Role of Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors in Diabetes Management

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Objectives:

- To understand the mechanism of action of SGLT2 inhibitors
- To learn about the efficacy, advantages, disadvantages/adverse effects of SGLT2 inhibitors
- To review the role of SGLT2 inhibitors in Type 2 Diabetes management
- To discuss studies of off-label use of SGLT2 inhibitors in patients with Type 1 Diabetes
Case 1: 63 yo female Referred to Clinic in 2013 for Diabetes Management

- Diagnosed with DM in 2004 (routine labs but in retrospect patient was having fatigue and polyuria)

- Never had DKA or any hospitalization due to DM

- Previously tried Metformin and Avandia but insulin started in 2006 due to poor control

- No evidence of diabetes complications
Case 1 – cont’

- PMHx: Tubal ligation; Tonsillectomy
- Meds: Lantus 9 units hs & 5 units am NovoRapid (breakfast 1:10; Lunch 1:6; dinner 1:7)
- Family Hx: no diabetes, HTN or thyroid disease
- Social Hx: non-smoker; minimal alcohol intake; retired teacher; exercises daily
Case 1 – cont’

- On P/E: W = 144 lbs; BMI = 22.5; BP = 110/66; P = 66; normal feet, thyroid and eye exam. Rest of exam unremarkable

- SMBG:
  - Fasting: quite variable: 3.8-13
  - Ac lunch: 5-11
  - Pc lunch: 12-14 (few around 18-21)
    - Pattern of hyperglycemia after weight training workouts

- Hypoglycemia: 2-3 episodes/week; not severe, feels symptoms
Case 1 – cont’

- Last visit: Sep/2015- In addition to insulin GP started patient on Forxiga (dapagliflozin) in July/2015

- Patient reported less glucose variability and reduction insulin dose since Forxiga started

- Labs:
  - Sep/2015: A1C 7.5%
  - April/2015: A1C 8.2%
  - Dec/2014: A1C 8.6%
Case 1  – cont’

- Anti-GAD = 16 (confirming diagnosis of LADA)
- Dec/2015: A1C 7.3%

What should be the next step?
Case 2: 27 yo female; T1DM since 10 yo

- On MDI (Lantus 17 units q HS + Humalog 1:12 ac breakfast, lunch and dinner)

- DKA only at diagnosis

- No hx of severe lows
  - 2-3 episodes hypoglycemia/week usually correlated to overcorrection, feels autonomic symptoms, treats properly, aware of driving guidelines

- No microvascular complications
Case 2- cont’

- A1C has been ranging from 8.7- 9.4%

- Patient frustrated as despite efforts to control her diabetes can’t get A1C at target and keeps gaining weight

- Has heard about a new oral medication for treating type 1 diabetes to be taken in addition to insulin that promotes weight loss

- Very interested in trying it and would like your opinion on that
Sodium Glucose Co-Transporter 2-(SGLT2) Inhibitors- Mechanism of Action

- Blocks glucose reabsorption by the kidney leading to ↑ urinary excretion glucose

- SGLT2 inhibitors available in Canada:
  - Canagliflozin (Invokana): 100-300 mg daily
  - Dapagliflozin (Forxiga): 5-10 mg daily
  - Empagliflozin (Jardiance): 10-25 mg daily
Hyperglycemia will increase SGLT2 expression and absorption capacity.

From Chao EC, Henry RR. Nat Rev Drug Discov. 2010;9:551-559.\(^7\)
SGLT2 Inhibitors:

- Modest A1C ↓ (~ 0.5-0.7%)
- Low risk of hypoglycemia
- Modest weight loss
- Modest drop in BP
- *Effect is insulin independent*
- Utility across the entire spectrum of diabetes stages
- Can be used in combination with several other OHA and insulin
- Associated with lower CVD event rate and mortality in T2DM patients with CVD (EMPA-REG Outcome)

Nat Rev Endocrinol 2012; 8:495-502
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woele, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

ABSTRACT

EMPA- REG OUTCOME

- 7,020 T2DM and known CVD
- Subjects randomized to receive Empa 10 mg or 25 mg or placebo
- Background of standard care
- Mean treatment duration: 2.6 years
Study Design: Outcomes

- **Primary Outcome**: Composite of death from cardiovascular causes, non fatal myocardial infarction, or nonfatal stroke

- **Secondary Outcome**: Composite of primary outcome, plus hospital for unstable angina
EMPA-REG Outcome: CV Benefits

**FIGURE 1**

**Cumulative Incidence of Nonfatal MI, Nonfatal Stroke, or CV Death with Empagliflozin or Placebo in the EMPA-REG OUTCOME Study (Primary Outcome)**

