Association between GLP1 receptor agonist (GLP1-RA) and sodium glucose co-transporter 2 inhibitor (SGLT2i) use and COVID-19 outcomes: A national retrospective cohort study

1. Overview

Emerging evidence from the COVID-19 pandemic suggest that patients with type 2 diabetes comprise a significant portion of the affected population and are at higher risk for severe outcomes including hospitalization and death,[1,2] yet it remains largely unknown how pre-morbid medication may impact outcomes of COVID-19 in patients with type 2 diabetes. Several medications have biologically plausible mechanisms with relevance for patients with diabetes among others including ACE inhibitors,[3] metformin,[4,5] and DPP4-inhibitors.[6,7] Recent large cardiovascular outcome trials and subsequent metanalyses[8] have demonstrated that some glucagon-like peptide-1 receptor agonists (GLP-1RA)[9,10] and sodium-glucose-linked cotransporter 2 inhibitors (SGLT2i)[11,12] are associated with a reduction of cardiovascular events and all-cause mortality among the same high-risk populations[13-15] who show higher susceptibility to severe COVID-19 and increased mortality. Yet, no studies have examined the class effect of these newer anti-hyperglycemic of mortality and other outcomes in the setting of COVID-19 infection. These data are critical because therapeutics represent a highly actionable intervention point to improve outcomes from both the inpatient and outpatient setting for a large population of patients with inherently high risk for COVID-19 associated mortality. To address this gap and inform evolving care guidelines for patients with medication-managed type 2 diabetes during the COVID-19 pandemic, this study aims to characterize the association of use of GLP1-RA and SLGT2i with COVID-19 outcomes using real world data from the National COVID Cohort Collaborative (N3C). We will consider the well-studied and commonly used class of dipeptidyl peptidase-4 inhibitors (DPP4i) as the active comparator drug to avoid confounding by indication.

2. Rationale and background

Diabetes is one of the three most significant comorbidities associated with severe COVID-19 disease in the US, alongside cardiovascular disease and hypertension.[1] Data from early in the pandemic reported approximately two times greater risk of death among patients with type 2 diabetes compared to those without,[2] as well as a greater risk of requiring hospitalization and ICU-level care.[16,17] Higher mortality has also been shown with common comorbidities associated with diabetes, including obesity, cardiovascular disease, heart failure, and chronic kidney disease.[1,2,17,18]

Evidence to suggest that pre-morbid medication may impact outcomes of COVID-19 is emerging but mixed. Several medications have biologically plausible mechanisms with relevance for patients with diabetes among others including ACE inhibitors,[3] metformin,[4,5] and DPP4-inhibitors;[6,7] key mechanisms or aspects of clinical relevance for various classes of diabetes medications in the setting of COVID-19 has been reviewed elsewhere.[19] While observational data has provided some evidence for protective effects associated with metformin use,[20,21] other retrospective studies have not provided clear insights.[22,23] To generate definitive data, there now exists an ongoing trial to study SGLT2-i in the setting of diabetes and COVID-19 (DARE-19, the randomized, double-blind, placebo-controlled, phase 3 Dapagliflozin in Respiratory Failure in Patients With COVID-19, sponsored by AstraZeneca).

No studies have examined the class effect of pre-morbid use of the newer anti-hyperglycemic medications, including GLP1-RA and SGLT2i, on COVID-19 outcomes. The association warrants investigations as both GLP1-RA and SGLT2i have been associated with a reduction of

cardiovascular events and all-cause mortality in large cardiovascular outcome trials[9-12] and subsequent metanalyses.[8] Critically, benefits associated with these medications appear to be most pronounced among patient populations with the highest risk for severe COVID-19, including individuals with comorbid cardiovascular disease, heart failure, chronic kidney disease, and obesity,[1,2,13,17,18] which has been formally recognized by the American Diabetes Association Standards of Care.[14,15] Characterizing the association between pre-morbid GLP1-RA and SGLT2-I use and COVID-19 mortality among patients with type 2 diabetes may reveal interventional strategies to improve outcomes for a large population of patients with inherently high risk for COVID-19 associated mortality.

Preliminary Data

Preliminary data from the US-based Explorys database showed class-based mortality differences for people on diabetes medications who had ICD-9/-10 COVID-19 diagnosis. Crude comparisons of the mortality associated with GLP1-RA vs DPP4i and SGLT2i vs DPP4i showed lower mortality with the two newer agents among individuals with COVID-19 diagnosis as well as among individuals with no COVID-19 diagnosis.

