

Thiazolidinediones and Glucagon-Like Peptide-1 Receptor Agonists and the Risk of Nonalcoholic Fatty Liver Disease: A Cohort Study

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BACKGROUND AND AIMS: Thiazolidinediones (TZDs) and glucagon-like peptide-1 (GLP-1) receptor agonists are potential pharmacological treatment options for patients at risk of NAFLD. Therefore, we examined the association between the risk of NAFLD and the use of TZDs and GLP-1 receptor agonists compared with the use of sulfonylureas (SUs) and insulins. Additionally, we calculated the incidence of HCC in users of TZDs and GLP-1 receptor agonists.

APPROACH AND RESULTS: We conducted a population-based cohort study using primary care data from the Clinical Practice Research Datalink database (2007-2018). All patients aged ≥ 18 with a prescription of an oral glucose-lowering agent or GLP-1 receptor agonist were included. The first prescription defined the start of follow-up. The primary outcome was a new diagnosis of NAFLD. Cox proportional hazards regression was used to estimate HRs and 95% CIs of the primary outcome. Incidence rates of HCC were determined per 1,000 person-years for all exposures. The study identified 207,367 adults with a prescription for a glucose-lowering agent. The risk of NAFLD was lower in patients prescribed a TZD than in those prescribed an SU (adjusted HR [aHR], 0.32; 95% CI, 0.20-0.51). No difference in risk of NAFLD was observed comparing GLP-1 receptor agonist use with insulin use (aHR, 1.22; 95% CI, 0.91-1.63).

CONCLUSIONS: Results of our study endorse the use of TZDs for selected patients at risk of NAFLD but do not support previous findings regarding the beneficial effect of GLP-1 receptor agonists. The low number of events in several subgroups may affect the generalizability of the current findings. (HEPATOLOGY 2021;74:2467-2477).

NAFLD is the most common liver disease in Western countries.⁽¹⁾ The prevalence of NAFLD has increased worldwide in parallel with the rise in obesity and is considered the “hepatic factor” of the metabolic syndrome.⁽¹⁾ The histological spectrum of NAFLD includes simple steatosis, NASH, fibrosis, and cirrhosis. Ultimately, NAFLD may progress to end-stage liver disease and/or HCC, which was the seventh most frequently diagnosed type of cancer and the fourth most common cause of cancer-related death worldwide in 2017.⁽²⁾

Currently, there are no U.S. Food and Drug Administration–approved treatments for NAFLD. However, glucose-lowering drugs that influence

Abbreviations: aHR, adjusted HR; BMI, body mass index; CPRD, Clinical Practice Research Datalink; DPP-4, dipeptidyl peptidase-4; FPG, fasting plasma glucose; GLP-1, glucagon-like peptide-1; HbA1c, hemoglobin A1c; RCT, randomized controlled trial; SU, sulfonylurea; TZD, thiazolidinedione.

Received June 25, 2020; accepted June 13, 2021.

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.32012/supinfo.

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DOI 10.1002/hep.32012

Potential conflict of interest: Dr. de Vries supervises three Ph.D. students who are employed with F. Hoffmann-La Roche Ltd. (Welwyn Garden City, UK, and Basel, Switzerland). The topics of their Ph.D.s are not related to the current work, and Dr. de Vries has not received any fees or reimbursements.

insulin sensitivity, weight, and metabolic profile have been proposed as potential therapies for NAFLD. Of these, thiazolidinediones (TZDs; in particular, pioglitazone) and liraglutide (a glucagon-like peptide-1 [GLP-1] receptor agonist) have shown beneficial effects on liver histology.⁽³⁻⁶⁾ In several randomized controlled trials (RCTs), treatment with pioglitazone resulted in beneficial effects on steatosis, inflammation, hepatocellular ballooning, and fibrosis.⁽⁴⁻⁶⁾ In another RCT, treatment with liraglutide resulted in resolution of NASH and slower fibrosis progression.⁽³⁾ However, these studies included small and selective patient populations with limited follow-up. Although these studies assessed the potential treatment of NAFLD, it is presumable that these drugs can also be beneficial for the prevention of NAFLD and its complications. To date, large real-world studies investigating the association between the use of TZDs and GLP-1 receptor agonists and the risk of developing NAFLD are lacking, and only a few studies with conflicting results on the use of TZDs and risk of HCC have been published.⁽⁷⁻⁹⁾

Thus, the primary objective of this study was to evaluate the association between current use of TZDs and GLP-1 receptor agonists and the risk of developing NAFLD compared with current use of sulfonylureas (SUs) and insulins. Because NAFLD may progress to HCC, our second objective was to investigate the incidence rate of HCC in users of TZDs and GLP-1 receptor agonists.

