The Role of SGLT-2 Inhibitors in the Management of Patients with Type 2 Diabetes

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Unmet Needs With Conventional Antihyperglycemic Therapies

- Many therapies are associated with weight gain
- Insulin and non incretin oral insulin secretagogue therapies are associated with significant risk for hypoglycemia
- Other AEs with some therapies include GI side effects and edema
- Many therapies fail to adequately control postprandial hyperglycemia
- Therapies often fail to maintain long-term glycemic control

New Classes Presently in Development

- Long-acting GLP-1 receptor agonists
- Ranolazine
- **Dual & Pan PPAR agonists**
- **11 Hydroxysteroid Dehydrogenase (HSD)- 1 inhibitors**
- Fructose 1,6-bisphosphatase inhibitors
- Glucokinase activators
- **G protein-coupled Receptor (GPR)- 40 & -119 agonists**
- Protein Tyrosine Phosphatase (PTB)- 1b inhibitors
- Camitine- Palmitoyltransferase (CPT)- 1 inhibitors
- Acetyl COA Carboxylase (ACC)- 1 & -2 inhibitors
- Glucagon receptor antagonists
- Salicylate derivatives
- Immunomodulatory drugs
- **Sodium- Glucose Cotransporter (SGLT) {-1} & -2 inhibitors**
The Kidneys Play an Important Role in Glucose Control

Normal Renal Glucose Physiology

- 180 g of glucose is filtered each day
- Virtually all glucose reabsorbed in the proximal tubules & reenters the circulation
- SGLT2 reabsorbs about 90% of the glucose
- SGLT1 reabsorbs about 10% of the glucose
- Virtually no glucose excreted in urine

### Sodium-Glucose Cotransporters

<table>
<thead>
<tr>
<th></th>
<th>SGLT1</th>
<th>SGLT2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Site</strong></td>
<td>Mostly intestine with some kidney</td>
<td>Almost exclusively kidney</td>
</tr>
<tr>
<td><strong>Sugar Specificity</strong></td>
<td>Glucose or galactose</td>
<td>Glucose</td>
</tr>
<tr>
<td><strong>Affinity for glucose</strong></td>
<td>High Km= 0.4 Mm</td>
<td>Low Km = 2 Mm</td>
</tr>
<tr>
<td><strong>Capacity for glucose transport</strong></td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td><strong>Role</strong></td>
<td>Dietary glucose absorption Renal glucose reabsorption</td>
<td>Renal glucose reabsorption</td>
</tr>
</tbody>
</table>

Targeting the Kidney

Renal Glucose Transport

Altered Renal Glucose Control in Diabetes

- Gluconeogenesis is increased in postprandial and postabsorptive states in patients with Type 2 DM
  - Renal contribution to hyperglycemia
  - 3-fold increase relative to patients without diabetes

- Glucose reabsorption
  - Increased SGLT-2 expression and activity in renal epithelial cells from patients with diabetes vs. normoglycemic individuals

Rationale for SGLT2 Inhibitors

- SGLT2 is a low-affinity, high capacity glucose transporter located in the proximal tubule and is responsible for 90% of glucose reabsorption.
- Mutation in SGLT2 transporter linked to hereditary renal glycosuria, a relatively benign condition in humans.
- Selective SGLT2 inhibitors have a novel & unique mechanism of action reducing blood glucose levels by increasing renal excretion of glucose.
- Decreased glycemia will decrease glucose toxicity leading to further improvements in glucose control.
- Selective SGLT2 inhibition, would also cause urine loss of the calories from glucose, potentially leading to weight loss.

SGLT2 Inhibitors in Phase 3 Development

- Empagliflozin
- Canagliflozin
- Dapagliflozin
- Ipragliflozin
Empagliflozin: Change in A1C

Randomized, double-blind, 12 week trial comparing empagliflozin and open-label metformin

*P<.001 vs. placebo
†500 mg BID for four weeks, then 1000 mg BID or the maximum tolerate dose

Empagliflozin: Change in Plasma Glucose in the Fasting State

Randomized, double-blind, 12 week trial comparing empagliflozin and open-label metformin

*P<.001 vs. placebo †500 mg BID for four weeks, then 1000 mg BID or the maximum tolerate dose

