Type 1 Diabetes Mellitus – In the Quest for an Oral Agent, Do Sodium-Glucose Cotransporter Inhibitors Summon the FURY or Leave Us TOOTHLESS?

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Learning Objectives:
1. Provide a basic overview of type 1 diabetes mellitus.
2. Discuss the significance of diabetic ketoacidosis.
3. Evaluate the literature pertaining to the utilization of sodium-glucose cotransporter inhibitors in the treatment of type 1 diabetes mellitus.
4. Recommend optimal pharmacotherapeutic regimen in an adult patient with type 1 diabetes mellitus given patient specific factors.
Type 1 Diabetes Mellitus (T1DM)

1. **Definition:** absolute insulin deficiency most commonly due to autoimmune β-cell destruction¹,²

2. **Epidemiology**
   A. 2017³
      i. 1.1 million individuals younger than 20 years (yrs) of age with T1DM globally
      ii. 216,300 North America and Caribbean; 169,900 United States (U.S.)
   B. 2015⁴,⁵
      i. 29 million adults worldwide with T1DM
      ii. Global incidence of T1DM increasing by approximately 3% annually
      iii. Roughly 1.5 million estimated to have T1DM in U.S.
   C. **Risk**
      i. Overall lifetime risk 1/250 people⁶
      ii. Increases with the number of relevant autoantibodies detected
      iii. Rate of progression to T1DM after autoantibody seroconversion⁷
         1. ≥ 2 autoantibodies (585 children): 5-year (yr) follow up: 43.5%, 10-yr follow up: 69.7%, and 15-yr follow up: 84.2%
         2. 1 autoantibody (474 children): 10-yr follow up: 14.5%
      iv. Geographic variability in annual incidence⁶,⁸
         1. 0.73/100,000 in China, 23/100,000 in U.S., and 60/100,000 in Finland
         2. Evidence that migrants from low incidence country soon develop higher rate of incidence of new country of residence
      v. Age and gender: incidence peaks at ages of 2, 4-6, and 10-14 yrs, with a slightly higher prevalence in males⁸,⁹
   D. Fewer than 33% of adults with T1DM achieve hemoglobin A1c (HbA1c) < 7.0% and most are overweight or obese⁴⁰-⁴²

3. **Etiology**
   A. Immune-mediated¹,⁸,¹³
      i. Previously referred to as insulin-dependent diabetes or juvenile-onset diabetes
      ii. 5-10% of diabetic population
      iii. Recent evidence suggests adult onset occurs in up to 50% of cases¹⁴
      iv. Non-obesity-related
      v. Genetically susceptible and exposed to poorly defined environmental trigger
         1. Presence of ≥ 1 autoimmune markers
            a. Islet-cell antibodies (ICA) – most common
            b. Antibodies present in 90% of individuals at time of diagnosis⁶
         2. Human leukocyte antigen (HLA)-DQA and DQB genes predispose or protect depending on HLA-DR/DQ allele
         3. 60 non-HLA loci also associated with risk of developing T1DM
      vi. Increased risk of developing additional autoimmune disorders²,¹⁵
   B. **Idiopathic:** no evidence of β-cell autoimmunity¹³

4. **Pathophysiology**
   A. **General overview**
      i. Preclinical period²
         1. Positive autoimmune markers
         2. β-cell destruction mediated by macrophages and T lymphocytes
         3. Remit or progress to β-cell failure
ii. T1DM: hyperglycemia resulting from 80-90% of β-cell population eradication
iii. Potential for honeymoon period2,8
   1. Transient fall in insulin requirement shortly after clinical onset of T1DM as β-cell function improves
   2. Significant and longer remission associated with older age of T1DM onset, less severe initial presentation, and absent to low levels of ICA or tyrosine phosphatase-like protein insulinoma antigen-2
iv. Total β-cell failure

B. Immunopathogenesis6
   i. Presentation of β-cell peptides by antigen-presenting cells \(\rightarrow\) migrate to pancreatic lymph nodes and interact with CD4+ T lymphocytes
   ii. CD4+ T lymphocytes activate CD8+ T cells \(\rightarrow\) lyse β-cells expressing antigen via major histocompatibility complex class 1 surface molecule
   iii. Innate immune cells \(\rightarrow\) release proinflammatory cytokines and reactive oxygen species causing further β-cell destruction
   iv. Defects in regulatory T lymphocytes \(\rightarrow\) fail to suppress autoimmunity
   v. Activated T cells in pancreatic lymph node \(\rightarrow\) stimulate B lymphocytes to produce autoantibodies

C. Rate of progression dependent on antibody: age of detection, number, titer, and specificity1

5. Symptoms3

<table>
<thead>
<tr>
<th>Abnormal thirst and dry mouth</th>
<th>Sudden weight loss</th>
<th>Frequent urination</th>
<th>Lack of energy and fatigue</th>
<th>Constant hunger</th>
<th>Blurred vision</th>
</tr>
</thead>
</table>

Figure 1 – Symptoms in T1DM

6. Complications

A. Acute: hypoglycemia, diabetic ketoacidosis (DKA), and infection
B. Chronic
   i. Macrovascular: cardiovascular (CV) (leading cause of death in T1DM of long duration), cerebrovascular, and peripheral vascular disease
   ii. Microvascular: retinopathy (leading cause of blindness), neuropathy, and nephropathy (leading cause of end-stage renal disease (ESRD))8

C. Landmark trial and long-term follow-up study

<table>
<thead>
<tr>
<th>Trial</th>
<th>Results</th>
</tr>
</thead>
</table>
| Diabetes Control and Complications Trial – 199316                  | • Strict glycemic control in T1DM delays onset and slows progression of microvascular complications
|                                                                     | • Severe hypoglycemia (SH) approximately 3x higher in intensive-therapy group (62/100 patient(pt)-yrs vs. 19/100 pt-yrs; P<0.001)
|                                                                     | • DKA event rates 2.0/100 pt-yrs intensive-therapy group vs. 1.8/100 pt-yrs conventional therapy group |
| Epidemiology of Diabetes Interventions and Complications study – 200517 | • Period of strict glycemic control reduced risk of first CV event by 42% (P = 0.02) and risk of nonfatal myocardial infarction (MI), stroke, or death from cardiovascular disease (CVD) by 57% |

7. Screening and diagnosis

A. Screening with autoantibody panel only recommended in setting of research trial or first-degree family members of proband with T1DM due to lack of approved therapeutic interventions in general1
B. Three distinct stages

Table 2: American Diabetes Association (ADA) Staging Based on Degree of Dysglycemia and Symptoms

<table>
<thead>
<tr>
<th>Stage</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td>Autoimmunity</td>
<td>Autoimmunity</td>
<td>New-onset hyperglycemia</td>
</tr>
<tr>
<td></td>
<td>Normoglycemia</td>
<td>Dysglycemia</td>
<td>Symptomatic</td>
</tr>
<tr>
<td></td>
<td>Presymptomatic</td>
<td>Presymptomatic</td>
<td></td>
</tr>
<tr>
<td>Diagnostic criteria</td>
<td>Multiple autoantibodies</td>
<td>Multiple autoantibodies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dysglycemia: IFG and/or IGT</td>
<td>Fasting plasma glucose (FPG) 100-125 mg/dL</td>
<td>Clinical symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-hour (hr) plasma glucose (PG) 140-199 mg/dL</td>
<td>Diabetes by standard criteria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HbA1c 5.7-6.4% or ≥ 10% increase in A1c</td>
<td></td>
</tr>
</tbody>
</table>

