Management: How Can We Do Better?

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2018 Virginia ACP Clinical Update
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Disclosures

I have no Disclosures
Objectives

• Use a case-based format to discuss diabetes management pearls
• Discuss diabetes management in the context of the 2018 ADA Practice Guideline
Epidemiology of Diabetes

Figure 2. Age-adjusted, county-level prevalence of diagnosed diabetes among adults aged ≥20 years, United States, 2013

2013 Diagnosed Diabetes Prevalence

Data source: United States Diabetes Surveillance System.
I Just Need Insulin Refills

- 21 y/o female with type 1 DM presents to your practice as a new patient
- Diagnosed with type 1 DM at age 7
- Previously on insulin pump therapy
- Reports her last endocrinologist stopped filling her prescriptions for insulin supplies
- HgbA1C% of 13%
- Current regimen: Lantus 34 units nightly and Novolog with meals based on carbohydrate count
- BMI 19
- Has received laser therapy for proliferative retinopathy
- 3 admissions in the last year for DKA
“I Just Need Insulin Refills”

What is your next best step?
   a. Pregnancy test
   b. Refill insulin and refer the patient to a new endocrinologist
   c. Refer the patient to a certified diabetes educator
   d. Ask the patient about prior admissions for DKA
   e. **Intensify the insulin regimen with correction factor**
   f. Ask the patient to describe techniques used for carbohydrate counting
   g. Ask the patient about symptoms of depression and/or anxiety
   h. Ask the patient about her perception of barriers to achieving glycemic control
   i. Ask about frequency and severity of hypoglycemia
# ADA Recommendations

Table 4.2—Situations that warrant referral of a person with diabetes to a mental health provider for evaluation and treatment

- If self-care remains impaired in a person with DD after tailored diabetes education
- If a person has a positive screen on a validated screening tool for depressive symptoms
- In the presence of symptoms or suspicions of disordered eating behavior, an eating disorder, or disrupted patterns of eating
- If intentional omission of insulin or oral medication to cause weight loss is identified
- If a person has a positive screen for anxiety or fear of hypoglycemia
- If a serious mental illness is suspected
- In youth and families with behavioral self-care difficulties, repeated hospitalizations for diabetic ketoacidosis, or significant distress
- If a person screens positive for cognitive impairment
- Declining or impaired ability to perform diabetes self-care behaviors
- Before undergoing bariatric or metabolic surgery and after surgery if assessment reveals an ongoing need for adjustment support
“I Just Need Insulin Refills”

- Patient returns to clinic after seeing mental health provider, and has been prescribed an antidepressant
- Overall glycemic control is improved by review of blood sugars
- Patient is very concerned regarding her weight gain of 15 pounds
- Patient is using Spark People app to calculate carbohydrates
- You recommend adding a correction factor if premeal blood sugars exceed 200 mg/dl
- At the next appointment, glycemic control has worsened
- What do you suspect?
<table>
<thead>
<tr>
<th>Table 2. Warning Signs of Eating Disorders in T1DM Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin manipulation</td>
</tr>
<tr>
<td>Unusually high A1C test results, unstable metabolic control, hyperglycemia</td>
</tr>
<tr>
<td>Deterioration in psychosocial functioning</td>
</tr>
<tr>
<td>Neglect of diabetes management</td>
</tr>
<tr>
<td>Weight loss or gain</td>
</tr>
<tr>
<td>Frequent dieting, preoccupation with meal planning</td>
</tr>
<tr>
<td>Anxiety about or avoidance of weigh-ins</td>
</tr>
<tr>
<td>Frequent bouts of hypoglycemia</td>
</tr>
<tr>
<td>Delayed onset of puberty</td>
</tr>
<tr>
<td>Poor self-esteem</td>
</tr>
<tr>
<td>Frequent diabetic ketoacidosis</td>
</tr>
<tr>
<td>Bingeing</td>
</tr>
<tr>
<td>Depressive symptoms</td>
</tr>
<tr>
<td>Early onset of microvascular complications</td>
</tr>
<tr>
<td>Severe family stress</td>
</tr>
<tr>
<td>Excessive exercise</td>
</tr>
</tbody>
</table>

