Diabetes: Putting it all together to design a high value diabetes regimen for your patient

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Disclosures

• None
Objectives

• Describe the benefits, side effects/risks, and costs of the newer diabetes medications
• Discuss the value of the newer diabetes medications
• Make high-value patient-centered decisions when intensifying diabetes therapy
Worsening HbA1c

• Ms L is a 48 year old woman here for routine f/u
• She has Type 2 diabetes (x 5 years; no complications), obesity (BMI 41), chronic knee pain from osteoarthritis, and is postmenopausal s/p TAH 6 yr ago for uterine leiomyomas
• You last saw her 6 months ago. At that time, her A1c was 6.4% on metformin 1000 mg BID
• You see that her A1c is now 8.5%.
• What other information do you need?
• How would you intensify her diabetes treatment?
“New-onset” diabetes

• Mr. B is a 53 year old M hospitalized for NSTEMI and underwent 3v CABG
• He had HTN but no other medical history and was on no medications prior to admission
• Admission point-of-care (POC) glucose: 263 mg/dL
• HbA1c: 11.5%
• He agrees that he needs to be on insulin upon discharge
• Are there any non-insulin medications that should be considered for him?
• How would you design his regimen?
ADVANCE: Diabetes complications and A1c relationship

- Linear relationship (no threshold) for eye complications
- J-curve: Increasing risk with A1c <6.5% for CV and renal complications

Even in 2019, people with diabetes still have more CVD, amputations and death

<table>
<thead>
<tr>
<th></th>
<th>T2DM</th>
<th>No DM</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LE amputations: # of</td>
<td>28.4</td>
<td>2.7</td>
<td>10.5</td>
</tr>
<tr>
<td>events /10,000 (95% CI)</td>
<td>(19.4-37.3)</td>
<td>(1.9-3.5)</td>
<td>(6.0-15.0)</td>
</tr>
</tbody>
</table>

Which glucose-lowering agent below has NOT been shown to reduce cardiovascular risk?

A. Liraglutide
B. Empagliflozin
C. Linagliptin
D. Canagliflozin
<table>
<thead>
<tr>
<th>Generic</th>
<th>Class</th>
<th>CV benefit</th>
<th>Risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empagliflozin</td>
<td>SGLT2i</td>
<td>CV death</td>
<td>↓14%</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>SGLT2i</td>
<td>MACE HF / DKD</td>
<td>↓14% ↓30% / ↓30%</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>SGLT2i</td>
<td>Hosp HF</td>
<td>↓27%</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>GLP-1RA</td>
<td>MACE (MI, stroke, CV death)</td>
<td>↓13%</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>GLP-1RA</td>
<td>MACE</td>
<td>↓26%</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>GLP-1RA</td>
<td>MACE</td>
<td>↓12%</td>
</tr>
</tbody>
</table>

Diabetes medications with clinical trial evidence for CV risk reduction
4 of these are now FDA-approved to reduce CV risk in diabetes

<table>
<thead>
<tr>
<th>Generic</th>
<th>Class</th>
<th>Date</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empagliflozin</td>
<td>SGLT2i</td>
<td>Dec 2016</td>
<td>CV death</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>GLP-1RA</td>
<td>Aug 2017</td>
<td>MACE (MI, stroke, CV death)</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>SGLT2i</td>
<td>Oct 2018</td>
<td>MACE Hosp HF, DKD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sep 2019</td>
<td></td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>SGLT2i</td>
<td>Oct 2019</td>
<td>Hosp HF</td>
</tr>
</tbody>
</table>

Type 2 diabetes

Established CVD or high CV risk
Overall approach to glucose-lowering in type 2 diabetes

First-line: metformin and comprehensive lifestyle change. Re-assess/modify every 3-6 months. If HbA1c above target, then...

Established ASCVD or CKD?

