Pharmacologic Management of Metabolic Syndrome: Navigating the Progression of Insulin Resistance

ANNE KNAPE, APRN-NP
DIVISION OF ENDOCRINOLOGY, NEBRASKA MEDICINE
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Objectives

• Identify pharmacologic treatment for insulin resistance prior to progression of disease
• Predict appropriate diabetes medications based on individual characteristics
• Evaluate comorbid condition to be considered when prescribing antihyperglycemic medications
Metabolic Syndrome Defined

A constellation of interrelated risk factors of metabolic origin—metabolic risk factors—that appear to directly promote the development of atherosclerotic cardiovascular disease (ASCVD).

1. Elevated waist circumference
2. Elevated triglycerides
3. Reduced HDL-C
4. Elevated blood pressure
5. Elevated fasting glucose

AHA/NHLBI 2005

Many variations of clinical criteria over the years

The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) is the most widely used (2005)
### NCEP-ATP III 2005 Criteria

<table>
<thead>
<tr>
<th>Any 3 of the 5 criteria constitutes diagnosis:</th>
<th>Categorical Cutpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated waist circumference</td>
<td>≥ 102cm (≥ 40 in) in men&lt;br&gt;≥ 88 cm (≥ 35 in) in women&lt;br&gt;(South Asians, Chinese and Japanese: ≥ 90cm in men and ≥ 80cm in women)</td>
</tr>
<tr>
<td>Elevated triglycerides</td>
<td>≥ 150mg/dL or on drug treatment</td>
</tr>
<tr>
<td>Reduced HDL-C</td>
<td>&lt; 40mg/dL in men - &lt; 50mg/dL in women&lt;br&gt;or on drug treatment</td>
</tr>
<tr>
<td>Elevated blood pressure</td>
<td>≥ 130mm Hg SBP or ≥ 85mm Hg DBP&lt;br&gt;or on drug treatment</td>
</tr>
<tr>
<td>Elevated fasting glucose</td>
<td>≥ 100mg/dL or on drug treatment</td>
</tr>
</tbody>
</table>

AHA/NHLBI 2005

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### Atherosclerotic cardiovascular disease (ASCVD)

**Coronary heart disease, cerebrovascular disease or peripheral arterial disease (presumed to be of atherosclerotic origin)**

- Leading cause of morbidity and mortality for individuals with diabetes
- $37.3$ billion in CV-related spending yearly associated with diabetes
- Hypertension and dyslipidemia are clear risk factors for ASCVD and diabetes itself is an independent risk factor for ASCVD
Case

Beth is a 23 year old female who presents as a new patient to primary care for routine physical. She reports steady weight gain after starting her period (age of menarche 12). Over the years her periods became more unpredictable, not always monthly, variable in flow, sometimes skipped completely. She is not sexually active. Says she was diagnosed with PCOS at age 18 by her gynecologist when her periods became irregular and is taking OCP which regulated her menses.

PMH: PCOS, obesity
VS: 145/96, HR 82, R 20, BMI 30
PE: hirsutism noted along chin and down midline of abdomen (Ferriman Gallwey score 10). Central obesity with waist circumference 36.5 inches. Well-groomed, otherwise unremarkable exam
Lab: CMP NL (creat 0.7, eGFR > 60, random gluc 105), electrolytes normal, TSH 2.1 (NL), A1c is 5.7%
You have records from her diagnosis of PCOS showing normal 8am dexamethasone-suppressed cortisol, 17OH-progesterone, prolactin and DHEA-S.
Medications: OCP, multivitamin

What are you concerned about?

7

Case

Beth confirms that she has checked BP in the community and has been >140/90 when she checks at the grocery store.

You discuss that she meets defined criteria for Metabolic Syndrome (elevated BP and waist circumference) and discussed starting antihypertensive medication.

