Targeting the Kidney in Managing the Patient with Type 2 Diabetes: A New Approach

Anaheim, California
April 11, 2012
Session 1: Targeting the Kidney in Managing the Patient with Type 2 Diabetes: A New Approach

Learning Objectives

1. Discuss the role of the kidney in glucose homeostasis.
2. Describe the contribution of the kidney to the sustained elevated glucose levels observed in individuals with uncontrolled type 2 diabetes.
3. Explain the mechanism of action of therapies that act through the kidney to reduce hyperglycemia in type 2 diabetes.
4. Assess clinical efficacy and safety data, and identify the potential place of therapies that target the kidney in the management of type 2 diabetes.

Faculty

Robert R. Henry, MD
Professor of Medicine
University of California, San Diego
Chief, Section of Diabetes, Endocrinology & Metabolism
Veterans Affairs Healthcare System
San Diego, California

Jaime A. Davidson, MD
Clinical Professor of Medicine
Division of Endocrinology, Diabetes and Metabolism
University of Texas Southwestern Medical School
Dallas, Texas

Robert R. Henry, MD, is professor of medicine at the University of California, San Diego and chief of the section of diabetes, endocrinology & metabolism and director of the Center for Metabolic Research at the Veterans Affairs Healthcare System in San Diego, California.

Dr Henry received his medical degree from the University of Manitoba Medical School, Manitoba, Canada, where he also completed his residency in internal medicine and fellowship in endocrinology. He is immediate past president, medicine and science, of the American Diabetes Association (ADA), and is a member of the European Association for the Study of Diabetes, the Obesity Society, the Endocrine Society, the Royal College of Physicians and Surgeons of Canada and Edinburgh, and the American Federation for Clinical Research. His research is funded by the National Institutes of Health-National Institute of Diabetes and Digestive and Kidney Diseases, the ADA, the Department of Veterans Affairs, and numerous pharmaceutical grants. Recent awards include the Distinguished Clinical Scientist Award and Banting Medal for service from the ADA, the Mary Jane Kugal Award of the Juvenile Diabetes Research Foundation International, the Robert H. Williams-Rachmiel Levine Award from the Western Metabolism Club, and the Frontiers in Science Award from the American Association of Clinical Endocrinologists.

Dr Henry has published more than 250 journal articles and chapters. His current research interests involve the metabolic and cardiovascular effects of human adipose tissue secretory products including adiponectin, signal interactions between skeletal muscle and adipose tissue, and defects of insulin signal transduction in these tissues of obese and type 2 diabetic patients.

Jaime A. Davidson, MD, FACP, MACE, is clinical professor of medicine at the University of Texas Southwestern Medical School, Dallas, Texas. Dr Davidson was one of the charter members in the formation of the American Association of Clinical
Endocrinologists (AACE). He was a member of the Texas Diabetes Council Professional Committee for the Texas Department of Health, the Council on Obesity Diabetes Education, and the International Diabetes Federation Task Force on Epidemiology. Dr Davidson served as a trustee of the American College of Endocrinology.

Dr Davidson is the recipient of numerous awards, most recently the AACE Outstanding Service Award for the Promotion of Endocrine Health of an Underserved Population for his work in addressing health disparities in Hispanic and Latino communities. He received the prestigious Harold Rifkin MD award at the 2006 American Diabetes Association meeting for distinguished international service in the cause of diabetes.

In 2006 he was honored as an honorary member of the Costa Rica College of Physicians and Surgeons and in 2007 as an honorary member of the Dominican Republic Endocrine Society. Dr Davidson is an honorary member of the National Academy of Medicine in Mexico.