If YES – established ASCVD or CKD

- And ASCVD predominates:
  - GLP-1RA or SGLT-2i (if adequate eGFR) with proven CVD benefit*
- And CHF or CKD predominates:
  - And eGFR adequate, then SGLT-2i with proven CVD or CKD benefit**
  - If SGLT-2i not tolerated, or contraindicated, then GLP-1RA with proven CVD benefit*

*FDA-approved:
liraglutide
epagliflozin
canagliflozin
Not FDA-approved:
Semaglutide
Dulaglutide

**FDA-approved:
Canagliflozin
Dapagliflozin
Not FDA-approved:
empagliflozin

Other benefits of diabetes agents

<table>
<thead>
<tr>
<th>No hypoglycemia</th>
<th>Weight loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>• GLP-1RA</td>
<td>• GLP-1RA</td>
</tr>
<tr>
<td>• SGLT-2i</td>
<td>• SGLT-2i</td>
</tr>
<tr>
<td>• DPP-4i</td>
<td></td>
</tr>
<tr>
<td>• Thiazolidinedione (TZD)</td>
<td></td>
</tr>
</tbody>
</table>
How to choose between a GLP-1RA or SGLT2i with CV benefit?

<table>
<thead>
<tr>
<th>SGLT2i</th>
<th>GLP1-RA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Consider Using an SGLT2 Inhibitor First When Patient and Clinician Priorities Include:</strong></td>
<td><strong>Consider Using a GLP-1RA First When Patient and Clinician Priorities Include:</strong></td>
</tr>
<tr>
<td>Reducing MACE and CV death</td>
<td>Reducing MACE and CV death</td>
</tr>
<tr>
<td>Preventing heart failure hospitalization</td>
<td>Substantial weight loss</td>
</tr>
<tr>
<td>Reducing blood pressure</td>
<td>Once weekly (subcutaneous) dosing</td>
</tr>
<tr>
<td>Orally administered therapies</td>
<td>Therapy when eGFR consistently &lt;45 ml/min/1.73 m²*</td>
</tr>
</tbody>
</table>

*Exception: oral semaglutide now avail.*

When to consider an alternative to an SGLT2i or GLP-1RA?

Consider an alternative to an SGLT2i if:
- Significant CKD*
- History of prior amputation, severe peripheral arterial disease, neuropathy, or diabetic foot ulcers (avoid canagliflozin)
- History of recurrent genital candidiasis
- History of diabetic ketoacidosis
- History of osteoporosis (avoid canagliflozin)

Consider an alternative to a GLP-1RA if:
- Persistent nausea, even at low doses
- History of pancreatitis
- History of gastroparesis
- History of MEN2 or medullary thyroid cancer
- History of proliferative retinopathy (semaglutide)

*The SGLT2i effect to lower glucose diminishes with worse CKD, but other benefits for CVD and CKD persist or are greater.

ARS #1

• Which glucose-lowering agent below has NOT been shown to reduce cardiovascular risk?

A. Liraglutide
B. Empagliflozin
C. Linagliptin
D. Canagliflozin
How do the agents compare for glucose-lowering?

- **GLP-1RA > SGLT2i > DPP-4i**

- **GLP-1RA**
  - Semaglutide = dulaglutide = exenatide weekly > liraglutide > exenatide

- **SGLT2i**
  - Canagliflozin = ertugliflozin > empagliflozin = dapagliflozin

- **DPP-4i**
  - Sitagliptin = linagliptin = alogliptin = saxagliptin
You are seeing a 76 yr old patient with T2DM, A1c 8.5% on metformin, h/o vertebral fracture and prior toe amputation, with good renal function. What drug class would the best option for A1c lowering?

A. Sulfonylurea
B. Thiazolidinedione
C. SGLT-2 inhibitor
D. GLP-1 receptor agonist
What about potential risks and side effects?
Biguanide: Metformin

GI side effects are common:
- Diarrhea
- Nausea

Vitamin B12 deficiency

Risk for lactic acidosis – Contraindicated if eGFR <30 mL/min
Titrate metformin to maximize tolerability – Epic dotphrase

When you start the metformin:

• Take one 500 milligram tablet once a day for one week. THEN
• Take one 500 milligram tablet twice a day for one week. THEN
• Take two 500 milligram tablets in the morning and one 500 milligram tablet in the evening for one week. THEN
• Take two 500 milligram tablets twice a day.
• The final dose is 1000 milligrams twice daily (total 2000 milligrams per day).
• If you develop intolerable symptoms of bloating or diarrhea after you increase the dose, go back to the previous lower dose for an additional week then try increasing it again.

