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Lower risks of cirrhosis and hepatocellular carcinoma with GLP-1RAs in type 2 diabetes: A nationwide cohort study using target trial emulation framework

Chun-Ting Yang, PhD[1]

Wen-Yu Yao, MS[1]

Chen-Yi Yang, MS[1]

Zi-Yang Peng, MS[1]

Huang-Tz Ou, PhD[1,2]

Shihchen Kuo, PhD[1,3]

[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan

[2]Department of Pharmacy, College of Medicine, National Cheng Kung University, Tainan, Taiwan

[3]Division of Metabolism, Endocrinology & Diabetes, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Michigan, United States

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Running title: Risks of cirrhosis and HCC with GLP-1RAs

Abstract

Background

To assess the association of cirrhosis and hepatocellular carcinoma (HCC) with the use of glucagon-like peptide-1 receptor agonists (GLP-1RAs) versus long-acting insulins (LAIs), which are the two commonly prescribed injectable glucose-lowering agents (GLAs) for patients with type 2 diabetes (T2D) after failure of multiple oral GLAs.

Methods

We emulated a target trial using the nationwide data of a Taiwanese cohort with T2D. Incident new users of GLP-1RAs and LAIs during 2013-2018 were identified and propensity score (PS) matching was applied to ensure between-group comparability in baseline patient characteristics. The primary outcome was the composite liver disease including cirrhosis or HCC. Each patient was followed until the occurrence of a study outcome, death, or the end of 2019, whichever came first. Subdistribution hazard models were employed to assess the treatment-outcome association. Sensitivity (e.g., stabilized inverse probability of treatment weighting analysis, time-dependent analysis), E-value, and negative control outcome analyses were performed to examine the robustness of study findings.

Results

We included 7,171 PS-matched pairs of GLP-1RA and LAI users with no significant between-group differences at baseline. Compared with LAIs, the use of GLP-1RAs was associated with significantly

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reduced risks of composite liver disease (subdistribution hazard ratio [95% confidence interval]: 0.56 [0.42-0.76]), cirrhosis (0.59 [0.43-0.81]), and HCC (0.47 [0.24-0.93]). Results were consistent across sensitivity analyses and among patients with different baseline characteristics.

Conclusion

Among T2D patients who require injectable GLAs, the use of GLP-1RAs versus LAIs was associated with lower risks of cirrhosis and HCC.

Keywords: GLP-1 receptor agonists, long-acting insulins, liver cirrhosis, hepatocellular carcinoma, type 2 diabetes

Introduction

With rising awareness of the burden caused by progressive liver diseases such as cirrhosis and hepatocellular carcinoma (HCC) in patients with type 2 diabetes (T2D) (1), interventions to ameliorate the progression of chronic liver diseases have emerged as a critical issue. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have weight-loss effect that is strongly linked to the improvement of hepatic steatosis (2). The phase II LEAN trial demonstrated that liraglutide could lead to histological resolution of non-alcoholic steatohepatitis (NASH) (3). Recent meta-analyses have reported that GLP-1RAs versus other glucose-lowering agents (GLAs) significantly improved hepatic adipose content, hepatic fibrosis markers, and liver enzyme levels in patients with T2D and non-alcoholic fatty liver disease (NAFLD) (4-6). However, whether these short-term clinical effects of GLP-1RAs could translate to long-term benefits on liver cirrhosis and HCC remains unclear.

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A retrospective cohort study reported no significant association of using GLP-1RAs versus thiazolidinediones (TZDs) with cirrhosis risk among patients with T2D (7). However, the generalizability and validity of this study were limited in that they only included patients aged ≥65 years, used data from a relatively outdated period (2007-2015) and had the possibility of imbalanced between-group baseline patient characteristics. Furthermore, patients who require injectable GLA therapies (GLP-1RAs, insulins) after failure on multiple oral GLAs in the later treatment course of T2D are at a high risk for progressive liver diseases (8, 9), but whether some glucose-lowering therapy would pose beneficial liver effects among such patients remains uncertain.

Given the limitations of the previous observational study (7) and the need for real-world evidence on liver effects of GLP-1RA therapy in T2D patients, we designed a nationwide retrospective cohort study to emulate a hypothetical pragmatic trial (10-13) for evaluating the comparative risk of cirrhosis and HCC associated with use of GLP-1RAs versus long-acting insulins (LAIs), which are two commonly prescribed injectables for real-world T2D patients who require intensive glycemic control after failure on multiple oral GLAs (14, 15).

Methods

This study was approved by the Institutional Review Board of National Cheng Kung University Hospital (A-EX-106-013) with a waiver of informed consent.

Emulation of a hypothetical target trial using observational data

We pursued a target trial design to emulate a randomized controlled, open-label, pragmatic trial with the nationwide data obtained from Taiwan's National Health Insurance Research Database (NHIRD). The NHIRD is a population-based database that contains individual-level, longitudinal

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healthcare claims data for around 23 million beneficiaries enrolled in the Taiwan NHI program (16). Details of the trial emulation are specified in Supplementary Table 1.

