Changing Focus in Type 2 Diabetes Management: Looking at the Kidney

Education Partner:

Rosemont, Illinois
November 30, 2011
Session 3: Changing Focus in Type 2 Diabetes Management: Looking at the Kidney

Learning Objectives

1. Describe the role of the kidney in glucose regulation, and discuss renal glucose transport in normoglycemia and hyperglycemia.
2. Explain the rationale for targeting renal glucose transport in treating type 2 diabetes (TD2), and interpret emerging clinical data.
3. Assess the potential role of TD2 therapies that target renal glucose transport in early though late stages of disease.

Faculty

George Bakris, MD
Professor of Medicine
Director, Hypertensive Diseases Unit
Pritzker School of Medicine
University of Chicago
Chicago, Illinois

Dr George Bakris is a professor of medicine and director of the Hypertensive Diseases Unit at the University of Chicago Pritzker School of Medicine. He received his medical degree from Chicago Medical School and trained as a resident in internal medicine at the Mayo Graduate School of Medicine, where he also completed a research fellowship in physiology and biophysics. He subsequently completed fellowships in nephrology and clinical pharmacology at the University of Chicago. From 1988 to 1991, Dr Bakris served on the faculty and was director of renal research at the Ochsner Clinic at Tulane University School of Medicine. He later was professor and vice chairman of preventive medicine and director of the Rush University Hypertension Center in Chicago from 1993 until 2006.

Dr Bakris has published over 500 articles and book chapters in the areas of diabetic kidney disease, hypertension, and progression of nephropathy. He is editor or co-editor of The Kidney and Hypertension; Hypertension: a Clinician’s Guide to Diagnosis and Treatment; Hypertension: Principles and Practice; Handbook of Hypertension Management; The Kidney in Cardiovascular Disease; Therapeutic Strategies in Hypertension; Microalbuminuria and Cardiovascular Risk; and Lower Extremity Arterial Disease. He is associate editor of the International Textbook of Cardiology and has served as co-principal investigator of a National Institutes of Health clinical research training grant. The current editor of the American Journal of Nephrology, the Journal of Human Hypertension, and the hypertension section editor of Up-to-Date, Dr Bakris serves on more than 14 editorial boards, including those of Kidney International, Nephrology, Dialysis & Transplant, Diabetes Care, Hypertension, the Journal of Hypertension, and the Journal of the American Society of Hypertension.

Dr Bakris chaired the National Kidney Foundation Consensus report on blood pressure and impact on renal disease progression, and has served on many other national committees. He was also a past-president of both the American College of Clinical Pharmacology and the American Society of Hypertension.
Dr Lawrence Leiter is professor of medicine and nutritional sciences at the University of Toronto, where he is head of the Division of Endocrinology and Metabolism and director of the Lipid Clinic. In addition, he is associate director of the Clinical Nutrition and Risk Factor Modification Centre at St Michael’s Hospital in Toronto.

Dr Leiter’s research includes clinical trials on atherosclerosis and diabetes prevention, and dietary and pharmacologic treatment of diabetes mellitus, hyperlipidemia, hypertension, and obesity. The author of over 260 publications in peer-reviewed journals, he was a co-investigator in the Diabetes Control and Complications Trial (DCCT) and serves on the steering committees of many ongoing outcome trials in both the diabetes and lipid areas.

Dr Leiter was past chair of the Canadian Diabetes Association (CDA) Clinical and Scientific Section and co-chair of the CDA Committee to revise the Clinical Practice Guidelines for the Management of Diabetes in Canada, published in 1998. He is also currently involved with the guidelines committees for the Canadian Hypertension Society and Obesity Canada. The former co-chair of the Seventh International Congress on Obesity, Dr Leiter was the founding chair of the Special Programs Committee of the US Endocrine Society from 1995 to 1998.

Faculty Financial Disclosure Statements

Dr Bakris reports he has received grant and research support from Forest Laboratories, Inc.; CVRx, Inc.; Novartis Pharmaceuticals Corporation; and PepsiCo, Inc. He has received honoraria for consulting and lectures from Takeda Pharmaceutical Company Limited; Abbott Laboratories; Walgreen’s; CVRx, Inc.; Johnson & Johnson; Medtronic, Inc.; and Servier Pharmaceuticals.

