Novel Treatments for the Management of Type 2 Diabetes: Focus on SGLT2 Inhibitors

Presented as a Midday Symposium and Live Webinar at the 49th ASHP Midyear Clinical Meeting and Exhibition

Wednesday, December 10, 2014
Anaheim, California
Please be advised that this activity is being audio and/or video recorded for archival purposes and, in some cases, for repurposing of the content for enduring materials.
Novel Treatments for the Management of Type 2 Diabetes: Focus on SGLT2 Inhibitors

Agenda

11:30 a.m. – 11:35 a.m.  | Welcome and Introduction

11:35 a.m. – 12:00 p.m.  | Understanding Sodium Glucose Transporter 2 (SGLT2) Inhibition in Type 2 Diabetes: Role of the Kidney in Glucose Homeostasis  
Susan Cornell, Pharm.D., CDE, FAPhA, FAADE

12:00 p.m. – 12:25 p.m.  | Safety and Efficacy of the SGLT2 Inhibitors in Type 2 Diabetes: Examining the Evidence  
Curtis L. Triplitt, Pharm.D., CDE

12:25 p.m. – 12:50 p.m.  | Incorporating the SGLT2 Inhibitors into Practice: Role of the Pharmacist  
Susan Cornell, Pharm.D., CDE, FAPhA, FAADE and Curtis Triplitt, Pharm.D., CDE

12:50 p.m. – 1:00 p.m.  | Faculty Discussion and Audience Questions  
All Faculty

Food and beverage are no longer provided at Midday Symposia. This ASHP policy considers the varied internal policies of commercial supporters related to the Physician Payments Sunshine Act.

Faculty

Susan Cornell, Pharm.D., CDE, FAPhA, FAADE, Activity Chair
Assistant Director of Experiential Education  
Associate Professor  
Department of Pharmacy Practice  
Midwestern University Chicago College of Pharmacy  
Downers Grove, Illinois

Curtis L. Triplitt, Pharm.D., CDE
Associate Director, Diabetes Research Center, Texas Diabetes Institute  
Associate Professor, Department of Medicine, Division of Diabetes  
University of Texas Health Science Center at San Antonio  
San Antonio, Texas
Disclosure Statement

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- Susan Cornell, Pharm.D., CDE, FAPhA, FAADE, declares she has served on the advanced practitioner advisory board for AstraZeneca and Sanofi.
- Curtis Triplitt, Pharm.D., CDE, declares he has served on the speakers bureau for AstraZeneca, Boehringer Ingelheim, and Janssen Pharmaceuticals, Inc.
- All other faculty and planners report no financial relationships relevant to this activity.
Activity Overview

This educational activity will provide health care practitioners with an overview of novel treatment options for type 2 diabetes, focusing on sodium glucose co-transporter 2 (SGLT2) inhibitors. The mechanism of action and role in therapy of novel agents for the management of type 2 diabetes will be described, and the importance of including patient-specific characteristics and preferences will be discussed.

Learning Objectives

At the conclusion of this application-based educational activity, participants should be able to

- Explain the role of the kidney in glucose homeostasis and regulation.
- Describe the mechanism of action and efficacy of SGLT2 inhibitors in the management of type 2 diabetes.
- Review safety and contraindications for SGLT2 inhibitors.
- Utilize monitoring parameters for the SGLT2 inhibitors in special populations.
- Apply the pharmacist’s role in ensuring appropriate use of these novel treatment options.

Your educational opportunities related to SGLT2 inhibitors extend beyond today’s symposium…

- Available in 2015
  - A live webinar on March 12, 2015 where faculty will explore issues raised by participant questions in today’s symposium (1 hour CPE)
  - Informational podcasts featuring interviews with the faculty
  - e-Newsletters featuring tips for incorporating information from this symposium into practice, as well as updates on emerging information on this topic
  - On-demand activity based on today’s live symposium (1.5 hours of CPE, please note that individuals who claim CPE credit for the live symposium or webinar are ineligible to claim credit for the on-demand activity)

For more information and to sign up to receive e-mail updates about this educational series, visit

www.ashpadvantage.com/splt2
Continuing Education Accreditation

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This activity provides 1.5 hours (0.15 CEUs – no partial credit) of continuing pharmacy education credit (ACPE activity 0204-0000-14-709-L01-P for the live activity and ACPE activity #0204-0000-14-709-H01-P for the on-demand activity).

Complete instructions for receiving your statement of continuing pharmacy education credit online are on the next page.

Webinar Information

Visit http://www.ashpadvantage.com/go/sglt2/webinar to find
• Webinar registration link
• Group viewing information and technical requirements

ACTION REMINDER EMAIL

Have ideas about what YOU want to remember to do as a result of what you are learning in this educational session? Use the Action Reminder tool via your smart device, and you will be sent an email reminder from YOURSELF next month.

If you do not have a smart device, access the Action Reminder for this activity at www.ashpadvantage.com/go/sglt2/remindme
CPE Instructions for Pharmacists and Technicians

Per ACPE, CPE credit must be claimed **no later than 60 days** from the date of the live activity or completion of a home study activity. All ACPE-accredited activities processed on the eLearning site will be reported directly to CPE Monitor. To claim pharmacy credit, you must have your NABP e-Profile ID, birth month, and birth day. If you do not have an NABP e-Profile ID, go to www.MyCPMonitor.net for information and application. Follow these instructions to process your CPE credit for this activity.

1. Access the e-Learning site at [http://elearning.ashp.org/my-activities](http://elearning.ashp.org/my-activities)

2. If you already have an ASHP account, log in using your username and password.

   **If you do not have an ASHP account**, click on the **Register** link and follow the registration instructions. You do not have to be a member to create an account.

**For Midyear Attendees in Anaheim**

- Once logged in, select “**Conferences**” and click on the conference name under **Your Conferences**.

- Under Add Sessions enter your attendance code announced during the activity, and click Submit.

  Helpful Tip: If your code is not redeeming successfully, verify that you have clicked on the title of your conference to access the **Attendance Code** field, not the Enrollment Code field.

- Each session will be listed under **Your Sessions**. Click Claim Credit for a particular session.

- Complete any requirements for each session by clicking on the name of the activity and following the instructions.

- Click Claim Credit. See steps 3-5 below.

**For Offsite Webinar Attendees**

- Once logged in, enter the enrollment code (announced during the webinar) into the “**ENROLLMENT CODE**” box for the activity and click Redeem.
Novel Treatments for the Management of Type 2 Diabetes:
Focus on SGLT2 Inhibitors

- The title of this activity will appear in a pop-up box on your screen. Click on the Go button or the activity title.
- Complete all required elements. A green check should appear as each required element is completed. You can now claim your credit.

3. Available credit(s) will appear beneath the completed required activities. Look for your profession in the list of available credits and click the appropriate Claim button. You might have to click to see more credit options if you do not see your profession listed.