Study population

Patients with T2D initiating a GLP-1RA or LAI during 1/1/2013-12/31/2018 were identified. The index date was defined as the date of treatment initiation, and the follow-up of patients began on the index date (observational analog of the intention-to-treat [ITT] effect). In the ITT analysis, patients were followed until the occurrence of study outcomes, death, loss to follow-up, or 12/31/2019, whichever came first. We excluded patients receiving GLP-1RAs or LAIs in the year before the index date (17). The one-year time period has been commonly applied in the literature to assess patients' baseline status and further determine the incident use of study treatments among real-world T2D populations (18-21). Patients with histories of cirrhosis, HCC, hepatectomy, or liver transplant in the year before the index date were excluded to avoid including prevalent cases of progressive liver diseases (Supplementary Figure 1).

The propensity score (PS) matching procedure was applied to generate a study population with similar probability of treatment assignment between the two study groups, which mimicked a randomized controlled trial (RCT) where all individuals possess the same likelihood of being assigned to each of the study groups (11,12). Logistic regression modeling was used to estimate the PS which indicated a patient's probability of receiving GLP-1RAs rather than LAIs conditional on a wide range of baseline patient demographic, clinical, and health behavior-related characteristics. GLP-1RA and LAI users were 1:1 matched using the 5-to-1 digit greedy PS matching procedure (22). Table 1 shows a list of baseline patient characteristics for PS estimation.

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Operational definitions of treatment exposure and study outcomes

Exposure to GLP-1RAs or LAIs was measured using the World Health Organization Anatomical Therapeutic Chemical Classification system. Primary outcome was a composite liver disease of cirrhosis or HCC. Secondary outcomes were cirrhosis or HCC. Cirrhosis and HCC were identified from inpatient or emergency department records using the International Classification of Diseases diagnosis codes (Supplementary Table 2). The validity of using these codes to identify study outcomes in administrative databases has been reported elsewhere (7, 23).

Statistical analyses

Differences in baseline characteristics between study groups were tested using standardized mean differences (SMDs), where an absolute SMD value greater than 0.1 indicated a significant between-group difference (24). The treatment-outcome association was estimated using subdistribution hazard models to account for the competing risk of death, and presented as subdistribution hazard ratios (SDHRs) with 95% confidence intervals (CIs) (25). A series of interaction tests were conducted by including the interaction terms between treatment and baseline patient characteristics as covariates in the models to explore potential heterogeneous treatment effects.

Several sensitivity analyses were performed to examine the robustness of study results from primary analyses under ITT scenario. First, a sensitivity analysis which evaluated the treatment-outcome association (hazard ratios [HRs]) using Cox proportional hazard models was performed to examine whether the conclusion of study findings remained consistent with the estimates of SDHRs in the primary analyses. Second, the per-protocol analysis was performed where patients were followed from the index date until treatment discontinuation, a switch to the other study drug, occurrence of study outcomes, death, loss to follow-up, or 12/31/2019, whichever came first. Third, stabilized inverse probability of treatment weighting (IPTW) (13,26) was applied to achieve a

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balanced distribution of confounders across study groups, thereby emulating the properties of a RCT. Different from the PS-matching method that estimates the average treatment effect on the treated, the stabilized IPTW approach includes the entire eligible study patients to measure the average treatment effect which would complement the concern of excluding unmatched patients in the PS-matching analysis. Fourth, to address the concern of biased estimates caused by time-varying confounders, the time-dependent survival analysis was re-iterated with adjustment of each patient's PS which was repeatedly measured every six months during the follow-up period. Fifth, patients were classified as having exposure to study drugs with a medication possession ratio (MPR) of either <0.8 or ≥ 0.8 within one year after the study drug initiation to explore whether treatment effects differed by patients' medication adherence. Sixth, an E-value analysis was conducted to assess how strongly a potential unmeasured confounder would negate the observed treatment-outcome association (27, 28). Because HbA1c levels are the major treatment indicator of glucose-lowering therapies in diabetes patients, we primarily considered the residual confounding effects attributable to the lack of HbA1c data in our E-value analysis. However, considering that other possible unmeasured confounders might exist, falsification analyses were performed to assess the presence of other potential unmeasured confounding using schizophrenia and herpes zoster virus reactivation as negative control outcomes, which have been adopted in previous studies to evaluate the effects of GLP-1RAs in T2D populations (29-32).

Subgroup analyses were performed to evaluate whether the treatment effects of study drugs differed by baseline patient characteristics, namely, gender, age, the histories of liver diseases (i.e., viral hepatitis, NASH, or alcoholic liver diseases), cancer, obesity, and NASH, and previous exposure to metformin and TZDs. PS matching and subdistribution hazard model analyses were re-iterated within each subgroup to ensure the comparability of patient characteristics between GLP-1RA and LAI users in analyses.

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A two-tailed *p*-value of <0.05 was considered a statistically significant difference. All analyses were conducted using SAS software version 9.4.

