What’s New in Type 2 Diabetes Management

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Disclosures
• None

Learning Objectives
• Understand ADA guidelines for medication use in type 2 diabetes
• Discuss categories of medications used to treat type 2 DM
• Review data on glycemic benefit and CV outcomes
Case #1

- 71 yo male, type 2 DM, BMI 37
- Metformin monotherapy
- A1C ↑ 8.4%
- Hypoglycemia with glipizide, refuses injections
- Recently hospitalized with CHF, AKI diagnosed
- Creatinine 1.7mg/dl, CrCl 40

Questions:
Continuation of his metformin:
1. Is contraindicated based on his creatinine
2. Is safe based on his creatinine
3. Is contraindicated based on his Crcl
4. Is safe based on Crcl

Case #2

- 64 yo man, type 2 DM diagnosed 9 years ago
- Hx of hyperlipidemia, myocardial infarct (MI) 2 yrs ago
- Metformin, glimepiride, statin, ACEI, BB
- A1c 8.8%, weight 280#, BMI 44, CrCl 40
- Refuses insulin, good insurance, doesn't want to gain weight.
Case #2

• What would you consider for next line therapy?
  1. DPP4
  2. TZD
  3. SGLT2 inhibitor
  4. GLP1 agonist

**TYPE 2 DIABETES**
Many Different Classes of Therapy

- **Reduce Hepatic Glucose Production**
  - Metformin + XR

- **Enhance Insulin Secretion/Effect**
  - Sulfonylureas
    - glipizide, glyburide, glimepiride
    - Meglitinides (short acting)
    - Repaglinide (Prandin), nateglinide (Starlix)
  - Insulin injectable

- **Attenuate Glucose Absorption**
  - a-glucosidase inhibitors
    - Acarbose (Precose)
    - Miglitol (Glyset)

**Other:**
- Bromocriptine
- Salsalate
- Colesevelam
- Pramlintide (Symlin)

**Thiazolidinediones**
- Pioglitazone (Actos), Rosiglitazone (Avandia)

**SGLT 2 Inhibitors**
- Canagliflozin (Invokana), Dapagliflozin (Farxiga), Empagliflozin (Jardiance)

**Incretin Therapies**
- GLP Analogs
  - Exenatide (Byetta), XR weekly
  - Liraglutide (Victoza), Albiglutide (Treziba), Dulaglutide (Trulicity), Lisocabastide (Adlyzo)
- DPP4 Inhibitors
  - Sitagliptin (Januvia), Saxagliptin (Onglyza), Linagliptin (Tradjenta), Alogliptin (Nesina)

**Drugs for DM Management**
Metformin

• Basics:
  – Mechanism of action (MOA): ↓ hepatic glucose
  – A1c lowering: 1-1.5%
  – Low cost: $4/month

• Pros:
  – Experience, less hypoglycemia, ↓ CVD (UKPDS),

• Cons:
  – Diarrhea/cramping (?less with XR)
  – B12 deficiency, periodic testing recommended
  – Rare acidosis, associated with illness, hypoxia, CHF, renal insufficiency

FDA Revises Metformin Warnings

NEW Labeling- 2016

• Then: Don’t use in women Cr ≥ 1.4mg/dL, Men ≥ 1.5mg/dL
• Now: Check eGFR
  – Contraindicated if < 30mL/min/1.73m2
  – Don’t start if between 30-45mL/min/1.73m2
  – If eGFR < 45mL/min/1.73m2, consider ↓ dose
  – Follow annually, or more often if at risk

www.fda.gov/drugs/drugsafety/ucm493244.htm
Sulfonylureas

- **Basics:**
  - MOA: ↑ insulin secretion from beta cells
  - A1c lowering: 1-2%
  - Cost: Low ($4/month)
- **Pros:**
  - Effective + long-experience
  - ↓ Micro-vascular risk (UKPDS)
- **Cons:**
  - Hypoglycemia, weight gain, durability

More on Sulfonylureas

- **Beta cell burnout:**
  - ADOPT: lost glucose control at 45 months with metformin vs 33 months with glyburide
  - No difference-UKPDS
  - Over 6 yrs, 34% with SU needed insulin, c/w 27% with DPP4
- **Weight gain:** 2-5kg on average
- **Hypoglycemia:**
  - Higher risk in elderly, erratic eating, renal issues

Which SU to choose?