She did not want to start medication for her blood pressure, so you discussed lifestyle changes and she met with the dietician in your office.
Lifestyle management

- Weight loss
- Physical activity
- Dietary modification
  - Calorie restriction for weight loss
  - Sodium <2300mg/day
  - Increased veggie and fruit consumption (8-10 servings per day)
  - Low fat dairy products (2-3 servings per day)
- Avoid excess alcohol consumption (no more than 2 drinks for men, 1 drink for women per day)

Weight loss medications

- Indicated for BMI ≥ 27 with a weight associated condition (DM2, HTN, HLP) or ≥ 30 without a comorbid condition
- Adjunct to diet, exercise and behavioral therapy
- Nearly all have been shown to delay progression to diabetes
- Approved for short term and long term use
- Insurance coverage is spotty, expensive $$$
- Many with unwanted/intolerable side effects
FDA approved weight loss medications

Table 8.2—Medications approved by the FDA for the treatment of obesity

<table>
<thead>
<tr>
<th>Medication name</th>
<th>Typical adult maintenance dose</th>
<th>Average wholesale price (30-day supply)</th>
<th>National Average Drug Acquisition Cost (30-day supply)</th>
<th>Treatment arm</th>
<th>Weight loss (% loss from baseline)</th>
<th>Common side effects</th>
<th>Possible safety concerns/considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-term treatment (≤12 weeks)</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Phentermine (108)</td>
<td>8–37.5 mg q.d.*</td>
<td>$5.56 (37.5 mg dose)</td>
<td>$9 (37.5 mg dose)</td>
<td>15 mg q.d</td>
<td>6.1</td>
<td>Dry mouth, insomnia, difficulty, irritability</td>
<td>Risk of severe hypertension, Contraindicated for use in combination with monoamine oxidase inhibitors</td>
</tr>
<tr>
<td><strong>Long-term treatment (&gt;12 weeks)</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Orlistat (3)</td>
<td>60 mg t.i.d. (OTC)</td>
<td>$43–$52</td>
<td>$42</td>
<td>120 mg t.i.d</td>
<td>9.6</td>
<td>Abdominal pain, flatulence, fecal urgency, back pain, headache</td>
<td>Potential malabsorption of fat-soluble vitamins (A, D, E, K) and of certain medications (e.g., cyclosporine, thyroid hormone, anticonvulsants, etc.)</td>
</tr>
<tr>
<td>Selective serotonin (5-HT) 5-HT2C receptor antagonist</td>
<td></td>
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<td></td>
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<tr>
<td>Lorcaserin (14)</td>
<td>10 mg b.i.d.</td>
<td>$333</td>
<td>$255</td>
<td>10 mg b.i.d.</td>
<td>4.5</td>
<td>Headache, nausea, dizziness, fatigue, nasopharyngitis</td>
<td>Serotonin syndrome and neuroleptic malignant syndrome-like reactions theoretically possible when coadministered with other serotonergic or antipsychotic agents</td>
</tr>
<tr>
<td>Lorcaserin SR</td>
<td>20 mg q.d.</td>
<td>$333</td>
<td>$254</td>
<td>20 mg q.d.</td>
<td>1.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 8.2—Continued

<table>
<thead>
<tr>
<th>Medication name</th>
<th>Typical adult maintenance dose</th>
<th>Average wholesale price (30-day supply)</th>
<th>National Average Drug Acquisition Cost (30-day supply)</th>
<th>Treatment arm</th>
<th>Weight loss (% loss from baseline)</th>
<th>Common side effects</th>
<th>Possible safety concerns/considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic amine anorectic/antiepileptic combination</td>
<td>7.5 mg/15 mg q.d.</td>
<td>$12.13 (7.5 mg/15 mg dose)</td>
<td>$178 (7.5 mg/15 mg dose)</td>
<td>15 mg/32 mg q.d</td>
<td>0.8</td>
<td>Constipation, pancreatitis, insomnia, nasopharyngitis, xerostomia</td>
<td>Birth defects, Cognitive impairment, Acute angle-closure glaucoma</td>
</tr>
<tr>
<td>Topiramate ER (209)</td>
<td></td>
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</tr>
<tr>
<td>Opioid antagonists/antidepressant combination</td>
<td>8 mg/90 mg q.d.</td>
<td>$334</td>
<td>$267</td>
<td>16 mg/180 mg b.i.d</td>
<td>5.0</td>
<td>Constipation, nausea, headache, xerostomia, insomnia</td>
<td>Contraindicated in patients with uncontrolled hypertension and/or severe disorders</td>
</tr>
<tr>
<td>Naltrexone and Bupropion ER (15)</td>
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<td></td>
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<tr>
<td>Glucagon-like peptide 1 receptor agonist</td>
<td></td>
<td></td>
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<tr>
<td>Liraglutide (16)</td>
<td>3 mg q.d.</td>
<td>$1,341</td>
<td>$1,154</td>
<td>3.0 mg q.d</td>
<td>6.0</td>
<td>Hypoglycemia, constipation, nausea, headache, indigestion</td>
<td>Acute pancreatitis, Black box warning</td>
</tr>
</tbody>
</table>

