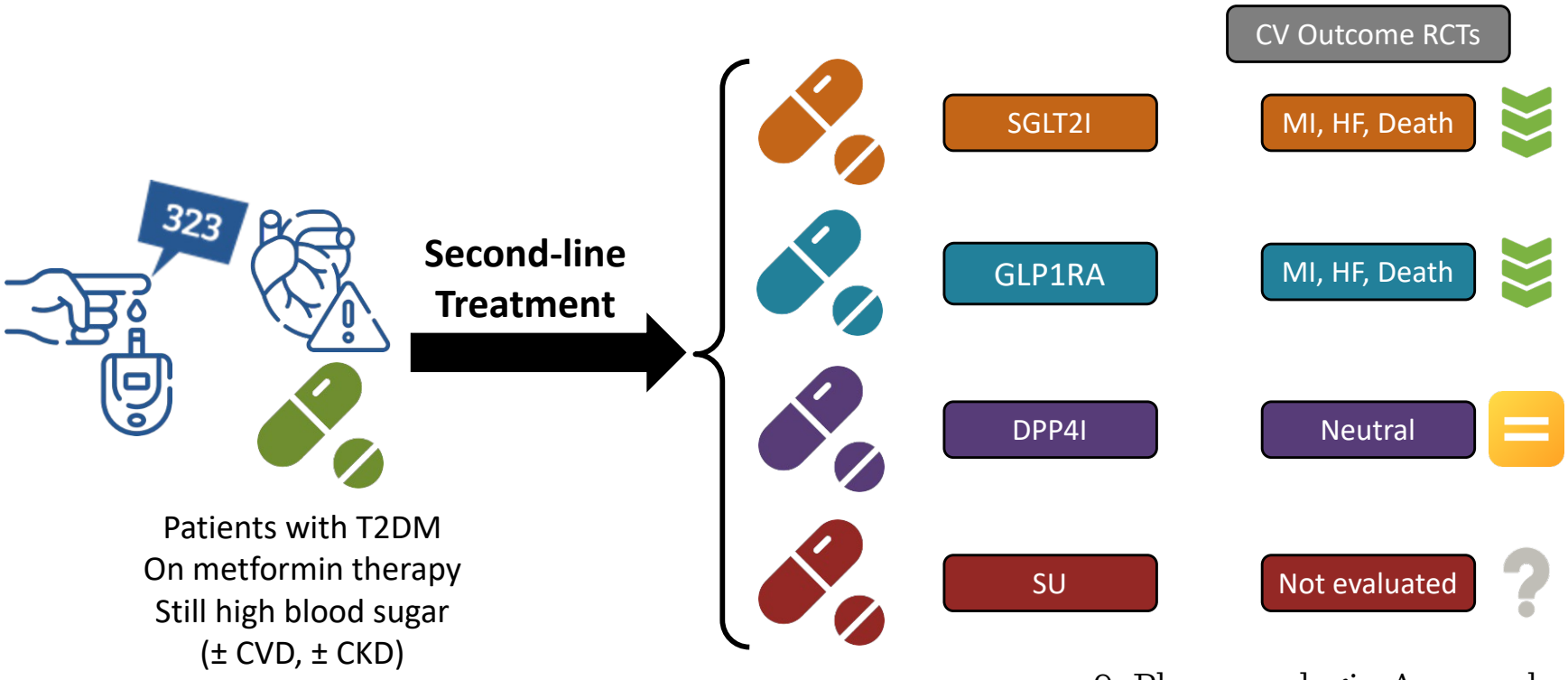
Insights from the large-scale evidence generation and evaluation across a network of databases for type 2 diabetes mellitus (LEGEND-T2DM)

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

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

2024 APAC OHDSI Symposium
6 December 2024

Type 2 diabetes mellitus (T2DM) treatment



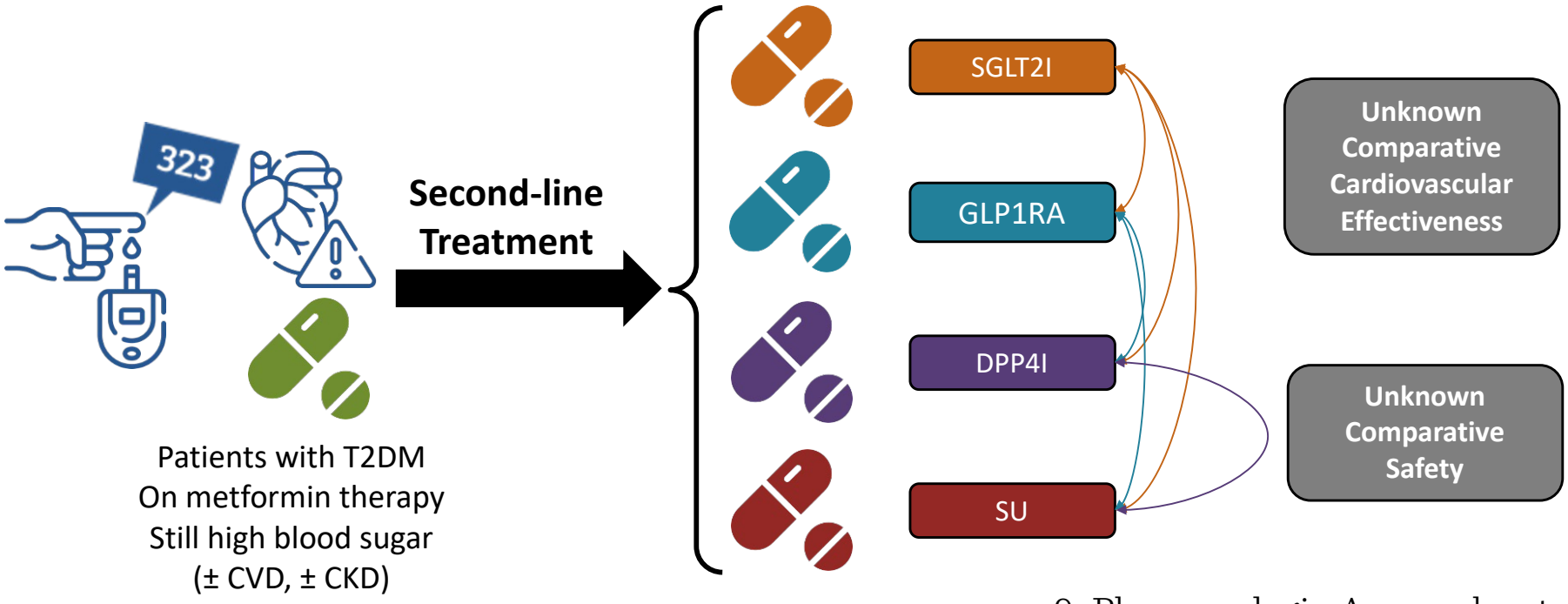
- American Diabetes Association: start with an SGLT2 inhibitor, GLP-1 receptor antagonist, DPP4 inhibitor or sulfonylurea
- Limited randomized controlled trials (RCTs) and clinical experience

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

Type 2 diabetes mellitus (T2DM) treatment



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

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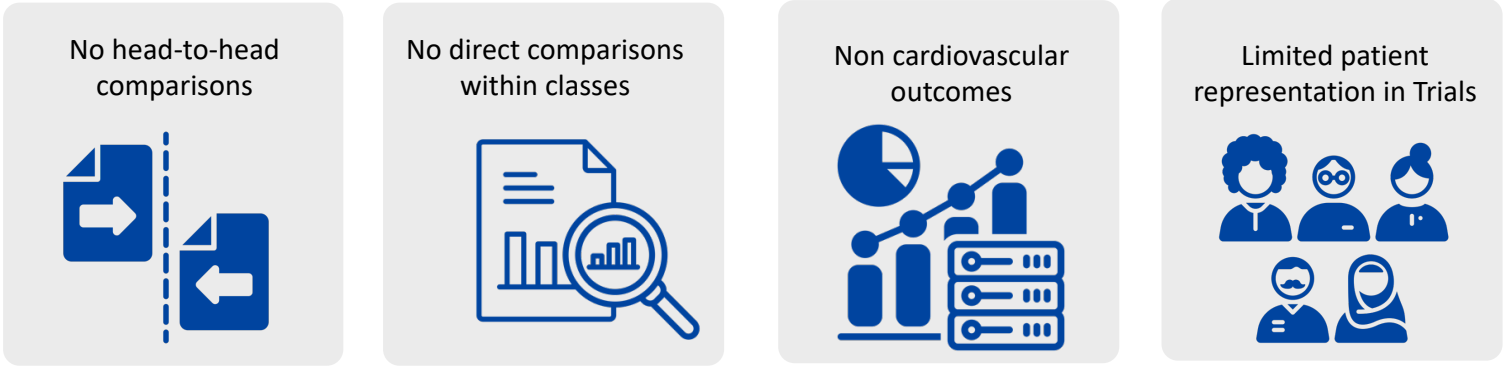
LEGEND in action

