Medication Make-Over: Contemporary Pharmacotherapy Options for Type 2 Diabetes

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Objectives

• Describe recent updates in the pharmacotherapy management recommendations for type 2 diabetes.

• Discuss the rationale regarding therapeutic decision making when adding on to, or replacing metformin in type 2 diabetes.

• Assess the appropriateness of SGLT-2 inhibitors, DPP-4 inhibitors, GLP-1 agonists, and newer concentrated insulins based on specific patient characteristics.
PATIENT CASE #1
Case #1: GL

- GL is a 60-year-old African-American male returning to his primary care clinic for routine follow-up. He has had T2D for 5 years, hypertension and dyslipidemia for 8 years and GERD for 3 years.

- Current Medications
  - Metformin 1000 mg PO BID
  - Lisinopril 20 mg PO daily
  - Atorvastatin 40 mg PO daily
  - Omeprazole 20mg PO daily

- SMBG:
  - Fingersticks three times a week in the morning
  - FPG = average 155 mg/dL (range 130-199 mg/dL)
Case #1: GL

Social History

- Employed full time as accountant
- Nonsmoking with no illicit drug use
- Occasional alcohol use (~3 drinks per week)
- Self-reported hectic and inconsistent eating schedule. Usually eats breakfast and dinner, but often times skips lunch during busy work day. Largest meal of day is dinner.
- Married with 2 grown children. His wife does the cooking.

Physical Exam, Vitals & Labs

- A1C 8.2%
- Weight - 194 lb
- BMI - 27 kg/m²
- BP - 132/80 mmHg
- HR - 70 bpm
- Slightly decreased sensation in both feet bilaterally
- Lipid panel – WNL
- Urinary albumin/creat - 215
- SCr - 1.0 mg/dL
- eGFR - > 100 mL/min/1.73 m²
Metformin is ** CURRENTLY ** most commonly used as “first line” therapy
Biguanides (Metformin)

- Impaired Insulin Secretion
- Increased Glucagon Secretion
- Increased Hepatic Glucose Production
- GI tract/Decreased Incretin Effect
- Increased Lipolysis
- Increased Glucose Reabsorption
- Decreased Glucose Uptake
- Neurotransmitter Dysfunction

Tips for Use: Metformin

• Dosing
  – Metformin immediate release
    • Start with 500mg daily to BID
    • Max effective dose is 2000mg/day
    • Individualize titration based on GI side effects
  – Metformin XR
    • May be helpful if immediate release GI effects are bothersome
    • Start XR 500mg – XR 750mg QD
  – Take with food to reduce GI side effects
  – Ideally take in evening/bedtime
  – Monitor: A1C, Serum Creatinine, eGFR, B12 levels
Metformin

- Historically, serum creatinine was the measure used to determine if a patient could be prescribed metformin.
- More recent studies support the use of the glomerular filtration rate estimating equation (eGFR).

<table>
<thead>
<tr>
<th>General Practice Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>eGFR 45 – 60 ml/min</strong></td>
</tr>
<tr>
<td><strong>eGFR 30 – 45 ml/min</strong></td>
</tr>
<tr>
<td><strong>eGFR &lt; 30 ml/min</strong></td>
</tr>
</tbody>
</table>

What comes after metformin?

How do you choose a second agent?
12 Pharmacotherapy Options

**Insulin (1)**
- **Bolus insulin**
  - Insulin lispro
    - U100
    - U200
  - Insulin aspart
  - Insulin glulisine
  - Insulin human inhaled
  - Regular human insulin

- **Basal insulin**
  - Insulin NPH
  - Insulin detemir
  - Insulin degludec
    - U100
    - U200
  - Insulin glargine
    - U100
    - U300

**Oral Medications (9)**
- α-glucosidase inhibitors (AGI)
- Biguanides
- Bile acid sequestrants (BAS)
- Dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins)
- Dopamine agonists
- Glinides
- Sulfonylureas (SU)
- Sodium Glucose Co-Transporter-2 inhibitors (SGLT-2i)
- Thiazolidinediones (TZDs or glitazones)

**Non-insulin injectable agents (2)**
- Glucagon-like peptide-1 (GLP-1) agonists
- Amylinomimetic

### ADA Standards of Medical Care (2017)

**Monotherapy**

<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>G/lactic acidosis</td>
<td>Low</td>
</tr>
</tbody>
</table>

- If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- & disease-specific factors).

