What's New in Diabetes for 2021-22?

Family Medicine Foundation of West Virginia Winter Meeting

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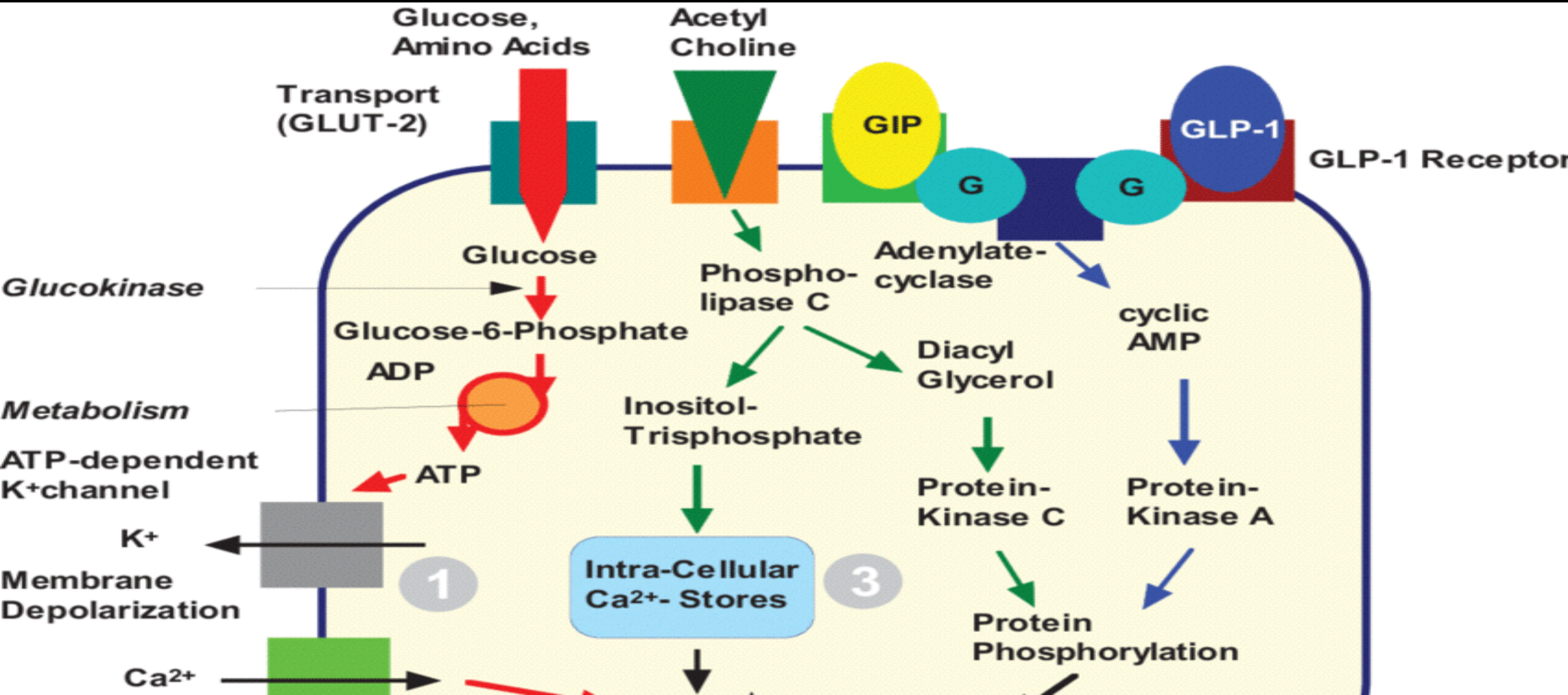
Objectives

- Review the pharmacology & benefits of a new class of T2DM medication; Tirzepatide(E Lilly)
- Review the pharmacology & clinical results of new once-weekly insulin preparation; insulin icodec (Novo Nordisc):
- Describe FDA approval of a biosimilar basal insulin to insulin glargine
- Review the recent impact of Covid-19 on diabetes & impact of diabetes on Covid-19
- Present a new paradigm for the pharmacologic approach to the treatment of T2DM in 2022

Tirzepatide

A dual glucose-dependent insulinotropic polypeptide (GIP)/ glucagon-like peptide-1 (GLP-1) receptor agonist

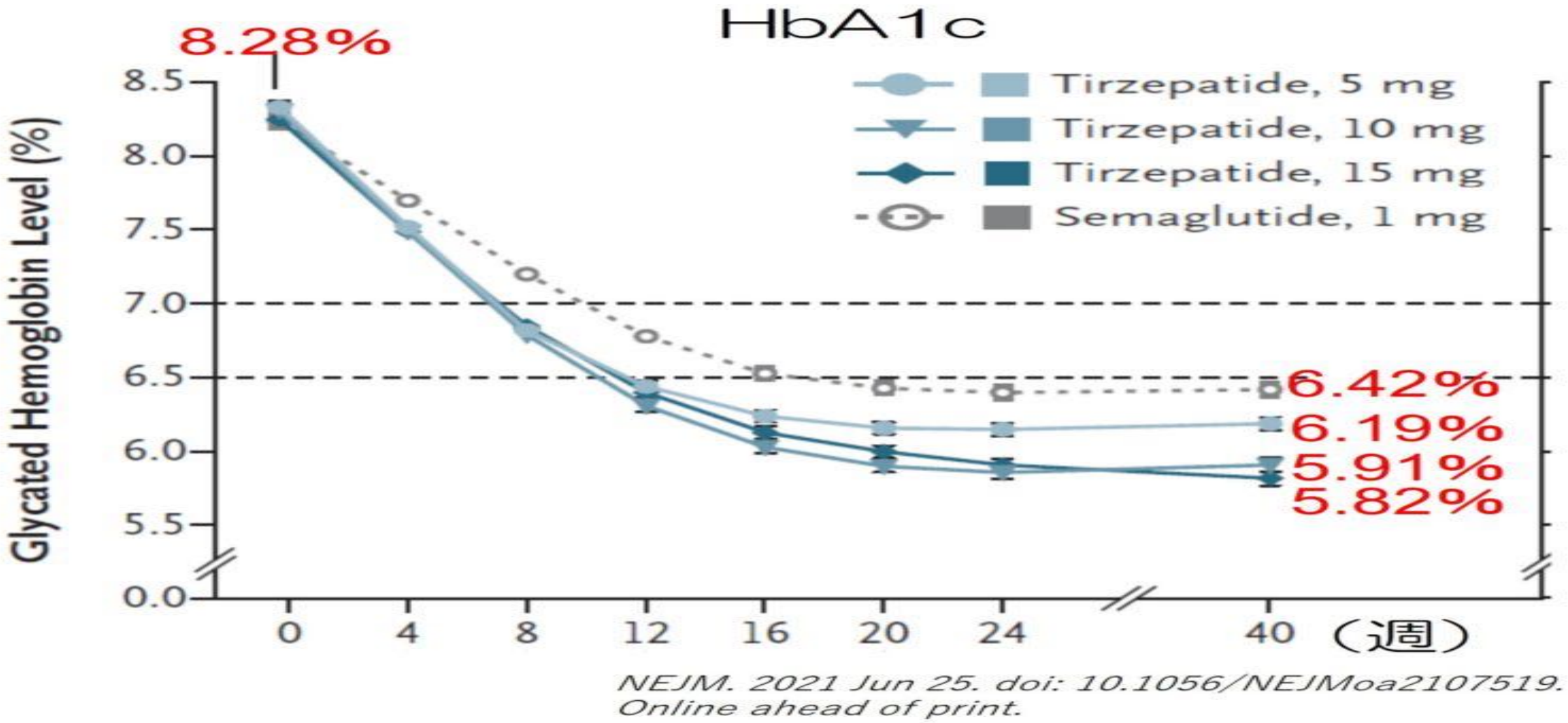
Tirzepatide: A Dual GIP/GLP-1 Agonist Which Increases β-Cell Insulin Synthesis& Release



