NEW THERAPIES FOR TYPE 2 DIABETES MELLITUS

Ramya Embar Srinivasan MBBS
Learning objectives

• Understand the mechanism of action and side effects of the new anti-diabetic drugs
• Understand the scenarios where the newer agents could be beneficial.
• Anti-diabetic drugs that can be used in Chronic Kidney Disease
Objectives

• Incretin Therapy
• Sodium Glucose Co-Transporter 2 Inhibitors (SGLT-2 Inhibitors)
• Anti-diabetic drugs used in Chronic Kidney Disease
Drug Availability for Diabetes
1950 to present

Number of unique classes


Insulin
GLP-1 Receptor Agonists
DPP-4 Inhibitors
SGLT-2 Inhibitors
Bromocriptine/Colesevelam
Pramlintide
Repaglinide, Nateglinide
α-glucosidase inhibitors
Metformin
Thiazolidinediones
SUs - Glipizide, Glyburide, Glimepiride

1 2 3 4 5 6 7 8 9 10/11 12
**Lifestyle Modification**

**Entry A1c < 7.5%**

- **Monotherapy**
  - Metformin
  - GLP-1 RA
  - SGLT-2i
  - DPP-4i
  - AGi
  - TZD
  - SU/GLN

  If not at goal in 3 months proceed to Double Therapy

**Entry A1c ≥ 7.5%**

- **Dual Therapy**
  - GLP-1 RA
  - SGLT-2i
  - DPP-4i
  - AGi
  - TZD
  - Basal Insulin
  - Colesevelam
  - Bromocriptine QR

  If not at goal in 3 months proceed to Triple Therapy

**Entry A1c > 9.0%**

- **Triple Therapy**
  - GLP-1 RA
  - SGLT-2i
  - DPP-4i
  - AGi
  - TZD
  - Basal Insulin
  - Colesevelam
  - Bromocriptine QR

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

**Symptoms**

- **NO**
  - Dual Therapy
- **YES**
  - Insulin ± Other Agents

**Add or Intensify Insulin**

- Refer to Insulin Algorithm

**Legend**

- ✓: Adverse events or possible benefits
- ▼: Use with caution

**Progression of Disease**
### Healthy eating, weight control, increased physical activity, and diabetes education

#### Metformin

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

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

<table>
<thead>
<tr>
<th>Metformin +</th>
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<th>Metformin +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonyleurea</td>
<td>Thiazolidinedione</td>
<td>DPP-4 inhibitor</td>
<td>SGLT2 inhibitor</td>
<td>GLP-1 receptor agonist</td>
<td>Insulin (basal)</td>
<td></td>
</tr>
<tr>
<td>high</td>
<td>high</td>
<td>intermediate</td>
<td>intermediate</td>
<td>high</td>
<td></td>
<td></td>
</tr>
<tr>
<td>moderate risk</td>
<td>low risk</td>
<td>low risk</td>
<td>low risk</td>
<td>high risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>gain</td>
<td>gain</td>
<td>neutral</td>
<td>low risk</td>
<td>high</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hypoglycemia</td>
<td>edema, HF, fx</td>
<td>rare</td>
<td>GU, dehydration</td>
<td>gain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>low</td>
<td>low</td>
<td>high</td>
<td>high</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

If A1C target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

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<tr>
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<td>DPP-4 inhibitor +</td>
<td>SGLT2 inhibitor +</td>
<td>GLP-1 receptor agonist +</td>
<td>Insulin (basal) +</td>
<td></td>
</tr>
<tr>
<td>TZD</td>
<td>SU</td>
<td>SU</td>
<td>SU</td>
<td>SU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or DPP-4-i</td>
<td>or DPP-4-i</td>
<td>or DPP-4-i</td>
<td>or DPP-4-i</td>
<td>or DPP-4-i</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or SGLT2-i</td>
<td>or SGLT2-i</td>
<td>or SGLT2-i</td>
<td>or SGLT2-i</td>
<td>or SGLT2-i</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or GLP-1-RA</td>
<td>or GLP-1-RA</td>
<td>or GLP-1-RA</td>
<td>or GLP-1-RA</td>
<td>or GLP-1-RA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or Insulin</td>
<td>or TZD</td>
<td>or TZD</td>
<td>or TZD</td>
<td>or TZD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or Insulin</td>
<td>or Insulin</td>
<td>or Insulin</td>
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<td>or Insulin</td>
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<td></td>
</tr>
</tbody>
</table>

