



Cardiovascular Effectiveness of Individual GLP-1RA and SGLT2 Drugs in T2DM: Findings from the LEGEND-T2DM Study

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LEGEND-T2DM: comparative effectiveness & safety of 2nd-line T2DM treatments

- 4 drug classes: GLP-1RA, SGLT2I, DPP4I, SU
 - GLP-1RA: semaglutide, dulaglutide, etc.
 - SGLT2I: empagliflozin, dapagliflozin, etc.
- 32 outcomes: cardiovascular, renal, gastrointestinal, etc.
- ~4.7M T2DM patients (already on metformin)
- 17 multinational databases
- Class-level comparisons: multiple publications
 - Cardiovascular benefits (JACC '24): $GLP1 \approx SGLT2 > DPP4, SU$
 - GLP1 thyroid tumor concern insignificant
 - GLP1 increased risk of NAION (eye neural stroke)

Comparative Effectiveness of Second-Line Antihyperglycemic Agents for Cardiovascular Outcomes



A Multinational, Federated Analysis of LEGEND-T2DM

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Protocol

BMJ Open Large-scale evidence generation and evaluation across a network of databases for type 2 diabetes mellitus (LEGEND-T2DM): a protocol for a series of multinational, real-world comparative cardiovascular effectiveness and safety studies

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This study: **individual drug-level** cardiovascular effectiveness

- GLP-1RA vs SGLT2I (both **cardio-protective**)
 - GLP-1RA (6 agents): semaglutide (19%), dulaglutide (17%), albiglutide, exenatide, liraglutide, lixisenatide.
 - SGLT2I (4 agents) : empagliflozin (32%), dapagliflozin (17%), canagliflozin, ertugliflozin.
- Cardiovascular outcomes: 3-pt MACE (**acute MI, stroke, cardiac death**), 4-pt MACE (+ **heart failure hospitalization**); individual MACE components.
- **1.2M** new-users of 2nd line drugs; 10 multinational databases.
- Hazard ratio (HR) via propensity-score adjusted Cox PH model; random-effects meta-analytic HR.



Main finding 1: **increased proportional use** of GLP-1RA & SGLT2 agents among all 2nd line drugs