All medications are contraindicated in women who are or may become pregnant. Women of reproductive potential must be counseled regarding the use of reliable methods of contraception. Select safety and side effect information is provided; for a comprehensive discussion of safety considerations, please refer to the prescribing information for each agent. B.i.d., twice daily; ER, extended release; MTC, multiple endocrine neoplasia syndrome type 2; MTC, medullary thyroid carcinoma; OTC, over the counter; PBO, placebo q.d., daily Rx, prescription: t.i.d., three times daily; XR, extended release. *Use lowest effective dose; maximum appropriate dose is 37.5 mg. 1Duration of treatment was 28 weeks in a general obese adult population. 2Enrolled participants had normal (79%) or impaired (21%) glucose tolerance. 3Maximum dose, depending on response, is 15 mg/32 mg q.d. Approximately 68% of enrolled participants had type 2 diabetes or impaired glucose tolerance.
Weight loss medication pearls

- Start with lowest dose and titrate according to side effects/response
- Monitor weight – if <5% of weight loss is achieved at 3 months, then medication should be discontinued and alternative approach considered (or if intolerable side effect profile)
- If possible, avoid starting medications that can cause weight gain for comorbidities (ex: gabapentin for nerve pain, select antipsychotics, etc.)

Case

Beth is back for 3 month follow-up, she was able to lose 10 lbs. BMI is now 28 and her BP is improved and is <130/80 when measured after her weight reduction.

She has a boyfriend, he’s in the military. They are moving to another state and they eventually plan to marry. You recommended following with a local PCP and wish her well.
Case – fast forward 5 years

Beth is back for follow-up. She is now 28 years old and is married. Has been 5 years since you’ve seen her. She has an IUD, no plans for children currently. She has gained 25 lbs over the last 5 years despite working at lifestyle interventions. No new complaints.

VS: BP 122/78, HR 70, R 20, BMI 35

PE: central adiposity, remains hirsute, she has new finding of nigricans acanthosis of neck

Lab: CMP (electrolytes NL, fasting glucose 106mg/dL, eGFR >60, LFTs normal)

Lipids: TC 197, Tg 185, HDL 30, LDL 90,

A1c is 6.0%

Medications: IUD, multivitamin

Insulin resistance

Pre-diabetes definition:

Fasting plasma glucose 100mg/dL – 125mg/dL

OR

75g OGTT with 2 hour glucose 140mg/dL - 199mg/dL

OR

A1c 5.7% - 6.4%

“Prediabetes should not be viewed as a clinical entity in its own right but rather as an increased risk for diabetes and cardiovascular disease (CVD). Prediabetes is associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension.” (ADA 2019)
Diabetes Prevention Program (DPP)

Intensive lifestyle changes and 7% weight reduction can reduce the incidence of type 2 diabetes by 58% over 3 years
- Calorie reduction
- 150 minutes/week of moderate physical activity (brisk walking)
- Consider technology for assistance in meeting goals (weight loss apps, etc.)
- Smoking cessation

Consider metformin for prevention of DM2 in those with pre-diabetes, especially those with BMI > 35, <60 yo and women with h/o GDM

Knowler et al. 2002, ADA 2019

Metformin (off-label use for prevention of DM2)

Biguanide – MOA: ↑peripheral glucose uptake and utilization, ↑hepatic response to blood sugar levels so that liver downregulates glucose production, ↓intestinal absorption of glucose

Monitoring: renal function, B12 in select patients, s/s of lactic acidosis (dehydration, acute illness)

Contraindications: renal disease and metabolic acidosis

Side effects: GI upset, bloating, diarrhea (up to 50% of people with IR and <20% with ER)