4. Review the information for the credit you are claiming. If all information appears to be correct, check the box at the bottom and click Claim. You will see a message if there are any problems claiming your credit.

5. After successfully claiming credit, you may print your statement of credit by clicking on Print. If you require a reprint of a statement of credit, you can return at any time to print a duplicate. For CPE credit for pharmacists and technicians, printed statements may not be necessary because your credit is reported directly to CPE Monitor.

NEED HELP? Contact eLearning@ashp.org

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<thead>
<tr>
<th>Date of Activity:</th>
<th>Code:</th>
<th>CPE Hours:</th>
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</thead>
<tbody>
<tr>
<td>Wednesday, December 10, 2014</td>
<td>- - - -</td>
<td>1.5</td>
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</tbody>
</table>
Novel Treatments for the Management of Type 2 Diabetes: Focus on SGLT2 Inhibitors

Susan Cornell, Pharm.D., CDE, FAPhA, FAADE, Activity Chair
Assistant Director of Experiential Education
Associate Professor
Department of Pharmacy Practice
Midwestern University Chicago College of Pharmacy
Downers Grove, Illinois

Susan Cornell, Pharm.D., CDE, FAPhA, FAADE, is Assistant Director of Experiential Education and Associate Professor, Department of Pharmacy Practice at Midwestern University Chicago College of Pharmacy in Downers Grove, Illinois. Dr. Cornell is also a certified diabetes educator and clinical pharmacy consultant, specializing in community and ambulatory care practice. Dr. Cornell has over 24 years of practice in community pharmacy where she has practiced as a clinical pharmacist, diabetes educator, and preceptor, as well as the inaugural coordinator of the American Diabetes Association (ADA)-recognized Dominick’s Pharmacy Diabetes Self-Management Education program. Dr. Cornell's current clinical practice is with the Access Community Health Network, where she trains, educates, and supervises students from the colleges of medicine, pharmacy, and health sciences as they provide diabetes education classes for patients in underserved community clinics.

Dr. Cornell received her Bachelor of Science degree in pharmacy from the University of Illinois, College of Pharmacy in 1986 and her Doctor of Pharmacy degree from Midwestern University in 2002.

Dr. Cornell recently completed her term as President of the Illinois Pharmacists Association in October 2011. She has received numerous awards and recognitions, including the 2010 Teacher of the Year Award, the 2010 American Association of Colleges of Pharmacy Student Engaged Community Service Award, and the 2005 Midwestern University Golden Apple Teaching Award. In 2008, she received fellow recognition from the American Association of Diabetes Educators (AADE) and the American Pharmacists Association. She is an active member of the ADA, as well as the AADE, where she served on the board of directors from 2004 to 2007.

Dr. Cornell has served as an invited speaker nationally and internationally on diabetes and its related conditions and is recognized as a key opinion leader in the field of diabetes education. She has contributed to many peer-reviewed print and online publications in this field.
Curtis L. Triplitt, Pharm.D., CDE
Associate Director, Diabetes Research Center, Texas Diabetes Institute
Associate Professor, Department of Medicine, Division of Diabetes
University of Texas Health Science Center at San Antonio
San Antonio, Texas

Curtis L. Triplitt, Pharm.D., CDE, is Associate Professor and Certified Diabetes Educator at the University of Texas Health Science Center at San Antonio (UTHSCSA) where he oversees many diabetes research projects. In addition, he clinically manages people with diabetes with an endocrinologist at the Texas Diabetes Institute.

Dr. Triplitt earned his Bachelor of Science degree in pharmacy from the University of Iowa and his Doctor of Pharmacy degree from the University of Texas at Austin and the Health Science Center at San Antonio. He completed a primary-care residency accredited by the American Society of Health-System Pharmacists at the William S. Middleton Veteran Administration's Hospital in Madison, Wisconsin.

Dr. Triplitt is well respected as a clinician, researcher, and author. He is an investigator in several ongoing research studies related to diabetes, and he has published several book chapters on diabetes, as well as articles in peer-reviewed journals, including Diabetes Care, Diabetes Spectrum, Expert Review of Endocrinology & Metabolism, Pharmacotherapy, and Drugs. Dr. Triplitt is currently Secretary of the Texas Diabetes Council (TDC), which is legislatively mandated to develop and implement a state plan for diabetes treatment, education, and training. The TDC’s mission is also to develop standards of care for the prevention, identification, and treatment of patients with diabetes mellitus in Texas.
Novel Treatments for the Management of Type 2 Diabetes Focus on SGLT2 Inhibitors

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Understanding Sodium Glucose Transporter 2 (SGLT2) Inhibition in Type 2 Diabetes: Role of the Kidney in Glucose Homeostasis

Susan Cornell, B.S., Pharm.D., CDE, FAPhA, FAADE
Midwestern University Chicago College of Pharmacy

It is estimated that...

- 1 in 3 babies born in 2012 will live to 100 years of age
- 1 in 3 babies born in 2000 will develop diabetes
  - 2 out of 3 in high-risk ethnic groups
- Therefore, the need for diabetes prevention and education is imperative
  - ALL healthcare professionals are needed


State of Diabetes Control

So, How are we doing?
What proportion of people with diabetes have

- Controlled BP (<130/80 mmHg)?
- LDL at the goal level (<100 mg/dL)?
- A1C at the goal level (<7%)?
- What proportion have met all three?

Survey says...

- Controlled BP (<130/80 mmHg)? 51%
- LDL at the goal level (<100 mg/dL)? 56%
- A1C at the goal level (<7%)? 52.5%
- What proportion have met all three? 18.82%

www.cdc.gov/diabetes/statistics/a1c/A1c_pct_overall.htm

Progressive Loss of β-Cell Function in Type 2 Diabetes Mellitus (T2DM)

Progressive loss of β-cell function occurs prior to diagnosis

- Sulfonylurea
- Diet
- Metformin

How many “broken” organs are involved in T2DM?

A. 1-2  
B. 3-5  
C. 6-8  
D. I have no idea

The Ominous Octet

How many classes of drugs are available to treat T2DM?
Pharmacotherapy Options

**Insulin**
- Bolus insulin
- Insulin lispro
- Insulin aspart
- Insulin glulisine
- Regular human insulin

**Basal insulin**
- Insulin NPH
- Insulin detemir
- Insulin glargine
- Insulin degludec*

**Oral Medications**
- α-glucosidase inhibitors (AGI)
- Biguanides
- Bile acid sequestrants (BAS)
- Dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins)
- Dopamine agonists
- Glitazones
- Sodium Glucose Cotransporter-2 inhibitors (SGLT2i)
- Thiazolidinediones (TZDs or glitazones)

**Non-insulin injectable agents**
- Glucagon-like peptide-1 (GLP-1) agonists
- Amylinomimetics

*not FDA approved at this time

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Take Away Moment

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- Record reminders to YOURSELF about what you are learning
- Will receive email reminder in January

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Pharmacotherapy to “Fix” T2DM Dysfunctional Organs

