

Foundations of Cardiometabolic Health Certification Course

**Certified
Cardiometabolic
Health Professional
(CCHP)**



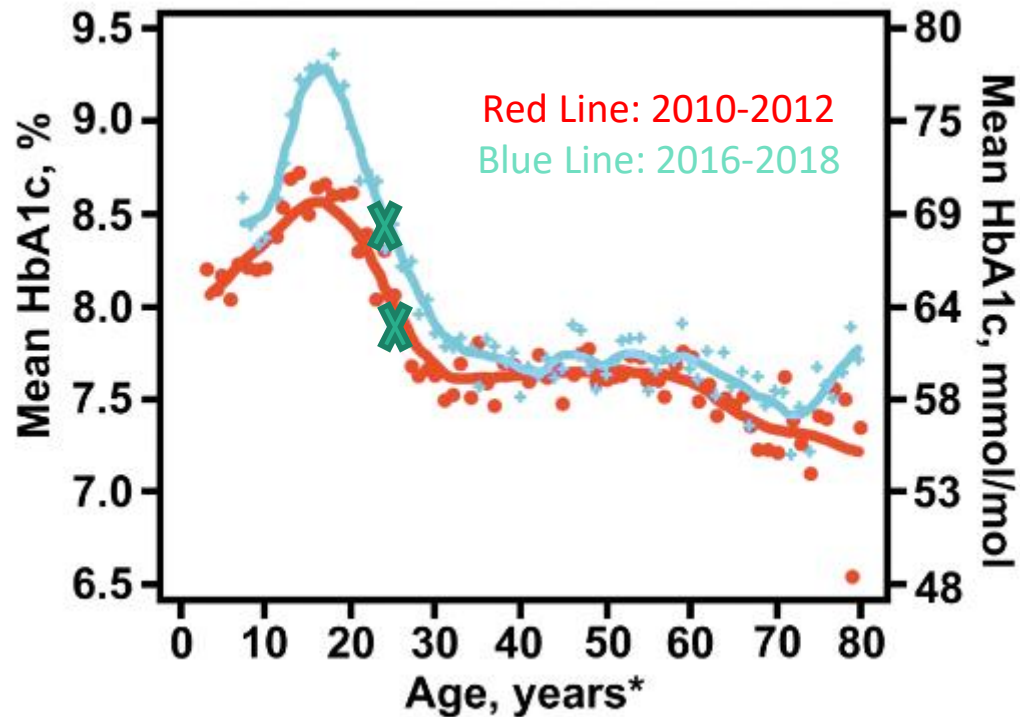
Advances in Insulin Therapy Using Non-Insulin and Insulin Injectables

Halis Kaan Akturk, MD
Associate Professor of Medicine and Pediatrics
Barbara Davis Center for Diabetes
University of Colorado

Dualities

Research: Medtronic, Tandem, Dexcom, Mannkind, Eli Lilly
Consulting: Medtronic, Tandem, Dexcom
All through University of Colorado

Glycemic Management is Hard



Only 21% adults
achieve ADA goal
of A1c <7%

Only 37% adults
achieve A1c
<7.5%

Average A1c
increased from
7.8% to 8.4%

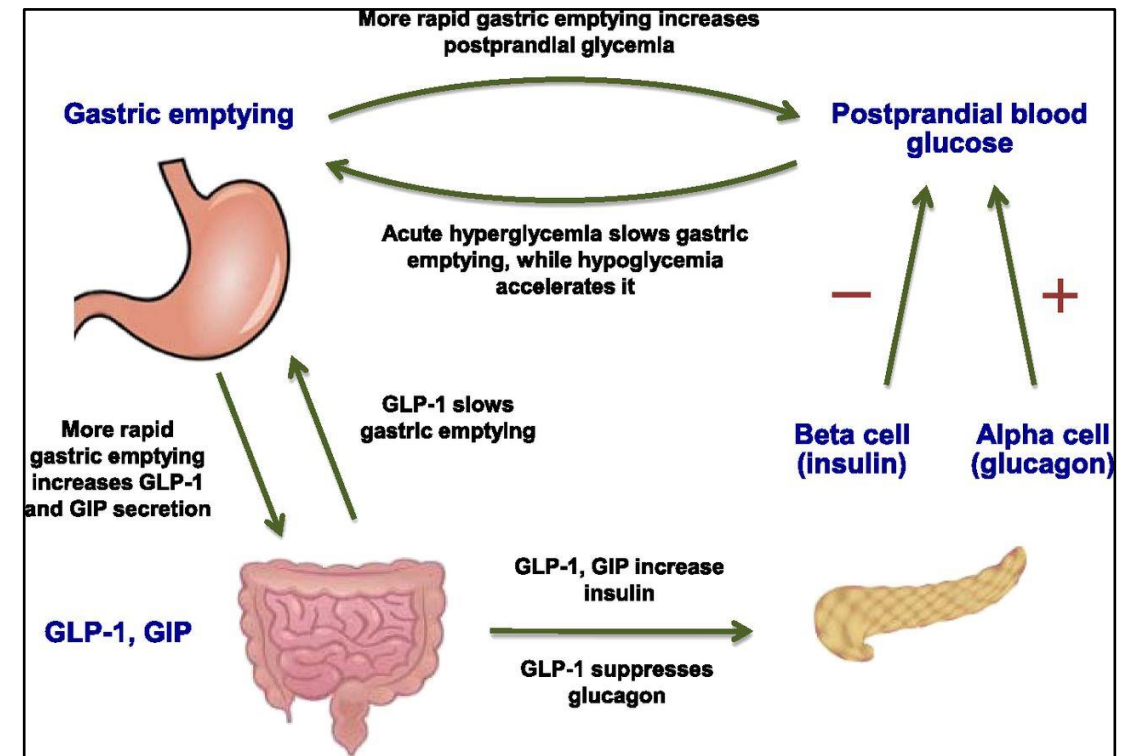
Despite advances
in technology and
therapeutics
many people
struggle to
achieve goals

Achieving Postprandial TIR is Even Harder

Postprandial glucose (PPG) > Fasting glucose (FPG) on glycemic management

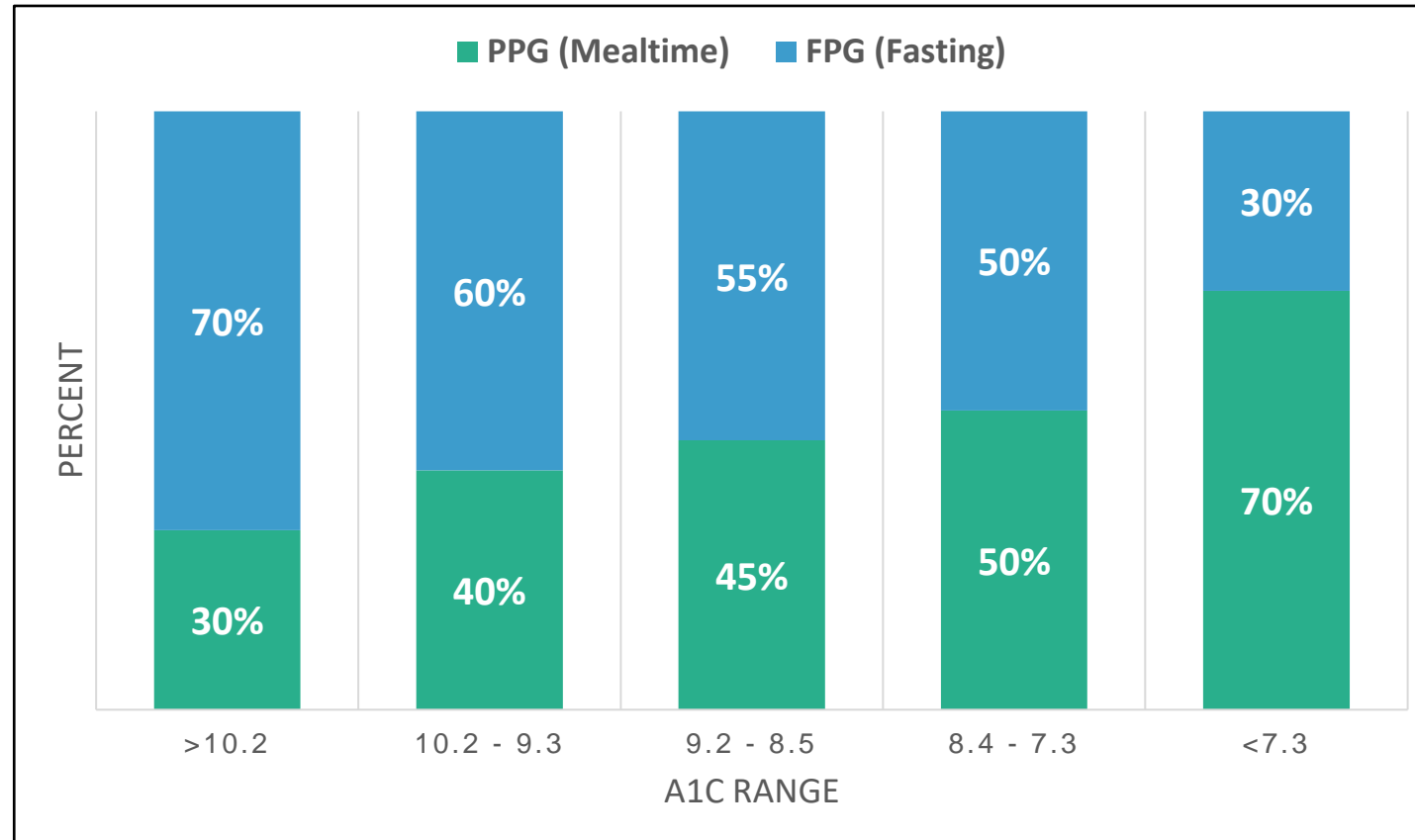
PPG management is complex and related to many other factors

In type 1 diabetes, the timing of insulin administration and insulin action can be challenging



