Use of GLP-1 receptor agonists and subsequent risk of acute liver injury

A cohort analysis in the OMOP CDM (GLP1-DILI)

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Background

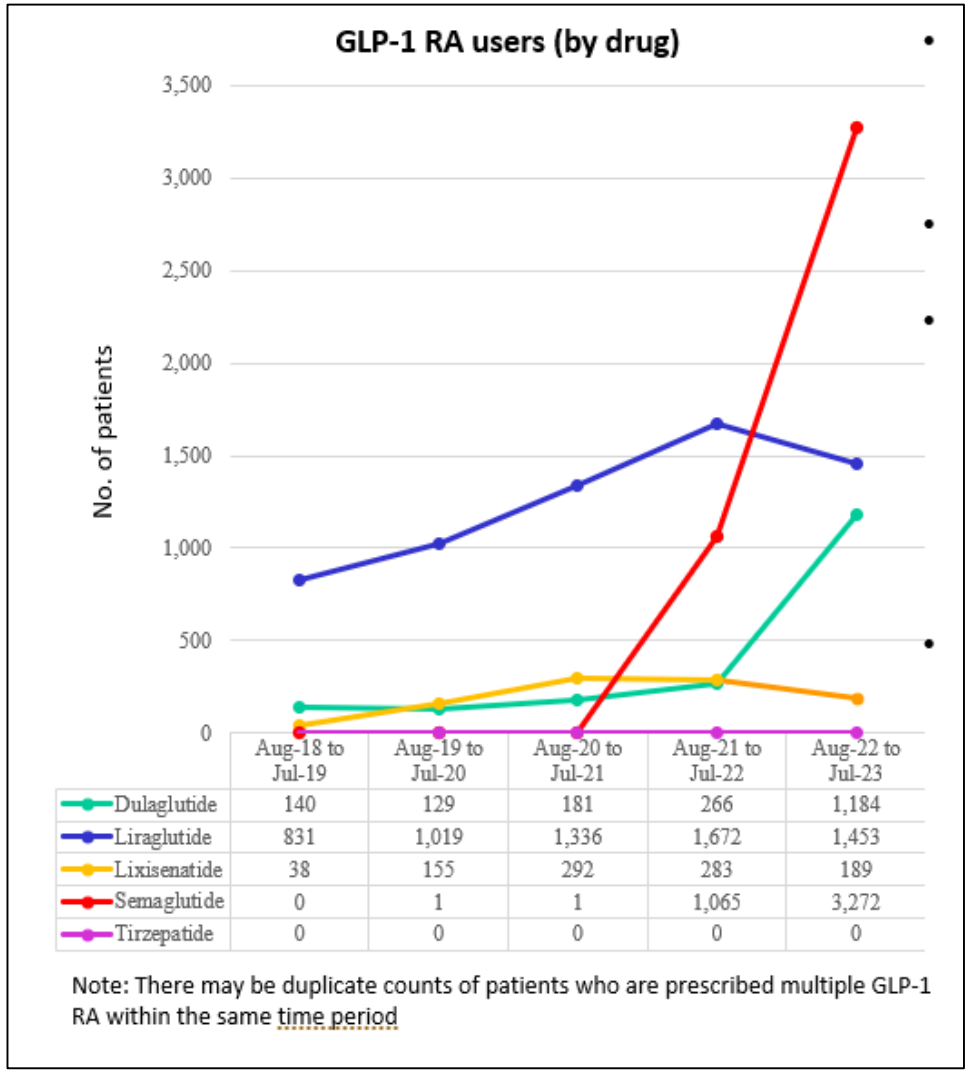
- GLP-1 receptor agonists (GLP-1RA) are increasingly used as treatment for T2DM and obesity.
- Several case reports have arisen on acute liver injury (ALI) post-prescription of GLP-1RA.
- Rising usage and seriousness of ALI warrants closer assessment to evaluate the risk, especially as second-line medication alongside other conventional prescriptions.