- Glipizide, glimepiride first-line
  - Glyburide increased risk for all hypoglycemia (1.44 RR ↑), 4.69x risk for severe lows Abrahamson MJ, Diab Care 2015
  - Also may inhibit ischemic preconditioning- in vitro studies Lee TM, JCEM 2003
- Consider rapid-acting meglitinides→ sulfa allergy, irregular meals hypoglycemia
  - $$$ however
Case # 1
• 71 yo male, type 2 DM, BMI 37
• Metformin monotherapy
• A1C ↑ 8.4%
• Hypoglycemia with glipizide, refuses injections
• Recently hospitalized with CHF, AKI diagnosed
• What would you add next to his therapy?

DPP 4’s
• Basics:
  – MOA: Inhibit metabolism of GLP1/GIP
  – A1C lowering: .5-1%
  – Cost: high ($370/month + coupon)
• Pros:
  – Less hypoglycemia, oral
  – Renal insufficiency → linagliptin (Tradjenta ®)
• Cons:
  – Angioedema/urticaria, pancreatitis, joint pain
  – ? ↑ CHF

<table>
<thead>
<tr>
<th></th>
<th>Sitagliptin (100 mg) v. Glipizide (5-20mg)</th>
<th>Saxagliptin (5 mg) v. Glipizide (5-20 mg)</th>
<th>Linagliptin (5 mg) v. Glimepiride (1-4 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1172</td>
<td>858</td>
<td>1551</td>
</tr>
<tr>
<td>Mean Age</td>
<td>57 yrs</td>
<td>58 yrs</td>
<td>60 yrs</td>
</tr>
<tr>
<td>Duration of DM</td>
<td>6.5 yrs</td>
<td>5.4 yrs</td>
<td>&gt;1 yr and ≤ 5 yrs: 40% &gt; 5 yrs: 52-54%</td>
</tr>
<tr>
<td>Mean A1C</td>
<td>7.7%</td>
<td>7.7%</td>
<td>7.7%</td>
</tr>
<tr>
<td>Follow-up</td>
<td>52 weeks</td>
<td>52 weeks</td>
<td>104 weeks</td>
</tr>
<tr>
<td>Reduction in A1C</td>
<td>-0.67% v. -0.67%</td>
<td>-0.74% v. -0.80%</td>
<td>-0.35% v. -0.53%</td>
</tr>
<tr>
<td>Hypoglycemia (%)</td>
<td>5.3% v. 34.1%</td>
<td>3.0% v. 36.3%</td>
<td>7% v. 36%</td>
</tr>
</tbody>
</table>

Lancet 2012; 380: 475-83
Diabetes Obes and Metabo 2007;9:194-205
Thiazolidinediones:

• Basics:
  – MOA: ↑ insulin sensitivity
  – A1c lowering: 1-1.5%
  – Cost: low ($30/month + coupon)

• Pros:
  – no hypoglycemia, durable
  – ↑HDL, ↓TG’s, ↓CVD events (PROactive), benefit in steatohepatitis

• Cons:
  – Fluid retention/CHF, weight gain, fractures, ↑LDL

Pioglitazone in Steatohepatitis

• 101 pts with pre-DM or dm, biopsy-proven nonalcoholic steatohepatitis (NASH)
  – Randomized to PBO or pioglitazone 45mg/d for 18 months

• 58% achieved ↓ score of liver disease
  – 51% with resolution of NASH

• Led to reduction in A1c, fasting insulin, AST/ALT, triglycerides

• Also noted: gain of 2.5 kg, no benefit with longer duration of treatment (up to 36 mos)

