Sodium glucose co-transporter type 2 (SGLT2) inhibitors – Moving Beyond Targets

Nicholas (Cole) Helbling PharmD
BCPS
Sanford Health

- Largest, not-for-profit rural health system in the nation
- 43 hospitals
- 243 clinics
- 27,000 employees
Sanford Medical Center Fargo

- Location: Fargo, ND
- Size: ~600 beds
- Teaching hospital
- Level II Trauma Center
Sanford Medical Home

• Position
  – 1 FTE: five pharmacist rotation, including a shared position with NDSU
  – Located in Sanford Southpointe Clinic, serves Fargo-Moorhead

• Collaborative practice agreement for disease state management: Diabetes

• Transition of care phone calls

• Post-hospital medication reconciliation

• Responds to drug information requests
Abbreviations

• DKA = Diabetic Ketoacidosis
• SGLT2-I = Sodium glucose like transporter 2 inhibitor
• UGE = Urinary Glucose Excretion
• T2DM = Type 2 Diabetes Mellitus
• PPG = Postprandial plasma glucose
• FPG = Fasting plasma glucose

• PK = pharmacokinetics
• PD = pharmacodynamics
Objectives

• Identify the mechanism of action and PK/PD properties of SGLT2-I

• Review important efficacy and safety information from SGLT2-I clinical trials

• Appropriately utilize SGLT2-I to obtain glycemic control targets and improve patient outcomes
Diabetes in the US

• 29.1 million people in the United States have diabetes

• 2012 total estimated economic impact of diabetes = $245 billion

Diabetes in ND

• 45,232 adults in North Dakota have diabetes

• 2012 total estimated cost of diabetes = $560 million

Diabetes in ND and US

Prevalence of Diabetes Among Adults in North Dakota and the United States

Source: Behavioral Risk Factor Surveillance System

What is Diabetes?

DeFronzo RA. *Diabetes* 2009;58:773-795
Objective #1:

Identify the mechanism of action and PK/PD properties of SGLT2-I
FDA Approval

• Canagliflozin  
  – March 2013

• Dapagliflozin  
  – January 2014

• Empagliflozin  
  – August 2014
SGLT2 and SGLT1

• SGLT2
  – Location: luminal membrane of the proximal renal tubules
  – High-capacity
  – Low-affinity

• SGLT1
  – Locations: distal segment of the proximal tubule, intestinal mucosa of small intestine, other tissues to a lesser extent
  – Low-capacity
  – High-affinity

Chao E. Clinical Diabetes 2014;31(1):4-11
SGLT2-I

- Selectivity for SGLT2 over SGLT1
  - Empagliflozin >2,500-fold selectivity
  - Dapagliflozin >1,200-fold selectivity
  - Canagliflozin >250-fold selectivity

Filtered glucose load ~180 g/day

SGLT2
(~90% glucose reabsorbed)

SGLT1
(~10% glucose reabsorbed)

Glucose reabsorption >179 g/day

Urine

Urinary glucose excretion <0.5 g/day
SGLT2-I

• Independent of insulin

• Independent of beta-cell function

• Independent of insulin resistance

• Results → limited loss of potency
Pharmacodynamics

<table>
<thead>
<tr>
<th></th>
<th>Canagliflozin</th>
<th>Dapagliflozin</th>
<th>Empagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased Urinary Glucose Excretion</td>
<td>• 100-300 mg/day → 100 grams/day</td>
<td>• 5-10 mg/day → 70 grams/day</td>
<td>• 10 mg/day → 64 grams/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 25 mg/day → 78 grams/day</td>
</tr>
<tr>
<td>Mean 24-hr Urinary Volume</td>
<td></td>
<td></td>
<td>Increased 341 mL/day on Day 1 and 135 mL/day on Day 5</td>
</tr>
<tr>
<td>QTc</td>
<td>Not associated with clinically significant prolongation</td>
<td>Not associated with clinically significant prolongation</td>
<td>Not associated with clinically significant prolongation</td>
</tr>
</tbody>
</table>

# Pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>Canagliflozin</th>
<th>Dapagliflozin</th>
<th>Empagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absorption (T&lt;sub&gt;max&lt;/sub&gt;)</strong></td>
<td>1-2 hours</td>
<td>2 hours</td>
<td>1.5 hours</td>
</tr>
<tr>
<td><strong>Absorption (bioavailability)</strong></td>
<td>65%</td>
<td>78%</td>
<td>75.5-77.4%</td>
</tr>
<tr>
<td><strong>Protein Binding</strong></td>
<td>99%</td>
<td>91%</td>
<td>86.2%</td>
</tr>
<tr>
<td><strong>Vd</strong></td>
<td>119 L</td>
<td>73.8 L</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>glucuronidation</td>
<td>glucuronidation</td>
<td>glucuronidation</td>
</tr>
<tr>
<td><strong>Half-life (t&lt;sub&gt;1/2&lt;/sub&gt;)</strong></td>
<td>10.6-13.1 h</td>
<td>12.9 h</td>
<td>12.4 h</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>51.7% feces</td>
<td>21% feces</td>
<td>41.2% feces</td>
</tr>
<tr>
<td></td>
<td>33% urine</td>
<td>75% urine</td>
<td>54.4% urine</td>
</tr>
</tbody>
</table>

## Pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>Canagliflozin</th>
<th>Dapagliflozin</th>
<th>Empagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Renal Impairment</strong></td>
<td>PD response declines with decreasing renal function</td>
<td>PD response declines with decreasing renal function</td>
<td>PD response declines with decreasing renal function</td>
</tr>
<tr>
<td><strong>Hepatic Impairment</strong></td>
<td>Increases in AUC and $C_{\text{max}}$</td>
<td>Increases in AUC and $C_{\text{max}}$</td>
<td>Increases in AUC and $C_{\text{max}}$</td>
</tr>
<tr>
<td><strong>Age, Gender, Race, and Body Weight</strong></td>
<td>No clinically meaningful effect on PK</td>
<td>No clinically meaningful effect on PK</td>
<td>No clinically meaningful effect on PK</td>
</tr>
</tbody>
</table>

Question #1

• In the setting of SGLT-2 inhibition, approximately how many kcal/day are excreted as glucose in urine?
  a) 100 kcal
  b) 250 kcal
  c) 500 kcal
  d) 1000 kcal

• Explanation: \(~50-80 \text{ g/day} \times \frac{4 \text{ kcal}}{1 \text{ g}} = 200-320 \text{ kcal/day}\)
Objective #2:
Review important efficacy and safety information from SGLT2 inhibitor clinical trials
### Healthy eating, weight control, increased physical activity, and diabetes education

#### Metformin
- **Efficacy**: high
- **Low risk**
- **Neutral/loss**
- **GI/lactic acidosis**
- **Low**

#### If A1C target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

<table>
<thead>
<tr>
<th>Metformin +</th>
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<th>Metformin +</th>
<th>Metformin +</th>
<th>Metformin +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea</td>
<td>Thiazolidinedione</td>
<td>DPP-4 inhibitor</td>
<td>SGLT2 inhibitor</td>
<td>GLP-1 receptor agonist</td>
<td>Insulin (basal)</td>
</tr>
<tr>
<td>high</td>
<td>high</td>
<td>intermediate</td>
<td>intermediate</td>
<td>high</td>
<td>highest</td>
</tr>
<tr>
<td>moderate risk</td>
<td>low risk</td>
<td>low risk</td>
<td>low risk</td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td>gain</td>
<td>gain</td>
<td>gain</td>
<td>loss</td>
<td>high</td>
<td>hypoglycemia</td>
</tr>
<tr>
<td>low</td>
<td>low</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>variable</td>
</tr>
</tbody>
</table>

#### If A1C target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

<table>
<thead>
<tr>
<th>Metformin +</th>
<th>Metformin +</th>
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<th>Metformin +</th>
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<th>Metformin +</th>
</tr>
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<tr>
<td>Sulfonylurea +</td>
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<td>SGLT2 inhibitor</td>
<td>GLP-1 receptor agonist</td>
<td>Insulin (basal)</td>
</tr>
<tr>
<td>TZD</td>
<td>SU</td>
<td>SU</td>
<td>SU</td>
<td>SU</td>
<td>TZD</td>
</tr>
<tr>
<td>or DPP-4-i</td>
<td>or DPP-4-i</td>
<td>or DPP-4-i</td>
<td>or DPP-4-i</td>
<td>or Insulin</td>
<td>or Insulin</td>
</tr>
<tr>
<td>or SGLT2-i</td>
<td>or SGLT2-i</td>
<td>or SGLT2-i</td>
<td>or SGLT2-i</td>
<td>or Insulin</td>
<td>or GLP-1-RA</td>
</tr>
<tr>
<td>or GLP-1-RA</td>
<td>or GLP-1-RA</td>
<td>or Insulin</td>
<td>or Insulin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### If A1C target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i.