B12 deficiency in chronic use – consider periodic monitoring of Vit B12 (esp if c/o neuropathy or in patients with anemias)
Metformin (cont)

Available in immediate release formulation and extended release formulation
- Immediate release tablet: 500 mg, 850 mg, 1000 mg strength
- Extended Release 24 Hour tablet: 500mg, 750mg or 1000mg tablets (typically only find 500mg tablets)

Clinically significant responses seen at 1500-2000mg daily typically
- Start 500mg q day, titrate up by 500mg every 1-2 weeks if tolerated
- Max dose 2500mg with normal renal function
- Extended release has less GI side effects

May reduce cardiovascular events

Metformin (cont)

New renal dosing guidelines implemented/recommended in 2016 by the FDA
- eGFR >45 – no dose adjustment, monitor renal functional annually
- eGFR 30-45 –
  - Preexisting impairment: controversial to start, if you do, start at ½ usual dose (250mg daily) and titrate slowly to max 1000mg daily. Follow eGFR q 3-6 months
  - eGFR falls during therapy: Consider benefits/risks of continuing therapy. If continuing reduce dose to max 1000mg/day. Follow eGFR q 3 months.
- eGFR < 30 – use is contraindicated

Liver disease – use cautiously, higher risk for lactic acidosis in selected patient (alcohol abuse, cirrhosis)
- Favorable impact on lipids because of it’s action in the liver
Case

Beth is started on metformin, she is tolerating fine and was able to titrate to 1000mg bid. She has lost 5 lbs since starting. They then move again for husband’s job and she’s lost to follow-up.

She returns to clinic for follow-up after another 5 years (now 33yo). She did have her IUD removed and they had a baby who is now 2 years old. She was diagnosed with GDM during pregnancy but was able to control it with diet. Her 6 week post delivery OGTT was normal (no DM2). Her husband had a vasectomy, they are not desiring fertility in the future. She also had her IUD replaced to control irregular menses.

More recently, tore meniscus exercising, so has been more sedentary following surgical repair. Her weight is climbing again and hasn’t been eating well. She hasn’t been able to lose “the baby weight.”

About 6 months ago, saw her interim PCP and restarted metformin when her A1c increased again to 6.2%. Also started on Atorvastatin for high LDL.

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Case

VS: BP 145/96, HR 84, R 20, BMI 37
PE: swelling of knee, otherwise unchanged from before
Lab: CMP (electrolytes NL, fasting glucose 130mg/dL, eGFR >60, LFTs NL)
  Lipids: TC 206, Tg 205, HDL 30, LDL 102,
  A1c is 7.6%
Meds: IUD, multivitamin, metformin 1000mg bid, atorvastatin 10mg qd

You discuss that you are concerned with her A1c (diabetes range) and her elevated BP.

Because she is now progressing to DM2, you check a urine MAB/creatinine ratio to screen for microvascular complications. It is elevated at 64ugAL/mgCR (NL <30)
Hypertension pharmacologic therapy

BP ≥ 140/90 mm/Hg = Lifestyle + 1 drug
BP ≥ 160/100 mm/Hg = Lifestyle + 2 drugs

Drug classes demonstrated to reduce CV events in diabetes:
• ACE inhibitors
• Angiotensin receptor blockers
• Thiazide-like diuretics
• Dihydropyridine calcium channel blockers

ACE inhibitors and ARBs

Inhibitors of renin-angiotensin system
• Angiotensin-converting enzyme inhibitors (ACE-i)
  Ex: Lisinopril, Benazapril, Captopril, Enalapril
  MOA: inhibits ACE activity -> decreased production of angiotensin

• Angiotensin Receptor Blockers (ARBs)
  Ex: Losartan, Irbesartan, Valsartan, Telmisartan
  MOA: Blocks angiotensin II receptor
ACE inhibitors and ARBs

Monitoring: serum creatinine and eGFR and serum K levels at least annually (consider more often with titrating doses or other changes in clinic status)

Absolute contraindications: Bilateral renal artery stenosis, angioedema and pregnancy (can cause fetal and neonatal morbidity and mortality - category C in 1st and D in 2nd/3rd trimesters)

• Drugs of choice for patients with albuminuria (urine albumin to creatinine ratio ≥ 30ugAL/mgCR) – demonstrated to reduce progression of kidney disease

• If one class not tolerated, the other should be substituted (ex: cough with ACE-I)

• Not recommended to use ACE-i and ARB in combination together (lack of ASCVD benefit and increased risk of adverse events - hyperkalemia, syncope and AKI)

FDA Recall of ARBs

Why are some valsartan, losartan, and irbesartan medicines being recalled?

