SGLT-2s: Potential Benefits and Risks
Anne Peters, MD
Saturday, March 5, 2016
11:30 a.m. – 12:15 p.m.

SGLT-2 inhibitors are the newest class of medication for the treatment of type 2 diabetes on the market. Their mechanism of action is different from any other anti-diabetes agent and can theoretically be used in combination with all other therapies, although RCT data is lacking when it comes to combination therapy with GLP-1 receptor agonists. In addition to lowering blood glucose levels they seem to have true cardiovascular benefits as shown in the landmark Empa-Reg Trial.

Because of the potential benefits of these agents for all individuals with diabetes, regardless of type, they have been used on-label for the treatment of type 2 diabetes and off-label for the treatment of type 1 diabetes. Unfortunately in the latter group rates of DKA appear to be increased, in particular with the higher doses of these agents.

This talk will touch on a variety of aspects of the use of these agents, starting with their potential to help reduce the risks of renal and cardiovascular complications. It will then move into a discussion of the risks of these agents, including DKA, bone fractures, and bladder and vaginal infections. Finally, an approach to risk mitigation will be described and a safe approach for use of these agents in all individuals with diabetes will be provided.

References:

SGLT-2 Inhibitors: Benefits and Risks

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Disclosure of Potential Conflicts of Interest

Consultantship
- Abbott Diabetes Care
- Astra Zeneca
- Bigfoot Biomedical
- BD; BI
- CVS/Caremark
- FDA
- Janssen, Lexicon, Lilly
- Medscape, Medtronic, Merck
- Novo Nordisk
- Omada Health
- OptumRX

Research Funding
- Janssen
- Medtronic Foundation

In healthy individuals, the renal glomeruli filter approximately 162 g of glucose per day. Virtually all of the filtered glucose is reabsorbed in the proximal tubules through the sodium glucose cotransporters SGLT2 and SGLT1.


SGLT1=sodium glucose cotransporter 1; SGLT2=sodium glucose cotransporter 2.

In the presence of SGLT-2 inhibitor, the less glucose is reabsorbed. The result is glycosuria.


Inhibitors of SGLT-2 Co-Transporter Increases Renal Glucose Excretion

In healthy individuals, the renal glomeruli filter approximately 162 g of glucose per day. Virtually all of the filtered glucose is reabsorbed in the proximal tubules through the sodium glucose cotransporters SGLT2 and SGLT1.


SGLT2 Inhibitors Lower Renal Threshold for Glucose Excretion (RTG)

Effect of Canagliflozin on A1C as Mono or Combination Therapy

Canagliflozin Added to

Baseline A1C (%)

Mono1 (N=524) 8.06 8.01
+Met (N=1284) 7.2±0.3 7.0±0.3
+innov (N=524) 8.9±0.4 8.6±0.3
+Fio (N=342) 7.6±0.3 7.4±0.3
+Insulin (N=1716) 8.3±0.3 8.2±0.3
Older subjects1,2 (N=714) 7.7

1Studies for combinations including SU or insulin were 18 weeks in duration; all others were 26 weeks in duration.
2P<0.001 for reduction vs control.

Adapted with permission from: diabetesIII.com, Infunce.Net,
Percent Change in Body Weight

<table>
<thead>
<tr>
<th>Time point (wk)</th>
<th>LS mean</th>
<th>% change</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>-3.9%</td>
<td>(-3.4 kg)</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>-2.8%</td>
<td>(-2.5 kg)</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>-0.6%</td>
<td>(-0.5 kg)</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>-2.2%</td>
<td>(-1.9 kg)</td>
<td></td>
</tr>
</tbody>
</table>

P <0.001

-3.3% (-2.9 kg)
P <0.001


Canagliflozin/Dapagliflozin/Empagliflozin

Warnings and Precautions
- Hypoglycemia: risk with secretagogues and/or insulin
- Genital mycotic infections
- Volume depletion/orthostatic changes
- Hypersensitivity
- Increased LDL
- Bladder cancer: don’t use if active; use with caution if prior history of bladder cancer (dapagliflozin only)

EMPA-REG OUTCOME®
- Randomised, double-blind, placebo-controlled CV outcomes trial
- Objective
To examine the long-term effects of empagliflozin versus placebo, in addition to standard of care, on CV morbidity and mortality in patients with type 2 diabetes and high risk of CV events

Dapa/Cana/Empa in Patients with Renal Impairment

Canagliflozin
Contraindicated in patients with eGFR <45 ml/min/1.73 m²
Dose is limited to 100 mg daily if eGFR 45-<60 ml/min/1.73 m²

Dapagliflozin
Contraindicated in patients with eGFR <60 ml/min/1.73 m²

Empagliflozin
Contraindicated if eGFR <45 ml/min/1.73 m²

Trials design
- Study medication was given in addition to standard of care
  - Glucose-lowering therapy was to remain unchanged for first 12 weeks
- Treatment assignment double masked
- The trial was to continue until at least 691 patients experienced an adjudicated primary outcome event