Materials and Methods

DATA SOURCES

Data were derived from the Clinical Practice Research Datalink (CPRD) GOLD, which contains prospectively collected health care information on approximately 7% of the primary care patients in the United Kingdom. Available information includes patient demographics, ethnicity, diagnoses, referrals to secondary care, laboratory results, prescription details, and lifestyle factors. Data in the CPRD GOLD have been shown to be valid and of high quality for a wide range of diseases⁽¹⁰⁾ and have been used to study HCC in patients with type 2 diabetes.⁽¹¹⁾

STUDY POPULATION

Data collection began June 1, 2007, and ended December 31, 2018. All patients aged ≥ 18 years with a first-ever prescription for an oral glucose-lowering agent or a GLP-1 receptor agonist during the study period were included. The date of the first glucose-lowering drug prescription during the study period defined the index date. As a result, patients could start on any oral glucose-lowering drug or GLP-1 receptor agonist and move between different treatment groups during follow-up. Patients with a history of polycystic ovarian syndrome, NAFLD, or HCC were excluded. However, patients with a history of NAFLD were not excluded from the secondary analyses, which

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evaluated the incidence of HCC. A lag period of 6 months following the index date was included in the HCC analysis to consider a latency time window and minimize possible detection bias. Here, patients diagnosed with HCC within the first 6 months of follow-up after the index date were excluded from the HCC incidence analyses. Supporting Figs. S1 and S2 show a flowchart of the study cohorts.

EXPOSURE TO GLUCOSE-LOWERING AGENTS

Follow-up time was divided into fixed intervals of 90 days, starting from the index date. Based on the time since the most recent oral glucose-lowering drug prescription, an interval was classified as “current use” (≤ 90 days) or “past use” (> 90 days). All patients were current users of one of the eligible drugs at the index date, and they could move between past and current use during follow-up. Based on the drug that was prescribed in the 90 days before a current use interval, current use was classified into the following mutually exclusive groups when comparing use of TZDs with use of SUs: current use of SUs, current use of TZDs, concurrent use of TZDs and SUs, current use of dipeptidyl peptidase-4 (DPP-4) inhibitors, and current use of other glucose-lowering agents (other than TZDs, SUs, and DPP-4 inhibitors). At the start of each current TZD interval, the cumulative prescribed TZD dosage, in pioglitazone equivalents, was reviewed. Defined daily doses were used to calculate the pioglitazone dose equivalents.⁽¹²⁾

Current use was classified into the following mutually exclusive groups when comparing use of GLP-1 receptor agonists with the use of insulins: current use of insulins, current use of GLP-1 receptor agonists, concurrent use of insulins and GLP-1 receptor agonists, and current use of other glucose-lowering agents (other than insulins and GLP-1 receptor agonists).

Users of SUs or insulins were chosen as the reference groups in our primary analyses because we anticipated that users of these agents would have the most comparable disease state and thus a similar risk of NAFLD. For instance, based on the 2009 and 2015 National Institute for Health and Care Excellence guidelines for type 2 diabetes management, TZDs and SUs are both second-line therapies, and GLP-1 receptor agonists and insulins are both third/fourth-line therapies.^(13,14)

STUDY OUTCOME

Data on incident NAFLD (our primary endpoint) and HCC (our secondary endpoint) were identified using Read Codes.⁽¹⁵⁾ Patients were followed from the index date until the outcome of interest (NAFLD or HCC), end of data collection, or death, whichever occurred first.