If A1C target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:

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

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If A1C target not achieved after ~3 months of combination injectable therapy:

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

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**Notes:**

1. Monotherapy
2. Dual therapy
3. Triple therapy
4. Combination injectable therapy
Objectives

- **Incretin Therapy**
  - GLP-1 Receptor Agonists (GLP-1 RA)
  - DiPetidyl Peptidase 4 (DPP-4) Inhibitors
- Sodium Glucose Co-Transporter 2 Inhibitors (SGLT-2 Inhibitors)
- Anti-diabetic drugs used in Chronic Kidney Disease
Question

- Incretins are gut derived hormones secreted in response to food intake
  - True
  - False
Incretins are gut derived hormones secreted in response to food intake

- True
- False
Incretins not only potentiate insulin secretion and suppress glucagon secretion, but also work on the feeding centers in the brain

- True
- False
Question

- Incretins not only potentiate insulin secretion and suppress glucagon secretion, but also work on the feeding centers in the brain
  - True
  - False
What is Incretin Therapy?

- Incretins are gut derived hormones
  - secreted in response to nutrients
  - potentiate insulin secretion
  - suppress glucagon secretion
- Two main types of incretins are:
  - GLP-1 – glucagon like peptide 1
  - GIP - glucose dependent insulino tropic peptide
- They are rapidly inactivated by dipeptidyl peptidase 4 (DDP4) enzyme
Food ingestion

GLP 1 and GIP release

GLP-1

Satiety

Delayed gastric emptying

DPP4 enzyme

Inactive GLP

Pancreas

Increased glucose uptake by muscle

Decrease gluconeogenesis is by liver

Increase Insulin release

Increased glucose uptake by muscle
GLP-1 Receptor Agonists (GLP-1 RA)

- **Short acting (<24 hrs)**
  - Exenatide BID (BYETTA)
- **Long acting (>24 hours)**
  - Liraglutide (VICTOZA) Once Daily
  - Dulaglutide OW (TRULICITY)
  - Exenatide OW (BYDUREON)
  - Albiglutide OW (TANZEUM)

OW = once weekly
Question

Long acting GLP1 RA decrease post prandial blood glucose more than fasting blood glucose

• True
• False
Long acting GLP1 RA decrease post prandial blood glucose more than fasting blood glucose

- True
- False
Question

Long acting GLP-1 RA cause more nausea and other GI side effects compared to the short acting GLP1 RA

• True
• False
Question

Long acting GLP1 RA cause more nausea and other GI side effects compared to the short acting GLP1 RA

- True
- False
Different effects of short and long acting GLP-1 RA

**Short acting GLP1 RA:**
- Slowed gastric motility – more nausea, but better post prandial glucose control

**Long acting GLP1 RA:**
- Modest slowing of gastric motility
- Tachyphylaxis
- Better fasting Blood glucose and A1C control
- Better with weight reduction
Question

Nausea improves with gradual dose titration with GLP-1 RA

- True
- False
Question

Nausea improves with gradual dose titration with GLP-1 RA

- True
- False
Question

GLP-1 RA are contraindicated in patients with a history of pancreatitis and cannot be used in patients who have developed pancreatitis while on treatment.

• True
• False
Question

GLP-1 RA are contraindicated in patients with a history of pancreatitis and cannot be used in patients who have developed pancreatitis while on treatment.

