Newer second-line glucose-lowering drugs versus thiazolidinediones on cirrhosis risk among older US adult patients with type 2 diabetes

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ABSTRACT

Aims: Type 2 diabetes (T2D) accelerates progression of chronic liver disease to cirrhosis, yet the effects of most glucose-lowering drugs (GLDs) on cirrhosis risk in T2D are unknown. To address this gap, we compared cirrhosis risk following initiation of newer second-line GLDs vs. thiazolidinediones (TZDs), which improve histology in non-alcoholic fatty liver disease.
Materials and methods: Using the US Medicare Fee-for-Service database (2007–2015) and an active comparator, new-user design, we estimated crude incidence rates (IRs) and propensity-score adjusted hazard ratios (aHR) for incident cirrhosis, comparing newer GLDs (dipeptidyl peptidase-4 inhibitors (DPP4i), glucagon-like peptide-1 receptor agonists (GLP1RA), and sodium-glucose co-transporter 2 inhibitors (SGLT2i)) vs. TZDs.
Results: Among 239,549 total initiators, we observed 318, 151, and < 30 cirrhosis events when comparing DPP4i vs. TZD, GLP1RA vs. TZD, and SGLT2i vs. TZD, respectively. IRs ranged from 1.7 [95% CI, 0.8–3.6] to 3.6 [2.5–5.2] events per 1000 person-years. Point aHR estimates for cirrhosis were elevated among newer GLD initiators vs. TZD (DPP4i: 1.15 [0.89–1.50]; GLP1RA: 1.34 [0.82–2.20]; SGLT2i: 1.16, [0.44–3.08]), although estimates were imprecise due to short durations of drug exposure.
Conclusions: We observed mildly elevated cirrhosis risk with newer GLDs vs. TZD; however, uncertainty remains due to imprecise and statistically non-significant effect estimates.

1. Introduction

Cirrhosis signifies late-stage chronic liver disease (CLD) resulting from many causes, including hepatitis B/C infection, alcohol-related liver disease and non-alcoholic fatty liver disease (NAFLD). Mortality due to cirrhosis has been rising,[1] increasing by 72% between 1999 and 2017.[2] Type 2 diabetes (T2D) is a potent risk factor for progression of hepatic steatosis to advanced fibrosis in NAFLD,[3] and the presence of T2D also heightens risk of cirrhosis from other etiologies,[4] including hepatitis B,[5] hepatitis C,[6] and alcoholic liver disease.[7] Despite T2D being a recognized risk factor for progressive liver disease, little is known about how glucose-lowering drugs (GLDs) influence risk of all-cause cirrhosis.

Thiazolidinediones (TZD) are insulin sensitizers with favorable lipid effects, and are known to improve steatosis and fibrosis in non-alcoholic steatohepatitis.[8,9] Notably, reduction of hepatic fat by TZDs may also be beneficial in other forms of liver disease, such as with viral hepatitis.[10] Newer GLDs, including dipeptidyl peptidase-4 inhibitors (DPP4i), glucagon-like peptide-1 receptor agonists (GLP1RA) and sodium-glucose cotransporter-2 inhibitors (SGLT2i), have only been explored for their benefits in NAFLD.[11,12] Both GLP1RA and SGLT2i improve NAFLD by promoting weight loss; weight-independent effects may also exist.[12,13] DPP4i do not appear to have a substantial impact on NAFLD, though data are mixed.[12–16]

Since T2D likely mediates progression of all-cause liver disease by promoting steatohepatitis, and since GLDs have varying liver effects, it is plausible that GLDs differentially modify cirrhosis risk in patients with T2D and CLD, regardless of etiology. Currently, there is insufficient evidence to recommend one GLD over another to reduce risk of cirrhosis in T2D. We aimed to address this gap by estimating the comparative effect of multiple newer second-line GLDs (DPP4i, GLP1RA, SGLT2i) vs.

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TZD on risk of incident cirrhosis of any etiology in older adult patients with T2D.

2. Materials and methods

2.1. Data source

We conducted an active comparator, new-user (ACNU) retrospective cohort study,[17] using a nationwide 20% random sample of the US Medicare Fee-for-Service (FFS) database. The Medicare FFS database is representative of the US population aged ≥65, with information on Part A (inpatient services), Part B (outpatient services), and Part D (prescription drug) coverage, as well as enrollment and demographic information.

2.2. Study population

The base population consisted of all patients with ≥1 prescription dispensing claim for a SGLT2i, DPP4i, GLP1RA, or TZD between January 1, 2007 and September 30, 2015, identified using National Drug Codes (NDCs). We conducted three pairwise comparisons (Appendix Tables 1, 2) to estimate the comparative risk of cirrhosis with newer GLDs vs. TZD (DPP4i vs. TZD, GLP1RA vs. TZD, and SGLT2i vs. TZD). Pairwise comparisons involving SGLT2i were only conducted using data from 2013 to 2015, since SGLT2i were not in routine use in the US before 2013. We additionally compared the three newer GLDs (SGLT2i vs. GLP1RA, SGLT2i vs. DPP4i, and DPP4i vs. GLP1RA); however, we observed generally unstable estimates due to limited drug use data in these comparisons, and report these analyses in the Appendix.

Eligible patients were adults aged ≥65 years with ≥12 months of continuous enrollment in Parts A, B, and D prior to first eligible prescription dispensing claim. To ensure new use of the study drugs, we excluded patients who received a prescription for either drug in each pairwise comparison during the 12-month baseline period leading up to drug initiation (washout period). To remove patients with prevalent cirrhosis, we excluded individuals with the following conditions in the 12-month baseline period: 1) previous diagnosis of cirrhosis in either clinic or hospital setting (ICD-9-CM diagnoses 456.0; 456.1; 456.2; 456.21; 567.23; 571.2; 571.5; 572.2; 572.3; 572.4; 789.59, which achieves a sensitivity of 98–99% for exclusion)[18]; 2) previous diagnosis of hepatocellular carcinoma or cholangiocarcinoma; or 3) prior hepatectomy or liver transplantation (Appendix Figs. 1, 2).

The study was exempted from full Institutional Review Board review by the University of North Carolina at Chapel Hill. The study protocol was registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance, prior to estimating treatment effects on cirrhosis (EU PAS Register Number 31539).

2.3. Exposure

Exposure was defined as ≥2 same-drug class prescription dispensing claims of the study drugs in each pairwise comparison. To simulate ongoing use of the initial treatment, we permitted the second prescription to occur within 30 days (grace period) following the first prescription's days' supply, to allow for leeway between prescription fills. The second prescription served as the index date for the analysis. We excluded patients who received a prescription for the comparator drug between the first and second prescriptions of the index drug, and vice versa.

2.4. Outcome

The primary outcome of interest (Appendix Table 3) was the first diagnosis of cirrhosis, defined by any of the following ICD-9-CM diagnosis codes in the hospital setting: 456.1, 571.2, or 571.5 (cirrhosis definition 1).[18] Due to the lack of a standard, validated claims-based definition for cirrhosis, we also assessed the impact of alternative definitions of cirrhosis (Appendix Table 3), including a more sensitive definition that uses the same codes as our primary definition, but in either outpatient or hospital settings (cirrhosis definition 2).[18]

2.5. Follow-up

We conducted the primary analysis using an "as-treated" approach, where follow-up started at the index date (date of the 2nd prescription) and ended at the time an individual experienced either an outcome of interest or censoring event (Appendix Fig. 3). Patients were censored for treatment discontinuation, switch or augmentation; disenrollment from Medicare Parts A, B, or D; or at the administrative study end (September 30, 2015), whichever came first.

