The Upsides And Downsides Of SGLT2 Inhibitors Within Our Choices Of Glucose Lowering Medications

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ADA-EASD Position Statement: Patient-Centered Approach

"...providing care that is respectful of and responsive to individual patient preferences, needs, and values - ensuring that patient values guide all clinical decisions."

- Gauge patient’s preferred level of involvement.
- Shared decision making – final decisions re: lifestyle choices ultimately lies with the patient.
- Explore, where possible, therapeutic choices.
- Utilize decision aids.

Disclosure to Participants

Notice of Requirements For Successful Completion
Please refer to learning goals and objectives
Learners must attend the full activity and complete the evaluation in order to claim continuing education credit hours

Conflict of Interest (COI) and Financial Relationship Disclosures:
Notice of Requirements For Successful Completion
Disclosure to Participants

Step 1: Set Glycemia Target

Patient Factors

Provider Factors

Normal Glucose Homeostasis Depends on Reabsorption in the Kidney

Healthy eating, weight control, increased physical activity & diabetes education

Medication

Normal Glucose

Filtered glucose, load = 180 g/day

Virtually all of the filtered glucose is reabsorbed in the proximal tubules through the sodium-glucose cotransporters SGLT2 and SGLT1

No Glycosuria

SGLT

~90% SGLT1 ~10%

SGLT1 = sodium glucose cotransporter 1; SGLT2 = sodium glucose cotransporter 2.
3  Add reference see below
   Carol Wysham, 5/2/2014
In the presence of SGLT-2 inhibitor, the less glucose is reabsorbed. The result is glycosuria.

SGLT1 ~10%
SGLT2 ~90%


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

SGLT2 Inhibitors Lower Renal Threshold for Glucose Excretion (RTG)

Canagliflozin/Dapagliflozin/Empagliflozin Warnings and Precautions
- Hypoglycemia: risk with secretagogues and/or insulin
- Genital mycotic infections
- Urinary tract infection, pyelo, urosepsis
- Volume depletion/orthostatic changes
- Acute renal insufficiency/failure
- DKA
- Bladder cancer (dapagliflozin only)
- Increased fracture risk (cana)
- Increased risk for amputation (cana)

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
My Approach for Prevention of Genital Mycotic Infections

Female:
- Warn of risk; reduce sugars slowly
- Make sure topical anti-fungal vaginal cream on hand to apply for even minimal irritation
- If history of vaginal yeast infection, give prescription for fluconazole 150 mg q72 hours x 3

Male:
- More common in uncircumcised men
- Discuss risk; genital hygiene
- Make sure topical anti-fungal vaginal cream on hand to apply for even minimal irritation
- If uncircumcised consider script for fluconazole

Use of Canagliflozin in T1D

Individual Tracings: After Efforts to Improve Lifestyle and Adherence

Individual Tracings: After Cana Added at the Patient’s Request

Case—Euglycemic DKA on Canagliflozin

- The patient is 27 yo female with T1D since the age of 2 with no DKA since Dx.
- A1C’s 9 – 10% for most of her life
- Feared weight gain and hypos; started on canagliflozin at 100 mg/day in 10/2014; uptitrated to 300 mg/day in mid-December.
- Dose of insulin: glargine 22 units qAM, CHO ratio 1:10, Correction 1:25.
- Went back to the East Coast for the holidays; developed symptoms of low grade viral syndrome

Canagliflozin in Person with T1DM—continued
Day -3…At work, still not feeling well. Normal insulin doses.

Day -2…Still not feeling great, eating less, BG's lower, doesn't give glargine. Continues canagliflozin.

Day -1…Still not feeling great, eating less, BG's lower, still doesn't give glargine. Continues canagliflozin. Has 2 glasses of wine at 8 pm. Thinks her DM is gone…gives no glargine.

Day 0. Wakes up vomiting uncontrollably at 8 AM. By noon goes to ER.

Day 1. In MICU being treated for DKA. Discharged home at 8 PM.
Euglycemic DKA in T2DM

- Case #9 is a 64 yo overweight female (32.8 kg/m²) with T2DM admitted for bilateral cervical foraminotomy.
- Anti-GAD - / C-peptide +
- Prior to cana she was on: an SA, sitagliptin and detemir 20 units BID with an A1C = 8.4%.
- Cana started, over the next 6 months she lost weight (BMI = 29.1 kg/m²), stopped her insulin and A1C fell to 7.8%.
- Her canagliflozin was held the morning of surgery.

