The Role of Combination or Co-formulation Products in the Treatment of Type 2 Diabetes

Jennifer M. Trujillo, PharmD, FCCP, BCPS, CDE, BC-ADM
University of Colorado
Skaggs School of Pharmacy and Pharmaceutical Sciences

Susan Cornell, PharmD, CDE, FAPhA, FAADE
Midwestern University Chicago College of Pharmacy
Target Audience: Pharmacists
ACPE#: 0202-0000-18-053-L01-P
Activity Type: Application-based
Disclosures

Dr. Trujillo serves on an advisory board for Sanofi. Dr. Cornell serves on an advisory board and speakers bureau for Novo Nordisk.

The American Pharmacists Association is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.
Learning Objectives

1. Review updates to the 2018 American Diabetes Association Standards of Medical Care in Diabetes related to the use of combination therapy or co-formulated products.
2. Describe the evidence that supports a physiologic approach to treatment intensification using combination or co-formulation products.
3. Discuss contraindications and side effect considerations when recommending co-formulated therapy for glycemic control.
4. Given a patient case, select among available co-formulation treatment options for add-on therapy.
1. Assessment Question

Which of the following medications is recommended by the American Diabetes Association to be used in combination with metformin in a patient with hyperglycemia and established atherosclerotic cardiovascular disease (ASCVD)?

A. Glyburide  
B. Pioglitazone  
C. Empagliflozin  
D. Sitagliptin
2. Assessment Question

Early treatment of type 2 diabetes with combination therapy:

A. May cause beta-cell failure due to overtreatment
B. Should be avoided due to the risk of hypoglycemia
C. Has been shown to be more effective than sequential intensification that is currently recommended
D. May be beneficial because it targets multiple physiologic defects but has not been shown to be more effective than sequential intensification
3. Assessment Question

Which of the following combination therapies can be used in a patient with renal impairment that has an eGFR $\leq 30$ mL/minute/1.73?

A. Ertugliflozin and sitagliptin
B. Liraglutide and degludec
C. Metformin and glipizide
D. Metformin and pioglitazone
4. Assessment Question

Which of the following is not a recommendation combination due to duplicate mechanism of action?

A. Dulaglutide and sitagliptin
B. Empagliflozin and linagliptin
C. Lixisenatide and glargine
D. Metformin and pioglitazone
Combination or co-formulation products

- 50% of Americans take at least two medications

- Advantages
  - Adherence
  - Cost
  - Pill burden
  - Better disease control

- Disadvantages
  - Dose limitations/Lack of flexibility
  - Side effect sense
Let’s Play
JEOPARDY
Which combination is it?? | A physiologic approach | What do the guidelines say?
---|---|---
100 | 100 | 100
200 | 200 | 200
300 | 300 | 300

Double Jeopardy
This oral co-formulation product approved in 2015 was the first-in-class to include a combination of an SGLT-2 inhibitor and a DPP-4 inhibitor.

A. Degludec + liraglutide (Xultophy®)
B. Empagliflozin + linagliptin (Glyxambi®)
C. Cangliflozin + alogliptin (Canlogin®)
<table>
<thead>
<tr>
<th>Metformin +</th>
<th>Glyburide</th>
<th>Glucovance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glipizide</td>
<td>Metaglip</td>
<td></td>
</tr>
<tr>
<td>Repaglinide</td>
<td>PrandiMet</td>
<td></td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Actoplus Met</td>
<td></td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>Avandamet</td>
<td></td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>Janumet or XR</td>
<td></td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>Kombiglyze XR</td>
<td></td>
</tr>
<tr>
<td>Alogliptin</td>
<td>Kazano</td>
<td></td>
</tr>
<tr>
<td>Linagliptin</td>
<td>Jentadueto or XR</td>
<td></td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>Synjardy or XR</td>
<td></td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>Invokamet or XR</td>
<td></td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>Xigduo XR</td>
<td></td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Glimepiride</td>
<td>Duetact</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>Glimepiride</td>
<td>Avandryl</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Alogliptin</td>
<td>Oseni</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>Linagliptin</td>
<td>Glyxambi</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>Saxagliptin</td>
<td>Qtern</td>
</tr>
<tr>
<td>Insulin glargine U-100</td>
<td>Lixisenatide</td>
<td>Soliqua</td>
</tr>
<tr>
<td>Insulin degludec U-100</td>
<td>Liraglutide</td>
<td>Xultophy</td>
</tr>
</tbody>
</table>
Which combination is it?: 200

The most commonly prescribed three drug combination pill includes these three generic medications used to treat diabetes, hypertension, and dyslipidemia.

