

# 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

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### Study ID

27791

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### DARWIN EU® study

No

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### Study countries

 United States

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### 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 ( $\geq 65$  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

**First published:** 01/02/2024

**Last updated:** 01/02/2024

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

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**Study start date**

Planned: 20/06/2017

Actual: 20/06/2017

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**Data analysis start date**

Planned: 20/06/2017

Actual: 20/06/2017

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**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

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

Not applicable

## Methodological aspects

### Study type

**Study type:**

Non-interventional study

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**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

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**Medical condition to be studied**

Diabetes mellitus management

Debridement

Diabetic foot

Peripheral vascular disorder

Peripheral revascularisation

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### **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)
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### **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.

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### **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...](#)

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## 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

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### **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

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### **Check completeness**

Unknown

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### **Check stability**

Unknown

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### **Check logical consistency**

Unknown

## Data characterisation

## **Data characterisation conducted**

No