A Change in Diabetes Treatment Paradigms
Improving Glucose Control Without Hypoglycemia and Without Weight Gain

Wednesday, March 13, 2013
1:30 PM – 3:00 PM
George R. Brown Convention Center
Houston, Texas

Educational Partner
Session 4: A Change in Diabetes Treatment Paradigms: Improving Glucose Control Without Hypoglycemia and Without Weight Gain

Learning Objectives
1. Assess current treatment goals for the comprehensive care of patients with type 2 diabetes.
2. Evaluate glucagon-like peptide–1 (GLP-1) receptor agonists’ and dipeptidyl peptidase–4 (DPP-4) inhibitors’ attributes relative to hypoglycemia and weight gain compared to other anti-glycemic therapies.
3. Distinguish among available DPP-4 inhibitors.
4. Describe the role of the kidney in glucose homeostasis.

Faculty
Frank Lavernia MD
Founder
North Broward Diabetes Center
Pompano Beach, Florida

Dr Frank Lavernia has been a practicing diabetologist for over 28 years in South Florida. He founded the North Broward Diabetes Center, at the North Broward Medical Center, in Pompano Beach, Florida. His most recent project has been the development of “Dr Frank’s Diabetes Workshops” to teach and empower people with diabetes. The American Diabetes Association has accredited Dr Lavernia’s private practice with the Certificate of Recognition for Diabetes Care for the past 10 years.

Dr Lavernia serves on various national faculties, including the Vascular Biology Working Group, the Coalition for the Advancement of Cardiovascular Health, and the National Diabetes Education Initiative, a think tank for type 2 diabetes and insulin resistance. As a member of numerous national speakers’ bureaus, he lectures about many diverse aspects of diabetes care around the country.

Richard E. Pratley, MD
Medical Director
Samuel E. Crockett, MD, Chair in Diabetes Research
Director, Florida Hospital Diabetes Institute
Senior Scientist
Florida Hospital–Sanford|Burnham Translational Research Institute for Metabolism and Diabetes
Professor
Sanford|Burnham Medical Research Institute
Orlando, Florida

Dr Richard Pratley is the Samuel E. Crockett, MD, Chair in Diabetes Research and medical director of the Florida Hospital Diabetes Institute (FHDI). He is also senior faculty at the Translational Research Institute for Metabolism and Diabetes, as well as a professor at the Sanford|Burnham Medical Research Institute at Lake Nona in Orlando.

Dr Pratley was head of the Diabetes and Metabolism Unit of the National Institutes of Health (NIH) Clinical Diabetes and Nutrition Section in Phoenix. He then served as senior director of the Cardiovascular and Metabolism Therapeutic areas at Novartis Pharmaceuticals, where he worked on the clinical development of new drugs for diabetes. From 2004 to 2011, Dr Pratley was director of the Diabetes and Metabolism Translational Medicine Unit at the University of Vermont (UVM), where he was also professor at the College of Medicine. There, he led many large-scale investigations, including NIH- and pharmaceutical company-sponsored studies.

Faculty Financial Disclosure Statements
The presenting faculty reports the following:

Dr Lavernia is a speaker for Abbott Laboratories and Novo Nordisk Inc., and an advisor for Amylin Pharmaceuticals.

Dr Pratley receives grant/research support from Eli Lilly and Company, Mannkind Corporation, Novartis Pharmaceuticals Corporation, Novo Nordisk Inc., Roche, Takeda Pharmaceuticals USA, and Merck & Co., Inc. He is a speaker for AstraZeneca–Bristol-Myers Squibb, Eli Lilly and Company, Mannkind Corporation, Novartis Pharmaceuticals Corporation, Novo Nordisk Inc., Roche, Takeda Pharmaceuticals USA, and, Eisai Co., Ltd.; and a consultant for AstraZeneca–Bristol-Myers Squibb, Eli Lilly and Company, Mannkind Corporation, Novartis Pharmaceuticals Corporation, Novo Nordisk Inc., Roche, Takeda Pharmaceuticals USA, Eisai Co., Ltd., and Merck & Co., Inc.
Education Partner Financial Disclosure Statement
The content collaborators at Global Directions in Medicine, Inc., report the following:
Anne Sendaydiego, PharmD, Medical Director, and Deanna Schuly, Program Manager, have no financial relationships to disclose.