A. Glipizide + lisinopril + simvastatin
B. Metformin + amlodipine + atorvastatin
C. Metformin + lisinopril + atorvastatin
## Top 5 combination products

<table>
<thead>
<tr>
<th>Rank</th>
<th>2-drug combinations</th>
<th>3-drug combinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lisinopril Atorvastatin</td>
<td>Metformin Lisinopril Atorvastatin</td>
</tr>
<tr>
<td>2</td>
<td>Lisinopril Metformin</td>
<td>Clopidogrel Lisinopril Atorvastatin</td>
</tr>
<tr>
<td>3</td>
<td>Amlodipine Lisinopril</td>
<td>Glipizide Metformin Lisinopril</td>
</tr>
<tr>
<td>4</td>
<td>Alprazolam Amphetamine salt combo</td>
<td>Atorvastatin Lisinopril Amlodipine</td>
</tr>
<tr>
<td>5</td>
<td>Amphetamine salt combo</td>
<td>Lisinopril Amlodipine HCTZ</td>
</tr>
<tr>
<td></td>
<td>Amphetamine salt combo XR</td>
<td></td>
</tr>
</tbody>
</table>
Which combination is it?: 300

This injectable co-formulation includes a short-acting GLP-1 receptor agonist and a basal insulin.

A. Insulin glargine U100 + lixisenatide (Soliqua®)
B. Insulin glargine U100 + liraglutide (Lanvicta®)
C. Insulin degludec U100 + liraglutide (Xultophy®)
Injectable Fixed-Ratio Combinations

- **IDegLira (Xultophy 100/3.6)**
  - Insulin degludec (basal insulin) + Liraglutide (GLP-1 RA)
  - Fixed ratio: Each dose step = 1 unit insulin degludec + 0.036 mg liraglutide
  - Indication: Type 2 diabetes inadequately controlled on basal insulin (<50 units/day) or liraglutide
  - Starting dose 16 units (16 units IDeg and 0.58 mg Lira)
  - Max dose 50 units (50 units IDeg and 1.8 mg Lira)

- **iGlarLixi (Soliqua 100/33)**
  - Insulin glargine (basal insulin) + Lixisenatide (GLP-1 RA)
  - Fixed ratio: Each dose step = 3 units insulin glargine + 1 μg lixisenatide
  - Indication: Type 2 diabetes inadequately controlled on basal insulin (<60 units/day) or lixisenatide
  - Starting dose if on <30 units/day of basal insulin
    - 15 units (15 units iGlar and 5 μg Lixi)
  - Starting dose if on 30-60 units/day of basal insulin
    - 30 units (30 units iGlar and 10 μg Lixi)
  - Max dose 60 units (60 units iGlar and 20 μg Lixi)
Using combination therapy early on in the diabetes disease process may help preserve the function of these cells.

A. Beta cells  
B. F cells  
C. Delta cells
Pathophysiology of Type 2 Diabetes

↓ Insulin Secretion
  • sulfonylureas

HYPERGLYCEMIA

↑ Hepatic Glucose Output
  • metformin

↑ Insulin Resistance
  • thiazolidinediones
Natural History of T2D: β-cell function

A Physiologic Approach: 200

The combination of these two drug classes improves glycemic control and decreases weight by increasing urinary glucose excretion, increasing glucose dependent insulin secretion, decreasing inappropriate glucagon secretion, slowing gastric emptying, and increasing satiety.

A. DPP4 inhibitors + TZDs
B. SGLT2 inhibitors + DPP4 inhibitors
C. SGLT2 inhibitors + GLP1 receptor agonists
Pathophysiology of Type 2 Diabetes

- GI Tract: ↓ GLP-1 secretion; ↑ rate of glucose absorption; Abnormal microbiota
- Pancreas: ↓ β-cell function, ↓ β-cell mass, ↓ Amylin
- Brain: ↑ appetite, ↓ morning dopamine surge, ↑ sympathetic tone
- Liver: ↑ glucose production
- Muscle: ↓ peripheral muscle uptake
- Adipose: ↑ lipolysis

Hyperglycemia due to ↓ Insulin, ↑ Glucagon

- Kidney: Upregulation of SGLT-2, ↑ glucose reabsorption
GLP-1 RAs: Actions on Target Tissues

- **GLP-1**
  - **Pancreas**
    - ↑Glucose-dependent insulin secretion
    - ↓Glucose-dependent glucagon secretion
  - **Stomach**
    - ↓Gastric emptying
  - **Brain**
    - ↑Satiety

---

Food → Gut ↓ Glucose ↓ Weight

---

GLP-1 → Inactive GLP-1

- **t_{1/2} = 1–2 min**
- **DPP-4**
DPP-4 inhibitors: Actions on Target Tissues

- **GLP-1**
  - Inactive
  - \( t_{1/2} = 1-2 \text{ min} \)

