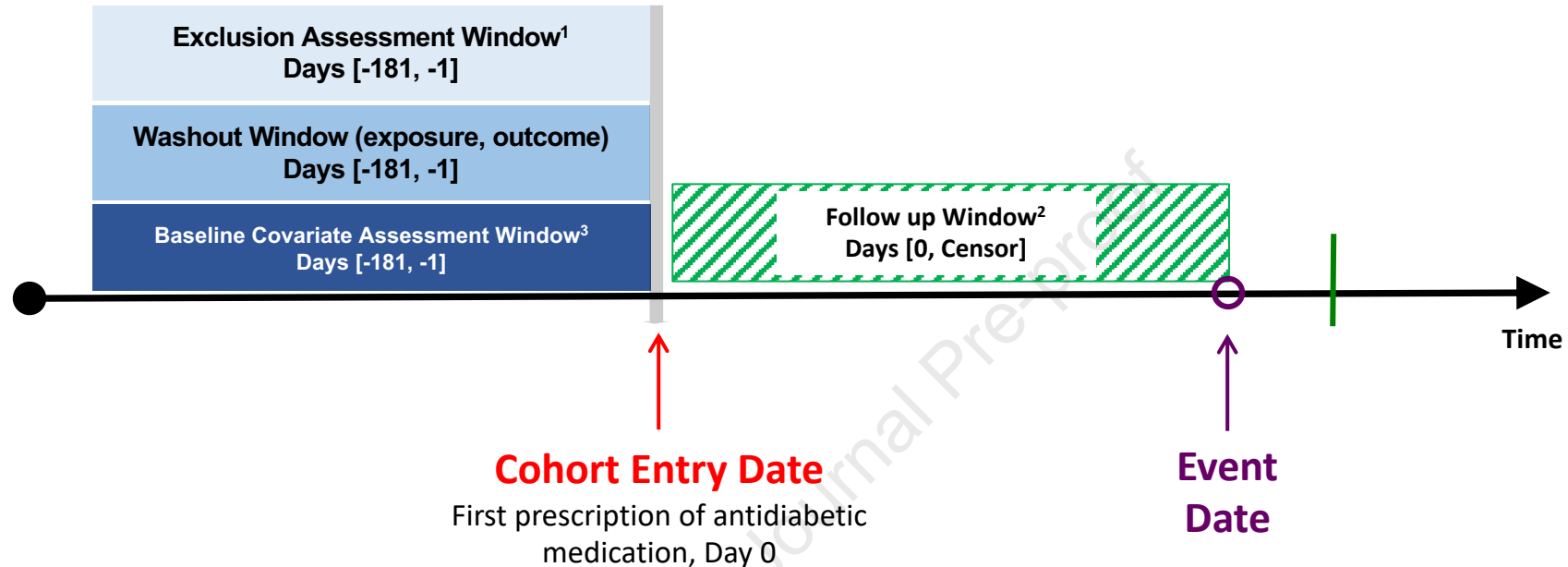


Figure S1. Study Schema*



*The study design was an event-exposure based cohort study. The event was defined by at least 1 diagnosis of a major hepatic decompensation event, defined using validated ICD-9/ICD-10 algorithms, as outlined in Table S1 and the Methods. The exposure was defined by new initiation of a second-line antidiabetic medication (in 3 pairwise comparisons), defined at the cohort entry date. The cohort entry date, in turn, was defined as the date on which the last requirement was fulfilled.

¹Individuals were excluded with type 1 diabetes, gestational diabetes, end-stage renal failure or human immunodeficiency virus (HIV), as per the Methods. Up to a 45-day grace period was allowed for each medication.

²First recorded outcome of interest, switching/stopping study drugs, death, disenrollment or end of study period.

³Baseline covariates were defined during the 180-day covariate assessment window, prior to the cohort entry date.

Supplementary Appendix

Supplementary Tables:

- **Table S1.** Definitions of Cirrhosis and Hepatic Decompensation Events
- **Table S2A.** Complete Baseline Characteristics in the Unmatched Cohorts of Patients with Cirrhosis and Type 2 Diabetes Initiating GLP-1 Receptor Agonists or Comparator Antidiabetic Medications
- **Table S2B.** Complete Baseline Characteristics in the Propensity Score-Matched Cohorts of Patients with Cirrhosis and Diabetes Initiating GLP-1 Receptor Agonists or Comparator Antidiabetic Medications
- **Table S3.** Risk of Hepatic Decompensation Among Propensity Score-Matched Patients with NAFLD Cirrhosis and Type 2 Diabetes Initiating GLP-1 Receptor Agonists or Comparator Antidiabetic Medications
- **Table S4.** Risk of Hepatic Decompensation in Propensity Score-Matched Subgroups of Patients with Cirrhosis and Type 2 Diabetes Initiating GLP-1 Receptor Agonists or Comparator Antidiabetic Medications
- **Table S5.** Risk of Hepatic Decompensation in Propensity Score-Matched Patients with Strictly Defined Cirrhosis and Type 2 Diabetes Initiating GLP-1 Receptor Agonists or Comparator Antidiabetic Medications
- **Table S6.** Risk of Hepatic Decompensation in Propensity Score-Matched Patients with Cirrhosis and Type 2 Diabetes Initiating GLP-1 Receptor Agonists versus Comparator Antidiabetic Medications, after Decreasing the Exposure Window to 15 days
- **Table S7.** Risk of Hepatic Decompensation in Propensity Score-Matched Patients with Cirrhosis and Type 2 Diabetes Initiating GLP-1 Receptor Agonists or Comparator Antidiabetic Medications, Using an Intention-To-Treat Approach
- **Table S8.** Risk of Hepatic Decompensation in Propensity Score-Matched Patients with Cirrhosis and Type 2 Diabetes Initiating a SGLT-2 inhibitor compared to a DPP-4 inhibitor
- **Table S9.** Risk of Fracture in Propensity Score-Matched Patients with Cirrhosis and Type 2 Diabetes Initiating a GLP-1 Receptor Agonist versus Comparator Antidiabetic Medications
- **Table S10.** Baseline Characteristics in Propensity Score-Matched Patients with Cirrhosis and Type 2 Diabetes Initiating GLP-1 Receptor Agonists or a Comparator Antidiabetic Medication, in the Optum Database
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Supplementary Figures:

- **Figure S1.** Study Schema

Supplementary References

Table S1. Definitions of Cirrhosis and Hepatic Decompensation Events

<i>Cirrhosis</i>	<i>Definition</i>
Cirrhosis (any)	At least 1 Inpatient or at least 2 Outpatient diagnosis codes: ICD-9: 571.2, 571.5, 571.6 ICD-10: K70.3, K74, K74.3, K74.4-K74.6
Strict Cirrhosis	At least 2 Inpatient or Outpatient codes for cirrhosis
Compensated Cirrhosis	Cirrhosis (defined above), without any prior decompensation event
Decompensated Cirrhosis	Cirrhosis (defined above) plus at least 1 code for a decompensation event, as defined below
<i>Hepatic decompensation events:</i>	
Hospitalization for any major hepatic decompensation event	Inpatient ICD-9 or ICD-10 discharge diagnosis for at least 1 individual decompensation outcome (defined below):
<ul style="list-style-type: none"> Ascites 	At least 1 inpatient discharge diagnosis: ICD-9: 789.5, 789.59 ICD-10: R18
<ul style="list-style-type: none"> Spontaneous Bacterial Peritonitis (SBP) 	At least 1 inpatient discharge diagnosis: ICD-9: 567.23, 567.0, 567.2, 567.8, 567.9 ICD-10: K65.0
<ul style="list-style-type: none"> Hepatorenal Syndrome (HRS) 	At least 1 inpatient discharge diagnosis: ICD-9: 572.4 ICD-10: K76.7
<ul style="list-style-type: none"> Esophageal Varices with Bleeding 	At least 1 inpatient discharge diagnosis: ICD-9: 456.0, 456.20 ICD-10: I85.0, I98.3
<ul style="list-style-type: none"> Hepatic Encephalopathy (HE) 	At least 1 of the following: (1) Inpatient discharge ICD-9 code for HE: 572.2, OR (2) Inpatient discharge ICD-10 code for cirrhosis (defined above) PLUS a prescription for lactulose and/or rifaximin
<i>Etiology of Cirrhosis:</i>	
Nonalcoholic Fatty Liver Disease (NAFLD)	At least 1 Inpatient or at least 2 Outpatient ICD-9 or ICD-10 diagnosis codes for NAFLD or steatohepatitis (NASH) in a patient with no other recorded etiology of liver disease*: ICD-9: 571.8 ICD-10: K76.9, K75.8 *See below for other etiologies of liver disease, to be excluded:
Alcohol-Related Liver Disease	At least 1 Inpatient or at least 2 Outpatient ICD-9 or ICD-10 diagnoses: ICD-9: 571.0-571.3 ICD-10: K70
Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) Infection	At least 1 Inpatient or at least 2 Outpatient ICD-9 or ICD-10 diagnoses: ICD-9: 070 ICD-10: B16-19
Other Liver Disease	At least 1 Inpatient or at least 2 Outpatient ICD-9 or ICD-10 diagnoses: <ul style="list-style-type: none"> Autoimmune liver disease (AIH, PBC, PSC): 571.6, 576.1; K83.01, K74.3, K75.4 Hemochromatosis: 275.0; E83.1 Wilson's Disease: 275.1; E83.01 Alpha-1-antitrypsin deficiency: 277.6; E88.01 Budd-Chiari Syndrome: 453.0; I82.0, K76.5 Chronic hepatitis unspecified: 571.4; K73.9, K73.2 Secondary/unspecified biliary cirrhosis: 571.6; K74.4-K74.5

Table S2A. Complete Baseline Characteristics in the Unmatched Cohorts of Patients with Cirrhosis and Type 2 Diabetes Initiating GLP-1 Receptor Agonists or Comparator Antidiabetic Medications

Baseline Characteristic	Cohort 1 GLP-1RA vs. DPP-4i		Cohort 2 GLP-1RA vs. Sulfonylurea		Cohort 3 GLP-1RA vs. SGLT2i	
	GLP-1RA N=2,084	DPP-4i N=4,537	GLP-1RA N=2,016	Sulfonylurea N=8,369	GLP-1RA N=2,191	SGLT-2i N=1,225
Male, %	1,168 (56.0)	2,517 (55.5)	1,124 (55.8)	4,858 (58.0)	1,218 (55.6)	640 (52.2)
Age, years - mean (SD)	57.3 (8.9)	60.9 (10.4)	57.4 (9.0)	61.4 (10.6)	57.4 (9.0)	57.8 (8.2)
<u>Etiology of Cirrhosis</u>						
Viral Hepatitis	149 (7.1)	476 (10.5)	141 (7.1)	923 (11.0)	162 (7.4)	123 (10.0)
Alcoholic Liver Disease	168 (8.1)	675 (14.9)	154 (7.6)	1,459 (17.4)	173 (7.9)	152 (12.4)
Nonalcoholic fatty liver disease	1,349 (64.7)	2,891 (63.7)	1,297 (64.3)	5,289 (63.2)	1,429 (65.2)	749 (61.1)
Other / Unspecified	418 (20.1)	495 (10.9)	424 (21.0)	698 (8.3)	427 (19.5)	201 (16.4)
<u>Cirrhosis Severity</u>						
Hospitalization for any decompensation	154 (7.4)	709 (15.6)	152 (7.5)	1,622 (19.4)	163 (7.4)	101 (8.2)
Ascites / SBP	85 (4.1)	533 (11.7)	85 (4.2)	1,218 (14.6)	92 (4.2)	60 (4.9)
Hepatic encephalopathy	71 (3.4)	316 (7.0)	72 (3.6)	596 (7.1)	79 (3.6)	54 (4.4)
Esophageal varices (any)	71 (3.4)	214 (4.7)	67 (3.3)	507 (6.1)	71 (3.2)	48 (3.9)
Bleeding esophageal varices	22 (1.1)	96 (2.1)	20 (1.0)	39 (0.5)	23 (1.0)	11 (0.9)
Hepatorenal syndrome	18 (0.4)	--	--	29 (0.3)	--	--
Hepatocellular carcinoma	50 (2.4)	184 (4.1)	48 (2.4)	395 (4.7)	50 (2.3)	33 (2.7)
<u>Diabetes Severity</u>						
Nephropathy	66 (3.2)	163 (3.6)	66 (3.3)	296 (3.5)	71 (3.2)	29 (2.4)
Neuropathy	193 (9.3)	394 (8.7)	183 (9.1)	689 (8.2)	199 (9.1)	102 (8.3)
Retinopathy	38 (1.8)	93 (2.0)	32 (1.6)	129 (1.5)	39 (1.8)	11 (0.9)
Circulatory complications	39 (1.9)	120 (2.6)	34 (1.7)	212 (2.5)	42 (1.9)	15 (1.2)
Diabetic foot	30 (1.4)	97 (2.1)	31 (1.5)	203 (2.4)	33 (1.5)	18 (1.5)
Dorsopathies	327 (15.7)	813 (17.9)	308 (15.3)	1,426 (17.3)	350 (16.0)	157 (12.8)
Hypoglycemia	51 (2.4)	188 (4.1)	49 (2.4)	294 (3.5)	55 (2.5)	33 (2.7)
Skin & soft tissue infections	127 (6.1)	376 (8.3)	125 (6.2)	780 (9.3)	135 (6.2)	61 (5.0)
Diabetes without complications	1,368 (65.6)	3,680 (81.1)	1,313 (65.1)	7,002 (83.7)	1,469 (67.0)	660 (53.9)
<u>Diabetes drugs in prior 180 days</u>						
Metformin	1,079 (51.8)	1,898 (41.8)	1,009 (50.0)	4,017 (48.0)	1,121 (51.2)	634 (51.8)
Glitazone	239 (11.5)	436 (9.6)	229 (11.4)	613 (7.3)	247 (11.3)	68 (5.6)
Insulin	544 (26.1)	514 (11.3)	546 (27.1)	674 (8.1)	556 (25.4)	275 (22.4)
SGLT2i	118 (2.6)	172 (8.3)	175 (8.7)	137 (1.6)	--	--
DPP-4i	--	--	426 (21.1)	1,045 (12.5)	464 (21.2)	346 (28.2)
Sulfonylurea	703 (33.7)	1,665 (36.7)	--	--	745 (34.0)	418 (34.1)
Meglitinides	19 (0.9)	33 (0.7)	20 (1.0)	39 (0.5)	19 (0.9)	6 (0.5)
<u>Comorbidities</u>						
Alcohol abuse / dependence	107 (5.1)	559 (12.3)	94 (4.7)	1,341 (16.0)	110 (5.0)	77 (6.3)
Cancer (any)	139 (6.7)	625 (13.8)	132 (6.5)	1,267 (15.1)	147 (6.7)	75 (6.1)
Drug abuse / dependence	15 (0.7)	42 (0.9)	13 (0.6)	132 (1.6)	15 (0.7)	10 (0.8)
Obesity	327 (15.7)	503 (11.1)	321 (15.9)	830 (9.9)	349 (15.9)	168 (13.7)
Ever smoker	141 (6.8)	382 (8.4)	132 (6.5)	702 (8.4)	139 (6.3)	115 (9.4)
Hypertension	862 (41.4)	2,323 (51.2)	832 (41.3)	4,288 (51.2)	920 (42.0)	468 (38.2)
Dyslipidemia	298 (14.3)	758 (16.7)	291 (14.4)	1,280 (15.3)	319 (14.6)	137 (11.2)
Ischemic heart disease	191 (9.2)	793 (17.5)	184 (9.1)	1,409 (16.8)	200 (9.1)	90 (7.3)