Results

There were 7,633 and 49,081 incident new-users of GLP-1RAs and LAIs during 2013-2018, respectively (Supplementary Figure 1). The GLP-1RA group was younger and had more females. More patients in the LAI group had macrovascular complications, but there were no between-group differences in microvascular complications. Liver diseases and exposure to medications with potential hepatotoxicity were generally comparable between study groups (Table 1). After the PS matching, 7,171 matched pairs of GLP-RA and LAI users with no significant between-group differences in baseline characteristics were included in the analyses (Table 1).

Table 2 shows the event rates and relative hazards of study outcomes associated with use of GLP-1RAs versus LAIs in the ITT and per-protocol analyses. In the ITT analysis, the use of GLP-1RAs versus LAIs was associated with decreased risks of composite liver disease, cirrhosis, and HCC by 44% (SDHR [95% CI]: 0.56 [0.42-0.76]), 41% (0.59 [0.43-0.81]), and 53% (0.47 [0.24-0.93]), respectively. GLP-1RA-associated lower risks of liver diseases were also shown in the per-protocol analysis although the statistical significance was not revealed for the HCC outcome. The estimated HRs using Cox proportional hazard models (Supplementary Table 3) were consistent with the estimated SDHRs shown in Table 2.

Overall, a reduced risk of liver diseases associated with use of GLP-1RAs versus LAIs was revealed across sensitivity analyses (Supplementary Table 4) and subgroup analyses (Figures 1 and 2) although an insignificant reduced risk was found in some scenarios (i.e., stratifying the study patients by adherence to the study drugs) or subgroups (e.g., male, having prior liver diseases or cancers). An

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insignificant increased risk of liver diseases associated with use of GLP-1RAs versus LAIs was observed among the patients aged ≥65 years.

The E-value for the composite liver disease was 2.97 for the point estimate and 1.96 for the upper 95% CI bound. This means that an unmeasured confounder (e.g., HbA1c) would need to have a relative risk of higher than 1.96 associated with both the treatment and outcome, conditional on measured confounders, to nullify the observed study findings. In falsification analyses, there were no significant associations of the risk of schizophrenia (SDHR [95% CI]: 0.97 [0.74-1.29]) or herpes zoster virus reactivation (SDHR [95% CI]: 1.13 [0.95-1.36]) with use of GLP-1RAs versus LAIs (Supplementary Table 5).

Discussion

To the best of our knowledge, this real-world retrospective cohort study comprising individual-level, longitudinal follow-up data is the largest and first analysis relevant to the clinically critical issue of long-term progressive liver outcomes (cirrhosis and HCC) associated with GLP-1RA therapy. Lower risks of cirrhosis and HCC associated with use of GLP-1RAs versus LAIs were observed in real-world T2D patients who require intensive injectable GLAs and are at high risk for progressive liver diseases.

Effect of GLP-1RAs versus insulins on cirrhosis

Evidence about the effect of GLP-1RAs versus insulins on the risk of chronic liver diseases is limited. Only one real-world study evaluated the risk of NAFLD between GLP-1RA and insulin therapies and reported an insignificant difference in developing NAFLD between treatments (33), but this finding should be interpreted with caution considering the potential residual bias, over-

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adjustments in the Cox regression analyses, and under-diagnosis and under-coding of NAFLD in administrative healthcare records (34). Our analyses defined cirrhosis as part of the primary outcome because 1) cirrhosis is a clinical condition that typically requires medical treatments, and thus should be more accurately identified in an administrative claims database, and 2) a cirrhosis risk with use of GLP-1RAs versus LAIs has not been investigated among a T2D population that requires intensive injectable GLAs after failure on multiple oral GLAs. Noticeably, the majority of such patients are severe diabetic cases with poor glycemic control and thus have an elevated risk for progressive liver diseases such as cirrhosis.

Nowadays, data on comparative treatment effects of glucose-lowering therapies in patients with T2D on cirrhosis remains lacking. Although a retrospective cohort study had assessed the cirrhosis risk associated with use of GLP-1RAs versus TZDs and reported an insignificant difference in the cirrhosis risk between treatments (7), the study results should be interpreted cautiously due to a wide range of study estimates (PS-weighted HR: 0.43-2.79) under different analysis scenarios and the limited generalizability of including only patients aged ≥65 years in the study.

Our findings of a lower cirrhosis risk associated with GLP-1RA use may be supported by recent meta-analyses which showed improved liver-related biomarkers, including hepatic steatosis markers, intrahepatic adipose, and alanine transaminase, following GLP-1RA therapy versus insulins among T2D patients with NAFLD (5, 6). Also, the GLP-1RA-associated weight-loss benefit which improves steatohepatitis and hepatic fibrosis (35-38) may partially explain the reduced risk of cirrhosis associated with GLP-1RA use. In other words, GLP-1RAs may mediate the progression pathway of simple steatosis, NASH, and fibrosis, through both weight-loss and weight-independent effects, and consequently reduce the risk of progressive liver diseases such as cirrhosis and HCC.

