Where Do SGLT2 Inhibitors Fit in the Spectrum of Treatment of T2DM?

Note: This is a downloadable version of a web-based presentation. Program interactivity only applies when viewing the activity online.

FACULTY

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Educational Objectives:

After completion of this activity, participants should be better able to:
- Identify key components of renal glucose handling and the contribution of the kidney to glucose homeostasis
- Describe the pharmacology and rationale for the use of SGLT2 inhibitors in T2DM and how they differ from other classes of antihyperglycemic medications
- Review observational and clinical trials regarding the efficacy and safety of SGLT2 inhibitors and explore potential advantages and disadvantages of their use in patients with T2DM

Introduction

Diabetes mellitus is a debilitating and burdensome disease that currently affects nearly 26 million persons in United States, more than 8% of the population.\(^1,2\) Patients with type 2 diabetes mellitus (T2DM) represent 90%-95% of these cases. The number of diagnosed cases of diabetes has been increasing over the past two decades, and the Centers for Disease Control and Prevention (CDC) projects that up to 1 in 3 adults in the United States could have diabetes by the year 2050 if these trends continue.\(^2\)

Persistent hyperglycemia in T2DM is associated with microvascular and macrovascular complications as well as progression of the underlying disease. Hyperglycemia in T2DM is secondary to a combination of underlying pathophysiologic processes, which include insulin resistance, progressive \(\beta\)-cell dysfunction, hypersecretion of glucagon, accelerated gastric emptying, an impaired incretin effect, and amylin deficiency. A wide range of therapies currently are available to treat underlying abnormalities, including metformin, insulin, sulfonylureas, non-sulfonylurea secretagogues, thiazolidinediones, incretin-based therapies, alpha-glucosidase inhibitors, and amylinomimetics (eg, pramlintide). However, only about half of treated T2DM patients achieve optimal glycemic control, and even fewer sustain it. Failure to reach and maintain target goals appears to be related to progression of underlying disease, therapeutic inertia in clinical practice, and therapy-limiting adverse effects of these agents.

Newer pharmacologic agents are needed, especially those not relying on insulin action. The kidneys play a vital role in maintaining normal glucose homeostasis, but this process is disturbed in patients with T2DM. Thus, pharmacologic agents targeting the altered renal response in patients with T2DM are an attractive therapeutic intervention.
The Kidneys and Glucose Homeostasis

Polling Question 2

Which of the following statements about sodium-glucose cotransporters (SGLTs) is true?

- The primary role of SGLT2 is active transport of glucose from the intestine
- SGLT1 is responsible for most of the renal reabsorption of glucose
- SGLTs facilitate passive transport of glucose across the brush-border membrane of proximal renal tubules
- SGLT2 is responsible for most of the renal reabsorption of glucose

SGLT2 is responsible for most of the renal reabsorption of glucose.

Sodium-glucose cotransporters (SGLT) are unique and differ from passive glucose transporters because they actively transport glucose across brush-border membranes. Found mainly in the S1 segment of the proximal tubule, SGLT2 actively transports 90% of filtered glucose into the tubule cells.

In healthy individuals, plasma glucose levels are maintained within a narrow range to ensure delivery of adequate amounts of energy to the brain (initially) and then to other organs. The body utilizes approximately 250 g of glucose daily, of which 180 g is derived from diet (ie, a normal Western diet). The difference between the amount of glucose obtained from food and the amount utilized is bridged by stored glucose and gluconeogenesis in the liver and to a lesser extent the kidneys (Figure 1). The kidneys contribute greatly to glucose homeostasis by controlling glucose filtration and reabsorption. Under normal circumstances (plasma glucose approximately 100 mg/dL), approximately 180 g of glucose is freely filtered from plasma by the glomeruli each day, and virtually all of this is reabsorbed in the renal tubules; no glucose appears in urine, attributed to the presence of glucose transporters in the proximal tubule.
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Figure 1. The Kidneys Play an Important Role in the Handling of Glucose

Glucose Transport and Metabolism in a Non-diabetic Individual

- Total glucose in body ~ 450 g
- Glucose utilization ~ 250 g/day
  - Brain ~ 125 g/day
  - Rest of body ~ 125 g/day
- Glucose in diet ~ 180 g/day
- Glucose production (gluconeogenesis + glycogenolysis) ~ 70 g/day
- Renal glucose filtration and reabsorption ~ 180 g/day

Polling Question 2

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SGLT2 is responsible for most of the renal reabsorption of glucose. Sodium-glucose cotransporters (SGLT) are unique and differ from passive glucose transporters because they actively transport glucose across brush-border membranes. Found mainly in the S1 segment of the proximal tubule, SGLT2 actively transports 90% of filtered glucose into the tubule cells.

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Glucose is a polar compound and is unable to permeate cell membranes. Absorption of glucose across the small intestine, reabsorption in renal tubules, transport across the blood-brain barrier, and uptake and release by all cells in the body are accomplished by two gene families of glucose transporters – the facilitative glucose transporters (GLUTs) and the sodium-glucose cotransporters (SGLTs). Glucose transporters (GLUTs) are expressed in every cell of the body. They work along the glucose gradient and are responsible for passive transport of glucose at cell membranes. The SGLTs actively transport glucose (against a concentration gradient) across the brush-border membrane of the proximal renal tubules and in the intestinal epithelium by a sodium-dependent transport process. Coordinated functions of sodium/potassium ATPase and SGLTs are required to mediate both intestinal and renal reabsorption of glucose. In this process, sodium and glucose are co-transported into cells via the sodium gradient produced by the Na+/K+ ATPase pump at the basolateral cell membranes.

Although six SGLTs have been identified on genetic analysis, only two have been well characterized in humans: SGLT1 and SGLT2. Comparative features of these two SGLTs are shown in Figure 2. SGLT2 is found primarily in the brush-border membrane of the convoluted S1 segment of the proximal tubule and accounts for most of the renal reabsorption of glucose (90%) (Figure 3). Residing in the distal straight S3 segment of the proximal tubule, SGLT1 is responsible for reabsorption of the remaining 10%. SGLT1 is found mainly in the intestine, and its central role is active transport of dietary glucose.
Figure 4 is a more specific depiction of glucose transport mechanisms across renal proximal tubule cells, showing active luminal transport mediated by SGLT2 in the S1 segment and SGLT1 in the S3 segment, coupled to sodium transport. Once glucose is inside the proximal tubular cell, GLUT2 and GLUT1 facilitate its exit across the basolateral cell membrane and into the interstitial fluid where it is picked up by the peritubular capillary.7,10
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Figure 4. Glucose Transport in Tubular Epithelial Cells

Polling Question 3

How does renal glucose handling differ in T2DM compared to healthy subjects?