C. C-peptide, measure of insulin secretion, negligible and useful if type of diabetes in question

D. Diagnostic criteria

Table 3: Diagnosis Criteria in Nonpregnant Patients (pts)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting blood glucose (FBG) ≥ 126 mg/dL OR</td>
<td>Without explicit hyperglycemia, confirm with repeat testing</td>
<td></td>
</tr>
<tr>
<td>2-hr PG ≥ 200 mg/dL during oral glucose tolerance test OR</td>
<td>*Dysglycemia potentially rapid in T1DM, and thus, HbA1c less sensitive</td>
<td></td>
</tr>
<tr>
<td>HbA1c ≥ 6.5%* OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classic symptoms of hyperglycemia/hyperglycemic crisis with random PG ≥ 200 mg/dL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

8. Management

A. Monitoring
   i. Glycemic goals
      1. HbA1c

Table 4: ADA HbA1c Goals

<table>
<thead>
<tr>
<th>Groups</th>
<th>General Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonpregnant adults</td>
<td>&lt; 7.0%</td>
</tr>
<tr>
<td>Pregnant adults</td>
<td>6.0-6.5%</td>
</tr>
<tr>
<td>Children/adolescents</td>
<td>&lt; 7.5%</td>
</tr>
</tbody>
</table>

2. ADA capillary point-of-care testing, continuous glucose monitoring (CGM), and laboratory measurement
   a. Nonpregnant adults
      i. Preprandial PG: 80-130 mg/dL
      ii. Peak postprandial PG: < 180 mg/dL
   b. Pregnant adults
      i. Fasting: < 95 mg/dL
      ii. 1-hr postprandial: < 140 mg/dL
      iii. 2-hr postprandial: < 120 mg/dL
   c. Children/adolescents
      i. Preprandial PG: 90-130 mg/dL
      ii. Bedtime/overnight: 90-150 mg/dL
      iii. Management of CV risk factors: blood pressure and lipid control
      iii. Microvascular complications

B. Lifestyle management
   i. Diabetes self-management education and support
ii. Medical nutrition therapy
iii. Physical activity
iv. Smoking cessation counseling
v. Psychosocial care

C. Pharmacotherapy\textsuperscript{22,23}

i. No Food and Drug Administration (FDA)-approved oral agents
   1. Metformin
      a. May reduce insulin requirement and improve metabolic control
      b. Does not improve glycemic control\textsuperscript{24}
      c. CV benefit remains under investigation
   2. Dipeptidyl peptidase 4 inhibitors: area of current study along with glucagon-like peptide 1 receptor agonists due to potential \(\beta\)-cell preservation and reduction in glucagon secretion
   iii. Amylin analog: pramlintide
      1. Mechanism of action (MoA): helps control postprandial glucose excursions by slowing gastric emptying, enhancing satiety, and reducing glucagon secretion
      2. Dosing: 15 mcg subcutaneously immediately prior to main meals titrated in 15-mcg increments, as tolerated, to a max dose of 60 mcg with each meal
         a. Titrate no more frequently than every 3 days
         b. Reduce preprandial insulin dose (including combination preparations) by 50% to avoid hypoglycemia
   iii. Insulin
      1. MoA: facilitates uptake of glucose by skeletal muscle and fat, inhibits hepatic glucose production, and suppresses free fatty acid release from adipocytes
      2. Modes of administration
         a. Multiple daily injections (MDI)
            i. Basal to control FBG and prevent ketosis
            ii. Bolus to control postprandial hyperglycemia
         b. Continuous subcutaneous insulin infusion (CSII)
            i. Pump utilizes rapid-acting insulins or U-500 to allow pt-specific hourly basal and bolus dosing
            ii. Pt education and carbohydrate counting essential
            iii. Approximately 64% of U.S. pts use insulin pump\textsuperscript{25}
      3. AEs: hypoglycemia, weight gain, and injection-site reactions
      4. Honeymoon phase caution

D. Surgical\textsuperscript{22,23}

i. Pancreas and islet transplantation – require life-long immunosuppression
ii. Reserve modalities for those
   1. Undergoing simultaneous or following renal transplantation
   2. Recurrent ketoacidosis or SH
Acute Life-Threatening Complications

1. Hypoglycemia
   A. Definition\textsuperscript{18}
      i. Hypoglycemia alert value: PG ≤ 70 mg/dL
      ii. Clinically significant hypoglycemia: PG < 54 mg/dL
      iii. SH: severe cognitive impairment requiring treatment assistance
   B. Epidemiology
      i. 4-10\% of T1DM-related deaths\textsuperscript{26,28}
      ii. SH\textsuperscript{6,8}
         1. Improvements in glucose monitoring and insulin now reveal similar rates between intensive and non-intensive glycemic control
         2. 26\% experience episode within 4 yrs of diagnosis
         3. 11.8\% of 7012 U.S. adults with ≥ 1 event in past 12 months (mos)\textsuperscript{29}
            a. HbA1c
               i. Lowest: 8.3\% with A1c 7.0-7.5\%
               ii. Highest: 13.9\% with A1c < 6.5\%, 13.7\% with A1c 8.0< 9.0\%
            b. Duration of diabetes
               i. Lowest: 8.6\% with duration < 20 yrs
               ii. Highest: 18.6\% with duration ≥ 40 yrs
            c. Higher frequency associated with lower socioeconomic status
   C. Signs and symptoms: sweating, anxiety, nausea, headache, tachycardia, hunger, shakiness, blurred vision, dizziness, irritability, confusion, weakness, fatigue, and paleness\textsuperscript{18,22}
   D. Treatment\textsuperscript{18,22}
      i. If hypoglycemia alert value:
         1. Ingest 15-20 g of glucose or equivalent
         2. Repeat if blood glucose (BG) remains < 70 mg/dL after 15 minutes
         3. Ingest snack or meal after glucose normalized
      ii. Clinically significant hypoglycemia with altered consciousness: utilize glucagon 1 mg intramuscularly and/or intravenous dextrose, and ease glucose targets

2. DKA
   A. Definition: metabolic decompensation characterized by hyperglycemia, ketonemia, and metabolic acidosis\textsuperscript{30}
   B. Epidemiology
      i. Initial presentation
         1. Initial manifestation of diabetes in 27-37\% of pts\textsuperscript{1,31,32}
         2. More common with disadvantaged socioeconomic background\textsuperscript{2}
      ii. Incidence
         1. Overall: 8/100 person-yrs and increases with age in girls, high reported insulin dose, higher HbA1c, and older children with limited access to care secondary to underinsurance or presence of psychiatric disorders\textsuperscript{8}
         2. Hospital admissions in U.S.\textsuperscript{30}
            a. > 130,000/yr, with majority of cases recurrent
            b. 30\% increase between 1995 to 2005
         3. Age group
            a. More common overall number of events in adults\textsuperscript{30}
b. Frequency in U.S. from T1D Exchange registry of > 30,000 pts

### Frequency of DKA in U.S. During 2015

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>4%</td>
</tr>
<tr>
<td>&lt; 6</td>
<td>6%</td>
</tr>
<tr>
<td>6-12</td>
<td>4%</td>
</tr>
<tr>
<td>13-17</td>
<td>5%</td>
</tr>
<tr>
<td>18-25</td>
<td>5%</td>
</tr>
<tr>
<td>26-49</td>
<td>2%</td>
</tr>
<tr>
<td>50-64</td>
<td>1%</td>
</tr>
<tr>
<td>&gt; 64</td>
<td>2%</td>
</tr>
</tbody>
</table>

Figure 2 – U.S. Frequency by Age Group

4. Percentage of 7012 U.S. adults with ≥ 1 event in past 12 mos: female (5.5%) vs. male (4.0%)^{29}

5. 2.3% with CSII and 4.3% with MDI^{10}

### Mortality

1. 1-5% of DKA episodes^{30,33,34}
   a. < 1% in adults, > 5% in elderly or those with life-threatening illnesses
   b. Death usually attributed to precipitating factor/illness