Suggested Reading List


SESSION 4
1:30 PM – 3:00 PM
A Change in Diabetes Treatment Paradigms: Improving Glucose Control without Hypoglycemia and without Weight Gain

SPEAKERS
Frank Lavernia, MD
Richard E. Pratley, MD

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Improving Glucose Control with Low Risks of Hypoglycemia and Low Risk of Weight Gain: Current Oral Therapy Options

Frank Lavernia, MD
Founder, North Broward Diabetes Center Broward Health
North Broward Medical Center
Pompano Beach, Florida

Learning Objectives
1. Assess current treatment goals for the comprehensive care of patients with type 2 diabetes
2. Evaluate GLP-1 receptor agonists and DPP-4 inhibitors attributes relative to hypoglycemia and weight gain compared with other antiglycemic therapies
3. Distinguish among available DPP-4 inhibitors
4. Describe the role of the kidney in glucose homeostasis
How many patients do you see each week with diabetes who are overweight and have poor glycemic control?

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

Outcomes Question 1
SB is 65 yrs old with a 7-year history of diabetes, dyslipidemia and hypertension. Her management goals are (choose all that apply):

1. LDL-C <100 mg/dL (<70 mg/dL if CAD)
2. LDL-C < 60 mg/dl
3. HbA1C <7%
4. HbA1C <6%
5. BP <140/80 mmHg
6. BP <130/85 mmHg
7. TG <150 mg/dL
8. HDL-C >40 mg/dL (men), >50 mg/dL (women)

Outcomes Question 2
Potential benefits of incretin-based therapies (GLP-1 Receptor Agonists and DPP-4 Inhibitors) include each of the following except:

1. Clinically relevant reductions in HbA1C
2. Low risk of hypoglycemia
3. Can be used safely in patients with renal impairment
4. Do not seem to increase CV risk
5. None of the above; all are potential benefits

Outcomes Question 3
Which of the following agents is associated with a low risk of hypoglycemia and a low risk of weight gain?

1. Any of the DPP-4 inhibitors
2. Metformin
3. Colesevelam
4. 1 and 3
5. 1, 2, and 3

Outcomes Question 4
Potential benefits of SGLT2 inhibition include all of the following except:

1. HbA1C reductions independent of insulin secretion
2. Modest BP reduction
3. Low risk of hypoglycemia
4. Modest weight loss
5. Lack of efficacy in patients with moderate to severe renal impairment
6. Complementary mechanism of action to other OADs

Correlation Between Diabetes and Obesity
Case Study

- 55-year-old obese (BMI 35 kg/m²) man with T2DM diagnosed 10 years ago
- A1C = 7.7%
- Current therapy:
  - Metformin 1000 mg twice a day
  - Glyburide 5 mg daily
- Tolerates metformin without gastrointestinal distress
- Occasional mild hypoglycemia when skips lunch (office worker with busy schedule)
- Well controlled hypertension and dyslipidemia (treated with ACE inhibitor and statin)

What is your next step regarding glucose-lowering therapy?

1. Increase glyburide
2. Discontinue glyburide and add DPP-4 inhibitor
3. Discontinue glyburide and add Colesevelam
4. Discontinue glyburide and add GLP-1 agonist
5. Discontinue glyburide and add TZD
6. Continue current therapy and add DPP-4 inhibitor
7. Continue current therapy and add Colesevelam
8. Continue current therapy and add GLP-1 agonist
9. Continue current therapy and add TZD

Newer Approaches and Thoughts About Treating T2DM

- Management of the diabetes patient is comprehensive—treat the ABCs (A1C, Blood pressure, Cholesterol)
- Individualize goals of therapy
- Always ask the year of diagnosis
  - Treat to goal aggressively in the first 10–12 years of disease
- Avoid hypoglycemia, weight gain, cardiovascular disease progression. DO NO HARM!
- Avoid contraindications with certain medications