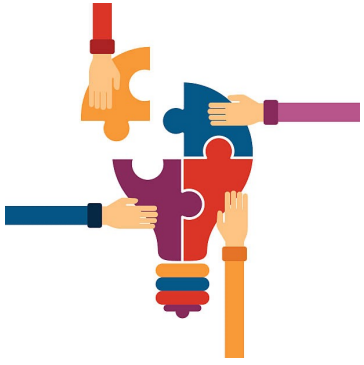
Huge knowledge gaps across $\mathcal{O}(10000)$ of **missing** RCT studies:



LEGEND aims to fill these gaps while overcoming current limitations of observational research (paradigm shift)

Observational Data

Evidence gaps

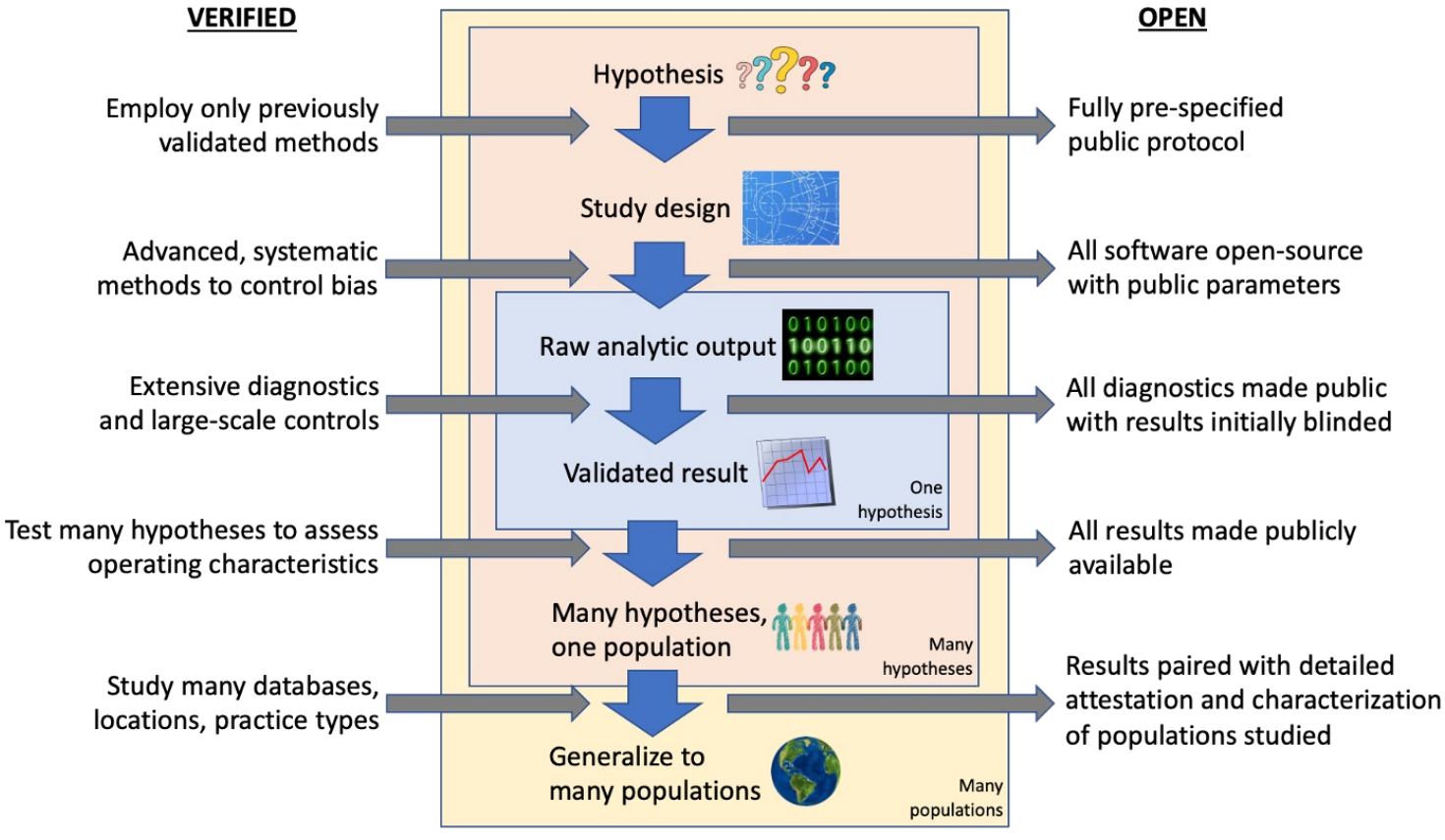


Limitations

- Residual confounding
- P hacking
- Publication bias

LEGEND philosophy

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

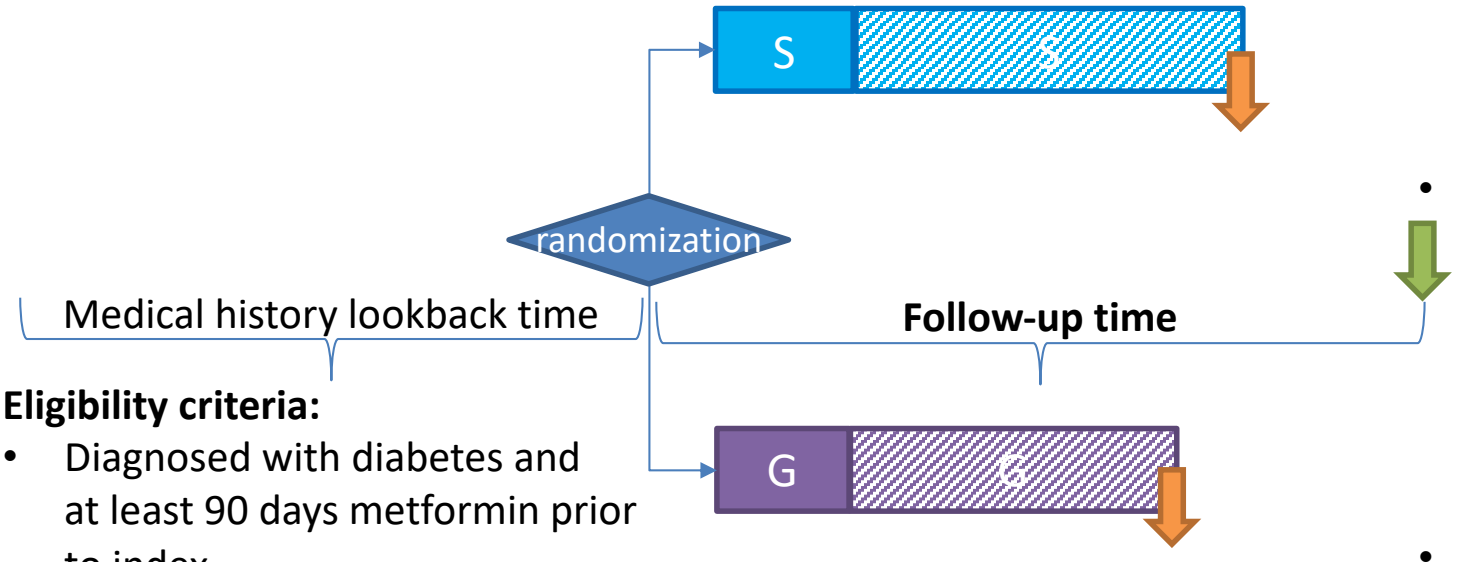


- rich, rigorous, and reliable (no one person has all necessary skills; central role for each of you)

Target trial for comparing two initial therapies

Treatment strategies:
- Initiation with SGLT2I (S)
- Initiation with GLP1RA (G)

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



Outcomes:
- CV efficacy:
  - Heart attack
  - Stroke
  - Heart Failure
- Safety:
  - Hypoglycemia
  - UTI
  - Cancer
  - Nausea
  - Vomiting
  - Diarrhea
- Negative controls

Eligibility criteria:
- Diagnosed with diabetes and at least 90 days metformin prior to index
- No prior 2nd-line drug use anytime prior to index