Congestive heart failure	102 (4.9)	526 (11.6)	101 (5.0)	1,091 (13.0)	16 (0.7)	17 (1.4)
Cardiac arrhythmia	70 (3.4)	363 (8.0)	70 (3.5)	714 (8.5)	74 (3.4)	24 (2.0)
Cerebrovascular disease	41 (2.0)	262 (5.8)	41 (2.0)	465 (5.6)	41 (1.9)	27 (2.2)
Obstructive Sleep Apnea	217 (10.4)	349 (7.7)	208 (10.3)	559 (6.7)	229 (10.5)	101 (8.2)
Chronic Obstructive Pulmonary disease	80 (3.8)	383 (8.4)	77 (3.8)	772 (9.2)	84 (3.8)	40 (3.3)
Non-diabetes chronic kidney disease	89 (4.3)	349 (7.7)	91 (4.5)	630 (7.5)	99 (4.5)	29 (2.4)
Depression	181 (8.7)	394 (8.7)	173 (8.6)	816 (9.8)	191 (8.7)	78 (6.4)
Dementia	17 (0.8)	117 (2.6)	16 (0.8)	254 (3.0)	18 (0.8)	4 (0.3)
Hypothyroidism	208 (10.0)	518 (11.4)	204 (10.1)	801 (9.6)	228 (10.4)	128 (10.4)
Osteoporosis	76 (3.6)	234 (5.2)	72 (3.6)	367 (4.4)	80 (3.7)	35 (2.9)
Falls	41 (2.0)	89 (2.0)	41 (2.0)	177 (2.1)	42 (1.9)	27 (2.2)
Fractures	42 (2.0)	165 (3.6)	69 (3.4)	375 (4.5)	42 (1.9)	28 (2.3)
Frailty ²	70 (3.3)	358 (7.9)	69 (3.4)	755 (9.0)	73 (3.3)	36 (2.9)
<i>Medications</i>						
Number of prescription medications, mean (SD)	12.0 (5.9)	10.6 (5.8)	12.0 (5.9)	9.5 (5.8)	12.0 (5.8)	11.6 (5.6)
ACE inhibitors	714 (34.3)	1,367 (30.1)	704 (34.9)	2,407 (28.8)	762 (34.8)	407 (33.2)
Angiotensin II receptor blockers	506 (24.3)	826 (18.2)	483 (24.0)	1,271 (15.2)	523 (23.9)	275 (22.4)
Anti-arrhythmic medications	22 (1.1)	91 (2.0)	21 (1.0)	157 (1.9)	22 (1.0)	11 (0.9)
Anticoagulants	110 (5.3)	314 (6.9)	103 (5.1)	609 (7.3)	108 (4.9)	54 (4.4)
Antiplatelets	120 (5.8)	320 (7.1)	120 (6.0)	500 (6.0)	126 (5.8)	78 (6.4)
Non-selective beta blockers	594 (28.5)	1,375 (30.3)	568 (28.2)	2,436 (29.1)	614 (28.0)	353 (28.8)
Bisphosphonates	40 (1.9)	119 (2.6)	37 (1.8)	199 (2.4)	41 (1.9)	20 (1.6)
Calcium channel blockers	341 (16.4)	803 (17.7)	336 (16.7)	1,361 (16.3)	356 (16.2)	187 (15.3)
Other diuretics	390 (18.7)	658 (14.5)	253 (12.5)	989 (11.8)	367 (16.8)	198 (16.2)
Loop diuretics	524 (25.1)	1,369 (30.2)	513 (25.4)	2,620 (31.3)	559 (25.5)	282 (23.0)
Statins	859 (41.2)	1,463 (32.2)	832 (41.3)	2,329 (27.8)	893 (40.8)	519 (42.4)
Non-statin lipid-lowering drugs	298 (14.3)	513 (11.3)	293 (14.5)	798 (9.5)	306 (14.0)	163 (13.3)
Antibiotics (any)	1,104 (53.0)	2,323 (51.2)	1,062 (52.7)	4,098 (49.0)	1,162 (53.0)	623 (50.9)
Antibiotics - fluoroquinolones	406 (19.5)	969 (21.4)	396 (19.6)	1,750 (20.9)	429 (19.6)	230 (18.8)
Anticonvulsants	390 (18.7)	658 (14.5)	384 (19.0)	1,155 (13.8)	393 (17.9)	234 (19.1)
Antidepressants	799 (38.3)	1,277 (28.1)	780 (38.7)	2,256 (27.0)	841 (38.4)	431 (35.2)
Benzodiazepines	374 (17.9)	746 (16.5)	358 (17.8)	1,348 (16.1)	390 (17.8)	211 (17.2)
Barbiturates	62 (3.0)	76 (1.7)	60 (3.0)	108 (1.3)	59 (2.7)	27 (2.2)
NSAIDs	366 (17.6)	608 (13.4)	359 (17.8)	981 (11.7)	380 (17.3)	234 (19.1)
Opioids	885 (42.5)	1,930 (42.5)	861 (42.5)	3,479 (41.5)	926 (42.3)	487 (39.8)
Rifaximin and/or Lactulose	223 (10.7)	648 (14.3)	220 (10.9)	1,148 (13.7)	240 (11.0)	152 (12.4)
<i>Healthcare Utilization in Prior 180 Days</i>						
Any hospitalization	391 (18.8)	1,569 (34.6)	377 (18.7)	3,398 (40.6)	403 (18.4)	224 (18.3)
Any ED visit	654 (31.4)	1,823 (40.2)	614 (30.5)	3,587 (42.9)	671 (30.6)	353 (28.8)
Any abdominal ultrasound	946 (45.4)	2,164 (47.7)	952 (47.2)	4,103 (49.0)	1,005 (45.9)	555 (45.3)
Any paracentesis	43 (2.1)	293 (6.5)	41 (2.0)	719 (8.6)	48 (2.2)	29 (2.4)
Any upper endoscopy	620 (29.8)	1,351 (29.8)	594 (29.5)	2,425 (29.0)	643 (29.3)	368 (30.0)
Any variceal banding	100 (4.8)	230 (5.1)	98 (4.9)	443 (5.3)	108 (4.9)	69 (5.6)
Any blood transfusion	42 (2.0)	229 (5.0)	116 (5.8)	1,183 (14.1)	125 (5.7)	69 (5.6)
Any visit to endocrinologist	543 (26.1)	672 (14.8)	530 (26.3)	741 (8.9)	564 (25.7)	306 (25.0)
Any visit to gastroenterologist / hepatologist	1,166 (56.0)	2,255 (49.7)	1,146 (56.8)	3,909 (46.7)	1,236 (56.4)	694 (56.7)
Medicare insurance + supplement	355 (17.0)	1,422 (31.3)	341 (16.9)	2,802 (33.5)	384 (17.5)	195 (15.9)

<i>Preventative Care in Prior 180 Days</i>						
Receipt of pneumonia vaccine	236 (11.3)	363 (8.0)	230 (11.4)	545 (6.5)	245 (11.2)	149 (12.2)
Receipt of flu vaccine	361 (17.3)	689 (15.2)	362 (18.0)	1,183 (14.1)	386 (17.6)	198 (16.2)
Colonoscopy	286 (13.7)	640 (14.1)	281 (13.9)	1,145 (13.7)	300 (13.7)	178 (14.5)
Mammogram	265 (12.7)	463 (10.2)	256 (12.7)	729 (8.7)	278 (12.7)	154 (12.6)
PSA or DRE	212 (10.2)	558 (12.3)	226 (11.2)	966 (11.5)	230 (10.5)	147 (12.0)
Any visit to primary care provider	1,837 (88.1)	3,950 (87.1)	1,784 (88.5)	7,073 (84.5)	1,931 (88.1)	1,109 (90.5)
HbA1c test ordered	1,599 (76.7)	2,933 (64.6)	1,554 (77.1)	4,734 (56.6)	1,676 (76.5)	984 (80.3)
Lipid panel ordered	1,216 (58.3)	2,230 (49.2)	1,184 (58.7)	3,579 (42.8)	1,270 (58.0)	766 (62.5)
Liver function tests ordered	789 (37.9)	1,684 (37.1)	763 (37.8)	2,959 (35.4)	835 (38.1)	422 (34.4)
Microalbuminuria test ordered	588 (28.2)	927 (20.4)	567 (28.1)	1,408 (16.8)	613 (28.0)	381 (31.1)

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).

