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Glucose-like Peptide-1 Receptor Agonists and Hepatic Decompensation Events in Patients with Cirrhosis and Diabetes

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Abstract

Background & Aims: To compare the effectiveness of glucose-like peptide-1 receptor agonists (GLP-1RA) with dipeptidyl peptidase-4 inhibitors (DPP-4i), sulfonylureas or sodium-glucose cotransporter 2 inhibitors (SGLT-2i) in reducing decompensation events, among patients with cirrhosis and type 2 diabetes.

Methods: This population-based, retrospective cohort study included patients with type 2 diabetes and cirrhosis, in a commercial healthcare database (IBM Marketscan). We constructed three pairwise, 1:1 propensity score (PS)-matched cohorts of adults initiating GLP-1RA or

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Acquisition of data: Simon, Schneeweiss
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All authors contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content and approved the final version of the manuscript. The corresponding author (TGS) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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The lead author (TGS) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and if relevant, registered) have been explained.

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The use of this dataset for research was approved by the institutional review board (#2011P002580) of the Brigham and Women's Hospital, Boston, MA, and a data use agreement is in place.

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a comparator medication (i.e. DPP-4i [2006-2020], sulfonylurea [2005-2020] or SGLT-2i [2013-2020]). Patients were followed in an astreated approach for decompensation events (i.e. ascites, spontaneous bacterial peritonitis [SBP], hepatorenal syndrome [HRS], hepatic encephalopathy [HE] or esophageal variceal hemorrhage [EVH]). Within each PS-matched cohort, we estimated HRs and 95%CIs, controlling for >90 baseline characteristics.

Results: Over 132 days of median follow-up (interquartile range=73, 290 days), PS-matched rates of any decompensation were significantly lower among GLP-1RA initiators, versus DPP-4i initiators (105.2 vs. 144.0/1000 person-years[PY]; HR=0.68 [95%CI=0.53-0.88]; n=1,431 pairs), and versus sulfonylureas (97.3 vs 144.0/1000PY; HR=0.64 [0.48-0.84]; n=1,246 pairs). Similar, inverse associations were found for individual decompensation events, including ascites/SBP/HRS (HRs=0.66 [0.45-0.97] and 0.66 [0.46-0.94], respectively), EVH (HRs=0.62 [0.41-0.92] and 0.59 [0.37-0.92], respectively), and HE (HRs=0.76 [0.55-1.06] and 0.60 [0.39-0.92], respectively). Results persisted in subgroups of patients with and without previously decompensated cirrhosis. In contrast, decompensation rates were similar, when GLP-1RA and SGLT-2i were directly compared (103.5 vs. 112.8/1000PY; HR=0.89 [0.62-1.28]).

Conclusion: Among cirrhotic patients with type 2 diabetes, we find high rates of decompensation, consistent with previous reports; these rates were substantially lower among GLP-1RA initiators, compared to DPP-4i or sulfonylureas.

Keywords

decompensated cirrhosis; antidiabetic therapy; comparative effectiveness; pharmacoepidemiology

Introduction

Cirrhosis is responsible for over 40,000 deaths each year in the U.S., and nearly 1.3 million deaths, worldwide[1 2], and cirrhosis-related mortality is increasing at an alarming pace[3]. Diabetes disproportionately affects over one-third of patients with cirrhosis, and contributes to substantial morbidity and mortality[4–6]. Specifically, hyperglycemia promotes the development of hepatocellular carcinoma (HCC)[5], and contributes to both hospitalizations and death from decompensation events, including ascites and spontaneous bacterial peritonitis (SBP), bleeding esophageal varices, hepatic encephalopathy (HE) and hepatorenal syndrome (HRS)[6–8]. Yet, for patients with cirrhosis, the benefit of intensive glucose control in patients remains controversial, and evidence regarding the optimal antidiabetic strategy is scarce, particularly for patients who do not tolerate metformin or require intensification of therapy. Thus, defining the safety and effectiveness of second-line antidiabetic strategies in this high-risk population remains an important unmet need.

Glucagon-like peptide-1 receptor agonists (GLP-1RA) exert numerous beneficial effects beyond reducing blood glucose and improving insulin sensitivity[9], including weight loss, improved blood pressure and lipid profiles, and reduced circulating inflammatory markers and adipokines[10]. In preclinical models, GLP-1RA therapy improves hepatic lipid oxidation, and in humans with non-cirrhotic nonalcoholic steatohepatitis (NASH), GLP-1RAs have demonstrated efficacy for reducing liver fat and lipotoxicity[11 12], and reversing NASH[13]. Despite this, clinical evidence regarding the safety and effectiveness of these medications

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in cirrhosis is scarce. Moreover, GLP-1RAs are associated with modest but significant increases in heart rate, which could increase the risk of variceal bleeding[14].

To date, randomized controlled trials (RCTs) of GLP-1RAs have excluded cirrhotic populations. Furthermore, as these trials did not perform head-to-head comparisons across antidiabetic drug classes, they cannot provide information regarding the comparative effectiveness of these medications. Thus, we directly compared GLP-1RAs to three comparable antidiabetic drug classes, with regard to risk of hepatic decompensation events, in a population-based cohort with established cirrhosis and type 2 diabetes.

Methods

Data Source

Data were collected from a large, nationwide U.S. commercial claims dataset (IBM MarketScan). MarketScan includes data for individuals who are commercially insured or who have primary traditional (part A & B but not D) Medicare insurance plus a supplemental health plan with a pharmacy benefit. For each insured individual, MarketScan includes demographic information, enrollment status and longitudinal patient-level information on all reimbursed medical services, including inpatient and outpatient diagnoses and procedures, and records of all dispensed prescription medications, including medication start date, number of refills, strength, quantity, and days' supply. This study was approved by the Brigham and Women's Hospital Institutional Review Board (IRB#2011P002580).