**Dual Therapy**

<table>
<thead>
<tr>
<th>Drug Combination</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>Intermediate</td>
<td>Intermediate</td>
<td>Rare</td>
<td>Low</td>
</tr>
</tbody>
</table>

- If A1C target not achieved after approximately 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- & disease-specific factors).

**Triple Therapy**

<table>
<thead>
<tr>
<th>Drug Combination</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>High</td>
<td>Rare</td>
<td>High</td>
</tr>
</tbody>
</table>

- If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e. adding a fourth antihyperglycemic agent).
Drug Selection: A Balancing Act

Clinical Outcomes

Patient Safety
Considerations in Drug Selection

• Patient factors to consider
  – Synergistic / complimentary mechanism of action
  – A1c lowering needed
    • Fasting, post-prandial
  – Weight/Obesity
    • High levels of insulin resistance
  – Cardiovascular disease
    • Hypoglycemia
  – Ease of medication administration
    • Side effect profile
  – Renal impairment
  – Cost, available medication coverage
Sulfonylureas

- **Islet b-cell**:
  - Impaired Insulin Secretion

- **Islet a-cell**:
  - Increased Glucagon Secretion

- **GI tract**:
  - Decreased Incretin Effect

- **Hepatic**:
  - Increased Hepatic Glucose Production

- **Neurotransmitter Dysfunction**

- **Increased**
  - Glucose Reabsorption
  - Lipolysis
  - Glucose Uptake

**Hyperglycemia**

Sulfonylureas

- Stimulates insulin release from the **pancreas**
  - Long acting stimulation (>6 hours)
  - Requires endogenous insulin to be effective; therefore better used early in the disease; if necessary
  - Short durability

- Lowers **fasting and postprandial glucose**
  Decreases A1c by 1.5-2% (~45-60 mg/dl)

- Most common side effects
  - Hypoglycemia
  - Weight gain
  - May inhibit ischemic pre-conditioning

Tips for Use

• Take in morning before/with breakfast
• If dosed BID, take with breakfast and supper.
  – Patient should check bedtime BG and have snack if needed
• Patients need to eat on schedule
  – Do not skip meals/snacks
    • Risk of hypo
Neurotransmitter Dysfunction

TZD’s (Glitazones)

Hyperglycemia

- Impaired Insulin Secretion
- Increased Glucagon Secretion
- Increased Hepatic Glucose Production
- Neurotransmitter Dysfunction
- GI tract/ Decreased Incretin Effect
- Increased Lipolysis
- Increased Glucose Reabsorption
- Decreased Glucose Uptake

TZD’s (Glitazones)

- Stimulates PPRA γ to increase GLUT-4 transporter production; thereby moving glucose from the blood into the peripheral tissue.
- Also reduces adipose fat
  - Can be used thru duration provided insulin is present
  - Good durability
- Lowers fasting and postprandial glucose
- Decreases A1c by 1.0-1.5% (~30-45 mg/dl)
- Most common side effects
  - Edema (swelling) usually in the legs
  - Weight gain
  - Possible ↑ risk of fractures.
- Takes 4-6 weeks (or more) to take affect and requires insulin (endogenous or exogenous)

Tips for Use

• Takes 4-8 weeks before effect is noticed.
• Patients need to give TZD’s 2-3 months use
• Best used early in the disease process
• Good combination with:
  – GLP-1 agonists
  – Metformin
  – SGLT-2i (?)
DPP4 Inhibitors (gliptins)

