

Cohort Study of Serious Adverse Events with Sodium-Glucose Cotransporter 2 Inhibitors

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LINKED-DM

SGLT2 inhibitors and serious adverse events

	Signal
Lower limb amputation	CANVAS
Bone fracture	CANVAS
Diabetic ketoacidosis	Case reports; Fralick et al (observational study) ¹
Acute kidney injury	Case reports
Serious urinary tract infection	Case reports
Venous thromboembolism	Yu et al (meta-analysis of RCTs) ²
Acute pancreatitis	Case reports

1. Fralick et al. **NEJM** (2017)
2. Wu et al. **Lancet Diabetes and Endocrinology** (2015)

Lower limb amputation

- **CANVAS** trials
 - 6.3 vs 3.4 per 1000 pyrs
 - HR **1.97** (1.41-2.75)
- No imbalance in rates in **EMPAREG OUTCOME**

Bone fracture

- **CANVAS** trials
 - CANVAS: HR 1.55 (1.21–1.97)
 - **But not** in CANVAS-R or in other SGLT2 inhibitor trials
- **Potential mechanisms**
 - Altered bone metabolism
 - Falls due to hypovolemia

Diabetic ketoacidosis

- Case reports
- **CANVAS** trials
 - 0.6 vs 0.3 events per 1000 pyrs (**p=0.14**)
- **Fralick et al.** (NEJM, 2017)
 - US insurance claims
 - **HR 2.2** (1.4-3.6) vs. DPP4 inhibitors

Acute kidney injury

- **Case reports**
(n >100 to the FDA Adverse Event Reporting System)
- **Decrease in GFR** after drug initiation

Acute kidney injury

- **EMPA-REG OUTCOME**
 - 1.0 (empagliflozin) VS 1.6% (placebo)
- **CANVAS trials**
 - HR 0.66 (0.39–1.11)

Serious urinary tract infection

- **Case reports** to FDA Adverse Event Reporting System
- **Urosepsis** in EMPAREG OUTCOME:
 - **0.4 vs 0.1%** (but no imbalance for complicated UTI)
- **No imbalance** in CANVAS trials for UTI

Venous thromboembolism

- Potential mechanism (**blood viscosity**)
- Meta-analysis in 2015¹
 - **HR = 1.54** (0.63–3.79)
- No imbalance in rates in **pooled RCTs**²
 - **OR = 0.88** (0.61–1.28)

1. Wu et al. **Lancet Diabetes and Endocrinology** (2015)

2. Zhang et al. **J Am Heart Assoc** (2018)

Acute pancreatitis

- **Case reports** to FDA
- **No imbalance** in RCTs (but few events)

Active comparator

Glucagon-like peptide 1 agonist (GLP1-RA)

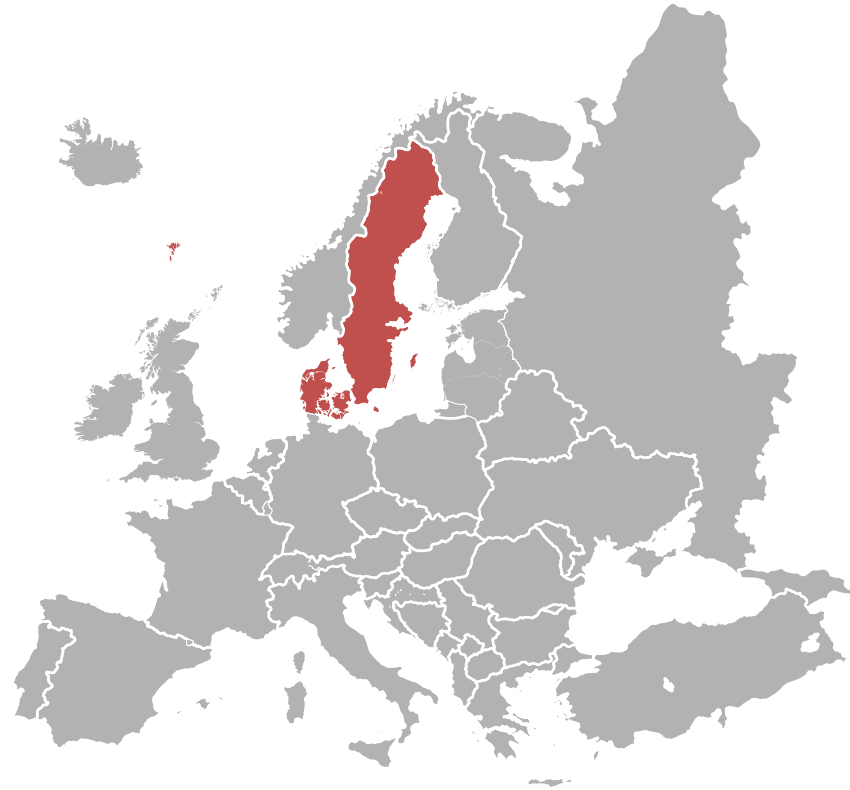
- Second/third-line glucose lowering drugs
- Cardiovascular benefit (Liraglutide)
- No known association with studied outcomes

