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

New York, New York
June 23, 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

Vivian Fonseca, MD, FRCP
Professor of Medicine
Chief of Endocrinology Section
Tulane University Medical Center
New Orleans, Louisiana

Vivian A. Fonseca, MD, FRCP, is professor of medicine, the Tullis–Tulane Alumni Chair in diabetes, and chief of the section of endocrinology at Tulane University Medical Center in New Orleans, Louisiana and is the president for Science and Medicine of the American Diabetes Association. Previously Dr Fonseca had served on and been chairman of the clinical practice committee of the American Diabetes Association (ADA), the ADA Disaster Task Force, the ADA strategic planning committee, and the joint ADA/ACC “Make the Link” Program. Dr Fonseca is a fellow of the American Association of Clinical Endocrinologists, the Royal College of Physicians (London), and the American College of Physicians. He is a member of the Endocrine Society, the American Diabetes Association, and the International Diabetes Federation.

Dr Fonseca’s current research interests include the prevention and treatment of diabetic complications and risk factor reduction in cardiovascular disease. He has a research program evaluating homocysteine and inflammation as risk factors for heart disease in diabetes. He is also an investigator in the National Institutes of Health (NIH)-funded Action to Control Cardiovascular Risk in Diabetes (ACCORD) study and serves on the glycemia control committee. Dr Fonseca is a co-investigator on the NIH TINSAL–T2D study and serves on the steering and ancillary studies committees. He is an ad hoc reviewer for several journals, including New England Journal of Medicine, JAMA, Diabetes, Diabetic Medicine, Kidney International, the American Journal of Clinical Nutrition, the British Medical Journal, and Metabolism. Dr Fonseca has authored over 250 papers and is the editor of the textbook Clinical Diabetes: Translating Research into Practice (Elsevier) and several monographs and book chapters.
Eugenio Cersosimo, MD, PhD, is the medical director of clinical research at the Texas Diabetes Institute and an associate professor of medicine at the University of Texas Health Science Center in San Antonio, Texas. He is board certified in endocrinology, diabetes, and metabolism and maintains an active practice in the adult outpatient clinic in San Antonio.

Dr. Cersosimo graduated from medical school at the Universidade Federal Fluminense in Rio de Janeiro, Brazil in 1975 and in 1986 obtained a doctorate degree in physiology at Vanderbilt University in Nashville, Tennessee. In 1994 he completed his training in internal medicine and endocrinology, diabetes, and metabolism in the clinician-investigator track at the Mayo Clinic, Rochester, Minnesota. He started his academic career as an assistant professor of medicine at the State University of New York at Stony Brook, New York, and in 2001 transferred to his current position.

Dr. Cersosimo has authored more than 60 original manuscripts and has received numerous research grants and awards from the National Institutes of Health, Juvenile Diabetes Foundation, American Diabetes Association, Kronkosky Foundation, Howard Hughes Institute, and from various pharmaceutical companies. Presently, he is directly involved in and supervises more than 20 different research projects in areas of his greatest interest: glucose regulation, the entero-pancreatic axis, and insulin therapy and insulin resistance with a focus on cardiovascular and renal complications.

Faculty Financial Disclosure Statements
The presenting faculty report the following:

Dr. Fonseca reports he has received research grant funding (to Tulane) from Novo Nordisk Pharmaceuticals, Inc., sanofi-aventis, Eli Lilly and Company, Daiichi Sankyo, Inc., Pamlab, Reata Pharmaceuticals, Inc., and Halozyme Therapeutics.
He has received honoraria for consulting and lectures from GlaxoSmithKline, Takeda, Novo Nordisk Pharmaceuticals, Inc., sanofi-aventis, Eli Lilly and Company, Daiichi Sankyo, Inc., Pamlabs, Xoma, Bristol-Myers Squibb Company and AstraZeneca Pharmaceuticals, LP.
Dr. Fonseca intends to reference unlabeled/unapproved uses of SGLT2 inhibitors in his presentation.

Dr. Cersosimo reports he has received honoraria from Takeda Pharmaceuticals, Amylin, and sanofi-aventis.
Dr. Cersosimo intends to reference unlabeled/unapproved uses of SGLT2 inhibitors in his presentation.