Extended-release formulations tend to be better tolerated
GLP-1 receptor agonists
dulaglutide, semaglutide, exenatide Qwk, liraglutide, exenatide

GI side effects are common:
- Nausea
- Vomiting
- Diarrhea

Injection site reactions

Risk of thyroid C-cell tumors
(liraglutide, dulaglutide, exenatide Qwk)

SQ (with 1 exception)
SGLT2-inhibitors

canagliflozin, empagliflozin, dapagliflozin, ertugliflozin

Genitourinary infections. Fournier’s gangrene

Risk of hypovolemia, hypotension

↑ LDL-cholesterol

Canagliflozin
- Amputation
- Fractures
DPP-4 inhibitors
sitagliptin, linagliptin, alogliptin, saxagliptin

Joint pain
Potential risk of acute pancreatitis
Thiazolidinediones (TZD)
rosiglitazone, pioglitazone

Congestive Heart Failure, Fluid retention/edema

Fractures

Bladder Cancer (Pioglitazone)

↑ LDL-Cholesterol (rosiglitazone)
Insulin
Glargine U-100 and U-300, detemir, degludec, lispro, aspart, glulisine, NPH, regular, 70/30, 75/25, 50/50

Hypoglycemia
More so with NPH, regular, 70/30

Injection site reactions

Weight gain
Sulfonylureas (SU)
glipizide, glyburide, glimepiride

Hypoglycemia

Increased risk of CV death based on studies of older SU tolvaptanamide

Weight gain
You are seeing a 76 yr old patient with T2DM, A1c 8.5% on metformin, h/o vertebral fracture and prior toe amputation, with good renal function. What drug class would be the best option for A1c lowering?

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“New-onset” diabetes

- Mr. B is a 53 year old M hospitalized for NSTEMI and underwent 3v CABG
- He had HTN but no other medical history and was on no medications prior to admission
- Admission point-of-care (POC) glucose: 263 mg/dL
- HbA1c: 11.5%
- He agrees that he needs to be on insulin upon discharge
- Which insulin is safe?
- Are there any non-insulin medications that should be considered for him?
Is it safe to use NPH instead of a basal insulin analog? Maybe.

Is it safe to use NPH instead of a basal insulin analog?

Switching from Glargine to NPH in a subpopulation of ACCORD caused more episodes of severe hypoglycemia but no difference in nocturnal hypoglycemia or health care resource utilization.

In the ACCORD population, NO

Observational data: All-cause mortality on insulin vs novel oral agents

- Lower all-cause mortality with novel agents in propensity score-matched groups treated with SGLT-2i and DPP-4i vs insulin

“New-onset” diabetes
Key aspects to consider

• Established ASCVD
• No heart failure or CKD
• Very high A1c of 11.5%
• Goals: improve/lower A1c, avoid hypoglycemia

• Basal insulin analog preferred over NPH
• Liraglutide (or dulaglutide or semaglutide)
• Canagliflozin (more glucose-lowering) or empagliflozin
Median monthly cost of max approved daily dose of non-insulin DM medications in US*