<table>
<thead>
<tr>
<th>Metformin +</th>
<th>Basal insulin +</th>
<th>Mealtime insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1-RA</td>
<td>or</td>
<td></td>
</tr>
</tbody>
</table>

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Monotherapy

- SGLT2-I vs Placebo
- Not comparative trials

<table>
<thead>
<tr>
<th></th>
<th>Baseline A1C</th>
<th>Change from Baseline</th>
<th>Difference from Placebo</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>8.01%</td>
<td>-1.03%</td>
<td>-1.16%</td>
<td>26 weeks</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>8%</td>
<td>-0.9%</td>
<td>-0.7%</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Emagliflozin</td>
<td>7.9%</td>
<td>-0.8%</td>
<td>-0.9%</td>
<td>24 weeks</td>
</tr>
</tbody>
</table>

Metformin + SGLT2-I

- Background therapy: Metformin dose ≥1500 mg
- SGLT2-I vs Placebo
- Not comparative trials

<table>
<thead>
<tr>
<th></th>
<th>Baseline A1C</th>
<th>Change from Baseline</th>
<th>Difference from Placebo</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>~7.9%</td>
<td>-0.94%</td>
<td>-0.77%</td>
<td>26 weeks</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>~8%</td>
<td>-0.8%</td>
<td>-0.5%</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Emagliflozin</td>
<td>~7.9%</td>
<td>-0.77%</td>
<td>-0.64%</td>
<td>24 weeks</td>
</tr>
</tbody>
</table>

**Metformin + Sulfonylurea + SGLT2-I**

- Background therapy: Metformin ≥ 1500 mg + Sulfonylurea at least half the maximum dose
- SGLT2-I vs Placebo
- Not comparative trials

<table>
<thead>
<tr>
<th></th>
<th>Baseline A1C</th>
<th>Change from Baseline</th>
<th>Difference from Placebo</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>~8.1%</td>
<td>-1.06%</td>
<td>-0.92%</td>
<td>26 weeks</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>~8.1%</td>
<td>-0.86%</td>
<td>-0.69%</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Emagliflozin</td>
<td>~8.1%</td>
<td>-0.8%</td>
<td>-0.6%</td>
<td>24 weeks</td>
</tr>
</tbody>
</table>

Insulin + SGLT2-I

- Background therapy: Insulin + other oral medications
- SGLT2-I vs Placebo
- Not comparative trials

<table>
<thead>
<tr>
<th></th>
<th>Baseline A1C</th>
<th>Change from Baseline</th>
<th>Difference from Placebo</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>~8.3%</td>
<td>-0.72</td>
<td>-0.73%</td>
<td>18 weeks</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>~8.5%</td>
<td>-0.9%</td>
<td>-0.6%</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Emagliflozin</td>
<td>~8.3%</td>
<td>-1%</td>
<td>-0.5%</td>
<td>18 weeks</td>
</tr>
</tbody>
</table>

## FPG and PPG

<table>
<thead>
<tr>
<th></th>
<th>Baseline FPG</th>
<th>Change from Baseline</th>
<th>Difference from Placebo</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>173</td>
<td>-35</td>
<td>-43</td>
<td>26 weeks</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>166.6</td>
<td>-28.8</td>
<td>-24.7</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Emagliflozin</td>
<td>153</td>
<td>-25</td>
<td>-36</td>
<td>24 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Baseline PPG</th>
<th>Change from Baseline</th>
<th>Difference from Placebo</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>254</td>
<td>-59</td>
<td>-64</td>
<td>26 weeks</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Emagliflozin</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>24 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Baseline weight (kg)</th>
<th>Change from Baseline</th>
<th>Difference from Placebo</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>86.9</td>
<td>-3.9</td>
<td>-3.3</td>
<td>26 weeks</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>94.2</td>
<td>-3.2</td>
<td>-3.2</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Emagliflozin</td>
<td>78</td>
<td>-3.2</td>
<td>-2.8</td>
<td>24 weeks</td>
</tr>
</tbody>
</table>

Blood Pressure

- Meta-analysis, 45 studies, N=11,232
  - SGLT2-I associated with significant reduction in SBP -4.45 mmHg compared to active competitors or placebo

- Mechanism → likely due to osmotic diuresis

- Potential for dehydration, hypotension, hypovolemia, and syncope

## Urinary Tract Infections

- Pooled data → 12 randomized, placebo-controlled trials
- Discontinuation due to UTI rare
- Mild to moderate intensity and respond to standard treatment