Beginning in Summer 2018, FDA learned and reported that some generic versions of the angiotensin II receptor blocker (ARB) medicines contain nitrosamine impurities that don’t meet the agency’s safety standards.

• Nitrosamine impurities, including N-Nitrosodimethylamine (NDMA), and N-Nitrosodiethyamine (NDEA), are probable human carcinogens (a substance that could cause cancer), and N-Nitros-N-methyl-4-aminobutyric acid (NMBA) is a potential human carcinogen.

• Nitrosamines are known environmental contaminants and found in water and foods, including meats, dairy products and vegetables.

• The presence of these nitrosamine impurities in ARB medicines was unexpected. Our ongoing effort has determined that these impurities may be generated when specific chemicals and reaction conditions are present in the manufacturing process of the drug’s API, and may also result from the reuse of materials, such as solvents.

What should I know as a health care professional?

FDA has determined the recalled ARBs pose an unnecessary risk to patients.

FDA recommends that pharmacists provide a replacement medicine not affected by the recall or prescribers consider other available treatment options for their patient’s medical condition.

A list of ARB medications affected by the recall are available on FDA’s website for healthcare professionals and patients to monitor. FDA has also posted a list of ARBs that are currently available, along with information regarding the status of FDA’s assessment for those medications.

FDA suggests health care professionals check the lists regularly for updates.

Samples can also be affected and part of the recall. Be certain to check samples to ensure affected products are not given to patients.

• If you have medication samples from these companies, quarantine the products, and do not provide them to patients.

Report any adverse reactions with ARB-containing products, to FDA’s MedWatch program to help the agency better understand the scope of the problem:

• Complete and submit the report online at www.fda.gov/medwatch/report.htm

• Download and complete the appropriate form, then submit it via fax at 1-800-FDA-0178

https://www.fda.gov/drugs/drug-safety-and-availability
Thiazide-like diuretics

- Ex: chlorthalidone, hydrochlorothiazide, metolazone
- **MOA:** act on distal renal tubule to inhibit sodium reabsorption
- **Monitoring:** electrolytes (hypokalemia, hypercalcemia, hyponatremia, hypomagnesemia)
- **Contraindications:** caution with h/o gout or renal calculi (risk for hyperuricemia), hypotension, pregnancy category C

Dihydropyridine Calcium Channel Blockers

- Ex: Amlodipine, Nicardipine, Nifedipine
- **MOA:** blocking of 3 different receptors: dipheylalkylamine-based and benzothiazepine-based (both type 1 receptors) and dihydropyrididine-based (type 2 receptors). CCBs relax arterial smooth muscles.
- **Monitoring:** liver function (extensively metabolized by liver), peripheral edema
- **Contraindications:** peripheral edema (prolonged vasodilation can worsen), unstable angina, use in caution with hepatic impairment, pregnancy category C (teratogenic effect demonstrated in animal studies)
Treat to target BP

≤ 140/90 without high cardiovascular disease risk (10 year ASCVD risk <15%)

≤ 130/80 in select patients with DM2 and HTN who are at higher CV risk (known CVD or 10 year ASCVD risk)

Progression to type 2 diabetes

Diagnostic criteria: A1c >6.5%, random glucose >200 with classic diabetes symptoms, 2 hr OGTT plasma glucose >140mg/dL or fasting glucose >126mg/dL
Prescribing for type 2 diabetes

- Metformin should be continued as long as tolerated and not contraindicated (renal function)
- Medications are added to achieve glycemic targets (not substituted)
- Adjust regimen/titrate every 3 months until target A1c is achieved (<7% or <6.5% if can be achieved without hypoglycemia)
- If A1c is >9%, consider starting insulin if symptoms of hyperglycemia
- Choose medications that benefit the individual patient – in most cases, preferred are those with weight loss or neutrality and CVD benefit
Glucagon-like peptide receptor agonists (GLP-1 RA)