*Actual out of pocket cost is usually different

<table>
<thead>
<tr>
<th>Class</th>
<th>Compound</th>
<th>Form/product</th>
<th>Max daily dose</th>
<th>Median Avg Wholesale Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea</td>
<td>Glipizide</td>
<td>10 mg XL</td>
<td>20 mg (XL)</td>
<td>$75</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>Pioglitazone</td>
<td>45 mg</td>
<td>45 mg</td>
<td>$348</td>
</tr>
<tr>
<td></td>
<td>Rosiglitazone</td>
<td>4 mg</td>
<td>8 mg</td>
<td>$407</td>
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<tr>
<td><strong>DPP-4i</strong></td>
<td>Alogliptin</td>
<td>25 mg</td>
<td>25 mg</td>
<td><strong>$234-516</strong></td>
</tr>
<tr>
<td></td>
<td>Saxagliptin</td>
<td>5 mg</td>
<td>5 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Linagliptin</td>
<td>5 mg</td>
<td>5 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sitagliptin</td>
<td>100 mg</td>
<td>100 mg</td>
<td></td>
</tr>
<tr>
<td><strong>SGLT2i</strong></td>
<td>Ertugliflozin</td>
<td>15 mg</td>
<td>15 mg</td>
<td><strong>$322-558</strong></td>
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<tr>
<td></td>
<td>Dapagliflozin</td>
<td>10 mg</td>
<td>10 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Canagliflozin</td>
<td>300 mg</td>
<td>300 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Empagliflozin</td>
<td>25 mg</td>
<td>25 mg</td>
<td></td>
</tr>
<tr>
<td><strong>GLP-1RA</strong></td>
<td>Exenatide Qwk</td>
<td>2 mg suspension/pen</td>
<td>2 mg</td>
<td><strong>$792-1044</strong></td>
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<tr>
<td></td>
<td>Exenatide Dose</td>
<td>10 mcg pen</td>
<td>20 mcg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dulaglutide</td>
<td>1.5/0.5 mL pen</td>
<td>1.5 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Semaglutide</td>
<td>1 mg pen</td>
<td>1 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Liraglutide</td>
<td>18 mg/3 mL pen</td>
<td>1.8 mg</td>
<td>$1044</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Compound</th>
<th>Form/product</th>
<th>Median Avg Wholesale Price</th>
<th>Walmart Price (&quot;Reli-On&quot;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal analog</td>
<td>Glargine (Lantus)</td>
<td>U-100 vial U-100 prefilled pen</td>
<td>$323</td>
<td></td>
</tr>
<tr>
<td>Concentrated Human Regular</td>
<td>U-500 Human Regular</td>
<td>U-500 vial U-500 prefilled pen</td>
<td>$178</td>
<td></td>
</tr>
<tr>
<td>Intermediate-acting</td>
<td>Human NPH</td>
<td>U-100 vial U-100 prefilled pen</td>
<td>$165</td>
<td>$25</td>
</tr>
<tr>
<td>Short-acting</td>
<td>Human Regular</td>
<td>U-100 vial</td>
<td>$165</td>
<td>$25</td>
</tr>
<tr>
<td>Rapid-acting</td>
<td>Lispro (Humalog)</td>
<td>U-100 vial U-100 3 mL cartridge U-100 or U-200 prefilled pen</td>
<td>$330 $408 $424</td>
<td></td>
</tr>
<tr>
<td>Pre-mixed</td>
<td>NPH/Regular 70/30</td>
<td>U-100 vial U-100 prefilled pen</td>
<td>$165</td>
<td>$25</td>
</tr>
<tr>
<td>Pre-mixed analog</td>
<td>Lispro 75/25</td>
<td>U-100 vial U-100 prefilled pen</td>
<td>$342</td>
<td>$424</td>
</tr>
</tbody>
</table>

*Actual out of pocket cost is usually different - Does not take into account discounts, rebates, other price adjustments

Inexpensive NPH, regular, or 70/30 insulin (no Rx needed) and supplies

<table>
<thead>
<tr>
<th>Item</th>
<th>Unit cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reli-On NPH insulin</td>
<td>$25 / vial</td>
</tr>
<tr>
<td>Reli-On Regular insulin</td>
<td>$25 / vial</td>
</tr>
<tr>
<td>Reli-On 70/30 insulin</td>
<td>$25 / vial</td>
</tr>
<tr>
<td>Reli-On Insulin syringes</td>
<td>$15.58 / box of 100</td>
</tr>
<tr>
<td>Reli-On Prime Glucose Monitor</td>
<td>$9</td>
</tr>
<tr>
<td>Reli-On Prime Test Strips</td>
<td>$17.88/100 strips</td>
</tr>
<tr>
<td>Reli-On Lancets</td>
<td>$1.58 for 100 lancets</td>
</tr>
</tbody>
</table>
Benefits

- Improve symptoms
- Decrease complications
- Weight loss/no weight gain
- CV, renal risk reduction

Risks

- Hypoglycemia
- Adverse effects
- Weight gain
- Invasiveness
What is high value diabetes care?