Study Population

Figure 1 outlines the study schema. We identified patients aged 18 or older with established cirrhosis and type 2 diabetes, who initiated GLP-1RA therapy (albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide or semaglutide), or one of 3 comparator classes: (1) dipeptidyl peptidase-4 inhibitors (DPP-4i: alogliptin, linagliptin, saxagliptin, or sitagliptin), between 19 October, 2006 (consistent with the marketing of sitagliptin, the first approved DPP-4i) and 17 June, 2020; or (2) sodium-glucose cotransporter 2 inhibitor (SGLT2i: canagliflozin, dapagliflozin, empagliflozin or ertugliflozin), between 29 March, 2013 (consistent with the marketing of canagliflozin, the first approved SGLT2i) and 17 June, 2020; or (3) second or third generation sulfonylureas (glimepiride, glipizide or glyburide), between 28 April 2005 (consistent with the marketing of exenatide, the first approved GLP-1RA) and 17 June 2020. The cohort entry date was the first filled prescription for GLP-1RA or comparator, after at least 180 days of continuous enrollment and no recorded use of either GLP-1RA or comparator during that period.

Patients were required to have a diagnosis of both type 2 diabetes (i.e. at least one inpatient or outpatient ICD-9 code of 250.x0 or 250.x2, or ICD-10 code E11.x) and cirrhosis (i.e. at least one inpatient or at least two outpatient ICD-9 codes [571.2, 571.5, 571.6] or ICD-10 code [K70.3, K74, K74.3, K74.4, K74.5, K74.6, K74.60, K74.69]), before the cohort entry date (Table S1). In previous validation studies, analogous ICD-9 and ICD-10 definitions of cirrhosis yielded positive predictive values (PPV) >85-90%[15–18]. We excluded anyone with

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diagnoses of type 1 diabetes, gestational diabetes, end stage renal disease or HIV. Patients meeting inclusion criteria contributed only once to each cohort, but they could contribute simultaneously to multiple cohorts. Figure S1 outlines the study schema for the 3 pairwise comparisons.

Outcomes and Patient Characteristics

The primary outcome was a hepatic decompensation event, a composite endpoint defined by hospitalization for ascites, SBP, HRS, bleeding esophageal varices or HE, using claims-based algorithms with demonstrated PPVs >85-95%[15–18] (Table S1). Secondary outcomes included individual decompensation events. Because rates of SBP and HRS were relatively low, these outcomes were categorized with ascites.

Follow-up began the day after cohort entry (i.e. drug initiation) and continued in an "as-treated" approach until the first occurrence of: discontinuation or switch to a comparator medication, study outcome, death, end of continuous health plan enrollment, or end of the study period. In cases of treatment interruption or discontinuation, we extended the exposure effect window until 45 days after the end of the last prescription's supply. Pre-exposure patient characteristics ascertained during the 180-day period before cohort entry are outlined in Tables S2A–B. We defined all comorbidities using ICD-9, ICD-10 and CPT codes.

Statistical analysis

Within the three cohorts, we compared baseline characteristics between initiators of GLP-1RA and each comparator. To address imbalances, we calculated propensity scores (PS) using three multivariable logistic regression models (i.e. one for each pairwise cohort), that predicted the probability of initiating medication (i.e. GLP-1RA or comparator), conditional on >90 baseline characteristics (outlined in Table S2A–B). Within each pairwise cohort, exposure groups were 1:1 PS-matched using the nearest neighbor approach with a maximum caliper width equal to 0.05 of the standard deviation of the logit of the PS[19]. Covariate balance between groups before and after PS matching was assessed using standardized mean differences, with significant imbalances defined as differences >0.1.[20]

For each comparison and for all outcomes, we calculated PS-matched incidence rates and corresponding hazard ratios (HRs) with 95% confidence intervals (CIs). Within each PS-matched cohort, we also estimated the cumulative incidence of study outcomes, accounting for the competing risk of all-cause mortality, using the Fine-Gray approach[21]. To assess the proportional hazards assumption, we tested the significance of the interaction term between exposure and time and confirmed it was not violated. In subgroups, we evaluated patients separately by sex, underlying nonalcoholic fatty liver disease (NAFLD), HBV- or HCV-related cirrhosis, alcohol-related liver disease (ALD), concurrent use of metformin, statins or non-selective beta-blockers (NSBB), insurance status and previous hepatic decompensation events (i.e. prior ascites, SBP, HRS, or bleeding esophageal varices or HE), during the initial 180-day period. For each subgroup, the PS was re-calculated and the PS-matching procedure was repeated[22].

We conducted several sensitivity analyses. First, we applied an alternative, strict definition of cirrhosis, that required at least two inpatient or outpatient diagnoses[16 17 23–25]. Second, to

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address informative censoring, we carried forward the exposure to an initiated drug for 365 days without censoring for drug discontinuation or switching, to mimic an intention-to-treat approach[26]. Third, because hepatic decompensation event rates were similar and low in SGLT2i initiators, we directly compared SGLT2i to DPP-4i initiators, after repeating the PS-matching procedure. Fourth, we examined the association between GLP-1RA initiation and a negative control outcome with an expected null finding (i.e. incident fractures). Next, to assess the generalizability of our findings and minimize potential residual confounding due to variable insurance status and missing race/ethnicity data in MarketScan, we repeated our primary analysis in an independent commercial database (Optum Clinformatics Datamart). Optum uses proprietary algorithms to define race, a derived ethnicity constructed from the member's name and geography. Once ethnicity is determined, the member is mapped to one of four categories (Asian, Black, Hispanic, White). For each of the aforementioned sensitivity analyses, we recalculated the PS and repeated the PS-matching procedure. Finally, we used an established, rule-out approach to test the sensitivity of our results to unmeasured confounding[27].

All analyses were performed using Aetion Evidence Platform[28], version 4.11, and SAS 9.4 Statistical Software (SAS Institute Inc, Cary, NC).

Results

We identified three unmatched, paired cohorts comprised of new initiators of: (1) either GLP-1RA (n=2,084) or DPP-4i (n=4,537); (2) either GLP-1RA (n=2,016) or a second-generation sulfonylurea (n=8,369); and (3) either GLP-1RA (n=2,191) or SGLT-2i (n=1,225) (Figure 1). From those unmatched cohorts, we then constructed three pairwise, 1:1 PS-matched cohorts, composed of new initiators of either: (1) GLP-1RA or DPP-4i (n=1,431 PS-matched pairs); (2) GLP-1RA vs. sulfonylureas (n=1,246 PS-matched pairs); and (3) GLP-1RA vs. SGLT-2i (n=845 PS-matched pairs).

