

What's New For Diabetes in 2023?

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Objectives

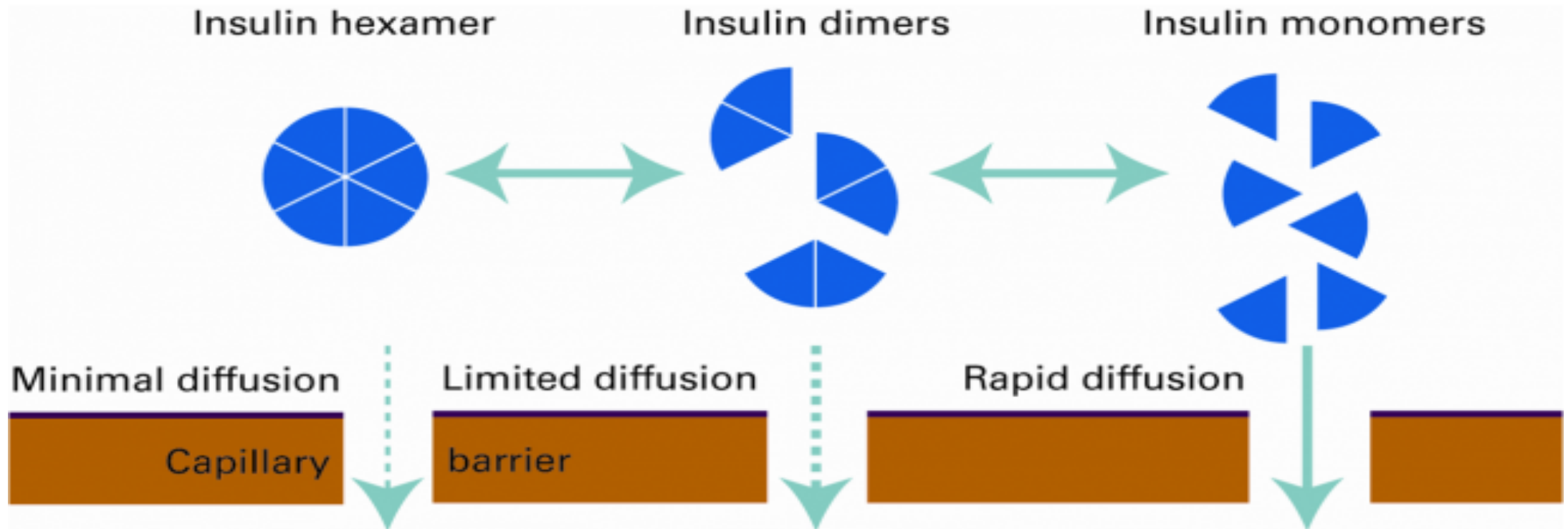
- Review the new FDA approved medications & insulin pumps available for diabetes management in 2023-24
- Insulin Icodec[®]; insulin analog with 7 day duration of action
- Retatrutide[®]; a Triple GIP/GLP-1/Glucagon Receptor Agonist
- Lantidra[®]; allogeneic pancreatic islet cells therapy for transplant in T1DM & severe hypoglycemia unawareness
- Tziel[®] (teplizumab); anti-CD3 inhibitor which delays new-onset of T1DM & provide evidence that verapamil, & semaglutide also preserve beta cell function at this stage!
- Present new insulin pumps & updates to current pumps

**Insulin Icodec (Aweekly®):
New 7 Day basal Insulin Preparation**

Now FDA approved & will be available by end of year

Insulin Inherently Crystallizes into Hexamers; But Then Disperses into Dimers & Then Monomers for Absorption

The rate of dispersion of insulin crystals into monomers contributes to rate on onset & duration of action

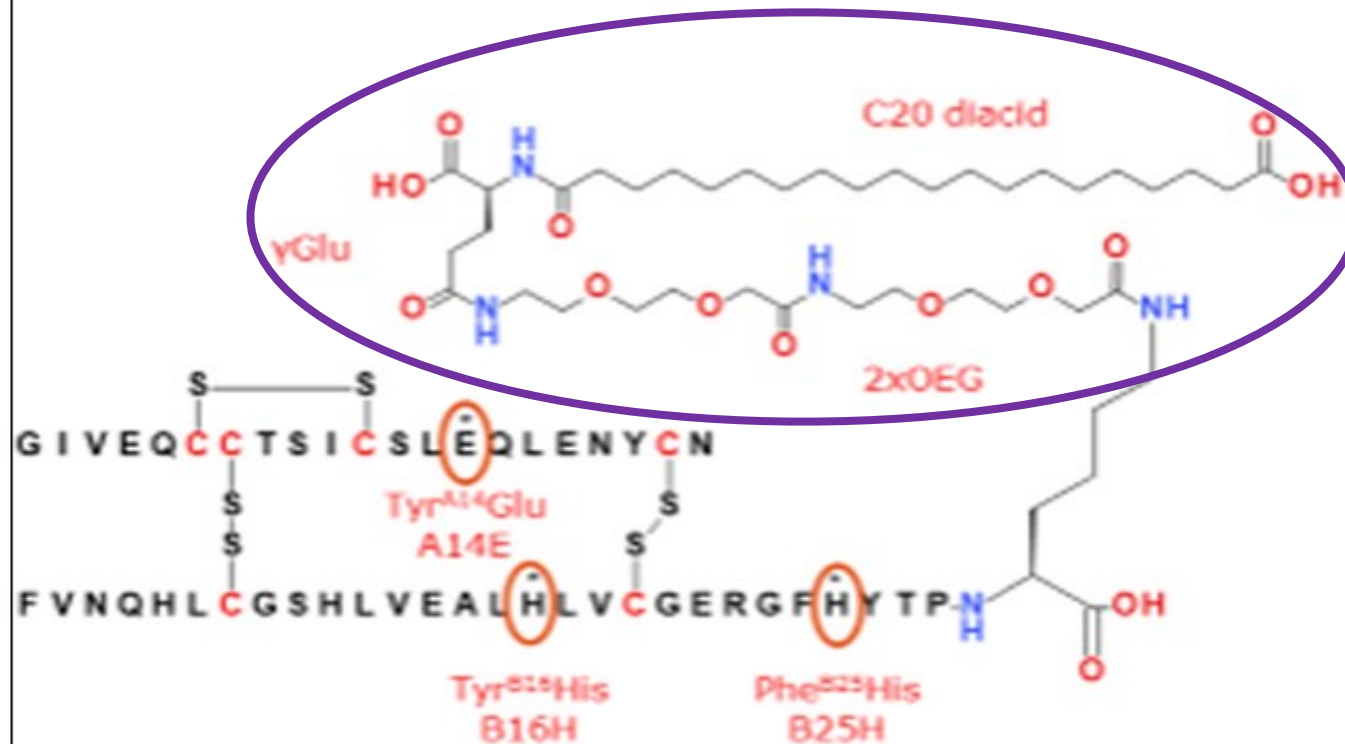


Structure of Insulin Icodec®

Analog of human insulin similar to insulin detemir®; it has 3 substitutions to the amino acid structure which reduces its clearance from the insulin receptor to prolong duration of action & an *attached C20 icosane fatty diacid chain that allows the molecule to bind reversibly to albumin prolonging the half-life to 196 hours (7 days) & achieving steady state after 2-3 days*