2. Accounts for 13-19% of T1DM-related deaths^{26,27,35}

3. By age group: Danish Cause of Death Registry: 1996 to 2000 revealed 55 deaths secondary to DKA in pts with T1DM^{36}

### Cost

iv. Cost: $2.4 billion dollars/yr for treatment^{30}

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C. Precipitating factors^{30,37}

i. Discontinuation or inadequate insulin

ii. Physiologic stressors (e.g., cerebrovascular accident (CVA), MI, and pancreatitis)

iii. Infections (30-50% cases worldwide)

iv. Other drugs (e.g., corticosteroids, thiazides, olanzapine, risperidone, and cocaine)

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D. Pathophysiology^{30,37}

i. Absolute or relative insulin deficiency stimulates elevation of counterregulatory hormones (glucagon, catecholamines, cortisol, and growth hormone)

ii. Inability to utilize glucose results in:
   1. Increased lipolysis that releases fatty acids and glycerol
      a. Free fatty acids precursor to ketoacids in the liver
      b. Glycerol substrate for gluconeogenesis in liver and kidney
   2. Increased proteolysis and glycogenolysis to produce glucose

iii. Hyperglycemia promotes osmotic diuresis causing dehydration, metabolic acidosis, and hyperosmolar state

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E. Signs and symptoms: polyuria, polydipsia, polyphagia, weight loss, fatigue, dyspnea, vomiting, preceding febrile illness, abdominal pain, dehydration, tachycardia, poor skin turgor, dry
mucous membranes, orthostatic hypotension, Kussmaul respirations, fruity breath, somnolence, lethargy, coma, hyponatremia, and hyperkalemia. F. Diagnostic criteria

<table>
<thead>
<tr>
<th>Severity</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>PG (mg/dL)</td>
<td>&gt; 250</td>
<td>&gt; 250</td>
<td>&gt; 250</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.25-7.30</td>
<td>7.00-7.24</td>
<td>&lt; 7.0</td>
</tr>
<tr>
<td>Serum bicarbonate (mEq/L)</td>
<td>15-18</td>
<td>10-14</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Urine ketone</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Serum ketone</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Effective serum osmolality</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Anion gap</td>
<td>&gt; 10</td>
<td>&gt; 12</td>
<td>&gt; 12</td>
</tr>
<tr>
<td>Mental status</td>
<td>Alert</td>
<td>Alert/drowsy</td>
<td>Stupor/coma</td>
</tr>
</tbody>
</table>

G. Treatment
- i. Underlying cause, fluid replacement, and insulin essential
- ii. May require administration of potassium, bicarbonate, phosphate, and magnesium

H. Complications: cerebral edema, hypoglycemia, hypokalemia, acute renal failure, and shock.

I. Prevention strategies
- i. Diabetes education programs, and improved follow-up and access to care
- ii. Access to supplies (e.g., glucose and ketone monitoring) and prescriptions (e.g., basal insulin prescription in case pump fails)
- iii. Sick-day management education

Sodium-Glucose Cotransporter (SGLT) Inhibitors

1. SGLT2 inhibitors

<table>
<thead>
<tr>
<th>Agent</th>
<th>Canagliflozin (Invokana®)</th>
<th>Dapagliflozin (Farxiga®)</th>
<th>Empagliflozin (Jardiance®)</th>
<th>Ertugliflozin (Steglatro®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MoA</td>
<td>Inhibit SGLT2 in proximal convoluted tubules, thereby reducing reabsorption of filtered glucose and lowering renal threshold for glucose, leading to increased glucose excretion in urine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FDA indication</td>
<td>Type 2 diabetes mellitus (T2DM)</td>
<td>T2DM</td>
<td>T2DM</td>
<td></td>
</tr>
<tr>
<td>FDA approval</td>
<td>March 2013</td>
<td>January 2014</td>
<td>August 2014</td>
<td>December 2017</td>
</tr>
<tr>
<td>Boxed warning</td>
<td>Lower limb amputations in T2DM pts with CVD or at risk for CVD</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Hypersensitivity</td>
<td>Severe renal impairment, ESRD, dialysis</td>
<td>Severe renal impairment, ESRD, dialysis</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td></td>
<td>Severe renal impairment, (estimated glomerular</td>
<td>Severe renal impairment, ESRD, dialysis</td>
<td>Severe renal impairment, ESRD, dialysis</td>
<td>Hypersensitivity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose</th>
<th>Total Dose (mg)</th>
<th>If eGFR 45-59 mL/min/1.73 m², 100 mg daily max dose</th>
<th>If eGFR &lt; 45 mL/min/1.73 m², discontinue or do not initiate</th>
<th>If eGFR &lt; 45 mL/min/1.73 m², discontinue or do not initiate</th>
<th>If eGFR &lt; 45 mL/min/1.73 m², discontinue or do not initiate</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mgonce daily; may increase to 300 mg once daily</td>
<td>5 mg once daily; may increase to 10 mg once daily</td>
<td>10 mg once daily; may increase to 25 mg once daily</td>
<td>5 mg once daily; may increase to 15 mg once daily</td>
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</table>

**Dosing in renal impairment**

- **Pediatric dosing**
  - Safety and efficacy not established in pediatric pts

**Administration**

- Prior to first meal of day
- Morning with or without food
- Morning with or without food

**AEs**

**Common**: urinary tract infection (UTI) and genital mycotic infection (GMI)

**Serious**: hypotension, DKA (including euglycemic), hypoglycemia, hypersensitivity, bone fracture, kidney injury/renal impairment, and urosepsis

**A. FDA Drug Safety Communication**

  **i. May 2015**

  1. SGLT2 inhibitor use may lead to ketoacidosis
  2. FDA Adverse Event Reporting System (FAERS) database: March 2013 to June 2014 revealed 20 cases of acidosis (DKA, ketoacidosis, or ketosis)
  3. Cases mostly T2DM pts with only slightly elevated blood sugar levels

  **ii. December 2015**

  1. FDA revised SGLT2 inhibitor labels with warning for ketoacidosis
  2. FAERS database: extended to May 2015 and reported 73 cases ketoacidosis
  3. Many cases not immediately recognized as BG levels below 250 mg/dL (i.e., euglycemic DKA)
  4. Required manufacturers conduct analysis of spontaneous postmarketing reports of ketoacidosis with follow-up for period of 5 yrs

**B. Landmark trials in T2DM**

  **i. EMPA-REG Outcome**: significant reduction in major adverse CV events and renal outcomes demonstrated

  **ii. CANVAS and CANVAS-R**: significant reduction in major adverse CV events, potential renoprotection, and increased risk of amputation

**2. SGLT1/SGLT2 inhibitor – sotagliflozin (Zynquista™)**

**A. Investigational dual inhibitor of SGLT1 and SGLT2**

**B. MoA**

  **i. SGLT2 inhibition**

  **ii. SGLT1 inhibition**

  1. Reduces glucose and galactose absorption in proximal intestine and augments release of gastrointestinal incretins, serving to blunt and delay postprandial hyperglycemia
  2. Not thought to have meaningful renal SGLT1 inhibition

**C. AEs**: nausea, bloating, diarrhea, DKA, genitourinary infections, and hypoglycemia

**D. Sanofi submitted New Drug Application to FDA March 2018 for use in T1DM**
E. May 2018, FDA accepted regulatory filing with a March 2019 targeted FDA action date

Clinical Controversy: SGLT Inhibitors, a Viable Option in T1DM?