Table S2A outlines the complete baseline characteristics of each treatment group, in the three unmatched cohorts. Compared to initiators of comparator medications, GLP-1RA initiators were younger, with fewer complications of cirrhosis or individual comorbidities, but they were more likely to use insulin and to have obesity. After PS-matching, all characteristics were well-balanced (Tables 1, S2B).

Hepatic Decompensation Events

Figure 2 depicts the cumulative incidence of the primary outcome (i.e. hospitalization for hepatic decompensation events), comparing PS-matched initiators of GLP-1RA to each of the three comparator groups, after accounting for the competing risk of death. Table 2 outlines absolute incidence rates and relative hazards of the primary outcome and the individual decompensation outcomes, after PS-matching. Median overall follow-up was 132 days (interquartile range=73, 290 days). Overall, we documented 96 decompensation events among GLP-1RA initiators, and 155 events among DPP-4i initiators (**cohort 1**; incidence rates, 105.2 vs. 144.0/1000 person-years [PY]), corresponding to HR=0.68 (95%CI=0.53-0.88)(Table 2). GLP-1RA initiators also had significantly lower rates of developing ascites, SBP or HRS (HR=0.66, 95%CI=0.45-0.97), or bleeding esophageal

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varices (HR=0.62, 95%CI=0.41-0.92), and a non-significant trend towards lower rates of HE (HR=0.76, 95%CI=0.55-1.06), compared to DPP-4i initiators.

Rates of decompensation events were also significantly lower among GLP-1RA initiators, compared to sulfonylurea initiators (**cohort 2**; 78 vs. 124 events; 97.3 vs. 144.0/1000PY, respectively), translating to HR=0.64 (95%CI=0.48-0.84). Similarly, initiators of GLP-1RAs had significantly lower rates of ascites, SBP or HRS (HR=0.66, 95%CI=0.46-0.94), bleeding esophageal varices (HR=0.59, 95%CI=0.37-0.92) and HE (HR=0.60, 95%CI=0.39-0.92), compared to sulfonylureas (Table 2). In contrast, when GLP-1RA and SGLT-2i initiators were directly compared, no significant differences were observed in rates of hepatic decompensation (**cohort 3**; 56 vs. 64 events; 103.5 vs. 112.8/1000PY, respectively; HR=0.89, 95%CI=0.62-1.28), or in individual decompensation endpoints (Table 2).

We repeated our primary analysis separately in PS-matched subgroups with compensated or decompensated cirrhosis, and our findings were consistent (Table 3). Similarly, among PS-matched patients with NAFLD cirrhosis, GLP-1RA initiators again demonstrated significantly lower rates of decompensation events, compared with DPP-4i (HR=0.63, 95%CI=0.47-0.85) or sulfonylureas (HR=0.71, 95%CI=0.51-0.98), but rates were similar when compared with SGLT-2i (HR=0.88, 95%CI=0.55-1.41)(Table S3). In further subgroup analyses, the observed benefits of GLP1RAs compared to DPP-4i or sulfonylureas did not differ substantially by gender, HBV/HCV status, underlying ALD, insurance status or concurrent use of metformin, statins or NSBB(Table S4). However, due to the small size of cohort 3 (GLP-1RA vs. SGLT-2i), the PS-matching procedure for these subgroup analyses could only be performed for comparisons of GLP-1RA with DPP-4i and sulfonylureas.

Sensitivity Analyses

Our findings were robust across all sensitivity analyses (Tables S5–S8). We also evaluated incident fractures as a negative control outcome and observed the expected null associations (Table S9). Additionally, we repeated our primary analysis within an independent study population (Optum), after PS-matching for the same covariates plus race/ethnicity (Table S10), and our results again remained similar (Table S11). Finally, we found that an unmeasured confounder would need to have an implausibly strong association with both exposure (i.e. OR=3.95 or stronger) and outcome (i.e. OR=0.1 or less) simultaneously, to move the point estimate to 1.0 (Tables S12A–B).

Discussion:

In a large, population-based cohort of U.S. adults with cirrhosis and type 2 diabetes, initiators of GLP-1RA therapy had lower rates of hepatic decompensation events, compared to initiators of two comparable and commonly-prescribed second-line antidiabetic drugs, DPP-4i and sulfonylureas. GLP-1RA initiators also demonstrated consistently lower rates of individual decompensation events, including ascites, SBP or HRS, bleeding esophageal varices and HE. The observed benefits of GLP-1RAs persisted after accounting for known and putative risk factors for adverse hepatic events, and they were robust in both men and women, in patients with compensated and decompensated cirrhosis, and in an independent study population. Importantly for this sick population, the benefits of GLP-1RA

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therapy were evident early, within 4 months of treatment initiation. In contrast, rates of major hepatic decompensation events were similarly low when GLP-1RA and SGLT-2i initiators were directly compared, suggesting that SGLT-2i may also confer important hepatoprotective effects, in patients with cirrhosis.

Emerging evidence supports a role for GLP-1RAs in cirrhosis and type 2 diabetes. Chronic hyperglycemia contributes to accelerated hepatic decompensation[6–8], and on preclinical studies, GLP-1RA treatment improves hepatic lipid oxidation[29], promotes hepatic stellate cell quiescence, diminishes cellular proliferation and improves microvascular function[30]. GLP-1RAs may also modulate cholangiocyte activation by inhibiting mitochondrial apoptosis[31], and by influencing *de novo* biosynthesis of primary bile acids[32]. Furthermore, in patients with non-cirrhotic NAFLD, RCTs demonstrate that GLP-1RAs can reduce liver fat, inflammation and lipotoxicity[11 12], and reverse NASH[13]. Collectively, these findings have led to the hypothesis that GLP-1RAs may offer unique benefits for patients with cirrhosis and diabetes. However, evidence to support this is scarce, as cirrhotic patients were previously excluded from all major RCTs of GLP-1RAs, and robust observational data is lacking. Thus, by performing direct, head-to-head comparisons across comparable antidiabetic drug classes in a large, nationwide cohort, the current study provides compelling real-world evidence that supports a role for GLP-1RAs in the setting of cirrhosis and diabetes.