Impaired Insulin Secretion

Increased Glucagon Secretion

Increased Hepatic Glucose Production

Neurotransmitter Dysfunction

Decreased Incretin Effect

Increased Lipolysis

Increased Glucose Reabsorption

Decreased Glucose Uptake

Hyperglycemia
DPP4 Inhibitors (gliptins)

• Inhibits DPP-4 enzyme in the GI tract that breaks down GLP-1 resulting in ↑ endogenous GLP-1.
  – glucagon suppression results in ↓ liver glucose production
  – Enhances appropriate insulin and amylin secretion from the pancreas
  – Can be used thru duration provided insulin is present
    • Promising durability

• Lowers postprandial glucose
  – Decrease A1c by 0.5 to 0.7% (~15-20 mg/dl; most postprandial)

• Most common side effects
  • Stuffy, runny nose
  • Headache
  • Upper respiratory tract infection

# DPP-4 Inhibitors: Comparisons

<table>
<thead>
<tr>
<th></th>
<th>sitagliptin</th>
<th>saxagliptin</th>
<th>linagliptin</th>
<th>alogliptin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose/frequency</strong></td>
<td>100 mg</td>
<td>5 mg</td>
<td>5 mg</td>
<td>25 mg</td>
</tr>
<tr>
<td></td>
<td>once daily</td>
<td>once daily</td>
<td>once daily</td>
<td>once daily</td>
</tr>
<tr>
<td><strong>Efficacy (A1C lowering): monotherapy</strong></td>
<td>↓ 0.6%</td>
<td>↓ 0.7%</td>
<td>↓ 0.4%</td>
<td>↓ 0.8%</td>
</tr>
<tr>
<td><strong>Efficacy (A1C lowering): combination therapy</strong></td>
<td>↓ 0.7%</td>
<td>↓ 1.2%</td>
<td>↓ 0.7%</td>
<td>↓ 0.9%</td>
</tr>
<tr>
<td><strong>Renal dosing</strong></td>
<td>50 mg daily (moderate)</td>
<td>2.5 mg daily (moderate-severe)</td>
<td><strong>No dose adjustment necessary</strong></td>
<td>12.5 mg daily (moderate)</td>
</tr>
<tr>
<td></td>
<td>25 mg daily (severe)</td>
<td></td>
<td>6.25 mg daily (severe)</td>
<td></td>
</tr>
<tr>
<td><strong>Approximate ex Vivo DPP-4 Inhibition, % (maximum)</strong></td>
<td>97</td>
<td>80</td>
<td>80</td>
<td>90</td>
</tr>
</tbody>
</table>

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Januvia® (sitagliptin). Prescribing information..  
Onglyza® (saxagliptin). Prescribing information.  
Tradjenta® (linagliptin). Prescribing information.  
Nesina™ (alogliptin). Prescribing information.
DPP-4 Inhibitors: Adverse Effects

**Joint Pain**
- FDA Alert (Aug, 2015): 33 cases from 2006-2013 in FAERS
- Occurred 1 day to years after initial use
- After discontinuation, symptoms relieved

**Heart Failure**
- FDA update April 2016 for alogliptin and saxagliptin
- EXAMINE:
  - Alogliptin increased HF hospitalizations (3.9% vs 3.3%)
- SAVOR-TIMI: Saxagliptin increased hospitalization rates for HF (3.5% vs. 2.8%,)

**Pancreatitis**
- FDA alert in 2009 due to post-market reports
- Higher rates in clinical trials compared to placebo
- Also seen with GLP-1 receptor agonists

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https://www.fda.gov/Drugs/DrugSafety/ucm459579.htm
Tips for Use

- Best used for patient with A1c near normal
  - Minimal A1c lowering
  - PPG target
- Minimal side effects
- Good combination with:
  - Metformin
  - SGLT-2i
Neurotransmitter Dysfunction


Increased Glucagon Secretion
Increased Hepatic Glucose Production
Increased Glucose Reabsorption
Decreased Glucose Uptake
GI Tract/Decreased Incretin Effect
Increased Lipolysis

