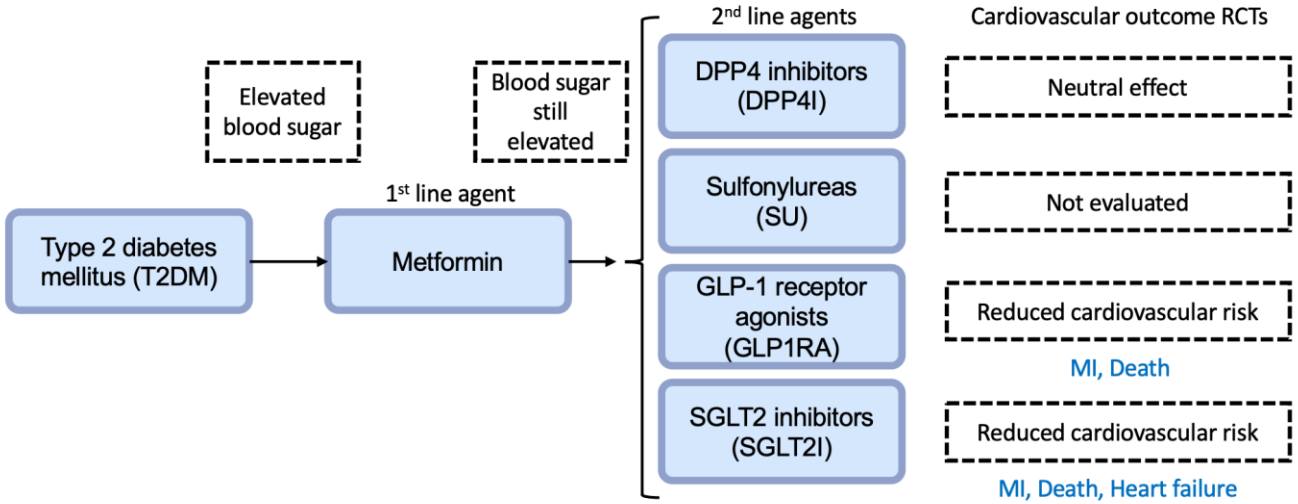
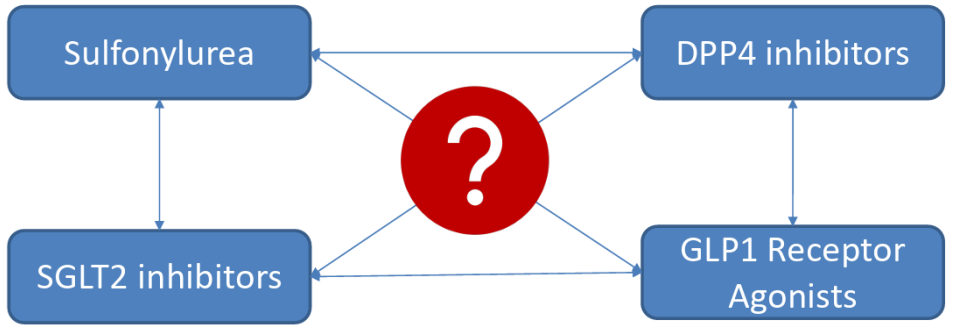
Comparative Safety of Second-Line Antihyperglycemic Agents in Older Adults with Type 2 Diabetes : Insight from the LEGEND-T2DM study

Chungsoo Kim

on behalf of the OHDSI Legend T2DM initiative

LEGEND-T2DM initiative





Critical need for evidence to improve choice between drug classes

- Are patients with cardiovascular disease (CVD) preferentially starting cardioprotective agents?
- Are cardioprotective agents more effective than others in real-world?
- Are cardioprotective agents safer than others in real-world?

2023 OHDSI Global Sympoisum Slides by Marc Suchard

LEGEND-T2DM initiative

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Multinational patterns of second line antihyperglycaemic drug initiation across cardiovascular risk groups: federated pharmacoepidemiological evaluation in LEGEND-T2DM

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjmed-2023-000651).

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ABSTRACT

OBJECTIVE To assess the uptake of second line antihyperglycaemic drugs among patients with type 2 diabetes mellitus who are receiving metformin.

DESIGN Federated pharmacoepidemiological evaluation in LEGEND-T2DM.

SETTING 10 US and seven non-US electronic health record and administrative claims databases in the Observational Health Data Sciences and Informatics network in eight countries from 2011 to the end of 2021.

PARTICIPANTS 4.8 million patients (≥18 years) across US and non-US based databases with type 2 diabetes mellitus who had received metformin monotherapy and had initiated second line treatments.

EXPOSURE The exposure used to evaluate each database was calendar year trends, with the years in the study that were specific to each cohort.

MAIN OUTCOMES MEASURES The outcome was the incidence of second line antihyperglycaemic drug use (ie, glucagon-like peptide-1 receptor agonists, sodium-glucose cotransporter-2 inhibitors, dipeptidyl peptidase-4 inhibitors, and sulfonylureas) among individuals who were already receiving treatment with metformin. The relative drug class level uptake across cardiovascular risk groups was also evaluated.

RESULTS 4.6 million patients were identified in US databases, 61 382 from Spain, 32 442 from Germany, 25 173 from the UK, 13 270 from France, 5580 from Scotland, 4614 from Hong Kong, and 2322 from Australia. During 2011-21, the combined proportional initiation of the cardioprotective antihyperglycaemic drugs (glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors) increased across all data sources, with the combined initiation of these drugs as second line drugs in 2021 ranging from 35.2% to 68.2% in the US databases, 15.4% in France, 34.7% in Spain, 50.1% in Germany, and 54.8% in Scotland. From 2016 to 2021, in some US and non-US databases, uptake of glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors increased more significantly among populations with no cardiovascular disease compared with patients with established cardiovascular disease. No data source provided evidence of a greater increase in the uptake of these two drug classes in populations with cardiovascular disease compared with no cardiovascular disease.