Analysis plan:
- Time-to-first-event analysis
- Cox proportional hazards

Observ. study for comparing two initial therapies

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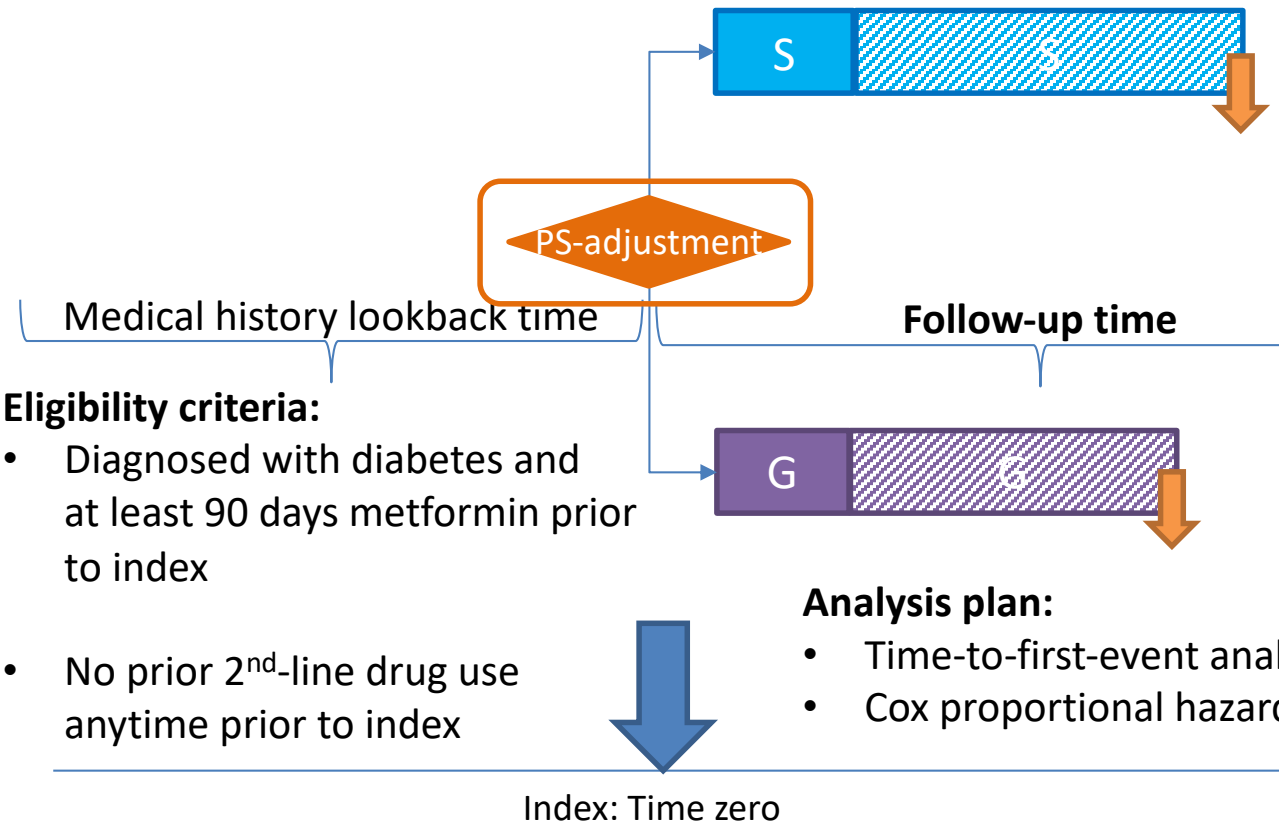

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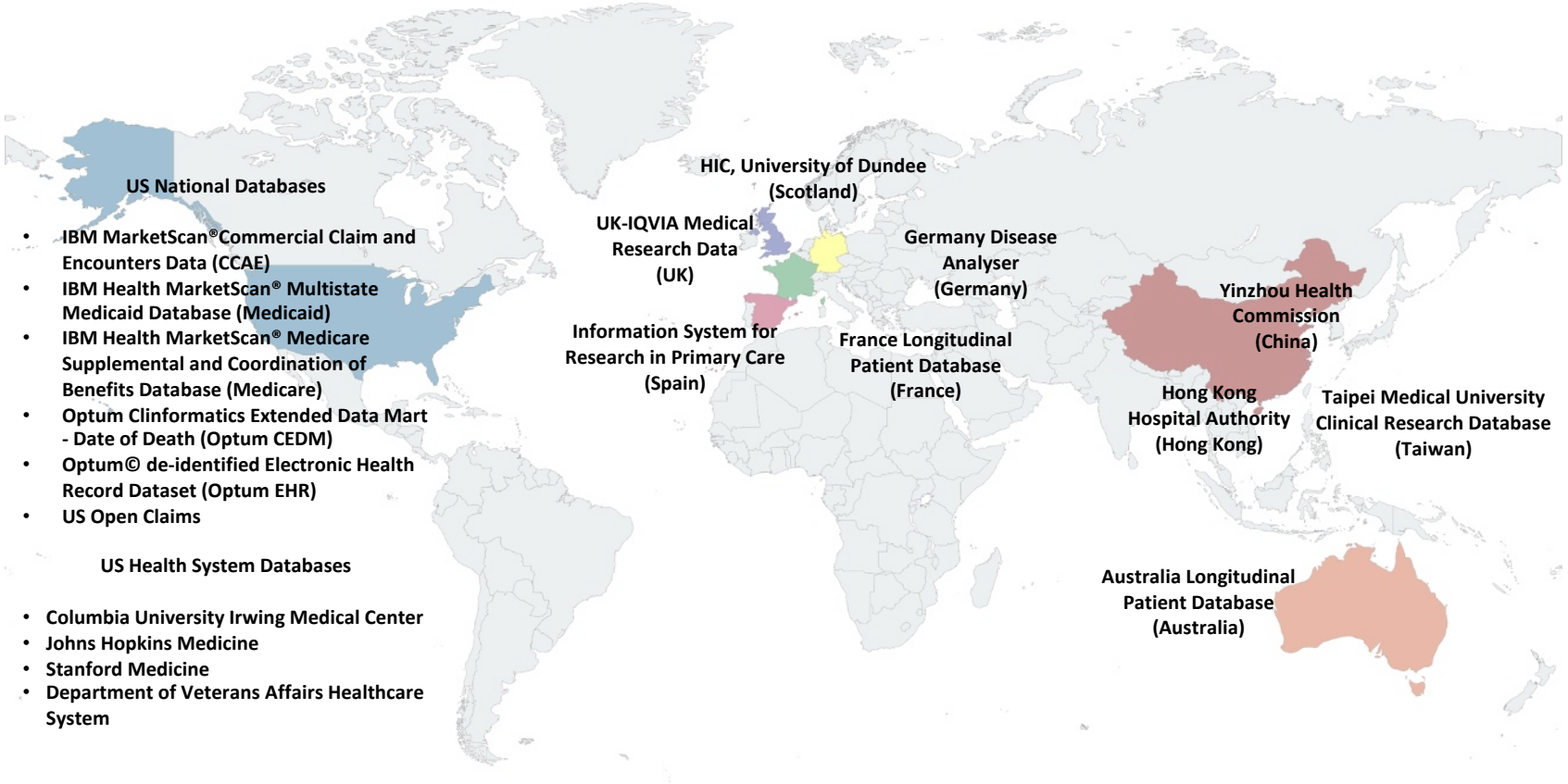
Second-line initiators across a global network

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

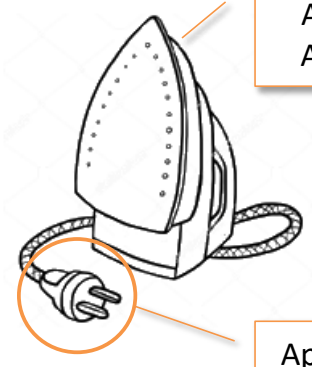


- 19 administrative claims and EHR data partners around the world

Current study approach does not scale

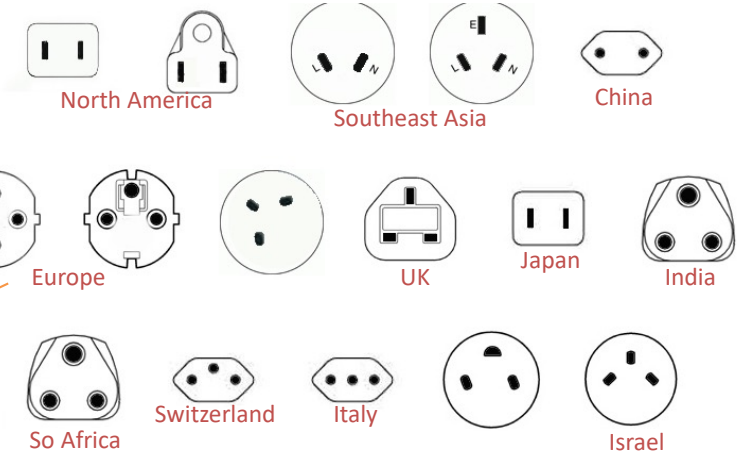
One study question - one database - one script

"What's the adherence to my drug in the data assets I own?"