Impaired Insulin Secretion

Hyperglycemia

SGLT-2i

SGLT-2i

- ↓ renal glucose reabsorption in the early proximal tubule of the kidney
  - body fat - Possibly due to ↑ water and fat urination (elimination)

- Lowers fasting glucose
  - Decreases A1c by 0.7-1% (~20-30 mg/dl)

- Most common side effects
  - Weight loss
  - Vaginal and male genital infections
  - Rash
  - UTI
  - Frequent urination
  - Increased thirst
  - GI problems (when combined with metformin)

## SGLT2 Inhibitors: Comparisons

<table>
<thead>
<tr>
<th></th>
<th>Canagliflozin</th>
<th>Dapagliflozin</th>
<th>Empagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy (A1c lowering)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>↓ 0.77 - 1.03%</td>
<td>↓ 0.8 – 0.9%</td>
<td>↓ 0.7 – 0.8%</td>
</tr>
<tr>
<td>Combination</td>
<td>↓ 0.79 - 0.94%</td>
<td>↓ 0.7 – 0.8%</td>
<td>↓ 0.7 – 0.8%</td>
</tr>
<tr>
<td><strong>Dose and Frequency</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>100-300 mg once daily</td>
<td>5-10 mg once daily</td>
<td>10-25 mg once daily</td>
</tr>
<tr>
<td><strong>Renal dose adjustment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl &lt;60 mL/min</td>
<td>100 mg once daily</td>
<td>Use not recommended</td>
<td>*No dosage adjustment</td>
</tr>
<tr>
<td>CrCl &lt;45 mL/min</td>
<td>Use not recommended</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Jardiance (empagliflozin) [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2014.*
<table>
<thead>
<tr>
<th><strong>Bone Loss</strong></th>
<th><strong>Acute Kidney Injury</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>A pooled analysis of 9 trials over 85 weeks compared canagliflozin to placebo: more bone fractures with Canagliflozin (1.5 vs. 1.1) per 100 patient-years</td>
<td>FDA received 101 confirmed cases of acute kidney injury</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Urosepsis</strong></th>
<th><strong>Diabetic Ketoacidosis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA warning added Dec 2015</td>
<td>FDA warning added May 2015 (updated Dec 2015)</td>
</tr>
<tr>
<td>19 cases of life-threatening urosepsis and pyelonephritis with canagliflozin(n=10) and dapagliflozin(n=9)</td>
<td>73 cases of DKA reported in FAERS canagliflozin(n=48) , dapagliflozin(n=21) , empagliflozin(n=4)</td>
</tr>
</tbody>
</table>

Tips for Use

• Educate patients on proper GU hygiene, importance of hydration, signs/symptoms of DKA, increase frequency of urination
• Use caution in patient on volume depleting drugs (e.g. diuretics)
• Good combination with:
  – Metformin
  – DPP-4i
  – GLP-1 agonist
GLP-1 Agonists

short-acting GLP-1 agonists

- Exenatide (Byetta®)
  - 5 mcg & 10 mcg
  - Twice-daily dosing

- Lixisenatide (Adlyxin®)
  - 10 mcg & 20 mcg
  - once-daily dosing

long-acting GLP-1 agonists

- Liraglutide (Victoza®)
  - 0.6 mg, 1.2 mg, & 1.8 mg
  - Once-daily dosing

- Exenatide (Bydureon®)
  - 2 mg
  - Once-weekly dosing

- Albiglutide (Tanzeum®)
  - 30mg & 50mg
  - Once-weekly dosing

- Dulaglutide (Trulicity®)
  - 0.75 mg & 1.5 mg
  - Once-weekly dosing
GLP-1 Agonists

- Impaired Insulin Secretion
- Increased Glucagon Secretion
- Increased Hepatic Glucose Production
- Neurotransmitter Dysfunction
- GI Tract/ Decreased Incretin Effect
- Increased Lipolysis
- Increased Glucose Reabsorption
- Decreased Glucose Uptake