Clinical Effects of Tirzepatide

		GLP-1	GIP
Pancreas	Beta cells	↑Insulin synthesis ↑Insulin secretion ↑Cell proliferation ↑Glucose sensing	↑Insulin synthesis ↑Insulin secretion ↑Cell proliferation ↑Glucose sensing
	Alpha cells	↓Glucagon secretion	↑Glucagon secretion
Brain		↑Satiety ↓Appetite	
Gastrointestinal		↓GI motility ↓Gastric emptying	
Adipose tissues			↑Lipolysis ↑Fatty acid synthesis ?Anti-lipogenic effect

Clinical Trial of Tirzepatide vs Semaglutide



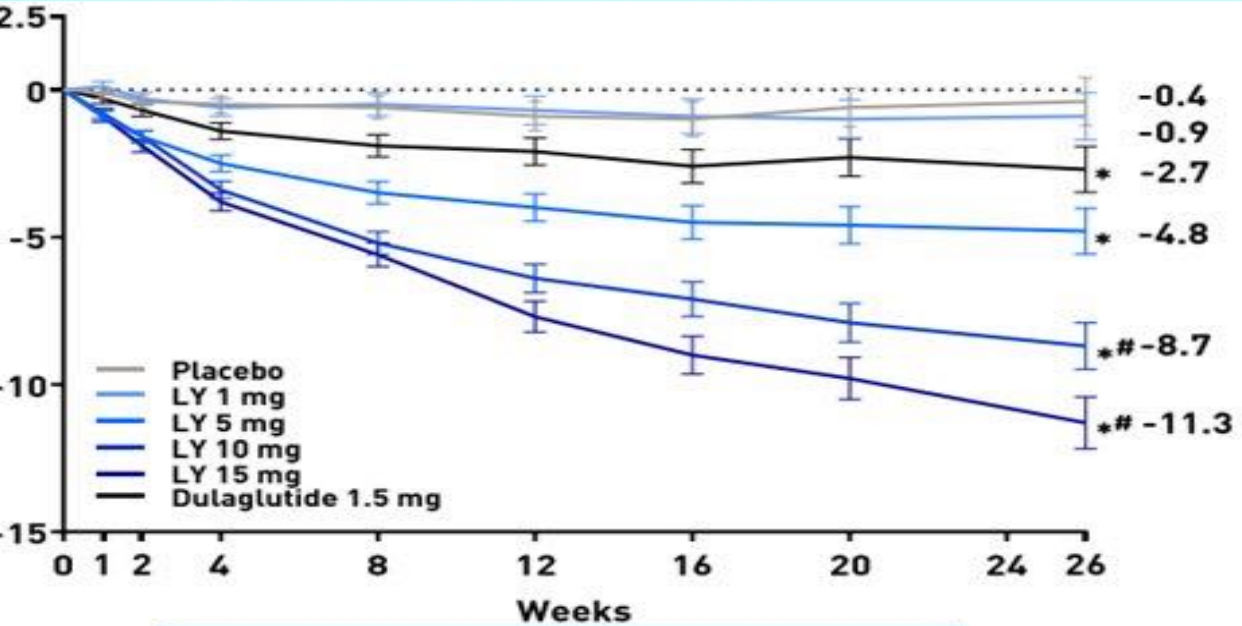
NEJM. 2021 Jun 25. doi: 10.1056/NEJMoa2107519. Online ahead of print.

TIRZEPATIDE PHASE 2

ACHIEVED POSITIVE RESULTS IN WEIGHT LOSS (ON TREATMENT ANALYSIS)

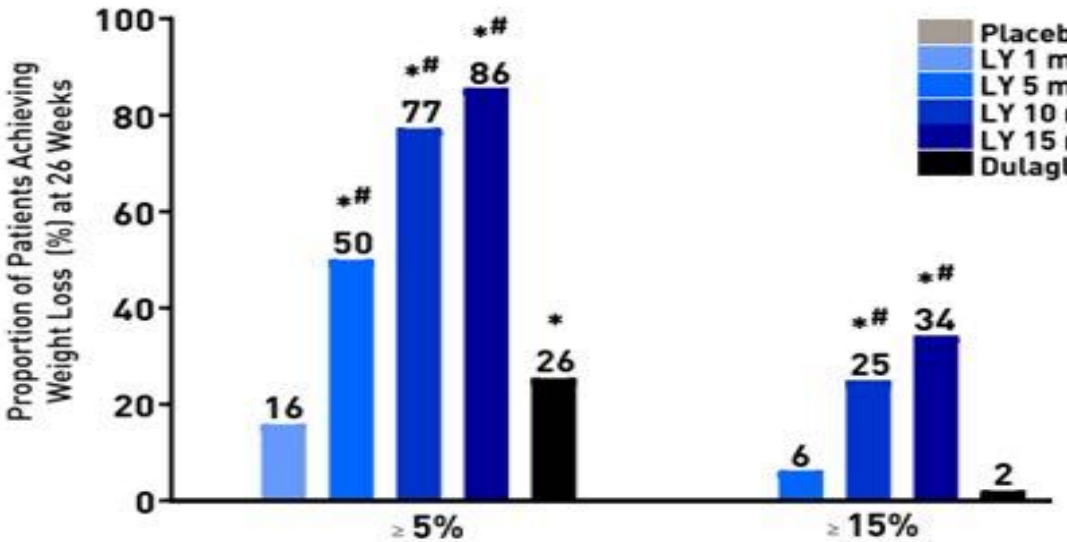
Lilly

WEIGHT LOSS (KG)