New user design

- No previous use of any study drug

Nationwide registers in **Sweden & Denmark**

- Population registers
- Patient registers
- Prescription registers
- Statistics Denmark/Statistics Sweden
- Swedish National Diabetes Register



New users

(aged ≥ 35 y; July 2013-2016)

Exclusion

Previous use of other study drug

Severe renal disease

End-stage illness

Drug misuse

Hospital admission <30 days

33,380 SGLT2 inhibitors

31,470 GLP1-RA

10,944

2,262

1,378

1,930

Propensity score estimation and 1:1 matching

Not matched

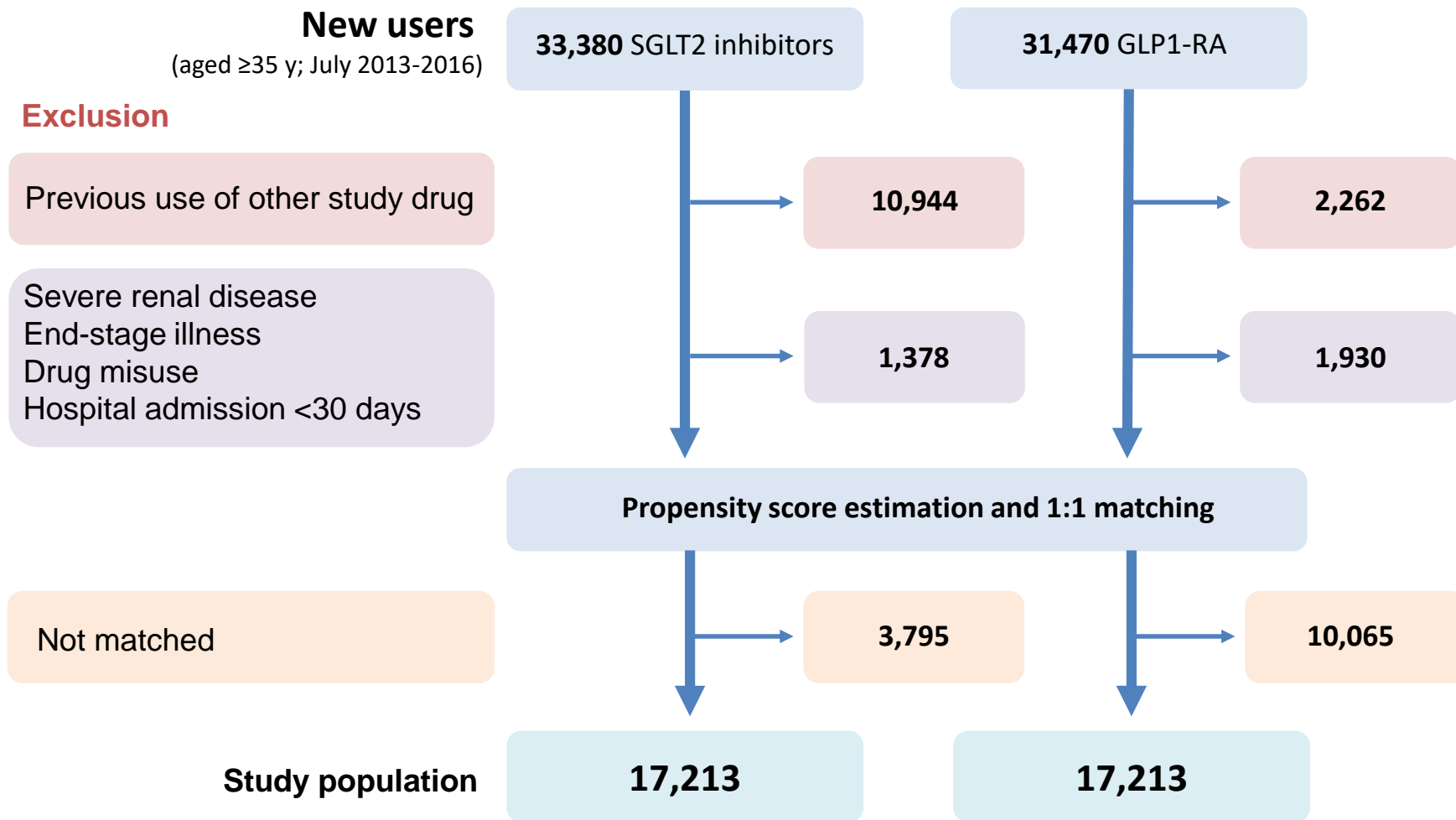
3,795

10,065

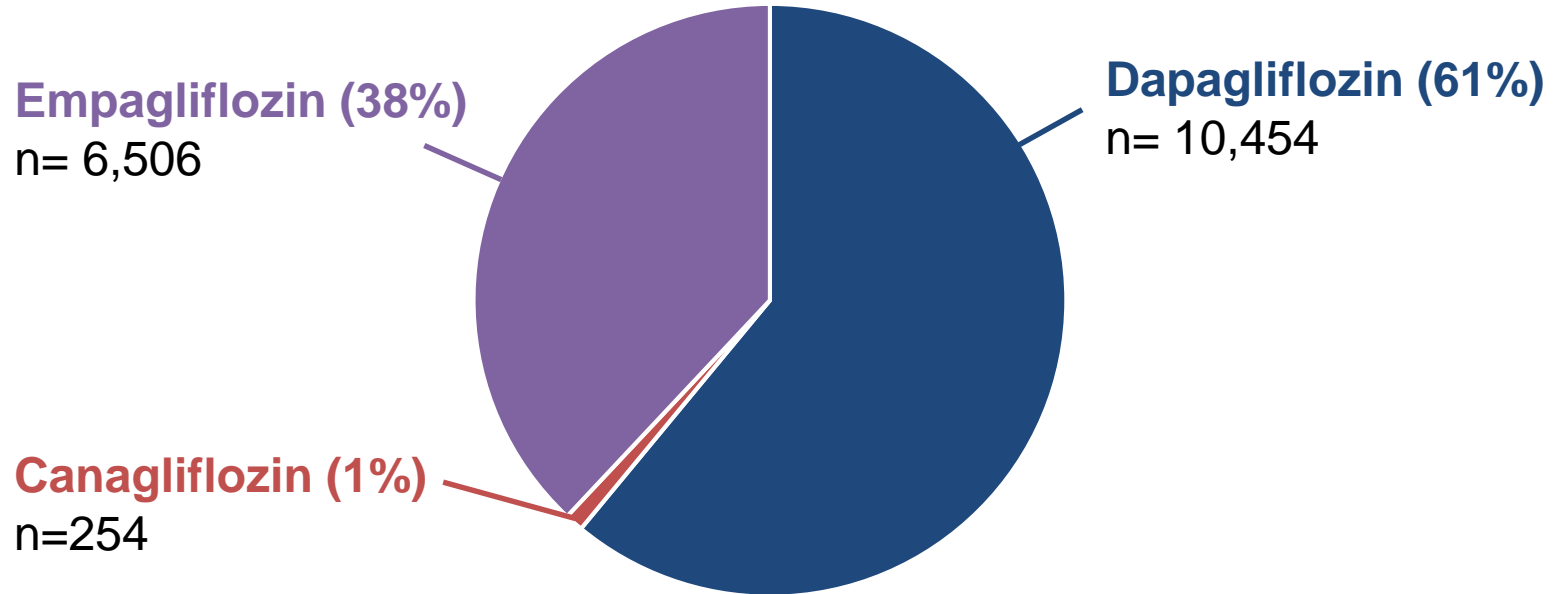
Study population

17,213

17,213

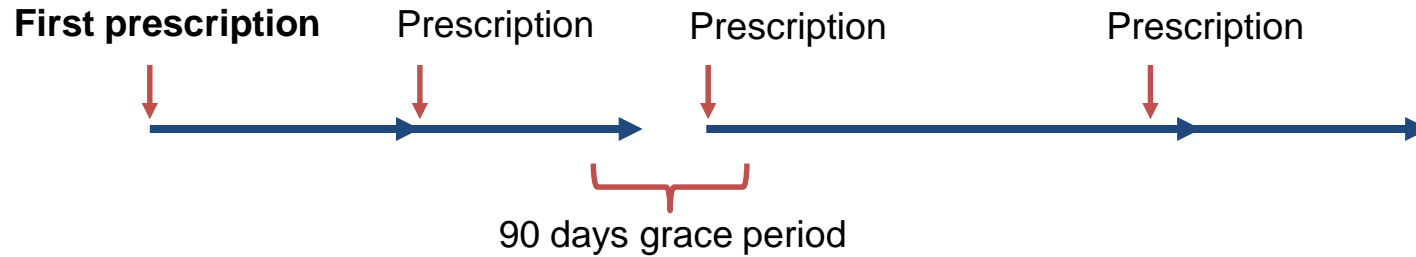


SGLT2 inhibitors



	SGLT2i (n=17,213)	GLP1-RA (n=17,213)
Male sex	61%	61%
Mean age (SD), yrs.	61 (10)	61 (10)
History of CVD	19%	19%
Metformin	80%	80%