Hyperglycemia

GLP-1 Agonists

- GLP-1 agonists “fix” 6 dysfunctional organs in T2DM
  - glucagon suppression
    - Results in ↓ liver glucose production
  - Enhances appropriate insulin and amylin secretion from the pancreas
    - Results in brain satiety
  - Regulates the GI tract to slow gastric emptying time
  - Can improve insulin uptake in peripheral tissue via weight loss
  - Can be used thru duration provided insulin is present
    - Promising durability

- Short acting agonists lowers postprandial glucose
  - Decreases A1c by 0.8-1.5% (~20-45 mg/dl; most postprandial)
- Long acting agonists lowers fasting and postprandial glucose
  - Decreases A1c by 0.8-1.8% (~20-50 mg/dl)

- Most common side effects
  - Weight loss
  - Stomach upset
  - Caution in patients at risk for pancreatitis

## GLP-1 RA: Adverse Effects

### Gallbladder Disease
- Increased risk of bile duct and gallbladder disease possibly due to rapid weight loss
- Higher rates seen in the SCALE and LEADER studies
- Patient counseling
  - Diet modifications and warning signs of right upper quadrant pain that can radiate to the shoulder

### Thyroid Disease
- Thyroid C-cell tumors have occurred in rats and mice at clinically relevant exposures
  - Black Box Warning
  - Higher rates with increased dose and duration
  - Avoid use in multiple endocrine neoplasia syndrome type 2 or personal or family history of medullary thyroid carcinoma

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# Differences in GLP-1 agonists

<table>
<thead>
<tr>
<th></th>
<th>Exenatide BID</th>
<th>Lixisenatide</th>
<th>Liraglutide</th>
<th>Exenatide QW</th>
<th>Albiglutide</th>
<th>Dulaglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>5 &amp; 10 mcg BID (within 30-60 min of am/pm meal)</td>
<td>10 &amp; 20 mcg (within 60 min of same meal once daily)</td>
<td>0.6 mg initial, then ↑ to 1.2 &amp; 1.8 mg Once daily, anytime</td>
<td>2 mg weekly</td>
<td>30mg &amp; 50mg weekly</td>
<td>0.75 mg &amp; 1.5 mg weekly</td>
</tr>
<tr>
<td><strong>Max dose</strong></td>
<td>10 mcg BID</td>
<td>20 mcg daily</td>
<td>1.8 mg daily</td>
<td>2mg weekly</td>
<td>50 mg weekly</td>
<td>1.5 mg weekly</td>
</tr>
<tr>
<td><strong>Half- life</strong></td>
<td>2-4 hours</td>
<td>2-4 hours</td>
<td>13 hours</td>
<td>5 days</td>
<td>5 days</td>
<td>5 days</td>
</tr>
<tr>
<td><strong>Homology to GLP-1</strong></td>
<td>53%</td>
<td>50%</td>
<td>97%</td>
<td>53%</td>
<td>97%</td>
<td>90%</td>
</tr>
<tr>
<td><strong>Antibodies</strong></td>
<td>44%</td>
<td>69.8%</td>
<td>8.6%</td>
<td>44%</td>
<td>2.5%</td>
<td>2%</td>
</tr>
</tbody>
</table>

FPG = fasting plasma glucose; PPG = postprandial plasma glucose
Tips for Use

• Educate and monitor injection technique
• Discuss/prepare patient on how to minimize nausea, GI side effects
• Good combination with:
  – Metformin
  – TZD
  – SGLT-2i
  – Basal insulin
Insulin