Effect of PPG on A1c

PPG values more accurately predicts A1c in patients with relatively lower A1c



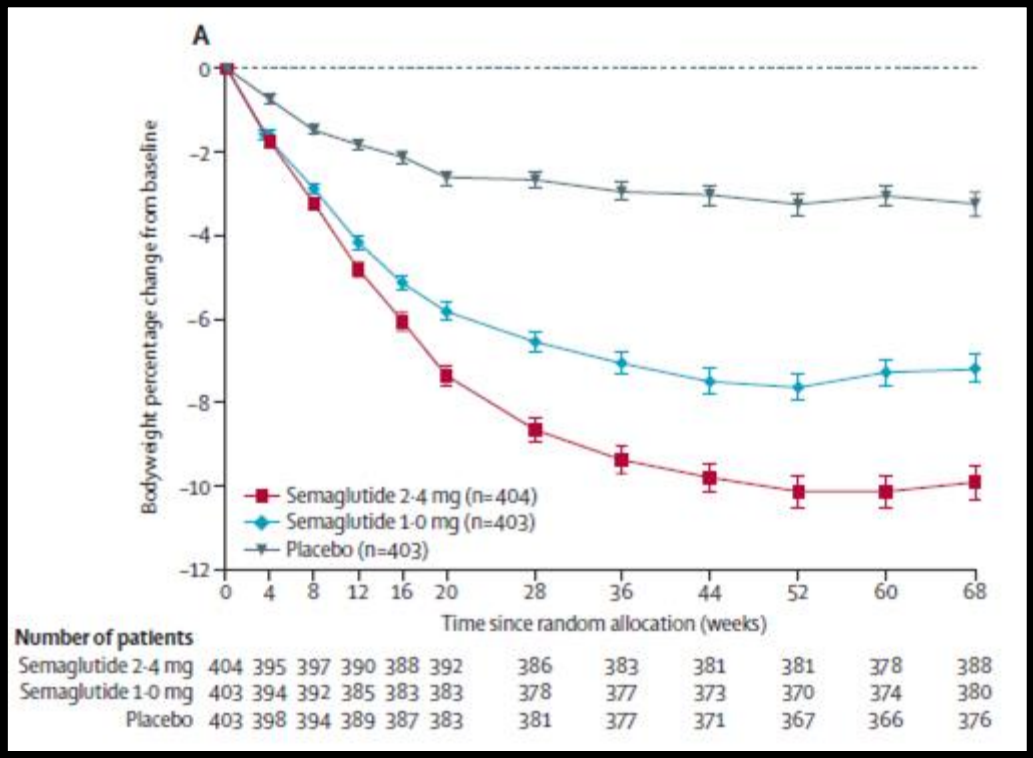
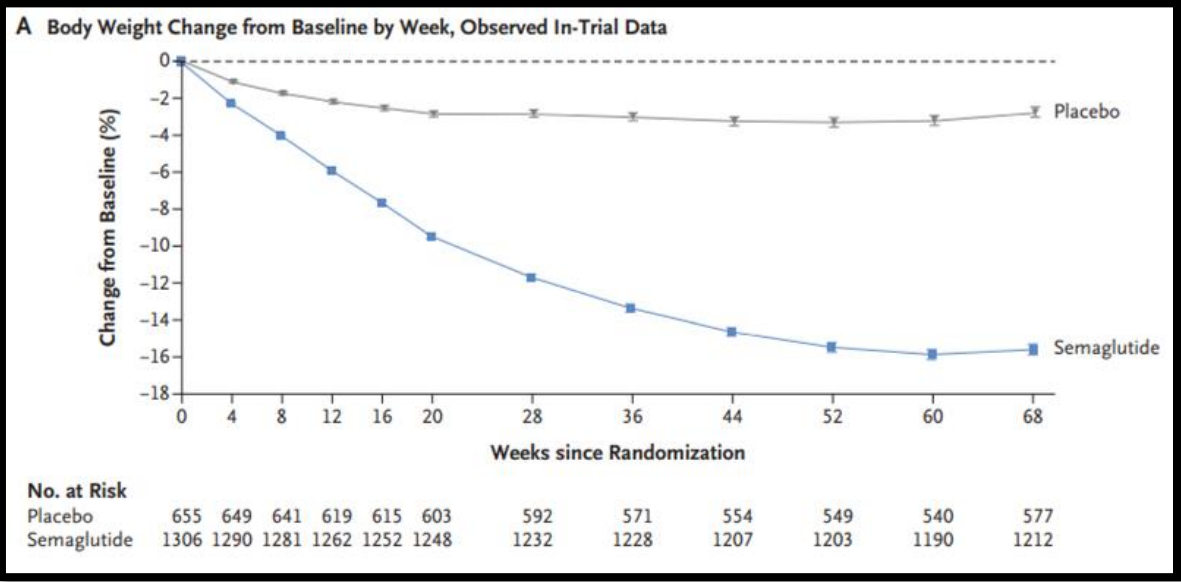
GLP1 RA Updates

- GLP-1 RAs are now the first-line injectable therapy for type 2 diabetes
- GLP-1 RAs (and SGLT-2i's) for CV or renal benefit for people with type 2 diabetes should now be *considered independently* of baseline or target A1c

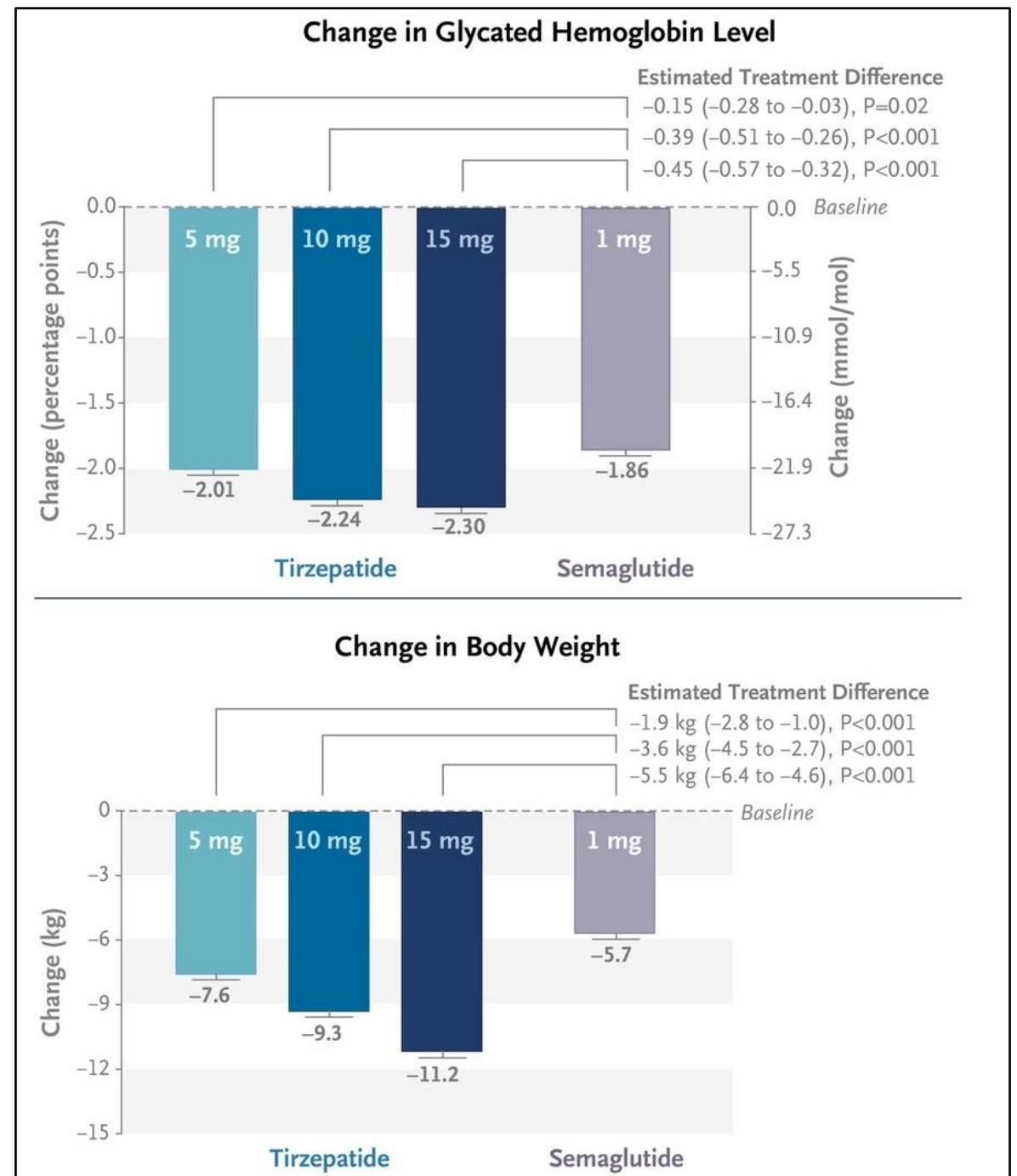
What is the evidence?



GLP1 RAs Continue to Be Developed for Weight Loss, With or Without Diabetes



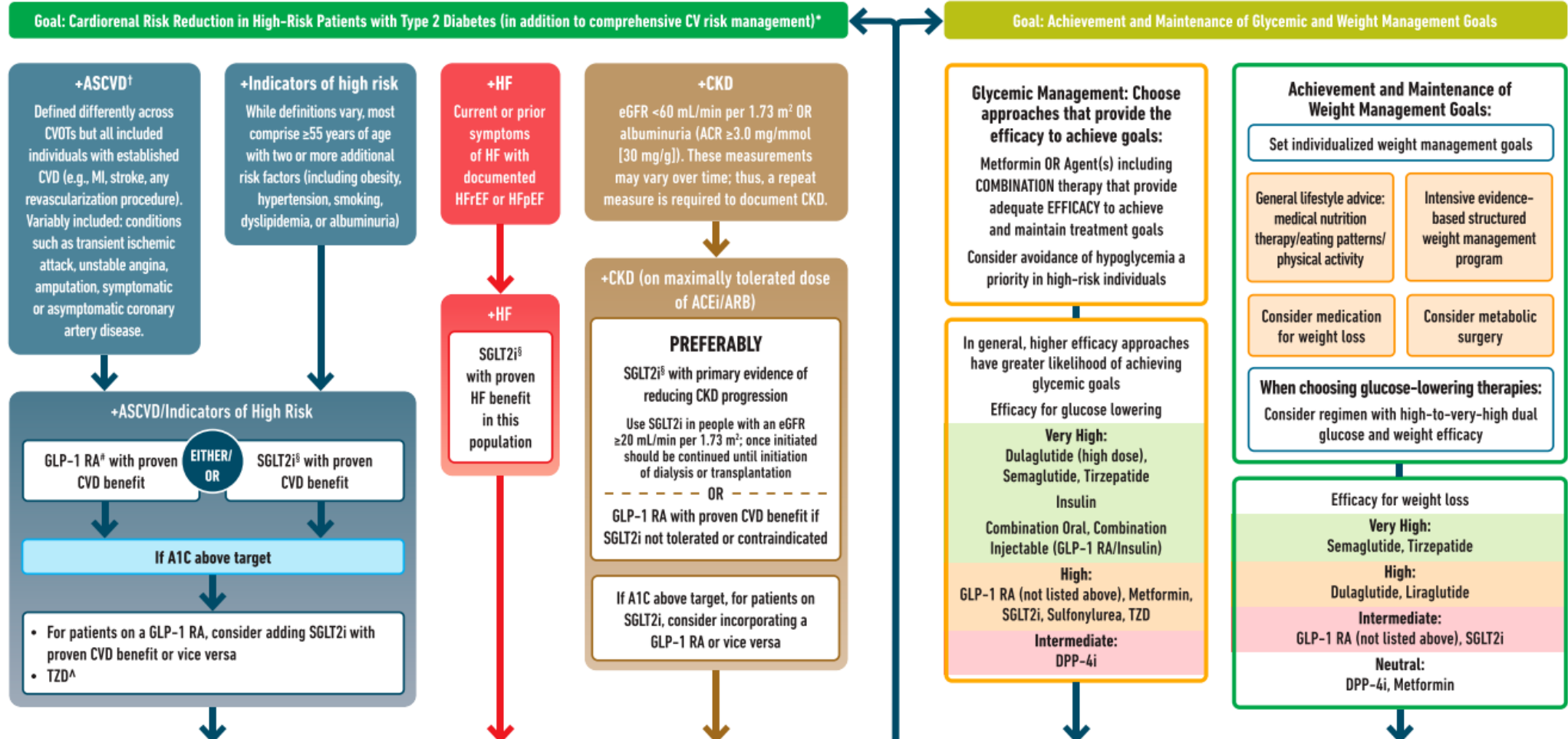
Tirzepatide vs Semaglutide in Type 2 Diabetes - SURPASS-2



