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

Baltimore, Maryland
December 8, 2012
Session 4: 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

John Gerich, MD
Emeritus Professor of Medicine
University of Rochester School of Medicine & Dentistry
Rochester, New York

Until 2011 John E. Gerich, MD, was professor of medicine at the University of Rochester School of Medicine and program director of the institution's Clinical Research Center, as well as head of its Diabetes Research Laboratory. Dr Gerich currently holds the title of emeritus professor of medicine at the university. Dr Gerich graduated from Cornell University magna cum laude and received his MD and residency training in internal medicine at Georgetown University.


Dr Gerich is internationally renowned as a diabetes investigator and has received numerous awards and lectureships.
Dr Serge A. Jabbour is professor of medicine and director in the division of endocrinology, diabetes & metabolic diseases in the department of medicine at Jefferson Medical College/Thomas Jefferson University in Philadelphia. He is also director of the Jefferson Diabetes Center and director of the Jefferson Weight Management Center.

Dr Jabbour completed his fellowship in endocrinology, diabetes, and metabolism at Thomas Jefferson University in 1999 and has been on faculty at Thomas Jefferson University since then.

Dr Jabbour was named “Top Doc in Endocrinology” by Philadelphia Magazine in 2011 and 2012. He holds many teaching awards, including Teacher of the Year by Residents and Students and the Dean’s Citation for Significant Contributions to the Advancement of Education at Jefferson Medical College. Dr Jabbour is a member of numerous professional organizations, including The Endocrine Society, American Diabetes Association, and American Association of Clinical Endocrinologists.

Dr Jabbour’s research is published in Clinical Nuclear Medicine, Expert Opinion in Clinical Pharmacotherapy, Current Opinion in Endocrinology, Diabetes and Obesity, and Endocrine Practice, among others, and he has been involved in many studies on diabetes and the metabolic syndrome. He serves on the editorial board of many journals and has lectured on various endocrine topics.

Faculty Financial Disclosure Statements
The presenting faculty report the following:

Dr Gerich has received honoraria from Bristol-Myers Squibb/AstraZeneca.
Dr Jabbour has no financial relationships to disclose.

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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</table>
Suggested Reading List


Session 4
2:00 PM - 3:15 PM

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

Speakers:
John Gerich, MD
Serge A. Jabbour, MD

Presenter Disclosure Information

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Off-Label/Investigational Discussion

In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

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>
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<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
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<tbody>
<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>

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

Demographic Question

Relative to diabetes: please indicate the approximate number of patients that you see each week with this condition.

1. None
2. 1 to 10
3. 11 to 20
4. 21 to 30
5. 31 to 40
6. 41 to 50
7. 51 to 60
8. >60

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
The Kidney, Glucose Regulation and Type 2 Diabetes

John E. Gerich, MD
University of Rochester School of Medicine

Key Factors responsible for Hyperglycemia in T2DM

“the terrible trioka”

1. Impaired α/β Cell Function
   - mainly genetic
2. Insulin Resistance
   - mainly secondary to obesity
3. Glucose toxicity
   – adverse effect of hyperglycemia on insulin secretion and action

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
Consequences of “the terrible trioka” on glucose metabolism

- Increased glucose production
  - liver, kidney
- Abnormal tissue glucose metabolism
  - decreased clearance, storage and oxidation, increased lactate production
- Increased renal tubular glucose reabsorption

Role of Kidney in Production of Glucose

Why Renal Glucose Release is Thought to be due to Gluconeogenesis

1. Kidney normally contains little glycogen
2. Cells that could store glycogen lack glucose-6-phosphatase
3. Renal uptake of gluconeogenic precursors approximates renal glucose release

Contribution of Kidney to Glucose Homeostasis

I: Production
II: Utilization
III: Reabsorption from Glomerular Filtrate

Why Renal Glucose Release is Thought to be due to Gluconeogenesis

1. Stumvoll et al 1995 28%
2. Meyer et al 1997 13%
3. Stumvoll et al 1998 22%
4. Stumvoll et al 1998 17%
5. Meyer et al 1998 21%
6. Meyer et al 2000 17%
7. Cersosimo et al 1999 25%
8. Cersosimo et al 1999 22%
9. Ekberg et al 1999 8%
10. Cersosimo et al 2000 21%
11. Cersosimo et al 2000 21%
12. Moller et al 2001 18%
13. Cersosimo et al 2001 32%
14. Meyer et al 2002 21%
15. Meyer et al 2002 11%
16. Woerle et al 2003 18%
17. Woerle et al 2003 20%
18. Meyer et al 2003 24%
19. Meyer et al 2005 12%