¹Hepatic 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.

²Frailty was defined using the validated index by Kim DH et al.¹

Table S2B. Complete Baseline Characteristics in the Propensity Score-Matched Cohorts of Patients with Cirrhosis and Diabetes Initiating GLP-1 Receptor Agonists or Comparator Antidiabetic Medications

Baseline Characteristic	Cohort 1 GLP-1RA vs. DPP-4i		Cohort 2 GLP-1RA vs. Sulfonylurea		Cohort 3 GLP-1RA vs. SGLT2i	
	GLP-1RA N=1,431	DPP-4i N=1,431	GLP-1RA N=1,246	Sulfonylurea N=1,246	GLP-1RA N=845	SGLT-2i 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)
<u>Etiology of Cirrhosis</u>						
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)
<u>Cirrhosis Severity</u>						
Prior hepatic decompensation event 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)
Hepatorenal syndrome	--	--	--	--	--	--
Hepatocellular carcinoma	36 (2.5)	37 (2.6)	28 (2.2)	29 (2.3)	24 (2.8)	23 (2.7)
<u>Diabetes Severity</u>						
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)
Circulatory complications	30 (2.1)	24 (1.7)	19 (1.5)	19 (1.5)	13 (1.5)	11 (1.3)
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)
<u>Diabetes Drugs in Prior 180 Days</u>						
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)
Meglitinides	9 (0.6)	8 (0.6)	11 (0.9)	11 (0.9)	4 (0.5)	3 (0.4)
<u>Comorbidities</u>						
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)
Ever smoker	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)

Cardiac arrhythmia	54 (3.8)	66 (4.6)	37 (3.0)	36 (2.9)	18 (2.1)	18 (2.1)
Cerebrovascular disease	33 (2.3)	20 (1.4)	26 (2.1)	24 (1.9)	13 (1.5)	11 (1.3)
Obstructive Sleep Apnea	151 (10.5)	158 (11.0)	119 (9.5)	111 (8.9)	77 (9.1)	78 (9.2)
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)
Hypothyroidism	143 (10.0)	150 (10.5)	132 (10.6)	121 (9.7)	72 (8.5)	77 (9.1)
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)
Frailty ²	54 (3.8)	48 (3.4)	51 (4.1)	46 (3.7)	27 (3.2)	22 (2.6)
<u>Medications</u>						
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)
Anti-arrhythmic medications	16 (1.1)	21 (1.5)	13 (1.0)	19 (1.5)	11 (1.3)	9 (1.1)
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)
Calcium channel blockers	221 (15.4)	225 (15.7)	193 (15.5)	194 (15.6)	141 (16.7)	141 (16.7)
Other diuretics	261 (18.2)	248 (17.3)	229 (18.4)	228 (18.3)	153 (18.1)	144 (17.0)
Loop diuretics	356 (24.8)	356 (24.8)	307 (24.6)	289 (23.2)	217 (25.7)	208 (24.6)
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)
Barbiturates	37 (2.6)	38 (2.6)	34 (2.7)	29 (2.3)	24 (2.8)	21 (2.5)
NSAIDs	230 (16.0)	233 (16.2)	215 (17.2)	210 (16.8)	158 (18.7)	160 (18.9)
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)
<u>Healthcare Utilization in Prior 180 Days</u>						
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 blood transfusion	93 (6.5)	85 (5.9)	66 (5.3)	69 (5.5)	45 (5.3)	46 (5.4)
Any visit to endocrinologist	322 (22.4)	321 (22.4)	276 (22.1)	294 (23.6)	204 (24.1)	201 (23.8)
Any visit to gastroenterologist	775 (54.0)	749 (52.2)	691 (55.4)	701 (56.2)	479 (56.7)	486 (57.5)
Medicare insurance + supplement	269 (18.8)	274 (19.1)	227 (18.2)	226 (18.1)	150 (17.8)	146 (17.3)
<u>Preventative Care in Prior 180 Days</u>						
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)
Any visit to primary care provider	1,260 (87.8)	1,248 (87.0)	1,088 (87.2)	1,088 (87.2)	766 (90.7)	771 (91.2)
HbA1c test	1,069 (74.5)	1,075 (74.9)	925 (74.2)	918 (73.6)	650 (76.9)	654 (77.4)
Lipid panel	820 (57.1)	822 (57.3)	707 (56.7)	711 (57.0)	488 (57.8)	495 (58.6)
Liver function tests	541 (37.7)	553 (38.5)	466 (37.4)	492 (39.5)	282 (33.4)	281 (33.3)
Microalbuminuria	379 (26.4)	385 (26.8)	319 (25.6)	303 (24.3)	250 (29.6)	253 (29.9)

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).

¹Hepatic 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.

²Frailty was defined using the validated index by Kim DH et al.¹

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Table S3. Risk of Hepatic Decompensation¹ Among Propensity Score-Matched Patients with NAFLD Cirrhosis* and Type 2 Diabetes Initiating GLP-1 Receptor Agonists or Comparator Antidiabetic Medications

	Cohort 2 (n=920 pairs)		Cohort 2 (n=791 pairs)		Cohort 3 (n=473 pairs)	
	GLP-1RA N=920	DPP-4 Inhibitor N=920	GLP-1RA N=791	Sulfonylurea N=791	GLP-1RA N=473	SGLT-2 Inhibitor N=473
Mean [IQR] follow-up, days	133 [73, 290]	135 [73, 341]	132 [73, 258]	133 [73, 307]	133 [73, 288]	152 [73, 360]
Hepatic Decompensation events¹						
• No. of events	69	116	60	82	34	37
• Incidence rate, per 1,000 PY	118.1	176.2	113.4	161.4	104.0	116.9
• Hazard ratio (95% CI)	0.63 (0.47-0.85)	1 (ref.)	0.71 (0.51-0.98)	1 (ref.)	0.88 (0.55-1.41)	1 (ref.)
Ascites, SBP or Hepatorenal Syndrome						
• No. of events	39	62	32	51	18	16
• Incidence rate, per 1,000 PY	64.5	88.2	59.2	96.3	57.0	47.2
• Hazard ratio (95% CI)	0.70 (0.47-1.04)	1 (ref.)	0.62 (0.40-0.96)	1 (ref.)	1.21 (0.62-2.38)	1 (ref.)
Bleed from esophageal varices						
• No. of events	27	61	23	37	15	22
• Incidence rate, per 1,000 PY	44.6	88.1	42.4	69.9	44.7	61.2
• Hazard ratio (95% CI)	0.48 (0.31-0.76)	1 (ref.)	0.60 (0.36-1.01)	1 (ref.)	0.72 (0.37-1.42)	1 (ref.)
Hepatic encephalopathy						
• No. of events	41	69	38	55	15	20
• Incidence rate, per 1,000 PY	68.7	99.8	72.0	104.4	46.8	59.5
• Hazard ratio (95% CI)	0.64 (0.43-0.94)	1 (ref.)	0.69 (0.46-1.04)	1 (ref.)	0.79 (0.40-1.54)	1 (ref.)

