Non-Insulin Pharmacotherapy for Type 2 Diabetes in 2016

Jim Chamberlain MD
ADA National Primary Care Advisory Group
Medical Director for Diabetes Services
St. Mark’s Hospital and St. Mark’s Diabetes Center
Salt Lake City, Utah
Son, someday you will make a girl very happy, for a short period of time. Then she’ll leave you and be with new men who are ten times better than you could ever hope to be. These men are called hockey players.
Non-Insulin Pharmacotherapy for Type 2 Diabetes in 1999 – The Triumvarate

- Impaired Insulin Secretion
- Hyperglycemia
- Increased HGP
- Decreased Glucose Uptake
Non-Insulin Pharmacotherapy for Type 2 Diabetes in 2016 – The Ominous Octet

Decreased Insulin Secretion

Decreased Incretin Effect

Increased Lipolysis

Islet-α cell

Increased Glucagon Secretion

Increased HGP

Hyperglycemia

Increased Glucose Reabsorption

Decreased Glucose Uptake

Neurotransmitter Dysfunction
Non-Insulin Pharmacotherapy for Type 2 Diabetes in 2016

There are 12 classes of drugs approved for the treatment of type 2 diabetes in 2016. How do they work, how well do they work, what are side effects, and where should we use them?

When sulfonylurea or insulin therapy is introduced, hypoglycemia appears to become the rate-limiting factor in our efforts to achieve aggressive glycemic control.

Monotherapy does NOT provide long-term sustained glycemic control, nor does the ‘sequential failure’ model.

There are many therapeutic options now to treat type 2 diabetes with advantages of weight control and negligible hypoglycemia risk – use them!
Antihyperglycemic therapy in type 2 diabetes - 2016

Healthy eating, weight control, increased physical activity, and diabetes education

<table>
<thead>
<tr>
<th>Drug</th>
<th>Efficacy*</th>
<th>Hypo risk</th>
<th>Weight</th>
<th>Side effects</th>
<th>Costs*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>high</td>
<td>low</td>
<td>neutral/loss</td>
<td>GI/lactic acidosis</td>
<td>low</td>
</tr>
</tbody>
</table>

If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

<table>
<thead>
<tr>
<th>Drug</th>
<th>Efficacy*</th>
<th>Hypo risk</th>
<th>Weight</th>
<th>Side effects</th>
<th>Costs*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin + Metformin</td>
<td>high</td>
<td>low risk</td>
<td>gain</td>
<td>edema, HF, fxs</td>
<td>low</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>high</td>
<td>moderate risk</td>
<td>gain</td>
<td>hypoglycemia</td>
<td>low</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>high</td>
<td>low risk</td>
<td>gain</td>
<td>edema, HF, fxs</td>
<td>low</td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td>intermediate</td>
<td>low risk</td>
<td>neutral</td>
<td>loss</td>
<td>rare</td>
</tr>
<tr>
<td>SGLT2 inhibitor</td>
<td>intermediate</td>
<td>low risk</td>
<td>loss</td>
<td>GU, dehydration</td>
<td>high</td>
</tr>
<tr>
<td>GLP-1 receptor agonist</td>
<td>high</td>
<td>low risk</td>
<td>gain</td>
<td>hypoglycemia</td>
<td>variable</td>
</tr>
</tbody>
</table>

If HbA1c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

<table>
<thead>
<tr>
<th>Drug</th>
<th>Efficacy*</th>
<th>Hypo risk</th>
<th>Weight</th>
<th>Side effects</th>
<th>Costs*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin + Metformin</td>
<td>high</td>
<td>low risk</td>
<td>gain</td>
<td>edema, HF, fxs</td>
<td>low</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>high</td>
<td>moderate risk</td>
<td>gain</td>
<td>hypoglycemia</td>
<td>low</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>high</td>
<td>low risk</td>
<td>gain</td>
<td>edema, HF, fxs</td>
<td>low</td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td>intermediate</td>
<td>low risk</td>
<td>neutral</td>
<td>loss</td>
<td>rare</td>
</tr>
<tr>
<td>SGLT2 inhibitor</td>
<td>intermediate</td>
<td>low risk</td>
<td>low risk</td>
<td>loss</td>
<td>high</td>
</tr>
<tr>
<td>GLP-1 receptor agonist</td>
<td>high</td>
<td>low risk</td>
<td>gain</td>
<td>hypoglycemia</td>
<td>variable</td>
</tr>
</tbody>
</table>

If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Efficacy*</th>
<th>Hypo risk</th>
<th>Weight</th>
<th>Side effects</th>
<th>Costs*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal insulin + Mealtime insulin</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>GLP-1-RA</td>
<td></td>
</tr>
</tbody>
</table>

©2015 by American Diabetes Association
**A1C 6.5 – 7.5%**
- **Monotherapy**
  - MET + GLP-1 or DPP4
  - TZD
  - Glinide or SU
- **TZD + GLP-1 or DPP4 + MET**
- **Colesevelam**

**A1C > 9.0%**
- **No Symptoms**
  - Drug Naive
  - Under Treatment
- **INSULIN ± Other Agent(s)**

**Symptoms**
- **INSULIN ± Other Agent(s)**

**A1C 7.6 – 9.0%**
- **Dual Therapy**
  - MET + GLP-1 or DPP4 ± SU
  - TZD
  - GLP-1 or DPP4 ± TZD

**A1C > 9.0%**
- **Triple Therapy**
  - MET + DPP4 ± GLP-1 ± TZD
  - AGI if PPG↑
  - SU or Glinide
  - Basal insulin
  - DPP4-i

**Progression of Disease**
- Order of medications listed are a suggested hierarchy of usage
- Based upon phase 3 clinical trials data