CONCLUSIONS Despite the increase in overall uptake of cardioprotective antihyperglycaemic

WHAT IS ALREADY KNOWN ON THIS TOPIC

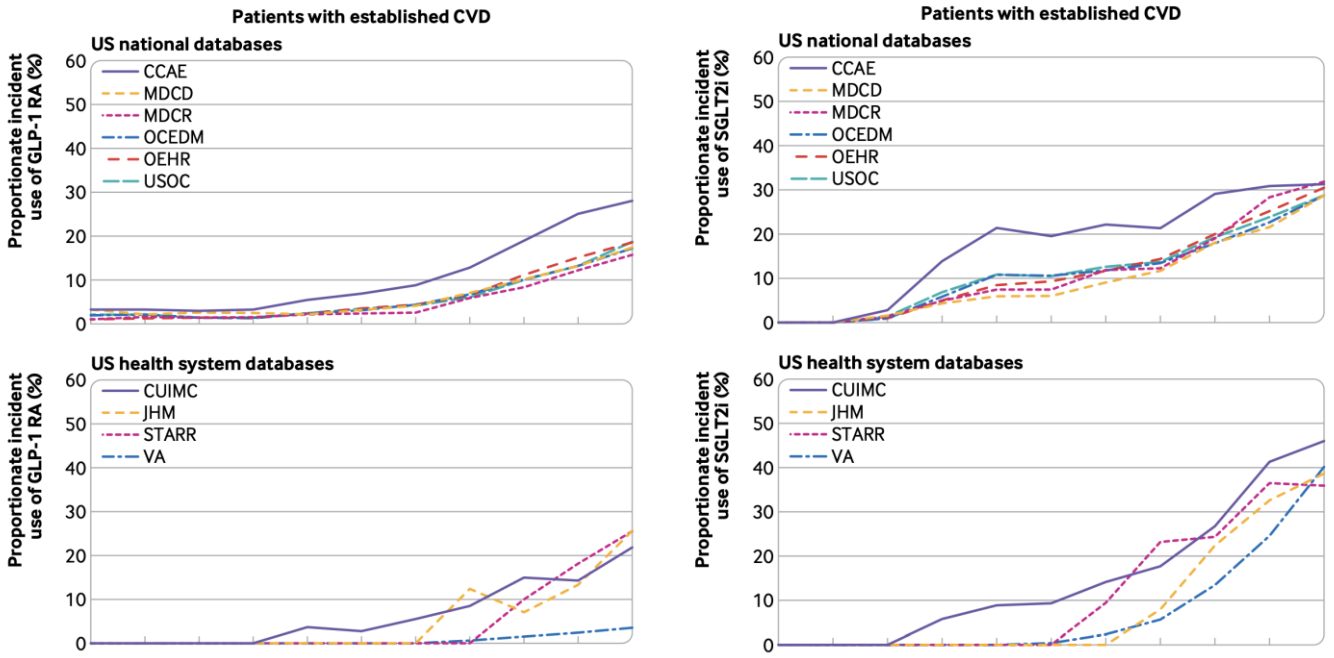
⇒ Glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter two inhibitors are cardioprotective second line antihyperglycaemic drugs
⇒ These drugs treat hyperglycaemia and improve risk for diabetes mellitus at high risk of cardiovascular disorders, but uptake of these drugs lags
⇒ Studies have focused on prevalent use, and US studies have focused on single payers or small populations included in national surveys

WHAT THIS STUDY ADDS

⇒ Uptake was large of cardioprotective antihyperglycaemic drugs among patients with type 2 diabetes mellitus initiating a second line agent, representing nearly half of all patients across US and non-US cohorts
⇒ Patterns suggest non-selective use of cardioprotective drugs, with an increasing uptake among people who do not have cardiovascular disease compared with people who have established cardiovascular disease
⇒ This finding is despite people with established cardiovascular disease representing the only group with a strong recommendation for use in clinical practice guidelines

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ This federated framework can guide future research to fill in the remaining knowledge gaps in the field
⇒ This approach acts as a benchmark for monitoring the uptake of antihyperglycaemic drugs in response to regional guidelines, insurance, and evidence



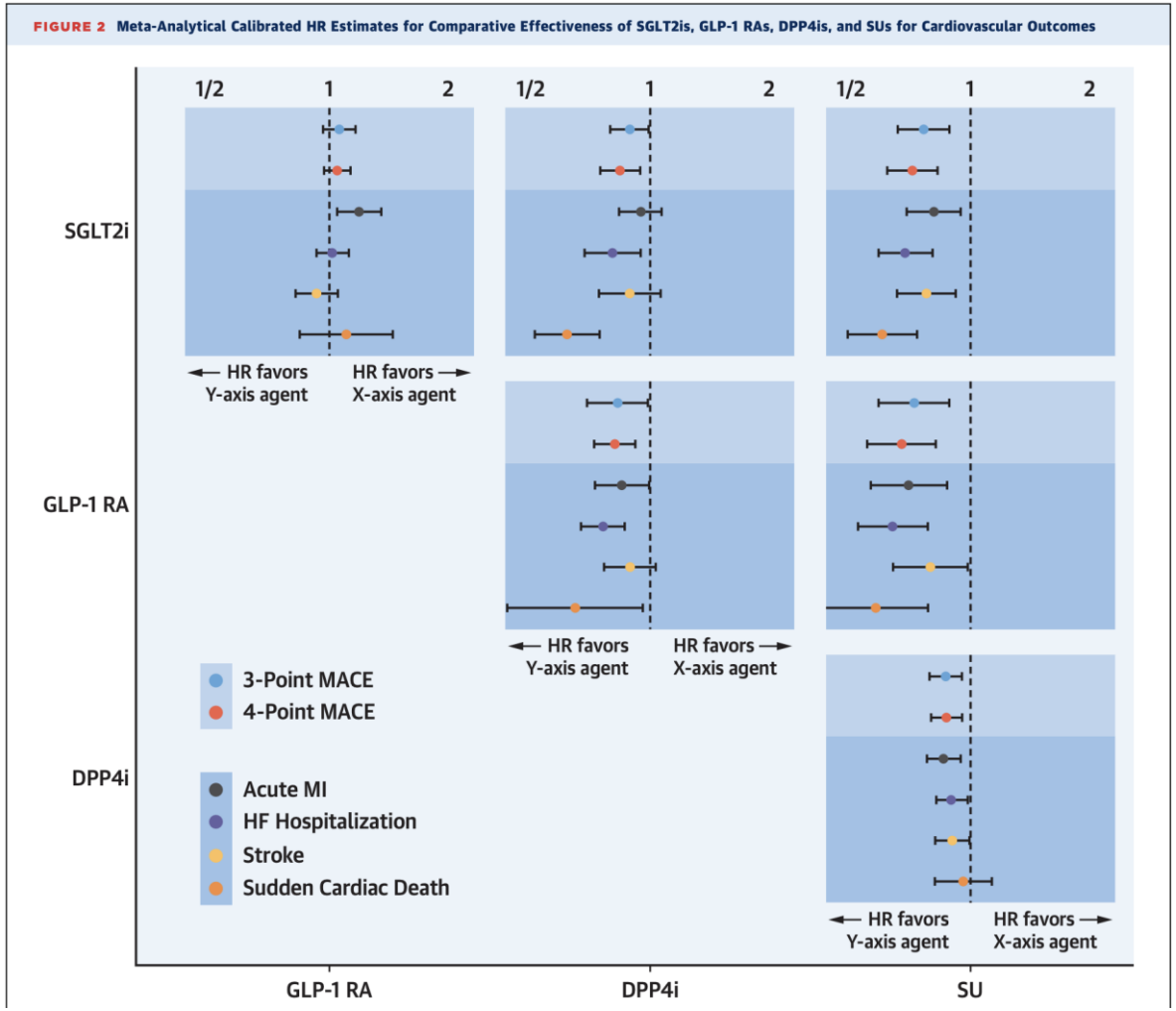
→ Despite the increase in overall uptake of cardioprotective antihyperglycemic drugs as second line treatments for type 2 diabetes mellitus, their **uptake was lower in patients with cardiovascular disease.**