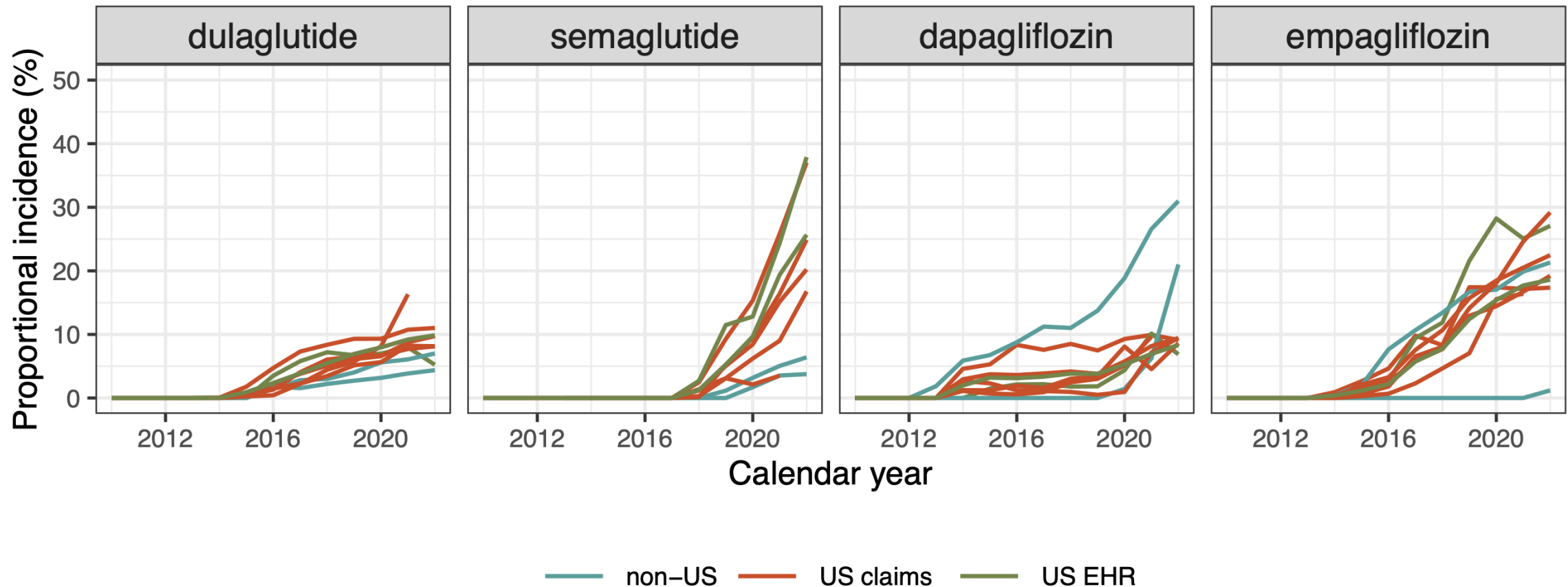
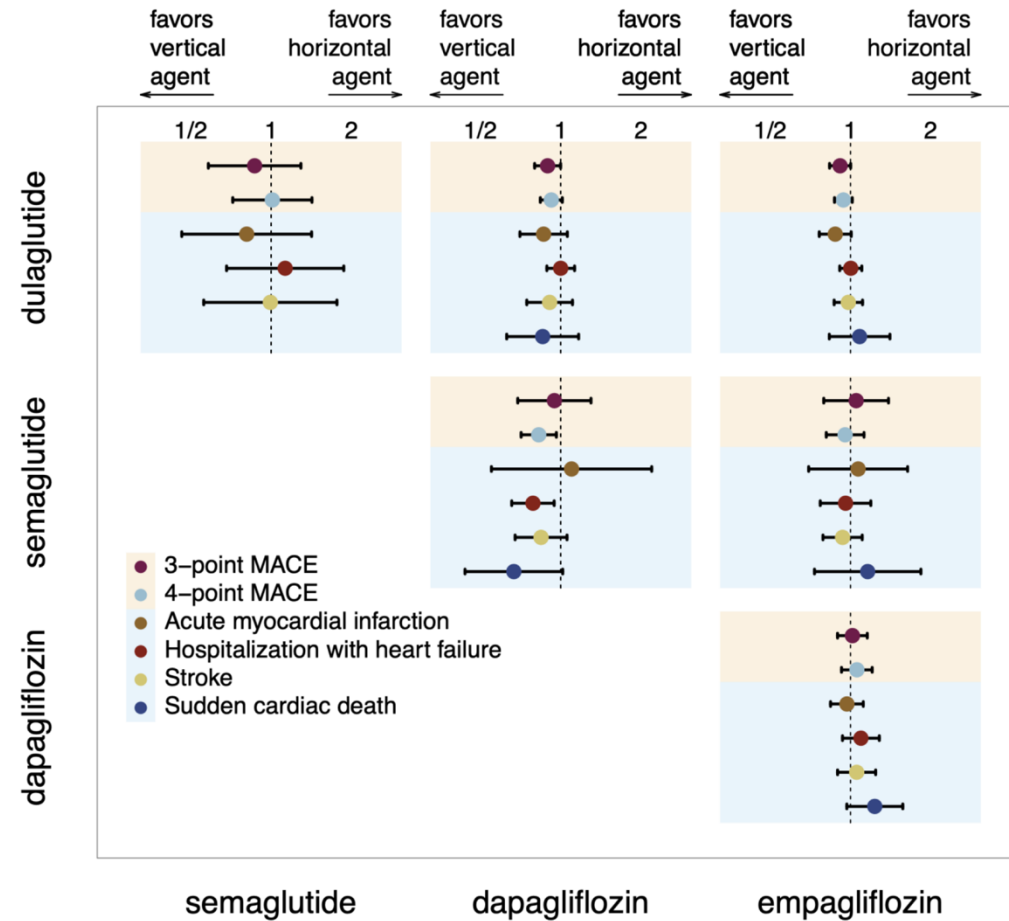


Figure. Yearly trends of proportional incidence of second-line drug initiation for a specific antihyperglycemic agent by year within each data source (one curve represents one data source for each drug).