- **Food** → **Gut** → **GLP-1** → **Pancreas**
  - \( \uparrow \text{Glucose-dependent insulin secretion} \)
  - \( \downarrow \text{Glucose-dependent glucagon secretion} \)

- **Stomach**
  - \( \downarrow \text{Gastric emptying} \)

- **Brain**
  - \( \uparrow \text{Satiety} \)

- **↓ Glucose**
- **↓ Weight**
Renal Pathophysiology of Diabetes

Gluconeogenesis
- Postabsorptive state: 20-25%
- Postprandial state: ~60%
- Mediated by insulin

Insulin resistance → increased renal glucose production

Glucose reabsorption
- Mediated by SGLTs and GLUTs
- Increases linearly until the tubular maximum glucose reabsorptive capacity ($T_mG$) is reached

Increased $T_mG$ → increased glucose reabsorption

Wilding JP. Metabolism 2014;63:1228-37.
Renal Glucose Handling

SGLT-2 Inhibitors

- Inhibits glucose reabsorption
- Lowers renal glucose threshold
- Increases urinary glucose excretion
- Glucose loss
  - 80–100 g/day
  - 320–400 kcal/day
A Physiologic Approach: 300

This triple drug combination was found to be superior to the standard sequential treatment approach at lowering A1C and weight and hypoglycemia in patients with newly diagnosed type 2 diabetes.

A. Metformin + glipizide + pioglitazone
B. Metformin + exenatide + pioglitazone
C. Metformin + exenatide + insulin glargine
EDICT: Initial combination therapy

- **Methods:**
  - Drug-naïve, recently diagnosed patients with T2D
  - Initial combination therapy: metformin + pioglitazone + exenatide (n=106) versus Sequential add-on therapy: escalating dose of metformin followed by sequential addition of SU or insulin glargine (n=115)

- **Results**
  - Lower A1C (5.95 v 6.5%), less hypoglycemia (7.5 fold lower rate), and weight loss instead of weight gain (-1.2 v +4.1kg) with initial combination therapy compared to sequential add-on therapy

Combination diabetes drug regimens should:

- Have ability to achieve desired level of A1C lowering
- Correct underlying pathophysiologic defect, have complementary mechanisms and additive effects
- Preserve beta cell function to ensure durability
- Target insulin resistance
- Exert beneficial effects on ASCVD risk
- Be weight neutral or promote weight loss
- Be safe and not exacerbate underlying medical conditions

The American Diabetes Association guidelines recommend consideration of dual combination therapy *initially* in patients with an A1C greater than this.

A. 7%
B. 8%
C. 9%
ADA Guidelines: Antihyperglycemic Therapy in Adults with T2D

Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes - 2018. Diabetes Care 2018; 41 (Suppl. 1): S73-S85
At diagnosis, initiate lifestyle management, set A1C target, and initiate pharmacologic therapy based on A1C:

- **A1C is less than 9%, consider Monotherapy.**
- **A1C is greater than or equal to 9%, consider Dual Therapy.**
- **A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, consider Combination Injectable Therapy** (See Figure 8.2).
The American Diabetes Association guidelines recommend that one of these medications be added to metformin in patients with established ASCVD.

A. Empagliflozin or dapagliflozin
B. Empagliflozin or liraglutide
C. An SGLT-2 inhibitor or a GLP-1 receptor agonist
ADA Guidelines: Antihyperglycemic Therapy in Adults with T2D

Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes - 2018.
Diabetes Care 2018; 41 (Suppl. 1): S73-S85
ADA Guidelines: Antihyperglycemic Therapy in Adults with T2D

<table>
<thead>
<tr>
<th>ASCVD?</th>
<th>Yes:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Add agent proven to reduce major adverse</td>
</tr>
<tr>
<td></td>
<td>cardiovascular events and/or cardiovascular</td>
</tr>
<tr>
<td></td>
<td>mortality (see recommendations with * on p. S75 and Table 8.1)</td>
</tr>
<tr>
<td>No:</td>
<td>- Add second agent after consideration of drug-specific effects and patient factors (See Table 8.1)</td>
</tr>
</tbody>
</table>

Pharmacologic Approaches to Glycemic Treatment:
*Standards of Medical Care in Diabetes - 2018. Diabetes Care 2018; 41 (Suppl. 1): S73-S85*
CVOT Results to Date

- Overall safety in major adverse cardiovascular events
  - SAVOR TIMI 53 – saxagliptin
  - EXAMINE – alogliptin
  - TECOS - sitagliptin
  - ELIXA - lixisenatide
  - EXSCEL – exenatide XR

- Overall reduction in major adverse cardiovascular events
  - EMPA-REG OUTCOME – empagliflozin
  - LEADER – liraglutide
  - CANVAS – canagliflozin
  - SUSTAIN 6 - semaglutide