Rohan K, Lovedeep Singh D, Arya A, et al. Multinational patterns of second line antihyperglycaemic drug initiation across cardiovascular risk groups: federated pharmacoepidemiological evaluation in LEGEND-T2DM. BMJ Medicine. 2023;2(1):e000651. doi:10.1136/bmjmed-2023-000651

LEGEND-T2DM initiative

Are GLP1RA/SGLT2I more effective than DPP4I/SU in real-world?

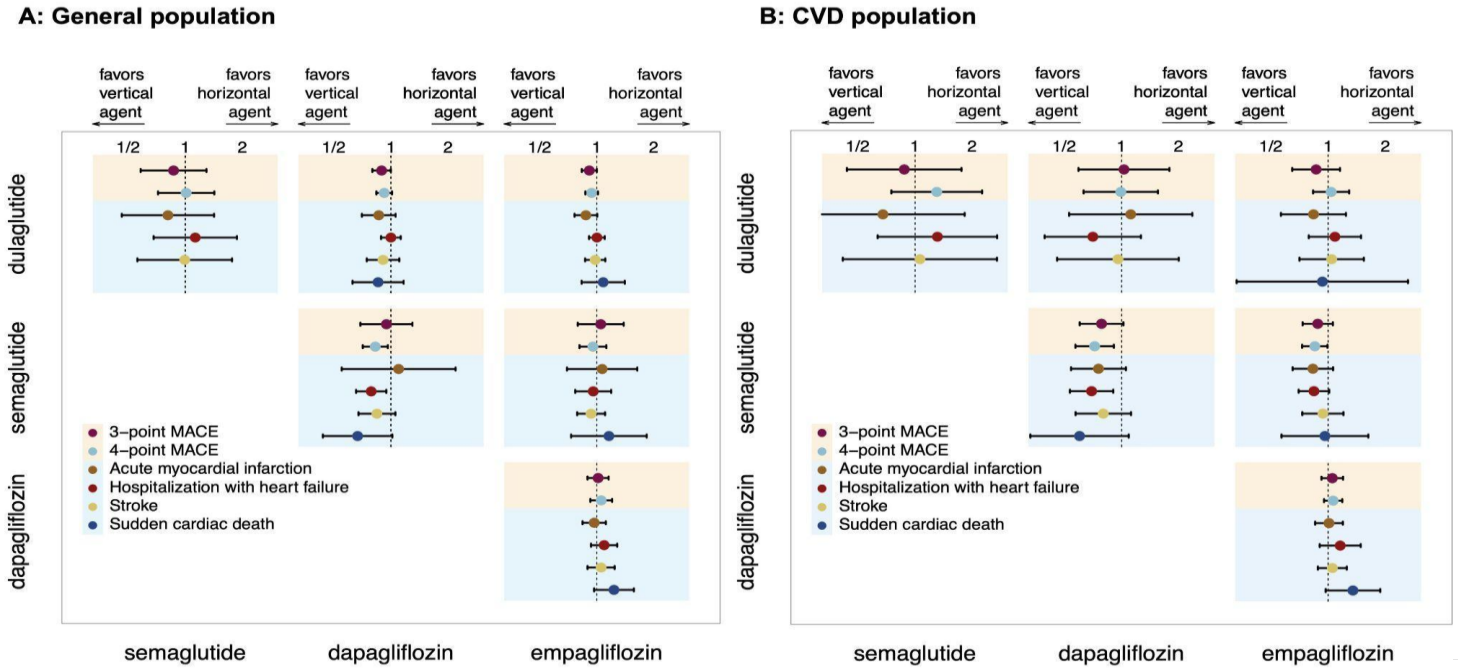
→ **GLP1RA/SGLT2Is showed beneficial effectiveness on most of CV outcomes** (MACE, MI, HF, sudden cardiac death) compared to DPP4Is and SUs

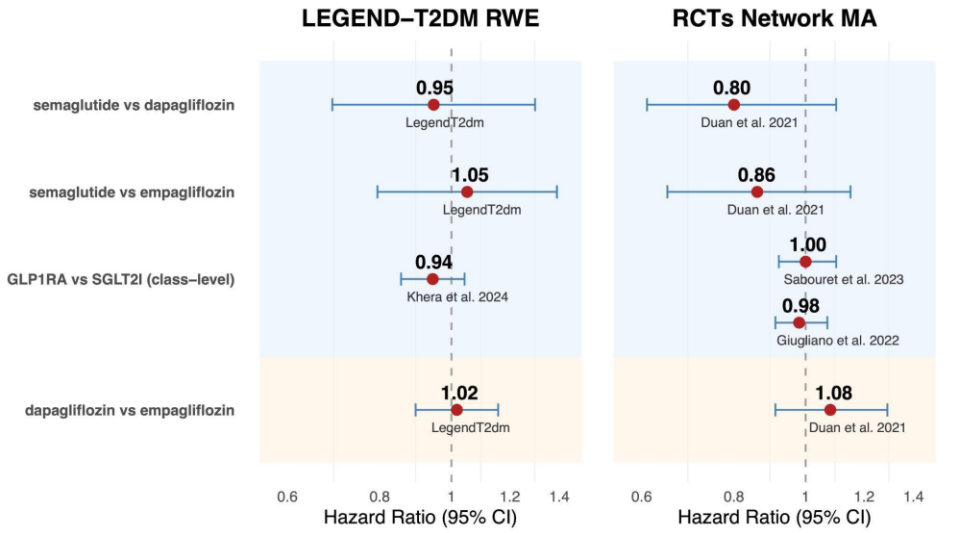


Khera R, Aminorroaya A, Dhingra LS, et al. Comparative Effectiveness of Second-Line Antihyperglycemic Agents for Cardiovascular Outcomes: A Multinational, Federated Analysis of LEGEND-T2DM. Journal of the American College of Cardiology. 2024/09/03/ 2024;84(10):904-917. doi:https://doi.org/10.1016/j.jacc.2024.05.069

LEGEND-T2DM initiative

Cardiovascular benefits are comparable between GLP-1RA and SGLT2I classes.
Could there be any differences between individual drugs?