Observed significant and dose-related decreases in body weight (kg)

WEIGHT LOSS (%) TARGET



34% of 15 mg dose patients achieve ≥15% body weight reduction

Data presented are LS mean ± SE. MMRM on treatment analysis.
Trial Description: 26 week randomized trial; 1mg, 5mg, 10mg: 2 week titration, 15mg: 6 week titration, dulaglutide 1.5mg
Baseline Characteristics: Mean age 57, weight 91.5 kg, BMI 32.6, A1c 8.1%, 90% on metformin

HbA1c (%) target data are logistic regression, on treatment analysis
*, #p<.05 vs placebo and vs. dulaglutide 1.5 mg, respectively

https://investor.lilly.com/static-files/ff772c9a-05f7-4d6a-a01d-340e2c4d9198

Summary of Clinical Effects

- Dose-dependent A1C reduction: -2.01% (5 mg), -2.24% (10 mg), -2.30% (15 mg) vs -1.86% (semaglutide)
- Dose-dependent weight reduction: -7.6 kg (5 mg), -9.3 kg (10 mg), -11.2 kg (15 mg) vs -5.7 kg (semaglutide)
- Very high percentage of participants achieving normal A1C; <7%: 82.0% (5 mg), 85.6% (10 mg), 86.2% (15 mg) vs 79.0% (semaglutide)
- Percent of participants achieving A1C <6.0%: 27.1% (5 mg), 39.8% (10 mg), 45.7% (15 mg) vs 18.9% (semaglutide)
- Dose-dependent decrease in hepatic fat stores; a 47% reduction for the 15 mg dose; will be used in FLD as well

Side-Effects Tirzepatide: Similar to GLP-1 Agonists Alone

- Gastrointestinal (GI) system; decreased appetite (nausea/satiety), diarrhea & vomiting were most common adverse events & demonstrated a dose-dependent behavior
- Pancreatitis (2 patients), cholecystitis (1 patient) which is similar to GLP-1 agonist

General Consensus for Tirzepatide

The Most Potent Diabetes Medication Class Developed so Far……..If Approved

A Once Weekly Insulin Formulation

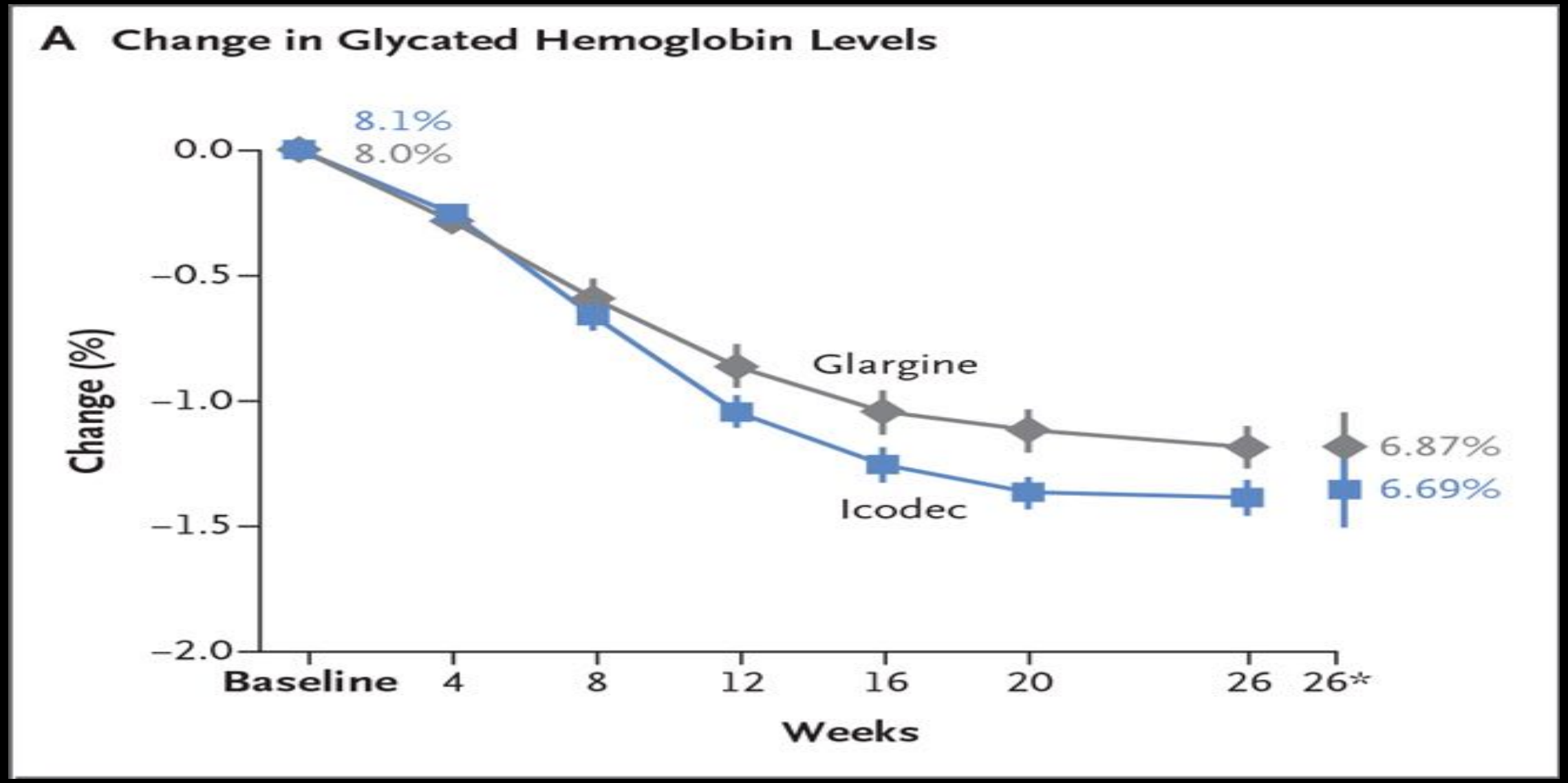
Insulin Isodec (NovoNordisc)

How Does It Not Cause Hypoglycemia?