ADA Standards of Care 2023

USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)

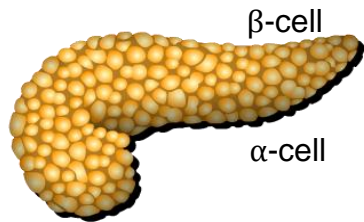


Limitations of GLP1 RA vs. Insulin Rx

- GLP1 RA
 - GI side effects
 - Pancreatitis
contraindication
 - Injection
 - Cost
- Insulin
 - Hypoglycemia
 - Weight gain
 - Need for frequent
glucose monitoring (CGM
ideal for prandial insulin)
 - Cost

GLP-1 RAs: Why They Make So Much Sense to Use With Basal Insulin

β and α cell dysfunction



GLP1 RAs: improves β and α cell function, delays gastric emptying, suppresses appetite

Fixed-Ratio GLP1-insulin
IGlar-Lixi
IDeg-Lira

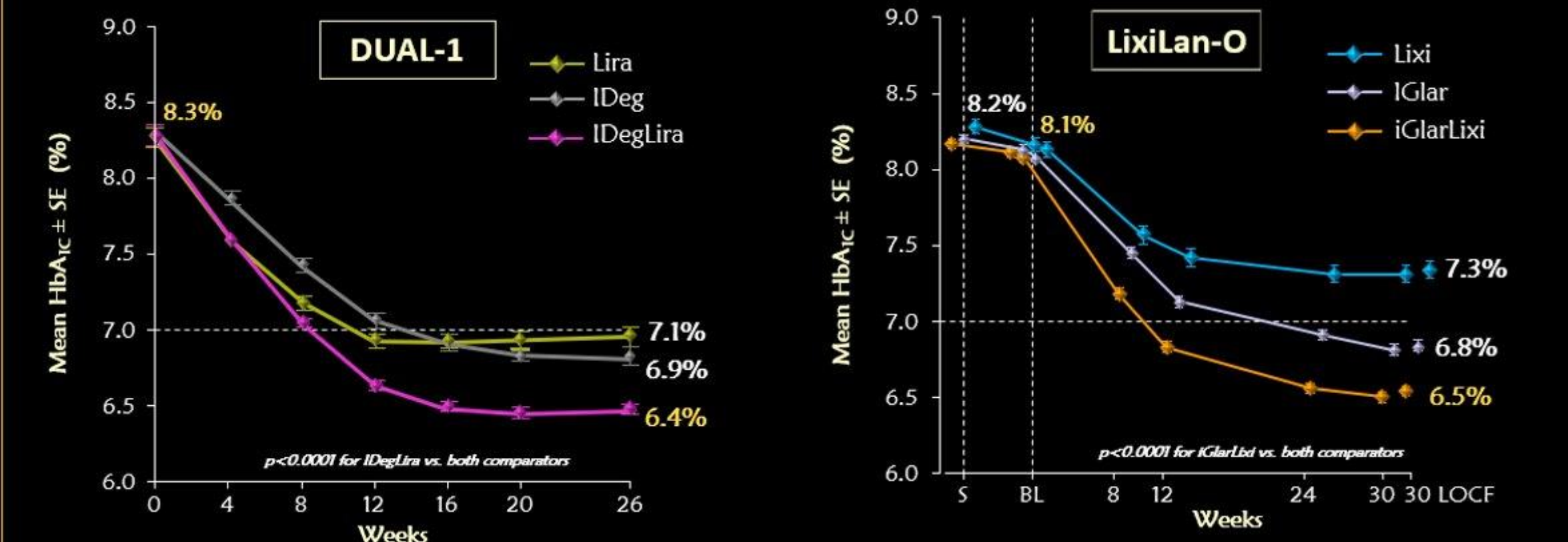
Increased HGP



Basal insulin: targets the Liver to suppress HGP by Reducing gluconeogenesis and glycogenolysis

Complementary Actions

Registration Studies: Fixed-Ratio Basal Insulin-GLP1RA Combo



IDegLira 100/3.6

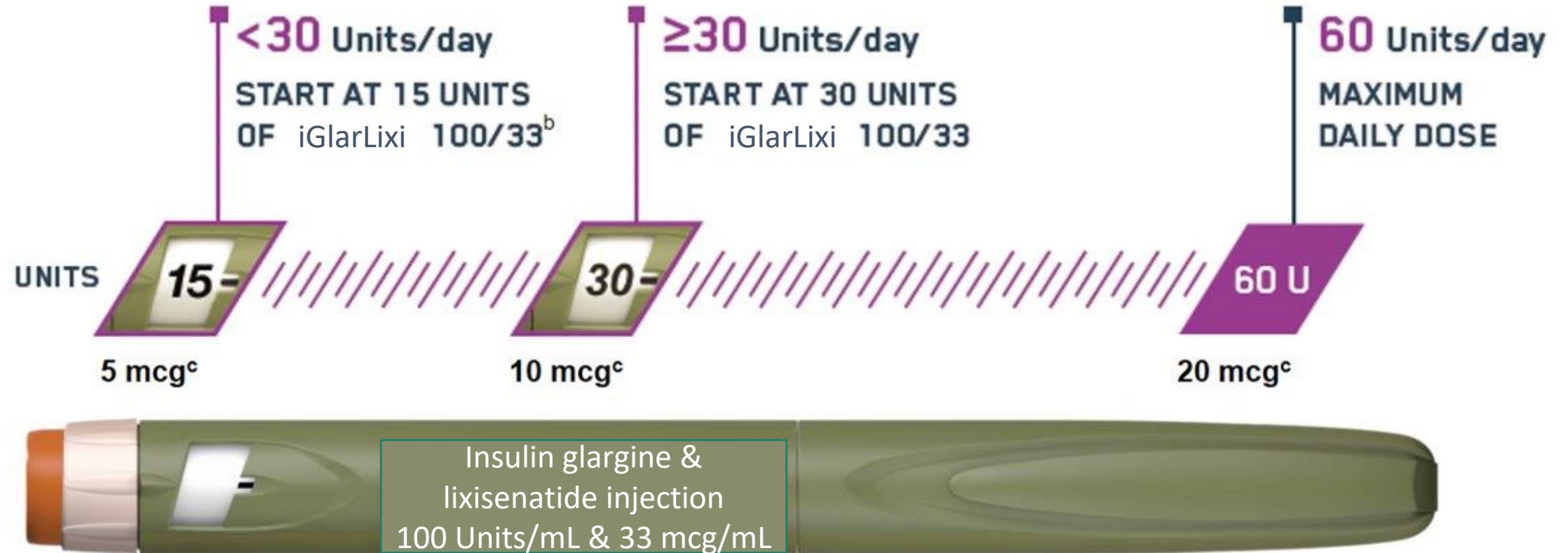
100 units = 100 units degludec, 3.6 mg liraglutide



1. Recommended starting dose (receiving basal insulin): 16 units (16 units degludec, 0.6 mg of liraglutide)
2. Recommendation is to titrate up or down by 2 units every 3 to 4 days based on SMBG
3. Pen delivers 10 units (10 units degludec, 0.4 mg liraglutide) to 50 units (50 units degludec, 1.8 mg liraglutide)

iGlarLixi 100/33

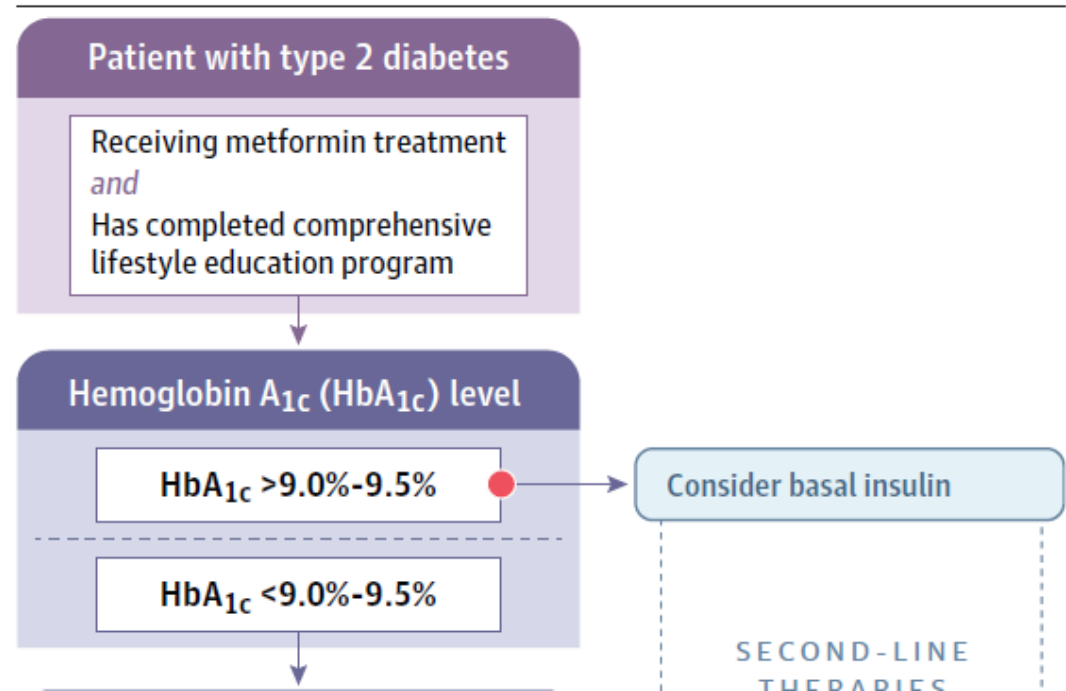
For patients uncontrolled on a basal insulin dose of^a:



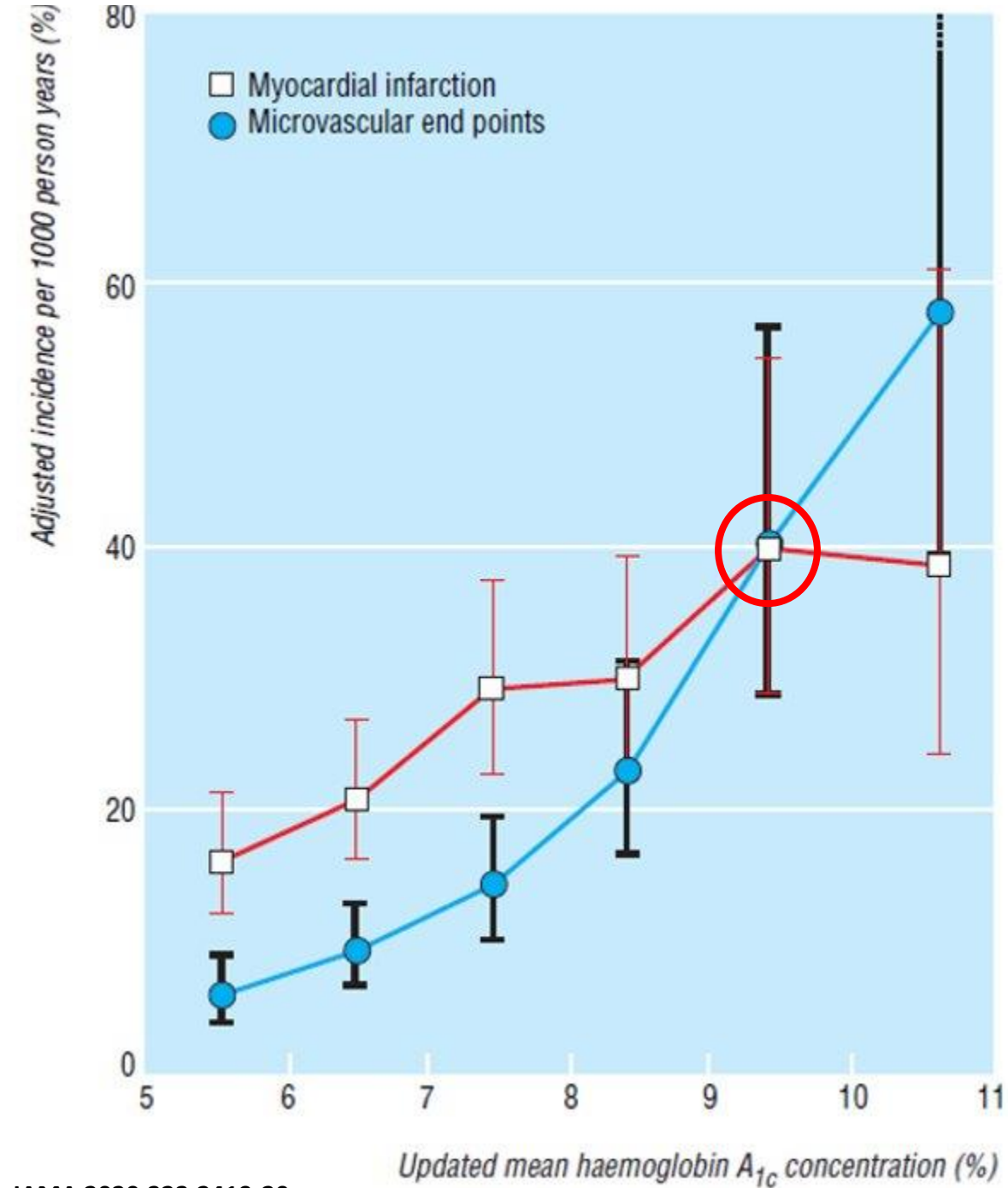
Talking to Patients About Starting a GLP1RA

- Discuss advantages – great efficacy, weight loss, blood pressure reduction
- Discuss CVD and probable renal benefits
- Discuss adverse events
 - Nausea, other GI adverse events; generally, resolves over time; consider in the context of satiety

If A1C is > 10% on metformin monotherapy, with or without ASCVD or CKD, the toxicity of the hyperglycemia needs to be treated while awaiting other drugs to take effect (not to mention the hassle with the PA, patients finding out they can't afford the med when they get to the pharmacy, etc.)

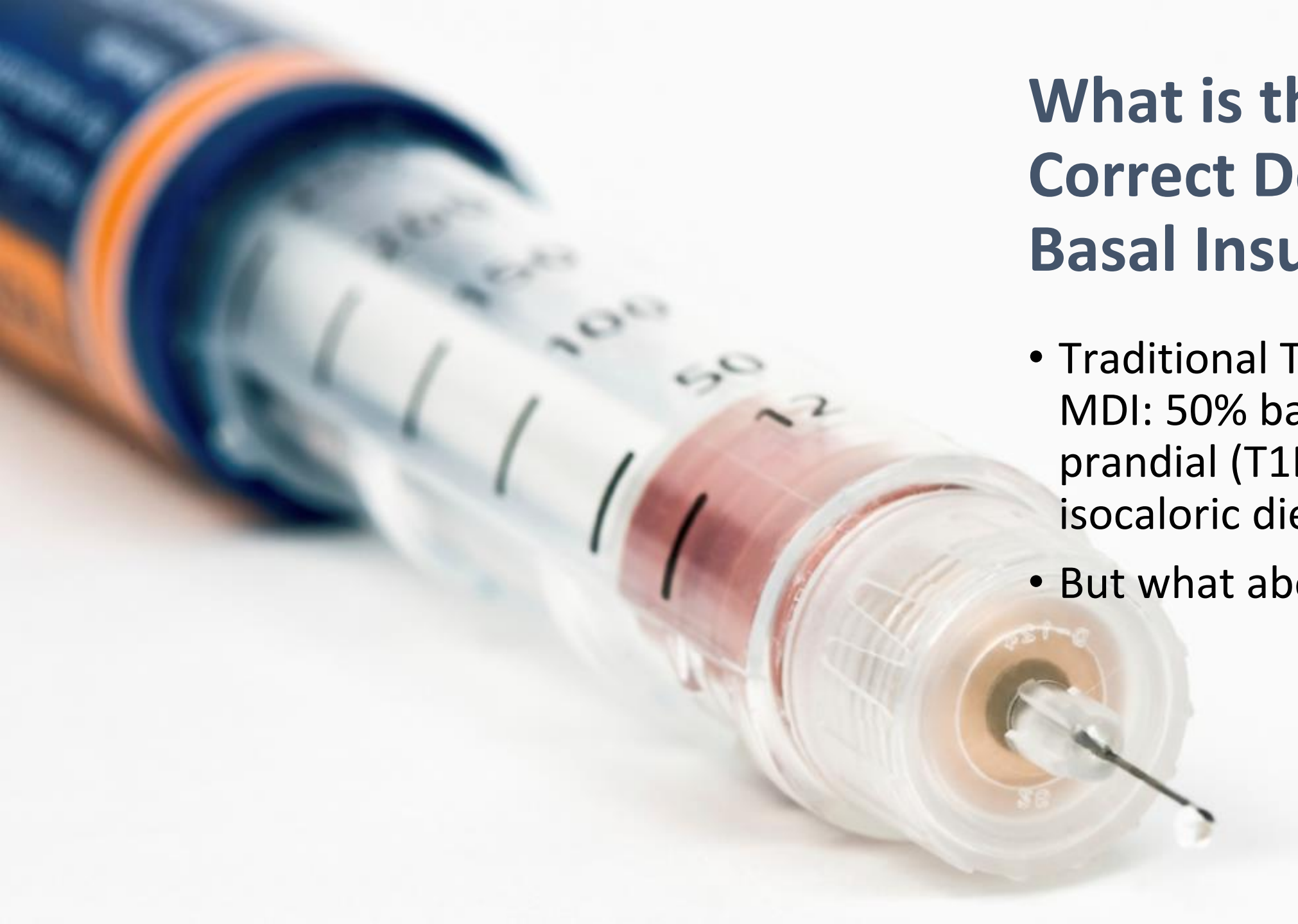


Why not just start basal insulin (or basal insulin with a GLP1 RA) while on the steep part of the curve (and avoid “clinical inertia”)?



Advances: Basal Insulin

- The primary role of endogenous basal insulin secretion is to fine tune lipolysis and hepatic glucose production in the fasting state, especially overnight, while maintaining sufficient glucose for brain function
- Goal of exogenous insulin with severe insulin deficiency
 - Attempts to recreate constant, low levels of insulin overnight and between meals which with the correct dose will maintain euglycemia for 24 hours in the fasting state



What is the Correct Dose of Basal Insulin?