- Dopamine agonists (brain)
- Amylinomimetics (GI tract, liver, pancreas, brain)
- GLP-1 Agonists (GI tract, liver, pancreas, brain)
- DPP4 Inhibitors (liver, pancreas, brain)
- Insulin (pancreas & peripheral tissue)
- TZDs (Peripheral tissue & fat)

Focus on Selection of Pharmacotherapy for T2DM

- Desired drug effects
  - Efficacious
  - Protect remaining β-cell function
  - Minimize hypoglycemic risks
  - Minimize weight gain
  - Minimize adverse effects and drug interactions
  - Cardiovascular benefit
Patients Are Willing to Pay More to Avoid Weight Gain or to Lose Weight

- Patients Value
  - Weight loss/avoiding weight gain
  - Avoiding hypoglycemia
  - Avoiding injection
  - Efficacy
  - Avoiding nausea


Willingness-to-Pay ($ USD / month)

\[ \downarrow \quad A1C (\%\) \]
\[ \downarrow \quad \text{Avoid Injection} \]
\[ \downarrow 1 \text{ kg weight} \]
\[ \downarrow \text{Weight (1 kg)} \]

Meta-Analysis: Weight Changes with Antihyperglycemic Agents Added to Metformin


\[ \Delta \text{Weight (kg)} \]

Hypoglycemic Risk of Antihyperglycemic Agents Added to Metformin

### Sodium Glucose Cotransporter-2 (SGLT2) Inhibitors

<table>
<thead>
<tr>
<th>Name</th>
<th>Approval Status or Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>Approved March 29, 2013</td>
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<tr>
<td>Dapagliflozin</td>
<td>Approved January 28, 2014</td>
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<tr>
<td>Empagliflozin</td>
<td>Approved August 1, 2014</td>
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<tr>
<td>Ipragliflozin</td>
<td>Phase III (approved in Japan)</td>
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<tr>
<td>Tofogliflozin</td>
<td>Phase III</td>
</tr>
<tr>
<td>Ertugliflozin</td>
<td>Phase III</td>
</tr>
<tr>
<td>Remogliflozin</td>
<td>Phase II</td>
</tr>
<tr>
<td>LX4211*</td>
<td>Phase IIb</td>
</tr>
</tbody>
</table>

*LX4211* is a dual sodium-dependent glucose cotransporter 1 (SGLT1) and SGLT2 inhibitor.

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### SGLT2/1 Inhibitors

- The kidney plays a major role in glucose homeostasis through gluconeogenesis and glomerular filtration, and reabsorption of glucose in the proximal convoluted tubules.
- Therefore, a new approach for therapeutic target was to inhibit SGLT, which is a large group of sodium substrate cotransporters.
- SGLT2 is responsible for the majority of renal glucose reabsorption in the early proximal tubule of the kidney.
- SGLT1 is responsible for approximately 10% of glucose reabsorption in the late proximal tubule of the kidney, as it is primarily responsible for glucose absorption in the GI tract.


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### Glucose Regulation by the Kidney

\[(180 \text{ L/day}) \times (1000 \text{ mg/L}) = 180 \text{ g/day}\]

- SGLT = Sodium glucose cotransporter

*See page 37 for enlarged view*
SGLT2 Mediates Glucose Reabsorption in the Kidney

- SGLT2 is located at S1 proximal tubular cell membrane (lumen):
  - Low affinity, high capacity for glucose (Na/K electro-chemical gradient)
  - Nearly exclusively expressed in the kidney
  - Responsible for ~90% of total renal glucose reabsorption

- GLUT2 is located at the baso-lateral membrane facing (interstitial space):
  - Facilitated glucose transport - glucose concentration gradient
  - Restores glucose to circulation (Reabsorbed + Gluconeogenesis)
  - Proximal tubules cannot oxidize glucose (FFA-energy dependent)

Renal Glucose Handling After SGLT2 Inhibition

- Urinary Glucose Excretion (g/day)
- Plasma Glucose (mg/dL)

Effect of SGLT2 Inhibition on Glycosuria

- A1C (%)
- Mean plasma glucose (mg/dL)


See page 37 for enlarged view
**Sodium Glucose Cotransporter-2 (SGLT2) Inhibitors**

- ↓ Renal glucose reabsorption in the early proximal tubule of the kidney
  - ↓ Body fat - possibly due to ↑ water and fat urination (elimination)
- Lowers **fasting** glucose
  - Decreases A1C by 0.7-1% (~20-30 mg/dl)
- Most common side effects
  - Weight loss
  - Vaginal and male genital infections
  - Rash
  - UTI
  - Frequent urination
  - Increased thirst
  - GI problems (when combined with metformin)


**Healthy Eating, Weight Control, Increased Physical Activity**


See page 38 for enlarged view
Glycemic Control Algorithm*, †

Progression of Disease

*Order of medications listed are a suggested hierarchy of usage;
†Based upon phase 3 clinical trials data.

Glycemic Control Algorithm*, †

Lifestyle Modification (including Medically Assisted Weight Loss)

ENTRY A1c < 7.5%
ENTRY A1c ≥ 7.5%
ENTRY A1c > 9.0%

Few Adverse Events
or Possible Benefits
Use with Caution

DUAL THERAPY
SYMPTOMS
TRIPLE THERAPY
NO SYMPTOMS

ADD or INTENSIFY INSULIN

Glucose Lowering Comparison

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Route of Administration</th>
<th>Target Glucose</th>
<th>A1C Reduction (%)</th>
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<tbody>
<tr>
<td>Sulfonylurea</td>
<td>Oral</td>
<td>Both</td>
<td>1.5-2.0</td>
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<tr>
<td>Meglitinide</td>
<td>Oral</td>
<td>FPG</td>
<td>1.5</td>
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<tr>
<td>Glitazones</td>
<td>Oral</td>
<td>Both</td>
<td>1.0-1.5</td>
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<tr>
<td>Meglitinides</td>
<td>Oral</td>
<td>PPG</td>
<td>0.5-2.0</td>
</tr>
<tr>
<td>AGLs</td>
<td>Oral</td>
<td>PPG</td>
<td>0.5-1.0</td>
</tr>
<tr>
<td>DDP-4 inhibitors</td>
<td>Oral</td>
<td>PPG</td>
<td>0.5-0.7</td>
</tr>
<tr>
<td>Bile acid sequestrant</td>
<td>Oral</td>
<td>PPG</td>
<td>0.4</td>
</tr>
<tr>
<td>Dipeptidyl peptidase-4 inhibitors</td>
<td>Oral</td>
<td>PPG</td>
<td>0.4</td>
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<td>SGLT-2 inhibitors</td>
<td>Injectable</td>
<td>PPG</td>
<td>0.7 – 1.1</td>
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<td>GLP-1 agonists</td>
<td>Injectable</td>
<td>Both</td>
<td>0.8-1.5</td>
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<tr>
<td>Amylin analogs</td>
<td>Injectable</td>
<td>PPG</td>
<td>0.6</td>
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| Glucose Lowering Comparison | | |
|-----------------------------|-----------------------------|