Insulin Isodec

- A C20 fatty acid modification (1,20-icosanedioic acid) to the insulin molecule produces a strong & reversible binding to serum albumin & slows insulin receptor mediated clearance & results in a 196 hr ½ life
- The slow, gradual release of insulin Isodec from albumin & slow insulin receptor activation results in steady-state insulin levels after a 3-4 week period

Insulin Isodec vs Insulin Glargine



Clinical Trial of Insulin Isodec vs Insulin Glargine Comparison

- Patients with T2DM & similar starting A1C's of ~8% were randomized to with 70U once-weekly insulin isodec vs 10U of daily insulin glargine for 26 weeks ….. target fasting BS was 70-112
- ~50% of patients were also on a dipeptidyl peptidase 4 inhibitor (DPP-4) for post-prandial glucose control
- Basal insulin doses were adjusted weekly with a fixed algorithm for 26 weeks…… to fasting glucose target

November 20, N Engl J Med
2020; 383:2107-2116
DOI: 10.1056/NEJMoa2022474

Insulin Isodec vs Insulin Glargine

- The mean patient-measured blood glucose levels were lower in the insulin icodec group than in the glargine group at all time points
- There was a greater reduction in the mean 9-point patient-measured blood glucose level (lower glycemic variability) from baseline to week 26 with insulin isodec
- A lower total weekly dose of insulin dose with insulin isodec
- A greater time spent within the tight glycemic range (70 to 140 mg per deciliter) during the last 2 weeks of treatment in the icodec group
- Change from baseline to week 26 in the fasting plasma glucose level & body weight were similar in the two groups

Insulin Isodec weekly is comparable to daily Insulin Glargine

Would be a good basal insulin for patients on other medications (weekly GLP-1 agonist) needing additional help achieving target fasting blood glucose levels

A Biosimilar Insulin?

“A biosimilar insulin is a biological product that is highly similar to, with no clinically meaningful differences from a biological product already manufactured”

FDA Approved
Semglee (insulin glargine-yfgn)

Both biosimilar to & interchangeable with Lantus (insulin glargine), a long-acting insulin analog

Major controversy;….. who controls the order to substitute; physician, pharmacist, insurance company?

Diabetes & Covid-19

Covid-19 & T2DM

- 21% of patients admitted to hospital with Covid-19 were elderly males with diabetes
- 21% of these patients were newly diagnosed diabetes & 28% had a history impaired GTT (half were induced by Covid-19?)
- High-dose glucocorticoids are standard care for outpatient & inpatient treatment of Covid 19 resulting in steroid-induced hyperglycemia as well
- Hospital mortality in T2DM/Covid-19 is 3X higher than non-diabetics & approaches 10%
- Pre-existing of T2DM increases susceptibility to Covid-19 & subsequent mortality from the infection

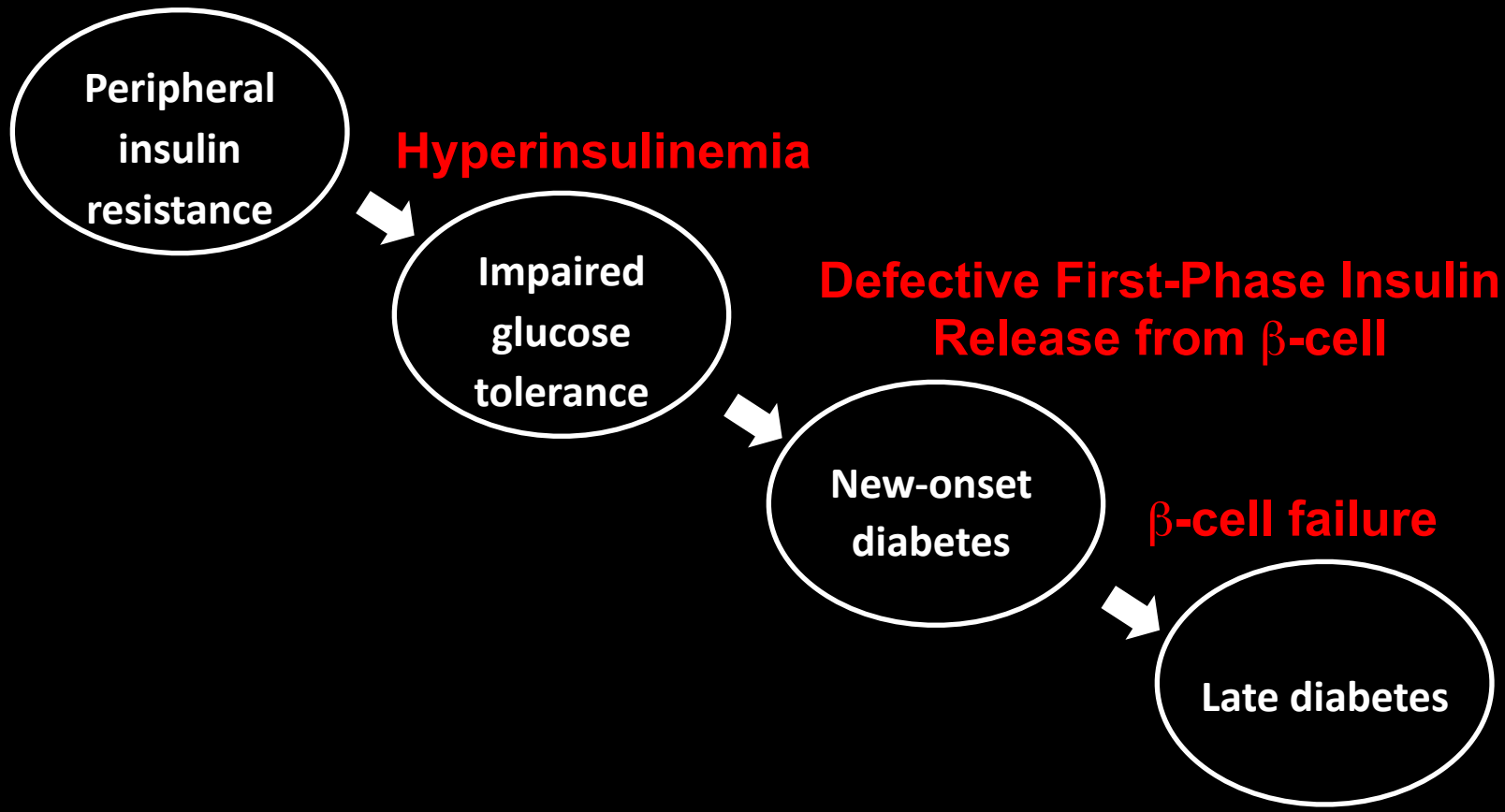
Covid-19 & T1DM

- **15% of new-onset T1DM cases admitted to hospital are Covid-19 positive**
- **Covid-19 positive T1DM patients present with a much higher frequency of severe DKA (>40%) or HHNK**
- ***The prevalence rate of new-onset T1DM has actually doubled during the Covid-19 epidemic in Europe!*** **(suggesting direct induction of insulinitis by Covid 19 virus)**