Mean ± SEM 19.8 ± 1.4%
Hepatic and Renal Gluconeogenesis as a % of total Glucose production

<table>
<thead>
<tr>
<th></th>
<th>Maximum Hepatic Gluconeogenesis (Feilig, Wahren, Alhborg)</th>
<th>Renal Glucose Release (presumed all Gluconeogenesis)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>22 ± 1.4%</td>
<td>20 ± 1.5%</td>
</tr>
</tbody>
</table>


Endogenous Glucose Release Before and After Removal of the Liver in Individuals Undergoing Liver Transplantation


Contribution of Renal Glucose Release During Hypoglycemia Counterregulation


Physiologic Postprandial Changes in Renal Glucose Release and Hepatic Glucose Release

Role of Kidney in Glucose Utilization

Contribution of Tissues to Glucose Uptake

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Postabsorptive State</th>
<th>Postprandial State</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>50%</td>
<td>10%</td>
</tr>
<tr>
<td>Muscle</td>
<td>20%</td>
<td>35%</td>
</tr>
<tr>
<td>Liver</td>
<td>10%</td>
<td>30%</td>
</tr>
<tr>
<td>Kidney</td>
<td>10%</td>
<td>15%</td>
</tr>
<tr>
<td>Other</td>
<td>10%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Overall Rate 2 mg/Kg/min (mainly insulin independent)

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

Role of Kidney in Reabsorption of Glucose from Glomerular Filtrate

SGLT family

<table>
<thead>
<tr>
<th>Protein</th>
<th>Substrates</th>
<th>Tissue distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT1</td>
<td>Glucose and galactose</td>
<td>Small intestine, heart, trachea and kidney</td>
</tr>
<tr>
<td>SGLT2</td>
<td>Glucose</td>
<td>Kidney</td>
</tr>
<tr>
<td>SGLT3</td>
<td>Glucose sensor</td>
<td>Small intestine, uterus, lungs, thyroid gland and testes</td>
</tr>
<tr>
<td>SGLT4</td>
<td>Mannose, glucose, fructose, 1,5-AG and galactose</td>
<td>Small intestine, kidney, liver, stomach and lung</td>
</tr>
<tr>
<td>SGLT5</td>
<td>Glucose and galactose</td>
<td>Kidney</td>
</tr>
<tr>
<td>SGLT6</td>
<td>Myo-inositol, glucose, xylose and chiro-inositol</td>
<td>Spinal cord, kidney, brain and small intestine</td>
</tr>
</tbody>
</table>


Sodium-Glucose Cotransporters

<table>
<thead>
<tr>
<th>SGLT1</th>
<th>SGLT2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td>Mostly intestine with some in kidney</td>
</tr>
<tr>
<td>Sugar specificity</td>
<td>Glucose or galactose</td>
</tr>
<tr>
<td>Affinity for glucose</td>
<td>Km = 0.4 mM</td>
</tr>
<tr>
<td>Capacity for glucose transport</td>
<td>Low</td>
</tr>
<tr>
<td>Role</td>
<td>Dietary glucose absorption</td>
</tr>
</tbody>
</table>


Renal Handling of Glucose, Non-Diabetic Individual

Virtual all the glucose filtered is reabsorbed and glucose does not appear in the urine.

