A NEW TAKE ON DIABETES MEDICATIONS: *RISKS AND BENEFITS, OLD MEDICATIONS VERSUS NEW, AND NEW INFORMATION ON OLD MEDICATIONS*

JESSICA CONKLIN, PHARMD, PHC, BCACP, CDE
VISITING ASSISTANT PROFESSOR
UNM COLLEGE OF PHARMACY

LEARNING OBJECTIVES

- Describe the difference between the manufactures dosing of metformin and new recommendations on the dosing of metformin
- Identify new diabetes treatment options and how they differ from older options
- Recognize the new FDA warnings for the use of DPP4 inhibitors and SGLT2 inhibitors

METFORMIN

Mechanism of Action:

1. ↑ insulin sensitivity
2. ↓ hepatic glucose production
3. ↓ intestinal glucose absorption

Efficacy: ↓ A1C 1.5%

No hypoglycemia as monotherapy

Weight neutral

Adverse Effects

- Primarily GI (up to 50%)
  - Titrate dose at weekly intervals to minimize AEs
  - Give with meals
- B12 Deficiency
- Lactic acidosis- rare

METFORMIN

DOSING

- Maximum dose: 2550mg/day
- Maximum effective dose: 2000mg/day

DOSAGE FORMS

- IR tablets
- ER tablets
  - ER formulation, anecdotally, may be associated with less GI adverse effects

OLD VS NEW

RENAL DOSING

- OLD
  - Manufacturer's dosing
    - SCr > 1.5mg/dL (males)
    - SCr > 1.4mg/dL (females)
- NEW PROPOSED RECOMMENDATIONS

eGFR level (mL/min)	Action
> 60 mL/min	No renal contraindication to metformin
<60 and >45	Continued use
<45 and >30	Prescribe metformin with caution Use lower dose (e.g. 50%, of half-maximum dose)
<30	Stop metformin

METFORMIN

Clinical Scenario:

- 43 y/o male with T2DM presents to clinic for a follow-up
  - PMH
    - HTN, HL, Obesity
  - LABS
    - A1C 13%
  - MEDS
    - Metformin 1000mg twice daily
    - Atorvastatin 20mg
    - Lisinopril 10mg once daily
    - Glimepiride 2mg once daily
- Patient is in agreement to start insulin glargine

Clinical Question:

- Do you continue patient's metformin or do you discontinue metformin?

METFORMIN

Mechanism of Action:

1. **↑ insulin sensitivity**
2. ↓ hepatic glucose production
3. ↓ intestinal glucose absorption

SULFONYLUREAS

Mechanism of Action:

↑ insulin secretion from pancreatic β-cells

Efficacy: ↓ A1C ~1.5%

- More rapid effect
- Dose in the morning
- Low durability
- Weight gain

Glyburide
Glipizide/Glipizide XL (Glucotrol)
Glimepiride (Amaryl)

OLD VS NEW

OLD

- 2nd Generation Sulfonylureas created equal
  - Glyburide
  - Glipizide/Glipizide XL
  - Glimepiride

NEW

- Avoid glyburide due to higher risk of hypoglycemia
- Consider glipizide XL or glimepiride for once daily dosing

Clinical Scenario:

- 43 y/o male with T2DM presents to clinic for a follow-up
  - PMH
    - HTN, HL, Obesity
  - LABS
    - A1C 13%
  - MEDS
    - Metformin 1000mg twice daily
    - Atorvastatin 20mg
    - Lisinopril 10mg once daily
    - Glimepiride 2mg once daily
- Patient is in agreement to start insulin glargine

Clinical Question:

- Do you stop the patient's sulfonylurea when initiating a basal insulin?