Abbreviations: NAFLD, nonalcoholic fatty liver disease; 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

¹Hepatic 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.

*NAFLD cirrhosis was defined using a validated ICD-based algorithm (see Supplementary Appendix).

Table S4. Risk of Hepatic Decompensation¹ in Propensity Score-Matched Subgroups of Patients with Cirrhosis and Type 2 Diabetes Initiating GLP-1 Receptor Agonists or Comparator Antidiabetic Medications

Subgroup*:	Cohort 1		Cohort 2	
	GLP-1RA	DPP-4i	GLP-1RA	Sulfonylurea
Men				
• No. of events / No. of subjects	75 / 760	103 / 760	46 / 811	82 / 811
• Hazard ratio (95% CI)	0.81 (0.60-1.04)	1 (ref.)	0.67 (0.47-0.97)	1 (ref.)
Women				
• No. of events / No. of subjects	45 / 975	71 / 975	50 / 999	86 / 999
• Hazard ratio (95% CI)	0.66 (0.45-0.96)	1 (ref.)	0.64 (0.45-0.91)	1 (ref.)
HBV/HCV Cirrhosis				
• No. of events / No. of subjects	9 / 131	22 / 131	5 / 132	17 / 132
• Hazard ratio (95% CI)	0.40 (0.19-0.88)	1 (ref.)	0.30 (0.11-0.81)	1 (ref.)
Alcohol-Related Cirrhosis				
• No. of events / No. of subjects	31 / 160	35 / 160	26 / 156	33 / 156
• Hazard ratio (95% CI)	0.98 (0.67-1.79)	1 (ref.)	0.77 (0.46-1.29)	1 (ref.)
Commercial Insurance				
• No. of events / No. of subjects	79 / 1,236	114 / 1,236	47 / 940	78 / 940
• Hazard ratio (95% CI)	0.73 (0.57-0.93)	1 (ref.)	0.60 (0.40-0.89)	1 (ref.)
Metformin use				
• No. of events / No. of subjects	59 / 1,067	89 / 1,067	49 / 1,161	98 / 1,161
• Hazard ratio (95% CI)	0.73 (0.53-1.02)	1 (ref.)	0.62 (0.44-0.87)	1 (ref.)
No Metformin use				
• No. of events / No. of subjects	66 / 753	106 / 753	44 / 799	68 / 799
• Hazard ratio (95% CI)	0.69 (0.54-0.94)	1 (ref.)	0.69 (0.47-1.01)	1 (ref.)
Non-selective Beta-Blocker use				
• No. of events / No. of subjects	48 / 437	77 / 437	32 / 446	67 / 446
• Hazard ratio (95% CI)	0.69 (0.48-0.99)	1 (ref.)	0.54 (0.35-0.82)	1 (ref.)
No Non-selective Beta-Blocker use				
• No. of events / No. of subjects	76 / 1,332	104 / 1,332	58 / 1,425	97 / 1,425
• Hazard ratio (95% CI)	0.82 (0.61-1.10)	1 (ref.)	0.70 (0.50-0.97)	1 (ref.)

Abbreviations: GLP-1RA, glucose-like peptide 1 receptor agonist; DPP-4 inhibitor, dipeptidyl peptidase-4 inhibitor; IQR, CI, confidence interval; HBV, hepatitis B virus infection; HCV, hepatitis C virus infection

¹Hepatic 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.

*For each subgroup, the propensity score (PS) was recalculated and the PS-matching procedure was repeated, to ensure appropriate balance between groups. For that reason, the numbers of patients in each PS-matched subgroup differ from the numbers of patients with and without specific characteristics, in Table 1.

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Table S5. Risk of Hepatic Decompensation in Propensity Score-Matched Patients with Strictly Defined Cirrhosis* and Type 2 Diabetes Initiating GLP-1 Receptor Agonists or Comparator Antidiabetic Medications

	Cohort 1 (n=1,147 pairs)		Cohort 2 (n=989 pairs)		Cohort 3 (n=700 pairs)	
	GLP-1RA N=1,147	DPP-4 inhibitor N=1,147	GLP-1RA N=989	Sulfonylurea N=989	GLP-1RA N=700	SGLT-2 inhibitor N=700
Mean [IQR] follow-up, days	133 [73, 280]	141 [73, 352]	127 [71, 248]	133 [73, 280]	133 [73, 286]	144 [73, 342]
Hepatic Decompensation events ¹						
• No. of events	86	136	72	103	44	61
• Incidence rate, per 1,000 PY	120.1	165.7	115.0	161.3	98.7	132.7
• Hazard ratio (95% CI)	0.69 (0.53-0.91)	1 (ref.)	0.70 (0.52, 0.94)	1 (ref.)	0.74 (0.50-1.10)	1 (ref.)
Ascites, SBP or hepatorenal syndrome						
• No. of events	41	69	44	66	31	37
• Incidence rate, per 1,000 PY	47.8	71.6	69.0	100.6	69.0	84.1
• Hazard ratio (95% CI)	0.72 (0.51-0.99)	1 (ref.)	0.67 (0.46-0.98)	1 (ref.)	0.81 (0.50-1.29)	1 (ref.)
Bleed from esophageal varices						
• No. of events	34	62	24	39	21	33
• Incidence rate, per 1,000 PY	44.0	70.4	31.7	48.2	46.2	69.5
• Hazard ratio (95% CI)	0.61 (0.40-0.93)	1 (ref.)	0.64 (0.39-1.07)	1 (ref.)	0.67 (0.38-1.15)	1 (ref.)
Hepatic encephalopathy						
• No. of events	58	79	46	76	31	30
• Incidence rate, per 1,000 PY	80.1	93.3	58.4	88.4	68.9	63.0
• Hazard ratio (95% CI)	0.80 (0.57-1.13)	1 (ref.)	0.64 (0.45-0.93)	1 (ref.)	1.07 (0.65-1.77)	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 this analysis, a diagnosis of cirrhosis required >2 inpatient or outpatient ICD-9 or ICD-10 diagnosis codes for cirrhosis, during the 180-day period prior to cohort entry.

For details see Methods and the Supplementary Appendix.

¹Hepatic 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.

Table S6. Risk of Hepatic Decompensation in Propensity Score-Matched Patients with Cirrhosis and Type 2 Diabetes Initiating GLP-1 Receptor Agonists versus Comparator Antidiabetic Medications, after Decreasing the Exposure Window to 15 days

	Cohort 1 (n=1,431 pairs)		Cohort 2 (n=1,246 pairs)		Cohort 3 (n=845 pairs)	
	GLP-1RA N=1,431	DPP-4 Inhibitor N=1,431	GLP-1RA N=1,246	Sulfonylurea N=1,246	GLP-1RA N=845	SGLT-2 Inhibitor N=845
Mean [IQR] follow-up, days	83 [43, 158]	103 [43, 200]	74 [43, 143]	99 [43, 183]	86 [43, 165]	103 [43, 224]
Hepatic Decompensation events ¹						
• No. of events	62	106	40	97	38	47
• Incidence rate, per 1,000 PY	119.7	151.7	86.4	180.5	114.3	121.9
• Hazard ratio (95% CI)	0.70 (0.51-0.96)	1 (ref.)	0.46 (0.32-0.66)	1 (ref.)	0.89 (0.58-1.36)	1 (ref.)
Ascites, SBP or hepatorenal syndrome						
• No. of events	42	57	26	59	27	31
• Incidence rate, per 1,000 PY	80.6	79.8	56.0	106.4	81.4	78.4
• Hazard ratio (95% CI)	0.91 (0.61-1.36)	1 (ref.)	0.51 (0.32-0.81)	1 (ref.)	0.99 (0.59-1.66)	1 (ref.)
Bleed from esophageal varices						
• No. of events	23	49	9	36	17	25
• Incidence rate, per 1,000 PY	43.7	68.6	19.1	64.7	50.6	63.6
• Hazard ratio (95% CI)	0.58 (0.35-0.95)	1 (ref.)	0.29 (0.14-0.60)	1 (ref.)	0.75 (0.41-1.39)	1 (ref.)
Hepatic encephalopathy						
• No. of events	42	58	37	56	24	25
• Incidence rate, per 1,000 PY	80.8	81.8	80.5	100.7	72.1	64.0
• Hazard ratio (95% CI)	0.87 (0.58-1.30)	1 (ref.)	0.74 (0.49-1.12)	1 (ref.)	1.04 (0.59-1.82)	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

¹Hepatic 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.