CONFOUNDERS

Potential confounders related to NAFLD and the exposure of interest were selected based on a review of the literature. These confounders were assessed at the index date or as a time-dependent risk factor. In all models investigating the risk of NAFLD, potential confounders that were assessed at baseline included sex, smoking status (nonsmoker, current smoker, former smoker, or unknown), and body mass index (BMI) (< 20.0 , 20.0 - 24.9 , 25.0 - 29.9 , 30 - 34.9 , ≥ 35 kg/m^2 , or unknown). Other potential confounders considered were determined time-dependently at the start of each new 90-day interval: age, alcohol use, a history of cardiovascular disease (excluding heart failure), chronic kidney disease, heart failure, chronic liver disease, hypertension, neuropathy, retinopathy, microalbuminuria, and macroalbuminuria. Furthermore, we determined the following most recently recorded laboratory values in the last year: alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), bilirubin, hemoglobin A1c (HbA1c), total cholesterol, LDL-cholesterol (C), HDL-C, fasting plasma glucose (FPG), systolic blood pressure, and diastolic blood pressure. If two or more laboratory measurements were recorded on the same date, the average value was used in the analysis. In addition, the use of any of the following drugs in the previous 6 months of an interval was considered as a potential confounder: amiodarone, methotrexate, systemic glucocorticoids, and valproate.

DATA ANALYSIS

Unadjusted incidence rates of NAFLD and HCC were calculated for each exposure group as events per 1,000 person-years. Time-dependent Cox proportional hazards models were used to estimate age/sex-adjusted and fully adjusted HRs (aHRs) and 95% CIs for NAFLD associated with current use of

TZDs compared with current use of SUs. A similar analysis was performed for current use of GLP-1 receptor agonists compared with current use of insulins. Furthermore, we stratified current TZD use by cumulative dose as a proxy for duration. Potential confounders were included in the analyses if they changed the beta coefficient for having NAFLD related to the exposure (current TZD use or current GLP-1 receptor agonist use) in an age/sex-adjusted analysis by at least 5% or when consensus about inclusion was reached within the team of researchers and supported by clinical evidence from the literature. After this study protocol had been approved by the Interdisciplinary Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency database research (protocol no. 19_037), we decided to no longer consider the following potential confounders because they have a strong association with the outcome and may act as intermediate variables rather than confounders: recent recordings of ALT, AST, GGT, ALP, and bilirubin. An indicator variable was used to account for missing data. All statistical analyses were performed using SAS statistical software, version 9.4 (SAS Institute, Inc., NC).

SENSITIVITY ANALYSES

We conducted multiple sensitivity analyses. The first sensitivity analysis investigated the influence of a different analytical method (i.e., propensity score matching) to control for confounding. Propensity score matching, which was used to balance users of TZDs with users of SUs and users of GLP-1 receptor agonists with users of insulin, is believed to be of value in situations in which the number of outcomes is low and correcting for several confounders is desirable.⁽¹⁶⁾ For the propensity score-matched analyses, we first identified all new users of TZDs, SUs, GLP-1 receptor agonists, and insulin from the study population that was used for the main analysis. We matched each TZD or insulin user to one patient (without replacement) initiating an SU or GLP-1 receptor agonist, respectively, on their estimated propensity score using nearest neighbor matching and a caliper of 0.02. Detailed information on the methods for this sensitivity analysis, such as the variables that were included in the propensity score, are provided in the Supporting Information. Additionally, Supporting Figs. S3-S6 show a flowchart of the study cohorts following propensity score matching.

Second, to assess the potential impact of unmeasured confounding factors in the association between the use of TZDs and NAFLD, a sensitivity analysis was conducted and an E-value was calculated.⁽¹⁷⁻¹⁹⁾ The E-value estimates how strong unmeasured confounding would have to be to overcome the observed association in this study.^(18,19)

The third sensitivity analysis evaluated the influence of different reference groups/disease stages. In our primary multivariable analysis, we compared the use of GLP-1 receptor agonists with the use of insulins because they are both used as third/fourth-line therapy in order to minimize confounding (e.g., controlling for diabetes duration and diabetes-related comorbidities).⁽¹⁴⁾ In the sensitivity analysis, we used current use of SUs as the reference group because this is a second-line therapy,⁽¹⁴⁾ thereby allowing us to investigate the influence of including a reference group with an earlier disease stage. All other methods were identical to the primary analysis.

In the fourth sensitivity analysis, we excluded all patients with a record of substantial alcohol consumption (>21 units per week for men and >14 units for women) before index date or during follow-up from our primary analysis (i.e., risk of NAFLD in users of TZDs compared with SUs).

In the fifth sensitivity analysis, we stratified our primary analyses (i.e., risk of NAFLD in users of TZDs compared with SUs and GLP-1 receptor agonists compared with insulins) by follow-up period into early (2007-2014) and late (2015-2018) follow-up.

In the sixth sensitivity analysis, we used a 2-year latency period instead of 6 months to calculate the HCC incidence rates.

