UTILIZING NEWER AGENTS TO PERSONALIZE MANAGEMENT OF TYPE 2 DIABETES MELLITUS

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Objectives

- Describe specific effects of antidiabetic agents on pathophysiologic deficits
- Distinguish patients who may benefit from individualized therapy, including older adults
- Select appropriate antidiabetic therapy utilizing evidence-based medicine and national guidelines
- Examine optimal antidiabetic therapy for different adult age groups, including older adults
Disclosure

I, Kristi W. Kelley, have no actual of potential conflict of interest in relation to this program.
PATHOGENESIS OF T2DM
PATHOGENESIS OF TYPE 2 DIABETES: Ominous Octet

### Pathogenesis of Type 2 diabetes

#### Insulin Resistance
- Leads to glucose intolerance
  - Genetics
  - Environmental

#### Compensation
- Leads to euglycemia
  - Healthy beta-cells

#### Beta-Cell Dysfunction
- Leads to imperfect compensation
  - Predisposed individuals
  - Worsened hyperglycemia ➔ glucotoxicity ➔ vicious cycle
  - Progression to pre-diabetes and diabetes

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THERAPY FOR TYPE 2 DIABETES: Sites of Action

- Metformin
  - Decreased incretin effect
  - Increased glucose uptake by insulin sensitivity

- Thiazolidinediones
  - Decreased glucose production
  - Increased glucose intake
  - Decreased FFA output

- SGLT2 Inhibitors
  - Increased glucose reabsorption

- Incretins
  - Appetite control

- Secretagogues
  - Simulate insulin secretion
  - Incretins
    - Increased insulin secretion
    - Decreased glucagon secretion

Question #1: Which of the following drug classes targets the stomach and the brain in patients with type 2 DM?

A. Incretins

B. Metformin

C. SGLT-2 inhibitors

D. Thiazolidinediones
Meet Doris

Image courtesy of imagerymajestic at FreeDigitalPhotos.net
Meet Doris

- 72 year old Caucasian female who lives with her husband
- Weight 180 lb, Height 5’8”, BMI 27.36 kg/m²
- A1c 9.2%, SCr 1.1 mg/dL, BP 145/82 mm Hg

Past Medical History:
- Type 2 DM (x 4 yr)
- Hypoglycemic episode requiring hospitalization 1 year ago
  - On metformin 1,000 mg po twice daily and glimepiride 4 mg po daily
- HTN (x 10 yr)
- Osteoarthritis
- No cognitive or functional impairment
Meet Doris

- **Current medications:**
  - Metformin 1,000 mg po twice daily
  - Lisinopril/HCTZ 20 mg/12.5 mg po daily
  - Acetaminophen 325 mg 2 capsules po three times daily
INDIVIDUALIZED THERAPY
ADA Guidelines: Individualized A1c Goals

Approach to the management of hyperglycemia

PATIENT / DISEASE FEATURES
- Risks potentially associated with hypoglycemia and other drug adverse effects
- Disease duration
- Life expectancy
- Important comorbidities
- Established vascular complications
- Patient attitude and expected treatment efforts
- Resources and support system

A1C 7%

more stringent

less stringent

Usually not modifiable

Potentially modifiable

Therapy considerations

- Safety*
- Efficacy*
- Hypoglycemia Risk*
- Weight*
- Side Effects
- Costs
- Ease of Use

*Priority
## Profiles of Antidiabetic Medications

<table>
<thead>
<tr>
<th></th>
<th>MET</th>
<th>GLP-1 RA</th>
<th>SGLT-2i</th>
<th>DPP-4i</th>
<th>AGi</th>
<th>TZD (moderate dose)</th>
<th>SU</th>
<th>GLN</th>
<th>COLSvl</th>
<th>BCR-QR</th>
<th>INSULIN</th>
<th>PRAML</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYPO</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate/Severe</td>
<td>Mild</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate to Severe</td>
<td>Neutral</td>
</tr>
<tr>
<td>WEIGHT</td>
<td>Slight Loss</td>
<td>Loss</td>
<td>Loss</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Gain</td>
<td>Gain</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Gain</td>
<td>Loss</td>
</tr>
<tr>
<td>GI Sx</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Mild</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASCVD</td>
<td>Benefit</td>
<td>Neutral</td>
<td>Possible Benefit</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Safe</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td></td>
</tr>
<tr>
<td>BONE</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate Fracture Risk</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td></td>
</tr>
</tbody>
</table>

- **Few adverse events or possible benefits**
- **Use with caution**
- **Likelihood of adverse effects**
- **? Uncertain effect**

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Type 2 DM Older Adults

- Assess functional abilities and cognitive status
  - Should include assessment of vision, hearing, dexterity
- Consider relaxing glycemic goals
  - Avoid hyperglycemic complications
- Be aware of need for depression screening and treatment
- Screen for DM complications that may produce functional impairment
- Treat cardiovascular risk factors with consideration of time frame of benefit
- Recognize physiological changes with aging that may affect pharmacotherapy

ADA. *Diabetes Care.* 2016;39(S1):S81-S85.
## Type 2 DM Older Adults

<table>
<thead>
<tr>
<th>Health Status</th>
<th>A1c Goal</th>
<th>Fasting BG Goal (mg/dL)</th>
<th>BP Goal (mm Hg)</th>
<th>Lipids</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Healthy</strong> (intact cognitive and functional status)</td>
<td>&lt; 7.5%</td>
<td>90 - 130</td>
<td>&lt;140/90</td>
<td>Statin unless contraindicated or not tolerated</td>
</tr>
<tr>
<td><strong>Complex/intermediate</strong> (multiple co-existing chronic illnesses (at least 3), 2+ instrumental ADL impairments or mild-to moderate cognitive impairment)</td>
<td>&lt; 8.0%</td>
<td>90 - 150</td>
<td>&lt;140/90</td>
<td></td>
</tr>
<tr>
<td><strong>Very Complex/Poor Health</strong> (long-term care or end-stage chronic illness, or moderate-to-severe cognitive impairment or 2+ ADL dependencies)</td>
<td>&lt; 8.5%</td>
<td>100 - 180</td>
<td>&lt;150/90</td>
<td>Consider likelihood of benefit with statin (more in secondary prevention)</td>
</tr>
</tbody>
</table>

Adapted Table 10.1 from ADA. *Diabetes Care*. 2016;39(S1):S81-S85.
Question #2: Which A1c goal would you choose for Doris within the body of your written assessment?