→ **Individual GLP-1RAs and SGLT2Is exhibited largely comparable cardiovascular benefits, including in patients with established CVD.**

Bu, F, Wu, R, Ostropolets, A. et al. Comparative Cardiovascular Effectiveness of Glucagon-Like Peptide 1 Receptor Agonists and Sodium-Glucose Cotransporter 2 Inhibitors in Diabetes Mellitus. JACC. 2026 Jun, 87 (21) 2963–2977. https://doi.org/10.1016/j.jacc.2026.02.5123

Background

Drug safety in Older adults

- The prevalence of diabetes in the elderly (approximately 30%) is 1.5 times that of the middle-aged.
- Multiple comorbidities, polypharmacy, and frailty can impede diabetes management and diminish the quality of life (ADA guidelines)
- Older adults are underrepresented in the randomized controlled trial.

American Diabetes Association Professional Practice Committee; 13. Older Adults: Standards of Care in Diabetes—2024. Diabetes Care 1 January 2024; 47 (Supplement_1): S244–S257. https://doi.org/10.2337/dc24-S013
Tyler Drake, Adrienne Landsteiner, Lisa Langsetmo, et al. Newer Pharmacologic Treatments in Adults With Type 2 Diabetes: A Systematic Review and Network Meta-analysis for the American College of Physicians. Ann Intern Med. [Epub 19 April 2024]. doi:10.7326/M23-1490

Background

Drug safety in Older adults

- Older adults are more vulnerable to safety issues, which can lead to worse diabetes outcomes.
- However, safety issues are hard to investigate because of the event rate or often overlooked compared to efficacy/effectiveness.
- The systematic safety profiles on second-line antihyperglycemic agents are fragmented and limited.
    - Recently published systematic reviews and new ACP guidelines also present only limited data such as hypoglycemia.

American Diabetes Association Professional Practice Committee; 13. Older Adults: Standards of Care in Diabetes—2024. Diabetes Care 1 January 2024; 47 (Supplement_1): S244–S257. https://doi.org/10.2337/dc24-S013

Tyler Drake, Adrienne Landsteiner, Lisa Langsetmo, et al. Newer Pharmacologic Treatments in Adults With Type 2 Diabetes: A Systematic Review and Network Meta-analysis for the American College of Physicians. Ann Intern Med. [Epub 19 April 2024]. doi:10.7326/M23-1490

Objectives

We aim to determine the comparative safety of second-line antihyperglycemic agents among older adults with type 2 diabetes.

Methods

Study design

Study population

- **Older adult (≥65) patients** with type 2 diabetes
  1) Previous observation ≥ 365 days
  2) Previous T2DM diagnosis but no T1DM or secondary DM
  3) ≥ 90 days metformin
  4) Exclude patients who used insulin as a long-term (> 30 days)

Target-comparator pairs

Target	Comparator
SGLT2I	GLP1RA
SGLT2I	DPP4I
SGLT2I	SU
GLP1RA	DPP4I
GLP1RA	SU
DPP4I	SU

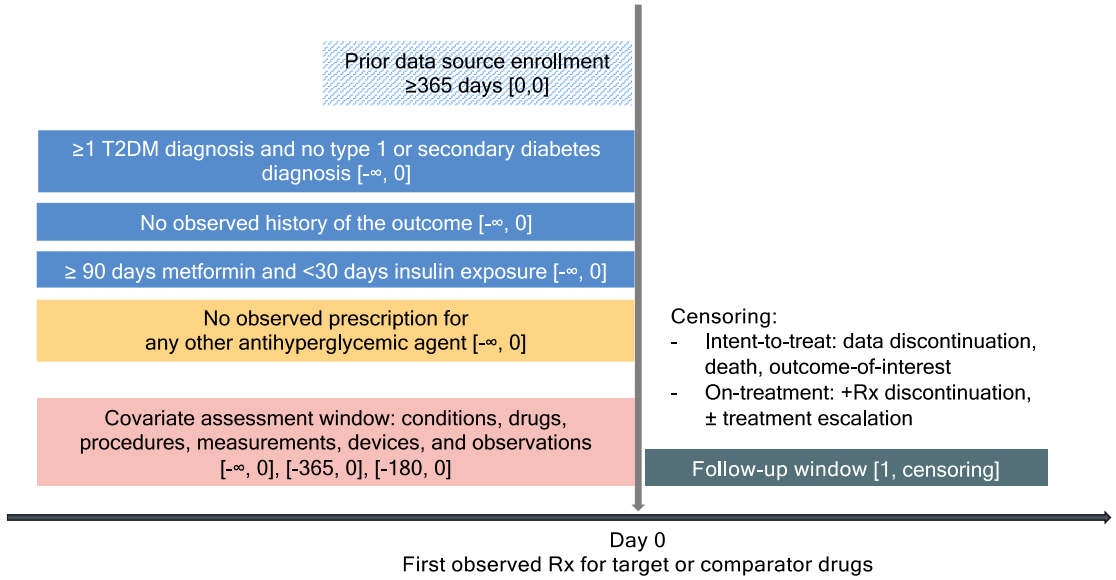


Figure 1. Study design scheme

Prespecified Protocol
https://ohdsi-studies.github.io/LegendT2dm/Protocol.html

Methods

Outcomes

Patient centric safety outcomes (22)		
Metabolic and endocrine complications (6)	**Organ system complications** Gastrointestinal, musculoskeletal, circulatory, skin and infection **(10)**	**Cancer and systemic complications (6)**
Abnormal weight gain	Acute pancreatitis	Bladder cancer
Abnormal weight loss	Nausea	Breast cancer
Diabetic ketoacidosis	Vomiting	Renal cancer
Hyperkalemia	Diarrhea	Thyroid tumor
Hypoglycemia	Bone fracture	All-cause mortality
Hypotension	Joint pain	Venous thromboembolism
	Lower extremity amputation	
	Peripheral edema	
	Genitourinary infection	
	Photosensitivity	

Reporting separately

Total 18 safety outcomes were included for this study

Methods

Data sources

Twenty databases were included the LEGEND T2DM projects.