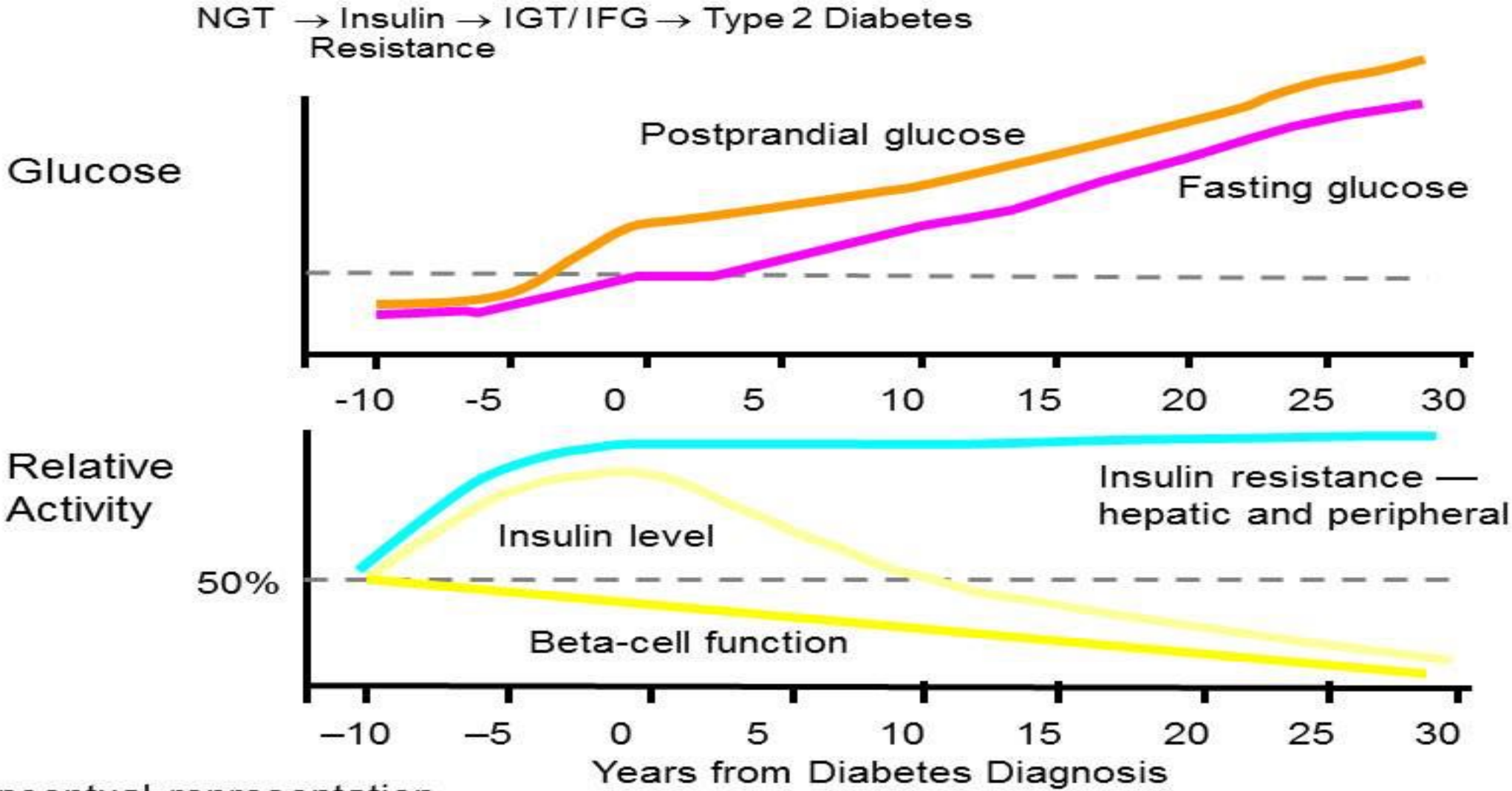
Is it Time For A Different Pharmacologic Approach To T2DM?

Historically, intervention by patients & health care providers has been too slow & often too late!

Metabolic Stages of T2DM



Development and Progression of Type 2 Diabetes*



*Conceptual representation.

NGT=normal glucose tolerance; IGT=impaired glucose tolerance; IFG=impaired fasting glucose.

Adapted from Ferrannini E. Presentation at 65th ADA in Washington, DC, 2006.; and Ramlo-Halsted et al. *Prim Care.* 1999;26:771–789.

Major Factors Involved in Pathogenesis of T2DM

1. **Ineffective Insulin action *(insulin resistance)***

   -caused by visceral obesity & lipotoxicity

2. **Impaired β-cell response to rising fasting blood glucose levels (due to *Glucotoxicity*)**