- The rate of glucose reabsorption is reduced
- There is evidence of reduced transport activity of SGLT2 and GLUT2 in animal models
- The maximum reabsorptive/transport capacity ($T_m$) for glucose is increased in the diabetic kidney
- The $T_m$ for glucose is reduced in the diabetic kidney, exacerbating hyperglycemia

The maximum reabsorptive/transport capacity ($T_m$) for glucose is increased in the diabetic kidney.

In patients with T2DM, the $T_m$ for glucose is increased, which increases glucose reabsorption. The contribution made by such increased reabsorption towards the worsening of hyperglycemia is unclear but under investigation.

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The filtered load of glucose by the kidneys is the product of plasma glucose multiplied by the glomerular filtration rate (GFR); the filtered load of glucose increases linearly with rising plasma glucose levels. The proximal renal tubule has a maximum reabsorptive capacity or transport maximum ($T_m$) for glucose. This varies between individuals, but on average it is about 375 mg/min. The $T_m$ typically is not reached in the healthy individual, and all filtered glucose is reabsorbed and returned to the circulation, conserving this energy source for the brain. This process usually is maintained at plasma glucose levels up to 200 mg/dL. At plasma glucose levels of 200-400 mg/dL, the $T_m$ is exceeded, with resultant glycosuria. There is variance in the threshold glucose levels required to overcome the $T_m$, related in part to heterogeneity in the $T_m$ for individual nephrons, glomerulotubular imbalance, or both.

The adaptation of SGLTs to chronic hyperglycemia has been a focus of investigation over the past two decades. In contrast to the beneficial renal conservation of glucose in nondiabetic subjects, this process appears maladaptive in type 1 and type 2 diabetes. The kidneys of diabetic patients appear to have an increased $T_m$ for glucose, which has the propensity to minimize glycosuria and exacerbate hyperglycemia and glucotoxicity (worsening of insulin resistance and beta-cell dysfunction in the presence of chronic hyperglycemia). Studies in animal models of diabetes have demonstrated an increased rate of proximal-tubular glucose reabsorption, related to increased gene expression and activity of both SGLT2 and GLUT2. An increase in messenger RNA (mRNA), protein expression, and transport activity of SGLT2 and GLUT2 also have been observed in cultured renal proximal tubule cells from patients with T2DM.

The $T_m$ for glucose has not been systematically examined in patients with T2DM. The contribution of increased glucose reabsorption to clinical exacerbation of hyperglycemia in T2DM patients is the focus of current investigations. An increased $T_m$ in type 1 diabetes has been demonstrated.

Based on these data, it seems that the kidneys contribute to the pathophysiologic process of hyperglycemia in patients with diabetes. Thus, selective inhibition of SGLT2 has been pursued as a rational therapeutic option in T2DM. Use of SGLT2 inhibitors in animal models and T2DM patients has improved hyperglycemia. Inhibition of SGLT1 has not been a focus of T2DM therapy because it only accounts for 10% of the glucose reabsorbed and preliminary studies have shown that this approach can result in glucose malabsorption and diarrhea.
Preclinical and Clinical Use of SGLT2 Inhibitors

Polling Question 4

Clinical studies in patients with T2DM have shown that treatment with the SGLT2 inhibitors:
- Increases urinary glucose excretion, lowers the A1C by 0.8%-0.9%, and reduces body weight and blood pressure
- Reduces postprandial plasma glucose levels, with A1C reductions of 0.5%
- Reduces hyperglycemia and urinary glucose excretion and is weight-neutral
- As add-on therapy to metformin was similar in efficacy to add-on glipizide, with similar reductions in body weight

Increases urinary glucose excretion, lowers the A1C by 0.8%-0.9%, and reduces body weight and blood pressure.

These effects have been observed consistently in phase 2-3 studies, without significant hypoglycemia. Weight loss has averaged 2-3 kg, with blood-pressure reductions of approximately 4/2-3 mm Hg. Significant decreases in postprandial plasma glucose and fasting blood glucose levels also have been observed. Efficacy as add-on therapy has been similar to glipizide, with less hypoglycemia; weight loss occurred with dapagliflozin compared to weight gain with glipizide.

Phlorizin, a nonselective inhibitor of SGLT1 and SGLT2, provided proof-of-concept for SGLT inhibition in animal models of diabetes by significantly increasing glycosuria, normalizing plasma glucose levels, and reversing insulin resistance; the latter effect appeared related to reversal of glucotoxicity. However, the nonselectivity of this agent (ie, also causing malabsorption of glucose and galactose from the small intestine) and its low oral bioavailability precluded further development.

Other animal studies have also shown that reduction of the glucotoxic effects of hyperglycemia with selective or nonselective SGLT2 inhibitors, including dapagliflozin, can improve insulin sensitivity and preserve or improve beta-cell function. Improvement of hyperglycemia with T-1095, which has a 30-fold greater selectivity for SGLT2 than SGLT1, has been associated with a significant increases in first-phase insulin secretion, and significant increases in fasting plasma insulin and the area under the plasma insulin curve with oral glucose tolerance testing when given to diabetic animals; these data are indicative of improvement of beta-cell function. In Zucker diabetic fatty rats, Macdonald and coworkers showed that dapagliflozin prevented the continual decline in functional adaptation of pancreatic beta cells during sustained lowering of glucose levels. The clinical relevance of these preclinical data remains to be determined.

Several selective SGLT2 inhibitors, most of which are structurally related to phlorizin, are in development for oral once-daily therapy for T2DM, including dapagliflozin, empagliflozin, ipragliflozin, canagliflozin. In preclinical and clinical studies, these agents have been shown to enhance glucose excretion and reduce hyperglycemia in an insulin-independent manner.

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Dapagliflozin, a C-aryl glucoside, is the SGLT2 inhibitor that has advanced the farthest in clinical trials. This agent is 1200-fold more selective for SGLT2 than SGLT1, and has shown 30-fold greater potency in vitro than phlorizin for SGLT2. In diabetic-animal models, dapagliflozin has significantly increased glycosuria and reduced fasting blood glucose (FBG) and postprandial plasma glucose (PPG) levels; insulin sensitivity was diminished, presumably via amelioration of glucotoxicity, similar to phlorizin.