Background Literature Review

<table>
<thead>
<tr>
<th>Author</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mudaliar et al.</td>
<td>First trial to explore administration of SGLT2 inhibitor – remogliflozin in T1DM • Ten individuals on CSII provided 5 randomized treatments including placebo (PBO), prandial insulin, 50 mg remogliflozin, 150 mg remogliflozin, and 500 mg remogliflozin as single doses at different treatment periods • Remogliflozin reduced mean glucose concentrations relative to PBO without AE</td>
</tr>
<tr>
<td>Perkins et al.</td>
<td>40 MDI/CSII pts completed 8 weeks (wks) of empagliflozin 25 mg daily • Significantly decreased HbA1c, fasting glucose, daily insulin use, symptomatic hypoglycemia, weight, and waist circumference • Two pts withdrawn secondary to DKA episodes within 3 days of initiation</td>
</tr>
<tr>
<td>Henry et al.</td>
<td>70 MDI/CSII adults randomized to dapagliflozin 1 mg, 2.5 mg, 5 mg (D5), 10 mg (D10), or PBO once daily for 2 wks to assess short-term safety • Hypoglycemia common across all treatments (60.0-92.3%) with no dose relation • One major hypoglycemic event requiring assistance among dapagliflozin groups related to not reducing insulin dose as investigator instructed, and no episodes of DKA</td>
</tr>
<tr>
<td>Sands et al.</td>
<td>33 MDI/CSII adults randomized to daily sotagliflozin 400 mg (S400) or PBO for 29 days • Sotagliflozin significantly decreased HbA1c, total daily insulin dose (TDD), bolus insulin dose, mean daily glucose, percentage of time in hyperglycemic range, and body weight • No severe hypoglycemic events • Two episodes of DKA in sotagliflozin group; deemed pump-related</td>
</tr>
<tr>
<td>Pieber et al.</td>
<td>Empagliflozin as Adjunctive to inSulin thErapy (EASE)-1 trial, 75 pts on MDI randomized to receive daily empagliflozin 2.5 mg, 10 mg, 25 mg, or PBO as insulin adjunct for 28 days • Empagliflozin significantly decreased HbA1c, TDD, and weight without episode of DKA or SH</td>
</tr>
</tbody>
</table>

Randomized Controlled Trials (RCTs)

**Henry RR, Thakkar P, Tong C, Polidori D, Alba M. Efficacy and safety of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to insulin in patients with type 1 diabetes. Diabetes Care. 2015;38(12):2258-2265.**

Objective
- Evaluate canagliflozin as an adjunct to insulin to achieve adequate glycemic control in adults with T1DM

Study Design
- Phase 2, multicenter, randomized, double-blind, PBO-controlled trial
  - May 2014 to June 2015 at multiple sites across U.S. and Canada
  - Randomized 1:1:1 to once daily canagliflozin 100 mg (C100), canagliflozin 300 mg (C300), or PBO prior to first meal of day for 18 wks; stratified by use of CSII vs. MDI
  - 2 wks of safety follow-up after 18-week (wk) treatment period
  - If HbA1c ≤ 8.0%, recommended basal reduced 20%; if > 8.0%, recommended basal reduced 10% prior to randomization
- Lab HbA1c and FPG masked after randomization
- Algorithms provided for pts to titrate basal insulin to achieve FBG of 80 to < 120 mg/dL and bolus insulin to achieve pre-lunch, pre-dinner, and bedtime glucose of 80 to < 120 mg/dL; investigators could also recommend adjustments

### Population

**Inclusion:**
- Adults 25-65 yrs of age with T1DM for ≥ 1 yr
- Fasting C-peptide of < 0.6 ng/mL at screening
- HbA1c 7.0-9.0%
- Body mass index (BMI) 21-35 kg/m²
- Stable insulin regimen and method of administration for ≥ 8 wks prior to screening

**Exclusion:**
- History (hx) of T2DM, pancreas or β-cell transplantation, or diabetes due to pancreatitis or pancreatectomy
- SH or DKA event within 6 mos of start
- MI, unstable angina, revascularization, or CVA ≤ 12 wks prior to screening
- New York Heart Association (NYHA) class III-IV
- Uncontrolled hypertension
- eGFR < 70 mL/min/1.73 mL²; if fell below 60 during study, dismissed from trial
- Antihyperglycemic agent other than insulin within 12 wks of screening

### Outcome(s)

**Primary:** proportion of adults with HbA1c reduction ≥ 0.4% and no weight increase; sensitivity analysis with HbA1c reduction ≥ 0.4% and < 1 kg change in weight

**Secondary:** change in baseline in HbA1c, FPG, weight, and basal/bolus dose requirements, proportion of adults with HbA1c < 7.0%, and incidence of documented hypoglycemia (including SH) and symptomatic hypoglycemia

**Safety:** adverse events including ketone-related events

### Statistical Methods

- Modified intent-to-treat (mITT) with pts randomized who received ≥ 1 dose
- Assumed 40% of C100 and C300 groups, along with 20% of PBO group, would meet primary endpoint to determine sample size of 100 pts/group to provide ~80% power to compare each dose with PBO; planned 110 pts/group
- 2-sided α of 0.05 for primary efficacy endpoint
- Primary efficacy endpoint analyzed with generalized linear mixed model
- Statistical comparisons between canagliflozin and PBO only performed for primary endpoint (P values); 95% confidence interval (CI) provided for non-prespecified endpoints for descriptive purposes

### Baseline Characteristics

- 614 enrolled → 352 randomized → 351 administered ≥ 1 dose: PBO (n = 117), C100 (n = 117), C300 (n = 117): 328 (93.4%) completed 18-wks
- C100 higher % male (59.0 vs. C300 55.6 vs. PBO 53.8) and white (94.9 vs. C300 87.2 vs. PBO 90.6), but lower % prior SH (12.8 vs. C300 16.2 vs. PBO 15.4)
- TDD baseline: 57.8 units/day PBO vs. 52.0 units/day C100 vs. 52.4 units/day C300
- Average (avg) age 42.3 yrs, BMI 28.1 kg/m², duration of T1DM 22.4 yrs, HbA1c 7.9%, and eGFR 96.4 mL/min/1.73 m²
- CSII 62.4% (61.5% PBO vs. 63.2% C100 vs. 62.4% C300)
- Hx of SH episode 14.8% and DKA event 12.0%

### Endpoints

**Primary:**
- Larger proportion of adults had HbA1c decrease ≥ 0.4% and no weight increase with canagliflozin: PBO 14.5%, C100 36.9%, C300 41.4%; P < 0.001 for both comparisons
  - HbA1c decrease ≥ 0.4%: PBO 22.7%, C100 45.0%, C300 43.2%
  - No weight increase: PBO 49.1%, C100 83.8%, C300 96.4%
Sensitivity analysis: proportion of participants with HbA1c reduction ≥ 0.4% and weight change < 1.0 kg: PBO 17.3%, C100 39.6%, C300 43.2%

Secondary:

### Secondary Efficacy Outcomes

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>C100 vs. PBO</th>
<th>C300 vs. PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LS Mean</td>
<td>95% CI</td>
</tr>
<tr>
<td></td>
<td>Difference from PBO</td>
<td></td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>-0.29</td>
<td>-0.43 to -0.14</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>-2.8</td>
<td>-3.5 to -2.1</td>
</tr>
<tr>
<td>FPG, mg/dL</td>
<td>-8.5</td>
<td>-22.5 to 5.5</td>
</tr>
<tr>
<td>TDD, units/d</td>
<td>-4.1</td>
<td>-7.9 to -0.3</td>
</tr>
<tr>
<td>Basal, units/d</td>
<td>-4.3</td>
<td>-6.2 to -2.4</td>
</tr>
<tr>
<td>Bolus, units/d</td>
<td>-0.3</td>
<td>-3.3 to 2.7</td>
</tr>
</tbody>
</table>