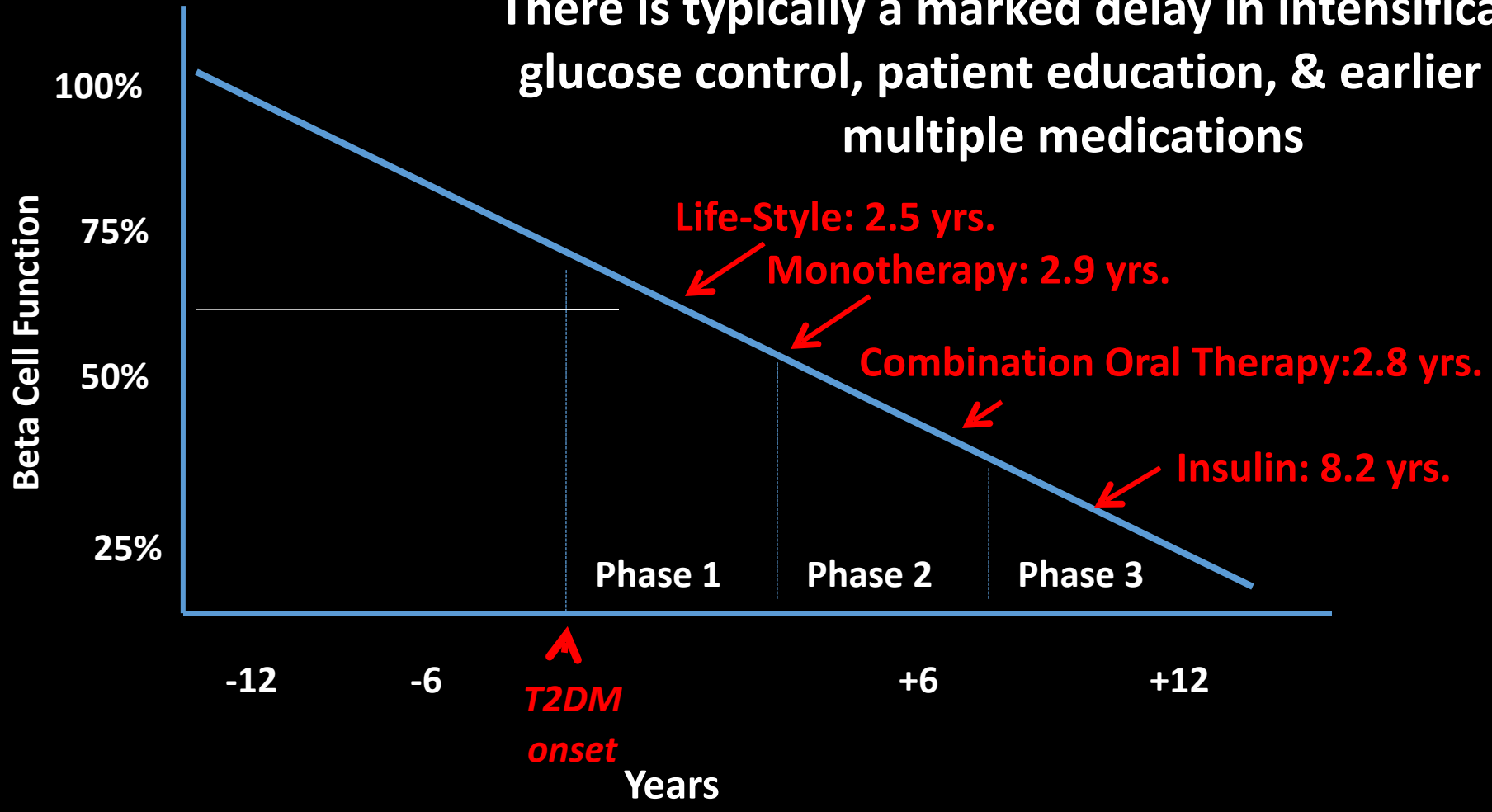
   - Resulting in defective first-phase insulin response to rising glucose levels leading to post-prandial hyperglycemia

3. **Loss of Incretin secretion *(GLP-1 & Amylin)***

4. ***Progressive β-cell loss due to stress-induced apoptosis resulting in insulin deficiency by ~ 7 yrs. following onset of T2DM***

The Old "Staged Pharmacologic Approach" to T2DM Resulted in Clinical Inertia

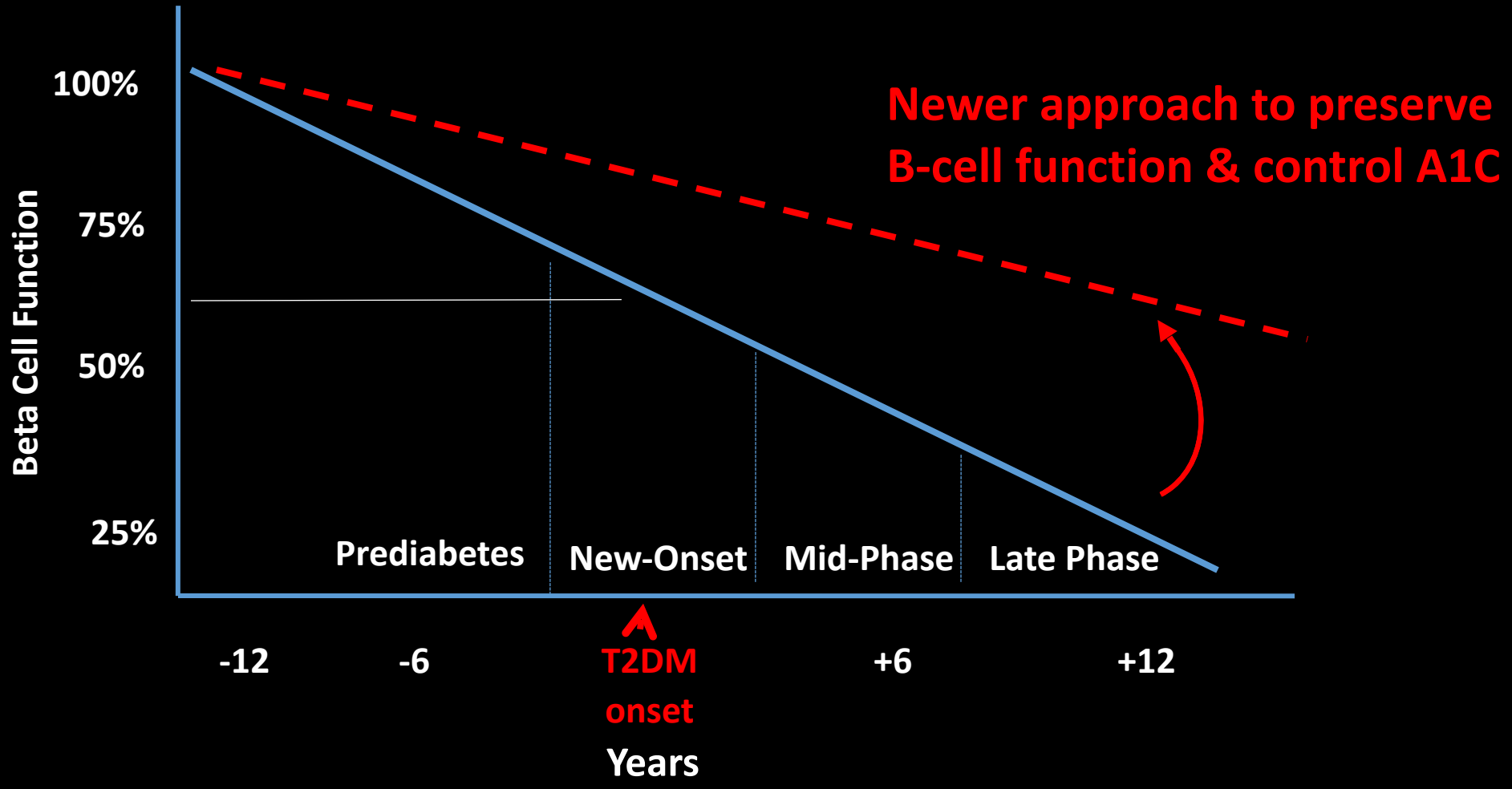
There is typically a marked delay in intensification of glucose control, patient education, & earlier use of multiple medications



Staged Approach to T2DM Failed to Control Glucose Levels or Prevent Long-Term Complications

Monotherapy with sulfonylureas actually accelerated weight gain (insulin resistance), β-cell failure, insulin deficiency & increased risk for CV disease & certain malignancies!!!

