Protocol 2018-7840; IMPACT #: I8R-MC-B008;

ENCePP Ref: EUPAS31111

Risk Factors Associated with Severe Hypoglycemia Among Patients with Type 2 Diabetes Mellitus Treated with Insulin

Confidential Information

Note to Regulatory Authorities: This document may contain protected personal data and/or commercially confidential information exempt from public disclosure. Eli Lilly and Company requests consultation regarding release/redaction prior to any public release. In the United States, this document is subject to Freedom of Information Act (FOIA) Exemption 4 and may not be reproduced or otherwise disseminated without the written approval of Eli Lilly and Company or its subsidiaries.

Original Protocol Electronically Signed and Approved by Lilly: Oct 30, 2019

Version 2.0 Electronically Signed and Approved by Lilly : Mar 3, 2020

Version 3: Non-substantial changes; no re-approval required ; Mar 10, 2020

Protocol Version 4.0 Electronically Signed and Approved by Lilly: approval date provided below

1. Table of Contents

Section **Page**

1. Table of Contents 2
2. List of Abbreviations 7
3. Abstract 8
4. Amendments and Updates 12
5. Milestones 13
6. Rationale and Background 14
7. Research Question and Objectives 16
7.1. Primary Objective 16
8. Research Methods 17
8.1. Study design 17
8.2. Setting 18
8.2.1. Study Time Periods 18
8.2.2. Selection Criteria 19
8.2.2.1. Inclusion Criteria 19
8.2.2.2. Exclusion Criteria 19
8.2.3. Cohort Selection 20
8.3. Variables 21
8.3.1. Pre-index Demographic and Clinical Characteristics 21
8.4. Data Sources 28
8.5. Study Size 30
8.6. Data Management 31
8.7. Data Analysis 31
8.7.1. Identification of SH Events 31
8.7.2. Matching 33
8.7.3. Missing Data 34
8.7.4. Significance Levels 34
8.7.5. Outcomes Analyses 34
8.7.5.1. Univariate Analyses 34
8.7.5.2. Multivariable Analyses 35
8.9 Limitations of the Research Methods 37
9. Protection of Human Subjects 38
10. Management and Reporting of Adverse Events/Adverse Reactions 39
10.1. Secondary Data Collection Study 39

10.2. Product Complaints 39
11. Plans for Disseminating and Communicating Study Results 40
13. References 43

List of Tables

Table **Page**

Table 8-1. Pre-index Potential Risk Factors and Definitions 22

List of Figures

Figure **Page**

Figure 8-1. Patient Selection Process.....18

Figure 8-2. Power analysis.....30

Figure 8-3. ICD-9/10-CM Diagnosis Codes for Identification of Hypoglycemic Events.....31

List of Annexes

Annex **Page**

Annex 1. List of Standalone Documents 46

Annex 2. Additional Information .....**Error! Bookmark not defined.**

2. List of Abbreviations

Term	Definition
PMTX+	PharMetrics Plus (IQVIA's Real World Adjudicated Claims Database)
ERB	Ethical review board
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AR	Adverse reaction
CCI	Charlson comorbidity index
CRF	Case report form
DRS	Disease risk score
DCSI	Diabetes complications severity index
T2DM	Type 2 diabetes mellitus
SH	Severe hypoglycemia
SAR	Serious adverse reaction

3. Abstract

Title

Risk Factors Associated with Severe Hypoglycemia Among Type 2 Diabetes Mellitus Patients Treated with Insulin

Rationale and background

Diabetes mellitus is one of the most common chronic health conditions in the world, affecting roughly 422 million (8.4%) adults around the world and an estimated 30.2 million (12.2%) adults in the U.S. While T2DM can initially be managed with noninsulin therapies, insulin therapy is typically required to achieve glycemic control after disease progression. However, progression of T2DM and insulin therapy can lead to a higher risk of hypoglycemia. Although hypoglycemia has been accepted by patients and providers as an inevitable consequence of preventing long-term diabetes complications, recent studies have found that hypoglycemia, including the severe form, is a potentially preventable cause of morbidity, mortality, high costs and impaired quality of life. Identification of additional risk factors will help clinicians recognize that there are factors which can lead to severe hypoglycemia and that it is essential that patients be prepared for hypoglycemia and severe hypoglycemia at all times if they are taking insulin.

Research question and objectives

The research question motivating this study is focused on risk factors for severe hypoglycemia in patients with type 2 diabetes (T2DM) mellitus treated with insulin.

- Besides well-established risk factors, what other patient clinical characteristics are associated with higher risk of developing severe hypoglycemia in patients with T2DM?

Primary study objective is detailed below:

Primary objective: To identify risk factors for severe hypoglycemic (SH) events in insulin-treated T2DM patients. Identification of patients at different risk of SH will be based on an evaluation of risk factors of SH using a retrospective nested case-control design.

Study design

For the primary objective, a retrospective nested case-control study with incidence density sampling utilizing adjudicated healthcare administrative claims data will be used to identify risk factors of SH based on demographic and clinical characteristics in insulin-treated T2DM patients. For the primary objective, patients with a SH event (ie, cases, index date defined as case occurrence date) and patients at risk for a SH event (ie, controls) while on insulin treatment will be exact matched on well-established risk factors and will be assessed for presence of potential additional risk factors during the 6-month pre-index period, with acute exposure to specific risk factors assessed during the 1-month period prior to the index date. Demographic and clinical characteristics will be assessed over a 6-month pre-index period.

Population

Patients with evidence of T2DM and insulin treatment in IQVIA's Real World Data Adjudicated Claims Database (PharMetrics Plus [PMTX+]) during the study period from 7/1/2012 – 12/31/2018 will be identified. Patients will have at least 6 months of continuous enrollment prior to the first insulin claim occurring. For the primary objective there will be no fixed follow-up period. Patients with other types of diabetes such as nonclinical, secondary, neonatal, gestational diabetes and type 1 diabetes, bariatric surgery, and data quality issues from 1/1/2012 – 12/31/2018 will be excluded. Patients with SH occurring while a patient is actively on insulin treatment will be included as cases in the study, with the index date defined as the date of first SH event. Patients on insulin therapy who have not had a SH event at the time of case identification will serve as potential controls. Once a patient has a SH event while on insulin therapy, they will be removed from the pool of potential controls. Cases will be direct matched to potential controls using incidence density sampling and on well-established risk factors, and the index date for controls will be defined as having the same amount of time at risk as the matched case (ie, number of days from cohort entry to the SH event for the case). Once a control patient is selected as a match, that patient will exit the control pool for the corresponding case. The excluded control will be put back to the sample when selecting controls for the next case and also may become a case later. If multiple cases occur at the same date, controls will be selected independently from the same pool of potential controls for each case.

Variables

Well-established risk factors of SH include older age, sulfonylurea use, renal insufficiency, and prior SH. Other potential risk factors for SH include type of insulin used, anti-diabetic use (by drug class), concomitant use of non-diabetes medications (including beta blockers, opioids, psychotropic medications, estrogen, corticosteroids), cognitive dysfunction, etc. Patient demographics (age, sex, region, payer type, health plan type) and clinical characteristics (Charlson comorbidity index [CCI], comorbid conditions, risk factors above, diabetes complications severity index [DCSI]) will also be described.

Data sources

Data from IQVIA's Real World Data Adjudicated Claims Database (PharMetrics Plus [PMTX+]) will be utilized. PMTX+ is comprised of adjudicated claims for more than 150 million unique enrollees across the United States. Enrollees with both medical and pharmacy coverage from 2011 represent approximately 40 million active lives annually. The database has diverse representation of geography, employers, payers, providers and therapy areas. Patients in each 3-digit zip code and every Metropolitan Statistical Area of the US are represented, with coverage of data from 90% of US hospitals, 80% of all US doctors, and representation from 85% of the Fortune 100 companies.

Study size

A power calculation estimated that the study will need approximately 440 to 2,250 patients with SH to have 80% power to detect odds ratios ranging from 1.5 to 1.2, respectively. A preliminary count of 4,815 patients with SH was found available to be matched to controls.