**Legend**
- = Few adverse events or possible benefits
- △ = Use with caution

*Available at www.aace.com/pub*

© AACE December 2009 Update. May not be reproduced in any form without express written permission from AACE.
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Expected decrease in $A_1c$ with monotherapy (%)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle changes</td>
<td>1.0-2.0</td>
<td>Broad benefits</td>
<td>Insufficient for most in 1st year</td>
</tr>
<tr>
<td>Metformin</td>
<td>1.0-2.0</td>
<td>Weight neutral, minimal hypoglycemia, cost effective</td>
<td>GI side effects, contraindicated in CRF?</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TZDs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulins</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The Primary Glucose-Lowering Effect of Metformin Resides in the Gut, Not the Circulation: Results From Short-term Pharmacokinetic and 12-Week Dose-Ranging Studies

Change in FPG and fasting metformin concentrations in the 12-week study

John B. Buse et al. Dia Care 2016;39:198-205

©2016 by American Diabetes Association
The Incretin Hormones

- Glucagon-like peptide-1 (GLP-1)
- Glucose-dependent insulinotropic peptide (GIP)
- Pancreatic peptide YY (PYY)
Metformin: Lactic Acidosis & Renal Dosing Adjustments

Systematic reviews of > 150,000 patients showed the incidence of lactic acidosis was ~3-5 cases/100,000 patients treated with metformin and ~4-6/100,000 patients treated with other drugs.

Accumulating observational data suggest that metformin may be safely continued down to glomerular filtration rate (GFR) of 45 mL/min/1.73 m² or even 30 mL/min/1.73 m².

If metformin is used in the lower GFR range, the dose should be reduced and patients should be advised to stop the medication for nausea, vomiting, and dehydration.


Bodmer M, et al. Metformin, sulfonylureas, or other antidiabetes drugs and the risk of lactic acidosis or hypoglycemia: a nested case-control analysis. *Diabetes Care* 2008;31:2086-2091


Standards of Medical Care in Diabetes—2016. *Diabetes Care* 2016;39(Suppl. 1) :S1–S112
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Expected decrease in A1c with monotherapy (%)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle changes</td>
<td>1.0-2.0</td>
<td>Broad benefits</td>
<td>Insufficient for most in 1st year</td>
</tr>
<tr>
<td>Metformin</td>
<td>1.0-2.0</td>
<td>Weight neutral, minimal hypoglycemia</td>
<td>GI side effects, contraindicated in CRF</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>1.0-2.0</td>
<td>Rapidly effective</td>
<td>Weight gain, hypoglycemia</td>
</tr>
<tr>
<td>TZDs</td>
<td>0.5-1.4</td>
<td>Improved lipid profile and ↓ MI</td>
<td>Weight gain, CHF, fluid retention</td>
</tr>
<tr>
<td>Insulins</td>
<td>1.5-3.5</td>
<td>No dose limit, rapidly effective,</td>
<td>Weight gain, hypoglycemia, newer insulins</td>
</tr>
<tr>
<td></td>
<td></td>
<td>improved lipids</td>
<td>expensive</td>
</tr>
<tr>
<td>Intervention</td>
<td>Expected decrease in A1c with monotherapy (%)</td>
<td>Advantages</td>
<td>Disadvantages</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------------------------------------</td>
<td>-------------------------------------------------</td>
<td>----------------------------------------------------</td>
</tr>
<tr>
<td>GLP-1 agonists</td>
<td>0.5-1.0</td>
<td>Weight loss</td>
<td>GI side effects, expensive, injection, long-term safety?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>minimal hypoglycemia</td>
<td></td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>0.5-0.8</td>
<td>Weight neutral</td>
<td>Expensive, long-term safety?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>minimal hypoglycemia</td>
<td></td>
</tr>
<tr>
<td>SLGT-2 inhibitors</td>
<td>0.8-1.2</td>
<td>Weight loss</td>
<td>Expensive, mycotic infections, orthostasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ SBP minimal hypoglycemia</td>
<td></td>
</tr>
<tr>
<td>α-Glucosidase inhibitor</td>
<td>0.5-0.8</td>
<td>Weight neutral</td>
<td>Frequent GI side effects, expensive, 3 times/day dosing</td>
</tr>
<tr>
<td>Glinides</td>
<td>0.5-1.5</td>
<td>Rapidly effective</td>
<td>Weight gain, 3 times/day dosing, hypoglycemia, expensive</td>
</tr>
<tr>
<td>Intervention</td>
<td>Expected decrease in A&lt;sub&gt;1c&lt;/sub&gt; with monotherapy (%)</td>
<td>Advantages</td>
<td>Disadvantages</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------------------------------------------------------</td>
<td>--------------------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>0.1-0.6</td>
<td>Weight loss</td>
<td>No one aware</td>
</tr>
<tr>
<td></td>
<td></td>
<td>minimal hypoglycemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colesevelam</td>
<td>0.6</td>
<td>Weight neutral lipid lowering</td>
<td>Expensive, 6 pills/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>minimal hypoglycemia</td>
<td></td>
</tr>
<tr>
<td>Pramlintide</td>
<td>0.7</td>
<td>Weight loss</td>
<td>Expensive, nausea, hypoglycemia</td>
</tr>
</tbody>
</table>
GLP-1 Modulates Numerous Functions in Humans