Dr Leiter reports he has received research funding, provided CME content on behalf of, and/or has acted as a consultant to Abbott Laboratories; AstraZeneca Pharmaceuticals; Boehringer Ingelheim Pharmaceuticals, Inc.; Bristol-Myers Squibb Company; Eli Lilly and Company; GlaxoSmithKline; Merek & Co., Inc.; Novartis Pharmaceuticals Corporation; Novo Nordisk Pharmaceuticals, Inc.; Roche Pharmaceuticals; sanofi-aventis; Servier Pharmaceuticals.

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>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>
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</table>
Suggested Reading List


**Drug List**

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
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<tr>
<td>colesevelam</td>
<td>Welchol</td>
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<tr>
<td>glipizide</td>
<td>Glucotrol</td>
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<tr>
<td>metformin</td>
<td>Glucophage</td>
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<tr>
<td>glibenclamide</td>
<td>Amaryl</td>
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<tr>
<td>glipizide, metformin</td>
<td>Metaglip</td>
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<tr>
<td>pioglitazone</td>
<td>Actos</td>
</tr>
<tr>
<td>sitagliptin</td>
<td>Januvia</td>
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</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 Kidney, Glucose Regulation, and Type 2 Diabetes

George L. Bakris, MD
Professor of Medicine
Director, Hypertensive Diseases Unit
Department of Medicine
The University of Chicago Hospitals
Chicago, Illinois

Disclosure Information
• Grant and Research Support (University): Forest Labs, Inc, Novartis Pharmaceutical Corporation, Medtronic, Relapysa
• Consulting: Takeda Pharmaceutical Company Limited, Abbott Laboratories, Servier

Incident Counts & Adjusted Rates, by Primary Diagnosis

Adverse Outcomes by eGFR and Albuminuria

Disorders of Glucose Metabolism Have Complex Origins

Normal Glucose Homeostasis

Adapted from Martin CL. Diabetes Educ. 2007;33(suppl 1):S5-13S.
Glucose is Reabsorbed in the Proximal Convoluted Tubule

Filtration occurs in Bowman's capsule: 110 L/day
- Proximal Convoluted Tubule
- Bowman's capsule
- Distal convoluted tubule
- Vasa recti
- Ascending tubule
- Descending tubule
- Collecting duct

Glucose is reabsorbed in the proximal convoluted tubule

1. **Glomerular Filtration**
   - 125 ml of filtrate formed every minute (180 L/24h)
   - Urine output 1.5 L/24h
   - 25,000 mEq of Na Filtered
   - Urine Na excretion 100 mEq/L
   - 144 g Glucose filtered/24h
   - Urine Glucose excretion - 0
   - Because **Reabsorption** occurs

2. **Two Families of Glucose Transporters**
   - **GLUT/SLC2A Family**
     - Facilitated glucose transporters
     - Passive, downhill transport
     - GLUT1 (widespread including the kidneys)
     - GLUT2 (kidneys and pancreas)
     - GLUT4 (muscle and adipose tissue)
   - **SGLT/SLC5A Family**
     - Sodium coupled glucose cotransporter
     - Active transport of glucose
     - SGLT1 (brush border of small intestine)
     - SGLT2 (proximal tubule)

3. **Renal Glucose Transport**
   - **Glucose Transporters (GLUTs)**
     - Facilitative or passive transporters work along a glucose gradient
     - Expressed in all cells – GLUT2 in kidney
   - **Sodium-Glucose Transporters (SGLTs)**
     - Active transport using the Na gradient produced by the Na/K ATPase pumps at membranes on luminal side of cell
     - SGLT2 in S1 and S2 segments of proximal convoluted tubule has low affinity but high capacity for glucose and is responsible for 90% of tubular reabsorption of glucose
     - SGLT1 in S3 segment of proximal convoluted tubule responsible for 10% of tubular reabsorption of glucose

4. **SGLT2 Is the Primary Glucose Transporter in the S1 Segment**
   - SGLT2 is a major transporter of glucose in the kidney
     - Low affinity, high capacity for glucose
     - Nearly exclusively expressed in the kidney
     - Responsible for ~90% of renal glucose reabsorption in the proximal tubule