*A1C: glycosylated hemoglobin; T1DM: type 1 diabetes mellitus.*

*Source: References 4, 8, 15, 29.*
“I Don’t Feel My Low Blood Sugars Anymore”

• 22 y/o female with type 1 DM presents to clinic for OCP renewal and for symptoms of feeling ”cold all the time”
• Diagnosed with type 1 DM at age 8
• Has a family history of thyroid disease
• Excellent glycemic control with HgbA1C% of 6.0%
• On academic scholarship, runs track
• On basal-bolus regimen with carb ratio of 1:10 and correction of 1:15 gm/dl
• Reports she had a “mild” motor vehicle accident
• Checks blood sugars 6-8 times per day
• BMI is 21, she has lost 7 pounds over 3 months
“I Don’t Feel My Low Blood Sugars Anymore”

You recommend:

a. Eat 15-20 grams of carbohydrate before exercise
b. Decrease the short-acting insulin dose by 50% for the meal before exercise
c. Keep track of blood sugars every 2 hours during a daytime fast
d. Check blood sugars at 2-3 am
e. Review medication list
f. Refer to Endocrinologist for continuous glucose monitor
g. Decrease total daily insulin doses by 10-15%
h. Check TSH
“I Don’t Feel My Low Blood Sugars Anymore”

- Physical exam demonstrates small diffuse goiter
- Thyroid peroxidase antibodies are elevated
- TSH is 11
- You prescribe 75 mcg levothyroxine per day
- She calls the office and reports that she is not tolerating the levothyroxine well, she complains of nausea, lightheadedness and describes having a near-syncopal event
- What happened?
Hypoglycemia Unawareness

Cycle of Recurrent Hypoglycemia (Nocturnal and Daytime) and Reduced Hypoglycemia Awareness

- Iatrogenic hyperinsulinemia (insulin replacement and/or OADs)
- Alcohol ingestion, unplanned exercise
- Impaired sympathetic and adrenal responses
- Severe hypoglycemia

Frequent hypoglycemia

- Tight glycemic control
- Reduced or absent glucagon (counterregulatory) response to hypoglycemia

Reduced cognition and sympathetic output during sleep

Initial symptom loss

Hypoglycemia unawareness
“Grandpa Passed Out”

- 82 y/o male with type 2 DM of 20 years duration
- PMH includes ASCAD (CABG), peripheral neuropathy, proliferative retinopathy s/p VEGF inhibitor therapy, Stage 3 CKD
- Regimen: Glargine 50 units nightly, 10 units Aspart with meals
- Recently admitted to the hospital for severe hypoglycemia
- HgbA1C% is 7.1%
“Grandpa Passed Out”

You do the following:

a. Ask about alcohol consumption
b. Review medication list
c. Recheck serum creatinine
d. Review blood sugar trends with emphasis on bedtime glucose values
e. Ask about colors of insulin pens
f. Liberalize glycemic goals
Depicted are patient and disease factors used to determine optimal A1C targets.

American Diabetes Association Clin Diabetes 2018;36:14-37
“I Am So Discouraged Doc”

- 57 y/o male returns to clinic for follow-up for type 2 DM
- Current regimen: Glargine 70 units bid, Aspart 45-60 units with meals
- HgbA1C% is 9.2%
- PMH: migraines, hypertension, chronic back pain
- Medications: amitriptyline, gabapentin, amlodipine
- BMI 37
- Progressive weight gain over the last one year
“I Am So Discouraged Doc”

Your next step:

a. Convert to U500 insulin tid with meals
b. Send a message to her neurologist suggesting topiramate as an alternative to amitriptyline
c. Refer for bariatric surgery
d. Recommend exercise 150 minutes per week
e. Increase basal insulin by 10%
f. Add GLP-1 based therapy
Watch your patient inject

- Removing the needle cap?
- Injecting in an area of lipohypertrophy or surgical scar?
- Injecting in thigh muscle?
- Priming the insulin pen device?
- Holding needle in position after injection for a few seconds?
## Antidepressants

- Venlafaxine
- Sertraline
- Citalopram
- Escitalopram
- Duloxetine
- Mirtazapine
- Amitriptyline

## Antipsychotics

- Aripiprazole
- Olanzapine
- Quetiapine
- Clozapine
- Risperidone
- Ziprasidone
- Paliperidone