GLP-1: Secreted upon the ingestion of food

Promotes satiety and reduces appetite

Alpha cells: ↓ Postprandial glucagon secretion

Beta cells: Enhances glucose-dependent insulin secretion

Liver: ↓ Glucagon reduces hepatic glucose output

Stomach: Helps regulate gastric emptying

<table>
<thead>
<tr>
<th>Drug</th>
<th>Generic</th>
<th>Dosing Schedule</th>
<th>Mixing Required</th>
<th>Pre-injection Waiting Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Byetta</td>
<td>Exenatide</td>
<td>BID</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Bydureon Kit</td>
<td>Exenatide extended release</td>
<td>Weekly</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>Bydureon Pen</td>
<td>Exenatide extended release</td>
<td>Weekly</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>Tanzeum</td>
<td>Albiglutide</td>
<td>Weekly</td>
<td>Yes</td>
<td>Yes 15-30 minutes</td>
</tr>
<tr>
<td>Trulicity</td>
<td>Dulaglutide</td>
<td>Weekly</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Victoza</td>
<td>Liraglutide</td>
<td>QD</td>
<td>No</td>
<td>None</td>
</tr>
</tbody>
</table>
# Updated GLP-1 Agonist Medication Chart

<table>
<thead>
<tr>
<th>Drug</th>
<th>Generic</th>
<th>Dosing</th>
<th>Approved for use with basal insulin</th>
<th>Auto injector</th>
</tr>
</thead>
<tbody>
<tr>
<td>Byetta</td>
<td>Exenatide</td>
<td>5 mcg, 10 mcg</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Bydureon Kit</td>
<td>Exenatide extended release</td>
<td>2 mg</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bydureon Pen</td>
<td>Exenatide extended release</td>
<td>2 mg</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Tanzeum</td>
<td>Albigrutide</td>
<td>30 mg, 50 mg</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Trulicity</td>
<td>Dulaglutide</td>
<td>0.75 mg, 1.5 mg</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Victoza</td>
<td>Liraglutide</td>
<td>0.6 mg, 1.2 mg, 1.8 mg</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
## Updated GLP-1 Agonist Medication Chart

<table>
<thead>
<tr>
<th>Drug</th>
<th>Generic</th>
<th>Hemoglobin A₁c reduction</th>
<th>Nausea</th>
<th>Weight Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Byetta</td>
<td>Exenatide</td>
<td>0.8-1.4%</td>
<td>34-57%</td>
<td>1.8-3.5 kg</td>
</tr>
<tr>
<td>Bydureon Kit</td>
<td>Exenatide extended release</td>
<td>1.3-1.9%</td>
<td>9-27%</td>
<td>2.1-2.3 kg</td>
</tr>
<tr>
<td>Bydureon Pen</td>
<td>Exenatide extended release</td>
<td>1.3-1.9%</td>
<td>9-27%</td>
<td>2.1-2.3 kg</td>
</tr>
<tr>
<td>Tanzeum</td>
<td>Albigrutide</td>
<td>0.6-0.9%</td>
<td>11%</td>
<td>0.4-1.2 kg</td>
</tr>
<tr>
<td>Trulicity</td>
<td>Dulaglutide</td>
<td>0.7-1.1%</td>
<td>12-21%</td>
<td>0.3-3.1 kg</td>
</tr>
<tr>
<td>Victoza</td>
<td>Liraglutide</td>
<td>0.8-1.1%</td>
<td>7.5-35%</td>
<td>0.4-2.8 kg</td>
</tr>
</tbody>
</table>
Summary of Physiologic Effects of GLP-1 Agonists

- Very effective glucose-lowering agents
- Nausea most common adverse effect ≈ 10-50%
- Typical weight reduction ≈ 1-3 kg
- Hypoglycemia rates negligible when not used in combination with sulfonylureas
# Updated DPP-4 Inhibitor Medication Chart

<table>
<thead>
<tr>
<th>Drug</th>
<th>Generic</th>
<th>Dosing Schedule</th>
<th>Dosing</th>
<th>Renal Dosing Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Januvia</td>
<td>Sitagliptin</td>
<td>QD</td>
<td>25, 50, 100 mg</td>
<td>50 mg (CrCl ≥ 30 to &lt; 50 mL/min)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25 mg (CrCl &lt; 30 mL/min) or ESRD requiring hemodialysis</td>
</tr>
<tr>
<td>Onglyza</td>
<td>Saxagliptin</td>
<td>QD</td>
<td>2.5, 5 mg</td>
<td>2.5 mg (CrCl ≤ 50 mL/min)</td>
</tr>
<tr>
<td>Tradjenta</td>
<td>Linagliptin</td>
<td>QD</td>
<td>5 mg</td>
<td>None</td>
</tr>
<tr>
<td>Nesina</td>
<td>Alogliptin</td>
<td>QD</td>
<td>6.25, 12.5, 25 mg</td>
<td>12.5 mg (CrCl ≥ 30 to &lt; 60 mL/min)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.25 mg (CrCl &lt; 30 mL/min) or ESRD requiring hemodialysis</td>
</tr>
</tbody>
</table>
## DPP-4 Inhibitors - Efficacy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Generic</th>
<th>Hemoglobin $A_1c$ reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Januvia</td>
<td>Sitagliptin</td>
<td>0.3-1.0%</td>
</tr>
<tr>
<td>Onglyza</td>
<td>Saxagliptin</td>
<td>0.4-0.9%</td>
</tr>
<tr>
<td>Tradjenta</td>
<td>Linagliptin</td>
<td>0.4-0.7%</td>
</tr>
<tr>
<td>Nesina</td>
<td>Alogliptin</td>
<td>0.6-1.0%</td>
</tr>
</tbody>
</table>
Summary of Physiologic Effects of DPP-4 Inhibitors

- Best tolerated class of glucose-lowering drugs
- Least effective of commonly used glucose-lowering drugs
- Typical weight reduction ≈ 0-2 kg
- Hypoglycemia rates negligible when not used in combination with sulfonylureas
Joint statement from FDA & European Medicines Agency (EMA)

- Pooled analysis from 14,611 patients from 25 clinical trials of sitagliptin
  = No increased risk of pancreatitis or pancreatic cancer