Notably, both GLP-1RA and SGLT-2i initiators had similar and low decompensation event rates, suggesting that SGLT-2i medications may also provide hepatoprotective benefits. This is biologically plausible, for SGLT-2i inhibit renal sodium reabsorption, reducing salt and water retention and attenuating the renin-angiotensin-aldosterone-system[33], which may improve fluid balance and correct the maladaptive neurohormonal signaling and pro-inflammatory responses that promote hepatic decompensation. However, SGLT-2i also represent the newest class of approved antidiabetic drugs, and their safety and efficacy in cirrhosis is unknown. Accordingly, we had relatively small numbers of SGLT-2i initiators, thus some of our secondary analyses were underpowered and should be interpreted cautiously. To that end, future large-scale studies are needed that directly compare SGLT-2i with comparable antidiabetic drug classes, and which also compare individual medications.

To our knowledge, this is the first study to evaluate the potential benefits of GLP-1RA use for preventing decompensation events in cirrhotic patients with type 2 diabetes, as directly compared with relevant treatment alternatives. It is strengthened by the inclusion of a large, nationwide population with validated definitions of cirrhosis and study outcomes, and comprehensive prescription medication use data. Careful PS-matching minimized both indication bias and residual confounding. Applying a new-user, active comparator design addressed selection and detection biases, while also aligning subjects at a uniform time (i.e. treatment initiation date), and minimizing potential healthy user bias. Moreover, we conducted numerous sensitivity and subgroup analyses to address potential misclassification and residual confounding, and our findings were consistent in an independent population.

We acknowledge several limitations. First, this was a retrospective study, and prospective studies including RCTs are needed. However, such studies are inherently costly, time-

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consuming and often exclude vulnerable populations, like patients with advanced cirrhosis. For this reason, comparative effectiveness research using administrative databases represents an innovative approach to efficiently generate robust data to help guide patient care, with findings that have been shown to recapitulate results from RCTs[34]. Second, although cirrhosis and outcomes were defined using validated algorithms with PPVs >85-90%[16 17 23–25], misclassification is still possible. Yet, our findings were robust in an independent cohort, across numerous sensitivity analyses, and after applying alternate definitions of cirrhosis. Third, despite careful PS-matching, confounding may nevertheless persist. This is particularly relevant for the comparison of GLP-1RAs with sulfonylureas, as sulfonylureas are older, less expensive and may be prescribed more frequently to patients with more advanced liver disease. We also lacked data regarding specific indications for other prescriptions, like NSBB. However, our findings were consistent after PS-matching for >90 covariates, including established markers of decompensation and other medication use. Further, our findings were consistent when GLP-1RAs were compared to DPP-4is, a medication class that is similarly new, costly and under-studied in cirrhosis. We also lacked more detailed data regarding indices of cirrhosis severity, laboratory data, the timing of initial cirrhosis diagnoses relative to initial diabetes diagnoses, regular alcohol use, body mass index, use of antiviral therapy during follow-up and duration of diabetes; however, our findings were robust across sensitivity analyses, and we demonstrated that it would be highly unlikely for an unmeasured confounder to fully explain our results. Fourth, because the marketing of GLP-1RAs, DPP-4i and SGLT-2i is relatively new — and cirrhotic patients were excluded from the original RCTs — some of our subgroups were small, and we lacked sufficient numbers to estimate risks in patients with and without previous ascites or esophageal varices, or to directly compare GLP-1RA to thiazolidinediones. Thus, large-scale, prospective studies are needed both to validate our findings and to directly compare the safety and effectiveness of individual antidiabetic medications, according to the adequacy of glycemic control, and also in relation to mortality and HCC. Finally, our results may not be generalizable to patients with different insurance types or those lacking insurance coverage, given differences in demographics, risk factors, socioeconomic status and drug adherence.

In conclusion, within a nationwide population of adults with cirrhosis and type 2 diabetes, initiators of GLP-1RA therapy had meaningfully reduced rates of decompensation events compared to two commonly prescribed, second-line antidiabetic alternatives, DPP-4i and sulfonylureas, consistent with preclinical data[29 30] and clinical studies of non-cirrhotic NAFLD[11–13]. Thus, our findings suggest substantial potential benefits of GLP-1RA therapy in patients with cirrhosis who are engaged in routine clinical care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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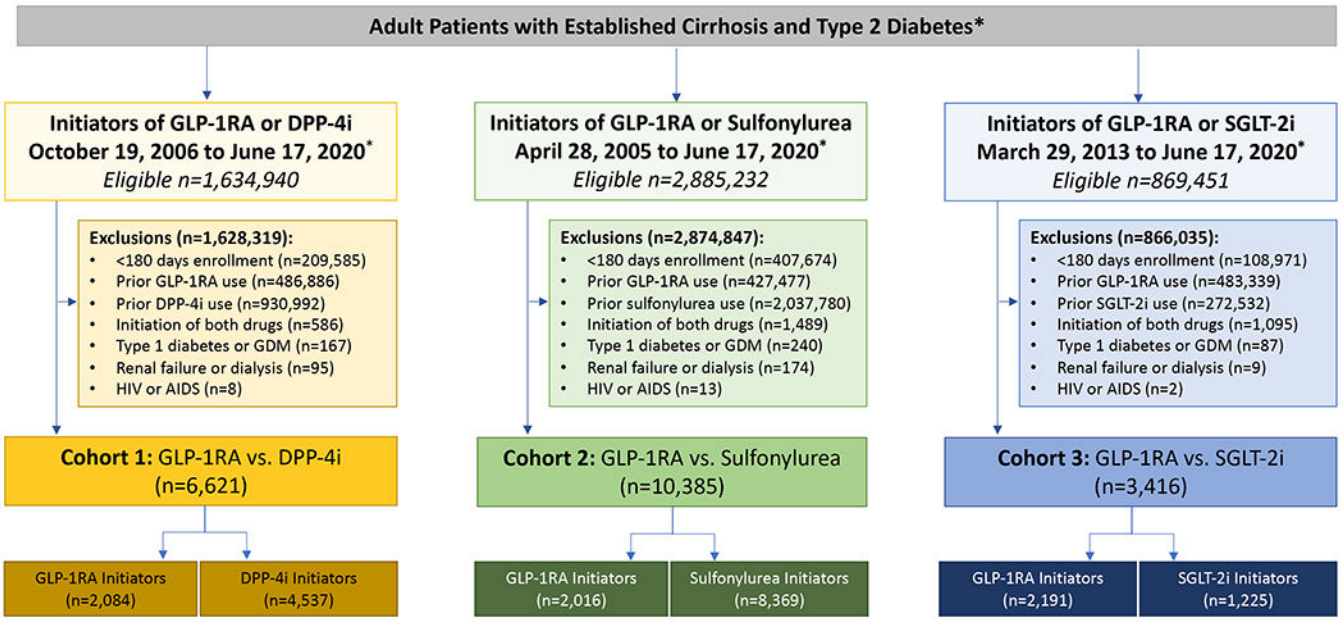

Figure 1.

