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

A cohort + SCCS analysis in the OMOP CDM (GLP-1RA-ALI)

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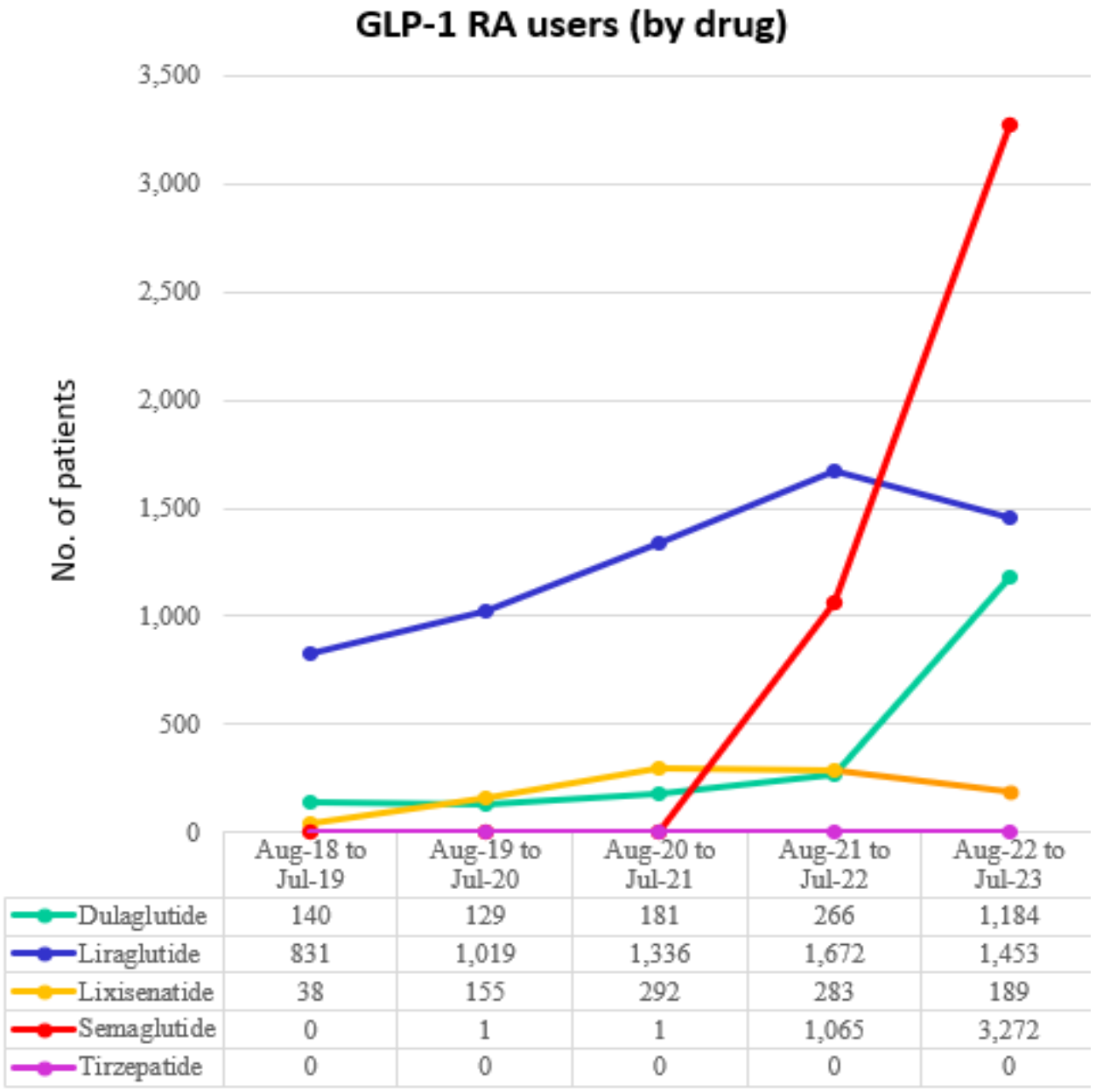
Study context

- GLP-1 receptor agonists (GLP-1 RA) increasingly used as treatment for T2DM (and obesity)
- Several case reports have arisen on acute liver injury (ALI) post-GLP-1 RA
- Rising usage and seriousness of ALI warrants closer assessment to evaluate the link

Clinical context

- GLP-1 receptor agonists (GLP-1 RA) are increasingly used



	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

Liver injury safety concerns have emerged

ABSTRACTS: CLINICAL VIGNETTES/CASE REPORTS - LIVER

Drug-induced Liver Injury Associated with the Glucagon-like Peptide 1 (GLP-1) Agonist Liraglutide

1131

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American Journal of Gastroenterology 108():p S335-S336, October 2013.