• True
• False
Question

GLP-1 RA are contraindicated in patients with family or personal history of medullary thyroid cancer

- True
- False
Question

GLP-1 RA are contraindicated in patients with family or personal history of medullary thyroid cancer

• True
• False
Liraglutide (Victoza) cannot be used if eGFR is <60ml/min
- True
- False
Question

• Liraglutide (Victoza) cannot be used if eGFR is <60ml/min
  - True
  - False
<table>
<thead>
<tr>
<th>Medication</th>
<th>In patients with impaired GFR</th>
<th>In dialysis patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 receptor agonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide</td>
<td>Not recommended with eGFR $&lt;30$ mL/min/1.73 m$^2$</td>
<td>Avoid use</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Not recommended with eGFR $&lt;60$ mL/min/1.73 m$^2$</td>
<td>Manufacturer does not recommend use (currently under study)</td>
</tr>
<tr>
<td>Albiglutide</td>
<td>No dose adjustment required</td>
<td>No clear guidelines exist—limited clinical experience in severe impairment of kidney function</td>
</tr>
</tbody>
</table>

Contraindications

- Exenatide (twice-daily and once-weekly formulations) should not be used in patients with
  a) GFR < 30 mL/min
  b) Severe gastrointestinal disease eg. gastroparesis

- GLP-1 RA should not be used in patients with:
  A personal or family history of
  a) medullary thyroid cancer
  b) multiple endocrine neoplasia 2A or 2B
Adverse effects

- GI side effects: nausea, vomiting, and diarrhea, and occur consistently 10 to 50 percent of patients
- Nausea may wane with duration of therapy and can be reduced with dose titration
- Nausea has been reported less frequently with once-weekly than with twice-daily administration (26 versus 50 percent)
- Meta-analysis of randomized trials comparing GLP-1 agonists with placebo or an active comparator experienced more nausea (8 to 40 percent more), diarrhea (3 to 118 percent more), and weight loss (-1.3 to -5.1 kg)
Adverse effects

• Pancreas — In patients with acute pancreatitis or history of pancreatitis GLP-1 agonists should not be started and should be discontinued if they are on therapy.
Candidates for therapy with GLP-1 RA

- In patients with A1C close to target (within 1 to 1.5% range from target)
- Weight loss is desired
- Avoidance of hypoglycemia is primary consideration
- In whom cost is not a major barrier
Question

GLP-1 RA can be used in combination with DPP-4 inhibitors.

• True
• False
GLP 1 RA can be used in combination with DPP4 inhibitors.

• True
• False
Question

GLP-1 RA are more potent compared to DPP-4 inhibitors.

- True
- False
Question

GLP-1 RA are more potent compared to DPP-4 inhibitors.

- True
- False
DPP4 inhibitors in combination with other oral agents or as Monotherapy

- Monotherapy decreases A1C by 0.54%
- Combination therapy with metformin decreases A1C by 0.58%
- Combination therapy with metformin and sulfonyl urea decreases A1C by 0.72%
- Typically used in patients with A1C levels < 8%
Summary

<table>
<thead>
<tr>
<th>GLP 1 Receptor Agonists</th>
<th>Dipeptidyl peptidase 4 inhibitors (DPP-4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide (Victoza) once daily</td>
<td>Sitagliptin (Januvia)</td>
</tr>
<tr>
<td>Exenatide (Byetta) BID</td>
<td>Saxagliptin (Onglyza)</td>
</tr>
<tr>
<td>Exenatide (Bydureon) Once weekly</td>
<td>Linagliptin (Tradjenta)</td>
</tr>
<tr>
<td>Albiglutide (Tanzeum) Once weekly</td>
<td></td>
</tr>
</tbody>
</table>
Objectives

- Incretin Therapy
- **Sodium Glucose Co-transporter 2 inhibitors (SGLT-2 inhibitors)**
- Anti-diabetic drugs and doses in Chronic kidney disease
Question

SGLT-2 inhibition
A) Increases Glycosuria
B) Causes weight loss
C) Reduces BP
D) Does not depend on beta cell function
E) All the above
Question