Cohort Construction

Abbreviations: GLP-1 RA, glucagon-like peptide receptor agonist; DPP-4, Dipeptidyl Peptidase-4; SGLT-2, sodium-glucose cotransporter-2; GDM, gestational diabetes

*included patients were adults over age 18 years with diagnoses of both type 2 diabetes and cirrhosis, as outlined in the Methods. Cohort 1 included new initiators of either GLP-1RA or DPP-4i starting on October 19, 2006 (consistent with the marketing of sitagliptin, the first approved DPP-4i); Cohort 2 included new initiators of either GLP-1RA or sulfonylureas, starting on April 28, 2005 (consistent with the marketing of exenatide, the first approved GLP-1RA); Cohort 3 included new initiators of either GLP-1RA or SGLT-2i, starting on March 29, 2013 (consistent with the marketing of canagliflozin, the first approved SGLT-2i). For details, see Methods.

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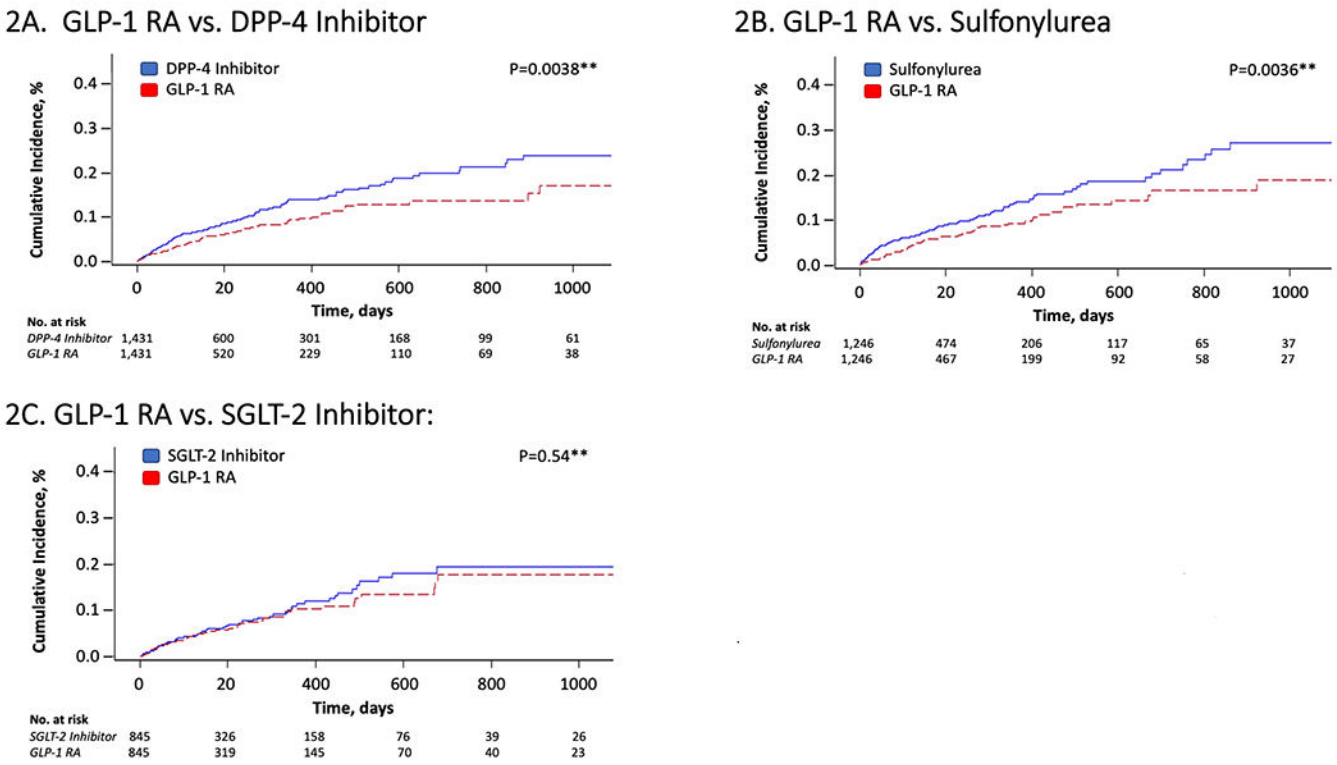

Figure 2.

Cumulative Incidence of Hepatic Decompensation* among Propensity Score-Matched Patients with Cirrhosis Initiating GLP-1 RA Therapy or Alternative Antidiabetic Medications

Abbreviations: GLP-1 RA, glucagon-like peptide receptor agonist; DPP-4, Dipeptidyl Peptidase-4; SGLT-2, sodium-glucose cotransporter-2; No., number

*Hepatic decompensation was defined as the first hospitalization for ascites, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome, bleeding esophageal varices or hepatic encephalopathy after the cohort entry date (i.e. date of drug initiation). For details, see Methods.

**P-values were obtained using Gray's test for equality of the cumulative incidence functions between each exposure group after propensity score-matching, accounting for the competing risk of all-cause mortality.

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Table 1.