Results

PATIENT CHARACTERISTICS

Table 1 and Supporting Table S1 show the baseline characteristics of the overall cohort and are stratified by use of glucose-lowering agent at index date (SUs, TZDs, insulins, and GLP-1 receptor agonists). A total of 207,367 patients met the study inclusion criteria, with a mean follow-up duration of 5.1 years. The median age of all users at the index date was 61 years, and 45.3% (n = 93,913) were female. At baseline, users of TZDs were younger (median age, 61

TABLE 1. Baseline Characteristics of All Glucose-Lowering Agent Users

Characteristic	All Users	TZD Users	SU Users	GLP-1 Receptor Agonist Users	Insulin Users
	n = 207,367	n = 2,104	n = 29,732	n = 871	n = 10,467
Follow-up time, years (mean)	5.1 (3.3)	5.4 (3.7)	4.3 (3.3)	3.8 (2.7)	4.6 (3.4)
Female, %	45.3	41.4	41.8	46.6	46.1
Age, years (median)	61 (50-71)	61 (53-71)	66 (54-77)	56 (47-63)	57 (45-70)
18-29 years, %	3.1	0.8	1.3	1.8	6
30-39 years, %	7.1	4.4	4.5	7.5	11.3
40-49 years, %	13.9	12.7	11.7	22.3	16.4
50-59 years, %	22.1	25.3	18.2	32.4	20.6
60-69 years, %	24.7	28.7	22.2	25.4	20.7
70-79 years, %	18.6	17.8	21.3	8.7	15.8
80+ years, %	10.6	10.3	20.7	2	9.2
Smoking status					
Current smoker, %	18.3	17.3	17.9	16.2	18.4
Former smoker, %	44.4	34.2	38.8	36.1	38.1
Never smoker, %	35.9	45.8	40.2	45.9	41.2
Unknown, %	1.3	2.7	3.2	1.8	2.4
Alcohol use					
Yes, %	59	43.5	46.5	45.6	47.1
No, %	26.8	25.7	27.7	25.8	29.6
Unknown, %	14.3	30.8	25.8	28.6	23.2
BMI, kg/m ² (median)	31.0 (27-36)	31.8 (28-37)	28.4 (25-33)	36.3 (32-41)	30.6 (27-35)
<20.0 kg/m ² , %	1.3	0.8	3.3	0.1	1.4
20.0-24.9 kg/m ² , %	11	9.5	19.8	2.3	11.5
25.0-29.9 kg/m ² , %	28.3	25.1	30	11.9	28
30.0-34.9 kg/m ² , %	27.5	25.9	20.5	24	27.1
≥35.0 kg/m ² , %	27	30.5	15.5	53.4	23.5
Unknown, %	4.9	8.3	11	8.3	8.5
History of disease					
Cardiovascular disease, %	7	6.7	10.2	3.7	8.7
Heart failure, %	3.1	1.4	5.7	2.2	4.2
Hypertension, %	37.9	41.1	37.7	42.5	35.6
Chronic liver disease, %	0.3	0.2	0.6	0.1	0.5
Chronic kidney disease, %	9.6	11.2	16.2	5.9	11.9
Neuropathy, %	1.6	2.7	1.9	3.3	6.2
Retinopathy, %	5.2	8.8	6.9	10.7	23.8
Microalbuminuria, %	9.4	5.9	8.5	5.5	14.1
Macroalbuminuria, %	1.1	0.6	1.4	0.7	2.7
Drug use in the previous 6 months					
Amiodarone, %	0.2	0	0.3	0.1	0.2
Methotrexate, %	0.5	0.2	0.4	0	0.4
Systemic glucocorticoids, %	6.7	1.4	8.6	2.3	4.8
Valproate, %	0.7	0.2	0.6	0.2	0.7

Note: Data are presented as means ± SD, medians (interquartile range), or proportions. Patients using other glucose-lowering agents (e.g., metformin) are included in users of all glucose-lowering agents but are not shown separately. Baseline laboratory values can be found in Supporting Table S1.

vs. 66 years), more obese (BMI, 31.8 kg/m² vs. 28.4 kg/m²), had a lower HbA1c (7.5% vs. 8.5%) and FPG (7.8 mmol/L vs. 10.6 mmol/L), and were less likely to have other comorbidities (e.g., cardiovascular diseases and chronic kidney disease) when compared with users of SUs. Users of GLP-1 receptor agonists had

a higher BMI (36.3 kg/m² vs. 30.6 kg/m²), a lower HbA1c (7.8% vs. 8.8%) and FPG (7.9 mmol/L vs. 9.6 mmol/L), and fewer diabetes-related complications (e.g., retinopathy and albuminuria) when compared with insulin users.