<table>
<thead>
<tr>
<th>Weight Effect</th>
<th>Hypoglycemia</th>
<th>CVD Protection</th>
<th>Cost</th>
<th>Other Considerations</th>
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<tbody>
<tr>
<td>Ailin</td>
<td>Neutral</td>
<td>Low risk</td>
<td>Possible</td>
<td>Possible</td>
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<tr>
<td>Amelogenetic</td>
<td>Loss</td>
<td>Low risk</td>
<td>Possible</td>
<td>Yes</td>
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<tr>
<td>Bile acid sequestrant</td>
<td>Neutral</td>
<td>Low risk</td>
<td>Possible</td>
<td>Yes</td>
</tr>
<tr>
<td>Biguanide</td>
<td>Loss</td>
<td>Low risk</td>
<td>Possible</td>
<td>Yes</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Neutral</td>
<td>Low risk</td>
<td>Possible</td>
<td>Yes</td>
</tr>
<tr>
<td>Dopamine agonists</td>
<td>Neutral</td>
<td>Low risk</td>
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<td>Yes</td>
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<tr>
<td>GLP-1 agonists</td>
<td>Loss</td>
<td>Low risk</td>
<td>Possible</td>
<td>Yes</td>
</tr>
<tr>
<td>Insulin</td>
<td>Gain or loss</td>
<td>Rapid-action</td>
<td>Possible</td>
<td>Possible</td>
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<tr>
<td>SGLT-2 inhibitors</td>
<td>Gain or loss</td>
<td>Slow-action</td>
<td>Both</td>
<td>Possible</td>
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<tr>
<td>TZDs (glitazones)</td>
<td>Gain</td>
<td>Risk</td>
<td>No</td>
<td>No</td>
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<tr>
<td>TZDs (thiazolidinediones)</td>
<td>Gain</td>
<td>Risk</td>
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</tbody>
</table>

FPG = fasting plasma glucose; PPG = postprandial glucose; GI = gastrointestinal; SMBG = self-monitoring of blood glucose.


See page 38 for enlarged view

See page 39 for enlarged view

See page 39 for enlarged view
Take-Home Message

- The number of people with diabetes continues to increase
- Type 2 diabetes is about 8 broken organs.
  - Of the 12 classes of drugs to treat type 2 diabetes, there is no single drug that fixes all 8 organs
  - Combination therapy is usually warranted
    • Use medications with complimentary actions
- Newer therapies focus on reducing:
  - Hypoglycemic risk
  - Weight loss
    • Both are favorable "side effects" for many people with type 2.

Take Away Moment

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Safety and Efficacy of the SGLT2 Inhibitors in Type 2 Diabetes: Examining the Evidence

Curtis Triplitt, Pharm.D., CDE
Clinical Associate Professor
Department of Medicine/Division of Diabetes
University of Texas Health Science Center at San Antonio
Texas Diabetes Institute
University Health System

SGLT2 Inhibitors

- Canagliflozin  FDA approved 2013
- Dapagliflozin  FDA approved 2014
- Empagliflozin  FDA approved 2014

SGLT2 Inhibitor Overview

- Pharmacokinetics and dosing
- Glycemic efficacy across the spectrum of diabetes
  - Monotherapy
  - Combination
    - Metformin
    - Sulfonylureas
    - Thiazolidinediones
    - Triple therapy
    - Insulin
  - Special populations
    - Renal insufficiency
    - Side effect profile
Pharmacokinetics

- Oral Bioavailability - Good for currently marketed
  - Phlorizin – Phloretin - poor bioavailability
  - Dapagliflozin - 78%
  - Empagliflozin - >60%
  - Canagliflozin - 65%
- $t_{1/2}$ - 12 ± 2 hours for all
- Metabolism/Drug-Drug Interactions
  - Major - glucuronidation - rifampin may decrease SGLT2i levels (others: ritonavir, phenobarbital, phenytoin)
  - Not inducers or inhibitors
    - Canagliflozin - weak P-glycoprotein (P-gp) inhibitor - may need to watch digoxin levels
  - Elimination - urine/feces glucuronidated or unchanged

Monotherapy - SGLT2 Inhibitors

Mean Change in HbA1c from baseline (%)

Combination with Metformin-SGLT2 Inhibitors

Mean Change in HbA1c from baseline (%)**

**NOT HEAD-TO-HEAD STUDIES


**Combination with Sulfonylurea-SGLT2 Inhibitors**

**Mean Change in HbA1c from baseline (%)**

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<th>Treatment</th>
<th>Baseline GLIMP100 300</th>
<th>Canagliflozin 52 week study</th>
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<th>Dapagliflozin 104 week study</th>
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<tbody>
<tr>
<td>GLIMP100 300</td>
<td>7.8%</td>
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<td>-0.18% (P&lt;0.021)</td>
<td>0.6%</td>
<td>-0.11% (P&lt;0.016)</td>
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</tr>
</tbody>
</table>

**NOT HEAD-TO-HEAD STUDIES**


---

**Pioglitazone- Dapagliflozin Added**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline GLIMP100 300</th>
<th>Canagliflozin 52 week study</th>
<th>Canagliflozin 52 week study</th>
<th>Dapagliflozin 104 week study</th>
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<td>0.6%</td>
<td>-0.11% (P&lt;0.016)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**Triple Therapy with SGLT2 inhibitors**

52 week study - canagliflozin 300 mg QD versus sitagliptin 100 mg QD

Background therapy: metformin and sulfonylurea

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline GLIMP100 300</th>
<th>Canagliflozin 52 week study</th>
<th>Canagliflozin 52 week study</th>
<th>Dapagliflozin 104 week study</th>
<th>Dapagliflozin 104 week study</th>
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<td></td>
<td></td>
</tr>
</tbody>
</table>


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SGLT2: In Combination with Insulin

Empagliflozin or placebo added to multiple daily insulin injections in obese patients with Type 2 Diabetes 52 week data
HbA1c: 8.3% BMI 34.8 kg/m² Insulin Dose Average: 92 units/day Insulin was titrated to maximize effect, but stayed stable (+/-10%) from week 40-52

<table>
<thead>
<tr>
<th></th>
<th>EMPA 10 mg/day</th>
<th>EMPA 25 mg/day</th>
<th>Placebo</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (% from baseline)</td>
<td>-1.18%</td>
<td>-1.27%</td>
<td>-0.81%</td>
<td>P&lt;0.001 vs. placebo</td>
</tr>
<tr>
<td>Weight (Δ kg)</td>
<td>7.2</td>
<td>7.1</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td>Insulin/day (Δ units)</td>
<td>1.95</td>
<td>2.04</td>
<td>0.44</td>
<td>P&lt;0.001 vs. placebo</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>-3.4</td>
<td>-3.8</td>
<td>-2.9</td>
<td>NS</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>-1.2</td>
<td>-2.5</td>
<td>-0.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