Value takes into account net clinical benefit, cost, and likelihood of patient adherence.
Drugs don’t work in patients who don’t take them.

- C. Everett Koop (US Surgeon General, 1982-1989)
Strategies to increase adherence

- **Useful** (demonstrate value) - educate about harms, benefits
- **Useable** (fits into real-life workflow)
  - lower cost
  - easy to take
  - minimize side effects
- **U** establish trust (and respect)
  - Show outcomes/effectiveness
  - Show that you are monitoring med adherence
Is it more cost-effective to start an SGLT-2i or NPH insulin as a 3rd agent?

- Cost-effectiveness analysis in U.K. from a payer perspective
- Type 2 DM not at A1c goal on metformin and DPP-4i
- Well-established, validated model, over a patient’s lifetime; conservative assumptions

• Conclusion: Treatment intensification with an SGLT2i prior to NPH was cost-effective or cost-neutral compared with immediately starting NPH. Higher drug costs offset by lower incidence of complications

Patient EV: 62 yr old F

- CC: shortness of breath x 2 days, fatigue x 1 month
- No fever, chest pain, cough, edema or weight change
- No other symptoms
- T2DM x 10 years, HTN
- Metformin XR 2000 mg QD, Glyburide 10 mg BID, enalapril 40 mg QD, NPH insulin 20 units QHS

- Exam: 128/64. HR 72. T 98.2    BMI  31
- Total Chol 199. LDL 126. HDL 37. TG 179.
- HbA1c 8.3%   Creatinine 0.9
EV: 62 yo F, T2DM x 10 yr on metformin, no CAD, A1c 8.3%, dyspnea x 2 days

• After workup, found to have CHF (EF 30%) and suspected to have had an MI in the past month
• Transferred out of ICU to step-down unit
• Paged by nurse: Unable to obtain blood pressure
• New STEMI

Do we have anything better for our diabetes patients now?

YES!
Key aspects to consider

- Established ASCVD
  - Heart failure (HFrEF)
- No CKD (creatinine 0.9 → eGFR 69 mL/min)
- A1c 8.3% - not at goal
  - How much lowering does she need?
  - Avoiding hypoglycemia is a priority
ARS #4 – 62 yo F with T2D x 10 yr on metformin, A1c 8.3%, established ASCVD and CHF, no CKD

• What class of diabetes agents would you add to her regimen of max dose metformin?
  • A. DPP-4i
  • B. GLP-1RA
  • C. SGLT2i
  • D. Sulfonylurea
62 yo F with T2D x 10 yr on metformin, A1c 8.3%, established ASCVD and CHF, no CKD

- Which SGLT2i would you select?
  - Empagliflozin or canagliflozin
    - FDA indications for lowering risk in ASCVD
    - Trial evidence to lower hospitalization for heart failure
  - Alternative agents but lower on list: dapagliflozin, ertugliflozin

- Stop glipizide

- Later, consider adding liraglutide if not at A1c goal or for further CV risk reduction
What if these are not “preferred” by her insurance company, or her out of pocket expense is too high?