- Proportion adults achieving HbA1c < 7.0%: PBO 5.7%, C100 10.1%, C300 11.2%
- Documented hypoglycemia: PBO 96.6%, C100 98.3%, C300 99.1%
  - Event rate/pt-yr exposure: PBO 80.6, C100 70.7, C300 79.2

### Safety:

### Adverse Event Summary

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>PBO (n = 117)</th>
<th>C100 (n = 117)</th>
<th>C300 (n = 117)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMI, females/total females (%) (*no GMI reported in males)</td>
<td>3/54 (5.6)</td>
<td>2/48 (4.2)</td>
<td>11/52 (21.2)</td>
</tr>
<tr>
<td>UTI, pts (%)</td>
<td>2 (1.7)</td>
<td>5 (4.3)</td>
<td>6 (5.1)</td>
</tr>
<tr>
<td>Ketone-related events, pts (%)*</td>
<td>0 (0)</td>
<td>6 (5.1)</td>
<td>11 (9.4)</td>
</tr>
<tr>
<td>DKA requiring hospitalization, n (%)</td>
<td>0 (0)</td>
<td>5 (4.3)</td>
<td>7 (6.0)</td>
</tr>
<tr>
<td>Increased urinary ketones and mild/moderate DKA or acidosis, n (%)</td>
<td>0 (0)</td>
<td>1 (0.9)</td>
<td>5 (4.3)</td>
</tr>
</tbody>
</table>

*17 pts experienced 18 events

### Author's Conclusion

Canagliflozin reduced HbA1c, weight, and insulin dose; however, increased DKA events, which will require additional mitigation strategies to reduce risk

### Critique

**Strengths:**
- RCT
- % CSII reflective of general population
- Self-titration
- Employed insulin dose adjustment algorithm
- Lack of home ketone monitoring increased real-world validity

**Limitations:**
- Soft primary outcome
- Lack clarity on generation of hypoglycemic event rate
- 3-page supplementary appendix and no protocol
- Low risk DKA population
- Unable to determine long-term safety and efficacy
- Glucose variability not addressed
- Blood pressure not evaluated

### Take Home Point(s)

Although canagliflozin improved glycemic control, reduced weight, and decreased insulin dose, DKA number needed to harm (NNH) 14 for ketone-related events and 20 for DKA requiring hospitalization unacceptably high given low-risk population
<table>
<thead>
<tr>
<th>Objective</th>
<th>Assess whether D5 or D10 added to adjustable insulin can safely improve glycemic control in individuals with T1DM</th>
</tr>
</thead>
</table>
| Study Design | Phase 3, multicenter, randomized, double-blind, PBO-controlled trial  
• Enrolled November 2014 to April 2016 at 43 sites in 17 countries  
• 8-wk lead-in period to optimize diabetes management  
• Randomized 1:1:1 to once daily D5, D10, or PBO for 24-wk treatment period  
  o Stratified by current use of CGM, method of insulin administration (MDI vs. CSII), and baseline HbA1c (≥ 7.5 to < 9.0% vs. ≥ 9.0 to ≤ 10.5%)  
  o Recommended TDD be reduced symmetrically in basal and bolus insulin by ≤ 20% after first study drug dose and then titrating back towards baseline levels  
  o Insulin adjusted by providers based on self-monitoring of blood glucose (SMBG)  
• Provided DKA education and ketone meters; required to monitor if symptomatic  
• DKA adjudication committee classified DKA events as definite, possible, or unlikely |
| Population | Inclusion:  
• Men and nonpregnant women 18 to 75 years old (y.o.)  
• Inadequately controlled T1DM, defined as HbA1c of 7.7-11.0% at screening and 7.5-10.5% at randomization  
• Prescription insulin ≥ 12 mos prior to enrollment, with TDD ≥ 0.3 units/kg/day for ≥ 3 mos before screening  
• C-peptide < 0.7 ng/mL  
• BMI ≥ 18.5 kg/m²  
Exclusion:  
• Hx of T2DM, maturity onset diabetes of the young, or diabetes insipidus  
• Symptoms of poorly controlled diabetes  
• Prior pancreatic surgery, chronic pancreatitis, or other pancreatic disorder leading to decreased β-cell capacity  
• DKA requiring medical intervention within 1 mo prior to screening  
• Hospital admission for hyper- or hypoglycemia within 1-mo pre-screening; frequent SH episodes  
• CVD within 6 mos pre-screening, unstable or rapidly progressing renal disease, significant hepatic disease, or malignancy within 5 yrs  
• Calculated creatinine clearance < 60 mL/min  
• Further criteria in supplementary appendix |
| Outcome(s) | Primary: change in baseline HbA1c after 24 wks of treatment  
Secondary: % change in TDD and bodyweight, change in mean value of 24-hr glucose readings and mean amplitude of glucose excursion (MAGE) of 24-hr CGM readings, % change of 24-hr CGM glucose readings within target range of > 70-180 mg/dL, and proportion with HbA1c decrease of ≥ 0.5% without SH  
Safety: hypoglycemia, DKA, hepatobiliary events, GMI, UTI, volume depletion, fractures, worsening renal function, hypersensitivity reactions, and CV AEs |
| Statistical Methods | • Sample size 243 pts/group for ~90% power to detect mean HbA1c difference of 0.35% between each dapagliflozin group and PBO at a 2-sided significance level of 0.0262 with a standard deviation of 1.1%; planned 256/group assuming no post-baseline assessment in 5% of pts  
• Efficacy analyses mITT with randomized pts receiving ≥ 1 dose, excluding initial 55 pts due to randomization error; treatment effects through pairwise comparisons  
  o Primary endpoint analyzed with longitudinal repeated-measures analysis  
  o Secondary endpoints only evaluated if primary endpoints significant |
• Safety analysis mITT with all randomized pts receiving ≥ 1 dose

Baseline Characteristics

• 1605 enrolled \(\rightarrow\) 833 randomized to D5 (n = 277), D10 (n = 296), PBO (n = 260); 758 (91.0%) completed 24-wks
• Groups well-matched – more women in D5 (57%) than D10 (50%) or PBO (49%)
  o Avg age 42.5 yrs, majority white and from Europe (~1/4 from North America), and mean baseline BMI was 28.3 kg/m²
  o Mean duration of diabetes 20.3 yrs, baseline HbA1c 8.53%
  o Avg baseline TDD of 62.1 units (0.76 units/kg) in D5, 59.4 units (0.71 units/kg) in D10, and 63.1 units (0.74 units/kg) in PBO
  o MDI 63% vs. CSII 37%, CGM 33%
  o ~75% of participants in HbA1c range ≥ 7.5% to 9.0% at randomization

Endpoints

Primary: significant HbA1c reduction over 24 wks with both D5 (n = 259) and D10 (n = 259) vs. PBO (n = 260); confirmed by sensitivity analyses
• D5 vs. PBO: adjusted mean change -0.42; 95% CI, -0.56 to -0.28; p < 0.0001
• D10 vs. PBO: adjusted mean change -0.45; 95% CI, -0.58 to -0.31; p < 0.0001

Secondary:

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>D5 vs. PBO</th>
<th>P Value</th>
<th>D10 vs. PBO</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin TDD, %</td>
<td>-8.8</td>
<td>&lt; 0.0001</td>
<td>-13.2</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>(95% CI: -12.6 to -4.9)</td>
<td></td>
<td></td>
<td>(-16.8 to -9.4)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Insulin TDD/kg, %</td>
<td>-5.5</td>
<td>0.0064</td>
<td>-9.8</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>(95% CI: -9.2 to -1.6)</td>
<td></td>
<td></td>
<td>(-13.4 to -6.1)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Weight, %</td>
<td>-2.96</td>
<td>&lt; 0.0001</td>
<td>-3.72</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>(95% CI: -3.63 to -2.28)</td>
<td></td>
<td></td>
<td>(-4.38 to -3.05)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>CGM Mean Value, mg/dL</td>
<td>-15.3</td>
<td>&lt; 0.0001</td>
<td>-18.0</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>(95% CI: -20.2 to -10.5)</td>
<td></td>
<td></td>
<td>(-23.0 to -13.1)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>CGM MAGE, mg/dL</td>
<td>-17.3</td>
<td>&lt; 0.0001</td>
<td>-18.9</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>(95% CI: -22.5 to -12.1)</td>
<td></td>
<td></td>
<td>(-24.1 to -13.7)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>24-hr CGM at goal of &gt; 70-180 mg/dL, %</td>
<td>9.1</td>
<td>&lt; 0.0001</td>
<td>10.7</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>(95% CI: 6.8 to 11.4)</td>
<td></td>
<td></td>
<td>(8.4 to 12.9)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