Table S7. Risk of Hepatic Decompensation in Propensity Score-Matched Patients with Cirrhosis and Type 2 Diabetes Initiating GLP-1 Receptor Agonists or Comparator Antidiabetic Medications, Using an Intention-To-Treat Approach²

	Cohort 1 (n=1,431 pairs)		Cohort 2 (n=1,246 pairs)		Cohort 3 (n=845 pairs)	
	GLP-1RA N=1,431	DPP-4 Inhibitor N=1,431	GLP-1RA N=1,246	Sulfonylurea N=1,246	GLP-1RA N=845	SGLT-2 Inhibitor N=845
Mean [IQR] follow-up, days	364 [163, 364]	364 [148, 364]	364 [169, 364]	364 [130, 364]	364 [165, 364]	364 [162, 364]
Hepatic Decompensation events ¹						
• No. of events	125	165	106	154	62	64
• Incidence rate, per 1,000 PY	116.4	155.2	111.8	174.4	101.2	103.3
• Hazard ratio (95% CI)	0.73 (0.57-0.94)	1 (ref.)	0.66 (0.51-0.86)	1 (ref.)	0.97 (0.67-1.39)	1 (ref.)
Ascites, SBP or hepatorenal syndrome						
• No. of events	65	108	62	106	41	39
• Incidence rate, per 1,000 PY	58.9	98.5	64.1	116.5	65.4	61.8
• Hazard ratio (95% CI)	0.58 (0.42-0.80)	1 (ref.)	0.56 (0.41-0.78)	1 (ref.)	1.05 (0.67-1.65)	1 (ref.)
Bleed from esophageal varices						
• No. of events	46	78	39	66	29	35
• Incidence rate, per 1,000 PY	41.3	70.5	39.8	71.3	46.1	55.5
• Hazard ratio (95% CI)	0.58 (0.40-0.84)	1 (ref.)	0.58 (0.39-0.87)	1 (ref.)	0.82 (0.50-1.36)	1 (ref.)
Hepatic encephalopathy						
• No. of events	56	66	50	66	27	27
• Incidence rate, per 1,000 PY	50.7	59.7	51.5	71.3	42.8	42.6
• Hazard ratio (95% CI)	0.84 (0.59-1.21)	1 (ref.)	0.75 (0.51-1.09)	1 (ref.)	1.00 (0.58-1.72)	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

¹Hepatic 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.

²To mimic an intention-to-treat approach, the exposure to an initiated drug was carried forward for 365 days without censoring for drug discontinuation or switching, as described in the Methods.

Table S8. Risk of Hepatic Decompensation in Propensity Score-Matched Patients with Cirrhosis and Type 2 Diabetes Initiating a SGLT-2 inhibitor compared to a DPP-4 inhibitor

	PS-Matched Cohort (n=723 pairs)	
	SGLT-2 Inhibitor N=723	DPP-4 Inhibitor N=723
Mean [IQR] follow-up, days	135 [73, 331]	133 [73, 276]
Hepatic Decompensation events¹		
• No. of events	60	64
• Incidence rate, per 1,000 PY	111.8	133.8
• Hazard ratio (95% CI)	0.89 (0.62-1.26)	1 (ref.)
Ascites, SBP or hepatorenal syndrome		
• No. of events	33	52
• Incidence rate, per 1,000 PY	59.5	108.5
• Hazard ratio (95% CI)	0.58 (0.38-0.90)	1 (ref.)
Bleed from esophageal varices		
• No. of events	17	19
• Incidence rate, per 1,000 PY	34.9	44.2
• Hazard ratio (95% CI)	0.81 (0.42-1.55)	1 (ref.)
Hepatic encephalopathy		
• No. of events	32	35
• Incidence rate, per 1,000 PY	58.6	72.1
• Hazard ratio (95% CI)	0.87 (0.54-1.41)	1 (ref.)

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

¹Hepatic 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.

Table S9. Risk of Fracture in Propensity Score-Matched Patients with Cirrhosis and Type 2 Diabetes Initiating a GLP-1 Receptor Agonist versus 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-4 Inhibitor N=1,431	GLP-1RA N=1,246	Sulfonylurea N=1,246	GLP-1RA N=845	SGLT-2 Inhibitor N=845
Mean [IQR] follow-up, days	133 [73, 282]	136 [73, 365]	132 [71, 250]	134 [73, 309]	134 [73, 290]	156 [73, 362]
Fracture						
• No. of events	53	58	42	53	22	25
• Incidence rate, per 1,000 PY	57.3	51.4	52.8	61.3	39.9	43.2
• Hazard ratio (95% CI)	1.06 (0.73-1.55)	1 (ref.)	0.84 (0.56-1.26)	1 (ref.)	0.90 (0.51-1.59)	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

Table S10. Baseline Characteristics in Propensity Score-Matched Patients with Cirrhosis and Type 2 Diabetes Initiating GLP-1 Receptor Agonists or a Comparator Antidiabetic Medication, in the Optum Database*