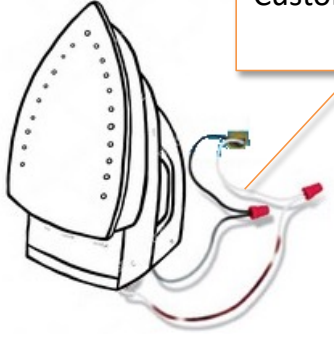


Analytical method: Adherence to Drug

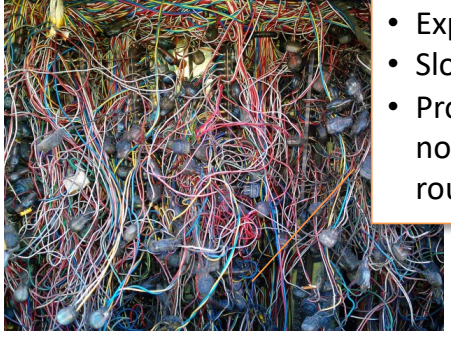
Application to data



Current solution:

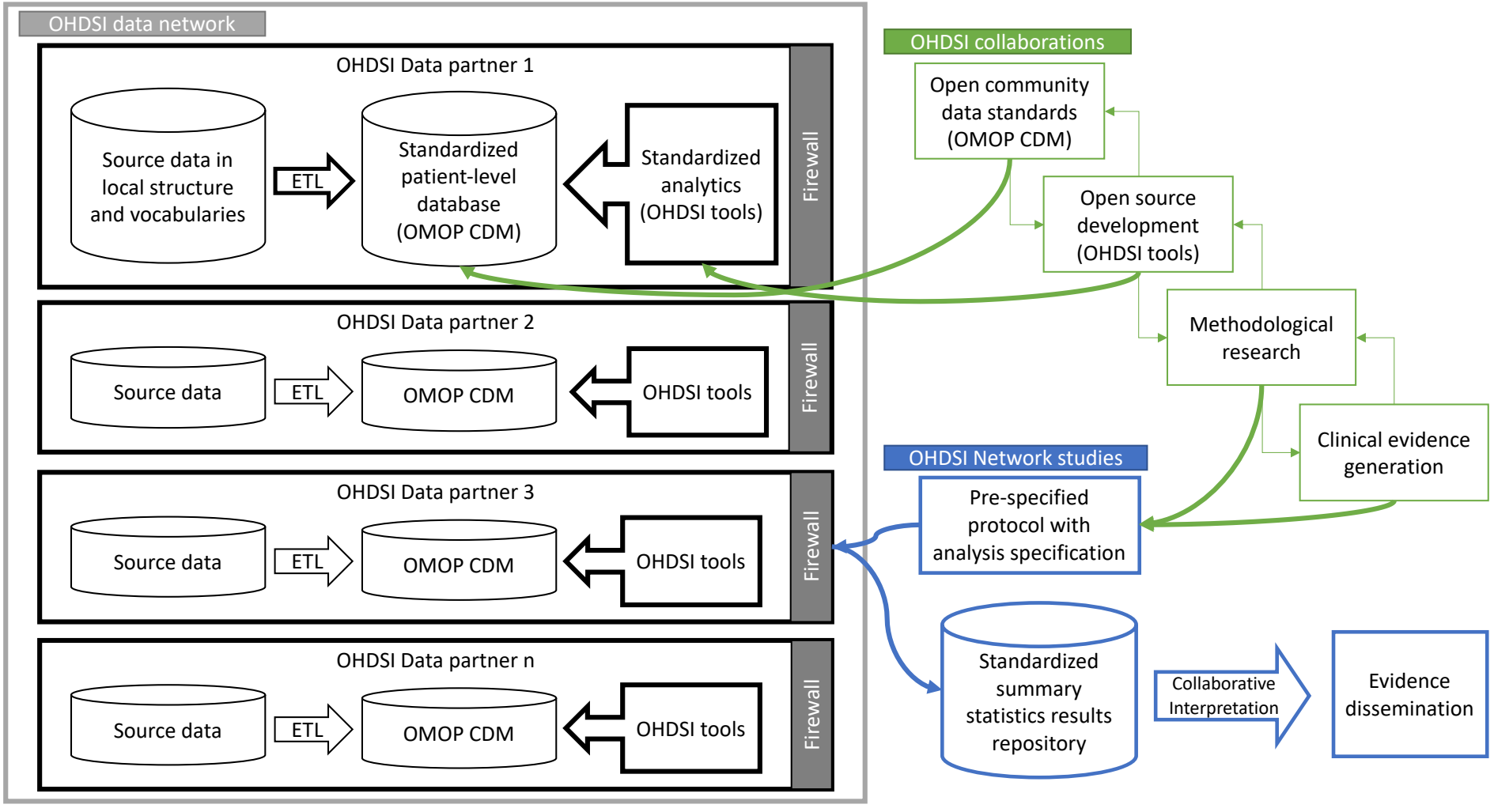


Custom script for each study

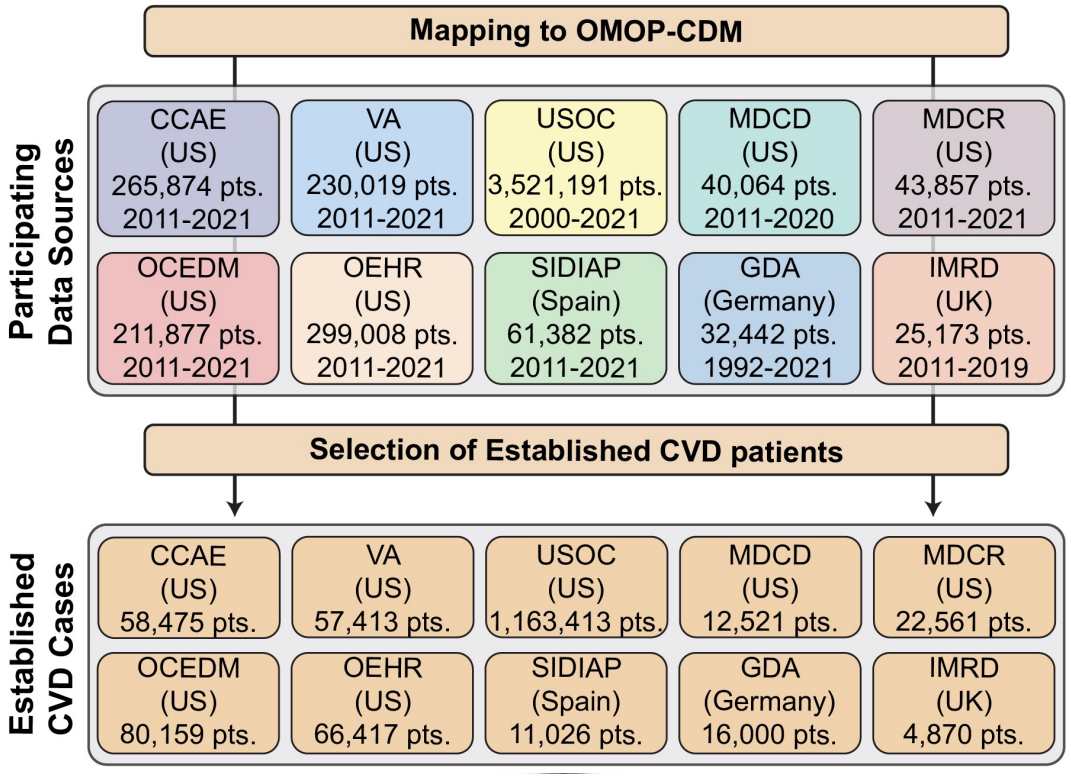


- Not scalable
- Expensive
- Slow
- Prohibitive to non-expert routine use

Open-science standards overcome the silos



New-initiators with T2DM and CVD (2011-2021)