Faculty Financial Disclosure Statements
The presenting faculty report the following:

Dr Henry reports he has received grants/research support (via the University of California San Diego and/or Veterans Military Research Foundation) from Amylin Pharmaceuticals, Inc., AstraZeneca Pharmaceuticals, Bristol-Myers Squibb Company, Johnson & Johnson, and Novartis. He is a consultant to Amgen, Inc., Boehringer Ingelheim Pharmaceuticals, Dainippon Sumitomo Pharma, Isis Pharmaceuticals, Novo Nordisk Pharmaceuticals, Roche Pharmaceuticals, sanofi-aventis, Tethys Bioscience, and Takeda Pharmaceutical Company. Dr Henry is a member of the advisory board of Amylin Pharmaceuticals, AstraZeneca Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals, Eli Lilly and Company, GlaxoSmithKline, Intarcia Therapeutics, Merck & Co., Novo Nordisk Pharmaceuticals, Orexigen Therapeutics, Roche Pharmaceuticals, sanofi-aventis, Tethys Bioscience, Versartis, and Vivus. Dr Henry reports he is a shareholder of Amylin Pharmaceuticals, Inc.

Dr Henry will discuss medications that target renal glucose reabsorption that are currently not approved by the FDA.

Dr Davidson reports he is a consultant, and/or an advisory or speaker’s board member for AstraZeneca Pharmaceuticals, Bristol-Myers Squibb Company, Bayer Pharmaceuticals, Eli Lilly & Co., Roche Diagnostic, Johnson & Johnson, Merck Sharp & Dohme, Novo Nordisk, and Takeda.

Dr Davidson intends to reference unlabeled/unapproved uses of SGLT 2 inhibitors in his presentation.

Education Partner Financial Disclosure Statement
The content collaborators at Voxmedia report the following:
John F. Kocsis, PhD, has no financial relationships disclose.

Acronym List

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>T2D</td>
<td>type 2 diabetes</td>
</tr>
<tr>
<td>GLUT</td>
<td>glucose transporter</td>
</tr>
<tr>
<td>SGLT</td>
<td>sodium glucose cotransporter</td>
</tr>
<tr>
<td>UGE</td>
<td>urinary glucose excretion</td>
</tr>
<tr>
<td>OAD</td>
<td>oral antidiabetic agents</td>
</tr>
<tr>
<td>ADA</td>
<td>American Diabetes Association</td>
</tr>
<tr>
<td>AACE</td>
<td>American Association of Clinical Endocrinologists</td>
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Suggested Reading List


Drug List

<table>
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<tr>
<th>Generic</th>
<th>Trade</th>
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<tbody>
<tr>
<td>colesvelam</td>
<td>Welchol</td>
</tr>
<tr>
<td>glimepiride</td>
<td>Amaryl</td>
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<tr>
<td>glipizide</td>
<td>Glucotrol</td>
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<tr>
<td>glipizide, metformin</td>
<td>Metaglip</td>
</tr>
<tr>
<td>metformin</td>
<td>Glucophage</td>
</tr>
<tr>
<td>pioglitazone</td>
<td>Actos</td>
</tr>
<tr>
<td>sitagliptin</td>
<td>Januvia</td>
</tr>
</tbody>
</table>

Question #1

- I am ______ in my understanding of the role of the kidney in glucose regulation.
  1) Very Confident
  2) Confident
  3) Somewhat Confident
  4) Unsure/Not Confident

Question #2

- ______ actively transports most of the glucose across the proximal convoluted tubule cells of the kidney.
  1) SGLT 1
  2) SGLT 2
  3) GLUT 1
  4) GLUT 2

Question #3

- I am ______ in my understanding of newer therapies that do not specifically target insulin resistance and impaired insulin secretion in type 2 diabetes.
  1) Very Confident
  2) Confident
  3) Somewhat Confident
  4) Unsure/Not Confident

Question #4

- Potential benefits of the SGLT2 inhibitors in addition to glucose lowering include:
  1) BP lowering
  2) Reduction in LDL-C
  3) Weight loss
  4) BP lowering and weight loss
  5) All of the above