- Amylase and lipase levels often increase with no GI adverse events

- “Assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer, as expressed recently in the scientific literature and in the media, are inconsistent with the current data”
Updated Safety Profile of GLP-1 Agonists and DPP-4 Inhibitors

✓ SAVOR-TIMI 53 Study

- 16,492 patients with history of or high-risk for CV disease treated with saxagliptin or placebo for 2.1 years:
  = Rates of acute and chronic pancreatitis same in both groups
  = More patients in saxagliptin group than in the placebo group were hospitalized for heart failure (3.5% vs. 2.8%; P=0.007)

✓ EXAMINE Study

- 5,380 patients with recent acute MI or unstable angina treated with alogliptin or placebo for up to 40 months:
  = Rates of acute and chronic pancreatitis same in both groups

SGLT2 Inhibitors

- Glucose (G) passes from the bloodstream into the nephron
- SGLT2 reabsorbs glucose from the nephron back into the bloodstream
- SGLT2 inhibitors block SGLT2 from reabsorbing glucose
- Glucose is lost in the urine, and blood glucose decreases

Nephron

Canagliflozin (Invokana®)
Dapagliflozin (Farxiga®)
Empagliflozin (Jardiance®)

BLOOD FLOW

G = Glucose

Lost in urine
<table>
<thead>
<tr>
<th>Drug</th>
<th>Generic</th>
<th>Dosing Schedule</th>
<th>Dosing</th>
<th>Renal Dosing Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farxiga</td>
<td>Dapagliflozin</td>
<td>QD</td>
<td>5, 10 mg</td>
<td>Discontinue when eGFR is persistently less than 60 mL/min/1.73 m²</td>
</tr>
<tr>
<td>Invokana</td>
<td>Canagliflozin</td>
<td>QD</td>
<td>100, 300 mg</td>
<td>100 mg once daily in patients with eGFR of 45 to less than 60 mL/min/1.73 m² Discontinue when eGFR is persistently less than 45 mL/min/1.73 m²</td>
</tr>
<tr>
<td>Jardiance</td>
<td>Empagliflozin</td>
<td>QD</td>
<td>10, 25 mg</td>
<td>Discontinue when eGFR is persistently less than 45 mL/min/1.73 m²</td>
</tr>
</tbody>
</table>
# SGLT-2 Inhibitors - Efficacy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Generic</th>
<th>Hemoglobin A1c reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farxiga</td>
<td>Dapagliflozin</td>
<td>0.5-1.0%</td>
</tr>
<tr>
<td>Invokana</td>
<td>Canagliflozin</td>
<td>0.7-1.0%</td>
</tr>
<tr>
<td>Jardiance</td>
<td>Empagliflozin</td>
<td>0.6-0.9%</td>
</tr>
</tbody>
</table>
Summary of Physiologic Effects of SGLT-2 Inhibitors

- Glucorectic effect of 60-80 grams of glucose per day = 240-320 kcal/day
- Typical weight reduction ≈ 2-4 kg
- Typical SBP reduction ≈ 3-5 mm Hg
- 2/3 of weight loss = adipose tissue
  - 1/3 of weight loss = lean tissue
- Of adipose tissue loss ½ = visceral fat
  - ½ = subcutaneous fat
SGLT-2 Inhibitors – Precautions

- Genital mycotic infection rate ≈ 5% in males
  ≈ 10% in females

- Bacterial urinary tract infections minimally increased

- Orthostatic symptoms more common in:
  - Age > 75 years of age
  - eGFR 30 to < 60 mL/min/1.73 m²
  - Patients using loop diuretics
SGLT-2 Inhibitors – Precautions

- Reports of diabetic ketoacidosis (DKA) in patient with both type 1 and type 2 diabetes:
  - 20 clinical cases requiring hospitalization between March 2013 and June 2014 in FDA Adverse Event Reporting System
  - Scarce clinical data initially suggested typical type 2 diabetics, but most likely insulin-treated type 2 diabetics or type 1 diabetics

*Diabetes Care* 2015;38:1638-1642
SGLT-2 Inhibitors – Precautions

- Reports of diabetic ketoacidosis (DKA) in patients with both type 1 and type 2 diabetes:
  - European Medicines Agency (EMA) reports 101 cases of DKA worldwide as of May 2015 in patients treated with SGLT-2 inhibitors
  - All cases were ‘serious’ with many requiring hospitalization and in a number of the reports blood sugar levels were only moderately increased
  - Has led to the term ‘euglycemic diabetic ketoacidosis’

*Diabetes Care* 2015;38:1638-1642
SGLT-2 Inhibitors – Precautions

- Reports of diabetic ketoacidosis (DKA) in patients with both type 1 and type 2 diabetes:
  - Rates of DKA were 0.5-0.8 per 1,000 patient years on canagliflozin compared to 0.2 per 1,000 patient years on comparator drugs in CANVAS study of 17,596 patients (most on insulin)
  - 6 of 12 cases of DKA on canagliflozin had evidence of LADA or type 1 diabetes with positive GAD65 antibodies
  - Rate of DKA less than 0.1% on dapagliflozin in DECLARE study of 17,150 patients
  - Rate of DKA less than 0.1% on empagliflozin in EMPA-REG OUTCOME study of 7,020 patients

*Diabetes Care* 2015;38:1638-1642
SGLT-2 Inhibitors – Precautions

✓ Risk factors for DKA on SGLT-2 inhibitors per FDA:
  - Intercurrent illness
  - Reduced food and fluid intake
  - Reduced insulin doses
  - History of alcohol intake

✓ Consensus (?) these drugs are NOT safe for use in type 1 diabetes

*Diabetes Care* 2015;38:1638-1642
# SGLT-2 Inhibitors – Cardiovascular Outcomes Trials