CV death

Cumulative incidence function. HR, hazard ratio
Hospitalisation for heart failure

Cumulative incidence function. HR, hazard ratio

EMPA-REG OUTCOME:
Therapeutic considerations

- Empagliflozin, as used in this trial, for 3 years in 1,000 patients with type 2 diabetes at high CV risk:
  - 25 lives saved (82 vs 57 deaths)
  - 22 fewer CV deaths (59 vs 37)
  - 14 fewer hospitalisations for heart failure (42 vs 28)
  - 53 additional genital infections (22 vs 75)

All-cause mortality

Kaplan-Meier estimate. HR, hazard ratio

Janssen Phase 2 Trial
Protocol 28431754DIA2004

To evaluate the efficacy and safety of CANA compared with PBO in patients with T1DM inadequately controlled with insulin therapy over 18 weeks.

Study Design

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Baseline Demographic and Disease Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1DM ≥ 1 year</td>
<td>PBO (n = 117)</td>
</tr>
<tr>
<td>Age, y</td>
<td>42 (12)</td>
</tr>
<tr>
<td>White, %</td>
<td>51</td>
</tr>
<tr>
<td>Black or African</td>
<td>0</td>
</tr>
<tr>
<td>American Asian</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>7.9 (0.6)</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>83 (15)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26 (4)</td>
</tr>
</tbody>
</table>

Values are Mean (SD)
Baseline Demographic and Disease Characteristics (cont)

<table>
<thead>
<tr>
<th></th>
<th>PBO</th>
<th>CANA 100 mg</th>
<th>CANA 300 mg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR, mL/min/1.73 m²</td>
<td>98 (15)</td>
<td>97 (15)</td>
<td>96 (17)</td>
<td>96 (15)</td>
</tr>
<tr>
<td>Duration of T1DM, y</td>
<td>23 (11)</td>
<td>22 (12)</td>
<td>22 (11)</td>
<td>22 (11)</td>
</tr>
<tr>
<td>CSII use, %</td>
<td>67</td>
<td>62</td>
<td>62</td>
<td>62</td>
</tr>
<tr>
<td>Prior severe hypoglycemia, %</td>
<td>15</td>
<td>13</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Prior DKA, %</td>
<td>12</td>
<td>11</td>
<td>13</td>
<td>12</td>
</tr>
</tbody>
</table>

Values are Mean (SD)

Primary Endpoint: Both Doses of CANA Increased the Proportion of Patients with DHbA1c ≤ -0.4% and No Weight Gain

Both Doses of CANA Decreased HbA1C

Both Doses of CANA Reduced Body Weight

Greater Reduction Seen with 300 mg Dose

Both Doses of CANA Reduced Fasting Glucose

However, 95% CIs for Differences Between CANA and PBO Included 0

Both Doses of CANA Reduced Insulin Doses

Greater Reductions Seen with 300 mg Dose

*P <0.001 versus PBO.

Data are LS mean change from baseline ± SE. Between-group differences are DLSM (95% CI).
**Treatment-Emergent Hypoglycemia Episodes**

<table>
<thead>
<tr>
<th></th>
<th>PBO (n = 117)</th>
<th>CANA 100 mg (n = 117)</th>
<th>CANA 300 mg (n = 117)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any documented hypoglycemia, %</td>
<td>97%</td>
<td>98%</td>
<td>99%</td>
</tr>
<tr>
<td>Event rate per patient-year of exposure</td>
<td>81</td>
<td>71</td>
<td>70</td>
</tr>
<tr>
<td>Patients with any documented symptomatic hypoglycemia, %</td>
<td>93%</td>
<td>96%</td>
<td>95%</td>
</tr>
<tr>
<td>Event rate per patient-year of exposure</td>
<td>56</td>
<td>51</td>
<td>47</td>
</tr>
<tr>
<td>Patients with any severe hypoglycemia, n (%)‡</td>
<td>2 (2%)</td>
<td>3 (3%)</td>
<td>8 (7%)</td>
</tr>
</tbody>
</table>

**Summary of Overall Safety and Selected AEs**

<table>
<thead>
<tr>
<th>Event</th>
<th>PBO (n = 117)</th>
<th>CANA 100 (n = 117)</th>
<th>CANA 300 (n = 117)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>84 (75)</td>
<td>105 (90)</td>
<td>79 (68)</td>
</tr>
<tr>
<td>AE leading to discontinuation</td>
<td>0</td>
<td>1 (1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>AE related to study drug</td>
<td>11 (10)</td>
<td>15 (13)</td>
<td>14 (12)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serious AEs leading to discontinuation</td>
<td>0</td>
<td>1 (1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Serious AEs related to study drug</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serious AEs leading to death</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>UTIs</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Genital mycotic infections</td>
<td>3 (6)</td>
<td>2 (4)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Osmotic diuresis-related AEs</td>
<td>0</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Volume depletion-related AEs</td>
<td>3 (6)</td>
<td>6 (5)</td>
<td>11 (9)</td>
</tr>
<tr>
<td>Ketone-related AEs</td>
<td>0</td>
<td>4 (4)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Serious DKA AEs</td>
<td>0</td>
<td>1 (1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Nonserious AEs</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Janssen Phase 2 Trial**

Protocol 28431754DIA2004

- Treatment with canagliflozin was associated with a dose-dependent increase in ketone-related adverse events including serious adverse events of DKA, which were associated with inciting factors and in some cases with BG levels <250 mg/dL (blood glucose levels ranged from 170 to >800 mg/dL).