Cusi K. Annals IM 2016

Sodium-Glucose Co-transporter 2 Inhibitors (SGLT2I)
SGLT2-Inhibitors

- Basics:
  - A1c lowering: 0.5-1%
  - Cost: $300-400/month

- Pros:
  - Oral, less hypoglycemia, wt loss (1-4kg), BP ↓, CV benefit, renal protection

- Cons:
  - Genital infections, DKA, bone loss/fracture risk, volume loss, increased creatinine, ? Efficacy with renal insufficiency

Second-agent Considerations

<table>
<thead>
<tr>
<th>Medication</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonfonyurea</td>
<td>- Cheap, no PA needed - Lots of experience</td>
<td>- Hypoglycemia - Weight gain</td>
</tr>
<tr>
<td>DPP-4</td>
<td>- No hypoglycemia - Few side effects (pancreatitis)</td>
<td>- Cost $$ - Potency - Likely PA</td>
</tr>
<tr>
<td>TZD</td>
<td>- Beneficial with fatty liver - No hypoglycemia - Less $$</td>
<td>- Edema, weight gain - Durability</td>
</tr>
<tr>
<td>SGLT-2</td>
<td>- ↓ wt, BP - ↓ CV events/mortality - renal protection</td>
<td>- GU infections - Polyuria/vol loss - DKA - Cost</td>
</tr>
</tbody>
</table>

Find one from each class to get experience with:
- Glimepiride (SU), sitagliptin (DPP4), pioglitazone, empagliflozin (SGLT2)
**GLP-1 Medications**

**Basics:**
- MOA: ↑insulin secretion, ↓glucagon, slows gastric emptying, ↓satiety
- A1C lowering: 1-1.5%
- Cost: high ($580-650/month+coupon)

**Pros:**
- no hypoglycemia, weight loss, CV benefit

**Cons:**
- injectable, pancreatitis, GI side effects, medullary thyroid cancer in animals, renal issues (exenatide)

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**GLP-1 Weekly**

- Useful for reluctant injectors
- Equivalent benefit to daily dosing
  - Wt loss, A1c lowering, hypoglycemia, SE

**Choose based on:**
tolerability, cost, and what is on formulary!

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**Comparing GLP-1s: Head-to-Head Summary**

**Glycemic Control (A1C lowering):**
- Dulaglutide ≈ Liraglutide ≈ ExQW > Albiglutide ≈ ExBID
  - (-1.1% to -1.6%)
  - (-0.8% to -0.9%)

**Nausea/GI Side Effects:**
- ExBID > Liraglutide > Once weekly formulations
  - (35%)
  - (20%)
  - (9-14%)

- All agents associated with low rates of hypoglycemia
- Typical weight loss – 3-8 lbs, significant variability between patients
GLP-1s: safety concerns

- Thyroid Cancer
  - Medullary only
  - Based on rodent models, increased levels of calcitonin
  - Not seen in humans
  Take home: would not recommend using in patients with family/personal history of medullary thyroid cancer

- Pancreatitis, pancreatic cancer
  - Cancer – no causal relationship determined
  - Pancreatitis in clinical trials ~occurrence rate low
  - Patients with DM have ↑ risk of pancreatitis
  Take home: avoid in those with history of pancreatitis or risk factors (ie alcoholism, hypertriglyceridemia)

CV Outcomes in DM Medications

- Motivated by high prevalence of CV in diabetes + concerns raised by rosiglitazone
- FDA Guidance to Industry, 2008
  - Sponsors should demonstrate that new type 2 DM drugs should not result in unacceptable CV risk
  - Require inclusion of higher risk CV patients, be long enough to detect adverse CV effects, include in protocol and committees to evaluate