Question #5

- If available, I would most likely use SGLT 2 inhibitors ______ in some of my type 2 diabetes patients.
  1) As monotherapy
  2) In combination with other antidiabetic agents (not including insulin)
  3) In combination with insulin
  4) 1 and 2
  5) 1 and 3
  6) 1, 2, and 3
  7) I am unsure
  8) I would not use them
The Pathophysiology of Glucose Regulation in the Kidney

Jaime A. Davidson, MD
Clinical Professor of Medicine
Division of Endocrinology, Diabetes and Metabolism
University of Texas Southwestern Medical School
Dallas, Texas

Glucose Control by the Kidney

- Gluconeogenesis
  - Proximal tubule
  - Renal contribution more substantial than previously believed
    - ≈ 20% of postabsorptive total-body glucose release
    - ≈ 40% of gluconeogenesis
  - Reabsorption of filtered glucose
    - > 99% of glucose in glomerular filtrate is reabsorbed in the proximal renal tubule

Glucose Transporters in the Proximal Renal Tubule

- S1 and S2 segments
  - SGLT2: 90% of reabsorption
- S3 segment
  - SGLT1: 10% of reabsorption

Renal Handling of Glucose

(180 L/day) (900 mg/L) = 162 g/day

Glucose Transport in Tubular Epithelial Cells

- SGLT2: High capacity, low affinity
- SGLT1: High capacity, high affinity

Sodium-Glucose Cotransporters

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

Renal Glucose Handling

- Tmax: Maximum rate of glucose reabsorption
- Threshold: Glucose filtration rate at which glucose reabsorption begins

Altered Renal Glucose Control in Diabetes

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

- Glucose reabsorption
  - Increased SGLT activity observed in diabetic versus normoglycemic mice
  - Increased SGLT2 expression and activity in renal epithelial cells from patients with diabetes versus normoglycemic individuals

Renal and Hepatic Glucose Release After Glucose Ingestion in Patients With Diabetes

- Increased baseline gluconeogenesis
- Insulin resistance with decreased suppression of gluconeogenesis
- Increased free fatty acids in DM stimulates gluconeogenesis in kidney & liver

**Schematic representation of the typical titration curve for renal glucose reabsorption in man.**


Renal SGLT2 Levels are Increased in Type 2 DM

Protein levels and glucose uptake in human exfoliated proximal tubular epithelial cells (HEPTECs) from individuals with normal glucose tolerance (NGT) or Type 2 DM

Renal SGLT2 Levels are Increased in Type 2 DM

Glucose Regulation: Summary

- Renal processes contribute to blood glucose regulation
- Glucose reuptake and production
- Renal processes of blood glucose regulation is altered in type 2 diabetes
- Gluconeogenesis increased
- Renal glucose reabsorption increased
- Alterations in blood glucose regulation contribute to hyperglycemia in diabetes

Functional Disorders

- Familial renal glucosuria
  - Due to SGLT2 gene mutations
  - Rare kidney disorder
  - Benign
  - No corresponding kidney complications
  - Urinary glucose excretion of 1-170 g/d
  - Absence of glucose reabsorption indicated by higher urinary glucose excretion

- Intestinal glucose-galactose malabsorption
  - Due to SGLT1 gene mutations
  - Severe diarrhea
  - Suggests major role for SGLT1 in intestinal reabsorption
  - Corrected by removing glucose, galactose, lactose from the diet
  - Mild glucosuria consistent with minor SGLT1 role in renal reabsorption

Lessons from Genetics

From Familial Renal Glucosuria to Type 2 Diabetes Intervention

Renal Glucose Handling After SGLT2 Inhibition

Summary: Rationale for SGLT2 Inhibitors

- SGLT2 is responsible for 90% of renal glucose reabsorption
- Mutations in SGLT2 transporter are benign
- Potentially lower blood glucose levels – due to increased renal excretion of glucose
- Potential weight loss – due to urine loss of the calories from glucose
Achieving Glycemic Control Through the Kidney in Type 2 Diabetes

Robert R. Henry, MD
Professor of Medicine
University of California San Diego

Renal Handling of Glucose in a Non-Diabetic Individual

Glucose Transport in Tubular Epithelial Cells

Sodium Glucose Co-Transporter 2 (SGLT2) Inhibition

A Novel Approach to Reduce Hyperglycemia

Summary of Renal Glucose Re-Absorption

Selective SGLT2 Inhibitors

A Potential Solution to Control Hyperglycemia?