1.5 million patients with T2DM and CVD

SGLT2i 16%

GLP-1 RA 8%

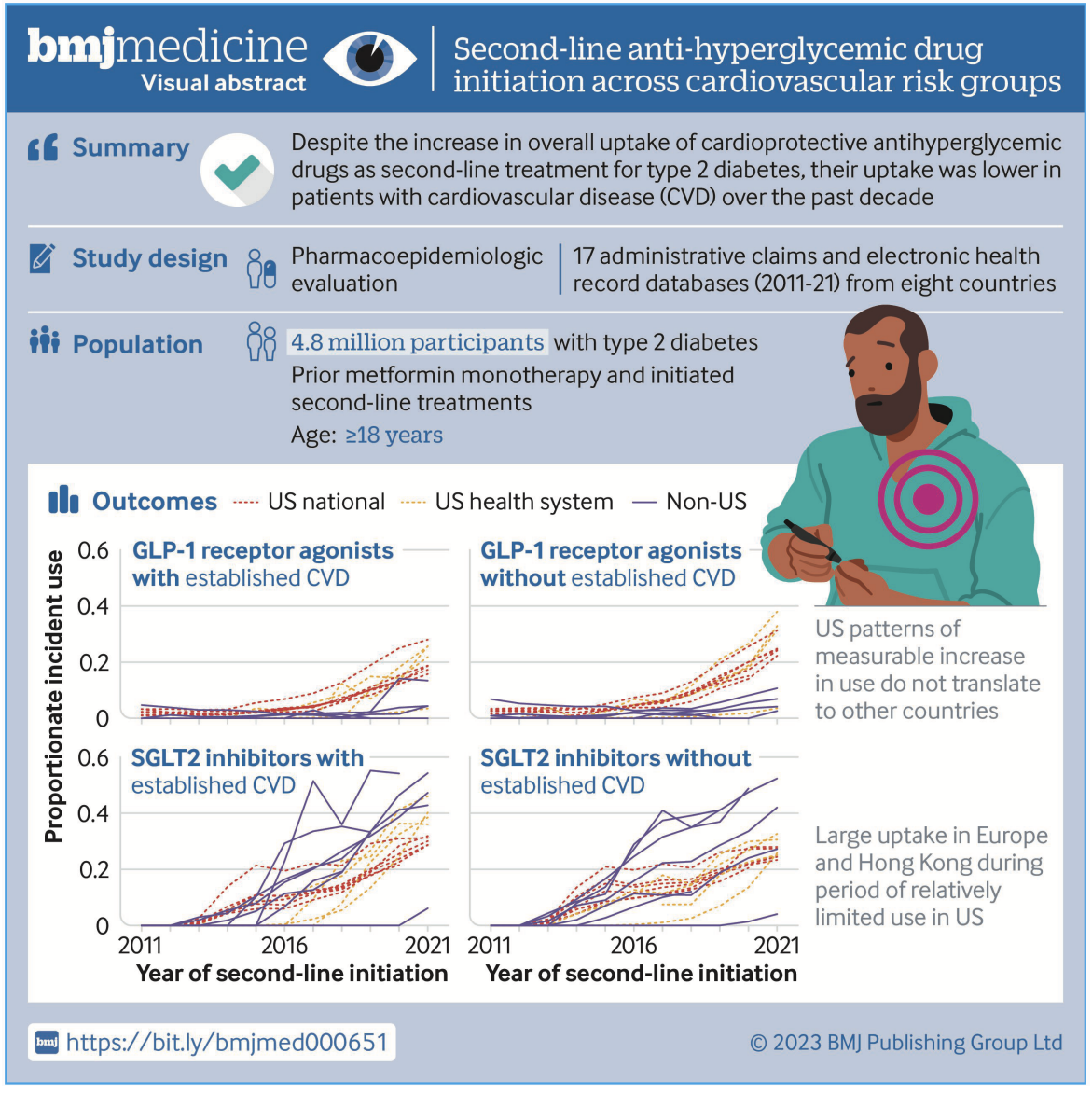
DPP4i 28%

SU 48%

Over 1.4 million patient-years of F/U
25,982 3-pt MACE
41,447 4-pt MACE

- 4.8 million new-initiators across the global network

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

Reducing MACE in T2DM+CVD patients

Via systematic best-practices:

New-user cohort design (emulate target trial)

LSPS adjustment (measured, unmeasured confounding)

Tian et al *IJE*

100 neg. controls (empirical calibration) Schuemie et al *PNAS*

Extensive objective diagnostics (improved reliability)

ELSEVIER

Journal of the American College of Cardiology

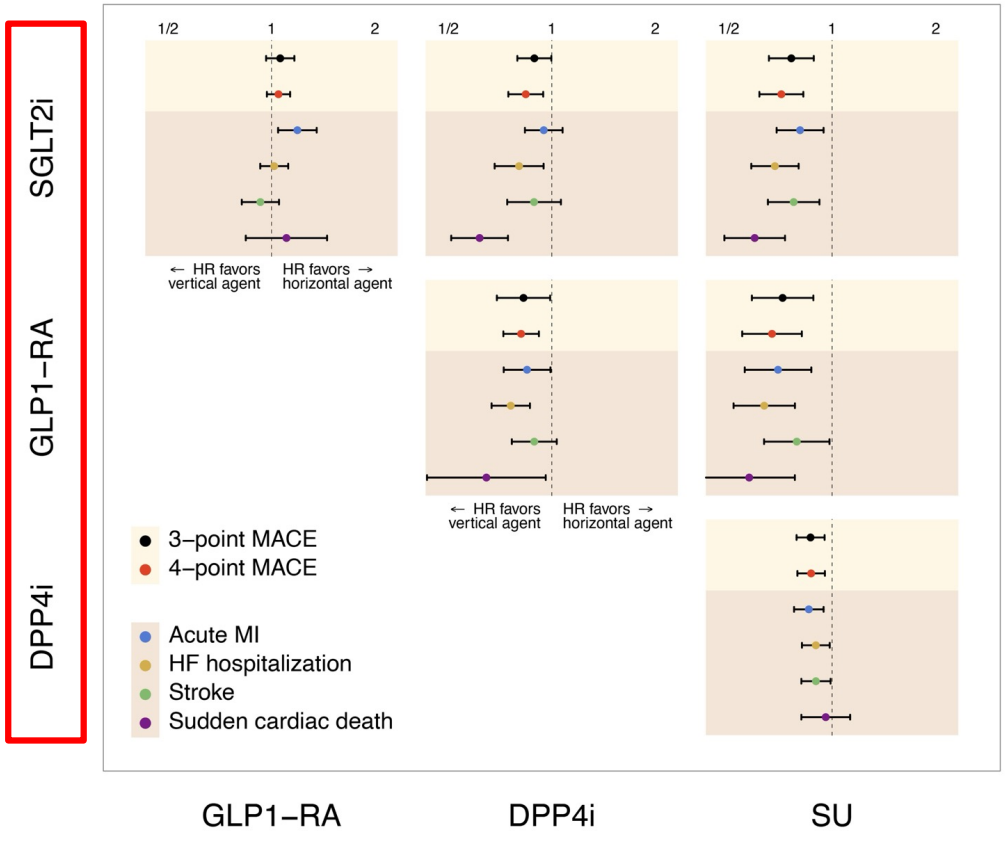
Volume 84, Issue 10, 3 September 2024, Pages 904-917

Original Research

Comparative Effectiveness of Second-Line Antihyperglycemic Agents for Cardiovascular Outcomes: A Multinational, Federated Analysis of LEGEND-T2DM

