Towards Honest Evidence from Observational Studies

George Hripcsak, David Madigan, Patrick Ryan, Martijn Schuemie, Marc Suchard

http://www.ohdsi.org

"The sole cause and root of almost every defect in the sciences is this: that whilst we falsely admire and extol the powers of the human mind, we do not search for its real helps."

— Novum Organum: Aphorisms [Book One], 1620, Sir Francis Bacon

Stroke, Systemic or Venous Thromboembolism

Real-world comparison of major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban, or warfarin

A propensity score matched analysis

Gregory Y. H. Lip, Allison Keshishian, Shital Kamble, Xianying Pan, Jack Mardekian, Ruslan Horblyuk, Melissa Hamilton

When comparisons were made between NOACs, matched rivaroxaban patients had a significantly higher risk of major bleeding (HR: 1.82; 95 % CI: 1.36–2.43) compared to apixaban patients.

Stroke, Systemic or Venous Thromboembolism

Real-world comparison of major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban, or warfarin
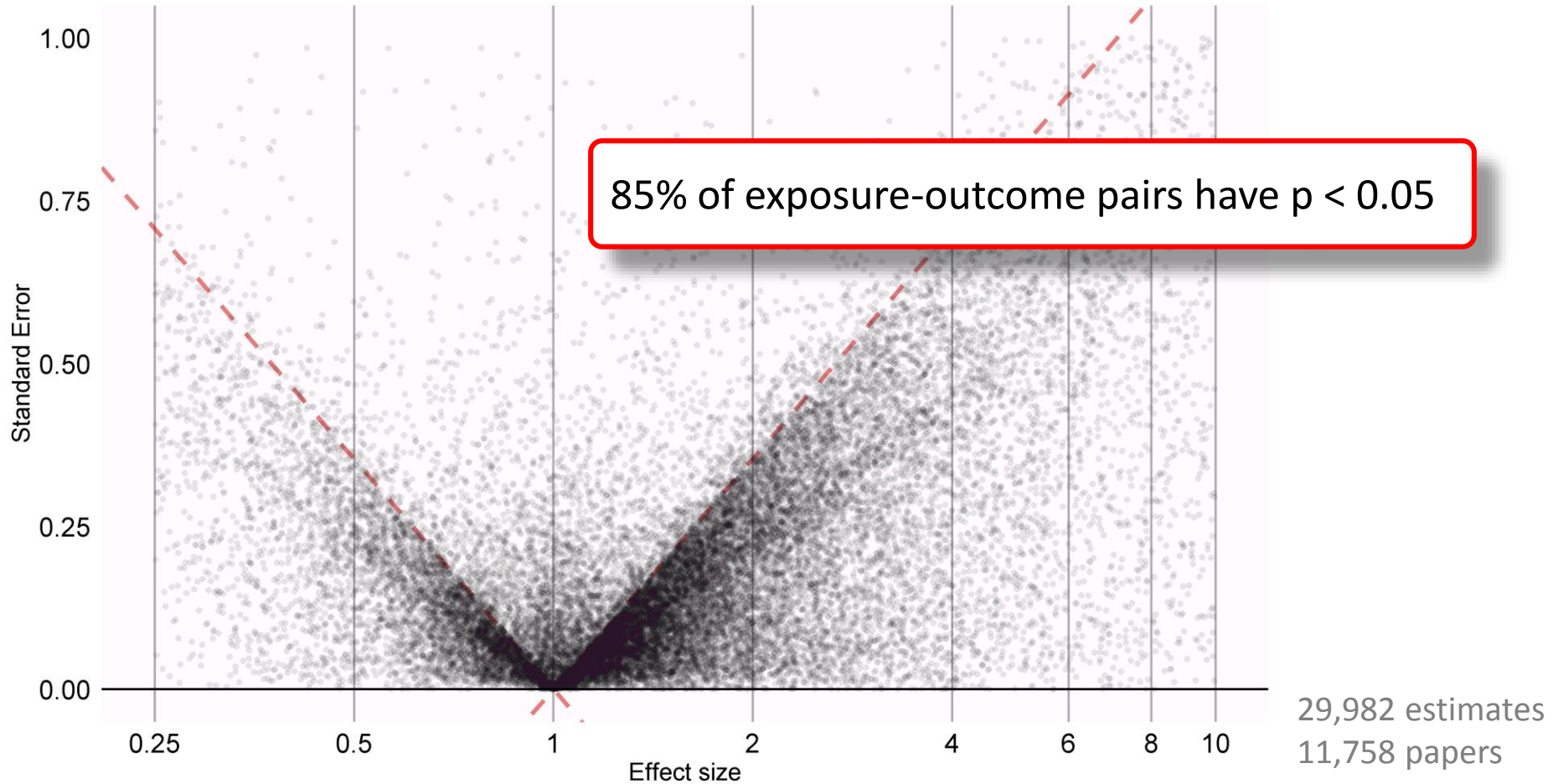
A propensity score matched analysis

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Reliable? Reproducible?

Observational research results in literature

85% of exposure-outcome pairs have p < 0.05

29,982 estimates
11,758 papers

Reliability: Analysis Ignores…

- Selection bias
- Measurement error
- Model misspecification
- Multiple modeling
- Unmeasured confounding

"Grave errors are commonplace, perhaps typical. It does no good to append a claim that you have included in the regression all relevant covariates, a claim that there are no unmeasured confounders and that you could not be mistaken in making this claim. Who are you that you could not be mistaken?"

- Paul Rosenbaum
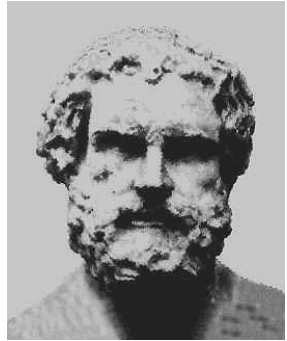
"I would rather discover one cause than gain the kingdom of Persia"
- Democritus 400 BCE

A New Approach

- Reproducible, systematized, open source approach at scale

- Negative controls
  - Drugs and outcomes "known" to have no causal association
  - Literature, product labels, spontaneous reports
  - Empirical p-values

- Positive Controls
  - Inject signals onto negative controls with known effect size
  - Calibrated confidence intervals

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Apps Courseworks David Madigan EJMS MedDRA – Terms | QScan iCloud – Find My iPh ScholarOne Manusc Continental Intellicast – Chatham New Jersey Transit CLIO » Other Bookmarks

OHDSI

OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

Who We Are   Who We Serve   Data Standardization   Analytic Tools   Resources   Join the Journey

Welcome to OHDSI!

The Observational Health Data Sciences and Informatics (or OHDSI, pronounced "Odyssey") program is a multi-stakeholder, interdisciplinary collaborative to bring out the value of health data through large-scale analytics. All our solutions are open-source.

OHDSI has established an international network of researchers and observational health databases with a central coordinating center housed at Columbia University.

Read more about us, about our goals, and how you can help support the OHDSI community.

Join the Journey

LEARN MORE
FROM YOUR
HEALTH DATA

ACHILLES Released

OHDSI released its first open-source software application, ACHILLES, at the 2014 EDM Forum in San Diego, CA. Congratulations to the ACHILLES

OHDSI on YouTube

Welcome to OHDSI

0:00 / 2:07

Latest News

- OHDSI paper published in Drug Safety

search here ...   Go

# Electronic Health Records ~ 700M

Major Use-Cases

- Population-level estimation
  - Effect estimation: Does metformin cause lactic acidosis?
  - Comparative effectiveness: Does metformin cause lactic acidosis more than glyburide?
- Patient-level prediction/Precision medicine
  - 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?
- Clinical characterization:
  - Natural history: Who are the patients that take metformin? What happens to them?
  - Quality improvement: what proportion of patients with diabetes experience disease-related complications?