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
<th>42</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with event (%)</td>
<td>0</td>
<td>2</td>
<td>5</td>
<td>10</td>
<td>17</td>
<td>25</td>
<td>34</td>
<td>45</td>
<td>60</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>4,667</td>
<td>4,580</td>
<td>4,455</td>
<td>4,328</td>
<td>3,851</td>
<td>2,821</td>
<td>2,359</td>
<td>1,534</td>
<td>370</td>
</tr>
<tr>
<td>Placebo</td>
<td>2,333</td>
<td>2,256</td>
<td>2,194</td>
<td>2,112</td>
<td>1,875</td>
<td>1,380</td>
<td>1,161</td>
<td>741</td>
<td>166</td>
</tr>
</tbody>
</table>

**Number of patients:**

HR 0.86  
95.02% CI 0.74-0.99  
$p = 0.0382^*$

Cumulative incidence function.

*Two-sided tests for superiority were conducted (statistical significance was indicated if $p \leq 0.0498$)
EMPA-REG Outcome: CV Benefits

FIGURE 2

Analysis of All-cause Mortality, CV Death, and Non-CV Death in the EMPA-REG OUTCOME Study\textsuperscript{10}

<table>
<thead>
<tr>
<th>Patients with event / analyzed</th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-point MACE*</td>
<td>490/4,687</td>
<td>282/2,333</td>
<td>0.86</td>
<td>0.74-0.99</td>
<td>0.0382</td>
</tr>
<tr>
<td>CV death</td>
<td>172/4,687</td>
<td>137/2,333</td>
<td>0.62</td>
<td>0.49-0.77</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>213/4,687</td>
<td>121/2,333</td>
<td>0.87</td>
<td>0.70-1.09</td>
<td>0.2189</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>150/4,687</td>
<td>60/2,333</td>
<td>1.24</td>
<td>0.92-1.67</td>
<td>0.1638</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>269/4,687</td>
<td>194/2,333</td>
<td>0.68</td>
<td>0.57-0.82</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Non-CV death</td>
<td>97/4,687</td>
<td>57/2,333</td>
<td>0.84</td>
<td>0.60-1.16</td>
<td>0.2852</td>
</tr>
</tbody>
</table>

Cox regression analysis.

*CV death, nonfatal MI, nonfatal stroke.
SGLT-2 Inhibitors- Disadvantages/AE

- ↑ urine volume
- volume depletion/hypotension/dizziness
- ↑ urinary tract infection
- ↑ genital fungal infections
- ↑ LDL-c; ↑ HDL-c; no change LDL-c/HDL-c ratio
SGLT-2 Inhibitors - Disadvantages/AE

- May predisposed to DKA (in T1DM and T2DM)
- ↑ creatinine (transient)
- Limited use in pts with CKD
  - Canagliflozin:
    - eGFR < 45: contraindicated
    - eGFR 45-60: maximum dose 100 mg/day
  - Dapagliflozin: eGFR < 60: contraindicated
  - Empagliflozin: eGFR < 45: contraindicated

J Clin Pharmacol. 2011 May 4
SGLT2 inhibitors may predispose to ketoacidosis?

- May/2015: FDA issued warning that SGLT2 inhibitors may lead to ketoacidosis- “Euglycemic Ketoacidosis”

- Based on 20 cases requiring hospitalization between March 2013-June 2014 in the FDA Adverse Event Reporting System Database

- In June 2015 European agencies announced that the Pharmacovigilance Risk Assessment Committee has started a review of all 3 drugs to evaluate risk DKA in T2DM
17,596 pts with T2DM

Incidence DKA and related events: 12 cases (0.07%)
- 4 of 5,337 - 0.07% (canagliflozin 100 mg)
- 6 of 5,350 - 0.11% (canagliflozin 300 mg)
- 2 of 6,909 - 0.03% (comparator)

After the episodes 6 pts on canagliflozin were reported to have LADA or T1DM
### Empagliflozin – T2D Clinical Trial Data - Diabetic Ketoacidosis Cases