NR = Not reported
NS = Not significant


---

SGLT2: Place in Therapy for Type 2 Diabetes Mellitus

- Mechanism independent of insulin production
- Potential for use across Type 1 and 2 DM
  - Caveat: renal insufficiency

Lifestyle | Monotherapy | Combination | Injectable Insulin

---

30 Second Table Discussion

- Why do you think that the A1C reduction with SGLT2 inhibitors is fairly equal whether it is used in monotherapy, combination, or even with insulin?
Weight Effects – Meta-analysis

<table>
<thead>
<tr>
<th></th>
<th>Mean difference</th>
<th>Upper 95% CI</th>
<th>Lower 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>-0.640</td>
<td>-0.768</td>
<td>-0.513</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>-0.592</td>
<td>-0.692</td>
<td>-0.491</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>-0.564</td>
<td>-0.745</td>
<td>-0.384</td>
</tr>
<tr>
<td>Ipragliflozin*</td>
<td>-0.504</td>
<td>-0.731</td>
<td>-0.277</td>
</tr>
<tr>
<td>SUMMARY</td>
<td><strong>-0.591 kg</strong></td>
<td>-0.663</td>
<td>-0.519</td>
</tr>
</tbody>
</table>

- Mechanism: 1 gram glucose = 4 kcal. Loss of potentially 200-300 kcal/day
- Maximum weight loss at approximately 6 months
- Weight loss is, in general, maintained

*Not approved in U.S.


Changes from Baseline in Body Weight in Phase 3 Dapagliflozin Studies

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Monotherapy</td>
<td>Met add-on</td>
<td>SU add-on</td>
<td>Insulin add-on</td>
</tr>
<tr>
<td>Dapa 2.5 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dapa 5 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dapa 10 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Strojek K et al. Abstract 870 presented at EASD 2010.

Meta-analysis - SGLT2 Inhibitor Blood Pressure Effects

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGLT2i vs. placebo</td>
<td>-3.77</td>
<td>-4.65 to -2.90</td>
</tr>
<tr>
<td>SGLT2i vs. active comparator</td>
<td>-4.49</td>
<td>-5.73 to -3.18</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGLT2i vs. placebo</td>
<td>-1.75</td>
<td>-2.27 to -1.23</td>
</tr>
<tr>
<td>SGLT2i vs. other antidiabetics</td>
<td>-2.01</td>
<td>-2.62 to -1.39</td>
</tr>
<tr>
<td>Odds Ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>2.68</td>
<td>1.14 to 6.39</td>
</tr>
</tbody>
</table>

- BP Lowering Mechanism
  - Not fully determined but likely due to osmotic diuresis
  - Orthostatic changes possible upon initiation
    * Early 24-48 hour increased sodium excretion
  - Caution in combination with other diuretics

Warnings/Precautions

- No FDA issued Black Box Warnings
- Warnings
  - Hypotension
  - Increased LDL-C levels
  - Genital Mycotic infections
  - Urinary Tract Infections
  - Impaired renal function

### Urinary Tract Infections

Pooled dapagliflozin data from 12 placebo controlled trials up to 24 weeks long

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Dapagliflozin 5 mg/day</th>
<th>Dapagliflozin 10 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall number of patients, N</td>
<td>1393</td>
<td>1145</td>
<td>1193</td>
</tr>
<tr>
<td>Patients with diagnosis of UTI, n (%)</td>
<td>52 (3.7)</td>
<td>65 (5.7)</td>
<td>51 (4.3)</td>
</tr>
<tr>
<td>Patients with history of recurrent UTI, n (%)</td>
<td>35 (2.5)</td>
<td>23 (2.0)</td>
<td>34 (2.8)</td>
</tr>
<tr>
<td>Patients with a prior history of recurrent UTI with clinical diagnosis of UTI, n (%)</td>
<td>6/35 (17.1)</td>
<td>4/23 (21.1)</td>
<td>6/34 (17.6)</td>
</tr>
</tbody>
</table>


### Urinary Tract Infections - continued

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Dapagliflozin 5 mg/day</th>
<th>Dapagliflozin 10 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>716</td>
<td>564</td>
<td>555</td>
</tr>
<tr>
<td>Women with diagnosed UTI, n (%)</td>
<td>45/677 (6.6)</td>
<td>55/581 (9.5)</td>
<td>46/598 (7.7)</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men with diagnosed UTI, n (%)</td>
<td>45/677 (6.6)</td>
<td>55/581 (9.5)</td>
<td>46/598 (7.7)</td>
</tr>
</tbody>
</table>

Rates of pyelonephritis:
- Dapagliflozin 5 mg 0.0%
- Dapagliflozin 10 mg 0.1%
- Placebo 0.1%

Which patients are at a higher risk of genital mycotic infections with SGLT2 inhibitors?

A. All patients have a higher risk  
B. Women with a prior history of infections  
C. Uncircumcised men  
D. All are correct

---

**Genital Mycotic Infections**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Dapagliflozin 5 mg/day</th>
<th>Dapagliflozin 10 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients, N</td>
<td>1393</td>
<td>1145</td>
<td>1193</td>
</tr>
<tr>
<td>Diagnosis of genital infection, n</td>
<td>12 (0.9)</td>
<td>65 (5.7)</td>
<td>57 (4.8)</td>
</tr>
<tr>
<td>History of recurrent genital infection, n (%)</td>
<td>10 (0.7)</td>
<td>13 (1.1)</td>
<td>12 (1.0)</td>
</tr>
<tr>
<td>Women</td>
<td>677</td>
<td>581</td>
<td>598</td>
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<tr>
<td>Diagnosis of genital infection, n (%)</td>
<td>10 (1.5)</td>
<td>49 (8.4)</td>
<td>41 (6.9)</td>
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<tr>
<td>Men</td>
<td>716</td>
<td>564</td>
<td>595</td>
</tr>
<tr>
<td>Diagnosis of genital infection, n (%)</td>
<td>2 (0.3)</td>
<td>36 (2.8)</td>
<td>16 (2.7)</td>
</tr>
</tbody>
</table>


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**Canagliflozin and eGFR**

### SGLT2 Inhibitors: Renal Dosing

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosing in CKD stages 3, 4 and 5 (non-dialysis)</th>
</tr>
</thead>
</table>
| Canagliflozin | - eGFR 45–59 ml/min/1.73m²  
                - Do not exceed 100 mg/day PO  
                - eGFR <45 ml/min/1.73m²  
                - Do not initiate and discontinue in patients currently receiving drug |
| Dapagliflozin | - eGFR <60 ml/min/1.73m²  
                - Do not initiate and/or discontinue                                                                 |
| Empagliflozin | - eGFR <45 ml/min/1.73m²  
                - Do not initiate and discontinue in patients currently receiving drug  
                - No limit on dosing                                                                                     |

- Glycemic efficacy becomes less pronounced with decreasing eGFR
- If the kidney doesn’t filter as much glucose, the SGLT2i can’t prevent reabsorption

---

30 Second Table Discussion

Concerns were raised that the small decrement in eGFR may lead to long-term worsening of renal insufficiency with SGLT2 inhibitors. Do you agree? Why or why not?

