Overarching Objective

This session will
• increase your knowledge of 8 of the 12 classes of FDA-approved diabetes medications, with an emphasis on those approved since 2012
• enhance your confidence when
  – assessing and educating patients
  – discussing patients taking these medications with physicians and other healthcare professionals

Specific Objectives

At the end of the program, you should be able to ...

1. explain the underlying metabolic defects of Type 2 diabetes for which medications have been developed:
   • insulin resistance
   • progressive decrease in insulin production
   • blunted incretin response
   • increased renal threshold for glucose
Objectives
At the end of the program, you should be able to ...

2. identify the metabolic defect(s) that each of the following classes of diabetes medications address:
   • biguanides
   • insulin secretagogues
   • insulin sensitizers
   • incretin-based therapies
   • sodium-glucose co-transporter-2 (SGLT2) inhibitors
   • insulin

Objectives
At the end of the program, you should be able to ...

3. accurately describe the mechanisms of action, safety, efficacy, contra-indications, and major patient-education teaching points for medications receiving FDA approval since 2012
   ➢ GLP-1 Receptor Agonists
     ➢ Bydureon (Exenatide Extended-Release) (2012)
     ➢ Tanzeum (Albiglutide) (April 2014)
     ➢ Trulicity (Dulaglutide) (Sept 2014)
   ➢ Dipeptidyl Peptidase 4 (DPP-4) Inhibitors
     ➢ Nesina (Alogliptin) (2013)
       ➢ Kazano (Alogliptin + Metformin)
       ➢ Oseni (Alogliptin + Pioglitazone)
     ➢ Nesina (Alogliptin) (2013)
       ➢ Kazano (Alogliptin + Metformin)
       ➢ Oseni (Alogliptin + Pioglitazone)

... cont’d ... Medications receiving FDA approval since 2012

➢ SGLT-2 Inhibitors
  ➢ Invokana (Canagliflozin) (2013)
  ➢ Invokamet: Canagliflozin / Metformin (Aug 2014)
  ➢ Farxiga (Dapagliflozin) (Jan 2014)
  ➢ Xigduo XR (Dapagliflozin + Metformin XR) (Oct 2014)
  ➢ Jardiance (Empagliflozin) (Aug 2014)
  ➢ Glyxambi (Empagliflozin + Linagliptin) (Feb 2015)
  ➢ Synjardy (Empagliflozin + Metformin HCl) (Aug 2015)

➢ Insulin
  ➢ Afrezza – insulin inhalation powder (June 2014)
  ➢ Toujeo (Glargine) SoloSTAR pen U-300 (Feb 2015)
  ➢ Humalog U-200 KwikPen (May 2015)
  ➢ Tresiba (Degludec) FlexTouch U-100 & U-200 (Sept 2015)
  ➢ Humulin R U-500 KwikPen (Jan 2016)
Objectives

At the end of the program, you should be able to ...

4. identify reliable resources for more information

A SHORT HISTORY OF MEDICATION OPTIONS FOR TYPE 2 DIABETES

From the 1950's until 1994, there were only 2 classes of diabetes medications:

- Sulfonylureas
- Insulin

1994: Metformin
1999: Thiazolidinediones
  (Rosiglitazone [Avandia] & Pioglitazone [Actos])

... Fast forward ...

March 2013: Invokana (Canagliflozin) – an SGLT2 inhibitor

12 Classes of Meds

Oral
1. Biguanides (Metformin)
2. Sulfonylureas
3. Meglitinides
4. Thiazolidinediones (TZD)
5. α-glucosidase inhibitors*
6. DPP-4 Inhibitors
7. Bromocriptine (Cycloset)*
8. Colesevelam (Welchol)*
9. Sodium-glucose co-transporter-2 (SGLT2) inhibitors

Injectable
10. GLP-1 Receptor Agonists
   11. Pramlintide (Symlin)*
   12 (a). Insulin

Inhalable
12 (b). Insulin

* α-glucosidase inhibitors, colesvelam, bromocriptine, pramlintide – generally not recommended due to modest efficacy, frequency of administration and/or limiting side effects.
Type 2 Diabetes (T2DM)

Type 2 diabetes is due to a **progressive loss of insulin secretion** on the background of **insulin resistance**

ADA. Diabetes Care. 2016;39 (Suppl 1), pg S13

Metabolic Defect #1 in T2DM: Insulin Resistance

- Decreased glucose uptake by muscles & adipose tissue
- Increased hepatic glucose output

Metabolic Defect #2 in T2DM: Progressive Loss of Insulin Secretion

![Graph showing the progression of diabetes over time]

*Figure 2: Representative depiction of the annual history of type 2 diabetes mellitus highlighting the role of insulin resistance, insulin deficiency, and impaired insulin effect. Both the immune system and beta-cell function are described. These 2 core pathophysiological defects likely contribute to the progressive nature of the disease, and may account for much of the deterioration in glucose control observed clinically in patients with type 2 diabetes. OGTT = oral glucose tolerance test; FPG = fasting plasma glucose; HOMA-IR = homeostasis model assessment of insulin resistance; HOMA-β = 0.59; p = 0.001. (Courtesy of the International Diabetes Center © 2006)*
Metabolic Defect #2 in T2DM: Progressive Loss of Insulin Secretion

Decreased insulin secretion from β-cells of the pancreas

Metabolic Defect #3 in T2DM: Blunted Incretin Effect

- Progressive deficiency of GLP-1 (glucagon-like peptide-1)
- Progressive β-cell resistance to the action of GIP (glucose-dependent insulino-tropic polypeptide)

Incretins:

GLP-1 (glucagon-like peptide-1) & GIP (glucose-dependent insulino-tropic polypeptide)

- Proteins that are secreted by the small intestine when food is ingested
- Stimulate β-cells to secrete insulin
- Inhibit glucagon secretion from α-cells
- Rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4)
- In T2DM, incretin effect is blunted

Figure 2. Representative injections of the natural history of type 2 diabetes mellitus highlighting the role of insulin resistance, insulin deficiency, and impaired incretin effect. Both the time course and relative function are descriptive. Three core pathophysiologic defects likely combine to contribute to the progressive nature of the disease, and may account for much of the abnormalities in glucose control observed clinically in patients with type 2 diabetes. In T2DM, incretin effect is blunted.