RISK OF NAFLD AND INCIDENCE OF HCC IN USERS OF TZDS

Overall, 2,526 patients were diagnosed with NAFLD during follow-up; 616 of these events occurred in the current SU use group and 18 in the current TZD use group. Current use of TZDs was associated with a decreased risk of NAFLD when compared with use of SUs (aHR, 0.32; 95% CI, 0.20-0.51) (Table 2). Stratification of TZDs by cumulative dose as a proxy for duration resulted in a significantly decreased risk of NAFLD in all categories (<5.4, 5.4-21.8, ≥21.9 g pioglitazone; Supporting Table S2). However, the number of events was very low in these subgroups.

Current combined use of TZDs and SUs was also associated with a decreased risk of NAFLD when compared with use of SUs only (aHR, 0.56; 95% CI, 0.36-0.87).

We tested the robustness of these findings with a propensity score-matched sensitivity analysis. Baseline characteristics of the propensity score-matched sensitivity analysis before (n = 68,979) and after

(n = 5,728) matching are presented in Supporting Table S3. Supporting Fig. S7 shows that there is a high degree of similarity in the propensity score distributions between the exposure groups after matching. The propensity score-matched analysis yielded a comparable result (aHR, 0.27; 95% CI, 0.14-0.52) (Supporting Table S4). Supporting Fig. S8 presents the Kaplan-Meier curve for NAFLD after propensity score matching for users of SUs and users of TZDs.

In our second sensitivity analysis, we calculated the E-value for the comparison of SUs with TZDs regarding NAFLD. The E-values were 5.7 for the HR point estimate and 3.3 for the upper bound of the CI. Exclusion of participants with substantial alcohol use did not substantially alter our results (aHR for current TZD use vs. current SU use, 0.27 [95% CI, 0.16-0.47]). Stratification of the follow-up period into early and late did not alter the results (aHR [2007-2014] current TZD use vs. current SU use, 0.39 [95% CI, 0.23-0.69], and aHR [2015-2018] current TZD use versus current SU use, 0.21 [95% CI, 0.09-0.51]).

The incidence rates of HCC in users of TZDs and SUs are shown in Supporting Table S5. Overall, 213 patients were diagnosed with HCC during follow-up. Crude incidence rates of HCC per 1,000 person-years were 0.3 for use of TZDs, 0.3 for use of SUs, and 0.2 with combined use. Results did not materially change when the latency period was extended to 2 years.

TABLE 2. Risk of NAFLD in Patients With Type 2 Diabetes Using TZDs Compared With SUs

Exposure to Glucose-Lowering Agents	No. of Events (n = 2,526)	Risk of NAFLD			
		PYs	IR/1,000 PYs	Age/Sex aHR (95% CI)	aHR (95% CI) [†]
Current Use of Glucose-Lowering Agents					
SUs	616	172,309	3.6	Reference	Reference
TZDs	18	14,732	1.2	0.32 (0.20-0.51)	0.32 (0.20-0.51)
DPP-4 inhibitors	159	45,677	3.5	0.92 (0.77-1.09)	0.86 (0.72-1.02)
Other glucose-lowering agents [†]	1,553	459,614	3.4	0.87 (0.79-0.95)	0.94 (0.85-1.03)
Concurrent use					
TZDs and SUs	20	9,624	2.1	0.56 (0.36-0.88)	0.56 (0.36-0.87)
Past use					
Past use of any glucose-lowering agent	160	363,620	0.4	0.10 (0.09-0.12)	0.15 (0.12-0.18)

Note: All groups in this table were mutually exclusive. Current use (1-90 days) or past use (>90 days) were defined by the time since the most recent prescription.

*Statistically adjusted for age, sex, BMI, HbA1c, and use of systemic glucocorticoids and all other exposure categories in this table.

[†]Use of glucose-lowering agents other than SUs, TZDs, and DPP-4 inhibitors.

Abbreviations: IR, incidence rate; PYs, person-years.