Structure of Insulin Icodec®

**Molecular Engineering of Insulin Icodec:
The first acylated insulin analogue for
once-weekly administration**



Tightly albumin-bound

Ultra-low insulin receptor affinity
hIR-A (@1.5% HSA) ~0.03%

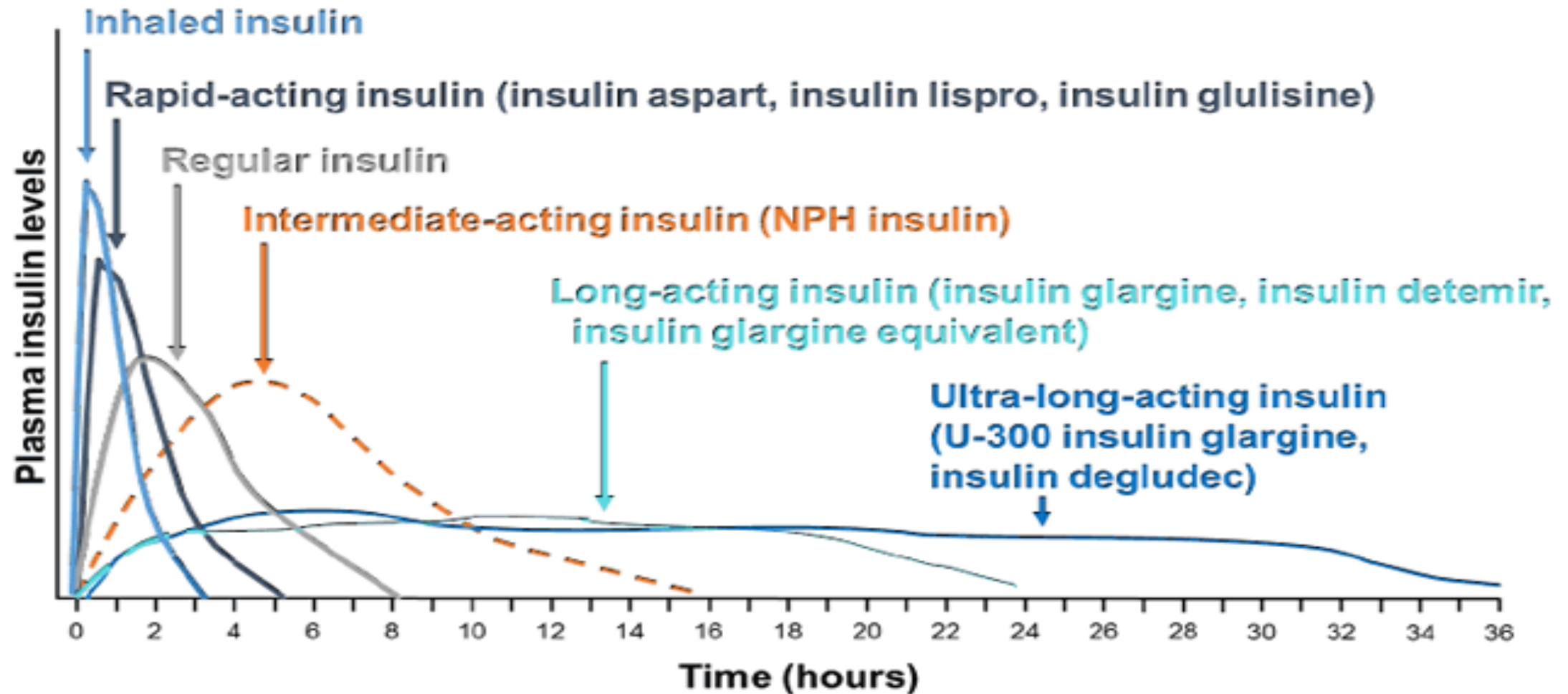
Ultra-long acting

Rat $t_{1/2}$ ~26 h
Dog $t_{1/2}$ ~60 h
Human $t_{1/2}$ ~196 h

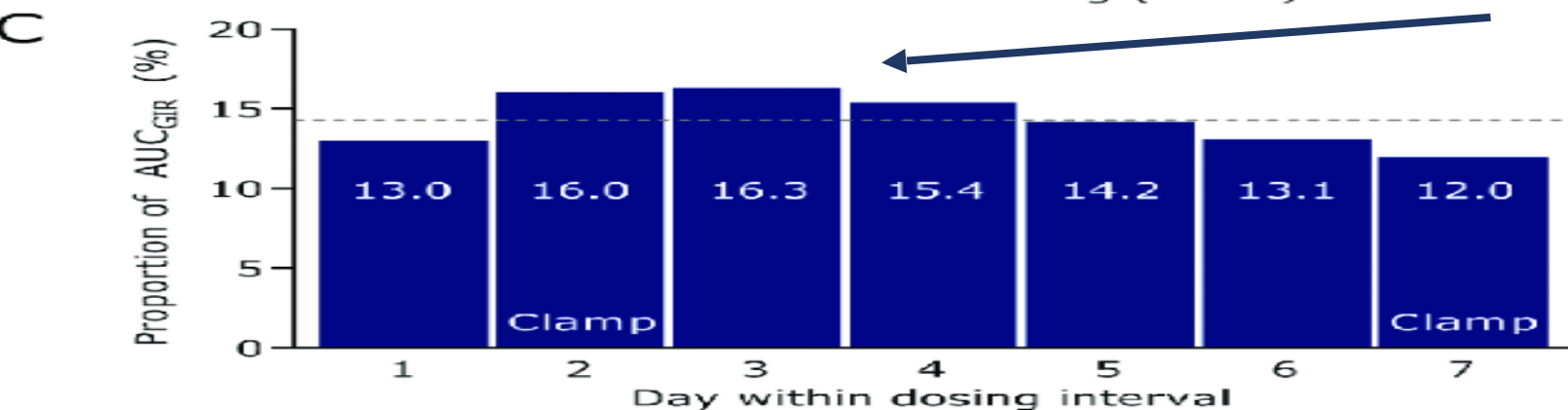
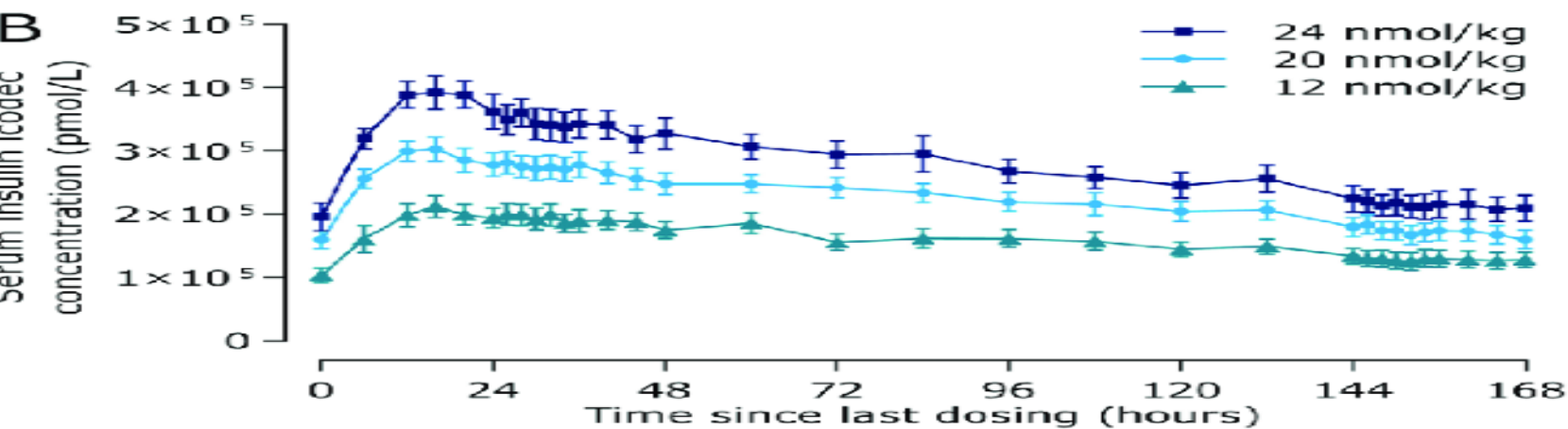
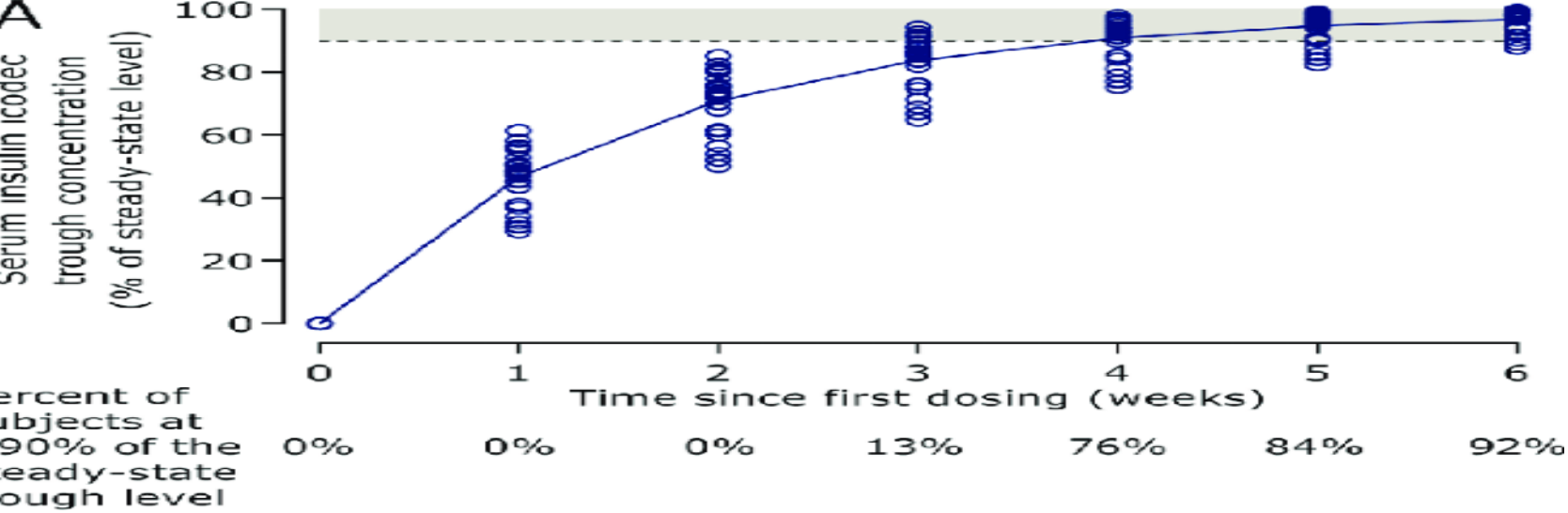
Fully *in vivo* potent

Once-weekly administration in humans demonstrated in phase 2 trials

Insulin Degludec Duration of Activity



Pharmacokinetic Properties of Insulin Icodec in T2DM



Steady-state after 3 days following injection

Erica Nishimura et al. BMJ Open Diab Res Care 2021;9:e002301

Insulin Icodec® Weekly Insulin Titration

- **Patients in the clinical trial were started on an initial dose of 70 U's of Insulin Icodec® SQ weekly**
- **Dosage was titrated upwards by 21U's or 28U's/week depending on the study with target fasting glucose of either; 70 or 80-130 mg/dl**
- **Hypoglycemia; BG <54 mg/dl requiring rescue was rare**

Summary of Onwards 1 & 3 Clinical Trials for Icodec® vs Daily insulin from Novo Nordisk®

- Icodec® demonstrated non-inferiority in HbA_{1c} reduction from baseline in insulin naïve patients @ week 52 compared to daily basal insulin injections (6.93% vs 7.12%)
- Icodec® treated patients achieved significantly more time in target blood glucose range (Time in Range) compared to daily basal insulin injections (71.9% vs 66.9%)
- More people achieved blood glucose targets with A1C <7% using Icodec® without clinically significant or severe hypoglycemia (0.30 vs 0.16) per-person yr.

Anticipated Clinical Role for Insulin Icodec® in Clinical Practice

- **Use as initial insulin add-on therapy for uncontrolled T2DM patients (A1C >8.5%) on maximum other therapy (orals & GLP1 or GLP1/GIP agonists)**
- **Hopefully it will help overcome clinical inertia of starting insulin in individuals not at target A1C levels (<7.0%) given once weekly injection & low risk of hypoglycemia**
- **Advanced practice providers could easily provide patient guidance for initial dose titration**

A GLP/GIP/Glucagon Triple Agonist! **(Retatrutide®)**

Weight loss

Glucose control

Cardiac & renal protection

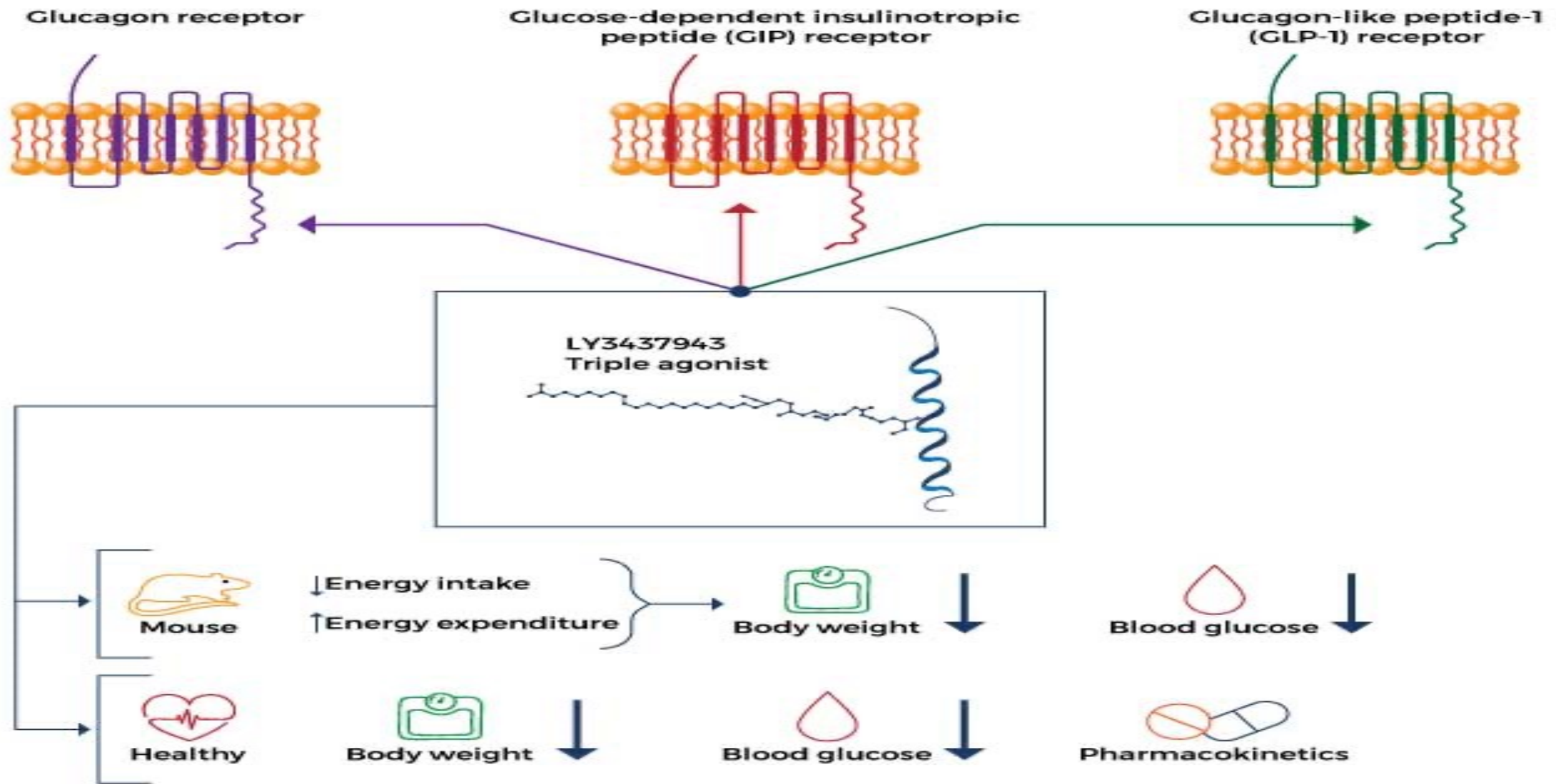
Fatty Liver Disease (FLD)