5. **Mechanism of Action of SGLT2 in Glucose Reabsorption**
   - SGLT2 is a major transporter of glucose in the kidney
     - Low affinity, high capacity for glucose
     - Nearly exclusively expressed in the kidney
     - Responsible for ~90% of renal glucose reabsorption in the proximal tubule


Post-absorptive Glucose Release

- Glycogenolysis from liver – 45%
- Gluconeogenesis – 55%
  - Liver – 60%, Kidney 40%
- Hormonal Control
  - Insulin: Liver ↓, Kidney ↓
  - Epinephrine: Liver ↑, Kidney ↑
  - Glucagon: Liver ↑, Kidney ↔

No Serious Consequences Associated With Renal Glucosuria

- Urinary glucose excretion with normal plasma glucose concentration
- Glucosuria varies from a few grams to >100 grams per day
- No evidence of renal tubular dysfunction
- Asymptomatic
- Hypoglycemia and hypovolemia are rarely, if ever, observed
  - Renal histology - normal
  - Renal function - normal
  - Incidence of chronic renal failure – not increased
  - Incidence of urinary tract infection – not increased
  - Incidence of diabetes – not increased
- In some individuals with severe forms of familial renal glucosuria, there is evidence for moderate volume depletion (renin activity and serum aldosterone 4.2- and 2.7-fold the upper limit of normal)

Summary – Renal Regulation of Blood Glucose

- Renal processes contribute to glucose regulation
  - Gluconeogenesis
  - Glucose reabsorption via SGLT1 and SGLT2
- Altered processes of renal glucose regulation contribute to hyperglycemia in diabetes
  - Increased postprandial and postabsorptive gluconeogenesis
  - Increased SGLT2 expression and activity

Summary: 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 SGLT2 expression and activity in renal epithelial cells from patients with diabetes versus normoglycemic individuals

Renal and hepatic glucose release after glucose ingestion in non-diabetic and diabetic subjects

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

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Changes in Glucose Metabolism in Patients with Advancing Chronic Kidney Disease

- Decreased renal clearance and metabolism of insulin
- Decreased hepatic clearance of insulin
- Decreased renal gluconeogenesis
- Insulin resistance from uremia
- Deficient catecholamine release
- Decreased food intake (uremia, gastroparesis)
- Weight loss


Conclusions

- Kidney important in postprandial hyperglycemia
  - Gluconeogenesis upregulated
  - Glucose reabsorption increased with upregulation of SGLT2
  - With advanced CKD, hypoglycemia may occur

SGLT2 Inhibition: Clinical Effects

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Lawrence Leiter, MD
Disclosure Information

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Effect of SGLT2 Inhibition (Mode of Action)

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

Potential Risks
- Hypoglycaemia
- Renal function
- Diuretic effect
- Hypovolaemia
- Hypotension
- Dehydration
- Bone mineral metabolism
- Urinary tract infections, vulvovaginitis, balanitis

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>
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<tr>
<td>LX4211</td>
<td>Phase II clinical trials</td>
<td>Unclear</td>
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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>N</th>
<th>BL Mean (%)</th>
<th>Adjusted Mean Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapa + MET</td>
<td>401</td>
<td>7.74</td>
<td>-0.5 ± 0.80*</td>
</tr>
<tr>
<td>Dapagliflozin + MET</td>
<td>400</td>
<td>7.69</td>
<td>+0.4 ± 0.80</td>
</tr>
</tbody>
</table>

*Adjusted mean change from baseline using ANCOVA (LOCF) ± 95% CI.
† Non-inferior compared to limit of 0.35% difference.
‡ Significantly superior to monotherapy (p<0.0001; statistical significance not reported).

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>BL Mean (%)</th>
<th>Adjusted Mean Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAPA + MET</td>
<td>202</td>
<td>7.74</td>
<td>-0.32% (−0.42, −0.21)</td>
</tr>
<tr>
<td>GLIP + MET (N=401)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAPA + MET (N=400)</td>
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</table>

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline Body Weight, kg</th>
<th>Mean Change in Body Weight</th>
<th>N</th>
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<tbody>
<tr>
<td>Dapagliflozin</td>
<td>87.18</td>
<td>0.53</td>
<td>80.78</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>87.18</td>
<td>0.53</td>
<td>80.78</td>
</tr>
<tr>
<td>Placebo</td>
<td>87.18</td>
<td>0.53</td>
<td>80.78</td>
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</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline Body Weight, kg</th>
<th>Mean Change in Body Weight</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapagliflozin</td>
<td>87.18</td>
<td>0.53</td>
<td>80.78</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>87.18</td>
<td>0.53</td>
<td>80.78</td>
</tr>
<tr>
<td>Placebo</td>
<td>87.18</td>
<td>0.53</td>
<td>80.78</td>
</tr>
</tbody>
</table>