Patients were considered to have discontinued treatment if they received no new prescription of the cohort drug class within a (prescription days' supply + pre-defined 30-day grace period) time window after the last prescription of the cohort drug class; censoring occurred at the end of this window. Similarly, patients were considered to have switched or augmented treatment if they filled a prescription for a comparator drug within the same time window after the last prescription of the cohort drug class; censoring occurred at the fill date of the comparator drug class. Patients who switched between, or augmented with, drugs within the same class were not censored.

2.6. Confounding control

We controlled for measured confounding using propensity score weighting, with the following baseline covariates, measured in the 12 months prior to index date, included in the propensity score model: 1) patient demographics (age, sex, race, low income subsidy); 2) diabetes-related comorbidities (retinopathy, nephropathy, neuropathy); 3) liver-related diseases (viral hepatitis B and C, alcoholic liver disease, non-alcoholic fatty liver disease, drug-induced liver injury); 4) cardiovascular comorbidities (hypertension, dyslipidemia, coronary artery disease, cerebrovascular disease, peripheral vascular disease, congestive heart failure); 5) general health comorbidities (chronic kidney disease, chronic obstructive pulmonary disease, depression, alcoholism, obesity, smoking status; 6) diabetic medication use (metformin, sulfonylurea, long-acting insulin, and any TZD, DPP4i, GLP-1RA, SGLT2i not used to define cohorts); 7) other medication use (angiotensin-converting enzyme inhibitor, angiotensin receptor blockers, beta-blockers, calcium channel blockers, statins, aspirin, prescription omega-3 fatty acids, and various diuretics [loop, thiazide, aldosterone antagonists, and other]); and 8) measures of healthcare utilization (number of hemoglobin A1c tests, number of low-density lipoprotein (LDL) tests, hospitalizations, emergency department visits, physician encounters, gastroenterologist encounters, endocrinologist encounters).

2.7. Statistical analysis

We estimated propensity scores using multivariable logistic regression and applied them via standardized mortality ratio (SMR) weighting to estimate the average treatment effect in the treated, by reweighting the comparator drug initiators by the propensity score odds (PS/(1-PS))[19] within each pairwise comparison. This approach seeks to address the question: "what would the observed cirrhosis risk have been if all patients who initiated a newer GLD instead initiated a TZD?" Covariate balance before and after SMR weighting was evaluated using the standardized mean difference (SMD). Asymmetric 1% propensity score trimming was used to remove some patients treated contrary to prediction to reduce the potential for unmeasured confounding.[20]

To compare incidence of cirrhosis, we estimated crude incidence rates (IR) and 95% confidence intervals (CIs) using Poisson regression, as well as crude and adjusted hazard ratios (aHRs) using SMR-

weighted Cox proportional hazards models. Finally, we generated cumulative incidence curves for cirrhosis using weighted Kaplan-Meier methods.

2.8. Sensitivity and subgroup analysis

We conducted a number of sensitivity and subgroup analyses to assess the impact of various study specifications and definitions. First, we used an initial treatment (IT) approach, ignoring censoring for treatment changes during follow-up (similar to intention-to-treat analyses in randomized clinical trials). Second, we applied 30-, 60-, 90-, 180-, and 270-day induction and latency periods to account for possible diagnostic delay of cirrhosis, where follow-up started e.g., 90 days after index date, and continued for outcomes 90 days after censoring for treatment discontinuation, switch, or augmentation. Third, we re-estimated HRs modeling death as a competing event in the Cox proportional hazards model, using the Aalen-Johansen estimator. To assess the robustness of the SMR weighting approach, we repeated the analysis using a multivariable Cox proportional hazard model. Finally, to assess whether the estimated HRs varied over calendar time, we restricted all analyses to the same 2013–2015 calendar period.

We also repeated the primary analysis within pre-defined, clinically-relevant patient subgroups: 1) patients with/without metformin use during the baseline period; 2) patients with/without baseline liver disease; 3) patients aged 66–75, >75; and 4) men vs. women. In post-hoc analyses, we additionally assessed effect measure modification among 1) patients with/without baseline insulin use; 2) patients with baseline claims for obesity; and 3) patients with self-identified white vs. non-white race.

3. Results

3.1. Study population

We identified 239,549 patients with initiation of any of the study drugs during the study window. Of those, 103,491 patients were included in the DPP4i (n = 69,027) vs. TZD (n = 34,464) comparison, 52,473 in the GLP1RA (n = 10,728) vs. TZD (n = 41,745) comparison, and 18,829 in the SGLT2i (n = 7849) vs. TZD (n = 10,980) comparison (Appendix Fig. 1, Table 1).

Initiators of TZDs exhibited higher proportions of male and non-white patients compared to initiators of the three newer second-line GLDs. Comorbidities were generally more prevalent among initiators of newer GLDs; we observed the largest crude differences between baseline covariate distributions in the SGLT2i vs. TZD comparison (Appendix Figs. 4, 5), relative to other comparisons. Prevalence of codes for baseline obesity, as well as the proportion of patients with DPP4i and insulin use during the baseline period, were notably elevated in GLP1RA and SGLT2i users. TZD initiators, on the other hand, had higher prevalence of renal disease compared to SGLT2i initiators, and generally more prior sulfonylurea and ACEI use. Covariate balance was improved by SMR weighting (Appendix Fig. 5).

3.2. Incidence of cirrhosis

In primary as-treated analysis, we observed 318, 151, and <30 cirrhosis events when comparing DPP4i vs. TZD, GLP1RA vs. TZD, and SGLT2i vs. TZD, respectively. Crude incidence rates of cirrhosis ranged from 1.7 [95% CI, 0.8–3.6] events per 1000 person-years in the SGLT2i cohort, to 3.6 [2.5–5.2] events per 1000 person-years in the GLP1RA cohort, and were generally higher among patients treated with DPP4i and GLP1RA, vs. TZD (Table 2). After weighting, we observed elevated aHR point estimates for all three newer second-line GLDs (Table 2). Compared to TZD initiators, the estimated hazard for cirrhosis was most elevated for GLP1RA initiators (aHR 1.34, 95% CI 0.82–2.20), followed by SGLT2i initiators (aHR 1.16, 95% CI 0.44–3.08) and DPP4i initiators (aHR 1.15, 95% CI 0.89–1.50). The elevated aHR estimates in the GLP1RA comparison were supported by separation of the cumulative incidence curves (Fig. 1), although curves crossed after 420 days of follow-up, likely due to low numbers of patients at-risk in the GLP1RA group. Alternative cirrhosis definitions yielded further-increased aHR estimates among newer GLD users for all TZD comparisons (Table 3, Fig. 1).

3.3. Subgroup and sensitivity analyses

Results remained generally consistent across a number of sensitivity analyses (Fig. 2). In all TZD comparisons, aHR estimates were elevated among patients who were younger (age ≤75), female, and who had a history of liver disease. Hazards also appeared to be increased among patients who self-identified as non-white in the GLP1RA and SGLT2i comparisons, while the reverse was observed in the DPP4i comparison. Subgroup aHR estimates were generally imprecise in all comparisons involving SGLT2i due to few observed events.

4. Discussion

This is the first study examining the comparative effect of second-line glucose-lowering drugs (GLDs) on risk of incident cirrhosis in patients with T2D. In general, point estimates suggested a possible trend towards lowest cirrhosis risk with TZD compared to newer second-line GLDs, which was largely consistent across a number of sensitivity analyses. However, short exposure durations to the study drugs yielded wide 95% CIs and limited our ability to draw strong conclusions from these data.

We chose to compare newer GLDs to TZD since less is known about the liver effects of these newer agents, whereas TZD have well-established benefits in NAFLD; including resolution of non-alcoholic steatohepatitis and improvement in fibrosis.[8,21,22] GLP1RA and SGLT2i are associated with weight loss and preliminary evidence also suggests benefit in NAFLD,[23–26] so we included these agents as comparisons. Additionally, we examined DPP4i since they are the most commonly prescribed branded second-line GLD,[27] and there is conflicting evidence regarding their impact on NAFLD.[13–16] Despite sulfonylureas being the most commonly prescribed second-line agent in T2D,[27] they are substantially cheaper than newer agents, so were excluded given potential for socioeconomic confounding.