Sleep Apnea

Cancer prevention

**Retatrutide[®];
a GIP/GLP-1/Glucagon Receptor
“Triple Agonist”**

Most potent incretin-based compound developed so far with an average –24.2% weight loss @ 48 months in the highest dose (12-mg group/week) as compared with –2.1% in the placebo group

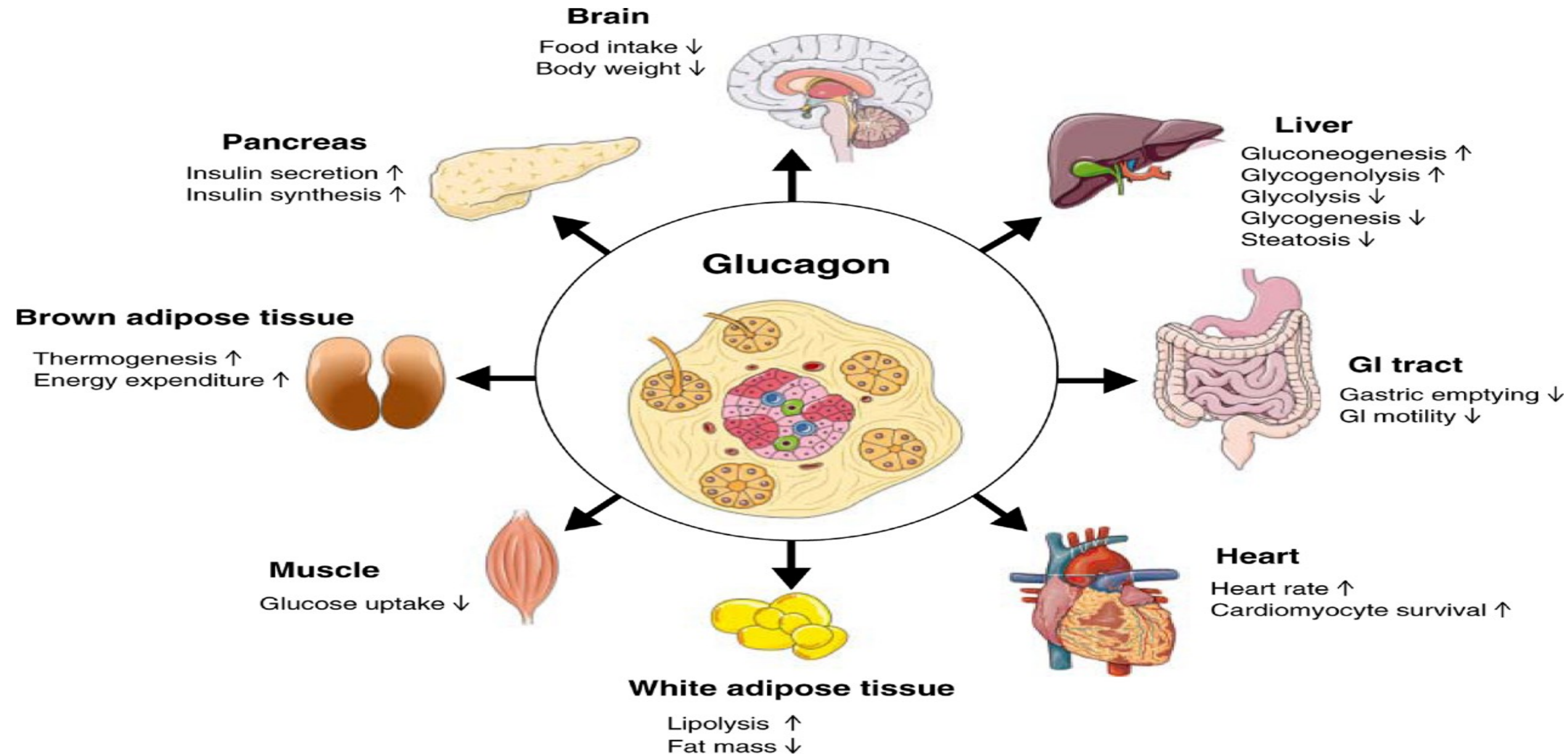


**Glucagon Reverses Hypoglycemia;
How Do It Help Improve Glucose Control??**

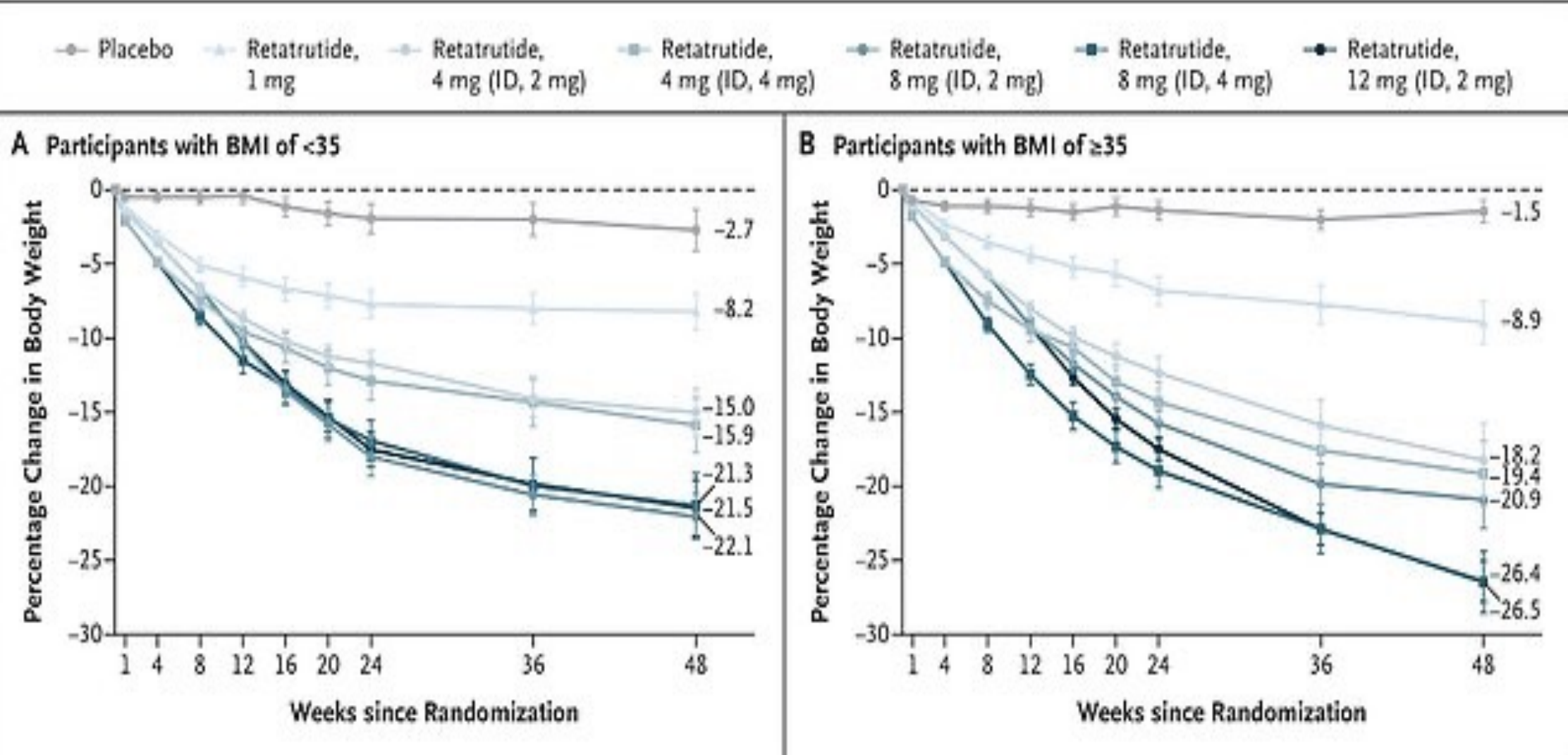
Glucagon Promotes Weight Loss by Suppressing Appetite & Increasing Thermogenesis Particularly; in Adipose Tissue

[Zeigerer, A. et. al. Compr Physiol. 2021 Apr 1; 11\(2\): 1759–1783.](#)