Standards of Medical Care in Diabetes: 2013

- LDL-C <100 mg/dL (<70 mg/dL if CAD)
- HDL-C >40 mg/dL (men), >50 mg/dL (women)
- TG <150 mg/dL
- A1C <7.0%
- BP <140/80 mmHg


Lifestyle Modifications

- Smoking cessation
- BMI <25 kg/m²
- Healthy diet
- Exercise

Rate the importance of hypoglycemia risk in your selection of glucose-lowering treatments

1. Not important; other factors like efficacy, cost, and contraindications are more important
2. Somewhat important
3. Important; balance with ability to lower blood glucose levels
4. One of the most important factors to ensure patients will be adherent
5. One of the most important factors to ensure safety
Which of these factors plays the major role in your day-to-day decision-making?

1. Risk for hypoglycemia
2. Risk for weight gain
3. Fluid retention risk
4. Fracture risk
5. Cardiovascular risks
6. Presence of contraindications
7. Renal impairment
8. Cost

Framework for Setting the Glycemic Target

<table>
<thead>
<tr>
<th>A1C Range</th>
<th>Most Intensive Level, Approximately 6.0%</th>
<th>Least Intensive Level, Approximately 8.0%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Highly motivated, adherent, knowledgeable, strong self-care capability</td>
<td>Less motivated, nonadherent, weak self-care capability</td>
</tr>
<tr>
<td></td>
<td>Adequate Resources or support systems</td>
<td>Inadequate</td>
</tr>
<tr>
<td></td>
<td>Low Risk of hypoglycemia</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Short (+ legacy effect) Duration of T2DM</td>
<td>Long (– legacy effect)</td>
</tr>
<tr>
<td></td>
<td>Long Life expectancy</td>
<td>Short</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>CVD Established</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>Coexisting conditions Multiple, severe, or both</td>
</tr>
</tbody>
</table>

Metformin

- Metformin is a cornerstone of oral antidiabetic pharmacotherapy
- ADA/EASD recommends starting metformin therapy along with lifestyle modification at the time T2DM is diagnosed
- Metformin acts to reduce hepatic gluconeogenesis and improve glucose uptake, and it may exert protective effects on pancreatic islet cells
- Metformin produces substantial reductions in A1C, but not:
  - Weight gain
  - Hypoglycemia
- Metformin has neutral to positive effects on lipids and BP
- Major adverse events associated with metformin are GI-related.
- Watch renal function

ADA/EASD Patient-Centered Approach to the Management of Hyperglycemia

If A1C goal not reached after 3 months of lifestyle + metformin monotherapy, proceed to two-drug combination

<table>
<thead>
<tr>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>SU*</td>
<td>T2D</td>
<td>DPP-4</td>
<td>GLP-1 RA</td>
<td>Insulin (usually basal)</td>
</tr>
<tr>
<td>Efficacy (↓ HbA1c)</td>
<td>High</td>
<td>High</td>
<td>Intermediate</td>
<td>High</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Moderate risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Weight</td>
<td>Gain</td>
<td>Gain</td>
<td>Neutral</td>
<td>Loss</td>
</tr>
<tr>
<td>Major side effect</td>
<td>Hypoglycemia</td>
<td>DKA, CHF, fractures</td>
<td>Rare</td>
<td>GI</td>
</tr>
<tr>
<td>Costs</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

If goal not reached after 3-6 months combo therapy with basal insulin, advanced combo therapy with multiple daily doses insulin.

*Use based on individual patient's needs and tolerance.
AACE Diabetes Algorithm for Glycemic Control

**LIFESTYLE MODIFICATION**
- Lifestyle modification
- A1C goal: 6.5% or lower

**GLP-1 Hormone Secretion and Metabolism**
- GLP-1 released into bloodstream and rapidly degraded by DPP-4 enzyme
- Remaining GLP-1 enters pancreas, suppresses glucagon secretion, stimulates insulin secretion, slows gastric emptying
- Oral DPP-4 inhibitors inhibit the actions of DPP-4, reduce degradation of existing GLP-1, providing pharmacologic GLP-1 concentrations