3. Research question and objective

It is currently not known how the classes of the newest anti-hyperglycemic *medications with established cardiovascular and mortality benefits* are associated with mortality among patients with type 2 diabetes and a COVID-19 diagnosis. In this study, two comparisons will be made between three anti-hyperglycemic agents, using one agent as the common comparator for the two drugs of interest.

This study aims to characterize whether 60-day in-house mortality is lower with use of:

1) GLIP1-RA versus DPP4i; **and**
2) SGLT2i versus DPP4i

The outcome is 60-day mortality following a COVID-19 diagnosis. Secondary outcomes will include markers of illness severity including hospital admission and level of respiratory support required.

Selection of DPP4i: DPP4i were selected as the comparator medication because these medications have been well-studied with minimal other clinical effects of concern which could reduce bias, DPP4i represent branded agents and thereby reduce some of the confounding by socioeconomic status, DPP4i are among the five recommended second line therapies with prevalent use[24] which may reduce confounding by indication.

For the primary analysis, insulin use was not selected as a comparator regimen because it often represents a salvage therapy and is associated with multiple comorbidities.[14,24] Glitazone use was not selected as a comparator regimen because this drug class is contraindicated in health failure and overall has low market penetration.[14] Sulfonylurea use was not selected as a comparator regimen because this class of medications is generic with low cost and therefore may introduce confounding by socioeconomic status. Use of these medications will be tested in an exploratory setting (see Secondary/Supplemental Analyses; below).

4. Research methods

Data source

This database study will use patient level de-identified U.S data from the National Covid Cohort Collaborative (N3C). [25]

Study design and population

The study population will include adult (age≥18), COVID-19 positive patients according to N3C standards with a record of a prescription of anti-hyperglycemic agents based on ATC-codes.

Inclusion criteria:

- At least 18 years of age in the year of the COVID-19 diagnosis
- COVID 19 positive defined consistently with N3C cohort paper (*in press*)
- At least one prescription of anti-hyperglycemic agents (GLP1-RA, SGLT2i or DPP4i) based on ATC-codes within the last 24 months prior to the COVID-19 diagnosis

Exclusion criteria:

- Patients with a history of concurrent DPP4i use and either GLP1-RA or SGLT2i, defined as one or more prescriptions within the last 24 months prior to COVID-19 diagnosis

Inclusion and exclusion criteria may be minorly modified based on constraints of the database. Inclusion and exclusion criteria are defined according to first COVID-19 diagnosis.

Measures

Outcomes: Outcome concept definitions will be aligned with the most updated criteria defined by the larger N3C collaborative analytics and clinical domain team working groups. Outcomes will be selected to be consistent with the most recent consensus statement on common outcome measures for COVID-19 clinical research.[26] The primary outcome is death within 60 days from diagnosis of COVID-19.

In addition to 60-day mortality, other key endpoints will include:

(1) All cause mortality (binary)
(2) Hospital admission (binary)

For patients requiring inpatient care, additional endpoints will include:

(3) Need for intubation/ventilation after COVID-19 diagnosis (binary)
(4) Hospitalization after COVID-19 diagnosis (binary)
(5) Emergency room visit after COVID-19 diagnosis (binary)

Outcomes are defined relative to any COVID-19 diagnosis.

Potential Covariates: Covariate concept definitions will be aligned with the most updated criteria defined by the larger N3C collaborative analytics and clinical domain team working groups. Potential baseline covariates include age, sex, race and ethnicity, hypertension (HTN), chronic kidney disease (CKD), cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD), cancer history, BMI/weight, insulin use (long-acting versus rapid-acting formulations), and ACE inhibitor use, smoking and glycemic control (HbA1c).

Additional comorbidities may be selected based on most recent evidence from the Centers for Disease Control and Prevention, which is updated and make publicly available on a regular basis,[27] as well as the most contemporary data from the US (NYC)[28] and diabetes-specific cohorts based in Europe[22] and Mexico.[29]

Statistical methods

The aim of the analysis is to estimate the relative odds of mortality 60 days following a COVID-19 diagnosis for patients with a history of SGLT2i/GLP1-RA use vs DPP4i use among eligible patients with COVID-19 in the N3C database.