- **Neurotransmitter Dysfunction**

- **Islet b-cell**
  - Impaired Insulin Secretion

- **Islet a-cell**
  - Increased Glucagon Secretion

- **GI Tract/Decreased Incretin Effect**

- **Increased Lipolysis**

- **Increased Glucose Reabsorption**

- **Decreased Glucose Uptake**

- **Increased Hepatic Glucose Production**

- **Neurotransmitter Dysfunction**

Pharmacokinetic Profile of Currently Available Basal Insulins

- Intermediate (NPH insulin)
- Long (Insulin detemir)
- Long (Insulin glargine)
- Ultralong (glargine U300)
- Ultralong degludec U100, U200

Time (h)

Plasma Insulin Levels
Concentrated Insulin Glargine (U-300)

- “Ultra long-acting” basal insulin
  - Smaller depot surface area
  - Reduced rate of absorption
- Relatively flat and prolonged PK/PD profiles
  - Half-life ~23 hours
  - Steady state in 4 days
  - Duration of action ≤ 36 hours
- Available only in pen
  - 450 units/pen (1.5 mL)
  - Maximum 80 units/injection
  - 3 pens per box
U-100 and U-200 Insulin Degludec

- Available only in a pen
  - U-200: 600 units/pen, max 160 units/inj
  - U-100: 300 units/pen, max 80 units/inj
- Can be used for patients on small and larger volumes of insulin
- Provides flatter and prolonged pharmacokinetic and pharmacodynamic profiles and more consistency
  - Duration of action >42 hours
  - Half-life ~25 hours
    - Detectable for at least 5 days
  - Steady state in 3-4 days

1. Garber AJ. Diabetes Obesity Metab; published online 31 Oct 2013.
Fixed Combination Products

Insulin glargine + lixisenatide (Soliqua™) – iGlarLixi

Insulin degludec + liraglutide (Xultophy®) - iDegLira
**Insulin + GLP-1 agonist**

**Insulin**
- GLP-1
- Impaired Insulin Secretion
- Increased Glucagon Secretion
- Increased Hepatic Glucose Production
- Neurotransmitter Dysfunction

**GLP-1**
- GI Tract/Decreased Incretin Effect
- Increased Lipolysis
- Decreased Glucose Uptake

**Hyperglycemia**

### Fixed Combination Products

**iGlarLixi — Administer within 1 hour before breakfast**
- Prime dose before every use (2 units)
- Starting dose
  - 15 units/5 mcg – previously treated with GLP-1RA or <30 units basal insulin
  - 30 units/10 mcg – previously treated with 30-60 units basal insulin
- Titrate by 2-4 units every week

**iDegLira — Administer once daily (anytime of day)**
- Prime dose before every use (priming symbol)
- Starting dose
  - 16 units/0.58 mcg
  - May be down titrated to 10 units/0.36 mcg
- Titrate by 2 units every 3-4 days

Comparison of Renal Considerations and CV Effects of DPP-4i, GLP-1 agonists and SGLT-2I
Renal Impairment

• Complicates treatment choices
  – Often result of poor glycemic control
  – Produces higher risk when using many medications
    • Hypoglycemia rate increases in CKD stage III-V
  – Can alter A1c interpretation
    • Shortens erythrocyte life span as eGFR decreases
    • Falsely lowers A1c values

Renal Impairment: Modified Algorithms

**eGFR 30-60 ml/min**
- Metformin (reduced dose)
  - DPP-4 (reduced dose), GLP-1 agonists, meglitinides
  - Pioglitazone, glipizide
  - Insulin

**eGFR <30 ml/min**
- DPP-4 (reduced dose), GLP-1 agonists, meglitinides
  - Pioglitazone, glipizide
  - Insulin

## GLP-1 Agonists

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drug/Dose</th>
<th>Reduce dose if:</th>
<th>Contraindicated if:</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 agonist</td>
<td>Exenatide IR: 5-10 mcg BID</td>
<td>---</td>
<td>Clcr &lt;30ml/min</td>
</tr>
<tr>
<td></td>
<td>ER: 2 mg weekly</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Liraglutide 0.6-1.8mg daily</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Lixisenatide 10-20 mcg daily</td>
<td>---</td>
<td>Clcr &lt; 15ml/min</td>
</tr>
<tr>
<td></td>
<td>Dulaglutide 0.75-1.5mg weekly</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Albiglutide 30-50 mg weekly</td>
<td>---</td>
<td>? &lt;15ml/min</td>
</tr>
</tbody>
</table>