• Discount/savings/copay cards?
• Are there any alternatives (without the FDA indication for lowering CV risk)?
  • Dapagliflozin (CV death, heart failure), ertugliflozin
  • GLP-1RA not as preferred since SGLT2i’s greatly benefit in HF, but data for CV risk reduction are available for: semaglutide, dulaglutide
Patient EV: 3 years later - CKD

- Age 65
- T2DM x 13 yr, HTN
- CAD with silent MI, HFrEF
- Creatinine 1.3 → eGFR 43 (CKD stage 3b)
- Metformin XR 2000 mg QD, empagliflozin 25 mg QD, liraglutide 1.8 mg QD
- A1c 7.9%
- How would you change her regimen?
Key aspects to consider

- Established ASCVD
- Heart failure
- CKD
- Goals: maintain A1c, avoid hypoglycemia

- Reduce metformin to 500 mg BID
- Continue SGLT-2i
- Certain GLP-1RA ok (semaglutide; liraglutide, lixisenatide)
  - Post marketing reports of AKI and worsening renal function requiring HD
  - Caution if severe GI side effects (monitor renal function, avoid uptitrating dose, consider stopping)
- Start insulin therapy with a basal analog
Metformin use

• CKD Stage 3a (45-59 mL/min): 500 mg QAM, 1000 mg QPM
• CKD Stage 3b (30-44 mL/min): 500 mg BID
• Monitor eGFR every 6 months
• Stop metformin if AKI likely or if eGFR <30
• D/C metformin if eGFR 30-60 mL/min and undergoing iodinated contrast study, liver disease, alcoholism, heart failure. Re-eval 48 hr after contrast study and restart if stable.

If your patient with T2DM and ASCVD has CKD

<table>
<thead>
<tr>
<th>Drug</th>
<th>Data available?</th>
<th>Renal dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empagliflozin</td>
<td>&gt;1800 pts studied with eGFR &lt;60; small CKD study (30-60)</td>
<td>Sparse data for eGFR &lt;60. D/C if eGFR &lt;45.</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>Small CKD study (30-50)</td>
<td>*Ok for eGFR 30-45 if albuminuria &gt;300 mg/day; contraindicated for eGFR &lt;30.</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>Small CKD study (45-60)</td>
<td>FDA: Avoid if eGFR &lt;45.</td>
</tr>
<tr>
<td>Liraglutide*</td>
<td>&gt;3000 pts studied with eGFR &lt;60 but not ESRD</td>
<td>No dose adjustment. Avoid in ESRD.</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>No data in eGFR &lt;30</td>
<td>GI side effects, renal fxn.</td>
</tr>
<tr>
<td>Semaglutide*</td>
<td></td>
<td>No dose adjustment.</td>
</tr>
<tr>
<td>Exenatide QW</td>
<td>Increased exposure with ↓eGFR</td>
<td>Avoid if eGFR &lt;45.</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>655 pts studied with eGFR 30-59</td>
<td>*Avoid if eGFR &lt;30.</td>
</tr>
</tbody>
</table>

Sources: Prescribing information for each drug listed above
No ASCVD, but with CKD

- LS is a 49 yr old woman with CKD
- T2DM x 10 yr, longstanding HTN
- Renal cell ca s/p nephrectomy
- Creatinine 2.2 → eGFR 44 (CKD stage 3b)
- Metformin XR 2000 mg QD, empagliflozin 25 mg QD, liraglutide 1.8 mg QD
- A1c 7.9%
- How would you change her regimen?
Key aspects to consider

- No known ASCVD
  - Any suspicion? Careful HPI/ROS for clues
- CKD (creatinine 2.2 → eGFR 44 mL/min)

Evidence for CV risk reduction by the new therapies is weaker without established ASCVD, but there is some evidence for renal benefits

- Reduce metformin to 500 mg BID. Stop empagliflozin
- Consider: reducing risk of nephropathy progression, cost, preference (route, dosing), comorbidities, potential side effects
- Limited options: GLP-1RA, linaglaptin/other DPP4i, insulin
What to do with DPP-4i dosing if renal function decreases

• Renal dysfunction:
  • Linagliptin ok to use at the same dose no matter what renal function

<table>
<thead>
<tr>
<th>If eGFR ↓ below...</th>
<th>Reduce:</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 mL/min</td>
<td>Alogliptin to 12.5</td>
</tr>
<tr>
<td>50 mL/min</td>
<td>Sitagliptin to 50, Saxagliptin to 2.5</td>
</tr>
<tr>
<td>30 mL/min</td>
<td>Sitagliptin to 25, Alogliptin to 6.25</td>
</tr>
</tbody>
</table>
Final thoughts (1)