Case reports from U.S., Middle East:

- Noted cases of acute liver injury between 2 weeks to 6 months of starting GLP-1RAs
- Fully resolved with cessation of GLP-1RAs

Previous EMA study conducted noted:

- No increased risk in overall population,
- Increased risk in **female** users of GLP-1RAs and DPP-4 inhibitors



	Aug-18 to Jul-19	Aug-19 to Jul-20	Aug-20 to Jul-21	Aug-21 to Jul-22	Aug-22 to Jul-23
Dulaglutide	140	129	181	266	1,184
Liraglutide	831	1,019	1,336	1,672	1,453
Lixisenatide	38	155	292	283	189
Semaglutide	0	1	1	1,065	3,272
Tirzepatide	0	0	0	0	0

Note: There may be duplicate counts of patients who are prescribed multiple GLP-1 RA within the same time period

Objective

- Evaluate risk of
  - Acute liver injury [outcome]
  - In T2DM users [cohort]
  - of GLP-1 RA [target exposure]
  - compared to DPP4 [comparator]

Target and Comparator Cohort

- Entry event: First drug exposure to **GLP-1 RA / DPP4i**
- Inclusion criteria:
  - >=365 days of prior observation
  - Age >= 18
  - At least 1 condition occurrence of Type 2 Diabetes Mellitus any time prior
  - 0 occurrences of Type 1 Diabetes Mellitus and Secondary Diabetes any time prior
  - Exposure to metformin (>90-day duration or >3 exposures) any time prior
  - No ‘liver or biliary-related conditions’ any time prior
- Cohort exit: No longer have continuous exposure persistence of 60 days between exposure records

Outcome definition

- Entry event: All condition occurrences of acute liver injury
  - Defined by OHDSI phenotype library diagnostic codes
- Inclusion criteria:
  - 0 condition occurrences of chronic hepatic failure on the index date
  - 0 occurrences of ‘acute liver injury’ in the 365d prior to the index date
- Cohort exit:
  - Condition end date + 90 days

Study design

- New user comparative cohort study
  - Executed within each data source across distributed network
- Large Scale Propensity Score (LSPS) model 1:1 matching between target (**GLP1RA**) and comparator (**DPP4i**) cohorts
- Hazard Ratio (HR) estimated using Cox proportional hazards model for outcome of interest (**acute liver injury**) during the 'on treatment' time-at-risk'
- 130 negative control outcomes
- Evidence synthesis across network to produce composite HR
  - Bayesian meta-analysis of all sources passing objective diagnostics

Data Quality Criteria

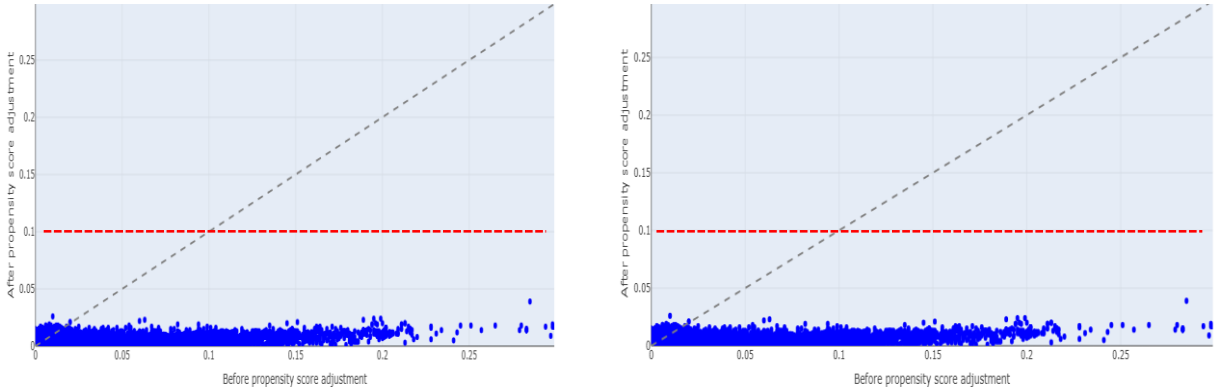
- Empirical equipoise
  - What proportion of target population is close to treatment indifference?
  - **PASS** if Equipoise (Preference score 0.3-0.7) > 0.20
- Covariate balance
  - Are baseline characteristics balanced?
  - **PASS** if Maximum Absolute Standardized Difference of Means after adjustment (Max ASDM) < 0.1
- Residual bias
  - Is the residual bias observed from negative controls small enough to accept that calibrated effect estimates can be trusted as unbiased?
  - **PASS** if Expected Absolute Systematic Error (EASE) < 0.25