Human studies have shown that dapagliflozin is well absorbed after oral doses. Once-daily dosing has produced dose-related increases in glycosuria in ascending-dose studies (2.5-100 mg/day), with near-maximal SGLT2 inhibition for ≥ 24 hours at doses of 20-50 mg. Pharmacokinetic parameters for dapagliflozin are shown in Table 1. No pharmacokinetic interaction was observed when dapagliflozin was combined with sitagliptin, pioglitazone, metformin, or glimepiride in recent open-label, randomized, crossover studies in healthy subjects.

Phase 2 and phase 3 randomized controlled trials have demonstrated the efficacy of dapagliflozin in significantly increasing urinary glucose excretion and reducing FBG and PPG levels, glycated hemoglobin (A1C), and body weight in patients with T2DM without clinically relevant hypoglycemia. Whether given as monotherapy or as add-on therapy to metformin, a sulfonylurea (glimepiride), or insulin therapy, A1C reductions of 0.8%-0.9% from baseline were consistently observed with dapagliflozin 10 mg/day (Figure 5), accompanied by weight loss of 1.5-3.2 kg (Figure 6). Reductions in blood pressure (by 3.6-5/2-3 mmHg), high-sensitivity C-reactive protein, and serum uric acid also have been observed with dapagliflozin in the aforementioned studies, which might prove...
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to be potential beneficial ancillary effects.

Figure 5. Dapagliflozin* Adjusted Mean Change from Baseline in A1C in Phase 3 Studies (10-mg Dose)

**P = 0.0001**

* Non-inferior mean difference, 0.0%; 95% CI -0.11% to 0.11%
In a phase 3, direct, head-to-head comparison over 1 year, add-on therapy with dapagliflozin ≤ 10 mg/day was noninferior to add-on glipizide ≤ 20 mg/day in improving A1C in T2DM patients inadequately controlled on metformin monotherapy (N=814). Weight loss was seen with dapagliflozin compared to weight gain with glipizide (Figure 6, H2H bars). The proportion of patients experiencing hypoglycemia was significantly lower with dapagliflozin (3.5% vs 40.8%). Two-year results of this study, with a one-time up-titration of dose allowed in the second year, found that there was sustained glycemic efficacy/weight loss with dapagliflozin and a similar low risk of hypoglycemia vs glipizide. Dapagliflozin currently is under review at the US Food and Drug Administration (FDA). Final action is expected in early to mid 2012. In January 2012, the FDA requested further data to assess the benefit-risk profile of dapagliflozin. Primary concerns of the FDA pertained to potential risks of breast and bladder cancer as well as potential liver and kidney risks, especially in the elderly. Adverse-effect data for dapagliflozin and other selective SGLT2 inhibitors from available clinical studies are discussed in a subsequent section of this activity.
At present, studies of other once-daily selective SGLT2 inhibitors are more limited. However, beneficial changes in T2DM patients have been similar to those observed with dapagliflozin. These are detailed briefly below.

**Empagliflozin** (BI 10773) has elicited changes in glycosuria and glycemia similar to dapagliflozin in animal models of diabetes. A 12-week, placebo-controlled, dose-finding study found significant reductions in A1C (about 0.7%) and body weight with empagliflozin 10 mg/day vs placebo when added to metformin therapy, with minimal hypoglycemia (1.1%) (Figure 7).
Canagliflozin: An increase in urinary glucose excretion and a reduction in the renal threshold for glucose, each dependent on dose, were seen with the selective SGLT2 inhibitor canagliflozin in a phase 1 study in healthy men.\textsuperscript{38} In a randomized, placebo-controlled study, the addition of canagliflozin 100-300 mg/day or 300 mg bid for 3 months to metformin therapy produced significant increases in glycosuria and reductions in A1C (-0.70 to -0.95%) and body weight (-2.5 to -3.4 kg) from baseline.\textsuperscript{39} Add-on sitagliptin 100 mg/day in this latter study was associated with a similar decrease in A1C, but weight reduction was significantly greater with canagliflozin (Figure 8). There was no increased risk of severe hypoglycemia with either canagliflozin or sitagliptin. Treatment with canagliflozin in doses of 100 mg qd and 300 mg qd is under evaluation in phase 3 studies.
Ipragliflozin (ASP1941) is another selective SGLT2 inhibitor which has produced significant dose-dependent increases in glucose excretion in healthy subjects and T2DM patients, and it has significantly lowered hyperglycemia and body weight in patients with T2DM. Changes with ipragliflozin have been similar to those seen with other selective SGLT2 inhibitors.

Ipragliflozin recently was investigated in T2DM patients with normal renal function and mild, moderate, or severe renal impairment by Veltkamp and colleagues. After single 100-mg oral doses, urinary excretion of glucose over 20 hours was substantially reduced in patients with moderate and severe renal insufficiency (estimated GFR [eGFR] 30-59 mL/min/1.73 m² and 15-29 mL/min/1.73 m², respectively) compared to patients with mild renal impairment (60-89 mL/min/1.73 m²) or normal renal function (Figure 9).
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Figure 9. Ipragliflozin* in Renal Impairment – 100-mg Single Dose

Following a single oral dose of ipragliflozin (IPRA) 100 mg in healthy subjects (HS) and T2DM patients with normal renal function (NRF), mild, moderate, or severe renal impairment (RI) (eGFR ≥90, 60-89, 30-59, and 15-29 mL/min/1.73 m², respectively) (n=8 per group):

- IPRA exposure ↑ ~50% in T2DM patients with moderate and severe RI
- t½ of IPRA similar in all T2DM groups (~20 h)
- UGE ↓ in T2DM patients with moderate or severe RI (see figure)

UGE, urinary glucose excretion


*ipragliflozin is not FDA approved

Polling Question 6

Which of the following statements regarding clinical adverse effects of selective SGLT2 inhibitors is true?

- Urinary tract infections (UTIs) occur more often than genital infections
- Canagliflozin has been associated with a higher incidence of urinary tract infections than dapagliflozin
- Hypoglycemia risk is minimal
- GI adverse effects are relatively common

Hypoglycemia risk is minimal.
In most clinical trials, the frequency of hypoglycemia has not exceeded that of placebo. Genital infections and UTIs also have been reported more frequently in patients taking selective SGLT2 inhibitors than placebo.

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All of the selective SGLT2 inhibitors mentioned above have been generally well tolerated in patients with T2DM. GI adverse effects have been minimal. Hypoglycemia has not occurred more frequently than with placebo in most phase 2 or phase 3 studies, and when observed, the incidence has been low (< 2% or 3%). 27-29,37,39,40 Genital infections and UTIs have tended to occur more often with selective SGLT2 inhibitors than placebo. 32,37,39,40,44,45 For canagliflozin, UTIs did not appear more frequently than in patients given placebo in 2 studies. 39,46 However, it is inappropriate to compare rates of UTIs between clinical trials with these agents, since multiple factors may play a role in the development of UTIs. Indeed, these factors need to be studied so that the incidence of UTIs can be minimized when these drugs are used in clinical practice.