**Episodes of DKA in the Clinical Trial over 18 weeks**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Cana 100 mg</th>
<th>Cana 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any ketone-related AE</td>
<td>0 (n = 0/117)</td>
<td>5.1% (n = 6/117)</td>
<td>9.4% (n = 11/117)</td>
</tr>
<tr>
<td>DKA Serious AE</td>
<td>0 (n = 0/117)</td>
<td>4.3% (n = 5/117)</td>
<td>6.0% (n = 7/117)</td>
</tr>
<tr>
<td>Nonserious ketone-related AE</td>
<td>0 (n = 0/117)</td>
<td>0.9% (n = 1/117)</td>
<td>4.3% (n = 5/117)</td>
</tr>
</tbody>
</table>

**Precipitating Factors**

- In all subjects with a serious adverse event of DKA, possible precipitating factors that could have caused or contributed to the event were present, with infections (pneumonia, influenza, bronchitis, infection of infusion site of insulin pump) and insufficient insulin dosing (pump failure, lack of compliance with insulin treatment) being the most common.
Undiagnosed LADA

- SN is a 32 yo female with diabetes referred to see me for evaluation of DKA on an SGLT-2 inhibitor.
- She had developed diabetes at the age of 30, 2 years previously. At that time her BMI was 24 m/kg². She is of Lebanese ancestry with family history positive for multiple family members with type 2 diabetes. No known autoimmunity.
- She was started on insulin for one month, but tapered of it after one month when anti-GAD antibodies negative came back with a positive C-peptide level.
- For ~2 years she was well controlled (by her report) on metformin, liraglutide and canagliflozin for her T2D.

Then she went on a 7 day cruise. At the end of the cruise she developed severe vomiting and abdominal pain.
- She was diagnosed on shipboard as having a "gastroenteritis" but went immediately to an ER once on land and was found to have DKA with BG’s around 180 mg/dl.
- After treatment for the DKA she was started on 75/25 twice daily insulin injections and came to see me due to her fluctuating BG’s and weight gain.
- Her C-peptide level was 0.15 ng/ml. Antibodies remain negative.

- At her first visit her 75/25 regimen was switched to MDI with long and rapid acting premeal insulin. Her goal was to lose weight to fit into her wedding dress which was handmade for her by a now-deceased relative.
- At her next visit I restarted her liraglutide along with her insulin with some improvement in her weight and BG’s.
- She begged to go back on an SGLT-2 I. I had her begin urine then serum ketone monitoring. On 5 mg empagliflozin her BG’s improved and serum ketones were 0.3 – 0.4. She was uptitrated to 10 mg and her ketones were 1.5 – 3.0. No symptoms. She was drinking 9 bottles of water daily.

T2D Database Review

- A recent analysis of serious AEs of DKA in the canagliflozin T2D clinical trial program (N = 17,596) showed that DKA occurred at a low frequency (<0.1%) similar to that seen in the general population of patients with T2D.
- Most patients with a serious AE of DKA were on insulin and had precipitating factors similar to those reported in the current study (eg, infection, noncompliance with insulin therapy); many of the patients had evidence of autoimmunity.
A U.S. Food and Drug Administration (FDA) safety review has resulted in adding warnings to the labels of a specific class of type 2 diabetes medicines called sodium-glucose cotransporter-2 (SGLT2) inhibitors about the risks of too much acid in the blood and of serious urinary tract infections. Both conditions can result in hospitalization.

Patients should stop taking their SGLT2 inhibitor and seek medical attention immediately if they have any symptoms of ketoacidosis, a serious condition in which the body produces high levels of blood acids called ketones. Symptoms of ketoacidosis include nausea, vomiting, abdominal pain, tiredness, and trouble breathing. Patients should also be alert for signs and symptoms of a urinary tract infection, such as a feeling of burning when urinating or the need to urinate often or right away; pain in the lower part of the stomach area or pelvis; fever; or blood in the urine. Contact a health care professional if you experience any of these symptoms.

Use of SGLT-2 inhibitors is off-label in individuals with T1DM other than in clinical trials. If an SGLT-2 inhibitor is used in an individual with T1DM the prescribing provider should employ a clear protocol for ketone monitoring and managing periods of illness, insulin reduction and physiological stress. Because DKA can be euglycemic as well as hyperglycemic, first-line providers need to be educated as to recognition and treatment of euDKA in people taking SGLT-2 inhibitors.

THANK YOU