Baseline Characteristic	Cohort 1 GLP-1RA vs. DPP-4 Inhibitor		Cohort 2 GLP-1RA vs. Sulfonylurea		Cohort 3 GLP-1RA vs. SGLT2 Inhibitor	
	GLP-1RA N=1,181	DPP-4i N=1,181	GLP-1RA N=1,240	Sulfonylurea N=1,240	GLP-1RA N=1,101	SGLT2i N=1,101
Male, %	54.7	55.1	55.4	53.6	54.0	53.2
Age, years - mean (SD)	62.6 (9.8)	62.7 (10.6)	62.3 (9.9)	62.5 (10.5)	62.5 (9.9)	62.7 (9.7)
Race/ethnicity	--	--	--	--	--	--
• White	66.8	68.5	67.2	67.2	65.8	66.3
• Black	10.2	9.9	9.5	8.8	10.4	9.8
• Asian	1.9	1.7	2.1	2.3	2.1	1.8
• Hispanic	21.1	19.9	21.2	21.7	21.7	22.1
• Unknown	0	0	0	0	0	0
<u>Etiology of Cirrhosis</u>						
Viral Hepatitis	16.6	17.0	16.3	15.6	15.3	15.5
Alcoholic Liver Disease	14.4	13.3	15.2	15.4	13.8	14.6
Nonalcoholic fatty liver disease	49.0	46.6	50.8	49.8	45.7	45.0
Other / Unspecified	20.0	23.1	17.7	19.2	25.2	24.9
<u>Cirrhosis Severity</u>						
Hospitalization for any decompensation ¹	7.5	7.8	7.2	7.0	6.8	6.1
Ascites / SBP	3.4	3.0	3.8	3.6	3.7	3.9
Hepatic encephalopathy	5.0	4.7	4.6	4.9	4.5	4.2
Esophageal varices (any)	3.3	2.7	3.0	3.2	1.4	1.3
Bleeding esophageal varices	0	0	0.2	0.1	0	0
Hepatorenal syndrome	0	0	0.3	0.4	0	0
Hepatocellular carcinoma	3.0	3.0	3.1	2.7	3.6	3.5
<u>Diabetes Severity</u>						
Nephropathy	2.8	2.7	2.6	2.3	1.2	1.3
Neuropathy	6.7	6.7	6.7	6.9	3.5	3.2
Retinopathy	2.1	2.5	1.9	2.3	1.4	1.2
Circulatory complications	1.3	1.4	1.2	1.5	0.5	0.7
Diabetic foot	1.0	1.0	0.8	0.9	0.5	0.4
Dorsopathies	8.6	8.4	8.1	9.0	4.2	4.5
Hypoglycemia	2.1	2.2	2.0	1.7	1.0	1.3
Skin & soft tissue infections	3.2	3.6	2.6	2.7	1.3	1.4
Diabetes without complications	26.3	23.7	27.8	26.4	13.8	14.4
<u>Diabetes drugs in prior 180 days</u>						
Metformin	51.7	50.6	49.3	50.7	55.6	55.7
Glitazone	7.5	7.7	7.7	8.1	4.8	5.3
Insulin	24.5	23.7	27.1	25.9	26.8	24.5
SGLT2i	8.1	7.0	8.8	8.6	--	--
DPP-4i	--	--	16.7	17.4	16.3	16.4
Sulfonylurea	30.1	29.0	--	--	28.1	28.4
Meglitinides	1.0	1.0	1.2	1.2	0.8	0.9
<u>Comorbidities</u>						
Alcohol abuse / dependence	3.5	3.8	3.7	3.7	1.8	2.3
Cancer ²	6.4	6.1	6.5	5.3	5.5	5.5

Drug abuse / dependence	0.6	0.4	0.9	0.8	0.4	0.4
Obesity	14.5	14.4	15.9	15.6	9.6	10.0
Ever smoker	5.4	6.1	5.4	5.2	4.9	5.4
Hypertension	21.1	19.6	40.0	41.5	11.6	11.7
Dyslipidemia	19.1	19.4	14.7	16.2	9.0	8.9
Ischemic heart disease	4.9	4.4	4.1	3.6	2.0	2.2
Congestive heart failure	3.4	4.2	5.1	4.7	0.8	1.0
Cardiac arrhythmia	2.1	2.0	1.4	1.4	1.6	1.5
Cerebrovascular disease	1.2	1.3	2.2	2.2	0.5	0.5
Obstructive Sleep Apnea	4.4	4.5	3.6	4.0	2.3	2.1
Chronic Obstructive Pulmonary disease	3.8	4.2	3.6	3.4	1.6	1.5
Non-diabetes chronic kidney disease	3.3	3.1	5.1	4.7	1.0	1.1
Depression	5.2	4.9	4.9	4.6	2.0	2.5
Dementia	0.5	0.4	0.6	0.7	0.3	0.3
Hypothyroidism	5.9	5.9	5.6	6.4	2.6	2.6
Osteoporosis	3.3	2.4	4.2	3.9	3.1	2.7
Falls	2.7	3.0	1.7	1.8	2.5	2.5
Fractures	1.2	1.3	1.9	1.8	0.5	0.4
Frailty ²	3.7	3.3	4.1	3.7	4.2	4.2
<i>Medications</i>						
Number of prescription medications, mean (SD)	12.7 (6.4)	12.6 (6.6)	12.7 (6.3)	12.6 (6.7)	13.0 (6.6)	13.0 (6.7)
ACE inhibitors	35.8	35.2	34.4	35.5	35.2	35.5
Angiotensin II receptor blockers	24.2	24.6	24.4	22.6	25.3	25.4
Anti-arrhythmic medications	2.1	2.0	1.0	1.2	1.0	1.4
Anticoagulants	7.5	7.0	4.6	4.0	6.8	7.4
Antiplatelets	9.5	9.4	6.1	5.9	9.6	9.9
Beta blockers	35.8	37.0	35.3	36.2	33.6	36.2
Bisphosphonates	2.5	2.0	2.6	2.7	2.5	2.4
Calcium channel blockers	20.9	21.7	20.4	20.8	21.3	20.8
Other diuretics	20.2	20.5	20.3	20.7	21.2	20.5
Loop diuretics	31.3	31.0	25.0	23.4	23.3	23.5
Statins	47.6	47.3	49.6	49.5	50.4	50.4
Non-statin lipid-lowering drugs	9.7	9.2	9.8	10.2	10.3	9.6
Antibiotics (any)	54.4	55.3	51.5	52.5	39.4	40.8
Antibiotics - fluoroquinolones	20.5	20.5	18.6	19.3	17.1	17.7
Anticonvulsants	28.7	28.3	29.4	30.7	28.2	28.1
Antidepressants	41.2	39.7	36.8	38.5	39.4	40.8
Benzodiazepines	17.1	16.3	17.3	17.7	16.2	15.7
Barbiturates	2.5	2.2	2.5	2.7	2.4	2.5
NSAIDs	16.2	15.9	17.3	17.9	17.9	17.0
Opioids	43.6	44.7	42.8	42.7	38.7	39.1
Rifaximin and/or Lactulose	13.6	13.0	13.7	14.1	14.6	15.4
<i>Healthcare Utilization in Prior 180 Days</i>						
Any hospitalization	20.1	20.6	19.0	17.3	23.9	23.5
Any ED visit	37.1	37.9	39.5	38.6	40.4	39.8
Any abdominal ultrasound	44.7	44.7	44.0	42.7	44.4	44.1
Any paracentesis	1.0	1.2	0.9	1.3	1.1	1.0
Any upper endoscopy	5.0	5.2	3.8	4.0	1.7	2.0
Any variceal banding	2.1	2.3	2.0	2.2	0.5	0.5

Any blood transfusion	6.2	6.6	6.1	5.7	5.3	5.4
Any visit to endocrinologist	21.2	22.5	23.0	21.6	20.7	21.8
Any visit to gastroenterologist / hepatologist	52.2	52.5	55.8	56.3	54.0	53.2
<i>Preventative Care in Prior 180 Days</i>						
Receipt of pneumonia vaccine	23.7	24.6	25.3	24.5	27.6	28.7
Receipt of flu vaccine	20.7	20.2	20.9	20.5	21.1	21.4
Colonoscopy	10.9	12.3	12.8	12.2	12.4	10.9
Mammogram	16.0	15.6	15.3	14.9	16.1	15.3
PSA or DRE	12.4	13.1	11.3	12.1	11.8	13.1
Any visit to primary care provider	84.4	84.0	83.9	84.0	84.7	84.4
HbA1c test ordered	84.6	83.5	84.4	85.4	86.7	86.6
Lipid panel ordered	67.1	65.3	65.6	66.9	67.1	67.3
Liver function tests ordered	34.7	33.8	36.1	34.4	35.6	35.5
Microalbuminuria test ordered	34.5	35.0	26.5	26.1	37.3	37.3

*The study population derived from the Optum Clinformatics Dataset, as outlined in the Methods. All characteristics presented as %, or mean (standard deviation, SD) unless noted otherwise.

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; NSAID, nonsteroidal anti-inflammatory drug; ED, emergency department; PSA, prostate-specific antigen; DRE, digital rectal examination; HbA1c, hemoglobin A1c).

¹Hepatic 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.

²Frailty was defined using the validated index by Kim DH et al¹.