**MOA:** activates GLP-1 receptors which leads to: ↑ glucose-dependent insulin secretion, ↓ glucagon secretion, ↓ gastric emptying, ↑ satiety

**Monitoring:** renal function, side effects

**Contraindications:** gastroparesis, personal or FH of MEN2, personal or FH of medullary thyroid cancer, h/o pancreatitis

**Renal considerations:**
- Exenatide not indicated eGFR <30
- Lixisenatide: caution eGFR<30
- Increased risk for AKI with starting GLP-1 or titrating
- **Progression of DKD benefit:** liraglutide (LEADER trial)

- Dulaglutide (Trulicity) - weekly
- Exenatide (Byetta) - bid
- Exenatide XR (Bydureon) – weekly
- Liraglutide (Victoza) – daily
- Lixisenatide (Adlyxin) – weekly
- Semaglutide (Ozempic) - weekly
- Albiglutide (Tanzeum) – weekly

(Shown to have CV benefit in CVOTs)

LEADER, SUSTAIN-6, HARMONY trials

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GLP-1 RAs

Non-insulin injectable medications – either daily or weekly

Beneficial side effect of weight loss, highly efficacious

Starting dose and titration varies per drug – limited mostly by GI side effects

CVOT’s showed CVD benefit in Liraglutide > Semaglutide > Exenatide XR

- Liraglutide has FDA approved indication for reduction of CV on label

Black Box warning: risk of thyroid C-cell tumors (? Incr risk for pancreatitis)

$$$ - National Average Drug Acquisition Cost (NADAC) = $792-$1,044
**Sodium-glucose cotransporter-2 inhibitors (SGLT-2 inhibitors)**

**MOA:** Inhibits SGLT2 in the proximal nephron and ↓ glucose reabsorption at level of kidney

**Monitoring:** renal function (transient drop in creatinine after starting), dehydration, blood pressure

**Contraindications:** h/o DKA, recurrent UTI or genital candidiasis, peripheral vascular disease or h/o foot ulceration/poor lower extremity circulation* (empagliflozin)

**Renal considerations:**
- Canagliflozin: not recommended eGFR <45
- Dapagliflozin: not recommended eGFR <60, contraindicated <30
- Empagliflozin: contraindicated eGFR <30
- Progression of DKD benefit: Empagliflozin and canagliflozin

**Canagliflozin (Invokana)**
**Dapagliflozin (Farxiga)**
**Empagliflozin (Jardiance)**
**Ertugliflozine (Steglatro)**

(Shown to have CV benefit in CVOTs)

**SGLT-2 inhibitors**

Once daily oral medication

Beneficial side effect of weight loss, moderately efficacious blood sugar lowering

Preferred agent for patients with ASCVD at high risk for or with heart failure

CVOT’s showed CVD benefit in Empagliflozin > Canagliflozin
- Empagliflozin has FDA approved indication for reduction of CV on label

Starting dose and titration varies per drug – monitor for hypotension, UTI’s, genital mycotic infections

Black box warning: risk of amputation (empagliflozin) (? Fournier’s gangrene)

$\$\$\$ - NADAC = $257 - $448
SGLT-2 inhibitors

Risk of bone fractures (canagliflozin) – FDA alert 2015

Euglycemic DKA risk (all agents) – FDA alert 2015
- seen in acute hospitalization settings (recent surgery, acute illness)
- in situations of insulin deficiency (reduction or stopping insulin, pancreatitis, DM1)
- Large diet changes (reducing calories, increased exercise)
- Alcohol use

*Take away: counsel patients of s/s of ketoacidosis, consider teaching use of keto sticks?, advise not to stop insulin

https://www.fda.gov/drugs/drug-safety-and-availability

SGLT-2 inhibitors and FDA warnings

Amputations:
Empagliflozin had incidentally noted increased risk of amputation (level of toe or metatarsal) -> Black box warning in 2017
2018 meta-analysis showed no significant increased risk for BKA with canagliflozin vs non-SGLT2 drug classes (OBSERVE-4D trial)
Take away: caution in prescribing with poor circulation or h/o amputations/ulcers

Fournier’s Gangrene:
FDA identified 12 cases on review from 5/2013-5/2018. Warning was issued and added to SGLT-2 labels
May 2019 report identified 55 cases – all severely ill and required hosp and management (3 died)
Take away: advise patients of s/s, have low threshold for considering the possibility

https://www.fda.gov/drugs/drug-safety-and-availability
Bersoff-Matcha et al. 2019
You and Beth discussed options, she started on once weekly semaglutide and has started testing sugars. Also started Lisinopril 10mg bid b/c of microalbuminuria and BP above goal.