Excluded

- Databases having no data for older adult population
- Databases having incomplete results for older adult population
  (Excluded Australia_LPD, CUIMC, China_WD, France_LPD, HIC Dundee, JHM, SG_KTPH, STARR, UK-IMRD)
- Databases with quality issue
  (Excluded HK-HA-DM
  due to median (IQR) f/u was 1 (1-1) in their results)

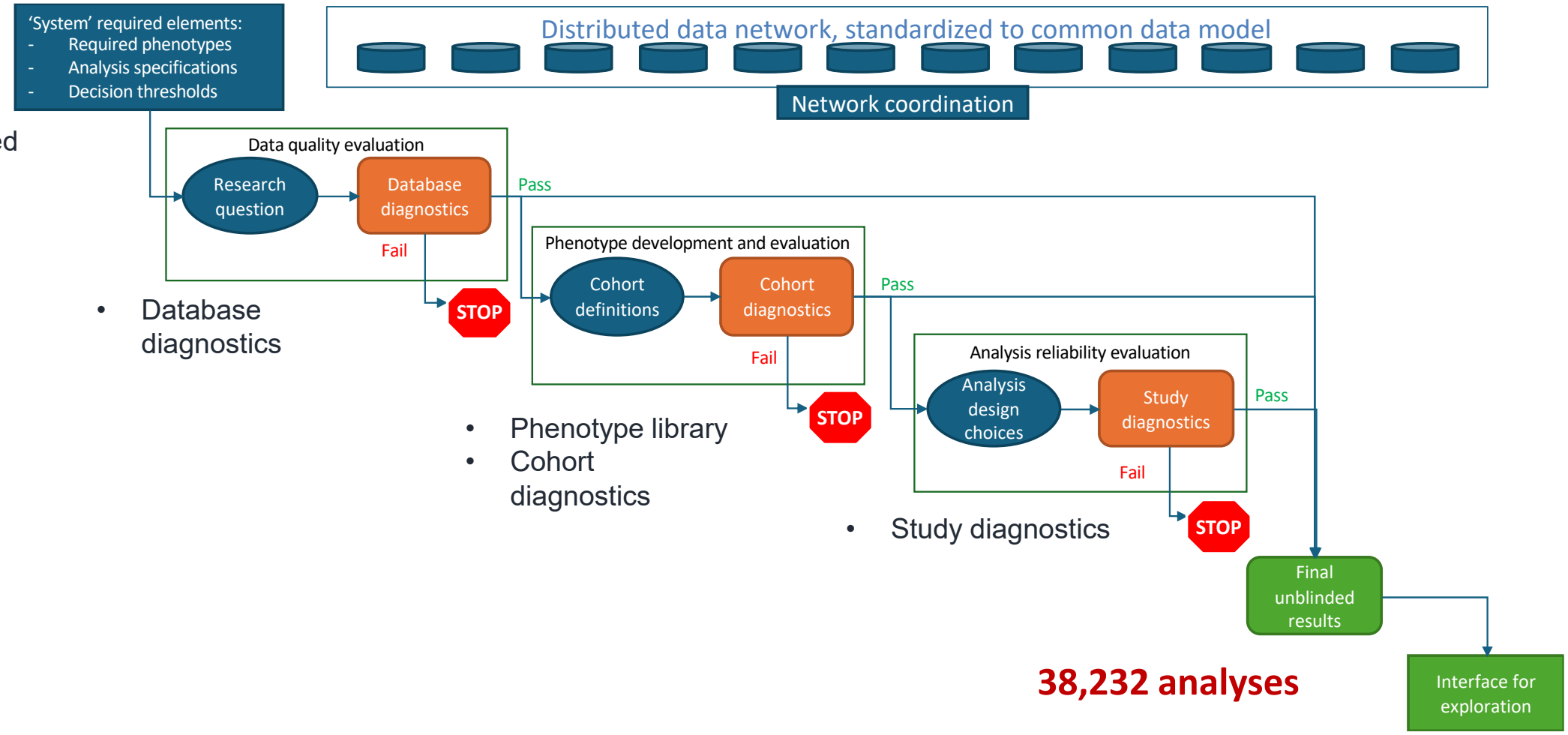
→ **Finally, 9 databases included**

→ We only used results when each arm meet the min number of patients (≥1000 patients)

Database	SGLT2I older-age	GLP1RA older-age	DPP4I older-age	SU older-age
Australia_LPD	326	10	732	40
CCAE	749	435	2089	3916
CUIMC	404	171	944	887
China_WD	145	8	222	244
France_LPD	41	165	4860	676
Germany_DA	2727	217	12158	4149
HIC Dundee	513	16	1620	465
HK-HA-DM	237	11	2087	3591
JHM	330	160	352	494
MDCD	178	101	1210	2488
MDCR	3511	2135	17961	43297
OptumDod	11619	5627	27244	66309
OptumEHR	7828	3573	23345	58387
SG_KTPH	<5	<5	9	50
SIDIAP	3746	289	26465	8667
STARR	195	118	316	742
UK-IMRD	921	184	8631	3014
US_Open_Claims	135495	62268	358700	741462
VA-OMOP	8539	848	15844	147244

Methods

- Prespecified Protocol



- Database diagnostics
- Phenotype library
- Cohort diagnostics
- Study diagnostics

38,232 analyses

= 9 database * 6 comparison pairs
* 118 outcomes (safety + NCO)
* 2 PS methods * 3 follow-up

https://ohdsi.org/sos-challenge/

Results

Table 1. Number of new users and followed days according to on-treatment or total follow-up within each database.