Objective diagnostics

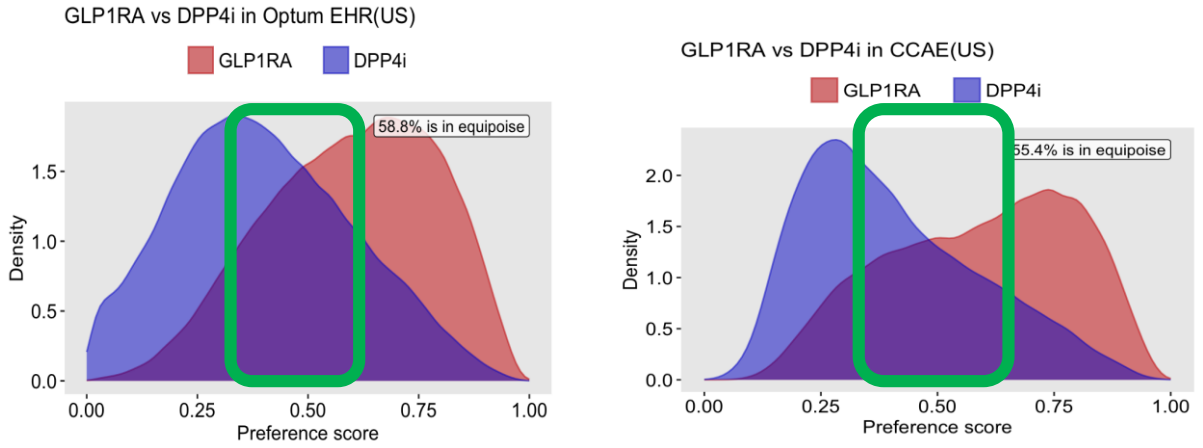
Diagnostic results:

- ~1.46M patients from U.S. and Japan after matching
- Kept databases that passed diagnostics criteria, with balanced covariates and sufficient PS overlap
- Negative control outcomes with EASE < 0.25

PS matching balanced covariates:



Good overlap in preference scores:



OPTUM EHR (US)

CCAE (US)

How many passed diagnostics?