Kidneys:
Renal glucose threshold is increased to ~200-250 mg/dL from normal threshold of ~180 mg/dL

Metabolic Defect #4 in T2DM

Medications that Address the Metabolic Defect of Insulin Resistance

Medication to Address:
Biguanides – ↓ hepatic glucose output
• Metformin (Glucophage, Glumetza, Fortamet)
  “First line therapy,” if not contraindicated
  • Lowers A1C by ~1 to 1.2 percentage points
  • Contraindicated in hepatic impairment and HF
  • Until April, contraindicated in all patients with renal impairment . . .
Metformin-containing Drugs: Drug Safety Communication - Revised Warnings for Certain Patients With Reduced Kidney Function

• After reviewing medical literature, FDA concluded that metformin can be used safely in some patients with mild or moderate kidney impairment

• FDA is requiring changes to metformin labeling:
  – Metformin is contraindicated if eGFR < 30 mL/min
  – Starting metformin if eGFR is between 30 and 45 mL/min is not recommended
  – Obtain an eGFR at least annually
  – In pts on metformin whose eGFR later falls < 45, assess benefits and risks


First-line therapy: Metformin

![Image of metformin chart]
Metabolic Defect:
Insulin resistance (decreased glucose uptake by muscles & adipose tissue)

Medications to Address:
Thiazolidinediones (TZD):
↑ insulin sensitivity in muscle & adipose tissue by increasing the production of glucose transporters (GLUT-4)
- Rosiglitazone (Avandia)
- Pioglitazone (Actos)

Disadvantages:
- Weight gain
- Edema / heart failure
- Bone fx (limbs, not hip)
- Bladder cancer (?)

A Tale of Two TZDs

Rosiglitazone (Avandia)
The FDA had restricted the distribution of Avandia in 2010 and ordered that the following boxed warning be placed on the package insert: "Taking rosiglitazone may increase the risk that you will experience a heart attack."
In 2013, the FDA lifted prescribing restrictions on the basis of a re-analysis of the data from the RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes) trial, concluding that there is insufficient evidence to conclude that Rosiglitazone increases the risk for CV outcomes.

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm376516.htm

A Tale of Two TZDs

Pioglitazone (Actos)
Possible association with bladder cancer
- “largely refuted” (AACE Consensus Statement, Garber 2016)
- “…pioglitazone is associated with an increased risk of bladder cancer” (145,806 pts followed between 2000 & 2014; 63% higher risk of bladder cancer)

(Dormandy 2009; Lewis 2011; Lewis 2015; Inzucchi 2015; Garber 2016; Tuccori 2016)
Decreased insulin secretion from $\beta$-cells of the pancreas

Medications to Address:
- Insulin Secretagogues - $\uparrow$ insulin secretion
  - Sulfonylureas (SFU)
    - Glipizide (Glucotrol)
    - Glyburide (Micronase)
    - Glimepiride (Amaryl)
  - Meglitinides ("glinides")
    - Nateglinide (Starlix)
    - Repaglinide (Prandin)

Disadvantages:
- Weight gain
- Hypoglycemia
- Low durability

Metabolic Defect:
- Medications to Address:
  - Sulfonylureas – low durability

Sulfonylureas – low durability

Medications that Address the Metabolic Defect of the “Blunted Incretin Effect” – Incretin-Based Therapies
Levels of Incretin Hormones Decrease as Diabetes Progresses

• Byetta (Exenatide) – a GLP-1 Receptor Agonist – FDA-approved in 2005
  ➢ injectable
• Januvia (Sitagliptin) – a DPP-4 inhibitor – FDA-approved in 2006
  ➢ oral

Today, we have 9 FDA-approved Incretin-Based Therapies

DPP-4 Inhibitors (oral)
• Sitagliptin (Januvia)
• Saxagliptin (Onglyza)
• Linagliptin (Tradjenta)
• Alogliptin (Nesina) (Jan 2013)

GLP-1 Receptor Agonists (injectable)
• Exenatide (Byetta)
• Liraglutide (Victoza)
• Exenatide extended-release (Bydureon) (Jan 2012)
• Albiglutide (Tanzeum) (April 2014)
• Dulaglutide (Trulicity) (Sept 2014)

Role of Incretin Hormones in Glucose Metabolism

When food is ingested, the intestines secrete the incretin hormones GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic polypeptide).

Incretin hormones stimulate insulin secretion in a glucose-dependent manner.
Incretin Hormones are then degraded by DPP-4

DPP-4 is an enzyme that rapidly breaks down the incretins (half-life of incretins is only ~2 minutes)

Incretin-Based Therapies:
DPP-4 Inhibitors (oral)

DPP-4 inhibitors slow down the inactivation of incretin hormones, thereby prolonging their survival.

The resulting higher concentration of active incretins:
• increases insulin secretion in a glucose-dependent manner
• suppresses glucagon secretion.