---

Summary

- SGLT2 inhibitors work across the spectrum of T2DM
- Moderate efficacy is similar when combined with other therapies
- Additional weight and blood pressure lowering benefits may be seen
  - No CV outcome trials have been completed
- Side Effects of Special Interest
  - GU infections
  - Renal Impairment
Medication-related Patient Care Concerns

- Medication errors cause at least one death every day and injure approximately 1.3 million people annually in the U.S.
- Delays in treatment and medication non-adherence are the major reasons behind avoidable costs in the healthcare system
  - Avoidable costs >$200 billion are incurred each year in the U.S. healthcare system, representing 8% of the country’s total annual healthcare expenditures
    - Significant cost to patients
    - Unnecessary utilization of healthcare resources
    - $400 million for hospital visits (annually)


Clinical Inertia

- Delays in evidence-based treatment to patients
  - >$40 billion per year in avoidable costs
- Diabetes is the largest avoidable impact to the U.S. healthcare system
  - Delays increased outpatient visits and hospitalizations
- Keys to adherence:
  - Identifying patients with chronic conditions
  - Creating a program that focuses on patient engagement
Adherence Declines
Over the First Year of Therapy

Patient Cases

Patient AL
• AL is a 83-year-old patient with T2DM x 21 years
• A1C is 7.9% (x 4 years); BMI – 24 kg/m²; SCr – 1.1 mg/dL
Current Medications
  – Metformin 1000 mg BID
  – Glimepiride 4 mg daily
• AL is discharged from the hospital following a hypoglycemic event; He resides in an assisted living apartment and has limited mobility
What should AL’s A1C goal be?

A. Less than 6.5 percent
B. Less than 7.0 percent
C. Less than 7.5 percent
D. Less than 8.0 percent
E. Unsure

Approach to Management of Hyperglycemia

Which changes to the existing treatment plan would you make?

A. Increase metformin to 2500 mg/day
B. Increase glimepiride to 8 mg/day
C. Decrease or discontinue metformin
D. Decrease or discontinue glimepiride
E. No changes to existing medications
What additional medications, if any, would you add?

A. Basal insulin  
B. DDP-4 inhibitor  
C. GLP-1 agonist  
D. SGLT2 inhibitor

Case Considerations

- AL has had T2DM for 21 years
  - Aggressive therapy and tight BG control may not be warranted
    - May do more harm than good
  - A1C goal would be acceptable near 7.5%
  - A1C needs ~0.4% lowering
    - Need to target postprandial, as well as fasting blood glucose
      - A1C of 7.9% is ~45% fasting and 55% postprandial
    - Adverse effects must be considered
      - Weight loss may not be necessary
      - Risk of hypoglycemia must be minimized
      - GI side effects should be considered
      - Fluid / electrolyte balance should be considered

Possible Pharmacotherapy for AL

<table>
<thead>
<tr>
<th>A1C Lowering Potential &amp; BG target</th>
<th>Weight Effect</th>
<th>Hypoglycemia Effect</th>
<th>β-Cell Protection</th>
<th>Other Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase Metformin</td>
<td>1.5% FPG</td>
<td>Loss</td>
<td>Low risk</td>
<td>Possible</td>
</tr>
<tr>
<td>Increase Sulfonylurea</td>
<td>1.5-2.0% FPG &amp; PPG Gain</td>
<td>增加</td>
<td>&lt; risk</td>
<td>No</td>
</tr>
<tr>
<td>Add Basal insulin (long-acting)</td>
<td>Open to target FPG</td>
<td>Gain or neutral</td>
<td>Low risk</td>
<td>Possible</td>
</tr>
<tr>
<td>Add a GLP-1 Agonist</td>
<td>0.5-1.5% Long – FPG &amp; PPG Loss</td>
<td>GI adverse effects</td>
<td>Low risk</td>
<td>Possible</td>
</tr>
<tr>
<td>Add a DPP-4 Inhibitor</td>
<td>0.0-0.7% FPG</td>
<td>Low risk</td>
<td>Possible</td>
<td>Minimal adverse effects, cost</td>
</tr>
<tr>
<td>Add a SGLT2 Inhibitor</td>
<td>0.5-1.5% FPG</td>
<td>Low risk</td>
<td>Possible</td>
<td>UTI and urogenital infections, fluid volume depletion/dysregulation</td>
</tr>
</tbody>
</table>

See page 41 for enlarged view
Patient GM

- GM is a 52-year-old Hispanic female with T2DM x 10 years
- A1C is 8.2%; BMI – 33 kg/m²; SCR – 0.8 mg/dL, BP 143/84 mmHg

<table>
<thead>
<tr>
<th>Current Medications</th>
<th>Past Medication History</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin 1000 mg BID</td>
<td>March 2014 - cotrimoxazole DS BID X 5 days</td>
</tr>
<tr>
<td>Linagliptin 5 mg QD</td>
<td>March 2014 - fluconazole 150 mg once</td>
</tr>
<tr>
<td>Lisinopril 20 mg QD</td>
<td></td>
</tr>
<tr>
<td>Hydrochlorothiazide 25 mg QD</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin 20 mg QD</td>
<td></td>
</tr>
<tr>
<td>Paroxetine 20 mg QD</td>
<td></td>
</tr>
</tbody>
</table>

OTC Medications
- PRN acetaminophen 500 mg (2 tablets) for occasional back pains
- Cream use occasionally

- She has been sent for intensification of her treatment regimen

Which changes to the existing treatment plan would you make?

A. Increase metformin to 2500 mg/day
B. Increase linagliptin to 10 mg/day
C. Switch linagliptin to empagliflozin 10 mg/day
D. Add dapagliflozin 5 mg/day
E. None of the above

What concerns would you have if an SGLT2 inhibitor was started?