Collective data from phase 3 studies on the incidence of hypoglycemia, genital infections, and UTIs with dapagliflozin therapy (10 mg/day) are shown in Figure 10. Results of patient questioning in several 12- to 24-week placebo-controlled studies designed to specifically assess the occurrence of UTIs and genital infections associated with dapagliflozin are shown in Figure 11 and Figure 12, respectively. As can be seen, placebo-subtracted incidences of diagnosed genital infections appear more common than diagnosed UTIs.

**Figure 10. Dapagliflozin* Safety Data – Phase 3 Studies (10-mg Dose)**

<table>
<thead>
<tr>
<th></th>
<th>Genital Infection&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Urinary Tract Infection&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy 10 mg&lt;sup&gt;c&lt;/sup&gt;</td>
<td>12.9% (vs 5%)</td>
<td>5.7% (vs 8%)</td>
<td>2.9%</td>
</tr>
<tr>
<td>Add-on to MET DAPA + MET (vs PBO)</td>
<td>9% (vs 5%)</td>
<td>8% (vs 8%)</td>
<td>4% (vs 3%)</td>
</tr>
<tr>
<td>Add-on to SU DAPA + GLIM (vs PBO)</td>
<td>6.6% (vs 0.7%)</td>
<td>5.3% (vs 6.2%)</td>
<td>7.9% (vs 4.9%)</td>
</tr>
<tr>
<td>H2H Add-on to MET Trial DAPA (vs 20 mg glipizide)</td>
<td>12.3% (vs 2.7%)</td>
<td>10.8% (vs 6.4%)</td>
<td>3.5% (vs 40.8%)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Add-on to Insulin (24 wks) DAPA + insulin (vs PBO)</td>
<td>7.2% (vs 2%)</td>
<td>8.4% (vs 4.1%)</td>
<td>No Difference</td>
</tr>
<tr>
<td>Add-on to Insulin (48 wks) DAPA + insulin (vs PBO)</td>
<td>6.4%-10.7% (vs 2.5%)</td>
<td>7.9%-10.8% (vs 5.1%)</td>
<td>50.6% (vs 50.3%)</td>
</tr>
</tbody>
</table>

<sup>a</sup> These events included signs, symptoms, and other reports suggestive of genital infections
<sup>b</sup> These events included signs, symptoms, and other reports suggestive of urinary tract infections
<sup>c</sup> Not placebo controlled
<sup>d</sup> P<0.001

*Dapagliflozin is not FDA approved

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Figure 11. Dapagliflozin* – Urinary Tract Infections

In 12 randomized, placebo-controlled 12-24 week studies, patients were actively questioned at each visit in order to identify possible urinary tract infection (UTI); most events were mild to moderate; few patients discontinued or interrupted treatment as a result.

<table>
<thead>
<tr>
<th></th>
<th>PBO</th>
<th>DAPA 2.5 mg</th>
<th>DAPA 5 mg</th>
<th>DAPA 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events suggestive of UTI, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N =</td>
<td>1393</td>
<td>814</td>
<td>1145</td>
<td>1193</td>
</tr>
<tr>
<td>Total</td>
<td>4.5</td>
<td>4.2</td>
<td>7.3</td>
<td>6.5</td>
</tr>
<tr>
<td>Clinically diagnosed UTI, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3.7</td>
<td>3.6</td>
<td>5.7</td>
<td>4.3</td>
</tr>
<tr>
<td>Women</td>
<td>6.6</td>
<td>5.8</td>
<td>9.6</td>
<td>7.7</td>
</tr>
<tr>
<td>Men</td>
<td>1.0</td>
<td>1.4</td>
<td>1.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
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</table>


Figure 12. Dapagliflozin* – Genital Infections

In 12 randomized, placebo-controlled 12-24 week studies, patients were actively questioned at each visit in order to identify possible genital infections; most events were mild to moderate; the majority of treated patients responded to a single course of therapy.

<table>
<thead>
<tr>
<th></th>
<th>PBO</th>
<th>DAPA 2.5 mg</th>
<th>DAPA 5 mg</th>
<th>DAPA 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events suggestive of genital infection, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N =</td>
<td>1393</td>
<td>814</td>
<td>1145</td>
<td>1193</td>
</tr>
<tr>
<td>Total</td>
<td>2.1</td>
<td>5.8</td>
<td>7.0</td>
<td>7.0</td>
</tr>
<tr>
<td>Diagnosed genital infection, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>0.9</td>
<td>4.1</td>
<td>5.7</td>
<td>4.8</td>
</tr>
<tr>
<td>Women</td>
<td>1.5</td>
<td>6.8</td>
<td>8.4</td>
<td>6.9</td>
</tr>
<tr>
<td>Men</td>
<td>0.3</td>
<td>2.4</td>
<td>2.8</td>
<td>2.7</td>
</tr>
</tbody>
</table>

Bladder and breast cancer have been observed rarely in patients receiving dapagliflozin.\textsuperscript{47,48} Analysis of data from published and unpublished trials has revealed 9 cases of breast cancer and 9 cases of bladder cancer among 5478 total patients treated with the drug compared to 1 case of each type of cancer in 3156 control patients.\textsuperscript{47} A causal relationship to dapagliflozin is unclear.

Evidence for specific drugs affecting cancer risk is limited. T2DM has been associated with an increased risk of some cancers, including bladder and breast cancer.\textsuperscript{49} A consensus report from the American Diabetes Association (ADA) and American Cancer Society suggests that cancer risk should not be a major factor in choosing between available therapies for T2DM in the average patient.\textsuperscript{49} Patients with a very high risk for cancer occurrence or recurrence may require more careful consideration.

**Polling Question 7**

**What will be the place in therapy of SGLT2 inhibitors in the treatment of T2DM?**

- First-line therapy in patients with renal impairment to enhance glycosuria
- Add-on therapy to any other antidiabetic agent, except insulin, in patients with good renal function
- First-line treatment for individuals with prediabetes, owing to the potential of these agents to reduce glucotoxicity
- \textbf{Place in therapy is yet to be determined}

\textbf{Place in therapy is yet to be determined.}

The ultimate place in therapy of selective SGLT2 inhibitors will depend on results of ongoing and future clinical trials, particularly direct comparisons with other antidiabetic agents. However, the non-insulin mechanism of action of selective SGLT2 inhibitors and their favorable characteristics support their use as add-on therapy in combination with any currently used medication, including insulin, as long as renal function is adequate.