“Smart secretagogues”

DPP-4 inhibitors (see hand-out packet, pg 3)

In general
• A1C by ~0.75 percentage points

Advantages
• Low risk of hypoglycemia
• Weight neutral

Dosing
• Once daily, without regard to time of day, without regard to food (take same time everyday)

Common side effects
• “Cold” symptoms

Most serious potential side effects
• Acute pancreatitis – no causality established (more on that later!)
• Joint pain – Aug 2015 FDA issued warning that DPP4i may cause joint pain that can be severe and disabling.
• Heart failure – to be discussed!
### DPP-4 inhibitors

#### Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Sitagliptin</th>
<th>Saxagliptin</th>
<th>Linagliptin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ A1C</td>
<td>± 0.75 percentage points</td>
<td>± 0.7 to 0.8 percentage points</td>
<td>± 0.5 to 0.7 percentage points</td>
</tr>
</tbody>
</table>

#### Advantages

- Low risk of hypoglycemia
- Weight neutral

#### Dosing

- Once daily, without regard to time of day, without regard to food (take same time everyday)
- 100 mg in normal renal function
- 50 mg in moderate renal impairment
- 25 mg in severe renal impairment

#### Common side effects

- Cold symptoms
- URI, UTI
- Ac. pancreatitis, nasopharyngitis, headache

#### Most serious potential side effects

- Ac. pancreatitis, allergic & hypersensitivity reactions, joint pain, heart failure [?]

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### DPP-4 inhibitors

#### Efficacy

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- Once daily, without regard to time of day, without regard to food (take same time everyday)
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#### Common side effects

- Cold symptoms
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#### Most serious potential side effects

- Ac. pancreatitis, allergic & hypersensitivity reactions, joint pain, heart failure [?]

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### DPP-4 inhibitors

#### Efficacy

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#### Advantages

- Low risk of hypoglycemia
- Weight neutral

#### Dosing

- Once daily, without regard to time of day, without regard to food (take same time everyday)
- 100 mg in normal renal function
- 50 mg / 25 mg in moderate renal impairment
- 25 mg in severe renal impairment

#### Common side effects

- Cold symptoms
- URI, UTI
- Ac. pancreatitis, nasopharyngitis, headache

#### Most serious potential side effects

- Ac. pancreatitis, allergic & hypersensitivity reactions, joint pain, heart failure [?]
DPP-4 inhibitors

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Sitagliptin</th>
<th>Saxagliptin</th>
<th>Linagliptin</th>
<th>Alogliptin (Nesina):</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C by 0.75% points</td>
<td>↓ A1C by ~0.7 to 0.8</td>
<td>↓ A1C by ~0.5 to 0.9</td>
<td>~0.4 to 0.7</td>
<td>↓ A1C by 0.4 to 0.6 percentage points</td>
</tr>
</tbody>
</table>

**Advantages**
- Low risk of hypoglycemia
- Weight neutral

**Dosing**
- Once daily, without regard to time of day
- 25 mg in normal renal function
- 12.5 mg in moderate/severe renal impairment

**Common side effects**
- URI, nasopharyngitis, headache

**Most serious potential side effects**
- Ac. pancreatitis, allergic reactions

<table>
<thead>
<tr>
<th>Newerest DPP-4 inhibitor (2013)</th>
</tr>
</thead>
</table>

- Only DPP-4 available in combination with a TZD (pioglitazon) or insulin.

**Side effects**
- "Cold" symptoms
- Ac. pancreatitis, Ac. pancreateitis, Pancreatitis
- Ac. renal failure, renal failure
- Severe hypersensitivity reactions (e.g., anaphylaxis)

**Patient Education: DPP-4 Inhibitors**

- Sx of acute pancreatitis:
  - Persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting

- Sx of hypersensitivity/allergic reactions:
  - Skin rash or itching, flaking or peeling of skin; hives; swelling of the face, lips, tongue and throat that may cause difficulty in breathing or swallowing

- Pt should stop taking DPP-4 inhibitor and seek medical advice immediately.
DPP-4 Inhibitors & Cardiovascular Outcomes

• No risk or benefit for all-cause mortality, CV mortality, MI or stroke among patients treated with DPP-4 inhibitors compared with placebo.
• RCTs that examined relationship b/t DPP-4i and heart failure (HF) have yielded mixed results.
  • SAVOR-TIMI 53 (2013): Pts treated with saxagliptin (Onglyza) were sig more likely to be hospitalized for HF than those given placebo (3.5% vs. 2.6%)
• Observational, cohort study 1.5 million pts, incretin-based drugs were not associated with increased risk of HF hospitalization (Fillon 2016)

Use cautiously, if at all, in pts with heart failure

(ADA Standards of Care in Diabetes – 2016; Inzucchi, 2015)

Injectable Incretin-based Therapies

GLP-1 Receptor Agonists:
  Exenatide (Byetta), Liraglutide (Victoza), Exenatide extended-release (Bydureon), Albiglutide (Tanzeum), Dulaglutide (Trulicity)
  [Note: Approved ONLY for adults with Type 2]

GLP-1 Receptor Agonists
(Exenatide, Liraglutide, Exenatide ER, Albiglutide, Dulaglutide)
Directly activate the GLP-1 receptors but are resistant to breakdown by DPP-4.

1. Promotes insulin secretion in a glucose-dependent manner
2. Decreases hepatic glucose production by decreasing glucagon secretion
3. Slows gastric emptying
4. Promotes satiety

NO GLP-1 RA has been approved for use with meal-time insulin.
Exenatide (Byetta), Liraglutide (Victoza), Albiglutide (Tanzeum) have been approved for use with basal insulin
GLP-1 Receptor Agonists

- Exenatide = Byetta
  - 2x/day
- Liraglutide = Victoza
  - 1x/day
- Exenatide ER = Bydureon
  - 1x/week
- Albiglutide = Tanzeum
  - 1x/week
- Dulaglutide = Trulicity
  - 1x/week