## Anticonvulsants

- Carbamazepine
- Valproic Acid
- Lamotrigine
- Gabapentin
- Phenobarbital

## Mood Stabilizers

- Lithium
- Sodium Valproate
- Lamotrigine

## Migraine Medications

- Sumatriptan
- Ergotamine

## Beta Blockers

- Propranolol
- Metoprolol
- Atenolol

## Calcium Channel Blockers

- Diltiazem
- Verapamil

## Alpha Agonists

- Clonidine

## Antihistamines

- Diphenhydramine

## Antiretrovirals

- AZT
- D4T
- 3TC

## Glucocorticoids

- Prednisone
- Methylprednisolone

## Other Common Medications

- Antibiotics
- Antibiotics
- Antifungals
- Antifungals
- Antivirals
- Antivirals

## Drug Interactions

- Interactions with antipsychotics, anticonvulsants, and mood stabilizers can occur. It is important to monitor for potential interactions and adjust dosages accordingly.
Combining Incretin-Based Therapies with Insulin

- Incretin based therapies are most effective in improving postprandial glucose (longer acting agents may have a greater effect on FPG than short acting agents)
- Promising: weight loss and decrease in total daily insulin dose, decreased rates of hypoglycemia
Combining Incretin-Based Therapies with Insulin

- Studies with Incretin based therapy as an add-on to insulin:
  - Resulted in 15-63% dose reduction in insulin dose
  - Resulted in 28% reduction in total daily dose of insulin in highly insulin resistant patients
  - GLP-IRAs have better glucose lowering results than DPP-4 inhibitors
Testing the Basal Insulin (with fasting)
Testing the Prandial Insulin

- Obtain premeal blood sugar and record
- Inject insulin at currently prescribed dose
- Check blood sugar at hourly intervals for 4 consecutive hours
- “Rule of 40 mg/dl”

- To little insulin: >180 mg/dl
- To much insulin: <100 mg/dl
Correction Factor/Sensitivity Factor

- Total amount of Insulin per day: (use a three day average)
- Basal daily total: ______units + Bolus daily total: ______units
- Divide: 1700 by Total Daily Insulin.
- This is the Sensitivity Factor/Correction Factor
- Example: 14 units basal insulin + 16 units bolus insulin = 30 units total daily insulin
- 1700/30 = 50
- This Correction Factor means that 1 unit of insulin will lower blood glucose by approximately 50mg/dl

Factors studied: 1500, 1700, 1800
Correction Factor to Calculate a Correction Bolus

• Correction Bolus Formula: \( (\text{Current BG}) - (\text{Target BG}) = \text{difference/correction factor} \)

• Example: Current BG = 200 mg/dl - Target BG = 100 mg/dl = difference 100 mg/dl

• \( 100/50 = 2 \) units of insulin

• Can be added to prandial insulin doses to create a “SMARTER” premeal dose
Once a starting TDD is determined, find your value in column one and look across that row for close estimates of your starting basal rate, carb factor, and correction factor.