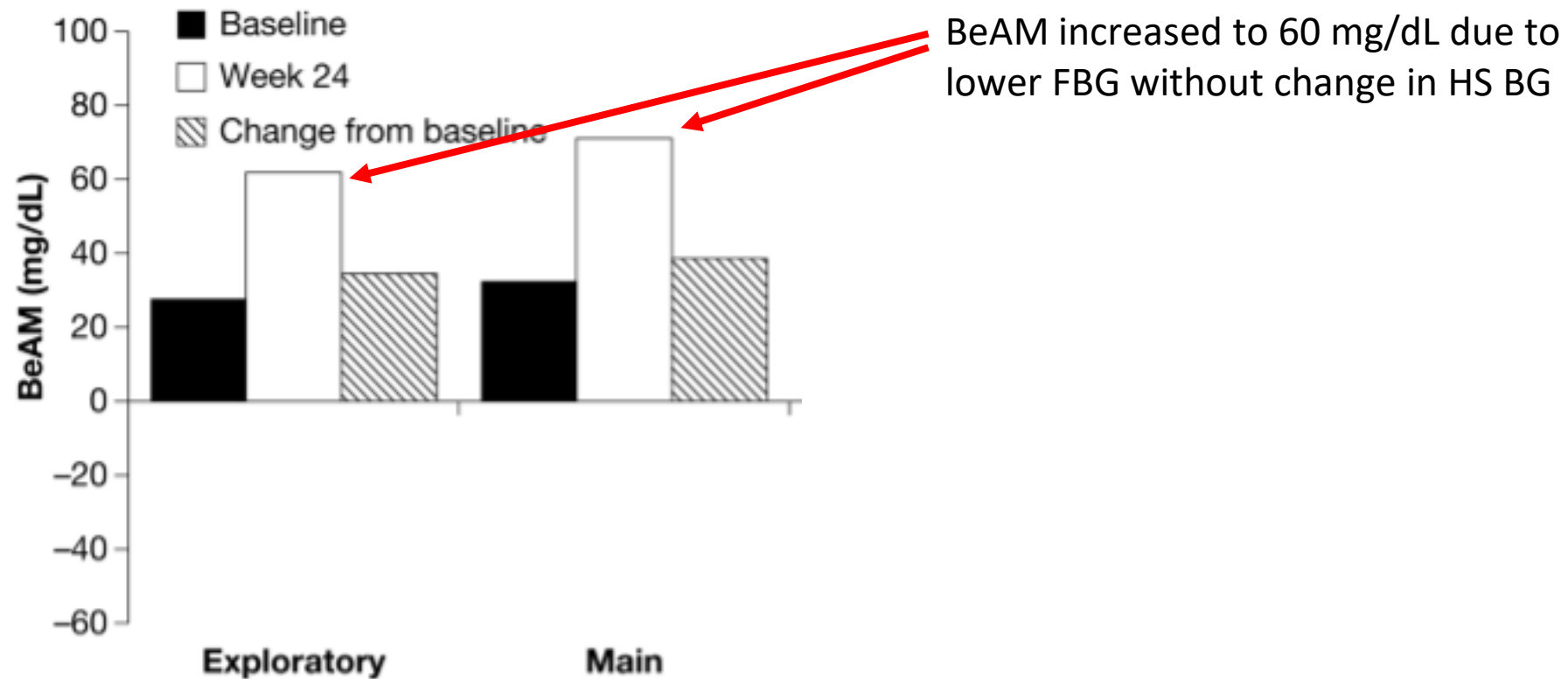
- Traditional Teaching: MDI: 50% basal/50% prandial (T1D, isocaloric diet)
- But what about T2D?

How to Dose Basal Insulin?

- BeAM factor = bedtime glucose – AM glucose
- A + BeAM factor: bedtime glucose is higher than AM glucose
 - For example, mean HS BG = 200, mean FBG = 100, BeAM = 100
- A – BeAM factor: bedtime glucose is lower than AM glucose
 - For example, mean HS BG = 120, mean FBG = 180, BeAM = -60

BeAM in T2D

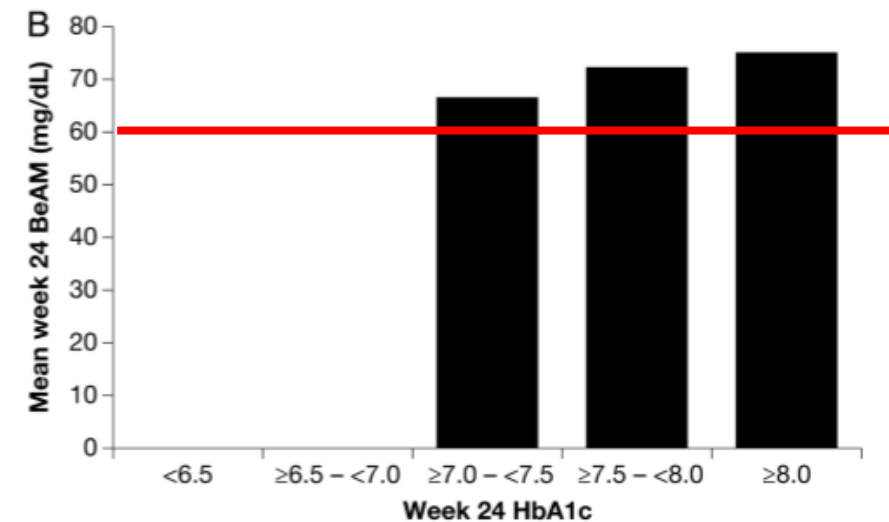
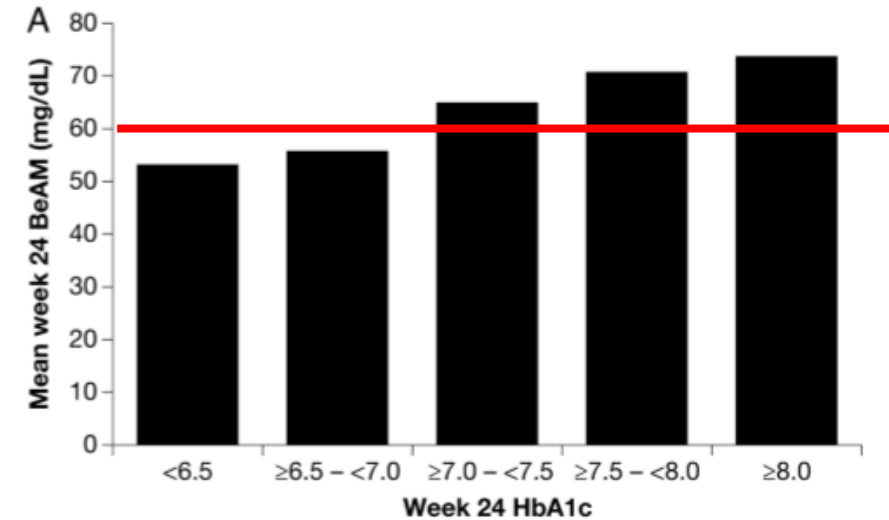
Adding basal insulin in T2D (N = 1401 and 553)



BeAM in T2D: Basal Insulin Only

The higher the BeAM, the higher the risk of early complications.

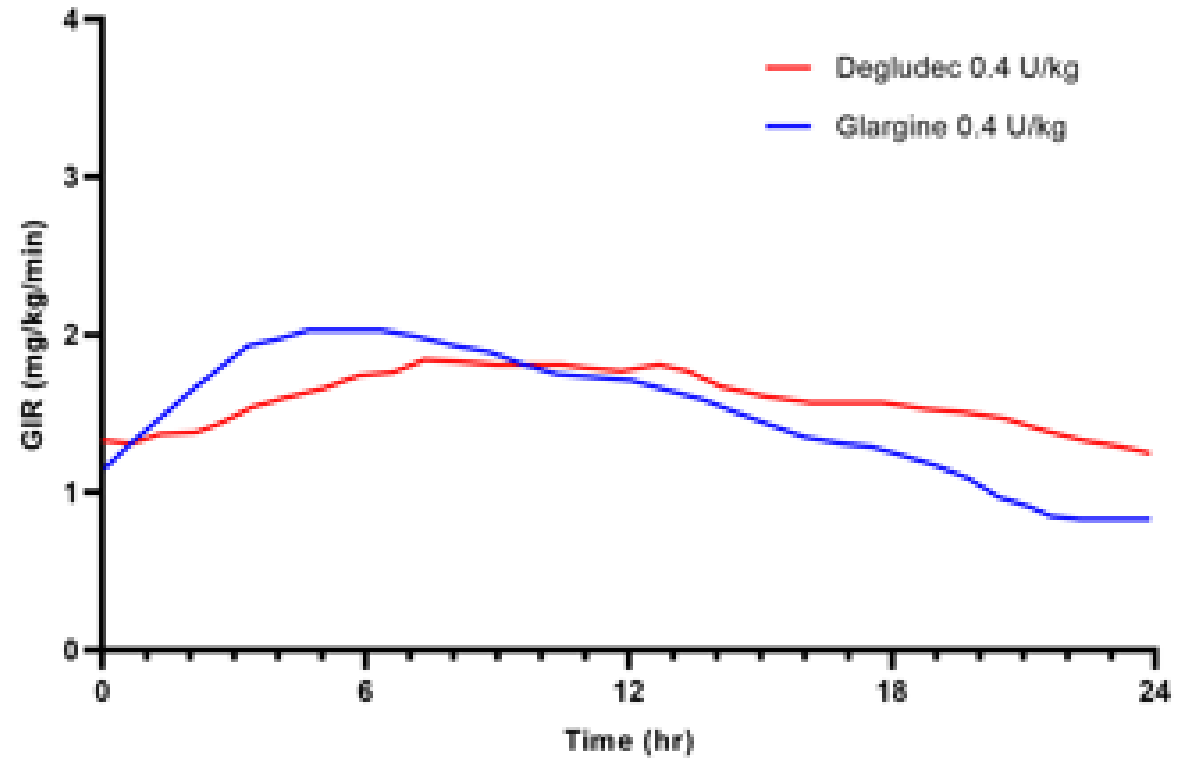
In T2D with basal insulin alone, it appears a BeAM level > 60 mg/dL is associated with A1C levels $> 7\%$. Should the goal in T2D on basal insulin be a BeAM < 60 mg/dL?