A. < 7.0%
B. < 7.5%
C. < 8.0%
D. < 8.5%
## Recommendations for Older Adults

<table>
<thead>
<tr>
<th>Category by MOA</th>
<th>Drug Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin sensitizers</td>
<td>Metformin – 1st line</td>
</tr>
<tr>
<td></td>
<td>Thiazolidinediones*</td>
</tr>
<tr>
<td>Insulin secretagogues</td>
<td>Sulfonylureas*</td>
</tr>
<tr>
<td></td>
<td>Meglitinide analogs*</td>
</tr>
<tr>
<td>Insulin</td>
<td>Insulin</td>
</tr>
<tr>
<td>Incretin-based therapies</td>
<td>GLP-1 RA</td>
</tr>
<tr>
<td></td>
<td>DDP-4 inhibitors</td>
</tr>
<tr>
<td>SGLT-2 inhibitors</td>
<td>SGLT-2 inhibitors</td>
</tr>
</tbody>
</table>

*Use with caution if at all

“Avoid using medications other metformin to achieve hemoglobin A1c < 7.5% in most older adults; moderate control is generally better.”
Remember Doris’ Current Therapy

- **Metformin**
  - Decreased incretin effect
  - Glucose production

- **Thiazolidinediones**
  - Glucose intake
  - FFA output

- **SGLT2 Inhibitors**
  - Glucose reabsorption

- **Incretins**
  - Appetite control
  - Simulate insulin secretion
  - Insulin secretion
  - Glucagon secretion

- **Secretagogues**
  - Insulin secretion

- **Glucose intake**
  - Upregulated

- **FFA output**
  - Downregulated

- **Insulin sensitivity**
  - Upregulated

Metformin is maximized but Doris’ A1c is 9.2%. What is next in her DM management?

- **GLP-1 agonists***
  - A1c reduction: 1%- 1.5%
  - ADRs: headache, nausea, diarrhea, ↑ risk of pancreatitis?

- **DPP-4 inhibitors***
  - A1c reduction: 0.5% - 1%
  - ADRs: ↑ risk of pancreatitis?, severe joint pain

- **TZDs**
  - A1c reduction: 1% - 1.5%
  - ADRs: ↑ weight, ↑ LDL

- **Sulfonylureas**
  - A1c reduction: 1% - 1.5%
  - ADRs: hypoglycemia, ↑ weight

- **α-glucosidase inhibitors**
  - A1c reduction: 0.5% - 1%
  - ADRs: flatulence, diarrhea

- **Bile acid sequestrant**
  - A1c reduction: 0.5% - 1%
  - ADRs: constipation, nausea, bloating, ↑ triglycerides

- **Insulin**
  - A1c reduction: 1.5% - 3.5%
  - ADRs: hypoglycemia, ↑ weight

- **SGLT2 inhibitors***
  - A1c reduction: 0.5% - 1%
  - ADRs: UTIs, ↑ urination, hypotension, ↑ LDL, fractures?

*Renal adjustment needed with some agents in class

Question #3: Based on Doris’ current A1c of 9.2% on metformin, what is the next BEST step in management of her type 2 DM?

A. d/c metformin, add Lantus® (insulin glargine) 30 units SQ daily

B. d/c metformin, add Starlix® (nateglinide) 120 mg po three times daily

C. Continue metformin, add Bydureon® (exenatide ER) 2 mg SQ once weekly

D. Continue metformin, add Invokana® (canagliflozin) 100 mg po daily
A FOCUS ON GLP-1 RECEPTOR AGONISTS (GLP-1 RAS)
GLP-1 RAs

- Approved for treatment of Type 2 DM as an adjunct to diet and exercise to improve glycemic control

- MOA:
  - Agonist of GLP-1 receptor
  - Augments glucose-dependent insulin secretion
  - Delays gastric emptying
Effects of GLP-1 Receptor Agonists

GLP-1 Agonist

- Insulin sensitivity

- Heart rate
- Myocardial contractility
- Blood pressure

- Appetite
- Energy expenditure
- Satiety

- Insulin secretion
- Glucagon secretion
- B-cell proliferation

- Natriuresis

- Gastric emptying
- Acid secretion
- GI motility

- Lipolysis
- FFA synthesis
- Glucose uptake

- Hepatic glucose output
- Glycogen synthesis
- Glucose oxidation

GLP-1 RA Efficacy

- **2012 meta-analysis (exenatide IR/ER and liraglutide)**
  - Max maintenance doses ↓ A1c by 1.1-1.6%
  - Exenatide ER and liraglutide ↓ FPG > exenatide IR

- **Daily and weekly GLP-1 RAs**
  - ↓ A1c 0.5 – 1.8%
  - Overall glycemic control
    - Weekly GLP-1 RAs ~ liraglutide > exenatide IR

## GLP-1 RA Comparison: Daily Dosing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Formulation</th>
<th>Special Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>exenatide IR</td>
<td>5 mcg SQ BID, titrate to 10 mcg BID after 1 month</td>
<td>Pre-filled, multi-dose pens: 5 mcg/dose OR 10 mcg/dose</td>
<td>Should be taken 60 min prior to meals</td>
</tr>
<tr>
<td>(Byetta®)</td>
<td></td>
<td></td>
<td>Do not use CrCl &lt; 30 mL/min</td>
</tr>
<tr>
<td>liraglutide</td>
<td>0.6 mg SQ daily, then titrate to 1.2 mg SQ daily</td>
<td>Pre-filled, multi-dose pens: all doses available in same pen</td>
<td>Administer without regard to meals</td>
</tr>
<tr>
<td>(Victoza®)</td>
<td>after 7 days; can further titrate to 1.8 mg SQ daily</td>
<td></td>
<td>If patient misses &gt; 3 days, restart titration to avoid GI side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Post-marketing concerns with worsening chronic renal function</td>
</tr>
</tbody>
</table>

