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

Rosemont, Illinois
September 19, 2012
Session 3: 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

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, 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 American Diabetes Association, the Department of Veterans Affairs, and numerous pharmaceutical grants. Recent awards include the Distinguished Clinical Scientist Award and Banting Medal for service from the American Diabetes Association, 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
Clinical Professor of Medicine
Division of Endocrinology, Diabetes and Metabolism
University of Texas Southwestern Medical School
Dallas, Texas

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 reports the following:

Dr Henry reports he has received grants/research support (via the University of California San Diego and/or Veterans Medical 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, Merek & Co., Novo Nordisk Pharmaceuticals, Orexigen Therapeutics, Roche Pharmaceuticals, sanofi-aventis, Tethys Bioscience, Versartis, and Vivus. 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 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 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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<tr>
<td>T2D</td>
<td>type 2 diabetes</td>
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<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>
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<tr>
<td>AACE</td>
<td>American Association of Clinical Endocrinologists</td>
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Suggested Reading List


Drug List

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<tr>
<th>Generic</th>
<th>Trade</th>
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<tr>
<td>colesuvelam</td>
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<tr>
<td>glimepiride</td>
<td>Amaryl</td>
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<td>glibizide</td>
<td>Glucotrol</td>
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<tr>
<td>glibizide, metformin</td>
<td>Metagliz</td>
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<tr>
<td>metformin</td>
<td>Glucophage</td>
</tr>
<tr>
<td>pioglitazone</td>
<td>Actos</td>
</tr>
<tr>
<td>sitagliptin</td>
<td>Januvia</td>
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<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
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<tr>
<td>canagliflozin</td>
<td>investigational</td>
</tr>
<tr>
<td>dapagliflozin</td>
<td>investigational</td>
</tr>
<tr>
<td>empagliflozin</td>
<td>investigational</td>
</tr>
<tr>
<td>ipragliflozin</td>
<td>investigational</td>
</tr>
<tr>
<td>LX4211</td>
<td>investigational</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 Davidson, MD
Disclosure Information
- Consultant, and/or an Advisory or Speaker’s Board member: AstraZeneca Pharmaceuticals, Bristol-Myers Squibb Company, Bayer Pharmaceuticals, Eli Lilly & Co., Roche Diagnostic, Johnson & Johnson, Merck-Sharp and Dome, Novo Nordisk, and Takeda.
- Dr. Davidson intends to reference unlabeled/unapproved uses of SGLT2 inhibitors in his presentation.

The Nephron and Collecting System

- Glomerulus
  - Filters: Water, Glucose, Salts, Small metabolites from plasma into Bowman’s space
- Renal tubule
  - Water and ions reabsorbed
- Proximal convoluted tubule
  - K+, HCO3-, Cl-, PO4-3, glucose, amino acids, Na+, water reabsorbed (Angiotensin)
- Distal convoluted tubule
  - Final Na+ reabsorption (Aldosterone)
- Loop of Henle
- Collecting Duct
  - Final water reabsorption (Vasopressin)

Guyton and Hall, Textbook of Medical Physiology, Ch. 24.

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


Glomerular Filtration

- 125 mL of filtrate formed/min (180 L/24 h)
  - Urine output 1.5 L/24 h
- 25,000 mEq of Na+ filtered
  - Urine Na+ excretion
  - 100 mEq/L
- 144 g glucose filtered/24 h
  - Urine glucose excretion=0
- Because reabsorption occurs


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

Two Families of Glucose Transporters

GLUT Family
- Facilitated glucose transporters
- Passive, downhill transport
- GLUT1 (widespread including the kidneys)
- GLUT2 (kidneys and pancreas)
- GLUT4 (muscle and adipose tissue)

SGLT Family
- Sodium coupled glucose cotransporter
- Active transport of glucose
- SGLT1 (brush border of small intestine)
- SGLT2 (proximal tubule)

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</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</td>
<td>Renal glucose reabsorption</td>
</tr>
</tbody>
</table>

Renal Glucose Handling

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

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

Glucose Regulation: Summary

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

Lessons from Genetics

From Familial Renal Glucosuria to Type 2 Diabetes Intervention

Functional Disorders

- Familial renal glucosuria
  - Due to SGLT2 gene mutations
  - Rare kidney disorder
  - No corresponding kidney complications
  - Suggests major role for SGLT1 in intestinal reabsorption
  - Absence of glucose reabsorption indicated by higher urinary glucose excretion

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

Renal Glucose Handling After SGLT2 Inhibition


Rate of Glucose Filtration/Reabsorption/Excretion (mg/min)

Plasma Glucose (mg/dL)

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

Robert Henry, MD—Disclosure Information

- **Grants/Research Support** (via the University of California San Diego and/or Veterans Medical Research Foundation): Amylin Pharmaceuticals, Inc., AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Johnson & Johnson, Novartis Pharmaceuticals Corporation
- **Consultant:** Amgen, Inc., Boehringer Ingelheim Pharmaceuticals Inc., Eisai Pharmaceuticals, Inc., Novo Nordisk Pharmaceuticals, Inc., Roche Pharmaceuticals, sanofi-aventis, Tethys Bioscience, Inc., Takeda Pharmaceuticals

