The Oasis in the Desert: *Miracle Medications*

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Advanced Practice Nurse and
Certified Diabetes Care and Education Specialist
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Case Study: Fred, 61 Years Old With T2D, Obesity, Dyslipidemia, Hypertension, and History of MI

- Physical Examination
  - No apparent distress
  - Height: 5 ft 10 in
  - Weight: 246 lb (BMI: 35.3 kg/m^2)
  - Blood pressure: 130/88 mm Hg. Pulse 72bpm
  - No edema noted
- Laboratory Findings
  - Fasting blood glucose: 133 mg/dL; A1C: 8.6%; UACR 25 mg/g; eGFR: 70 mL/min/1.73 m^2
  - All other labs normal

PMH

-MI 4 years ago

- Medications
  - Atorvastatin 80 mg daily
  - Lisinopril 40 mg daily
  - Metoprolol tartrate 25 mg twice daily
  - Metformin 1000 mg twice daily
  - Aspirin 81 mg daily
- Allergies/Adverse Drug Events: GI issues when first starting Metformin
- Family Hx: Mother: dylsipidemia, MI age 68. Father HTN, Obesity
- Social
  - Lives alone, retired
  - Has BC/BS insurance

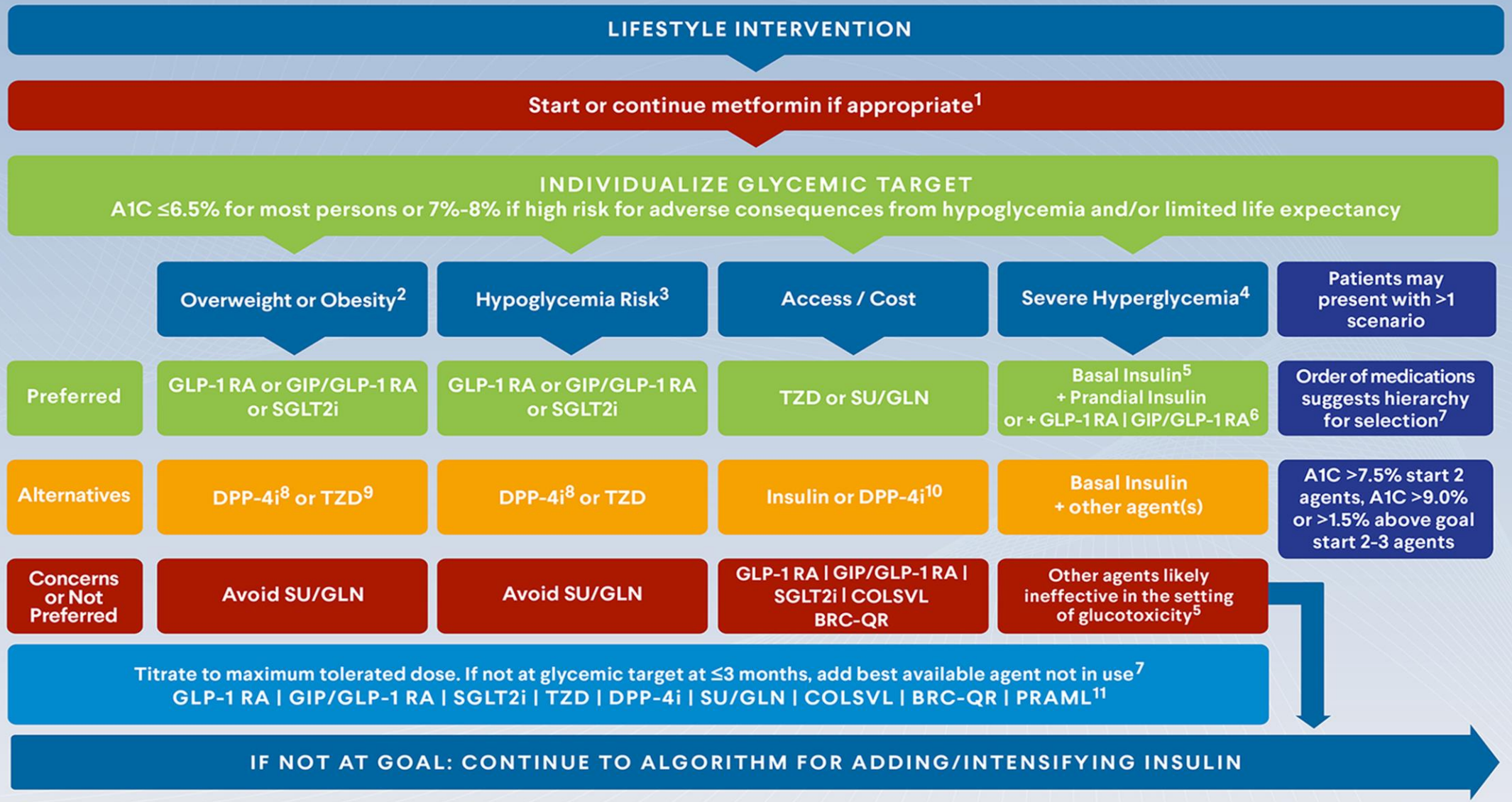
A1C = glycated hemoglobin; eGFR = estimated glomerular filtration rate; UACR = urine albumin-creatinine ratio.

What are next steps for Fred?

- Change Metformin to XR?
- Add a GLP1? GLP/GIP?
- Add an SGLT2?
- Add an Sulfonylurea?
- Other?

- Refer to Diabetes Self Management Education and Support?
- Continuous Glucose Monitoring (CGM)?

GLUCOSE-CENTRIC ALGORITHM FOR GLYCEMIC CONTROL



[1]Take with food with dose titration for enhanced tolerance. [2]See also COMPLICATIONS-CENTRIC MODEL FOR THE CARE OF PERSONS WITH OVERWEIGHT/OBESITY and PROFILES OF WEIGHT-LOSS MEDICATIONS table. [3]Evaluate for issues leading to hypoglycemia or hypoglycemia unawareness and manage with patient-centered strategies. [4]If A1C >10% and/or BG ≥300 with symptomatic hyperglycemia, reduce glucose/A1C as promptly and safely as possible. [5]See also ALGORITHM FOR ADDING/INTENSIFYING INSULIN. [6]GLP-1 RA requires titration phase which can delay glycemic control. After glucose toxicity is resolved,consider adding other agents. [7]See also PROFILES OF ANTIHYPERGLYCEMIC MEDICATIONS table. [8]GLP-1 RA and DPP-4i should not be combined. [9]TZD can cause fluid retention but have benefit for NAFLD, CVD prevention, dyslipidemia. [10]Access/Cost are dependent on location of the market. Insulin costs vary widely with devices (e.g., pens versus vials) and formulations (e.g., analogues versus combinations such as 70/30). [11]PRAML is used as an adjunct with prandial insulin.

Downloaded from https://journals.lww.com/clinicalpharmacology by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8K2+Ya6H515kE=

Use of Glucose-Lowering Medications in Management of Type 2 Diabetes

To avoid therapeutic inertia, reassess and modify treatment regularly (3-6 mo)

HEALTHY LIFESTYLE BEHAVIORS, DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT, SOCIAL DETERMINANTS OF HEALTH

Goal: Cardiorenal Risk Reduction in High-Risk Patients With Type 2 Diabetes (in addition to comprehensive CV risk management)

+ ASCVD

Defined differently across CVOTs but all included individuals with established CVD (eg, MI, stroke, any revascularization procedure). Variably included conditions such as transient ischemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease

+ Indicators of High Risk

Definitions vary, but most comprise ≥55 yr of age with 2 or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria)

+ HF

Current or prior symptoms of HF with documented HFrEF or HFpEF

+ CKD

eGFR <60 mL/min/1.73 m^2 OR albuminuria (ACR ≥3.0 mg/mmol [30 mg/g])
These measurements may vary over time; thus, a repeat measure is required to document CKD

+ ASCVD/Indicators of High Risk

GLP-1 RA with proven CVD benefit — Either/or — SGLT2i with proven CVD benefit

IF A1C ABOVE TARGET

- For patients receiving GLP-1 RA, consider adding SGLT2i with proven CVD benefit and vice versa
- TZD

+ HF

SGLT2i with proven HF benefit in this population

+ CKD (receiving maximally tolerated dose of ACEi/ARB)

PREFERABLY
SGLT2i with primary evidence of reducing CKD progression
Use SGLT2i in people with eGFR ≥20 mL/min/1.73 m^2; once initiated, should be continued until initiation of dialysis or transplantation
OR
GLP-1 RA with proven CVD benefit if SGKT2i not tolerated or contraindicated

IF A1C above target, for patients **receiving SGLT2i, consider incorporating GLP-1 RA or vice versa**

Additional Cardiorenal Risk Reduction or Glycemic Lowering Needed

Goal: Achievement and Maintenance of Glycemic and Weight Management Goals

Glycemic Management: Choose approaches that provide the efficacy to achieve goals

Metformin OR agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals
Consider avoidance of hypoglycemia a priority in high-risk individuals

have greater likelihood of achieving glycemic goals

Efficacy for Glucose Lowering

VERY HIGH: Dulaglutide (high dose), semaglutide, tirzepatide Insulin Combination oral, combination injectable (GLP-1 RA/insulin)
HIGH: GLP-1 RA (not listed above), metformin, SGLT2i, sulfonylurea, TZD
INTERMEDIATE: DPP-4i

Achievement and Maintenance of Weight Management Goals

Set individualized weight management goals

General lifestyle advice: medical nutrition therapy/ eating patterns/physical activity	**Intensive evidence-based structured weight management program**
Consider medication for weight loss	**Consider metabolic surgery**

When Choosing Glucose-Lowering Therapies: Consider regimen with high to very high dual glucose and weight efficacy

Efficacy for Weight Loss

VERY HIGH: Semaglutide, tirzepatide
HIGH: Dulaglutide, liraglutide
INTERMEDIATE: GLP-1 RA (not listed above), SGLT2i
NEUTRAL: DPP-4i, metformin

If A1C Above Target

Identify Barriers to Goals:

- Consider DSMES referral to support self-efficacy in achievement of goals
- Consider technology (eg, diagnostic CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that affect achievement of goals

Adapted from Davies. Diabetes Care. 2022;45:2753.

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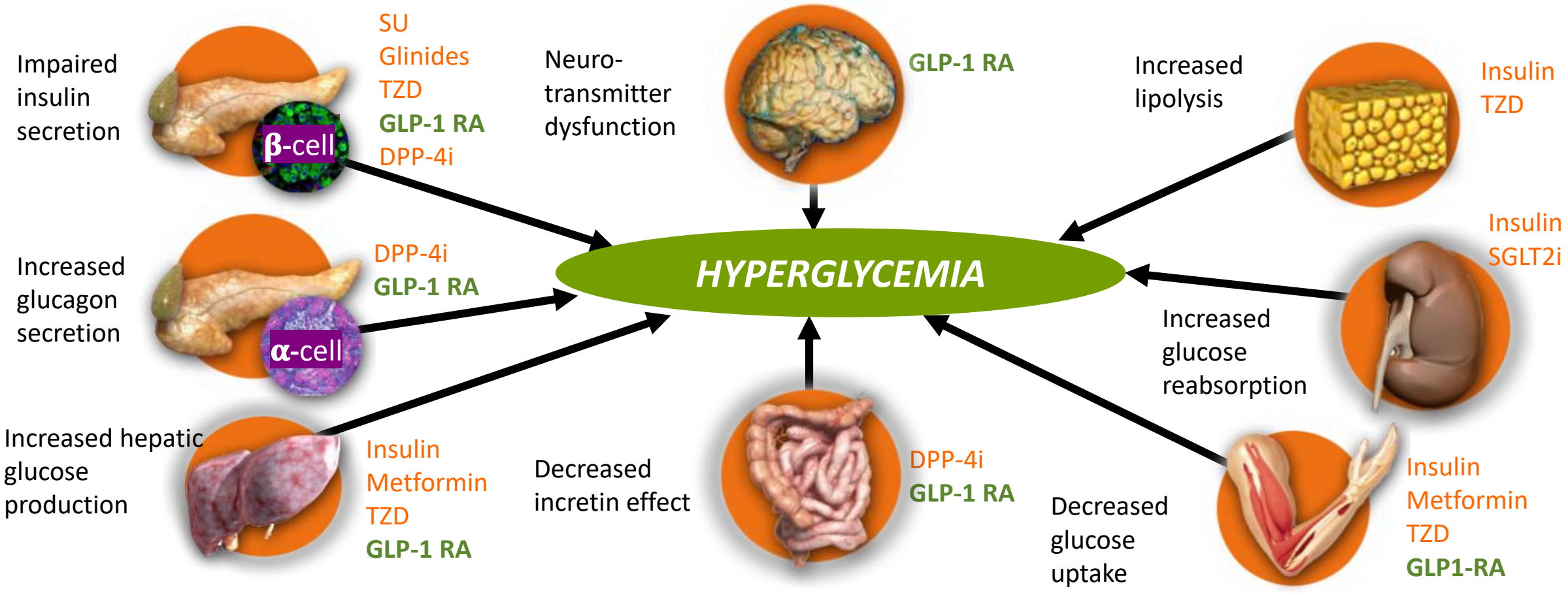
The "Ominous Octet": Multiple, Complex Pathophysiologic Abnormalities in T2D



DPP-4i = dipeptidyl peptidase-4 inhibitor; SGLT2i = SGLT2 inhibitor; SU = sulfonylurea; TZD = thiazolidinedione.