- Remaining questions
  - Generalizability – patient population
  - Mechanism
  - Potential additive effects with combinations

## CV Effects of Diabetes Medications

<table>
<thead>
<tr>
<th>ASCVD</th>
<th>CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Potential benefit</td>
</tr>
<tr>
<td>SGLT-2 inhibitors</td>
<td>Benefit (cana, empa)</td>
</tr>
<tr>
<td>GLP-1 RAs</td>
<td>Neutral (lixisenatide, exenatide XR)</td>
</tr>
<tr>
<td>GLP-1 RAs</td>
<td>Benefit (liraglutide)</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Neutral</td>
</tr>
<tr>
<td>TZDs</td>
<td>Potential benefit (pioglitazone)</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Neutral</td>
</tr>
<tr>
<td>Insulin</td>
<td>Neutral</td>
</tr>
</tbody>
</table>
In a patient who is maximized on basal insulin therapy but still has an elevated A1C, the American Diabetes Association guidelines recommend this as a next treatment step.

A. Add a GLP-1 receptor agonist  
B. Add sliding scale insulin  
C. Switch to Regular insulin U-500
ADA Guidelines: Antihyperglycemic Therapy in Adults with T2D

**Dual Therapy**

**Lifestyle Management + Metformin + Additional Agent**

- **ASCVD?**
  - **Yes:** Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations with * on p. 575 and Table 8.1)
  - **No:** Add second agent after consideration of drug-specific effects and patient factors (See Table 8.1)

- **A1C at target after 3 months of dual therapy?**
  - **Yes:** Monitor A1C every 3–6 months
  - **No:** Assess medication-taking behavior
    - Consider Triple Therapy

**Triple Therapy**

**Lifestyle Management + Metformin + Two Additional Agents**

Add third agent based on drug-specific effects and patient factors (See Table 8.1)

- **A1C at target after 3 months of triple therapy?**
  - **Yes:** Monitor A1C every 3–6 months
  - **No:** Assess medication-taking behavior
    - Consider Combination Injectable Therapy (See Figure 8.2)

**Combination Injectable Therapy**

(See Figure 8.2)
Combination Injectable Therapy in T2D

**Initiate Basal Insulin**
Usually with metformin +/- other noninsulin agent

- **Start**: 10 U/day or 0.1-0.2 U/kg/day
- **Adjust**: 10-15% or 2-4 units once or twice weekly to reach FBG target
- **For hypo**: Determine & address cause; if no clear reason for hypo, ↓ dose by 4 units or 10-20%

- If A1C not controlled, consider combination injectable therapy

**Add 1 rapid-acting insulin injection before largest meal**

- **Start**: 4 units, 0.1 U/kg, or 10% basal dose. If A1C <8%, consider ↓ basal by same amount
- **Adjust**: ↓ dose by 1-2 units or 10-15% once or twice weekly until SMBG target reached
- **For hypo**: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2-4 units or 10-20%

- If A1C not controlled, advance to basal-bolus

**Add GLP-1 RA**

- **If not tolerated or A1C target not reached, change to 2 injection insulin regimen**
- **Change to premixed insulin twice daily (before breakfast and supper)**

- **Start**: Divide current basal dose into ½ AM, ½ PM or ⅛ AM, ⅛ PM
- **Adjust**: ↓ dose by 1-2 units or 10-15% once or twice weekly until SMBG target reached
- **For hypo**: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2-4 units or 10-20%

- If A1C not controlled, consider changing to alternative insulin regimen

**Change to premixed analog insulin 3 times daily (breakfast, lunch, supper)**

- **Start**: Add additional injection before lunch
- **Adjust**: ↓ doses by 1-2 units or 10-15% once or twice weekly to achieve SMBG target
- **For hypo**: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2-4 units or 10-20%

- If goals not met, consider changing to alternative insulin regimen

**Add ≥2 rapid-acting insulin injections before meals (‘basal-bolus’)**

- **Start**: 4 units, 0.1 U/kg, or 10% basal dose/meal. If A1C <8%, consider ↓ basal by same amount
- **Adjust**: ↓ dose(s) by 1-2 units or 10-15% once or twice weekly to achieve SMBG target
- **For hypo**: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2-4 units or 10-20%

- If goals not met, consider changing to alternative insulin regimen
Combination Injectable Therapy in T2D

**Add 1 rapid-acting insulin injection before largest meal**

- **Start:** 4 units, 0.1 U/kg, or 10% basal dose. If A1C <8%, consider ↓ basal by same amount.
- **Adjust:** ↑ dose by 1-2 units or 10-15% once or twice weekly until SMBG target reached.
- **For hypo:** Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2-4 units or 10-20%.

If A1C not controlled, **advance to basal-bolus**

**Add GLP-1 RA**

- If not tolerated or A1C target not reached, change to 2 injection insulin regimen.