Dapagliflozin not FDA approved.
Dapagliflozin Adjusted Mean Change from Baseline in Body Weight in Phase 3 Studies (10 mg dose)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>Monotherapy</th>
<th>Add-on to Metformin</th>
<th>Add-on to SU2</th>
<th>Add-on to Insulin (24 wks)</th>
<th>Add-on to Insulin (48 wks)</th>
<th>H2H DAPA + MET</th>
<th>H2H GLIP + MET</th>
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</thead>
<tbody>
<tr>
<td>(Baseline values)</td>
<td></td>
<td>(94.2 kg)</td>
<td>(86.3 kg)</td>
<td>(80.6 kg)</td>
<td>(94.6 kg)</td>
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<tr>
<td>24 wk</td>
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<td>-3.5 kg</td>
<td>-2.7 kg</td>
<td>-2.1 kg</td>
<td>-2.3 kg</td>
<td>-2.3 kg</td>
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</table>

*p<0.0001; **Difference -4.7 kg 95% CI -5.1 to -4.2 p<0.0001


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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>Monotherapy</th>
<th>Add-on to Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Baseline values)</td>
<td></td>
<td>(94.2 kg)</td>
<td>(86.3 kg)</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
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<td>24 wk</td>
<td>Add-on to Metformin</td>
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<tr>
<td>Diastolic BP (mm Hg)</td>
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<td>24 wk</td>
<td>Add-on to Metformin</td>
</tr>
</tbody>
</table>

Studies examining effects of other SGLT2 inhibitors on BP underway

Potential Effects of SGLT2 Inhibition (Mode of Action)

- **Insulin-independent Glucometabolism**
  - Hypoglycaemia
  - Renal function
  - Diuretic effect
  - Hypovolaemia
  - Hypertension
  - Dehydration
  - Bone mineral metabolism
  - Urinary tract infections, vulvovaginitis, balanitis

- **Hypoglycaemia**
  - Fasting plasma glucose (FPG)
  - Postprandial glucose (PPG)

- **Weight Reduction**

- **Blood Pressure Reduction**

Potential Effects of SGLT2 Inhibition

- **Glucosuria**
  - Rect excretion of glucose and its associated calories

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

- **Balanitis and other related infections**
  - Statistical significance not reported

- **Urinary Tract Infections**

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

- **Vulvovaginitis and other related 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

- Poised CANA group
- SITA
- PBO

Canagliflozin not FDA approved
Genital Infections and UTI with Empagliflozin

- An increase in genital infections was observed with empagliflozin

N=495

0 2 4 6 8 10 12

Genital infections (% incl signs & symptoms)

UTIs (UTI, cystitis excl. signs & symptoms)