In general:
- ↓ A1C by ~1.0 percentage point
- low risk of hypoglycemia
- weight loss (~2 to 3 kg)
- ? CV protection (↓ BP, ↓ chol)
  - Mar 2016 LEADER trial results – Liraglutide (Victoza) reduces the risk of major adverse CV events in people with T2DM (details to be presented at 76th Scientific Sessions of the ADA in June).
- May preserve (possibly improve) β-cell function

GLP-1 Receptor Agonists

(Exenatide, Liraglutide, Exenatide ER, Albiglutide, Dulaglutide)

In general:
- In patients not able to achieve A1C goal with ≥ 1 oral agent + basal insulin, GLP-1 RAs are increasingly preferred to meal-time insulin as next “add-on” agent
  - (Inzucchi 2015)
- Common S/E
  - GI – Nausea, vomiting, diarrhea
  - Injection site reactions – Pruritus, nodule formation (more common with those that require mixing)
- Dose of insulin, SFU, glinide may need to be ↓
GLP-1 Receptor Agonists
(Exenatide, Liraglutide, Exenatide ER, Albiglutide, Dulaglutide)

In general:
WARNING (all GLP-1 RAs except Exenatide)
• Risk of thyroid C-cell tumors
• Contraindicated in pts with personal or family h/o medullary thyroid cancer (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN 2)

Cases of MTC reported during post-marketing period in pts on Liraglutide (Victoza), but causal relationship NOT established (http://www.novo-pi.com/victoza.pdf)

GLP-1 Receptor Agonists
(Exenatide, Liraglutide, Exenatide ER, Albiglutide, Dulaglutide)

In general: Contraindications / Cautions
• Contraindicated in pts with h/o
  • Pancreatitis
  • GI problems (gastroparesis, IBD)
• Renally impaired patients
  • Exenatide (Byetta & Bydureon) contraindicated if Cr CI < 30 (renally excreted)
  • Use caution when initiating or increase dose in renally impaired pts (eGFR 30-50)
  • Monitor renal function in renally impaired pts reporting severe GI reactions

GLP-1 Receptor Agonists
(Exenatide, Liraglutide, Exenatide ER, Albiglutide, Dulaglutide)

Patient Education
• Self-Monitoring of Blood Glucose (SMBG) is needed to assess effects of GLP-1 and guide adjustments to doses of insulin or secretagogue (SFU, glinide) to prevent hypoglycemia

<table>
<thead>
<tr>
<th>Therapeutic concentration achieved</th>
<th>Exenatide (Bydureon)</th>
<th>Albiglutide (Tanzeum)</th>
<th>Dulaglutide (Trulicity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steady state concentration achieved</td>
<td>at about week 7</td>
<td>after 4 to 5 weeks</td>
<td>within 2 to 4 weeks</td>
</tr>
</tbody>
</table>
GLP-1 Receptor Agonists
(Exenatide, Liraglutide, Exenatide ER, Albiglutide, Dulaglutide)

Patient Education (continued)
• Sx of acute pancreatitis
• Correct injection technique
• How to reconstitute Exenatide ER (Bydureon) and Albiglutide (Tanzeum) prior to administration

Bydureon Single Dose Tray ("kit") – vial & syringe:

1. Powder (Bydureon)
2. Liquid microspheres
3. Orange connecting device
4. Needle

Bydureon Pen:


GLP-1 Receptor Agonists
(Exenatide, Liraglutide, Exenatide ER, Albiglutide, Dulaglutide)

Patient Education (continued)
• Albiglutide (Tanzeum) must be reconstituted prior to administration
GLP-1 Receptor Agonists

(Exenatide, Liraglutide, Exenatide ER, Albiglutide, Dulaglutide)

Patient Education (continued)

- Trulicity (Dulaglutide) is a pen
  - no reconstitution necessary
  - pen must be unlocked to release “no-see” needle
  - pt places pen against skin; presses & holds the injection button (hear a click)
  - continues holding against skin until hear a 2nd click or “pop” (5-10 seconds); can then remove pen from skin

<table>
<thead>
<tr>
<th>GLP-1 Receptor Agonists</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>In general</th>
<th>Exenatide (Byetta)</th>
<th>Liraglutide (Victozza)</th>
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<th>Albiglutide (Tanzeum)</th>
<th>Dulaglutide (Trulicity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>0.7 to 1.0</td>
<td>0.8 to 1.5</td>
<td>1.0 (12 mo)</td>
<td>0.6 to 1.0</td>
<td>0.7 to 1.6</td>
</tr>
<tr>
<td>Dosing</td>
<td>Variable; Byetta can be given without regard to meals</td>
<td>1 mcg; start with 1 mcg, ↑ to 1.2 mg after 1 wk, max dose 1.8 mg</td>
<td>1/4, 1/2, 1 mg; start with 0.5 mg, ↑ to 1.5 mg if needed</td>
<td>1/4, 1/2 mg; start with 0.75 mg, ↑ to 1.5 mg if needed</td>
<td></td>
</tr>
<tr>
<td>Common S/E</td>
<td>Nausea: 8-12%; Vomiting: 1-5%</td>
<td>Nausea: 5-15%; Vomiting: 6-12%</td>
<td>Nausea: 9-14%; Vomiting: 6-14%</td>
<td>Nausea: 12-15%; Diarrhea: 4-9%; Abdominal pain: 7-9%</td>
<td></td>
</tr>
<tr>
<td>Patient Educa-tion</td>
<td>How to reconstitute Byetta &amp; Tanzeum; Components of a single-dose tray (&quot;kit&quot;)</td>
<td>How to use Victoza pen</td>
<td>How to reconstitute powder in pen</td>
<td>Available as a pen (no reconstitution necessary but some training still needed)</td>
<td></td>
</tr>
</tbody>
</table>
The text appears to be a table discussing GLP-1 Receptor Agonists, including their efficacy, dosing, common adverse effects, and patient education. The table is divided into columns for each agonist, with details on efficacy, dosing, and adverse effects. The text also mentions the lower rate of nausea with quarterly dosing compared to twice daily or daily dosing.