<table>
<thead>
<tr>
<th>SAF-5+ (broadest safety pool with all T2D patients treated with empagliflozin – does not include Emp-REG Outcome)(^#)</th>
<th>Placebo n (%) [Rate/ 100 PY]</th>
<th>Empagliflozin 10 mg n (%) [Rate/ 100 PY]</th>
<th>Empagliflozin 25 mg n (%) [Rate/ 100 PY]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>3695 (100.0)</td>
<td>3806 (100.0)</td>
<td>4782 (100.0)</td>
</tr>
<tr>
<td>Events consistent with DKA</td>
<td>5 (0.1) [0.20]</td>
<td>2 (0.1) [0.05]</td>
<td>1 (&lt;0.1) [0.02]</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>4 (0.1) [0.12]</td>
<td>2 (0.1) [0.05]</td>
<td>1 (&lt;0.1) [0.02]</td>
</tr>
<tr>
<td>Ketoacidosis</td>
<td>1 (&lt;0.1) [0.01]</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Acetonaemia</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Empa-REG Outcome(^\dagger)</th>
<th>Placebo n (%) [Rate/ 100 PY]</th>
<th>Empagliflozin 10 mg n (%) [Rate/ 100 PY]</th>
<th>Empagliflozin 25 mg n (%) [Rate/ 100 PY]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>2333 (100.0)</td>
<td>2345 (100.0)</td>
<td>2342 (100.0)</td>
</tr>
<tr>
<td>Diabetic ketoacidosis*</td>
<td>1 (&lt;0.1) [0.02]</td>
<td>3 (0.1) [0.05]</td>
<td>1 (&lt;0.1) [0.02]</td>
</tr>
</tbody>
</table>

\(^\ast\)Based on 4 MedDRA preferred terms.

\(^\#\)Kohler S, et. al Safety and tolerability of empagliflozin in patients with type 2 diabetes.American Diabetes Association (ADA) 75th Scientific Sessions, 5–9 June 2015, Boston, Massachusetts, USA; poster presentation 1173-P

\(^\dagger\)Zinman B et. al 2015. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. NEJM
Case series: 13 episodes of SGLT2-inhibitior associated DKA (7 pts with T1DM; 2 pts with T2DM)

Main characteristic: Euglycemic-DKA- delayed recognition by patients and providers

2 cases in T2DM occurred postoperatively

In patients with T1DM contributing factors were not always identified
Potential mechanisms whereby SGLT2 inhibitors may promote ketosis

- To minimize hypoglycemia patients usually need to decrease insulin dose, leading to potential increase in lipolysis and hepatic ketogenesis

- SGLT2-i have been shown to increase plasma glucagon level in patients with T2DM

- ? Decrease renal clearance of ketone bodies
  - Phlorizin (non-selective inhibitor of SGLT1 and 2) increases renal tubular reabsorption of acetoacetate- animal studies only
    - J Clin Invest 2014; 124:499
    - Am J Physiol 1956; 184:91
Potential mechanisms whereby SGLT2 inhibitors may promote ketosis
Role of SGLT2-inhibitors in Type 2 Diabetes Management
Pharmacotherapy in T2DM

- Metformin - “Foundation Therapy”
- Insulin Secretagogues:
  - Meglitinide
  - SU
- TZDs
- Incretin Agents:
  - DPP4-inhibitors
  - GLP1-Receptors Agonists
- Alpha-glucosidase inhibitors (Acarbose)
- Sodium Glucose co-transporter 2 (SGLT2) inhibitors
- Insulin
“Personalizing” Type 2 Diabetes Therapy

- Anticipation of Drug Efficacy
- Concerns of Adverse Effects
- Desired for added benefits

- Patient’s Preferences
- Cost & Coverage
- No contra indication

Medication of choice?
Use of SGLT2-inhibitors in T2DM:

**Indications:**
- A1C not at target
- Weight loss desirable
- BP not at target
- Concerns about hypoglycemia
- Intact kidney function

**Contra-indications (or should be avoided):**
- eGFR < 60
- Baseline orthostatic symptoms
- Recurrent UTI
Sodium-Glucose Cotransporter 2 Inhibition and Glycemic Control in Type 1 Diabetes: Results of an 8-Week Open-Label Proof-of-Concept Trial

Diabetes Care 2014;37:1480–1483 | DOI: 10.2337/dc13-2338

- 40 patients with T1DM on MDI or CSII
- Objective: glycemic efficacy and safety of empagliflozin 25 mg daily
- Single-arm, open-label, proof of concept trial
- A1C 6.5%-11%
- 8 weeks of treatment
- 2 weeks post-treatment follow-up
Results:

Figure 1—Mean A1C (A), fasting capillary glucose (B), symptomatic hypoglycemia (C), total insulin dose (D), and weight (E) at each study time point. Bar graphs indicate the mean for each variable, and the error bars indicate the SEM. Mean and SDs, the change in mean from baseline with its SD, and the P value for comparison with baseline are shown in each panel for each study time point.
18-week, randomized, double-blind, placebo-controlled trial
351 adults with T1DM (25-65 yo) on MDI or CSII
A1C 7-9%
Canagliflozin 100 mg, 300 mg or placebo
Primary objective: % of pts achieving A1C reduction >=0.4% and no increase in body weight
Other: change A1C, body weight, insulin dose, hypo incidence, AE report
Results:
### Results - Ketone-related AE