Education Partner Financial Disclosure Statement
The content collaborator at Voxmedia reports the following:
John F. Kocsis, PhD, has no financial relationships to 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>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
</tr>
</thead>
<tbody>
<tr>
<td>colesevelam</td>
<td>Welchol</td>
</tr>
<tr>
<td>glimepiride</td>
<td>Amaryl</td>
</tr>
<tr>
<td>glipizide</td>
<td>Glucotrol</td>
</tr>
<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>

**Generic** | **Trade** | **Investigational**
---|---|---
| canagliflozin | | investigational |
| dapagliflozin | | investigational |
| empagliflozin | | investigational |
| ipragliflozin | | investigational |
| LX4211        | | investigational |

**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

INSIGHTS INTO GLUCOSE REGULATION BY THE KIDNEY

Eugenio Cersosimo, M.D., Ph.D.
Associate Professor of Medicine
Medical Director, Clinical Research
Texas Diabetes Institute
University of Texas HSC at San Antonio

Eugenio Cersosimo, M.D., Ph.D.
Disclosure Statement

Research funding: Merck & Co., Inc.

INSIGHTS INTO GLUCOSE REGULATION BY THE KIDNEY

I: Glomerular Filtration and Reabsorption
II: Glucose Production (Gluconeogenesis)
III: Glucose Utilization

- Glycogen storage
- Lactate formation
- Glucose oxidation

Gerich J. Baillieres Clin Endocrinol Metab. 1993;7:551-86

INSIGHTS INTO GLUCOSE REGULATION BY THE KIDNEY


INSIGHTS INTO GLUCOSE REGULATION BY THE KIDNEY

SGLT-2 Mediates Glucose Reabsorption in the Kidney

E Gerszonimo, R Judd and JM Miles. J Clin Invest. 1994;93:584-89,

SGLT-2 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 Threshold “Maladaptation” in Diabetes

- Renal threshold for glucose reabsorption ($T_{mG}$) is increased by 20-40% in type 2 diabetes
  (Farber SJ et al. J Clin Invest 1951; 30:125-29)
- Similar elevations have been reported in type 1 diabetes
- Cultured human renal tubular cells show enhanced SGLT-2 expression, its protein concentration with augmented glucose transport capacity

This represents a maladaptive response in diabetes aimed at conservation of glucose for energy needs

Rationale for Selective SGLT-2 Inhibition in Diabetes

- Correction of the overactive renal tubular glucose reabsorption rates
- Minimize gastrointestinal side effects associated with SGLT-1 inhibition by nonselective agents
- Potential to cause negative energy balance with “desired” body weight loss and maintenance
- No effect on insulin secretion or risk of hypoglycemia
- Unique mechanism of plasma glucose lowering

Familial Renal Glucosuria

- Autosomal recessive deficiency or decreased affinity of SGLT2
- Characterized by persistent urinary glucose excretion within normal plasma glucose concentration
- No evidence of renal glomerular or tubular dysfunction
- Hypoglycemia is rare; Renal histology & Renal function are normal
- The incidence of diabetes, chronic renal failure & urinary tract infection are not increased
- Homozygous individuals have severe glucosuria (15-200 g/day)

Effect of Non-selective SGLT Inhibition on Plasma Glucose in Diabetic Rats
Phlorizin injection in partially-pancreatectomized rat model of diabetes

SGLT 2 INHIBITION: MEETING THE NEEDS IN DIABETES CARE

- Corrects a Novel Pathophysiologic Defect
- Reduces HbA1c
- Promotes Weight Loss
- Improves Glycemic Control and Decreases CV Risk Factors
- Complements Action of Other Anti-diabetic Agents
- Reduces Blood Pressure
- No Hypoglycemia
- Reversal of Glucotoxicity

Summary

- The kidney helps to maintain glucose homeostasis by free glomerular filtration and complete tubular reabsorption with simultaneous glucose production and utilization
- SGLT-2 is located in the S1 segment of proximal tubules and is responsible for 90% of all glucose reabsorbed
- Normal renal threshold is reached at plasma glucose concentrations of 180-220 mg/dl; glucosuria follows
- In diabetes, a maladaptive increase in the renal glucose reabsorption threshold contributes to hyperglycemia
- Selective SGLT-2 inhibition could become an important treatment target & play a role in diabetes management