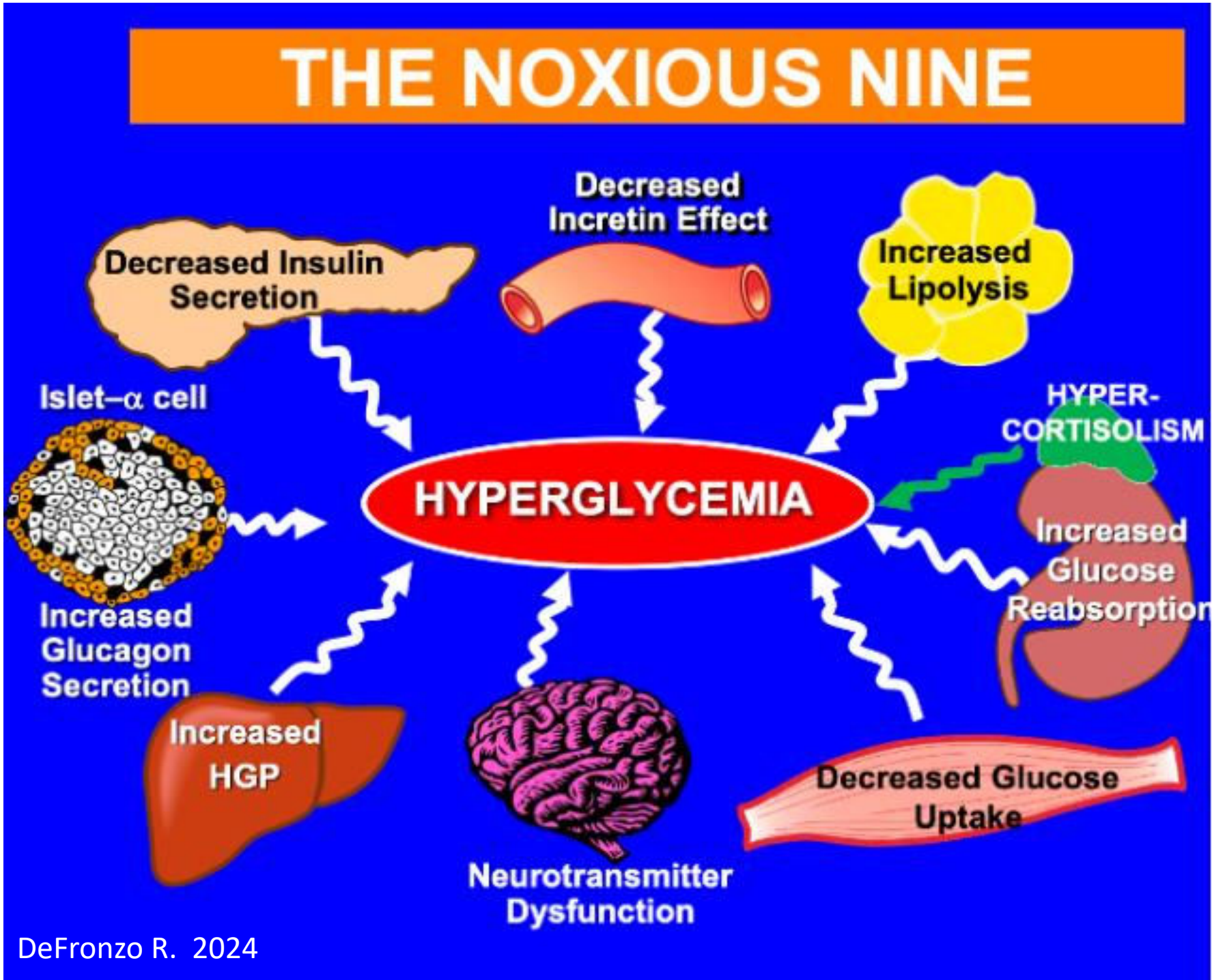
Adapted from: Inzucchi SE, Sherwin RS. In: Cecil Medicine. 2011; DeFronzo RA. Diabetes. 2009;58:773-795.

CATALYST trial ADA 2024

-Hypercortisolism in 24% of T2D pts on 2 orals
-33% of participants had an adrenal adenoma.

Screening: with an overnight 1 mg dexamethasone suppression test. Specifically, individuals with cortisol >1.8 µg/dL and dexamethasone levels >140 ng/dL in the morning following administration would be diagnosed with hypercortisolism.

Cortisol raises glucose



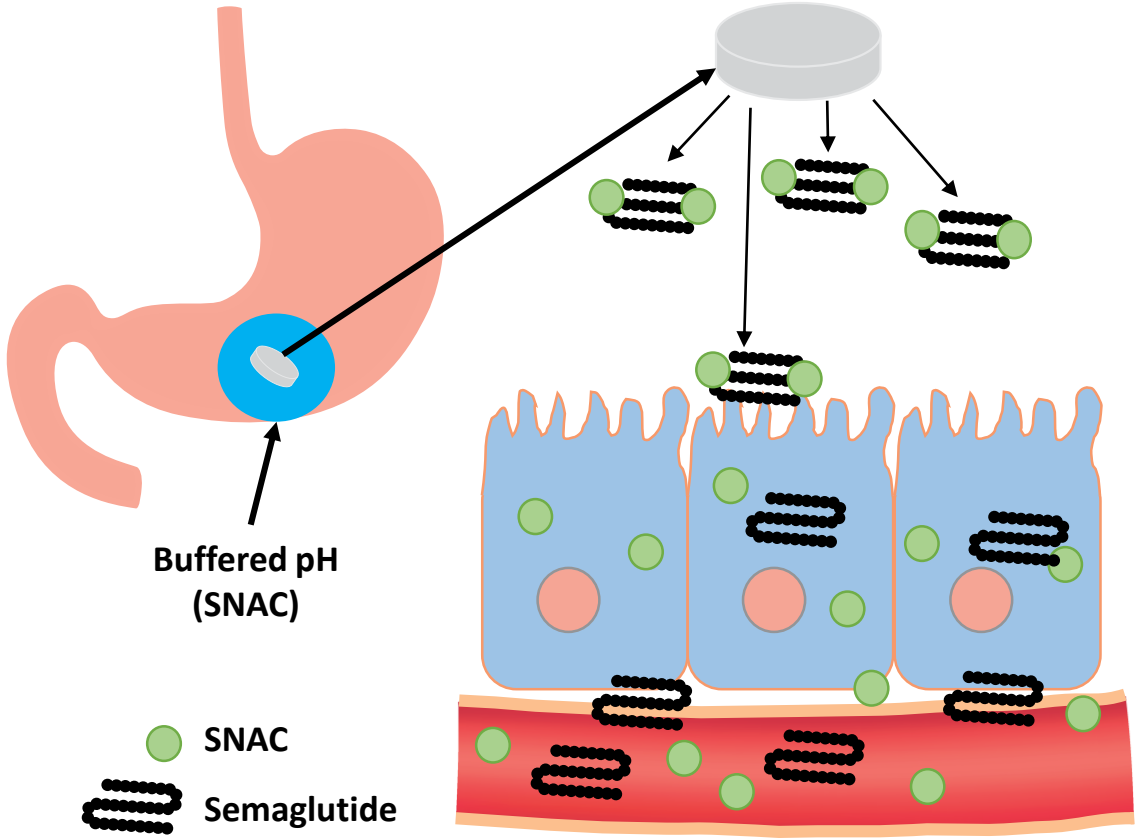
GLP-1 RA Dosage Guidelines and Benefits in T2D

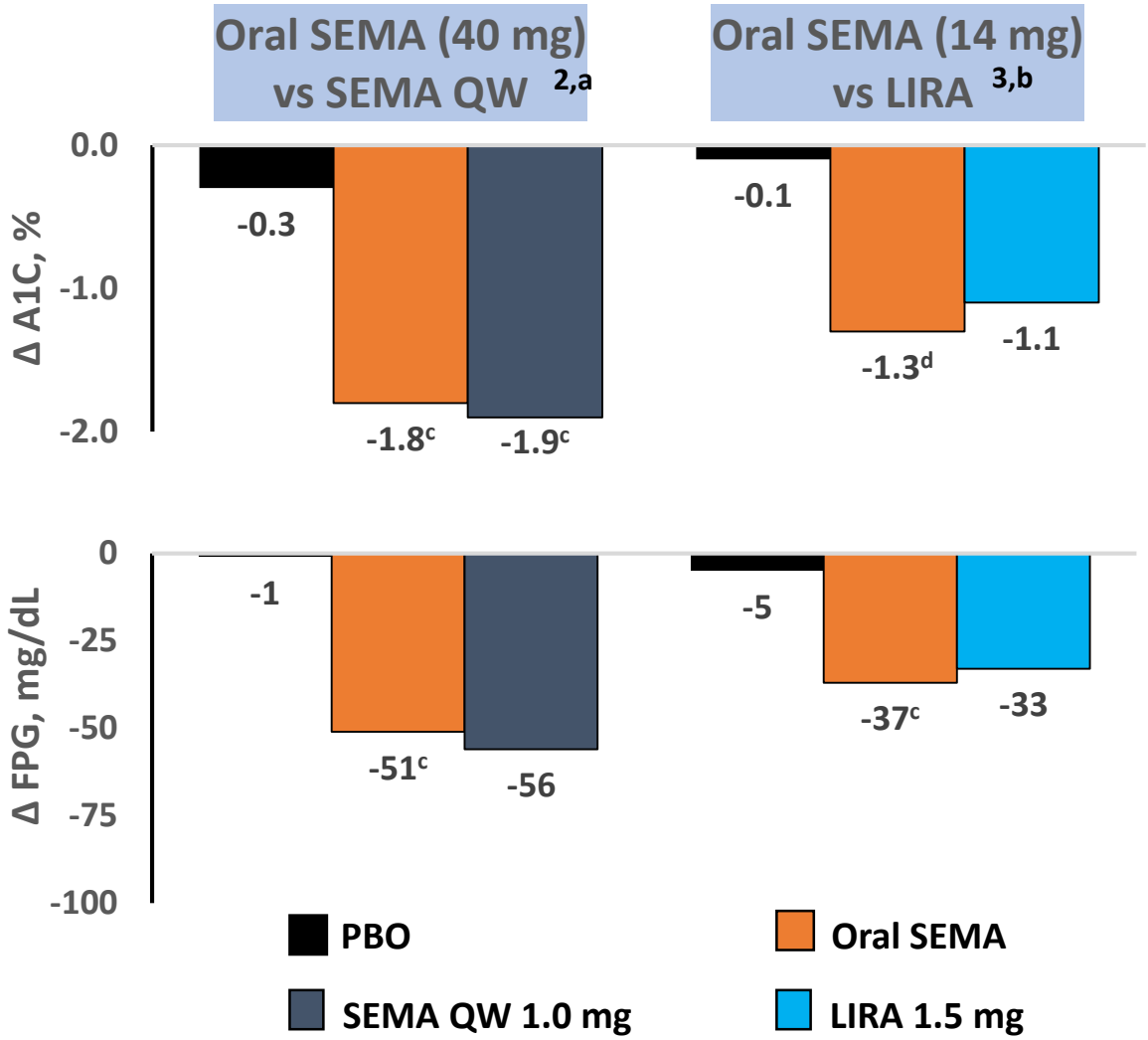
GLP-1 RA	Dosing Frequency	Starting Dose	Max Dose	Titration Frequency	Cardiovascular Benefit	Kidney Benefit
Exenatide BID	Twice daily	5 mcg	10 mcg	1 month		
Lixisenatide	Once daily	10 mcg	20 mcg	14 days		
Liraglutide	Once daily	0.6 mg	1.8 mg	1 week	Yes	Yes
Semaglutide PO	Once daily	3 mg	14 mg	30 days		
Dulaglutide	Once weekly	0.75 mg	4.5 mg	≥4 weeks	Yes	Yes
Semaglutide SC	Once weekly	0.25 mg	2 mg	4 weeks	Yes	Yes
Exenatide ER	Once weekly	2 mg	2 mg	NA		

American Diabetes Association. Diabetes Care. 2022;45:S133. Dulaglutide PI. Exenatide BID PI. Exenatide ER PI. Liraglutide PI. Lixisenatide PI. Semaglutide SC PI. Semaglutide tablets PI.

How Does *Oral* Semaglutide Compare With Other GLP-1 RAs?

SEMA Formulation With SNAC: Protection and Absorption[1]

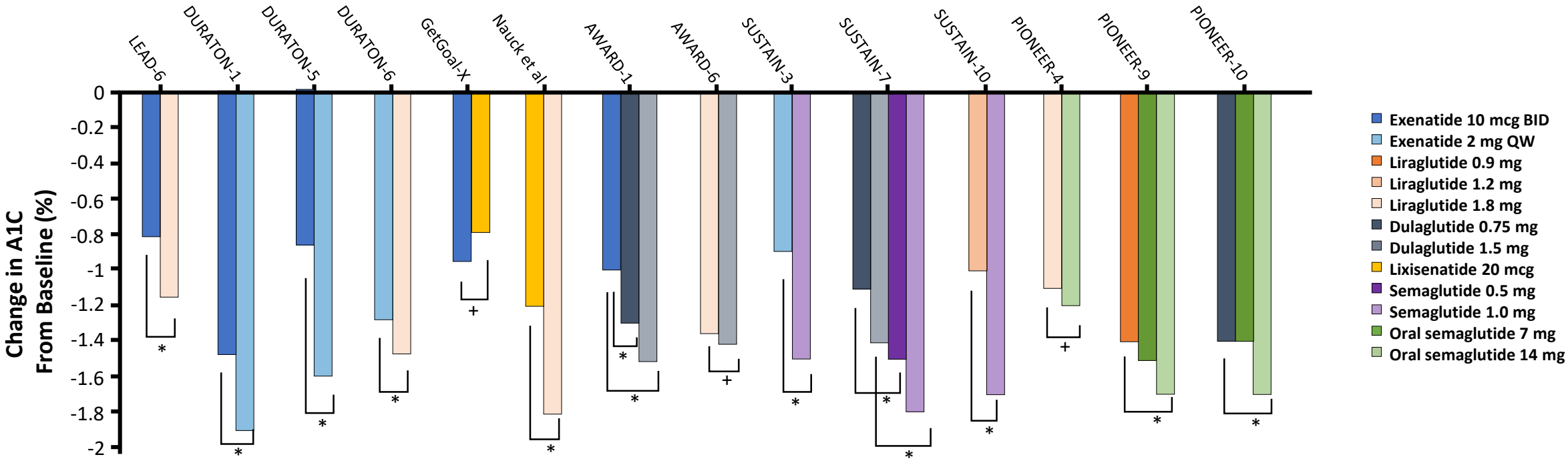




[a] Randomized trial; 26 weeks; N = 632; BL A1C 7.9%.
[b] Randomized trial; 52 weeks (26-week data, trial product estimand presented); N = 711; BL A1C 8.0%.
[c] *P* < .05 vs PBO.
[d] *P* < .05 vs PBO and LIRA.

1. Bucheit JD, et al. *Diabetes Technol Ther*. 2019 Oct 1. [Epub ahead of print];
2. Davies M, et al. *JAMA*. 2017;318:1460-1470; 3. Pratley R, et al. *Lancet*. 2019;394:39-50.

GLP-1 RA Comparative Studies: Change in A1C

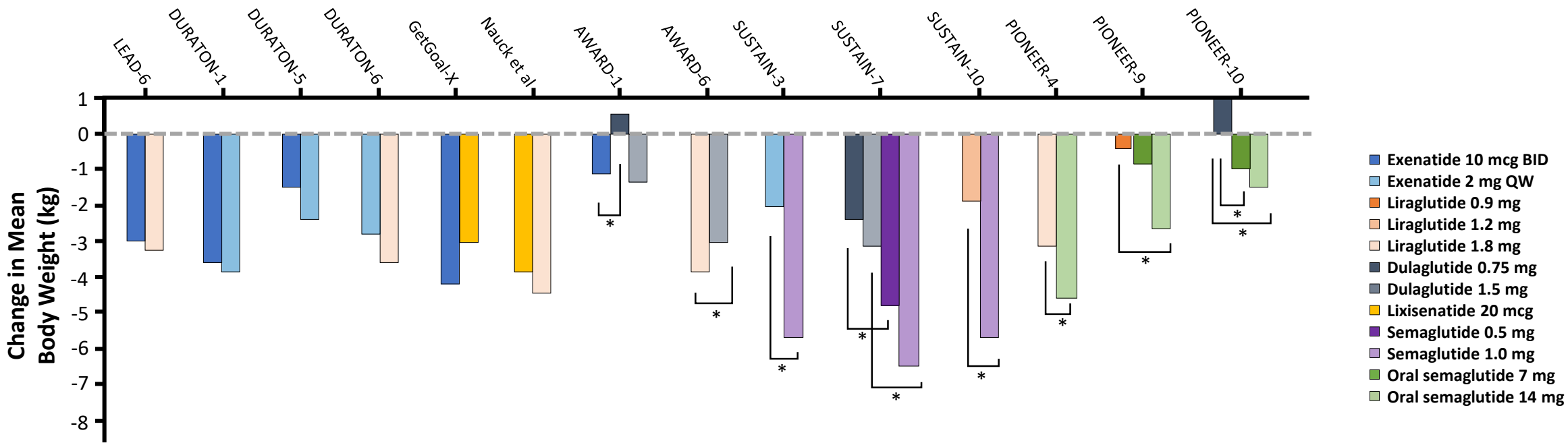


*P <0.05. †P <0.05, meeting predefined noninferiority margin.

