Sodium-Glucose Cotransporter-2 Inhibitor Use and Risk of Fournier's Gangrene: Validating the US Food and Drug Administration Drug Warning (SGLT2i Use and FG Risk)

First published: 06/06/2019

Last updated: 01/04/2024

Study Finalised

Administrative details

EU PAS number

EUPAS30018

Study ID

33386

DARWIN EU® study

No

Study countries

United States

Study description

In August 2018, the US Food and Drug Administration (FDA) released a safety warning associating sodium-glucose cotransporter-2 inhibitors (SGLT2i), the newest class of antihyperglycemic drugs, with increased incidence of Fournier's gangrene (FG), a rare, necrotizing fasciitis of the perineum. To validate this warning using real-world data, we propose to evaluate the association between SGLT2i initiation and FG risk using a large healthcare administrative claims database from the commercially-insured U.S. population (IBM Watson MarketScan Commercial Claims and Encounters). We will apply the active comparator, new user (ACNU) study design to estimate and compare the incidence of FG between patients who initiated SGLT2i and those who initiated comparable second-line glucose-lowering drugs (GLDs), dipeptidyl peptidase-4 inhibitors (DPP4i) and sulfonylureas (SU). Exposure to a study drug will be defined by at least two same-drug class prescription dispensing claims of either a SGLT2i or an active comparator drug. Fournier's gangrene will be defined using combinations of ICD-9 and ICD-10 diagnosis codes, as well as ICD-9 procedure, ICD-10 procedure, Common Procedural (CPT), and National Drug Codes (NDCs) for systemic antibiotics, debridement, and related surgery.We will use propensity score methods to control for baseline confounding and estimate the average treatment effect in the treated. We will estimate the crude incidence rates of FG during follow-up for both the SGLT2i and comparator drug cohort, by dividing total number of observed cases during follow-up by the total person-time at risk. We will additionally estimate and compare the cumulative incidence of study outcomes for each study cohort using weighted Kaplan-Meier methods. Finally, crude and adjusted hazard ratios (HRs) for study outcomes will be estimated using weighted Cox proportional hazards models.

Study status

Finalised

Research institutions and networks

Institutions

Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill

Contact details

Study institution contact

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Study contact

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Primary lead investigator

Til Stürmer

Primary lead investigator

Study timelines

Date when funding contract was signed

Planned: 05/06/2019

Actual: 05/06/2019

Study start date

Planned: 05/06/2019

Actual: 05/06/2019

Data analysis start date
Planned: 05/06/2019

Actual: 05/06/2019

Date of final study report
Planned: 31/12/2019

Actual: 15/01/2020

Sources of funding

- No external funding

Study protocol

SGLT2_fournier's_gangrene_study_protocol_20190605_final.pdf (602.4 KB)

Regulatory

Was the study required by a regulatory body?

No

Is the study required by a Risk Management Plan (RMP)?

Not applicable

Methodological aspects

Study type

Study type list

Study topic:

Disease /health condition

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Assessment of risk minimisation measure implementation or effectiveness

Data collection methods:

Secondary use of data

Main study objective:

To evaluate and compare the association between SGLT2i initiation, relative to other second-line glucose lowering drugs (GLDs), on the incidence and risk of Fournier’s gangrene, based on an active comparator, new-user (ACNU) study design.

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Anatomical Therapeutic Chemical (ATC) code

(A10BB) Sulfonylureas

Sulfonylureas

(A10BH) Dipeptidyl peptidase 4 (DPP-4) inhibitors

Dipeptidyl peptidase 4 (DPP-4) inhibitors

(A10BK) Sodium-glucose co-transporter 2 (SGLT2) inhibitors

Sodium-glucose co-transporter 2 (SGLT2) inhibitors

Medical condition to be studied

Scrotal gangrene

Diabetic gangrene

Population studied

Short description of the study population

All MarketScan CCAE beneficiaries with at least one prescription dispensing claim for a SGLT2i or an active comparator drug between April 1, 2013 and June 30, 2017.

Age groups

- Adults (18 to < 46 years)
- Adults (46 to < 65 years)

Special population of interest

Other

Special population of interest, other

Diabetes mellitus patients

Estimated number of subjects

300000

Study design details

Outcomes

Fournier’s gangrene will be defined using combinations of ICD-9 and ICD-10 diagnosis codes, and ICD-9 procedure, ICD-10 procedure, Common Procedure Terminology (CPT) and National Drug Codes (NDCs) for systemic antibiotics, debridement, and related surgery.

Data analysis plan

We will use an active comparator, new user study design, which tends to synchronize patients with respect to diabetes severity and duration, to compare new users of SGLT-2i with new users of DPP-4i and sulfonylureas. We will use propensity scores to remove imbalances in measured potential confounders between study cohorts. We will estimate the crude incidence rates of FG during follow-up for both the SGLT2i and comparator drug cohort. We will additionally estimate and compare the cumulative incidence of FG 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.

Documents

Study results

8. e000985.full (1).pdf (1021.88 KB)

Study publications

Yang JY, Wang T, Pate V, Buse JB, Stürmer T. Real-world evidence on sodium-gluc…

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data sources (types)

Administrative healthcare records (e.g., claims)

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

No