Renal Glucose Handling

Role of Kidney in Diabetes

Renal Glucose Release: Studies in Diabetic Animals

Teng, 1954 Rat Cortical Slices 4X
Landau, 1960 Rat Cortical Slices 2.5X
Flinn, et al., 1961 Rat Cortical Slices 6X
Joseph and Subrahmanyam, 1968 Rat Cortical Slices 2X
Kamm and Cahill, 1969 Rat Cortical Slices 1.5X
Chong and Schneder, 1970 Chinese Hamster Cortical Slices 2X
Triscari, et al., 1979 Rat Cortical Slices 1.5X
Lemieu, et al., 1982 Rat Cortical Slices 4X

Systemic, Renal and Hepatic Glucose Release

<table>
<thead>
<tr>
<th></th>
<th>Nondiabetics</th>
<th>Diabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic Release*</td>
<td>10.2 ± 0.3</td>
<td>15.0 ± 0.9**</td>
</tr>
<tr>
<td>Renal Release*</td>
<td>1.5 ± 0.2</td>
<td>3.7 ± 0.4**</td>
</tr>
<tr>
<td>(increment)</td>
<td>−</td>
<td>(2.2 ± 0.3)</td>
</tr>
<tr>
<td>Hepatic Release*</td>
<td>8.7 ± 0.3</td>
<td>11.3 ± 0.7**</td>
</tr>
<tr>
<td>(increment)</td>
<td>−</td>
<td>(2.6 ± 0.7)</td>
</tr>
</tbody>
</table>

*μmol · kg⁻¹ · min⁻¹
**p<0.001

Postprandial Tissue Glucose Uptake

<table>
<thead>
<tr>
<th></th>
<th>Nondiabetic</th>
<th>Diabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splanchnic (liver)</td>
<td>~30%</td>
<td>~20% ↓</td>
</tr>
<tr>
<td>Muscle</td>
<td>~25%</td>
<td>~20% ↓</td>
</tr>
<tr>
<td>Brain</td>
<td>~15%</td>
<td>~15%</td>
</tr>
<tr>
<td>Kidney</td>
<td>~10%</td>
<td>~20% ↑</td>
</tr>
<tr>
<td>Other</td>
<td>~20%</td>
<td>~25% ↑</td>
</tr>
</tbody>
</table>


Maximum Tubular Glucose Reabsorption (TmG) in Diabetes

<table>
<thead>
<tr>
<th></th>
<th>Type 1 Diabetes (N=10)</th>
<th>Controls (N=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>419 ± 16</td>
<td>352 ± 24 mg/min</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Type 2 Diabetes (N=12)</th>
<th>Controls (N=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>424 ± 30</td>
<td>357 ± 46 mg/min</td>
</tr>
</tbody>
</table>

Summary

The kidney makes an important contribution to normal glucose homeostasis in terms of glucose production, glucose disposal and glucose reabsorption from glomerular filtrate.

In type 2 diabetes, renal glucose production, disposal and reabsorption from glomerular filtrate are all increased.

Conclusion

Suppression of increased renal tubular glucose reabsorption may be a useful therapeutic strategy in diabetes mellitus.

Achieving Glycemic Control Through the Kidney in Type 2 Diabetes (clinical efficacy and safety data with SGLT 2 inhibitors)

Serge Jabbour, MD, FACP, FACE
Professor of Medicine
Director, Division of Endocrinology, Diabetes & Metabolic Diseases
Thomas Jefferson University
Philadelphia, PA

SGLT2 Inhibitors in Clinical Development

<table>
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<th>Compounds in development</th>
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<th>Anticipated filing date</th>
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<tr>
<td>Dapagliflozin</td>
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<td>Filed in December, 2010</td>
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<td>Phase III clinical trials</td>
<td>Filed May 2012</td>
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<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>
</tr>
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</table>

Comparison of Increases in Glucose Production and Renal Glucose Reabsorption in Type 2 Diabetes

Glucose Production

~50 gm/24 hrs

Glucose Reabsorption

~150 gm/24 hrs

2Assumes HbA1c 8%, MBG 183 mg/dl; normal GFR

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</table>
SGLT2 Inhibitors Increase Urinary Glucose Excretion

**Dapagliflozin monotherapy**
- 12-week (phase 2)

**Canagliflozin monotherapy**
- 2-week (phase 1b)

Increased Urinary Glucose Excretion with Dapagliflozin

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

Dapagliflozin: Change in FPG at Week 24 Across Studies
Change in HbA1c in 12-Week Add-on to Metformin Studies of SGLT2 Inhibitors


Mean change in HbA1c (%) from baseline

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Change in HbA1c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg qd</td>
<td>-0.8</td>
</tr>
<tr>
<td>100 mg qd</td>
<td>-0.7</td>
</tr>
<tr>
<td>200 mg qd</td>
<td>-0.6</td>
</tr>
<tr>
<td>300 mg qd</td>
<td>-0.5</td>
</tr>
<tr>
<td>300 mg bid</td>
<td>-0.4</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>-0.3</td>
</tr>
</tbody>
</table>

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

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Canagliflozin: Mean A1C Over Time

PBO, placebo; CANA, canagliflozin; SE, standard error; mITT, modified intent-to-treat; LOCF, last observation carried forward.