Changing The Natural History of T2DM: Beta Cell Death May Be Preventable!



Basic Tenants of Intensive T2DM Management In Addition to Medications

- Regular exercise & weight loss
- Aggressive CV Risk Factor Reduction to secondary intervention levels
- ACE/*ARB* for microalbuminuria (ARB now preferred)
- Smoking cessation
- Continuous surveillance for early indicators of impending complications such as: annual dilated fundus exam of eyes, foot exam (neurofilament), routine labs, & early cardiac stress testing

T2DM Can Be Prevented!

The Diabetes Prevention Trial 2 (DPT2)

Risk for T2DM was reduced by up to 58% …… & sustained for up to 15 years with life-style intervention alone!

Pharmacologic Interventions Which Preserve β-Cell Function & Delay T2DM Onset

- **Metformin** reduces insulin resistance, changes gut microbiome to a more healthy one, reduces hepatic inflammation, produces marginal weight loss & reduces risk for DM progression ~ 30%
- **TZD's** reduce TG's, raise HDL, & are 3X more effective than metformin at reducing T2DM progression
- **GLP-1 agonists** promote satiety, weight loss, induces β-cell regeneration & are 3X more effective than metformin reducing T2DM progression
- **SGLT-2 Inhibitors** improve post-prandial glucose levels & reduce A1C levels by nearly 1% as single agent (current prevention studies)

There have been no clinical trials combining metformin, plus a GLP-1 agonist, & SGLT-2 inhibitor in Prevention or Long-Term Treatment Trials!

Why? Most Clinical Trials are funded by the manufacturers looking for clinical superiority of their own (still patented) medication

T2DM Management if I Were King

Diabetes Medications, Durable Medical Equipment, & Medical Supplies would be 100% covered by insurance

T2DM Management if I Were King

- All patients at diagnosis would be placed on low dose metformin & titrated up to 850-1000 mg BID as tolerated (unless CRF)
- All patients with BMI >28 would be placed on weekly, low dose GLP-1 agonist & dose titrated up
- Patients with BMI> 35 would be titrated to maximum tolerable GLP-1 agonist dose
- All patients with post-prandial hyperglycemia documented by CGM &/or a HX of ASCVD, CVA, CKD or diabetic retinopathy would be placed on a SGLT-2 inhibitor plus Yeast Guard (protect against monilial infection)
- All patients would get periodic CGM assessment ("Flash CGM") at least q 6 months for glucose pattern analysis

T2DM Management if I Were King

- The combination of metformin, a GLP-1 agonist, & an SGL-2 inhibitor would be a desired combination of medications to control glucose & preserve β-cell function
- A TZD could be added for TG's >200 (NASH) or significant insulin resistance
- Patients whose fasting BS's not at target (< 150) on these 3 classes of medications would be placed on basal insulin; starting @ 10U/day.. with dose increased 3-5U q week until at target
- Patients with long-standing T2DM & low c-peptide requiring basal/ bolus insulin or with hypoglycemia unawareness would have a Dexcom or Freestyle 2 CGM for personal use

The Diabetes Medications with Cardioprotection Actions

- SGLT-2 inhibitors
- GLP-1 antagonists
- Pioglitizone (only TZD with this effect)
- Metformin (weak benefits compared to the others)

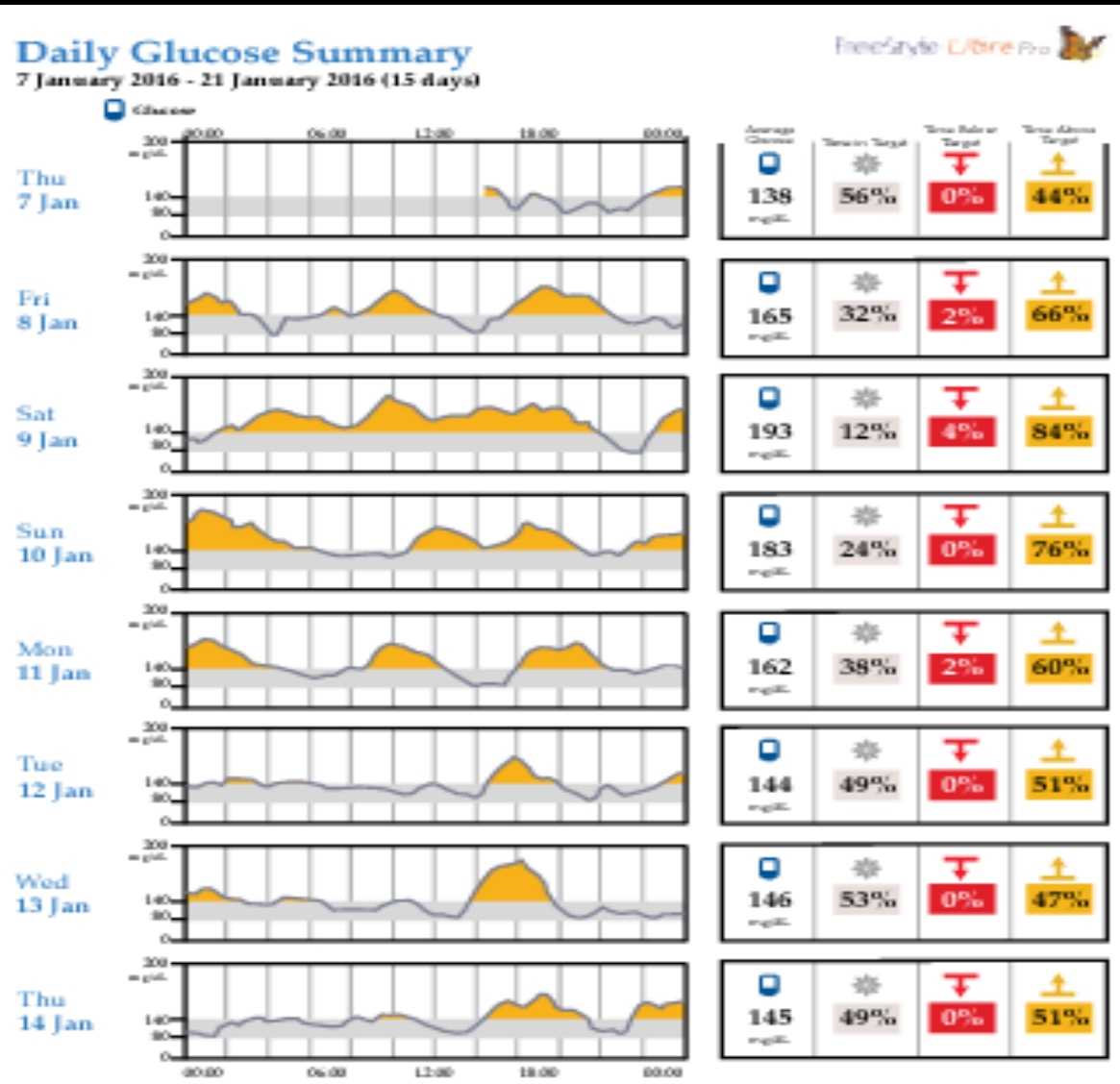
SGLT-2 Inhibitors Are Also Protective Against Microvascular Complications