Selected Baseline Characteristics in Propensity Score Matched Cohorts of Patients with Cirrhosis and Diabetes Initiating GLP-1 Receptor Agonists or a Comparator Medication

	Cohort 1 GLP-1RA vs. DPP-4i		Cohort 2 GLP-1RA vs. Sulfonylurea		Cohort 3 GLP-1RA vs. SGLT2i	
Baseline Characteristic	**GLP-1RA** ***N=1,431***	**DPP-4i** ***N=1,431***	**GLP-1RA** ***N=1,246***	**Sulfonylurea** ***N=1,246***	**GLP-1RA** ***N=845***	**SGLT2i** ***N=845***
Male, %	778 (54.2)	785 (54.7)	704 (56.5)	693 (55.6)	502 (52.0)	498 (51.6)
Age, years - mean (SD)	57.6 (9.1)	57.6 (9.5)	57.5 (9.1)	57.6 (9.6)	58.0 (8.7)	58.1 (8.4)
Etiology of Cirrhosis						
Viral Hepatitis	111 (7.7)	107 (7.5)	90 (7.2)	92 (7.4)	78 (9.2)	78 (9.2)
Alcoholic Liver Disease	128 (8.9)	125 (8.7)	114 (9.2)	127 (10.2)	85 (10.1)	94 (11.1)
Nonalcoholic fatty liver disease	922 (64.3)	927 (64.6)	788 (63.2)	773 (62.0)	511 (60.5)	501 (59.3)
Other / Unspecified	274 (19.1)	276 (19.2)	255 (20.4)	255 (20.4)	171 (20.2)	172 (20.4)
Cirrhosis Severity						
Hospitalization for hepatic decompensation[1]	117 (8.2)	115 (8.0)	89 (7.1)	97 (7.8)	66 (7.8)	63 (7.5)
Ascites / SBP	68 (4.7)	66 (4.6)	56 (4.5)	64 (5.1)	42 (5.0)	42 (5.0)
Hepatic encephalopathy	58 (4.0)	60 (4.2)	55 (4.4)	54 (4.3)	37 (4.4)	33 (3.9)
Esophageal varices (any)	53 (3.7)	46 (3.2)	36 (2.9)	36 (2.9)	30 (3.6)	27 (3.2)
Bleeding esophageal varices	17 (1.2)	14 (1.0)	10 (0.8)	5 (0.4)	7 (0.8)	6 (0.7)
Hepatocellular carcinoma	36 (2.5)	37 (2.6)	28 (2.2)	29 (2.3)	24 (2.8)	23 (2.7)
Diabetes Severity						
Nephropathy	42 (2.9)	45 (3.1)	37 (3.0)	35 (2.8)	22 (2.6)	22 (2.6)
Neuropathy	126 (8.8)	128 (8.9)	106 (8.5)	108 (8.7)	67 (7.9)	70 (8.3)
Retinopathy	26 (1.8)	26 (1.8)	21 (1.7)	17 (1.4)	5 (0.6)	7 (0.8)
Diabetic foot	25 (1.7)	27 (1.9)	17 (1.4)	20 (1.6)	11 (1.3)	12 (1.4)
Dorsopathies	240 (16.7)	237 (16.5)	195 (15.6)	186 (14.9)	102 (12.1)	104 (12.3)
Hypoglycemia	41 (2.9)	34 (2.4)	25 (2.0)	21 (1.7)	17 (2.0)	16 (1.9)
Skin & soft tissue infections	97 (6.8)	91 (6.3)	74 (5.9)	73 (5.9)	35 (4.1)	40 (4.7)
Diabetes without complications	978 (68.2)	971 (67.7)	810 (65.0)	797 (63.9)	408 (48.3)	407 (48.2)
Diabetes Medication Use						
Metformin	724 (50.5)	724 (50.5)	581 (46.6)	605 (48.5)	449 (53.1)	453 (53.6)
Glitazone	150 (10.5)	136 (9.5)	114 (9.1)	126 (10.1)	45 (5.3)	48 (5.7)
Insulin	294 (20.5)	300 (20.9)	125 (10.0)	139 (11.1)	83 (9.8)	77 (9.1)
SGLT2i	87 (6.1)	86 (6.0)	81 (6.5)	85 (6.8)	--	--
DPP-4i	--	--	76 (6.1)	70 (5.6)	201 (23.8)	196 (23.2)
Sulfonylurea	463 (32.3)	459 (32.0)	--	--	270 (32.0)	254 (30.1)
Meglinitides	9 (0.6)	8 (0.6)	11 (0.9)	11 (0.9)	4 (0.5)	3 (0.4)

