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

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## SGLT2 inhibitors and serious adverse events

<table>
<thead>
<tr>
<th>Condition</th>
<th>Signal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower limb amputation</td>
<td>CANVAS</td>
</tr>
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<td>Bone fracture</td>
<td>CANVAS</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>Case reports; Fralick et al (observational study)(^1)</td>
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<td>Acute kidney injury</td>
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<td>Serious urinary tract infection</td>
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<tr>
<td>Venous thromboembolism</td>
<td>Yu et al (meta-analysis of RCTs)(^2)</td>
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<tr>
<td>Acute pancreatitis</td>
<td>Case reports</td>
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</table>

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 RCTs²
  - 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

Not matched

Propensity score estimation and 1:1 matching

Study population

33,380 SGLT2 inhibitors
10,944
1,378
3,795
17,213

31,470 GLP1-RA
2,262
1,930
10,065
17,213
SGLT2 inhibitors

Dapagliflozin (61%)  
n= 10,454

Empagliflozin (38%)  
n= 6,506

Canagliflozin (1%)  
n= 254
<table>
<thead>
<tr>
<th></th>
<th>SGLT2i (n=17,213)</th>
<th>GLP1-RA (n=17,213)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>61%</td>
<td>61%</td>
</tr>
<tr>
<td>Mean age (SD), yrs.</td>
<td>61 (10)</td>
<td>61 (10)</td>
</tr>
<tr>
<td>History of CVD</td>
<td>19%</td>
<td>19%</td>
</tr>
<tr>
<td>Metformin</td>
<td>80%</td>
<td>80%</td>
</tr>
</tbody>
</table>
Exposure (As treated)

First prescription \[\rightarrow\] Prescription \[\rightarrow\] Prescription \[\rightarrow\] Prescription

90 days grace period
### 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
<table>
<thead>
<tr>
<th>Event</th>
<th>SGLT2i (n=17,213)</th>
<th>GLP1RA (n=17,213)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Lower limb amputation</td>
<td>40 (2.7)</td>
<td>22 (1.1)</td>
<td>2.32 (1.37-3.91)</td>
</tr>
<tr>
<td>Bone fracture</td>
<td>228 (15.4)</td>
<td>263 (13.9)</td>
<td>1.11 (0.93-1.33)</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>19 (1.3)</td>
<td>11 (0.6)</td>
<td>2.14 (1.01-4.52)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>34 (2.3)</td>
<td>62 (3.2)</td>
<td>0.69 (0.45-1.05)</td>
</tr>
<tr>
<td>Serious urinary tract infection</td>
<td>80 (5.4)</td>
<td>114 (6.0)</td>
<td>0.89 (0.67-1.19)</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>63 (4.2)</td>
<td>79 (4.1)</td>
<td>0.99 (0.71-1.38)</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>20 (1.3)</td>
<td>23 (1.2)</td>
<td>1.16 (0.64-2.12)</td>
</tr>
</tbody>
</table>
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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