<table>
<thead>
<tr>
<th></th>
<th>Dapagliflozin 2.5 mg N=814</th>
<th>Dapagliflozin 5 mg N=1145</th>
<th>Dapagliflozin 10 mg N=1193</th>
<th>Placebo N=1393</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosed Infections</td>
<td>3.6%</td>
<td>5.7%</td>
<td>4.3%</td>
<td>3.7%</td>
</tr>
</tbody>
</table>

Urinary Tract Infections

• FDA warning [12-4-15]
  – 19 cases of urosepsis reported w/SGLT2-I
  – All cases resulted in hospitalization
  – No deaths reported
Genital Mycotic Infections

- Pooled data → 12 randomized, placebo-controlled trials
- Female → vulvovaginitis
- Male → balanitis
- Mild to moderate intensity and responds to standard treatment

<table>
<thead>
<tr>
<th></th>
<th>Dapagliflozin 2.5 mg N=814</th>
<th>Dapagliflozin 5 mg N=1145</th>
<th>Dapagliflozin 10 mg N=1193</th>
<th>Placebo N=1393</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosed Infections</td>
<td>4.1%</td>
<td>5.7%</td>
<td>4.8%</td>
<td>0.9%</td>
</tr>
</tbody>
</table>

Lipid Profile

- **LDL-C**
  - Dose related increases 4.5-8%

- **HDL-C**
  - Dose related increases 1.5-3.6%

- **Triglycerides**
  - Small decreases not clinically significant

- **Clinical relevance unknown**

Euglycemic DKA

• FDA warning [12-4-15]
  – 73 cases of ketoacidosis associated w/SGLT2-I
  – All cases considered serious and some required hospitalization
  – Uncharacteristically mild to moderate glucose elevations

• Suggested pathophysiology
  – Lower insulin-to-glucagon ratio stimulated lipolysis
  – Enhanced lipid oxidation in the setting of lower carbohydrate oxidation

Euglycemic DKA

- Reported incidence of DKA in clinical trials
  - < 0.1%

- Triggering factors
  - Illness, reduced food/fluid intake, reduced insulin doses, and alcohol intake

- Symptoms of ketoacidosis
  - Nausea, vomiting, abdominal pain, tiredness, and trouble breathing
“Half the diabetics were given the new drug and responded well. The other half got a placebo and went into shock.”
Approach to the management of hyperglycemia

**PATIENT / DISEASE FEATURES**

- **Risks potentially associated with hypoglycemia and other drug adverse effects**
  - more stringent
  - low
  - less stringent
  - high

- **Disease duration**
  - newly diagnosed
  - long-standing

- **Life expectancy**
  - long
  - short

- **Important comorbidities**
  - absent
  - few / mild
  - severe

- **Established vascular complications**
  - absent
  - few / mild
  - severe

- **Patient attitude and expected treatment efforts**
  - highly motivated, adherent, excellent self-care capacities
  - less motivated, nonadherent, poor self-care capacities

- **Resources and support system**
  - readily available
  - limited

CV Outcomes

- Diabetes is a major risk factor for CV disease
- T2DM + CV disease = ↑ risk of death
- Evidence that glucose lowering reduces CV events and death has not been convincingly shown
- Modest CV benefit may be observed after a prolonged follow-up period
- Intensive glucose lowering or the use of specific glucose-lowering agents maybe associated with adverse CV outcomes

CV Outcomes

• EMPA-REG OUTCOME
  – T2DM with established CV disease, 2.6 years
  – Empagliflozin vs placebo against background standard of care
  – Baseline A1C 7-9%
  – Primary outcome = composite of death from CV causes, non-fatal MI, or non-fatal stroke
  – Secondary outcomes
## CV Outcomes

### Highlights

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Empagliflozin (N=4687)</th>
<th>Placebo (N=2333)</th>
<th>Hazard Ratio (95% CI)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome</strong></td>
<td>10.5%</td>
<td>12.1%</td>
<td>0.86 (0.74-0.99)</td>
<td>63</td>
</tr>
<tr>
<td><strong>Death from any cause</strong></td>
<td>5.7%</td>
<td>8.3%</td>
<td>0.68 (0.57-0.82)</td>
<td>39</td>
</tr>
<tr>
<td><strong>Death from CV causes</strong></td>
<td>3.7%</td>
<td>5.9%</td>
<td>0.62 (0.49-0.77)</td>
<td>46</td>
</tr>
<tr>
<td><strong>Hospitalization for HF</strong></td>
<td>2.7%</td>
<td>4.1%</td>
<td>0.65 (0.5-0.85)</td>
<td>72</td>
</tr>
</tbody>
</table>