If goals not met, **consider changing to alternative insulin regimen**

**Change to premixed insulin twice daily (before breakfast and supper)**

- **Start:** Divide current basal dose into 1/3 AM, 1/3 PM or 1/2 AM, 1/2 PM.
- **Adjust:** ↑ dose by 1-2 units or 10-15% once or twice weekly until SMBG target reached.
- **For hypo:** Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2-4 units or 10-20%.

If A1C not controlled, **advance to 3rd injection**
**Algorithm for Adding/Intensifying Insulin**

**Start Basal (Long-Acting Insulin)**

- **A1C < 8%**
  - TDD: 0.1–0.2 U/kg
- **A1C > 8%**
  - TDD: 0.2–0.3 U/kg

**Insulin Titration every 2–3 days to reach glycemic goal:**
- **Fixed regimen:** Increase TDD by 2 U
- **Adjustable regimen:**
  - FBG > 180 mg/dL: add 20% of TDD
  - FBG 140–180 mg/dL: add 10% of TDD
  - FBG 110–139 mg/dL: add 1 unit
  - If hypoglycemia, reduce TDD by:
    - BG < 70 mg/dL: 10%–20%
    - BG < 40 mg/dL: 20%–40%

Consider discontinuing or reducing sulfonylurea after starting basal insulin (basal analogs preferred to NPH)

**Glycemic Goal:**
- <7% for most patients with T2D; fasting and premeal BG < 110 mg/dL; absence of hypoglycemia
- A1C and FBG targets may be adjusted based on patient’s age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk

**Intensify (Prandial Control)**

- **Add GLP-1 RA**
  - Or SGLT-2i
  - Or DPP-4i
- **Add Prandial Insulin**
  - Basal Plus 1, Plus 2, Plus 3
  - Basal Bolus
    - Begin prandial insulin before largest meal
    - If not at goal, progress to injections before 2 or 3 meals
      - Start: 10% of basal dose or 5 units
    - Basal Bolus
      - Begin prandial insulin before each meal
      - 50% Basal / 50% Prandial TDD 0.3–0.5 U/kg
      - Start: 50% of TDD in three doses before meals

**Insulin Titration every 2–3 days to reach glycemic goal:**
- Increase prandial dose by 10% or 1-2 units if 2-h postprandial or next premeal glucose consistently > 140 mg/dL
- If hypoglycemia, reduce TDD basal and/or prandial insulin by:
  - BG consistently < 70 mg/dL: 10%–20%
  - Severe hypoglycemia (requiring assistance from another person) or BG < 40 mg/dL: 20%–40%
GLP-1 Receptor Agonists + Basal Insulin

GLP-1 Agonists
- Fasting and postprandial glycemic control
- Weight reduction
- Low hypoglycemic risk
- GI adverse effects

Basal Insulin
- Fasting glycemic control
- Individualized dosing
- Hypoglycemic risk
- Weight gain
GLP-1 RAs + Basal Insulin

- Meta-analysis: 15 studies included
- GLP-1 RA + basal insulin vs. other treatments
- Variety of background therapies and active comparators
- Results
  - Improved mean reduction in A1C of -0.44% (95% CI, -0.60 to -0.29)
  - No increased relative risk of hypoglycemia (HR 0.99; 95% CI, 0.76–1.29)
  - Mean reduction in weight of -3.22 kg (95% CI, -4.90 to -1.54)
## Fixed-Ratio Combinations: Clinical Evidence

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>Treatment</th>
<th>Δ A1C From Baseline (%)</th>
<th>Δ Wt From Baseline (kg)</th>
<th>Hypoglycemia (%)</th>
<th>Nausea (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LixiLan-O (metformin ± 2nd OAD)</td>
<td>iGlarLixi</td>
<td>-1.6</td>
<td>-0.3</td>
<td>25.6</td>
<td>9.6</td>
</tr>
<tr>
<td></td>
<td>iGlar</td>
<td>-1.3</td>
<td>+1.1</td>
<td>23.6</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td>Lixisenatide</td>
<td>-0.9</td>
<td>-2.3</td>
<td>6.4</td>
<td>24</td>
</tr>
<tr>
<td>LixiLan-L (basal ± 2 OADs)</td>
<td>iGlarLixi</td>
<td>-1.1</td>
<td>-0.7</td>
<td>40</td>
<td>10.4</td>
</tr>
<tr>
<td></td>
<td>iGlar</td>
<td>-0.6</td>
<td>+0.7</td>
<td>42.5</td>
<td>0.5</td>
</tr>
<tr>
<td>DUAL-1 (metformin ± pioglitazone)</td>
<td>iDegLira</td>
<td>-1.9</td>
<td>-0.5</td>
<td>32</td>
<td>8.8</td>
</tr>
<tr>
<td></td>
<td>iDeg</td>
<td>-1.4</td>
<td>+1.6</td>
<td>39</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td>Liraglutide</td>
<td>-1.3</td>
<td>-3.0</td>
<td>7</td>
<td>19.7</td>
</tr>
<tr>
<td>DUAL-2 (basal + metformin ± SU)</td>
<td>iDegLira</td>
<td>-1.9</td>
<td>-2.7</td>
<td>24</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td>iDeg</td>
<td>-0.9</td>
<td>0</td>
<td>25</td>
<td>3.5</td>
</tr>
</tbody>
</table>

Double Jeopardy
That a “No-No”

What’s the problem?

