SGLT-2 Inhibitors:
Overview and Place in Therapy

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Disclosure
• Nothing to disclose

Objective
• Describe the appropriate clinical use of SGLT-2 inhibitors for treating diabetes
  – Canagliflozin
  – Dapagliflozin
  – Empagliflozin

• SGLT = Sodium-Glucose Cotransporter
Indication

- Treatment of type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycemic control

Mechanism of Action

SGLT2 inhibition reduces reabsorption of glucose into the bloodstream resulting in glucose passing through the urine. Schematic View of the Kidney in People with Poorly Controlled T2D

Comparative Efficacy

<table>
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<tr>
<th>Medication</th>
<th>Mean A1c Decrease</th>
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<tbody>
<tr>
<td>Canagliflozin 100-300mg daily</td>
<td>Monotherapy: 0.77-1.03%&lt;sup&gt;1&lt;/sup&gt; Combo therapy: 0.63-1.06%&lt;sup&gt;2,3,4&lt;/sup&gt;</td>
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<tr>
<td>Dapagliflozin 5-10mg daily</td>
<td>Monotherapy: 0.41-1.11%&lt;sup&gt;5,6&lt;/sup&gt; Combo therapy: 0.5-0.97%&lt;sup&gt;3,8,10,11&lt;/sup&gt;</td>
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<tr>
<td>Empagliflozin 10-25mg daily</td>
<td>Monotherapy: 0.5-0.85%&lt;sup&gt;12,13&lt;/sup&gt; Combo therapy: 0.6-1%&lt;sup&gt;14,15,16,17&lt;/sup&gt;</td>
</tr>
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</table>
Other Effects Noted in Clinical Trials

- Decreased fasting and postprandial glucose
- Systolic blood pressure decrease
  - Approximately 2-10mmHg
- Weight loss
  - Up to 4.7kg
- Decreased uric acid
- Small increases in LDL and HDL cholesterol

Renal Dose Adjustments

- Canagliflozin
  - eGFR 45-60 do not exceed 100mg daily
  - eGFR <45 do not use
- Dapagliflozin
  - eGFR <60 do not use
- Empagliflozin
  - eGFR <45 do not use

Safety

- Side effects:
  - Genital mycotic infections (females>males)
  - Urinary tract infection
  - Postural dizziness/orthostatic hypotension
  - Polyuria
- Low risk of hypoglycemia
  - Unless used in combination with sulfonylurea or insulin
- Dapagliflozin: risk of bladder cancer

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Safety

- FDA Warning: Ketoacidosis
  - FDA review identified 20 cases of acidosis in patients treated with SGLT2 inhibitors from March 2013-June 2014
  - S/S: Difficulty breathing, nausea, vomiting, abdominal pain, confusion, unusual fatigue/sleepiness
  - Risk factors: major illness, reduced food and fluid intake, and reduced insulin dose

Convenience

- Once-daily dosing
- Also a few combination products available:
  - Canagliflozin + IR metformin: dosed twice daily
  - Dapagliflozin + ER metformin: dosed once daily
  - Empagliflozin + linagliptin
- Cost:
  - Approximately $400 per month
  - “$0” copay cards available through manufacturers for private insurance

Place in Therapy

- ADA guidelines:
  - Second line therapy in addition to metformin if not at goal
- AACE guidelines:
  - Can be used as monotherapy or in addition to other agents as part of dual or triple therapy
- Key advantages:
  - Oral medication
  - Low risk of hypoglycemia
  - Potential for weight loss
Case

- XY is a 51 year old Caucasian male who presents to clinic today for follow-up DM appointment.
  - Current diabetes medications:
    - Metformin XR 2000mg daily
  - Labs prior to visit:
    - A1c 7.6%, Scr 1.1, eGFR >60
  - Vitals:
    - BMI 32.5, BP 136/78 mmHg, Pulse 88 bpm

What would be the advantages of adding an SGLT-2 inhibitor to this patient’s regimen?

a) A1c reduction adequate to reach goal (<7%)
b) Weight loss
c) Low risk of hypoglycemia when added to metformin
d) All of the above

References

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