<table>
<thead>
<tr>
<th>Time point (wk)</th>
<th>PBO</th>
<th>CANA 100 mg</th>
<th>CANA 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6.8</td>
<td>7.0</td>
<td>7.2</td>
</tr>
<tr>
<td>6</td>
<td>6.8</td>
<td>7.0</td>
<td>7.2</td>
</tr>
<tr>
<td>12</td>
<td>6.8</td>
<td>7.0</td>
<td>7.2</td>
</tr>
<tr>
<td>18</td>
<td>6.8</td>
<td>7.0</td>
<td>7.2</td>
</tr>
<tr>
<td>26</td>
<td>6.8</td>
<td>7.0</td>
<td>7.2</td>
</tr>
</tbody>
</table>

Canagliflozin not FDA approved

Stenlof K et al. ADA 2012, Abstract 81-OR.

**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)

---

Canagliflozin: Proportion of Subjects Reaching A1C Goals

<table>
<thead>
<tr>
<th>A1C &lt;7.0%</th>
<th>A1C &lt;6.5%†</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO</td>
<td>CANA 100 mg</td>
</tr>
<tr>
<td>36.6</td>
<td>6.3</td>
</tr>
<tr>
<td>46.5</td>
<td>7.4</td>
</tr>
<tr>
<td>62.4</td>
<td>17.8</td>
</tr>
</tbody>
</table>

†P < 0.001 for cana 100 mg and cana 300 mg vs placebo

N = 192 placebo, 195 cana 100 mg, 197 cana 300 mg.

---

Change in HbA1c at 52 Weeks in Dapagliflozin Initial Combination with Metformin XR Study


**Statistically significant by heirarchical testing rule.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>BL Mean (%)</th>
<th>Week 52 Mean (%)</th>
<th>Difference</th>
<th>95% CI (Week 52 – Baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapa 10 mg vs. MET XR</td>
<td>7.69</td>
<td>5.71</td>
<td>-1.98</td>
<td>-2.22 to -1.74</td>
</tr>
<tr>
<td>Combination vs. Monotherapies</td>
<td>7.74</td>
<td>6.29</td>
<td>-1.45</td>
<td>-1.70 to -1.21</td>
</tr>
</tbody>
</table>

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


Dapagliflozin not FDA approved

**Statistically significant by heirarchical testing rule.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>BL Mean (%)</th>
<th>Week 104 Mean (%)</th>
<th>Difference</th>
<th>95% CI (Week 104 – Baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAPA + MET</td>
<td>7.69</td>
<td>6.75</td>
<td>-0.94</td>
<td>-1.11 to -0.77</td>
</tr>
<tr>
<td>GLIP + MET</td>
<td>7.74</td>
<td>6.72</td>
<td>-1.02</td>
<td>-1.21 to -0.83</td>
</tr>
</tbody>
</table>

---

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

Del Prato S, et al. Presented at the Annual Meeting of the EASD, 10-14 September, 2011 (Presentation no #852). Dapagliflozin not FDA approved

**Statistically significant by heirarchical testing rule.
**Change in HbA1c with Dapagliflozin across 24-Week Studies**

- **Monotherapy** (N=558):
  - Baseline: 8.53%
  - Adjusted mean change from baseline: -0.72%
- **Add-on to SU** (N=596):
  - Baseline: 8.06%
  - Adjusted mean change from baseline: -0.81%
- **Add-on to PIO** (N=420):
  - Baseline: 8.11%
  - Adjusted mean change from baseline: -0.97%
- **Add-on to Insulin** (N=807):
  - Baseline: 8.00%
  - Adjusted mean change from baseline: -1.09%

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

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

- **Canagliflozin** (12 wk study in Japanese patients, N=383):
  - Baseline body weight, kg: 69.37
  - Mean change in body weight: -3.5 kg
- **Empagliflozin** (12 wk study, N=408):
  - Baseline body weight, kg: 67.18
  - Mean change in body weight: -3 kg
- **Ipragliflozin** (16 wk study in Japanese patients, N=129):
  - Baseline body weight, kg: 68.5
  - Mean change in body weight: -2.5 kg

Statistical significance not reported.