RISK OF NAFLD AND INCIDENCE OF HCC IN USERS OF GLP-1 RECEPTOR AGONISTS

Table 3 shows the incidence rates and risk of NAFLD in users of GLP-1 receptor agonists. There were 155 events of NAFLD in the current insulin use group and 64 in the current GLP-1 receptor agonist group. There was no difference in risk of NAFLD between users of GLP-1 receptor agonists and users of insulins (aHR, 1.22; 95% CI, 0.91-1.63). A similar result was found for combined use of a GLP-1 receptor agonist and insulin (aHR, 1.39; 95% CI, 0.86-2.24).

In the sensitivity analysis in which we performed a propensity score-matched analysis, the risk of NAFLD was similar with use of GLP-1 receptor agonists versus use of insulins (aHR, 1.08; 95% CI, 0.66-1.77) (Supporting Table S7). Additional information can be found in Supporting Figs. S9 and S10 and Supporting Table S6.

In our sensitivity analysis with SUs as a reference group, the risk of NAFLD in users of GLP-1 receptor agonists was lower. However, it was also not a statistically significant difference from this reference group (aHR, 0.85; 95% CI, 0.64-1.13) (Supporting Table S8). Stratification of the follow-up period resulted in a nonsignificant increased risk of NAFLD with GLP-1 receptor agonist use in the earlier years (aHR [2007-2014] current GLP-1 receptor agonist use versus current insulin use, 2.31 [95% CI, 0.46-3.65]), whereas GLP-1 receptor agonist use was not associated with

NAFLD in the later years (aHR [2015-2018] current GLP-1 receptor agonist use versus current insulin use, 0.82; [95% CI, 0.56-1.22]).

The incidence rates of HCC in users of GLP-1 receptor agonists and insulins are shown in Supporting Table S9. Crude incidence rates of HCC per 1,000 person-years were 0.1 for use of GLP-1 receptor agonists, 0.4 for use of insulins, and 0.5 with combined use. The incidence rates of HCC for insulin use and combined use decreased in the sensitivity analyses with a latency period of 2 years (0.2 and 0.3 events per 1,000 person-years, respectively).

Discussion

The results of this large, population-based study showed that current use of TZDs was associated with a 68% reduced risk of NAFLD compared with current use of SUs. In contrast, current use of GLP-1 receptor agonists was not associated with a decreased risk of NAFLD compared with current use of insulins. Our findings remained consistent in subsequent sensitivity analyses.

Studies have investigated the association between TZDs and the development or resolution of NAFLD,^(4-6,20-22) including RCTs that used liver biopsies and a maximum follow-up of 2 years.⁽⁴⁻⁶⁾ Use of pioglitazone resulted in improvement and resolution of NASH and improvement in fibrosis scores.⁽⁴⁻⁶⁾ A recently published retrospective cohort study also

TABLE 3. Risk of NAFLD in Patients With Type 2 Diabetes Using GLP-1 Receptor Agonists Compared With Insulins

Exposure to Glucose-Lowering Agents	No. of Events (n = 2,526)	PYs	Risk of NAFLD		
			IR/1,000 PYs	Age/Sex aHR (95% CI)	aHR (95% CI) [†]
Current use of glucose-lowering agents					
Insulins	155	59,399	2.6	Reference	Reference
GLP-1 receptor agonists	64	13,738	4.7	1.71 (1.28-2.29)	1.22 (0.91-1.63)
Other glucose-lowering agents [†]	2,128	625,056	3.4	1.57 (1.33-1.85)	1.35 (1.14-1.60)
Concurrent use					
GLP-1 receptor agonists and insulins	19	3,763	5.0	1.87 (1.16-3.01)	1.39 (0.86-2.24)
Past use					
Past use of any glucose-lowering agent	160	363,620	0.4	0.18 (0.14-0.22)	0.30 (0.24-0.38)

Note: All groups in this table were mutually exclusive. Current use (1-90 days) or past use (>90 days) were defined by the time since the most recent prescription.

*Statistically adjusted for age, sex, BMI, HDL-C, diastolic blood pressure, retinopathy, and use of systemic glucocorticoids and all other exposure categories in this table.

[†]Use of glucose-lowering agents other than insulins and GLP-1 receptor agonists.

Abbreviation: IR, incidence rate; PYs, person-years.

found a significantly decreased risk (HR, 0.39) of cirrhosis in patients using TZDs compared with nonusers of TZDs.⁽²²⁾ However, the database that was used in that study did not contain information on important confounders, including lifestyle factors, such as BMI and smoking status, and laboratory values, such as HbA1c.