4.1. Impact of glucose-lowering drugs on cirrhosis appears to mirror NAFLD literature

Our findings on the impact of GLDs and cirrhosis risk follow similar patterns to those seen in NAFLD. For instance, TZD have the strongest evidence for benefit in NAFLD, and we likewise observed HR estimates consistently above 1 for newer GLD vs. TZD comparisons in as-treated, propensity score-weighted analyses. Both GLP1RA and SGLT2i have been shown to improve liver enzymes and reduce hepatic steatosis in patients with T2D and NAFLD.[23,25,26,28] Few randomized controlled trials (RCTs) have compared these agents to TZD, and they position GLP1RA and SGLT2i as either similar or better than TZD at improving liver enzymes and histology.[29–32] In our study, we observed slightly higher estimated hazards of incident cirrhosis among both GLP1RA and SGLT2i initiators compared to TZD initiators, although aHR estimates were reduced in the GLP1RA analysis when including outpatient and expanded cirrhosis diagnosis codes. Precision was also limited for our SGLT2i comparisons, with fewer years of SGLT2i data (2013–2015) likely contributing to this uncertainty.

DPP4i use was associated with higher estimated hazard of incident cirrhosis compared to TZD, particularly when using cirrhosis definitions with greater sensitivity (i.e., definitions 2 and 4). This trend may reflect DPP4i's more neutral effect observed in NAFLD.[12] Interestingly, serum dipeptidyl peptidase 4 (DPP4) levels are elevated in NASH, and are positively associated with histopathological grade and fibrosis.[33,34] A recent

Table 1
Baseline characteristics of eligible initiators of DPP4i vs. TZD, GLP1RA vs. TZD, and SGLT2i vs. TZD, before and after implementation of standardized mortality ratio (SMR) Weighting[a] (365-day washout period, 1% asymmetric propensity score trimming).