<table>
<thead>
<tr>
<th>Table 3—Summary of overall safety and selected AEs over 18 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
</tr>
<tr>
<td><strong>(n = 117) n (%)</strong></td>
</tr>
<tr>
<td>Any AE</td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
</tr>
<tr>
<td>AEs related to the study drug*</td>
</tr>
<tr>
<td>Serious AEs</td>
</tr>
<tr>
<td>Deaths</td>
</tr>
<tr>
<td>Urinary tract infections</td>
</tr>
<tr>
<td>Genital mycotic infections</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female†‡</td>
</tr>
<tr>
<td>Osmotic diuresis–related AEs§</td>
</tr>
<tr>
<td>Volume depletion–related AEs‖</td>
</tr>
<tr>
<td>Ketone-related AEs¶</td>
</tr>
<tr>
<td>Serious DKA AEs**</td>
</tr>
<tr>
<td>Nonserious AEs††</td>
</tr>
</tbody>
</table>

*Possibly, probably, or very likely related to study drug, as assessed by investigators. †Placebo, n = 54; canagliflozin 100 mg, n = 48; canagliflozin 300 mg, n = 52. ‡Including vaginal infection, vulvovaginal candidiasis, and vulvovaginal mycotic infection. §Including dry mouth, nocturia, polydipsia, polyuria, thirst, and urine output increased. †Including dehydration, dizziness postural, hypotension, and syncope. ‖Including DKA, ketoacidosis, and urine ketone body present. †#One patient had an initial serious DKA event and a subsequent nonserious DKA event of increased urine ketones. **Requiring hospitalization. ††Including increased urinary ketones and mild and moderate DKA or acidosis.
Back to the Case 1…
63 yo female with LADA started on Dapagliflozin

- Discussed with patient:
  - off label use of SGLT2 inhibitors in T1DM
  - recent warnings from FDA and Health Canada that SGLT2 inhibitors may lead to DKA in patients with T1DM and T2DM

- After extensive discussion and counseling patient opted to remain on Forxiga in combination with insulin
Back to the Case ...

27 yo female with T1DM since the age of 10 yo frustrated about poor control and progressive weight gain

- Discussed with patient:
  - off label use of SGLT2 inhibitors in T1DM
  - Discussed about ongoing clinical trials recruiting patients with T1DM

- After understanding mechanism of action and potential side effects patient willing to obtain more information about research trials and will consider participation
Empagliflozin as Adjunctive to Insulin Therapy in Type 1 Diabetes Over 52 Weeks (EASE-2)

- **ClinicalTrials.gov Identifier:** NCT02414958
- Comparison of 2 doses of empagliflozin vs placebo in T1DM on MDI or CSII
- Randomization to 3 treatments arms (equal assignment)
- 52 week double-blind treatment period, and 3 week follow-up period
- Estimated Enrollment: 720 patients
- HbA1c 7.5%- 10.0%
- Age >/= 18 years
EASE-2 Trial

Primary Outcome Measures:
- Change from baseline in HbA1c

Secondary Outcome Measures:
- Change from baseline in body weight
- Incidence rate of symptomatic and/or severe hypoglycaemic
- Change from baseline in the percentage of time spent in target glucose range of 3.9-10.0 mmol/L by CGM
- Change from baseline in total daily insulin dose (TDID)
- Change from baseline in SBP and DBP
Empagliflozin as Adjunctive to insulin therapy in Type 1 Diabetes Over 52 Weeks

This study is currently recruiting participants. (see Contacts and Locations)

Verified January 2016 by Boehringer Ingelheim

Sponsor:
Boehringer Ingelheim

Collaborator:
Eli Lilly and Company

Information provided by (Responsible Party):
Boehringer Ingelheim

Purpose

Comparison of 2 doses of empagliflozin vs placebo in patients already using either an insulin regimen or oral treatments arms (equal assignment) following a screening period, an optimisation period and a run-in period, and a 3 week follow-up period.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Mellitus, Type 1</td>
<td>Drug: Empagliflozin Drug: Placebo</td>
</tr>
</tbody>
</table>
Take Home Messages

- SGLT2 inhibitors reduce blood glucose by inducing glycosuria (reduce A1C ~ 0.5-0.7%)
- Related to modest weight loss and BP drop
- Low risk of hypoglycemia
- Reduction in CV death in T2DM + known CVD (Empa)
  - mechanism not clear/awaiting findings of other studies with SGLT2-i
- Side effects include genital mycotic infections, UTI and volume depletion
- ??? associated with euglycemic DKA
  - multiple biologically plausible mechanism
  - Ongoing trials should further define the risk in T1DM and T2DM
- Utility in special populations (T1DM, pediatric) remains to be determined