Pancreatic disease and Incretin-based Therapies

Epidemiologic studies, rodent studies, and a human autopsy have raised concerns that these therapies may be associated with pancreatitis and/or pancreatic cancer.

- **ADA**: “...assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer … are inconsistent with the current data.” (Egan 2014)
- **AACE/ACE**: “No studies have confirmed that incretin agents cause pancreatitis” … however, GLP-1 RA and DPP-4 inhibitors “should be used with caution in patients with a history of pancreatitis and discontinued if pancreatitis develops” (Garber, 2016, pg 89)
Medications that Address the Increased Renal Glucose Threshold

Metabolic Defect:
> Increased Renal Glucose Threshold

Medications to Address:
> Sodium-glucose co-transporter-2 (SGLT2) inhibitors ("glucuretics")
  > Canagliflozin (Can'a-gli-fLOZ-in)
  > Invokana – March 2013
  > Dapagliflozin
  > Farxiga – Jan 2014
  > Empagliflozin
  > Jardiance – Aug 2014

Sodium-glucose co-transporter-2

> SGLT2 actively transports glucose across the proximal convoluted tubule of the kidney so it can be reabsorbed into the blood
**Sodium-glucose co-transporter-2**

- The renal glucose threshold in someone without diabetes is ~180 mg/dL.
- In diabetes, the renal glucose threshold is increased to ~200-250 mg/dL.
- When the maximum capacity of the renal tubule to reabsorb glucose is exceeded, glucose is excreted into the urine.

---

**When SGLT2 is blocked**

- Renal threshold is lowered.
- Less glucose is reabsorbed by the kidneys.
- More glucose is excreted into the urine.
- Plasma glucose decreases.

[Image: http://www.invokanahcp.com/mechanism-of-action]

---

Invokana (Canagliflozin) blocking SGLT2 from reabsorbing glucose from kidney.

[Image: invokana-sglt2-glucose-block.png]
SGLT2 inhibitors

- ↓ A1C by ~0.5 to 1 percentage point
- eGFR must be ≥ 45 mL/min (Invokana & Jardiance) and ≥ 60 mL/min (Farxiga)
- Low risk of hypoglycemia (~3%)
- ↓ weight (~3 to 5 lb)
  - 1/3 is LBM (including fluid) & 2/3 is fat loss
  - ~50 to 70 g gluc (= 200-280 kcal) “spilled” into urine/day
- ↓ systolic BP by ~3 to 5 mm Hg

SGLT2 inhibitors

- ↑ LDL by ~3 to 8%
  - Canagliflozin (Invokana) ↑ HDL by ~8%
  - Empagliflozin (Jardiance) associated with significantly lower rates of all-cause and cardiovascular death; lower hospitalizations for heart failure

(Garber, 2016)

SGLT2 inhibitors

- Genital yeast infections
- UTI
- Increased urination
- Dehydration → hypotension
- Hyperkalemia (Invokana only)
**SGLT2 inhibitors**

- Patients > 65-75 years old
  - Higher incidence of adverse reactions related to volume depletion (hypotension, postural dizziness, syncope, dehydration)
  - Higher incidence of UTIs (Jardiance)
  - Lower efficacy (Invokana)
- Patients at risk for hyperkalemia (on ACEi or ARB) (Invokana)
- Patients with h/o bladder cancer, bladder cancer risk factors, hematuria (Farxiga)
- Patients in whom DKA may develop

**SGLT2 inhibitors: DKA & UTI**

**FDA Warnings** (5/15/15 & 12/4/15)

- **DKA**
  - From Mar 2013 to May 2015, FDA identified 73 cases of ketoacidosis in pts with T1 or T2 DM treated w/ SGLT2i
  - All patients required hospitalization or treatment in an ED
  - Ketoacidosis not immediately recognized – BG levels were below those typically seen in DKA (“euglycemic DKA”)
- **UTI**
  - FDA also identified 19 cases of life-threatening blood infections (urosepsis) and kidney infections (pyelonephritis) that started as UTIs between Mar 2013 and Oct 2014.
  - All pts were hospitalized; few required dialysis.
  - An FDA safety review has resulted in adding warnings to the labels of SGLT2 inhibitors about the risks of too much acid in the blood and of serious UTIs.

http://www.fda.gov/Drugs/DrugSafety/ucm475463.htm

**SGLT2 Inhibitors: DKA**

Use with caution in pts predisposed to DKA.
Factors that predispose to DKA:

- insulin deficiency (e.g., T1DM, h/o pancreatitis or pancreatic surgery)
- insulin dose reduction
- acute febrile illness
- reduced calorie intake d/t illness or surgery
- calorie restriction disorders
- alcohol abuse
### SGLT2 Inhibitors

#### Patient Education
- **Drink plenty of fluids** to prevent dehydration!
- **Symptoms of ketoacidosis**
  - Nausea, vomiting, abdominal pain, tiredness, and trouble breathing.
- **Symptoms of UTI**
  - A feeling of burning when urinating or the need to urinate often or right away; pain in the lower part of the stomach area or pelvis; fever; or blood in the urine.

