Let’s CUT to it: Is there a class effect with sodium glucose transporter-2 inhibitors (SGLT2i) and the risk of amputations?

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Objectives

- Discuss relative background information regarding SGLT-2 inhibitors
- Explain the relationship between amputations and type 2 diabetes mellitus
- Evaluate current literature discussing the risk of amputations with SGLT-2 inhibitors
- Develop recommendations for the implementation of SGLT-2 inhibitors in practice

Disclosures

- The author has no conflicts of interest to disclose

Background

Sodium Glucose Cotransporters
- Mediators of glucose transport across apical cell membranes
- Two types
  - SGLT-1
    - Expressed in the intestine and kidneys
    - Renal glucose reabsorption is ~10%
    - Late proximal straight tubule
  - SGLT-2
    - Expressed in the kidneys
    - Renal glucose reabsorption is ~90%
    - Early proximal convoluted tubule
Background

Mechanism of Action of SGLT-2i
- Decrease glucose reabsorption
- Decrease blood glucose
- Decrease sodium reabsorption
- Increase urinary glucose excretion

Examples of SGLT-2i
- Canagliflozin (Invokana®)
  - 100 mg once daily before meals (Max = 300 mg once daily)
- Empagliflozin (Jardiance®)
  - 10 mg once daily (Max = 25 mg once daily)
- Dapagliflozin (Farxiga®)
  - 5 mg once daily (Max = 10 mg once daily)

Pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>Canagliflozin</th>
<th>Empagliflozin</th>
<th>Dapagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>65% - 80%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Half life</td>
<td>~10-13 hours</td>
<td>~12 hours</td>
<td>~13 hours</td>
</tr>
<tr>
<td>Time to Peak</td>
<td>1-2 hours</td>
<td>1.5 hours</td>
<td>2 hours</td>
</tr>
<tr>
<td>Protein binding</td>
<td>99% to albumin</td>
<td>~86%</td>
<td>91%</td>
</tr>
<tr>
<td>Renal Adjustments</td>
<td>C/r with eGFR &lt; 30 mL/min *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic Adjustments</td>
<td>None ¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effect on A1c</td>
<td>0.7-1.0%</td>
<td></td>
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</tbody>
</table>

Warnings
- Amputations
- Necrotizing fasciitis of the perineum
- Side effects
  - Weight loss
  - Genitourinary infections
  - Hyperkalemia
  - Bone fractures
  - Ketoacidosis

FDA Black Box Warning
- An approximately 2-fold increased risk of lower limb amputations associated with canagliflozin use was observed
- Prior to initiation consider risk factors for amputation
- Discontinue therapy if any of the following occur: signs and symptoms of new infection (including osteomyelitis), new pain or tenderness, or sores/ulcers involving the lower limbs

ADA Place in Therapy
- Monotherapy
- Dual Therapy
- Triple Therapy

* not recommended to initiate with eGFR 30-45 mL/min
¹ avoid canagliflozin in Child Pugh Class C/D

Reference:
AMPUTATIONS IN TYPE 2 DIABETES MELLITUS

Type 2 Diabetes Mellitus
- Considered the “epidemic of the 21st century”

Epidemiology
- Diabetic patients are 10-20% more likely to experience an amputation compared to the general public
- 15% of diabetic patients will experience an amputation
- Amputations are the most feared adverse health outcome in diabetic patients
- African Americans and Hispanics have as high of a 10-fold risk

Direct Medical Costs
- According to a study evaluating 20 million diabetic patients in the United States
  - The total cost per episode of lower extremity amputations was $70,434
  - The incidence was approximately 0.8% or 166,000 patients
  - The total adjusted health cost was ~$12 billion

Cost of Diabetes in Texas
- Direct Medical Costs
- Indirect Costs

Diabetes Impact in Texas in 2012
- According to the Diabetes Care Journal:
  - Direct medical costs = ~$13.35 billion
  - Indirect costs = ~$4.89 billion
- The rate of diabetes has continued to increase since 2008
Amputations in Type 2 Diabetes Mellitus

- Lower extremity amputations (LEA) per 1,000 persons on Medicare with diabetes in 2008

Mechanism of Action
- Not well established

Potential Theories
- Peripheral arterial disease (PAD)
- Diabetic neuropathy
- Infections
- Thiazide diuretics
  - Volume depletion
  - Increased A1c