Data analysis

Descriptive statistics will be reported using frequency and percentage distributions for categorical variables. Mean, median, and standard deviation will be generated as measures of central tendency and variance for continuous and count variables. Conditional logistic regression will be used to identify potential risk factors for SH after matching on known risk factors.

Forward or backward variable selection procedures may be used to determine which variables to include in the final model.

Milestones

Milestone	Planned date
Data extraction	12/15/2019
Cohort build, matching, and descriptive analysis of matched/unmatched populations	3/15/2020
Data analysis and presentation of results tables	4/15/2020
Draft report of study results	12/30/2020

4. Amendments and Updates

Amendement 2

5. Milestones

Milestone	Planned date
Data extraction	12/15/2019
Cohort build, matching, and descriptive analysis of matched/unmatched populations	3/15/2020
Data analysis and presentation of results tables	4/15/2020
Final report of study results	12/30/2020

6. Rationale and Background

Diabetes mellitus is one of the most common chronic health conditions in the world, affecting roughly 422 million (8.4%) adults around the world (Silbert et al., 2018) and an estimated 30.2 million (12.2%) adults in the U.S. Type 2 diabetes mellitus (T2DM) accounts for roughly 95% of diabetes cases. It is one of the leading causes of blindness, heart attacks, kidney failure, stroke, and lower extremity amputation and is the 7th leading cause of death in the U.S (CDC, 2017).

While T2DM can initially be managed with noninsulin therapies, insulin therapy is typically required to achieve glycemic control after disease progression. However, insulin therapy contributes to a higher risk of hypoglycemia when administered incorrectly or in the presence of patient-related risk factors (e.g. inadequate or erratic carbohydrate consumption following administration of insulin). While mild or nocturnal hypoglycemia is usually resolved at home, severe hypoglycemia (SH) requires assistance from others to recover (e.g. family members, caregivers) that may require medical assistance which may result in an emergency room or inpatient visit (ADA 2019, Holstein et al., 2012, Leese et al., 2003). While commonly accepted by patients and their healthcare providers as an inevitable consequence of preventing long-term diabetes complications, hypoglycemia is increasingly recognized an important and potentially preventable cause of morbidity, mortality, high costs, diminished productivity, and impaired quality of life (Silbert et al., 2018). In a recent observational healthcare claims database study of patients with T2DM treated with basal insulin, patients with a SH event in the first year after basal insulin initiation had nearly $10,000 more in healthcare expenditures at baseline compared to patients who did not have a SH event. Total healthcare expenditures during 1-year follow-up increased by over $11,000 in the SH group, while there was no change in the non-SH group (Fonseca et al., 2017).

While the risk of SH is known to be elevated in the T1DM population, the risk has been understudied in the T2DM population, which makes up the majority of all diabetes patients. Among the T2DM population, a strong risk factor for SH is insulin use (Geller et al. 2014, Misra-Hebert et al., 2018, Lee et al., 2017, Karter et al. 2017, Han et al. 2018), however, there is a paucity of knowledge about the range of SH risk factors among the insulin-treated sub-population. Frequently reported risk factors of SH among patients with T2DM are older age

(Fonseca et al. 2017, Lee et al., 2017, Karter et al. 2017, Han et al. 2018, Shao et al. 2018), sulfonylurea use (Misra-Hebert et al. 2018, Karter et al. 2017), previous history of hypoglycemia-related medical visit (severe or non-severe) (Fonseca et al. 2017, Misra-Hebert et al. 2018), duration of diabetes (Han et al. 2018, Shao et al. 2018), and renal disease (Lin et al. 2010, Fonseca et al. 2018, Karter et al. 2017, Han et al. 2018). Other understudied but potential risk factors include concomitant medication use (e.g., beta blockers, psychotropics, opioids, estrogen hormone replacement therapy, corticosteroids) (Kenny et al. 2013, Graveling & Frier 2009, White et al. 2007, Martin-Timon & Ganizo-Gomez, 2015), oral anti-diabetic medications (Misra-Hebert et al. 2018, Han et al. 2018, Lee et al. 2017), and cognitive impairment (Kostev et al. 2014, Lee et al. 2017). Specifically, Karter et al. 2017 identified six most important risk factors for severe hypoglycemia including prior episodes of hypoglycemia, ED visits, insulin use, sulfonylurea use, severe or end-stage kidney disease, and age using recursive portioning. The classification tree was pruned to optimize predictive accuracy, model simplicity, practicality of implementation, and intuitive clinical interpretation. This study focuses on identifying additional risk factors beyond well-established ones using a nested case control design. Contribution of each risk factor to SH risk (ie, odds ratio) will be estimated by conditional logistic regression, enabling a comparison of associated risk across different risk factors.

This study aims to identify risk factors other than those that have already been reported (such as older age, sulfonylurea use, renal insufficiency, and prior SH) among insulin-treated adults with T2DM using an administrative healthcare claims database. Furthermore, the comparative safety study will describe and compare demographic and clinical characteristics in insulin-treated patients with T2DM who do and do not experience a SH event.

7. Research Question and Objectives

The research question motivating this study is focused on risk factors for severe hypoglycemia in patients with T2DM treated with insulin.

- Besides well-established risk factors, what other patient clinical characteristics are associated with higher risk of developing severe hypoglycemia in patients with T2DM?

7.1. Primary Objective

1. To identify risk factors for severe hypoglycemic (SH) events in insulin-treated patients with type 2 diabetes mellitus (T2DM). Risk factors will be evaluated using a retrospective nested case-control study design. Risk factors will be grouped into those that are well-established, as reported in the literature, and other potential risk factors. Conditional logistic regression will be used after direct matching on well-established risk factors to uncover new risk factors for SH in this patient population.

8. Research Methods

8.1. Study design

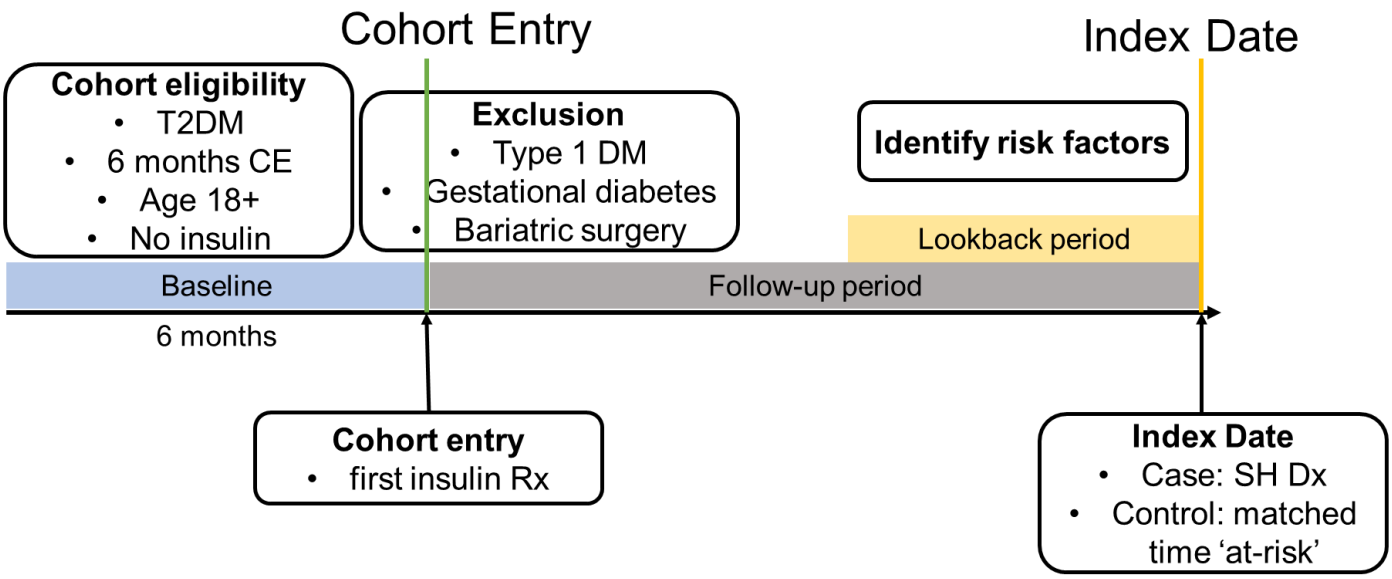
For the primary objective, a retrospective nested case-control study with incidence density sampling (Richardson DB. 2004) utilizing adjudicated healthcare administrative claims data (IQVIA's Read World Data Adjudicated Claims Database (PharMetrics Plus [PMTX+]) will be used to identify risk factors of SH among patients with insulin-treated type 2 diabetes mellitus (T2DM). The study will be comprised of the following patients:

- Patients who experience a SH event while on insulin therapy (cases)
- Patients who are at risk of a SH event while on insulin therapy (noncases)

Patients with a first insulin claim (defined as cohort entry) during the study period (7/1/2012 – 12/31/2018) and evidence of T2DM during 6 months before or at first insulin claim date will be identified. Patients with insulin use during 6 months prior to cohort entry will be excluded. Patients will be followed from the first insulin claim until the earliest of the following (denoted as follow-up period): loss of insulin coverage (defined as a gap in treatment of > 90 days after insulin prescription claim date plus days of supply) (Moura et al. 2018), evidence of first SH during insulin treatment period plus 30 days after last insulin supply runs out, loss of continuous enrollment for pharmacy/medical benefits, or end of the study period. Patients will be evaluated for SH occurring during the follow-up period. Cases will be defined as patients with at least 1 SH occurring during the follow-up period, indexed on the first SH date defined as number of days of SH occurrence after cohort entry, and exact-matched to control patients on well-established risk factors (i.e., age, use of sulfonylurea, prior SH, renal insufficiency) during 6 months pre-index. Controls will be selected using incidence density sampling from all patients still at risk for SH at the time a case is found, and will be indexed on the same index date to have the same amount of time at risk as the matched case after cohort entry as the matched case. When a control exits the cohort due to loss of insulin coverage, its at-risk period will have the same number of days (30) added after insulin supply runs out as for cases. Once a control patient is selected as a match, that patient will exit the control pool for the corresponding case. The excluded control will be put back to the sample when selecting controls for the next case and also may become a case later. If multiple cases occur at the same date, controls will be selected independently from the same pool

of potential controls for each case. Figure 8-1 illustrates the cohort selection process and the overall study design.

Figure 8-1. Patient Selection Process



Cohort exit: enrollees followed until lose CE, 90+ without insulin Rx, SH event, or end of observation window

(Note that an SH event may occur during insulin treatment period plus 30 days after insulin supply runs out, and similarly controls that exit the cohort for loss of insulin coverage may be at risk 30 days after insulin supply runs out.)

8.2. Setting

8.2.1. Study Time Periods

- Study period: 7/1/2012 to 12/31/2018
- Cohort entry: First insulin prescription during the study period
- Baseline period: 6 months prior to cohort entry
- Follow-up period: cohort entry to cohort exit
- Cohort exit: individuals will be followed until the first of the following events:

  - First SH event during insulin treatment period plus 30 days after insulin supply runs out
  - Loss of insulin coverage (defined as a gap in insulin treatment of > 90 days after last insulin supply runs out) (Moura et al. 2018)
  - Loss of continuous enrollment for pharmacy/medical benefits (>= 30 days of gap)
  - End of study period
- Index date:
  - Cases: date of first SH during the follow-up period defined as number of days of SH occurrence after cohort entry
  - Controls: same as index date of a matched case so they have the same amount of time at risk as the matched case after cohort entry
- Pre-index period:
  - 6 months prior to index date

8.2.2. Selection Criteria

Patients will be included in the study if they meet the below selection criteria:

8.2.2.1. Inclusion Criteria

1) ≥ 1 claims for insulin between 7/1/2012 and 12/31/2018. The date of the first insulin claim will be the cohort entry date.
2) ≥1 diagnoses for T2DM (ICD-9-CM codes: 250.x0, 250.x2; ICD-10-CM codes: E11.xx) during the baseline period including the first insulin prescription (cohort entry) date
3) ≥ 18 years of age on the date of cohort entry
4) ≥ 6 months of continuous health plan enrollment with both medical and pharmacy benefits during the baseline period

8.2.2.2. Exclusion Criteria

Patients will be excluded if they meet any of the below criteria:

1) Any insulin prescription during the baseline period

2) Diagnosis of type 1 diabetes (ICD-9-CM: 250.x1, 250.x3; ICD-10-CM: E10.xx), gestational diabetes (ICD-9-CM: 648.8x; ICD-10-CM: O24.4), nonclinical diabetes ((ICD-9-CM: 790.29; ICD-10-CM: R73.09), secondary diabetes (ICD-9-CM: 249.x; ICD-10-CM: E13.x), neonatal diabetes mellitus (ICD-9-CM: 75.1; ICD-10-CM: P70.2) and baratric surgery from 1/1/2012-12/31/2018.
3) Data quality issues, defined as missing or invalid year of birth, unknown sex, unknown region, aged ≥ 65 years not covered by Medicare Advantage, missing or invalid payer type (i.e., covered by Medicare Supplemental, State Children's Health Insurance Program (SCHIP), or pharmacy only coverage due to incomplete data capture)

8.2.3. Cohort Selection

Once the cohort of insulin-treated T2DM patients is selected, the time at risk will be established as the time from the cohort entry until the earliest of: loss of insulin coverage, the end of the study period, the end of continuous medical and pharmacy benefits, or evidence of SH during insulin treatment plus 30 days after last insulin supply runs out.

Cases will be defined as patients with ≥ 1 SH event occurring during the follow-up period and will be indexed based on the date of the first SH as number of days after case occurrence, based on ICD-9-CM and ICD-10-CM diagnosis codes proposed by Karter et al. (Karter et al., 2019), described in Section 8.7.1. Patients still at risk for SH at the index date of case identification will serve as potential controls for that case with incidence density sampling. A control that later became a case within 6 months after the occurrence date of the current case will be excluded from the risk set of controls for each case to avoid potential overlap of 6-month pre-index risk factor assessment periods.

Potential controls will be direct matched to cases on well-established risk factors (described in Section 8.7.2), with a ratio of up to 2 controls to 1 case, and the index date will be defined as having the same amount of time at risk as the matched case (ie, number of days from cohort entry to the SH event for the case). If there is a sufficient sample size of cases, 1:1 matching will be used (Strom, Kimmel and Hennessy 2012).

8.3. Variables

8.3.1. Pre-index Demographic and Clinical Characteristics

Demographic and clinical characteristics will be collected during the 6-month pre-index period. Some variables will also be reported within 1-month prior to the index date, to capture acute exposure. The demographic and clinical characteristics of interest are detailed in Table 8-1. These potential risk factors include those identified through literature review of both manuscripts and congress presentations as well as medications associated with a disease state that has reported higher risk of SH in the literature (ie, psychiatric patients). Forward or backward variable selection procedures may be used to determine which variables to include in the final conditional logistic regression model. For the small number of variables that may have acute impact on SH defined both during the 6 months and 1 month prior to index date in the following table, to avoid overlapping of the 2 periods, 6 months pre-index will not include the last month pre-index.