Negative control: ingrowing nail

Crude estimate: duloxetine versus sertraline

HR = 1.16 (1.01 – 1.32), p = 0.03
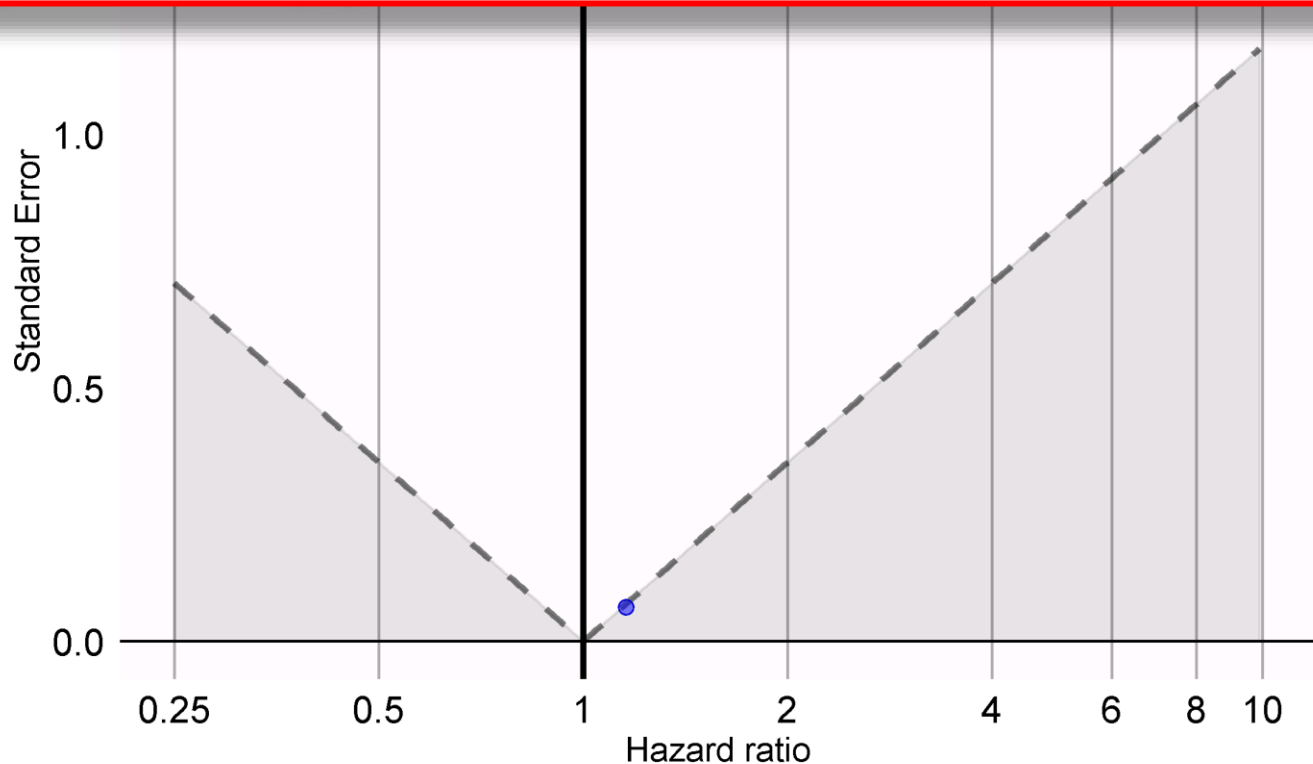
All negative controls - crude
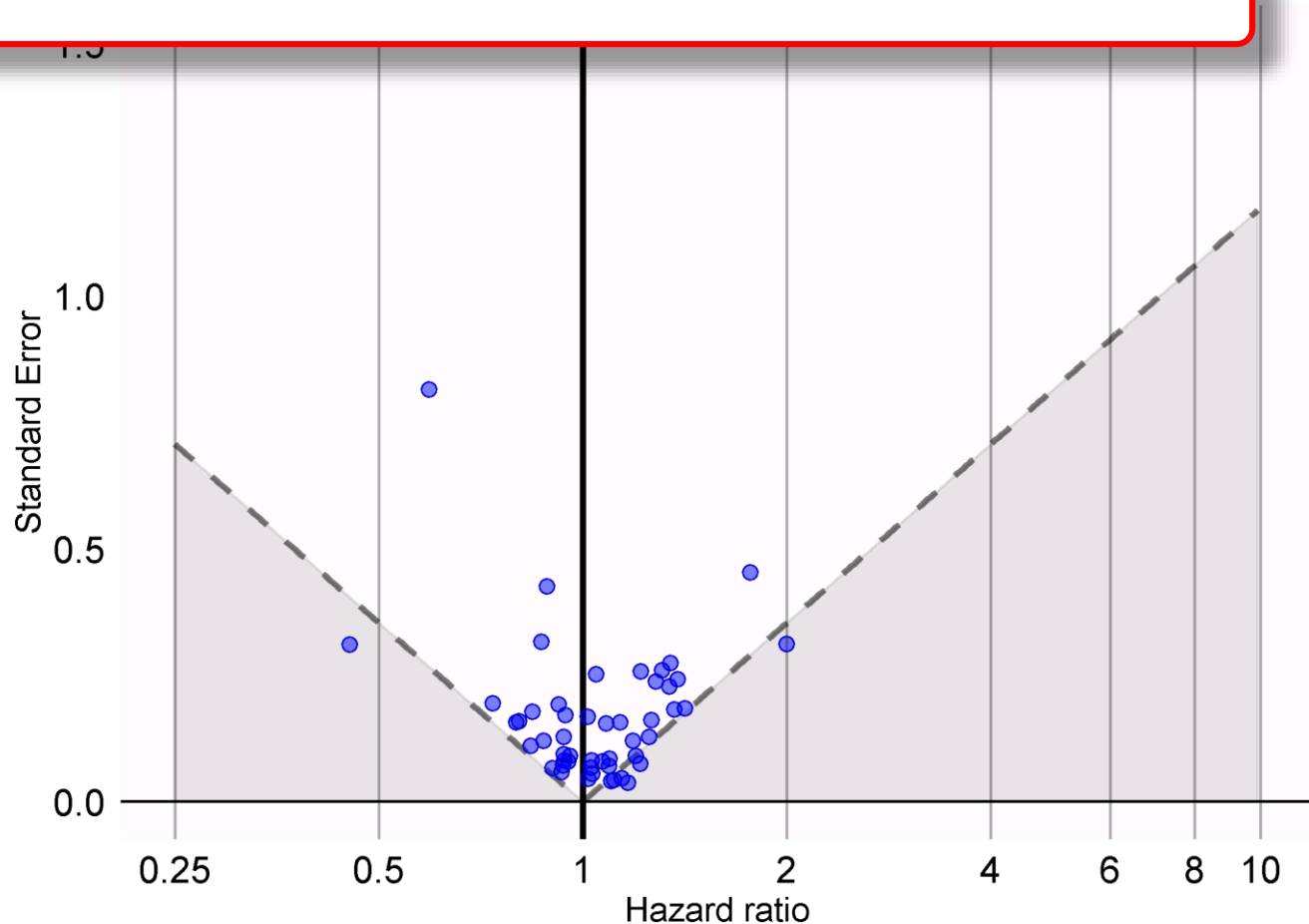
We would expect 5% of negative controls to have p < 0.05

Instead, 68% have p < 0.05!
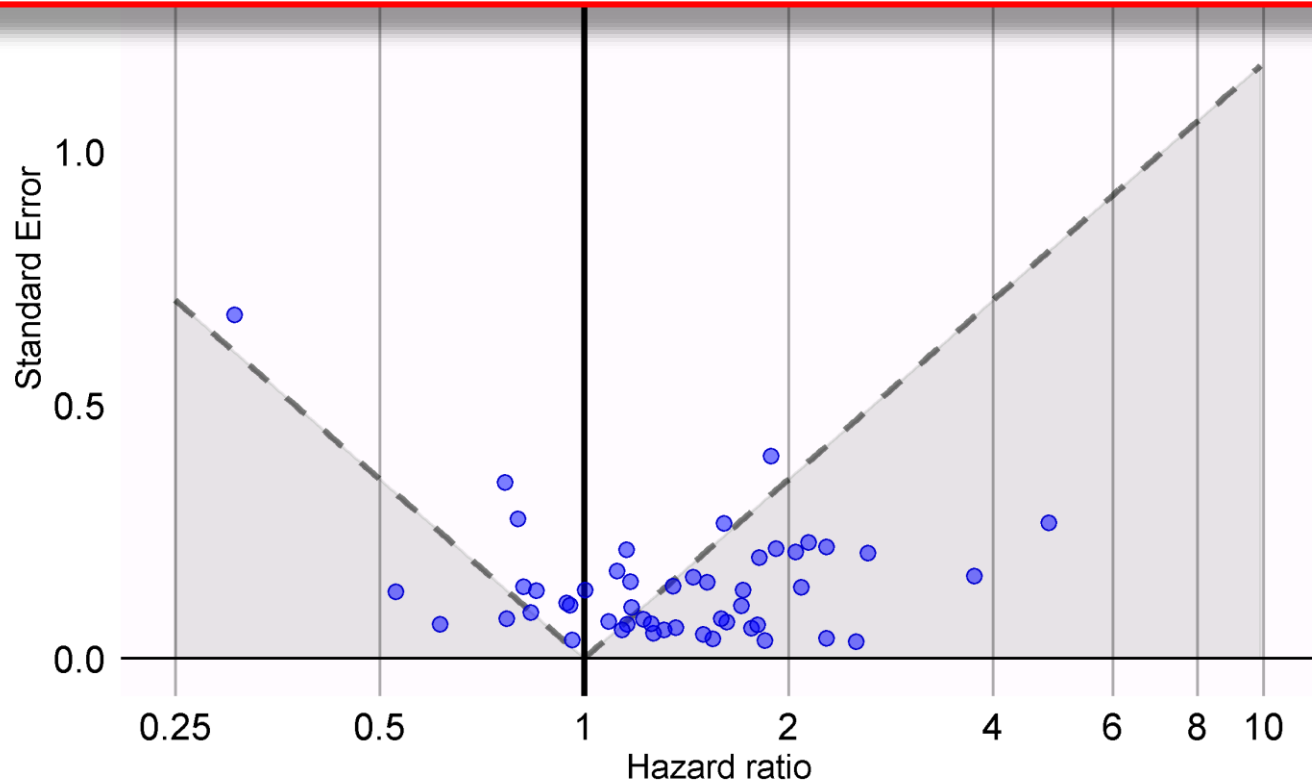
All negative controls - adjusted