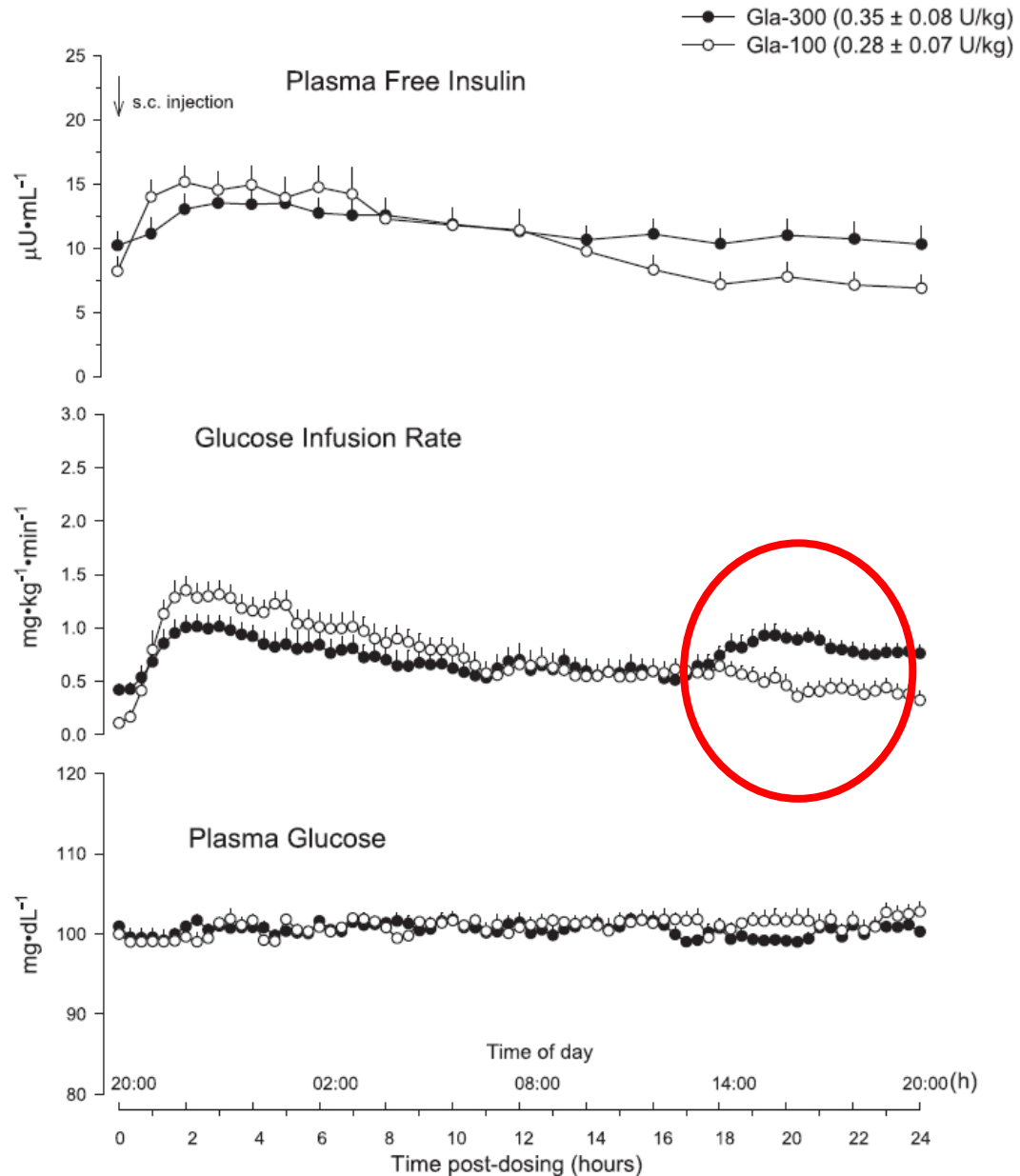
Basal Insulins

- Not all the same!
- NPH-occasionally used for severe dawn phenomenon in T1D, morning steroids, more nocturnal hypoglycemia compared to analogues in both T1D and T2D
- Glargine (U-100): most commonly used basal insulin
- U-300 glargine
- Degludec

Insulin Action Curves: Degludec vs. Glargine



What About U100 Glargine vs. U300 Glargine?



U300 lasts longer
than U100 BUT
requires about 15%
more in the dose

U-100 Glargine vs. Degludec/U-300 Glargine

- Degludec: consistently less hypoglycemia
- U300 glargine: some but not all studies with less hypoglycemia
- Bottom line: Degludec and U300 glargine are better basal insulins than U100 glargine; as a rule of thumb if you can get them, you should (especially for T1D)

Fast Acting Insulin Aspart



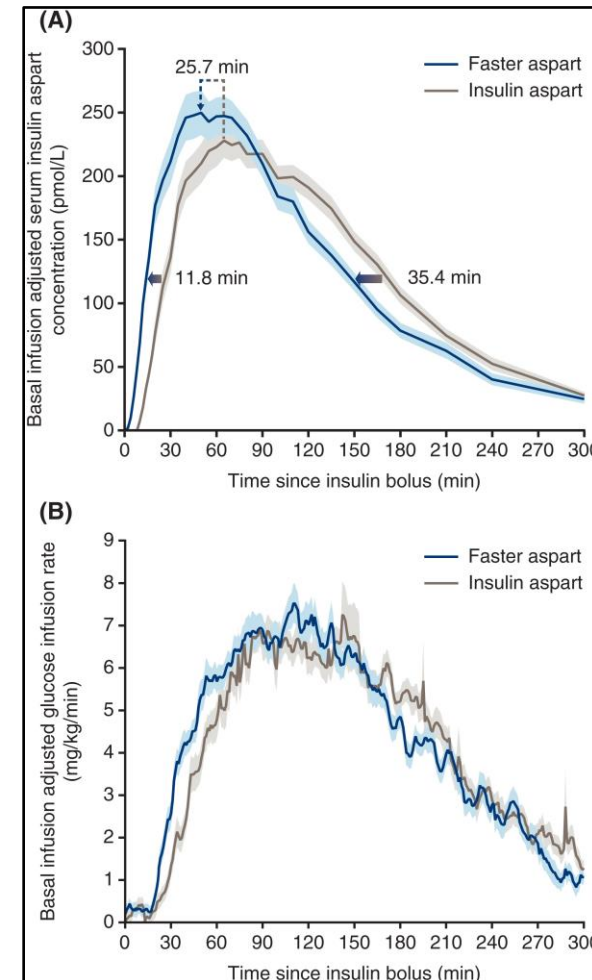
Insulin aspart + Vitamin B3 + L-arginine



Vitamin B3
(Niacinamide) → Increase
absorption



L-arginine → Stabilizer

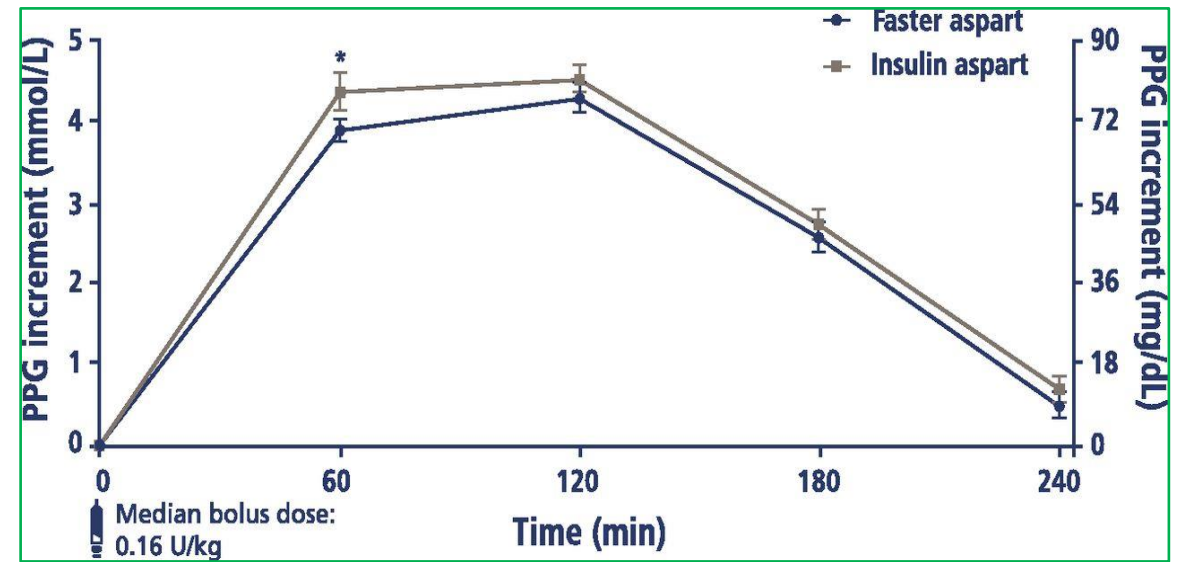
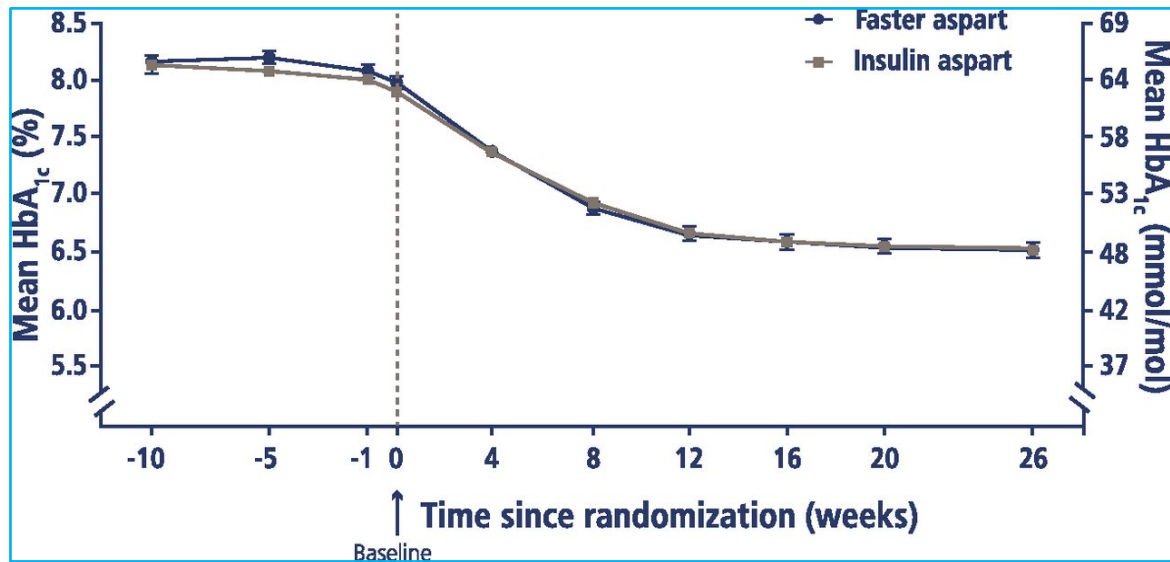