Byetta (exenatide) PI. Wilmington, DE: AstraZeneca Pharmaceuticals; 2015.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Formulation</th>
<th>Special Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>exenatide ER (Bydureon®)</td>
<td>2 mg once weekly</td>
<td>Pre-filled, single-use pen – must be “mixed” prior to use</td>
<td>3 day dosing window; DO NOT USE CrCl &lt; 30 mL/min (same as exenatide IR)</td>
</tr>
<tr>
<td>dulaglutide (Trulicity®)</td>
<td>0.75 mg once weekly, may increase to 1.5 mg once weekly</td>
<td>Pre-filled, single-use pen</td>
<td>3 day dosing window; no renal dosing adjustment</td>
</tr>
</tbody>
</table>
| albiglutide (Tanzeum®)   | 30 mg once weekly, titrate to 50 mg once weekly | Pre-filled, single-use pen – 30 mg/dose OR 50 mg/dose – must be reconstituted prior to use | 3 day dosing window  
No renal dosing adjustment BUT caution if GFR < 15 mL/min/1.73 m² |
## Daily Dosing ADRs

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>Exenatide IR</th>
<th>Liraglutide 1.2 mg</th>
<th>Liraglutide 1.8 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exenatide BID N=155</td>
<td>Placebo BID N=77</td>
<td>Liraglutide 1.2 mg N=645</td>
</tr>
<tr>
<td>Nausea</td>
<td>8%</td>
<td>0%</td>
<td>18%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4%</td>
<td>0%</td>
<td>6%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>&lt;2%</td>
<td>Not reported</td>
<td>10%</td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>12.70%</td>
<td>Not reported</td>
<td>2%</td>
</tr>
</tbody>
</table>

*Information from package inserts

Byetta (exenatide) PI. Wilmington, DE: AstraZeneca Pharmaceuticals; 2015.
# Weekly Dosing ADRs

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>Exenatide ER N=248</th>
<th>Dulaglutide 0.75 mg N=836</th>
<th>Dulaglutide 1.5 mg N=834</th>
<th>Placebo N=568</th>
<th>Albiglutide N=923</th>
<th>Placebo N=468</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>11.30%</td>
<td>12.40%</td>
<td>21.10%</td>
<td>5.30%</td>
<td>11.10%</td>
<td>9.60%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Not reported</td>
<td>6.00%</td>
<td>12.70%</td>
<td>2.30%</td>
<td>4.20%</td>
<td>2.60%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10.90%</td>
<td>8.90%</td>
<td>12.60%</td>
<td>6.70%</td>
<td>13.10%</td>
<td>10.50%</td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>10.50%</td>
<td>0.50%</td>
<td>0.50%</td>
<td>0.00%</td>
<td>11%</td>
<td>2%</td>
</tr>
</tbody>
</table>

*Information from package inserts

GLP-1 RA ADRs

- **Hypoglycemia**
  - Risk is lower with monotherapy (2 – 9.7%)
  - Risk increases with:
    - Combo - Greatest with sulfonylurea (7- 36%) or basal insulin (~14 – 25%)
    - Higher doses
    - Frequency of administration (daily > weekly)
  - Severe hypoglycemia < 1%
Lisa

- 58 yo Caucasian female, 220 lb, BMI: 32.2 kg/m²
- A1c 7.7% [estimated average glucose (eAG) = 174 mg/dL], SCr 1.8 mg/dL, estimated GFR 36 mL/min/1.73 m²
- Past Medical History:
  - Type 2 DM (x 5 yr)
  - HTN (x 5 yr)
- Allergies: NKDA
Lisa’s current medications:
- pioglitazone 45 mg po daily
- amlodipine 10 mg po daily
- valsartan 160 mg po daily

Lisa reports:

<table>
<thead>
<tr>
<th>Timing of BG values</th>
<th>Range of BG values (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM waking</td>
<td>150 – 180</td>
</tr>
<tr>
<td>Noon preprandial</td>
<td>75 – 180</td>
</tr>
<tr>
<td>PM preprandial</td>
<td>200 – 220</td>
</tr>
<tr>
<td>HS (3 hr postprandial)</td>
<td>190 - 220</td>
</tr>
</tbody>
</table>
Question #4: In addition to encouraging intensive lifestyle modifications, which of the following would be the next BEST therapy to optimize Lisa’s diabetes management?

A. Add Amaryl® (glimepiride) 1 mg po daily

B. Add Byetta® (exenatide IR) 5 mcg SQ twice daily

C. Add metformin 1,000 mg po BID

D. Add Victoza® (liraglutide) 0.6 mg SQ daily
GLP-1 RA: Warnings and Precautions

- Pancreatitis
- Thyroid C-cell tumors
- Hypoglycemia
- Renal impairment
- Severe gastrointestinal disease
- Injection-site reactions
Pancreatitis Warning

- Acute pancreatitis (AP)
  - Initial FDA warning with exenatide in 2007, subsequent updates 2008, 2013 – adding other incretin agents

- Evidence for pancreatitis
  - Post hoc analysis
  - Mainly observational case reports

Approach to Pancreatitis Warning

- Watch patients for s/s of pancreatitis
- If suspected, stop GLP-1 RA
- Pancreatitis confirmed
  - Do NOT restart GLP-1 RA
- Patients with history of pancreatitis
  - Use alternative therapy
Jack

- 62 year old African American male, BMI 32.1 kg/m²
- A1c 8.2%, SCr 0.9 mg/dL, BMP WNL
- Past Medical History:
  - Type 2 DM (x 1 yr)
  - Pancreatitis (x 2 yrs ago)
- John’s BG log book reveals:

<table>
<thead>
<tr>
<th>Timing of BG values</th>
<th>Range of BG values (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting BG</td>
<td>100 – 180</td>
</tr>
<tr>
<td>2hr postprandial</td>
<td>&gt; 200</td>
</tr>
</tbody>
</table>

- Current medication:
  - Metformin 1,000 mg po twice daily
Question #5: Which A1c goal would you choose for Jack within the body of your written assessment?

A. < 7.0%
B. < 7.5%
C. < 8.0%
D. < 8.5%
Question #6: In addition to encouraging intensive lifestyle modifications, which of the following would be the BEST option to add to optimize Jack's diabetes management?

A. Actos® (pioglitazone) 45 mg po daily

B. Invokana® (canagliflozin) 100 mg po daily

C. Onglyza® (saxagliptin) 5 mg po daily

D. Tanzeum® (albiglutide) 30 mg SQ once weekly
GLP-1 RA: Warnings and Precautions

- **Thyroid C-cell tumors**
  - In rodents – increase in “dose-related and treatment-duration-dependent thyroid C-cell tumors”
  - Black box warning – “contraindicated in patients with personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)”

- **Hypersensitivity**
  - Contraindication
GLP-1 RA and CVD Advantages?