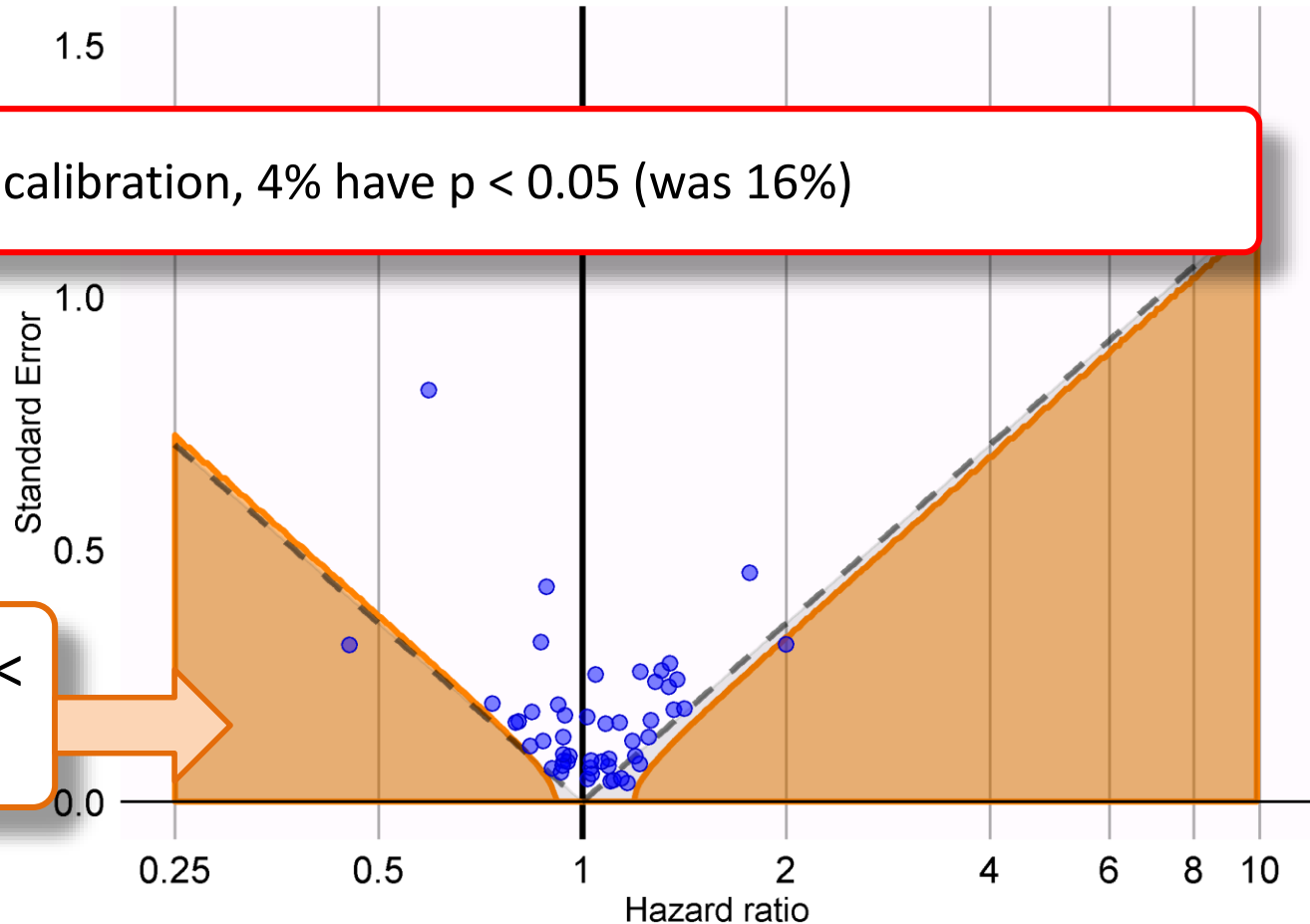When using propensity-based method, 16% have p < 0.05

P-value calibration

duloxetine vs. Sertraline - Adjusted

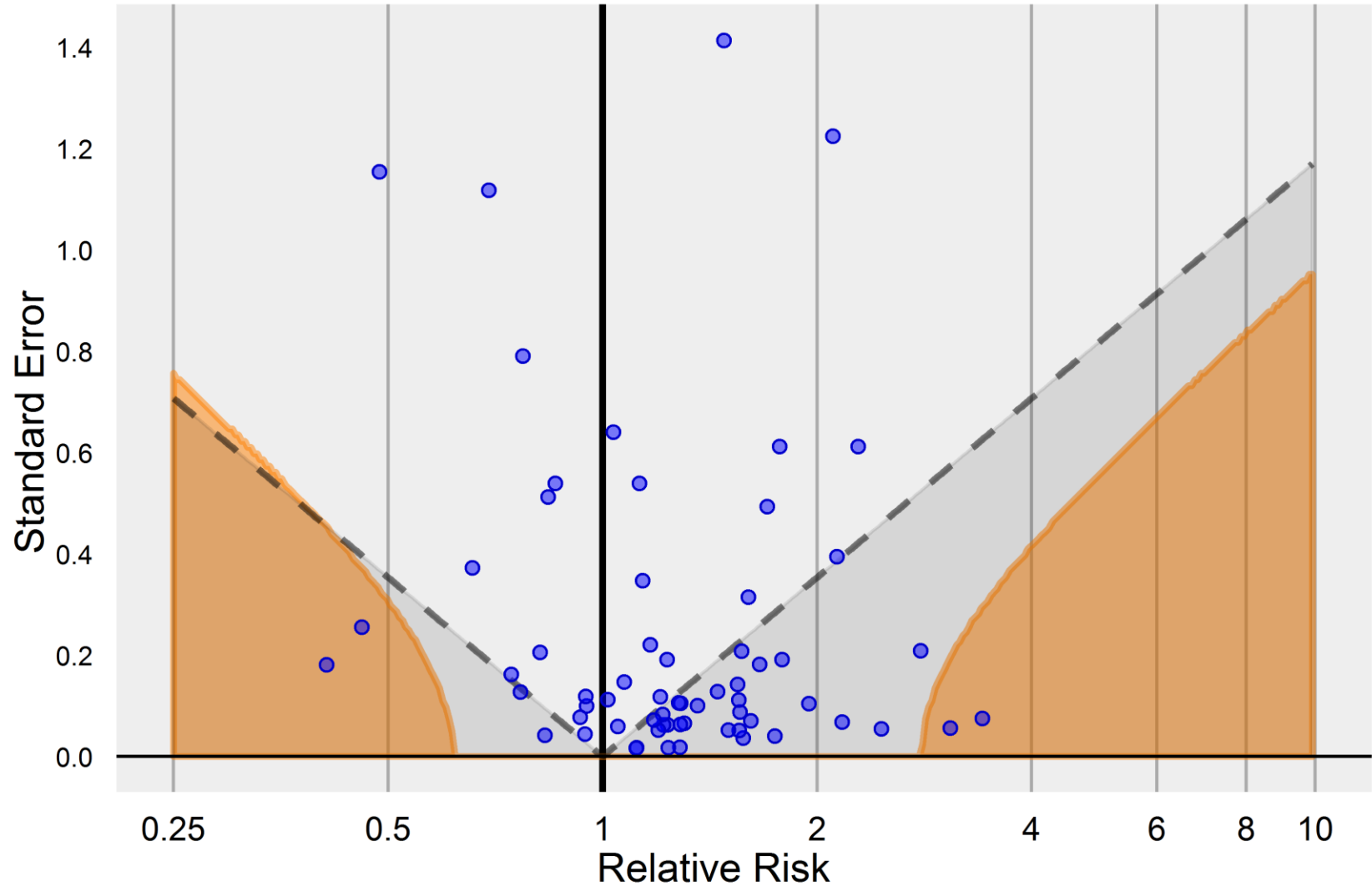After calibration, 4% have p < 0.05 (was 16%)

Calibrated p < 0.05

p-value calibration plot

2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

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56 pages containing **106** recommendations
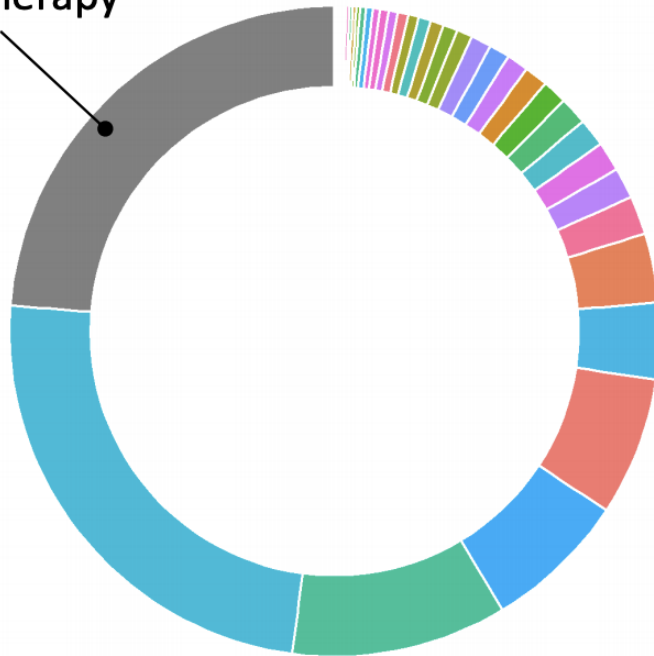
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Hypertension mono-therapy