The primary estimand is the odds of mortality following 60 days from diagnosis with COVID-19. The ratio of the odds (OR) between the two drugs will be estimated using targeted maximum likelihood estimation (TMLE). TMLE is used to analyze observational data from a non-controlled experiment in a way that allows effect estimation even in the presence of confounding factors.[30,31] A super learner approach will be used to improve precision. Since the outcome is binary in nature—i.e. mortality or not 60 days after the COVID-19 diagnosis; there are no expected censoring issues. Additionally, the number of deaths following sixty days is rare compared to the number of individuals studied, hence the OR and the RR will be comparable. The first analysis will generate the OR comparing mortality between GLP1-RA and DPP4i. The second analysis will generate the OR comparing SGLT2i versus DPP4i.

For comparison the estimated OR will also be based on an inverse probability of treatment weighted (IPTW) logistic regression model. Logistic regression is chosen as all defined outcomes are binary in nature. IPTW will be used to balance patient covariates across drug-class users.

The risk of death for a given patient with estimated weights w_i is estimated as

$$log(\frac{\mathrm{p}}{1-\mathrm{p}}) = \beta_0 + \beta_1(DPP4 = 1) \; + \; w_i$$

The IPTW weights (unstabilized) are defined for the ith subject as

$$weight_i \; = \frac{Z_i}{e(X_i)} + \frac{(1-Z_i)}{1-e(X_i)}$$

where $e(X_i)$ is the propensity score defined as the ith subject's covariates X_i, and Z_i is 1 or 0 for treatment or active control. Stabilized weights for the ith subject can be written as

$$stabilized\ weight_i \; = \frac{Z_i \cdot P(Z=1)}{e(X_i)} + \frac{(1-Z_i)\cdot(1-P(Z=1))}{1-e(X_i)}$$

where $e(X_i)$ is the propensity score defined as the ith subject's covariates X_i, and Z_i is 1 or 0 for treatment or control, and $P(Z=1)$ is calculated as the proportion of subjects in the sample that received treatment $Z=1$.

Using unstabilized weights, the sum of weights among the treated and untreated are equal, thereby mimicking a 1:1 allocation. However, with stabilized weights, the sum of weights in each treatment group will equal the observed group sizes. The analysis will use stabilized weights.

Weights will be truncated at the 5 and 95th percentile determined from the distribution of weights, this is aligned with standard approaches.

Selection of Covariates:
Initial baseline covariate selection to address confounding will be informed by data availability. Minimal baseline confounders will include age, sex, race/ethnicity, body weight, HTN, CKD, CVD, metformin use and insulin use (long-acting and short-acting).

For IPTW we will use standardized mean differences (SMD) to evaluate covariate balance across DDP4i and SGLT2i/GLP1-RA users before and after IPTW weighting. Any covariates not balanced after IPTW weighting will be controlled in the regression analysis for outcomes. Adjustments may be made to the final set of confounders based on availability of data. If the SMD is greater than 0.2 it is considered an important moderator for the comparison.

Missing data:
Missing covariate information will affect estimation and who is included in the analysis. Sensitivity analysis using a minimal set of covariates will be performed.

Continuous covariates such as body weight and hba1c will be imputed based on patients treatment arm, gender and age using a linear regression model.
Categorical covariates such as ethnicity and race will be imputed based on the majority category within the patients treatment arm.
For covariates like medical history and drug use, patients with no data indicating events will be assumed to have had no events and hence these type of variables will never be missing.

Timing of Analyses,
Primary analysis will be conducted at the accrual of at least 125 events in the GLP1 and DPP4i arms pooled, which will give a power of 80% with an OR of 0.6.

80% power	*OR*						
	0.3	*0.4*	*0.5*	*0.6*	*0.7*	*0.8*	*0.9*
Event number	*23*	*39*	*68*	*125*	*257*	*657*	*2946*

The N3C database is a living database with ongoing ingestion of clinical data over time.

Secondary Analysis and Supplementary Analyses

1. Comparison of mortality differences to non-COVID-19 cohort

A second set of cohorts will be constructed to get an estimate of the mortality ratio in a non-COVID adult (age≥18) population. The purpose of this supplemental analysis is whether there are *added* benefits related to use of SGLT2i and/or GLP1-RA versus DPP4i for patients with a COVID-19 diagnosis in addition to the type 2 diabetes diagnosis that exceed benefits occurring among patients with a diagnosis of type 2 diabetes with no COVID-19 diagnosis. Thus, the mortality risk among the population with type 2 diabetes and COVID-19 will be compared against those estimated non-COVID-19 population with diabetes (where the mortality risk

associated with SGLT2i and/or GLP1-RA versus DPP4i should be significantly lower in the COVID-19 population).