Effect of GLP-1RAs on HCC

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There are no previously available data on HCC outcomes following GLP-1RA therapy (39). Our study is thus the first to show a reduction in HCC risk associated with use of GLP-1RAs versus LAIs. This result might be explained by the pharmacological mechanisms proposed in previous *in vitro* and animal studies (40-50), including the direct effects of GLP-1RAs on the attenuation of hepatocyte apoptosis (41, 42), modulation of liver Kupffer cell M1/M2 polarization (43, 44), and activation of AMP-activated protein kinase (AMPK), which is associated with anti-inflammation and the prevention of cancer development (45, 46). Additionally, the anti-hepatocarcinogenesis effect of GLP-1RAs may be partially explained by the amelioration of hyperglycemia that produces reactive oxygen species and advanced glycation endpoints and further induces hepatic inflammation, DNA damage, and carcinogenesis (47-50). However, our study findings should be interpreted with caution given the potentially increased risk of liver cancer with insulin therapy reported in previous studies (39, 51, 52). Specifically, a meta-analysis of cohort and case-control studies showed that insulin versus non-insulin use in patients with diabetes had a 90% increased risk of liver cancer (relative risk [95% CI]: 1.90 [1.44-2.50]) although a considerable heterogeneity (I^2=76.1%) existed in the included studies (51). Another retrospective cohort study found that compared with use of metformin alone, insulin alone or insulin in combination with other GLAs (e.g., metformin, sulfonylureas) significantly increased the HCC risk by 0.44- to 1.86-fold in patients with diabetes and NAFLD (52). Whether the lower risk of HCC associated with GLP-1RA use observed in the present study can be attributed to the actual benefit of GLP-1RAs or is merely caused by the relative effect compared with insulins is worthy of further investigation.

GLP-1RA therapy-associated liver outcomes across patient characteristics

The limited number of sample sizes and event numbers may contribute to the non-significantly lower risks of liver outcomes associated with GLP-1RA versus LAI therapy among several patient

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subgroups (Figures 1 and 2). Additionally, an insignificant increased risk of liver outcomes associated with GLP-1RA versus LAI use was observed among those aged ≥65 years. However, caution should be made while interpreting the analysis results considering the uncertainty in study inference arisen from the wide confidence intervals of the relative hazard estimates. Hence, future research with larger sample sizes is warranted to explore whether heterogeneous treatment effects exist across the patient subgroups.

Strengths and limitations

This real-world study bridges the current evidence gap regarding comparative treatment effects on progressive liver diseases between GLP-1RA and LAI therapies among T2D patients. With several methodological efforts made to ensure the internal validity (e.g., trial emulation design, PS-matching analysis) and support the external validity (e.g., PS-weighting analysis, sensitivity and subgroup analyses) of the study findings, the present study generated supporting real-world evidence on reductions in the risks of cirrhosis and HCC associated with use of GLP-1RAs versus LAIs in T2D populations who require intensive injectable GLAs. The methodological efforts included 1) the target trial design of emulating an idealized clinical trial to estimate causal treatment effects, 2) the adoption of an incident new user and active comparator design to avoid time-related bias (e.g., prevalent-user and survivor bias) and the effect of confounding by indication that typically arises in the comparative analysis of treatment versus non-treatment; 3) the application of PS-based methods (i.e., matching, weighting) to enhance the between-group comparability and minimize residual confounding effects; and 4) the use of a series of sensitivity and subgroup analyses to confirm the robustness of study findings and study generalizability to diverse real-world patient populations.

Several study limitations should be acknowledged. First, like other real-world studies based on administrative claims data, there might be unmeasurable confounding effects due to a lack of clinical

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laboratory and health behavioral data. However, several efforts were made to minimize these effects. Specifically, PS matching was employed to carefully consider a wide range of variables as proxies for patient baseline status of diabetes severity (e.g., previous use of GLAs, diabetes-related complications), liver diseases (e.g., viral hepatitis, alcoholic and non-alcoholic liver diseases), and general health conditions (e.g., comorbidities, health behaviors) in the primary analysis. A greater level of between-group comparability in patient baseline characteristics was achieved after PS matching.

In addition, an E-value analysis was performed to determine whether our study findings would be reversed by possible residual confounding effects arisen from unmeasured HbA1c levels which are the major treatment indicator of glucose-lowering therapies. Specifically, previous real-world studies revealed that initiators of basal insulins tended to have a 0.6% to 1% higher HbA1c level compared with those of GLP-1RAs (15, 53). Every 1% increase in mean HbA1c was reported to have 15%-increased odds (odds ratio: 1.15 [1.01, 1.31]) of progressed hepatic fibrosis stages (i.e., stages 0 to 4) (54). Namely, a 1% higher HbA1c elevates the risk of incident cirrhosis (i.e., from hepatic fibrosis stages 0 to 4) with an odds ratio ranging from 1.04 (i.e., 1.01 x 1.01 x 1.01 x 1.01) to 2.94 (i.e., 1.31 x 1.31 x 1.31 x 1.31), which is lower than the estimated E-value of 2.97 in our primary analysis. Considering the odds ratio of 2.94 was close to the estimated E-value of 2.97 and our hypothetical calculation only accounted for residual confounding by HbA1c levels, we further performed a negative control outcome analysis to detect the possibility of residual confounding effects in this observational study (30). The negative control outcome analysis demonstrated no differences in schizophrenia or herpes zoster virus reactivation risk between GLP-1RA and LAI users, suggesting that residual confounding due to unmeasured factors might be less likely.