- The newer DM medications do not cause hypoglycemia or weight gain but are costly.
- Continue metformin for as long as possible. Uptitrate for adherence.
- NPH insulin can be safely used in many/most pts with type 2 DM.
- DO NOT prescribe a GLP-1RA with a DPP-4i.
Final thoughts (2)

- All of the SGLT2i reduce CV, HF and/or CKD risk
- Some of the GLP-1RA reduce CV and/or CKD risk
- SGLT2i and GLP-1RA are high value therapies in patients with ASCVD, HF and/or CKD
On the near horizon

• Dulaglutide (GLP-1RA) reduced risk of MACE by 12%. Also renal, microvascular (eye or kidney)
• FDA approval for broader patient population?

• Comparative effectiveness trial of sulfonylurea (glimepiride) vs DPP-4i (sitagliptin) vs GLP-1RA (liraglutide) vs insulin (glargine)
• Estimated completion: July 2021
Resources

• ADA. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes – 2020. *Diabetes Care* 2020;43(Suppl. 1).

• ADA. Cardiovascular disease and risk management: Standards of Medical Care in Diabetes – 2020. *Diabetes Care* 2020;43(Suppl. 1).

What is one thing you will do differently when you see your next diabetes patient?

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Reinforce lifestyle recommendations for type 2 DM

• Lifestyle changes
  • Less calorie-dense foods
  • Emphasis on:
    • Complex carbohydrates higher in fiber
    • Lean/plant proteins
    • Smaller portions
  • Increase physical activity
• Weight loss if overweight
  • Mediterranean or DASH diet
  • Meal replacement shakes (1-2 meals/day)
Classes of diabetes therapies

1922 Animal insulins
1950’s Sulfonylureas
1982 Recombinant human insulin
1995 Metformin
1996 Insulin analog (Humalog)
1997 Repaglinide
1999 TZD
2005 Acarbose
2005 Pramlintide
2005 Exenatide
2006 Sitagliptin
2013 Canagliflozin
The most commonly-used diabetes medications

<table>
<thead>
<tr>
<th>Category</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanide</td>
<td>metformin</td>
</tr>
<tr>
<td>Glucagon-like peptide-1 receptor agonist</td>
<td>exenatide, exenatide QW, liraglutide, dulaglutide, lixisenatide, semaglutide (PO)</td>
</tr>
<tr>
<td>Sodium glucose co-transport-2 inhibitor</td>
<td>canagliflozin, dapagliflozin, empagliflozin, ertugliflozin</td>
</tr>
<tr>
<td>Dipeptidyl peptidase-4 inhibitor</td>
<td>sitagliptin, saxagliptin, linagliptin, alogliptin</td>
</tr>
<tr>
<td>Insulin Insulin analogs</td>
<td>NPH, Regular, 70/30, Lispro, Aspart, Glulisine, Glargine, Detemir, Degludec, inhaled</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>glimepiride, glyburide, glipizide</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>pioglitazone, rosiglitazone</td>
</tr>
<tr>
<td>Insulin</td>
<td>Onset</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------</td>
</tr>
<tr>
<td>inhaled</td>
<td>&lt;5-10 min</td>
</tr>
<tr>
<td>rapid acting*</td>
<td>5-15 min</td>
</tr>
<tr>
<td>regular</td>
<td>30-60 min</td>
</tr>
<tr>
<td>NPH</td>
<td>1-2 hr</td>
</tr>
<tr>
<td>U500</td>
<td>1-2 hr</td>
</tr>
<tr>
<td>detemir</td>
<td>1-2 hr</td>
</tr>
<tr>
<td>glargine U100</td>
<td>1-2 hr</td>
</tr>
<tr>
<td>glargine U300</td>
<td>6 hr</td>
</tr>
<tr>
<td>degludec</td>
<td>1-2 hr</td>
</tr>
</tbody>
</table>

*lispro U100, U200; aspart, FiAsp, glulisine