As there may be selection bias related to who gets a COVID-19 test, The IBM Explorys database will be used to estimate the OR for a non-COVID-19 population. Inclusion criterias are as above: participants must have a prescription of either one of the investigational drugs (GLP1-RA, SGLT2i, or DPP4i) within the last 24 months but no concurrent use within 24 months, they must also be 18 years of age in year 2020 and alive on Jan 01 2020. Mortality rates are estimated in the total cohorts and in age and gender stratified cohorts.
The comparison of the OR for the N3C COVID population will be compared with the non-COVID-19 population using a simple T-test.

3. Exploratory analyses of additional clinical outcomes

Additional outcomes may include other clinical complications: AKI (either by diagnosis code, receipt of renal replacement therapy, or doubling of baseline creatinine), cardiac injury (evidence of acute thrombosis on angiogram), sepsis syndromes, stroke, thrombosis (elevation in d-dimer levels), and inflammatory markers (IL-6), as well as acute diabetes-specific outcomes: diabetic ketoacidosis, hyperglycemic hyperosmolar syndrome.
Stratification and additional comparisons will be done on an explorative nature and for sensitivity of the primary analysis.

Together, the hierarchy of testing for the full analysis plan described above is as follows:

1. GLP1-RA vs DPP4i using TMLE in COVID-19 positive patients
2. SGLT2i vs DPP4i using TMLE in COVID-19 positive patients
3. OR from 1) versus the OR based on a non-COVID-19 positive population
4. OR from 2) versus the OR based on a non-COVID-19 positive population
5. Primary and secondary analyses (1, 2) using IPTW

Limitations of the research methods

Several limitations should be considered, some of which are due to the limitations and biases inherent to retrospective analyses of EMR data.

- Study population is defined by prescription of antihyperglycemic medication rather than diabetes ICD-10 code
- EMR data, including diagnoses, prescriptions, and procedures, are only available when the patient is seen by a provider who contributes to the EMR system; any services conducted by providers external to contributing EMR systems were not captured. This may limit data on outpatient diabetes regimen for new patient encounters. Of note, the EXPLORYS data referenced in the supplemental analyses does integrate EMR data with claims data.
- EMR data provides evidence of whether a drug was prescribed, not whether the drug was acquired or used. Adherence to prescription medications in the US is variable.
- Measures of BMI may be missing due to missing height variables. Height may be imputed for individuals missing this measure. Alternatively, in the event of significant missing data, the BMI variable will be replaced by weight in kilograms.

- There are likely inherent patient profile differences between individuals who use GLP1-RA and SGLT2i versus DPP4i, raising concern for unmeasured or residual confounding.
- There is heterogeneity in when individuals are tested and/or assigned a diagnosis of COVID-19. Therefore, COVID-19 diagnosis code does not represent a standardized time point in clinical course.
- Sample size is limited to stratify by insulin users versus non-users.

2) Significance of Results

The proposed analysis may generate results that carry implications for large patient population[1] in great clinical need.[32] There are currently no other diabetes-specific interventions to reduce COVID-19 risk (outside recommendations for the general population).[16] Testing the association between antihyperglycemic medications and outcomes in patients with a COVID-19 diagnosis builds on evidence for patient factors that confer risk for unfavorable outcomes by generating potentially actional evidence which may inform best practices for care of patients with type 2 diabetes during the COVID-19 pandemic.

3) Protection of human subjects

This is non-interventional study with use of secondary data sources (i.e. EMR database) and patients will not be contacted during any phase of the study. This study will be performed in accordance with ethical principles that are consistent with the Declaration of Helsinki, ICH GCPs, GPP and the applicable legislation on Non-Interventional Studies and/or Observational Studies.

Written consent from patients is not needed, because patient linked data are anonymised before being made available to research. All database records are statistically de-identified and certified to be fully compliant with U.S. patient confidentiality requirements set forth in the Health Insurance Portability and Accountability Act of 1996. Because this study used only deidentified patient records and did not involve the collection, use, or transmittal of individually identifiable data, institutional review board approval to conduct this study was not necessary.

The final protocol of this study must be approved or given a favourable opinion in writing in accordance with local regulation and must also approve any amendment to the protocol

4) References

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PROTOCOL LOCKED

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