Targeting the Kidney in Managing Hyperglycemia: Exploring the Evidence

Vivian Fonseca, MD
Tulane University Medical Center
New Orleans, LA

Vivian Fonseca, MD Disclosure Statement

- Dr. Fonseca will discuss or present information that is related to an off-label or investigational use of SGLT inhibitors.
Major Targeted Sites of Oral Drug Classes

Pancreas
Muscle and fat
Liver
Kidney

Hepatic glucose overproduction

Effect of SGLT2 Inhibition (Mode of Action)

Potential Benefits
- Insulin-independent
- Glycemic benefits
- HbA1c
- Fasting plasma glucose (FPG)
- Postprandial glucose (PPG)
- Body weight benefits
- Blood pressure benefits

Potential Risks
- Hyperglycemia
- Renal function
- Diabetic effect
- Hypoglycemia
- Hypertension
- Dehydration
- Bone mineral metabolism
- Urinary tract infections, vulvovaginitis, balanitis

DPP-4=dipeptidyl peptidase 4; TZDs=thiazolidinediones.

Effect of Non-selective SGLT Inhibition on Plasma Glucose in Diabetic Rats

Phlorizin injection in a part-pancreatectomized rat model of diabetes

SGLT2 Inhibitors in Clinical Development

Compounds in development
Development status
Anticipated filing date

Dapagliflozin
Phase III clinical trials; FDA complete response letter issued Jan. 2012 requesting add'l clinical data
Filed in December, 2010

Canagliflozin
Phase III clinical trials
Filed May 2012

Empagliflozin
Phase III clinical trials
2H 2013 (US & EU)

Ipragliflozin
Phase III clinical trials
Japan – 2013
US – 2H 2013
EU – 2H 2013

LX4211
Phase II clinical trials
Unclear

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

Increased Urinary Glucose Excretion in Longer Term with Dapagliflozin

SGLT: sodium-glucose co-transporter

aP<0.05; bP<0.001

Fasting glucose values are means ± SD

Sha S et al. Diabetologia 2011;54:666-673

Canagliflozin not FDA approved

FDA Advisory Committee 19th July 2011: http://www.fda.gov
**Significantly superior to monotherapy (p<0.0001);**

Adjusted mean change from baseline using ANCOVA, excluding data after rescue (LOCF).

Dapagliflozin not FDA approved.

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Baseline FPG, mg/dL (mmol/L)</th>
<th>Change in FPG, mg/dL (mmol/L)</th>
<th>Mean Baseline FPG, mg/dL (mmol/L)</th>
</tr>
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<tbody>
<tr>
<td>Dapagliflozin</td>
<td>162.0 (9.0)</td>
<td>-1.68 (0.11)</td>
<td>175 (8.7)</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>164.0 (9.5)</td>
<td>-1.54 (0.33)</td>
<td>179 (9.3)</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>165.0 (9.7)</td>
<td>-1.48 (0.32)</td>
<td>183 (9.9)</td>
</tr>
</tbody>
</table>

Statistical significance not reported.

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

<table>
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<tr>
<th>Treatment</th>
<th>Mean Baseline FPG, mg/dL (mmol/L)</th>
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Statistical significance not reported.

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Baseline HbA1c, %</th>
<th>Change in HbA1c, %</th>
<th>Mean Baseline HbA1c, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>8.00</td>
<td>-0.54**</td>
<td>7.92</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>8.32</td>
<td>-0.54**</td>
<td>8.28</td>
</tr>
</tbody>
</table>

Statistical significance not reported.

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

<table>
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<tr>
<th>Treatment</th>
<th>Mean Baseline HbA1c, %</th>
<th>Change in HbA1c, %</th>
<th>Mean Baseline HbA1c, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>7.7</td>
<td>-0.54**</td>
<td>7.66</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>7.9</td>
<td>-0.54**</td>
<td>7.86</td>
</tr>
</tbody>
</table>

Statistical significance not reported.