Empagliflozin Safety Summary

• In Phase 2b study
  - Reported adverse events were comparable among treatment groups
  - Most frequently reported AEs
    • Frequent urination, thirst, and nasopharyngitis
  - Urinary tract infection frequency was low (1.2%) and comparable to placebo (1.2%) and metformin (1.2%)
  - Incidence of genital infection was low: mycosis (0.8%) and pruritis (1.2%) with Empagliflozin versus none with metformin or placebo
  - Rates of hypoglycemia were similar between groups

Canagliflozin

Mean Baseline A1C (%) 7.71 8.01 7.81 7.57 7.70 7.71 7.62

*P<.001 vs. placebo calculated using LS means


*P<.001 vs. placebo calculated using LS means
Canagliflozin Trials

• Symptomatic genital infections in 3-8% canagliflozin arms
  – 2% placebo
  – 2% SITA

• Urinary tract infections in 3-9% canagliflozin arms
  – 6% placebo
  – 2% SITA

• Hypoglycemia in 0-6% canagliflozin arms
  – 2% placebo
  – 5% SITA

Changes from Baseline in A1C in Phase 3 Dapagliflozin Studies

Changes from Baseline in Fasting Plasma Glucose in Phase 3 Dapagliflozin Studies

Changes from Baseline in Body Weight in Phase 3 Dapagliflozin Studies

Monotherapy Study: Summary and Conclusion

- In treatment-naïve patient with newly-diagnosed Type 2 DM, dapagliflozin monotherapy resulted in
  - Clinically meaningful decreased in A1C and fasting plasma glucose with a near absence of hypoglycemia
  - Favorable effects on weight and blood pressure

- In the exploratory evening dose cohort, changes from baseline in A1C, fasting plasma glucose, and body weight at week 24 were similar to those seen in the main patient cohort

- In the high A1C (QAM) exploratory cohort, dapagliflozin elicited a considerable improvement in glycemia

Perspectives on SGLT2 Inhibition

• Potential advantages
  – Insulin Independence
  – Weight loss (75g urine glucose = 300kcal/day)
  – Low risk of hypoglycemia
  – Blood pressure lowering?

• Concerns
  – Polyuria
  – Electrolyte disturbances
  – Bacterial urinary tract infections
  – Fungal genital infections
  – Malignancies
  – Hypovolemia
<table>
<thead>
<tr>
<th>Benefits</th>
<th>Metformin</th>
<th>DPP-4 Inhibitor</th>
<th>GLP-1 Agonist</th>
<th>Sulfonylurea</th>
<th>Glinide</th>
<th>TZD</th>
<th>Colesevelam</th>
<th>AGI</th>
<th>Insulin</th>
<th>Pramlintide</th>
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<tbody>
<tr>
<td><strong>PPG - lowering</strong></td>
<td>Mild</td>
<td>Moderate</td>
<td>Moderate to Marked</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Mild</td>
<td>Mild</td>
<td>Moderate to Marked</td>
<td>Moderate to Marked</td>
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<tr>
<td><strong>FPG - lowering</strong></td>
<td>Moderate</td>
<td>Mild</td>
<td>Mild</td>
<td>Moderate</td>
<td>Mild</td>
<td>Moderate</td>
<td>Mild</td>
<td>Neutral</td>
<td>Moderate to Marked</td>
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<tr>
<td><strong>Nonalcoholic fatty liver disease (NAFLD)</strong></td>
<td>Mild</td>
<td>Neutral</td>
<td>Mild</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
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<td><strong>Risks</strong></td>
<td></td>
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<tr>
<td><strong>Hypoglycemia</strong></td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Mild</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
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<tr>
<td><strong>GI Symptoms</strong></td>
<td>Moderate</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate</td>
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<tr>
<td><strong>Risk of use with renal insufficiency</strong></td>
<td>Severe</td>
<td>Reduce Dosage</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Mild</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td><strong>Contraindicated if liver failure or predisposition to lactic acidosis</strong></td>
<td>Severe</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
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<tr>
<td><strong>Heart failure/Edema</strong></td>
<td>Contra-indicated in CHF</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Mild/Moderate</td>
<td>Neutral</td>
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<tr>
<td><strong>Weight Gain</strong></td>
<td>Benefit</td>
<td>Neutral</td>
<td>Benefit</td>
<td>Mild</td>
<td>Mild</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Mild to Moderate</td>
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<tr>
<td><strong>Fractures</strong></td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
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<td>Moderate</td>
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<td>Neutral</td>
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<tr>
<td><strong>Drug-Drug Interactions</strong></td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Neutral</td>
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