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

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; FDA complete response letter issued Jan. 2012 requesting addtl data</td>
<td>Filed in December, 2010</td>
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<tr>
<td>Canagliflozin</td>
<td>Phase III clinical trials</td>
<td>Filed May 2012</td>
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<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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Sodium Glucose Co-Transporter 2 (SGLT2) Inhibition
A Novel Approach to Reduce Hyperglycemia

![Sodium Glucose Co-Transporter 2 (SGLT2) Inhibition Diagram]

Canagliflozin not FDA approved

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

48 healthy males; RTG, renal threshold for glucose
Shia S et al. Diabetes Obes Metab. 2011;13:689-697
Increased Urinary Glucose Excretion in Longer Term with Dapagliflozin Titration Period Maintenance Period

Study Week
Dapagliflozin + Metformin (n = 406)
Glipizide + Metformin (n = 408)


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

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


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

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


Mean Baseline HbA1c, % 8.09 7.9 8.32
Statistical significance not reported

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

Dapagliflozin not FDA approved
Adjusted mean change from baseline using ANCOVA (LOCF) N's at Week 52 equal N's at baseline.

† Non-inferior compared to limit of 0.35%

Dapa
+ MET
Glip + MET

\[
\begin{array}{c|c|c|c|c|c}
& \text{N=400} & \text{N=401} \\
\hline
\text{BL Mean (%)} & 7.69 & 7.74 \\
\text{difference} & 0.00 & (95\% \text{ CI} -0.11 \text{ to } 0.11) \\
\end{array}
\]

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


Dapagliflozin not FDA approved


Dapagliflozin not FDA approved

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


Canagliflozin & Empagliflozin not FDA approved

Baseline body weight, kg

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


Canagliflozin & Empagliflozin not FDA approved

Baseline body weight, kg

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


Canagliflozin & Empagliflozin not FDA approved

Baseline body weight, kg

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


Canagliflozin & Empagliflozin not FDA approved

Baseline body weight, kg

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


Canagliflozin & Empagliflozin not FDA approved

Baseline body weight, kg

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


Canagliflozin & Empagliflozin not FDA approved

Baseline body weight, kg
**Weight Loss Characterization with Dapagliflozin**

- Dapagliflozin 10 mg/d or placebo added to open-label metformin (182 pts inadequately controlled on metformin)
- At 24 weeks, dapagliflozin reduced (vs placebo):
  - Total body weight (2.08 kg—placebo-corrected, p < 0.0001)
  - Waist circumference (P = 0.0001)
  - Fat mass (2/3 of weight loss attributed to reduction in fat mass), p = 0.0001
  - Lean mass (incorporates the fluid component), nominal p = 0.0211
  - Visceral adipose tissue, nominal p = 0.0084
  - Subcutaneous adipose tissue, nominal p = 0.0385


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

- Balanitis and other related infections
- Urinary Tract Infections

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

- Vulvovaginitis and other related infections
- Urinary Tract Infections

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

Genital Infections and UTI with Empagliflozin


N=495

An increase in genital infections was observed with empagliflozin

Events of Hypotension / Hypovolaemia / Dehydration in Dapagliflozin Studies

Number (%) of Patients

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dapa 2.5 mg</th>
<th>Dapa 5 mg</th>
<th>Dapa 10 mg</th>
<th>Pbo</th>
</tr>
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<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 (0.1)</td>
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<tr>
<td>Dehydration</td>
<td>3 (0.4)</td>
<td>0</td>
<td>1 (0.1)</td>
<td>0</td>
</tr>
<tr>
<td>Urine Flow Decreased</td>
<td>0</td>
<td>0</td>
<td>1 (0.1)</td>
<td>0</td>
</tr>
<tr>
<td>Blood Pressure Decreased</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (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>
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<tr>
<td>Urine Output Decreased</td>
<td>1 (0.1)</td>
<td>0</td>
<td>0</td>
<td>1 (0.1)</td>
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</table>