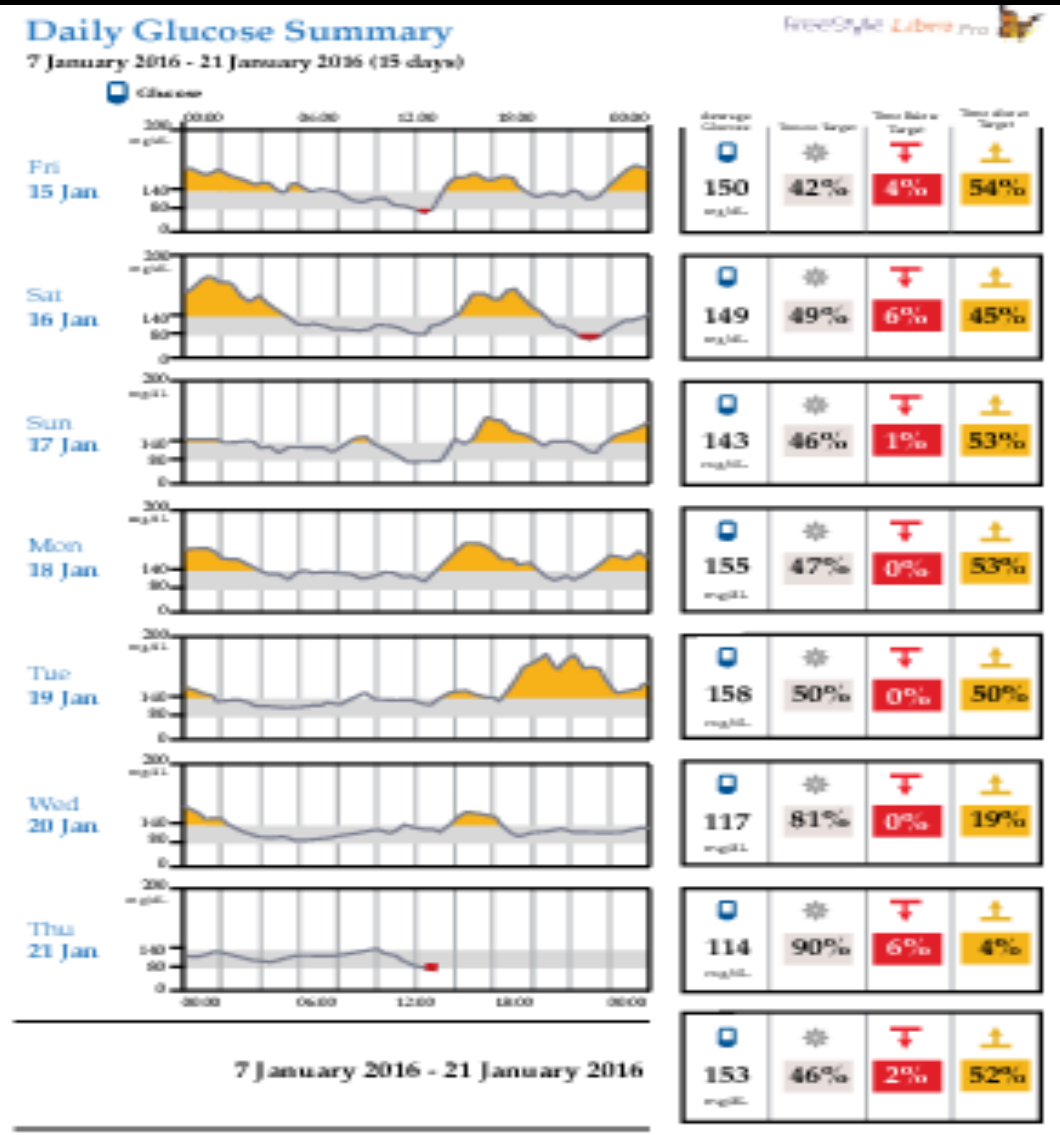
Clinical Evidence of Eye & Kidney Protection in T2DM

Impact of CGM in Diabetes Management

- Allows both the provider *& the patient* see abnormal patterns of glucose excursion… which in turn allows for adjustments in life-style &/or medications to correct the problem
- The *detection of asymptomatic hypoglycemia* in patients in which it was previously unrecognized
- CGM's have allowed intensive control of glucose & reductions in A1C while reducing risk of long-term complications & hypoglycemia
- Patients with personal CGM devices often "autocorrect" when looking at their own data & reduce their A1C's ~ 1%

Example of 14 Days of Freestyle Libre Data





Clinical Benefits of Flash & rtCGM

- Improves glucose control & lowers of A1C by 0.6-1.1% depending of study & initial A1C
- Decreases frequency of severe hypoglycemia 35-50%
- Time spent in hypoglycemic range is reduced nearly 40% *which decreases frequency of CV events, seizures, brain injury (Dead Man in Bed Syndrome)*
- Decreases frequency of DKA, ER, & hospital admissions ……*which decreases costs*
- Improves quality of life (QoL) scores

Conclusions of Presentation

- Tirzepatide is a new dual GIP/GLP-1 receptor agonist which is the most potent diabetes medication developed so far & will probably replace the GLP-1 agonists
- Insulin Isodec is a new once weekly insulin formulation being developed
- Semglee (insulin glargine-yfgn) is a new biosimilar molecule to glargine (Lanus) insulin just approved by the FDA
- Diabetes & Covid-19 are synergistic in susceptibility/morbidity
- We now have oral/injectable medications capable of controlling T2DM & reducing the progression to insulin deficiency, controlling glucose levels, & dramatically reducing the risk for long-term complications

Thank you!