#### SGLT-2 Inhibitor Comparison Chart

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>2-drug combination therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td><strong>Efficacy</strong></td>
</tr>
<tr>
<td>↓ A1C by ~ 0.7 to 1 percentage point</td>
<td>↓ A1C by ~ 0.5 to 0.7 percentage points</td>
</tr>
<tr>
<td>↓ A1C by ~ 0.4 to 0.9 percentage points</td>
<td></td>
</tr>
<tr>
<td><strong>eGFR must be</strong></td>
<td><strong>eGFR must be</strong></td>
</tr>
<tr>
<td>&gt; 45 mL/min</td>
<td>&gt; 60 mL/min</td>
</tr>
<tr>
<td>&gt; 45 mL/min</td>
<td></td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td><strong>Dose</strong></td>
</tr>
<tr>
<td>100 mg/day, before 1st meal of day; ↑ to 300 mg if needed and if eGFR &gt; 60</td>
<td>5 mg/day, taken in morning, with or w/out food; ↑ to 10 mg if needed</td>
</tr>
<tr>
<td>10 mg/day, taken in morning, with or w/out food; ↑ to 25 mg if needed</td>
<td></td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td><strong>Advantages</strong></td>
</tr>
<tr>
<td>Low risk of hypoglycemia</td>
<td>Low risk of hypoglycemia</td>
</tr>
<tr>
<td>↓ wgt by 2.2-3.3% (~ 5 lb)</td>
<td>↓ wgt by &gt; 3 lb</td>
</tr>
<tr>
<td>↓ systolic BP by &gt;3 to 5 mm Hg</td>
<td>↓ systolic BP by &gt;5 to 6 mm Hg</td>
</tr>
<tr>
<td>↓ HDL by ~8%</td>
<td>↓ HDL by ~8%</td>
</tr>
<tr>
<td>Low risk of hypoglycemia</td>
<td>Low risk of hypoglycemia</td>
</tr>
<tr>
<td>↓ wgt by &gt; 3 lb</td>
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</tr>
<tr>
<td>↓ systolic BP by &gt;3 to 5 mm Hg</td>
<td>↓ systolic BP by &gt;5 to 6 mm Hg</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td><strong>Disadvantages</strong></td>
</tr>
<tr>
<td>↑ LDL by ~4 to 8%</td>
<td>↑ LDL by 2.9%</td>
</tr>
<tr>
<td>↑ LDL by ~5-7%</td>
<td></td>
</tr>
<tr>
<td><strong>Common side effects</strong></td>
<td><strong>Common side effects</strong></td>
</tr>
<tr>
<td>Genital yeast infections (women: 10-11%, men: 4%)</td>
<td>Genital yeast infections (women: 7-8%, men: 1-2%)</td>
</tr>
<tr>
<td>UTI: 4 to 6%</td>
<td>UTI: 4 to 6%</td>
</tr>
<tr>
<td>Increased urination</td>
<td>Increased urination</td>
</tr>
<tr>
<td>Dehydration</td>
<td>Dehydration</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>Hypokalemia</td>
</tr>
<tr>
<td>↑ LDL by ~4 to 8%</td>
<td>↑ LDL by 2.9%</td>
</tr>
<tr>
<td>↑ LDL by ~5-7%</td>
<td></td>
</tr>
<tr>
<td><strong>Use with Caution in Patients</strong></td>
<td><strong>Use with Caution in Patients</strong></td>
</tr>
<tr>
<td>&gt; 65 years old (more prone to volume depletion; lower efficacy)</td>
<td>&gt; 65 years old (more prone to volume depletion; lower efficacy)</td>
</tr>
<tr>
<td>At risk for hyperkalemia (ACEi or ARB)</td>
<td>At risk for hyperkalemia (ACEi or ARB)</td>
</tr>
<tr>
<td>Prone to DKA</td>
<td>Prone to DKA</td>
</tr>
<tr>
<td>Prone to DKA</td>
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</tr>
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<td>Prone to DKA</td>
<td>Prone to DKA</td>
</tr>
</tbody>
</table>

#### Monotherapy – vs – 2-drug combination therapy
Monotherapy – vs –
2-drug combination therapy

• In general, monotherapy with an oral diabetes medication reduces A1C by ~1 percentage point
  – Metformin ↓ A1C to a greater degree than do the DPP-4i (~1.2% - vs - ~0.8%)
• Combination therapies reduce A1C by an additional ~1%
  – Metformin + any other drug (SU, TZD, DPP-4i, GLP-1): similar efficacy

AHRQ. Comparing Medicines for Adults with Type 2 Diabetes. www.effectivehealthcare.gov/diabetesmeds.cfm

Combination Oral Medications

• Secretagogues + Metformin
  – Metaglip: Glipizide / Metformin
  – Glucovance: Glyburide / Metformin
  – PrandiMet: Repaglinide / Metformin
• Secretagogue + TZD
  – Duetact: Glimepiride / Pioglitazone
  – Avandaryl: Glimepiride / Rosiglitazone
• TZD + Metformin
  – Actoplus Met: Pioglitazone / Metformin
  – Avandamet: Rosiglitazone / Metformin

Combination Oral Meds (cont’d)

• DPP-4 Inhibitor + Metformin
  – Janumet: Sitagliptin / Metformin
  – Janumet XR: Sitagliptin / Metformin XR
  – Kombiglyze XR: Saxagliptin / Metformin
  – Jentadueto: Linagliptin / Metformin
  – Kazano: Alogliptin / Metformin
• DPP-4 Inhibitor + TZD
  – Oseni: Alogliptin / Pioglitazone
Combination Oral Meds (cont’d)

- SGLT2 Inhibitor + Metformin
  - Invokamet: Canagliflozin / Metformin (Aug 2014)
  - Xigduo XR: Dapagliflozin + Metformin XR (Oct 2014)
  - Synjardy: Empagliflozin + Metformin (Aug 2015)

- SGLT2 Inhibitor + DPP-4 Inhibitor
  - Glyxambi: Tradjenta / Jardiance (Feb 2015)