Characteristic[b]	DPP4i vs. TZD			GLP1RA vs. TZD			SGLT2i vs. TZD		
	DPP4i initiators (n = 69,027)	TZD initiators (n = 34,464)	Weighted TZD initiators (n = 68,979)	GLP1RA initiators (n = 10,728)	TZD initiators (n = 41,745)	Weighted TZD initiators (n = 10,689)	SGLT2i initiators (n = 7849)	TZD initiators (n = 10,980)	Weighted TZD initiators (n = 7984)
Age, mean (std. dev.)	74.1 (7.1)	72.9 (6.9)	74.0 (7.1)	70.7 (5.3)	73.1 (6.9)	70.6 (5.3)	71.6 (5.6)	73.0 (6.8)	71.6 (5.6)
Male	28,015 (40.6)	15,281 (44.3)	27,907 (40.5)	4349 (40.5)	18,512 (44.3)	4263 (39.9)	3840 (48.9)	5371 (48.9)	3887 (48.7)
Race									
White	52,040 (75.4)	25,123 (72.9)	52,178 (75.6)	9074 (84.6)	30,056 (72.0)	9059 (84.7)	6446 (82.1)	8263 (75.3)	6622 (82.9)
Black	7499 (10.9)	4035 (11.7)	7315 (10.6)	873 (8.1)	4765 (11.4)	883 (8.3)	565 (7.2)	1056 (9.6)	553 (6.9)
Other	9488 (13.7)	5306 (15.4)	9486 (13.8)	781 (7.3)	6924 (16.6)	748 (7.0)	838 (10.7)	1661 (15.1)	809 (10.1)
Diabetes comorbidities[b]									
Nephropathy	5769 (8.4)	2353 (6.8)	5791 (8.4)	1182 (11.0)	3115 (7.5)	1176 (11.0)	634 (8.1)	1178 (10.7)	661 (8.3)
Neuropathy	13,480 (19.5)	5465 (15.9)	13,640 (19.8)	2666 (24.9)	7096 (17.0)	2685 (25.1)	1959 (25.0)	2169 (19.8)	2043 (25.6)
Retinopathy	10,414 (15.1)	4893 (14.2)	10,392 (15.1)	1925 (17.9)	6248 (15.0)	1913 (17.9)	1438 (18.3)	1609 (14.7)	1430 (17.9)
Peripheral vascular disease	9521 (13.8)	3977 (11.5)	9508 (13.8)	1208 (11.3)	5000 (12.0)	1231 (11.5)	920 (11.7)	1213 (11.0)	964 (12.1)
General health comorbidities[b]									
Alcoholic liver disease	31 (0.0)	16 (0.0)	30 (0.0)	NTSR[c]	17 (0.0)	NTSR	NTSR	NTSR	NTSR
Alcohol abuse	320 (0.5)	179 (0.5)	314 (0.5)	29 (0.3)	212 (0.5)	27 (0.3)	19 (0.2)	20 (0.2)	23 (0.3)
AMI	3283 (4.8)	1176 (3.4)	3247 (4.7)	465 (4.3)	1446 (3.5)	457 (4.3)	320 (4.1)	389 (3.5)	290 (3.6)
Cerebrovascular disease	13,204 (19.1)	5518 (16.0)	13,124 (19.0)	1564 (14.6)	6842 (16.4)	1596 (14.9)	1233 (15.7)	1563 (14.2)	1287 (16.1)
CHF (exclusion)	–	–	–	–	–	–	–	–	–
CKD	12,073 (17.5)	4743 (13.8)	12,080 (17.5)	1888 (17.6)	6173 (14.8)	1894 (17.7)	939 (12.0)	2208 (20.1)	975 (12.2)
Coagulopathy	2377 (3.4)	935 (2.7)	2417 (3.5)	287 (2.7)	1167 (2.8)	287 (2.7)	213 (2.7)	278 (2.5)	204 (2.6)
COPD	15,371 (22.3)	6704 (19.5)	15,265 (22.1)	2431 (22.7)	8182 (19.6)	2387 (22.3)	1585 (20.2)	2064 (18.8)	1678 (21.0)
Decompensation	3532 (5.1)	1182 (3.4)	3525 (5.1)	391 (3.6)	1505 (3.6)	378 (3.5)	195 (2.5)	446 (4.1)	199 (2.5)
Depression	10,174 (14.7)	4163 (12.1)	10,116 (14.7)	1717 (16.0)	5087 (12.2)	1685 (15.8)	1088 (13.9)	1388 (12.6)	1132 (14.2)
Diabetes	66,541 (96.4)	31,795 (92.3)	66,456 (96.3)	10,289 (95.9)	38,887 (93.2)	10,252 (95.9)	7750 (98.7)	10,290 (93.7)	7885 (98.8)
Drug induced liver	513 (0.7)	281 (0.8)	537 (0.8)	66 (0.6)	371 (0.9)	67 (0.6)	44 (0.6)	53 (0.5)	50 (0.6)
Dyslipidemia	57,787 (83.7)	26,207 (76.0)	57,698 (83.6)	9130 (85.1)	32,418 (77.7)	9069 (84.8)	7053 (89.9)	8936 (81.4)	7186 (90.0)
HIV	125 (0.2)	72 (0.2)	133 (0.2)	13 (0.1)	93 (0.2)	15 (0.1)	NTSR	19 (0.2)	NTSR
Ischemic heart disease	22,087 (32.0)	9052 (26.3)	21,991 (31.9)	3295 (30.7)	11,359 (27.2)	3324 (31.1)	2409 (30.7)	2827 (25.7)	2451 (30.7)
Liver disease	155 (0.2)	65 (0.2)	153 (0.2)	13 (0.1)	90 (0.2)	13 (0.1)	23 (0.3)	19 (0.2)	17 (0.2)
Non-alcoholic liver disease	1840 (2.7)	680 (2.0)	1874 (2.7)	400 (3.7)	885 (2.1)	416 (3.9)	332 (4.2)	323 (2.9)	356 (4.5)
Obesity	9142 (13.2)	3344 (9.7)	9097 (13.2)	2900 (27.0)	4119 (9.9)	2860 (26.8)	1916 (24.4)	1599 (14.6)	1965 (24.6)
Peptic ulcer disease	1358 (2.0)	639 (1.9)	1368 (2.0)	136 (1.3)	799 (1.9)	135 (1.3)	91 (1.2)	176 (1.6)	85 (1.1)
Renal disease	13,316 (19.3)	5325 (15.5)	13,311 (19.3)	2099 (19.6)	6917 (16.6)	2104 (19.7)	1068 (13.6)	2383 (21.7)	1098 (13.7)
Smoking	6542 (9.5)	2410 (7.0)	6534 (9.5)	1085 (10.1)	2979 (7.1)	1074 (10.0)	887 (11.3)	1181 (10.8)	952 (11.9)
Viral hepatitis	504 (0.7)	218 (0.6)	528 (0.8)	52 (0.5)	281 (0.7)	47 (0.4)	36 (0.5)	58 (0.5)	34 (0.4)
History of cancer	11,034 (16.0)	4599 (13.3)	11,068 (16.0)	1564 (14.6)	5699 (13.7)	1559 (14.6)	1240 (15.8)	1576 (14.4)	1279 (16.0)
Peritoneal dialysis	33 (0.0)	27 (0.1)	36 (0.1)	NTSR	32 (0.1)	NTSR	NTSR	NTSR	NTSR
Prior medication use[b]									
ACEI	32,481 (47.1)	17,161 (49.8)	32,399 (47.0)	4995 (46.6)	20,722 (49.6)	5004 (46.8)	3534 (45.0)	5175 (47.1)	3657 (45.8)
ARB	21,700 (31.4)	8771 (25.4)	21,739 (31.5)	3637 (33.9)	11,293 (27.1)	3587 (33.6)	2962 (37.7)	3267 (29.8)	3021 (37.8)
Aspirin	2570 (3.7)	1236 (3.6)	2570 (3.7)	568 (5.3)	1485 (3.6)	559 (5.2)	378 (4.8)	361 (3.3)	391 (4.9)
Beta blockers	34,125 (49.4)	14,687 (42.6)	34,161 (49.5)	5116 (47.7)	18,203 (43.6)	5086 (47.6)	3817 (48.6)	5020 (45.7)	3920 (49.1)
Calcium channel blockers	25,268 (36.6)	11,387 (33.0)	25,178 (36.5)	3587 (33.4)	14,127 (33.8)	3535 (33.1)	2629 (33.5)	3834 (34.9)	2713 (34.0)
Lactulose	896 (1.3)	376 (1.1)	882 (1.3)	90 (0.8)	477 (1.1)	89 (0.8)	50 (0.6)	102 (0.9)	62 (0.8)
Omega-3	2068 (3.0)	712 (2.1)	2135 (3.1)	389 (3.6)	1038 (2.5)	389 (3.6)	341 (4.3)	318 (2.9)	358 (4.5)
Rifaximin	58 (0.1)	19 (0.1)	60 (0.1)	11 (0.1)	25 (0.1)	NTSR	NTSR	NTSR	NTSR
Statins	49,068 (71.1)	22,641 (65.7)	48,928 (70.9)	7841 (73.1)	28,040 (67.2)	7720 (72.2)	5980 (76.2)	8011 (73.0)	6061 (75.9)
Loop diuretics	11,631 (16.8)	4933 (14.3)	11,642 (16.9)	2196 (20.5)	5926 (14.2)	2172 (20.3)	1095 (14.0)	1403 (12.8)	1069 (13.4)
Other diuretics	16,826 (24.4)	8056 (23.4)	16,910 (24.5)	2766 (25.8)	9954 (23.8)	2808 (26.3)	1944 (24.8)	2544 (23.2)	2031 (25.4)
Thiazide diuretics	10,457 (15.1)	5183 (15.0)	10,334 (15.0)	1671 (15.6)	6157 (14.7)	1634 (15.3)	1116 (14.2)	1562 (14.2)	1140 (14.3)
Aldosterone antagonists	1529 (2.2)	593 (1.7)	1491 (2.2)	349 (3.3)	712 (1.7)	332 (3.1)	197 (2.5)	235 (2.1)	225 (2.8)
Metformin	49,045 (71.1)	22,373 (64.9)	49,086 (71.2)	7144 (66.6)	27,765 (66.5)	7127 (66.7)	6051 (77.1)	7409 (67.5)	6182 (77.4)
Sulfonylureas	35,193 (51.0)	18,047 (52.4)	35,504 (51.5)	5094 (47.5)	22,742 (54.5)	5128 (48.0)	4008 (51.1)	5910 (53.8)	4102 (51.4)
Thiazolidinediones	–	–	–	–	–	–	–	–	–
DPP4i	–	–	–	3254 (30.3)	7456 (17.9)	3430 (32.1)	3369 (42.9)	3331 (30.3)	3592 (45.0)
GLP1RA	1469 (2.1)	815 (2.4)	1596 (2.3)	–	–	–	1198 (15.3)	501 (4.6)	1317 (16.5)
SGLT2i	331 (0.5)	100 (0.3)	351 (0.5)	247 (2.3)	174 (0.4)	239 (2.2)	–	–	–
Long-acting insulin	10,803 (15.7)	5058 (14.7)	10,852 (15.7)	3919 (36.5)	5896 (14.1)	3902 (36.5)	2458 (31.3)	1754 (16.0)	2629 (32.9)
Measures of healthcare utilization in year prior to index date[b]									
Low-income subsidy (LIS) status									
0 – no subsidy	38,026 (55.1)	17,261 (50.1)	38,242 (55.4)	7000 (65.2)	20,815 (49.9)	6735 (63.0)	5656 (72.1)	6889 (62.7)	5719 (71.6)
1–100 premium subsidy	27,451 (39.8)	15,013 (43.6)	27,120 (39.3)	3172 (29.6)	18,398 (44.1)	3575 (33.4)	1914 (24.4)	3626 (33.0)	2034 (25.5)
2 – partial (25–75) premium subsidy	3550 (5.1)	2190 (6.4)	3617 (5.2)	556 (5.2)	2532 (6.1)	380 (3.6)	279 (3.6)	465 (4.2)	232 (2.9)
Number of HbA1c tests in the past year									
0	7352 (10.7)	6513 (18.9)	7658 (11.1)	1102 (10.3)	7250 (17.4)	1153 (10.8)	353 (4.5)	1507 (13.7)	410 (5.1)
1	11,907 (17.2)	6649 (19.3)	11,533 (16.7)	1474 (13.7)	7574 (18.1)	1426 (13.3)	900 (11.5)	1684 (15.3)	826 (10.3)
2	16,796 (24.3)	7635 (22.2)	16,000 (23.2)	2282 (21.3)	9236 (22.1)	2236 (20.9)	1825 (23.3)	2442 (22.2)	1700 (21.3)
≥3	32,972 (47.8)	13,667 (39.7)	33,788 (49.0)	5870 (54.7)	17,685 (42.4)	5874 (55.0)	4771 (60.8)	5347 (48.7)	5048 (63.2)
Number of LDL tests in the past year									
0	11,682 (16.9)	8413 (24.4)	12,065 (17.5)	1758 (16.4)	9506 (22.8)	1798 (16.8)	801 (10.2)	2119 (19.3)	849 (10.6)
1	19,513 (28.3)	9703 (28.2)	19,084 (27.7)	2901 (27.0)	11,506 (27.6)	2802 (26.2)	2114 (26.9)	3124 (28.5)	2086 (26.1)