- **Surrogate CV markers**
  - Modest ↓ in TC, LDL and TG
  - Modest ↑ in HDL
  - Modest ↓ SBP 4-5 mm Hg/DBP 1-2 mm Hg
  - Slight ↑ HR (2-3 bpm)

GLP-1 RA and CVD Advantages?

- Macrovascular outcomes –
  - All PIs state “no clinical studies establishing conclusive evidence of macrovascular risk reduction”

- Pending CV outcomes trials:
  - EXSCEL (exenatide ER)
  - REWIND (dulaglutide)

- Completed CV outcomes trials:
  - ELIXA (lixisenatide)
  - LEADER (liraglutide)
GLP-1 RA and CVD Advantages?

ELIXA (lixisenatide)
- 6068 patients with MI or unstable angina within last 180 days
- Median follow-up – 2.1 years
- Primary endpoint of CV death, MI, stroke, or hospitalization for unstable angina
  - Lixisenatide noninferior to placebo (p< 0.001) but not superior (p= 0.81)

LEADER (liraglutide)
- 9340 patients with high cardiovascular risk
- Median follow-up – 3.8 years
- Primary composite outcome – time to the first occurrence of death from CV causes, nonfatal MI, or nonfatal stroke
  - Liraglutide 13.0% vs. placebo 14.9% (p< 0.001 for noninferiority, p=0.01 for superiority)

Doi: 10.1056/NEJMoa1603827
GLP-1 RAS PLACE IN THERAPY
Candidates for GLP-1 RA Therapy

Individuals who:

- are relatively early in the disease process
- could benefit from monotherapy but are NOT good candidates for metformin or a sulfonylurea
- have a hazardous occupation that makes hypoglycemia especially dangerous
- are overweight
- want to lose weight, especially if they have suboptimal glycemic control with oral therapy
- are reluctant to transition to insulin, especially if concerned about weight gain and/or hypoglycemia

GLP-1 RA: Implications in the Elderly

- No difference in efficacy or safety when comparing younger patients to those >65 yo
- May be useful in patients who experience hypoglycemia unawareness

- **Things to Consider:**
  - Renal function, especially if using exenatide IR/ER and liraglutide
  - Ease of administration
  - Dosing with meals
Which GLP-1 RA is Superior?

<table>
<thead>
<tr>
<th>Factors to consider</th>
<th>Agent(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Least nausea</td>
<td>Exenatide* or albiglutide</td>
</tr>
<tr>
<td>Highest risk of injection site reactions</td>
<td>Exenatide* or albiglutide</td>
</tr>
<tr>
<td>A1c reduction</td>
<td>Exenatide*, liraglutide, and dulaglutide (additional ↓ - 0.4%)</td>
</tr>
<tr>
<td>FPG reduction</td>
<td>Exenatide* and dulaglutide</td>
</tr>
<tr>
<td>PPG reduction</td>
<td>Exenatide BID (and lixisenatide)</td>
</tr>
<tr>
<td>Body weight</td>
<td>Dulaglutide</td>
</tr>
<tr>
<td>Greatest patient satisfaction</td>
<td>Exenatide weekly higher than BID</td>
</tr>
<tr>
<td></td>
<td>Similar between liraglutide vs. albiglutide or dulaglutide</td>
</tr>
</tbody>
</table>

*weekly dosing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patient Assistance Program</th>
<th>Manufacturer's Coupons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide IR (Byetta®)</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>Exenatide ER (Bydureon®)</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Dulaglutide (Trulicity®)</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Albiglutide (Tanzeum®)</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Liraglutide (Victoza®)</td>
<td>YES</td>
<td>YES</td>
</tr>
</tbody>
</table>

Needymeds.org
William

- 70 year old Caucasian male
- A1c 8.8%, SCr 1.5 mg/dL, eGFR 46 mL/min/1.73 m², BP 154/96 mm Hg
- Past Medical History:
  - Type 2 DM (diagnosed today)
  - HTN (x 6 yr)
  - Depression (x 4 yr)
  - CHF (x 4 yr)
- Current medications:
  - lisinopril/HCTZ 20 mg/25 mg po daily
  - carvedilol 12.5 mg po BID
  - citalopram 20 mg po daily
  - acetaminophen 650 mg po TID
Question #7: The provider and William are agreeable to starting a GLP-1 RA. Which GLP-1 RA would be the **BEST** to initiate in William to maximize efficacy and minimize adverse effects?

A. Byetta® (exenatide IR)

B. Tanzeum® (albiglutide)

C. Trulicity® (dulaglutide)

D. Victoza® (liraglutide)
Potential Benefits of GLP-1 RA and Insulin

- Improve post-prandial glucose (PPG) control
- Maximize endogenous prandial insulin response
- Influence alpha-cell function
- Do not impair alpha-cell response to hypoglycemia
- No carbohydrate counting or frequent blood glucose monitoring
- Minimize or avoid weight gain
- Incretin actions complement those of metformin
- Proposed cardioprotection/↑ Cardiac Output

Incretin and Insulin Combination: Pearls

- More convenient intensification strategy vs. prandial insulin
- Overweight patients → consider GLP-1 RA before meal-time insulin
- N/V/D is generally only during first 1-2 weeks of therapy

- Adding GLP-1 RAs to insulin
  - If A1c < 8% reduce insulin dose
    - Recommended reduction ranges from 15-63%
    - At initiation of GLP-1 RA - ↓ basal dose by 10% and prandial by 30 – 40%
    - If only on a small amount of prandial insulin, consider withholding
    - May be able to discontinue insulin

GLP-1 RA Effect on Bolus Insulin

- Randomized (N = 134) to either:
  - Exenatide + basal insulin (n = 76)
  - Exenatide + basal insulin + bolus insulin (n = 58)

- With the addition of exenatide:
  - Bolus insulin doses decreased 35% (p = 0.0053)
  - 45% able to discontinue bolus insulin (p < 0.001)
  - 22% discontinued exenatide due to ADRs