Second, the comparisons of GLP-1RAs with other GLAs besides LAIs were not considered in the present study. Future research is encouraged to extensively evaluate the comparative effectiveness of GLP-1RA versus other GLA therapies on liver outcomes for providing more information to support

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clinical treatment decisions. Third, the validity of some disease diagnosis codes such as obesity or NASH in the administrative claims database is uncertain (e.g., under-diagnosis, under-recording) (34) and may further introduce misclassification bias although such bias is usually nondifferential between study groups. Lastly, the generalizability of our study findings might be limited to T2D populations who are in need of injectable GLAs and have universal healthcare coverage.

Conclusion

Among a real-world patient cohort with T2D, the use of GLP-1RAs versus LAIs was associated with significantly lower risks of cirrhosis and HCC. Future research with larger sample sizes or different study designs that allow to corroborate our study findings and explore heterogeneous treatment effects of GLP-1RAs on progressive liver diseases is encouraged to provide comprehensive evidence for facilitating personalized medicine.

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Conflict of interest

All authors have no competing interests to declare.

Author contributions

Yang CT, Yang CY, Yao WY, and Ou HT had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: All authors.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: All authors.

Critical revision of the manuscript for important intellectual content: Ou HT, Kuo S.

Statistical analysis: Yang CT, Yang CY, Yao WY.

Obtained funding: Ou HT.

Administrative, technical, or material support: Ou HT.

Supervision: Ou HT, Kuo S.

Data availability statement

Data sharing is not applicable to this study as data management and analysis were only allowed to be conducted in the Health and Welfare Data Science Center in Taiwan due to data privacy and safety concerns.

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Correspondence

Huang-Tz Ou, PhD

Institute of Clinical Pharmacy and Pharmaceutical Sciences

College of Medicine, National Cheng Kung University

1 University Road

Tainan 701, Taiwan

Telephone: 886-6-2353535 ext. 5685

Fax: 886-6-2373149

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Email: huangtz@mail.ncku.edu.tw

Table 1: Baseline characteristics of study population stratified by GLP-1RA and LAI use before and after propensity score matching

Characteristics	Before PSM			After PSM[§]		
	GLP-1RAs	LAIs	SMD	GLP-1RAs	LAIs	SMD
Number of subjects	7,633	49,081		7,171	7,171	
Demographic characteristics at index date						
Age at index date (years), mean (SD)	48.6 (12.5)	56.3 (14.8)	-0.56	49.3 (12.4)	49.1 (13.3)	0.01
Female (%)	50.3%	41.0%	0.19	49.6%	49.3%	0.01
Year of index date (%)						
2013	3.0%	10.9%	-0.32	3.2%	3.2%	0
2014	4.7%	13.1%	-0.30	5.0%	5.0%	0
2015	9.3%	15.2%	-0.18	9.7%	9.6%	0
2016	14.1%	16.8%	-0.08	14.4%	14.8%	-0.01
2017	27.8%	20.1%	0.18	27.6%	27.8%	-0.01
2018	41.2%	23.9%	0.37	40.2%	39.6%	0.01
Previous GLA exposure in year before index date						
Number of oral GLAs per subject, mean (SD)	2.7 (1.2)	2.3 (1.5)	0.30	2.7 (1.2)	2.7 (1.2)	-0.04

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Specific type of GLAs (%)						
Metformin	89.5%	68.1%	0.54	88.9%	89.8%	-0.03
Sulfonylurea	63.8%	61.0%	0.06	65.7%	67.7%	-0.04
Meglitinide	7.8%	11.1%	-0.11	8.0%	7.7%	0.01
Alpha-glucosidase inhibitor	18.5%	19.2%	-0.02	18.8%	19.4%	-0.02
Thiazolidinedione	20.6%	15.7%	0.12	20.9%	21.0%	0
Dipeptidyl peptidase-4 inhibitor	65.2%	50.0%	0.31	65.5%	66.5%	-0.02
Sodium-glucose cotransporter-2 inhibitor	0.5%	0.2%	0.05	0.4%	0.4%	0
Rapid-acting insulin*	0.3%	0.4%	-0.03	0.3%	0.2%	0.01
Intermediate-acting insulin*	0.2%	0.6%	-0.07	0.2%	0.2%	-0.01
Mixed insulin*	3.8%	4.0%	-0.01	3.9%	4.1%	-0.01
Diabetes-related complications in year before index date (%)						
Cardiovascular and cerebrovascular diseases	18.9%	26.2%	-0.17	19.5%	19.1%	0.01
Ischemic heart diseases	12.2%	14.3%	-0.06	12.5%	12.1%	0.01
Heart failure	3.4%	5.8%	-0.11	3.5%	3.7%	-0.01
Arrhythmia	3.7%	5.5%	-0.09	3.9%	3.9%	0
Atherosclerosis	0.7%	1.0%	-0.02	0.8%	0.8%	0
Arteriosclerotic cardiovascular disease	3.5%	3.1%	0.02	3.6%	3.4%	0.01
Cardiogenic shock	0.0%	0.1%	-0.03	0.0%	0.1%	-0.01

