Newer glucose-lowering agents versus thiazolidinediones on risk of incident cirrhosis and clinical decompensation events in patients with diabetes

1. Background

Cirrhosis signifies late-stage, chronic liver disease from any cause, which may include hepatitis B/C infection, alcoholism or non-alcoholic fatty liver disease (NAFLD). Mortality due to cirrhosis has been rising [1], increasing by 65% between 1999 and 2016 [2]. While diabetes is a recognized, potent risk factor for the progression of early NAFLD to more advanced fibrosis [3], the presence of diabetes may increase the risk of cirrhosis from other etiologies as well [4], such as hepatitis B infection [5], hepatitis C infection [6], and alcoholic liver disease [7]. Furthermore, patients with diabetes who develop cirrhosis are at higher risk of liver-related complications and mortality than those without diabetes [4, 8-13].

Multiple glucose-lowering agents have been explored for their impact on NAFLD, however their influence on other types of chronic liver disease is less clear. While NAFLD is a diagnosis of exclusion, this does not preclude metabolic factors, such as diabetes and obesity, from contributing to hepatic steatosis and worsening other forms of chronic liver disease. Therefore, diabetes represents a risk factor for cirrhosis and its complications, and glucose-lowering agents have the potential to modulate this risk. We hypothesize that risk of cirrhosis and liver-related complications in patients with diabetes and chronic liver disease can be modified differentially by glucose-lowering medications.

Thiazolidinediones (TZD) are insulin sensitizers with favorable lipid effects, and are well-known to improve advanced fibrosis in non-alcoholic steatohepatitis [14, 15]. Reduction of hepatic fat by TZD may be beneficial in other forms of liver disease, such as with hepatitis C virus/HIV coinfection [16], and even in patients without diabetes [15]. Newer glucose-lowering agents are being explored for their benefits in NAFLD, including sodium-glucose cotransporter-2 (SGLT2) inhibitors [15, 17-19], dipeptidyl dipeptidase-4 (DPP4) inhibitors, and glucagon-like

peptide 1 (GLP-1) receptor agonists [15, 20, 21]. DPP4 inhibitors and GLP-1 receptor agonists are incretin-based therapies which increase GLP-1 levels to enhance glucose-stimulated insulin secretion, while SGLT2 inhibitors lower glucose by inhibiting glucose reabsorption in the kidney; an action which is independent of insulin secretion [22]. Both GLP-1 receptor agonists and SGLT2 inhibitors improve NAFLD by promoting glycemic control and weight loss [15, 23] - more research is needed to determine whether glucose- and/or weight-independent mechanisms of improving NAFLD exist for these agents. Furthermore, additional studies are required to determine the liver effects of these newer glucose-lowering agents compared to the fairly well-established benefits of TZD in NAFLD. However, TZD have a number of undesirable effects including fluid retention exacerbating prevalent heart failure, weight gain and increased fracture risk. Thus if newer, weight-neutral/beneficial agents impart similar or better liver effects, it may be preferable to use these agents over TZD for high-risk liver patients with diabetes.

Even in the absence of diagnosed NAFLD, diabetes is a risk factor for incident cirrhosis [4-7], as well as for decompensation events in patients with compensated cirrhosis [12]. While other mechanisms may exist, diabetes likely mediates this risk by fueling non-alcoholic steatohepatitis, be it in the presence or absence of other chronic liver injury such as alcohol or hepatitis B/C infection. Therefore, it is reasonable to believe that glucose-lowering agents may differentially modify risk of cirrhosis and decompensation events in individuals with diabetes and any form of chronic liver disease. Currently, there is insufficient evidence to recommend one glucose-lowering agent over another to reduce risk of cirrhosis and its complications in diabetes. Here we propose a study to explore the comparative effect of newer glucose-lowering agents versus TZD on risk of incident cirrhosis and clinical decompensation events in patients with diabetes.

2. Objectives

Aim 1) To estimate the effects of newer glucose-lowering agents versus TZD on risk of incident cirrhosis in patients with diabetes. Newer glucose-lowering agents to be examined are SGLT2 inhibitors and the incretin therapies, dipeptyl peptidase-4 (DPP4) inhibitors and GLP-1 receptor agonists.