**Change in Body Weight in 12-16 Week Add-on to Metformin Studies of SGLT2 Inhibitors**

- **Canagliflozin** (placebo adjusted values):
  - Baseline body weight, kg: 87
  - Mean change in body weight: -3.5 kg
- **Empagliflozin**:
  - Baseline body weight, kg: 87
  - Mean change in body weight: -3 kg

**Weight Loss Characterization with Dapagliflozin**

- **Dapagliflozin 10 mg/d or placebo added to open-label metformin (182 diabetics on metformin, A1c 7.17, BMI 31.0 kg/m2)**
  - At 24 weeks, dapagliflozin reduced (vs placebo):
    - Total body weight (-2.08 kg, p < 0.0001)
    - Waist circumference (-1.52 cm, p = 0.0001)
    - Fat mass by DEXA (-1.48 kg, 2/3 of weight loss attributed to reduction in fat mass, p = 0.0001)
    - Visceral adipose tissue by MRI (-258.4 cm³, nominal p = 0.0084)
    - Subcutaneous adipose tissue by MRI (-184.9 cm³, nominal p = 0.0385)

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

- **24 wk Monotherapy**:
  - Adjusted mean change from baseline (kg): -4.7 kg
  - 95% CI: -5.1 to -4.2
  - p<0.001
- **Add-on to Monotherapy/Metformin**:
  - Adjusted mean change from baseline (kg): -4.3 kg
  - 95% CI: -4.7 to -3.9
  - p<0.001

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

- **Systolic BP (mm Hg)**
  - 24 wk Monotherapy/Metformin:
    - Adjusted mean change from baseline (mm Hg): -0.6
  - 24 wk Monotherapy/Metformin to Sitagliptin:
    - Adjusted mean change from baseline (mm Hg): -5.1

- **Diastolic BP (mm Hg)**
  - 24 wk Monotherapy/Metformin:
    - Adjusted mean change from baseline (mm Hg): -1.6
  - 24 wk Monotherapy/Metformin to Sitagliptin:
    - Adjusted mean change from baseline (mm Hg): -5.1

Studies examining effects of other SGLT2 inhibitors on BP underway.
Urinary Tract Infections: SGLT2 Inhibitors With Metformin

- Occurrence of signs and symptoms suggestive of urinary tract infection was similar across treatments.
- Reports indicate that urinary tract infections:
  - Were generally mild to moderate and not recurrent.
  - Responded to standard treatments.
  - Rarely led to discontinuation.
  - One discontinuation.

\[ P < .05 \] for DAPA vs GLIM based on post hoc analysis.

- Rosenstock J, et al. *Diabetes*. 2010;59(suppl 1):77-OR;

### Agent Urinary Tract Infections (% of Participants)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Urinary Tract Infections (% of Participants)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAPA (24 wk)</td>
<td>DAPA: 4-8 PBO: 8</td>
</tr>
<tr>
<td>DAPA (102 wk)</td>
<td>DAPA: 8-13 PBO: 8</td>
</tr>
<tr>
<td>DAPA (52 wk)</td>
<td>DAPA: 11b GLIM: 6</td>
</tr>
<tr>
<td>CANA (12 wk)</td>
<td>CANA: 3-9 PBO: 6</td>
</tr>
<tr>
<td>EMPA (12 wk)</td>
<td>EMPA: 3 PBO: 3</td>
</tr>
</tbody>
</table>

Genital Infections: SGLT2 Inhibitors With Metformin

- Most events mild to moderate.
- Most resolved with conventional intervention.
- Rarely led to study discontinuation.
- One discontinuation.
- One severe and 3 led to discontinuation in DAPA group.

\[ P < .05 \] for DAPA vs GLIM based on post hoc analysis.