Smith RJ, Diabetes Care 2016

Completed CV Outcome Trials

<table>
<thead>
<tr>
<th>Trial, n of subjects</th>
<th>MACE*</th>
<th>Hosp for CHF</th>
<th>All-cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAVOR-TIMI (exenatide), n=10,492</td>
<td>1.02 (.89-1.12)</td>
<td><strong>1.27 (1.07-1.55)</strong></td>
<td>1.11 (.96-1.27)</td>
</tr>
<tr>
<td>EXAMINE (albiglutide), n=3650</td>
<td>.96 (.8-1.16)</td>
<td>1.19 (1.0-1.4)</td>
<td>.85 (1.7-1.09)</td>
</tr>
<tr>
<td>TECOS (albiglutide), n=14,071</td>
<td>.98 (.86-1.09)</td>
<td>1.0 (.83-1.2)</td>
<td>1.01 (1.01-1.14)</td>
</tr>
<tr>
<td>EMPA-REG (empagliflozin), n=11,020</td>
<td>.83 (.74-.94)</td>
<td>.95 (1.0-1.0)</td>
<td>.98 (1.01-1.02)</td>
</tr>
<tr>
<td>ELIXA (lixisenatide), n=6,068</td>
<td>1.02 (.89-1.17)</td>
<td>.96 (.82-1.16)</td>
<td>.94 (1.78-1.13)</td>
</tr>
<tr>
<td>LEDAER (tegliglutide), n=5046</td>
<td>.87 (.78-.97)</td>
<td>.87 (1.73-1.05)</td>
<td>.95 (1.74-1.07)</td>
</tr>
<tr>
<td>SUSTAIN 6 (exenatide), n=1,297</td>
<td>.74 (.58-.95)</td>
<td>1.11 (1.77-1.61)</td>
<td>1.05 (1.74-1.5)</td>
</tr>
</tbody>
</table>
**DPP4’s and CHF?**

- No increase noted in retrospective cohort of 376,677 pts comparing risks for CHF with saxagliptin/sitagliptin (Toh et al, Annals IM 2016)
- Explanations:
  - Chance finding, differences in studies/patients enrolled, background care provided, differences in drugs
- FDA Warning- April 2016
  - Consider d/c of saxagliptin and alogliptin in those who develop CHF

**Completed CV Outcome Trials**

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<td>SAVOR-TIMI (saxagliptin), n=10,492</td>
<td>1.00 (.89-1.12)</td>
<td>1.27 (.97-1.65)</td>
<td>1.11 (.96-1.27)</td>
</tr>
<tr>
<td>EXAMINE (alogliptin), n=3,380</td>
<td>0.96 (.8-1.16)</td>
<td>1.19 (.9-1.58)</td>
<td>.95 (.75-1.19)</td>
</tr>
<tr>
<td>TECCOS (sitagliptin), n=4,971</td>
<td>0.98 (.88-1.09)</td>
<td>1.0 (.85-1.2)</td>
<td>1.01 (.8-1.14)</td>
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<tr>
<td>EMPA-REG (empagliflozin), n=7020</td>
<td>.85 (.74-99)</td>
<td>.88 (.57-82)</td>
<td></td>
</tr>
<tr>
<td>LEADER (liraglutide), n=9,340</td>
<td>.87 (.78-97)</td>
<td>.87 (.73-1.05)</td>
<td>.85 (.74-97)</td>
</tr>
<tr>
<td>SUSTAIN 6 (semaglutide), n=3,297</td>
<td>.74 (.58-95)</td>
<td>1.11 (.77-1.61)</td>
<td>1.05 (.74-1.5)</td>
</tr>
</tbody>
</table>

**EMPA-REG OUTCOME Trial**

- 7028 patients, type 2 DM + CVD
  - Followed 3.1 years
  - Empagliflozin 10mg vs 25mg vs PBO
- Primary outcome: Composite CVD death, non-fatal MI, non-fatal stroke
  - 97% completed study
- With empagliflozin:
  - ↓ rates of death from CV causes, CHF admits, death from any cause
  - A1c ↓: 12 wks: -.54-.6%, 206 wks: -.24-.36%

Zinman B et al, NEJM 2015;373:2117
### SGLT-2’s Cardioprotective?