Aim 2) To estimate the effect of newer glucose-lowering agents (described above) versus TZD on risk of clinical decompensation events in patients with cirrhosis and diabetes.

3. Study Design

We will implement an active comparator, new-user (ACNU)[24] cohort design using 1) nationwide data on commercially-insured patients (MarketScan Commercial Claims and Encounters), aged 18-64, with inpatient, outpatient, and prescription drug insurance coverage between 2007-2017; and 2) a nationwide 20% random sample of fee-for-service U.S. Medicare beneficiaries, age ≥ 65 years with Parts A (inpatient services), B (outpatient services) and D (prescription drug) coverage between 2007-2017. Since SGLT2 inhibitors were not in routine use before 2013, comparisons including SGLT2 inhibitors will only be conducted for 2013-2017; the rest of the comparisons will utilize years 2007-2017. For aim 1 we will identify cohorts of patients with diabetes without cirrhosis who are newly starting either of the following drug classes: TZD, SGLT2 inhibitors, DPP4 inhibitors, and GLP-1 receptor agonists. For aim 2 we will identify cohorts of patients with diabetes and known cirrhosis who are newly starting any of the abovementioned drug classes, and assess comparative incidence of decompensation events following drug initiation.

4. Data Sources

- MarketScan Commercial Claims and Encounters (CCAE) Database, 2007-2017 (2013-2017 for SGLT2 inhibitor comparisons)

- Medicare Fee-for-Service (FFS) Database (Parts A, B, and D), 20% random sample, 2007-2017 (2013-2017 for SGLT inhibitor comparisons)

5. Study population inclusion and exclusion criteria

Aim 1

The eligible population will consist of MarketScan enrollees aged 18-64, and Medicare enrollees aged ≥ 65 with a diagnosis of type 2 diabetes and without a diagnosis of cirrhosis in the 12 months prior to drug initiation date (index date). We will include patients with and without underlying chronic liver disease, such as known hepatitis B/C infection, alcoholism and/or non-alcoholic fatty liver disease. Type 2 diabetes will be defined as International Classification of Disease, 9th and 10th edition, Clinical Modification (ICD-9 CM) codes seen below. For the purpose of excluding cirrhosis at baseline, cirrhosis will be defined as having any of the codes in Table 1 at a physician visit, which achieves a sensitivity of 98-99% for exclusion. [25]

Table 1: ICD-9 and ICD-10 code definitions for type 2 diabetes and cirrhosis

	Type 2 diabetes	**Cirrhosis**
ICD-9 CM codes	250.xx	456.1; 571.2; 571.5
ICD-10 CM codes	E11.xx	I85.0*; I85.1*; K70.3; K71.7, K74.6

*codes were converted to U.S. equivalents [25]. Other codes were the same between U.S. and Canada.

We will identify new users of glucose-lowering therapies of interest based on the first dispensing of a prescription in that drug class. Participants will be entered into the cohort on the date of dispensing of the first prescription. We will identify new users of the following comparisons:

I. DPP4 inhibitor versus TZD

II. GLP-1 receptor agonist versus TZD

III. SGLT-2 inhibitor versus TZD

IV. SGLT2 inhibitor versus GLP-1 receptor agonist

V. SGLT2 inhibitor versus DPP4 inhibitor

VI. DPP4 inhibitor versus GLP-1 receptor agonist

We will exclude the following patients:

1. Individuals without at least 12 months of continuous enrollment in MarketScan CCAE, or in Medicare Parts A, B and D prior to the first prescription dispensing claim.
2. Patients who have received any of the study drugs part of the pairwise comparison in the 12 months preceding the first prescription dispensing claim
3. Individuals with the following conditions in the 12-month period leading up to drug initiation:
    - Previous diagnosis of cirrhosis
    - Previous diagnosis of hepatocellular carcinoma or cholangiocarcinoma
    - Prior hepatectomy or liver transplantation