## CV Outcomes

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Pooled Empagliflozin (N=4687)</th>
<th>Placebo (N=2333)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>90.2%</td>
<td>91.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe AE</td>
<td>23.5%</td>
<td>25.4%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Serious AE</td>
<td>38.2%</td>
<td>42.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>D/C</td>
<td>17.3%</td>
<td>19.4%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>27.8%</td>
<td>27.9%</td>
<td></td>
</tr>
<tr>
<td>UTI</td>
<td>18%</td>
<td>18.1%</td>
<td></td>
</tr>
<tr>
<td>Genital Infection</td>
<td>6.4%</td>
<td>1.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Volume Depletion</td>
<td>5.1%</td>
<td>4.9%</td>
<td></td>
</tr>
<tr>
<td>ARF</td>
<td>5.2%</td>
<td>6.6%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>AKI</td>
<td>1%</td>
<td>1.6%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>DKA</td>
<td>0.1%</td>
<td>&lt;0.1%</td>
<td></td>
</tr>
<tr>
<td>Thrombosis</td>
<td>0.6%</td>
<td>0.9%</td>
<td></td>
</tr>
<tr>
<td>Bone Fracture</td>
<td>3.8%</td>
<td>3.9%</td>
<td></td>
</tr>
</tbody>
</table>
Class Effect?

- Caution → different selectivity for SGLT2 vs SGLT1

- CANVAS – CANagliflozin cardioVascular Assessment Study ~ March 2017

- DECLARE-TIMI58 – Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI58) ~ April 2019
Summary

• A1C: ↓ ~0.6-1%

• FPG: ↓ ~30 mg/dL
  – PPG lowering w/Canagliflozin

• Weight: ↓ ~3 kg

• BP: ↓ SBP ~4 mmHg and ↓ DBP ~2 mmHg

• T2DM + CV disease → CV outcomes data
Summary

• Urinary tract infections: $\uparrow \sim 1\%$

• Genital mycotic infections: $\uparrow \sim 4\%$

• Impaired renal function: generally avoid use

• LDL-C: $\uparrow \sim 5\%$, clinical significance unknown

• Euglycemic DKA: rare but serious ADE
Objective #3:

 Appropriately utilize SGLT2 inhibitors to obtain glycemic control targets and improve patient outcomes
Healthy eating, weight control, increased physical activity, and diabetes education

### Metformin

- **Efficacy**: high
- **Hypo risk**: low risk
- **Weight**: neutral / loss
- **GI / lactic acidosis**: low

*If A1C target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):*

- **Metformin + Sulfonylurea**
  - **Efficacy**: high
  - **Hypo risk**: moderate risk
  - **Weight**: gain
  - **Side effects**: hypoglycemia
  - **Costs**: low

- **Metformin + Thiazolidinedione**
  - **Efficacy**: high
  - **Hypo risk**: low risk
  - **Weight**: gain
  - **Side effects**: edema, HF, fxS
  - **Costs**: low

- **Metformin + DPP-4 inhibitor**
  - **Efficacy**: intermediate
  - **Hypo risk**: low risk
  - **Weight**: low risk
  - **Side effects**: rare
  - **Costs**: high

- **Metformin + SGLT2 inhibitor**
  - **Efficacy**: intermediate
  - **Hypo risk**: low risk
  - **Weight**: low risk
  - **Side effects**: rare
  - **Costs**: high

- **Metformin + GLP-1 receptor agonist**
  - **Efficacy**: high
  - **Hypo risk**: highest
  - **Weight**: high risk
  - **Side effects**: hypoglycemia
  - **Costs**: variable

*If A1C target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):*

- **Metformin + Sulfonylurea + TZD**
  - **Efficacy**: high
  - **Hypo risk**: moderate risk
  - **Weight**: gain
  - **Side effects**: hypoglycemia
  - **Costs**: low

- **Metformin + Thiazolidinedione + SU**
  - **Efficacy**: high
  - **Hypo risk**: low risk
  - **Weight**: gain
  - **Side effects**: edema, HF, fxS
  - **Costs**: low

- **Metformin + DPP-4 inhibitor + TZD**
  - **Efficacy**: intermediate
  - **Hypo risk**: low risk
  - **Weight**: low risk
  - **Side effects**: rare
  - **Costs**: high