A. She is currently taking a diuretic
B. She has a history of UTI’s
C. She may have a history of recurrent mycotic infections
D. All of the above
Role of the Pharmacist for SGLT2 inhibitors

- Monitor renal function
  - A small drop in eGFR may be expected
  - Most clinicians will not notice because it is small and SCr does not change significantly

- Assess Blood Pressure
  - Consider reduction of concomitant diuretic if BP at goal or patient is close to “pre-renal dry” currently
  - Tell patient about possible orthostatic changes
  - Counsel to increase water intake PRN

- Review profile/ask patient for UTI and GU infection history
  - Counsel on risks
  - Tell uncircumcised males about risk

WUZZLE #2

Take-Home Message

- Managing diabetes can be challenging
  - Set the patient up for success by using effective drug therapy that:
    - Fixes the dysfunctional organs
    - Saves the beta cell
    - Minimizes hypoglycemia
    - Does not cause weight gain
    - Has a favorable CV profile

- Pharmacists must routinely assess patients for:
  - Appropriate drug use
  - Adherence
  - Clinical inertia
  - Medication related concerns/problems
**Glucose Regulation by the Kidney**

\[(180 \text{ L/day}) (1000 \text{ mg/L}) = 180 \text{ g/day}\]

\[\text{SGLT} = \text{Sodium glucose cotransporter}\]

**SGLT2 Mediates Glucose Reabsorption in the Kidney**

- **SGLT2** is located at S1 proximal tubular cell membrane (lumen):
  - Low affinity, high capacity for glucose (Na/K electro-chemical gradient)
  - Nearly exclusively expressed in the kidney
  - Responsible for ~90% of total renal glucose reabsorption

- **GLUT2** is located at the baso-lateral membrane facing (interstitial space):
  - Facilitated glucose transport - glucose concentration gradient
  - Restores glucose to circulation (Reabsorbed + Gluconeogenesis)
  - Proximal tubules cannot oxidize glucose (FFA-energy dependent)

Glycemic Control Algorithm*,†

**Lifestyle Modification** *(Including Medically Assisted Weight Loss)*

**ENTRY A1c <7.5%**
- **MONOTHERAPY**
  - Metformin
  - DPP-4i
  - SGLT2i
  - GLP-1RA
- Few Adverse Events or Possible Benefits
- Use with Caution

**ENTRY A1c ≥7.5%**
- **DUAL THERAPY**
  - Metformin + GLP-1RA
  - Metformin + DPP-4i
  - Metformin + SGLT2i
  - Metformin + Insulin
- If not at goal in 3 months proceed to triple therapy

**ENTRY A1c >9.0%**
- **NO SYMPTOMS**
  - DUAL THERAPY
  - TRIPLE THERAPY
- **SYMPTOMS**
  - INSULIN + OTHER AGENTS
  - ADD or INTENSIFY INSULIN

**Progression of Disease**
- Order of medications listed are a suggested hierarchy of usage;
- Based upon phase 3 clinical trials data.

## Glucose Lowering Comparison

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Route of Administration</th>
<th>Target Glucose: FPG or PPG</th>
<th>A1C Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea</td>
<td>Oral</td>
<td>Both</td>
<td>1.5-2.0</td>
</tr>
<tr>
<td>Metformin</td>
<td>Oral</td>
<td>FPG</td>
<td>1.5</td>
</tr>
<tr>
<td>Glitazones</td>
<td>Oral</td>
<td>Both</td>
<td>1.0-1.5</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Oral</td>
<td>PPG</td>
<td>0.5-2.0</td>
</tr>
<tr>
<td>AGIs</td>
<td>Oral</td>
<td>PPG</td>
<td>0.5-1.0</td>
</tr>
<tr>
<td>DDP-4 inhibitors</td>
<td>Oral</td>
<td>PPG</td>
<td>0.5-0.7</td>
</tr>
<tr>
<td>Bile acid sequestrant</td>
<td>Oral</td>
<td>PPG</td>
<td>0.4</td>
</tr>
<tr>
<td>Dopamine agonists</td>
<td>Oral</td>
<td>PPG</td>
<td>0.4</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>Oral</td>
<td>FPG</td>
<td>0.7 – 1.1</td>
</tr>
<tr>
<td>GLP-1 agonists</td>
<td>Injectable</td>
<td>Short-acting—PPG</td>
<td>0.8-1.5</td>
</tr>
<tr>
<td>Amylin analogs</td>
<td>Injectable</td>
<td>PPG</td>
<td>0.6</td>
</tr>
<tr>
<td>Insulin</td>
<td>Injectable</td>
<td>Basal - FPG Bolus – PPG</td>
<td>Open to target</td>
</tr>
</tbody>
</table>

FPG = fasting plasma glucose; PPG = postprandial glucose


<table>
<thead>
<tr>
<th>AGIs</th>
<th>Weight Effect</th>
<th>Hypoglycemia</th>
<th>β-Cell Protection</th>
<th>CVD Benefits</th>
<th>Cost</th>
<th>Other Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amylinomimetic</td>
<td>Loss</td>
<td>Low risk</td>
<td>Possible</td>
<td>Possible</td>
<td>$ to $$</td>
<td>GI adverse effects (nausea), gastrointestinal impairment</td>
</tr>
<tr>
<td>Bile acid sequestrant</td>
<td>Neutral or loss</td>
<td>Low risk</td>
<td>Possible</td>
<td>Yes</td>
<td>$</td>
<td>GI adverse effects (constipation), dose frequency</td>
</tr>
<tr>
<td>Biguanides</td>
<td>Loss</td>
<td>Low risk</td>
<td>Possible</td>
<td>Yes</td>
<td>$</td>
<td>GI adverse effects (diabetes), renal and hepatic impairment</td>
</tr>
<tr>
<td>DPP-4 inhibitors (gliptins)</td>
<td>Neutral</td>
<td>Low risk</td>
<td>Possible</td>
<td>Yes</td>
<td>$$</td>
<td>Minimal adverse effects</td>
</tr>
<tr>
<td>Dopamine agonist</td>
<td>Neutral or loss</td>
<td>Low risk</td>
<td>Unknown</td>
<td>Yes/no</td>
<td>$$</td>
<td>GI adverse effects (nausea), gastrointestinal impairment</td>
</tr>
<tr>
<td>GLP-1 agonists</td>
<td>Loss</td>
<td>Low risk</td>
<td>Possible</td>
<td>Yes</td>
<td>$$</td>
<td>GI adverse effects (nausea), gastrointestinal impairment</td>
</tr>
<tr>
<td>Insulin</td>
<td>Gain or loss</td>
<td>Risk—bolus</td>
<td>Low risk—basal</td>
<td>Possible</td>
<td>$ to $$</td>
<td>Injectable, dose frequency (bolus), increased SMIBG</td>
</tr>
<tr>
<td>Secretagogues, sulfonylureas and glinides</td>
<td>Gain</td>
<td>Risk</td>
<td>No</td>
<td>No</td>
<td>$ to $$</td>
<td>Immediate short-term response, increased SMIBG, dose frequency (glucagon)</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>Loss</td>
<td>Low risk</td>
<td>??</td>
<td>Yes</td>
<td>$$$</td>
<td>Urinary tract and urogenital infections</td>
</tr>
</tbody>
</table>

FPG = fasting plasma glucose; PPG = postprandial glucose; GI = gastrointestinal; SMBG = self-monitoring of blood glucose.