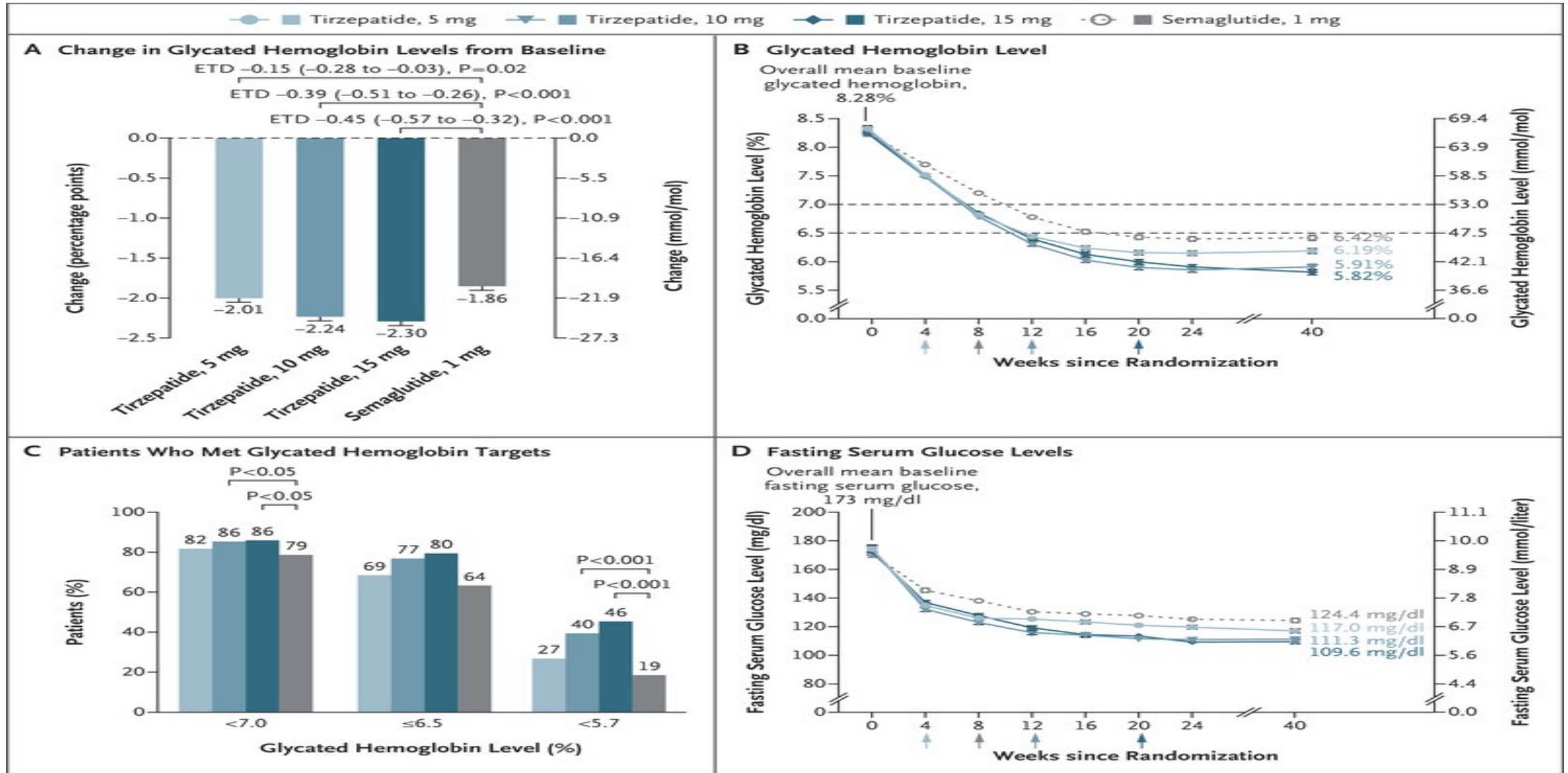
Metabolic Effects of Glucagon



Clinical Trial; Effect of Retatrutide on Weight Loss



Clinical Trial; Effect of Retatrutide on A1C Levels



The GLP/GIP/G Agonists; Additional Benefits of These Drugs; Suppress Inflammation

Improves endothelial function, inhibits pro-inflammatory cytokines, & theoretically decreasing risk for CV disease, CVA, CKD, GERD, & oncogenesis

Summary of Beneficial Effects of Retatrutide®

- **Most potent “GLP-1 like drug yet”**
- **Weight loss**
- **Improved glucose control**
- **Lower blood pressure**
- **Improved lipid profile & LFT's (improved fatty liver disease)**

Lantidra®

**CellTrans' donislecel allogeneic pancreatic islet cell
therapy**

**The first FDA approved allogeneic pancreatic
islet cellular therapy made from cadaver donor
pancreatic cells**

Indications for Lantidra®

For T1DM patients with severe uncontrolled diabetes from hypoglycemia unawareness..... in spite of the use of “autonomous hybrid” insulin pumps with CGM

Impact of Hypoglycemia Unawareness

- **Increased risk for severe hypoglycemia with loss of consciousness, seizures, or coma & permanent brain injury**
- **Increased risk for accidents, physical injury to self & others**
- **Fear of hypoglycemia results in reluctance to intensively control glucose levels which increases risk for all of the long-term complications of diabetes**
- **Continuous glucose monitors with hypoglycemia alarms & “smart” insulin pumps with hypoglycemia prediction algorithms have dramatically improved outcomes & patient safety.....however**

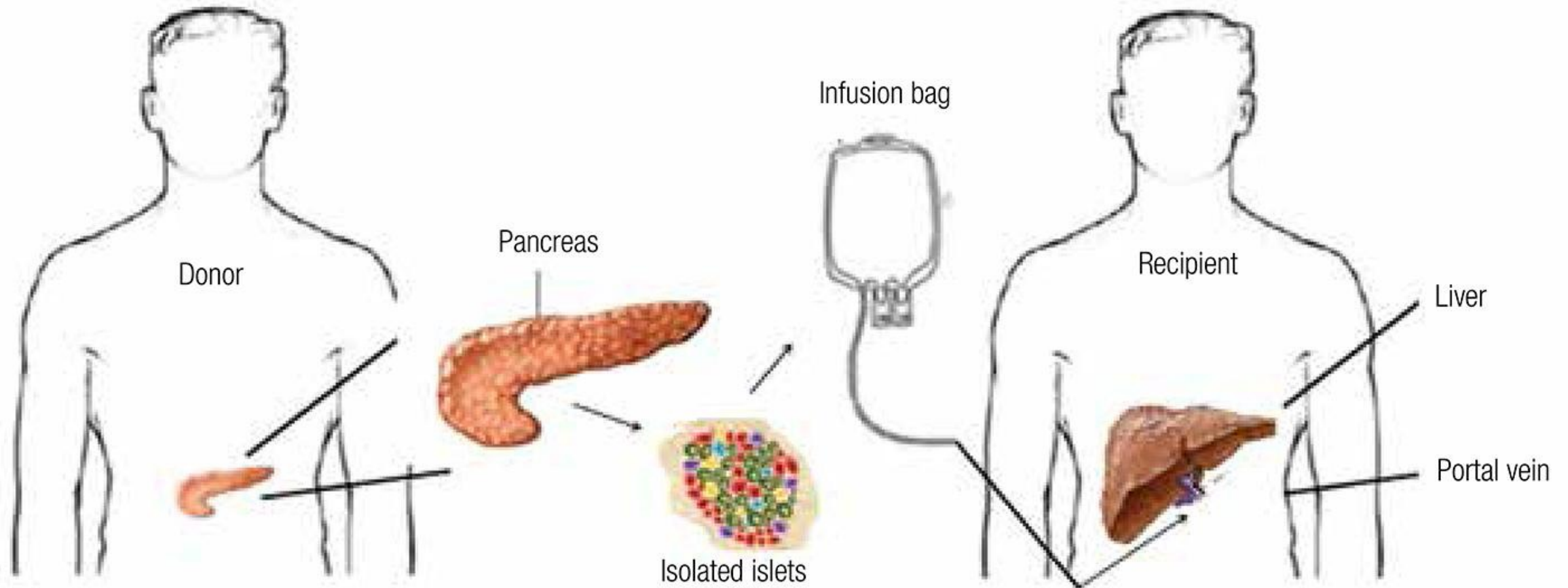
Factors Contributing to Hypoglycemia Unawareness

- **25% of patients with T1DM have experienced some hypoglycemia without being aware that it is happening**
- **Attenuation or loss of sympathoadrenal mechanisms results in impaired catecholamine stimulation of beta-adrenergic symptoms, increased hepatic gluconeogenesis, & normal increase in cortisol release**
- **Autonomic neuropathy**
- **Sleep, psychological stress, alcohol abuse, & beta-adrenergic blockers also blunt symptoms**

Hypoglycemia Begets Hypoglycemia

Recurrent hypoglycemia induces an adaptive response in which the blood-brain barrier, neurons, &/or astrocytes increase their capacity to uptake fuels other than glucose, which contributes to hypoglycemia unawareness

Lantidra[®] Protocol



Source of Islet Cells for Lantidra®

- Human islet cells containing both α & β cells containing glucagon & insulin were isolated from cadaver donor pancreases, digested by specific enzymes, & purified by density gradient
- Islet cells are then cultured for a short period of time to confirm viability & then transplanted via ultrasound guided cannulation of the portal vein similar to previous islet cell transplantation procedures (Edmonton Protocol)
- Immunosuppressant medications are required to prevent islet cell rejection

Lantidra[®] Protocol

- **5,000 equivalent islet number (EIN) per kg patient body weight for initial infusion (transplant)**
- **A dose of 4,500 EIN/kg for subsequent infusions (same recipient) if required**
- **Cells infused through the hepatic portal vein**
- **The estimated cell infusion volume should not exceed 10 cc per transplant infusion**

Clinical Trial Results for Lantidra®

- Lantidra® was evaluated in two non-randomized, single-arm studies in a total of 30 participants with uncontrolled T1DM & hypoglycemic unawareness
- The composite efficacy endpoint consisted of A1C <6.5% & absence of severe hypoglycemic events through one year after a patient's last transplant
- Nineteen patients (63%) met the composite efficacy endpoint, 20 (67%) were insulin independent at one year after last transplant & 8 were insulin independent @ six-years post-last transplant

Safety of Protocol

- Of the 1,319 adverse events reported during the first year after transplantation, 8 were life-threatening, 75 were severe, & 1 patient died of multi-organ failure from immunosuppression
- Donislecel safety outcomes were comparable to those of similar islet products published from other islet transplant centers & probably safer than whole pancreas transplants
- Most risks appeared to mirror those observed for patients on immunosuppression
- A major criticism was that it was an uncontrolled study

Preserving Beta Cells To Prevent or Treat New-Onset T1DM

*Newly diagnosed T1DM patients still have ~50% of their
beta cells remaining*

Several different medications with intriguing success @
preserving beta cell function have been published this year

Tziel[®] (teplizumab) Injection is FDA Approved to Delay Onset of T1DM

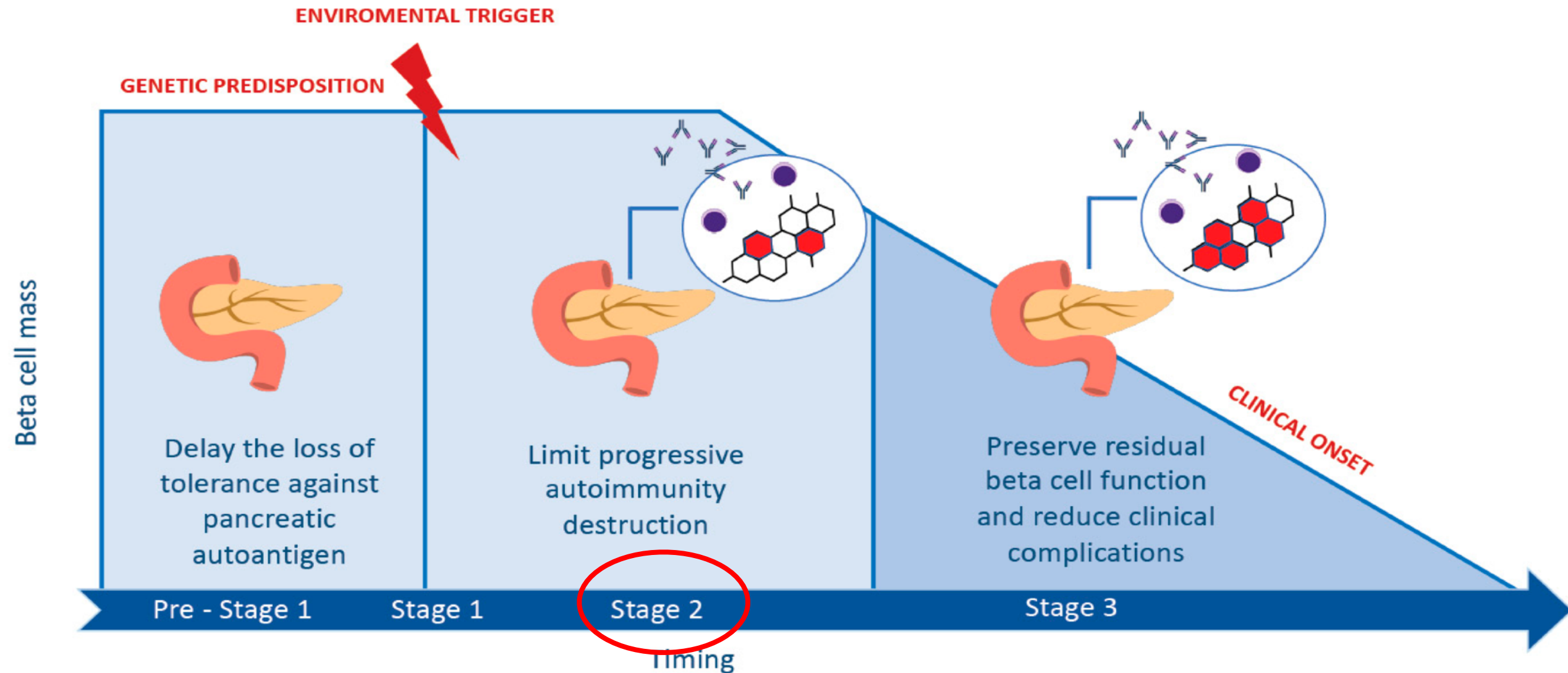
FDA approved for adults & pediatric patients (>8 years) who are stage 2 of beta cell destruction in the pathogenesis of T1DM to delay onset of overt diabetes (stage 3)