It’s all in the timing.

<table>
<thead>
<tr>
<th>200</th>
<th>200</th>
<th>200</th>
</tr>
</thead>
<tbody>
<tr>
<td>400</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>600</td>
<td>600</td>
<td>600</td>
</tr>
</tbody>
</table>

Final Jeopardy
The renal function (mL/minute/1.73 m²) when metformin should be discontinued.

a. What is <60mL/minute/1.73 m²?
b. What is <450mL/minute/1.73 m²?
c. What is <30mL/minute/1.73 m²?
Metformin: Renal Impairment

- eGFR between 30 to 45 mL/minute/1.73 m².
  - Not recommended
- eGFR below 30 mL/minute/1.73 m²
  - Contraindicated

If a patient is already on metformin
- eGFR falls below 45 mL/minute/1.73 m²
  - Weigh benefits of continuation versus discontinuation.
- eGFR falls below 30 mL/minute/1.73 m²
  - Discontinue metformin
Renal Impairment Comparison

**eGFR 30-60 ml/min**
- Metformin (reduced dose)
- DPP-4 (reduced dose)
- GLP-1 agonists
- Meglitinides (low dose)
- TZDs
- Glipizide (low dose)
- Glimepiride (low dose)
- Insulin

**eGFR <30 ml/min**
- DPP-4 (reduced dose)
- GLP-1 agonists (some)
- Meglitinides (low dose)
- TZDs
- Glipizide (low dose)
- Glimepiride (low dose)
- Insulin

*Standards of Medical Care in Diabetes - 2018. Diabetes Care 2018; 41 (Suppl. 1): S73-S85*
### DPP-4i: Renal Impairment

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drug/Dose</th>
<th>Reduce dose if:</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP-4 inhibitors</td>
<td>Sitagliptin</td>
<td>eGFR 30-50: 50mg daily</td>
</tr>
<tr>
<td></td>
<td>25-100mg daily</td>
<td>eGFR &lt;30: 25mg daily</td>
</tr>
<tr>
<td></td>
<td>Saxagliptin</td>
<td>eGFR &lt;50: 2.5mg daily</td>
</tr>
<tr>
<td></td>
<td>2.5-5mg daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alogliptin</td>
<td>eGFR 30-60: 12.5mg daily</td>
</tr>
<tr>
<td></td>
<td>25mg daily</td>
<td>eGFR &lt;30: 6.25mg daily</td>
</tr>
<tr>
<td></td>
<td>Linagliptin</td>
<td>No dose adjustment required</td>
</tr>
<tr>
<td></td>
<td>5mg daily</td>
<td></td>
</tr>
</tbody>
</table>
# SGLT-2i: Renal Impairment

<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</td>
<td>eGFR 45-59: 100 mg daily</td>
<td>eGFR &lt;45ml/min</td>
</tr>
<tr>
<td></td>
<td>100-300 mg daily</td>
<td>100 mg daily</td>
<td></td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>Not recommended if eGFR 30-60</td>
<td>eGFR &lt;30ml/min</td>
<td></td>
</tr>
<tr>
<td>5-10 mg daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>---</td>
<td></td>
<td>eGFR &lt;30ml/min</td>
</tr>
<tr>
<td>10-25 mg daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ertugliflozin</td>
<td>Not recommended if eGFR 30-60</td>
<td>eGFR &lt;30ml/min</td>
<td></td>
</tr>
<tr>
<td>5-15 mg daily</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## GLP-1 Agonists: Renal Dosing

<table>
<thead>
<tr>
<th>Renal dosing</th>
<th>Exenatide (Byetta)</th>
<th>Lixisenatide (Lyxumia)</th>
<th>Liraglutide (Victoza)</th>
<th>Exenatide QW (Bydureon)</th>
<th>Albiglutide (Tanzeum)</th>
<th>Dulaglutide (Trulicity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30 not rec</td>
<td>&lt; 15 avoid</td>
<td>No adjustment</td>
<td>&lt;30 not rec</td>
<td>&lt;15 no recommendation</td>
<td>No adjustment</td>
<td></td>
</tr>
<tr>
<td>15–59 use caution and monitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
That a “No-No” - $400