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Adjusted % of patients with ≥ 1 episode of hypoglycaemia</th>
<th>Difference 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapagliflozin vs. Metformin XR</td>
<td>1.1%</td>
<td>-0.00(-0.60 to 0.60)</td>
</tr>
</tbody>
</table>

**Statistically significant by heirarchical testing rule.**

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### Change in HbA1c at 52 Weeks in Dapagliflozin vs. SU Add-on to Metformin Study

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Adjusted mean change from baseline using ANCOVA (LOCF)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapagliflozin vs. Glipizide</td>
<td>-0.59</td>
<td>-0.60 to 0.07</td>
</tr>
</tbody>
</table>

Dapagliflozin not FDA approved.

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### Change in HbA1c at 52 Weeks in Dapagliflozin vs. Glipizide Study

<table>
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<td>Dapagliflozin vs. Glipizide</td>
<td>0.00%</td>
<td>0.00% (-0.60 to 0.60)</td>
</tr>
</tbody>
</table>

Adjusted mean change from baseline using ANCOVA (LOCF). **p<0.0001.**

Dapagliflozin not FDA approved.
Change in HbA1c to 104 Weeks in Dapa vs. SU Add-on to Met Study

Change in HbA1c with Dapagliflozin across 24-Week Studies

Change in Body Weight in 12-16 Week Monotherapy Studies of SGLT2 Inhibitors

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

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

Dapagliflozin not FDA approved

Studies examining effects of other SGLT 2 inhibitors on BP underway

Statistical significance not reported

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

Balanitis and other related infections

Urinary Tract Infections

Statistical significance not reported

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

Vulvovaginitis and other related infections

Urinary Tract Infections

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

Statistical significance not reported

Genital Infections and UTI with Empagliflozin

An increase in genital infections was observed with empagliflozin

Statistical significance not reported

Events of Hypotension / Hypovolaemia / Dehydration in Dapagliflozin Studies

Placebo-controlled Pool – Short-Term Period

Pooled data from placebo-controlled dapagliflozin studies

Statistical significance not reported

Dapagliflozin not FDA approved
Events All Phase 2b and 3 Pool, All Cases as of May 2011

FDA Advisory Committee 19th July 2011: http://www.fda.gov

Dapagliflozin not FDA approved

Incidence Rate Difference with 95% CI

Malignant and Unspecified Tumors by Tumor Origin in Dapagliflozin Studies

Gender-specific tumor types:
- Breast (Female)
- Prostate (Male)
- Female Reproductive (Female)

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

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

Dapagliflozin Update
- Letter requests additional clinical data to allow a better assessment of the benefit-risk profile for dapagliflozin.

Targets for Oral Antidiabetic Therapies
Case Presentation
Karen

- 45-year-old Caucasian woman with a 2-year history of type 2 diabetes mellitus; initial A1c = 8.5 %
- Started on metformin, increased to a dose of 1000 mg twice daily. A1c with level to approx. 7.5 % at 12 months
- 1.5 years after diagnosis, A1c = 7.8 % and glipizide 10 mg daily 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, she discontinued sulfonylureas

Case Presentation
Karen

- Currently working as Administrative Ass’t, walks 3-5 days a week, 30 minutes per day
- 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”
- She has heard about injections for weight loss, not excited about injecting but will try if it will help
- She also is concerned about the complications and knows her A1c needs to be lower

Two years after diagnosis, and on metformin only, A1c = 7.9 %
SMBG: her fasting plasma glucose (FPG) averages 140 mg/dL and her postprandial glucose (PPG) ranges from 190-235 mg/dL.
5 feet 4 inches tall (body mass index [BMI] = 36 kg/m²)
Blood pressure is 135/84 mmHg; and her lipids are within the target range according to laboratory tests performed last week

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
  
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**Question # 4**  
- Potential benefits of the SGLT2 inhibitors in addition to glucose lowering include:
  
  1) BP lowering  
  2) Reduction in LDL-C  
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  4) BP lowering and weight loss  
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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
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  6) 1, 2, and 3
  7) I am unsure
  8) I would not use them