Characteristics of currently available therapies for T2DM are shown in Figure 13 and Figure 14. All therapies have adverse effects, which can limit their use, lead to nonadherence, or adversely affect the health of the patient. Moderate weight loss may improve insulin resistance, glycemia, and blood pressure in patients with T2DM and is recommended in overweight or obese individuals; however, weight gain is an adverse effect of insulin as well as many non-insulin antidiabetic medications, including sulfonylureas, glinides, and thiazolidinediones (TZDs).\textsuperscript{50-52}
### Figure 13. T2DM: Non-Insulin Therapeutic Landscape: 2011

<table>
<thead>
<tr>
<th>Agent</th>
<th>Examples</th>
<th>Mechanism</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>glyburide, glipizide,</td>
<td>Closes Kᵢ₅₅ channels</td>
<td>↑ Pancreatic insulin secretion</td>
</tr>
<tr>
<td></td>
<td>glimepiride</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Glinides”</td>
<td>repaglinide, nateglinide</td>
<td>Closes Kᵢ₅₅ channels</td>
<td>↑ Pancreatic insulin secretion</td>
</tr>
<tr>
<td>Biguanides</td>
<td>metformin</td>
<td>activates AMP kinase</td>
<td>↓ Hepatic glucose production</td>
</tr>
<tr>
<td>TZDs</td>
<td>rosiglitazone, pioglitazone</td>
<td>activates PPAR-γ</td>
<td>↑ Peripheral insulin sensitivity</td>
</tr>
<tr>
<td>Alpha-GIs</td>
<td>acarbose, miglitol</td>
<td>inhibits small bowel alpha-GI enzymes</td>
<td>↓ Intestinal carbohydrate absorption</td>
</tr>
<tr>
<td>Amylinomiectins</td>
<td>pramlintide</td>
<td>activates amylin receptors</td>
<td>↓ Pancreatic glucagon secretion, delays gastric emptying, ↑ satiety</td>
</tr>
<tr>
<td>GLP-1R agonists</td>
<td>exenatide, liraglutide</td>
<td>activates GLP-1 receptors</td>
<td>↑ Pancreatic insulin secretion, ↓ glucagon secretion, delays gastric emptying, ↑ satiety</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>sitagliptin, saxagliptin, linagliptin</td>
<td>inhibits DPP-4 to ↑ endogenous incretin hormones</td>
<td>↑ Pancreatic insulin secretion, ↑ pancreatic glucagon secretion</td>
</tr>
<tr>
<td>Bile-acid sequestrants</td>
<td>colesevelam</td>
<td>binds bile-acid cholesterol</td>
<td></td>
</tr>
<tr>
<td>D2 agonists</td>
<td>bromocriptine</td>
<td>activates dopaminergic receptors</td>
<td></td>
</tr>
</tbody>
</table>

### Figure 14. T2DM: Non-Insulin Therapeutic Landscape: 2011

<table>
<thead>
<tr>
<th>Agent</th>
<th>↓A₁c</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>1%-2%</td>
<td>↓Microvascular risk, inexpensive</td>
<td>Hypoglycemia, wt gain, beta-cell exhaustion</td>
</tr>
<tr>
<td>“Glinides”</td>
<td>1%-1.5%</td>
<td>↓postprandial plasma glucose (PPG)</td>
<td>Hypoglycemia, wt gain, beta-cell exhaustion, dose frequency (tid), expensive</td>
</tr>
<tr>
<td>Biguanides</td>
<td>1%-2%</td>
<td>Wt loss, no hypoglycemia, ↓ CVD, ↑ satiety, inexpensive</td>
<td>GI adverse effects (AEs), lactic acidosis, B12-deficiency (long-term use)</td>
</tr>
<tr>
<td>TZDs</td>
<td>1%-1.5%</td>
<td>No hypoglycemia, beta-cell preservation,*</td>
<td>Wt gain, edema, heart failure, bone fractures, ↑ CVD (ros), expensive</td>
</tr>
<tr>
<td>Alpha-GIs</td>
<td>0.5%-1%</td>
<td>↓PPG, ↑ CVD, moderate expense</td>
<td>GI AEs, dose frequency (tid), rare hepatic failure (acarbose)</td>
</tr>
<tr>
<td>Amylinomiectins</td>
<td>0.5%</td>
<td>Wt loss, ↓ PPG</td>
<td>GI AEs, dose frequency (tid), infections, expensive</td>
</tr>
<tr>
<td>GLP-1R agonists</td>
<td>1%</td>
<td>Wt loss, beta-cell preservation, ↓ CV benefits (ira &gt; exen) ↓ FBG, but not PPG</td>
<td>GI AEs, ? pancreatitis, renal failure, infections, expensive</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>0.6%-0.8%</td>
<td>No hypoglycemia, wt-neutral, oral incretin therapy</td>
<td>Uticaria (angiowodem, ? Pancreatitis (sitagliptin and linagliptin), expensive</td>
</tr>
<tr>
<td>Bile-acid sequestrants</td>
<td>0.5%</td>
<td>No hypoglycemia, ↓ LDL-C</td>
<td>GI AEs, ↑ TGs, expensive</td>
</tr>
<tr>
<td>D2 agonists</td>
<td>0.5%</td>
<td>No hypoglycemia</td>
<td>Nausea, vomiting, dizziness, expensive</td>
</tr>
</tbody>
</table>

* Rosiglitazone did not arrest the long-term decline in beta-cell function in the ADOPT study.

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Where Do SGLT2 Inhibitors Fit in the Spectrum of Treatment of T2DM?

The UK Prospective Diabetes Study (UKPDS) 34 found that overweight T2DM patients initially randomized to insulin progressively gained weight over a follow-up period of 13 years (mean up to 8 kg). Weight gain also was significant with glyburide (+ 4 kg), but least with metformin (+ 1-2 kg, which was similar to a control group of mainly diet). Fasting plasma insulin levels decreased significantly in the metformin group throughout the follow-up period.

In a more recent randomized controlled trial, A Diabetes Outcome Progression Trial (ADOPT), mean change in body weight from baseline over 5 years was + 4.8 kg with rosiglitazone and + 1.6 kg with glyburide, but −2.9 kg with metformin, all given as monotherapy. Weight gain with glyburide occurred during the first year and then remained stable (Figure 15).

The favorable effect of metformin on body weight may be due in part to its adverse gastrointestinal (GI) effects, such as nausea, diarrhea, and abdominal pain. However, the latter effects can lead to nonadherence unless adjustments are made (eg, taking the medication with food, dividing doses, starting with a low dose).