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	Cohort 1 GLP-1RA vs. DPP-4i		Cohort 2 GLP-1RA vs. Sulfonylurea		Cohort 3 GLP-1RA vs. SGLT2i	
Baseline Characteristic	**GLP-1RA** ***N=1,431***	**DPP-4i** ***N=1,431***	**GLP-1RA** ***N=1,246***	**Sulfonylurea** ***N=1,246***	**GLP-1RA** ***N=845***	**SGLT2i** ***N=845***
Comorbidities						
Alcohol abuse / dependence	83 (5.8)	82 (5.7)	65 (5.2)	59 (4.7)	34 (4.0)	32 (3.8)
Cancer (any)	105 (7.3)	104 (7.2)	76 (6.1)	78 (6.3)	47 (5.6)	48 (5.7)
Drug abuse / dependence	10 (0.7)	9 (0.6)	10 (0.8)	10 (0.8)	5 (0.6)	2 (0.2)
Obesity	219 (15.3)	228 (15.9)	200 (16.0)	203 (16.3)	120 (14.2)	117 (13.8)
Smoking (ever)	98 (6.8)	98 (6.8)	75 (6.0)	83 (6.7)	73 (8.6)	80 (9.5)
Hypertension	617 (43.0)	630 (43.9)	503 (40.3)	495 (39.7)	292 (34.6)	275 (32.5)
Dyslipidemia	215 (15.0)	215 (15.0)	187 (15.0)	180 (14.4)	78 (9.2)	76 (9.0)
Ischemic heart disease	144 (10.0)	149 (10.4)	104 (8.3)	107 (8.6)	67 (7.9)	60 (7.1)
Congestive heart failure	78 (5.4)	77 (5.4)	62 (5.0)	60 (4.8)	29 (3.4)	25 (3.0)
Cerebrovascular disease	33 (2.3)	20 (1.4)	26 (2.1)	24 (1.9)	13 (1.5)	11 (1.3)
Chronic obstructive pulmonary disease	61 (4.3)	66 (4.6)	43 (3.4)	33 (2.6)	26 (3.1)	23 (2.7)
Non-diabetes chronic kidney disease	62 (4.3)	65 (4.5)	57 (4.6)	50 (4.0)	28 (3.3)	23 (2.7)
Depression	125 (8.7)	133 (9.3)	112 (9.0)	106 (8.5)	59 (7.0)	55 (6.5)
Dementia	14 (1.0)	16 (1.1)	13 (1.0)	14 (1.1)	4 (0.5)	4 (0.5)
Osteoporosis	52 (3.6)	55 (3.8)	51 (4.1)	52 (4.2)	21 (2.5)	24 (2.8)
Falls	24 (1.7)	14 (1.7)	22 (1.8)	20 (1.6)	26 (3.1)	21 (2.5)
Fractures	29 (2.0)	29 (2.0)	23 (1.8)	18 (1.4)	14 (1.7)	15 (1.8)
Medication Use						
Number of prescription drugs, mean (SD)	11.2 (5.7)	11.2 (5.9)	11.2 (5.9)	11.2 (6.2)	12.0 (5.9)	11.8 (5.6)
ACE inhibitors	475 (33.1)	466 (32.5)	380 (30.5)	405 (32.5)	285 (33.7)	279 (33.0)
Angiotensin II receptor blockers	321 (22.4)	345 (24.0)	275 (22.1)	265 (21.3)	200 (23.7)	195 (23.1)
Anticoagulants	70 (4.9)	80 (5.6)	58 (4.7)	64 (5.1)	36 (4.3)	34 (4.0)
Antiplatelets	82 (5.7)	75 (5.2)	75 (6.0)	73 (5.9)	52 (6.2)	54 (6.4)
Non-selective beta blockers	389 (27.1)	409 (28.5)	334 (26.8)	343 (27.5)	255 (30.2)	244 (28.9)
Bisphosphonates	27 (1.9)	27 (1.9)	27 (2.2)	31 (2.5)	12 (1.4)	11 (1.3)
Loop diuretics	356 (24.8)	356 (24.8)	307 (24.6)	289 (23.2)	217 (25.7)	208 (24.6)
Other diuretics	261 (18.2)	248 (17.3)	229 (18.4)	228 (18.3)	153 (18.1)	144 (17.0)
Statins	539 (37.6)	523 (36.4)	464 (37.2)	477 (38.3)	357 (42.2)	362 (42.8)
Non-statin lipid-lowering drugs	176 (12.3)	177 (12.3)	166 (13.3)	165 (13.2)	114 (13.5)	104 (12.3)
Antibiotics (any)	755 (52.6)	742 (51.7)	628 (50.4)	626 (50.2)	447 (52.9)	432 (51.1)
Antibiotics-fluoroquinolones	276 (19.2)	270 (18.8)	226 (18.1)	229 (18.4)	154 (18.2)	160 (18.9)
Anticonvulsants	261 (18.2)	248 (17.3)	229 (18.4)	228 (18.3)	166 (19.6)	163 (19.3)
Antidepressants	514 (35.8)	514 (35.8)	468 (37.5)	460 (36.9)	311 (36.8)	314 (37.2)
Benzodiazepines	245 (17.1)	241 (16.8)	221 (17.7)	209 (16.8)	154 (18.2)	148 (17.4)
Opioids	608 (42.4)	582 (40.6)	519 (41.6)	492 (39.5)	343 (40.6)	329 (38.9)
Rifaximin and/or Lactulose	164 (11.4)	173 (12.1)	153 (12.3)	151 (12.1)	112 (13.3)	103 (12.2)

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	Cohort 1 GLP-1RA vs. DPP-4i		Cohort 2 GLP-1RA vs. Sulfonylurea		Cohort 3 GLP-1RA vs. SGLT2i	
Baseline Characteristic	**GLP-1RA** ***N=1,431***	**DPP-4i** ***N=1,431***	**GLP-1RA** ***N=1,246***	**Sulfonylurea** ***N=1,246***	**GLP-1RA** ***N=845***	**SGLT2i** ***N=845***
Healthcare Utilization in Prior 180 Days						
Any hospitalization	300 (20.9)	289 (20.1)	225 (18.0)	231 (18.5)	155 (18.30	143 (16.9)
Any ED visit	460 (32.1)	474 (33.0)	366 (29.4)	384 (30.8)	267 (31.6)	249 (29.5)
Any abdominal ultrasound	650 (45.3)	639 (44.5)	560 (44.9)	569 (45.6)	385 (45.6)	393 (46.5)
Any paracentesis	33 (2.3)	32 (2.2)	28 (2.2)	36 (2.9)	20 (2.4)	18 (2.1)
Any upper endoscopy	429 (29.9)	431 (30.0)	365 (29.3)	355 (28.5)	259 (30.7)	263 (31.1)
Any variceal banding	74 (5.2)	69 (4.8)	58 (4.7)	65 (5.2)	45 (5.3)	47 (5.6)
Any visit to gastroenterologist	775 (54.0)	749 (52.2)	691 (55.4)	701 (56.2)	479 (56.7)	486 (57.5)
Preventative Care in Prior 180 Days						
Receipt of pneumonia vaccine	148 (10.3)	160 (11.1)	139 (11.1)	147 (11.8)	121 (4.3)	125 (14.8)
Receipt of flu vaccine	238 (16.6)	256 (17.8)	225 (18.0)	235 (18.8)	147 (17.4)	152 (18.0)
Colonoscopy	198 (13.8)	193 (13.4)	165 (13.2)	160 (12.8)	120 (14.2)	132 (15.6)
Mammogram	170 (11.8)	169 (11.8)	170 (13.6)	168 (13.5)	99 (11.7)	103 (12.2)
PSA or DRE	149 (10.4)	161 (11.2)	139 (11.1)	157 (12.6)	95 (11.2)	99 (11.7)
HbA1c testing	1,069 (74.5)	1,075 (74.9)	925 (74.2)	918 (73.6)	650 (76.9)	654 (77.4)
Liver function testing	541 (37.7)	553 (38.5)	466 (37.4)	492 (39.5)	282 (33.4)	281 (33.3)

Abbreviations: GLP-1RA, glucose-like peptide 1 receptor agonist; DPP-4 inhibitor, dipeptidyl peptidase-4 inhibitor; SGLT-2 inhibitor, sodium-glucose cotransporter-2 inhibitor; SD, standard deviation; SBP, spontaneous bacterial peritonitis; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ED, emergency department; PSA, prostate-specific antigen; DRE, digital rectal examination; HbA1c, hemoglobin A1c).