Duo-therapy

Amlodipine	Labetalol
Atenolol	Lisinopril
Azilsartan	Losartan
Benazepril	Methyldopa
Bisoprolol	Metoprolol
Candesartan	Nadolol
Captopril	Nebivolol
Carvedilol	Nicardipine
Chlorthalidone	Nifedipine
Clonidine	Olmesartan
Diltiazem	Propranolol
Doxazosin	Quinapril
Enalapril	Ramipril
Felodipine	Spironolactone
Fosinopril	Telmisartan
Furosemide	Terazosin
Hydralazine	Torsemide
Hydrochlorothiazide	Valsartan
Indapamide	Verapamil
irbesartan	

Truven Health MarketScan CCAE. Therapies > 2 ingredients not shown

58 outcomes of interest

Abdominal pain	Dementia	Ischemic stroke
Abnormal weight gain	Depression	Kidney disease
Abnormal weight loss	Diarrhea	Malignant neoplasm
Acute myocardial infarction	Edema	Measured renal dysfunction
Acute pancreatitis	End stage renal disease	Nausea
Acute renal failure	Fall	Neutropenia or agranulocytosis
All-cause mortality	Gastrointestinal bleeding	Rash
Anaphylactoid reaction	Gout	Rhabdomyolysis
Anemia	Headache	Stroke
Angioedema	Heart failure	Sudden cardiac death
Anxiety	Hemorrhagic stroke	Syncope
Bradycardia	Hepatic failure	Thrombocytopenia
Cardiac arrhythmia	Hospitalization with heart failure	Transient ischemic attack
Cardiovascular disease	Hospitalization with preinfarction syndrome	Type 2 diabetes mellitus
Cardiovascular-related mortality	Hyperkalemia	Vasculitis
Chest pain or angina	Hypokalemia	Venous thromboembolic events
Chronic kidney disease	Hypomagnesemia	Vertigo
Coronary heart disease	Hyponatremia	Vomiting
Cough	Hypotension	
Decreased libido	Impotence	

76 negative controls

Abnormal cervical smear

Abnormal pupil

Abrasion and/or friction burn of trunk without infection

Absence of breast

Absent kidney

Acid reflux

Acquired hallux valgus

Acquired keratoderma

Acquired trigger finger

Acute conjunctivitis

Amputated foot

Anal and rectal polyp

Burn of forearm

Calcaneal spur

Cannabis abuse

Cervical somatic dysfunction

Changes in skin texture

Chondromalacia of patella

Cocaine abuse

Colostomy present

Complication due to Crohn's disease

Contact dermatitis

Contusion of knee

Crohn's disease

Derangement of knee

Difficulty sleeping

Disproportion of reconstructed breast

Effects of hunger

Endometriosis

Epidermoid cyst

Feces contents abnormal

Foreign body in orifice

Ganglion cyst

Genetic predisposition

Hammer toe

Hereditary thrombophilia

Herpes zoster without complication

High risk sexual behavior

Homocystinuria

Human papilloma virus infection

Ileostomy present

Impacted cerumen

Impingement syndrome of shoulder region

Ingrowing nail

Injury of knee

Irregular periods

Kwashiorkor

Late effect of contusion

Late effect of motor vehicle accident

Leukorrhea

Macular drusen

Melena

Nicotine dependence

Noise effects on inner ear

Nonspecific tuberculin test reaction

Non-toxic multinodular goiter

Onychomycosis due to dermatophyte

Opioid abuse

Passing flatus

Postviral fatigue syndrome

Presbyopia

Problem related to lifestyle

Psychalgia

Ptotic breast

Regular astigmatism

Senile hyperkeratosis

Somatic dysfunction of lumbar region

Splinter of face, without major open wound

Sprain of ankle

Strain of rotator cuff capsule

Tear film insufficiency

Tobacco dependence syndrome

Vaginitis and vulvovaginitis

Verruca vulgaris

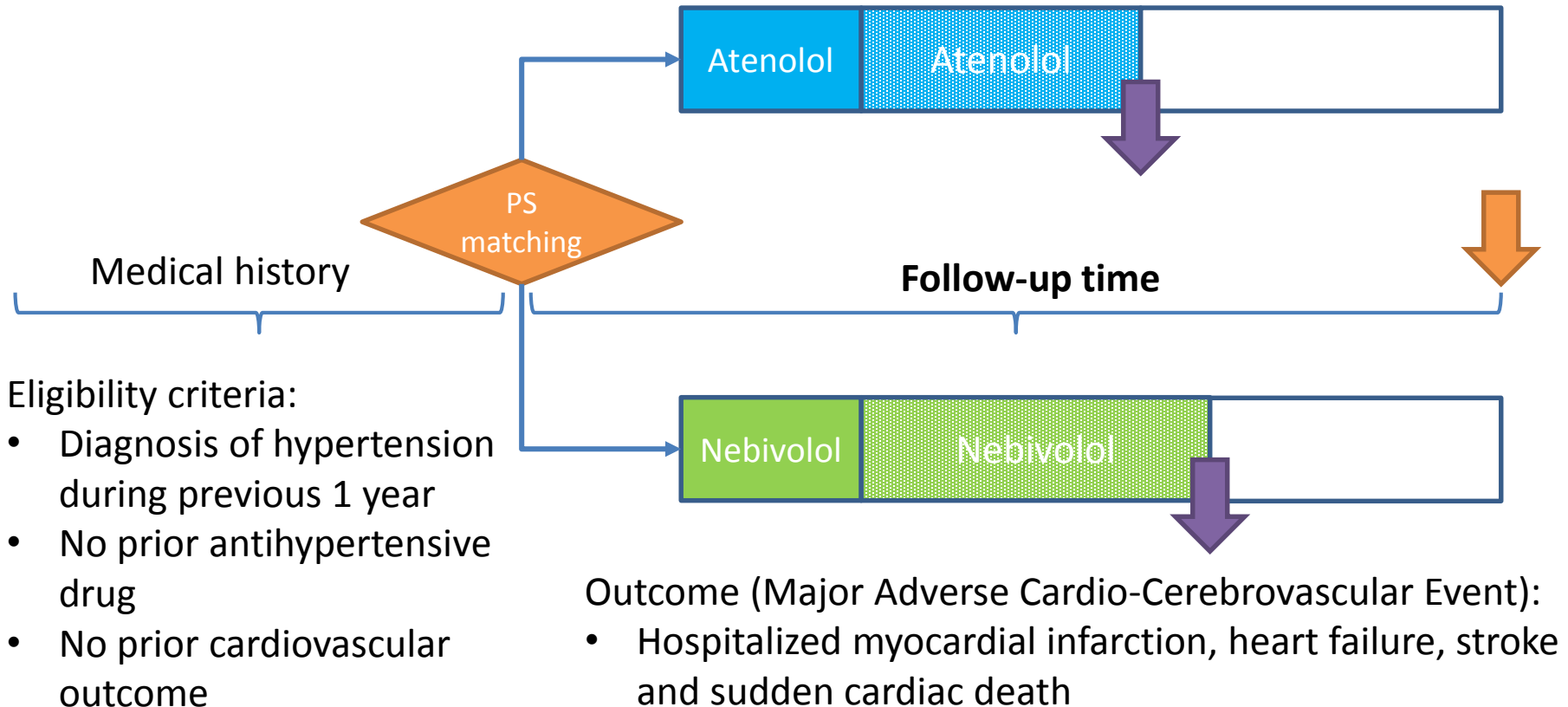Wrist joint pain

Wristdrop

Method: Study design (LEGEND)

Treatment strategies:
- **Atenolol**
- **Nebivolol**

Causal contrasts of interest:
- On-treatment effect
- Intent-to-treat effect

Medical history

Eligibility criteria:
- Diagnosis of hypertension during previous 1 year
- No prior antihypertensive drug
- No prior cardiovascular outcome

PS matching

| Atenolol | Atenolol | |

Follow-up time

| Nebivolol | Nebivolol | |

Outcome (Major Adverse Cardio-Cerebrovascular Event):
- Hospitalized myocardial infarction, heart failure, stroke and sudden cardiac death

Method: **LEGEND** (Large-scale Evidence Generation and Evaluation in a Network of Databases

All randomized trials

LEGEND

40 trials
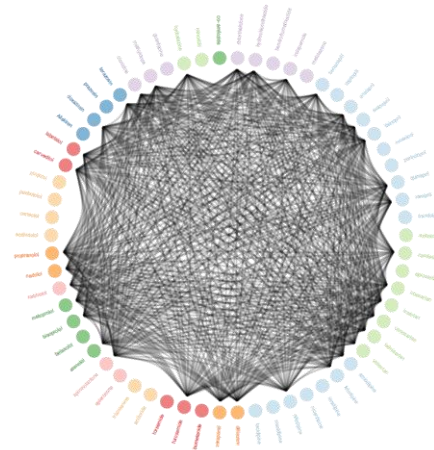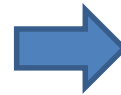
10,278 comparisons