Pharmacokinetics

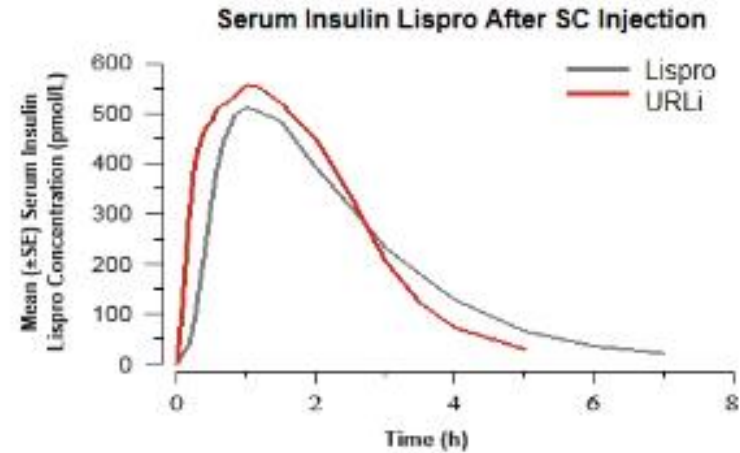
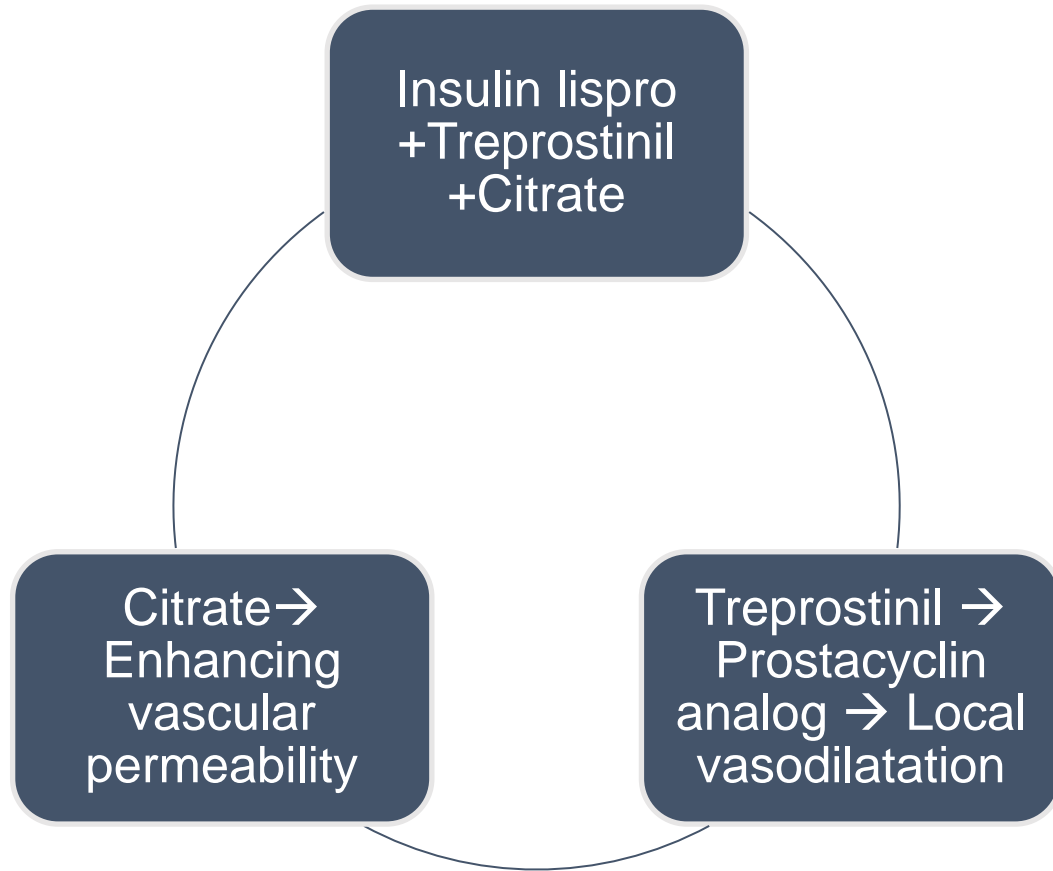
Pharmacodynamics

Fiasp in T2D: ONSET-2

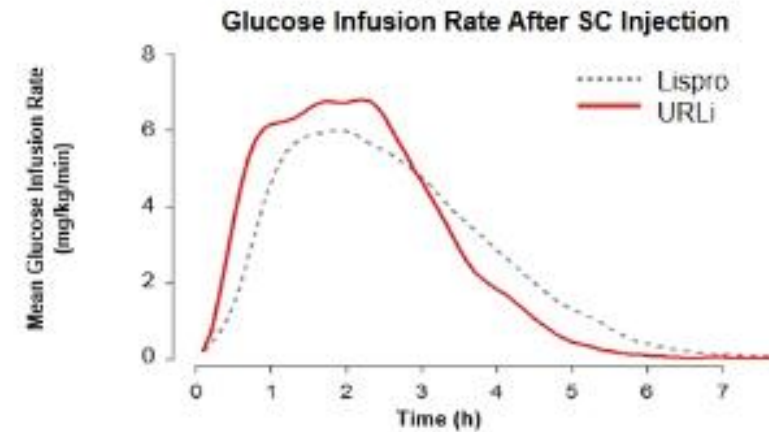
Faster aspart improved 1-h PPG with no differences in 2–4-h PPG versus IAsp



Insulin Lispro-aabc



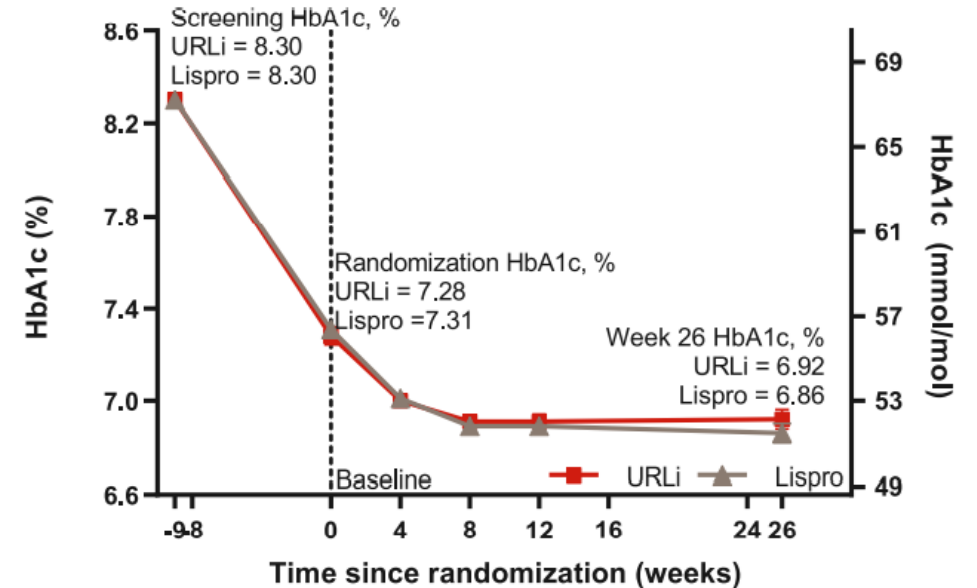
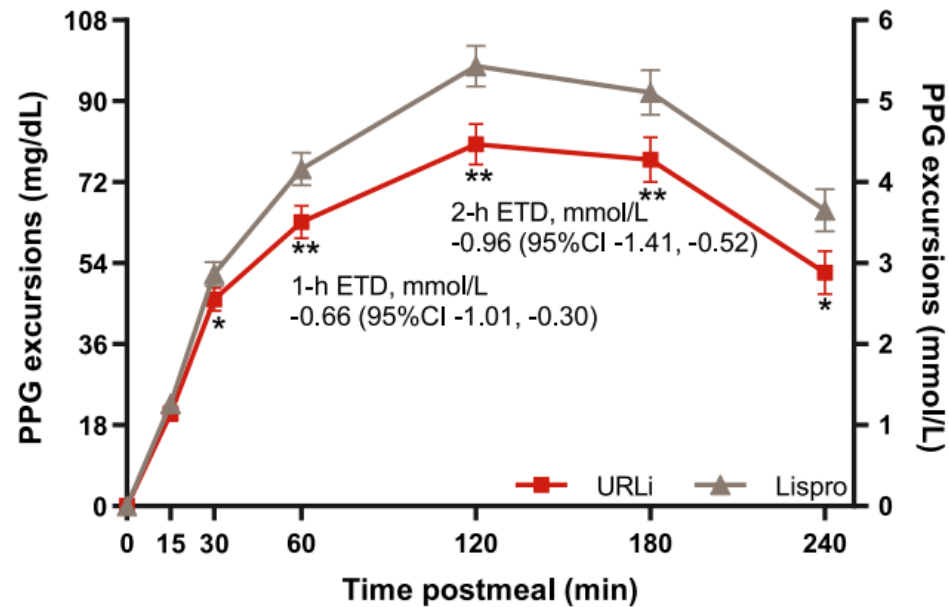
Pharmacokinetics