<table>
<thead>
<tr>
<th>Starting TDD(^1) =</th>
<th>Day’s Basal(^2)</th>
<th>Average Basal(^3)</th>
<th>Carb Factor(^4) 1u covers:</th>
<th>Corr. Factor(^5) 1u lowers BG:</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 units</td>
<td>7 units</td>
<td>0.30 u/hr</td>
<td>25 grams</td>
<td>100 mg/d (5.5 mmol)</td>
</tr>
<tr>
<td>22 units</td>
<td>9 units</td>
<td>0.37 u/hr</td>
<td>20 grams</td>
<td>82 mg/dl (4.5 mmol)</td>
</tr>
<tr>
<td>26 units</td>
<td>10 units</td>
<td>0.43 u/hr</td>
<td>17 grams</td>
<td>69 mg/dl (3.8 mmol)</td>
</tr>
<tr>
<td>30 units</td>
<td>12 units</td>
<td>0.50 u/hr</td>
<td>15 grams</td>
<td>60 mg/dl (3.3 mmol)</td>
</tr>
<tr>
<td>35 units</td>
<td>14 units</td>
<td>0.58 u/hr</td>
<td>13 grams</td>
<td>51 mg/dl (2.9 mmol)</td>
</tr>
<tr>
<td>40 units</td>
<td>16 units</td>
<td>0.67 u/hr</td>
<td>11 grams</td>
<td>45 mg/dl (2.5 mmol)</td>
</tr>
<tr>
<td>45 units</td>
<td>18 units</td>
<td>0.75 u/hr</td>
<td>10 grams</td>
<td>40 mg/dl (2.2 mmol)</td>
</tr>
<tr>
<td>50 units</td>
<td>20 units</td>
<td>0.83 u/hr</td>
<td>9 grams</td>
<td>36 mg/dl (2.0 mmol)</td>
</tr>
<tr>
<td>60 units</td>
<td>24 units</td>
<td>1.00 u/hr</td>
<td>8 grams</td>
<td>30 mg/dl (1.6 mmol)</td>
</tr>
<tr>
<td>70 units</td>
<td>28 units</td>
<td>1.17 u/hr</td>
<td>6 grams</td>
<td>26 mg/dl (1.4 mmol)</td>
</tr>
<tr>
<td>80 units</td>
<td>32 units</td>
<td>1.33 u/hr</td>
<td>6 grams</td>
<td>23 mg/dl (1.3 mmol)</td>
</tr>
<tr>
<td>90 units</td>
<td>36 units</td>
<td>1.50 u/hr</td>
<td>5 grams</td>
<td>20 mg/dl (1.1 mmol)</td>
</tr>
<tr>
<td>100 units</td>
<td>40 units</td>
<td>1.67 u/hr</td>
<td>5 grams</td>
<td>18 mg/dl (1.0 mmol)</td>
</tr>
</tbody>
</table>

\(^1\) Calculate the starting TDD on page 117.
\(^2\) Day’s basal is 40% of the TDD
\(^3\) Avg Basal = day’s basal/24 hrs
\(^4\) Carb Factor = 450/TDD
\(^5\) Correction Factor = 1800/TDD in mg/dl or 100/TDD in mmol
## Converting to U-500

### Table 2. Administration and Dosing of U-500 Insulin

<table>
<thead>
<tr>
<th>TDD (U/day)</th>
<th>Injection Schedule</th>
<th>How Doses Are Weighted</th>
<th>Dosing Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>200-299</td>
<td>2 injections per day (8 AM, 6 PM)</td>
<td>60/40</td>
<td>BG level &lt;50 mg/dL above or below target range: Increase or decrease U-500 in increments of 5 U (0.01 mL) per dose</td>
</tr>
<tr>
<td></td>
<td>3 injections per day (8 AM, 12 noon, 6 PM)</td>
<td>40/30/30, 45/35/20, or 40/40/20</td>
<td>BG level ≥50 mg/dL above or below target range: Increase or decrease U-500 in increments of 10 U (0.02 mL) per dose</td>
</tr>
<tr>
<td>300-599</td>
<td>3 injections per day (8 AM, 12 noon, 6 PM)</td>
<td>40/30/30, 45/35/20, or 40/40/20</td>
<td>BG level within 100 mg/dL above or below target range: Increase or decrease U-500 in increments of 25 U (0.05 mL) per dose</td>
</tr>
<tr>
<td></td>
<td>4 injections per day (8 AM, 12 noon, 5 PM, 10 PM)</td>
<td>30/30/30/10</td>
<td>BG level &gt;100 mg/dL above or below target range: Increase or decrease U-500 in increments of 50 U (0.1 mL) per dose</td>
</tr>
<tr>
<td>≥600</td>
<td>4 injections per day</td>
<td>30/30/30/10</td>
<td>Increase or decrease U-500 in increments of 50 U (0.1 mL) per dose</td>
</tr>
</tbody>
</table>

*As a percentage of TDD. BG: blood glucose; TDD: total daily dose. Used with permission from Drs. Cochrane and Gordon. Source: Reference 12.*
## Converting to U-500

### Table 1: Conversion Information for Humulin R U-500 Insulin Dose
When Using a U-100 Insulin Syringe or a Tuberculin Syringe