US Insurance databases

    IBM® MarketScan® CCAE (Commercial Claims and Encounters)

    IBM® MarketScan® MDCD (Multi-state Medicaid)

    IBM® MarketScan® MDCR (Medicare Supplemental Beneficiaries)

    Optum® Clinformatics®

Japanese insurance database

    Japan Medical Data Center (JMDC)

Korean National insurance database

    NHIS-national sample cohort (NHIS-NSC) DB

US EHR databases

    Columbia University medical Center

    Optum® PANTHER®

German EHR database
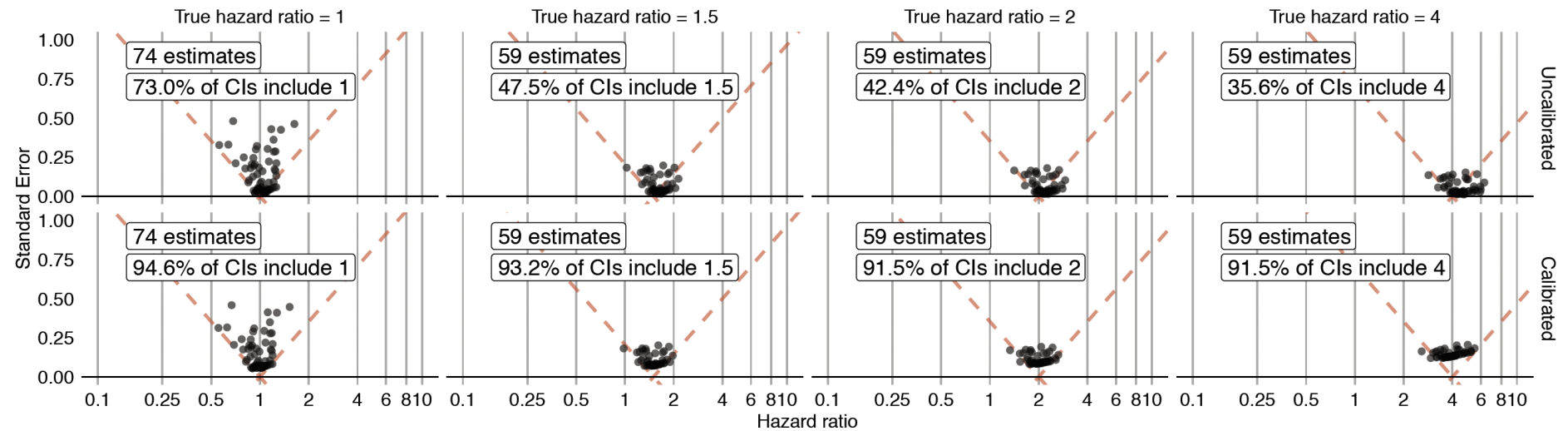
    QuintilesIMS Disease Analyzer (DA) Germany

https://github.com/OHDSI/LEGEND

LEGEND results

1,321,696 estimates

83.4% of CIs includes 1

Observational research results in literature

85% of exposure-outcome pairs have p < 0.05

29,982 estimates
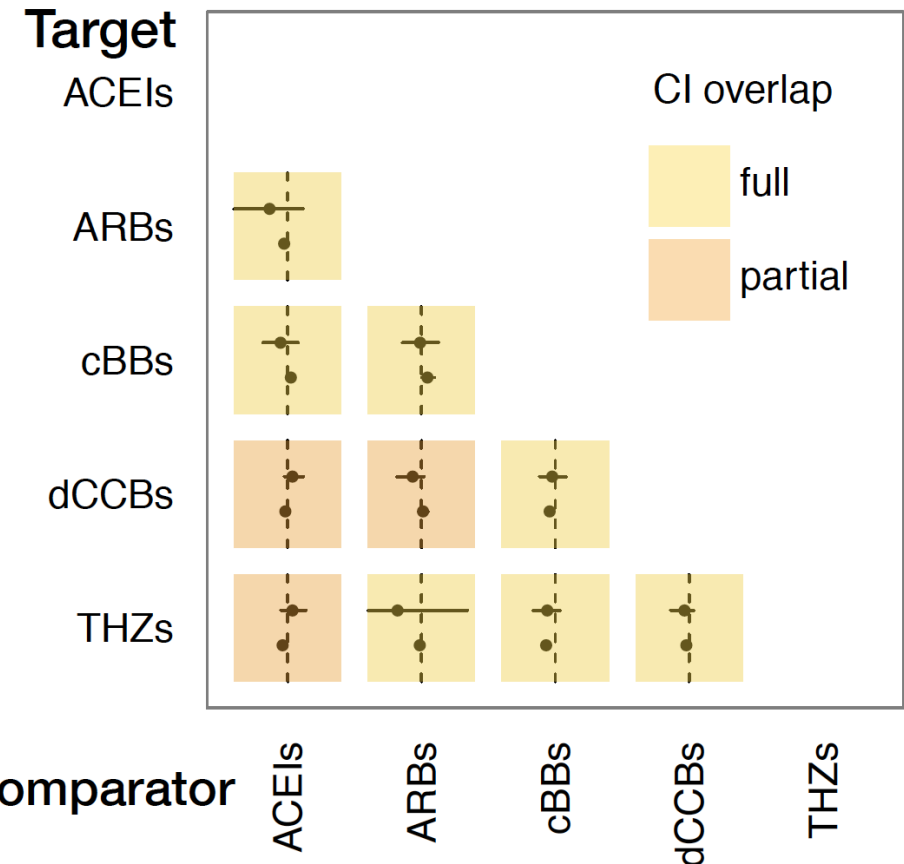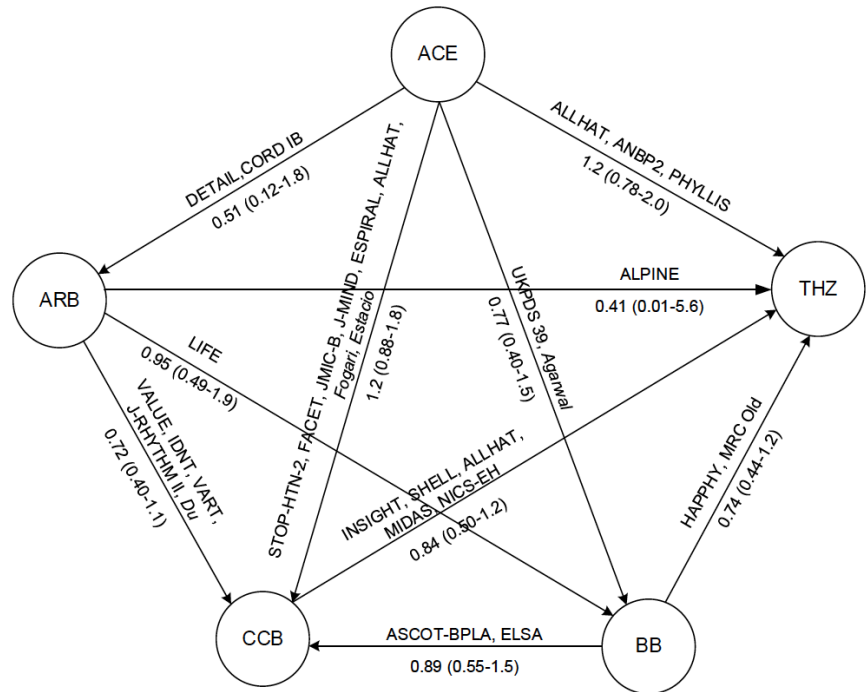11,758 papers
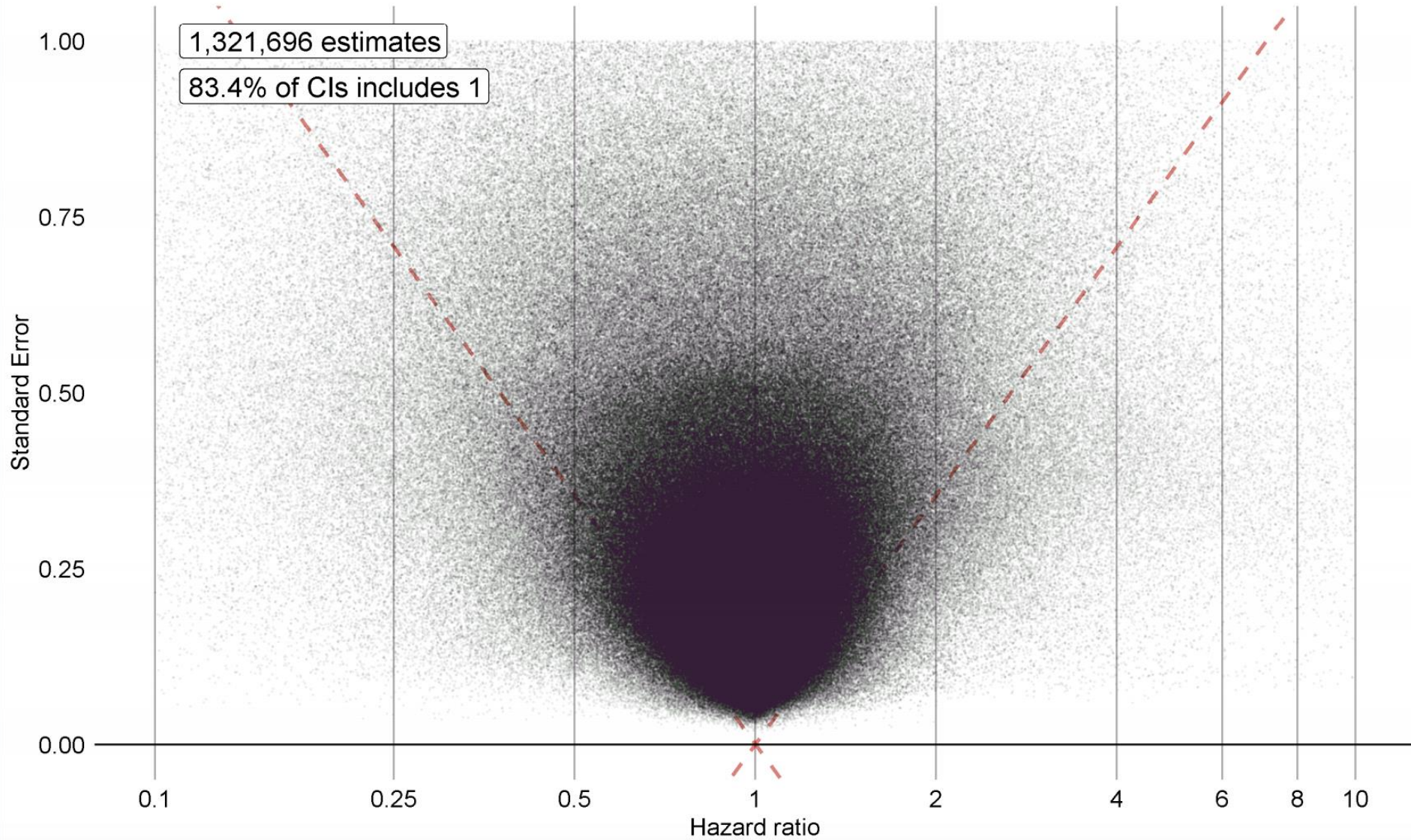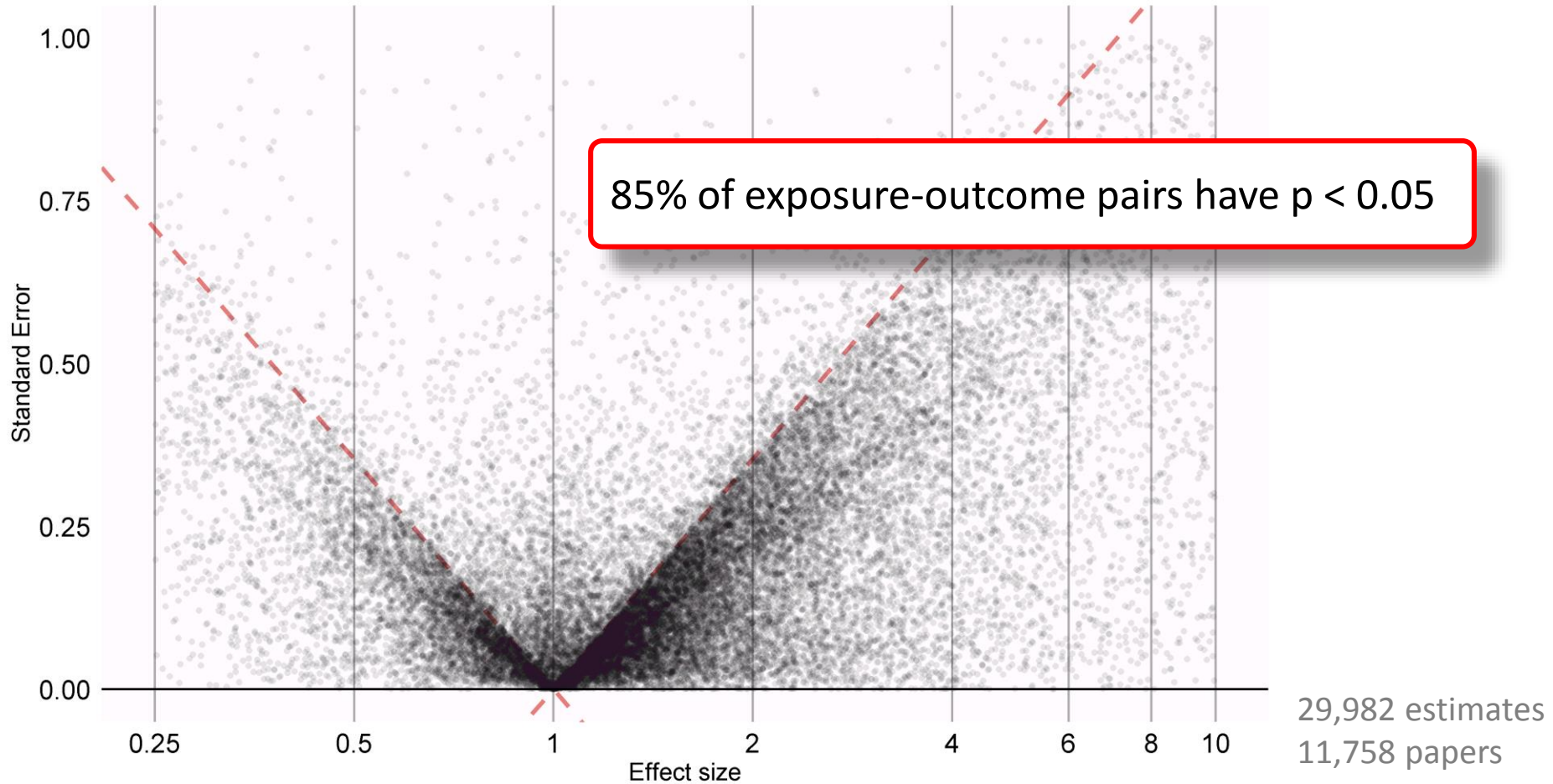
Thiazide vs. ACEi, MI