Table 1 (*continued*)

Characteristic[b]	DPP4i vs. TZD			GLP1RA vs. TZD			SGLT2i vs. TZD		
	DPP4i initiators (n = 69,027)	TZD initiators (n = 34,464)	Weighted TZD initiators (n = 68,979)	GLP1RA initiators (n = 10,728)	TZD initiators (n = 41,745)	Weighted TZD initiators (n = 10,689)	SGLT2i initiators (n = 7849)	TZD initiators (n = 10,980)	Weighted TZD initiators (n = 7984)
2	18,132 (26.3)	7979 (23.2)	17,383 (25.2)	2715 (25.3)	9937 (23.8)	2699 (25.3)	2173 (27.7)	2745 (25.0)	2110 (26.4)
≥3	19,700 (28.5)	8369 (24.3)	20,447 (29.6)	3354 (31.3)	10,796 (25.9)	3391 (31.7)	2761 (35.2)	2992 (27.2)	2938 (36.8)
Flu shot received in past year	37,731 (54.7)	16,254 (47.2)	37,780 (54.8)	6089 (56.8)	20,200 (48.4)	6013 (56.3)	4883 (62.2)	5907 (53.8)	4968 (62.2)
Number of hospitalizations in the past year									
0	56,180 (81.4)	28,873 (83.8)	56,191 (81.5)	9311 (86.8)	34,944 (83.7)	9228 (86.3)	7073 (90.1)	9536 (86.8)	7161 (89.7)
1	7204 (10.4)	3313 (9.6)	7266 (10.5)	939 (8.8)	4009 (9.6)	970 (9.1)	553 (7.0)	904 (8.2)	598 (7.5)
2	3321 (4.8)	1333 (3.9)	3184 (4.6)	319 (3.0)	1627 (3.9)	303 (2.8)	168 (2.1)	341 (3.1)	141 (1.8)
≥3	2322 (3.4)	945 (2.7)	2337 (3.4)	159 (1.5)	1165 (2.8)	188 (1.8)	55 (0.7)	199 (1.8)	84 (1.0)
Number of days spent in the hospital in the past year									
0	56,180 (81.4)	28,873 (83.8)	56,191 (81.5)	9311 (86.8)	34,944 (83.7)	9228 (86.3)	7073 (90.1)	9536 (86.8)	7161 (89.7)
1–2	3133 (4.5)	1490 (4.3)	3145 (4.6)	452 (4.2)	1825 (4.4)	473 (4.4)	275 (3.5)	414 (3.8)	302 (3.8)
3–5	3289 (4.8)	1435 (4.2)	3305 (4.8)	433 (4.0)	1739 (4.2)	430 (4.0)	244 (3.1)	429 (3.9)	244 (3.1)
5–10	1732 (2.5)	780 (2.3)	1705 (2.5)	168 (1.6)	916 (2.2)	173 (1.6)	101 (1.3)	156 (1.4)	105 (1.3)
>10	4693 (6.8)	1886 (5.5)	4632 (6.7)	364 (3.4)	2321 (5.6)	385 (3.6)	156 (2.0)	445 (4.1)	172 (2.2)
Number of emergency department visits in the past year									
0	48,019 (69.6)	25,361 (73.6)	47,994 (69.6)	8080 (75.3)	30,621 (73.4)	8013 (75.0)	6028 (76.8)	8211 (74.8)	6099 (76.4)
1	13,052 (18.9)	5816 (16.9)	13,114 (19.0)	1769 (16.5)	7090 (17.0)	1807 (16.9)	1247 (15.9)	1833 (16.7)	1255 (15.7)
≥2	7956 (11.5)	3287 (9.5)	7871 (11.4)	879 (8.2)	4034 (9.7)	870 (8.1)	574 (7.3)	936 (8.5)	630 (7.9)
Number of physician encounters in the past year									
0	2055 (3.0)	2317 (6.7)	2054 (3.0)	391 (3.6)	2547 (6.1)	406 (3.8)	76 (1.0)	580 (5.3)	76 (1.0)
1–3	4183 (6.1)	3641 (10.6)	4177 (6.1)	689 (6.4)	4030 (9.7)	704 (6.6)	298 (3.8)	994 (9.1)	293 (3.7)
4–6	5713 (8.3)	3454 (10.0)	5728 (8.3)	757 (7.1)	4030 (9.7)	755 (7.1)	592 (7.5)	1045 (9.5)	575 (7.2)
≥7	57,076 (82.7)	25,052 (72.7)	57,021 (82.7)	8891 (82.9)	31,138 (74.6)	8824 (82.6)	6883 (87.7)	8361 (76.1)	7040 (88.2)
Number of gastroenterologist visits in the past year									
0	59,121 (85.6)	30,507 (88.5)	59,234 (85.9)	9140 (85.2)	36,733 (88.0)	9166 (85.7)	6673 (85.0)	9679 (88.2)	6763 (84.7)
1	4077 (5.9)	1653 (4.8)	3862 (5.6)	689 (6.4)	2074 (5.0)	653 (6.1)	528 (6.7)	588 (5.4)	549 (6.9)
2	2813 (4.1)	1094 (3.2)	2686 (3.9)	491 (4.6)	1393 (3.3)	416 (3.9)	336 (4.3)	359 (3.3)	351 (4.4)
≥3	3016 (4.4)	1210 (3.5)	3197 (4.6)	408 (3.8)	1545 (3.7)	455 (4.3)	312 (4.0)	354 (3.2)	322 (4.0)
Number of endocrinologist visits in the past year									
0	60,351 (87.4)	32,025 (92.9)	60,986 (88.4)	8029 (74.8)	38,296 (91.7)	8233 (77.0)	6078 (77.4)	9750 (88.8)	6145 (77.0)
1	2947 (4.3)	818 (2.4)	2080 (3.0)	819 (7.6)	1114 (2.7)	502 (4.7)	372 (4.7)	357 (3.3)	382 (4.8)
2	1944 (2.8)	504 (1.5)	1619 (2.3)	504 (4.7)	706 (1.7)	455 (4.3)	323 (4.1)	242 (2.2)	301 (3.8)
≥3	3785 (5.5)	1117 (3.2)	4293 (6.2)	1376 (12.8)	1629 (3.9)	1499 (14.0)	1076 (13.7)	631 (5.7)	1156 (14.5)
Year of initiation									
2008	4123 (6.0)	7099 (20.6)	14,059 (20.4)	427 (4.0)	7696 (18.4)	1594 (14.9)	–	–	–
2009	5085 (7.4)	7892 (22.9)	15,362 (22.3)	466 (4.3)	8874 (21.3)	1852 (17.3)	–	–	–
2010	6187 (9.0)	6298 (18.3)	12,420 (18.0)	578 (5.4)	7373 (17.7)	1715 (16.0)	–	–	–
2011	9232 (13.4)	3829 (11.1)	7319 (10.6)	934 (8.7)	4765 (11.4)	1129 (10.6)	–	–	–
2012	10,825 (15.7)	2101 (6.1)	4025 (5.8)	1484 (13.8)	2740 (6.6)	721 (6.7)	0 (0)	281 (2.6)	189 (2.4)
2013	11,457 (16.6)	2345 (6.8)	4881 (7.1)	2148 (20.0)	3247 (7.8)	1026 (9.6)	550 (7.0)	3408 (31.0)	2359 (29.5)
2014	12,749 (18.5)	2794 (8.1)	6202 (9.0)	2473 (23.1)	4085 (9.8)	1467 (13.7)	3279 (41.8)	4257 (38.8)	3193 (40.0)
2015	9369 (13.6)	2106 (6.1)	4711 (6.8)	2218 (20.7)	2965 (7.1)	1185 (11.1)	4020 (51.2)	3034 (27.6)	2242 (28.1)

Abbreviations: SGLT2i, sodium-glucose cotransporter-2 inhibitors; DPP4i, dipeptidyl peptidase-4 inhibitors; GLP1RA, glucagon-like peptide-1 receptor agonist; TZD, thiazolidinediones; AMI, acute myocardial infarction; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blockers; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; NTSR, number too small to report[c].