DPP-4 INHIBITORS

Mechanism of Action:

Inhibition of dipeptidyl peptidase 4 enzyme resulting in prolonged activation of incretin levels (e.g GLP-1)

Efficacy: ↓ A1C 0.4-0.7%

- Approved for monotherapy or combination therapy
- Weight Neutral
- Minimal risk of hypoglycemia

Sitagliptin (Januvia®)

Linagliptin (Tradjenta ®)

Saxagliptin (Onglyza®)

Alogliptin (Nesina®)

DPP-4 INHIBITORS

OLD: Well tolerated

NEW: FDA says DPP-4 inhibitors for diabetes may cause severe joint pain *FDA MedWatch (08/28/15)*

FDA warning:

- DPP-4 inhibitors **could cause severe and disabling joint pain**.
- If patients experience these symptoms, should be counseled to talk to their health care provider immediately.
- Health care professionals should be alerted to DPP-4 inhibitors as a potential cause of severe joint pain. Discontinue medication, if appropriate.

Clinical Scenario:

AA is 71 y/o male with a PMH of T2DM, HTN, BPH and HL for a follow up visit. His A1C has increased from 6.9% to 8.0%. He walks 30minutes daily and tends to eat one large meal (dinner). He is currently taking metformin ER 500mg once daily (GFR= 42), lisinopril, tamsulosin, atorvastatin.

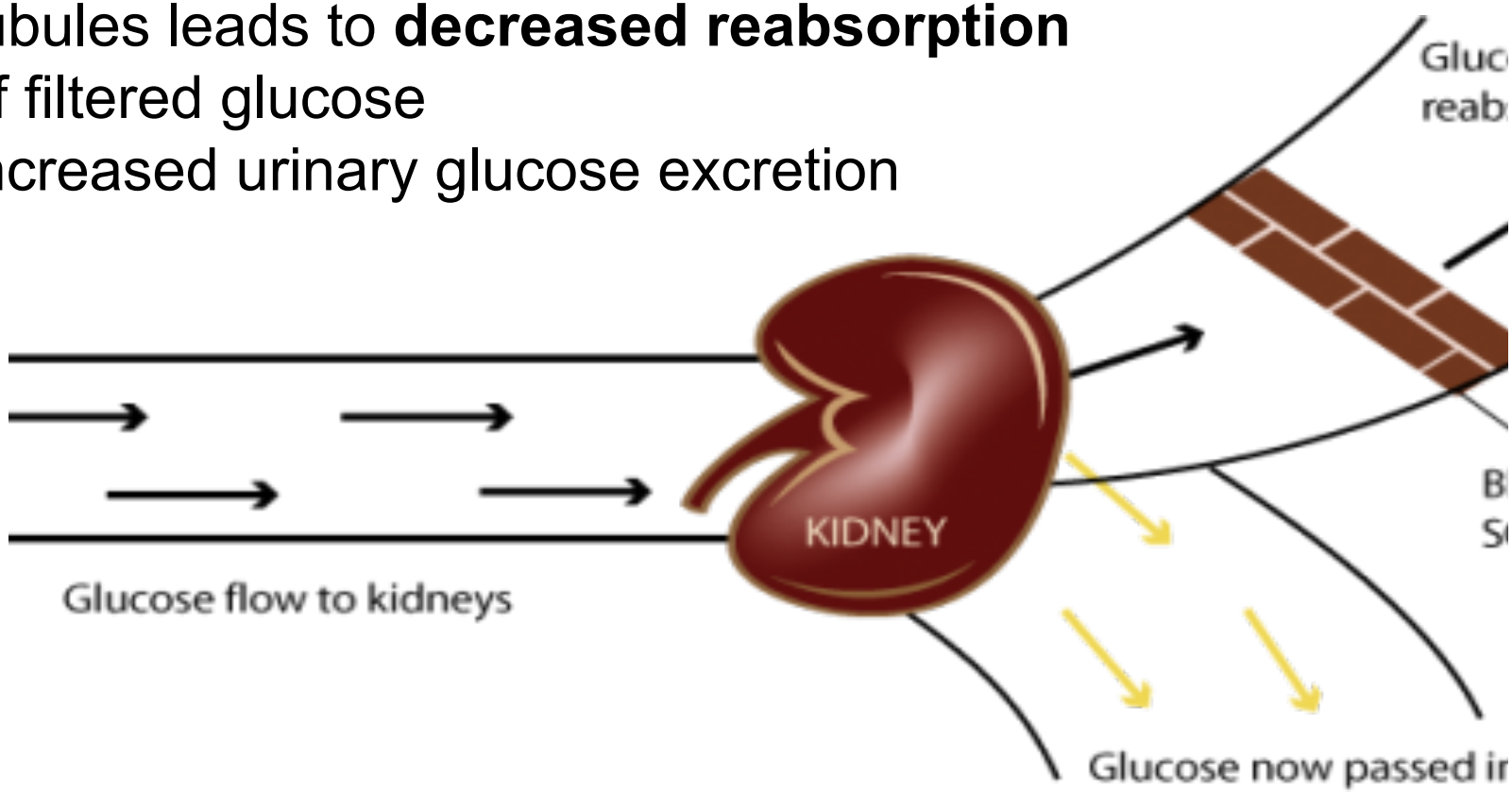
Clinical Question:

What oral agent would you consider adding to AA's regimen?

SGLT2 INHIBITORS

Mechanism of Action

- Inhibition of **S**odium-**GL**ucose co**T**ransportor**2** in the proximal renal tubules leads to **decreased reabsorption** of filtered glucose
- Increased urinary glucose excretion



SGLT2 INHIBITORS

Canagliflozin (Invokana™)

Dapagliflozin (Farxiga™)

Empagliflozin (Jardiance™)

Efficacy: ↓ A1C 0.5-1.0%

- Once daily oral medications
- Dose in the morning
- Correct volume depletion prior to initiating

NEW VS NEWER

NEW

- Well tolerated
  - Genital mycotic infections, UTI
  - Increased urination, weight loss

NEWER

- FDA says SGLT2 inhibitors for diabetes may carry **acidosis risk** (*FDA MedWatch (05/2015)*
- >50 cases of acidosis (ketoacidosis & metabolic)
  - 35 hospitalizations (4 off-label use)
    - Possible contributing factors: low carb diet, decreased food and fluids, reduced insulin and major illness

Clinical Scenario:

JM is a 39 year old female with a PMH of T2DM and obesity. She presents to your clinic stating that she joined Weight Watchers and is really trying to lose weight.

MEDICATIONS

Metformin 1000mg twice daily

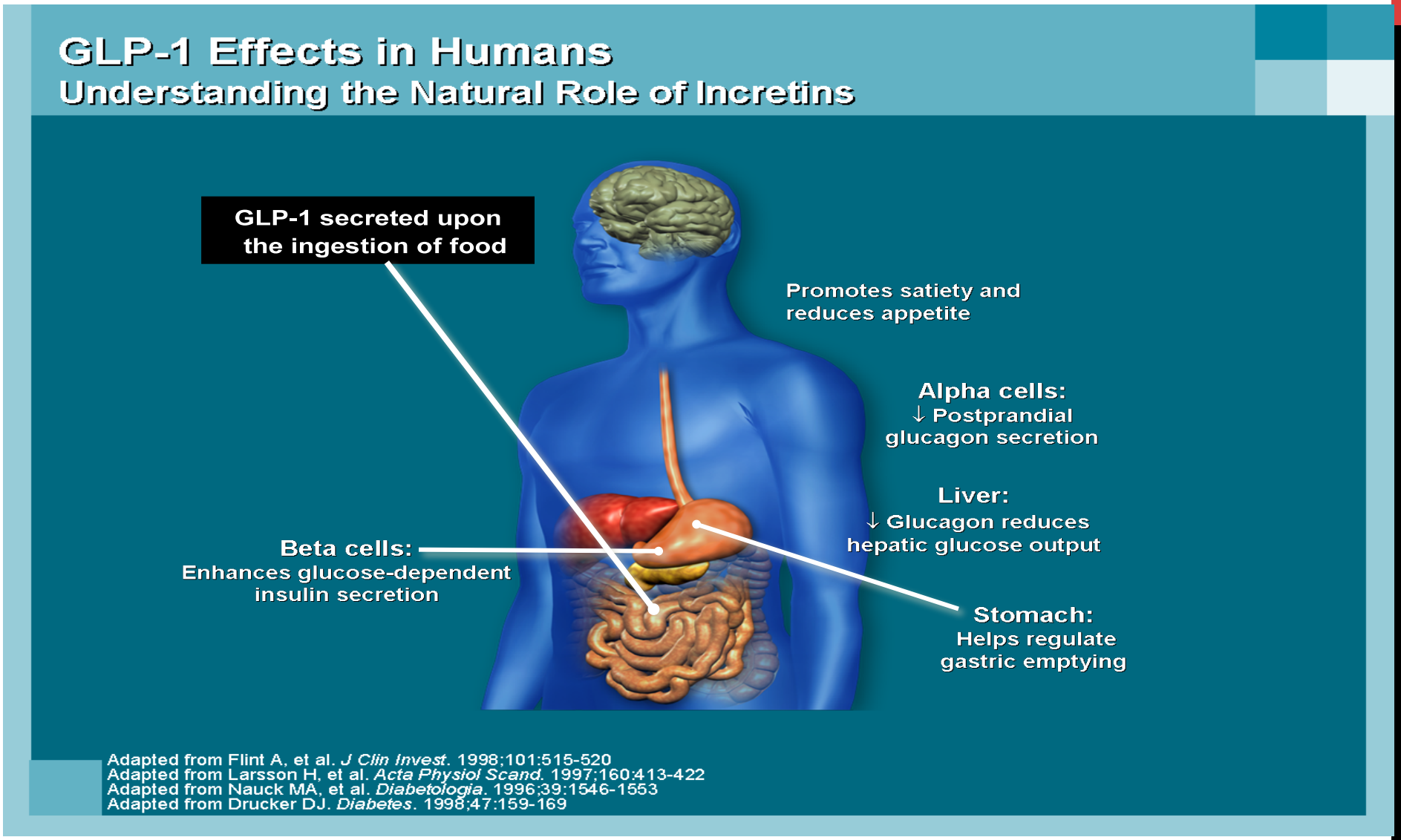
LABS

A1C 8.5%

Clinical Question:

What additional therapy would you consider for JM?

GLP-1 PHYSIOLOGY



GLUCAGON-LIKE PEPTIDE 1 (GLP-1) AGONISTS

Mechanism of Action:

Glucagon-like-peptide-1 (GLP-1) analogs

- Incretin mimetic
- Resistant to degradation by dipeptidyl peptidase-4 (DPP-4)
- Suppresses high glucagon levels
- Delays gastric emptying (**can affect absorption of other medications**)

Efficacy: ↓ A1C 0.5-1.6%

- Weight loss
- GI side effects
- CI in patients with gastroparesis

GLUCAGON-LIKE PEPTIDE 1 (GLP-1) AGONISTS

OLD:

- FDA approved for type 2 diabetes in patients on oral drugs or long-acting basal insulin

Exenatide (Byetta®): BID

Liraglutide (Victoza®): daily

Exenatide LAR (Bydureon®): weekly

Dulaglutide (Trulicity): Q weekly

Albiglutide (Tanzeum) Q weekly

NEW:

FDA approved for weight loss in patients without diabetes

- **Liraglutide (Saxenda):**
  - Approved for adults with a BMI >30 or BMI>27 with a weight related condition
  - ~4.5% weight loss from baseline compared to placebo

Clinical Scenario:

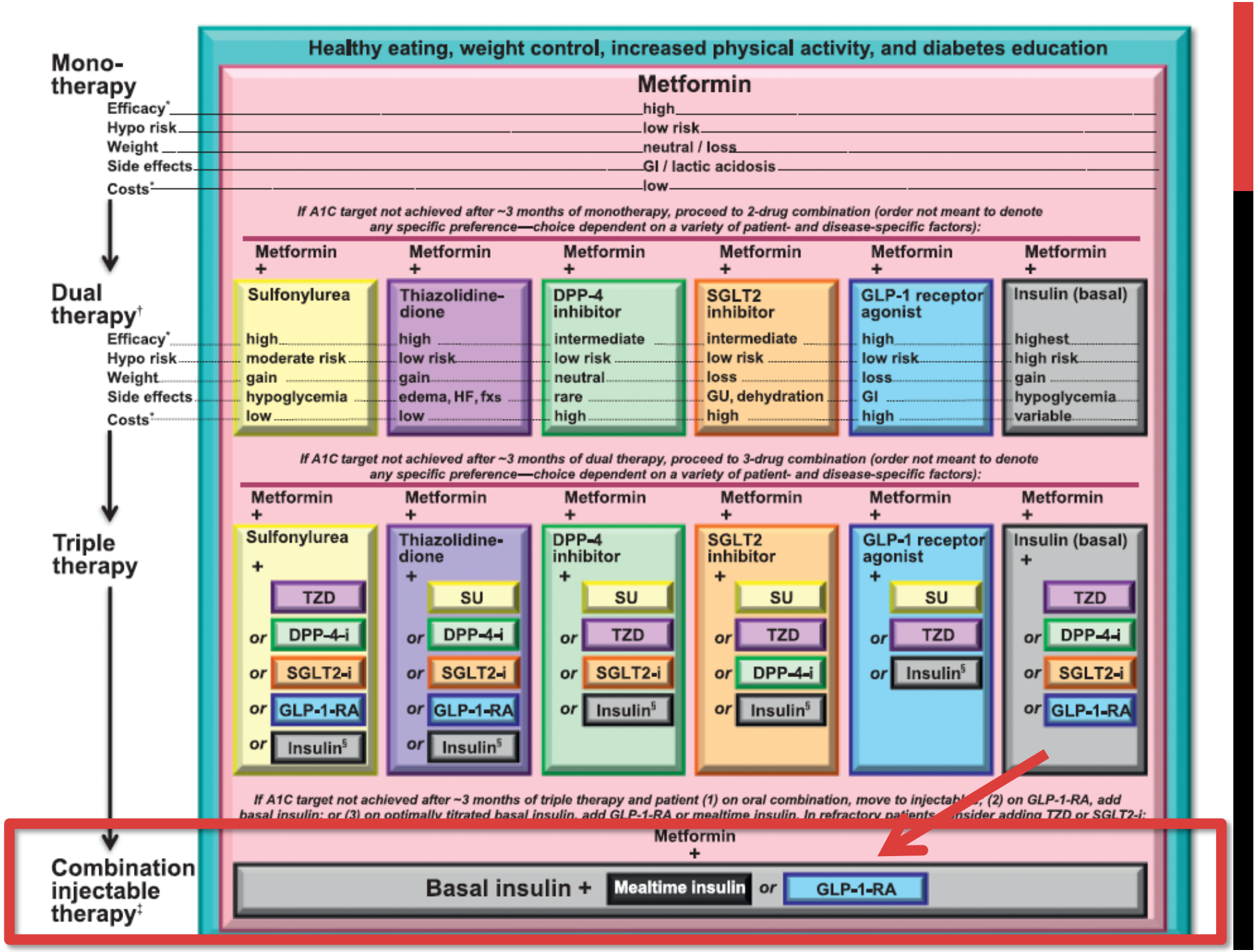
JJ is a 52 y/o male who has titrated his Lantus to 30 units. He presents to clinic with his blood glucose log. He is checking his blood sugar 3 times a day. His fasting blood sugars ranging from 99-129mg/dL and his postprandial blood glucose levels range from 212-270mg/dL. His A1C remains elevated at 9% (3 months after starting Lantus**)**

PMH: T2DM, Obesity, HTN

MEDICATIONS: Metformin, Lantus, Lisinopril

Clinical Question:

What agent would you start to control JJ's elevated postprandial blood glucose?