• Reductions in TDD proportional for basal and bolus insulin requirements
  o D5: adjusted mean change from baseline -11.6% (basal), -14.3% (bolus)
  o D10: adjusted mean change from baseline -13.7% (basal), -18.0% (bolus)
  o PBO: adjusted mean change baseline -0.6% (basal), -4.6% (bolus)

• HbA1c reduction ≥ 0.5% without SH significant for both groups
  o D5 vs. PBO: odds ratio (OR), 3.09; 95% CI, 2.10 to 4.56; p < 0.0001
  o D10 vs. PBO: OR, 3.29; 95% CI, 2.23 to 4.85; p < 0.0001

Safety:

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>D5 (n = 277)</th>
<th>D10 (n = 296)</th>
<th>PBO (n = 260)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMI, pts (%)</td>
<td>34 (12)</td>
<td>33 (11)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>UTI, pts (%)</td>
<td>19 (7)</td>
<td>11 (4)</td>
<td>13 (5)</td>
</tr>
<tr>
<td>Renal worsening/failure, pts (%)</td>
<td>4 (1)</td>
<td>2 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Fractures, pts (%)</td>
<td>4 (1)</td>
<td>3 (1)</td>
<td>3 (1)</td>
</tr>
</tbody>
</table>
### Hypoglycemia

<table>
<thead>
<tr>
<th></th>
<th>SH, pts (%)</th>
<th>SH, events (%)</th>
<th>SH, events/100 pt-yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Documented, pts (%)</td>
<td>220 (79)</td>
<td>31 (1)</td>
<td>25.2</td>
</tr>
<tr>
<td>SH, pts (%)</td>
<td>21 (8)</td>
<td>19 (6)</td>
<td>29.5</td>
</tr>
<tr>
<td>SH, events (%)</td>
<td>19 (7)</td>
<td>54 (1)</td>
<td>47.8</td>
</tr>
<tr>
<td>SH, events/100 pt-yrs</td>
<td>207 (80)</td>
<td>235 (79)</td>
<td>23 (8)</td>
</tr>
</tbody>
</table>

### DKA

<table>
<thead>
<tr>
<th></th>
<th>Definite, pts (%)</th>
<th>Euglycemic DKA, events</th>
<th>Possible, pts (%)</th>
<th>Unlikely, pts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite, pts (%)</td>
<td>4 (1)</td>
<td>0</td>
<td>5 (2)</td>
<td>9 (3)</td>
</tr>
<tr>
<td>Euglycemic DKA, events</td>
<td>2 (2)</td>
<td>1 (&lt; 1)</td>
<td>7 (2)</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Possible, pts (%)</td>
<td>3 (1)</td>
<td></td>
<td>8 (3)</td>
<td></td>
</tr>
</tbody>
</table>

### Author’s Conclusion

As the first oral adjunct to insulin for T1DM to show HbA1c and weight loss benefit, along with reduced hypoglycemia risk, compared with insulin alone, concomitant dapagliflozin represents a promising addition to insulin therapy.

### Critique

**Strengths:**
- Large RCT
- Glucose variability
- No insulin adjustment algorithm more closely reflects clinical practice
- DKA adjudicated by blinded committee
- Evaluated many AEs

**Limitations:**
- Generalizability
- Lack of long-term efficacy and safety data
- Excluded pts with common comorbidities
- Insulin adjustment done solely by investigator
- No set criteria to define possible or unlikely DKA
- Outcome bias
- Blood pressure not evaluated

### Take Home Point(s)

Potential T1DM FDA indication for dapagliflozin based on findings; however, when possible DKA added to definitive events, less favorable profile revealed (NNH 47)

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**Objective**

Determine safety and efficacy of sotagliflozin as adjunct to insulin in T1DM

**Study Design**

Phase 3, multicenter, randomized, double-blind, PBO-controlled trial
- October 2015 to April 2017 at 133 sites across 19 countries
- Randomized 1:1 to once daily PBO or S400 prior to first meal of day for 24 wks
- Continued approved insulin regimen with exception of receiving 30% lower bolus insulin dose with first meal of study period
- Insulin adjusted by providers based on SMBG using algorithms targeting ADA goals
- Lab HbA1c, fasting plasma, and urinary glucose levels masked after randomization
- Wk 16 to 24, investigators informed of HbA1c > 11.0% to make necessary changes
- Pts provided information/supplies for detection of ketosis (urine ketone strips, β-hydroxybutyrate meter and strips), urogenital hygiene, and proper hydration

**Population**

- Men and nonpregnant women ≥ 18 y.o. with T1DM for ≥ 1 yr
- Stable basal insulin dose ≥ 2 wks prior to screening visit
- HbA1c 7.0-11.0%
- BMI ≥ 18.5 kg/m²

**Exclusion:**
- SH within 1 mo prior to screening
- DKA within 1 mo or ≥ 2 events within 6 mos
- T2DM or severely uncontrolled T1DM
- eGFR < 45 m/min/1.73 m²
- Chronic corticosteroids within 6 mos of screening
- β-hydroxybutyrate > 0.6 mmol/L at screening
- Severely immunocompromised
- Pancreatitis within 12 mos of screening
• Able and willing to perform SMBG
• Adequate contraception by women
• Hepatitis or lab-confirmed abnormal liver function
• NYHA class III-IV
• CVD within 3 mos of screening
• Further criteria in supplementary appendix

Outcome(s)

Primary: HbA1c < 7.0% with no episodes of SH or DKA
Secondary: change from baseline sotagliflozin vs. PBO in HbA1c, weight, mean daily bolus insulin dose, and systolic blood pressure (SBP) in pts with SBP ≥ 130 mmHg
Other: HbA1c < 7.0% with no weight gain, DKA, number of documented hypoglycemic events, SH, change from baseline in diastolic blood pressure (DBP), FPG, mean daily basal insulin dose, mean daily total insulin, and eGFR

Statistical Methods

• mITT with pts who underwent randomization and received ≥ 1 dose
• Sample size 700 pts/group to provide ~90% power to detect effect size of 0.10 for primary endpoint, assuming 50% of pts would achieve endpoint
• 2-sided α of 0.05 for primary and secondary efficacy variables
• Sensitivity analysis performed to account for missing data
• Categorical variables analyzed as proportions and results summarized as % points
• Safety analysis descriptive

Baseline Characteristics

• 1755 screened → 1405 randomized → 1402 received dose of S400 (n = 699) or PBO (n = 703): 1229 (87.7%) completed 24-wks
• Groups well-matched
  o Avg age 43.3 y.o. S400 vs. 42.4 y.o. PBO, female 48.8% S400 vs. 51.8% PBO, white 88.6% S400 vs. 88.3% PBO, and mean BMI 28.3 kg/m² S400 vs. 28.1 kg/m² PBO
  o Mean duration of diabetes 20.5 yrs S400 vs. 19.6 yrs PBO, baseline HbA1c 8.3% S400 vs. 8.2% PBO, FPG 165.1 mg/dL S400 vs. 163.4 mg/dL PBO
  o Mean TDD 56.9 units/d (0.69 units/kg) S400 vs. 58.4 units/d (0.71 units/kg) PBO
  o MDI 60.7% S400 vs. 60.2% PBO
  o Avg SBP 122.0 mmHg S400 vs. 121.8 mmHg PBO, DBP 76.4 mmHg S400 vs. 76.7 mmHg PBO, SBP ≥ 130 mmHg 29.0% S400 vs. 28.9% PBO