[a] Weighted by standardizing the comparator drug initiators to the population of index treatment initiators, using the propensity score odds (PS/(1-PS)), to estimate the treatment effect in the treated (ATT).

[b] All baseline characteristics measured in the one year (365 days) prior to date of cohort drug initiation.

[c] Number too small to report (<11), per Medicare Data Use Agreement.

randomized study by Yan et al comparing the efficacy of liraglutide, sitagliptin or insulin glargine (on background metformin) for NAFLD found that add-on liraglutide and sitagliptin led to comparable reductions in liver fat, whereas insulin glargine did not.[35] However, a dedicated RCT by Cui et al examining the effects of sitagliptin (vs placebo) on NAFLD in patients with T2D did not demonstrate improvement in hepatic fat content.[14]

4.2. Gender and other subgroup differences

In subgroup analyses, we observed higher estimated aHRs for cirrhosis among women, in particular for the DPP4i vs. TZD comparison (Fig. 2, primary definition, women, aHR 1.50 [95% CI 1.04, 2.16]; men; 0.86 [95% CI 0.59–1.25]). We observed similar trends for GLP1RA and SGLT2i, vs. TZD, though estimates were more imprecise in these comparisons. The reasons for this gender difference are unclear, although data on NAFLD suggest an important role of sex hormones, as men are at higher risk during reproductive years, while women are at higher risk after menopause.[36] It is therefore feasible that the metabolically distinct livers of men and women interact differently with medications, including GLDs. Some studies have reported TZD to be more effective in women than in men, though data are mixed.[37,38] Evidence does not suggest meaningful differences in efficacy of GLP1RA and SGLT2i by gender,[37–39] though women are more likely to experience side effects of these medications (e.g., nausea and vomiting associated with GLP1RA).[37,38] It is plausible that more frequent examinations and testing in response to medication-related symptoms could lead to earlier discovery of cirrhosis (e.g., via abdominal imaging or endoscopy) in women compared to men. It is notable that sex differences also exist in other forms of CLD[40] – how this is influenced by GLDs is largely unknown, and an interesting area for future research.

We additionally observed a higher estimated hazard of cirrhosis among initiators of GLP1RA vs. TZDs (aHR 1.82 [95% CI 1.09, 3.06]) in patients *not* on baseline insulin, whereas this was not the case for those on

Table 2
Crude and adjusted hazard ratio (HR) estimates for incident liver cirrhosis with second-line glucose-lowering drug initiation (365-day washout period, As-treated analysis, 1% asymmetric propensity score trimming).

Comparison	Cohort	Number of patients	Median (IQR) follow-up time, years[a]	Total person-years	Number of events[b]	Crude incidence rate, per 1000 person-years	Crude HR (95% CI)	PS-weighted HR (95% CI)
DPP4i vs. TZD								
AT Analysis	DPP4i	69,027	0.66 (0.33–1.51)	78,778	220	2.8 (2.4–3.2)	1.09 (0.86–1.39)	1.15 (0.89–1.50)
	TZD	34,464	0.64 (0.33–1.45)	38,393	98	2.6 (2.1–3.1)		
IT Analysis	DPP4i	69,027	2.08 (0.91–3.00)	131,309	392	3.0 (2.7–3.3)	1.03 (0.88–1.21)	1.06 (0.89–1.26)
	TZD	34,464	3.00 (1.52–3.00)	79,036	232	2.9 (2.6–3.3)		
GLP1RA vs. TZD								
AT Analysis	GLP1RA	10,728	0.45 (0.25–0.96)	8264	30	3.6 (2.5–5.2)	1.41 (0.95–2.11)	1.34 (0.82–2.20)
	TZD	41,745	0.64 (0.33–1.42)	45,741	121	2.6 (2.2–3.2)		
IT Analysis	GLP1RA	10,728	1.66 (0.67–3.00)	18,355	57	3.1 (2.4–4.0)	1.06 (0.80–1.41)	0.95 (0.67–1.34)
	TZD	41,745	3.00 (1.40–3.00)	93,420	281	3.0 (2.7–3.4)		
SGLT2i vs. TZD								
AT Analysis	SGLT2i	7849	0.40 (0.21–0.70)	NTSR[b]	NTSR	1.7 (0.8–3.6)	0.91 (0.38–2.21)	1.16 (0.44–3.08)
	TZD	10,980	0.58 (0.30–1.11)	8507	17	2.0 (1.2–3.2)		
IT Analysis	SGLT2i	7849	0.60 (0.31–1.03)	NTSR	NTSR	1.6 (0.8–3.1)	0.62 (0.30–1.29)	0.80 (0.38–1.67)
	TZD	10,980	1.10 (0.51–1.75)	12,953	35	2.7 (1.9–3.8)		

Abbreviations: SGLT2i, sodium-glucose cotransporter-2 inhibitors; DPP4i, dipeptidyl peptidase-4 inhibitors; GLP1RA, glucagon-like peptide-1 receptor agonists; TZD, thiazolidinediones; IQR, interquartile range; PS, propensity score; AT, as-treated; IT, initial treatment (similar to intention-to-treat approach in randomized controlled trials); NTSR, number too small to report[b].
[a] Follow-up in IT analyses were capped at 3 years following index date.
[b] Number too small to report (<11), per Medicare Data Use Agreement.

insulin. One potential explanation is that GLP1RA are often initiated in patients whose glycemic control has worsened such that they necessitate insulin, but who decline or prefer to delay recommended insulin therapy. Also, patients prescribed GLP1RA in the absence of insulin may have worse obesity. In both cases, poor metabolic health in this subgroup may contribute to more rapid progression of liver disease. Conversely, patients with baseline insulin use, which is a surrogate measure of increased diabetes duration or severity, may have experienced higher baseline cirrhosis risk in both drug groups, which may have contributed to the attenuated aHR estimates in that subgroup. We did not observe these trends in the SGLT2i vs. TZD comparison, although estimates in that analysis were generally difficult to interpret due to low precision.

4.3. Implication of findings

Our findings suggest a possible trend towards greater benefit of TZD over newer GLDs in terms of cirrhosis risk. Since we included an older population of patients with T2D, it is likely that NAFLD accounted for a large proportion of CLD in this study. Thus, while our results reflect the impact of GLDs on all-cause cirrhosis, this may be largely driven by known effects in NAFLD, rather than impact on other forms of CLD (i.e. viral, alcoholic). One small study examining hepatic steatosis by magnetic resonance spectroscopy found that pioglitazone was able to reduce hepatic steatosis in individuals with human immunodeficiency virus and hepatitis C coinfection.[10] However, data examining use of pioglitazone and other GLDs in non-NAFLD CLD are limited, and further