- Rosenstock J, et al. *Diabetes*. 2010;59(suppl 1):77-OR;

### Agent Genital Infections (% of Participants)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Genital Infections (% of Participants)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAPA (24 wk)</td>
<td>DAPA: 8-13 PBO: 5</td>
</tr>
<tr>
<td>DAPA (102 wk)</td>
<td>DAPA: 12-15 PBO: 5</td>
</tr>
<tr>
<td>DAPA (52 wk)</td>
<td>DAPA: 12 GLIM: 3</td>
</tr>
<tr>
<td>CANA (12 wk)</td>
<td>CANA: 3-8 PBO: 2</td>
</tr>
<tr>
<td>EMPA (12 wk)</td>
<td>EMPA: 2.5 PBO: 0</td>
</tr>
</tbody>
</table>

Dapagliflozin, canagliflozin, empagliflozin not FDA approved.

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

<table>
<thead>
<tr>
<th>Agent</th>
<th>Vulvovaginitis and other related infections</th>
<th>Urinary Tract Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRO</td>
<td>2.5 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>N=716</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
</tr>
<tr>
<td>PRO</td>
</tr>
<tr>
<td>N=814</td>
</tr>
<tr>
<td>Hypotension</td>
</tr>
<tr>
<td>Syncope</td>
</tr>
<tr>
<td>Dehydration</td>
</tr>
<tr>
<td>Orthostatic</td>
</tr>
</tbody>
</table>

Women

<table>
<thead>
<tr>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
</tr>
<tr>
<td>PRO</td>
</tr>
<tr>
<td>N=1193</td>
</tr>
<tr>
<td>Hypotension</td>
</tr>
<tr>
<td>Syncope</td>
</tr>
<tr>
<td>Dehydration</td>
</tr>
</tbody>
</table>

Incidence of Vulvovaginal Candidiasis in Female Patients with T2DM on Canagliflozin

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

Pooled data from placebo-controlled canagliflozin studies.

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

Dapagliflozin not FDA approved

Statistical significance not reported.

Incidence of Hypovolaemia / Dehydration in Dapagliflozin Studies

<table>
<thead>
<tr>
<th>Agent</th>
<th>Number (% of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapa 2.5 mg</td>
<td>N = 814</td>
</tr>
<tr>
<td>Dapa 5 mg</td>
<td>N = 1145</td>
</tr>
<tr>
<td>Dapa 10 mg</td>
<td>N = 1193</td>
</tr>
<tr>
<td>Pbo</td>
<td>N = 1393</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event</th>
<th>Number (% of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Subjects</td>
<td>10 (1.2)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>6 (0.7)</td>
</tr>
<tr>
<td>Syncope</td>
<td>3 (0.4)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>3 (0.4)</td>
</tr>
<tr>
<td>Urine Flow Decreased</td>
<td>0 (0.1)</td>
</tr>
<tr>
<td>Blood Pressure Decreased</td>
<td>0 (0.1)</td>
</tr>
<tr>
<td>Orthostatic Hypotension</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Urine Output Decreased</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Pooled data from placebo-controlled dapagliflozin studies.

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

Dapagliflozin not FDA approved

Statistical significance not reported.
All Phase 2b and 3 Pool, All Cases as of May 2011