Well-Established Risk Factors Measurable in Claims

- Age at index date
    - Categorical: grouped into 5-year increments
- Sulfonylurea use
    - During 6-months prior to index
- Prior SH event 6 months pre-index
    - Binary indicator flag
- Renal disease: A binary indicator variable for patients with any claims for chornic renal disease or ESRD
    - During 6-months prior to index

Other Potential Risk Factors Measurable in Claims:

Table 8-1. Pre-index Potential Risk Factors and Definitions

Variable	Definition
Sex	Male/Female as reported in the data
Geographic region	5 regions as reported in the data: Northeast, Midwest, South, West, Unknown
Insurance type	Insurance type at index, as reported in the data and grouped into the following categories: Commercial, Medicaid, Medicare Risk, Self-Insured, other/unknown
Health plan type	Health plan type, as reported in the data and grouped into the following categories: HMO, PPO, POS, Consumer-directed, Indemnity, Other
Index year	The year of the index date will be extracted and reported as follows: 2013, 2014, 2015, 2016, 2017, 2018
Charlson comorbidity index (CCI), continuous	A CCI score will be assigned by assessing all claims occurring in the 6-month pre-index period for ICD-9-CM and ICD-10-CM codes indicative of comorbid conditions for the Dartmouth-Manitoba modification of the Charlson Comorbidity Index. the distribution of raw CCI scores will be reported
CCI, categorical	CCI score will be grouped into the following categories: 0, 1, 2, 3, 4+
Diabetes Complications Severity Index (DCSI)	A DCSI score will be assigned by assessing all claims occurring in the 6-month pre-index period for ICD-9-CM and ICD-10-CM codes indicative of diabetes complications. A higher DCSI score is indicative of more severe diabetes. The distribution of raw DCSI will be reported.
DCSI, categorical	DCSI will be grouped into the following categories: 0, 1, 2, 3, 4, 5+.
Alcohol/Drug Abuse	A binary indicator variable will be created for patients with any claims for alcohol/drug abuse occurring during the 6-month pre-index period

Variable	Definition
Anxiety	A binary indicator variable will be created for patients with any claims for anxiety occurring during the 6-month pre-index period
Asthma	A binary indicator variable will be created for patients with any claims for asthma occurring during the 6-month pre-index period
Cancer	A binary indicator variable will be created for patients with any claims for cancer (not including non-melanoma skin cancer) occurring during the 6-month pre-index period
Cardiac Arrhythmia	A binary indicator variable will be created for patients with any claims for cardiac arrhythmia occurring during the 6-month pre-index period
Cardiac Valvular Disease	A binary indicator variable will be created for patients with any claims for cardiac valvular disease occurring during the 6-month pre-index period
Cerebrovascular Disease	A binary indicator variable will be created for patients with any claims for cerebrovascular disease occurring during the 6-month pre-index period
Chronic Pain/Fibromyalgia	A binary indicator variable will be created for patients with any claims for chronic pain or fibromyalgia occurring during the 6-month pre-index period
Congestive Heart Failure	A binary indicator variable will be created for patients with any claims for congestive heart failure occurring during the 6-month pre-index period
COPD	A binary indicator variable will be created for patients with any claims for COPD occurring during the 6-month pre-index period
Dementia	A binary indicator variable will be created for patients with any claims for dementia occurring during the 6-month pre-index period

Variable	Definition
Depression	A binary indicator variable will be created for patients with any claims for depression occurring during the 6-month pre-index period
Diabetic retinopathy	A binary indicator variable will be created for patients with any claims for diabetic retinopathy occurring during the 6-month pre-index period
Dyslipidemia	A binary indicator variable will be created for patients with any claims for dyslipidemia occurring during the 6-month pre-index period
Epilepsy/Seizure Disorder	A binary indicator variable will be created for patients with any claims for epilepsy/seizure disorders occurring during the 6-month pre-index period
Hepatitis	A binary indicator variable will be created for patients with any claims for hepatitis occurring during the 6-month pre-index period
HIV/AIDS	A binary indicator variable will be created for patients with any claims for HIV/AIDS occurring during the 6-month pre-index period
Hypertension	A binary indicator variable will be created for patients with any claims for hypertension occurring during the 6-month pre-index period
Liver/Gallbladder/Pancreatic Disease	A binary indicator variable will be created for patients with any claims for liver/gallbladder/pancreatic disease occurring during the 6-month pre-index period
Myocardial Infarction(MI)/CAD	A binary indicator variable will be created for patients with any claims for MI/CAD occurring during the 6-month pre-index period
Osteoarthritis	A binary indicator variable will be created for patients with any claims for osteoarthritis occurring during the 6-month pre-index period

Variable	Definition
Paralysis/Hemiplegia/Paraplegia	A binary indicator variable will be created for patients with any claims for paralysis/hemiplegia/paraplegia occurring during the 6-month pre-index period
Peptic Ulcer Disease	A binary indicator variable will be created for patients with any claims for peptic ulcer disease occurring during the 6-month pre-index period
Peripheral Vascular Disease	A binary indicator variable will be created for patients with any claims for peripheral vascular disease occurring during the 6-month pre-index period
Rheumatologic Disease (SLE, RA, AS, PsA)	A binary indicator variable will be created for patients with any claims for rheumatologic disease occurring during the 6-month pre-index period
Schizophrenia	A binary indicator variable will be created for patients with any claims for schizophrenia occurring during the 6-month pre-index period
Sleep Disorders	A binary indicator variable will be created for patients with any claims for sleep disorders occurring during the 6-month pre-index period
Smoking or History of Smoking	A binary indicator variable will be created for patients with any claims for smoking or history of smoking occurring during the 6-month pre-index period
Thyroid Disease	A binary indicator variable will be created for patients with any claims for thyroid disease occurring during the 6-month pre-index period
Pregnancy	Pregnancy during 6 month pre-index period
Prior diabetes medication use	A series of binary indicator variables will be created for patients with claims for the following anti-diabetics: long-acting insulin, rapid-acting insulin, short-acting insulin, NPH, insulin mixes, and oral anti-diabetics by drug class (alpha-glucosidase inhibitors, amylin analogs, antidiabetic combos, biguanides, dipeptidyl peptidase IV inhibitors, GLP-1 agonistsincretin mimetic agents, meglitinides, sodium-

Variable	Definition
	glucose cotransporter inhibitor, thiazolidinediones) occurring during the 6-month pre-index period and during 1 month pre-index. Insulin use alone vs. in combination with oral/injectable anti-diabetic medication use (as broken out above
Average daily dose for insulin	Average daily dose for insulin, for each insulin class as mentioned above and for all insulins combined, used during 6 months pre-index
CGM use	Continuous glucose monitoring during 6 months pre-index
Use of beta-blockers	A binary indicator variable will be created for patients with any claims for beta-blockers during the 6-month pre-index period. Please break out new and old generations of beta-blockers and test if it makes a difference.
Acute use of beta-blockers	A binary indicator variable will be created for patients with any claims for beta-blockers within 1-month pre-index. Please break out new and old generations of beta-blockers and test if it makes a difference.
Use of opioids	A binary indicator variable will be created for patients with any claims for opioids during the 6-month pre-index period
Acute use of opioids	A binary indicator variable will be created for patients with any claims for opioids within 1-month pre-index
Use of psychotropic medications	A series of binary indicator variables will be created for patients with any claims for psychotropic medications (by drug class) during the 6-month pre-index
Acute use of psychotropic medications	A series of binary indicator variables will be created for patients with any claims for psychotropic medications (by drug class) within 1-month pre-index: Antidepressants

Variable	Definition
	• Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, citalopram, sertraline, paroxetine, escitalopram • Serotonin and norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine and duloxetine • Tricyclics • Bupropion Anti-anxiety medications • Benzodiazepines, such as clonazepam, alprazolam, and lorazepam • Buspirone Stimulants, such as methylphenidate, amphetamine, dextroamphetamine, and lisdexamfetamine dimesylate Antipsychotics • Typical antipsychotics, such as chlorpromazine, haloperidol, perphenazine, and fluphenazine • Atypical antipsychotics, such as risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, and lurasidone
Mood disorder	Defined as evidence of anxiety or depression within the 6-month pre-index period and within 1-month prior to index
Use of estrogen	A binary indicator variable will be created for patients with any claims for estrogen during the 6-month pre-index period
Acute use of estrogen	A binary indicator variable will be created for patients with any claims for estrogen within 1-month pre-index