- Inhibition of SGLT2-mediated glucose re-absorption in the renal proximal tubule leads to increased glycosuria and reduced plasma glucose levels
- In animals (diabetic rats) results in:
  - Enhanced insulin sensitivity
  - Suppressed hepatic glucose production
  - Improved insulin secretion via reduced glucose toxicity
- Mechanism of action is independent of insulin resistance or the severity of beta-cell dysfunction
### SGLT2 Inhibitors in Clinical Development

<table>
<thead>
<tr>
<th>Compounds in development</th>
<th>Development status</th>
<th>Anticipated filing date</th>
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<tbody>
<tr>
<td>Dapagliflozin</td>
<td>Phase III clinical trials</td>
<td>Filed in December, 2010</td>
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<tr>
<td>Canagliflozin</td>
<td>Phase III clinical trials</td>
<td>2H 2012</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>Phase III clinical trials</td>
<td>2H 2013 (US &amp; EU)</td>
</tr>
<tr>
<td>LX4211</td>
<td>Phase II clinical trials</td>
<td>Unclear</td>
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</table>

### Calculated 24-hr Mean Renal Threshold for Glucose on Day 1 after Canagliflozin Dosing

48 healthy males; RTilm renal threshold for glucose

Sha S et al., Diabetes Obes Metab. 2011;13:669-672

### Increased Urinary Glucose Excretion in Longer Term with Dapagliflozin

Nauck MA, et al., Diabetes Care 2011;34:2015-22. Dapagliflozin not FDA approved

### Change in FPG in 12-16 Week Monotherapy Studies of SGLT2 Inhibitors


### Change in HbA1c in 12-16 Week Monotherapy Studies of SGLT2 Inhibitors


### Change in FPG in 12-Week Add-on to Metformin Studies of SGLT2 Inhibitors

Change in HbA1c in 12-Week Add-on to Metformin Studies of SGLT2 Inhibitors


<table>
<thead>
<tr>
<th>Mean Baseline HbA1c, %</th>
<th>7.7</th>
<th>7.9</th>
</tr>
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<tbody>
<tr>
<td>Mean change in HbA1c (% from baseline)</td>
<td>-0.8</td>
<td>-0.7</td>
</tr>
</tbody>
</table>

50 mg qd 100 mg qd 200 mg qd 300 mg qd 300 mg bid Sitagliptin 1 mg qd 5 mg qd 10 mg qd 25 mg qd 50 mg qd

Canagliflozin (placebo adjusted values) 12 wk study (N=451)

Empagliflozin (placebo adjusted values) 12 wk study (N=495)

Canagliflozin & Empagliflozin not FDA approved

Statistical significance not reported

**Significantly superior to monotherapy (p<0.0001); † Non-inferior compared to limit of 0.35% Adjusted mean change from baseline using ANCOVA, excluding data after rescue (LOCF)

Change in HbA1c in 24-Week Dapagliflozin Initial Combination with Metformin XR Study


<table>
<thead>
<tr>
<th>BL mean (%)</th>
<th>9.03</th>
<th>9.03</th>
<th>9.10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapa 10 mg vs. MET XR</td>
<td>-0.01 (-0.22, 0.20) †</td>
<td>-0.53**</td>
<td></td>
</tr>
</tbody>
</table>

Combination vs. Monotherapies -0.54**

Adjusted % of patients with ≥1 episode of hypoglycaemia #


*Statistically significant vs. placebo using Dunnett’s correction Adjusted mean change from baseline using ANCOVA, excluding data after rescue (LOCF)