Several systematic reviews and meta-analyses have endorsed the beneficial effects of TZDs on NAFLD, also with similar effect sizes as found in our real-world observational study.⁽²³⁻²⁷⁾ In addition to glycemic control, TZDs reduce chronic systemic inflammation, stimulate adipocyte differentiation (with subsequent redistribution of excess triglycerides away from the liver), and increase plasma adiponectin. This may explain the advantageous effects on liver histology.^(28,29) TZDs, however, have become one of the most controversial groups of glucose-lowering agents. Different side effects of TZDs, including weight gain, bone fractures, and heart failure, are of concern for many clinicians.⁽³⁰⁻³⁴⁾ Furthermore, there is an ongoing debate on the risk of bladder cancer, which remains inconclusive.^(35,36) On the other hand, there is increasing evidence that pioglitazone has beneficial effects on risk of major adverse cardiovascular events, stroke, and myocardial infarction, especially in patients with a history of cardiovascular disease.^(28,31-34) Therefore, careful patient selection and treatment monitoring may justify pioglitazone treatment in patients with NAFLD, as was recently advocated in European clinical practice guidelines for the management of NAFLD.⁽³⁷⁾ The results of our study confirm the beneficial effects of pioglitazone in a real-life setting that includes an active treatment comparator and hence provide an important addition to the existing literature.

In contrast to the results found for TZDs, we did not observe any difference in risk of NAFLD between users of GLP-1 receptor agonists and insulins. This was confirmed in a sensitivity analysis in which SUs were used as a reference group. Also, in contrast to TZDs, current literature is not consistent regarding the effects of GLP-1 receptor agonists on the development of NAFLD. Although studies investigating the effect of GLP-1 receptor agonists on liver enzymes suggested beneficial effects,⁽³⁸⁻⁴¹⁾ other studies (including RCTs) that used liver fat (assessed noninvasively) as the primary outcome reported inconsistent results.⁽⁴²⁻⁴⁶⁾ Several studies reported a reduced intrahepatic fat

content after 22 to 26 weeks of GLP-1 receptor agonist use,⁽⁴³⁻⁴⁵⁾ whereas others could not detect a statistically significant reduction.^(42,46) The only RCT that used liver histology as a primary outcome—and reported beneficial effects on the resolution of NASH—may be flawed by imbalanced randomization (BMI differed 3.5 kg/m² between intervention and placebo) due to a small sample size.⁽³⁾ Although it is suggested that the positive effects of liraglutide on NASH resulted from a direct hepatic effect and weight loss,⁽³⁾ the precise mechanisms are still not clear. However, confounding by indication, such as a high BMI that prompted clinicians to prescribe a GLP-1 receptor agonist,⁽⁴⁷⁾ may have masked a true beneficial effect in the present study because BMI is also a risk factor for NAFLD. It is possible that this is explained by residual confounding, despite the conduct of two multivariable regression analyses with different reference groups. Therefore, based on previous and current findings, additional research is warranted to allow definite conclusions regarding the effects of GLP-1 receptor agonists on NAFLD.

Because of our observational study design, the reported associations may be (partly) explained by various types of unmeasured confounding. To minimize confounding, we used different statistical techniques and sensitivity analyses. Although we selected active comparator groups with a similar indication within the disease stage to our exposure of interest (i.e., second-line therapy compared with second-line therapy), our baseline table suggests that users of SUs or insulins (our reference groups) had a more advanced stage of diabetes and were less healthy compared with users of TZDs or GLP-1 receptor agonists, respectively. Because patients with a more advanced disease stage might have a higher *a priori* risk of developing NAFLD,^(29,48) this could have led to an overestimation of beneficial effects of our exposures of interest. TZDs have a drug regulatory history of side effects related to liver disease (troglitazone), cardiac events, and bone fractures (among women) and may therefore be more likely prescribed to healthier people. However, in our sensitivity analysis, we have tried to overcome this imbalance by using propensity score matching, and results remained similar. Although we have not used high-dimensional propensity scores, both options cannot be considered as a “magic wand” to fully control for all unmeasured confounding. Unmeasured confounding may also have been introduced by missing data on