Pooled data from placebo-controlled dapagliflozin studies

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

Dapagliflozin not FDA approved

Malignant and Unspecified Tumors by Tumor Origin in Dapagliflozin Studies

<table>
<thead>
<tr>
<th>Tumor Origin</th>
<th>N = 4559</th>
<th>Control</th>
<th>Difference from Control</th>
<th>Δ</th>
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<tbody>
<tr>
<td>Overall Malignancies and Unspecified Tumors</td>
<td>45 29</td>
<td>4 1</td>
<td>0.716</td>
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<tr>
<td>Bladder * (squamous)</td>
<td>7 6</td>
<td>1</td>
<td>0.158</td>
<td></td>
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<tr>
<td>Thyroid and Endocrine</td>
<td>7 3</td>
<td>1</td>
<td>0.034</td>
<td></td>
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<tr>
<td>Gastrointestinal</td>
<td>4 4</td>
<td>2</td>
<td>0.028</td>
<td></td>
</tr>
<tr>
<td>Pancreatic</td>
<td>4 1</td>
<td>3</td>
<td>0.015</td>
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<tr>
<td>Hepatobiliary</td>
<td>1 1</td>
<td>1</td>
<td>0.011</td>
<td></td>
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<tr>
<td>Musculoskeletal and Soft Tissue</td>
<td>1 2</td>
<td>2</td>
<td>0.009</td>
<td></td>
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<tr>
<td>Metastases and Site Unspecified</td>
<td>1 2</td>
<td>1</td>
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<td>Blood and lymphatics</td>
<td>2 1</td>
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<td>0.003</td>
<td></td>
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<td>Site</td>
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<td>0.000</td>
<td></td>
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<tr>
<td>Rectal</td>
<td>6 4</td>
<td>2</td>
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<tr>
<td>Respiratory and Mediastinal</td>
<td>5 1</td>
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<tr>
<td>Gender-specific tumor types:</td>
<td></td>
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<tr>
<td>Breast (Female)</td>
<td>9 1</td>
<td>0</td>
<td>0.029</td>
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<tr>
<td>Prostate (Male)</td>
<td>8 2</td>
<td>0</td>
<td>0.018</td>
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<tr>
<td>Female Reproductive (Female)</td>
<td>1 1</td>
<td>0</td>
<td>0.016</td>
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</table>

Incidence Rate Difference with 95% CI

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

Dapagliflozin: Proportion of Patients with Elevated Liver Tests

<table>
<thead>
<tr>
<th>Test Type</th>
<th>ALT Elevation</th>
<th>Total Bilirubin Elevation</th>
<th>Combined Elevations</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Dapa</td>
<td>N = 4310</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3x ULN</td>
<td>62/4281 (1.4%)</td>
<td>18/4281 (0.4%)</td>
<td>5/4281 (0.1%)</td>
</tr>
<tr>
<td>&gt;5x ULN</td>
<td>17/4281 (0.4%)</td>
<td>4/4281 (0.1%)</td>
<td>4/4281 (0.1%)</td>
</tr>
<tr>
<td>&gt;10x ULN</td>
<td>4/4281 (0.1%)</td>
<td>2/4281 (0.1%)</td>
<td>1/4281 (0.1%)</td>
</tr>
<tr>
<td>&gt;20x ULN</td>
<td>2/4281 (&lt;0.1%)</td>
<td>1/4281 (0.1%)</td>
<td>0</td>
</tr>
<tr>
<td>All Control N = 1942</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3x ULN</td>
<td>31/1943 (1.6%)</td>
<td>15/1943 (0.8%)</td>
<td>5/1942 (0.3%)</td>
</tr>
<tr>
<td>&gt;5x ULN</td>
<td>11/1943 (0.6%)</td>
<td>3/1943 (0.2%)</td>
<td>3/1943 (0.2%)</td>
</tr>
<tr>
<td>&gt;10x ULN</td>
<td>3/1943 (0.2%)</td>
<td>1/1943 (0.1%)</td>
<td>0</td>
</tr>
<tr>
<td>&gt;20x ULN</td>
<td>1/1943 (0.1%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total Bilirubin Elevation</td>
<td>18/4281 (0.8%)</td>
<td>5/4281 (0.3%)</td>
<td></td>
</tr>
<tr>
<td>Combined Elevations</td>
<td>5/4281 (0.1%)</td>
<td>3/1942 (0.2%)</td>
<td></td>
</tr>
</tbody>
</table>

One possible case of liver toxicity in patient taking dapagliflozin

FDA Advisory Committee 9th July 2011: http://www.fda.gov
Dapagliflozin Update

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

Perspectives on SGLT2 Inhibition

Potential Advantages

- Once daily administration
- Decreases FPG, PPG, A1c
- Weight loss (60g urine glucose = 240 kcal/day = ½ lb/week)
- No/ Low risk of hypoglycemia
- Blood pressure lowering
- Effect independent of insulin secretion or insulin resistance
- Use complementary with other T2D Rx - T1D, Pre-diabetes

Concerns

- Weight loss may wane over time
- Polyuria
- Hypotension/dehydration
- Electrolyte disturbances
- Bacterial urinary tract infections
- Fungal genital infections
- May not be effective in patients with renal impairment
- Unexpected side effects and safety - eg. BMD not yet known

Targets for Oral Antidiabetic Therapies

Reduce Hyperglycemia

- Metformin
- Thiazolidinediones
- GLP-1 analogues
- DPP-4 inhibitors
- SGLT2 inhibitors

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

Case Presentation Karen

- 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

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

ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

KEY POINTS

- Glycemic targets & BG-lowering therapies must be individualized.
- Diet, exercise, & education: foundation of any T2DM therapy program
- Unless contraindicated, metformin = optimal 1st-line drug.
- After metformin, data are limited. Combination therapy with 1-2 other oral / injectable agents is reasonable; minimize side effects.
- Ultimately, many patients will require insulin therapy alone / in combination with other agents to maintain BG control.
- All treatment decisions should be made in conjunction with the patient (focus on preferences, needs & values.)
- Comprehensive CV risk reduction: a major focus of therapy.
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