Figure adapted from Trujillo. Ther Adv Endocrinol Metab. 2021;12:2042018821997320. Note that direct comparisons between clinical trials cannot be made.

Ahmann. Diabetes Care. 2018;41:258. Blevins. J Clin Endocrinol Metab. 2011;96:1301. Buse. Lancet. 2009;374:39. Buse. Lancet. 2013;381:117. Capehorn. Diabetes Metab. 2020;46:100-109. Drucker. Lancet. 2008;372:1240. Dungan. Lancet. 2014;384:1349. Nauck. Diabetes Care. 2016;39:1501. Pratley. Lancet. 2019;394:39-50. Pratley. Lancet Diabetes Endocrinol. 2018;6:275. Rosenstock. Diabetes Care. 2013;36:2945. Wysham. Diabetes Care. 2014;37:2159. Yabe. Lancet Diabetes Endocrinol. 2020;8:392-406. Yamada. Lancet Diabetes Endocrinol. 2020;8:377-391.

Trials of GLP-1 RAs: Changes in Body Weight



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Drug shortages allow FDA to authorize “Compounding” FDA alert on “Faux-zempic”

. **FDA warns HCPs and patients of dosing errors with compounded injectable semaglutide** - Last Friday, the FDA issued an alert to HCPs, compounders, and patients about recent reports of dosing errors and overdoses with compounded injectable semaglutide. The majority of these reports were largely due to incorrect dose measurements by patients and miscalculations by HCPs, leading to the administration of five to 20 times more than the intended dose of semaglutide. Resulting adverse events included severe nausea, vomiting, hypoglycemia, and hospitalization.

To prevent challenges with dosing errors and overdoses, the FDA encourages patients to talk to HCPs about how to measure and administer correct doses and clarify any confusion with units. The FDA also recommends raising awareness on dosing, especially as most reports indicated that patients were unfamiliar with measuring the intended dose with a syringe.

FDA’s warning comes amid challenges with global shortages of GLP-1 RAs, including Novo Nordisk’s Wegovy (semaglutide 2.4 mg) and Ozempic (semaglutide 1.0 mg). While the FDA acknowledges use of compounded versions may occur when a drug is in shortage, it continues to acknowledge concerns with reports of adverse events.

CloseConcerns. Kelly L. Close <kelly_close@closeconcerns.com Accessed 7-30-24

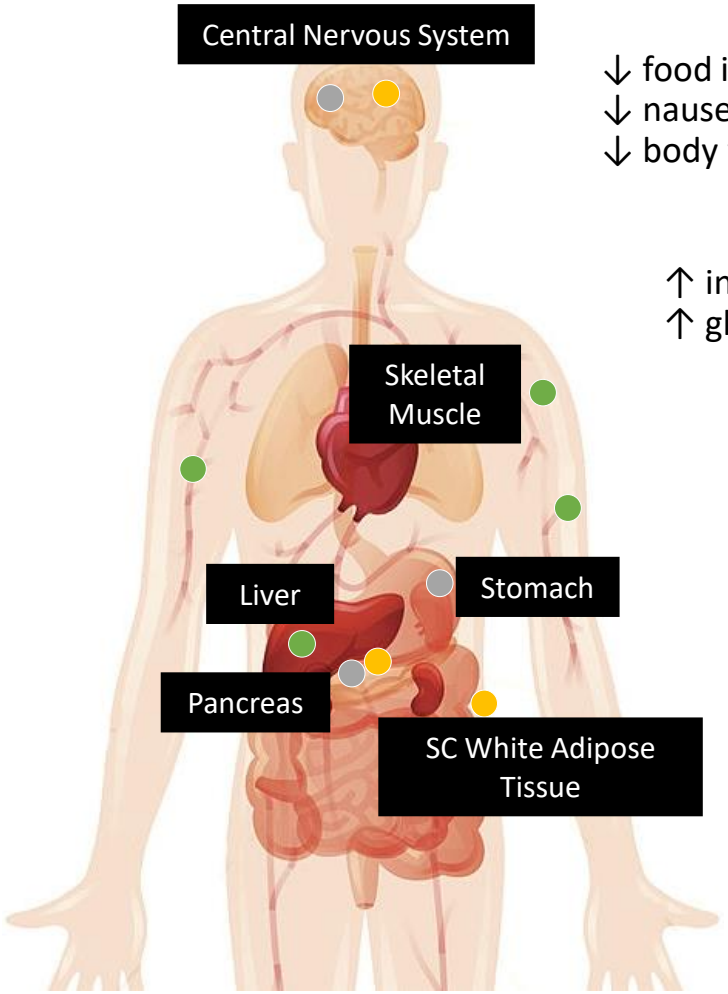
GLP-1 RA Cardiovascular Outcomes Trials

Agent	Lixisenatide SC, Daily	Liraglutide SC, Daily	Semaglutide SC, Weekly	Exenatide ER SC, Weekly	Albiglutide SC, Weekly	Dulaglutide SC, Weekly	Semaglutide PO, Daily
Study	ELIXA	LEADER	SUSTAIN-6	EXSCEL	HARMONY	REWIND	PIONEER-6
N	6068	9340	3297	14,752	9463	9901	3183
Trial duration	25 mo	3.8 yr	2.1 yr	3.2 yr	1.5 yr	>5 yr	16 mo
Mean diabetes duration, yr	9.3	12.8	13.9	12	14	10.5	14.9
Mean age, yr	60	64	65	62	64	66	66
Female, %	30	36	39	38	30	47	32
Prior CVD, %	100	72	59	73	100	31	85
Mean BMI, kg/m^2	30	33	33	32	32	32	32
Mean A1C, %	7.7	8.7	8.7	8.0	8.7	7.3	8.2

Pfeffer. NEJM. 2015;373:2247. Marso. NEJM. 2016;375:311. Marso. NEJM. 2016;375:1834. Holman. NEJM. 2017;377:1228.
Green. Am Heart J 2018;203:30. Gerstein. Diabetes Obes Metab 2017;20:42. Husain. NEJM. 2019;381:841.

Glucagon-Like Peptide-1 (GLP-1) Receptor Agonism

Glucose-Dependent Insulinotropic Polypeptide (GIP) Receptor Agonism



↑ satiety
↓ food intake
↑ nausea
↓ body weight

↑ insulin
↓ glucagon

↓ gastric emptying

↓ hyperglycemia

↑ insulin sensitivity
↓ hepatic glucose production
↓ ectopic lipid accumulation

↓ food intake
↓ nausea
↓ body weight

↑ insulin
↑ glucagon

↑ insulin sensitivity
↑ lipid buffering capacity
↑ blood flow
↑ storage capacity
↓ proinflammatory immune cell infiltration

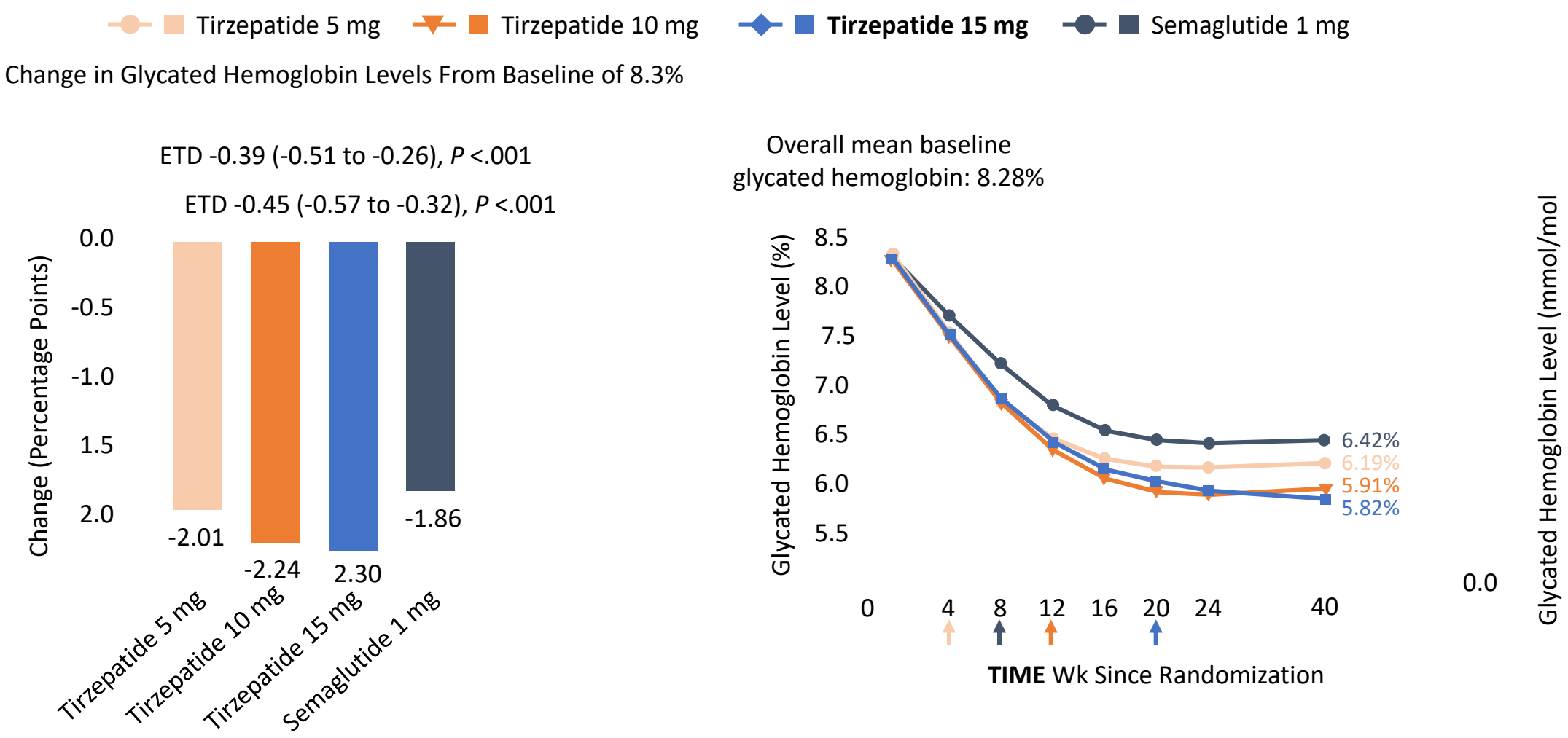
↓ hyperglycemia
↓ dietary triglyceride

↑ insulin sensitivity
↑ metabolic flexibility
↓ ectopic lipid accumulation

- Glucose-dependent insulinotropic polypeptide receptor agonism
- Glucagon-like peptide-1 receptor agonism
- Indirect action

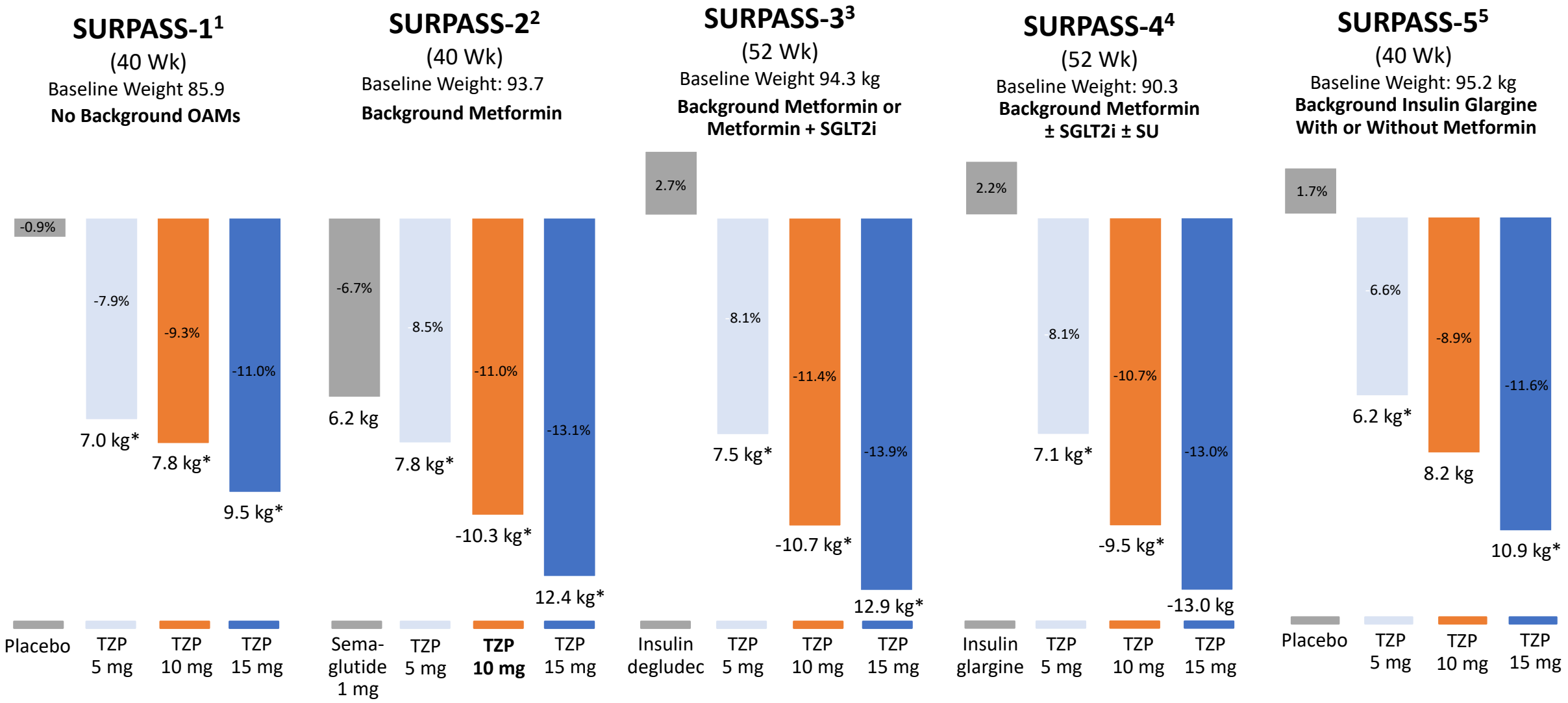
Samms. Trends Endocrinol Metab. 2020;31:410

Tirzepatide vs Semaglutide in T2D: Change in A1C



Frias. NEJM. 2021;385:5035.