She’s back for 3 month follow-up after starting meds. She is having trouble with side effects from the semaglutide, although, she has lost 10 lbs. Her BP has been improved since starting Lisinopril and is at goal (132/80 today).

You recheck labs: A1c is 7%, eGFR >60, random glucose 98 and urine MAB/creat is now <30

Medications: IUD, multivitamin, metformin 1000mg bid, atorvastatin 10mg qd, Lisinopril 10mg bid

**Next step? A1c better, but not tolerating GLP-1 very well.**
**Dipeptidyl peptidase-4 inhibitors (DPP-4)**

**MOA:** Inhibits DPP-4 (enzyme that breaks down endogenous GLP-1), ↑ GLP-1 & GIP, ↑ glucose dependent insulin secretion and ↓ glucose dependent glucagon secretion

**Monitoring:** renal function

**Contraindications:** ? History of pancreatitis

**Renal considerations:** okay for use in CKD. All require renal dose adjustment except for Linagliptin

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**DPP-4 inhibitors**

Generally well tolerated, no risk for hypoglycemia

Weight neutral with moderate efficacy (less than GLP-1)

Once daily oral – no dose titration

Do not use in conjunction with GLP-1 (no notable benefit and ? higher pancreatitis risk)

CVOTs – no benefit (yet), but possible risk for CHF patients with saxagliptin and alogliptin

$$ - NADAC = $170 - $314$$
Case Finale

Beth stopped the semaglutide and started empagliflozin. She is tolerating well without side effects. She has been able to reduce her weight by another 20 lbs and is working hard at lifestyle improvements.

Labs: A1c 6.7%, eGFR >60, lipids: TC 195, Tg 130, HDL 35, LDL 100

You plan to follow-up with her every 6 months for now.

References


DeFronzo R. From the triumvirate to the Ominous Octet: A new paradigm for the treatment of Type 2 Diabetes Mellitus. Diabetes. 2009 Apr; 58(4): 773-795. https://doi.org/10.2337/db09‐9028


* Information on how to find the cardiovascular outcome trials referenced in this presentation available on request*
### Profiles of Antidiabetic Medications

<table>
<thead>
<tr>
<th>MET</th>
<th>GLP-1 RA</th>
<th>SGLT2i</th>
<th>DPP4i</th>
<th>AGI</th>
<th>TZD</th>
<th>SU</th>
<th>GLN</th>
<th>COLSUL</th>
<th>BCR-QR</th>
<th>INSULIN</th>
<th>PRAML</th>
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### Renal/GU
- Contraindicated: eGFR < 30 mL/min/1.73 m²
- Not indicated for eGFR 45 mL/min/1.73 m²
- Renal Myocardial infarctions
- Effect in Reducing Albuminuria
- Possible Benefit of LDL/LDL
- Possible CHD Benefit

### GI/Sx
- Upper: Moderate
- Lower: Moderate

### Cardiovascular
- Normal: See #1
- Severe: See #3
- Moderate: See #2

### Bone
- Neutral

### Ketoadeosis
- DKA Can Occur in Various Stress Settings

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### Grading of severity of hirsutism in women

![Grading of severity of hirsutism in women](image)

Ferriman–Gallwey hirsutism scoring system. Each of the nine body areas that is most sensitive to androgens is assigned a score from 0 (no hair) to 4 (frankly virile), and these are summed to provide a hormonal hirsutism score. "Focal" hirsutism (score 1 to 7) is a common normal variant, whereas generalized hirsutism (score of 8 or more) is abnormal in the general United States population. The normal score is lower in Asian populations and higher in Mediterranean populations.

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