Clinical Stages in Development of T1DM

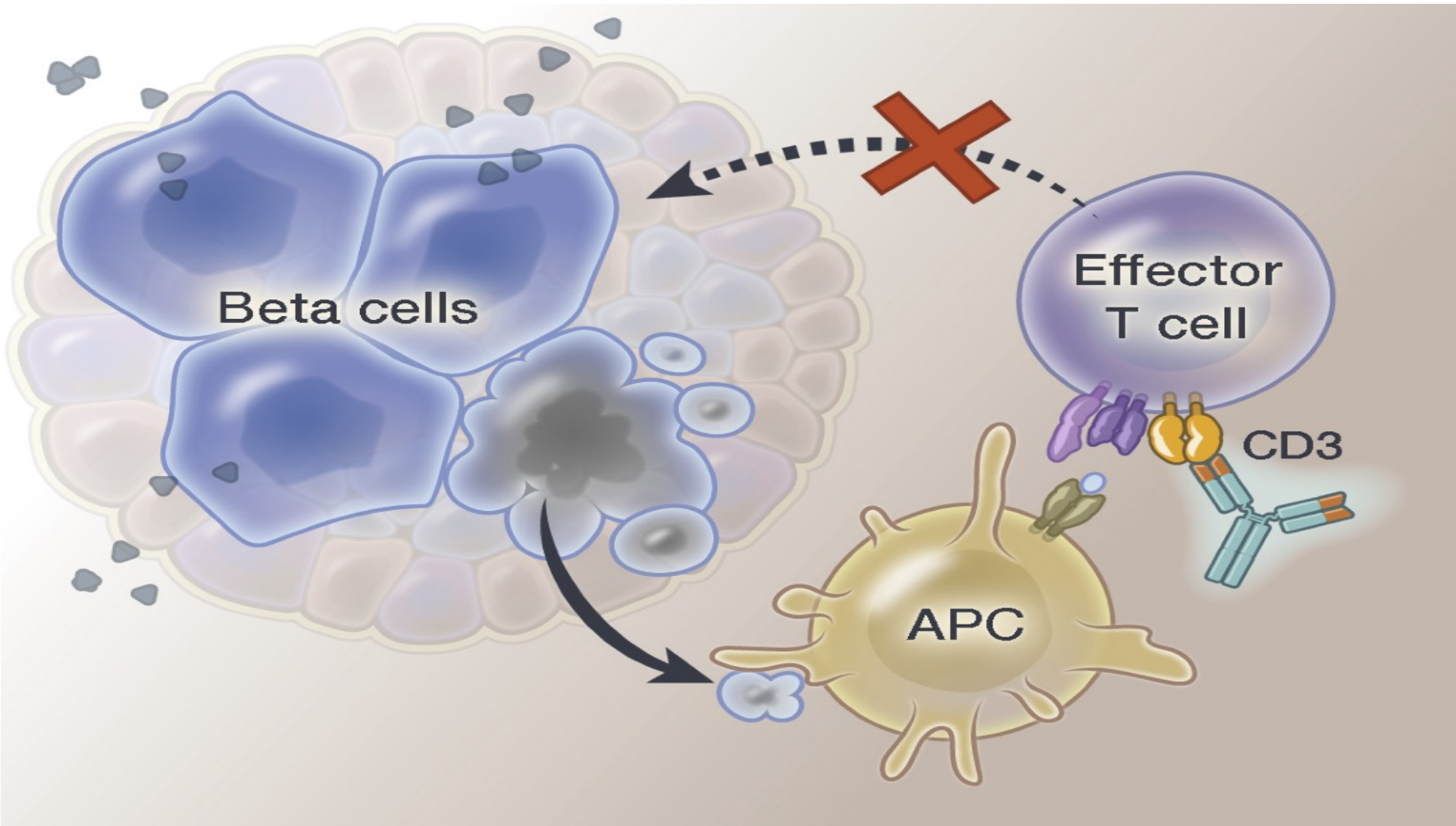
PRIMARY PREVENTION

SECONDARY PREVENTION

TERTIARY PREVENTION



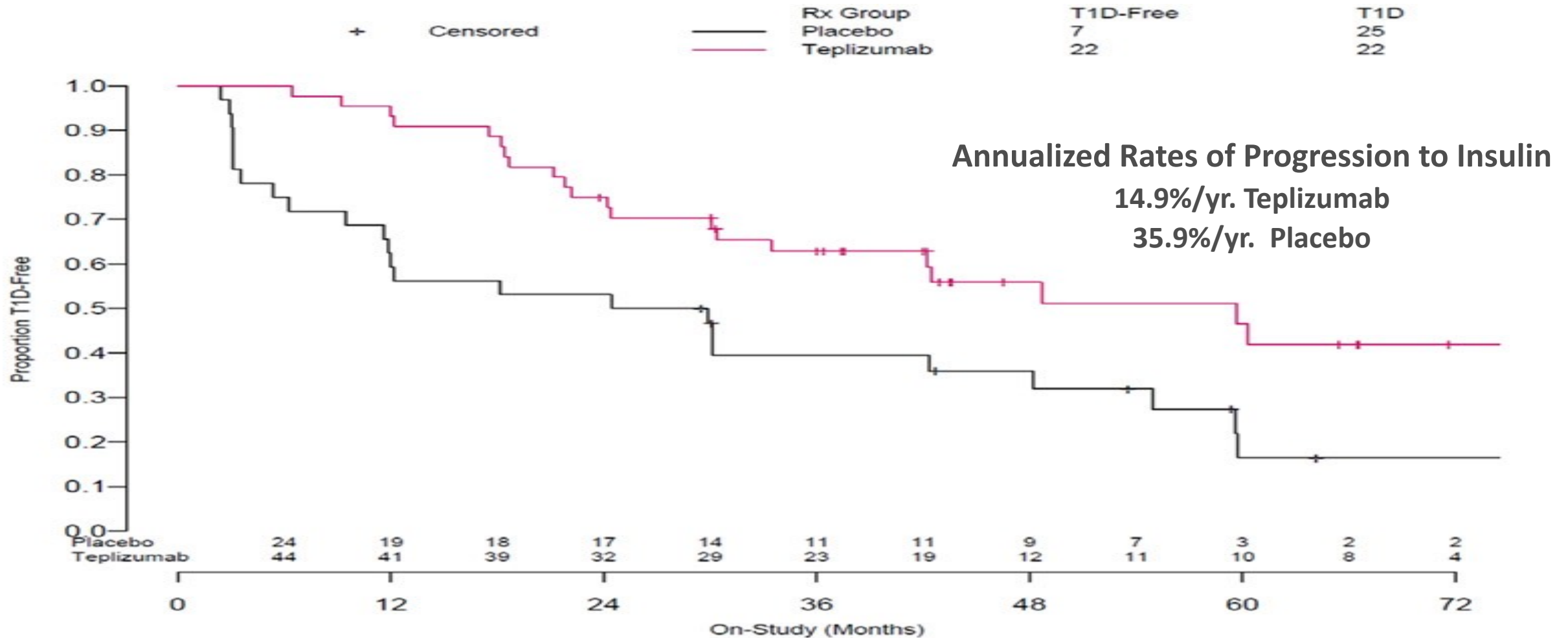
Teplizumab is a humanized mAb That Recognizes the CD3 Cell-Surface Protein Complex on T Cells & Inhibits the Autoimmune Destruction of β Cells



Clinical Trial Requirements, Protocol, Results

- Patient must demonstrate 2 different islet cell antibodies (ICA, Insulin Antibodies, Anti-GAD) on 2 separate occasions within 6 months & be >8 yrs old
- They must demonstrate evidence of impaired glucose tolerance without overt diabetes; FBS >110-125 mg/dl or 2 hr. PP >140-200
- Protocol includes a daily IV infusion of escalating doses of Teplizumab (days 1-4) followed by 10 additional days of IV infusion of the higher dose
- *Patients have were followed for 7 yrs, the treatment delayed onset by 24 months & decreased annualized risk by 60%*

Teplizumab Delays Onset of T1DM in High Risk Islet Cell Antibody Patients @ 6 Years



[Sims, E. et. al. Sci Transl Med. 2021 Mar 3; 13\(583\)](#)

Teplizumab Improves & Stabilizes Beta Cell Function in ICA Positive High-Risk Individuals

- Teplizumab treatment improved quantitative OGTT glucose AUC values over the course of the study
- Teplizumab treatment increased stimulated C-peptide responses
- Teplizumab treatment reversed declines in C-peptide AUC seen during the first 6 months of treatment
- Insulin secretory dynamics improve & were stabilized by teplizumab treatment