The secretagogue combination that should not be used.

a. What is glyburide and metformin?
b. What is glipizide and sitagliptin?
c. What is glimipreride and a meglitinide?
Sulfonylureas and Meglitinides have same mechanism of action

That a “No-No” - $600

The incretin agents (classes) that should not be used in combination.

a. What is dulaglutide and metformin?
b. What is empagliflozin and sitagliptin?
c. What is liraglutide and a linagliptin?
GLP-1 target defects:

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

DPP-4i target defects:

- **Islet b-cell**: Impaired Insulin Secretion
- **Islet a-cell**: Increased Glucagon Secretion
- **GI tract**: Decreased Incretin Effect
- **Increased Glucose Reabsorption**
- **Increased Glucagon Secretion**
- **Increased Hepatic Glucose Production**
- **Increased Lipolysis**
- **Decreased Glucose Uptake**

**Neurotransmitter**

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
This is post-market FDA reported adverse effect of DPP-4 inhibitors.

a. What is hypoglycemia?
b. What is joint pain?
c. What is nausea?
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

[https://www.fda.gov/Drugs/DrugSafety/ucm459579.htm](https://www.fda.gov/Drugs/DrugSafety/ucm459579.htm)


DPP4 Inhibitors: Adverse Effects and Tips

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

- Best used for patient with A1c near normal
  - Minimal A1c lowering
  - PPG target

- Good combination with:
  - Metformin
  - SGLT-2i
# DPP-4 Inhibitors: Comparisons

<table>
<thead>
<tr>
<th>Dose/ frequency</th>
<th>sitagliptin</th>
<th>saxagliptin</th>
<th>linagliptin</th>
<th>alogliptin</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg once daily</td>
<td>0.6%</td>
<td>0.7%</td>
<td>0.4%</td>
<td>0.8%</td>
</tr>
<tr>
<td>5 mg once daily</td>
<td>0.7%</td>
<td>1.2%</td>
<td>0.7%</td>
<td>0.9%</td>
</tr>
<tr>
<td>25 mg once daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Efficacy (A1C lowering): monotherapy | ↓ 0.6% | ↓ 0.7% | ↓ 0.4% | ↓ 0.8% |
| Efficacy (A1C lowering): combination therapy | ↓ 0.7% | ↓ 1.2% | ↓ 0.7% | ↓ 0.9% |

| Approximate ex Vivo DPP-4 Inhibition, % (maximum) | 97 | 80 | 80 | 90 |

What's the problem: 400

This is NOT a post-market FDA reported adverse effect of SGLT-2 inhibitors.

a. What is bone loss?
b. What is ketoacidosis?
c. What is pancreatitis?
## SGLT-2i: Post Market - Adverse Effects

<table>
<thead>
<tr>
<th>Bone Loss</th>
<th>Acute Kidney Injury</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>Urosepsis</th>
<th>Diabetic Ketoacidosis</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>

SGLT-2i: Adverse Effects and Tips

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

- 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

What's the problem: 600

This is a post-market FDA reported adverse effect of GLP-1 agonists.

a. What is gall bladder disease?
b. What is hair loss?
c. What is heart failure?
### 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

GLP-1 agonists: Adverse Effects and Tips

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

- 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
## 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>30 mg &amp; 50 mg 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>2 mg 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
It’s all in the timing: 200

The best time to inject ultra long-acting basal insulins, such as Glargine U-300 and Degludec U-100 or U-200.

a. What is any time of day, with or without food?
b. What is in the morning before breakfast?
c. What is in the evening near bedtime?
Pharmacokinetic Profiles of Ultra Long-Acting Basal Insulins

Flood TM. *J Fam Pract.* 2007; 56(suppl 1):S1-S12.
After injecting NPH insulin, this is the time a patient is at greatest risk of experiencing hypoglycemia.

a. What is 2-3 hours after the dose?
b. What is 6-8 hours after the dose?
c. What is NPH has a low risk of hypoglycemia?
Pharmacokinetic Profile of Basal Insulins

Intermediate (NPH)

Flood TM. *J Fam Pract*. 2007; 56(suppl 1):S1-S12.
It’s all in the timing: 600

This fixed dose combination product must be dosed 30 minutes prior to the first meal if the day.

a. What is Ertugliflozin/Sitagliptin?
b. What is IDeqLira?
c. What is IGlarLixi?
Fixed Combination Products

**IGlarLixi**
- Administer once daily, 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, any time 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