Performance on the controls

Efficacy outcomes: **myocardial infarction**, heart failure, stroke

- 28 / 30 estimates are concordant (discordant in BBs for HF)

http://data.ohdsi.org/LegendBasicViewer

http://data.ohdsi.org/LegendMedCentral/   (gimmick?)

Concluding thoughts

- An international community and global data network can be used to generate real-world evidence in a secure, reliable and efficient manner

- Common data model critically important

- Much work remains on establishing (and improving) <u>actual</u> operating characteristics of current approaches to causal inference

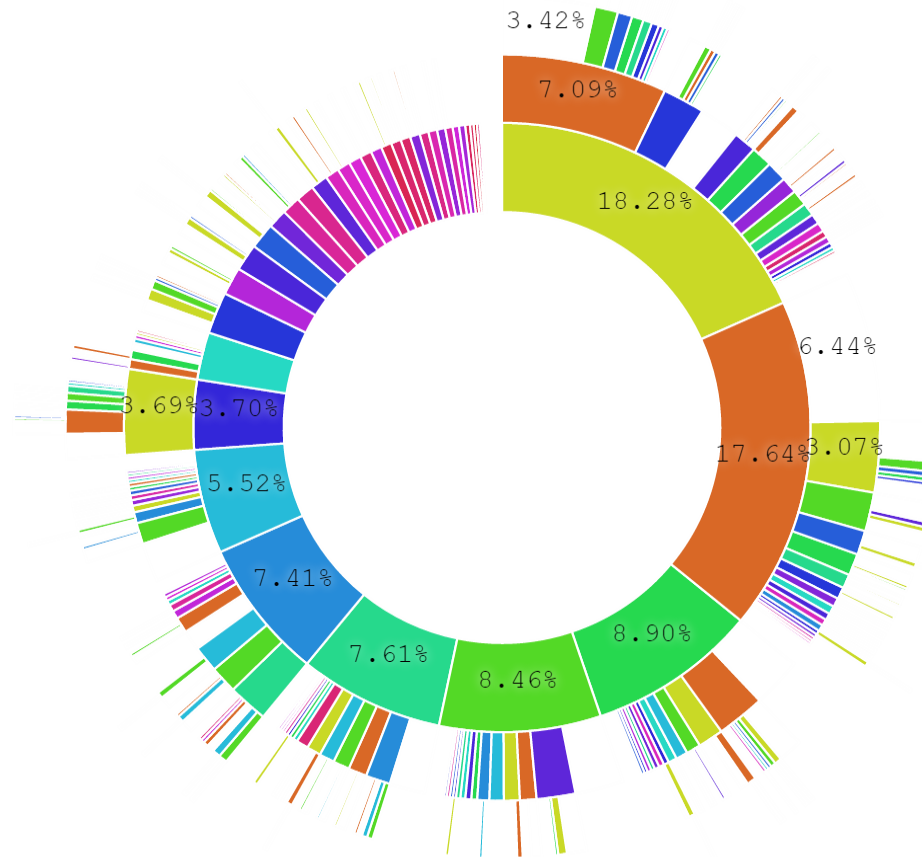# Treatment pathways for diabetes

T2DM : All databases

Only drug

First drug

Second drug

(Hripcsak et al, 2016, PNAS)
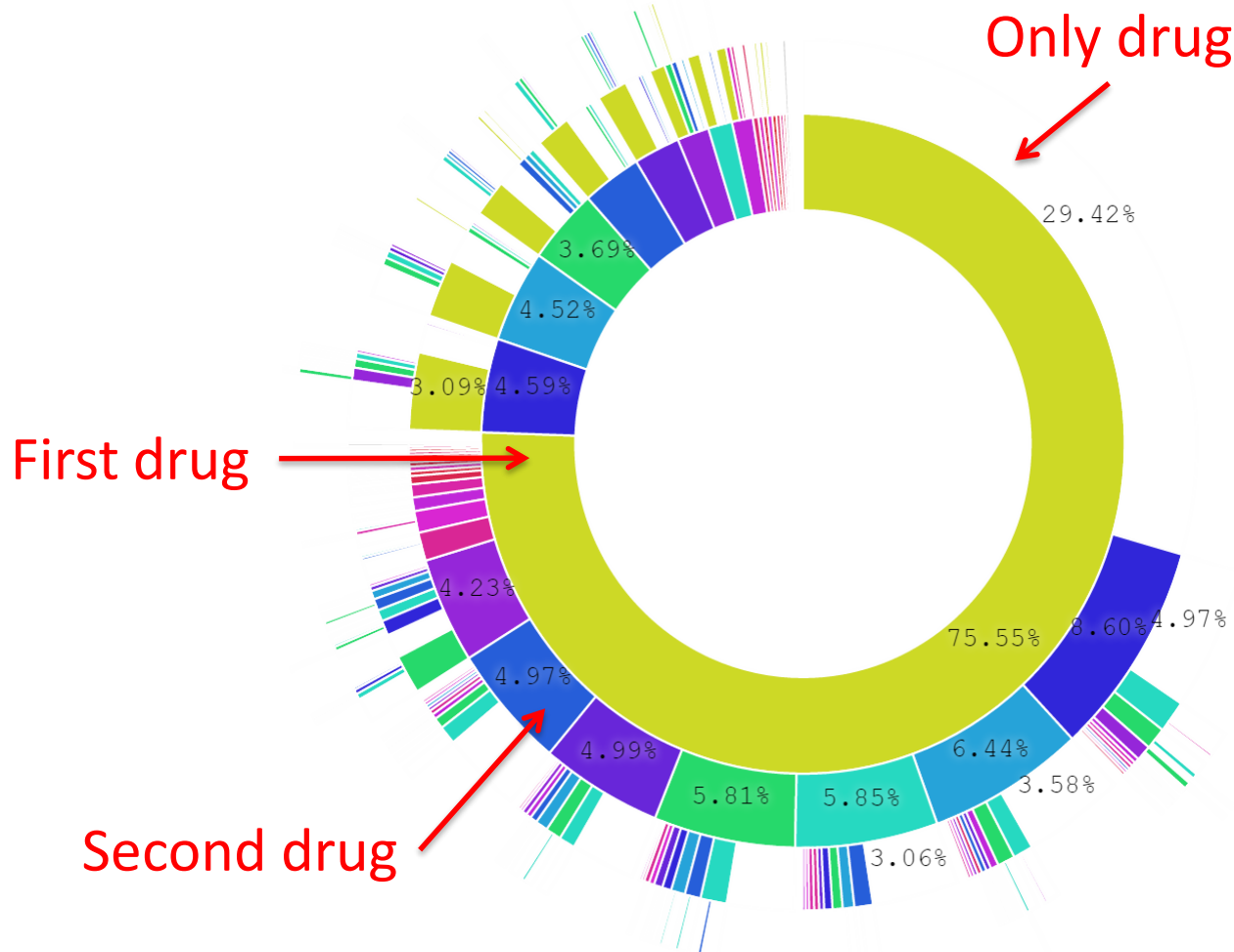
Legend:
- Metformin
- pioglitazone
- sitagliptin
- Glipizide
- glimepiride
- Gliclazide
- Glyburide
- rosiglitazone
- Insulin, Glargine, Human
- exenatide
- Insulin, Aspart, Human
- liraglutide
- saxagliptin
- Insulin, Lispro, Human
- Glucose
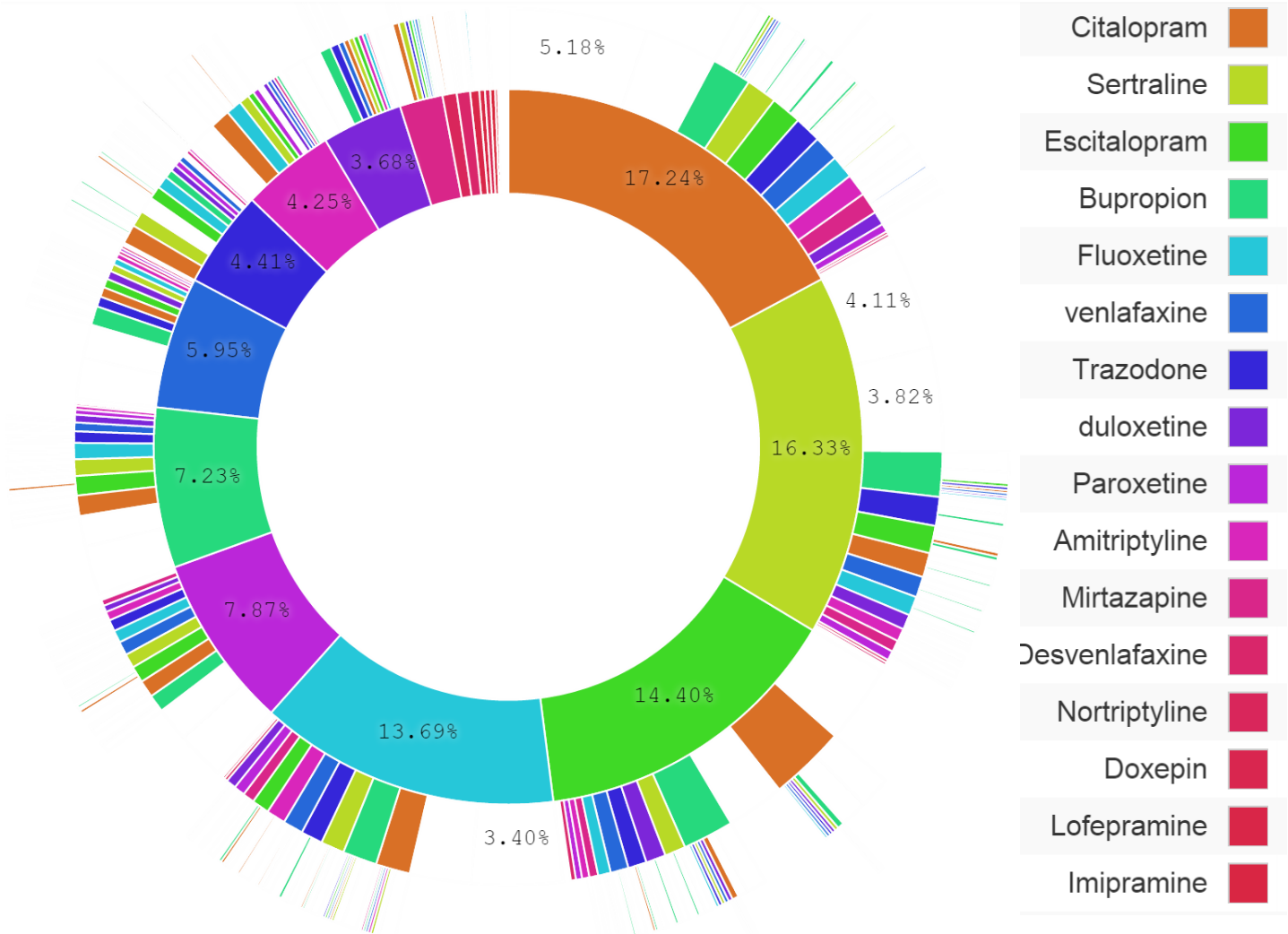- Insulin, Isophane, Human