SGLT-2 inhibition
A) Increases Glycosuria
B) Causes weight loss
C) Reduces BP
D) Does not depend on beta cell function
E) All the above
FROM THE FOLLOWING ARTICLE:
SGLT2 inhibition — a novel strategy for diabetes treatment
Edward C. Chao & Robert R. Henry
Nature Reviews Drug Discovery 9, 551-559 (July 2010)
SGLT-2 inhibitors

- Inhibit glucose reabsorption in the proximal renal tubule
- Glycosuria results in decline in plasma glucose
- Can be used in patients with refractory type 2 diabetes
- Gluconeogenesis is increased in post prandial state in patients with type 2 diabetes
Question

In patients with type 2 Diabetes and mild CKD (eGFR 58), which of the following is an appropriate choice of therapy?
A) Dapagliflozin (farxiga) 5mg with no dose titration.
B) Canagliflozin (invokana) 100mg with no titration
C) Canagliflozin 100mg and titrated to 300mg daily if tolerated
D) Neither drug should be used
Question

In patients with type 2 Diabetes and mild CKD (eGFR 58), which of the following is an appropriate choice of therapy?

A) Dapagliflozin (farxiga) 5mg with no dose titration.

B) Canagliflozin (invokana) 100mg with no titration

C) Canagliflozin 100mg and titrated to 300mg daily if tolerated

D) Neither drug should be used
Oral diabetic agents and CKD

- **Dapagliflozin** (Farxiga) contraindicated in patients with eGFR <60
- **Canagliflozin** (Invokana) contraindicated in patients with eGFR <45
  - Dose is limited to 100mg daily if eGFR 45- <60
- **Empagliflozin** (Jardiance) contraindicated if eGFR <45
Question

Most common side effect from SGLT-2 inhibitors compared to placebo with metformin is:

A) Genital mycotic infections  
B) Headaches  
C) GI side effects  
D) Nasopharyngeal infection  
E) Urinary tract infection
Question

Most common side effect from SGLT-2 inhibitors compared to placebo with metformin is:

A) Genital mycotic infections
B) Headaches
C) GI side effects
D) Nasopharyngeal infection
E) Urinary tract infection
Adverse Events

- Genital mycotic infections: increased both in males and females
- Balanitis, especially in circumcised men
- Intravascular volume depletion (osmotic diuresis), more common in elderly and patients on high dose diuretics
- Electrolyte imbalance; hypermagesemia
- Hyperkalemia only seen in patients on ACE inhibitors or ARBs
- Bladder cancer (only with dapagliflozin 0.17% compared to 0.03% placebo)
- UTI – similar rates in both control and treatment group
Trials comparing SGLT-2 inhibitors with other anti-diabetic agents

- Metformin + SGLT-2 inhibitor vs Metformin + Glipizide
  - Mean A1C 7.7%
  - Decreased A1C similarly
  - Decreased weight (-3.2 kg vs +2.0 kg)
  - Less hypoglycemia
SGLT-2 inhibitors – Euglycemic Ketoacidosis

Rother et al SGLT 2 inhibitors may predispose to ketoacidosis  JCEM April 2015
Objectives

• Incretin Therapy
• Sodium Glucose Co-transporter 2 inhibitors (SGLT-2 inhibitors)

• Anti-diabetic drugs in Chronic Kidney Disease
Question

42 year female with type 2 diabetes with nephropathy and eGFR of 40. Her A1C is 8.2%. She is unable to afford many of her medications. She requests medication on the 4$ list, if possible. Given her kidney disease which of the following would you choose?

A) Glimepiride
B) Glipizide
C) Glyburide
Question

42 year female with type 2 diabetes with nephropathy and eGFR of 40. Her A1C is 8.2%. She is unable to afford many of her medications. She requests medication on the 4$ list, if possible. Given her kidney disease which of the following would you choose?