Change in HbA1c at 104 Weeks in Dapa vs. SU Add-on to Met Study


Dapagliflozin not FDA approved

Data are adjusted mean change from baseline ± 95% CI derived from a repeated measures mixed model. DAPA, dapagliflozin. DB, double-blind. MET, metformin

Change in FPG at Week 24 Across Studies

Dapagliflozin: Change in FPG at Week 24 Across Studies

Dapagliflozin not FDA approved

<table>
<thead>
<tr>
<th>Δ FPG (mg/dL) with 95% CI</th>
<th>-21.7</th>
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<tbody>
<tr>
<td>Mono-therapy (N=558)</td>
<td>162.7</td>
</tr>
<tr>
<td>Add-on to MET (N=548)</td>
<td>163.3</td>
</tr>
<tr>
<td>Add-on to SU (N=596)</td>
<td>172.9</td>
</tr>
<tr>
<td>Add-on to PIO (N=420)</td>
<td>164.8</td>
</tr>
<tr>
<td>Add-on to Insulin (N=807)</td>
<td>177.6</td>
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</tbody>
</table>

Dapagliflozin not FDA approved

<table>
<thead>
<tr>
<th>Δ HbA1c (%) with 95% CI</th>
<th>-0.14% (-0.25, -0.03)</th>
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<tbody>
<tr>
<td>DAPA + MET (N=400)</td>
<td>7.69</td>
</tr>
<tr>
<td>GLIP + MET (N=401)</td>
<td>7.74</td>
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</tbody>
</table>

Dapagliflozin not FDA approved

| Statistical significance vs. placebo by hierarchical testing rule. *p<0.05; **p<0.001 Adjusted mean change from baseline using ANCOVA, excluding data after rescue (LOCF) | -0.32% (-0.42, -0.21) |

Del Prato S, et al. Presented at the Annual Meeting of the EASD, 12-16 September, 2011 (Presentation no #852). Dapagliflozin not FDA approved
Change in Body Weight in 12-16 Week Monotherapy Studies of SGLT2 Inhibitors

Mean change in body weight (kg) from baseline


Baseline body weight, kg 69.37 67.18 -3.5 -3 -2.5 -2 -1.5 -1 -0.5 0

50 mg qd 100 mg qd 200 mg qd 300 mg qd Placebo 5 mg qd 10 mg qd 25 mg qd Placebo 50 mg

Cangliflozin 12 wk study in Japanese patients (N=383)
Empagliflozin 12 wk study (N=408)
Ipragliflozin 16 wk study in Japanese patients (N=129)

Canagliflozin, Empagliflozin, & Ipraglifloxin not FDA approved
Statistical significance not reported

Change in Body Weight in 12-Week Add-on to Metformin Studies of SGLT2 Inhibitors

Mean change in body weight (kg) from baseline


Baseline body weight, kg 87 -3.5 -3 -2.5 -2 -1.5 -1 -0.5 0

0.5 1

50 mg qd 100 mg qd 200 mg qd 300 mg qd 300 mg bid Sitagliptin
1 mg qd 5 mg qd 10 mg qd 25 mg qd 50 mg qd Placebo

Sitagliptin Placebo

Canagliflozin (placebo adjusted values) 12 wk study (N=451)
Empagliflozin 12 wk study (N=495)

Canagliflozin & Empagliflozin not FDA approved
Statistical significance not reported

Dapagliflozin Adjusted Mean Change from Baseline in Body Weight in Phase 3 Studies (10 mg dose)

Baseline values

Adjusted mean change from baseline in Body Weight (kg)

24 wk Monotherapy 1
Add-on to Metformin 2 Add-on to SU 3 Add-on to Insulin (24 wks) 4 Add-on to Insulin (48 wks) 5


Dapagliflozin not FDA approved

Dapagliflozin Adjusted Mean Change from Baseline in Blood Pressure in Phase 3 Studies (10 mg dose)

Systolic BP (mm Hg) Diastolic BP (mm Hg)