GLP-1 RA Effect on Bolus Insulin

- 52-week, phase 3, non-inferiority study comparing:
  - Bolus insulin (lispro) + Basal insulin (glargine)
  - Bolus insulin (lispro) + GLP-1 RA (dulaglutide 0.75/1.5 mg)

- Change in A1c
  - Significant decrease with weekly dulaglutide 0.75 mg (0.17%) & 1.5 mg (0.22%) compared to glargine

- Change in weight
  - Significant decrease in dulaglutide 1.5 mg arm (-0.87 kg)
  - Significant increase in glargine arm (+2.33 kg)

- Insulin requirement
  - Bolus insulin: 30% more in dulaglutide arms
  - Total daily dose (TDD) of insulin: 30% lower in dulaglutide arms

- Hypoglycemia
  - No significant differences

Conclusion: Reduction in A1c, weight loss, and potentially more bolus insulin with an overall lower total daily dose of insulin

GLP-1 RA Effect on High-Dose Insulin

- 6 month trial comparing:
  - High-dose insulin (TDD > 1.5 units/kg/day) + GLP-1 (liraglutide titrated to 1.8 mg daily)
  - High-dose insulin (TDD > 1.5 units/kg/day) + placebo

- Change in A1c
  - Significant decrease in liraglutide arm (0.9%) compared to placebo (0.0%) (p=0.002)

Conclusion: Reduction in A1c, weight loss, and increased patient satisfaction and potentially less TDD of insulin

- Change in weight
  - Significant decrease in liraglutide arm (-2.0 kg)
  - Significant increase in placebo arm (+0.4 kg)

- Insulin requirement
  - Liraglutide arm (-28 units) vs. placebo (p=0.06)
  - If A1c < 9% - suggest decrease 25-30%

A FOCUS ON
DPP-4 INHIBITORS
DPP-4 Inhibitors

- Approved for treatment of Type 2 DM as an adjunct to diet and exercise to improve glycemic control

- MOA:
  - Inhibits dipeptidyl peptidase-4 (DPP-4) → ↑incretin hormones
  - Augments glucose-dependent insulin secretion (like GLP-1RA)
  - Decreases circulating glucagon
  - Delays gastric emptying (like GLP-1 RA)

- Administration
  - Once daily without regard to meals
## DPP-4 Inhibitors (DPP-4i)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Special Considerations</th>
</tr>
</thead>
</table>
| alogliptin    | 25 mg daily   | CrCl 30 – 60 mL/min: 12.5 mg daily  
CrCl < 30 mL/min: maximum dose 6.25 mg daily                                                                                                               |
| (Nesina®)     |               |                                                                                                                                                    |
| linagliptin   | 5 mg daily    | No dosage adjustment  
Strong P-gp or CYP3A4 inducer may ↓ linagliptin’s efficacy  
– use alternative treatments                                                                                                                          |
| (Tradjenta®)  |               |                                                                                                                                                    |
| saxagliptin   | 2.5 mg or 5 mg daily | CrCl ≤ 30 mL/min: 2.5 mg daily  
Concomitant use with strong CYP450 3A4/5: 2.5 mg daily                                                                                               |
| (Onglyza®)    |               |                                                                                                                                                    |
| sitagliptin   | 100 mg daily  | CrCl 30 – 50 mL/min: 50 mg daily  
CrCl < 30 mL/min: 25 mg daily                                                                                                                              |
| (Januvia®)    |               |                                                                                                                                                    |
Effects of DPP-4 Inhibitors

- **DDP-4 inhibitors** Inhibit the degradation of endogenous incretins

- **Glycogen synthesis**
- **Glucose oxidation**

- **Insulin secretion**
- **Glucagon secretion**
- **B-cell proliferation**

- **Blood pressure**
- **Heart rate**
- **Myocardial contractility**

- **Appetite**
- **Energy expenditure**
- **Satiety**

- **Gastric emptying**
- **Acid secretion**
- **GI motility**

- **Natriuresis**

- **Lipolysis**
- **FFA synthesis**
- **Glucose synthesis**
- **Glucose uptake**

- **Hepatic glucose output**


DPP-4 Inhibitor Efficacy

- Meta-analysis
  - ↓ A1c 0.5 – 0.9%

- All DPP-4 inhibitors have similar efficacy
  - A1c change from baseline
  - Achievement of A1c < 7%

- Compared with metformin monotherapy
  - Lower ↓ A1c, ↓ FPG level, weight loss
  - Lower risk of adverse CV events, hypoglycemia, and GI ADRs

DPP-4 Inhibitors: Common Side Effects

- Nasopharyngitis
- UTIs
- Headache
- Upper respiratory infection

Low Risk of Hypoglycemia
DPP-4 Inhibitors: Warnings and Precautions

- Pancreatitis
- Hypoglycemia
- Hypersensitivity
- Arthralgia
- Macrovascular outcomes
- Heart failure
  - alogliptin, saxagliptin

DPP-4 Inhibitors and Pancreatitis

- Acute pancreatitis (AP)
  - Initial FDA warning with sitagliptin in 2009 – on all other incretin agents
- Evidence for pancreatitis
  - Post-marketing and RCT

- Watch patients for s/s of pancreatitis
- If suspected, stop DPP-4 inhibitor
- Pancreatitis confirmed
  - Do NOT restart DPP-4 inhibitor
- Patients with history of pancreatitis
  - Use alternative therapy
DPP-4 Inhibitors and Severe Joint Pain

- FDA Warning added to all package inserts in August 2015
- October 2006 – December 2013
  - 33 total cases – “substantial reduction” in activity level
    - Most cases with sitagliptin (n=28) vs. saxagliptin (n=5), linagliptin (n=2), alogliptin (n=1), vildagliptin (n=2)
    - Severe arthralgia with two different DPP-4 inhibitors (n =5)
    - Patients hospitalized (n = 10)
    - Symptoms appeared within 1 month of initiation of DPP-4 inhibitor (n= 22)
    - Symptoms resolved within 1 month of d/c DPP-4 inhibitor (n=23)

- Management:
  - Consider DPP-4 inhibitors as a possible cause if severe and persistent joint pain
  - Consider d/c of DPP-4 inhibitor

DPP-4 Inhibitors and Heart Failure

- FDA Warning added to alogliptin-containing products in February 2014
  - Result of EXAMINE (alogliptin use after ACS)
    - Note that alogliptin did NOT increase incidence of major CV events
- FDA Warning added to saxagliptin-containing products in April 2016
  - Result of SAVOR-TIMI 53 (saxagliptin in patients who had a history of, or were at risk for, CV events)
    - Note that saxagliptin did NOT increase or decrease incidence of major CV events
- More risk if pre-existing CV or kidney problems
- Monitor patients for s/s of heart failure

DPP-4 Inhibitors and CVD Advantages?