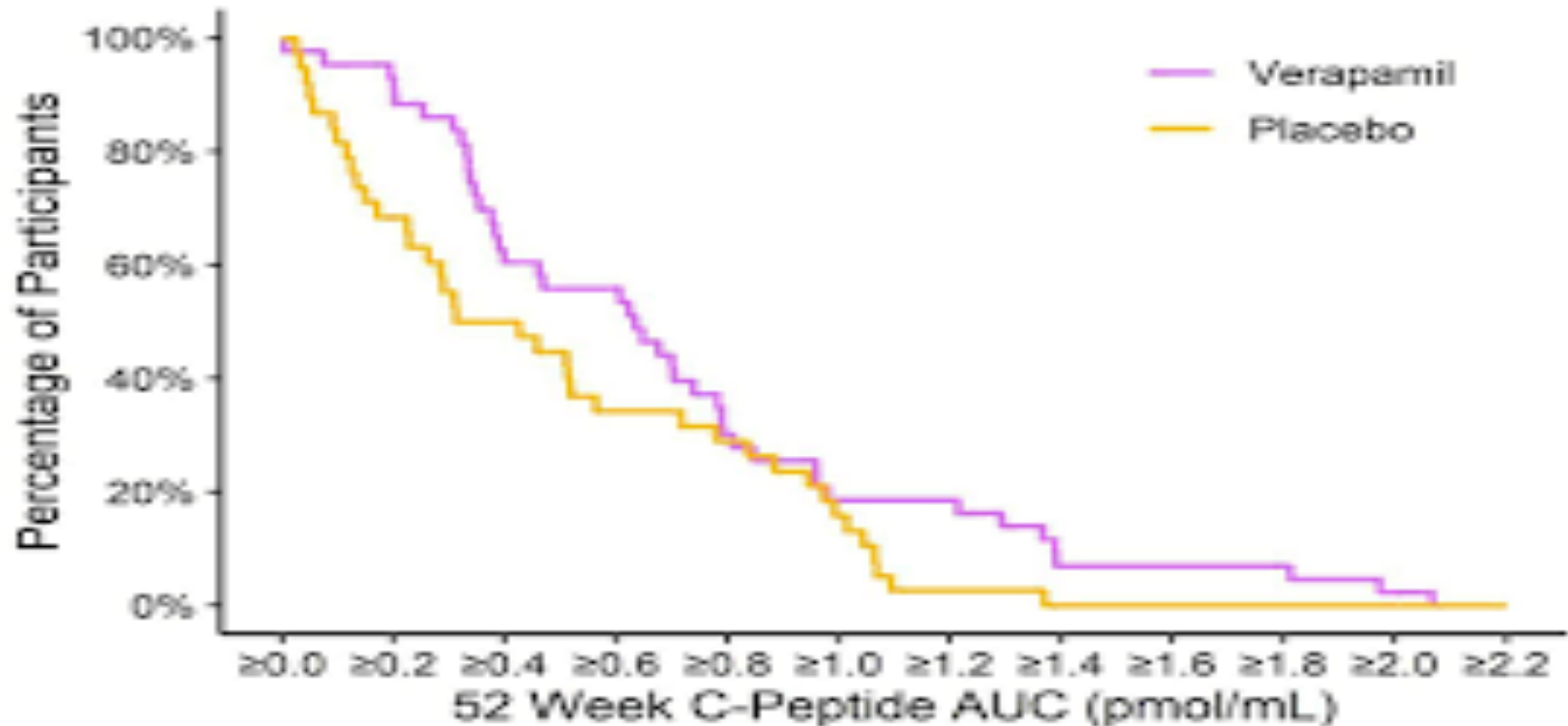
What Is The Benefit of Delaying Onset of T1DM for 5 Years?

Reduces risk of long-term complications, chances to develop better behavioral habits with better education, increased research opportunities for additional new treatment to delay onset, & potentially decreased healthcare costs

However....

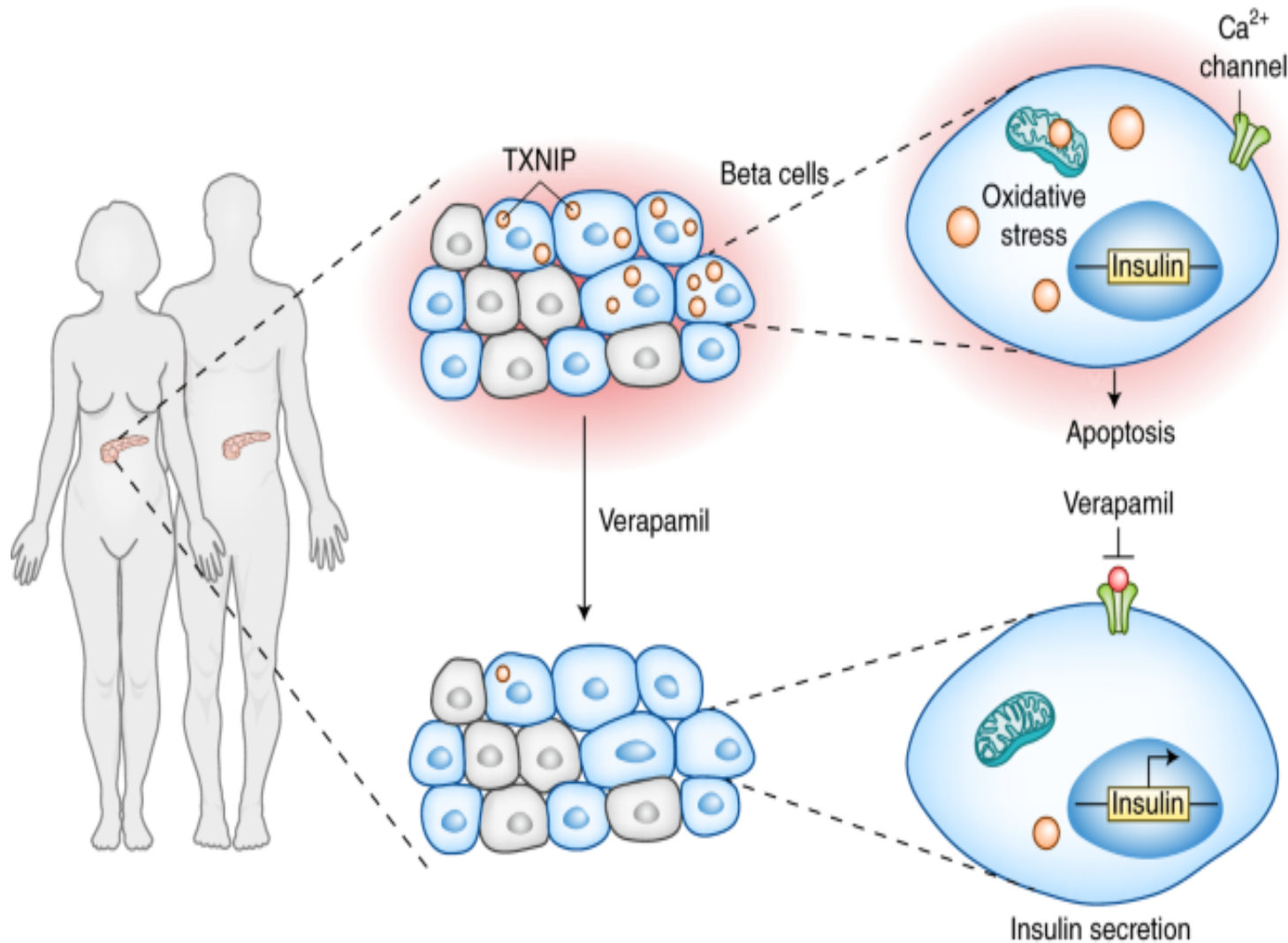
**Calcium Channel Blockers & GLP-1 Agonists
May Also Restore/Preserve Beta Cell Function
in New-Onset (Stage 3) T1DM!!**

Verapamil Restored/Preserved Beta Cell Secretion in 88 Children/Adolescents for 52 Weeks



Forlenza, G. et. Al. JAMA. 2023;329(12):990-999.

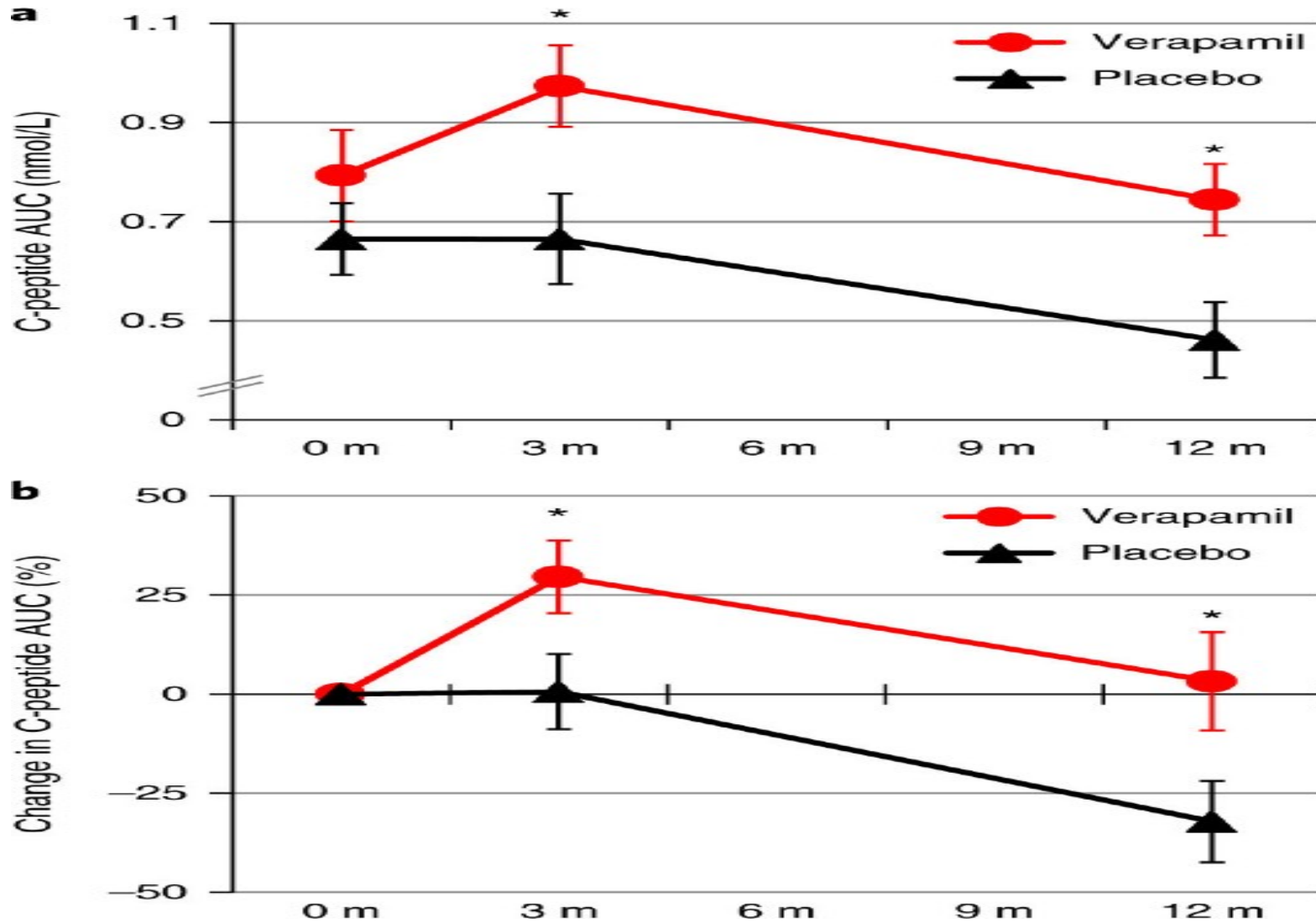
How?? Verapamil Reduces Oxidative Stress, Restores Insulin Secretion, & Protects Beta Cells



Verapamil reduces the amount of a protein called TXNIP in β -cells.