Exposure (As treated)



Primary outcomes

National Patient Registers

Lower limb amputation

Bone fracture

Diabetic ketoacidosis

Acute kidney injury

Serious urinary tract infection

Venous thromboembolism

Acute pancreatitis

Statistical analysis

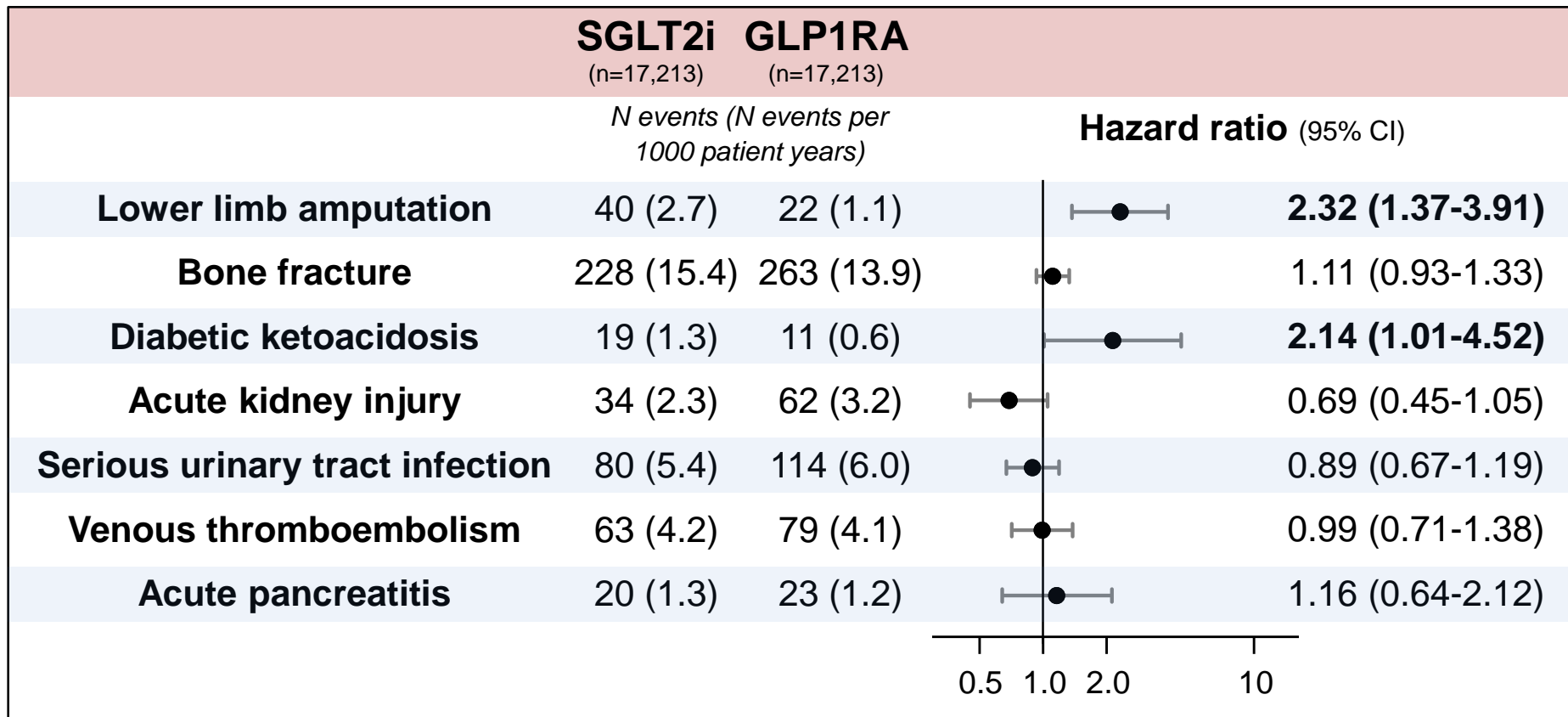
Separate for each outcome

Cox regressions

Follow-up (days)

Median	270
Lower quartile	132
Upper quartile	508

Results



Sensitivity analyses

- **Intention to treat** exposure definition
- **Sweden** (61% of cohort)

National Diabetes Register - adjustment for:

- Glycated haemoglobin
- BMI
- Smoking
- Albuminuria
- eGFR

Limitations

- **Observational study**
- Analysed SGLT2 inhibitors as a **drug class**

Dapagliflozin	61%
Empagliflozin	38%

LINKED-DM Investigators

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