**Efficacy of GLP-1 Receptor Agonists and DPP-4 Inhibitors: Meta-analysis and Systematic Review**

<table>
<thead>
<tr>
<th></th>
<th>GLP-1 RA</th>
<th>DPP-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline A1C</td>
<td>7.4% to 10.3%</td>
<td>7.2% to 9.3%</td>
</tr>
<tr>
<td>A1C reductions*</td>
<td>1.1% to -1.8%</td>
<td>0.6% to 1.1%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>&gt;2 kg</td>
<td>0.2 to -0.6 kg</td>
</tr>
</tbody>
</table>

Mean reductions in FPG with exenatide once weekly (qw) or liraglutide once daily (qd) were greater than those with exenatide twice daily (bid) and the DPP-4 inhibitors

*At highest maintenance doses

**Incretin-Based Therapies: 2 Different Approaches to Enhance the Action of GLP-1**

GLP-1, an incretin hormone, is released after meals
- Stimulates insulin secretion
- Slows gastric emptying
- Enhances satiety and reduces food intake

**Traditional Antihyperglycemic Therapies Are Often Associated with Multiple Challenges: Can Incretin-Based Agents Help?**

- Inability to meet glycemic goals
- Hypoglycemia is a commonly cited concern with regard to diabetes medications
- Adherence to diabetes medications is lower among patients who are concerned about their weight
- Often difficult to use in patients with comorbidities (CKD, CVD)
- Can be used safely in patients with CKD and renal impairment; do not seem to increase CV risk

**Hypoglycemia in T2DM**

- Risks greater for
  - Older patients
  - Those with longer diabetes duration
  - Patients using certain antihyperglycemic medications (ie, SUs, insulin)
- Potential financial savings incurred with SUs is often negated by the need for additional physician visits or even hospital admissions to manage hypoglycemic episodes
- Patients with drive for strict glycemic control (perhaps)
- Incidence of self-reported severe hypoglycemia
  - 25% of patients taking insulin >5 years
- Effects
  - Mild/moderate: self-care effects, anxiety/fear
  - Severe: cognitive impairment, injury, seizures, transient paralysis/coma, arrhythmias, death
**Hypoglycemia Risk is Low With DPP-4 Inhibitors: Review of Randomized, Controlled Trials**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Hypoglycemia RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any DPP-4 inhibitor compared to placebo</td>
<td>0.92 (0.74, 1.15)</td>
</tr>
<tr>
<td>Any DPP-4 inhibitor compared to SU in absence of SU combination therapy</td>
<td>0.20 (0.17, 0.24)</td>
</tr>
<tr>
<td>Sitagliptin or linagliptin in combination with insulin or a SU</td>
<td>1.86 (1.46, 2.37)</td>
</tr>
</tbody>
</table>

DPP-4 inhibitors have a glucose-dependent mechanism of action (ie, they stimulate insulin secretion only during hyperglycemia), resulting in low hypoglycemia risk.

*80 (4 alogliptin, 8 linagliptin, 8 saxagliptin, 20 sitagliptin, and 27 vildagliptin) double-blind, randomized, placebo or active-controlled trials with ≥18 weeks duration in patients with T2D reporting safety outcomes were included.

Gooßen K, Gräber S. Diabetes Obes Metab. 2012 Apr 20.

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**Prevalence of CKD in US Adults by Diabetes Status**

<table>
<thead>
<tr>
<th>CKD Status</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosed diabetes</td>
<td>41.70</td>
</tr>
<tr>
<td>Undiagnosed diabetes</td>
<td>39.00</td>
</tr>
<tr>
<td>Pre-diabetes</td>
<td>18.00</td>
</tr>
<tr>
<td>No diabetes</td>
<td>10.60</td>
</tr>
</tbody>
</table>

Chronic kidney disease (CKD) defined as estimated glomerular filtration rate (GFR) 15–59 mL/min per 1.73 m² or albumin-creatinine ratio ≥30 mg/g.


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**Declining Renal Function Increases Hypoglycemia Risk**

<table>
<thead>
<tr>
<th>Glucose (mg/dL)</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 90</td>
<td>1.62</td>
</tr>
<tr>
<td>90–110</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Groups adjusted for race, gender, age, cancer, diabetes and cardiovascular disease (all rate ratios P < .0001 vs. control).