SURPASS: Weight Loss With Tirzepatide in T2D



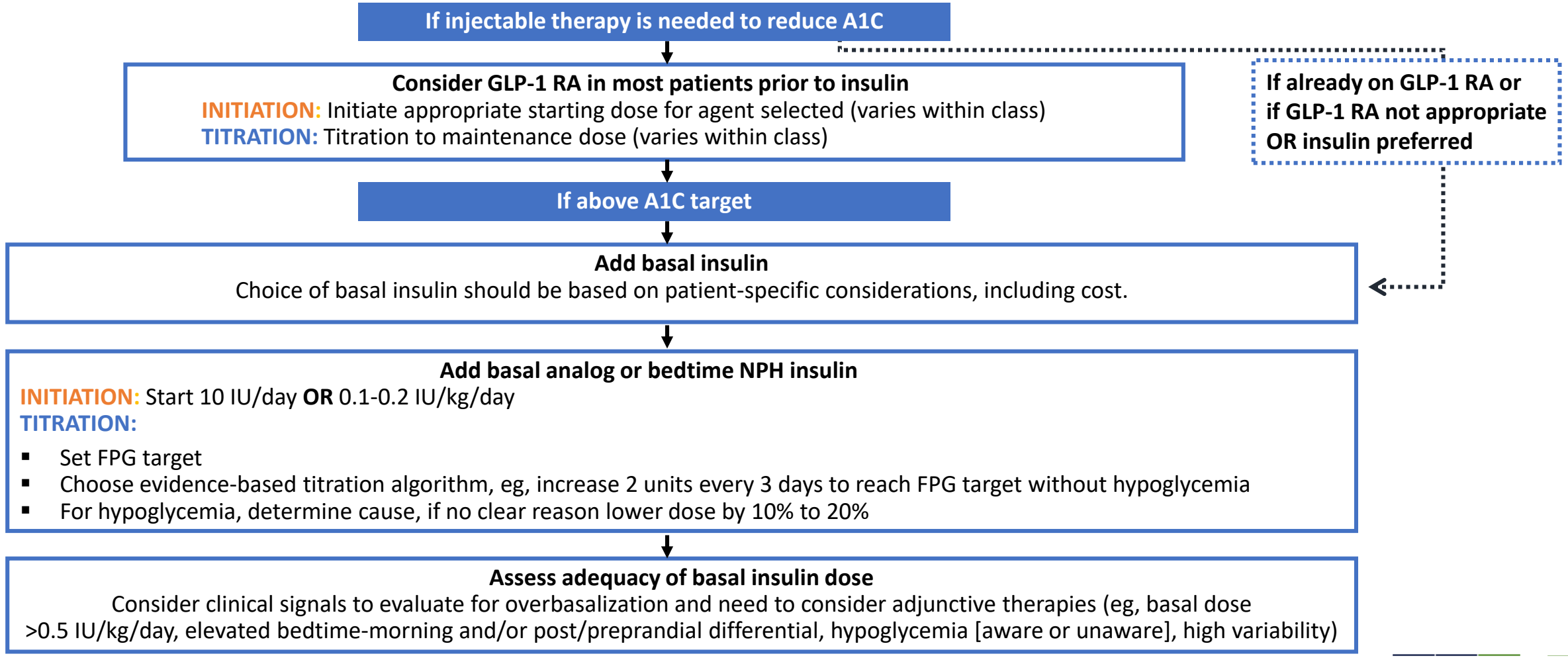
Denotes statistical significance to comparator.

1. Rosenstock. Lancet. 2021;398:143. 2. Frias. NEJM. 2021;385:503. 3. Giorgino. ADA 2021. Abstr 78-LB.
4. Del Prato. Lancet. 2021;398:1811. 5. Dahl. ADA 2021. Abstr 80-LB.

Terzepatide/(Mounjaro)

- Once a week auto injector
- 2.5mg/5/mg/7.5mg/10mg/12.5mg/15mg per 0.5 mL
- Works on fasting and post meal glucose
- Helps you feel full, can contribute to weight loss (13-25lb)
- Potential Side effects: Nausea/Vomiting/↓ Appetite /Diarrhea or Constipation
  - Acute kidney diseases can occur if you get dehydrated
- Contraindicated: personal or family history of medullary thyroid carcinoma (MTC), or in patients with Multiple Endocrine neoplasia syndrome type 2 (MEN2),
- Risk of Thyroid c-cell tumors, acute pancreatitis, hypoglycemia if used with SU or Insulin (dose needs to be adjusted).
- A1c reduction 1.8% to 2.
- Cost: $$$, co-pay card

Choose GLP-1 RA Before Insulin Nearly Always



FPG = fasting plasma glucose.

ADA. Diabetes Care. 2022;45:S125.

Starting Therapies in Patients With T2D

Coverage Search App

Apple App Store
https://apps.apple.com/us/app/coverage-search/id834992816

Google Play Store
https://play.google.com/store/apps/details?id=testformularysearch.mmit.com.formulary&hl=en_US&gl=US&pli=1

1. Use *Coverage Search* or another formulary search resource
   - Requires the drug, state, and insurance category to determine coverage
2. Review the mechanism of action and benefits of the drug (eg, A1C reductions, weight reductions, CV or renal protection)
3. Review the side effects and how to mitigate
   - For GLP-1 RA GI adverse effects: snack for the first few days, eat about one-half of what you usually eat, stop eating when full, follow or slow the titration schedule
   - For SGLT2i adverse effects: good genital hygiene (clean and dry), drink extra water
4. Show patients how to inject with demo pen or sample and supervise self injection
5. Call (or have an MA call) the pharmacy to verify prescription was received, run the prescription, and determine out-of-pocket cost
6. Print (or have an MA print) co-pay card for patients with commercial insurance

Case →Fred

- Fred followed your advice and
  - started semaglutide at 0.25mg.
  - He was queasy, so week 2 decreased to 10 clicks. Week 3: 0.25mg, and week 4: 0.5mg
  - Weeks 5-8 and 9-12 he took 0.5mg/weekly injection
  - Weeks 13-20 he increased to 1mg/week
  - His early nausea abated with “click” titration, and after 4 months, he was able to increase to 1 mg weekly.
  - 2 months later, he was taking 2mg weekly with no further side effects
- Since originally starting a GLP-1, he has lost a total of 25 lb. He states he has more energy, and has started walking daily
- Physical Examination
  - Height: 5 ft 10 in
  - Weight: 221 lb (BMI: 31.7kg/m^2)
  - Blood pressure: 128/80 mm Hg
  - Pulse: 70 beats/min
- Laboratory Findings
  - Fasting blood glucose: 108 mg/dL; A1C: 7.2%
  - All other repeat labs normal

IS THIS ENOUGH?

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PMH

-MI 4 years ago

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- Allergies/Adverse Drug Events: GI issues when first starting Metformin
- Family Hx: Mother: dylsipidemia, MI age 68. Father HTN, Obesity
- Social
  - Lives alone, retired
  - Has MCare with BC/BS supplement

A1C = glycated hemoglobin; eGFR = estimated glomerular filtration rate; UACR = urine albumin-creatinine ratio.

So what do we do next for Fred?

- SGLT2
- Basal Insulin
- Upgrade to GLP/GIP
- Add Pioglitazone
- Refer for bariatric surgery

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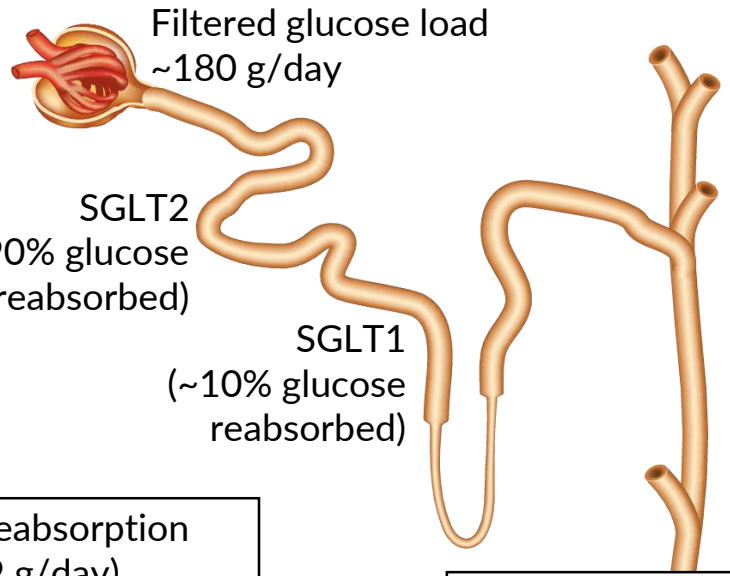
Cardiorenal Risk Reduction or Glycemic Lowering Needed

ADA Standards of Care, 2023

Role of SGLT2 Inhibitors

Nephron



Glucose reabsorption
(>179 g/day)

SGLT2 inhibition

Glucose reabsorption reduced to ~100-130 g/day

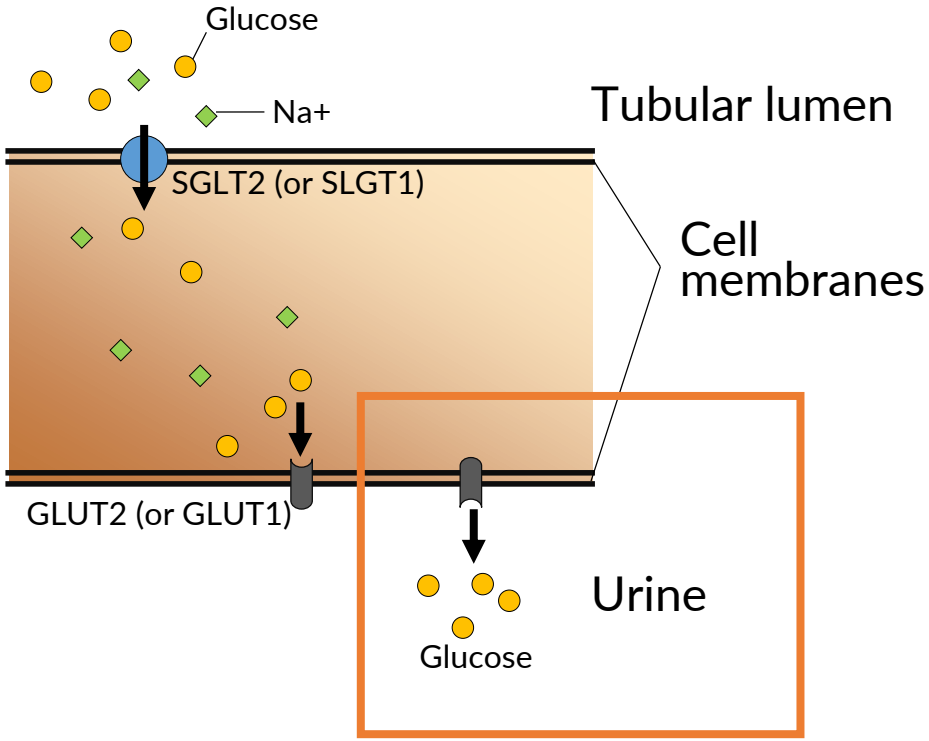
Urinary glucose excretion
<0.5 g/day

SGLT2 inhibition

Urinary glucose excretion increased to ~50-100+ g/day

Hyperglycemia reduced in T2D

Renal proximal tubule cell



Nauck MA. *Drug Des Devel Ther*. 2014;8:1335-1380.

SGLT2 Inhibitor Summary

SGLT2 inhibitor	FDA Approval for Risk Reduction			A1C Reduction	Dose	Renal dosing
	CVD	HF	CKD			
Brenzavvy® (bexagliflozin)	No indication	No indication	No indication	-0.5%	20 mg/day	• **<30 mL/min/1.73 m^2:** not recommended
Invokana® (canagliflozin)	✓	No indication	✓	-0.77% to -1.03%	100-300 mg/day	• **30-59 mL/min/1.73 m^2:** 100 mg • **<30 mL/min/1.73 m^2:** not recommended
Farxiga® (dapagliflozin)	✓	✓ (HFrEF only)	✓	-0.6% to -0.8%	5-10 mg/day	• **25-<45 mL/min/1.73 m^2:** 10 mg • **<30 mL/min/1.73 m^2:** not recommended
Jardiance® (empagliflozin)	✓	✓	Under FDA review	-0.7% to -0.8%	10-25 mg/day	• **<30 mL/min/1.73 m^2:** not recommended
Steglatro® (ertugliflozin)	No indication	No indication	No indication	-0.7% to -0.9%	5-15 mg/day	• **<45 mL/min/1.73 m^2:** not recommended

Brenzavvy: No PA, No insurance required: ~ $47/mo

US FDA accepts supplemental New Drug Application for Jardiance® for adults with chronic kidney disease. January 24, 2023. Accessed March 9, 2023. https://www.boehringer-ingelheim.com/human-health/metabolic-diseases/fda-accepts-new-chronic-kidney-disease-treatment-application.

Case Summary: Fred

- Fred followed your advice and
  - started empagliflozin 10mg
  - No adverse events reported
  - No hypoglycemia
- Laboratory Findings after 3 months
  - Fasting blood glucose: 104 mg/dL; A1C: 6.8%
  - All other repeat labs normal

AND he attended diabetes education classes!

Meet Sarah,
46 y/0 F Uncontrolled DM ~ 9 years:
T2, T1 or LADA?

DX:

- peripheral neuropathy,
- hyperlipidemia,
- iron deficiency anemia
- persistently elevated A1C
- BMI 30.78 (wt 185, ht 65 inches)

MEDS:

- 54 units of Glargine (lantus) at bed time,
- 1.8mg Liraglutide (Victoza) injection daily,
- Metformin 1000mg twice a day and
- Dapagliflozin (Farxiga) 10mg daily.

PMH:

- She has a strong family history of diabetes
- hx of gestational diabetes when she was pregnant some ago.

LABS:

- Her sugars range from 70-400mg/dl and she complains of daily nausea and dyspepsia.
- GAD 65 (results +) and other labs ordered to evaluate for type 1
- eGFR 52
-

Questions about Sarah's case….

1. Does she have late onset T1 diabetes?
2. Since GAD65 was positive, do we need to test other antibodies? What are they?
3. If LADA, should she continue other meds or just insulin?
    1. Dapagliflozin? Other renal protection?
    2. Continue Metformin? Switch to GLP?
    3. Insulin? Adjust current 54u glargine (basal)?
        1. How do you switch to Multiple daily insulin (MDI)? How to titrate basal/bolus
    4. When should she do Blood glucose testing? What about a CGM? Insulin Pump?
    5. What other auto immune issues should be checked?
    6. Other?