Main finding 2: **GLP1 $\approx$ SGLT2** at ingredient-level in cardiovascular effectiveness, among general & CVD populations

A: General population



B: CVD population

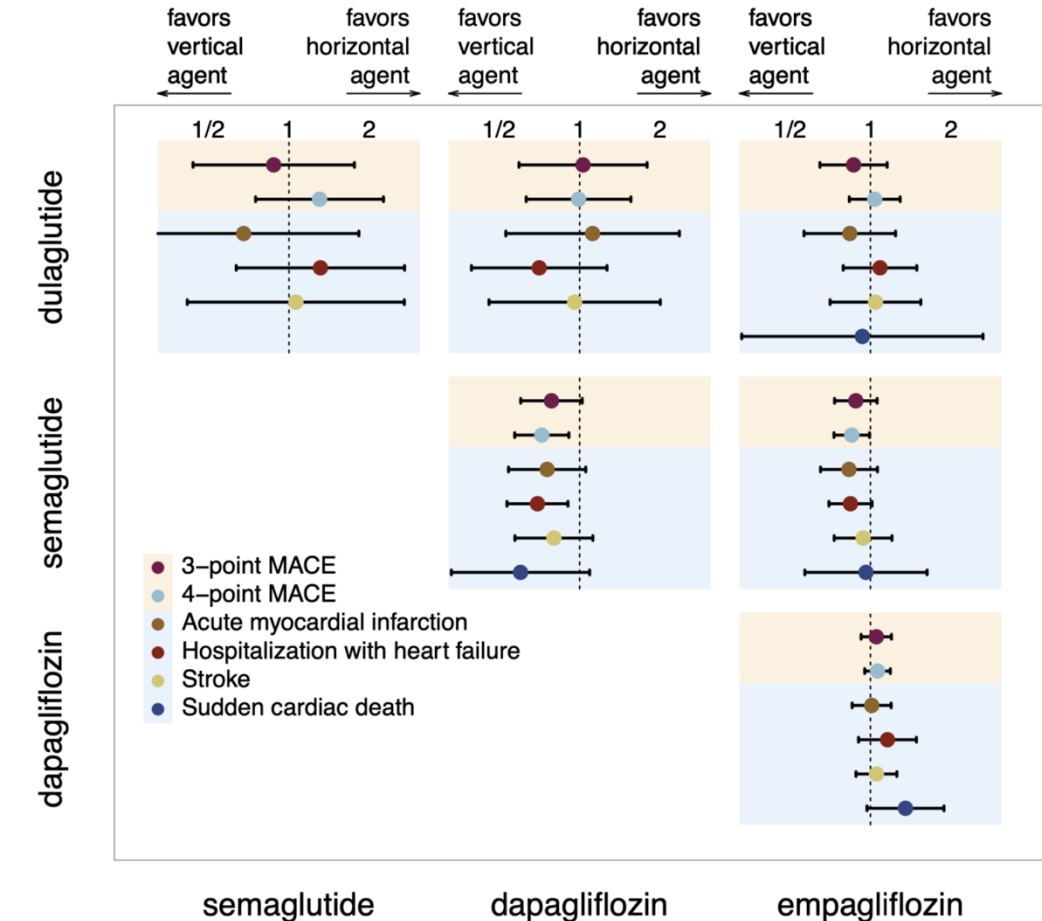


Figure. Meta-analytic HR estimates for cardiovascular effectiveness between GLP-1RA and SGLT2I drug new-users, among general population (A) & CVD subpopulation (B).



Discussion

- Findings **support guideline flexibility** between GLP-1RA and SGLT2I for **cardiovascular** benefits **at ingredient level**
- Future work:
 - Safety outcomes: gastrointestinal outcomes, DKA risks, etc.
 - Expanding treatments: newer agents (tirzepatide), combo therapy, etc.
 - **More data partners (!!)** for more generalizability
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