Healthy eating, weight control, increased physical activity, and diabetes education
Mono-therapy
Metformin
Efficacy* high
Hypo risk low risk
Weight neutral / loss
Side effects GI / lactic acidosis
Costs* low
If A1C target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):
Dual therapy†
Metformin + Sulfonylurea
Efficacy* high
Hypo risk moderate risk
Weight gain
Side effects hypoglycemia
Costs* low
Metformin + Thiazolidine-dione
high
low risk
gain
edema, HF, fxs
low
Metformin + DPP-4 inhibitor
intermediate
low risk
neutral
rare
high
Metformin + SGLT2 inhibitor
intermediate
low risk
loss
GU, dehydration
high
Metformin + GLP-1 receptor agonist
high
low risk
loss
GI
high
Metformin + Insulin (basal)
highest
high risk
gain
hypoglycemia
variable
If A1C target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):
Triple therapy
Metformin + Sulfonylurea + TZD or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin§
Metformin + Thiazolidine-dione + SU or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin§
Metformin + DPP-4 inhibitor + SU or TZD or SGLT2-i or Insulin§
Metformin + SGLT2 inhibitor + SU or TZD or DPP-4-i or Insulin§
Metformin + GLP-1 receptor agonist + SU or TZD or Insulin§
Metformin + Insulin (basal) + TZD or DPP-4-i or SGLT2-i or GLP-1-RA
If A1C target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectable; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients, consider adding TZD or SGLT2-i:
Combination injectable therapy‡
Metformin +
Basal insulin + Mealtime insulin or GLP-1-RA

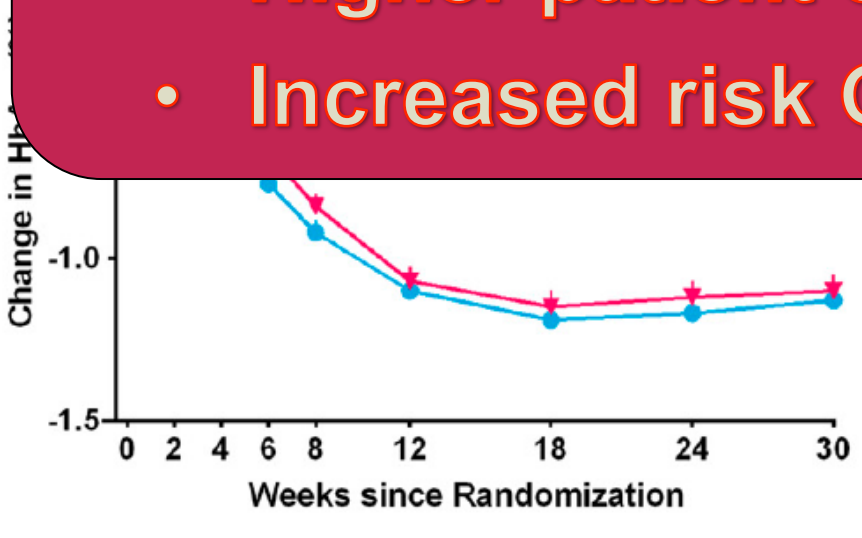
Glucagon-Like Peptide 1 Receptor Agonist or Bolus Insulin With Optimized Basal Insulin in Type 2 Di