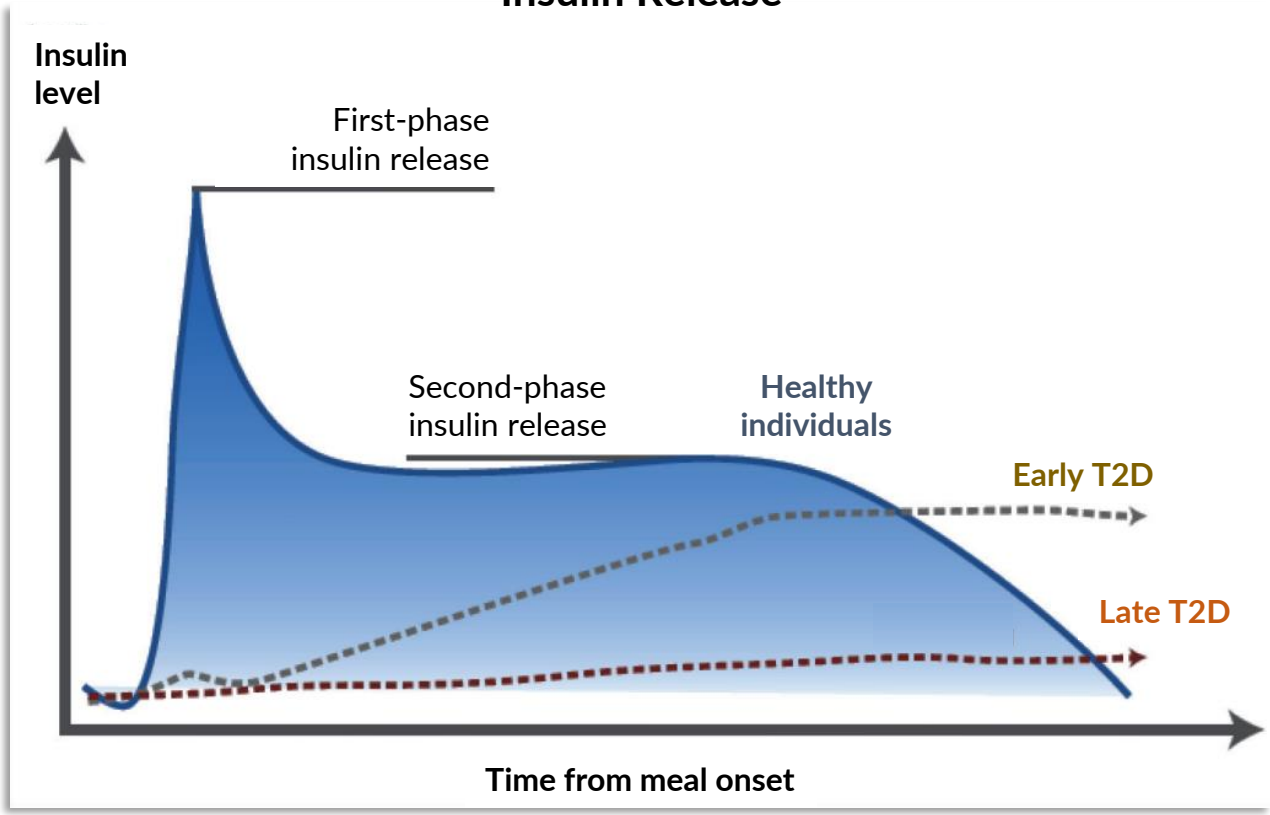
Goals of Basal Insulin Therapy

Goals of Basal Insulin Therapy in Patients With T2D

- Supplement normal physiologic insulin production, providing steady insulin levels throughout the day
- Improve glycemic control after noninsulin therapies prove insufficient
- Control fasting blood glucose (FBG) levels

NOTE: Basal insulin therapy assumes sufficient beta-cell function for prandial insulin secretion and has minimal effects on postprandial glucose (PPG) levels.

Effects of Insulin Resistance on Postprandial Insulin Release



Vargas-Uricoechea H. *J Clin Med Res*. 2022;14(1):8-21.

Meece J. *Diabetes Ther*. 2018;9(3):877-890.
Vargas-Uricoechea H. *J Clin Med Res*. 2022;14(1):8-21.

5 Steps to Fredom

Insulin titration schedule for

Change date (when new doses start)	**Units of pre-meal rapid-acting analog** c lispro (Humalog) c aspart (Novolog) c glulisine (Apidra)	**Units of peakless insulin glargine (Lantus)** c Before breakfast c Before bedtime
	8	24
	10	24
	10	30
	12	30
	12	36
	14	36
	14	42
	16	42
	16	48
	18	48
	18	54
	20	54
	20	60
	22	60
	22	66
	24	66
	24	72
	26	72
	26	78
	28	78
	28	84
	30	84
	30	90
	32	90
	32	96
	34	96

While we are trying to discover the amount of insulin that you need, please eat _____ (c gm) (c servings) of carbohydrate at every meal. The instruction to eat the same amount at each meal is a temporary restriction. Our goal is to discover the amount of insulin that is needed to get good results for a certain amount of carbohydrate. Then, once we discover the matching rule, you will be free to change the amount that you eat from meal to meal.

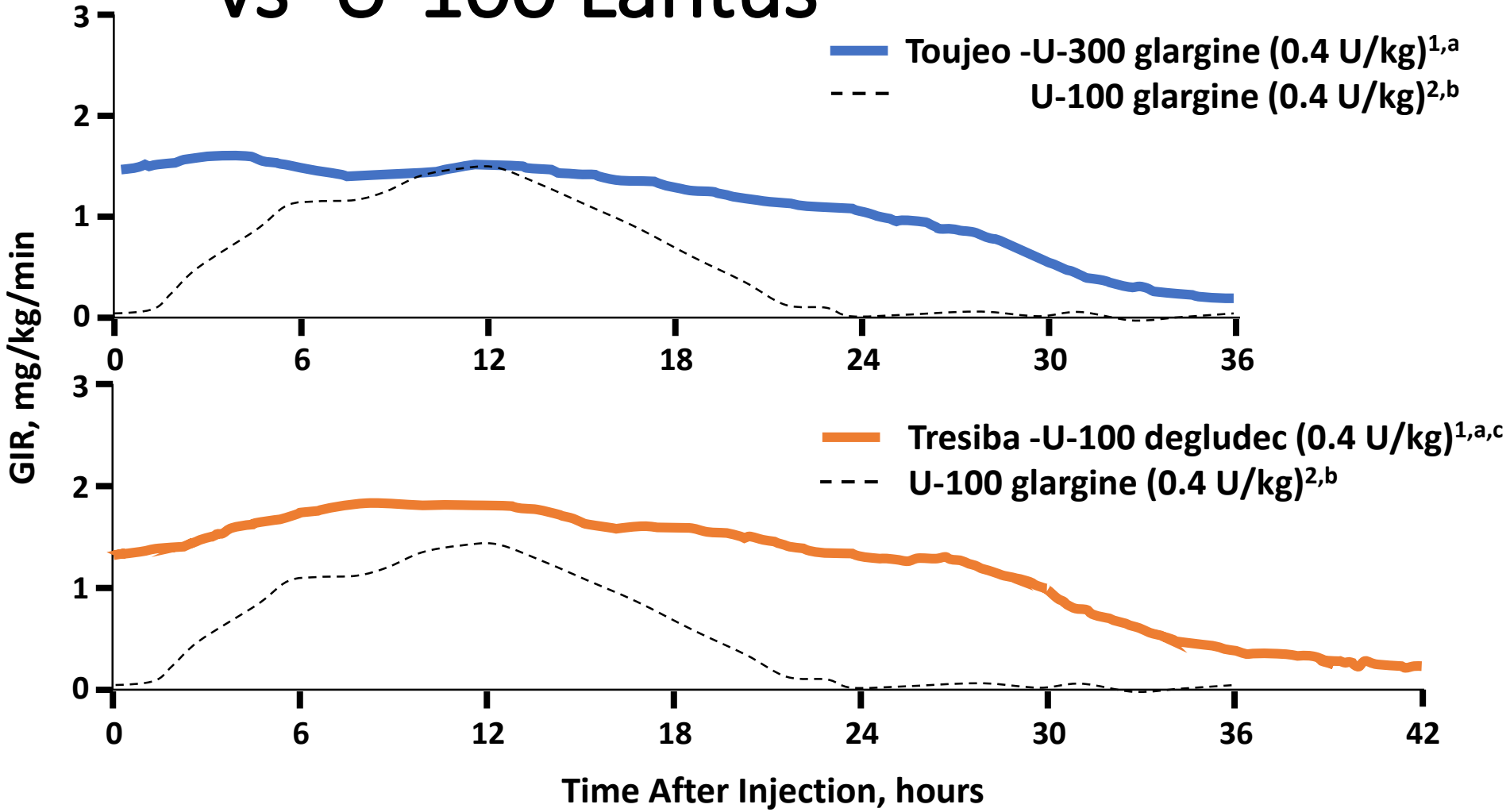
Call me if you begin to show any readings under 80 or if you have symptoms of hypoglycemia. If you begin to show some blood glucose readings before meals that are in the target range of _____ to _____ mg/dL, please hold with the dose you are taking, make no further changes of insulin dose, and come in to visit me to review your logbook. Be sure to carry in your meter and one week of log-

Moore. University of Kansas, endocrinology. 2023

Time Action of Insulins

Insulin	Starts (m-hr)	Peak (hr)	Duration (hrs)
Aspart,Lispro,Gulisine Novolog, Humalog, Apidra	10-15m	1–1.5	3-4
Lyumjev, FiAsp Ultra fast	1-5 m	30-90m	3
Afrezza(inhaled rapid)	12-15	53min	180min
Regular	30+m	2–3	4–6
NPH (Walmart $25 no Rx)	2–4h	6–8	10–12
Glargine (Lantus) u-100 (Toujeo) - U300	2+h	~Flat VERY flat	24+/- 32 hr
Detemir (Levemir)	2+h	6+/-	20-24
Degludec (Tresiba)	2+ hr	VERY flat	42 hr

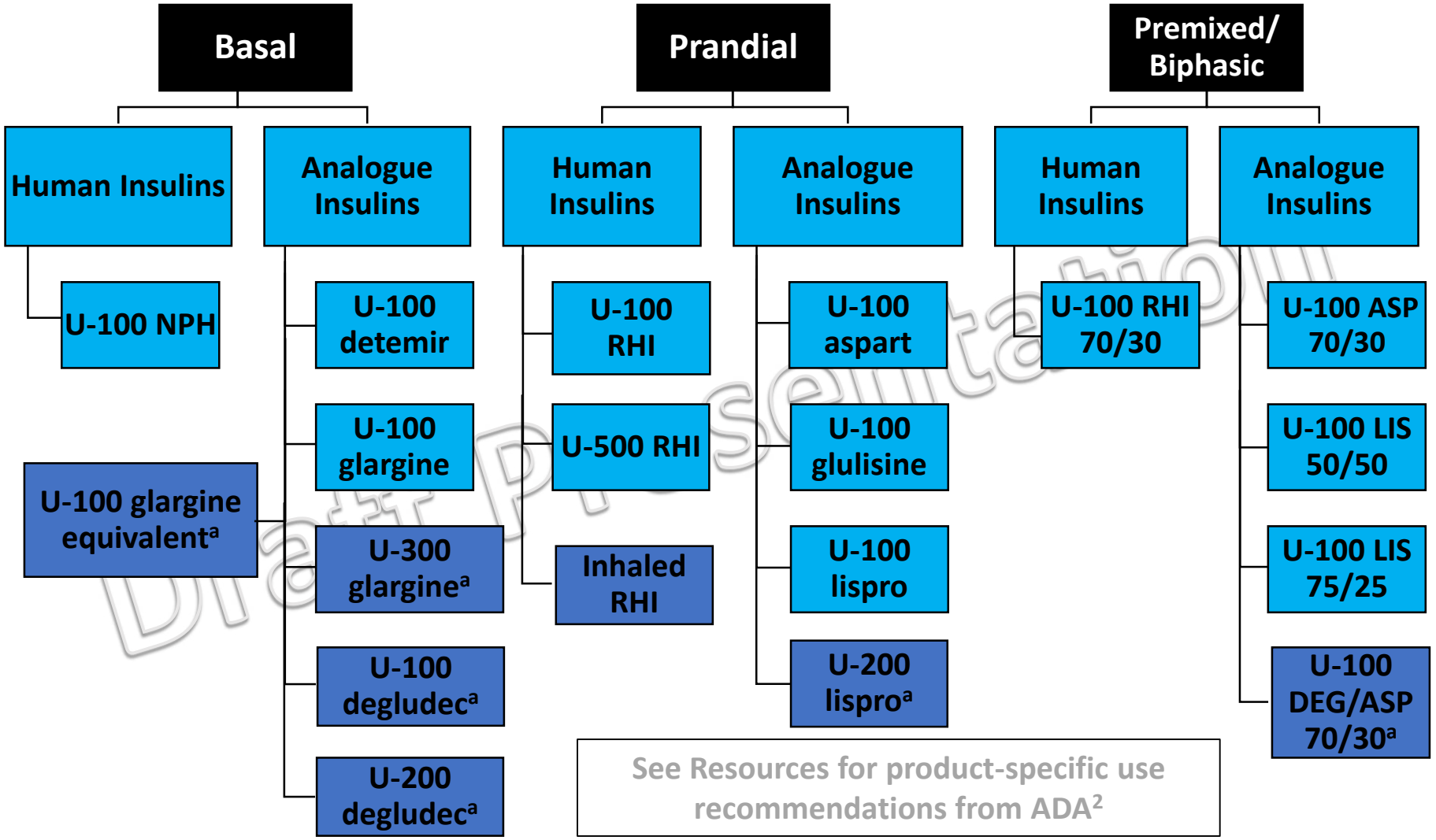
Time Action of Ultralong-Acting Insulins vs U-100 Lantus



[a] Results shown for individuals with T1DM; [b] Individuals with and without T1DM; [c] U-200 degludec curve is similar.[3]

1. Drugs@FDA. http://www.accessdata.fda.gov/scripts/cder/daf/.
2. Google Patents. http://www.google.com/patents/US20120122774.
3. Heise T, et al. *Diabetes*. 2012;61(suppl 1):A91 [abstract 349-OR].

Approved Insulins: United States



Draft Presentation

[a] Available only in prefilled pens.

1. Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA;

Basal Insulin Time Actions

Concentration	Insulin	Duration of Action	Classification	Mixing Needed?
U-100	NPH	Variable, up to 24 h	Intermediate	Yes
U-100	Detemir	7.6 to > 24 h	Long	No
U-100	Glargine[a]	10.8 to > 24 h	Long	No
U-100	Degludec	> 42 h	Longer	No

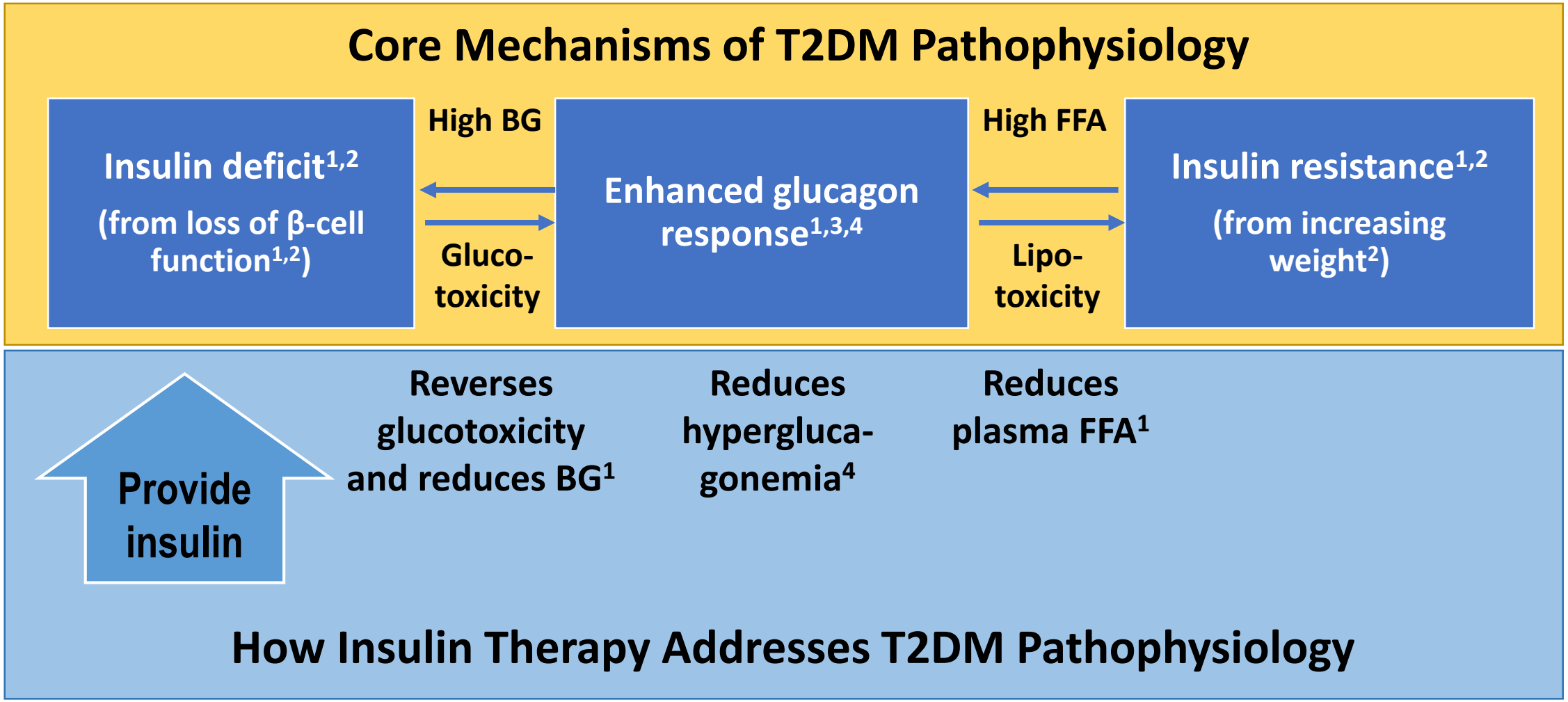
Concentration	Insulin	Duration of Action	Classification	Mixing Needed?
U-200	Degludec	> 42 h	Longer	No
U-300	Glargine	16 to > 36 h	Longer	No
U-500	Human regular[b]	13 to 24 h	Intermediate	No

- The number after "U" represents the concentration in terms of units of insulin per 1 mL
-
- Concentrated insulins may have different time-action profiles than their U-100 versions

[a] Includes equivalent and follow-on formulations; [b] Has both basal and prandial action at U-500 concentration.

1. Drugs@FDA. https://www.accessdata.fda.gov/scripts/cder/daf/;
2. ADA. *Diabetes Care*. 2018;41(suppl 1):S1-S159.

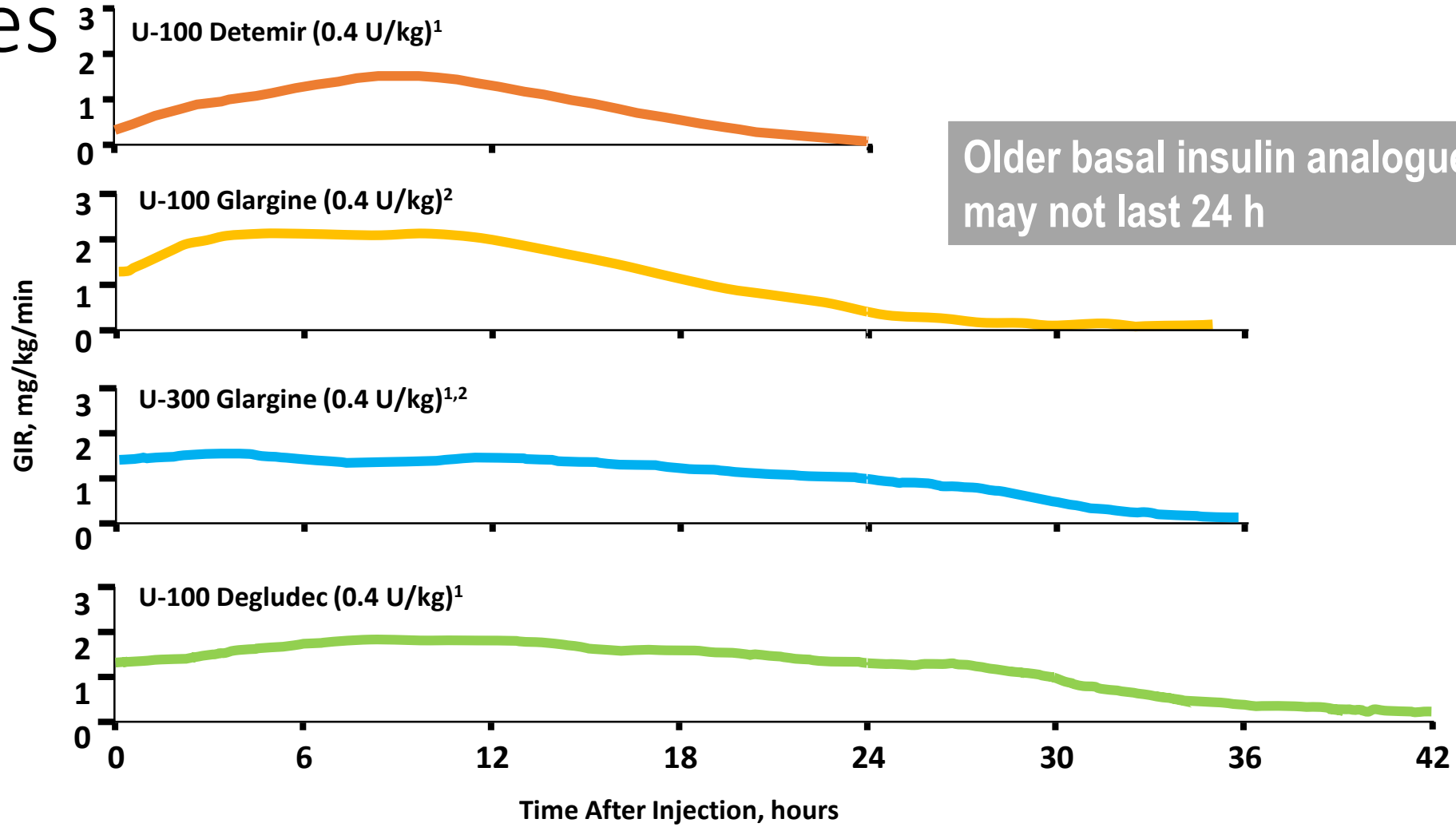
Role of Basal Insulin Therapy in T2DM



1. Hanefeld M, et al. *Diabetes Ther*. 2016;7:187-201; 2. Kahn SE. *Diabetologia*. 2003;46:3-19; 3. Mitrakou A, et al. *N Engl J Med*. 1992;326:22-29; 4. Kramer CK, et al. *J Clin Endocrinol Metab*. 2015;100:2987-2995.

Clamp Study Results: Current Basal Insulin Analogues

Graphs depict the adjustments needed to a glucose infusion to keep blood glucose levels as flat as possible



Older basal insulin analogues may not last 24 h

1. Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA.
2. Becker RH, et al. *Diabetes Care*. 2015;38:637-643.

Initiating Ultra long Basal Insulins in Patients With T2DM: Guidelines and Evidence

General Guidelines for Any Basal Insulin

Specific Guidelines for Newer Insulins

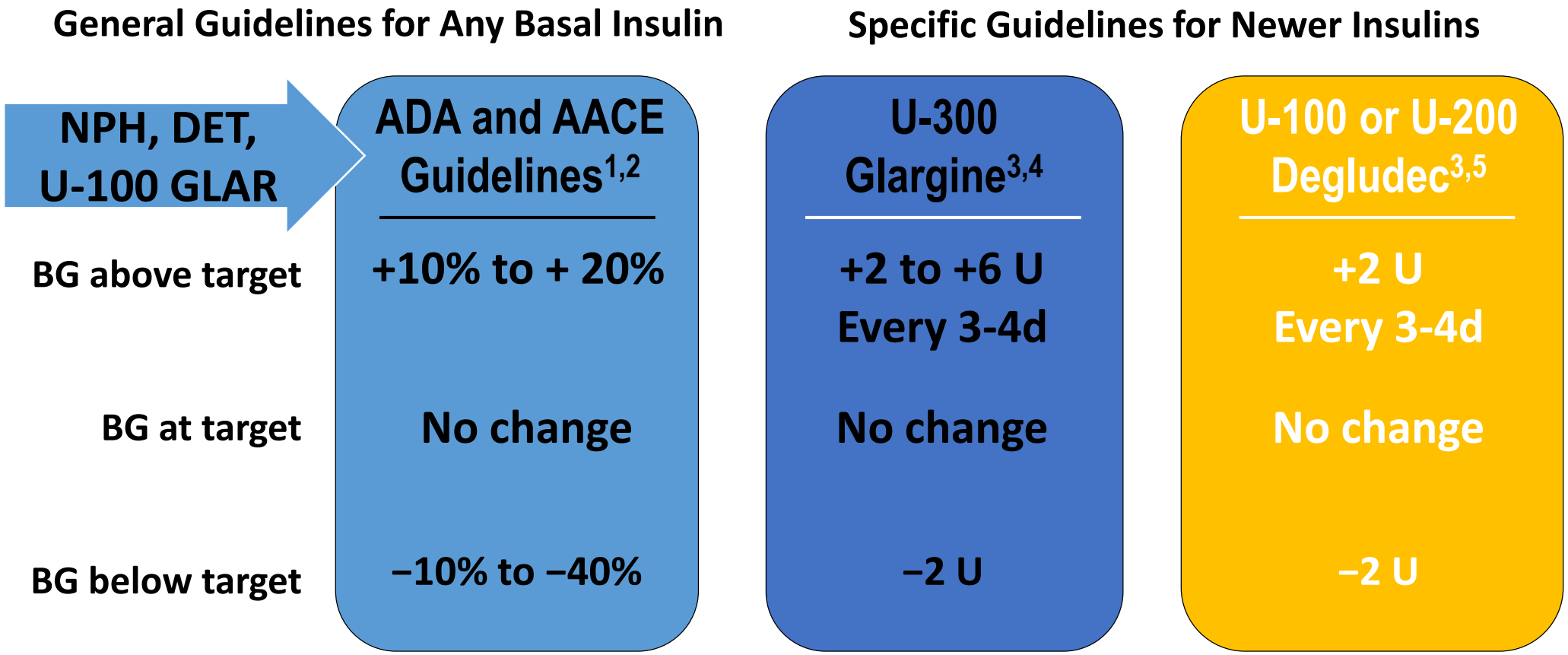
AACE Guidelines[1]	ADA Guidelines[2]	U-300 Glargine[3]	U-100 or U-200 Degludec[3]
0.1-0.2 U/kg/d if A1C < 8% 0.2-0.3 U/kg/d if A1C > 8%	0.1-0.2 U/kg/d *or* 10 U/d	0.2 U/kg/d	10 U/d
Smallest dose increment:		450 U pen: 1 U 900 U pen: 2 U	U-100: 1 U U-200: 2 U

****Short Cut**: **Weight in lbsX10%. Ex 220 lbs=22u basal {on formulary}**

1. dhinnen clinical practice.

1. Garber AJ, et al. *Endocr Pract*. 2018;24:91-120;
2. ADA. *Diabetes Care*. 2018;41(suppl 1):S1-S159;

Titrating Basal Insulins: Guidelines and Evidence



- **Compute average FBG from 2-3 (or median of 3) previous measurements[4-6]**

1. Garber AJ, et al. *Endocr Pract*. 2018;24:91-120; 2. ADA. *Diabetes Care*. 2018;41(suppl 1):S1-S159;
4. Rosenstock J, et al. *Diabetes Care*. 2018 Aug
13. [Epub ahead of print]; 5. Vora J, et al. *Diabetes Res Clin Pract*. 2015;109:19-31.

Considerations for Using Ultralong-Acting Basal Insulins in Patients With Renal Impairment

U-100 and U-200 Degludec

- No differences in PK activity in patients with mild to severe CKD[1]
- Steady-state half-life is ≈ 25 hours in individuals with T2DM and normal renal function[2]
- < 10% of participants in clinical trials had eGFR < 60[3]

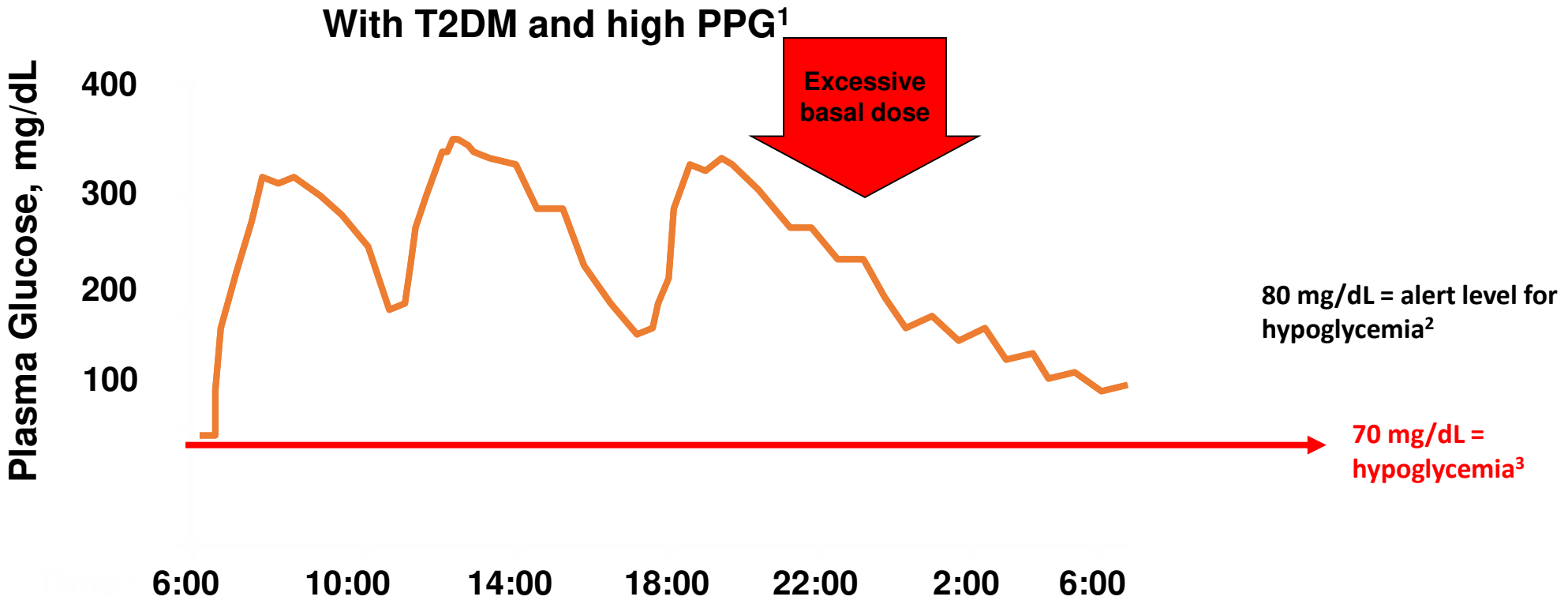
U-300 Glargine

- U-100 and U-300 GLAR have equivalent efficacy if eGFR ≥ 30[4]
- Less nocturnal hypoglycemia with U-300 if eGFR ≥ 30[4]
- Less overall hypoglycemia with U-300 if eGFR ≥ 30 and < 90[4]