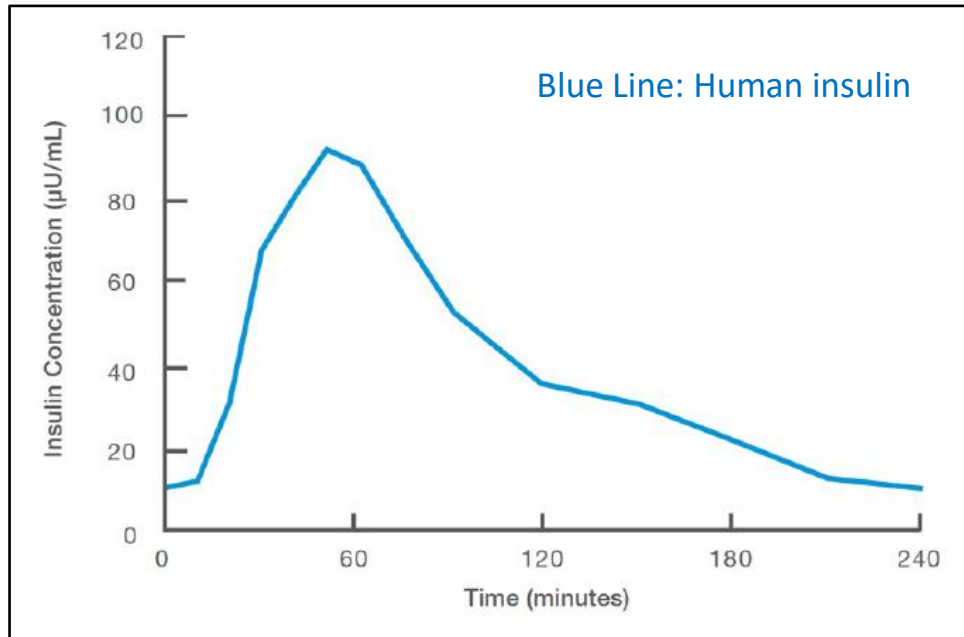
Pharmacodynamics

Lispro-aabc in T2D: PRONTO-T2D

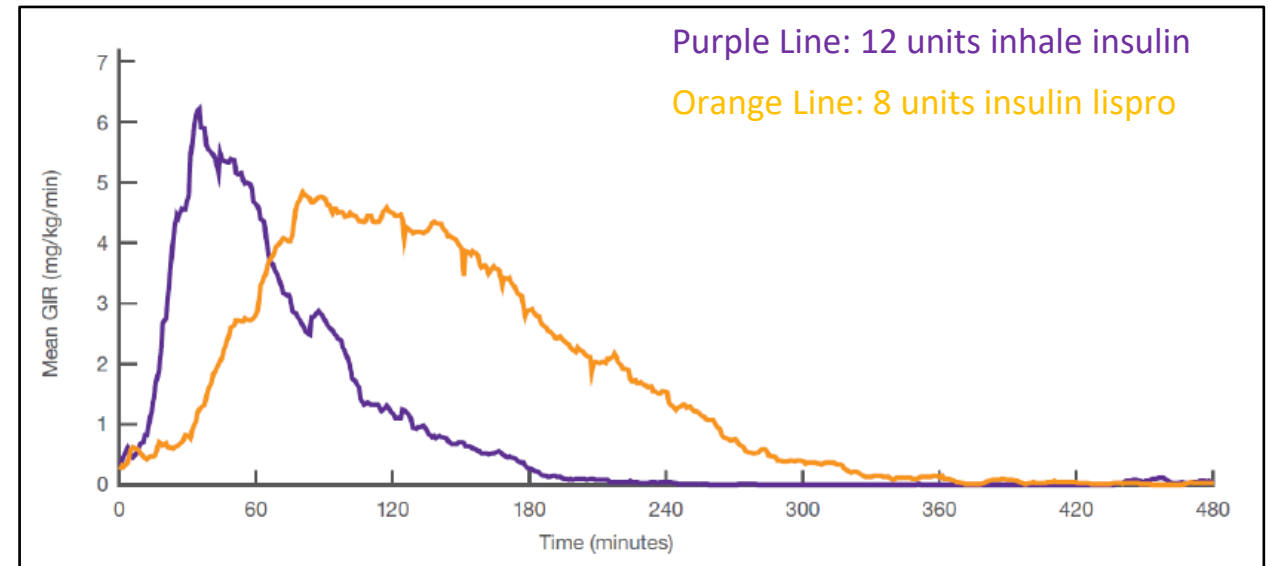
N=673



Inhaled Insulin Mimics Endogenous Insulin

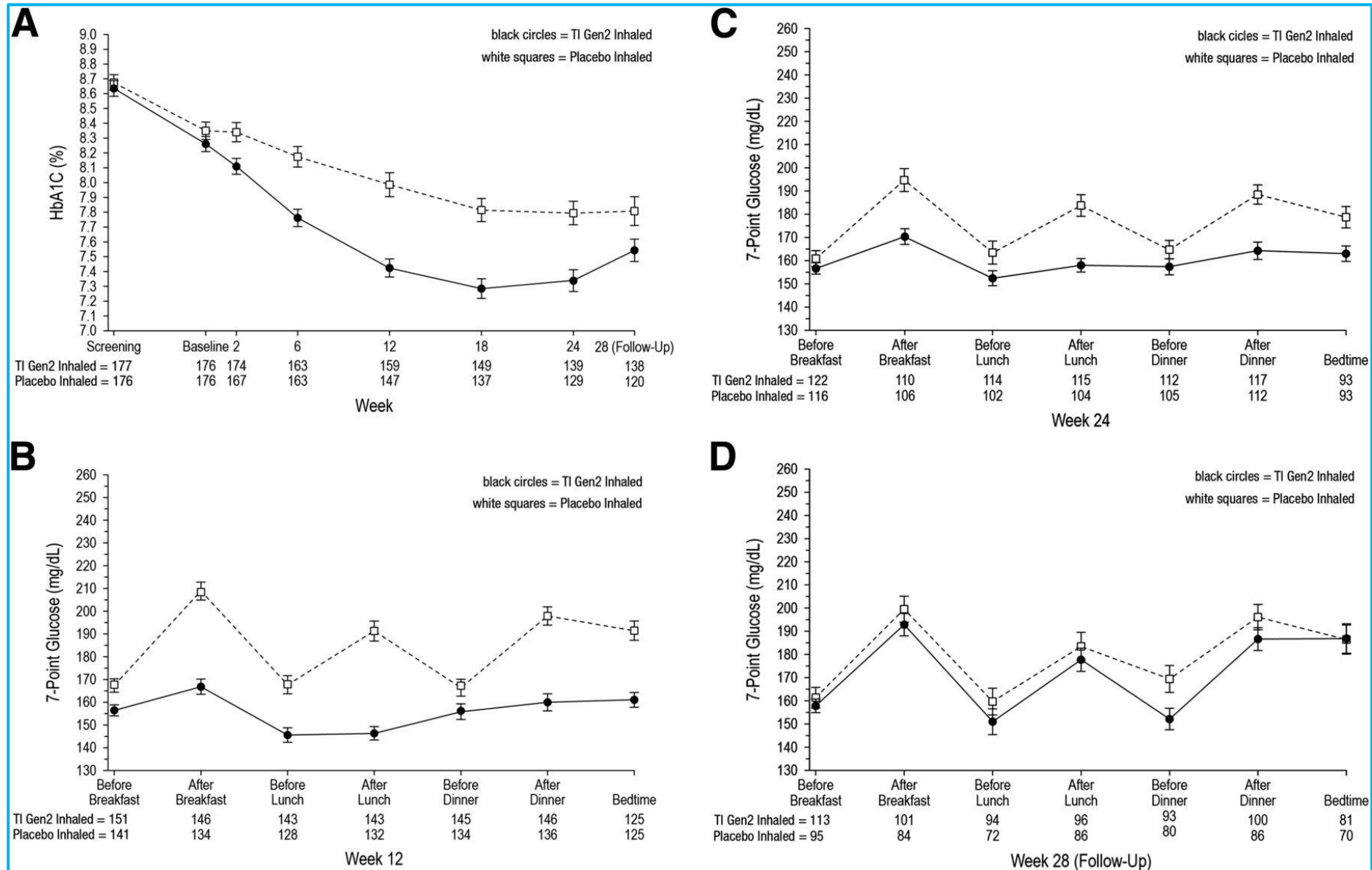


Adults without diabetes



Adults with T1D

Inhaled Insulin in T2D- AFFINITY-2



Summary of Inhaled Insulin

Advantages	Disadvantages
<ul style="list-style-type: none">• Ultra rapid acting, in and out, faster than any insulin in the market• Better postprandial blood glucose• Less risk of hypoglycemia• No needles, easy to carry and use• Good for snacks coverage (touch on)• Good for young adults and busy professionals• Ideal for patients can't wait 10-15 mins to eat after injections	<ul style="list-style-type: none">• Requirement of FEV₁ testing• High fat/protein meals may need additional dosing• People tend to under-dose (1.5-2X dose needed)• Confusion with dosing units• Only available in 4-, 8-, and 12-unit cartridges• No pediatric indication yet• Insurance coverage

What is Another Tool to Reduce the After-Meal Spike?

- Post-meal exercise: reduces after-meal spike
- Pre-meal exercise: reduces BOTH pre-meal and post-meal glucose levels



Conclusions

- GLP1-RAs have been a tremendous benefit to people with diabetes due to their ability to lower glucose and weight in addition to CVD and probable renal benefits
- Although expensive (very), the cost of these agents to those with insurance have not increased
- GI side effects are usually but not always manageable.
- Fixed-ratio GLP1-RAs with basal insulin is an important tool to remember

Conclusions

- There are many choices of basal insulin, all with slight differences, but these agents should be started sooner than they currently are with very high HbA1c levels
- BeAM scores are an excellent tool to assess basal insulin dosing
- For postprandial BG control faster rapid analogs or inhaled insulin can be used.
- In type 2 diabetes, dosing of prandial insulins does not need to be complex (compared to type 1 diabetes) and fixed doses with or without corrections often works well.

Foundations of Cardiometabolic Health Certification Course

**Certified
Cardiometabolic
Health Professional
(CCHP)**



Patient Case – Advanced Glycemic Management

Halis Kaan Akturk, MD
Associate Professor of Medicine and Pediatrics
Barbara Davis Center for Diabetes
University of Colorado

Patient Case - Introduction

You are seeing a new patient, a 54-year-old woman with 5 years of T2D who has not seen a physician in 2 years before the pandemic. She takes metformin monotherapy.

She has no CVD but takes atorvastatin and lisinopril; her father died from CVD and had an MI at the age of 61 years old. Her BMI is 36.

She has since gained 12 pounds, and on metformin monotherapy her HbA1c has increased from 7.1% to 11.2%.

What is the best option at this time?

- A. Add dulaglutide
- B. Add long-acting exenatide
- C. Add bedtime glargine
- D. Add bedtime glargine with mealtime lispro
- E. Add the combination of insulin degludec and liraglutide

Patient Case - Continued

- The same patient was started on IDegLira and after 6 months her HbA1c improved from 11.2% to 8.3% at the highest dose (50 units degludec, 1.8 mg liraglutide). Her BMI now is reduced from 36 to 34.
- Fasting and premeal glucose levels are generally in the low-to-mid-100s, but after eating she is often in the mid-to-high 200s.
- What is the best option now?
 - A. mealtime lispro or inhaled insulin
 - B. pioglitazone
 - C. dapagliflozin
 - D. Change the liraglutide to semaglutide and take the degludec separately

Patient Case - Conclusion

- This same patient wants to start an exercise program of fast walks alternating with swimming. What is the best time of day for her exercise?
 - A. In the morning before breakfast
 - B. Immediately after dinner when her blood sugars are highest
 - C. In the middle of the afternoon
 - D. At bedtime

THANK YOU



Barbara Davis
Center for Diabetes

UNIVERSITY OF COLORADO
ANSCHUTZ MEDICAL CAMPUS