<table>
<thead>
<tr>
<th>Humulin R U-500 dose (units)</th>
<th>U-100 insulin syringe (unit markings)</th>
<th>Tuberculin syringe (volume in mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>5</td>
<td>0.05</td>
</tr>
<tr>
<td>50</td>
<td>10</td>
<td>0.1</td>
</tr>
<tr>
<td>75</td>
<td>15</td>
<td>0.15</td>
</tr>
<tr>
<td>100</td>
<td>20</td>
<td>0.2</td>
</tr>
<tr>
<td>125</td>
<td>25</td>
<td>0.25</td>
</tr>
<tr>
<td>150</td>
<td>30</td>
<td>0.3</td>
</tr>
<tr>
<td>175</td>
<td>35</td>
<td>0.35</td>
</tr>
<tr>
<td>200</td>
<td>40</td>
<td>0.4</td>
</tr>
<tr>
<td>250</td>
<td>50</td>
<td>0.5</td>
</tr>
<tr>
<td>275</td>
<td>55</td>
<td>0.55</td>
</tr>
<tr>
<td>300</td>
<td>60</td>
<td>0.6</td>
</tr>
<tr>
<td>325</td>
<td>65</td>
<td>0.65</td>
</tr>
<tr>
<td>350</td>
<td>70</td>
<td>0.7</td>
</tr>
<tr>
<td>375</td>
<td>75</td>
<td>0.75</td>
</tr>
<tr>
<td>400</td>
<td>80</td>
<td>0.8</td>
</tr>
<tr>
<td>425</td>
<td>85</td>
<td>0.85</td>
</tr>
<tr>
<td>450</td>
<td>90</td>
<td>0.9</td>
</tr>
<tr>
<td>475</td>
<td>95</td>
<td>0.95</td>
</tr>
<tr>
<td>500</td>
<td>100</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**Dose (actual Humulin R U-500 units)**

- **Divide dose (actual Humulin R U-500 units) by 5**
- **Divide dose (actual Humulin R U-500 units) by 500**
Patients will require significant reduction in or stoppage of prandial insulin doses/secretagogues while on the liquid protein diet before and after surgery, need for basal reduction is variable.
Patients having a milder form of diabetes and who achieve greater weight loss after surgery are more likely to achieve complete resolution of diabetes mellitus.

Roux-en-Y gastric bypass improves diabetes through rapid weight loss, by exclusion (bypassing) of the initial portion of the jejunum from the flow of nutrients and by altering production of various gut hormones leading to improvement of insulin secretion and resistance.

Roux-en-Y gastric bypass is the most powerful operation to control diabetes. Patients will require significant reduction in or stoppage of prandial insulin doses/secretagogues while on the liquid protein diet before and after surgery, need for basal reduction is variable.
“Aunt Sue Calls For Advice”

- Your Aunt Sue calls to “chat” after her recent visit to her primary care provider
- 61 y/o with type 2 DM for two years on monotherapy (metformin 1000 mg bid)
- PMH: hypertension, hyperlipidemia, ASCAD s/p MI
- HgbA1C% is 8%
- Her physician has recommended addition of sulfonylurea and she is asking for your advice
Antihyperglycemic Therapy in Adults with Type 2 Diabetes

At diagnosis, initiate lifestyle management, set A1C target, and initiate pharmacologic therapy based on A1C:

- **A1C is less than 9%**, consider Monotherapy.
- **A1C is greater than or equal to 9%**, consider Dual Therapy.
- **A1C is greater than or equal to 10%**, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, consider Combination Injectable Therapy (See Figure 8.2).

### Monotherapy

**Lifestyle Management + Metformin**

Initiate metformin therapy if no contraindications* (See Table 8.1)

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

### Dual Therapy

**Lifestyle Management + Metformin + Additional Agent**

- **ASCVD?**
  - Yes: - Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations with * on p. 75 and Table 8.1)
  - No: - Add second agent after consideration of drug-specific effects and patient factors (See Table 8.1)