A1c correlation
- Deshpande et al
  - A1c < 7.5% = higher mortality and increased amputations
  - A1c > 7.5% = 20% higher risk of amputations than the strictly controlled group
- Meta Analysis (Papanas et al)
  - The risk of LEA increases with higher A1c
  - Patients with an A1c > 9% had an increase in LEA
- Meta Analysis (Zhou et al)
  - Higher A1c is correlated with an increased risk of LEA
  - Glucose control is important in reducing LEA incidence

Literature
- Risks of Diabetic Foot Syndrome and Amputation Associated with Sodium Glucose Co-Transporter 2 Inhibitors
- A real-world meta-analysis of 4 observational databases (OBSERVE-4D)
- Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes (CANVAS)
- Association Between Sodium-Glucose Cotransporter 2 Inhibitors and Lower Extremity Amputation Among Patients With Type 2 Diabetes
Risks of Diabetic Foot Syndrome and Amputation Associated with SGLT-2 Inhibitors (Li, et al)

**Purpose**
- To evaluate the risk of diabetic foot syndrome (DFS) and amputations associated with SGLT-2i

**Methods**
- Meta analysis of 14 randomized controlled trials (RCT) including 26,167 patients that reported DFS or amputation as an adverse event

**Limitations**
- Limited number of studies available for analysis that met criteria

**Baseline Characteristics**
- Average age range 54-69 years old, A1c ranges 7.8-8.3%, 10 trials had a primary race of white

**Interventions**
- Empagliflozin (6), canagliflozin (2), or dapagliflozin (1) vs. placebo

**Follow up**
- CANVAS: 188 weeks
- EMPA-REG outcome: 156 weeks
- Other RCT: 50-76 weeks

**Results**
- No class effect associated with SGLT-2i and amputations when compared with placebo
  - 95% CI: 0.81-2.41
- Canagliflozin was associated with higher amputation risks than other groups
  - 95% CI: 1.37-2.60

**Author’s Critique**
- Inconsistency between the drugs evaluated
- Short follow up period and limited sample size
- Patient population differences

A real-world meta-analysis of 4 observational databases (OBSERVE-4D, Ryan et al)

**Purpose**
- To compare the risk of canagliflozin vs. SGLT-2i and non-SGLT-2i for below knee lower amputations and heart failure hospitalizations

**Methods**
- Real world meta-analysis of 4 observational databases containing a total of 714,582 patients

**Baseline Characteristics**
- Average age range 50-64 years old, 55% male, 11% with neuropathy associate with T2DM

**Results**
- No differences observed between canagliflozin and the other SGLT-2i in any database
  - On-treatment:
    - Hazard ratio (95% CI) = 1.14 (0.67 - 1.93)
  - Intention to treat:
    - Hazard ratio (95% CI) = 1.13 (0.99 - 1.29)
A real-world meta-analysis of 4 observational databases (OBSERVE-4D, Ryan et al)

**Author’s Conclusions**
- First real-world comparison of the risk of amputations with canagliflozin, other SGLT-2i, and non SGLT-2i
- Included privately insured populations, Medicaid, and Medicare
- No observed differences in the risk of amputations among all groups

**Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes (CANVAS, Neal et al)**

**Inclusion Criteria**
- Type 2 diabetes and A1c between 7.0% - 10.5%
- ≥ 30 years old with a history of ASCVD
- Or >50 years old with ≥ 2 risk factors for CVD

**Exclusion Criteria**
- History of DKA, type 1 diabetes, pregnant, current use of an SGLT2 inhibitor
- eGFR < 30; fasting BG >270 mg/dL

**Baseline Characteristics**
- Both groups relatively equal
- Mean age 63 years, diabetes duration 14 years, A1c 8.2%

**Results**
- **Primary endpoint**
  - Hazard ratio 0.86; 95% CI 0.75-0.97
- **Safety**
  - Amputation
    - 6.3 vs. 3.4 participants per 1000 patient years
    - p value < 0.001
  - Male genitalia infection
    - 34.9 vs. 10.8 participants per 1000 patient years
    - p value < 0.001

**Conclusion**
- Higher risk when history of risk factors present
- **Strengths**
  - Large sample size
  - Long duration of follow up and trial
- **Weaknesses**
  - Discontinuation of agents could have affected A1c levels

**Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes (CANVAS, Neal et al)**

**Purpose**
- To evaluate if the use of canagliflozin in type 2 diabetic patients with a high risk for CV disease had a lower risk of death from CV causes

**Methods**
- Multicenter, randomized, double-blind, placebo-controlled trial including 10,142 patients
- Limited patients with CKD
- Fewer ESRD events