Adverse effects of other current therapies that can interrupt therapy and lead to poorer outcomes are hypoglycemia with sulfonylureas or glinides, adverse cardiovascular effects or peripheral edema with TZDs, and GI upset with exenatide or liraglutide or alpha-glucosidase inhibitors (see Figures 13 and 14, above). Another disadvantage of current therapies is their inability to maintain glycemic control over the long term. Other UKPDS studies (UKPDS 28 and 49) and ADOPT have demonstrated that current oral antidiabetic therapies, including drug combinations, eventually will fail (Table 2). Although some T2DM treatment failures could be attributed to therapeutic inertia, the inexorable
progression of underlying beta-cell dysfunction likely plays a major role.\textsuperscript{7,16} It is unclear if the incretin mimetics will ultimately show benefit in preserving beta-cell health, as has been shown in vitro.

<table>
<thead>
<tr>
<th>Table 2. Current Therapy: Failure to Maintain Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UKPDS 49\textsuperscript{1}</strong></td>
</tr>
<tr>
<td>- Monotherapy with either metformin, a sulfonylurea (glyburide, chlorpropamide), or insulin in newly diagnosed T2DM patients increased the number of those achieving A1C levels &lt;7% (goal) compared to diet alone</td>
</tr>
<tr>
<td>- This waned with time, and only about half of these patients maintained goal at 3 years</td>
</tr>
<tr>
<td>- Only 25% remained controlled after 9 years of therapy</td>
</tr>
<tr>
<td>- These data indicate that addition of a second or third agent would be required to improve control over time</td>
</tr>
</tbody>
</table>

| **UKPDS 28\textsuperscript{2}** |
| - Combination therapy also has fallen short |
| - Only one-third of newly diagnosed T2DM patients receiving metformin combined with a sulfonylurea maintained control (A1C <7%) after 3 years |

| **ADOPT\textsuperscript{3}** |
| - In recently diagnosed T2DM patients, initial therapy with rosiglitazone initially slowed the rate of loss of beta-cell function, improved insulin sensitivity, and prolonged the time to treatment failure compared to glyburide or metformin |
| - However, A1C data reveal that rosiglitazone was only marginally more effective than metformin at 4 years and rosiglitazone did not prevent rises in A1C levels over time (increasing from about 5.6% at year 1 to 7% at year 4) |
| - Although TZDs do have some beta-cell preserving effects, results of ADOPT suggest that rosiglitazone does not arrest the long-term decline in beta-cell function.\textsuperscript{4,5} |

Advantages and disadvantages of selective SGLT2 inhibitors are shown in Table 3. The ultimate place in therapy of these agent has yet to be determined, pending further results of clinical trials assessing their efficacy and safety in various types of T2DM patients (eg, newly diagnosed, poorly controlled) and head-to-head comparisons with other agents. However, because of the non-insulin mechanism of action of SGLT2 inhibitors, the potential of these agents as an add-on therapy option in combination with any other antidiabetic agents (including insulin) in inadequately controlled patients with an eGFR ≥ 60 mL/min/1.73 m\textsuperscript{2} is of great interest. Some investigators also suggest a role for SGLT2 inhibitors as monotherapy in patients with newly diagnosed T2DM and in individuals with prediabetes, since glucotoxicity may contribute to beta-cell dysfunction in the setting of impaired glucose tolerance or fasting glucose.\textsuperscript{9} Further studies will determine the potential role of SGLT2 inhibitors in these indications.
Upon review of the most recent consensus algorithms for optimizing glycemic control in T2DM from the American Association of Clinical Endocrinologists (AACE)\textsuperscript{52} and the ADA/European Association for the Study of Diabetes (EASD)\textsuperscript{31} (Figure 16 and Figure 17), it is evident that a selective SGLT2 inhibitor might serve as an option in dual or triple therapy drug regimens for patients adhering to lifestyle changes but not achieving goal. Addition of an SGLT2 inhibitor in patients who remain uncontrolled on insulin may be particularly useful, since there are few options for patients in this high-risk group.
Where Do SGLT2 Inhibitors Fit in the Spectrum of Treatment of T2DM?

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It should be noted that the 2008 ADA/EASD consensus algorithm is being updated by combined efforts of both the ADA and EASD. These new guidelines will be published in early 2012 and will be less prescriptive than prior algorithms and present both the advantages and disadvantages of available therapies.

Metformin is the sole initial pharmacologic agent listed for T2DM at diagnosis in the 2008 ADA/EASD guidelines, and one of the most attractive uses of a selective SGLT2 inhibitor would be in combination with metformin in early T2DM to enhance the glucose-lowering effects and weight loss afforded by metformin, perhaps as a first-line therapy. SGLT2 inhibitors also might be positioned as first-line monotherapy pending further studies and direct comparisons. Individual patient characteristics can further dictate the place in therapy of selective SGLT2 inhibitors. Examples of good candidates are shown in Table 4.

### Table 4. Examples of Good Candidates for Treatment with an SGLT2 Inhibitor

<table>
<thead>
<tr>
<th>Condition</th>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive T2DM patients</td>
<td>Although effects on blood pressure are relatively modest, add-on therapy in hypertensive patients may augment antihypertensive effects of angiotensin-receptor blockers or angiotensin-converting enzyme inhibitors, one of which should be included in regimens for managing hypertension in T2DM</td>
</tr>
<tr>
<td>Overweight or obese T2DM patients</td>
<td>Weight loss with SGLT2 inhibitors can enhance benefits of lifestyle changes and weight loss with other oral agents (eg, metformin, GLP-1 analogs)</td>
</tr>
<tr>
<td>The T2DM patient with frequent hypoglycemic episodes and weight gain on another antidiabetic agent (eg, glipizide)</td>
<td>A switch to an SGLT2 inhibitor could be beneficial by promoting weight loss and decreasing hypoglycemic excursions</td>
</tr>
<tr>
<td>The T2DM patient experiencing therapy-limiting adverse GI effects on another antidiabetic agent (eg, exenatide)</td>
<td>A switch to an SGLT2 inhibitor could minimize GI effects and elicit similar A1C reductions</td>
</tr>
<tr>
<td>The T2DM patient with poor control of PPG with another antidiabetic agent (eg, repaglinide, acarbose)</td>
<td>A switch to an SGLT2 inhibitor could eliminate or decrease PPG excursions</td>
</tr>
<tr>
<td>Waning clinical efficacy of single or combination antidiabetic agents over time</td>
<td>Adding an SGLT2 inhibitor, or switching from one agent in a combination to an SGLT2 inhibitor, may enhance clinical efficacy</td>
</tr>
</tbody>
</table>