Total N of older adults = 1,808,003

Drug class and database	n	Median (IQR) in On-treatment time, day	Median (IQR) in total follow-up time, day
SGLT2I			
ODOD	11,619	114 (55-273)	390 (146-799)
MDCR	3,511	121 (38-344)	419 (156-880)
USOC	135,495	125 (59-309)	681 (293-1,342)
OEHR	7,828	59 (29-99)	596 (295-1,081)
DAG	2,727	157 (97-372)	598 (293-1,155)
SIDIAP	3,746	246 (84-617)	498 (155-875)
VA	8,539	144 (71-306)	283 (124-592)
Total	**173,465**		
GLP1RA			
ODOD	5,627	95 (40-219)	345 (124-728)
MDCR	2,135	108 (36-300)	513 (159-1,129)
USOC	62,268	105 (50-258)	585 (241-1,130)
OEHR	3,573	55 (29-102)	527 (273-983)
Total	**73,603**		
DPP4I			
CCAE	2,089	86 (29-144)	110 (56-180)
ODOD	27,244	157 (63-375)	832 (342-1,581)
MDCR	17,961	191 (87-491)	815 (333-1,533)
MDCD	1,210	130 (56-330)	834 (357-1,539)
USOC	358,700	158 (59-416)	1,575 (806-2,430)
OEHR	23,345	90 (89-194)	1,076 (537-1,827)
DAG	12,158	219 (97-509)	1,174 (564-2,065)
SIDIAP	26,465	719 (200-1464)	1,207 (567-2,137)
VA	15,844	235 (90-523)	756 (348-1,337)
Total	**485,016**		
SU			
CCAE	3,916	84 (29-146)	113 (57-189)
ODOD	66,309	193 (89-504)	882 (352-1,709)
MDCR	43,297	186 (72-496)	890 (354-1,780)
MDCD	2,488	126 (48-311)	1,020 (464-1,874)
USOC	741,462	203 (89-547)	1,498 (717-2,419)
OEHR	58,387	102 (89-231)	1,219 (587-2,042)
DAG	4,149	211 (119-467)	2,043 (1003-3,325)
SIDIAP	8,667	741 (188-1615)	2,879 (1674-3,808)
VA	147,244	224 (90-544)	2,071 (1043-3,330)
Total	**1,075,919**		

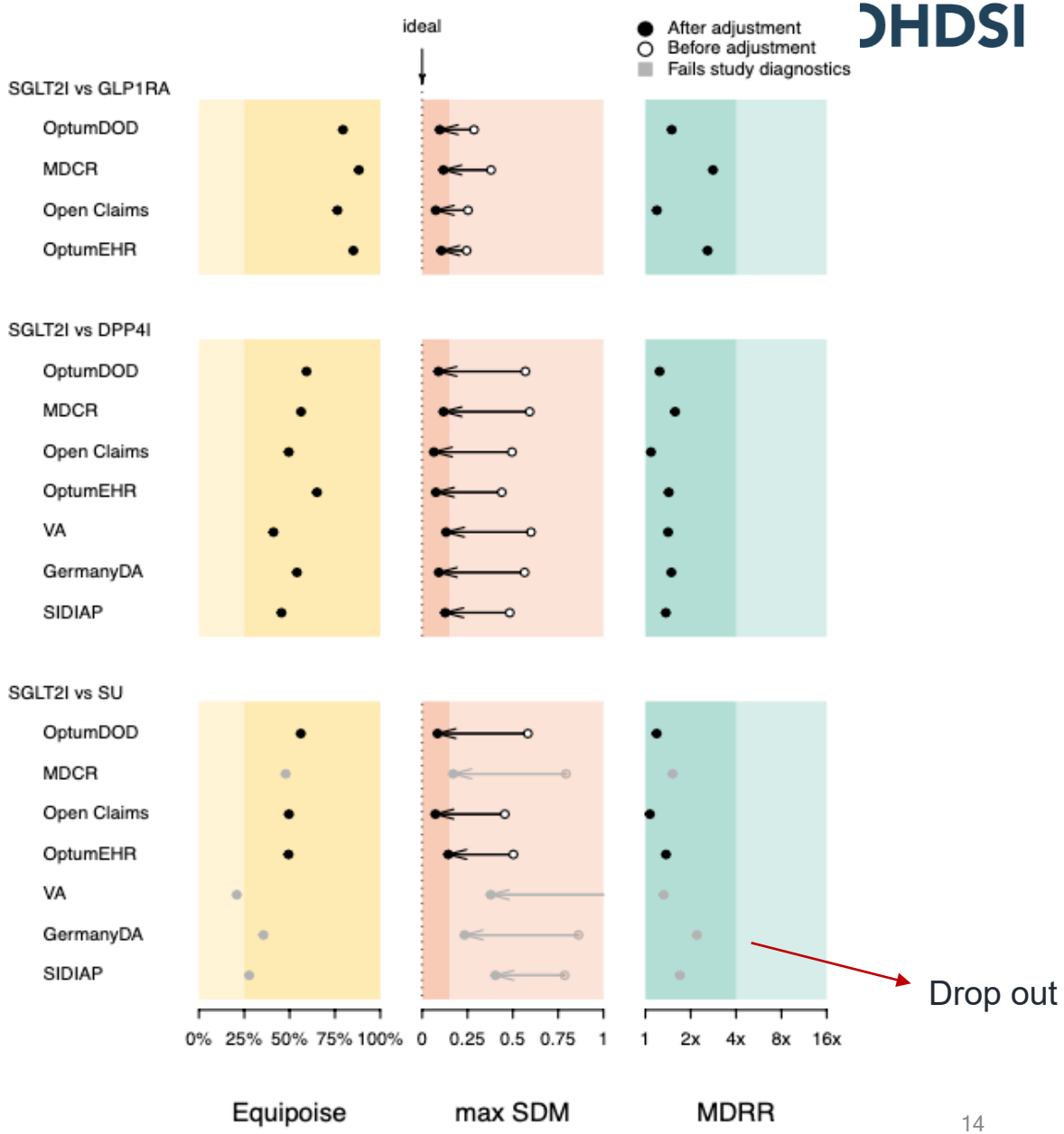
IQR: interquartile range; DPP4I: dipeptidyl peptidase inhibitor 4; GLP1RA: glucagon-like peptide-1 receptor agonist; SGLT2I: sodium glucose cotransporter 2 inhibitor; SU: sulfonylurea; MDCR: IBM MarketScan Medicare Supplemental and Coordination of Benefits Database; Optum DOD: Optum© Clinformatics Extended Data Mart - Date of Death Database; Optum EHR: Optum© de-identified Electronic Health Records Database.

Results

Study diagnostics

- **Comparability - Empirical equipoise (Proportion of preference score in equipoise >0.25)**
- **Covariate balance – max SDM (<0.15)**
- **Statistical Power – MDRR (<4.0)**

"Methodological rigor"