[1] Hepatic decompensation events included any hospitalization for which primary cause included ascites, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome, hepatic encephalopathy or bleeding esophageal varices. For details see Methods.

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Table 2.

Risk of Hepatic Decompensation among Propensity Score-Matched Patients with Cirrhosis and Type 2 Diabetes Initiating GLP-1 Receptor Agonists or Comparator Antidiabetic Medications

	Cohort 1 (n=1,431 pairs)		Cohort 2 (n=1,246 pairs)		Cohort 3 (n=845 pairs)	
	GLP-1RA ***N=1,431***	**DPP-4i** ***N=1,431***	**GLP-1RA** ***N=1,246***	**Sulfonylurea** ***N=1,246***	**GLP-1RA** ***N=845***	**SGLT-2 Inhibitor** ***N=845***
Median [IQR] follow-up, days	133 [73, 277]	136 [73, 342]	127 [71, 246]	133 [73, 286]	133 [73, 288]	152 [73, 360]
Hepatic Decompensation events[1]						
• No. of events	96	155	78	124	56	64
• Incidence rate, per 1,000 PY	105.2	144.0	97.3	147.7	103.5	112.8
• Hazard ratio (95% CI)	0.68 (0.53-0.88)	1 (ref.)	0.64 (0.48-0.84)	1 (ref.)	0.89 (0.62-1.28)	1 (ref.)
Ascites, SBP or Hepatorenal Syndrome						
• No. of events	56	87	48	76	38	37
• Incidence rate, per 1,000 PY	62.2	82.0	58.8	87.3	69.5	63.0
• Hazard ratio (95% CI)	0.66 (0.45-0.97)	1 (ref.)	0.66 (0.46-0.94)	1 (ref.)	1.07 (0.68-1.68)	1 (ref.)
Bleed from esophageal varices						
• No. of events	38	69	29	51	28	37
• Incidence rate, per 1,000 PY	40.5	61.0	35.4	58.6	50.7	63.5
• Hazard ratio (95% CI)	0.62 (0.41-0.92)	1 (ref.)	0.59 (0.37-0.92)	1 (ref.)	0.78 (0.48-1.27)	1 (ref.)
Hepatic encephalopathy						
• No. of events	59	87	46	77	35	34
• Incidence rate, per 1,000 PY	64.0	77.6	58.4	88.4	64.0	58.8
• Hazard ratio (95% CI)	0.76 (0.55-1.06)	1 (ref.)	0.60 (0.39-0.92)	1 (ref.)	1.07 (0.67-1.71)	1 (ref.)

Abbreviations: GLP-1RA, glucose-like peptide 1 receptor agonist; DPP-4 inhibitor, dipeptidyl peptidase-4 inhibitor; SGLT-2 inhibitor, sodium-glucose cotransporter-2 inhibitor; IQR, interquartile range; PY, person-years; CI, confidence interval; SBP, spontaneous bacterial peritonitis

[1]Hepatic decompensation was defined as the first recorded hospitalization for which the primary cause included ascites, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome, bleeding esophageal varices or hepatic encephalopathy. For details see Methods.

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Table 3.

Risk of Hepatic Decompensation Events[1] among Propensity Score-Matched Patients with Compensated or Decompensated Cirrhosis[*] and Type 2 Diabetes Initiating GLP-1 Receptor Agonists or Comparator Antidiabetic Medications

	Cohort 1		Cohort 2		Cohort 3	
	GLP-1RA	**DPP-4 Inhibitor**	**GLP-1RA**	**Sulfonylurea**	**GLP-1RA**	**SGLT-2 Inhibitor**
Compensated Cirrhosis[1], N.	1,294	1,294	1,167	1,167	769	769
• Median [IQR] follow-up, days	133 [73, 286]	160 [73, 382]	132 [71, 251]	135 [73, 314]	135 [73, 290]	157 [73, 363]
• No. of events	69	111	53	86	38	44
• Incidence rate, per 1,000 PY	81.9	116.3	71.1	109.7	76.9	81.7
• Hazard ratio (95% CI)	0.68 (0.51-0.93)	1 (ref.)	0.63 (0.44-0.88)	1 (ref.)	0.93 (0.60-1.43)	1 (ref.)
Decompensated Cirrhosis[1], N.	173	173	161	161	64	64
• Median [IQR] follow-up, days	88 [44, 182]	83 [36, 204]	88 [40, 160]	77 [36, 179]	98 [54, 217]	104 [53, 183]
• No. of events	43	67	40	62	19	19
• Incidence rate, per 1,000 PY	521.8	702.9	572.2	884.0	654.7	556.4
• Hazard ratio (95% CI)	0.68 (0.46-0.98)	1 (ref.)	0.65 (0.44-0.97)	1 (ref.)	1.15 (0.61-2.18)	1 (ref.)

Abbreviations: GLP-1RA, glucose-like peptide 1 receptor agonist; DPP-4 inhibitor, dipeptidyl peptidase-4 inhibitor; SGLT-2 inhibitor, sodium-glucose cotransporter-2 inhibitor; IQR, interquartile range; PY, person-years; CI, confidence interval; SBP, spontaneous bacterial peritonitis

[*] For each subgroup (i.e. compensated cirrhosis and decompensated cirrhosis), the propensity score-matching procedure was repeated to ensure appropriate balance between drug exposure groups. Thus, the total number of patients and the total number of recorded events differs from that shown in Table 2.

[1] Hepatic decompensation was defined as the first recorded hospitalization for which the primary cause included ascites, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome, hepatic encephalopathy or bleeding esophageal varices. For details see Methods.