12 Classes of Diabetes Meds

Oral
1. Biguanides (Metformin)
2. Sulfonylureas (SU)
   a. Glipizide (Glucotrol)
   b. Glyburide (Micronase)
   c. Glimepiride (Amaryl)
3. Meglitinides (glinides)
   a. Repaglinide (Prandin)
   b. Nateglinide (Starlix)
4. Thiazolidinediones (TZD)
   a. Rosiglitazone (Avandia)
   b. Pioglitazone (Actos)
5. α-glucosidase inhibitors
   a. Acarbose (Precose)
   b. Miglitol (Glyset)
6. DPP-4 Inhibitors
   a. Sitagliptin (Januvia)
   b. Saxagliptin (Onglyza)
   c. Linagliptin (Tradjenta)
   d. Alogliptin (Nesina)
7. Bromocriptine (Cycloset)
8. Colesevelam (Welchol)
9. SGLT2 inhibitors
   - Canagliflozin (Invokana)
   - Dapagliflozin (Farxiga)
   - Empagliflozin (Jardiance)

Injectable / Inhalable
12. Insulin
   - Injectable
   - Inhalable

+ 17 combination oral meds!
Insulin Types (before Feb 2015)

- Traditional (human) insulin
  - Short-acting insulin (Regular)
    • Humulin R, Novolin R
  - Intermediate-acting (NPH)
    • Humulin N, Novolin N
- Insulin analogs
  - Rapid-acting (bolus)
    • Faster onset, higher peak, shorter duration than Regular
    • Humalog, Novolog, Apidra
  - Long-acting (basal)
    • Lantus, Levemir
- Premixed insulins

All these are “U-100” (100 units insulin/mL)

Until Feb 2015 the only insulin that was NOT U-100 was “U-500 Regular insulin”

12 Classes of Diabetes Meds (cont’d)

Injectable / Inhalable

12. Insulin (only new insulins listed)

- Injectable
  - Rapid acting:
    • Humalog U-200 (May 2015)
  - Long acting:
    • Toujeo (Glargine) U-300 (Feb 2015)
  - Ultra-long acting:
    • Tresiba (Degludec) U-100 & U-200 (Sept 2015)
- U-500
  • Humulin R U-500 KwikPen (Jan 2016)
- Inhalable
  • Afrezza – insulin inhalation powder (June 2014)

New Insulins

- Humalog KwikPen U-200 (May 2015)
  - Recommended if taking >15 u Humalog/meal
  - Holds double the amount of Humalog as U100 pen
    • U-200 pen contains 600 units (U-100 pen = 300 units)
  - More for convenience (less likely to run out of insulin)
- No dose conversions required
- Dialing 1 unit delivers 1 unit of insulin
New Insulins

• Toujeo® (Insulin Glargine)
  SoloSTAR pen U-300 (Feb 2015)
  
  – a once-daily long-acting basal insulin (~36 hr duration)
  – 3x as concentrated as Lantus
  – approved for adults with type 1 and type 2 diabetes
  – to be administered at same time every day
  – dose counter shows number of units to be injected – no dose conversion is required

New Insulins

• Toujeo® SoloSTAR pen U-300
  
  – released more gradually than Lantus
    – onset of action ~6 hr (vs ~1-2 hr)
    – maximum glucose lowering effect may take 5 days
  – when titrating dose, wait 3 to 4 days between dose increases
  – “for patients controlled on Lantus, expect that a higher daily dose of Toujeo will be needed…”
    (http://products.sanofi.us/toujeo/toujeo.pdf)
    • in clinical trials, 11% to 17.5% more Toujeo was needed to achieve same glycemic target
  – Compared to Lantus:
    • significantly lower risk of nocturnal hypoglycemia
    • less weight gain
  
  (Riddle 2014; White 2016)

New Insulins

• Tresiba (Degludec) – Ultra long-acting (Sept 2015)
  
  – 1st basal insulin molecule approved by FDA in 10 yr
    • Others: Glargine (Lantus) & Detemir (Levemir)
  – Duration of action: ≥ 42 hr (d/t delayed absorption)
  – Indicated for adults 18 years and older
  – Available in U-100 & U-200 formulations
New Insulins

• Tresiba (Degludec)
  – Injection is given once a day, virtually any time of day (within 8 to 40 hr after last injection)
    • Sunday: 8:00 p.m.
    • Monday: 7:00 a.m. (11 hr after last injection)
    • Tuesday: 10:00 p.m. (39 hr after last injection)... and achieve same glycemic control as Glargine (Lantus) administered at same time every day

New Insulins

• Tresiba (Degludec)
  – When titrating the dose, wait 3 to 4 days between dose increases
  – Available in U-100 and U-200 FlexTouch pens
  – The dose window for both pens shows the number of insulin units to be delivered
  – NO conversion is needed

Tresiba (Degludec)
New Insulins

• Humulin R U-500 KwikPen (Jan 2016)
  – **not** a new insulin
  – **what is new:**
    • pen vs vial
    • no dose conversion needed

New Insulins

• Inhaled insulin
  – Exubera (Pfizer)
    • FDA approved in 2006
    • Pfizer withdrew it from the market in 2007
  – Afrezza – insulin inhalation powder (2014)

New Insulins

• Afrezza – insulin inhalation powder (2014)
  – Rapid-acting inhaled insulin
  – Administered at beginning of a meal
  – Available as single-use cartridges of 4, 8 and 12 units
New Insulins

- Afrezza – insulin inhalation powder
  - Inhaler:
  - Cartridges:

  Fully assembled:

New Insulins

- Afrezza – insulin inhalation powder

  **WARNING: RISK OF ACUTE BRONCHOSPASM IN PATIENTS WITH CHRONIC LUNG DISEASE**

  See full prescribing information for complete boxed warning.
  - Acute bronchospasm has been observed in patients with asthma and COPD using AFREZZA.
  - AFREZZA is contraindicated in patients with chronic lung disease such as asthma or COPD.
  - Before initiating AFREZZA, perform a detailed medical history, physical examination, and spirometry (FEV₁) to identify potential lung disease in all patients.