<table>
<thead>
<tr>
<th>Effect</th>
<th>Likelihood</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic actions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ BG</td>
<td>Unlikely</td>
<td>BG a weak CV risk factor, benefit of A1c on CVD takes 10 yrs</td>
</tr>
<tr>
<td>↓ fat oxidation or ketone</td>
<td>Unlikely</td>
<td>↑O2 demand per ATP generated</td>
</tr>
<tr>
<td>concentration</td>
<td>Unlikely</td>
<td>Modest changes</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Unlikely</td>
<td></td>
</tr>
<tr>
<td>Hemodynamic actions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ BP</td>
<td>Likely</td>
<td>Proven CV protection in prior studies</td>
</tr>
<tr>
<td>Diuretic effect</td>
<td>Likely</td>
<td>Proven against CHF in prior trials</td>
</tr>
<tr>
<td>Impaired arterial elasticity</td>
<td>Possible</td>
<td>? Some effect of empagliflozin</td>
</tr>
<tr>
<td>Direct effect on myocardium</td>
<td>Unlikely</td>
<td>No evidence</td>
</tr>
<tr>
<td>Decreased sympathetic tone</td>
<td>Possible</td>
<td>No ↑ in HR with ↓ in BP and volume</td>
</tr>
</tbody>
</table>

Abdul-Ghani M, Diab Care 2016

### EMPA-REG: Bottom Line

- The addition of empagliflozin is associated with lower CVD event rates and mortality
  - More trials to confirm whether this is class effect
- **Clinical Implication:** this trial shows meaningful effect on CVD events from using empagliflozin in addition to standard T2DM care and option should be individualized

### New label for Empagliflozin

```
INDICATIONS AND USAGE

JARDIANCE is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated:
- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus,
- to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease. (1)
```
Empagliflozin and Kidney Disease

- Secondary analysis of EMPA-REG
  - Does adding empagliflozin affect renal outcomes?
- Same population, eGFR > 30ml/min

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>RRR (95%CI)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>New/worsening nephropathy</td>
<td>48</td>
<td>76</td>
<td>37% (28-44)</td>
<td>15</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>42</td>
<td>65</td>
<td>36% (26-44)</td>
<td>18</td>
</tr>
<tr>
<td>Doubling Cr/EGFR&gt;45</td>
<td>5.5</td>
<td>9.7</td>
<td>44% (21-61)</td>
<td>89</td>
</tr>
<tr>
<td>Dialysis</td>
<td>1.0</td>
<td>2.1</td>
<td>55% (37-79)</td>
<td>304</td>
</tr>
</tbody>
</table>

Wanner C, NEJM 2016

Liraglutide and CV Outcomes

LEADER Trial:
9340 pts, followed for 3.8 yrs, randomized to liraglutide or placebo
NNT to prevent one event in 3 yrs was 66 (primary outcome), 98 (death)

LEADER vs EMPA-REG

<table>
<thead>
<tr>
<th></th>
<th>LEADER</th>
<th>NNT</th>
<th>EMPA-REG</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Comp Outcome</td>
<td>.87</td>
<td>53</td>
<td>.86</td>
<td>63</td>
</tr>
<tr>
<td>CV Death</td>
<td>.78</td>
<td>77</td>
<td>.62</td>
<td>46</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>-----</td>
<td>NS</td>
<td>-----</td>
<td>NS</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>-----</td>
<td>NS</td>
<td>-----</td>
<td>NS</td>
</tr>
<tr>
<td>Death-any cause</td>
<td>.85</td>
<td>72</td>
<td>.68</td>
<td>39</td>
</tr>
<tr>
<td>HF hosp</td>
<td>-----</td>
<td>NS</td>
<td>.65</td>
<td>72</td>
</tr>
</tbody>
</table>