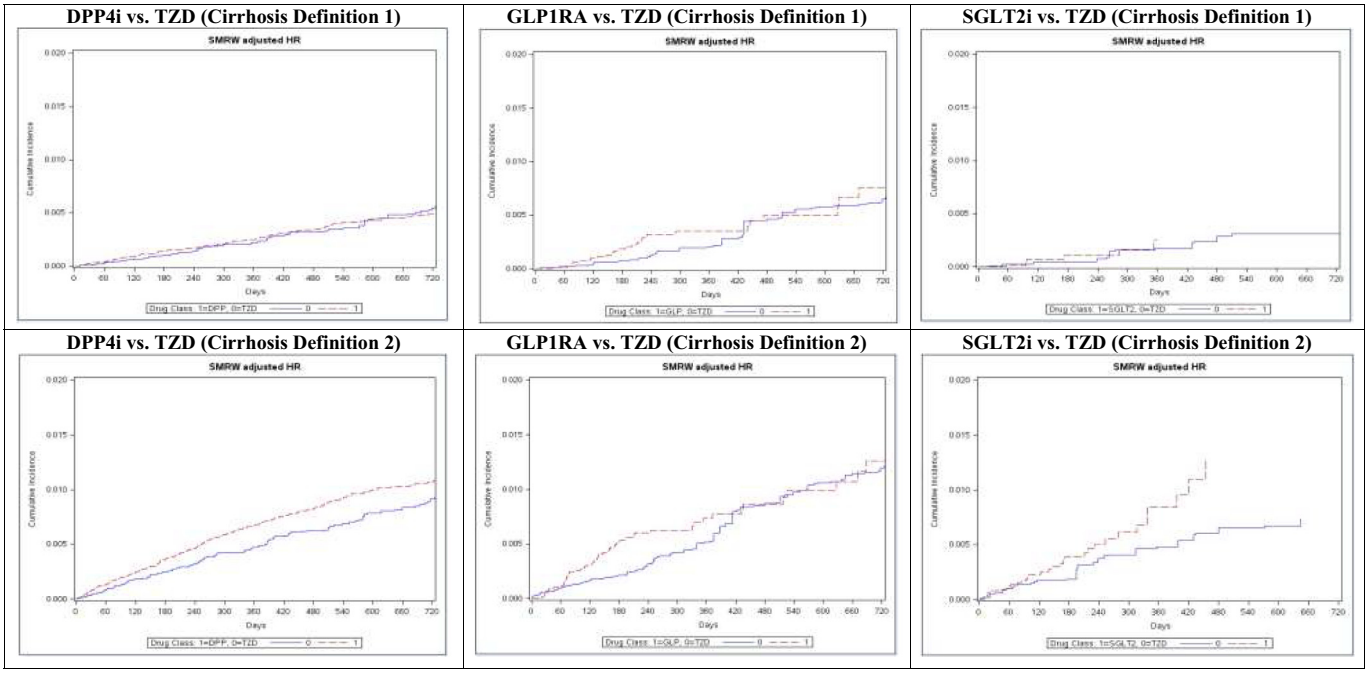

Fig. 1. SMR-weighted[a] cumulative incidence (Kaplan-Meier) curves for incident liver cirrhosis following second-line glucose-lowering drug initiation (365-day washout period, as-treated analysis, 1% asymmetric propensity score trimming). Abbreviations: SMR, standardized mortality ratio; SGLT2i, sodium-glucose cotransporter-2 inhibitors; DPP4i, dipeptidyl peptidase-4 inhibitors; GLP1RA, glucagon-like peptide-1 receptor agonists; TZD, thiazolidinediones; HR, hazard ratio. [a]Weighted by standardizing the comparator drug initiators to the population of index drug initiators, using the propensity score odds (PS/(1-PS)), to estimate the treatment effect in the treated (ATT).

Table 3
Crude and adjusted hazard ratio (HR) estimates for incident liver cirrhosis under Alternative Outcome Definitions (365-day washout period, as-treated analysis, 1% asymmetric propensity score trimming).

Comparison	Cohort	Number of patients	High specificity definitions[a]			High sensitivity definitions[a]		
			Crude incidence rate, per 1000 person-years	Crude HR (95% CI)	PS-weighted HR (95% CI)	Crude incidence rate, per 1000 person-years	Crude HR (95% CI)	PS-*weighted HR* (95% CI)
DPP4i vs. TZD								
Lapointe et al., 2018 **(Definitions 1 & 2)**	DPP4i	69,027	2.8 (2.4–3.2)	1.09 (0.86–1.39)	1.15 (0.89–1.50)	6.2 (5.7–6.8)	1.34 (1.13–1.59)	1.38 (1.14–1.66)
	TZD	34,464	2.6 (2.1–3.1)			4.6 (4.0–5.4)		
Nehra et al, 2013 **(Definitions 3 & 4)**	DPP4i	69,027	1.0 (0.8–1.2)	1.03 (0.69–1.52)	1.03 (0.68–1.56)	6.9 (6.3–7.5)	1.20 (1.02–1.40)	1.25 (1.05–1.48)
	TZD	34,464	1.0 (0.7–1.3)			5.8 (5.1–6.6)		
GLP1RA vs. TZD								
Lapointe et al, 2018 **(Definitions 1 & 2)**	GLP1RA	10,728	3.6 (2.5–5.2)	1.41 (0.95–2.11)	1.34 (0.82–2.20)	7.0 (5.4–9.1)	1.37 (1.03–1.83)	1.21 (0.85–1.70)
	TZD	41,745	2.6 (2.2–3.2)			4.9 (4.3–5.6)		
Nehra et al, 2013 **(Definitions 3 & 4)**	GLP1RA	10,728	1.9 (1.2–3.2)	1.93 (1.09–3.41)	1.77 (0.79–3.97)	8.3 (6.5–10.5)	1.32 (1.02–1.73)	1.19 (0.86–1.65)
	TZD	41,745	1.0 (0.7–1.3)			5.9 (5.3–6.7)		
SGLT2i vs. TZD								
Lapointe et al, 2018 **(Definitions 1 & 2)**	SGLT2i	7849	1.7 (0.8–3.6)	0.91 (0.38–2.21)	1.16 (0.44–3.08)	7.8 (5.5–11.1)	1.48 (0.92–2.39)	1.64 (0.94–2.86)
	TZD	10,980	2.0 (1.2–3.2)			4.8 (3.6–6.6)		
Nehra et al, 2013 **(Definitions 3 & 4)**	SGLT2i	7849	0.7 (0.2–2.3)	1.04 (0.26–4.17)	1.99 (0.49–8.02)	7.8 (5.5–11.1)	1.28 (0.81–2.04)	1.38 (0.80–2.38)
	TZD	10,980	0.8 (0.4–1.7)			5.5 (4.2–7.4)		

Abbreviations: SGLT2i, sodium-glucose cotransporter-2 inhibitors; DPP4i, dipeptidyl peptidase-4 inhibitors; GLP1RA, glucagon-like peptide-1 receptor agonists; TZD, thiazolidinediones; IQR, interquartile range; PS, propensity score; AT, as-treated; IT, initial treatment (similar to intention-to-treat approach in randomized controlled trials). [a]**Definition 1**: 456.1; 571.2; 571.5; INPATIENT ONLY (specificity 91–96%; sensitivity 57–77%); **Definition 2**: 456.1; 571.2; 571.5; INPATIENT (INPT) & OUTPATIENT (OUTPT) (specificity 61–77%; sensitivity 98–99%); **Definition 3**: 456.0; 456.2; 456.21; 572.4; INPT/OUTPT (specificity 98.3%; sensitivity 11.3%); **Definition 4**: 456.0; 456.1; 456.2; 456.21; 571.2; 571.5; 572.2; 572.3; 572.4; 567.23; INPT/OUTPT (specificity 43%; sensitivity 97.7%).

studies would be needed before TZD could be recommended above other GLDs for the purpose of reducing risk of progression to cirrhosis.

4.4. Strengths and limitations

Ours is the first study to examine the impact of second-line GLDs on risk of incident cirrhosis in a large, nationally-representative population of older adult patients. The active comparator, new user design provides implicit control for confounding by indication among patients receiving similar-line GLDs, and the restriction to patients with ≥2 prescriptions of a study drug increases confidence that patients are continuously taking those drugs. Finally, as shown in standardized difference plots, propensity score weighting methods were successful in controlling for measured confounders.