24 Wk Monotherapy 1
Add-on to Metformin 2 Add-on to SU 3


Statistical significance not reported

Studies examining effects of other SGLT 2 inhibitors on BP underway

Infections in the Setting of Pharmacologically-Induced Glucosuria in Men on Dapagliflozin

Balanitis and other related infections Urinary Tract Infections

Men

Women

FDA Advisory Committee 19th July 2011: http://www.fda.gov
Dapagliflozin not FDA approved

Statistical significance not reported

Infections in the Setting of Pharmacologically-Induced Glucosuria in Women on Dapagliflozin

Vulvovaginitis and other related infections Urinary Tract Infections

Women

FDA Advisory Committee 19th July 2011: http://www.fda.gov
Dapagliflozin not FDA approved

Statistical significance not reported
Incidence of Vulvovaginal Candidiasis in Female Patients on Canagliflozin


An increase in vulvovaginal candidiasis in female patients was observed with canagliflozin.

- N=158
- Canagliflozin not FDA approved
- Statistical significance not reported

Genital Infections and UTI with Empagliflozin


An increase in genital infections was observed with empagliflozin.

- N=495
- Empagliflozin not FDA approved
- Statistical significance not reported

Events of Hypotension / Hypovolaemia / Dehydration in Dapagliflozin Studies

<table>
<thead>
<tr>
<th>Number (%) of Patients</th>
<th>Dapa 2.5 mg N = 814</th>
<th>Dapa 5 mg N = 1145</th>
<th>Dapa 10 mg N = 1193</th>
<th>Pbo N = 1393</th>
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</thead>
<tbody>
<tr>
<td>Total Subjects with an Event</td>
<td>10 (1.2)</td>
<td>7 (0.6)</td>
<td>9 (0.8)</td>
<td>5 (0.4)</td>
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<tr>
<td>Hypotension</td>
<td>6 (0.7)</td>
<td>5 (0.4)</td>
<td>5 (0.4)</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Syncope</td>
<td>0</td>
<td>0</td>
<td>2 (0.2)</td>
<td>1 (&lt;0.1)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>3 (0.4)</td>
<td>0</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
</tr>
<tr>
<td>Urine Flow Decreased</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
</tr>
<tr>
<td>Blood Pressure Decreased</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;0.1)</td>
</tr>
<tr>
<td>Orthostatic Hypotension</td>
<td>1 (0.1)</td>
<td>2 (0.2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Urine Output Decreased</td>
<td>1 (0.1)</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;0.1)</td>
</tr>
</tbody>
</table>

Bladder Cancer in Dapagliflozin Studies

- 9 Bladder Cancers in 5,501 pts (0.16%) treated with dapa vs 1 in 3,184 (0.03%) treated with placebo/comparator
- All bladder cancers in male patients
- 7 of these 10 pts had hematuria prior to study treatment
  - In the overall study population, in males, hematuria reported at baseline in 7.8% of dapa pts and 8.2% of control pts
- 8 pts with bladder cancer were current or former smokers
- 5 pts were diagnosed at < 6 months from start of study treatment; none at > 24 months
- Too few events to establish causality
- No carcinogenicity or mutagenicity signal in animal studies
- Note: SGLT 2 has not been shown to be expressed in human bladder tissue

Breast Cancer in Dapagliflozin Studies

- 10 Breast Cancers in 2,531 women (0.40%) treated with dapa vs 3 in 1,359 women (0.22%) treated with placebo/comparator
- All breast cancers in female patients & > 50 yrs old
  - 10/13 > 60 yrs old
- All but one patient were post-menopausal
- All cases detected < 1 yr after exposure to dapa
  - 2 reported within first 8 weeks of treatment
- Too few events to establish causality
- No carcinogenicity or mutagenicity signal in animal studies
- Note: SGLT 2 has not been shown to be expressed in human breast tissue
### Case Presentation: Karen