Variable	Definition
Use of testosterone	A binary indicator variable will be created for patients with any claims for testosterone during the 6-month pre-index period
Acute use of testosterone	A binary indicator variable will be created for patients with any claims for testosterone within 1-month pre-index
Use of corticosteroids	A binary indicator variable will be created for patients with any claims for corticosteroids during the 6-month pre-index period
Acute use of corticosteroids	A binary indicator variable will be created for patients with any claims for corticosteroids within 1-month pre-index
Use of glucagon	A binary indicator variable will be created for patients with any claims for glucagon during the 6-month pre-index period
Pre-index healthcare resource utilization	Variables for pre-index healthcare utilization occurring during the 6-month pre-index period (not including the index date) will be tabulated, as described in Section **Error! Reference source not found.**.
Use of thyroid medications	A binary indicator variable will be created for patients with any claims for thyroid medications during the 6-month pre-index period
Acute use of thyroid medications	A binary indicator variable will be created for patients with any claims for thyroid medications within 1-month pre-index
Use of thiazides	A binary indicator variable will be created for patients with any claims for thiazides during the 6-month pre-index period
Acute use of thiazides	A binary indicator variable will be created for patients with any claims for thiazides within 1-month pre-index
Acute use of epinephrine	A binary indicator variable will be created for patients with any claims for epinephrine within 1-month pre-index
Use of niacin	A binary indicator variable will be created for patients with any claims for niacin during the 6-month pre-index period

8.4. Data Sources

The aggregated IQVIA Real World Data Adjudicated Claims Database (PharMetrics Plus [PMTX+]) is comprised of adjudicated claims for more than 150 million unique enrollees across the United States. Enrollees with both medical and pharmacy coverage from 2011 represent approximately 40 million active lives annually. Data are available from 2006 onwards; with a typical 3-4-month lag due to claims adjudication.

The PMTX + database has diverse representation of geography, employers, payers, providers and therapy areas. Patients in each 3-digit zip code and every Metropolitan Statistical Area of the US are represented, with coverage of data from 90% of US hospitals, 80% of all US doctors, and representation from 85% of the Fortune 100 companies.

In addition to standard fields such as inpatient and outpatient diagnoses and procedures, retail and mail order prescription records, PMTX + has detailed information on the pharmacy and medical benefit (co-payment, deductible), the inpatient stay (admission type and source, discharge status) and provider details (specialty, provider ID). All 3-digit zip codes in the US are covered and reported allowing more granular patient segmentation and comparisons by geography.

Payment amounts include the negotiated rate between the plan and providers (allowed) and the actual amount paid by health plans to the provider for all services rendered. Charge amount is also available for a subset of claims. Other data elements include dates of service, demographic variables (age, sex, and geographic region), product type (e.g., HMO, PPO), payer type (e.g., commercial, self-pay), and start and stop dates of health-plan enrolment. Due to the broad reach of the data, records in the PMTX + database are representative of the national, commercially insured population in terms of age and sex for individuals aged 65 and under. The data are also longitudinal, with more than 30 million patients who have both medical and pharmacy coverage with 3 or more years of continuous enrollment. All data are HIPAA compliant to protect patient privacy.

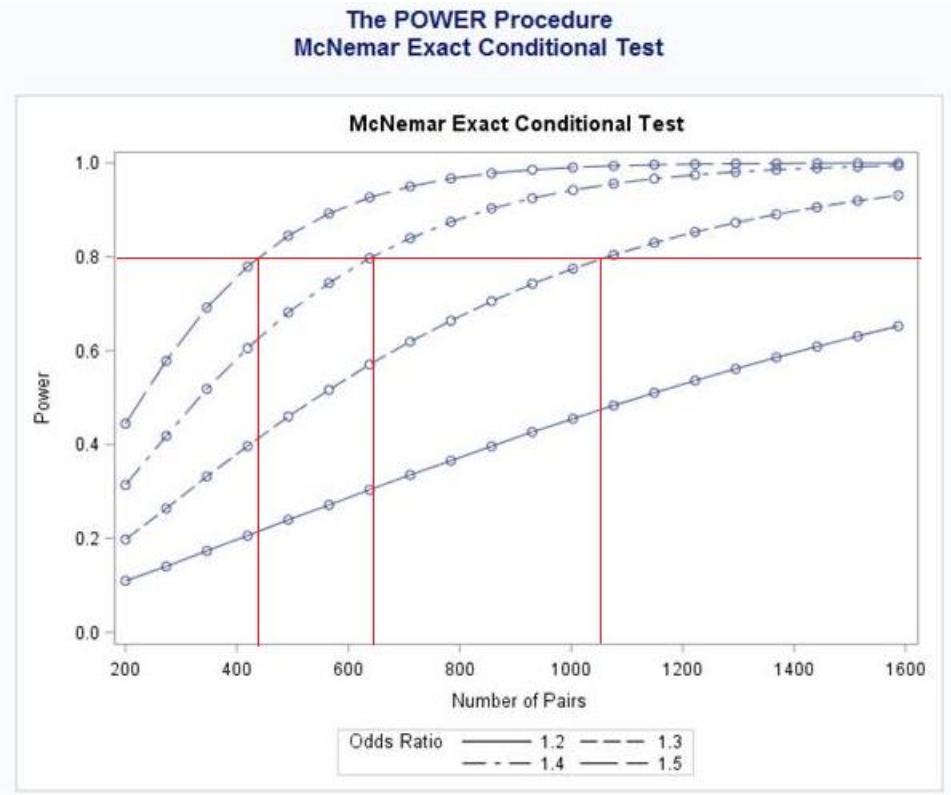
The PMTX+ database includes the following patient level information:

- Year of birth, sex
- Geography
- Diagnoses codes
- Procedure codes (CPT4, ICD, HCPCS, Revenue Center)
- Date of service
- Location of care
- Amounts allowed and paid by payer
- Patient liability amount (copay, coinsurance, deductible)
- Payer types
- Enrollment status

8.5. Study Size

A power calculation using the McNemar Exact Conditional test with alpha = 0.05 and assuming a 21% prevalence of the risk factor for SH in the population of T2DM patients on insulin (Edridge CL et al., 2015) with estimated correlation between SH and non-SH patients (R^2) of 0.2 was conducted. Roughly 440 to 2,250 cases would be needed to detect odds ratios ranging from 1.5 to 1.2, respectively (Figure 8-2).

Figure 8-2. Power analysis



A preliminary count of 4,815 patients with SH was found to meet the cohort selection criteria and can be matched to controls.

8.6. Data Management

Datasets and analytic programs will be kept on a secure server and archived per Lilly record retention procedures. If the study is being conducted by a third party, the datasets and analytic programs will be stored according to the vendor's (IQVIA) procedures.

8.7. Data Analysis

8.7.1. Identification of SH Events

Identification of SH events

SH events will be identified using ICD-9/10-CM codes below recently validated (Figure 8-3; Ginde et al., 2008; Karter et al., 2019). All ICD-9/10-CM codes listed in Figure 8-3 will be used to define a SH event depending on whether the event occurred before or after October 1, 2015. Events occurring within 24 hours of each other will count as one episode. To ensure that rule-out diagnoses are not captured, only non-ancillary claims will be used to identify SH events. Non-ancillary claims include inpatient/ED claims, physician office visits, medical procedures, etc. We limit to non-ancillary claims to ensure that we were not picking up things like rule-out diagnoses of hypoglycemia. For outpatient claims, we only use primary diagnosis to identify SH events. For inpatient/ED claims, we use diagnosis codes in all positions to be consistent with Ginde et al. 2008. We note that these events are those severe enough to require health care encounters – as such any healthcare visit with these codes will be considered as a SH event. The study investigates risk factors for the events as defined, which do not necessarily capture all hypoglycemia events.