There were important limitations to this study. First, longer drug exposure times may be necessary to detect significant differences between GLDs, since it can take many years to develop and diagnose cirrhosis. In our study, the relatively short (0.40–0.66 years) on-treatment times observed in the Medicare FFS population precluded our ability to establish a robust causal relationship between second-line GLD use and incidence of cirrhosis. Second, our study was not linked to the electronic health record, so we were unable to adjust for several relevant confounding factors, such as blood pressure, HbA1c, lipids, and importantly, body mass index. Notably, obesity is known to be sub-optimally captured in administrative claims data, with high specificity but poor sensitivity. We observed higher prevalence of obesity codes among new users of GLP1RA and SGLT2i than in TZD users; while reasonable covariate balance was achieved after propensity score weighting, we acknowledge the possibility for residual confounding. We conducted a sensitivity analysis to examine the impact of baseline obesity and found no meaningful difference in results, though this should be interpreted with caution since coding for obesity may be incomplete in clinical practice. Future head-to-head pragmatic randomized trials comparing liver effects of TZDs to other second-line GLDs may help to address issues of baseline unmeasured confounding.

Finally, when interpreting results of our study, it is important to consider the natural history of cirrhosis and outcome definitions used. Cirrhosis can take years to develop, and diagnoses often occur when patients transition from compensated to decompensated disease; the latter of which may necessitate hospitalization.[41] Since we anticipated low counts for cirrhosis over our 8-year study period, we examined multiple validated coding definitions (Appendix Table 3). Our primary coding definition required ICD-9 codes to be placed in the hospital setting only, while our secondary definition included the same codes but allowed them to be placed in either inpatient or outpatient settings. Since most cases of compensated cirrhosis receive care in the primary care setting,[42] our secondary definition had greater sensitivity for detecting cirrhosis and likely captured more individuals with both stable and decompensated disease, vs. only hospitalized patients with more severe disease or clinical decompensation (i.e., primary definition). Event rates for cirrhosis were expectedly higher with our secondary definition, and comparisons were better powered. Larger studies with higher event rates would be needed to provide additional insight into the impact of GLDs on cirrhosis risk when very specific (yet less sensitive) outcomes definitions are used.

5. Conclusion

In conclusion, we observed a possible trend towards lower risk of incident cirrhosis with TZD use vs. newer second-line GLDs, although some uncertainty remains due to imprecise estimates resulting from short durations of on-treatment follow-up in this population. Our results mirror preliminary data on the impact of GLDs on NAFLD, and these findings merit further study to better understand which GLDs should be prioritized for reducing cirrhosis risk among patients with type 2 diabetes.

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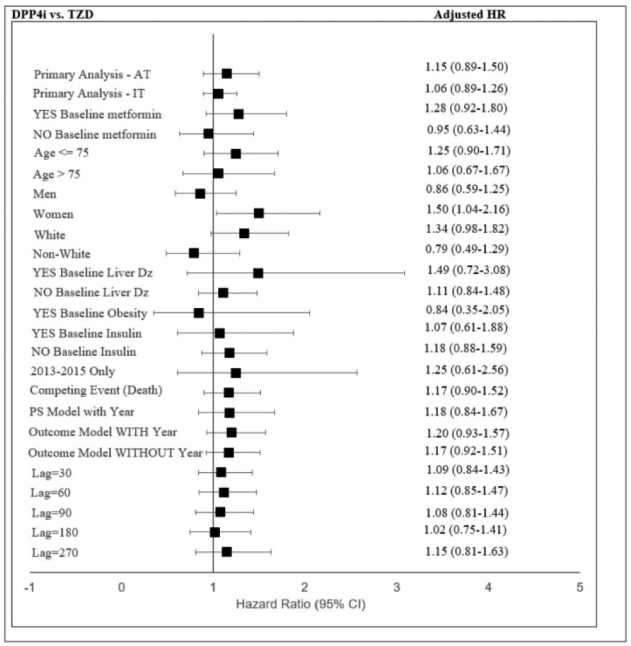

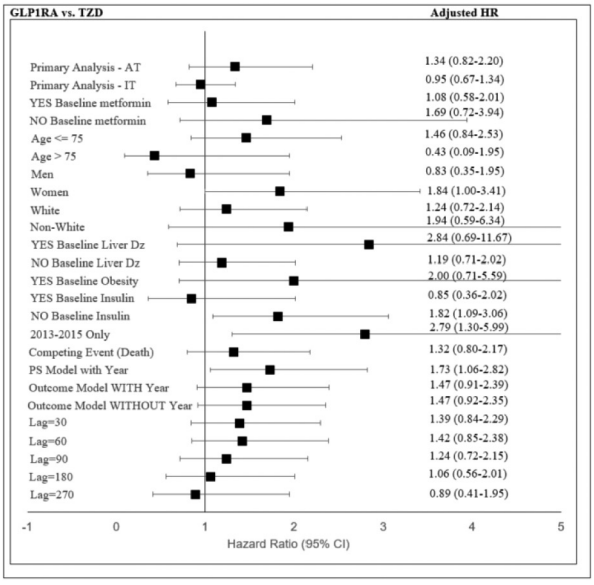

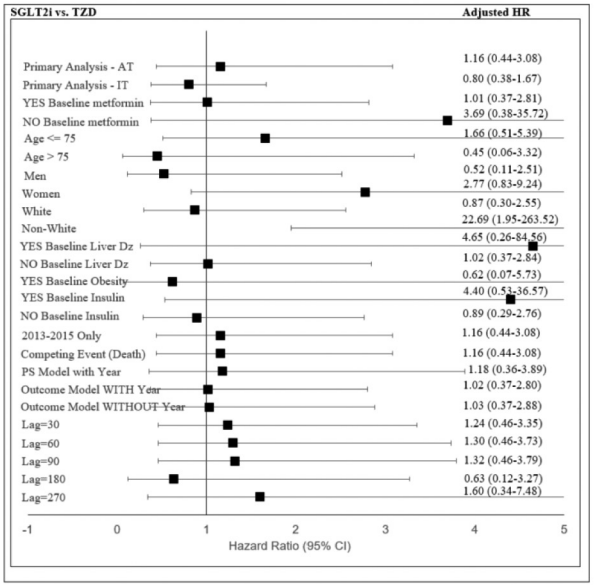

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Declaration of competing interest

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Fig. 2. Adjusted hazard ratio (HR) estimates for incident liver cirrhosis with second-line glucose-lowering drug, sensitivity and subgroup analyses, TZD comparisons[b] Abbreviations: SGLT2i, sodium-glucose cotransporter-2 inhibitors; DPP4i, dipeptidyl peptidase-4 inhibitors; SU, sulfonylureas; IQR, interquartile range; SMR, standardized mortality ratio; HR, hazard ratio; AT, as-treated; IT, initial treatment; Hx, history. [a]Weighted by standardizing the comparator drug initiators to the population of SGLT2i initiators, using the propensity score odds (PS/(1-PS)), to estimate the treatment effect in the treated (ATT). [b]Primary analyses performed with both induction and latency periods = 0 [c]Propensity scores were re-estimated within each subgroup.

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Author contributions

Yang JY: Designed the study, performed analyses, interpreted results and drafted the manuscript.

Alexopoulos AS: Conceived study idea, designed the study, interpreted results and drafted the manuscript.

Moon A: Provided clinical input, interpreted results and edited the manuscript.

Kim H: Provided clinical input, interpreted results and edited the manuscript.

Pate V: Performed data extraction, provided data analysis support and verification.

Barritt AS: Provided clinical input, interpreted results and edited the manuscript.

Crowley MJ: Provided clinical input, interpreted results and edited the manuscript.

Buse JB: Provided clinical oversight and expertise, contributed to study design decisions, interpreted results and edited the manuscript.

Stürmer T: Provided methods oversight and expertise, contributed to study design decisions, interpreted results and edited the manuscript.

Guarantors' statement

JY Yang and AS Alexopoulos served as the guarantors for the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jdiacomp.2020.107706.

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