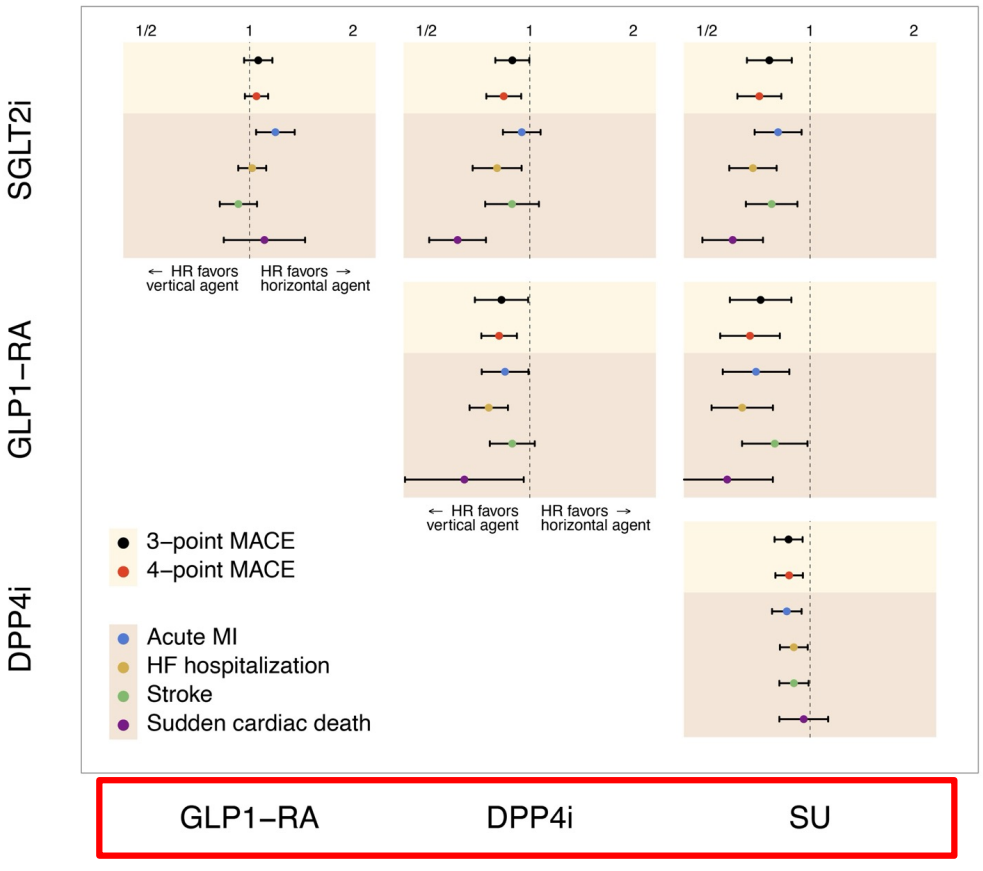
Rohan Khera MD, MS [a b c], Arya Aminorroaya MD, MPH [a], Lovedeep Singh Dhingra MBBS [a], Phyllis M. Thangaraj MD, PhD [a], Aline Pedroso Camargos PhD [a], Fan Bu PhD [d], Xiyu Ding MS [e], Akihiko Nishimura PhD [e], Tara V. Anand BS [f], Faaizah Arshad BS [g], Clair Blacketer MPH [h], Yi Chai PhD [i], Shounak Chattopadhyay PhD [g], Michael Cook BSc [e], David A. Dorr MD, MS [j], Talita Duarte-Salles PhD [k l], Scott L. DuVall PhD [m n], Thomas Falconer MS [f], Tina E. French RN, CPHQ [o p], Elizabeth E. Hanchrow RN, MSN [o p], Guneet Kaur MS [q], Wallis C.Y. Lau BSc, PhD [r s t u], Jing Li MS [v], Kelly Li BS [g], Yuntian Liu MPH [a b], Yuan Lu ScD [a], Kenneth K.C. Man BSc, MPH, PhD [r s t u], Michael E. Matheny MD, MS, MPH [o p], Nestoras Mathioudakis MD, MHS [w], Jody-Ann McLeggon MPH [f], Michael F. McLemore RN [o p], Evan Minty MD, MSc [x], Daniel R. Morales MD [q], Paul Nagy PhD [w], Anna Ostropolets MD, PhD [h], Andrea Pistillo MSc [k], Thanh-Phuc Phan MBA [y], Nicole Pratt PhD [z], Carlen Reyes MD, PhD [k], Lauren Richter MD [f], Joseph S. Ross MD, MHS [b aa], Elise Ruan MD [f], Sarah L. Seager BS [bb], Katherine R. Simon AA [o p], Benjamin Viernes PhD [m n], Jianxiao Yang MS [cc], Can Yin MS [dd], Seng Chan You MD, PhD [ee ff], Jin J. Zhou PhD [g gg], Patrick B. Ryan PhD [f], Martijn J. Schuemie PhD [hh], Harlan M. Krumholz MD, SM [a b ii], George Hripcsak MD, MS [f], Marc A. Suchard MD, PhD [g m jj kk]

Reducing MACE in T2DM+CVD patients



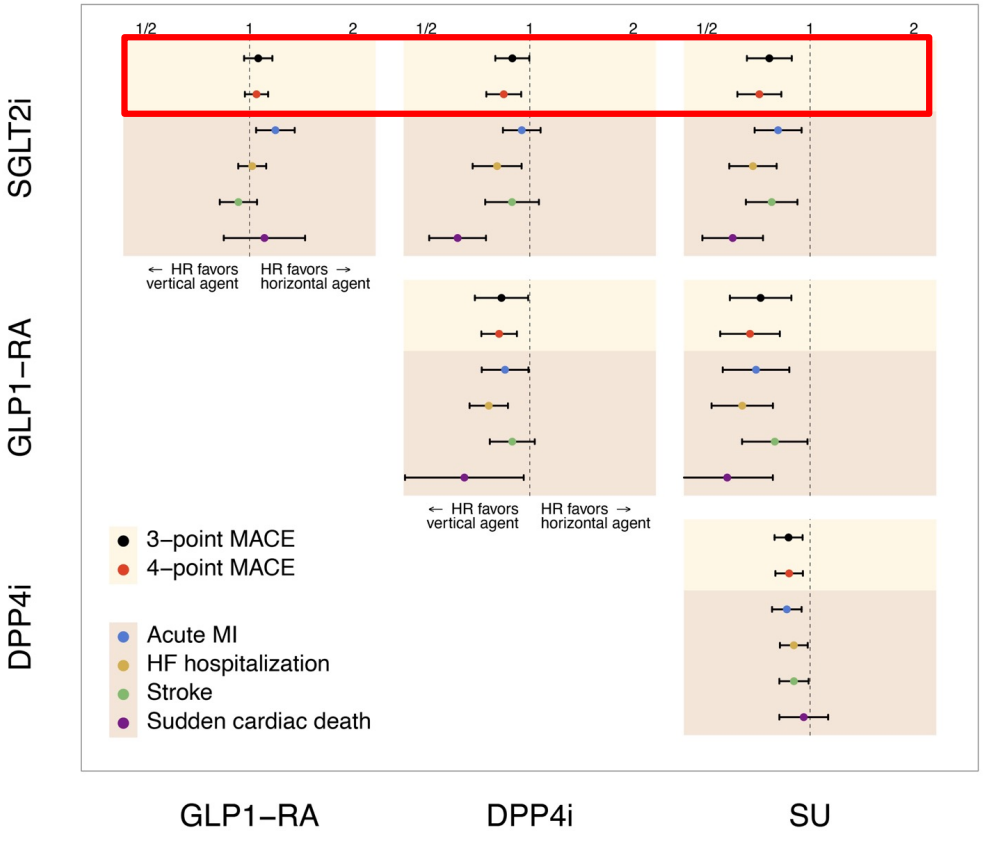
- HRs $< 1 \rightarrow$ vertical class (T) is more effective