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**Case Study**

- 60-year old obese (BMI 35 kg/m²) African American woman with T2DM diagnosed 9 years ago
- A1C = 7.4%
- Current therapy:
  - Metformin 1000 mg twice a day
  - Glyburide 10mg daily
- Tolerates metformin without gastrointestinal distress
- Occasional mild hypoglycemia when skips lunch (office worker with busy schedule)
- Well controlled hypertension and dyslipidemia (treated with ACE inhibitor and statin)
- GFR 45 ml/min

**What is your next step regarding glucose-lowering therapy?**

1. Continue metformin, switch glyburide to glipizide and add Alogliptin
2. Continue metformin, switch glyburide to glipizide and add Linagliptin
3. Continue metformin, switch glyburide to glipizide and add Saxagliptin
4. Continue metformin, switch glyburide to glipizide and add Sitagliptin
5. Discontinue sulfonylurea and start Alogliptin
6. Discontinue sulfonylurea and start Linagliptin
7. Discontinue sulfonylurea and start Saxagliptin
8. Discontinue sulfonylurea and start Sitagliptin
**Metformin**

- Eliminated unchanged by urinary excretion
- Contraindicated in renal insufficiency due to lactic acidosis
- Avoid with serum creatinine ≥ 1.4 mg/dl in women and ≥ 1.5 mg/dl in men
- Lactic acidosis risk increased by CHF, alcohol, cimetidine, and acute renal failure after surgery or iodinated dyes
- Stop 2-3 days before surgery or iodinated dyes, and resume when it is clear that renal function has not been affected

**Sulfonylureas**

In contrast with incretin axis drugs, all SUs induce insulin secretion regardless of ambient glucose

- **Gliburide**
  - Metabolized by liver to ACTIVE metabolites cleared by the kidney, which accumulate in renal failure. HIGH RISK for hypoglycemia
- **Glimepiride**
  - Metabolized by liver to ACTIVE metabolites cleared by the kidney, which accumulate in renal failure. MODERATE RISK hypoglycemia
- **Glipizide**
  - Metabolized by liver to INACTIVE metabolites. PREFERRED SULFONYLUREA in renal failure

**Excretion of DPP-4 Inhibitors**

- **Linagliptin**
  - No dose adjustment and/or no additional drug monitoring required
  - All other DPP-4 inhibitors are primarily excreted via the kidneys.
  - They require dose-adjustments or are not recommended in patients with declining renal fx.
  - Drug-related kidney monitoring may also be required.

**Dosing Adjustments of DPP-4 Inhibitors in the Presence of Renal Impairment**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Metabolism/Clearance</th>
<th>Dose Adjustment in CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin</td>
<td>Renal</td>
<td>50 mg/d if GFR 30-60 mL/min</td>
</tr>
<tr>
<td></td>
<td>25 mg/d if GFR &lt; 30 mL/min</td>
<td></td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>Hepatic/renal</td>
<td>2.5 mg/d if GFR &lt; 30 mL/min</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>Hepatic</td>
<td>No dose adjustment necessary</td>
</tr>
<tr>
<td>Alogliptin</td>
<td>Renal</td>
<td>12.5 mg once daily if GFR 230 to &lt;60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.25 mg once daily if GFR&lt;30</td>
</tr>
</tbody>
</table>

DPP-4 Inhibition: Role in T2DM Therapy

- Oral therapy, once daily
  - Inhibits the action of DPP-4 and reduce degradation of existing GLP-1, providing physiologic GLP-1 concentrations
- Can be used as monotherapy or in combination with other antihyperglycemic agents
  - Add on to metformin, TZD; triple combo particularly effective
  - All can be used with insulin, but lower doses of insulin may be needed


DPP-4 Inhibition: Role in T2DM Therapy (cont'd)

- Clinically important A1C reductions
  - Comparable efficacy to rosiglitazone, glipizide
- Very well tolerated
  - Low risk of hypoglycemia, no weight gain, no GI symptoms, no edema
  - Low risk for drug-drug interactions
- Can be used in patients with co-morbid disease
  - No dose adjustments required with linaglipin in patients with CKD
  - Does not increase CV risk


Case Study

- 49-year-old (BMI 33 kg/m²) Mexican-American man with T2DM diagnosed 2 years ago
- A1C = 7.2%
- LDL 130 mg/dL
- Current therapy:
  - Metformin 500 mg twice a day
  - Atorvastatin 40 mg once a day

What is your next step therapy?