Case Presentation: First- and Second-Line Treatment of T2DM

A 56-year-old Caucasian man presents to you for follow-up. Six months earlier, the patient was found to have a FBG of 138 mg/dL at his annual physical exam. He has a 10-year history of hypertension and dyslipidemia, controlled by lisinopril 20 mg bid, amlodipine 10 mg/day, and simvastatin 40 mg/day. Family history revealed diagnosed thyroid cancer in his living mother and hypothyroidism in his sister. Blood pressure at his annual physical was 118/76 mmHg, and lipid profile results included total cholesterol 190 mg/dL, triglycerides 123 mg/mL, LDL-C 95 mg/dL, and HDL-C 43 mg/dL. Renal and hepatic function tests were normal.
On follow-up blood tests 2 weeks after his annual physical, FBG was 132 mg/dL and A1C was 6.8%, confirming the diagnosis of T2DM. At the time of diagnosis, his weight was 243 pounds (BMI, 33.1 kg/m²), and the patient felt he did not have T2DM but rather that the tests were wrong or related to his being overweight. At that visit, you informed the patient and his wife that T2DM was a progressive disease, but that the patient could delay initiation of medication if he changed his diet and increased his activity level. You referred him to a dietician and a diabetes self-management education (DSME) class; however, the patient acknowledged neither. The patient’s concerned wife immediately began restricting food portions and eliminating foods containing sugar. They took walks in the evenings for several months, but discontinued this activity when the weather turned colder in the winter. The patient then entered a period of noncompliance.

At this follow-up visit, the patient is surprised to learn that his A1C has increased to 7.2% and he had gained 8 pounds. Blood pressure also was slightly increased (128/84 mmHg) and his lipid profile reveals total cholesterol 202 mg/dL, triglycerides 160 mg/dL, LDL-C 105 mg/dL, and HDL-C 42 mg/dL. He adheres to your repeat referrals to a DMSE program and individual sessions with a dietician for medical nutrition therapy (MNT). He also is started on metformin 500 mg bid, which is increased to 1 g bid, but he experiences abdominal discomfort and diarrhea on the higher dose, necessitating dose reduction to 1500 mg/day.
Renal-function tests probably should have been repeated in this patient at this visit, and should be ongoing (at least annually). Maintaining kidney function for as long as possible is an important goal for every patient with diabetes. Persistent microalbuminuria (30-299 mg/24 hrs) is a marker for subsequent development of nephropathy in patients with T2DM, as well as an increased risk for cardiovascular disease. Intensive glucose control will not improve kidney function if compromise is already present, but optimizing control of glucose levels and blood pressure before renal damage occurs can delay the onset of nephropathy or slow its progression.

Monitoring of renal function is essential for early detection and management of nephropathy, to assess the efficacy of preventive treatment measures, and for evaluation of its progression. Testing for urinary albumin excretion (with spot urine-to-albumin ratio) is recommended annually in all T2DM patients, starting at the time of diagnosis. Monitoring serum creatinine also is recommended annually in all T2DM patients, regardless of degree of albumin excretion, with calculation of the eGFR to determine level of chronic kidney disease (CKD) (Table 5). An angiotensin receptor blocker or angiotensin-converting enzyme inhibitor is indicated in patients with micro- or macro-albuminuria.

### Table 5. CKD Stages

<table>
<thead>
<tr>
<th>Stage</th>
<th>eGFR (mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥ 90 (normal renal function)</td>
</tr>
<tr>
<td>2</td>
<td>60-89 (mild renal impairment)</td>
</tr>
<tr>
<td>3</td>
<td>30-59 (moderate renal impairment)</td>
</tr>
<tr>
<td>4</td>
<td>15-29 (severe renal impairment)</td>
</tr>
<tr>
<td>5</td>
<td>&lt; 15 or on dialysis (renal failure)</td>
</tr>
</tbody>
</table>

The GFR is the best overall index of kidney function. The Kidney Disease Outcomes Quality Initiative (KDOQI) clinical guidelines from the National Kidney Foundation (NKF) recommend use of the Modification of Diet in Renal Disease (MDRD) Study equation to estimate GFR. A rapid eGFR calculator is available from the National Kidney Disease Education Program (NKDEP) at http://www.nkdep.nih.gov/professionals/gfr_calculators/idms_con.htm.

Renal function also should play a role in the treatment decision-making process, since many
antidiabetic medications require dose reduction in the face of renal impairment or should be avoided. In addition, some medications can adversely affect renal function and require periodic monitoring. Examples of these are shown in Table 6. Use of metformin in patients with RI has been somewhat controversial. The drug typically has been avoided in males and females with serum creatinine of ≥ 1.5 and ≥ 1.4, respectively, due the risk of lactic acidosis. However, using eGFR is preferred to serum creatinine measurement for monitoring and adjusting treatment in clinical practice. A recent review suggests that metformin may be used with caution when the eGFR is < 60 mL/min/1.73 m², with a dose reduction when eGFR is < 45 mL/min/1.73 m² and discontinuance of therapy when eGFR falls to < 30 mL/min/1.73 m². For SGLT2 inhibitors specifically, preliminary data suggest that they may be ineffective in patients with an eGFR < 60 mL/min/1.73 m².

Table 6. Antidiabetic Agents and the Kidneys

| Dose Adjustment Needed in Renal Impairment | Acarbose | Avoid in patients with serum creatine (Cr) > 2 mg/dL |
| Antagonists | Exenatide | Dose adjustment not required if Cr clearance (CrCl) is 50-80 mL/min; caution when increasing dose from 5 mg to 10 mg in patients with CrCl of 30-50 mL/min and in renal transplant patients |
| | Insulin | Pharmacokinetics altered; dose should be based on clinical response |
| | Linagliptin | No dose adjustment needed |
| | Liraglutide | Can be used without dose reduction in patients with renal impairment (RI) |
| | Metformin | Lactic acidosis risk. Recent evidence suggests cautious use with eGFR between 30 and 60 mL/min/1.73 m²; avoid use if < 30 mL/min/1.73 m² |
| | Saxagliptin | Dose of 2.5 mg once daily recommended if CrCl < 50 mL/min |
| | Sitagliptin | Reduce dose to 50 mg once daily if CrCl ≥ 50.50 mL/min |
| | | Reduce to 25 mg once daily if creatinine clearance < 30 mL/min |
| Selective SGLT2 Inhibitors | | Preliminary data suggest loss of efficacy (reduced glycosuria) if eGFR falls below 60 mL/min/1.73 m² (UKD Degrade: 3) |
| Sulfonylureas | | Potential for worsening of hypoglycemia in RI, particularly in the elderly |
| | | Avoid glyburide |
| | | Glibizide dose adjustment not generally needed in mild-moderate RI |