T2DM Case--continued

- ~10 hours after surgery she developed nausea. By the next morning her CO2 =13 mmol/L, BG = 169 mg/dl and AG = 16 mEq/L. She had N/V and was treated with anti-emetics.
- The next morning her BG =179 mg/dl, CO2 = 5 mmol/L, AG = 19 mEq/L. That evening her serum acetone level was measured (positive at a 1:32 dilution) and started on an IV insulin and dextrose drip.
- Over the next few days her CO2 increased to normal, her BG levels were in the range of 116 - 190 mg/dl.

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.

My Approach for Pre-Op Management SGLT-2 I

- If patient undergoing general anesthesia, hold SGLT-2 inhibitor for 3 days in advance of major surgery (it can take up to 3 days for effect of SGLT-2 inhibitor to dissipate)
- If this not possible and metabolic acidosis develops, remember it could be DKA
- Not necessary to hold for 3 days if more minor procedure, BUT hold on fasting days (e.g. for colonoscopy) and/or if patient is NPO.
RCT: Canagliflozin in T1D

- Study initiated May 28, 2014
- Completed June 5, 2015
- Primary objective was to determine efficacy, safety and tolerability of canagliflozin in people with type 1 diabetes compared to placebo.
- Cana 100 and 300 mg doses vs placebo were evaluated over 18 weeks. Each of the three groups consisted of 117 randomized subjects.


Study Design

Study Design Diagram:
- Pretreatment Period
- Double-blind Treatment Period
- Titrated background insulin to goal
- Baseline BW (kg)
- Baseline (%)
- Treatment-Emergent Hypoglycemia Episodes
- Baseline (%)
- Event rate per patient-year of exposure

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>DHbA1c ≤ -0.4%</th>
<th>ΔBW ≤ 0</th>
<th>ΔDHbA1c ≤ -0.4% and ΔBW ≤ 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO</td>
<td>23</td>
<td>45</td>
<td>49</td>
</tr>
<tr>
<td>CANA 100 mg</td>
<td>49</td>
<td>84</td>
<td>96</td>
</tr>
<tr>
<td>CANA 300 mg</td>
<td>41</td>
<td>96</td>
<td>96</td>
</tr>
</tbody>
</table>

Both Doses of CANA Decreased HbA1C

Both Doses of CANA Reduced Body Weight

Both Doses of CANA Decreased HbA1C

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline (%)</th>
<th>1.0</th>
<th>0.1</th>
<th>0.01%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO</td>
<td>7.9</td>
<td>7.9</td>
<td>7.9</td>
<td>0.01%</td>
</tr>
<tr>
<td>CANA 100 mg</td>
<td>7.9</td>
<td>-0.1</td>
<td>-0.2</td>
<td>-0.27%</td>
</tr>
<tr>
<td>CANA 300 mg</td>
<td>7.9</td>
<td>-0.2</td>
<td>-0.3</td>
<td>-0.24%</td>
</tr>
</tbody>
</table>

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

Both Doses of CANA Reduced Body Weight

<table>
<thead>
<tr>
<th>Treatment</th>
<th>DHbA1c (% change)</th>
<th>ΔBW (% change)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO</td>
<td>-0.25 (95% CI)</td>
<td>-0.3% (95% CI)</td>
</tr>
<tr>
<td>CANA 100 mg</td>
<td>-0.20 (95% CI)</td>
<td>-0.5% (95% CI)</td>
</tr>
<tr>
<td>CANA 300 mg</td>
<td>-0.15 (95% CI)</td>
<td>-0.7% (95% CI)</td>
</tr>
</tbody>
</table>