1. Increase metformin
2. Increase metformin and start colesevelam
3. Add a DPP-4 inhibitor
4. No change in therapy, encourage more exercise

Prevalence of Diagnosed T2DM in U.S. Hispanic Populations

The age-adjusted percentage for Hispanics with diagnosed diabetes overall was 6.3% in 1997 and 9.3% in 2010 for an increase of 48%.


Colesevelam

- Approved as adjunct therapy for dyslipidemia (2000)
- Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (2008 approval)
  - Not for treatment of type 1 DM or DKA
  - Mechanism of action of glucose lowering uncertain
  - Available as tablets or powder for oral suspension

DKA, diabetic ketoacidosis
Initial Combination Therapy with Metformin Plus Colesevelam in Drug-Naïve Hispanic Patients with Early Type 2 Diabetes*

<table>
<thead>
<tr>
<th>A1C Results</th>
<th>Lipid Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1.2</td>
<td>LDL-C (-19.4%)</td>
</tr>
<tr>
<td>-1.0</td>
<td>Non-HDL-C (-10.3)</td>
</tr>
<tr>
<td>-1.5</td>
<td>TC (-11.1)</td>
</tr>
</tbody>
</table>

*Unapproved indication; a $P = 0.001$ vs metformin plus placebo; b $P < 0.05$ vs metformin plus placebo; only patients who were not at treatment target at baseline were included.


Colestevalam: Safety Profile

- Generally well tolerated
  - Gastrointestinal side effects most common drug-related adverse events
  - Constipation
  - Dyspepsia
- Colesevelam did not increase risk of hypoglycemia when added to existing metformin-, sulfonylurea- or insulin-based therapy in patients with T2DM
- Colesevelam can increase triglyceride levels in patients with T2DM
  - Caution is recommended in patients with TG levels >300 mg/dL
  - Contraindicated in patients with TG levels >500 mg/dL and in patients with hypertriglyceridemia-induced pancreatitis


Colestevalam: Drug Interactions

- Colesevelam reduces the absorption of:
  - Cyclosporin
  - Glyburide
  - Levothyroxine sodium
- Oral contraceptives containing ethinyl estradiol or norethindrone
- Colesevelam also may reduce the activity of phenytoin and warfarin

Drugs that interact with colesvelam should be administered four hours before the administration of colesvelam and, when possible, drug levels should be monitored

Which of the following agents is associated with a low risk of hypoglycemia and a low risk of weight gain?

1. Any of the DPP-4 inhibitors
2. Metformin
3. Colesevelam
4. 1 and 3
5. 1, 2, and 3

Conclusions

- T2DM is a progressive disease; combination therapy and lifestyle modification are important aspects of comprehensive approaches to improving patient outcomes
- Metformin is a cornerstone of therapy
  - Low risk of hypoglycemia and weight gain
- Newer treatment options offer physicians choices for monotherapy or combination therapy regimens that balance efficacy and tolerability for patients with T2DM
  - DPP-4 inhibitors are effective in lowering A1C levels either as monotherapy or in combination therapy, with a low incidence of hypoglycemia and no weight gain
  - Colesevelam has dual indication for glucose-lowering and lipid-lowering, with low risk of hypoglycemia and weight gain

Emerging Treatment Options: SGLT-2 Inhibitors in Clinical Context

Richard Pratley, MD
Samuel Crockett Chair in Diabetes Research
Director, Florida Hospital Diabetes Institute
Senior Scientist, Translational Research Institute
Professor, Sanford Burnham Medical Research Institute
Orlando, Florida
Off Label Disclosure

• All SGLT 2 Inhibitors Are Currently Investigational in the United States

Please rate your current understanding of emerging SGLT inhibitors on a scale from 1 (low) to 5 (high)

1. 1
2. 2
3. 3
4. 4
5. 5

Which of the following is the target for the mechanism of action of SGLT2 Inhibitors?