### DPP-4i

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drug/Dose</th>
<th>Reduce dose if:</th>
<th>Contraindicated if:</th>
</tr>
</thead>
</table>
| DPP-4 inhibitors | **Sitagliptin**  
|                  | 25-100mg daily          | eGFR 30-50: 50mg daily <30: 25mg daily | ---                 |
|                  | **Saxagliptin**  
|                  | 2.5-5mg daily           | eGFR<50: 2.5mg daily              | ---                 |
|                  | **Alogliptin**  
|                  | 25mg daily              | eGFR 30-60: 12.5mg daily <30: 6.25mg daily | ---                 |
|                  | **Linagliptin**  
|                  | 5mg daily               | ---                              | ---                 |

# SGLT-2i

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drug/Dose</th>
<th>Reduce dose if:</th>
<th>Contraindicated if:</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT2 inhibitors</td>
<td>Canagliflozin 100-300 mg daily</td>
<td>eGFR 45-59: 100 mg daily</td>
<td>eGFR &lt;45ml/min</td>
</tr>
<tr>
<td></td>
<td>Dapagliflozin 5-10 mg daily</td>
<td>---</td>
<td>eGFR &lt;60ml/min</td>
</tr>
<tr>
<td></td>
<td>Empagliflozin 10-25 mg daily</td>
<td>---</td>
<td>eGFR &lt;45ml/min</td>
</tr>
</tbody>
</table>

Renal Protection

• **EMPA-REG OUTCOME**
  – Empagliflozin: 39% relative risk reduction in incident or worsening nephropathy compared to placebo

• **LEADER**
  – Liraglutide: 22% relative risk reduction in new onset or worsening kidney disease compared to placebo

## Cardiovascular Disease
(from AACE 2017)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Benefit</th>
<th>Neutral</th>
<th>Caution</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCVD</td>
<td>GLP-1 agonists</td>
<td>Metformin</td>
<td>SU</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TZD (stroke risk)</td>
<td>SGLT-2i</td>
<td>GLN</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>DPP-4i</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pramlintide</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>AGI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Failure</td>
<td>GLP-1 agonists</td>
<td>Metformin</td>
<td>DPP-4i</td>
<td>SU</td>
</tr>
<tr>
<td></td>
<td>SGLT-2i</td>
<td>AGI</td>
<td>TZD</td>
<td>GLN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pramlintide</td>
<td></td>
<td>Insulin</td>
</tr>
</tbody>
</table>

ASCVD = atherosclerotic cardiovascular disease
# Cardiovascular Disease – Clinical Trials

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drug</th>
<th>Impact on CVD</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 agonist</td>
<td>Exenatide</td>
<td><em>Ongoing trial</em></td>
<td>EXSCEL</td>
</tr>
<tr>
<td></td>
<td>Liraglutide</td>
<td>↓ Risk of CV death and total death</td>
<td>LEADER</td>
</tr>
<tr>
<td></td>
<td>Dulaglutide</td>
<td><em>Ongoing trial</em></td>
<td>REWIND</td>
</tr>
<tr>
<td></td>
<td>Albiglutide</td>
<td>No ↑ CV Risk</td>
<td>HARMONY program meta-analysis</td>
</tr>
<tr>
<td></td>
<td>Lixisenatide</td>
<td>No ↑ CV Risk</td>
<td>ELIXA</td>
</tr>
</tbody>
</table>

Adapted from: Handelsman Y. Endocrine Today. 2016
## Cardiovascular Disease – Clinical Trials