**Association Between SGLT-2i and Lower Extremity Amputation Among Patients With Type 2 Diabetes (Chang et al)**

**Purpose**
- To quantify the association between the use of oral medications for T2DM and 5 outcomes

**Methods**
- Retrospective cohort study evaluating 953,906 patients and the use of SGLT-2i, DPP-4i, GLP-1 agonists alone, or other T2DM medications
- Insured individuals only
- Low event rate
- Limited follow up time period
**Literature**

**Association Between SGLT-2i and Lower Extremity Amputation Among Patients With Type 2 Diabetes**  
(Chang et al)

**Inclusion**
- Insured patients with at least one of the following medications: SGLT-2i, DPP-4i, or GLP-1 agonists, sulfonylureas, metformin and TZDs

**Exclusion**
- <18 years old, new antidiabetic medication during the baseline period, any insulin use, and any outcome of interest in the baseline period

**Baseline Characteristics**
- >50 years old, 60% on metformin, 60% HTN, 30% on thiazide diuretics, 2% neuropathy

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**Results**
- **Follow up time**  
  - 99-120 days based on the medication
- **Incident rates**  
  - SGLT-2i: 10.53 per 10,000 person years  
  - Metformin, sulfonylureas, etc.: 4.90 per 10,000 person years
- **Amputation risk with SGLT-2i vs. DPP-4i/GLP-1 agonists**  
  - CI 0.85-2.67, CI 0.64-3.36
- **Amputation risk with SGLT-2i vs. metformin/TZD, etc.**  
  - CI 1.19-3.77

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**Back to the guidelines...**
- ADA recommends that in patients with established ASCVD on metformin, addition of canagliflozin may be considered to reduce major adverse cardiovascular events, based on drug-specific/patient factors

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**CONCLUSIONS AND RECOMMENDATIONS**

- The CANVAS trial showed a statistically significant increase in amputations in patients taking canagliflozin
- Based on the meta analyses, the amputation risk is not a class effect with SGLT-2 inhibitors
- Various patient/disease factors contribute to the overall amputation risk

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**Recommendations**
- **Patient specific factors**  
  - Prior amputation, peripheral vascular disease, etc.
- **Engage in a care system that provides preventative care**  
  - A1c check  
  - Foot exam  
  - New infection
- **Evaluate risk vs. benefit**  
  - CV benefit vs. amputation risk  
  - Lifetime risk of amputation is high in T2DM
Looking Forward

- Recently approved SGLT-2i
  - Ertugliflozin (Strata®)  
    - No safety endpoint for amputations

- Future studies
  - Dapagliflozin Effect on Cardiovascular Events
    - DECLARE-TIMI 58
    - Ongoing trial

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References


Questions?
Appendices

Appendix A: Abbreviations

Appendix B: SGLT-2i timeline of discovery

Appendix C: Mechanism of Action of SGLT-2i
Appendix A: Abbreviations

SGLT-2i: Sodium glucose transporter 2 inhibitors
eGFR: Estimated glomerular filtration rate
ADA: American Diabetes Association
ASCVD: Atherosclerotic Cardiovascular Disease
DPP-IV: Dipeptidyl peptidase-4 inhibitor
GLP-1: Glucagon-like peptide-1
CHF: Congestive Heart Failure
T2DM: Type 2 Diabetes Mellitus
LEA: Lower extremity amputation
PAD: Peripheral Arterial Disease
DFS: Diabetic Foot Syndrome
RCT: Randomized controlled trial
CI: Confidence interval
CV: Cardiovascular
CKD: Chronic Kidney Disease
ESRD: End Stage Renal Disease
BG: Blood glucose
CVD: Cardiovascular disease
TZD: Thiazolidinedione
HTN: Hypertension
Appendix B: SGLT-2i timeline of discovery

1836
Phlorizin isolated from bark of apple tree

1933
Phlorizin shown to completely block renal glucose absorption in humans

1938
Renal glucose kinetics characterized, clearly demonstrating maximal reabsorptive capacity and threshold for glucose excretion

1960
Active co-transport concept proposed for intestinal glucose absorption

1987
SGLT1 cloned

1992
SGLT2 cloned

1995
Phlorizin treatment shown to reverse glucotoxicity in diabetic rodents

First report of treatment potential of a selective SGLT2 inhibitor

2012-2014
First SGLT2 inhibitors approved for treatment of type 2 diabetes

Dapagliflozin
Empagliflozin
Canagliflozin
T-1095
Appendix C: Mechanism of Action of SGLT-2i