**Malignant and Unspecified Tumors by Tumor Origin in Dapagliflozin Studies**

<table>
<thead>
<tr>
<th>Tumor Origin</th>
<th>N =</th>
<th>Control</th>
<th>Dapa 2.5 mg</th>
<th>Difference from Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Malignant and</td>
<td>65</td>
<td>29</td>
<td>36</td>
<td>0.018</td>
<td></td>
</tr>
<tr>
<td>Unspecified Tumors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder a (Obstructed)</td>
<td>7</td>
<td>0</td>
<td>1 (1)</td>
<td>0.138</td>
<td></td>
</tr>
<tr>
<td>Thyroid and Endocrine</td>
<td>1</td>
<td>3</td>
<td>2 (2)</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>6</td>
<td>2</td>
<td>4 (4)</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>Pancreatic</td>
<td>4</td>
<td>1</td>
<td>3 (3)</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td>2</td>
<td>0</td>
<td>2 (2)</td>
<td>0.014</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and</td>
<td>1</td>
<td>0</td>
<td>1 (1)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Soft Tissue</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastases and Site</td>
<td>1</td>
<td>2</td>
<td>0 (0)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Unspecified</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and Lymphatic</td>
<td>2</td>
<td>2</td>
<td>0 (0)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>13</td>
<td>6</td>
<td>7 (7)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Female Reproductive</td>
<td>9</td>
<td>1</td>
<td>8 (8)</td>
<td>0.018</td>
<td></td>
</tr>
<tr>
<td>Female Reproductive</td>
<td>8</td>
<td>2</td>
<td>6 (6)</td>
<td>0.028</td>
<td></td>
</tr>
<tr>
<td>Respiratory and</td>
<td>5</td>
<td>5</td>
<td>0 (0)</td>
<td>0.030</td>
<td></td>
</tr>
<tr>
<td>Mediastinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Gender-specific tumor types:
  |       |         |              |                         |         |
| Breast (Female)       | 9   | 1       | 8 (8)        | 0.030                   |         |
| Prostate (Male)       | 9   | 2       | 7 (7)        | 0.030                   |         |
| Female Reproductive (Female) | 1 | 1 | 0 (0) | 0.030 |         |

**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 Update**

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

**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

**Canagliflozin: Summary of Overall Safety**

<table>
<thead>
<tr>
<th>Subjects, n (%)</th>
<th>PBO (n = 192)</th>
<th>CANA 100 mg (n = 195)</th>
<th>CANA 300 mg (n = 197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>191 (100%)</td>
<td>119 (61%)</td>
<td>118 (60%)</td>
</tr>
<tr>
<td>AEs leading to discontinue</td>
<td>9 (5)</td>
<td>4 (2%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>AEs related to study drug*</td>
<td>18 (10)</td>
<td>34 (17)</td>
<td>50 (26)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>8 (5)</td>
<td>2 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Deaths</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*PBO: placebo; CANA, canagliflozin; AE, adverse event.

One possible case of liver toxicity in patient taking dapagliflozin.
Canagliflozin: Selected Safety Parameters

<table>
<thead>
<tr>
<th></th>
<th>PBO (n = 192)</th>
<th>CANA 100 mg (n = 195)</th>
<th>CANA 300 mg (n = 197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UTI</td>
<td>8 (4.2)</td>
<td>14 (7.2)</td>
<td>10 (5.1)</td>
</tr>
<tr>
<td>Genital mycotic infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0</td>
<td>2 (1.0)</td>
<td>5 (2.5)</td>
</tr>
<tr>
<td>Female†</td>
<td>4 (2.1)</td>
<td>10 (5.1)</td>
<td>8 (4.1)</td>
</tr>
<tr>
<td>Osmotic diuresis-related AEs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pollakiuria (increased frequency)</td>
<td>1 (0.5)</td>
<td>5 (2.6)</td>
<td>6 (3.1)</td>
</tr>
<tr>
<td>Polyuria</td>
<td>0</td>
<td>6 (3.1)</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>Volume-related AEs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postural dizziness</td>
<td>1 (0.5)</td>
<td>2 (1.0)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td></td>
<td>0</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Hypoglycemia episodes‡</td>
<td>5 (2.6)</td>
<td>7 (3.6)</td>
<td>6 (3.0)</td>
</tr>
</tbody>
</table>

PBO, placebo; CANA, canagliflozin; AE, adverse event; UTI, urinary tract infection.

*PBO, n = 88; CANA 100 mg, n = 81; CANA 300 mg, n = 89; †PBO, n = 104; CANA 100 mg, n = 114; CANA 300 mg, n = 108; ‡Includes episodes that were either biochemically documented (<70 mg/dL) or reported as severe by the investigator.

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
- Effective independent of insulin secretion or insulin resistance
- Use complementary with other T2D Rx - T1D, Pre-diabetes

Concerns
- Bacterial urinary tract infections
- Fungal genital infections
- May not be as effective in patients with renal impairment
- Safety concerns (cancer, etc) need to be addressed in more studies

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

THANK YOU
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

Questions & Answers