New Insulins

- Afrezza – insulin inhalation powder

  - Afrezza causes ↓ in lung function over time
  - Pulmonary function should be assessed
    - before initiating
    - after 6 months
    - annually
    - even in the absence of pulmonary symptoms
  - 27% pts treated w/ Afrezza reported cough
New Insulins
Afrezza – insulin inhalation powder
• suffering from a low level of prescriptions!

Summary of the 11 Classes of Non-Insulin Therapies for Diabetes (hand-out pg 6)

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Medications</td>
<td>Injectable Medications</td>
<td>Metformin</td>
</tr>
<tr>
<td>Thiazolidinediones (TZDs)</td>
<td>Ex: Amaryl, Avandia</td>
<td></td>
</tr>
<tr>
<td>α-glucosidase inhibitors</td>
<td>Ex: Miglitol, Metaglip</td>
<td></td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Ex: Januvia, Onglyza</td>
<td></td>
</tr>
<tr>
<td>Bromocriptine (Cycolset)</td>
<td>Ex: Bromocriptine</td>
<td></td>
</tr>
<tr>
<td>Colesevelam (Welchol)</td>
<td>Ex: Colesevelam</td>
<td></td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>Ex: Xigduo, EMPA</td>
<td></td>
</tr>
<tr>
<td>GLP-1 receptor agonists</td>
<td>Ex: Exenatide, Liraglutide</td>
<td></td>
</tr>
<tr>
<td>Amylin analog (Symlin)</td>
<td>Ex: Amylin</td>
<td></td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Ex: Nateglin, Jantoven</td>
<td></td>
</tr>
<tr>
<td>Meglitindes</td>
<td>Ex: Daonil, Congestin</td>
<td></td>
</tr>
</tbody>
</table>

Mechanism of Action
- ↓ hepatic glucose production;
- ↑ insulin sensitivity
- ↑ insulin secretion from β-cells in pancreas
- ↑ insulin sensitivity in peripheral tissue (muscle, fat, liver)
- ↓ rate of carbohydrate digestion
- Prolong survival of GLP-1, thereby ↑ insulin & ↓ glucagon secretion in a glucose dependent manner
- Unknown; may ↓ the hypothalamic drive that stimulates early morning hepatic glucose output
- Unknown; may ↓ glucose absorption

Glucuretics:
- ↑ urinary glucose excretion

Mimics GLP-1:
- ↑ insulin & ↓ glucagon secretion in a glucose dependent manner;
- ↓ rate of gastric emptying;
- stimulates satiety center in brain

Amylin-like effect (inhibits glucagon secretion; slows gastric emptying)

A1C reduction
- 1.0 – 1.2 Nat 0.75; Rep ~1
- 1.25 rosi 1.0 pio 1.0 (at dose of >150 mg/d) ~0.75
- 0.1 – 0.6 0.5 ~1.0 0.5 – 0.7

Adverse Events / Risks / Cautions
- GI disturbances, lactic acidosis (rare but serious), HOLD before & after contrast dye studies
- Hypoglycemia, weight gain, low durability
- Heart failure, edema, wgt gain, bone fractures
- GI disturbances; only glucose tabs or gel will be effective in treating hypoglycemia
- Acute pancreatitis, URI, cold sx, hyper sensitivity/allergic rxns, joint pain, heart failure
- Hypotension if taking ergot meds (eg, Cafergot); syncope
- May ↑ TG - not recommended if TG > 500; Constipation, nausea, dyspepsia
- Genital yeast infections, UTI, polyuria, dehydration → hypotension, DKA
- Pancreatitis, N/V, injection site rxns, gastroparesis; monitor renal function
- Nausea, hypoglycemia

Summary of Diabetes Medications
Most medications for Type 2 diabetes address the underlying pathophysiologic defects
- Progressive ↓ in insulin secretion
- Insulin resistance
- ↑ hepatic glucose output
- Blunted incretin response
- ↑ renal glucose threshold

• Other medications (not discussed in this presentation)
  - Modify physiologic processes related to nutrient absorption (α-glucosidase inhibitors) or have mechanisms of action that are not completely understood (Cycolset, Welchol)
Summary of Guidelines

- Metformin, unless contraindicated, is considered first-line therapy
- If Metformin is contraindicated or poorly tolerated, or if pt needs dual or triple therapy, medications should be chosen on the basis of factors such as
  - Efficacy
  - Complementary mechanisms of action
  - Risks / potential side effects (hypoglycemia, wgt gain, nausea, DKA, pancreatitis, heart failure)
  - Cardiovascular outcomes
  - Cost / insurance coverage
  - Dosing frequency (QD, TID, QW) or complexity
  - Consideration of patient’s goals and values

Reliable resources for more information

- ADA Position Statements
- AACE Consensus Statement
- NIH’s Daily Med website
- Prescribing Information
- DiabetesPro SmartBrief (email alerts)
Position & Consensus Statements


See hand-out packet, pg 1

See hand-out packet, pg 2

“The drug labeling information on this website . . . has been reformatted to make it easier to read . . .”

Prescribing Information

For example: Let’s say you can’t remember if Bydureon is contraindicated in renal impairment or not. Simply use Google to search for “Bydureon Prescribing Information.”


Once you’ve got the pdf, go to “Edit” and choose “Find.”
Type “renal” in the search box

Renal Impairment: Postmarketing reports with exenatide, sometimes requiring hemodialysis and kidney transplantation. Not recommended if patient has severe renal impairment or end-stage renal disease. Use with caution in patients with renal transplantation or moderate renal impairment (5.4, 8.6, 12.3).

DiabetesPro SmartBrief
https://www.smartbrief.com

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The smarter way to stay on top of news for diabetes health professionals