Aim 2

The eligible population will consist of MarketScan enrollees aged 18-64, and Medicare enrollees aged ≥ 65 with a diagnosis of type 2 diabetes (defined by ICD-9 CM codes 250.xx), and compensated cirrhosis at baseline. Compensated cirrhosis will be defined as any of the following physician visit ICD codes: ICD-9: 456.1; 571.2; 571.5; or ICD-10: I85.0; I85.1; K70.3; K71.7, K74.6. [25] As with aim 1, we will identify new users of glucose-lowering therapies of interest based on the first dispensing of a prescription in that drug class. Participants will be entered into the cohort on the date of dispensing of the first prescription. We will identify new users of the following comparisons:

I. DPP4 inhibitor versus TZD

II. GLP-1 receptor agonist versus TZD

III. SGLT-2 inhibitor versus TZD

IV. SGLT2 inhibitor versus GLP-1 receptor agonist

V. SGLT2 inhibitor versus DPP4 inhibitor

VI. DPP4 inhibitor versus GLP-1 receptor agonist

We will exclude the following patients:

1. Individuals without at least 12 months of continuous enrollment in MarketScan CCAE, or in Medicare Parts A, B and D prior to the first prescription dispensing claim.
2. Patients who have received any of the study drugs part of the pairwise comparison in the 12 months preceding the first prescription dispensing claim
4. Individuals with the following conditions in the 12-month period leading up to drug initiation:
   - Previous diagnosis of hepatocellular carcinoma or cholangiocarcinoma
   - Prior hepatectomy or liver transplantation
   - Any clinical decompensation event (as defined below in 7. Outcomes)
   - We will also exclude patients who have an ICD, CPT or HCPCS code related to peritoneal dialysis as detailed in Table 2. [26]

Table 2: Codes associated with peritoneal dialysis

ICD-9 codes	996.56; 996.68; V56.2; V56.32; V56.8
ICD-10 codes	T85.611A; T85.621A; T85.631A; T85.71XA; Z49.02; Z49.32;
CPT codes	49420; 49421; 90945; 90947
HCPCS codes	A4653; A4671; A4672; A4673; A4719; A4720; A4721; A4722; A4723; A4724; A4725; A4726; A4728; A4760; A4765; A4766; A4860; A4880; A4900; A4901; A4905; E1632; E1592; E1594; E1630; E1634; E1638; E1640

6. Exposure and comparison

For both aims, exposure will be defined at least **two** same-drug class prescriptions dispensing claims of the comparator drugs of interest between 2007-2017 identified using the National Drug Codes (NDC). The second prescription will serve as the index date for the analysis.

Comparisons	Index Drug	Comparator Drug
I	DPP4 inhibitors	Thiazolidinediones[d]
II	SGLT2 inhibitors	Thiazolidinediones
III	GLP-1 receptor agonists[c]	Thiazolidinediones
IV	SGLT2 inhibitors	GLP-1 receptor agonists
V	SGLT 2 inhibitors	DPP4 inhibitors
VI	DPP4 inhibitors	GLP-1 receptor agonists

a. Sitagliptin, vildagliptin, saxagliptin, linagliptin
b. Canagliflozin, dapagliflozin, empagliflozin
c. Albiglutide, dulaglutide, exenatide (short- and long-acting), liraglutide, lixisenatide, semaglutide
d. Pioglitazone, rosiglitazone

7. Outcomes

Aim 1: The primary outcome of interest is the first diagnosis of cirrhosis during follow-up. Incident cirrhosis will be defined as any of the following diagnosis codes in the hospital setting, and this achieves a specificity of 91-96% for diagnosis (sensitivity of 57-77%): ICD-9: 456.1; 571.2; 571.5; or ICD-10: I85.0; I85.1; K70.3; K71.7, K74.6. [25]

Aim 2: Our primary outcome of interest for this aim is any clinical decompensation event. A decompensation event will be defined as any of the below diagnosis codes in the hospital setting (with concurrent physician visit code for cirrhosis as defined in Table 1), and this achieves a specificity of 89-98% for diagnosis, with sensitivities ranging 79-89%. [25]