Article

Liraglutide-Induced Hepatotoxicity

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TIRZEPATIDE-RELATED ACUTE LIVER INJURY

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LIVER: CLINICAL VIGNETTES/CASE REPORTS

S3653 Semaglutide-Induced Hepatotoxicity: A Rare Case of Drug Induced Liver Injury

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The American Journal of Gastroenterology 118(10S):p S2370, October 2023. | *DOI:* 10.14309/01.ajg.0000964252.91007.e2

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Metrics

Introduction:

Semaglutide is a GLP-1 analogue approved for the treatment of type 2 diabetes and weight loss. Drug-induced liver injury (DILI) is a rare but significant cause of liver disease associated with various medications. We present a case of a 67-year-old woman who developed acute hepatocellular injury after initiation of semaglutide therapy for weight loss.

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Association between exposure to liraglutide versus active comparators and risk of acute hepatic injury

First published: 05/07/2024 **Last updated:** 14/10/2024

EU PAS number: EUPAS1000000243

Study Finalised

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Methods applied

- IQVIA™ DA Germany database
- New-user, active comparator design
- Diagnosis codes only for ALI
- Propensity score matching
- Intention-to-treat analysis
- Time-to-event, Cox regression

Box 1. Summary of study methods	
	• Those with recorded history of the outcome prior index-date (Excluded conditions are specific to each outcome, see more details in Section 5.3).
Treatment protocols	Initiate any of the following substances at **index-date** (as monotherapy). *Target arms (exposure of interest):* • liraglutide (target arm [Cohort 1], class: GLP-1 receptor agonist) *Comparator arms:* • empagliflozin (comparator arm [Cohort 2], class: SGLT-2 inhibitor) • dapagliflozin (comparator arm [Cohort 3], class: SGLT-2 inhibitor) • sitagliptin (comparator arm [Cohort 4], class: DPP-4 inhibitor)
Assignment procedures	We assumed treatments are randomly assigned conditional on the propensity score (PS) [see Section 5.6, Potential confounding factors]
Index-date (cohort entry, beginning of follow-up)	The index-date was the date of the initiation of treatment defined as a prescription date for liraglutide, empagliflozin, dapagliflozin or sitagliptin.
Outcome	First ever recorded occurrence of any of the conditions (incident event) included in the definition for each outcome: "Diseases of liver" (comparison 1), acute hepatic injury (comparison 2), acute hepatic injury with no chronic hepatic failure (comparison 3) [See section 5.6, Outcomes, and Annex II]
Follow-up	Patients were followed-up from index-date up to maximum of 90 days. Thus, patients were followed-up from index-date to the earliest of: date of first occurrence of outcome, loss to follow-up, death, end of follow-up (90 days) or end of the study period [See Section 5.5, Follow-up period]

Some notable differences between liraglutide and comparator

Table S3. Predefined[(1)] baseline characteristics before and after PS matching in **T2DM patients** in the IQVIA™ DA Germany database

	Before matching			After matching		
	Target	Comparator		Target	Comparator	
Characteristic	%	%	SMD	%	%	SMD
Age group						
10 - 14		0.0				
15 - 19	0.1	0.0	0.04	0.1	0.1	0.00
20 - 24	0.3	0.1	0.06	0.3	0.3	0.01
25 - 29	0.6	0.2	0.08	0.5	0.7	-0.02
30 - 34	1.4	0.5	0.11	1.4	1.5	0.00
35 - 39	2.9	1.2	0.13	2.5	2.5	0.00
40 - 44	5.3	2.3	0.18	4.3	4.6	-0.02
45 - 49	8.1	4.7	0.15	7.7	7.6	0.01
50 - 54	14.5	9.2	0.17	13.1	14.4	-0.04
55 - 59	17.6	13.8	0.11	17.1	17.3	-0.01
60 - 64	17.0	16.5	0.01	16.5	16.4	0.00
65 - 69	14.3	16.0	-0.05	15.2	15.9	-0.02
70 - 74	9.6	13.9	-0.13	9.8	8.0	0.06
75 - 79	5.4	10.7	-0.18	7.3	6.8	0.02
80 - 84	2.5	7.4	-0.20	3.5	3.2	0.02
85 - 89	0.3	2.9	-0.17	0.5	0.6	-0.01
90 - 94	0.0	0.5	-0.07	0.1	0.0	0.02
95 - 99		0.0			0.1	
Gender: female	45.6	35.8	0.20	47.1	49.5	-0.05
Medical history: General						