Older Participants SAVOR-TIMI 53 (saxagliptin)
- 8,561 elderly (≥ 65yo) and 2,330 very elderly (≥ 75 yo) with history of, or at risk for, CV events
- Median follow-up – 2.1 years
- Primary endpoint of CV mortality, MI, or ischemic stroke
  - HR 0.92 for elderly vs. 1.15 (< 65 yo)
  - HR 0.95 for very elderly
- Saxagliptin ↑ risk for hospitalization for HF – no age-based interaction

TECOS (sitagliptin)
- 14,671 patients with CVD sitagliptin or placebo added to usual care
- Median follow-up – 3.0 years
- Primary CV outcome of composite CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina
  - Sitagliptin noninferior to placebo (HR 0.98; p< 0.001)
- Rates of hospitalization for HF
  - No difference between 2 groups (HR 1.00; p=0.98)

Eva

- 75 year old African American female
- A1c 8.2%, SCr 1.1 mg/dL, eGFR 59 mL/min/1.73 m², BP 146/76 mm Hg
- Past Medical History:
  - Type 2 DM (x 1 yr)
  - OA (knees) (x 15 yr)
- Current medications:
  - metformin 1,000 mg po twice daily
  - lisinopril 10 mg po daily
  - acetaminophen 650 mg po three times daily
Question #8: In addition to encouraging intensive lifestyle modifications, which of the following would be the BEST option to add to optimize Eva's diabetes management?

A. Amaryl® (glimepiride) 4 mg po daily

B. Jardiance® (empagliflozin) 10 mg po daily

C. Tanzeum® (albiglutide) 30 mg SQ once weekly

D. Tradjenta® (linagliptin) 5 mg po daily
DPP-4 INHIBITORS PLACE IN THERAPY
DPP-4 Inhibitors: ADA Standards of Care

[Diagram showing the use of DPP-4 inhibitors in combination with other medications for diabetes management, including Metformin, Sulfonylureas, Thiazolidinediones, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 agonists, and basal insulin.]
DPP-4 Inhibitor Place in Therapy

**Added to metformin**
- DPP-4 inhibitors vs. sulfonylureas or pioglitazone
- No difference in A1c
- ↓ weight by ~2.2 kg
- Less hypoglycemia

**Added to insulin**
- Meta-analysis [Januvia® (sitagliptin) - 3 studies, Onglyza® (saxagliptin), vildagliptin, Tradjenta® (linagliptin), and Nesina® (alogliptin)]
  - ↓ A1c by 0.52%
  - ↓ 2h-PPG by 32.6 mg/dL
  - ↓ weight by ~0.11 kg
  - Low risk of hypoglycemia

Candidates for DPP-4 Inhibitor Therapy

Individuals who:

- are relatively early in the disease process
- could benefit from monotherapy but are NOT good candidates for metformin or a sulfonylurea
  - Especially if A1c < 7.5%
- have a hazardous occupation that makes hypoglycemia especially dangerous
- are overweight
- are reluctant to inject themselves
DPP-4 Inhibitors: Implications in the Elderly

- No difference in efficacy or safety when comparing younger patients to those > 65 yo
  - A1c ↓0.7% - no difference vs. younger patients
  - Safety profile similar to placebo
- Few contraindications (relative)
- Hypoglycemia still rare as monotherapy or with insulin sensitizers
- Consider renal function
  - Dosing adjustment needed, except linagliptin

# DPP-4 Inhibitor Availability

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patient Assistance Program</th>
<th>Manufacturer’s Coupons</th>
<th>Available in combination with</th>
</tr>
</thead>
<tbody>
<tr>
<td>alogliptin (Nesina®)</td>
<td>YES</td>
<td>YES</td>
<td>metformin (Kazano®, pioglitazone (Oseni®))</td>
</tr>
<tr>
<td>linagliptin (Tradjenta®)</td>
<td>YES</td>
<td>YES</td>
<td>metformin (Jentadueto®, empagliflozin (Glyxambi®))</td>
</tr>
<tr>
<td>saxagliptin (Onglyza®)</td>
<td>YES</td>
<td>YES</td>
<td>metformin (Onglyza®)</td>
</tr>
<tr>
<td>sitagliptin (Januvia®)</td>
<td>YES</td>
<td>YES</td>
<td>metformin (Janumet®, Janumet XR®)</td>
</tr>
</tbody>
</table>
A FOCUS ON
SGLT2 INHIBITORS
Figure 3 | Renal handling of glucose in a non-diabetic individual. Virtually all the glucose filtered is reabsorbed, and none appears in the urine. The locations for sodium–glucose co-transporter 2 (SGLT2) and SGLT1 are shown. Adapted from REF. 12.
SGLT2 Inhibitors (SGLT2i)

- Approved for treatment of Type 2 DM as an adjunct to diet and exercise to improve glycemic control

- MOA:
  - Inhibits SGLT2 found specifically in the S1 segment of the proximal convoluted tubule of the kidney.
  - Blocks renal reabsorption of glucose

- Administration
  - Without regard to meals
  - Once daily in the morning

Invokana (canagliflozin) PI. Titusville, NJ: Janssen Pharmaceuticals; 2016.
Jardiance (empagliflozin) PI. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals; 2016.
### SGLT2 Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Special Considerations*</th>
</tr>
</thead>
<tbody>
<tr>
<td>canagliflozin</td>
<td>100 mg daily (titrate to 300 mg daily)</td>
<td>eGFR 45-60 maximum dose 100 mg daily; eGFR 30-45 use not recommended (however studies show generally well tolerated in stage 3 CKD); eGFR &lt;30 contraindicated; Adjust dosing for concomitant therapy with UGT inducers</td>
</tr>
<tr>
<td>(Invokana®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dapagliflozin</td>
<td>5 mg daily (titrate to 10 mg daily)</td>
<td>Use is not recommended eGFR &lt;60, discontinue if eGFR persistently &lt;60</td>
</tr>
<tr>
<td>(Farxiga®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>empagliflozin</td>
<td>10 mg daily (titrate to 25 mg daily)</td>
<td>eGFR &lt;45 do not initiate; discontinue if eGFR is persistently &lt;45</td>
</tr>
<tr>
<td>(Jardiance®)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*eGFR is reported in mL/min/1.73 m²
SGLT2 Inhibitor Efficacy