- **Current Diagnoses: Type 2 Diabetes Mellitus**
- **Medical History:** 2-year history of Type 2 Diabetes Mellitus, initial A1c = 8.5%
- **Medication history:**
  - Started on metformin, increased to a dose of 1000 mg twice daily. A1c was lowered to approx. 7% at 12 months.
  - After 1.5 years, A1c was lowered to 7.8% and glipizide was added to her treatment regimen; had experienced a weight gain of 5 pounds as well as several episodes of mild hypoglycemia over the next 6 months. Sulfonylureas were discontinued.
- **Current Activity: Working as Administrative Assistant, walks 3-5 days a week, 30 minutes per day.
- **Diet:** States diet isn’t great, because she’s “human”, but feels she does as well as she can. Tries to prepare meals at home at night; for lunch, has to grab something “quick, and not always ideal”.
- **Concerns:** She is concerned about injection side effects and safety. Not excited about injections but willing to try if it will help to lower her A1c.
- **Blood pressure:** 135/84 mmHg
- **BMI:** 36 kg/m²
- **Blood glucose:** FPG averages 140 mg/dL and PPG ranges from 190-235 mg/dL
- **SMBG:** Self-Monitoring of Blood Glucose
Which of the following statements is most likely correct with regard to treatment considerations for this patient?

1) Her lack of more exercise is the most likely contributing factor to her weight gain
2) She should be counseled to adhere to her glipizide treatment because metformin is more likely to contribute to her weight gain than glipizide
3) A positive energy balance and her glipizide treatment are the most likely contributing factors to her weight gain
4) It was prudent for her to stop taking the sulfonylurea

What is your A1C glycemic goal for this patient?

1) <7.5
2) <7.0
3) <6.5
4) Lowest possible without hypoglycemia

My add-on drug to metformin for management of hyperglycemia in this patient is:

1) Another trial of Sulfonylurea (lower dose) or glinide
2) TZD
3) SGLT 2 inhibitor (if available)
4) DPP-4 inhibitor
5) GLP-1 analog
6) Alpha-glucosidase inhibitor
7) Colesevelam
8) Insulin

If this patient were 65 years old instead of 45 yo, and has had diabetes for 20 years, my A1c goal for this patient would be:

1) < 8
2) < 7.5
3) < 7
4) < 6.5
5) Lowest possible without hypoglycemia

If this patient were 65 years old instead of 45 yo, and has had diabetes for 20 years, my add-on drug to metformin for management of hyperglycemia would be:

1) Sulfonylurea or glinide
2) TZD
3) SGLT 2 inhibitor (if available)
4) DPP-4 inhibitor
5) GLP-1 analog
6) Alpha-glucosidase inhibitor
7) Colesevelam
8) Insulin
9) No add-on drug

Question # 1

I am _____ in my understanding of the role of the kidney in glucose regulation.

1) Very Confident
2) Confident
3) Somewhat Confident
4) Unsure/Not Confident
Question # 2

• ______ actively transports most of the glucose across the proximal convoluted tubule cells of the kidney.

1) SGLT 1  
2) SGLT 2  
3) GLUT 1  
4) GLUT 2

Question # 3

• I am ______ in my understanding of newer therapies that do not specifically target insulin resistance and impaired insulin secretion in type 2 diabetes.

1) Very Confident  
2) Confident  
3) Somewhat Confident  
4) Unsure/Not Confident

Question # 4

• Potential benefits of the SGLT2 inhibitors in addition to glucose lowering include:

1) BP lowering  
2) Reduction in LDL-C  
3) Weight loss  
4) BP lowering and weight loss  
5) All of the above

Question # 5

• If available, I would most likely use SGLT 2 inhibitors ______ in some of my type 2 diabetes patients.

1) As monotherapy  
2) In combination with other antidiabetic agents (not including insulin)  
3) In combination with insulin  
4) 1 and 2  
5) 1 and 3  
6) 1, 2, and 3  
7) I am unsure  
8) I would not use them