Figure 8-3. ICD-9/10-CM Diagnosis Codes for Identification of Hypoglycemic Events

ICD-9 Code	**Description**
251.0	Hypoglycemic coma
251.1	Other specified hypoglycemia
251.2	Hypoglycemia, unspecified
962.3	Poisoning by insulins and antidiabetic agents
250.8	Diabetes with other specified manifestations (without the following co-diagnoses codes on the same claim: 259.8, 272.7, 681.xx, 682.xx, 686.9x, 707.1-707.9, 709.3, 730.0-730.2, 731.8)
ICD-10 Code	**Description**
E08.641	Diabetes mellitus due to underlying condition with hypoglycemia with coma
E08.649	Diabetes mellitus due to underlying condition with hypoglycemia without coma
E09.641	Drug or chemical induced diabetes mellitus with hypoglycemia with coma
E09.649	Drug or chemical induced diabetes mellitus with hypoglycemia without coma
E11.641	Type 2 diabetes mellitus with hypoglycemia with coma
E11.649	Type 2 diabetes mellitus with hypoglycemia without coma
E13.641	Other specified diabetes mellitus with hypoglycemia with coma
E13.649	Other specified diabetes mellitus with hypoglycemia without coma

E15	Nondiabetic hypoglycemic coma
E16.0	Drug-induced hypoglycemia without coma
E16.1	Other hypoglycemia
E16.2	Hypoglycemia, unspecified
T38.3X1A	Poisoning by insulin and oral hypoglycemic [antidiabetic] drugs, accidental (unintentional), initial encounter
T38.3X1D	Poisoning by insulin and oral hypoglycemic [antidiabetic] drugs, accidental (unintentional), subsequent encounter
T38.3X1S	Poisoning by insulin and oral hypoglycemic [antidiabetic] drugs, accidental (unintentional), sequela
T38.3X2A	Poisoning by insulin and oral hypoglycemic [antidiabetic] drugs, intentional self-harm, initial encounter
T38.3X2D	Poisoning by insulin and oral hypoglycemic [antidiabetic] drugs, intentional self-harm, subsequent encounter
T38.3X2S	Poisoning by insulin and oral hypoglycemic [antidiabetic] drugs, intentional self-harm, sequela
T38.3X3A	Poisoning by insulin and oral hypoglycemic [antidiabetic] drugs, assault, initial encounter
T38.3X3D	Poisoning by insulin and oral hypoglycemic [antidiabetic] drugs, assault, subsequent encounter
T38.3X3S	Poisoning by insulin and oral hypoglycemic [antidiabetic] drugs, assault, sequela
T38.3X4A	Poisoning by insulin and oral hypoglycemic [antidiabetic] drugs, undetermined, initial encounter
T38.3X4D	Poisoning by insulin and oral hypoglycemic [antidiabetic] drugs, undetermined, subsequent encounter
T38.3X4S	Poisoning by insulin and oral hypoglycemic [antidiabetic] drugs, undetermined, sequela
T38.3X5A	Adverse effect of insulin and oral hypoglycemic [antidiabetic] drugs, initial encounter
T38.3X5D	Adverse effect of insulin and oral hypoglycemic [antidiabetic] drugs, subsequent encounter
T38.3X5S	Adverse effect of insulin and oral hypoglycemic [antidiabetic] drugs, sequela

8.7.2. Matching

In addition to incidence density sample matching, cases and controls will be exact matched on well-established risk factors as detailed in Section **Error! Reference source not found.** for the primary analysis.

- Age: Age will be calculated at index date, and grouped into 5-year increments
- Prior sulfonylurea use: A binary indicator variable will be created for the 6-month pre-index period

- Renal disease: A binary indicator variable will be created for the 6-month pre-index period
- Prior SH: A binary indicator variable will be created for the 6-month pre-index period

For each case, a risk set composed of all potential controls that fall within the same 5-year age category will be created. The remaining matching variables will be calculated for patients in the risk set and patients within each risk set will be exact matched on the remaining variables, beginning with the hardest to match cases (those with the least potential controls). A random sample of up to 2 controls who match on all variables will be selected. This will be repeated until all cases have been matched, or no further matches can be made. If the sample size for cases is sufficient, patients will be matched with a ratio of 1:1 (Strom, Kimmel and Hennessy 2012).

If exact matching fails to attain an acceptable level of matching, disease risk score (DRS) matching may be used. A multivariable logistic regression model will be used to assign a disease risk score (Wyss et. al., 2016) to each patient, based on the presence of well-established risk factors. The dependent variable for the disease risk score model will be SH. All well-established risk factors will be included as independent variables in the model. The disease risk score is the predicted probability of having SH, conditioned on presence of well-established risk factors. Greedy nearest neighbor DRS matching without replacement with a caliper width of 0.2 of the SD of the logit of the propensity score will be used to create a cohort of final matched SH and non-SH patients at a ratio of 1:2 in order to identify new risk factors for SH.

8.7.3. Missing Data

Patients with missing data on demographics (age, sex, and geographic region) will be excluded from all analyses. Data cleaning measures may be applied to days' supply of insulin claims prior to cohort eligibility pending data exploration, and may include setting missing or extreme values to the median by NDC/HCPCS code. Any and all cleaning to be done before they create the cohort sample. Since the study is utilizing adjudicated claims with available healthplan enrolment information, the absence of diagnoses/procedures/medications are not assumed to be missing data.

8.7.4. Significance Levels

All tests will be 2-sided with a 0.05 alpha level of significance. All analyses will be conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC).

8.7.5. Outcomes Analyses

8.7.5.1. Univariate Analyses

Descriptive statistics will be reported using frequency and percentage distributions for categorical variables. Mean, median, and standard deviation will be generated as measures of central tendency and variance for continuous and count variables. Comparison of pre-index demographics, clinical characteristicsbetween cases and controls will be made using McNemar's/Stuart-Maxwell (Sun X, Yang Z, 2008; matched samples) and Chi-Square (unmatched samples) tests for binary/categorical variables and paired t-test (matched samples) and t-tests (unmatched samples) for continuous variables.

To identify the initial set of variables for the multivariable model we will conduct univariate analyses of the relationships between SH and each of the potential risk factors described in Section 8.3.1 that were not used as matching variables. Risk factors with a P-value < 0.10 will be kept for further evaluation in the multivariable analysis (see below).

8.7.5.2. Multivariable Analyses

Evaluation of risk factors for severe hypoglycaemia (Primary Objective)

A conditional logistic regression model will be used to evaluate the relative contribution of independent variables as risk factors according to the intensity of their influence on the development of SH events. The dependent variable will be the occurrence of a SH event during the follow-up period. Independent variables for the model will include demographic and clinical characteristics that are kept from the univariate analysis. For variables defined both during the 6 months and 1 month prior to index date, to avoid overlapping of the 2 periods, 6 months pre-index shall not include the last month pre-index.

Some interactions, especially for significant covariates or those defined by the study team a priori may be considered for inclusion in the model. Correlation matrice and Spearman's rank correlation will be used to determine correlation between variables, with a value of >0.5 indicating high correlation. For correlated variables, those of most clinical significance will be included in the model.

Results for the model will be presented in terms of odds ratios (OR) along with corresponding 95% confidence intervals (CI). A forward (or backward) elimination procedure will be applied to keep only significant covariates (at level 0.05) in the model. Dropped covariates will be identified with their last in-model OR p-value. Variables with OR > 1.0 having a 95% CI that does not include 1.0 will be identified as risk factors for SH. Some variables may also be found to be protective (OR < 1.0 and 95% CI excludes 1.0).

Sensitivity Analysis

A nested case-control study with no matching will be employed as a sensitivity analysis for the primary objective to determine which covariates emerge as risk factors, including those known risk factors in the study sample. All patients with a SH occurring during the insulin treatment period will be designated as cases and patients with no SH occurring during the insulin treatment period will be designated as controls. To define the index date for controls, the distribution of time from the first insulin claim during the follow-up period until the index date in cases will be grouped into deciles. Patients in the control group will be randomly assigned to one of ten subgroups and index dates will be generated by adding to the first insulin claim a random number of days that falls within the assigned decile among the cases. For example, if a patient in the control pool is randomly assigned to the 4^{th} decile, the index date for this patient would be generated by adding a random number of days between 122 and 210 to the date of first insulin claim observed during the index period (Table 8-). This method will ensure that the distribution of time between insulin and the index date will have similar distributions in the case and control samples. After the index dates are generated for the controls, a logistic regression model will be used to evaluate the relative contribution of independent variables as risk factors according to the intensity of their influence upon the development of SH events. The dependent variable will be the occurrence of a SH event during the follow-up period. Independent variables for the model

will include demographic and clinical characteristics described in Section 8.3.1 and Section **Error! Reference source not found.**, including the well-established risk factors. The correlation matrix produced by the model will be used to determine correlations between parameter estimates, with a value of >0.5 indicating high correlation.