- A meta-analysis of canagliflozin and dapagliflozin
  - ↓ A1c by -0.79% (monotherapy) and -0.61% (add on therapy)
- As a class, A1c reduction is ~0.7-1%
- A1c levels > 10% → potentially greater A1c reductions of
  - 2.6% with canagliflozin 300mg
  - 3.7% with empagliflozin 25mg
- Within the class, SGLT2 inhibitors have similar efficacy
  - As monotherapy, canagliflozin 300 mg may lower A1c more
- *SGLT-2 inhibitors have similar efficacy to metformin and sulfonylureas.*
Donna

- 65 year old Caucasian female, 195 lb, BMI 32.2 kg/m²
- A1c 8.3%  SCr 0.9 mg/dL  eGFR >60 mL/min/1.73m²
- Past Medical History
  - Type 2 Diabetes (x 3 yr)
  - Hypertension (x 10 yr)
- Medications
  - metformin 1,000 mg po twice daily
  - Januvia® (sitagliptin) 50 mg po daily
  - amlodipine 10 mg po daily
Question #9: What is the next BEST therapy to optimize Donna’s diabetes management?

A. Add Actos® (pioglitazone) 45 mg po daily
B. Add Byetta® (exenatide IR) 10 mcg SQ BID
C. Add Farxiga® (dapagliflozin) 10 mg po daily
D. Add Invokana® (canagliflozin) 100 mg po daily
SGLT-2 Inhibitors: Common Side Effects

- UTIs
- Female Genital Mycotic Infections
- Male GU Fungal Infections
- Hypotension/Hypovolemia
- Polyuria
- Low Risk of Hypoglycemia

Invokana (canagliflozin) PI. Titusville, NJ: Janssen Pharmaceuticals; 2016.
Jardiance (empagliflozin) PI. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals; 2016.
SGLT2 Inhibitors: Warnings and Precautions

- Hypotension
- Ketoacidosis
- Genital mycotic infections
- Impairment in renal function
  - Acute renal injury (canagliflozin)
- Urosepsis and pyleonephritis
- Hypoglycemia
- Hypersensitivity reactions
- Increased LDL-C
- Macrovascular outcomes
- Hyperkalemia (canagliflozin)
- Bladder Cancer (dapagliflozin)
- Amputation (canagliflozin)

Invokana (canagliflozin) PI. Titusville, NJ: Janssen Pharmaceuticals; 2016.
Jardiance (empagliflozin) PI. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals; 2016.
**SGLT2 Inhibitors and Ketoacidosis**

- FDA Warning added to all package inserts in May 2015
  - Updated in December 2015
  - 73 cases of DKA in T1DM and T2DM (60% type 2 diabetes)
  - Occurred within 1 year of initiation or dose adjustment
  - Required ED visit or hospitalization
- More cases with canagliflozin (n=48) and dapagliflozin (n=21) vs. empagliflozin (n=4)
- Signs and symptoms consistent with metabolic acidosis
  - Nausea, vomiting, abdominal pain, malaise, shortness of breath

SGLT2 Inhibitors and Ketoacidosis

- Atypical cases
  - Only slightly elevated glucose

- Potential triggers for the ketoacidosis cases included major illness, reduced food and fluid intake, and reduced insulin dose.

- Postulated mechanisms:
  - A decrease in insulin use with the addition of the SGLT-2 inhibitor
  - Increased glucagon levels that promote ketogenesis (a potential direct effect on alpha islet cells)
  - Decreased clearance of ketone bodies

- Discontinue SGLT2i if DKA is suspected

SGLT2 Inhibitors and Urosepsis

- FDA Warning added to all package inserts in December 2015

- May 2013 – October 2014
  - 19 cases of life-threatening urosepsis and pyelonephritis
  - Required ED visits or hospitalization (including ICU)
  - 2 patients required hemodialysis
  - Almost half reported *E. coli* as causative organism

- Reports only with canagliflozin (n=10) and dapagliflozin (n=9)

SGLT2 Inhibitors and Amputations

- FDA issued Drug Safety Communication to the public – May 2016 regarding canagliflozin
- Ongoing trial with canagliflozin (Canagliflozin Cardiovascular Assessment Study – CANVAS)
  - Amputations occurred ~2 times as often in canagliflozin arms
    - 7 out of every 1,000 patients treated with canagliflozin 100 mg daily
    - 5 out of every 1,000 patients treated with canagliflozin 300 mg daily
    - 3 out of every 1,000 patients treated with placebo
- Monitor patients’ legs and feet for:
  - New pain/tenderness, sores, ulcers, infections

SGLT2 Inhibitors and Bone Loss?

- **Dapagliflozin data**
  - 6-9% of patients in one study had bone fractures over 104 weeks

- **Canagliflozin data**
  - A polled analysis of eight trials over 68 weeks showed a 30% increase in fracture risk
  - FDA added a new warning/precaution about fracture risk to the canagliflozin label September 2015

- May be due to increased concentrations of phosphate in the serum or an increase in parathyroid hormone (PTH)

Invokana (canagliflozin) PI. Titusville, NJ: Janssen Pharmaceuticals; 2016.
SGLT2 Inhibitors and CVD Advantages?

- **BP Reduction**
  - Blood pressure reductions versus placebo
    - Systolic blood pressure (SBP) → 3-5 mmHg
    - Diastolic blood pressure (DBP) → 0.5-2.5 mmHg
  - Only canagliflozin was shown to have a dose-dependent relationship with SBP
  - Low risk of orthostatic hypotension
  - Likely a result of the chronic natriuretic and osmotic diuretic effects
- **SBP reductions typically seen with weight loss**
  - However, meta-analysis of randomized controlled trials with SGLT-2 inhibitors → no significant relationship between changes in body weight to SBP

SGLT2 Inhibitors and CVD Advantages?