Results

Metabolic and endocrine complications

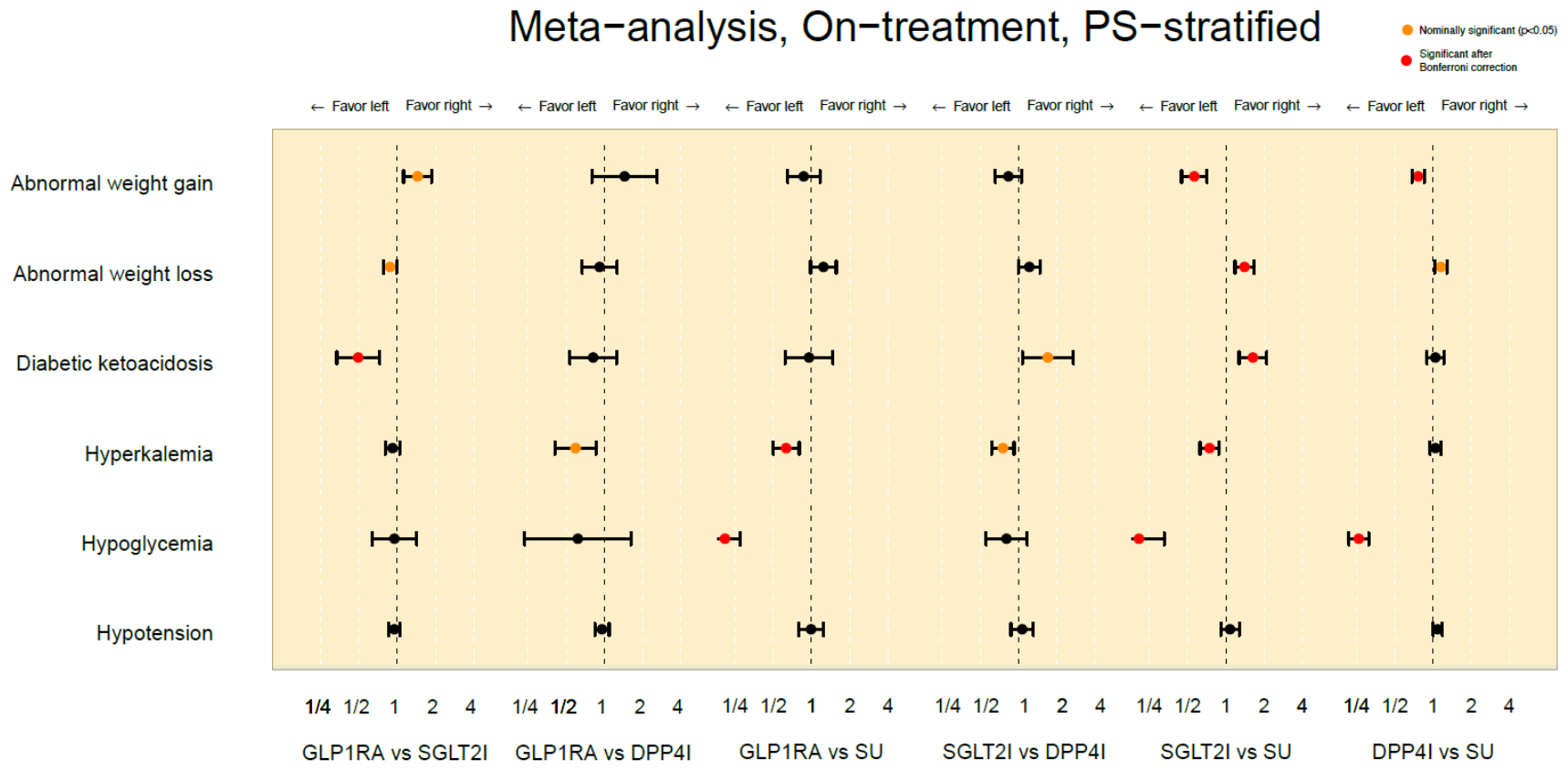
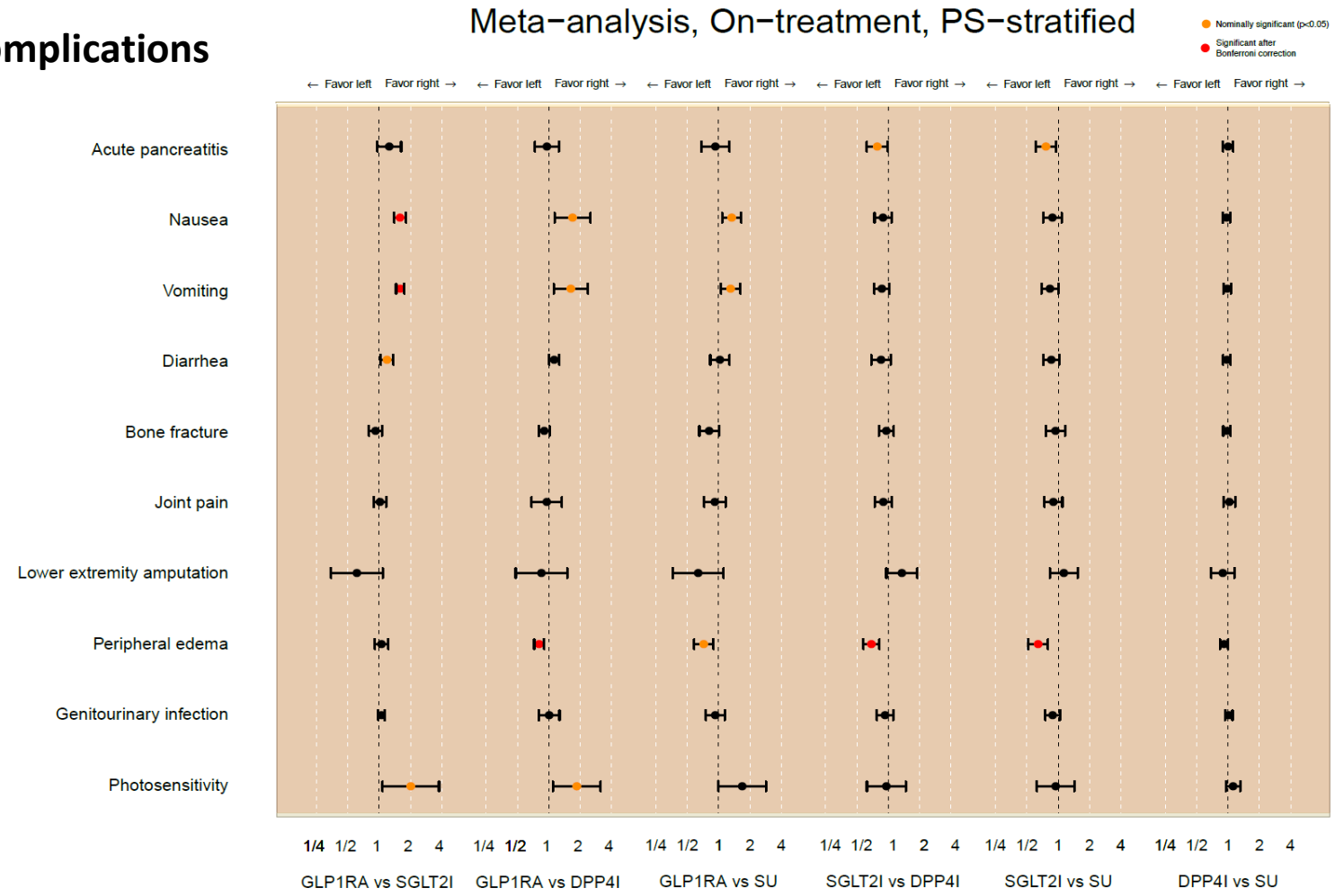


Figure 2. Meta-analytic safety profiles comparing new users of SGLT2I to GLP1RA, DPP4I, and SU across 22 outcomes. Points and lines identify HR estimates with their 95% CIs, respectively. Outcomes in orange mean that $p<0.05$ and outcomes in red mean statistically significant after Bonferroni correction ($p<0.00227$) for the multiple testing. Result for all-cause mortality in the GLP1RA vs SU comparison was not presented because there was no valid result after the study diagnostic process.