Table 8-2. Example of time between insulin and SH per decile in cases.

Decile	Range of number of days between insulin date and index date
1	0-20
2	21-75
3	76-121
4	122-210
5	211-268
6	269-300
7	301-330
8	331-353
9	354-380
10	381-405

8.8 Quality Control

Programming for this project will be conducted by a primary analyst and validated by a separate analyst (validation analyst). For all data processing steps, the validation analyst will review the programme along with input and output datasets. For the analysis steps of the project, double-programming techniques to reduce the potential for programming errors may be employed.

Dual programming will be limited to the conditional logistic regression model for the primary objective, and to the logistic regression model in the sensitivity analysis.

8.9 Limitations of the Research Methods

Studies conducted using administrative claims databases have inherent limitations. Data were collected for billing rather than research purposes so some variables that may be of interest are not available. Specifically, the absence of claims with diagnosis codes for hypoglycaemia does not imply that patients do not experience any hypoglycaemic events. It is possible that patients in the non-SH group experience hypoglycemic events, however, these events are not considered severe since they did not trigger a billable visit to healthcare provider. Among patients who seek clinical care, the algorithms adopted (Ginde et al., 2008; Karter et al., 2019) are considered the gold standard to identify SH events using diagnosis codes as they were validated based on a chart review and was recently updated to ICD-10-CM codes. Similarly, behavioural and social-economic factors which may be associated with severe hypoglycaemia are not available for study. The PMTX+ database is nationally representative of commercially/self-insured patients. Patients aged ≥ 65 years are underrepresented as Medicare fee-for-service claims are not included in the data, and the Medicaid population is not well represented.

9. Protection of Human Subjects

This study will use only de-identified patient records and will not involve the collection of any prospective data from patients, nor will it involve any transmission of individually identifiable data, therefore it is expected that no IRB review or approval is required. An IRB waiver will be obtained prior to analysis.

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Pharmacoepidemiology Practices (GPPs) and applicable laws and regulations of the country or countries where the study is being conducted, as appropriate.

10. Management and Reporting of Adverse Events/Adverse Reactions

10.1. Secondary Data Collection Study

This is a non-interventional study based on secondary data use, and therefore no individual case safety report (ICSR) reporting is required. The study protocol-defined AEs include: severe hypoglycemia. All protocol-defined adverse events collected will be summarized in the final study report. No other AEs will be collected.

10.2. Product Complaints

Not applicable, as the study does not involve identifiable patient data associated with an Eli Lilly and Company product. No requirement for protocol-defined AE collection and reporting (there are no protocol-defined AEs). Any ADRs associated with any Lilly or non-Lilly product are not actively collected, but should be reported per local laws and regulations.

11. Plans for Disseminating and Communicating Study Results

A final report in Microsoft Word will be developed at the conclusion of the study, with result tables included in a Microsoft Excel workbook in the Appendix. The study findings may be submitted to a scientific congress and/or to a peer reviewed journal.

12. Post-hoc sensitivity analysis after analysis completion

The primary analysis focused on estimating the influence on the main effects on SH risk of drug exposure within 1 month and 2-6 months prior to SH occurrence in addition to other potential risk factors. After the protocol specified analysis was completed, it was proposed to conduct a post-hoc sensitivity analysis to further clarify the effects of timing of drug exposure by considering interaction between drug exposures within 1 month and within 2-6 months prior to events.

Note that this is a post hoc sensitivity analysis proposed after analysis completion. It is also ad hoc by nature as we only test a subset of variables from the final estimated model (see the Appendix) as opposed to rerun the entire analysis from the beginning. It does not alter the study itself or any results from the primary analysis. The sensitivity analysis results are intended to be included in the Discussion section of a manuscript in anticipation of potential questions from journal reviewers regarding second-order effects of timing of drug exposure to support main findings, and will not be included in either Methods or Results due to its post hoc and ad hoc nature.

Proposal:

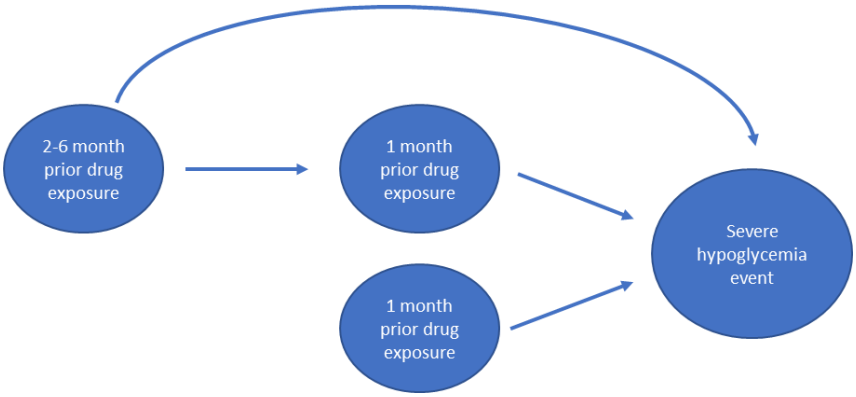
For all the drugs kept as significant in the final primary conditional logistic regression model (see the Appendix), the 2-6 month drug exposure variables are kept unchanged. However, the 1-month drug exposure variables are split into 2 variables, conditional on whether there was 2-6 month prior exposure or not.

This is a case of longitudinal drug exposure where we can use directed acyclic graph to illustrate causal relationships (figure 1). There are 3 causal arrows impacting the outcome: (1) 2-6 month drug exposure can influence the outcome directly; (2) 1-month prior exposure without 2-6 month prior exposure (ie, new script) can influence the outcome; (3) 2-6 month exposure can influence 1-month exposure and the “contaminated” 1-month exposure subsequently influences the

outcome. One key insight illuminated by the DAG is that 2-6 month variable influences the outcome in a way completely independent of 1 month drug exposure, due to the longitudinal sequence of drug exposure.

The three sets of drug exposure variables, namely, 2-6 month prior drug exposure, 1-month drug exposure without 2-6 month drug exposure, and 1-month drug exposure with 2-6 month drug exposure, are forced into the same final conditional logistic regression model (see the appendix) to further illuminate timing of drug exposure effects.

Figure 1: A causal diagram for impacts of drug exposure on SH event



Appendix:

Final conditional logistic regression estimates from the primary analysis: cases and controls matched with incidence density sampling and four well-established risk factors

Conditional logistic regression model for evaluation of risk factors for SH among patients with SH (cases) and patients at risk of SH (controls): Matched