A) Glimepiride
B) Glipizide
C) Glyburide
Diabetic kidney disease: a report from an ADA Consensus Conference

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<thead>
<tr>
<th>Medication</th>
<th>In patients with impaired GFR</th>
<th>In dialysis patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second-generation sulfonylureas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glipizide</td>
<td>No dose adjustment required</td>
<td>No dose adjustment required</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>Initiate conservatively at 1 mg daily</td>
<td>Initiate conservatively at 1 mg daily</td>
</tr>
<tr>
<td>Glyburide</td>
<td>Avoid use</td>
<td>Avoid use</td>
</tr>
</tbody>
</table>

Oral diabetic agents in CKD

- **Sulfonylureas – Glipizide** is the drug of choice
- Glipizide is metabolized by the liver and primarily excreted in the urine as inactive metabolite
- Glyburide has weak active metabolites that are excreted in the urine
- Glimepiride is primarily metabolized by the liver, with renal excretion of active metabolite
Question

65 year male with DM type 2 for the past 5 years, A1C of 7.9% on Metformin 2gm and Sitagliptin 100mg daily, is found to have worsening kidney function with eGFR of 48, with creatinine of 1.4. What would you do to treat this patient?

A) Stop both metformin and sitagliptin
B) Decrease doses of metformin to 1gm and sitagliptin to 25mg daily
C) Decrease sitagliptin to 50mg daily and metformin to 1gm daily
D) Do nothing
65 year male with DM type 2 for the past 5 years A1C of 7.9% on Metformin 2gm and sitagliptin 100mg daily, is found to have worsening kidney function with eGFR of 48, with creatinine of 1.4. What would you do to treat this patient?

A) Stop both metformin and sitagliptin

B) Decrease doses of metformin to 1gm and sitagliptin to 25mg daily

C) Decrease sitagliptin to 50mg daily and metformin to 1gm daily

D) Do nothing
Oral diabetic agents in CKD

- **Metformin** – susceptible to drug accumulation and lactic acidosis
- The precise serum creatinine limits and eGFR thresholds for the safe use remain uncertain.
- In clinical practice, eGFR of >30 mL/min is used as a threshold for the safe use of metformin
- For a patient with an eGFR between 30 and 60 mL/min, metformin dose is halved
<table>
<thead>
<tr>
<th>Medication</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td>U.S. prescribing information states “do not use if serum creatinine ≥1.5 mg/dL in men, ≥1.4 mg/dL in women”</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Metformin</td>
<td>British National Formulary and the Japanese Society of Nephrology recommend cessation if eGFR &lt; 30 mL/min/1.73 m²</td>
<td></td>
</tr>
</tbody>
</table>

Diabetic kidney disease: a report from an ADA Consensus Conference
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<td></td>
<td></td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>100 mg daily if eGFR &gt;50 mL/min/1.73 m²</td>
<td>25 mg daily</td>
</tr>
<tr>
<td></td>
<td>50 mg daily if eGFR 30-50 mL/min/1.73 m²</td>
<td></td>
</tr>
<tr>
<td></td>
<td>25 mg daily if eGFR &lt;30 mL/min/1.73 m²</td>
<td></td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>5 mg daily if eGFR &gt;50 mL/min/1.73 m²</td>
<td>2.5 mg daily</td>
</tr>
<tr>
<td></td>
<td>2.5 mg daily if eGFR ≤50 mL/min/1.73 m²</td>
<td></td>
</tr>
<tr>
<td>Linagliptin</td>
<td>No dose adjustment required</td>
<td>No dose adjustment required</td>
</tr>
<tr>
<td>Alogliptin</td>
<td>25 mg daily if eGFR &gt;60 mL/min/1.73 m²</td>
<td>6.25 mg daily</td>
</tr>
<tr>
<td></td>
<td>12.5 mg daily if eGFR 30-60 mL/min/1.73 m²</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.25 mg daily if eGFR &lt;30 mL/min/1.73 m²</td>
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Diabetic kidney disease: a report from an ADA Consensus Conference
You note that your patient who is on liraglutide 1.8mg daily for diabetes has an eGFR of 55. What would you do for this patient?
A) Continue the liraglutide at the same dose
B) Decrease liraglutide dose in half
C) Stop liraglutide
Question

You note that your patient who is on liraglutide 1.8mg daily for diabetes has an eGFR of 55. What would you do for this patient?