Results

Organ system complications



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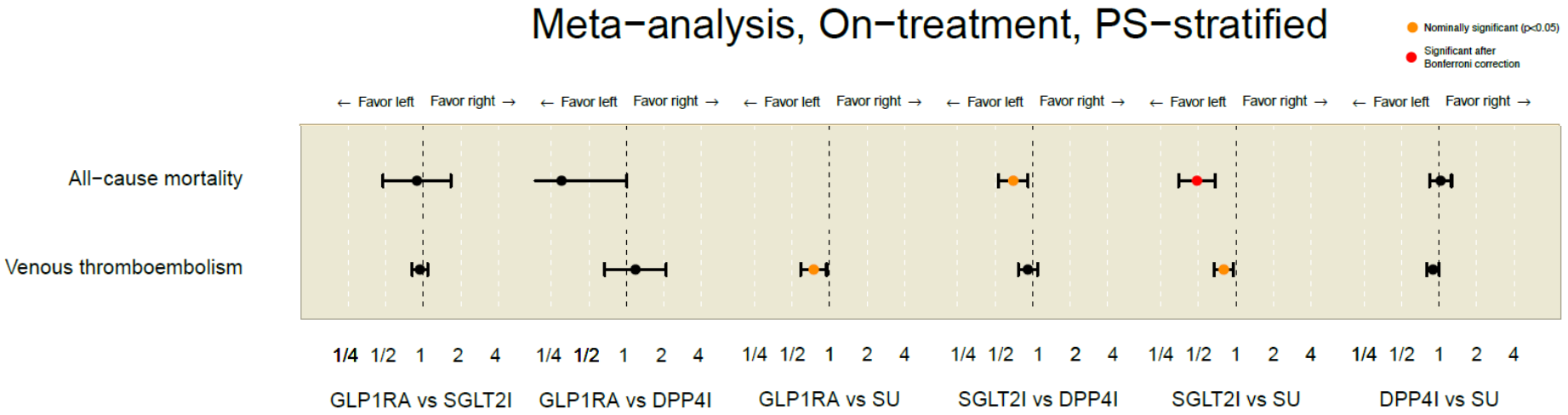
Results

Systemic outcomes



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Discussion

Highlights

- In older adults with type 2 diabetes, the safety profile of each second line antihyperglycemic agent was diverse.
- The GLP-1 RA and SGLT2 inhibitor showed not only better effectiveness *(Khera et al., JACC, 2024)* but also generally safe across multiple outcomes, esp., hypoglycemia, hyperkalemia, and peripheral edema, than DPP4i and SU in older adults.
- However, there were unique challenges for those agents, SGLT2 inhibitors showed elevated diabetic ketoacidosis and GLP-1RAs showed a higher risk of GI adverse events, which may affect drug compliance and continuity of care in older adults.

Discussion

Novelty

- Even though most of the results are reassuring, however, a direct head-to-head safety study between drug classes with large sample size is still novel.
- This fill the gap in evidence regarding the older adult population, which generally underrepresented in randomized controlled trials.
- We applied sophisticated analysis pipelines (e.g., study diagnostics) to enhance the quality of observational studies.

Limitation

- Inherit fundamental problems (misclassification/unmeasured/residual bias) of the observational study
- Short follow-up period, no labs.
- Not included neuropsychiatric outcomes (e.g., impaired cognition, suicide, dementia), even though those are crucial for older adults

Paper

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Article | Open access | Published: 04 April 2026

Real-world evidence for comparative safety of second-line antihyperglycemic agents in older adults with type 2 diabetes

Chungsoo Kim, Fan Bu, Clair Blacketer, Anna Ostropolets, Talita Duarte-Salles, Benjamin Viernes, Thomas Falconer, Andrea Pistillo, Jing Li, Can Yin, Mui Van Zandt, Paul Nagy, Akihiko Nishimura, Evan Minty, Seng Chan You, Mitsuaki Sawano, Shoko Sawano, Ja Young Jeon, Arya Aminorroaya, Lovedeep S. Dhingra, Aline F. Pedroso, Phyllis Thangaraj, David A. Dorr, Nicole Pratt, ... Yuan Lu + Show authors

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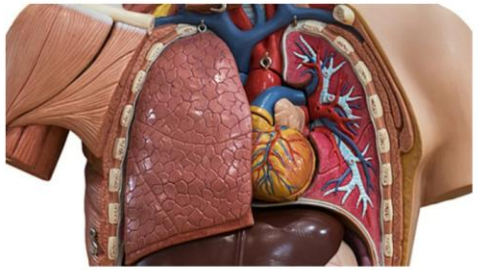
Focus | 26 January 2021

Translational and clinical research

Translational research describes the process of converting basic scientific findings into novel treatments and diagnostics aimed to address unmet clinical needs. Here, we showcase a plethora of diverse studies, ranging from the investigation of the molecular mechanisms underlying the onset and course of a disease using preclinical models, to the development of innovative interventions in human subjects with the goal to guide health care policy and clinical practice.



Article
Open Access
4 Apr 2026
Nature Communications

Real-world evidence for comparative safety of second-line antihyperglycemic agents in older adults with type 2 diabetes

Here the authors report real-world evidence through a retrospective analysis of a multinational cohort of 1.8 M older adults showing that GLP1RAs and SGLT2 inhibitors carry lower risk for hyperkalemia than sulfonylureas. However, SGLT2 inhibitors increased risk of ketoacidosis. Findings support safety-conscious prescribing for older adults, who are often underrepresented in clinical trials.

Chungsoo Kim, Fan Bu ... Yuan Lu

Featured in the journal's "Translational and clinical research" focus section!!

Thank you