1. Brain
2. Incretin system
3. Kidney
4. Liver
5. Pancreas

What percentage of filtered glucose does the kidney reabsorb in otherwise healthy individuals?

1. 10%
2. 30%
3. 50%
4. 70%
5. 90%

Which of the following is the most common adverse effect of SGLT2 inhibitors?

1. Gastrointestinal side effects
2. Genitourinary infections
3. Weight gain
4. Hypoglycemia

Renal Handling of Glucose in a Non-diabetic Individual

SGLT = sodium-glucose transporter
Mechanism of Action of SGLT1 and SGLT2

ATP = adenosine triphosphate; GLUT = glucose transporter; K+ = potassium; Na+ = sodium


Renal Glucose Handling in Diabetes


Effect of SGLT2 Inhibition on Renal Glucose Handling

T2DM = type 2 diabetes mellitus


Mechanism of Action of SGLT2 Inhibitors


SGLT 2 Inhibition in T2DM: Physiologic Consequences


SGLT2 Inhibitors: Multiple Investigational Agents in Development

<table>
<thead>
<tr>
<th>Compound</th>
<th>Stage of Development</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapagliflozin</td>
<td>First to complete phase III trials; submitted to FDA (more data required)</td>
<td>10 mg QD</td>
<td></td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>Phase III trials complete; submitted to FDA (advisory committee recommended to approve)</td>
<td>300 mg QD</td>
<td>Mechanism may include delayed intestinal glucose absorption; increased urinary glucose excretion</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>Phase III; 10 trials with, 14,500 patients currently underway</td>
<td>10–25 mg QD</td>
<td>Most selective of investigational SGLT2 inhibitors</td>
</tr>
<tr>
<td>Ipragliflozin</td>
<td>Just entering phase III;</td>
<td>12.5–300 mg QD</td>
<td></td>
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</table>
Dapagliflozin 10 mg vs. Metformin XR vs. Combination Therapy: A1C at Week 24

Dapagliflozin 10 mg vs. Glipizide as Add-on to Metformin

Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycemic control with metformin (≥1500 mg)

Dapagliflozin monotherapy in drug-naïve patients with diabetes: a randomized-controlled trial of low-dose range

Dapagliflozin Safety: Malignancies

• Bladder cancer incidence rate:
  - 0.16% patients (n=5,478) treated with dapagliflozin vs 0.03% patients (n=3,156) in placebo group (p = 0.15)
• Breast cancer incidence rate:
  - 0.4% patients (n=2,223) treated with dapagliflozin vs 0.09% patients (n=1,053) in placebo group (p = 0.27)
**A1C change in response to Canagliflozin vs Sitagliptin in Patients with T2DM**


**Empagliflozin: Change in A1C in T2DM Patients at Week 12**

*P < 0.001 vs. placebo
500 mg twice daily for 4 weeks, then 1,000 mg twice daily or the maximum tolerated dose

**Empagliflozin: Change in FPG in T2DM Patients at Week 12**

*P < 0.001 vs. placebo
† 500 mg twice daily for 4 weeks, then 1,000 mg twice daily or the maximum tolerated dose

**Empagliflozin: Change in Body Weight in T2DM Patients at Week 12**

*P < 0.001 vs. placebo
† 500 mg twice daily for 4 weeks, then 1,000 mg twice daily or the maximum tolerated dose

**Empagliflozin: Add-on to Metformin**


**Empagliflozin Lowers Blood Pressure Independent of Weight or A1C Change**

Blood Pressure Changes in Hypertensive (SBP >140 mmHg) T2DM Treated with Empagliflozin for Glucose Control

Summary: Efficacy of SGLT2 Inhibitors

- Targeted and specific mechanism
- Can be combined with other antihyperglycemic agents and insulin
- Effects on A1C comparable to other OADs
- Modest weight loss
- Low risk of hypoglycemia