Package insert: Soliqua. Package insert: Xultophy
Insulin + GLP-1 agonist

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

**Neurotransmitter Dysfunction**
<table>
<thead>
<tr>
<th>Agent</th>
<th>Initial Dose (Duration)</th>
<th>Regular Dose</th>
<th>Dose Frequency and Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide</td>
<td>5 μg (1 month)</td>
<td>5 or 10 μg</td>
<td>Twice daily; given within 60-min period before morning and evening meals (or before 2 main meals of day, ~6 h or more apart)</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>10 µg (2 weeks)</td>
<td>20 µg</td>
<td>Once daily, given within 60-min period before morning meal.</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>0.6 mg (1 week)</td>
<td>1.2 or 1.8 mg</td>
<td>Once daily at any time of day (with or without meals)</td>
</tr>
</tbody>
</table>
| Exenatide extended release     | 2 mg                   | 2 mg         | • Once weekly at any time of day (with or without meals)  
• If a dose is missed, should be administered as soon as possible if there are ≥3 d until next scheduled dose |
| Albiglutide                    | 30 mg                  | 30 or 50 mg  |                                                                                          |
| Dulaglutide                    | 0.75 mg                | 0.75 or 1.5 mg |                                                                                          |
Patient Case
Case #1: TP

- TP is a 58-year-old Hispanic-American male returning to his primary care clinic for routine follow-up. He has had T2D for 1 year, hypertension and dyslipidemia for 3 years.

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

- SMBG:
  - FBG three times a week
    - average 155 mg/dL (range 130-199 mg/dL)
Case #1: TP

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 3 grown children. His wife does the cooking.

Physical Exam, Vitals & Labs

- A1C 8.2%
- Weight - 194 lb
- BMI - 28 kg/m²
- BP - 132/80 mmHg
- HR - 70 bpm
- Lipid panel – WNL
- SCr - 1.0 mg/dL
- eGFR - > 100 mL/min/1.73 m²
What pharmacotherapy would you recommend adding to TP’s metformin?

A. DPP-4 inhibitor
B. SGLT-2 inhibitor
C. GLP-1 receptor agonist
D. Basal Insulin
E. SGLT-2i + DPP-4i combo
F. GLP-1 agonist/basal Insulin combo
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/protection
    - ASCVD profile
    - Hypoglycemia risk
  - Ease of medication administration
    - Side effect profile
  - Renal impairment
  - Cost, available medication coverage
## 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 inhibitor 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 A₁c: 8.7%
- Patients taking 2 OADs: > 7.2 y*; mean HbA₁c: 9.1%
- Patients taking 3 OADs: > 7.1 y*; mean HbA₁c: 9.7%

*Indicates that < 50% of subjects have intensified treatment. Mean time between HbA₁c measurements was 6.2 to 7 months. Khunti K, et al. Diabetes Care. 2013;36:3411-3417.

OAD = oral antidiabetes drug
Considerations for TP

- TP has had diabetes for 1 year
  - Aggressive therapy and good BG is warranted
- A1c goal < 7% would be reasonable
  - A1c needs ~1.2% lowering
    - Needs FPG and PPG lowering

- Adverse effects must be considered
  - Weight loss would be ideal, weight neutral at best
  - Risk of hypoglycemia must be considered, especially considering is inconsistent eating patterns
  - CV protection is warranted
## Possible Pharmacotherapy for TP

<table>
<thead>
<tr>
<th></th>
<th>Efficacy</th>
<th>Weight Effect</th>
<th>Hypoglycemia</th>
<th>CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP-4 Inhibitor</td>
<td>Intermediate</td>
<td>Neutral</td>
<td>Low risk</td>
<td>Neutral</td>
</tr>
<tr>
<td>SGLT-2 inhibitor</td>
<td>Intermediate</td>
<td>Loss</td>
<td>Low risk</td>
<td>benefit</td>
</tr>
<tr>
<td>GLP-1 Agonist</td>
<td>High</td>
<td>Loss</td>
<td>Low risk</td>
<td>Yes</td>
</tr>
<tr>
<td>Basal insulin</td>
<td>High</td>
<td>Gain</td>
<td>Low risk</td>
<td>Neutral</td>
</tr>
<tr>
<td>SGLT-2i/DPP4i</td>
<td>Intermediate</td>
<td>Loss</td>
<td>Low risk</td>
<td>Benefit</td>
</tr>
<tr>
<td>GLP-1/Basal insulin</td>
<td>High</td>
<td>Loss/neutral</td>
<td>Low risk</td>
<td>Benefit</td>
</tr>
</tbody>
</table>
Take Away Message

- Combination therapy is often warranted to properly manage T2D.
  - Pharmacist need to watch for clinical inertia
- Various co-formulations are available to enhance medication adherence.
  - Effective combination therapy needs to target different mechanisms (defects in T2D).
- Drugs that support CVD safety or benefit should be considered for patients with T2D and ASCVD.
Final Jeopardy
The year insulin was first made available for patient use.

a. What is 1922?
b. What is 1938?
c. What is 1947?