SGLT2i: Place in Therapy for Type 2 Diabetes Mellitus

- Mechanism independent of insulin production
- Potential for use across Type 1 and 2 DM
  - Caveat - renal insufficiency

<table>
<thead>
<tr>
<th>Lifestyle</th>
<th>Monotherapy</th>
<th>Combination</th>
<th>Injectable Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGT</td>
<td>Endogenous Insulin</td>
<td>Insulin Resistance</td>
<td>Postprandial BG</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td>Normal Insulin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Normal Blood Glucose</td>
</tr>
</tbody>
</table>

SGLT2 inhibitors

SGLT2 Inhibitors: Renal Dosing

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosing in CKD stages 3, 4 and 5 (non-dialysis)</th>
</tr>
</thead>
</table>
| Canagliflozin  | • eGFR 45—59 ml/min/1.73 m²  
                    Do not exceed 100 mg/day PO  
                    • eGFR <45 ml/min/1.73 m²  
                    Do not initiate and discontinue in patients currently receiving drug |
| Dapagliflozin  | • eGFR <60 mL/min/1.73 m²  
                    Do not initiate and/or discontinue |
| Empagliflozin  | • eGFR <45 ml/min/1.73 m²  
                    Do not initiate and discontinue in patients currently receiving drug. No limit on dosing |

- Glycemic efficacy becomes less pronounced with decreasing eGFR
- If the kidney doesn’t filter as much glucose, the SGLT2i can’t prevent reabsorption

Invokana (canagliflozin) prescribing information. 2014 May.
Farxiga (dapagliflozin) prescribing information. 2014 Aug.
Jardiance (empagliflozin) prescribing information. 2014 Aug.
### Approach to Management of Hyperglycemia

<table>
<thead>
<tr>
<th>Patient attitude and expected treatment efforts</th>
<th>More Stringent</th>
<th>Less Stringent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risks potentially associated with hypoglycemia, other adverse events</td>
<td>highly motivated, adherent, excellent self-care capacities</td>
<td>less motivated, non-adherent, poor self-care capacities</td>
</tr>
<tr>
<td>Disease duration</td>
<td>low</td>
<td>high</td>
</tr>
<tr>
<td>Life expectancy</td>
<td>long</td>
<td>short</td>
</tr>
<tr>
<td>Important comorbidities</td>
<td>absent</td>
<td>severe</td>
</tr>
<tr>
<td>Established vascular complications</td>
<td>absent</td>
<td>severe</td>
</tr>
<tr>
<td>Resources, support system</td>
<td>readily available</td>
<td>limited</td>
</tr>
</tbody>
</table>


### Possible Pharmacotherapy for AL

<table>
<thead>
<tr>
<th>A1C Lowering Potential &amp; BG target</th>
<th>Weight Effect</th>
<th>Hypoglycemia</th>
<th>β-Cell Protection</th>
<th>Other Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase Metformin</td>
<td>1.5% FPG</td>
<td>Loss</td>
<td>Low risk</td>
<td>Possible</td>
</tr>
<tr>
<td>Increase Sulfonylurea</td>
<td>1.5-2.0% FPG &amp; PPG</td>
<td>Gain</td>
<td>+ risk</td>
<td>No</td>
</tr>
<tr>
<td>Add Basal insulin (long-acting)</td>
<td>Open to target FPG</td>
<td>Gain or neutral</td>
<td>Low risk</td>
<td>Possible</td>
</tr>
<tr>
<td>Add a GLP-1 Agonist</td>
<td>0.8-1.9% Short – PPG</td>
<td>Loss</td>
<td>Low risk</td>
<td>Possible</td>
</tr>
<tr>
<td>Add a DPP-4 Inhibitor</td>
<td>0.5-0.7% PPG</td>
<td>Neutral</td>
<td>Low risk</td>
<td>Possible</td>
</tr>
<tr>
<td>Add a SGLT2 Inhibitor</td>
<td>0.6-1.0% FPG</td>
<td>Loss</td>
<td>Low risk</td>
<td>Possible</td>
</tr>
</tbody>
</table>
Novel Treatments for the Management of Type 2 Diabetes: Focus on SGLT2 Inhibitors

Abbreviations List

AGI = α-glucosidase inhibitor
A1C = hemoglobin A1c
BAS = Bile acid sequestrant
BG = blood glucose
BMI = body mass index
CANA = canagliflozin
CKD = chronic kidney disease
CV = cardiovascular
DAPA = dapagliflozin
DBP = diastolic blood pressure
DPP-4 = Dipeptidyl peptidase-4
DPP-4i = DPP-4 inhibitor
eGFR = estimated glomerular filtration rate
EMPA = empagliflozin
FPG = fasting plasma glucose
GI = gastrointestinal
GLIM = glimepiride
GLIP = glipizide
GLP-1 = Glucagon-like peptide-1
GLP-1 RA = glucagon-like peptide-1 receptor agonist
GU = genitourinary
HbA1c = hemoglobin A1c
HDL = high density lipoprotein
IGT = impaired glucose tolerance
LDL = low density lipoprotein
MET = metformin
NS = non-significant
PBO = placebo
PLAC = placebo
PPG = postprandial glucose
SBP = systolic blood pressure
Scr = serum creatinine
SGLT-2 = Sodium Glucose Co-Transporter 2
SGLT2i = Sodium Glucose Co-Transporter-2 inhibitor
SMBG = self-monitoring of blood glucose
SU = sulfonylurea
TZD = Thiazolidinedione
T2DM = Type 2 Diabetes Mellitus
UTI = urinary tract infection
Self-Assessment Questions

1. At the time of diagnosis of Type 2 Diabetes, approximately what percentage of beta cell function has been lost?
   a. 5-10%
   b. 15-35%
   c. 30-50%
   d. 50-80%

2. Which of the following diabetes therapy (class of drugs) does not have a weight loss benefit?
   a. Biguanides
   b. DPP-4 inhibitors
   c. GLP-1 agonists
   d. SGLT-2 inhibitors

3. Which of the following diabetes therapy (class of drugs) has a high risk for hypoglycemia?
   a. DPP-4 inhibitors
   b. GLP-1 agonists
   c. SGLT-2 inhibitors
   d. Sulfonylureas

4. Patient JR has had type 2 diabetes for 4 years and his recent A1c was 8.3%. He is currently taking metformin 1000 mg twice daily. JR was just prescribed an SGLT-2 inhibitor. Which of the following is NOT a potential side effect of you need to review with JR?
   a. Frequent urination
   b. Genital infections
   c. GI problems
   d. Weight gain

5. Which of the following statements is true regarding the use of SGLT-2 inhibitors?
   a. According to the ADA guidelines, SGLT-2 inhibitors can be used as first-line treatment, monotherapy.
   b. According to the ADA guidelines, SGLT-2 inhibitors can be used as second-line treatment, added to metformin.
   c. According to the AACE guidelines, SGLT-2 inhibitors can be used as first-line treatment, monotherapy, but should be used with caution.
   d. According to the ADA and AACE guidelines, SGLT-2 inhibitors are not included in the current recommendations.

Answers

1. d
2. b
3. d
4. d
5. c