Treatment-Emergent Hypoglycemia Episodes

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients with any documented hypoglycemia, %</th>
<th>Event rate per patient-year of exposure</th>
<th>Patients with any documented symptomatic hypoglycemia, %</th>
<th>Event rate per patient-year of exposure</th>
<th>Patients with any severe hypoglycemia, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO</td>
<td>97% (n = 117)</td>
<td>81 (n = 117)</td>
<td>93% (n = 117)</td>
<td>56 (n = 117)</td>
<td>2 (2%) (n = 117)</td>
</tr>
<tr>
<td>CANA 100 mg</td>
<td>98% (n = 117)</td>
<td>71 (n = 117)</td>
<td>96% (n = 117)</td>
<td>51 (n = 117)</td>
<td>3 (3%) (n = 117)</td>
</tr>
<tr>
<td>CANA 300 mg</td>
<td>99% (n = 117)</td>
<td>79 (n = 117)</td>
<td>95% (n = 117)</td>
<td>47 (n = 117)</td>
<td>8 (7%) (n = 117)</td>
</tr>
</tbody>
</table>
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</td>
<td>5.1% (n = 6/117)</td>
<td>9.4% (n = 11/117)</td>
</tr>
<tr>
<td>DKA Serious AE</td>
<td>0</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</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.

Follow-Up

- After ~1 year on cana she developed pneumonia.
- Although warned of the risk of euDKA she continued to take the cana 300 mg/d and reduced her insulin due to lack of CHO intake.
- She developed euDKA and was hospitalized for treatment.
- Off cana her BG’s were higher and more variable. She restarted at 50 mg/d and increased to 100 mg/d with daily ketone testing (first for a baseline week, then as she uptitrated).
- She has done well since except when she goes out for a few drinks on the weekend which causes strongly positive serum ketones the next morning. Now she holds the cana if planning to go out.

Patient Satisfaction


Changes in Measures of Glycemic Variability at Week 18 (CGM Substudy)

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>PBO (n = 24)</th>
<th>CANA 100 mg (n = 25)</th>
<th>CANA 300 mg (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean glucose, mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>162.1 ± 31.1</td>
<td>175.7 ± 27.3</td>
<td>164.9 ± 24.4</td>
</tr>
<tr>
<td>Change</td>
<td>10.2 ± 35.2</td>
<td>-20.9 ± 22.2</td>
<td>-12.3 ± 21.7</td>
</tr>
<tr>
<td>Glucose standard deviation, mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>68.1 ± 12.8</td>
<td>63.5 ± 16.3</td>
<td>69.3 ± 12.7</td>
</tr>
<tr>
<td>Change</td>
<td>1.6 ± 14.0</td>
<td>-5.2 ± 15.8</td>
<td>-12.2 ± 15.9</td>
</tr>
<tr>
<td>MAGE, mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>163.8 ± 31.5</td>
<td>149.9 ± 36.1</td>
<td>166.6 ± 28.8</td>
</tr>
<tr>
<td>Change</td>
<td>5.1 ± 33.8</td>
<td>-11.4 ± 36.3</td>
<td>-32.7 ± 37.0</td>
</tr>
</tbody>
</table>

*Data are mean ± SD.

My Personal Approach for Off-Label Use of SGLT-2 I’s in T1D

- Patient needs to be adherent, aware of risks of DKA, hypoglycemia, off-label use. Must be eating at least 100 grams of carbs/day
- Start by testing ketones once in the morning x 2 weeks to establish baseline (serum or urine)
- Start with ¼ - ½ of the lowest dose pill qAM
- Increase every 2 weeks based on ketones; max dose = 100 mg cana; 5 mg dapa; 10 mg empa
- No change in insulin dose initially
- Continue morning ketone testing until stable on maximal achieved dose

Change in Proportion of Time Spent in Glycemic Ranges at Week 18 (CGM Substudy)

My Personal Approach for Off-label Use of SGLT-2 I's in T1D

- Stop ketone testing 2 weeks after stable on one pill daily, but have ketone testing available
- EDUCATE: Don’t switch to low carb diet, hold SGLT-2 I if sick, in situation where more likely to become dehydrated, if planning much more exercise, if pump failure, perhaps if traveling
- EDUCATE: teach that if ketones rise (above 0.5 on serum ketone testing) to INCREASE carb intake, give more insulin, drink fluids, hold SGLT-2 inhibitor until ketones fall to baseline

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.
Undiagnosed LADA

- 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.

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
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)

Conclusions

- SGLT-2 inhibitors have many benefits and some risks
- Be aware of risks and minimize as much as possible; patient and provider education vital
- Listen to the patient, in terms of their preferences and goals
- Report abnormal events to the FDA if you think they are medication related—it helps define risk
  http://www.fda.gov/Safety/MedWatch/