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Aortic aneurysm and aortic dissection	0.2%	0.2%	-0.01	0.2%	0.2%	0
Ischemic stroke	2.5%	7.1%	-0.21	2.7%	2.6%	0
Hemorrhagic stroke	0.5%	1.8%	-0.12	0.5%	0.5%	0
Transient ischemic attack	1.0%	1.7%	-0.06	1.1%	1.0%	0.01
Peripheral vascular diseases	2.8%	5.1%	-0.12	2.9%	2.8%	0
Nephropathy	24.9%	27.1%	-0.05	25.2%	25.2%	0
Neuropathy	7.6%	9.8%	-0.08	7.9%	8.3%	-0.01
Retinopathy	11.1%	12.4%	-0.04	11.4%	12.0%	-0.02
Non-proliferative retinopathy	4.6%	5.1%	-0.02	4.7%	4.9%	-0.01
Proliferative retinopathy	2.2%	3.6%	-0.08	2.3%	2.3%	0
Diabetic macular edema	2.5%	2.9%	-0.02	2.6%	2.8%	-0.01
Hypoglycemia	0.6%	1.3%	-0.07	0.6%	0.7%	-0.01
Comorbidities in year before index date (%)						
Liver diseases						
Viral hepatitis	4.8%	4.8%	0	4.9%	4.9%	0
Nonalcoholic steatohepatitis	2.1%	1.3%	0.06	2.0%	1.9%	0.01
Alcoholic liver disease	0.3%	0.6%	-0.06	0.3%	0.3%	0
Hypertension	54.6%	53.6%	0.02	54.8%	54.6%	0
Dyslipidemia	67.9%	53.0%	0.31	68.1%	69.1%	-0.02
Cancer	12.5%	12.6%	0	12.5%	12.7%	-0.01

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Chronic obstructive pulmonary diseases	3.2%	6.0%	-0.14	3.3%	3.4%	-0.01
Gastrointestinal diseases[†]	9.5%	12.1%	-0.09	9.7%	9.5%	0.01
Gastrointestinal symptoms[‡]	7.3%	8.7%	-0.05	7.4%	7.5%	0
Gout	7.5%	7.5%	0	7.5%	7.6%	0
Hypothyroidism	1.6%	0.9%	0.06	1.4%	1.5%	0
Bipolar disorders	1.3%	0.7%	0.05	1.2%	1.1%	0.01
Major depressive disorders	2.8%	2.7%	0.01	2.8%	2.6%	0.01
Schizophrenia	1.0%	0.8%	0.02	1.0%	1.0%	0
Sleep apnea	2.1%	0.6%	0.13	1.7%	1.5%	0.02
Human immunodeficiency virus infection	0.1%	0.1%	-0.01	0.1%	0.1%	0
Exposure to medications for comorbidities in year before index date (%)						
Lipid-lowering medications	74.7%	53.1%	0.46	74.8%	74.2%	-0.01
Alpha-blockers	3.4%	4.3%	-0.05	3.5%	3.4%	0
Beta-blockers	28.2%	26.3%	0.04	28.2%	28.5%	-0.01
RAS agents	54.3%	44.3%	0.2	54.1%	53.8%	0.01
Diuretics	12.9%	17.3%	-0.12	13.2%	12.9%	0.01
Calcium channel blockers	22.9%	27.9%	-0.12	23.3%	23.1%	0
Anti-arrhythmias	1.5%	2.0%	-0.04	1.5%	1.4%	0.01
Cardiac glycosides	0.8%	1.9%	-0.1	0.8%	0.8%	0.01

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Vasodilators	18.4%	23.4%	-0.12	18.9%	19.2%	-0.01
Antiplatelets	22.3%	27.7%	-0.13	23.0%	23.1%	0
Anticoagulants	1.8%	3.5%	-0.11`	1.9%	2.0%	-0.01
Medication with potential hepatotoxicity in year before index date (%)						
Androgen deprivation therapy	0.2%	0.7%	-0.07	0.2%	0.2%	0.01
Amiodarone	0.7%	1.1%	-0.04	0.7%	0.6%	0.01
Glucocorticoid	25.2%	25.2%	0	25.2%	24.9%	0.01
Griseofulvin	0.9%	0.9%	0	0.9%	0.9%	-0.01
Hormone replacement therapy	5.6%	3.2%	0.12	5.4%	5.4%	0
Methotrexate	0.4%	0.4%	0	0.4%	0.4%	0
Tamoxifen	0.2%	0.2%	0.01	0.2%	0.3%	-0.01
Valproic acid	0.9%	1.4%	-0.05	0.9%	0.8%	0.01
Health behavior-related characteristics in year before index date						
Obesity (%)	9.1%	1.4%	0.35	6.5%	5.9%	0.03
Alcoholism (%)	0.3%	0.8%	-0.07	0.3%	0.3%	-0.01
Smoking cessation therapy (%)	1.9%	1.9%	0	1.9%	2.0%	0
Number of HbA1c tests, mean (SD)	7.8 (3.9)	5.5 (4.1)	0.58	7.7 (3.7)	7.7 (4.3)	-0.02
Number of LDL tests, mean (SD)	5.5 (3.6)	3.6 (3.3)	0.55	5.4 (3.5)	5.4 (3.8)	-0.01

Abbreviations: PSM, propensity score matching; GLP-1RAs, glucagon-like peptide-1 receptor agonists; LAIs, long-acting insulins; SMD, standardized mean difference; SD, standard deviation;

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GLAs, glucose-lowering agents; RAS, renin-angiotensin system; HbA1c, glycated hemoglobin; LDL, low-density lipoprotein cholesterol.