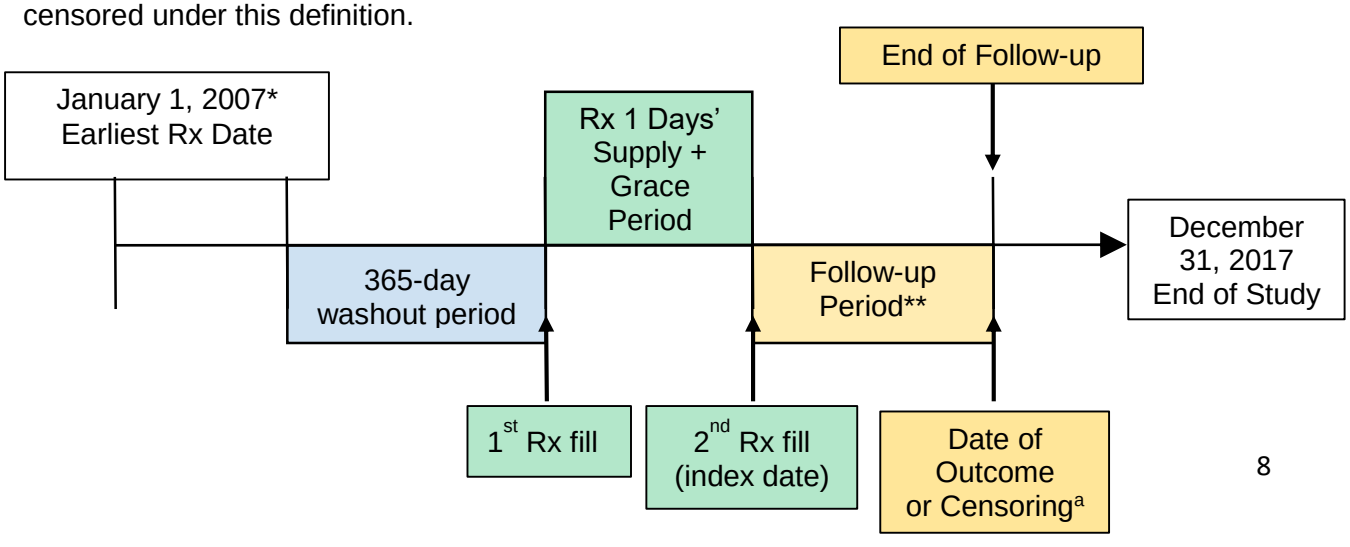
ICD-9	456.0, 456.2; 572.2, 572.4, 782.4, 789.5
ICD-10	I85.0, I86.4, I98.20, I98.3, K72.1, K72.9, K76.7, R17, R18

8. Follow-up

The primary analysis for both aims will be carried out in an "as-treated" fashion. Follow-up will begin 180 days after the index date (date of 2nd prescription) and end at the time an individual experiences either an outcome of interest or censoring event. Patients will be censored for treatment discontinuation/switch/ augmentation, disenrollment from the insurance plan, or study end (December 31, 2017), whichever comes first. Once patients are censored, we will include a latent period of 180 days for the outcome of incident cirrhosis (aim 1), and 30 days for the outcome of clinical decompensation event (aim 2).

Treatment discontinuation, switch, and augmentation will be defined using a combination of days' supply, found on each prescription dispensing claim, and a pre-defined 30-day "grace period". Patients will be considered to have discontinued treatment if they have no new prescription of the cohort drug class within a (days' supply + grace period) time window after the last prescription of the cohort drug class. Censoring will occur at the end of the same (days' supply + grace period) time window. We will vary the length of this grace period in sensitivity analyses to examine the robustness of the primary analysis results to changes in grace period.

Patients will be considered to have switched or augmented treatment if they fill a prescription for a comparator drug within the (days' supply + grace period) time window after the last prescription of the cohort drug. Censoring will occur at the fill date of the comparator drug class. Patients who switch between or augment with drugs within the same class will not be censored under this definition.