- **Metformin + SGLT2 inhibitor + Insulin**
  - **Efficacy**: intermediate
  - **Hypo risk**: low risk
  - **Weight**: low risk
  - **Side effects**: rare
  - **Costs**: high

*If A1C target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:

- **Basal insulin + GLP-1-RA**
- **Basal insulin + Mealtime insulin or GLP-1-RA**

---

# Profiles of Antidiabetic Medications

<table>
<thead>
<tr>
<th></th>
<th>MET</th>
<th>GLP-1 RA</th>
<th>SGLT-2i</th>
<th>DPP-4i</th>
<th>AGi</th>
<th>TZD (moderate dose)</th>
<th>SU</th>
<th>GLN</th>
<th>COLSVL</th>
<th>BCR-QR</th>
<th>INSULIN</th>
<th>PRAML</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HYPO</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate/Severe</td>
<td>Mild</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate to Severe</td>
<td>Neutral</td>
</tr>
<tr>
<td><strong>WEIGHT</strong></td>
<td>Slight Loss</td>
<td>Loss</td>
<td>Loss</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Gain</td>
<td>Gain</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Gain</td>
<td>Loss</td>
<td></td>
</tr>
<tr>
<td><strong>RENAL/GU</strong></td>
<td>Contraindicated CKD Stage 3B,4,5</td>
<td>Exenatide Not Indicated CrCl &lt; 30</td>
<td>Not Effective with eGFR &lt; 45</td>
<td>Genital Mycotic Infections</td>
<td>Dose Adjustment Necessary (Except Linagliptin)</td>
<td>Neutral</td>
<td>Neutral</td>
<td>More Hypo Risk</td>
<td>Neutral</td>
<td>More Hypo Risk</td>
<td>Neutral</td>
<td></td>
</tr>
<tr>
<td><strong>GI Sx</strong></td>
<td>Moderate</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Mild</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>CHF</strong></td>
<td>Neutral</td>
<td>Neutral</td>
<td>Possible Benefit</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td><strong>CARDIAC</strong></td>
<td>Neutral</td>
<td>Neutral</td>
<td>Benefit</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td><strong>ASCVD</strong></td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate Fracture Risk</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
</tbody>
</table>

- Few adverse events or possible benefits
- Use with caution
- Likelihood of adverse effects
- ? Uncertain effect

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Patient Case #1

• 55 year old male presents to internal medicine clinic for diabetes follow-up.
  – PMH: T2DM, HTN, CAD, and dyslipidemia
  – Meds: ASA 81 mg/day, Metformin 2gm/day, Lisinopril 10 mg/day, HCTZ 12.5 mg/day, and Atorvastatin 10 mg/day
  – CrCl=90 mL/min and A1C=11.2%
Patient Case #1

• For the management of T2DM, what is the most appropriate intervention?
  a) Add sulfonylurea
  b) Add SGLT2-I
  c) Add sulfonylurea + SGLT2-I
  d) Add Insulin
Patient Case #2

• 55 year old male presents to internal medicine clinic for diabetes follow-up.
  – PMH: T2DM, HTN, CAD, and dyslipidemia
  – Meds: ASA 81 mg/day, Metformin 2gm/day, Lisinopril 10 mg/day, HCTZ 12.5 mg/day, and Atorvastatin 10 mg/day
  – CrCl=90 mL/min and A1C=7.9%
Patient Case #2

• For the management of T2DM, what is the most appropriate intervention
  a) Add sulfonylurea
  b) Add SGLT2-I
  c) Add sulfonylurea + SGLT2-I
  d) Add Insulin
Patient Case #3

- 92 year old male presents to internal medicine clinic for diabetes follow-up.
  - PMH: T2DM, HTN, CAD, BPH, and dyslipidemia
  - Meds: ASA 81 mg/day, Metformin 2gm/day, Lisinopril 10 mg/day, Finasteride 5 mg/day, HCTZ 12.5 mg/day, and Atorvastatin 10 mg/day
  - CrCl=35 mL/min and A1C=7.9%
Patient Case #3

• For the management of T2DM, what is the most appropriate intervention
  a) Add sulfonylurea
  b) Add SGLT2-I
  c) Add sulfonylurea + SGLT2-I
  d) Add Insulin
  e) Probably no intervention or add DPP4-I
References

• DeFronzo RA. From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus. *Diabetes* 2009;58:733-795
References


Sodium glucose co-transporter type 2 (SGLT2) inhibitors – Moving Beyond Targets

Nicholas (Cole) Helbling PharmD
BCPS