- eGFR stated in mL/min/1.73 m^2

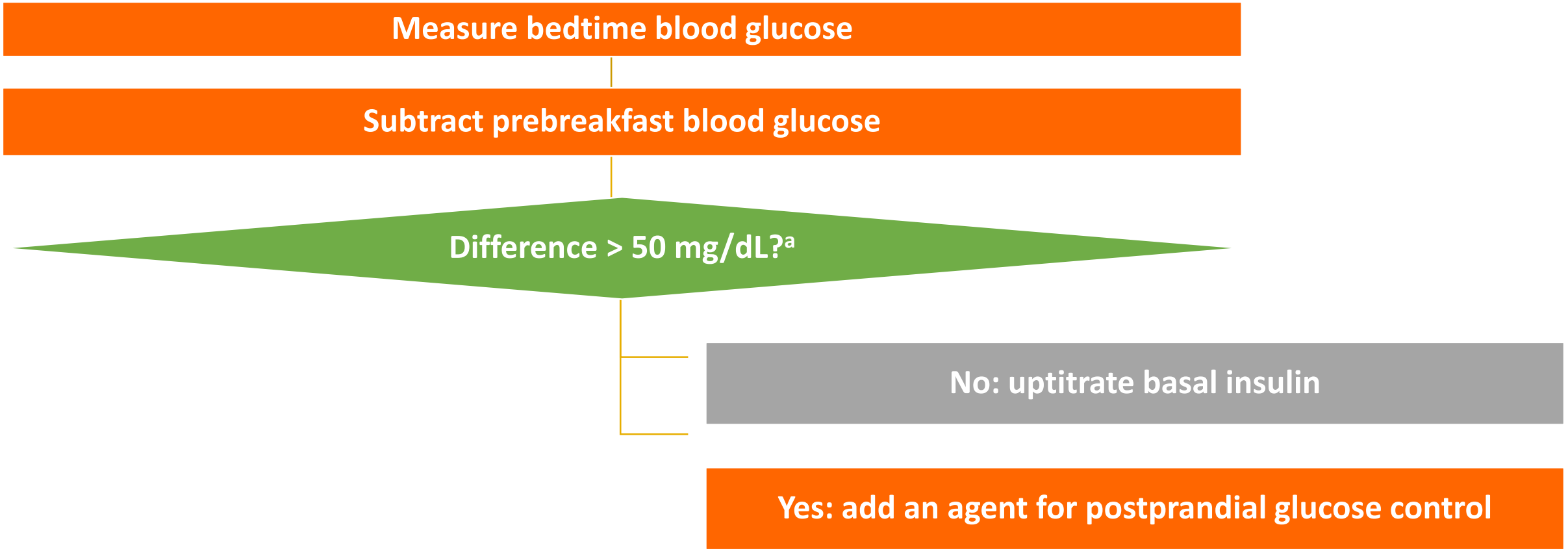
1. Kiss I, et al. *Clin Pharmacokinet*. 2014;53:175-183; 2. Heise T, et al. *Diabetes Obes Metab*. 2012;14:944-950; 3. Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA; 4. Escalada J, et al. *Diabetes*. 2016;65(suppl 1):A18 [69-OR].

Overly Aggressive Basal Insulin Titration (**Overbasalization**) is also Dangerous



1. Polonsky KS, et al. *N Engl J Med*. 1988;318:1231-1239; 2. Seaquist ER, et al. *J Clin Endocrinol Metab*. 2013;98:1845-1859.; 3. Cryer PE. In: *Hypoglycemia in Diabetes: Pathophysiology, Prevalence, and Prevention*. Alexandria, VA: ADA;2009:17-44.

Avoiding Overbasalization in T2DM



- **Overly aggressive basal insulin dosing increases the risk of severe hypoglycemia without reducing A1C—do not overbasalize to address PPG excursions![1,2]**

[a] Retrospective analysis used > 50 mg/dL as a cutoff value, but the study authors suggest that values of 45-55 mg/dL merit consideration for additional intervention.

1. Zisman A, et al. *BMJ Open Diabetes Res Care*. 2016;4:e000171.
2. Tanenberg RJ, et al. *Diabetes*. 2006;55(suppl 1):A135 [abstract 567-P].

Calculating the Number of Pens to Prescribe

Parameter	U-300 Glargine	U-100 Degludec	U-200 Degludec
Minimum dose increment	1	1	2
Insulin units/pen[a]	450	300	600

Doing the math (with sample calculations for 50 units/day):

Daily dose × 30 d/mo = monthly dose	50 units/d × 30 d = 1500 units/mo
$\frac{\text{Pens needed}}{\text{Pens/carton}} = \text{cartons needed}^*$	U-300 glargine: 4/5 = 0.8 → 1 carton U-100 degludec: 5/5 = 1 carton U-200 degludec: 3/3 = 1 carton

*** Remember to round *up* if there is a fraction so your patient has enough insulin!**

[a] Calculated from dosage form information given in the prescribing information: units/mL × mL/pen.

Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA.

Comparing and Contrasting Long-Acting and Ultralong-Acting Basal Insulins

What Stays the Same

- Basal insulin is administered once a day (except Detemir)
- 1 unit of insulin is still the same, no matter what *concentration* you are using.
- “Start low and go slow” when titrating to minimize hypoglycemia
- No need to refrigerate after opening

What’s Different

- Ultra long acting insulins are available in pens (Deg U200 also in vial)
- Ultra long insulins have a duration >24 hrs
- Do not titrate ultra long basals more often that every 3-4 days
- Ultralong-acting insulins have more flexible dosing than older insulins
  - 24 ± 3 hours for U-300 glargine
  - 24 ± 16 hours for degludec
- Flatter profile, less nocturnal hypoglycemia

Current Basal Insulins vs U-100 Glargine: Clinical Characteristics in T2DM

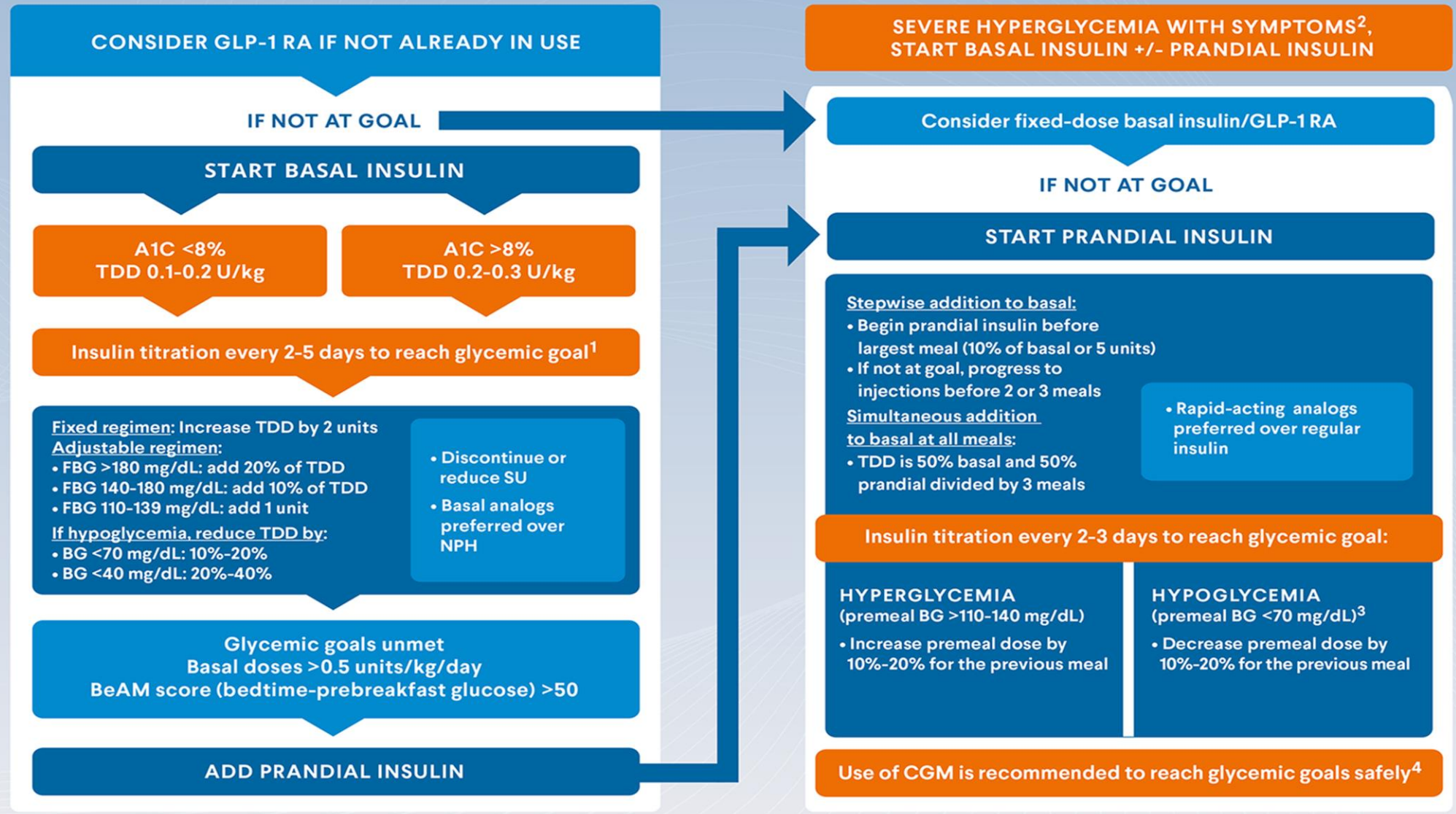
	U-100 NPH[1]	U-100 Detemir[1]	U-100 Glargine Equivalent[2]	U-300 Glargine[3]	U-100 Degludec[4,5]
Δ A1C	=	=	=	=	=
Overall hypoglycemia	=	=	=	⇓ 14%	⇓ 26%[a]
Nocturnal hypoglycemia	⇑ 37%	=	=	⇓ 31%	⇓ 29%
Severe hypoglycemia	=	=	=	=	⇓ 30%-40%

Newer basal insulin analogues are associated with less hypoglycemia than older basal insulins

Arrows indicate statistically significant differences at $P < .05$ or better.
[a] All confirmed hypoglycemia during maintenance period, in meta-analysis.

1. Rys P, et al. *Acta Diabetol*. 2015;52:649-662; 2. Rosenstock J, et al. *Diabetes Obes Metab*. 2015;17:734-741; 3. Ritzel R, et al. *Diabetes Obes Metab*. 2015;17:859-867; 4. Zhang XW, et al. *Acta Diabetol*. 2018;55:429-441; 5. Marso SP, et al. *N Engl J Med*. 2017;377:723-732.

ALGORITHM FOR ADDING/INTENSIFYING INSULIN



[1]Glycemic goals: A1C ≤6.5%-7% without hypoglycemia, fasting and premeal glucose <110 mg/dL, A1C should be individualized in people with comorbidities and at high adverse consequences of hypoglycemia and/or limited life expectancy. Longer-acting basal insulins (e.g., glargine U300, degludec U100 or U200) require slower titration ≥3 days because of a longer time to steady state. [2]For symptomatic hyperglycemia with A1C >10% and/or BG ≥300 mg/dL, reduce glucose/A1C as promptly and safely as possible. Consider testing for autoimmune diabetes. GLP-1 RA requires titration phase which can delay glycemic control. [3]Oral administration of rapidly absorbed source of glucose (tablet, fruit juice) if person can safely swallow. If unresponsive or unable to swallow, subcutaneous/Intramuscular/intranasal glucagon or glucagon analogue can be given by a trained member of the household. [4]See also American Association of Clinical Endocrinology Clinical Practice Guideline: The Use of Advanced Technology in the Management of Persons with Diabetes Mellitus.

