Sodium-Glucose Cotransporter-2 Inhibitor (SGLT-2i) Use and Risk of Subsequent Amputation

First published: 24/10/2017

Last updated: 23/04/2024

Study Ongoing

Administrative details

EU PAS number

EUPAS21368

Study ID

27791

DARWIN EU® study

No

Study countries

United States

Study description

Recent findings from the CANVAS clinical trials suggest a possible increase in the risk of amputation associated with use of canagliflozin, a SGLT-2i drug, versus placebo. To our knowledge, there has been no study of the association between SGLT-2i initiation and amputation risk performed using large healthcare databases, which may be more representative of real-world clinical practice in a broader target population of patients with Type II diabetes mellitus, and using an active comparator, new user study design.To address this gap in knowledge, we propose to evaluate and compare the association between SGLT-2i initiation, relative to initiation of other second-line glucose lowering drugs, on the incidence and risk of diabetes-related amputation, using observational data from the commercially-insured U.S. population (<65 years old patients) and Medicare (≥65 years old patients) from 2013-2015, and based on an active comparator, new user study design.New users of SGLT-2i drugs will be compared to new users of other second-line active comparators (DPP-4 inhibitors and sulfonylureas). Exposure will be defined by at least two same-drug class prescription dispensing claims of either a SGLT-2i or an active comparator drug. The primary outcome of interest is lower-extremity amputation, additional secondary outcomes will be considered. The primary analysis will be carried out in an "as-treated" fashion.We will use propensity scores to minimize imbalances in measured potential confounders between study cohorts. We will estimate and compare the cumulative incidence of both primary and secondary outcomes for each study cohort using weighted Kaplan-Meier methods. Crude and adjusted hazard ratios 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. A number of sensitivity analyses are planned

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Study status

Ongoing

Research institutions and networks

Institutions

University of North Carolina at Chapel Hill

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Institution

Department of Epidemiology,Gillings School of Global Public Health

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: 20/06/2017

Actual: 20/06/2017

Study start date
Planned: 20/06/2017

Actual: 20/06/2017

Data analysis start date
Planned: 20/06/2017

Actual: 20/06/2017

Date of final study report
Planned: 31/12/2018

Sources of funding

- Other

More details on funding

Unfunded

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:

Non-interventional study

Scope of the study:

Assessment of risk minimisation measure implementation or effectiveness

Main study objective:

To evaluate and compare the association between SGLT-2 inhibitor initiation, relative to other second-line glucose lowering drugs DPP-4 inhibitors and sulfonylureas, on the incidence and risk of diabetes-related amputation, based on a new-user, active comparator 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

Diabetes mellitus management

Debridement

Diabetic foot

Peripheral vascular disorder

Peripheral revascularisation

Additional medical condition(s)

Lower-extremity amputation

Population studied

Age groups

- Adults (18 to < 46 years)
- Adults (46 to < 65 years)
- Adults (65 to < 75 years)
- Adults (75 to < 85 years)
- Adults (85 years and over)

Estimated number of subjects

300000

Study design details

Outcomes

The primary outcome of interest is lower extremity amputation (LEA), defined using ICD-9 or CPT procedure codes. In secondary outcome analysis, we will assess the association between SGLT-2i initiation and other consequences of diabetic disease, including the following conditions: debridement, diabetic foot

ulcer and gangrene, peripheral vascular disease (PVD), and peripheral revascularization. These conditions will be identified using ICD-9 diagnosis and procedure codes as well as CPT procedure codes.

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 and compare the cumulative incidence of both primary and secondary outcomes for each study cohort using weighted Kaplan-Meier methods. Crude and adjusted hazard ratios (HRs) for both primary and secondary outcomes will be estimated using weighted Cox proportional hazards models, controlling for age, sex, as well as any potential confounders that remain unbalanced after propensity score implementation.

Documents

Study publications

Yang JY, Wang T, Pate V, Gower EW, Crowley MJ, Buse JB, Stürmer T. Sodium-Gluco...

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 source(s)

Ambulatory EMR - OMOP

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