Endpoints

Primary: Significant Primary Efficacy Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>S400 (n = 699) pts (%)</th>
<th>PBO (n = 703) pts (%)</th>
<th>Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c &lt; 7.0% and no SH or DKA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All pts</td>
<td>200 (28.6)</td>
<td>107 (15.2)</td>
<td>13.4 (9.0 to 17.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CSII pts</td>
<td>88 (32.0)</td>
<td>45 (16.1)</td>
<td>15.9 (8.6 to 23.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MDI pts</td>
<td>112 (26.4)</td>
<td>62 (14.7)</td>
<td>11.8 (6.1 to 17.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HbA1c ≥ 7.0% and ≥ 1 DKA episode</td>
<td>18 (2.6)</td>
<td>4 (0.6)</td>
<td>2.0 (0.7-3.3)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Secondary: Efficacy Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>S400 (n = 699)</th>
<th>PBO (n = 703)</th>
<th>LS Mean Difference from PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c, % (95% CI)</td>
<td>-0.79</td>
<td>-0.33</td>
<td>-0.46 (0.34 to 0.54)</td>
</tr>
<tr>
<td>P Value</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Metric</td>
<td>S400 (n = 699)</td>
<td>PBO (n = 703)</td>
<td>Difference</td>
</tr>
<tr>
<td>----------------------------</td>
<td>---------------</td>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>Weight, kg (95% CI) P Value</td>
<td>-2.21 (-2.45 to -1.97)</td>
<td>0.77 (0.53 to 1.01)</td>
<td>-2.98 (-3.31 to -2.66)</td>
</tr>
<tr>
<td>SBP in pts with SBP ≥ 130 mmHg, mmHg (95% CI) P Value</td>
<td>-9.2 (-11.0 to -7.4)</td>
<td>-5.7 (-7.5 to -3.9)</td>
<td>-3.5 (-5.7 to -1.3)</td>
</tr>
<tr>
<td>Daily bolus insulin dose, units/d (95% CI) P Value</td>
<td>-3.39 (-4.85 to -3.01)</td>
<td>-1.09 (-2.00 to -0.17)</td>
<td>-2.84 (-4.05 to -1.64)</td>
</tr>
</tbody>
</table>

Other:
- HbA1c < 7.0% with no weight gain: 171/699 (24.5%) S400 vs. 51/703 (7.3%) PBO
- S400 LS mean difference from PBO
  - FPG: -23.2 mg/dL; 95% CI (-30.4 to -16.0); P < 0.001
  - TDD: -5.25 units/day; 95% CI (-6.67 to -3.83); P < 0.001
  - Daily basal insulin dose: -2.60 units/day; 95% CI (-3.39 to -1.81); P < 0.001
  - DBP, mITT population: -1.3 mmHg; 95% CI (-2.1 to -0.6); P < 0.001
  - eGFR: -0.24 mL/min/1.73 m2; 95% CI (-1.52 to 1.04); P = 0.71

### Adverse Event Summary

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>S400 (n = 699)</th>
<th>PBO (n = 703)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMI, pts (%)</td>
<td>45 (6.4)</td>
<td>15 (2.1)</td>
</tr>
<tr>
<td>UTI, pts (%)</td>
<td>25 (3.6)</td>
<td>27 (3.8)</td>
</tr>
<tr>
<td>Diarrhea, pts (%)</td>
<td>29 (4.1)</td>
<td>16 (2.3)</td>
</tr>
<tr>
<td>Fractures, pts (%)</td>
<td>4 (0.6)</td>
<td>5 (0.7)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Documented hypoglycemia, pts (%)</td>
<td>673 (96.3)</td>
<td>670 (95.3)</td>
</tr>
<tr>
<td>≤ 55 mg/dL, pts (%)</td>
<td>528 (75.5)</td>
<td>559 (79.5)</td>
</tr>
<tr>
<td>SH, pts (%)</td>
<td>21 (3.0)</td>
<td>17 (2.4)</td>
</tr>
<tr>
<td>CSII, pts (%)</td>
<td>10 (3.6)</td>
<td>5 (1.8)</td>
</tr>
<tr>
<td>MDI, pts (%)</td>
<td>11 (2.6)</td>
<td>12 (2.8)</td>
</tr>
<tr>
<td>Serious and nonserious acidosis-related adverse events, pts (%)</td>
<td>60 (8.6)</td>
<td>17 (2.4)</td>
</tr>
<tr>
<td>DKA, pts (%)</td>
<td>21 (3.0)</td>
<td>4 (0.6)</td>
</tr>
<tr>
<td>CSII, pts (%)</td>
<td>12 (4.4)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>MDI, pts (%)</td>
<td>9 (2.1)</td>
<td>2 (0.5)</td>
</tr>
</tbody>
</table>

### Author’s Conclusion
Significantly larger proportion of adults in S400 group achieved primary endpoint; however, DKA rate significantly higher in S400 pts not meeting HbA1c < 7.0%

### Critique
**Strengths:**
- Large RCT
- Employed insulin dose adjustment algorithms
- Included DKA results by administration method
- Pts with CV comorbidities
- Evaluated blood pressure
- Independent agencies involved

**Limitations:**
- Masking HbA1c favored active intervention
- Infrequent participant-provider visits
- Low risk DKA population
- Lack of long-term efficacy and safety data
- Glucose variability not addressed

### Take Home Point(s)
Increased DKA risk (NNH 42), especially in CSII users (NNH 27), in relatively low risk population potentially offsets benefits of sotagliflozin
Table 8: Recent Trial Results