Adverse Effect on Renal Function

GLP-1 Analogues
- Periodic monitoring for deterioration of renal function is indicated in patients receiving GLP-1 agonists and exenatide has been associated with RI and acute renal failure, at times requiring hemodialysis or kidney transplantation; these events have often occurred in patients experiencing nausea and vomiting who have preexisting kidney disease or in patients using agents with nephrotoxic potential, such as non-steroidal anti-inflammatory medications |
- Linagliptide also has been associated with acute renal failure or worsening of chronic renal failure, sometimes requiring hemodialysis; unlike exenatide, dose reductions of linagliptide are not required in patients with RI |

Where Do SGLT2 Inhibitors Fit in the Spectrum of Treatment of T2DM?

Polling Question 9

Which of the following current FDA-approved drug therapies could be added to metformin in this patient to improve glycemic control and promote loss of weight without a significant risk of hypoglycemia?

- Exenatide
- Glipizide
- Pioglitazone
- Repaglinide

Exenatide.

Exenatide, given with metformin, can enhance weight loss and further lower the A1C without inducing significant hypoglycemia.

There is no consensus among diabetes experts on what second-line therapy is best. Sulfonylureas are used frequently due to their low cost, but hypoglycemia and weight gain would be problematic in many patients, including the current case. These adverse effects also are seen with glinides. In recent years, the use of DPP-4 inhibitors as second-line therapy has increased substantially; they are well-tolerated, essentially weight-neutral, and may exert a synergistic effect with metformin. However, the ability of DPP-4 inhibitors to lower A1C and sustain significant reductions is somewhat limited, and less so than is seen with GLP-1 agonists. Adding a GLP-1 agonist to metformin would be a reasonable choice in this patient to promote weight loss and improve the A1C. Of note, however, is that GI adverse effects are relatively frequent with GLP-1 agonists and some patients may resist the injections. GI effects in this patient may be minimized by slow upward titration of dose (over 1 month for exenatide, 1 week for liraglutide).

Basal insulin is another option, but it is used mainly after combination oral therapy. The weight gain and peripheral edema seen with pioglitazone are deterrents to its use as add-on therapy to metformin. Another option is colesevelam, a bile-acid sequestrant, which can be combined with metformin, a sulfonylurea, or insulin. Colesevelam effectively lowers LDL-C (which is not required in this patient) and can provide a 0.5% further reduction in A1C. Acarbose is another option; it lowers PPG, but it is not generally well-tolerated because of GI effects (e.g., abdominal pain, flatulence).

Either an oral DPP-4 inhibitor or an injectable GLP-1 agonist would be a rational choice for add-on therapy to metformin in this patient to prevent additional weight gain or promote weight loss, respectively, and to reduce A1C. Hypoglycemia with either class of drugs should be minimal when combined with metformin. These add-on therapies are consistent with AACE and ADA/EASD.
Where Do SGLT2 Inhibitors Fit in the Spectrum of Treatment of T2DM?

When available, a selective SGLT2 inhibitor also would be a logical choice to add to metformin. The resulting reductions in blood pressure and weight, with favorable effects on A1C and no increased hypoglycemic risk, would benefit this patient.

Case Presentation – Continued

The patient continues to see you over a number of years, during which time he has periods of compliance and noncompliance, with corresponding ups and downs in his lab values and body weight. As his T2DM progresses, you adjust his diet and exercise program and help him adjust his drug therapy, based on lab results and adverse effects.

He has moved through treatment with glipizide, with some weight gain. Sitagliptin was introduced instead at that point, but glycemic control deteriorated and it was replaced by exenatide, which caused nausea and vomiting, necessitating a switch to liraglutide, which caused a rash. From liraglutide, he moved to pioglitazone, then insulin glargine, which was titrated up to 65 units. At that time, FBG was 112 mg/dL with an A1C of 7.3%. Insulin aspart was added (5-8 units with each meal) and A1C subsequently fell to 6.8%, but he gained 12 pounds and had occasional hypoglycemia.

Three years later, he returns to you for routine follow up. He is no longer taking insulin aspart due to recurring hypoglycemia and is now on insulin glargine 80 units at bedtime. He is also taking metformin extended-release 1 g/day, pioglitazone 15 mg/day, sitagliptin 100 mg/day, simvastatin, lisinopril, and amlodipine. His A1C is 7.4% and he would like to know if any new medications will be available for T2DM in the next 1-2 years.
In an analysis of phase 2 study data, Zhang and colleagues found dapagliflozin to be effective in both the early and late stages of T2DM. A1C lowering from baseline and urinary glucose excretion were similar in each group, and weight loss was greater in the late stages. Both groups of patients had adequate renal function. Late-stage patients were receiving aggressive treatment with insulin. This study suggests benefits of dapagliflozin on glycemia are seen in T2DM patients with early disease (eg, treatment-naïve) as well as late-stage patients on insulin. Thus, an SGLT2 inhibitor may be a rational choice in the current patient with advancing disease, as long as renal function is still normal or only mildly impaired (eGFR > 60 mL/min/1.73 m²). Renal function should be assessed in this patient prior to its use.

SGLT2-inhibition therapy might be substituted for pioglitazone in this patient's current regimen, to eliminate any further weight gain. Studies have shown a benefit in using dapagliflozin combined with insulin therapy.

However, one concern of beginning SGLT2-inhibition therapy in this particular patient is his family history of cancer. Although cancer risk with SGLT2 inhibitors will require additional long-term observation, the patient should be apprised of the available data. If he agrees to therapy when it becomes available, appropriate cancer screenings should be considered. Clinicians should follow any guidance given by the FDA on such screening when it becomes available.
Conclusion

Selective SGLT2 inhibitors differ from current pharmacologic modalities for T2DM by their mechanism to lower hyperglycemia (ie, glycosuria), which is independent of insulin action. This mechanism has enabled improved glycemic control regardless of the stage of the disease, as seen in the study by Zhang and colleagues. In animal models, SGLT2 inhibitors have augmented beta-cell function and improved insulin sensitivity by reducing glucotoxicity. Data on the efficacy of these agents in clinical trials are accumulating, and SGLT2 inhibitors may offer a welcome to addition to the therapeutic landscape for the treatment of T2DM.
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References


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