TXNIP is toxic to the β -cells & results in β -cell dysfunction & apoptosis

Verapamil Restores Beta Cell Secretory Response in IVGTT



Verapamil reduces the amount of a protein called TXNIP in cells. TXNIP concentration increases as the the beta cells try to process higher levels of blood sugar. At a certain level, TXNIP can be toxic to the beta cells & result in beta cell dysfunction/death.

Forlenza, G. et. Al. JAMA. 2023;329(12): 990-999.

Verapamil Protocol: FDA Approved Calcium Channel Blocker

- **Children/adolescents were started on 30 mg BID (1.7 mg/kg/d)**
- **Dose was escalated by 30 mg q 2 weeks as tolerated.... up to a total dose of 120-180 mg BID**
- **Except for mild hypotension.....this is a nontoxic FDA approved drug!**

Semaglutide to Preserve Beta Cell Function in Early New-Onset T1DM in Small Case Series

Dandona, P. et al. N Engl J Med 2023; 389:958-95

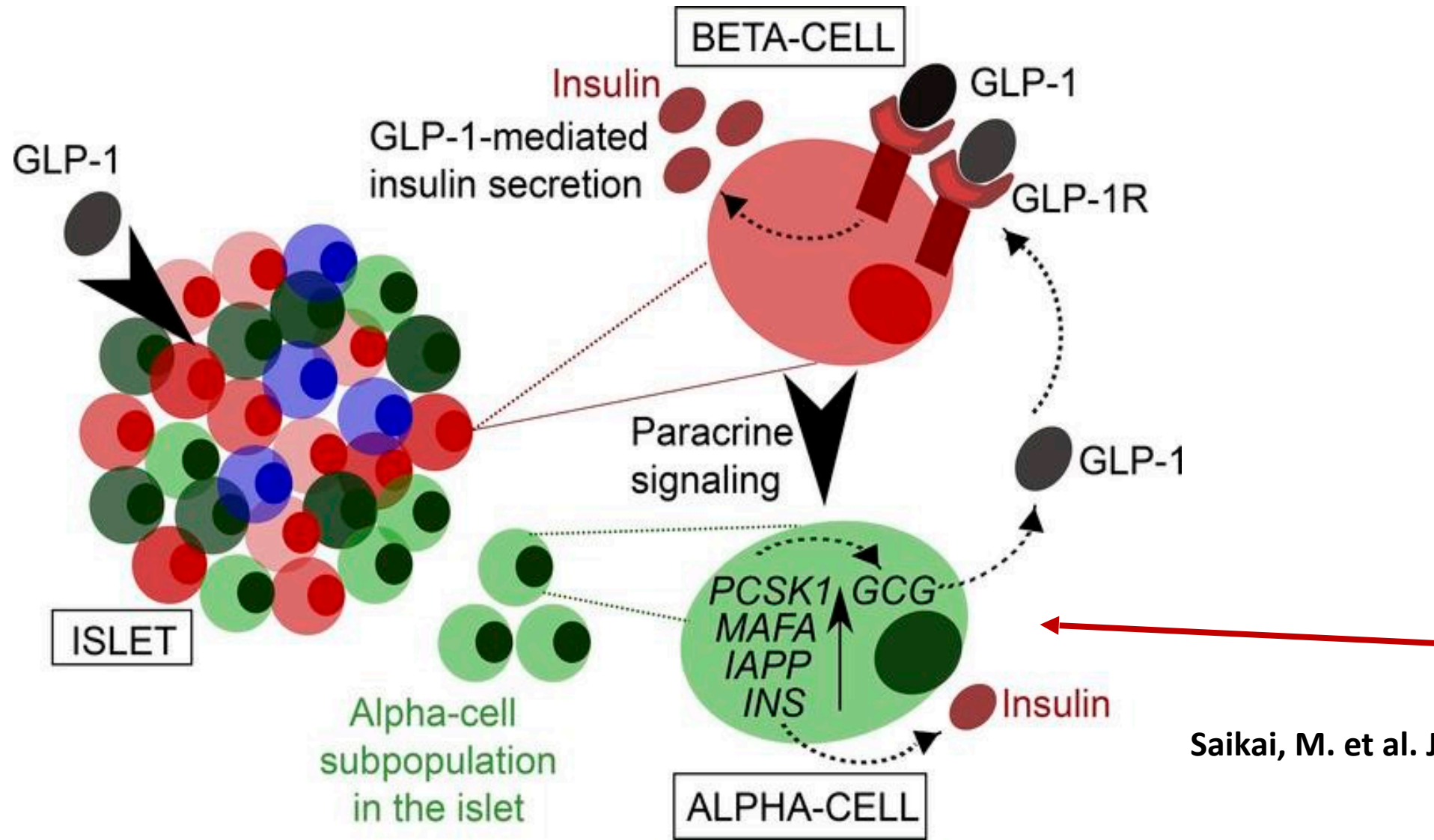
Semaglutide in Early Type 1 Diabetes

- **Early intensive insulin therapy @ new-onset of T1DM itself has been used to “preserve” beta cell function/c-peptide secretion for up to 5 yrs.**
- **GLP-1 agonists preserve beta cell function in T2DM & in animal models of T1DM**
- **Early use of a GLP-1 agonist led to better glucose control & to elimination of need for prandial insulin in all patients & withdraw of basal insulin in most individuals**

Results of Semaglutide Treatment in New-Onset T1DM

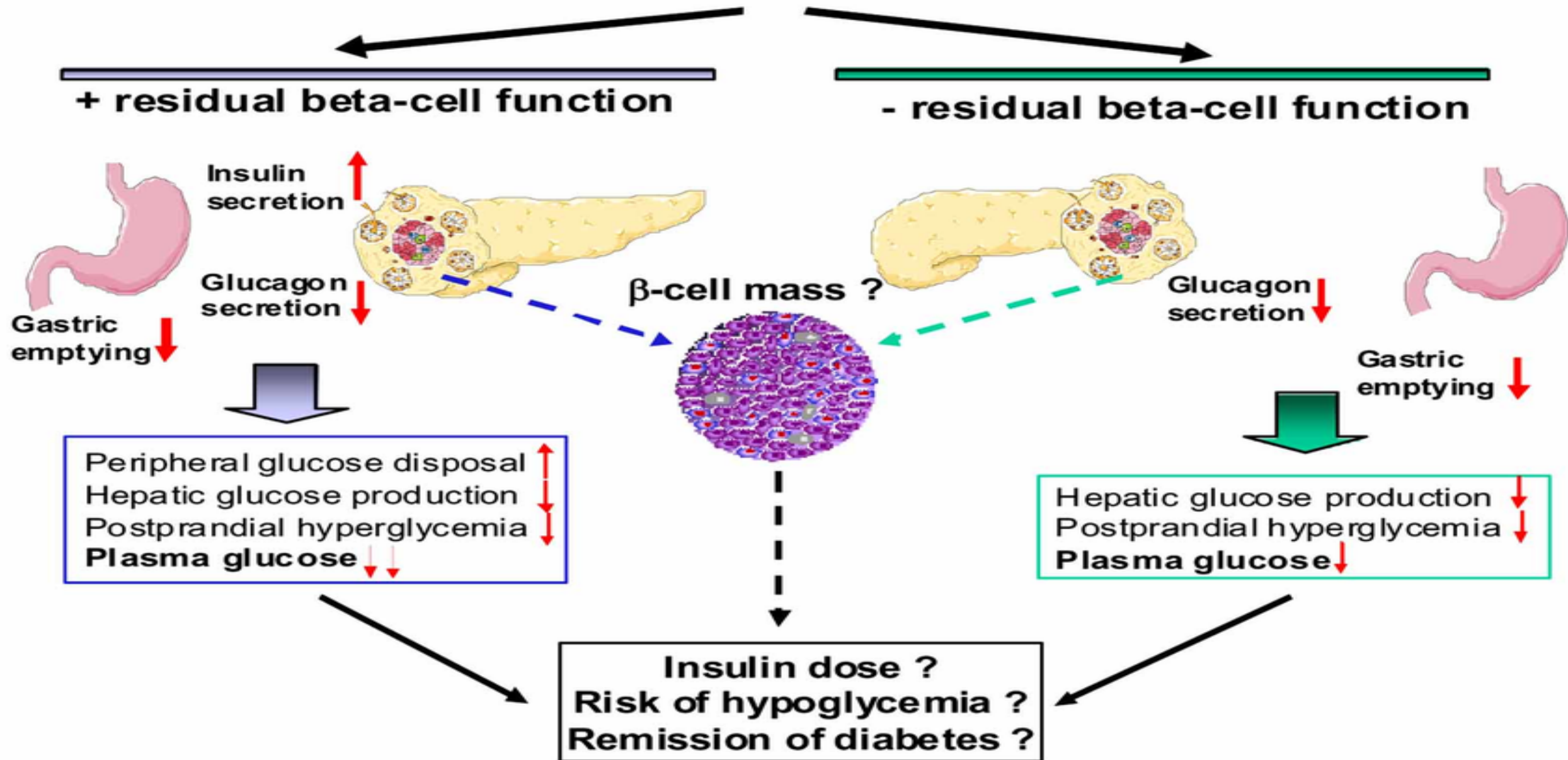
- **10 patients with uncontrolled (ave. A1C 11.6%) new-onset T1DM (<6 months) were placed on Tandem[®] insulin pumps/CGM**
- **They were then placed on semaglutide & titrated to full weekly dose with minimal side-effects**
- **Initially, meal bolus insulin was able to be tapered off followed by basal insulin in 8/10 patients**

GLP-1 Agonists Stimulate Beta Cell Regeneration & Expression β Cell–Like Genes in Alpha Cells



Saikai, M. et al. JCI Insight. 2021;[6\(3\)](#)

GLP-1 treatment in subjects with type 1 diabetes

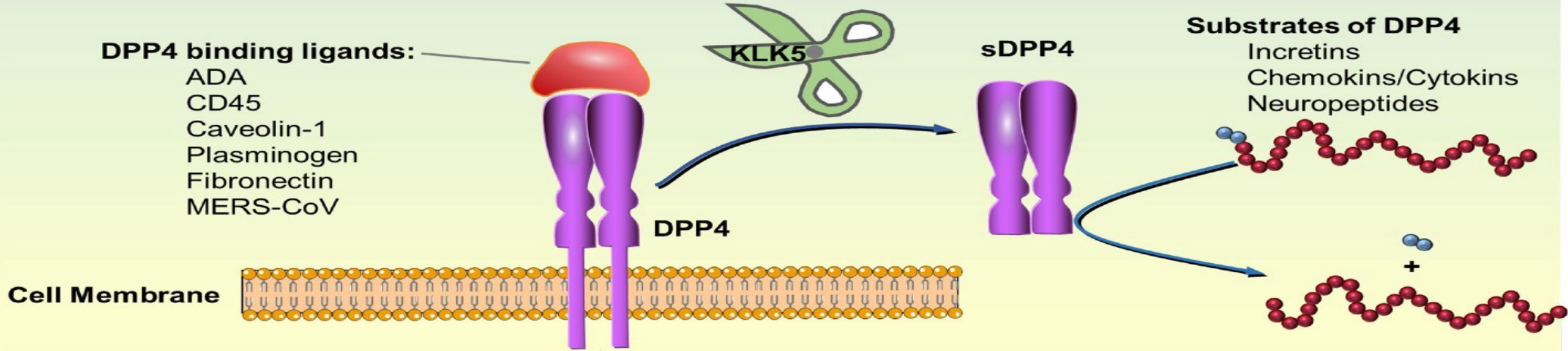


DPP4 Inhibitors in New Onset T1DM?