Table S11. Risk of Hepatic Decompensation Events in Propensity Score-Matched Patients with Cirrhosis and Type 2 Diabetes Initiating a GLP-1 Receptor Agonist versus Comparator Antidiabetic Medications, in the Optum Database*

	Cohort 1 (n=1,181 pairs)		Cohort 2 (n=1,240 pairs)		Cohort 3 (n=1,101 pairs)	
	GLP-1RA N=1,181	DPP-4 Inhibitor N=1,181	GLP-1RA N=1,240	Sulfonylurea N=1,240	GLP-1RA N=1,101	SGLT-2 Inhibitor N=1,101
Mean [IQR] follow-up, days	127 [71, 249]	133 [73, 312]	127 [71, 249]	133 [73, 312]	133 [73, 268]	133 [73, 281]
Hepatic Decompensation events ¹						
• No. of events	39	70	50	91	39	44
• Incidence rate, per 1,000 PY	43.5	71.0	52.0	76.5	59.6	55.3
• Hazard ratio (95% CI)	0.72 (0.55-0.93)	1 (ref.)	0.65 (0.46-0.92)	1 (ref.)	0.91 (0.59-1.40)	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

*The study population derived from the Optum Clinformatics Dataset, as outlined in the Methods.

¹Hepatic 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.

Tables S12A-B. Rule-out approach sensitivity analysis for an unmeasured confounder

Scenario:

1. We fixed the observed relative risk (ARR) to the point estimate of the propensity score-matched hazard ratio for major decompensation events, comparing GLP-1RA initiators to DPP-4 initiators (hazard ratio, 0.68, 95% CI 0.53-0.88 [Table 2]).
2. We varied the prevalence of the unmeasured confounder (P_C) from 0.1 to 0.6.
3. We then examined the parameter combinations of (a) the association between drug exposure and the confounder (OR_{EC}), and (b) the association between the confounder and the primary outcome (RR_{CD}), that would be necessary to move the point estimate of the association between GLP-1RA initiation and incident hepatic decompensation events to 1.0.

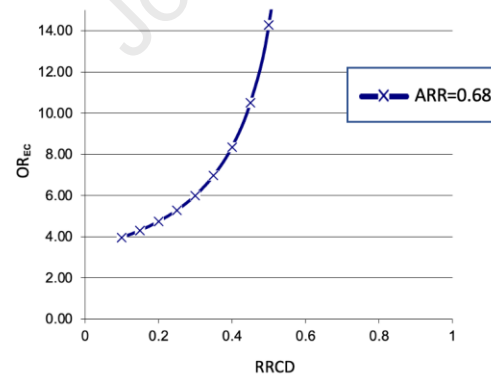
Definitions:

OR_{EC} =Association between drug exposure and confounder
 RR_{CD} =Association between confounder and disease outcome
 ARR=apparent exposure relative risk
 P_E =Prevalence of drug exposure
 P_C =Prevalence of the unmeasured confounder

Results and explanation:

S12A. An unmeasured confounder with a prevalence of 0.2 with a RR_{CD} of 0.6 for hepatic decompensation events would need to have an implausibly strong, positive association with GLP-1RA drug exposure ($OR_{EC}=55.0$ or more) to move our point estimate to 1.0. If such a confounder had a more modest association with the drug exposure (i.e. $OR_{EC}=3.95$), then it would also need to have a very strong, inverse association with hepatic decompensation outcomes (i.e. $RR_{CD}=0.1$ or less), to move the point estimate to 1.0.

RR_{CD}	P_C	P_E	ARR	OR_{EC}
0.97	0.2	0.02	0.68	83.34
0.95	0.2	0.02	0.68	999.0
0.9	0.2	0.02	0.68	999.0
0.85	0.2	0.02	0.68	999.0
0.8	0.2	0.02	0.68	999.0
0.75	0.2	0.02	0.68	999.0
0.7	0.2	0.02	0.68	999.0
0.65	0.2	0.02	0.68	999.0
0.6	0.2	0.02	0.68	55.00
0.55	0.2	0.02	0.68	22.54
0.5	0.2	0.02	0.68	14.27
0.45	0.2	0.02	0.68	10.50
0.4	0.2	0.02	0.68	8.35
0.35	0.2	0.02	0.68	6.97
0.3	0.2	0.02	0.68	6.00
0.25	0.2	0.02	0.68	5.28
0.2	0.2	0.02	0.68	4.73
0.15	0.2	0.02	0.68	4.30
0.1	0.2	0.02	0.68	3.95



S12B. Alternatively, an unmeasured confounder with a prevalence of 0.6 and a weaker association with the drug exposure (i.e. $OR_{EC}=2.16$) would need to have a very strong, inverse association with hepatic decompensation outcomes (i.e. $RR_{CD}=0.1$ or less) to move the point estimate to 1.0.

RR_{CD}	P_C	P_E	ARR	OR_{EC}
0.97	0.6	0.02	0.68	999.0
0.95	0.6	0.02	0.68	999.0
0.9	0.6	0.02	0.68	999.0
0.85	0.6	0.02	0.68	999.0
0.8	0.6	0.02	0.68	999.0
0.75	0.6	0.02	0.68	999.0
0.7	0.6	0.02	0.68	999.0
0.65	0.6	0.02	0.68	999.0
0.6	0.6	0.02	0.68	999.0
0.55	0.6	0.02	0.68	999.0
0.5	0.6	0.02	0.68	999.0
0.45	0.6	0.02	0.68	43.70
0.4	0.6	0.02	0.68	10.14
0.35	0.6	0.02	0.68	5.90
0.3	0.6	0.02	0.68	4.24
0.25	0.6	0.02	0.68	3.35
0.2	0.6	0.02	0.68	2.80
0.15	0.6	0.02	0.68	2.43
0.1	0.6	0.02	0.68	2.16

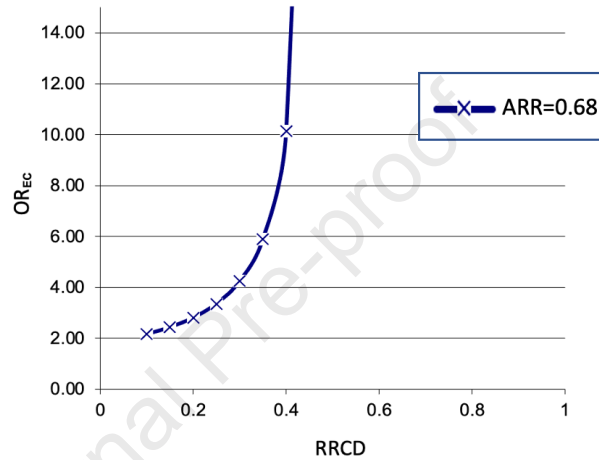




Figure S1. Study Schema

The study design was an event-exposure based cohort study. The event was defined by at least 1 diagnosis of type 2 diabetes and at least 1 diagnosis of cirrhosis, defined using a validated ICD-9/ICD-10 algorithm (see Methods). The exposure was defined by new initiation of a second-line antidiabetic medication (in 3 pairwise comparisons), defined at the cohort entry date. The cohort entry date, in turn, was defined as the date on which the last requirement was fulfilled.

¹Individuals were excluded with type 1 diabetes, gestational diabetes, end-stage renal failure or human immunodeficiency virus (HIV), as per the Methods. Up to a 45-day grace period was allowed for each medication.

²First recorded outcome of interest, switching/stopping study drugs, death, disenrollment or end of study period.

³Baseline covariates were defined during the 180-day covariate assessment window, prior to the cohort entry date.

Supplementary References:

1. Kim DH, Schneeweiss S, Glynn RJ, et al. Measuring Frailty in Medicare Data: Development and Validation of a Claims-Based Frailty Index. *J Gerontol A Biol Sci Med Sci* 2018;73(7):980-87. doi: 10.1093/gerona/glx229 [published Online First: 2017/12/16]

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