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drug</th>
<th>Impact on CVD</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT2 inhibitors</td>
<td>Canagliflozin</td>
<td>↓ Risk of CV death</td>
<td>CANVAS</td>
</tr>
<tr>
<td></td>
<td>Dapagliflozin</td>
<td><em>Ongoing trial</em></td>
<td>DECLARE-TIMI</td>
</tr>
<tr>
<td></td>
<td>Empagliflozin</td>
<td>↓ Risk of CV death</td>
<td>EMPA-REG</td>
</tr>
</tbody>
</table>

Adapted from: Handelsman Y. Endocrine Today. 2016
# Cardiovascular Disease – Clinical Trials

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drug</th>
<th>Impact on CVD</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP-4 inhibitors</td>
<td>Sitagliptin</td>
<td>No ↑ CV Risk, No ↑ HF hospitalization</td>
<td>TECOS</td>
</tr>
<tr>
<td></td>
<td>Saxagliptin</td>
<td>No ↑ CV Risk, ↑ HF hospitalization</td>
<td>SAVOR-TIMI</td>
</tr>
<tr>
<td></td>
<td>Alogliptin</td>
<td>No ↑ CV Risk</td>
<td>EXAMINE</td>
</tr>
<tr>
<td></td>
<td>Linagliptin</td>
<td><em>Ongoing trials</em></td>
<td>CAROLINA* CARMELINA</td>
</tr>
</tbody>
</table>

Adapted from: Handelsman Y. Endocrine Today. 2016
## Weight Considerations

<table>
<thead>
<tr>
<th>Gain</th>
<th>Neutral</th>
<th>Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>SU Meglitinides Insulin TZD</td>
<td>Metformin DPP-4 inhibitor AG inhibitor Bile acid sequestrants Dopamine agonist</td>
<td>GLP-1 agonist SGLT-2 inhibit Amylin mimetic</td>
</tr>
</tbody>
</table>

Clinical Inertia Leaves Patients Unnecessarily Exposed to Hyperglycemia

Median Time to Addition of Another OAD or Insulin

- Patients taking 1 OAD: 2.2 y; mean $A_1c$: 8.7%
- Patients taking 2 OADs: > 7.2 y*; mean $HbA_1c$: 9.1%
- Patients taking 3 OADs: > 7.1 y*; mean $HbA_1c$: 9.7%

*Indicates that < 50% of subjects have intensified treatment.
Mean time between $HbA_1c$ measurements was 6.2 to 7 months.
Combination & Co-formulation Considerations
Do NOT Use Combinations

- **Duplicate Mechanisms of Action**
  - Sulfonylurea + meglitinide
  - GLP-1 agonist + DPP4 inhibitor
  - 2 long acting/intermediate insulins
  - 2 rapid/short acting insulins
  - Sulfonylurea/meglitinide + rapid/short acting insulin
Effective Metformin Combinations

• **Need FPG lowering**
  - Met + SU
  - Met + TZD
  - Met + SGLT-2i
  - Met + GLP-1 agonist (long)
  - Met + Basal

• **Need PPG lowering**
  - Met + DPP-4i
  - Met + SGLT-2i
  - Met + GLP-1 agonist (short)
Effective Non-Met Combinations

- Modest A1c reduction (primarily PPG)
  - DPP-4i + SGLT-2i

- High A1c lowering (FPG + PPG)
  - GLP-1 agonist + TZD
  - GLP-1 agonist + SGLT-2i
  - GLP-1 agonist + Basal insulin
Key Points

• Diabetes guidelines encourage individualizing therapy

• Several factors guide drug therapy selection including:
  – patient safety,
  – blood glucose lowering potential
  – weight effects
  – cost
  – adherence
  – patient preferences
Key Points

• Metformin is currently recommended as initial therapy for most patients with type 2 diabetes.
  – Although, most patients will require additional therapy, particularly as the disease progresses.

• Newer medications offer additional treatment options with other positive effects

• Liraglutide and empagliflozin have cardiovascular benefits.
  • More data on other (newer) drugs to come soon
Thank you for your participation.

What questions can I answer for you?

scorne@midwestern.edu