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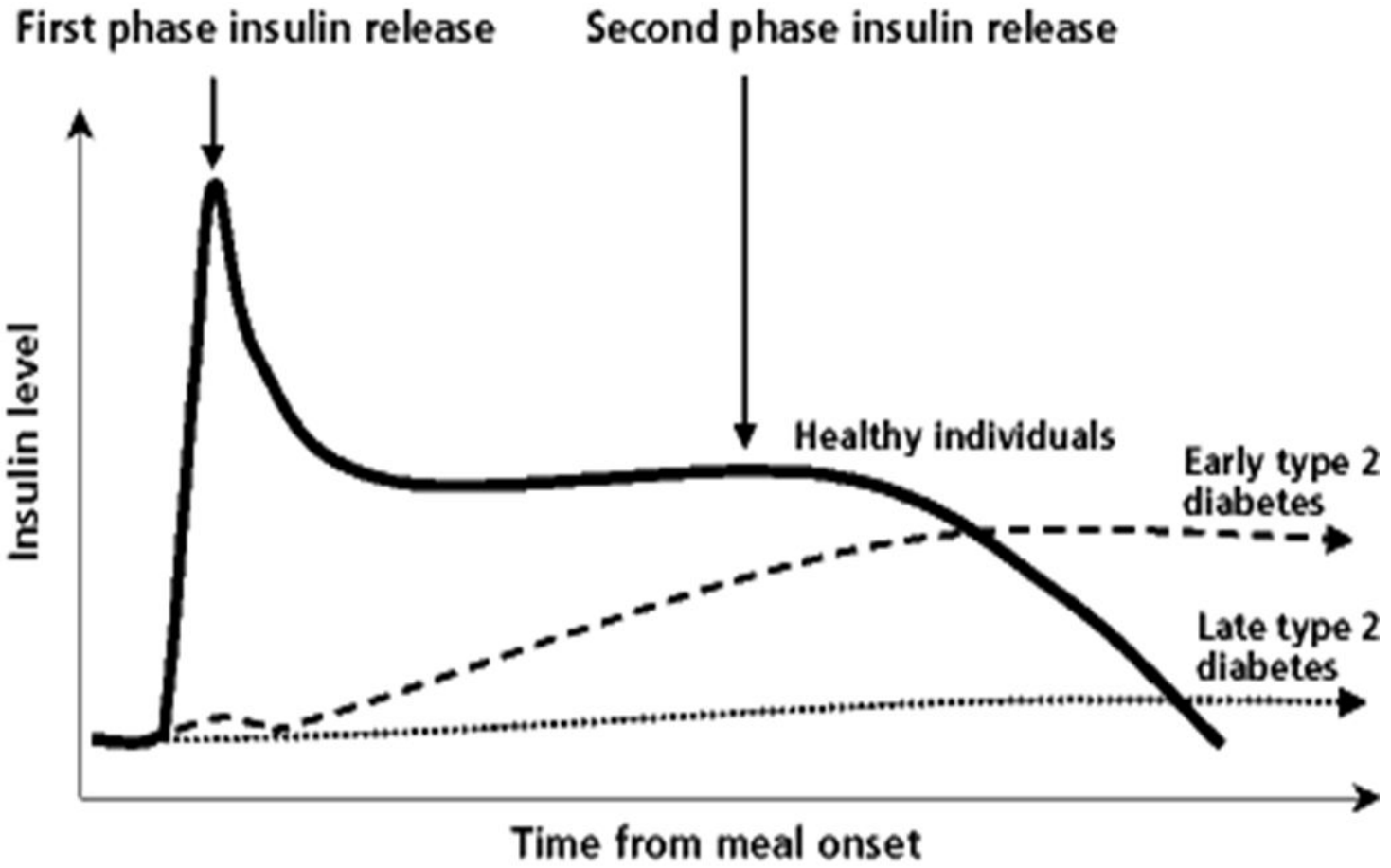
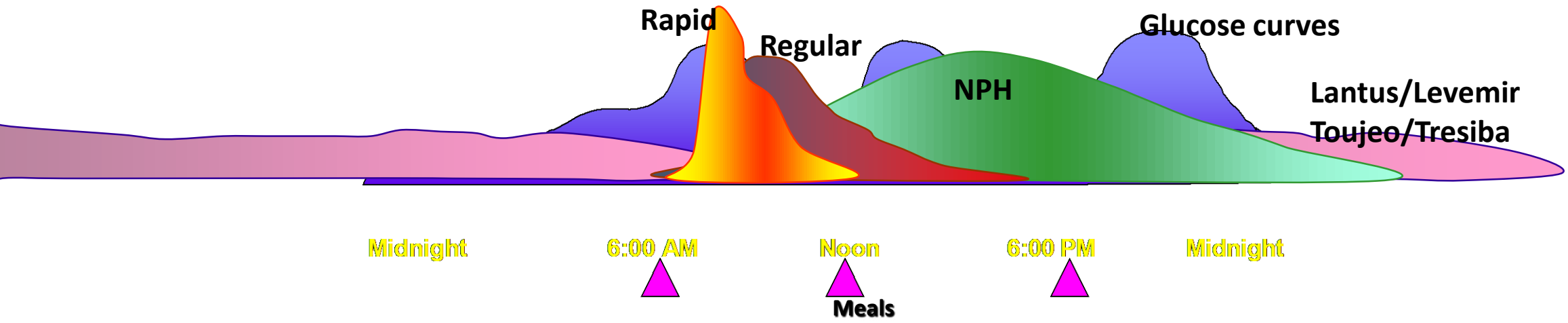
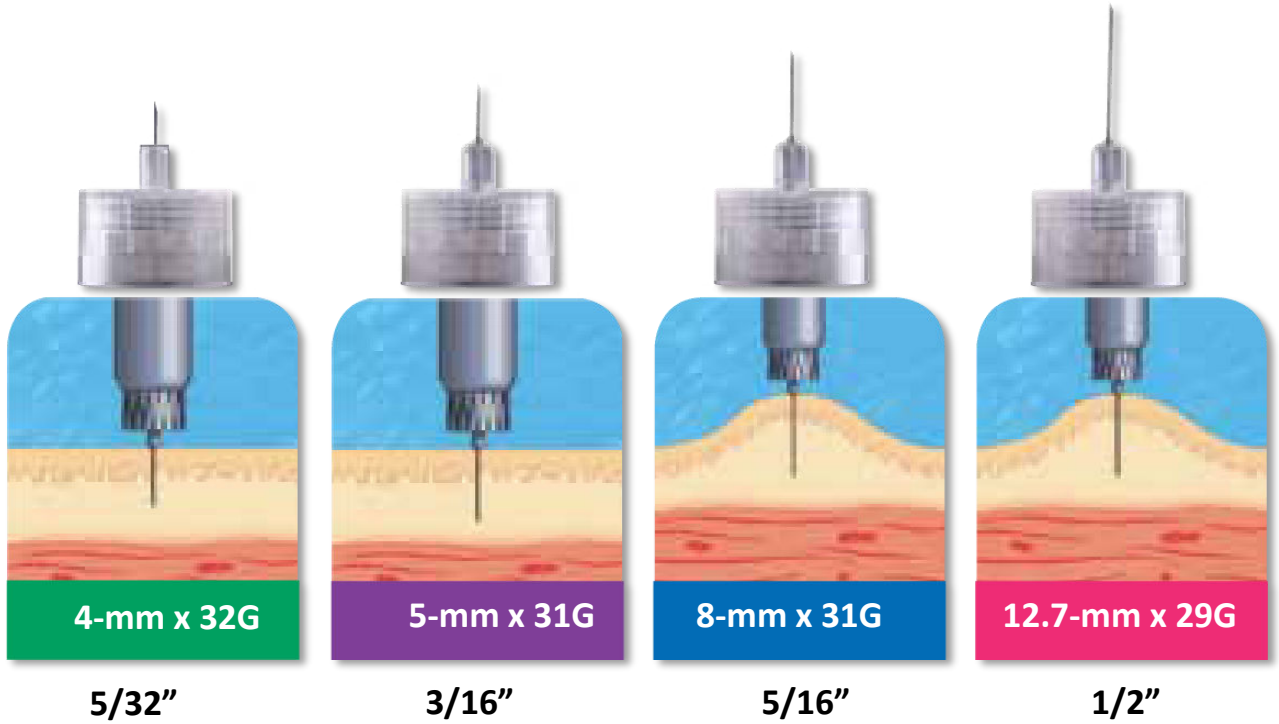
Impaired Insulin Secretion



A Variety of Insulins are Available, Including Insulin Analogs



Overcoming Patient Fears of Injection



- Use the shortest needle possible
- Demonstrate and administer first injection in the office
- Ensure injection into subcutaneous tissue, not intramuscularly
- Penetrate skin quickly, but inject slowly
- Use a new needle with every injection

Becton Dickinson Diabetes. *Step by step injection guide.* 2012; www.bd.com/us/diabetes.
Becton Dickinson Diabetes. BD pen needles fit these pens.
http://www.bd.com/us/diabetes/hcp/main.aspx?cat=3067&id=3156
King L, et al. *Nurs Stand.* 2003;17:45-52;Frid A, et al. *Diabetes Metab.* 2010; 36 (suppl 1):S3-S18.

Not Everything that happens is a Miracle:
Other Non-Insulin Therapies

- Old clinical management:
  - Metformin (for years)
  - Sulfonylurea (for years)
  - Insulin

Sulfonylureas/Secretagogues:

Glipizide, Glyburide, Glimiperide
Prandin and Starlix

- Formulations:
  - Glimepiride (Amaryl) 1, 2, 4mg (max: 8mg) 30 min before meals. 1-2x/d
  - Glyburide (Glynase) 1.5mg,3,6mg (max 12mg) 30 min before meals. 1-2x/d
  - Glipizide (Glucatrol XL) :5,10mg (max: 20mg) 30 min before meals. 1-2/d
  - Repaglinide (Prandin) 0.5, 1, 2mg (max 16mg)5-30 min before meals. 3x/d
  - Natelinide (Starlix) 60, 120mg (Max 360mg) 5-30 min before meals 3x/d
- AE: Hypoglycemia. Weight gain after treating hypoglycemia
- Pt Ed: Squeezes insulin out of pancreas. Glipizide/glyburide have similar time actions to NPH. When taking before breakfast, DON'T miss lunch. If dose before dinner, BedTime snack with protein.
- Amaryl is more renal friendly and flatter time action
- dc or cut dose in half when starting GLP, GLP/GIP
- Sulfonylureas increase risk of all cause mortality by 26% and CV mortaility by 46%. Crest study. Clinicalendocrinologynews.com 10(11) 2015

DPP4s

- Formulations: Oral. Distant cousin to the GLP's
  - Sitagliptin (Januvia) 100mg (renal dose 50mg, GFR<50)
  - Alogliptin (Nesina) 12.5, 25mg half
  - Saxaglipin (Onglyza) 5mg half

  **Linagliptin (Tradjenta) 5mg No renal dosing required. Excreted in bile and feces
- MOA: glucose activated, nudges the pancreas
- AE: low risk of hypoglycemia
- Why Not? Not generic $$$, only average about 0.5 % A1C drop

Some things still have benefit….

Metformin

- Formulations: XR=Extended Release: 500mg (on the $4 list), 750, 1000mg
  (IR Immediate Release= GAS/DIARRHEA: 500mg, 850mg, 1000mg
- Clinically Therapeutic Dose: 2000mg (Max dose 2,550mg – no additional benefit)
- Titrate 500mg XR weekly until Fasting Glucose in target and tolerability
- Approved in kids >10yrs
- MOA: Inhibits hepatic gluconeogenesis, decreases intestinal absorption and improvers peripheral glucose uptake. **For Pts**: Stops the "Leaky Liver"
- AE's: Gas, Cramps, Diarrhea.
- Monitor B12 annually. Renal fn if GFR dropping
- Contraindications: GFR<30, hx lactic acidosis, severe hepatic disease, alcohol abuse
- Hold for IV contract or acute dehydration
- Guidelines don't require this as first Rx started. Insurance does sometimes though.

Thiazolidones TZDs: Pioglitazone (Actos)

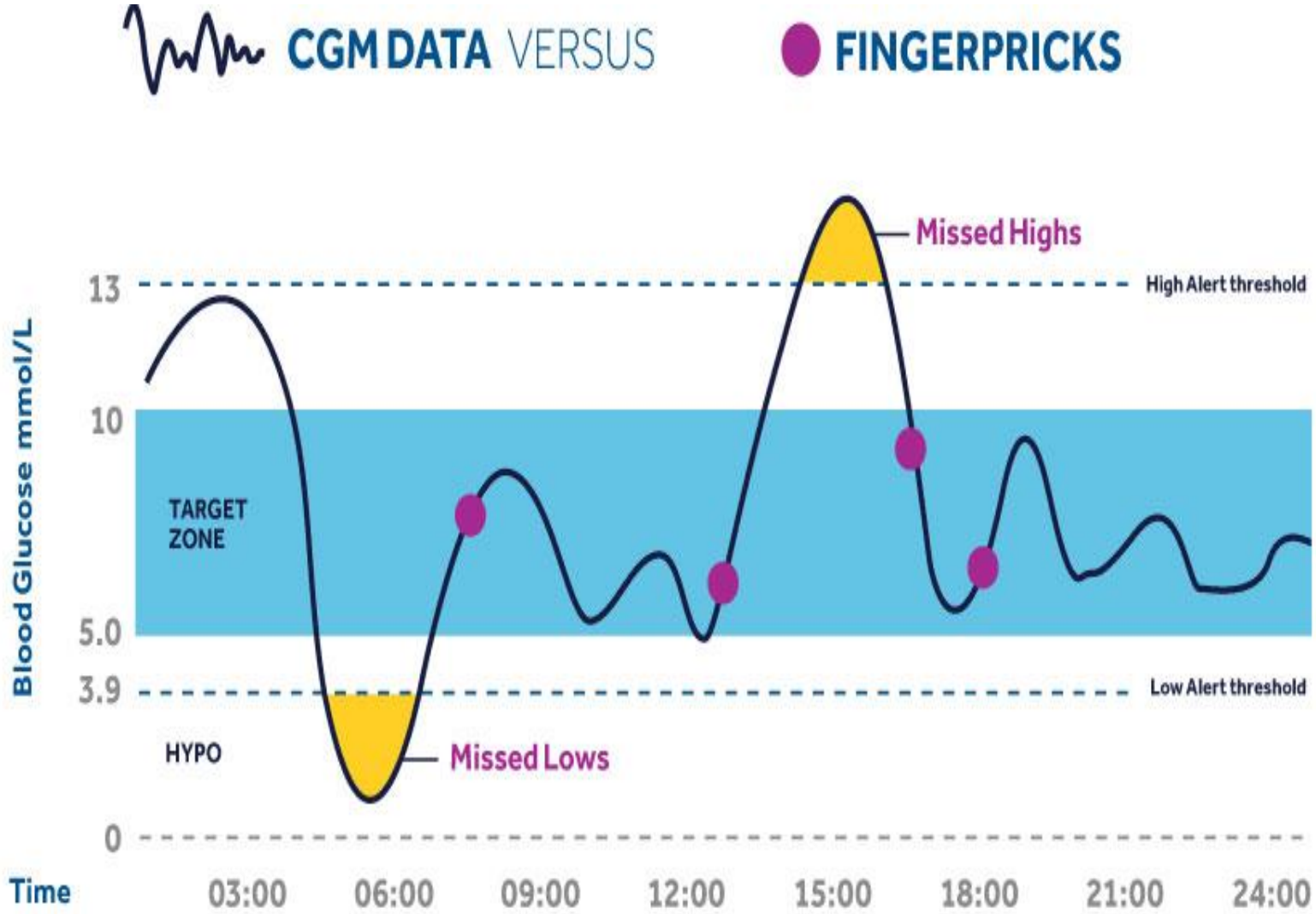
- Pio: **15mg**, 30mg, 45mg. Pro Tip: Weight GAIN >15mg
- Rosiglitazone (Avandia):4mg, 8mg (Controversial = Cardiac AE/s)
- MOA: Works intracellularly to improve signaling: adipose, muscle, liver
  - Very effective to improve insulin resistance (Even Pio 7.5mg –R. DeFronzo)
- AE's: Weight gain, edems (esp if subclinical CHF)
- Do not use if CHF
- Monitor LFT;s prior and following initiation, sx of HF, wt gain, bladder CA
- Takes 2-3 months for therapeutic benefit
- Anti-inflammatory, Reduces visceral fat – NASH/NAFLD, improved heart fn BP and A-Fib

Glucose-Lowering Agents: T2DM Overview

		Metformin	DPP-4 inhibitors	GLP-1 receptor agonists	SGLT2 inhibitors	SUs (second generation)	TZDs	Insulin
Glucose-lowering efficacy		High	Intermediate	High	Intermediate	High	High	Highest
Hypoglycemia						Yes		Yes
Weight		Neutral (potential for modest weight loss)	Neutral	Loss	Loss	Gain	Gain	Gain
CV effect	**ASCVD**	Potential benefit	Neutral	Benefit/neutral[a]	Benefit[a]	Neutral	Potential benefit[a]	Neutral
	HF	Neutral	Potential risk[a]	Neutral -benefit	Benefit[a]	Neutral	Increased risk	Neutral
Adverse events		GI effects, potential B12 deficiency	Joint pain, potential acute pancreatitis	GI effects, potential acute pancreatitis, thyroid C-cell tumors	Genitourinary infection, volume depletion,	GI effects, increased risk of CV mortality	Congestive HF, fluid retention, fractures	Injection site reactions

[a] Depending upon specific agent; always check the product label.
ASCVD, atherosclerotic cardiovascular disease; DKA, diabetic ketoacidosis; HF, heart failure.

ADA. *Diabetes Care*. 2024;47(Suppl 1):S1–S232.


CGM DATA VERSUS
FINGERPRICKS
Missed Highs
13
High Alert threshold
10
TARGET ZONE
5.0
3.9
Low Alert threshold
HYPO
Missed Lows
0
Blood Glucose mmol/L
Time
03:00
06:00
09:00
12:00
15:00
18:00
21:00
24:00

Pumps ***PLUS*** CGM ***automated insulin delivery***

Summary

- You can now *Treat Diabetes*, not just *Chase* Glucose
- SGLT2s and GLP's; GLP/GIPs offer simplicity in treatment, Glucose improvement with additional weight loss and very low hypoglycemia risk
- SGLT2s and GLP's also offer Renal, Cardiac, and Stroke protection. (The big uglies if diabetes is out of control long term)
- Help your PWD get the best they can afford: Check the formulary, other resources. It might require a PA
- New technology is empowering. CGMs, Pumps, communication back and forth…
- Ultra long acting insulins are like I-70 through W Ks.
- Plus: Less hypoglycemia, intra patient, intra day variability
- **You Can Do It**!