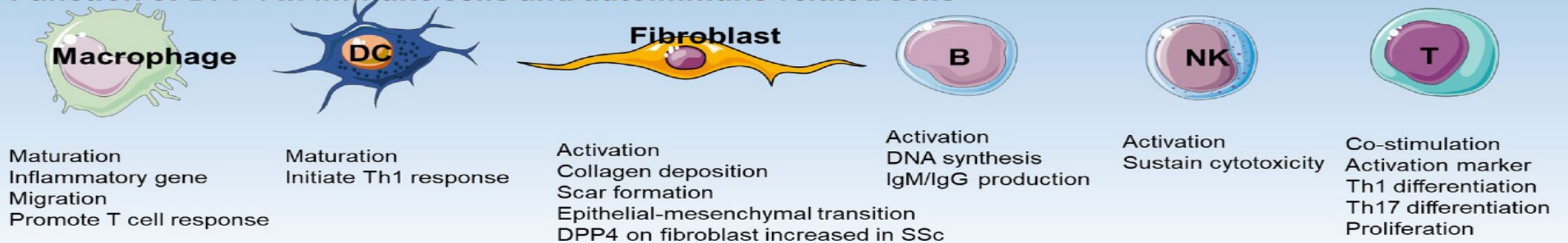
Improve β -cell function, attenuate autoimmune destruction of β -cells & decreases insulin requirements in New-Onset T1DM

[Penaforte-Saboia, J. et. al. Diabetes Metab Syndr Obes. 2021; 14: 565–573](#)

Immune Modulating Effects of the DPP4 Inhibitors



Function of DPP4 in immune cells and autoimmune-related cells



Is a New Paradigm Evolving for Initial Treatment of New-Onset T1DM To Preserve β -Cell Function?

- Intensive insulin therapy to “rest β -cells”
- Immunosuppression to “protect β -cells” from further T-cell mediated destruction
- Verapamil to “protect β -cells” from oxidative stress-induced apoptosis
- GLP-1 agonist to stimulate β -cell regeneration...or
- DPP4-Inhibitor to increase GLP-1 levels & direct, immune regulatory effects??

New Insulin Pumps FDA Approved in 2023

- **Roche's Accu-Chek 'Solo' micropump system**
- **Beta Bionics 'iLet ACE Pump' & iLet Dosing Decision Software which eliminates carbohydrate counting**
- **Tandem's 'Mobi' is billed as the "world's smallest"**
- **Medtronic's MiniMed™ 780G pump upgrade with automated "meal detection" software which helps cover missed meal boluses or inaccurate carb estimates with supplemental insulin**

Roche's Accu-Chek 'Solo'® Tubing-Free "Patch" Pump



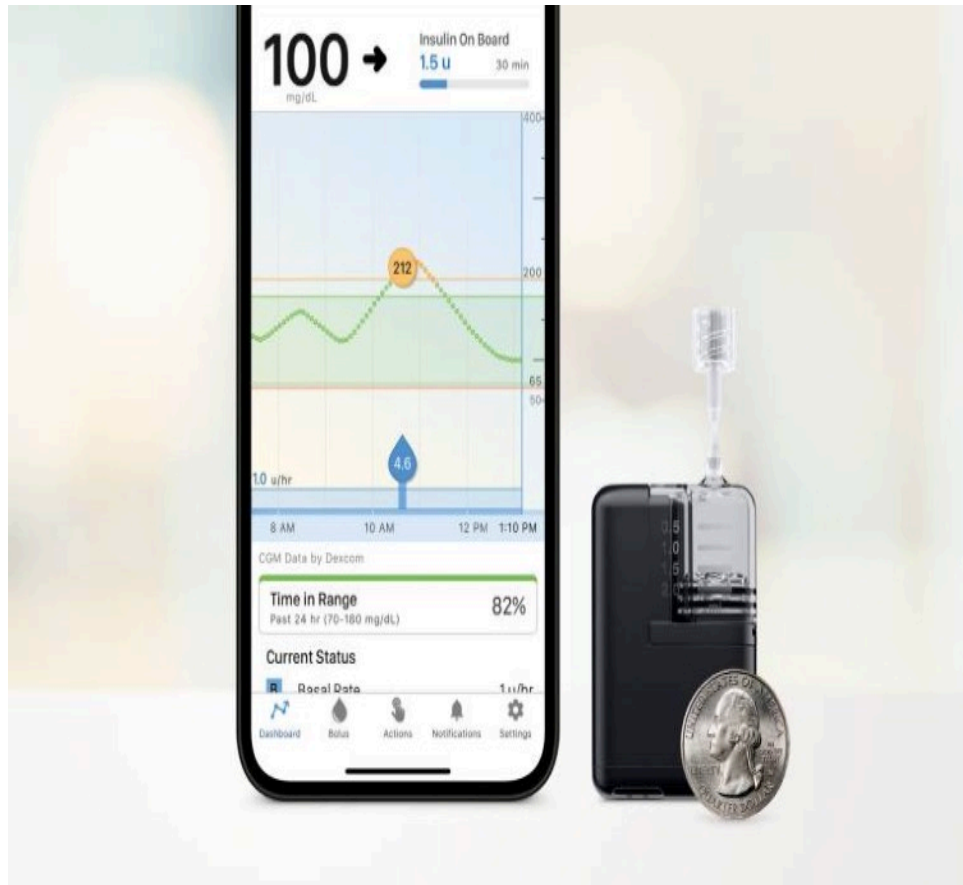
Similar to Tandem's T-Slim X2 insulin pump eliminating infusion set tubing

Beta Bionics 'iLet ACE Pump'



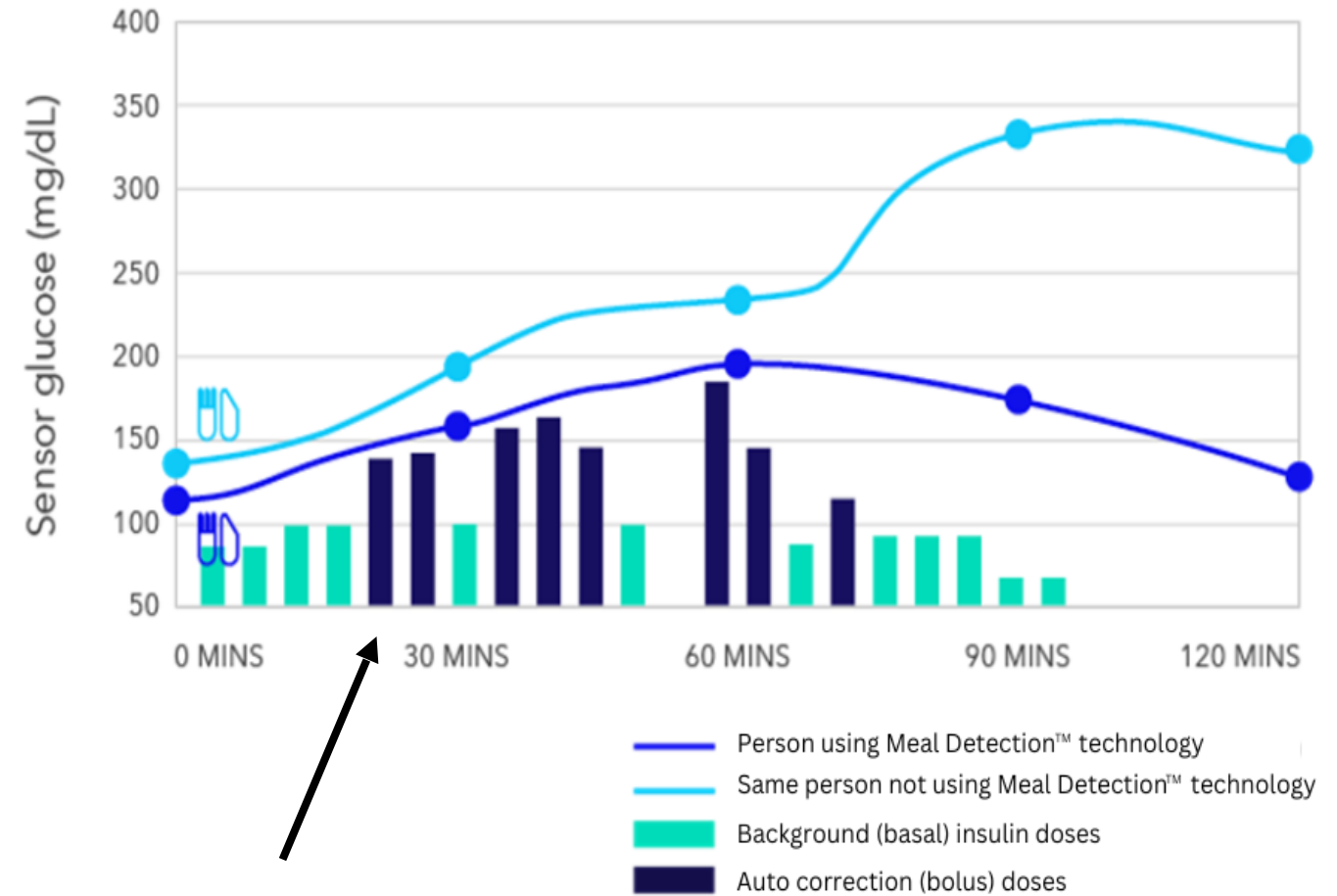
Eliminates carbohydrate countingbut patient must notify pump of impending meal & estimate “high or low carb” content

Tandem 'Mobi' Insulin Pump



“World’s smallest durable automated insulin delivery device”

Medtronic's MiniMed™ 780G Pump with Automated “Meal Detection” Software



The iLet ACE® & MiniMed 780G® insulin pumps are overcoming the major patient complaint/obstacle to self-directed intensive glucose control which is.....

Missed meal boluses!

Take Home This Year

- **Insulin Icodec[®] is the first weekly duration of action insulin analog should help overcome the clinical inertia of starting insulin therapy in patients with uncontrolled T2DM**
- **GLP-1/GIP/G “Triple Agonists” are even more potent compounds for use in treatment of weight loss, glucose control, HT, & NASH**
- **Lantidra[®] is a the first FDA approved source of allogeneic pancreatic islet cells available to transplant centers for treatment of severe hypoglycemia unawareness**

Take Home This Year

- **Tziel[®] (teplizumab) an anti-CD3 Ab given by daily infusion for 2 weeks can significantly delay the onset of T1DM in ICA⁺ children & adults for 6 yearsfar**
- **Verapamil (Ca⁺⁺ channel inhibitor) & semaglutide (GLP-1 agonist) are FDA approved medications (as well as DPP4-Inhibitors) can also preserve β -cell function & insulin secretion in new-onset T1DM without immunosuppression**
- **Smarter, “semi-closed loop” insulin pumps are evolving & one eliminates need for carbohydrate counting & another now can detect-meal induced hyperglycemia administer supplemental insulin automatically**