**Table 2. Cardiovascular outcome trials with SGLT-2 inhibitors**

<table>
<thead>
<tr>
<th></th>
<th>EMPA-REG OUTCOME</th>
<th>CANVAS</th>
<th>DECLARE-TIMI 58</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ClinicalTrials.gov</strong></td>
<td>NCT01131676</td>
<td>NCT01032629</td>
<td>NCT01730534</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Empagliflozin/placebo (2:1)</td>
<td>Canagliflozin/placebo (2:1)</td>
<td>Dapagliflozin/placebo (1:1)</td>
</tr>
<tr>
<td><strong>Enrollment</strong></td>
<td>7020</td>
<td>4411</td>
<td>17,276</td>
</tr>
<tr>
<td><strong>Key inclusion criteria</strong></td>
<td>Established vascular complications, HbA1c 7.0%–10.0%, age ≥18 years</td>
<td>Established vascular complications (age ≥30 years) or ≥2 CV risk factors (age &gt;50 years), HbA1c 7.0%–10.5%</td>
<td>High risk for CV events, T2DM, age ≥40 years</td>
</tr>
<tr>
<td><strong>Primary end point</strong></td>
<td>CV death, nonfatal MI, nonfatal stroke</td>
<td>CV death, nonfatal MI, nonfatal stroke</td>
<td>CV death, nonfatal MI, nonfatal stroke</td>
</tr>
<tr>
<td><strong>Estimated reporting</strong></td>
<td>2015</td>
<td>2017</td>
<td>2019</td>
</tr>
</tbody>
</table>


*Adapted from Inzucchi et al.*
SGLT-2 Inhibitors – Cardiovascular Outcomes

Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME)

7,020 patients in 42 countries with type 2 diabetes randomized to empagliflozin 10 or 25 mg or placebo added to standard care for up to 5 years. 3.1 years median follow up:

- 32% reduction in all-cause mortality
- 38% reduction in CV mortality (primary outcome)
- 35% reduction in hospitalization for CHF
- No change in non-fatal MI or stroke (primary outcomes)

Data presented at European Association for the Study of Diabetes, Stockholm, Sweden, September 17, 2015.

SGLT-2 Inhibitors – Renal Protection?

↓ hyperfiltration
↓ albuminuria
↓ glomerular BP
↓ systemic BP
↓ arterial stiffness
↓ HbA₁c
↓ weight
↓ inflammation
↓ intravascular volume

Škrtić M and Cherney D. Curr Opin Nephrol Hypertens 2015;24:96–103
When sulfonylurea or insulin therapy is introduced, hypoglycemia appears to become the rate-limiting factor in our efforts to achieve aggressive glycemic control.
Hypoglycemia – Clinical Impact

Drugs Causing Most ED Visits in Patients > Age 65 in United States

1. Warfarin (33%)
2. Insulins (14%)
3. Other anti-platelet drugs (13%)
4. Sulfonylureas (11%)

Hypoglycemia – Clinical Impact

Vital Signs, QT Prolongation, and Newly Diagnosed Cardiovascular Disease During Severe Hypoglycemia in Type 1 and Type 2 Diabetic Patients in Japan (n=414, blood glucose = 31-32 mg/dl)

- Hypoglycemia-induced QTc interval prolongation (> 0.44 s):
  - 50.0% in type 1 DM
  - 59.9% in type 2 DM

- Hypoglycemia-induced severe HTN (> 180/120 mm Hg):
  - 19.8% in type 1 DM
  - 38.8% in type 2 DM

- Hypoglycemia-induced hypokalemia (< 3.5 mEq/L):
  - 42.4% in type 1 DM
  - 36.3% in type 2 DM

Hypoglycemia – Clinical Impact

Potential Mechanisms for Adverse Cardiovascular Events

- Hypoglycemia-induced QT prolongation
- Hypoglycemia-induced hypokalemia
- Direct effect of hypoglycemia on myocardial blood flow
- Acute inflammatory effects on vascular endothelium
- Rises in circulating epinephrine concentrations
  - vasoconstriction
  - platelet aggregation
- Hypoglycemia-induced seizure activity
### RR for Experiencing at Least One Hypoglycemic Episode: Glyburide Versus Other Secretagogues

<table>
<thead>
<tr>
<th>Study</th>
<th>Glyburide n/N</th>
<th>Secretagogue n/N</th>
<th>RR (random) 95% CI</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baba 1983</td>
<td>20/131</td>
<td>10/146 Glic</td>
<td>2.23 [1.08, 4.59]</td>
<td></td>
</tr>
<tr>
<td>Dills 1996</td>
<td>48/288</td>
<td>34/289 Glim</td>
<td>1.42 [0.94, 2.13]</td>
<td></td>
</tr>
<tr>
<td>Draeger 1996</td>
<td>74/520</td>
<td>60/524 Glim</td>
<td>1.24 [0.90, 1.71]</td>
<td></td>
</tr>
<tr>
<td>Haider 1976</td>
<td>2/76</td>
<td>0/80 Chlp</td>
<td>5.26 [0.26, 107.81]</td>
<td></td>
</tr>
<tr>
<td>Hamblin 1970</td>
<td>7/50</td>
<td>2/47 Chlp</td>
<td>3.29 [0.72, 15.05]</td>
<td></td>
</tr>
<tr>
<td>Harrower 1994</td>
<td>7/84</td>
<td>2/86 Glic</td>
<td>3.58 [0.77, 16.76]</td>
<td></td>
</tr>
<tr>
<td>Landgraf 1999</td>
<td>9/101</td>
<td>9/94 Repg</td>
<td>0.93 [0.39, 2.24]</td>
<td></td>
</tr>
<tr>
<td>Mafauzy 2002</td>
<td>19/119</td>
<td>15/116 Repg</td>
<td>1.23 [0.66, 2.31]</td>
<td></td>
</tr>
<tr>
<td>Marbury 1999</td>
<td>37/182</td>
<td>59/362 Repg</td>
<td>1.25 [0.86, 1.81]</td>
<td></td>
</tr>
<tr>
<td>Rosenstock 1993</td>
<td>3/70</td>
<td>1/69 Glip</td>
<td>2.96 [0.32, 27.74]</td>
<td></td>
</tr>
<tr>
<td>Wollenbuttel 1999</td>
<td>13/139</td>
<td>26/286 Repg</td>
<td>1.03 [0.55, 1.94]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>2199</td>
<td>2513</td>
<td></td>
<td>1.52 [1.21, 1.92]</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $I^2 = 42.1\%$