<table>
<thead>
<tr>
<th>Author</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buse et al.58 Sep 2018</td>
<td>inTandem1 study: 52-wk, phase 3, multicenter, double-blind, PBO-controlled trial, randomized North American adults with T1DM to once daily PBO (n = 268), sotagliflozin 200 mg (S200) (n = 263), and S400 (n = 262) post 6-wk insulin optimization period</td>
</tr>
<tr>
<td></td>
<td>• Significant efficacy outcomes</td>
</tr>
<tr>
<td></td>
<td>o PBO-adjusted HbA1c reduction 24 wks: 0.36% S200, 0.41% S400 (P &lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td>o PBO-adjusted HbA1c reduction 52 wks: 0.25% S200, 0.31% S400 (P &lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td>o PBO-adjusted mean SBP reduction 12 wks: 3.5 mmHg S200, 4.2 mmHg S400 (P &lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td>o Mean treatment differences vs. PBO 52 wks</td>
</tr>
<tr>
<td></td>
<td>▪ FBG: S200 12.2 mg/dL lower (P = 0.028), S400 19.4 mg/dL lower (P &lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td>▪ Bolus dose: S400 15.6% lower; basal dose: S400 11.9% lower (P &lt; 0.001)</td>
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<tr>
<td></td>
<td>▪ Time in range: S400 increased 10.4% (P &lt; 0.001) relative to PBO</td>
</tr>
<tr>
<td></td>
<td>▪ Weight: S200 3.1 kg lower (P &lt; 0.001), S400 4.3 kg lower (P &lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td>• Notable safety outcomes</td>
</tr>
<tr>
<td></td>
<td>o SH: 26 pts (9.7%) PBO, 17 pts (6.5%) S200, 17 pts (6.5%) S400</td>
</tr>
<tr>
<td></td>
<td>o DKA: 1 pt (0.4%) PBO, 9 pts (3.4%) S200, 11 pts (4.2%) S400; 7 episodes euglycemic</td>
</tr>
<tr>
<td></td>
<td>▪ CSII: 1/160 pts (0.6%) PBO, 8/156 pts (5.1%) S200, 7/157 pts (4.5%) S400</td>
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<tr>
<td></td>
<td>▪ MDI: 0 pts (0%) PBO, 1/107 pts (0.9%) S200, 4/105 pts (3.8%) S400</td>
</tr>
<tr>
<td></td>
<td>• Conclusion: sotagliflozin with optimized insulin associated with improved clinical outcomes (i.e., sustained HbA1c reduction, weight loss, lower insulin dose, longer time in range, and fewer episodes of SH), but more cases of DKA</td>
</tr>
<tr>
<td>Danne et al.59 Sep 2018</td>
<td>inTandem2 study: 52-wk, phase 3, multicenter, double-blind, PBO-controlled trial, randomized European (and Israeli) adults with T1DM to once daily PBO (n = 258), S200 (n = 261), and S400 (n = 263) post 6-wk insulin optimization period</td>
</tr>
<tr>
<td></td>
<td>• Significant efficacy outcomes</td>
</tr>
<tr>
<td></td>
<td>o PBO-adjusted HbA1c reduction 24 wks: 0.37% S200, 0.35% S400 (P &lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td>o PBO-adjusted HbA1c reduction 52 wks: 0.21% S200, 0.32% S400 (P &lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td>o Mean treatment differences vs. PBO 24 wks</td>
</tr>
<tr>
<td></td>
<td>▪ FBG: S200 21.6 mg/dL lower, S400 25.6 mg/dL lower (P &lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td>▪ Time in range: S200 increased 8.4% (P = 0.044), S400 increased 13.4% (P &lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td>▪ 2-hr PG: S200 50.4 mg/dL lower (P = 0.009), S400 75.6 mg/dL lower (P &lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td>▪ Bolus insulin dose: S200 12.9% lower (P &lt; 0.001), S400 16.4% lower (P &lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td>▪ Basal insulin dose: S200 5.8% lower (P = 0.007), S400 4.7% lower (P = 0.03)</td>
</tr>
<tr>
<td></td>
<td>o Mean treatment differences vs. PBO 52 wks</td>
</tr>
<tr>
<td></td>
<td>▪ FBG: S400 15.7 mg/dL lower (P &lt; 0.008)</td>
</tr>
<tr>
<td></td>
<td>▪ Weight: S200 2.18 kg lower (P &lt; 0.001), S400 2.92 kg lower (P &lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td>o PBO-adjusted mean SBP reduction 12 wks: S400 2.8 mmHg lower (P = 0.001)</td>
</tr>
<tr>
<td></td>
<td>• Notable safety outcomes</td>
</tr>
<tr>
<td></td>
<td>o SH: 13 pts (5.0%) PBO, 13 pts (5.0%) S200, 6 pts (2.3%) S400</td>
</tr>
<tr>
<td></td>
<td>o DKA: 0 pts (0%) PBO, 6 pts (2.3%) S200, 9 pts (3.4%) S400</td>
</tr>
<tr>
<td></td>
<td>▪ CSII: 0 pts (0%) PBO, 1/68 pts (1.5%) S200, 5/67 pts (7.5%) S400</td>
</tr>
<tr>
<td></td>
<td>▪ MDI: 0 pts (0%) PBO, 5/193 pts (2.6%) S200, 4/196 pts (2.0%) S400</td>
</tr>
<tr>
<td></td>
<td>o Acidosis-related adverse events</td>
</tr>
<tr>
<td></td>
<td>▪ Any: 3 (1.2%) PBO, 23 (8.8%) S200, 30 (11.4%) S400</td>
</tr>
<tr>
<td></td>
<td>▪ Serious: 0 (0%) PBO, 7 (2.7%) S200, 13 (4.9%) S400</td>
</tr>
</tbody>
</table>
• Conclusion: sotagliflozin with optimized insulin associated with significant HbA1c reductions, but more DKA episodes

<table>
<thead>
<tr>
<th>Mathieu et al.⁶⁰ Sep 2018</th>
<th>DEPICT-2 study: 24-wk, phase 3, multicenter, double-blind, PBO-controlled trial, randomized adults with T1DM and inadequate glycemic control to once daily PBO (n = 272), D5 (n = 271), and D10 (n = 270)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Significant efficacy outcomes</td>
<td></td>
</tr>
<tr>
<td>o PBO-adjusted HbA1c reduction: 0.37% D5, 0.42% D10 (P &lt; 0.0001)</td>
<td></td>
</tr>
<tr>
<td>o PBO-adjusted mean TDD % reduction: 10.8% D5, 11.1% D10 (P &lt; 0.0001)</td>
<td></td>
</tr>
<tr>
<td>o Adjusted mean basal insulin change: 1.5% PBO, -11.2% D5, -16.7% D10</td>
<td></td>
</tr>
<tr>
<td>o Adjusted mean bolus insulin change: -2.59% PBO, -11.6% D5, -8.3% D10</td>
<td></td>
</tr>
<tr>
<td>o PBO-adjusted weight reduction: 3.2% D5, 3.7% D10 (P &lt; 0.0001)</td>
<td></td>
</tr>
<tr>
<td>o Mean treatment differences vs. PBO</td>
<td></td>
</tr>
<tr>
<td>▪ 24-hr CGM mean value: -15.7 mg/dL D5, -19.7 mg/dL D10 (P &lt; 0.0001)</td>
<td></td>
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<tr>
<td>▪ 24-hr CGM in target range: 9.0% D5, 10.7% D10 (P &lt; 0.0001)</td>
<td></td>
</tr>
<tr>
<td>• Notable safety outcomes</td>
<td></td>
</tr>
<tr>
<td>o SH: 7.7% PBO, 6.3% D5, 8.5% D10</td>
<td></td>
</tr>
<tr>
<td>o DKA: 0 pts (0%) PBO, 7 pts (2.6%) D5, 6 pts (2.2%) D10; 3 episodes euglycemic</td>
<td></td>
</tr>
<tr>
<td>▪ CSII: 0 pts (0%) PBO, 6 pts (6.5%) D5, 3 pts (3.3%) D10</td>
<td></td>
</tr>
</tbody>
</table>

• Conclusion: dapagliflozin associated with significant reduction in HbA1c, mean glucose, glycemic variability, time in glycemic target range, weight, and TDD, but more DKA events

**Recommendations**

1. **SGLT inhibitor summary**
   - A. Enhanced glycemic control
   - B. Decreased TDD
   - C. Reduced weight
   - D. Improved BP (particularly SBP)
   - E. Commonly associated AEs as expected
   - F. Similar hypoglycemia, including SH events
   - G. Increased risk of DKA, particularly with CSII
   - H. No long-term CV or renal outcomes

2. **Recommendation**
   - A. Consider dapagliflozin or sotagliflozin in inadequately controlled T1DM as adjunct to insulin in adherent, non-elderly adults preferably on MDI with high health literacy, willing to undergo extensive education and perform home ketone monitoring
   - B. Caution with adults using CSII
   - C. Alternatively, could initiate if inadequate glycemic control and adult unwilling to titrate insulin secondary to weight concerns
   - D. Reduce TDD by no more than 20% at time of initiation and titrate, as necessary
   - E. Avoid if age < 18 y.o. or ≥ 65 y.o.; BMI < 18.5 kg/m²; hx of DKA, GMI, or UTI; serious CV, renal, or hepatic comorbidities; hx of pancreatitis or pancreatectomy; and initiating for sole purpose of CV or renal benefit