A) Continue liraglutide at the same dose
B) Decrease liraglutide dose in half
C) Stop liraglutide
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<th>GLP-1 receptor agonists</th>
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<tbody>
<tr>
<td>Exenatide</td>
<td>Not recommended with eGFR &lt; 30 mL/min/1.73 m²</td>
<td>Avoid use</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Not recommended with eGFR &lt; 60 mL/min/1.73 m²</td>
<td>Manufacturer does not recommend use (currently under study)</td>
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<td>No clear guidelines exist—limited clinical experience in severe impairment of kidney function</td>
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</table>
Question

Your previous patient with eGFR of 55 in whom you stopped liraglutide, asks you regarding the new SGLT-2 inhibitors and their use in chronic kidney disease. What would you advise her?

A) Start canagliflozin 100mg daily
B) Start canagliflozin 300mg daily
C) Start Dapagliflozin at 5mg daily
D) Tell her the eGFR is too low and SGLT-2 inhibitors are contraindicated.
Question

Your previous patient with eGFR of 55 in whom you stopped liraglutide, asks you regarding the new SGLT-2 inhibitors and their use in chronic kidney disease. What would you advise him to do?

A) Start canagliflozin 100mg daily
B) Start canagliflozin 300mg daily
C) Start Dapagliflozin at 5mg daily
D) Tell her the eGFR is too low and SGLT-2 inhibitors are contraindicated
Oral diabetic agents and CKD

- **Dapagliflozin** (Farxiga) contraindicated in patients with eGFR <60

- **Canagliflozin** (Invokana) contraindicated in patients with eGFR <45ml/min/1.73m
  - Dose is limited to 100mg daily if eGFR 45 - <60

- **Empagliflozin** (Jardiance) contraindicated if eGFR <45
Retail Cost: 2015

Cost of a 10 ml vial ($)

<table>
<thead>
<tr>
<th></th>
<th>NPH</th>
<th>Glarg</th>
<th>Det</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barringer</td>
<td>40</td>
<td>75</td>
<td>40</td>
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<tr>
<td>Wal-Mart*</td>
<td>137</td>
<td>288</td>
<td>294</td>
</tr>
<tr>
<td>Target</td>
<td>125</td>
<td>284</td>
<td>269</td>
</tr>
</tbody>
</table>

Cost of 5 pens (15ml) ($)

<table>
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<tr>
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<th>NPH</th>
<th>Glarg</th>
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</thead>
<tbody>
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<tr>
<td>Wal-Mart</td>
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<tr>
<td>Target</td>
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<td>448</td>
<td>403</td>
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</tbody>
</table>

* Wal-Mart ReliOn brands are $25 per 10ml vial (Novolin-N, Novolin-R, & Novolin 70/30)
Summary

Goals are to limit weight gain, avoid hypoglycemia, lower risk of CV disease, improve beta cell function

<table>
<thead>
<tr>
<th>GLP 1 Receptor Agonists</th>
<th>Dipeptidyl peptidase 4 inhibitors (DPP-4)</th>
<th>SGLT-2 inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide (Victoza) once daily</td>
<td>Sitagliptin (Januvia)</td>
<td>Canagliflozin (Invokana)</td>
</tr>
<tr>
<td>Exenatide (Byetta) BID</td>
<td>Saxagliptin (Onglyza)</td>
<td>Dapagliflozin (Farxiga)</td>
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<tr>
<td>Exenatide (Bydureon) Once weekly</td>
<td>Linagliptin (Tradjenta)</td>
<td>Empagliflozin (Jardiance)</td>
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<tr>
<td>Albiglutide (Tanzeum) Once weekly</td>
<td></td>
<td></td>
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</tbody>
</table>