Non-Insulin Pharmacotherapy for Type 2 Diabetes in 2016

Monotherapy does NOT provide long-term sustained glycemic control nor does the ‘sequential failure’ model
Antihyperglycemic therapy in type 2 diabetes - 2015

Healthy eating, weight control, increased physical activity, and diabetes education

Metformin
- high
- low risk
- neutral / loss
- GI / lactic acidosis
- low

If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

- Metformin + Sulfonlurea
  - high
  - moderate risk
  - gain
  - hypoglycemia
  - low
- Metformin + Thiazolidinedione
  - high
  - low risk
  - gain
  - edema, HF, fxs
  - low
- Metformin + DPP-4 inhibitor
  - intermediate
  - low risk
  - neutral
  - rare
  - high
- Metformin + SGLT2 inhibitor
  - intermediate
  - low risk
  - loss
  - GU, dehydration
  - high
- Metformin + GLP-1 receptor agonist
  - high
  - low risk
  - gain
  - GI
  - variable
- Metformin + Insulin (basal)
  - highest
  - high risk
  - loss
  - gain
  - hypoglycemia
  - variable

If HbA1c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

- Metformin + Sulfonlurea + TZD
- Metformin + Thiazolidinedione + SU
- Metformin + DPP-4 inhibitor + SU
- Metformin + SGLT2 inhibitor + SU
- Metformin + GLP-1 receptor agonist + SU
- Metformin + Insulin (basal)

If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-I.
**Glycemic Control Algorithm**

**Lifestyle Modification**
( Including Medically Assisted Weight Loss)

**ENTRY A1c < 7.5%**
- MONOTHERAPY
  - Metformin
  - GLP-1 RA
  - DPP4-i
  - SGLT-2
  - TZD
  - SU/AGI

If A1c > 6.5% in 3 months add second drug (Dual Therapy)

**ENTRY A1c ≥ 7.5%**
- DUAL THERAPY
  - GLP-1 RA
  - DPP4-i
  - TZD
  - Basal insulin
  - Colesevelam
  - Bromocriptine QR
  - AG-i
  - SU/AGI

If not at goal in 3 months proceed to triple therapy

**ENTRY A1c > 9.0%**
- NO SYMPTOMS
  - DUAL THERAPY
  - OR
  - TRIPLE THERAPY
  - INSULIN ± OTHER AGENTS

- SYMPTOMS
  - ADD OR INTENSIFY INSULIN

**Triple Therapy**
- MET or other first-line agent
  - GLP-1 RA
  - DPP4-i
  - TZD
  - Basal insulin
  - Colesevelam
  - Bromocriptine QR
  - AG-i
  - SU/AGI

If not at goal in 3 months proceed to or intensify insulin therapy

**Progression of Disease**

* Order of medications listed are a suggested hierarchy of usage
** Based upon phase 3 clinical trials data

*May not be reproduced in any form without express written permission from AACE.

---

© AACE December 2009 Update.

---
HbA1c Over Time

Rosiglitazone vs Metformin
-0.13 (-0.22 to -0.05), P=0.002

Rosiglitazone vs Glyburide
-0.42 (-0.50 to -0.33), P<0.001
Monotherapy does NOT provide long-term sustained glycemic control nor does the “sequential failure” model – need to strongly consider early combination therapy
Glycemic Control Continues to Deteriorate After Sulfonylureas Are Added to Metformin Among Patients With Type 2 Diabetes

Early combination therapy provides better initial and more sustained glycemic control – especially combinations of drugs with complementary mechanisms of action (metformin plus...).
Antihyperglycemic therapy in type 2 diabetes - 2015

<table>
<thead>
<tr>
<th>Healthy eating, weight control, increased physical activity, and diabetes education</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metformin</strong></td>
</tr>
<tr>
<td>high</td>
</tr>
<tr>
<td>low risk</td>
</tr>
<tr>
<td>neutral / loss</td>
</tr>
<tr>
<td>GI / lactic acidosis</td>
</tr>
<tr>
<td>low</td>
</tr>
</tbody>
</table>

If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

<table>
<thead>
<tr>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Sulfonlurea</td>
<td>Thiazolidinedione</td>
<td>DPP-4 inhibitor</td>
<td>SGLT2 inhibitor</td>
<td>GLP-1 receptor agonist</td>
<td>Insulin (basal)</td>
</tr>
<tr>
<td>high</td>
<td>high</td>
<td>high</td>
<td>intermediate</td>
<td>intermediate</td>
<td>highest</td>
</tr>
<tr>
<td>low risk</td>
<td>low risk</td>
<td>low risk</td>
<td>low risk</td>
<td>low risk</td>
<td>high</td>
</tr>
<tr>
<td>gain</td>
<td>gain</td>
<td>neutral</td>
<td>loss</td>
<td>GI</td>
<td>gain</td>
</tr>
<tr>
<td>edema, HF, fxs</td>
<td>neutral</td>
<td>rare</td>
<td>hypoglycemia</td>
<td>hypoglycemia</td>
<td>variable</td>
</tr>
<tr>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
</tr>
</tbody>
</table>