NEJM 2015, 373:2117-2128; NEJM 2016;375:311-22

Slide courtesy of Abby Frye, PharmD
LEADER v. EMPA-REG

Slide courtesy of Abby Frye, PharmD

In-Progress CVD Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug</th>
<th>Planned #</th>
<th>Planned date</th>
</tr>
</thead>
<tbody>
<tr>
<td>CANVAS</td>
<td>Canagliflozin</td>
<td>4407</td>
<td>June 2017</td>
</tr>
<tr>
<td>CARMELINA</td>
<td>Linagliptin</td>
<td>8300</td>
<td>Jan 2018</td>
</tr>
<tr>
<td>EXCEL</td>
<td>Exenatide</td>
<td>14000</td>
<td>Jan 2018</td>
</tr>
<tr>
<td>ITCA 850</td>
<td>Exenatide</td>
<td>4000</td>
<td>July 2018</td>
</tr>
<tr>
<td>CAROLINA</td>
<td>Linagliptin</td>
<td>6000</td>
<td>Sept 2018</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>Dapagliflozin</td>
<td>17150</td>
<td>April 2019</td>
</tr>
<tr>
<td>REWIND</td>
<td>Dulaglutide</td>
<td>9622</td>
<td>April 2019</td>
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<tr>
<td>HARMONY</td>
<td>Albiglutide</td>
<td>9400</td>
<td>May 2019</td>
</tr>
<tr>
<td>CV OUTCOMES ETUGLIFLOZIN</td>
<td>Ertugliflozin</td>
<td>3900</td>
<td>Oct 2020</td>
</tr>
<tr>
<td>CV OUTCOMES OMARIGLIPTIN</td>
<td>Omaripliltin</td>
<td>4202</td>
<td>Dec 2020</td>
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</table>

Smith RJ, Diab Care 2016

Third Agent Options

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 Agonist</td>
<td>- Wt loss</td>
<td>- Cost</td>
</tr>
<tr>
<td></td>
<td>- No hypoglycemia</td>
<td>- Injectable</td>
</tr>
<tr>
<td></td>
<td>- CV benefit</td>
<td>- Pancreatitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- GI side effects</td>
</tr>
<tr>
<td>SGLT-2</td>
<td>- Wt loss</td>
<td>- Cost</td>
</tr>
<tr>
<td></td>
<td>- No hypoglycemia</td>
<td>- Infections</td>
</tr>
<tr>
<td></td>
<td>- CV benefit</td>
<td>- DKA</td>
</tr>
<tr>
<td></td>
<td>- Oral</td>
<td>- Less effect- renal insufficiency</td>
</tr>
</tbody>
</table>
Bariatric Surgery for DM

- STAMPEDE Trial
  - 5 year follow up of 150 pts with type 2 dm randomized to intensive medical therapy (IMT) vs IMT + gastric bypass or sleeve gastrectomy
  - Primary outcome: A1c < 6% with/without dm medications
  - 90% completed follow up

Schauer PR, NEJM 2017

Mean Changes in Measures of Diabetes Control from Baseline to 5 Years


Objectives:

- Understand ADA guidelines for medication use in type 2 diabetes
- Discuss categories of medications used to treat type 2 DM
- Review data on glycemic benefit and CV outcomes
Case #1
• 71 yo male, type 2 DM, BMI 37
• Metformin monotherapy
• A1C ↑ 8.4%
• Hypoglycemia with glipizide, refuses injections
• Recently hospitalized with CHF, AKI diagnosed
• Creatinine 1.7mg/dl, CrCl 40

Questions:
Continuation of his metformin:
1. Is contraindicated based on his creatinine
2. Is safe based on his creatinine
3. Is contraindicated based on his Crcl
4. Is safe based on crcl

Case #2
• 64 yo man, type 2 DM diagnosed 9 years ago
• Hx of hyperlipidemia, myocardial infarct (MI) 2 yrs ago
• Metformin, glimepiride, statin, ACEI, BB
• A1c 8.8%, weight 280#, BMI 44, CrCl 40
• Refuses insulin, good insurance, doesn’t want to gain weight.
Case #2

- What would you consider for next line therapy?
  1. DPP4
  2. TZD
  3. SGLT2 inhibitor
  4. GLP1 agonist

THE END