- **Weight loss**
  - One of the only oral antidiabetic agents with weight loss
  - Weight reductions of 2-4 kg have been seen across the class
  - In combination therapy, the addition of dapagliflozin offset the weight gain caused by pioglitazone
  - Body composition testing showed reduction in visceral fat/subcutaneous fat

SGLT2 Inhibitors and CVD Advantages?

- **Additional Hypothesized CV Risk Reduction**
  - Reduction in glucose variability and uric acid levels
  - Reduction in urinary albumin excretion
  - Potential reduction the rate of GFR decline in patients with diabetic nephropathy

- **Small, dose related increase in LDL and TC**
  - Some studies found mild reductions

- **May increase in HDL and lower TG**

- **No cardiovascular outcomes trials at this time demonstrating LDL increases translate into an increase in real-life cardiovascular events**

SGLT2 Inhibitors and CVD Advantages?

- **EMPA-REG OUTCOME** (empagliflozin vs. placebo)
  - Patients with established cardiovascular disease

- **Primary outcome**: death from CV causes and nonfatal MI or stroke
  - Significantly reduced with empagliflozin (10.5% vs 12.1%)

- **Secondary outcomes**
  - No differences in individual CV event rates
  - Decreased CV death (3.7%, vs. 5.9% in the placebo group; 38% RRR)
  - Decreased hospitalizations for heart failure (2.7% vs. 4.1%; 35% RRR)
  - Decreased death from any cause (5.7% vs. 8.3%; 32% RRR)

SGLT2 Inhibitors: ADA Standards of Care
SGLT2 Inhibitors: AACE/ACE Guidelines

Glycemic Control Algorithm

Lifestyle Therapy

Entry A1C < 7.5%

Mono Therapy*

- Metformin
- GLP-1 RA
- SGLT-2

Entry A1C ≥ 7.5%

Dual Therapy*

- GLP-1 RA
- DPP-4i
- TZD
- Diabetic 
- AGI
- SGLT-2

Triple Therapy*

- GLP-1 RA
- DPP-4i
- TZD
- Basal insulin
- Colistatin
- Bromocriptine
- AG
- SGLT-2

Entry A1C > 9.0%

Symptoms

- No

- Yes

- Dual Therapy

- Insulin + Other Agents

Progression of Disease

SGLT2 Inhibitor Place in Therapy

Added to metformin
- Invokana® (canagliflozin) vs. glimepiride
  - ↓ weight by ~4 kg
  - ↓ SBP by ~3.3-4.6 mmHg
  - Less hypoglycemia

Added to insulin
- Farxiga® (dapagliflozin) vs. placebo and Jardiance® (empagliflozin) vs. placebo
  - ↓ weight by ~1-2 kg
  - Reduced insulin requirements (~8-18 units)
  - Low risk of hypoglycemia

Candidates for SGLT2 Inhibitor Therapy

Individuals who:

- are relatively early in the disease process
- could benefit from monotherapy but are NOT good candidates for metformin or a sulfonylurea
  - Especially if A1c < 7.5%
- are reluctant to inject themselves but could benefit from dual- or triple-therapy
  - Within 1-2% of A1c goal
- have a hazardous occupation that makes hypoglycemia especially dangerous
- are overweight
- have good renal function/stable volume status
- could benefit from modest BP ↓

SGLT2 Inhibitors: Implications in the Elderly

- > 65 years → higher incidence of adverse events (AE) related to intravascular volume depletion particularly with Invokana® (canagliflozin) 300 mg/day dose
  - Hypotension
  - Postural dizziness
  - Orthostatic hypotension
  - Syncope
  - Dehydration

- More prominent increase in AE >75 years old
- Hypoglycemia still rare
- Efficacy may be diminished (A1c -0.61% vs. -0.74%)
- Polyuria concerns?

SGTL2 Inhibitor Availability

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<tr>
<td>canagliflozin (Invokana®)</td>
<td>YES</td>
<td>YES</td>
<td>metformin (Invokamet®)</td>
</tr>
<tr>
<td>dapagliflozin (Farxiga®)</td>
<td>YES</td>
<td>YES</td>
<td>metformin (Xigduo®)</td>
</tr>
<tr>
<td>empagliflozin (Jardiance®)</td>
<td>YES</td>
<td>YES</td>
<td>metformin (Synjardy®) linagliptin (Glyxambi®)</td>
</tr>
</tbody>
</table>
Cheryl

- 64 year old African American female, 264 lb, 5’4”, BMI 45 kg/m²
- A1c 8.3%, GFR >60 mL/min/1.73m², BP 110/60 mm Hg
- Past Medical History:
  - Type 2 DM
- Current medications:
  - metformin 1,000 mg po twice daily
  - Januvia® (sitagliptin) 100 mg po daily
  - lisinopril 5 mg po daily
  - aspirin 81 mg po daily
  - pravastatin 40 mg po daily
Question #10: Cheryl is starting Jardiance® (empagliflozin) today. What would be MOST appropriate to discuss with the patient prior to initiating therapy?

A. Discontinue Januvia® (sitagliptin) because of duplicate MOAs
B. Hypotension because of BP 110/60 mm Hg today
C. Concerns about weight gain
D. Concerns about renal function
Question #11: Thomas is a 69 yo male with Type 2 DM. Which of the following medications would MOST likely need to be discontinued when adding an SGLT2 inhibitor?

A. Actos® (pioglitazone)

B. Aldactone® (spironolactone)

C. Lasix® (furosemide)

A. Microzide® (hydrochlorothiazide)
Key Takeaways

- Guidelines encourage individualization of A1c goals based on patient specific factors.

- Guidelines emphasize that GLP-1 RAs, DPP-4 inhibitors, and SGLT2i are preferred add-on therapy to metformin for treatment of type 2 diabetes.

- GLP-1 RAs, DPP-4 inhibitors, and SGLT2i can be used safely in older adults but renal function must be considered.

- Utilizing GLP-1 RAs, DPP-4 inhibitors, and SGLT2i to target pathophysiological deficits in type 2 diabetes can avoid or minimize weight gain and may improve cardiovascular disease risk.

- GLP-1 RAs, DPP-4 inhibitors, and SGLT2i in combination with insulin have been shown to be a safe and effective approach to reducing insulin requirements and minimizing weight gain associated with insulin use.
UTILIZING NEWER AGENTS TO PERSONALIZE MANAGEMENT OF TYPE 2 DIABETES MELLITUS

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