Some notable differences between liraglutide and comparator

Table S3. Predefined[(1)] baseline characteristics before and after PS matching in **T2DM patients** in the IQVIA™ DA Germany database

	Before matching			After matching		
	Target	Comparator		Target	Comparator	
Characteristic	**%**	**%**	**SMD**	**%**	**%**	**SMD**
Medical history: Cardiovascular disease						
Atrial fibrillation	2.3	3.4	-0.06	1.9	1.8	0.01
Cerebrovascular disease	3.8	4.9	-0.05	2.9	2.5	0.03
Coronary arteriosclerosis	4.0	8.7	-0.18	4.3	4.0	0.01
Heart disease	21.7	32.0	-0.22	18.8	17.8	0.03
Heart failure	6.5	9.7	-0.11	5.4	5.1	0.01
Ischemic heart disease	10.1	16.1	-0.17	8.7	7.7	0.04
Peripheral vascular disease	9.9	9.2	0.02	7.3	7.3	0.00

Results

No increased ALI risk observed, relative to new users of SGLT2i / DPP4i

Treatment arm	Follow-up (person-years)	n events	IR	95% CI		HR	95% CI	
365 days								
Sitagliptin	7710.90	25	**3.24**	2.07	4.54	**1.00**	[Reference]	
Liraglutide	7760.48	10	**1.29**	0.52	2.19	**0.40**	0.18	0.80
180 days								
Sitagliptin	4007.91	11	**2.74**	1.25	4.49	**1.00**	[Reference]	
Liraglutide	4016.81	7	**1.74**	0.50	3.24	**0.63**	0.23	1.61
90 days								
Sitagliptin	2080.46	5	**2.40**	0.48	4.81	**1.00**	[Reference]	
Liraglutide	2071.77	<5	(*)	(*)	(*)	**0.80**	0.20	3.04

Incretin-Based Drugs and the Risk of Acute Liver Injury Among Patients With Type 2 Diabetes

Richeek Pradhan,[1,2] Hui Yin,[2] Oriana H.Y. Yu,[2,3] and Laurent Azoulay[1,2,4]

Diabetes Care 2022;45:2289–2298 | https://doi.org/10.2337/dc22-0712

OBJECTIVE

To determine whether the use of dipeptidyl peptidase 4 (DPP-4) inhibitors and glucagon-like peptide 1 receptor agonists (GLP-1 RAs), separately, is associated with an in
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RESULTS

Compared
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RAs were
1.11, 95%
users of both DPP-4 inhibitors (HR 3.22, 95% CI 1.67–6.21) and GLP-1 RAs (HR 3.23, 95% CI 1.44–7.25).

CONCLUSIONS

In this population-based study, DPP-4 inhibitors were associated with an increased risk of acute liver injury compared with SGLT-2 inhibitors in patients with type 2 diabetes. In contrast, an increased risk of acute liver injury was observed only among female GLP-1 RA users.

RESULTS

Compared with SGLT-2 inhibitors, DPP-4 inhibitors were associated with a 53% increased risk of acute liver injury (HR 1.53, 95% CI 1.02–2.30). In contrast, GLP-1 RAs were not associated with an overall increased risk of acute liver injury (HR 1.11, 95% CI 0.57–2.16). However, an increased risk was observed among female users of both DPP-4 inhibitors (HR 3.22, 95% CI 1.67–6.21) and GLP-1 RAs (HR 3.23, 95% CI 1.44–7.25).

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Objectives

- Evaluate risk of ALI in T2DM users of GLP-1 RA
  - Cohort:
    - In patients with T2DM, what are the **absolute and relative risks** of ALI incidence when prescribed with second-line GLP-1 RA compared to other classes of diabetes prescriptions?
  - Self-controlled case series (SCCS):
    - In patients with T2DM prescribed second-line GLP-1 RA, what is the **relative incidence** of developing ALI within an exposure risk period compared to baseline periods?