If HbA1c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

<table>
<thead>
<tr>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Sulfonlurea</td>
<td>Thiazolidinedione</td>
<td>DPP-4 inhibitor</td>
<td>SGLT2 inhibitor</td>
<td>GLP-1 receptor agonist</td>
<td>Insulin (basal)</td>
</tr>
<tr>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
</tr>
<tr>
<td>TZD</td>
<td>DPP-4-I</td>
<td>SGLT2-I</td>
<td>GLP-1-RA</td>
<td>Insulin</td>
<td>Insulin</td>
</tr>
<tr>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
</tr>
<tr>
<td>DPP-4-I</td>
<td>SGLT2-I</td>
<td>GLP-1-RA</td>
<td>Insulin</td>
<td>Insulin</td>
<td>Insulin</td>
</tr>
<tr>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
</tr>
<tr>
<td>Insulin</td>
<td>Insulin</td>
<td>Insulin</td>
<td>Insulin</td>
<td>Insulin</td>
<td>Insulin</td>
</tr>
<tr>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
</tr>
</tbody>
</table>

If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-I:

<table>
<thead>
<tr>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
</tr>
<tr>
<td>Basal insulin +</td>
</tr>
<tr>
<td>Mealtime insulin or</td>
</tr>
<tr>
<td>GLP-1-RA</td>
</tr>
</tbody>
</table>

©2015 by American Diabetes Association
**A1C 6.5 – 7.5%**

**Monotherapy**
- MET + GLP-1 or DPP4
- TZD
- Glinide or SU

**Dual Therapy**
- MET + GLP-1 or DPP4 + TZD
- MET + Colesevelam
- AGI

**Triple Therapy**
- MET + GLP-1 or DPP4 + TZD + AGI

**A1C > 9.0%**

**No Symptoms**
- Drug Naive
- Under Treatment
- INSULIN ± Other Agent(s)

**Symptoms**
- INSULIN ± Other Agent(s)

**ENTRY A1c < 7.5%**

**ENTRY A1c ≥ 7.5%**

**ENTRY A1c > 9.0%**

**Lifestyle Modification**
(Including Medically Assisted Weight Loss)

**MONOTHERAPY**
- Metformin
- GLP-1 RA
- DPP4-i
- AG-i
- SGLT-2
- TZD
- SU/GLN

If A1c > 6.5% in 3 months add second drug (Dual Therapy)

**DUAL THERAPY**
- GLP-1 RA
- DPP4-i
- TZD
- **SGLT-2**
- Basal insulin
- Colesevelam
- Bromocriptine QR
- AG-i
- SU/GLN

If not at goal in 3 months proceed to triple therapy

**TRIPLE THERAPY**
- GLP-1 RA
- DPP4-i
- TZD
- Basal insulin
- DPP4-i
- Colesevelam
- Bromocriptine QR
- AG-i
- SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

**Progression of Disease**

Copyright © 2013 AACE. May not be reproduced in any form without express written permission from AACE.
Initial Combination Therapy With Sitagliptin Plus Metformin

Patients with T2DM not on therapy or on mono- or low-dose combo-OHA

If on OHA, discontinue therapy

Screening period

Diet and exercise run-in period

Single-blind placebo run-in period

Eligible if A1C 7.5%–11%

Week –2 Day 1

Screening period

If on OHA, discontinue therapy

Week 54

Week 104

24-week phase¹ with 30-week continuation phase²

50-week extension study³

Sitagliptin 100 mg qd

Sitagliptin 50 mg bid + metformin 500 mg bid

Sitagliptin 50 mg bid + metformin 1,000 mg bid

Placebo

Metformin 500 mg bid

Metformin 1,000 mg bid

Metformin 1,000 mg bid

Glycemic rescue criteria

FPG criteria to week 24

A1C >8% to week 54

A1C >7.5% to week 104

6–12 weeks

Week –2

Day 1

Week 24

Week 54

Week 104

3. Data available on request from Merck & Co., Inc. Please specify 20852883(2)-JAN.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Sitagliptin 100mg q day</th>
<th>Metformin 500 mg BID</th>
<th>Metformin 1000 mg BID</th>
<th>Sitagliptin 50 mg+ metformin 500 mg BID</th>
<th>Sitagliptin 50 mg+ metformin 1000 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c Δ</td>
<td>---</td>
<td>-0.66</td>
<td>-0.82</td>
<td>-1.13</td>
<td>-1.40</td>
<td>-1.90</td>
</tr>
<tr>
<td>FPG</td>
<td>5.8</td>
<td>-17.5</td>
<td>-27.3</td>
<td>-29.3</td>
<td>-47.1</td>
<td>-63.9</td>
</tr>
<tr>
<td>2-hour PPG</td>
<td>0.3</td>
<td>-51.9</td>
<td>-53.4</td>
<td>-78.0</td>
<td>-92.5</td>
<td>-116.9</td>
</tr>
<tr>
<td>A1c &lt; 7%</td>
<td>9%</td>
<td>20%</td>
<td>23%</td>
<td>38%</td>
<td>43%</td>
<td>66%</td>
</tr>
<tr>
<td>A1c &lt; 6.5%</td>
<td>2%</td>
<td>10%</td>
<td>9%</td>
<td>20%</td>
<td>22%</td>
<td>44%</td>
</tr>
</tbody>
</table>

Initial Combination Therapy With Sitagliptin Plus Metformin Study: A1C Results at 104 Weeks (Extension Study)

APT Population (Extension Study)

- Sitagliptin 100 mg qd (n=50)
- Metformin 500 mg bid (n=64)
- Sitagliptin 50 mg bid + metformin 500 mg bid (n=96)
- Metformin 1,000 mg bid (n=87)
- Sitagliptin 50 mg bid + metformin 1,000 mg bid (n=105)

Mean baseline A1C = 8.5%–8.7%

APT=all-patients-treated; bid=twice a day; LSM=least-squares mean; qd=daily.