Risk for SH (N=6,136 [3,153 matched pairs])	Parameter	SE	Odds Ratio*	95% Confidence Interval	
				Lower Limit	Upper Limit
Independent variables:					
Gender (vs.Male)	0.102	0.058	1.107	0.988	1.240
Index year binary variable (pre-Oct 2015 vs. Oct. 2015 and later)	0.754	0.066	2.125	1.865	2.420
CCI (vs. 0 and 1 combined)					
2	0.243	0.081	1.275	1.089	1.493
3	0.340	0.108	1.405	1.138	1.736
≥4	0.448	0.119	1.566	1.240	1.976
Standard comorbidities :					
Alcohol abuse	0.886	0.223	2.426	1.568	3.753
Cardiac arrythmia	0.251	0.092	1.285	1.072	1.539
Congestive heart failure	0.384	0.103	1.468	1.199	1.797
Dementia/alzheimers	0.549	0.231	1.732	1.101	2.724
Hepatitis	0.403	0.186	1.496	1.039	2.154
Hypertension	0.171	0.071	1.187	1.032	1.364
Liver disease/gallbladder/pancreas	0.232	0.098	1.261	1.040	1.529
Paralysis/hemiplegia/paraplegia	0.411	0.202	1.508	1.016	2.239
Peripheral vascular disease	0.461	0.112	1.585	1.274	1.973
Smoking or history of smoking	0.248	0.088	1.281	1.078	1.523
Cancer during 1-month prior to index date	0.628	0.141	1.874	1.422	2.471
Pregnancy during 1-month prior to index	1.164	0.322	3.203	1.703	6.025
Medications (used within 2-6-months pre-index, not including the last month pre-index): n, %					
Beta adrenergics	-0.243	0.121	0.784	0.618	0.994
Adrenergic combinations	0.368	0.154	1.445	1.070	1.953
Medications (used within 1-month pre-index): n, %					
Type of insulin					
Rapid-acting insulin	0.382	0.066	1.466	1.289	1.667
Short-acting insulin	0.798	0.173	2.220	1.581	3.118
Oral anti-diabetics	-0.217	0.063	0.805	0.712	0.911
Opioids	0.321	0.076	1.379	1.187	1.602
Anti-anxiety medications	0.413	0.128	1.512	1.177	1.942
Antipsychotics	0.466	0.169	1.593	1.144	2.220
Corticosteroids	0.303	0.126	1.354	1.058	1.732
Beta adrenergics	0.339	0.149	1.404	1.049	1.879

13. References

American Diabetes Association. Standards of Medical Care in Diabetes – 2019. Diabetes Care (2019);42(Suppl. 1):S1–S187.

CDC. National Diabetes Statistics Report, 2017: estimates of diabetes and its burden in the United States. Centers for Disease Control and Prevention. National Center for Chronic Disease Prevention and Health Promotion. 2017. https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf. Accessed September 4, 2018.

Edridge CL, Dunkley AJ, Bodicoat DH, et al. Prevalence and Incidence of Hypoglycaemia in 532,542 People with Type 2 Diabetes on Oral Therapies and Insulin: A Systematic Review and meta-Analysis of Population Based Studies. PLOS ONE (2015); 10(6): e0126427.

Fonseca V, Chou E, Chung H-W, Gerrits C. Economic Burden of Hypoglycemia with Basal Insulin in Type 2 Diabetes. Am J Manag Care (2017); 23(2): 114-122.

Geller et al. National Estimates of Insulin-related Hypoglycemia and Errors Leading to Emergency Department Visits and Hospitalizations. JAMA Intern Med. 2014 May ; 174(5): 678–686. doi:10.1001/jamainternmed.2014.136.

Ginde AA, Blanc PG, Lieberman RM, Camargo CA Jr. Validation of ICD-9-CM coding algorithm for improved identification of hypoglycemia visits. BMC Endocr Disord 2008;8:4

Glasheen WP, Renda A, Dong Y. Diabetes Complications Severity Index (DCSI)-Update and ICD-10 translation. J Diabetes Complications. 2017 Jun;31(6):1007-1013. doi: 10.1016/j.jdiacomp.2017.02.018. Epub 2017 Mar 14.

Han K, Yun JS, Park YM et al. Development and validation of a risk prediction model for severe hypoglycemia in adult patients with type 2 diabetes: a nationwide population-based cohort study. Clin Epidemiol. 2018 Oct 23;10:1545-1559. doi: 10.2147/CLEP.S169835. eCollection 2018.

Holstein A, Patzer OM, Machalke K et al. Substantial increase in incidence of severe hypoglycemia between 1997-2000 and 2007-2010: a German longitudinal population-based study. Diabetes Care (2012) May;35(5):972-5. doi: 10.2337/dc11-1470. Epub 2012 Mar 12.

Karter AJ, Warton EM, Lipska KJ, et al. Development and Validation of a Tool to Identify Patients With Type 2 Diabetes at High Risk of Hypoglycemia-Related Emergency Department or Hospital Use. JAMA Intern Med. 2017 Oct 1;177(10):1461-1470. doi: 10.1001/jamainternmed.2017.3844.

Karter AJ, Warton EM, Moffet HH, et al. Revalidation of the Hypoglycemia Risk Stratification Tool Using ICD-10 Codes. Diabetes Care. 2019 Apr;42(4):e58-e59. doi: 10.2337/dc18-2154. Epub 2019 Feb 14.

Kenny C. When hypoglycemia is not obvious: diagnosing and treating under-recognized and undisclosed hypoglycemia. Primary care diabetes. 2014 Apr 1;8(1):3-11.

Kostev K, Dippel FW, Rathmann W. Predictors of hypoglycaemia in insulin-treated type 2 diabetes patients in primary care: a retrospective database analysis. Prim Care Diabetes. 2014;8(2):127–31. https://doi.org/10.1016/j.pcd.2013.10.001.

Lee AK, Lee CJ, Huang ES et al. Risk Factors for Severe Hypoglycemia in Black and White Adults With Diabetes: The Atherosclerosis Risk in Communities (ARIC) Study. Diabetes Care. 2017 Dec;40(12):1661-1667. doi: 10.2337/dc17-0819. Epub 2017 Sep 19.

Leese GP, Wang J, Broomhall J et al. Frequency of severe hypoglycemia requiring emergency treatment in type 1 and type 2 diabetes: a population-based study of health service resource use. Diabetes Care. 2003 Apr;26(4):1176-80.

Lin Y et al. Risk factors for recurrent hypoglycemia in hospitalized diabetic patients admitted for severe hypoglycemia. Yonsei Med J. 2010 May;51(3):367-74. doi: 10.3349/ymj.2010.51.3.367.

Martín-Timón I, del Cañizo-Gómez FJ. Mechanisms of hypoglycemia unawareness and implications in diabetic patients. World journal of diabetes. 2015 Jul 10;6(7):912.

Misra-Hebert AD, Pantalone KM, Ji X et al. Patient Characteristics Associated With Severe Hypoglycemia in a Type 2 Diabetes Cohort in a Large, Integrated Health Care System From 2006 to 2015. Diabetes Care. 2018 Jun;41(6):1164-1171. doi: 10.2337/dc17-1834. Epub 2018 Mar 16.

Moura CS, Rosenberg ZB, Abrahamowicz M et al. Treatment Discontinuation and Clinial Events in Type 2 Diabetes Patients Treated with Dipeptidyl Peptidase-4 Inhibitors or NPH Insulin as Third-Line Therapy. Journal of Diabetes Research. 2018; vol. 2018, Article ID 4817178, 7 pages. https://doi.org/10.1155/2018/4817178.

Richardson DB. An incidence density sampling program for nested case-control analyses. Occup Environ Med. 2004; 61:e59.

Shao H, Fonseca V, Stoecker C et al. Novel Risk Engine for Diabetes Progression and Mortality in USA: Building, Relating, Assessing, and Validating Outcomes (BRAVO). Pharmacoeconomics. 2018 Sep;36(9):1125-1134. doi: 10.1007/s40273-018-0662-1.

Silbert, R., Salcido-Montenegro, A., Rodriguez-Gutierrez, R. et al. Hypoglycemia Among Patients with Type 2 Diabetes: Epidemiology, Risk Factors, and Prevention Strategies. Curr Diab Rep (2018) 18: 53. https://doi.org/10.1007/s11892-018-1018-0.

Strom BL, Kimmel ES, Hennessy S. *Pharmacoepidemiology.* 5th Edition. West Sussex, John Wiley & Sons, Ltd., 2012.

Sun X, Yang Z. Generalized McNemar's Test for Homogeneity of the Marginal Distributions. SAS Global Forum. 2008.

White JR. The contribution of medications to hypoglycemia unawareness. Diabetes Spectrum. 2007 Apr 1;20(2):77-80.

Wyss R, Glynn RJ, Gagne JJ. A Review of Disease Risk Scores and Their Application in Pharmacoepidemiology. Curr Epidemiol Rep. 2016;3:277-284.

Annex 1. List of Standalone Documents

Not applicable.