Notes:

*Previous exposure to these types of insulin was defined as having at least 28 days of drug exposure during the one-year baseline period.

†Gastrointestinal diseases included gastric ulcer, peptic ulcer, inflammatory bowel disease, and diverticulitis.

‡Gastrointestinal symptoms included nausea/vomiting, diarrhea, flatulence, eructation, and gas pain.

§Among the 7,171 matched cohorts, 45.9% (n=3,293) and 54.1% (3,878) of the GLP-1RA users initiated dulaglutide and liraglutide at the index date, respectively, and 31.1% (n=2,231) and 68.9% (n=4,940) of the LAI users initiated insulin detemir and insulin glargine at the index date, respectively.

Table 2: Event rates and hazard ratios of study outcomes associated with use of GLP-1RAs and LAIs

	GLP-1RAs (n=7,171)		LAIs (n=7,171)		
	Number of events	Event rate (events/100 pys)	Number of events	Event rate (events/100 pys)	SDHR (95% CI) of GLP-1RAs versus LAIs
Intention-to-treat analysis					
Composite liver disease	66	0.35	119	0.63	0.56 (0.42-0.76)
Cirrhosis	60	0.32	103	0.55	0.59 (0.43-0.81)
Hepatocellular carcinoma	12	0.06	26	0.14	0.47 (0.24-0.93)
Per-protocol analysis					
Composite liver disease	34	0.26	68	0.50	0.52 (0.35-0.79)

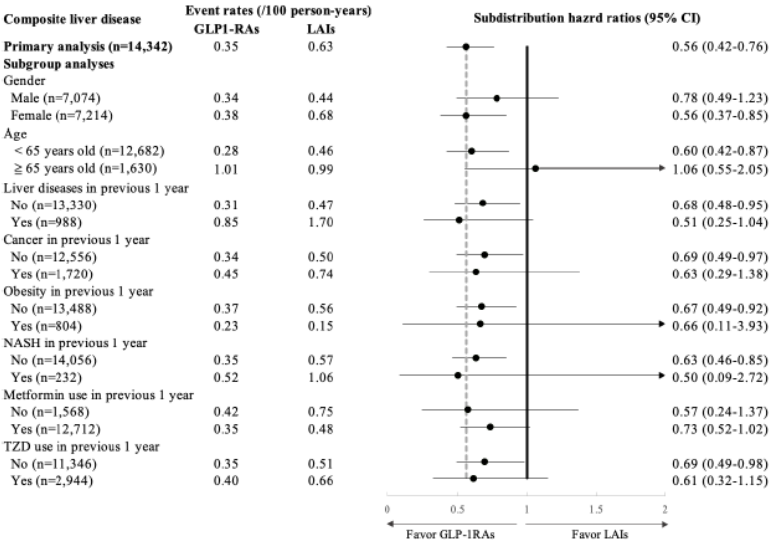
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Cirrhosis	29	0.22	58	0.43	0.52	(0.33-0.81)
Hepatocellular carcinoma	6	0.05	13	0.10	0.49	(0.18-1.29)

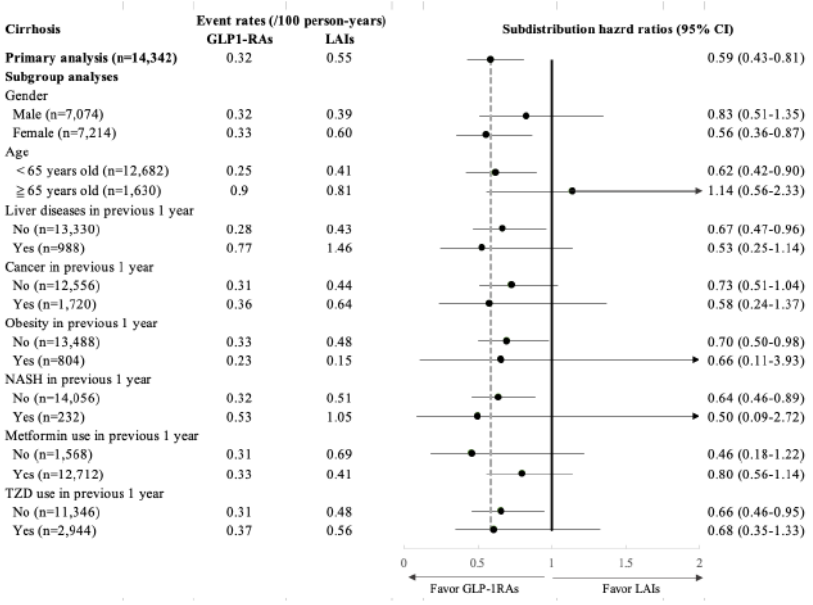
Abbreviations: GLP-1RAs, glucagon-like peptide-1 receptor agonists; LAIs, long-acting insulins; pys, person-years; SDHR, subdistribution hazard ratio; CI, confidence interval.