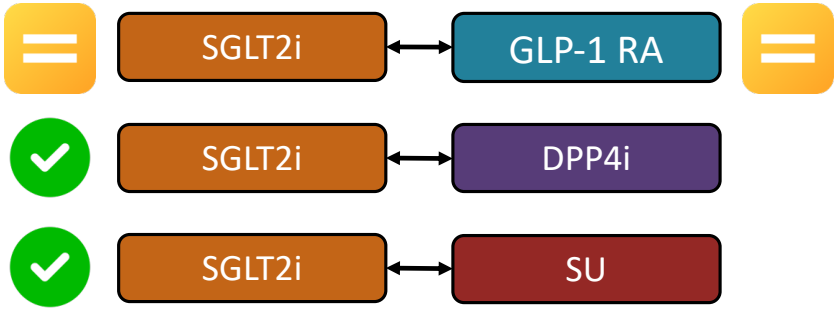
Reducing MACE in T2DM+CVD patients



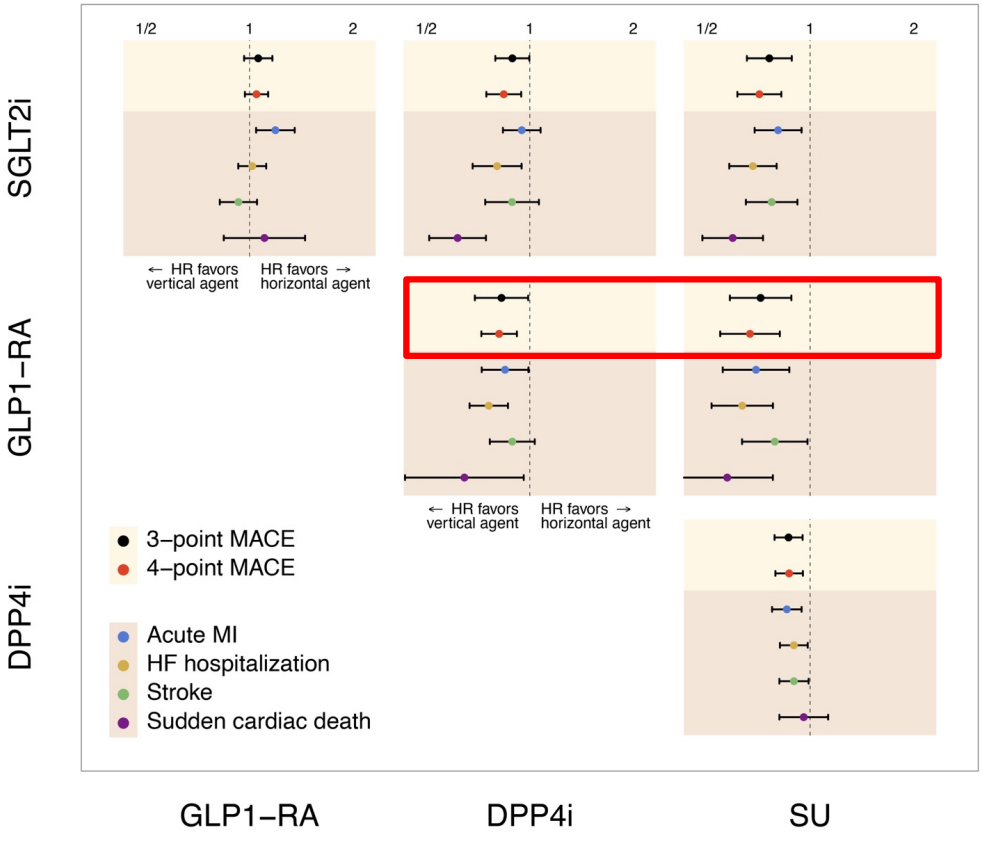
- HRs $> 1 \rightarrow$ horizontal class (C) is more effective

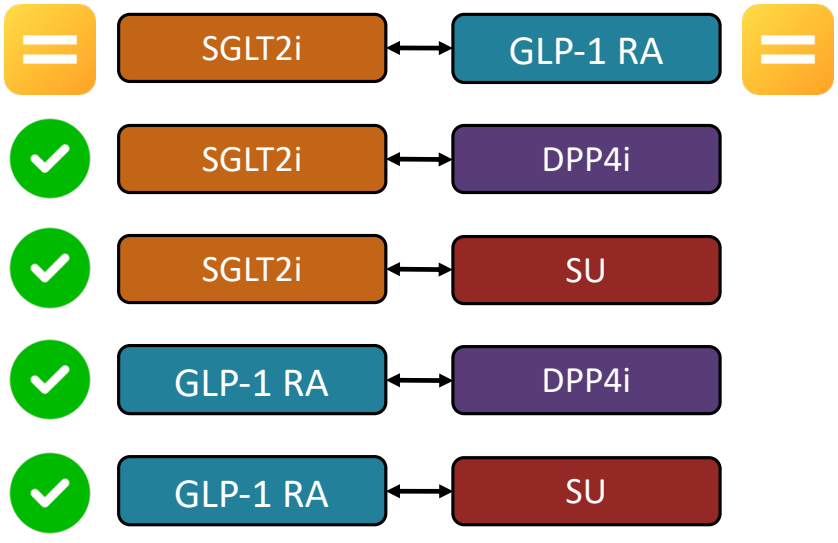
Reducing MACE in T2DM+CVD patients



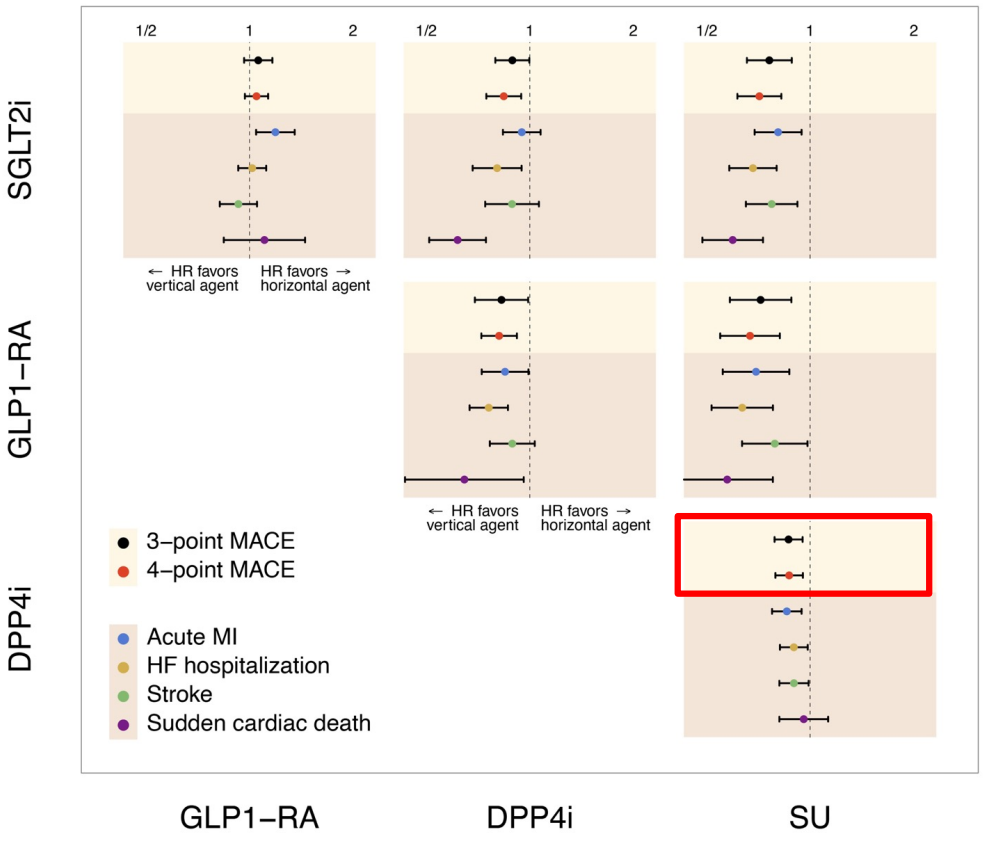


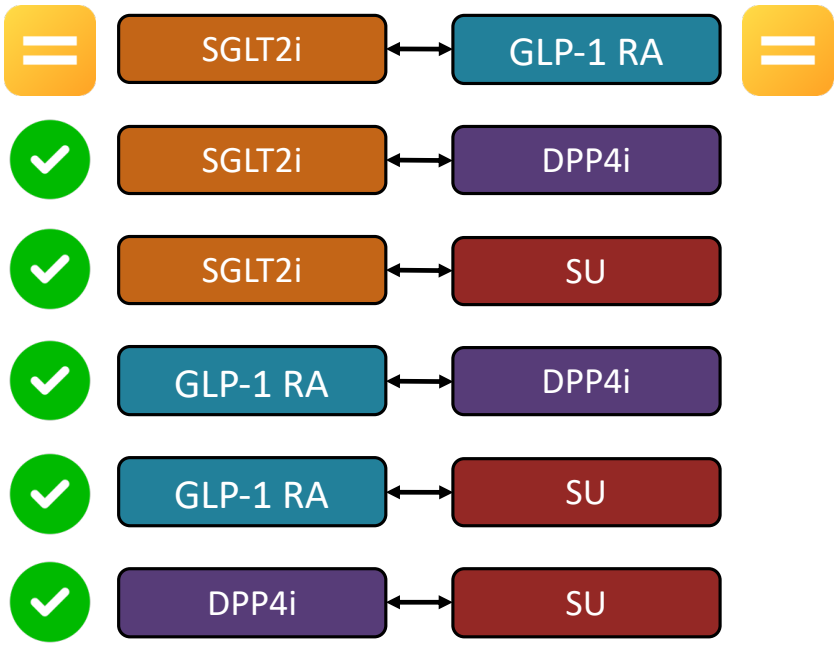
Reducing MACE in T2DM+CVD patients





Reducing MACE in T2DM+CVD patients





- SGLT2I ≈ GLP1RA (consistent with RCT)
- GLP1RA > DPP4I > SU (RWE fills in for missing RCTs)