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

### Triple Therapy

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

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

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

### Combination Injectable Therapy

(See Figure 8.2)
Table 8.1—Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

<table>
<thead>
<tr>
<th>Medication</th>
<th>Efficacy</th>
<th>Hypoglycemia</th>
<th>Weight Change</th>
<th>CV Effects</th>
<th>Cost</th>
<th>Oral/SQ</th>
<th>Renal Effects</th>
<th>Additional Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>High</td>
<td>No</td>
<td>Neutral (Potential for Bladder Low)</td>
<td>Potential benefits</td>
<td>Neutral</td>
<td>Low</td>
<td>Oral</td>
<td>Neutral</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Intermediate</td>
<td>No</td>
<td>Less</td>
<td>Neutral</td>
<td>High</td>
<td>Oral</td>
<td>Neutral</td>
<td>• Blood glucose, fasting glucose, total cholesterol, triglycerides increased with eGFR &lt; 50</td>
</tr>
<tr>
<td>GLP-1 RAs</td>
<td>High</td>
<td>No</td>
<td>Less</td>
<td>Neutral</td>
<td>High</td>
<td>SQ</td>
<td>Neutral</td>
<td>• Blood glucose, fasting glucose, total cholesterol, triglycerides increased with eGFR &lt; 50</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Intermediate</td>
<td>No</td>
<td>Neutral</td>
<td>Neutral</td>
<td>High</td>
<td>Oral</td>
<td>Neutral</td>
<td>• Blood glucose, fasting glucose, total cholesterol, triglycerides increased with eGFR &lt; 50</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>High</td>
<td>No</td>
<td>Gain</td>
<td>Potential benefits</td>
<td>High</td>
<td>Oral</td>
<td>Neutral</td>
<td>• Blood glucose, fasting glucose, total cholesterol, triglycerides increased with eGFR &lt; 50</td>
</tr>
<tr>
<td>Sulfonylureas (second generation)</td>
<td>High</td>
<td>Yes</td>
<td>Gain</td>
<td>Neutral</td>
<td>High</td>
<td>Oral</td>
<td>Neutral</td>
<td>• Blood glucose, fasting glucose, total cholesterol, triglycerides increased with eGFR &lt; 50</td>
</tr>
<tr>
<td>Insulin</td>
<td>Highest</td>
<td>Yes</td>
<td>Gain</td>
<td>Neutral</td>
<td>Low</td>
<td>SQ</td>
<td>Neutral</td>
<td>• Lower risk, increased with eGFR, decreased triglycerides, increased lipids</td>
</tr>
<tr>
<td>Antagonists</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>High</td>
<td>SQ</td>
<td>Neutral</td>
<td>• Gastrointestinal side effects common (diarrhea, nausea)</td>
</tr>
</tbody>
</table>

*See ref. 31 for description of efficacy. FDA approved for CVD benefit. CVD, cardiovascular disease; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; NASH, nonalcoholic steatohepatitis; RAs, receptor agonists; SQ, subcutaneous; TLDM, type 2 diabetes.
FDA label: Liraglutide

- FDA News Release
- The U.S. Food and Drug Administration approved a new indication for Liraglutide (Victoza, Novo Nordisk) to reduce the risk of myocardial infarction, stroke, and cardiovascular death in adults with type 2 diabetes mellitus who have established cardiovascular disease.

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm531517.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery
The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.
FDA label: Empagliflozin

- FDA News Release
- The U.S. Food and Drug Administration approved a new indication for empagliflozin (Jardiance Boehringer Ingelheim Pharmaceuticals Inc.) to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and cardiovascular disease
EMPA-REG-OUTCOME study
RCT n=7,020

- **Benefits:** oral pill! weight loss!; improved blood pressure, some specific SGLT2i have shown reduced CV risk, rare to cause hypoglycemia as monotherapy

- **Drawbacks:** caution with CKD, cost, long-term CV effects being investigated (may not be a class effect (empagliflozin benefit, canagliflozin benefit but risk amputations seen)

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Zinman et al. “Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes.” N Engl J Med 2015. 373; 22. (Note: funded by Boehringer Ingelheim and Eli Lilly.)
FDA Safety Alert 05/16/2017: Canagliflozin

• FDA News Release
• Based on new data from two large clinical trials, the FDA has concluded that the type 2 diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR) causes an increased risk of leg and foot amputations. FDA is requiring new warnings, including the most prominent Boxed Warning to be added to the canagliflozin drug labels to describe this risk
## CANVAS Trials