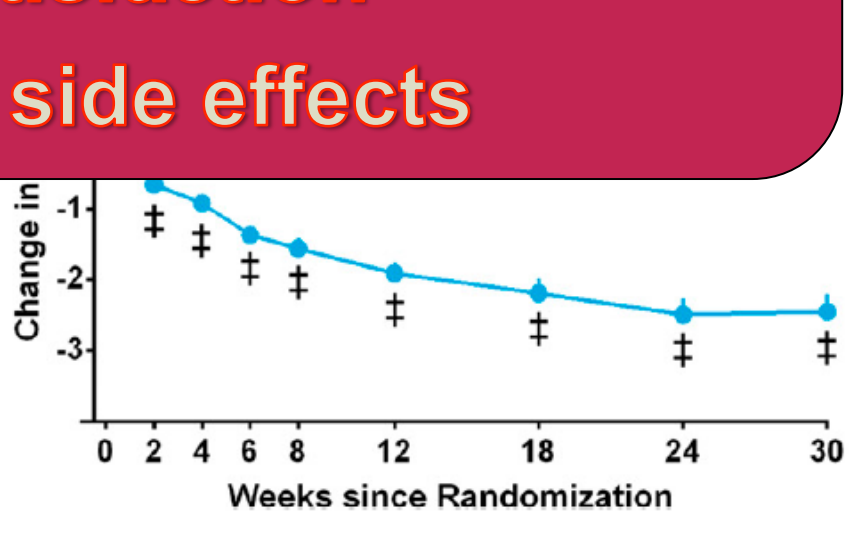
*Michaela Diamant,[1†] Michael A. Nauck,[2] Rimma Shaginian,[3] James K. Malone,[4] Simon Cleall,[5] Matthew Reaney,[5] Danielle de Vries,[3] Byron J. Hoogwerf,[4] Leigh MacConell,[6] and Bruce H.R. Wolffenbuttel,[7] for the 4B Study Group**

Diab

Exenatide therapy:

- Less nocturnal hypoglycemia
- Higher patient-satisfaction
- Increased risk GI side effects





RAPID-ACTING INSULIN

Onset 5-15 minutes

- Inject immediately before or 15 min before meals

Peak: ½ to 1 ½ hrs

Duration 3.5- 5 hours

RAPID ACTING INSULIN

OLD:

- **SQ insulin**
  - Insulin Lispro (Humalog®)
  - Insulin Aspart (Novolog®)
  - Insulin Glulisine (Apidra®)

New:

- **Inhaled insulin**
  - Insulin Human (Afrezza®)

INHALED INSULIN

Afrezza ™ (insulin human)

- Only available inhaled insulin
- Available in 4, 8 & 12 units
- PK differs from Rapid acting insulin
  - Faster onset, Faster off set
- Potentially less risk of dose stacking
- FEV1 prior to initiation
- Contraindicated in patients with asthma/COPD
- Not intended to replace injectable rapid acting insulin but rather used in a select patient population

Clinical Scenario:

KJ is a 21 year old T1DM who has been on insulin for 8 years. He presents to clinic asking if he could switch his rapid acting insulin to the “new inhaled insulin” as he is tired of giving himself injections.

PMH: T1DM, Asthma, depression

MEDICATIONS: insulin glargine, insulin aspart, albuterol, fluoxetine

Clinical Question: Is KJ a candidate for inhaled insulin?

INSULIN GLARGINE

Mechanism of Action

- Long acting/basal insulin
- 100units/mL
  - Onset: 4 to 5 hours
  - Peak: blunted
  - Duration of action: ~22+ hours

OLD VS NEW

OLD

Insulin glargine (U100) Lantus ™

NEW

Insulin glargine (U300) Toujeo ™

INSULIN GLARGINE U300

- 3x as much insulin in 1mL
- Reduced volume compared to U100
- Reduced surface area of SQ depot
- Slower and more constant rate of absorption
- Comparable glycemic control
- Less hypoglycemia-nocturnal

Clinical Scenario:

A 57 y/o male presents to clinic for diabetes management. He currently takes 48 units of glargine U100 once daily. He asks you about the new insulin as he has seen on TV.

PMH: Obesity, HTN, HL

MEDICATIONS: glargine, lisinopril, atorvastain

You are willing to meet the patient's request and start insulin glargine U300.

Clinical Question: What dose would you start?

INSULIN

Rapid Acting

- Humalog® (lispro)
- Novolog ® (aspart)
- Apidra ® (glulisine)
- **Afrezza® (human)**

Short Acting-Regular Insulin (R)

- Novolin® R
- Humulin® R

Intermediate Acting-NPH (N)

- Novolin® N
- Humulin ® N

Long Acting – Basal Insulin

- Levemir® (detemir)
- Lantus® (glargine)
- **Toujeo® (glargine)**

QUESTIONS?