lifestyle factors, such as diet or exercise. At baseline, TZD users had a higher median BMI than users of SUs. Under the assumption that a higher BMI is associated with lower exercise levels and an unhealthier diet, we speculate that statistical adjustments for these potential confounders may yield even smaller inverse associations between TZD use and risk of NAFLD than currently reported. Furthermore, because the recommended amount of physical activity in the United Kingdom (at least 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity physical activity) gives an 18% risk reduction of NAFLD,^(49,50) it is unlikely that our results are completely the result of not adjusting for physical activity. In addition, only 57.6% of the adult population in the United Kingdom meet these physical activity criteria.⁽⁴⁹⁾ Moreover, under the assumption that the 68% reduced risk of NAFLD with use of TZDs versus use of SUs is fully explained by unmeasured confounding, our E-value suggested that the association between the residual confounding and NAFLD is reflected by an HR of at least 5.7.⁽¹⁷⁻¹⁹⁾ This large E-value implies that considerable unmeasured confounding would be needed to discredit our observed effect estimate.

During the design of our study, we decided to evaluate the risk of HCC as a secondary outcome. Because HCC is a known complication of NAFLD,⁽⁵¹⁾ it could indirectly support our main analysis, and an overall good concordance in recording of malignancies has been reported between CPRD and the National Cancer Registration and Analysis Service or Hospital Episode Statistics.^(52,53) However, because of small numbers, we decided to only descriptively report crude incidence rates.

In addition to those already mentioned, the study has various limitations. A main limitation is the low number of events, particularly in some of our subgroup analyses, which may affect the generalizability of the current findings. Studies have shown an underreporting of NAFLD in real-life data,⁽⁵⁴⁾ which also appears to be the case in the current study. Although it cannot be fully excluded, we do not believe that the underreporting of NAFLD would be different between users of TZDs and SUs. Persistently elevated liver enzymes, which often lead to the diagnosis NAFLD, are generally not a reason to prescribe a specific glucose-lowering agent. Moreover, nondifferential misclassification of the outcome would result in

bias toward the null (i.e., HR = 1), leading to insignificant findings.⁽⁵⁵⁾ Because we found a highly significant effect, we do not believe our result regarding the association between the use of TZDs and NAFLD is influenced by this nondifferential misclassification. In contrast, however, nondifferential misclassification could theoretically account for the absent difference in NAFLD risk between GLP-1 receptor agonists and insulins. Second, because the diagnosis of NAFLD was based on Read Codes, there is no information on the diagnostic method (either imaging or biopsy) nor the stage of the disease (i.e., steatosis, NASH, or fibrosis). Finally, because the CPRD contains prescription data and not dispensed data, misclassification of exposure is possible. Moreover, the CPRD records prescriptions written by general practitioners (GPs) and not specialists, who are more likely to start patients on GLP-1 receptor agonists. However, refill prescriptions are generally issued by a GP. Therefore, we expect this misclassification to be minimal.

This study also has several strengths. First, we used a new user design and incident outcome cohort. The inclusion of only new users of glucose-lowering agents eliminated the potential influence of prevalent use; patients with a known history of NAFLD were also excluded. Second, we assessed exposure time-dependently, which prevents the introduction of immortal time bias. Third, we excluded patients with a diagnosis of HCC within the first 6 months of follow-up after the index date to account for a minimal latency period. Finally, the results remained consistent in several sensitivity analyses in which we used a different statistical method and a different reference group to investigate the influence of the analytical method and disease stage, thereby confirming the robustness of our findings.

In conclusion, results of our study endorse the use of TZDs for selected patients at risk of NAFLD provided that contraindications and side effects are considered. Studies investigating the effect of GLP-1 receptor agonists on NAFLD are inconclusive and have several shortcomings, and therefore, large and well-executed RCTs are likely required to assess the effect of GLP-1 receptor agonists on NAFLD resolution. In addition, further longitudinal studies that include a larger sample size are warranted to investigate the risk of HCC in users of glucose-lowering agents and translate the results into clinical practice.

Author Contributions: M.C.G.J.B. initiated the study. J.D. performed the literature review and wrote the first draft of the paper. J.H.M.D. analyzed the data. J.D., M.C.G.J.B., F.V., A.M.B., and J.H.M.D. were responsible for study concept and design. J.H.M.D. and F.V. took responsibility for the integrity of the data and accuracy of the data analyses. All authors participated in the interpretation of the data, critically revised the paper for intellectual content, and approved the final version to be published.

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