Treatment pathways for HTN
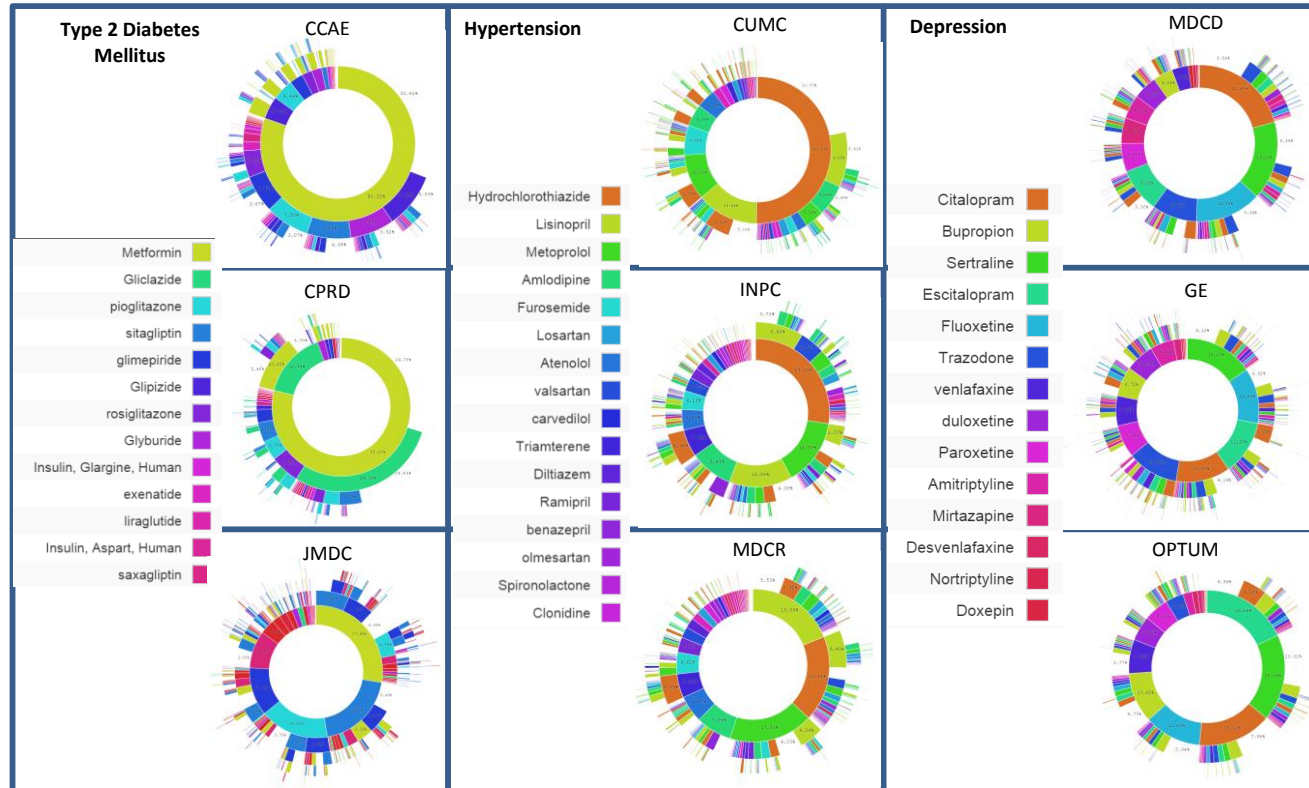
HTN: All databases

Treatment pathways for depression
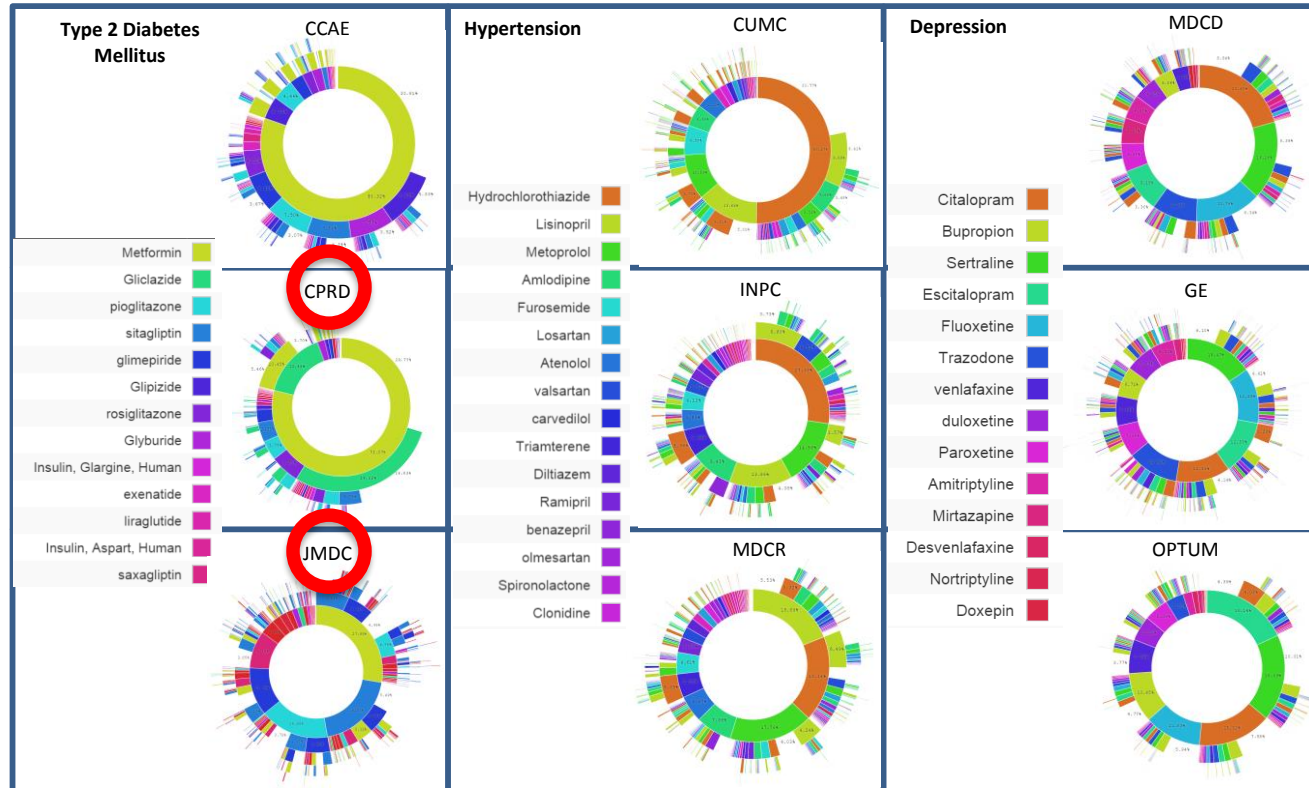
Depression: All databases

Population-level heterogeneity
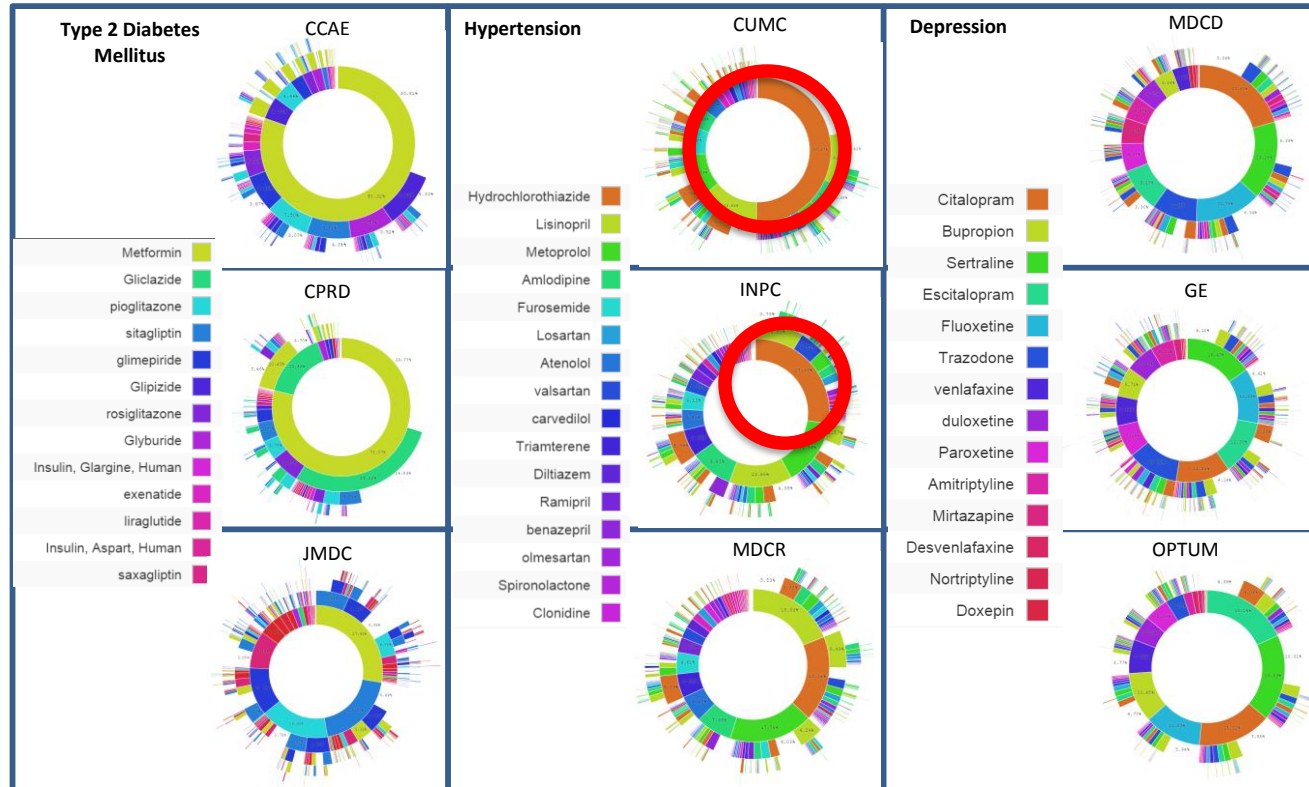
Population-level heterogeneity

Differences by country

Population-level heterogeneity

Differences by medical center