Statistical significance not reported

Empagliflozin not FDA approved

Genital Infections and UTI with Empagliflozin

Events of Hypotension / Hypovolaemia / Dehydration in Dapagliflozin Studies

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

Pooled data from placebo-controlled dapagliflozin studies

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

Malignant and Unspecified Tumors by Tumor Origin in Dapagliflozin Studies

<table>
<thead>
<tr>
<th>Tumor Origin</th>
<th>All Dapa N = 4559</th>
<th>All Control N = 2239</th>
<th>Difference from Control</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Malignancies and Unspecified Tumors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder 6 (3.5)</td>
<td></td>
<td></td>
<td>0.010</td>
<td></td>
</tr>
<tr>
<td>Thyroid and Endocrine 7 (3.2)</td>
<td></td>
<td></td>
<td>0.034</td>
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</tr>
<tr>
<td>Gastrointestinal 6 (2.1)</td>
<td></td>
<td></td>
<td>0.028</td>
<td></td>
</tr>
<tr>
<td>Pancreatic 4 (1.7)</td>
<td></td>
<td></td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>Hematopoietic 2 (0.9)</td>
<td></td>
<td></td>
<td>0.014</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and Soft Tissue 1</td>
<td></td>
<td></td>
<td>0.060</td>
<td></td>
</tr>
<tr>
<td>Metastases and site Unspecified 1</td>
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<td></td>
<td>0.080</td>
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</tr>
<tr>
<td>Blood and Lymphoid 2 (1.1)</td>
<td></td>
<td></td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Skin 12 (6.6)</td>
<td></td>
<td></td>
<td>0.053</td>
<td></td>
</tr>
<tr>
<td>Renal Tract 0 (0.2)</td>
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<tr>
<td>Respiratory and Mediastinal 5</td>
<td></td>
<td></td>
<td>0.139</td>
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<tr>
<td>Gender-specific tumor types:</td>
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<td>0.186</td>
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<tr>
<td>Breast 6 (3.5)</td>
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<td>0.029</td>
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<tr>
<td>Prostate 5 (2.7)</td>
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<td>0.176</td>
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<tr>
<td>Female Reproductive 1 (0.2)</td>
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<td>0.103</td>
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</table>

Malignant and Unspecified Tumors by Tumor Origin in Dapagliflozin Studies

<table>
<thead>
<tr>
<th>Event</th>
<th>All Dapa N = 4310</th>
<th>All Control N = 1942</th>
<th>Difference from Control</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Bilirubin Elevation</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>&gt; 2x ULN</td>
<td>18/4281 (0.4)</td>
<td>5/1942 (0.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined Elevations</td>
<td>5/4281 (0.1)</td>
<td>3/1942 (0.2)</td>
<td></td>
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</tr>
</tbody>
</table>

One possible case of liver toxicity in patient taking dapaglifloxin

Summary of SGLT2 Inhibitors

- Glucosuria and resultant decrease in HbA1c, FPG and PPG
- Effective as monotherapy and in combination with other oral agents and insulin
  - Mitigates the need for increased insulin requirements (shown with dapagliflozin); insulin dose used in combination with dapagliflozin was 50% of patients’ daily insulin dose
- Weight loss
- Blood pressure lowering
- Efficacy shown for duration of 12-week (canagliflozin, empagliflozin), 16-week (ipragliflozin) and 104-week (dapagliflozin) studies.
- Increase in frequency of genital infections and possibly in UTIs

Potential Effects of SGLT2 Inhibition (Mode of Action)

Potential benefits
- Insulin-independent
- HbA1c lowering
- Reduction in:
  - FPG
  - PPG
  - Weight
- Reduction in blood pressure
- Insulin-independent
- HbA1c lowering
- Reduction in:
  - FPG
  - PPG
  - Weight
- Reduction in blood pressure

Potential risks
- Hypoglycaemia
- Renal function
- Diabetic effect
  - Hypoglycaemia
  - Hypertension
  - Dehydration
- Bone mineral metabolism
- Urinary tract infections, vulvovaginitis, balanitis
- Rare or unexpected events
Panel Discussion

- Importance of combination therapy in achieving glycemic goals
- Matching the right antihyperglycemic agent to the right patient
- Potential role of SGLT 2 inhibitors in the management of type 2 diabetes

Considerations for Therapy Selection

- Baseline HbA1c
- Efficacy profile
- Risk for hypoglycemia
- Risk for fractures
- Weight effects
- Adverse event profile
  - Edema
  - GI side effects (nausea, vomiting, diarrhea)
- Comorbidities
  - Cardiovascular disease
  - Renal impairment
- Costs and formulary availability

Properties of the Ideal Drug

- Robust ↓ HbA1c
- No hypoglycemia
- No weight gain
- Complimentary actions
- Durability
- Well tolerated
- Long-term safety
- Simple administration
- Added value
  - e.g., ↓BP, lipids, β cell function, CVD etc,
ADA/EASD Treatment Algorithm

Tier 1: Well-validated core therapies
- At diagnosis: Lifestyle + Metformin
- LIFESTYLE + Metformin + Basal insulin
- LIFESTYLE + Metformin + Sulfonylurea
- LIFESTYLE + Metformin + GLP-1 analogue

Tier 2: Less well-validated therapies
- LIFESTYLE + Metformin + Pioglitazone
- LIFESTYLE + Metformin + Sulfonylurea
- LIFESTYLE + Metformin + Basal insulin

Reduce Hyperglycemia

Targets for Oral Antidiabetic Therapies

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