Values represented are rounded. Actual values are 1.15 for sitagliptin 100 mg qd and 1.06 for metformin 500 mg bid.

Data available on request from Merck & Co., Inc. Please specify 20852883(2)-JAN.
### Initial Combination Therapy With Sitagliptin Plus Metformin Study: Change in Body Weight at 104 Weeks\(^a\) (Extension Study)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LS mean change in weight from baseline, kg (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin 100 mg qd n=50</td>
<td>0.5 (–0.7, 1.7)</td>
</tr>
<tr>
<td>Metformin 500 mg bid n=65</td>
<td>–0.8 (–1.9, 0.3)</td>
</tr>
<tr>
<td>Metformin 1,000 mg bid n=88</td>
<td>–2.4(^b) (–3.3, –1.5)</td>
</tr>
<tr>
<td>Sitagliptin 50 mg bid + Metformin 500 mg bid n=100</td>
<td>0.0 (–0.8, 0.9)</td>
</tr>
<tr>
<td>Sitagliptin 50 mg bid + Metformin 1,000 mg bid n=107</td>
<td>–1.2(^b) (–2.0, –0.3)</td>
</tr>
</tbody>
</table>

\(b\)95% confidence interval for least squares mean change from baseline excluded “0.”

Data available on request from Merck & Co., Inc. Please specify 20852883(2)-JAN.

\(a\)Results include only randomized patients who entered the extension study, had not received glycemic rescue therapy through week 54, took at least 1 dose of study medication after week 54, and had at least 1 post-54-week A1C measurement.

bid=twice a day; CI=confidence interval; LS=least-squares; qd=daily.
## Initial Combination Therapy With Sitagliptin Plus Metformin Study: Adverse Experience Profiles at 24 Weeks

### Summary of Adverse Experiences

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Sitagliptin 100 mg qd</th>
<th>Metformin 500 mg bid</th>
<th>Metformin 1,000 mg bid</th>
<th>Sitagliptin 50 mg + metformin 500 mg bid</th>
<th>Sitagliptin 50 mg + metformin 1,000 mg bid</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>176</td>
<td>179</td>
<td>182</td>
<td>182</td>
<td>190</td>
<td>182</td>
</tr>
<tr>
<td>≥1 AE, %</td>
<td>50.6</td>
<td>53.6</td>
<td>55.5</td>
<td>62.1</td>
<td>57.9</td>
<td>57.7</td>
</tr>
<tr>
<td>Drug-related AEs, %</td>
<td>9.7</td>
<td>6.7</td>
<td>11.5</td>
<td>16.5</td>
<td>12.6</td>
<td>15.4</td>
</tr>
<tr>
<td>Serious AEs, %</td>
<td>5.7</td>
<td>5.0</td>
<td>2.2</td>
<td>1.1</td>
<td>3.2</td>
<td>0.5</td>
</tr>
<tr>
<td>Hypoglycemia, %</td>
<td>0.6</td>
<td>0.6</td>
<td>0.5</td>
<td>1.1</td>
<td>1.1</td>
<td>2.2</td>
</tr>
<tr>
<td>All gastrointestinal AEs, %</td>
<td>10.8</td>
<td>15.1</td>
<td>15.9</td>
<td>25.3</td>
<td>17.9</td>
<td>24.7</td>
</tr>
</tbody>
</table>

AE=adverse experience; bid=twice a day.
Multi-Drug Add-On Therapy

Dual Add-on Therapy in Type 2 Diabetes Poorly Controlled With Metformin Monotherapy: A Randomized Double-Blind Trial of Saxagliptin Plus Dapagliflozin Addition Versus Single Addition of Saxagliptin or Dapagliflozin to Metformin (n = 534)

**Multi-Drug Add-On Therapy**

Dual Add-on Therapy in Type 2 Diabetes Poorly Controlled With Metformin Monotherapy: A Randomized Double-Blind Trial of Saxagliptin Plus Dapagliflozin Addition Versus Single Addition of Saxagliptin or Dapagliflozin to Metformin (n = 534)

### Table 3—AEs

<table>
<thead>
<tr>
<th>AEs</th>
<th>SAXA+DAPA+MET (n = 179)</th>
<th>SAXA+MET (n = 176)</th>
<th>DAPA+MET (n = 179)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 1 AE</td>
<td>87 (49)</td>
<td>93 (53)</td>
<td>87 (49)</td>
</tr>
<tr>
<td>At least 1 serious AE</td>
<td>2 (1)</td>
<td>6 (3)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>AE leading to discontinuation</td>
<td>1 (0.6)</td>
<td>0</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Serious AE leading to discontinuation</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AEs of special interest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>1 (0.6)</td>
<td>9 (5)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Genital infections</td>
<td>0</td>
<td>1 (0.6)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>GFR decrease</td>
<td>3 (2)</td>
<td>1 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>Fractures</td>
<td>0</td>
<td>2 (1)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>0</td>
<td>1 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>Hypoglycemia*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Minor</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.6)</td>
<td>2 (1)</td>
<td>1 (0.6)</td>
</tr>
</tbody>
</table>

Provider Perceptions of Diabetes Education

USU IRB Approval: 2/10/2015
Approval Terminates: 2/9/2018
Protocol #6344

http://tinyurl.com/dmedresearch
Non-Insulin Pharmacotherapy for Type 2 Diabetes in 2016

There are many therapeutic options now to treat type 2 diabetes with advantages of weight control and negligible hypoglycemia risk – use them!