Figure 1: Event rates and hazard ratios of composite liver diseases associated with use of GLP-1RAs and LAIs in primary and subgroup analyses



Abbreviations: GLP-1RAs, glucagon-like peptide-1 receptor agonists; LAIs, long-acting insulins; CI, confidence interval; NASH, non-alcoholic steatohepatitis; TZD, thiazolidinedione.

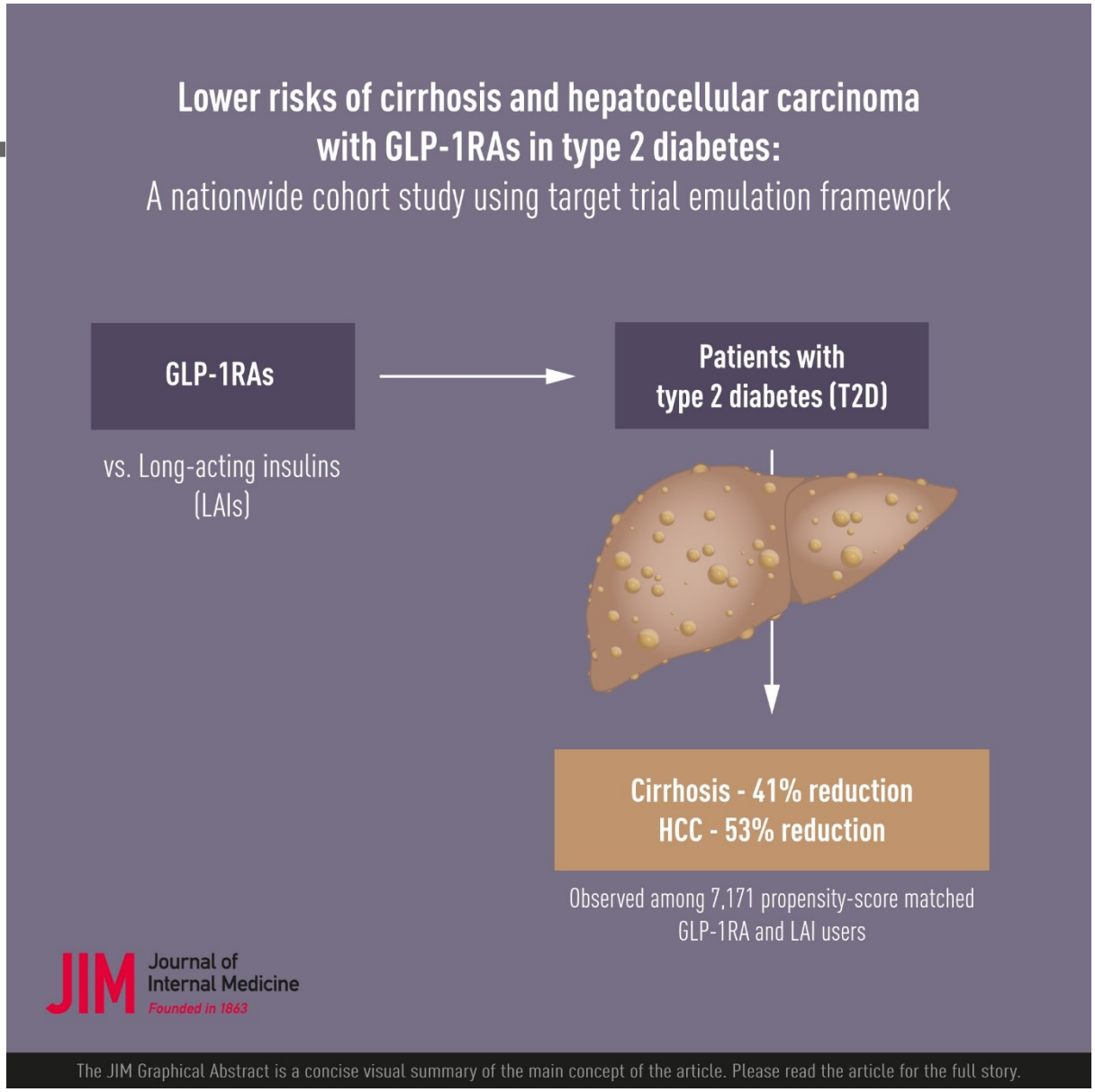
Figure 2: Event rates and hazard ratios of cirrhosis associated with use of GLP-1RAs and LAIs in primary and subgroup analyses



Abbreviations: GLP-1RAs, glucagon-like peptide-1 receptor agonists; LAIs, long-acting insulins; CI, confidence interval; NASH, non-alcoholic steatohepatitis; TZD, thiazolidinedione.

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