*January 1, 2013 for SGLT2 inhibitor comparisons
**A lag time of 180 days after index date precedes the follow-up period

9. Covariates

Baseline covariates will be measured in the 12 months prior to index date. The following covariates will be included:

1) Demographics: age, gender, race (Medicare only), smoking status, calendar year, low income subsidy (Medicare only)
2) Diabetes comorbidities: retinopathy, nephropathy, neuropathy
3) Liver disease: viral hepatitis (B, 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) Other health comorbidity: chronic kidney disease, chronic obstructive pulmonary disease, depression, alcoholism, obesity
6) Diabetic medication use: metformin, sulfonylurea, TZD (if applicable), DPP4 inhibitor (if applicable), GLP-1 receptor agonist (if applicable), SGLT2 inhibitor (if applicable), long-acting insulin
7) Other medication use: angiotensin-converting enzyme inhibitor, angiotensin receptor blockers, beta-blockers, calcium channel blockers, statins, prescription omega-3 fatty acids (Epanova [omega-3-carboxylic acids], Lovaza [omega-3-acid ethyl esters], Omtryg [omega-3-acid ethyl esters] and Vascepa [icosapent ethyl]), loop diuretics (furosemide, torsemide, bumetanide), aldosterone antagonists (spironolactone, eplenerone), thiazide diuretics (hydrochlorothiazide, chlorthalidone), other diuretics, aspirin
8) Measures of healthcare utilization: hyperglycemia/diabetes diagnosis, hospitalization due to hyperglycemia/diabetes, emergency department visit due to

hyperglycemia/diabetes, physician encounters, gastroenterologist encounters, endocrinologist encounters

10. Statistical analysis

The active comparator, new user study design tends to synchronize patients with respect to diabetes severity and duration. We will assess this balance by looking at the crude distribution of claims data based covariates across treatment cohorts. We will consider strong predictors of treatment choice as additional exclusion criteria. Once balanced cohorts have been identified, we will use propensity scores to remove remaining imbalances in measured potential confounders between study cohorts. Our primary aim is to identify active comparator drug initiators that will allow us to estimate what would have happened to the index drug initiators if they had instead initiated the comparator drug. To achieve this goal, we will estimate the average treatment effect in the treated (ATT) by reweighting the comparator drug initiators by the propensity score odds (PS/(1-PS)) [27]. We will estimate and compare the cumulative incidence of both primary outcomes for each study cohort using weighted Kaplan-Meier methods. Crude and adjusted hazard ratios (HRs) for both primary and secondary outcomes will be estimated using weighted Cox proportional hazards models, controlling for age, sex, as well as any potential confounders that remain unbalanced after propensity score implementation.

11. Sensitivity analysis

For both aims of the study we plan to perform the following sensitivity analyses:

1) We will perform an analysis based on initial treatment (IT), ignoring censoring for treatment changes during follow-up (similar to intention-to-treat analyses in randomized clinical trials). IT analysis will be compared to “as-treated” in the primary statistical analysis.
2) We will additionally perform an analysis whereby we censor for switch to, or addition of, all other second-line glucose-lowering drugs and compare this to “as-treated” in the primary statistical analysis.
3) Repeat analysis with varying grace periods (60-day, 90-day).
4) Repeat analysis with varying lag times (90-day, 270-day, 360-day).
5) Repeat analysis with varying latent periods (aim 1: 90-day, 270-day; aim 2: 14-day, 60-day)
6) If time and resources permit, we will perform the following additional sensitivity analyses:
    - Repeat analysis requiring metformin use at baseline.
    - Repeat analysis using different outcome (ICD-9) definitions for cirrhosis, based on U.S. data with varying sensitivity/specificity cut-offs [28]:
    - Repeat analysis using a different outcome (ICD-9) definition for decompensation event, described in a U.S. study by Liu *et al* [12]:

7) **Subgroup analyses:**
    a. Baseline chronic liver disease status (NAFLD, hepatitis B infection, hepatitis C infection, alcoholic liver disease)
    b. Age (Medicare: 65-75 years, >75 years; MarketScan: <50 years, >50 years)
    c. Sex (male, female)

12. References

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