LEGEND-T2DM is a rich, open resource

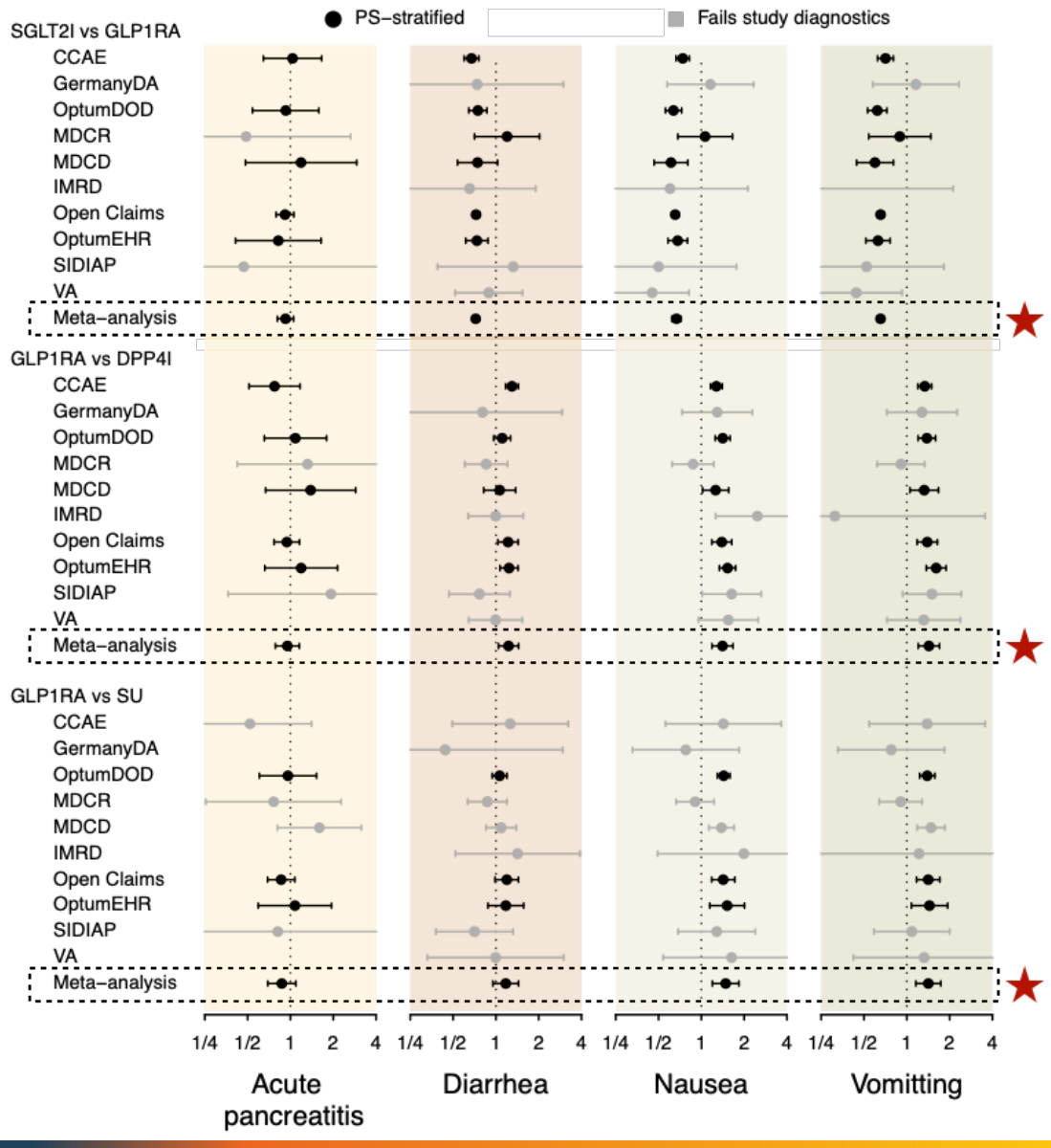
32 outcomes: CV, safety, patient-centered (PC)

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)

Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 23-26 October 2023

27 October 2023

News | Human | Pharmacovigilance | Referrals

GLP-1 receptor agonists: available evidence not supporting link with thyroid cancer

EMA's safety committee (PRAC) has concluded that the available evidence does not support a causal association between the Glucagon-Like Peptide-1 Receptor Agonists (GLP-1) - exenatide, liraglutide, dulaglutide, semaglutide, and lixisenatide - and cancer of the thyroid (a small gland in the front and lower part of the neck which makes and releases hormones).

Emerging directions in LEGEND-T2DM

Patients with renal disease or heart failure

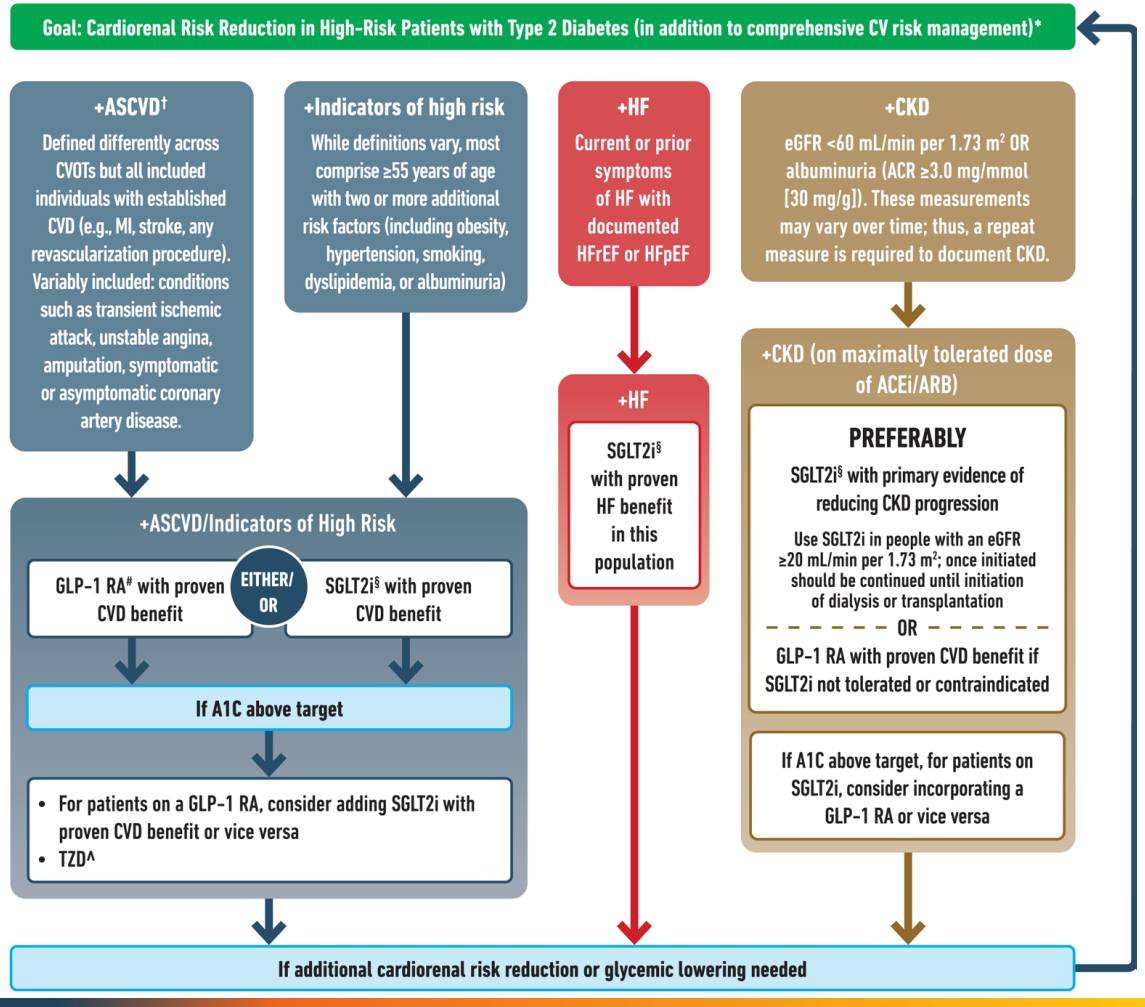
Older adults, risk differences in women

Ingredient (drug-level) comparisons

Scalable robust methods (Bayesian data integration)

Public health-driven outcomes (APAC is leading the way)

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 Phuc, 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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