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Canagliflozin (N=5795)</th>
<th>Placebo (N=4347)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke</td>
<td>26.9</td>
<td>31.5</td>
<td>0.86 (0.75–0.97)</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>11.6</td>
<td>12.8</td>
<td>0.87 (0.72–1.06)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>9.7</td>
<td>11.6</td>
<td>0.85 (0.69–1.05)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>7.1</td>
<td>8.4</td>
<td>0.90 (0.71–1.15)</td>
</tr>
<tr>
<td>Fatal or nonfatal myocardial infarction</td>
<td>11.2</td>
<td>12.6</td>
<td>0.89 (0.73–1.09)</td>
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<td>Fatal or nonfatal stroke</td>
<td>7.9</td>
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<tr>
<td>Hospitalization for any cause</td>
<td>118.7</td>
<td>131.1</td>
<td>0.94 (0.88–1.00)</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>5.5</td>
<td>8.7</td>
<td>0.67 (0.52–0.87)</td>
</tr>
<tr>
<td>Death from cardiovascular causes or hospitalization for heart failure</td>
<td>16.3</td>
<td>20.8</td>
<td>0.78 (0.67–0.91)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>17.3</td>
<td>19.5</td>
<td>0.87 (0.74–1.01)</td>
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<tr>
<td>Progression of albuminuria</td>
<td>89.4</td>
<td>128.7</td>
<td>0.73 (0.67–0.79)</td>
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<td>40% reduction in eGFR, renal-replacement therapy, or renal death</td>
<td>5.5</td>
<td>9.0</td>
<td>0.60 (0.47–0.77)</td>
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“My blood sugars were crazy when they gave me prednisone last year”

• 59 y/o male with type 2 DM and A1C% of 7.5%
• Current insulin regimen: 24 units of glargine and 5 units aspart with meals
• PMH: COPD with frequent exacerbations
• Just prescribed prednisone taper starting at 60 mg/dl
• What is your next step?
Half-life is the Key

<table>
<thead>
<tr>
<th>Glucocorticoid</th>
<th>Relative anti-inflammatory potency</th>
<th>Biological half-life</th>
<th>Relative mineralocorticoid effect</th>
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<tbody>
<tr>
<td>Cortisol/hydrocortisone</td>
<td>1</td>
<td>8-12 hrs</td>
<td>1</td>
</tr>
<tr>
<td>Prednisone/prednisolone</td>
<td>4</td>
<td>12-36 hrs</td>
<td>0.8</td>
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<tr>
<td>Methylprednisolone (not injectable)</td>
<td>5</td>
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<td>0.5</td>
</tr>
<tr>
<td>Triamcinolone (not injectable)</td>
<td>3-5</td>
<td>24-48 hrs</td>
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<tr>
<td>Dexamethasone</td>
<td>29</td>
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Prednisone and NPH

- 0.1 units kg for every 10 mg of prednisone or equivalent up to a maximum dose of 0.4 units/kg
- Given as a morning dose in addition to current regimen of insulin with the prednisone dose
A 64 y/o male followed in your practice for type 2 DM

Presents for follow-up and informs you of a recent diagnosis of lymphoma

He is scheduled to begin a 7 day course of chemotherapy which will include a morning dose of 10 mg dexamethasone each day

He was diagnosed with Type 2 diabetes mellitus 8 years ago, and he has been treated with metformin 1000 mg twice daily and his most recent hemoglobin A1C% is 7.5%

He feels well currently and has had no difficulty tolerating liquids or solid foods

Recent labs demonstrated a serum creatinine of 0.8 mg/dl

Physical exam is notable for mild central adiposity, other physical exam findings are generally unremarkable
Recent fingerstick glucose ranges from home record: before breakfast (119 to 145 mg/dl) before lunch (175 to 187 mg/dl) before dinner (190-220 mg/dl) before bed (195-245 mg/dl). Which is the following is the best management plan?

- a. Supplemental aspart insulin 30 minutes before meals if glucose exceeds 130 mg/dl
- b. Insulin glargine once daily and insulin apart before meals
- c. Premixed 70/30 Novolin insulin before each meal
- d. NPH insulin every morning before dexamethasone administration
- e. Insulin glargine once daily every morning before dexamethasone administration
# Half-life is the Key

## Table 1

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Natural Selection?

The End