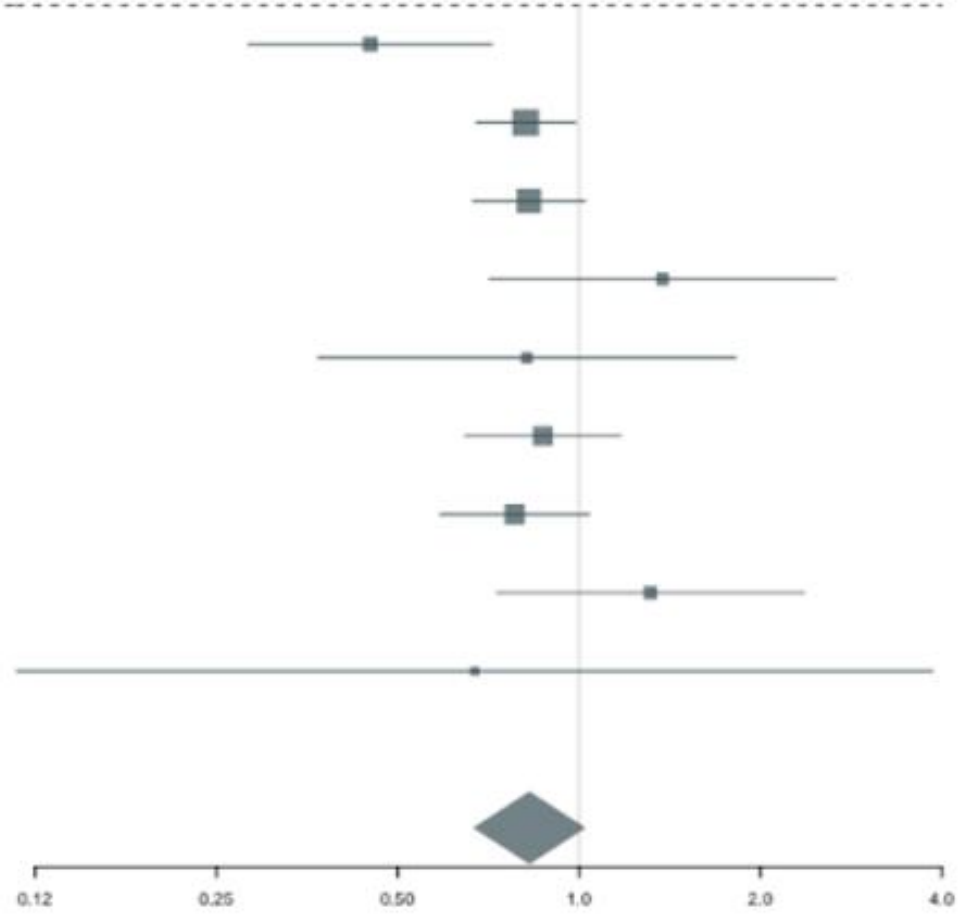
9 have passed so far

Database	OVERALL	COVARIATE BALANCE	EMPIRICAL EQUIPOISE	RESIDUAL BIAS (EASE)
France Disease Analyzer	Fail✗	FAIL✗	PASS✓	FAIL✗
Healthverity CC	Pass✓	PASS✓	PASS✓	PASS✓
MarketScan Commercial Claims (CCAE)	Pass✓	PASS✓	PASS✓	PASS✓
MarketScan Multi-State Medicaid	Pass✓	PASS✓	PASS✓	PASS✓
MarketScan Medicare Supplemental (MDCR)	Pass✓	PASS✓	PASS✓	PASS✓
Japan Medical Data Center	Pass✓	PASS✓	PASS✓	PASS✓
LPD Australia	Fail✗	FAIL✗	PASS✓	NOT EVALUATED
Iqvia LRx-US-9-LAAD	Pass✓	PASS✓	PASS✓	PASS✓
Optum EHR	Pass✓	PASS✓	PASS✓	PASS✓
PharMetrics	Pass✓	PASS✓	PASS✓	PASS✓
Yonsei University Severance CDM	Fail✗	FAIL✗	PASS✓	FAIL✗
Taipei Medical University CRD	Fail✗	FAIL✗	PASS✓	PASS✓
US Department of Veterans Affairs (VA)	Pass✓	PASS✓	PASS✓	PASS✓

Meta analysis results

GLP1RA vs DPP4i

Source	Event Rate GLP1RA	Event Rate DPP4i	Hazard ratio (95% CI)
CCAE(US)	0.70	1.48	0.45(0.28–0.72)
HVCC(US)	1.96	2.44	0.82(0.67–0.99)
LAAD(US)	0.78	0.97	0.83(0.67–1.02)
MDCD(US)	2.61	1.83	1.38(0.71–2.67)
MDCR(US)	2.37	3.17	0.82(0.37–1.82)
Optum EHR(US)	1.95	2.26	0.87(0.65–1.17)
PharMetrics(US)	1.11	1.42	0.78(0.59–1.04)
VA(US)	0.94	0.67	1.31(0.73–2.36)
JMDC(JP)	<1.80	1.05	0.67(0.12–3.86)
Meta–analysis	**<1.05**	**1.31**	**0.83(0.67–1.02)**



Summary

- Does exposure to **GLP-1 receptor agonists** have a different risk of experiencing **acute liver injury** within **time from day after exposure start to exposure end**, relative to **DPP-4 inhibitors**, among the population with **Type 2 diabetes mellitus**?

- **No evidence** of difference in risk

Next

- Evaluate risk of acute liver injury (and related secondary outcomes) in T2DM users of GLP-1 RA compared to DPP4 and SGLT2 inhibitors

Next Up

Target Cohort	Comparator Cohorts
New second-line users of GLP-1 RA	New second-line users of DPP4 inhibitors
	New second-line users of SGLT2 inhibitors

Primary outcome (executed)	Acute liver injury
Secondary outcomes (planned)	*Elevated ALP and AST liver enzymes* • *Alanine aminotransferase (ALT) ≥ 120 U/L + total bilirubin ≥ 2.0mg/dL OR* • *International normalized ratio (INR) ≥ 1.5 + total bilirubin ≥ 2.0mg/dL recorded within first 2 days of admission.* • *At least 1 confirmation of normal liver enzyme during the 90 days prior to index date.* • *At least 90 days of observation period*
	Cholelithiasis, cholecystitis
	Diagnosis of chronic liver injury within 30-, 60-, and 365-days post-index date, based on OHDSI Phenotype Library

Where are we?

- Code has just been tested on Yonsei University Severance CDM
  - Cohort was not big enough to pass matching ☹
- Looking for more test cohorts – especially Asian cohorts!
  - Test on larger cohorts that allow matching
  - Validate results

Thank you very much!