Safety of SGLT-2 Inhibitors

- SGLT-2 inhibitors do not cause gastrointestinal side effects, hypoglycemia, or weight gain
- Genitourinary infections appear to be the main novel side effect of SGLT-2 inhibitors, and are presumably linked to high levels of glucose excreted in the urine
- Data on potential carcinogenicity in the dapagliflozin trials were largely responsible for the FDA advisory committee’s recommendation against approval

Genitourinary Infections

- In short-term placebo-controlled trials of dapagliflozin:
  - urinary tract infections occurred in 10% of women and 2.7% of men
  - genital infections occurred in 10% of women and 3.5% of men.
- In the study of canagliflozin as add-on to metformin
  - 3% to 9% of patients developed urinary tract infections
  - 3% to 8% developed genital infections.
- In the study of empagliflozin added to metformin,
  - urinary tract infection occurred in 3.1% of empagliflozin-treated patients versus 2.8% in the placebo arm.
  - Genital infections were reported in 2.5% of the empagliflozin arms, 1.4% of the sitagliptin arm, and none of the placebo group.
SGLT2 Inhibitors Potential Role in Managing Hyperglycemia in T2DM

Monotherapy
- Efficacy (↓A1C): High
- Hypoglycemia: Low risk

Lifestyle Changes

2-drug combinations
- Efficacy (↓A1C): More complex
- Hypoglycemia: Neutral
- Weight: Gain
- Side effects: GI/lactic acidosis
- Costs: Low

3-drug combinations
- Proceed after 3 mo. if needed
- Insulin usually in combination with 1-2 noninsulin agents

SGLT2 Inhibitors

Benefits
- Improves glycemic control
- Reduces body weight
- Not dependent on insulin secretion
- Complementary mechanism of action to other OADs
- Effective when used as monotherapy or as add-on therapy to commonly used T2DM diabetes medications
- Effective in patients with a short duration of disease and in those with a long history of type 2 diabetes who are receiving insulin therapy
- Modest BP reduction

Limitations
- NOT effective in patients with moderate to severe renal impairment
- May predispose individuals to genital and urinary tract infections
- Unknown long-term durability
- Unknown long-term safety profile

Unanswered Questions About SGLT2 Inhibition

Durability
- The efficacy of SGLT2 inhibition may wane once blood glucose falls into the normal range

Safety and tolerability
- The long-term safety of this class remains to be proven
- Risk of nocturia and genitourinary infections may limit use in some patients

Renal impairment
- SGLT2 inhibition may not be effective in patients with renal impairment

Conclusions

- SGLT2 inhibition represents a novel approach to the treatment of type 2 diabetes
- Studies in experimental models of diabetes have demonstrated that induction of glucosuria reverses glucotoxicity
  - Restores normoglycemia
  - Improves β-cell function and insulin sensitivity
- More safety data are needed

Outcomes Question 1
SB is 65 yrs old with a 7-year history of diabetes, dyslipidemia and hypertension. Her management goals are (choose all that apply):

1. LDL-C <100 mg/dL (<70 mg/dL if CAD)
2. LDL-C < 60 mg/dl
3. HbA1C <7%
4. Hb A1C <6%
5. BP <140/80 mmHg
6. BP <130/85 mmHg
7. TG <150 mg/dL
8. HDL-C >40 mg/dL (men), >50 mg/dL (women)

Outcomes Question 2
Potential benefits of incretin-based therapies (GLP-1 Receptor Agonists and DPP-4 Inhibitors) include each of the following except:

1. Clinically relevant reductions in HbA1C
2. Low risk of hypoglycemia
3. Can be used safely in patients with renal impairment
4. Do not seem to increase CV risk
5. None of the above; all are potential benefits
Outcomes Question 3
Which of the following agents is associated with a low risk of hypoglycemia and a low risk of weight gain?

1. Any of the DPP-4 inhibitors
2. Metformin
3. Colesevelam
4. 1 and 3
5. 1, 2, and 3

Outcomes Question 4
Potential benefits of SGLT2 inhibition include all of the following EXCEPT:

1. HbA1C reductions independent of insulin secretion
2. Modest BP reduction
3. Low risk of hypoglycemia
4. Modest weight loss
5. Lack of efficacy in patients with moderate to severe renal impairment
6. Complementary mechanism of action to other OADs

Question & Answer