



Diabete tipo 1: Solo insulina?

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Disclosure

Il Prof. Paolo Pozzilli dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

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Obesity in people living with type 1 diabetes

Bart Van der Schueren, Darcy Ellis, Raquel N Faradji, Eeba Al-Ozairi, Jonathan Rosen, Chantal Mathieu

Lancet Diabetes Endocrinol, 2021

REVIEW ARTICLE

Clinical Research

The emergence of obesity in type 1 diabetes

Martin T. W. Kueh^{1,2}, Nicholas W. S. Chew³, Ebaa Al-Ozairi^{4,5} and Carel W. le Roux⁶

International Journal of Obesity (2024)

Expert Review of Endocrinology & Metabolism



EXPERT
REVIEW

OF ENDOCRINOLOGY & METABOLISM

Obesity in type 1 diabetes: an overlooked immune-metabolic issue

Ernesto Maddaloni & Dario Tuccinardi

Expert Review of Endocrinology & Metabolism, 2024



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Review

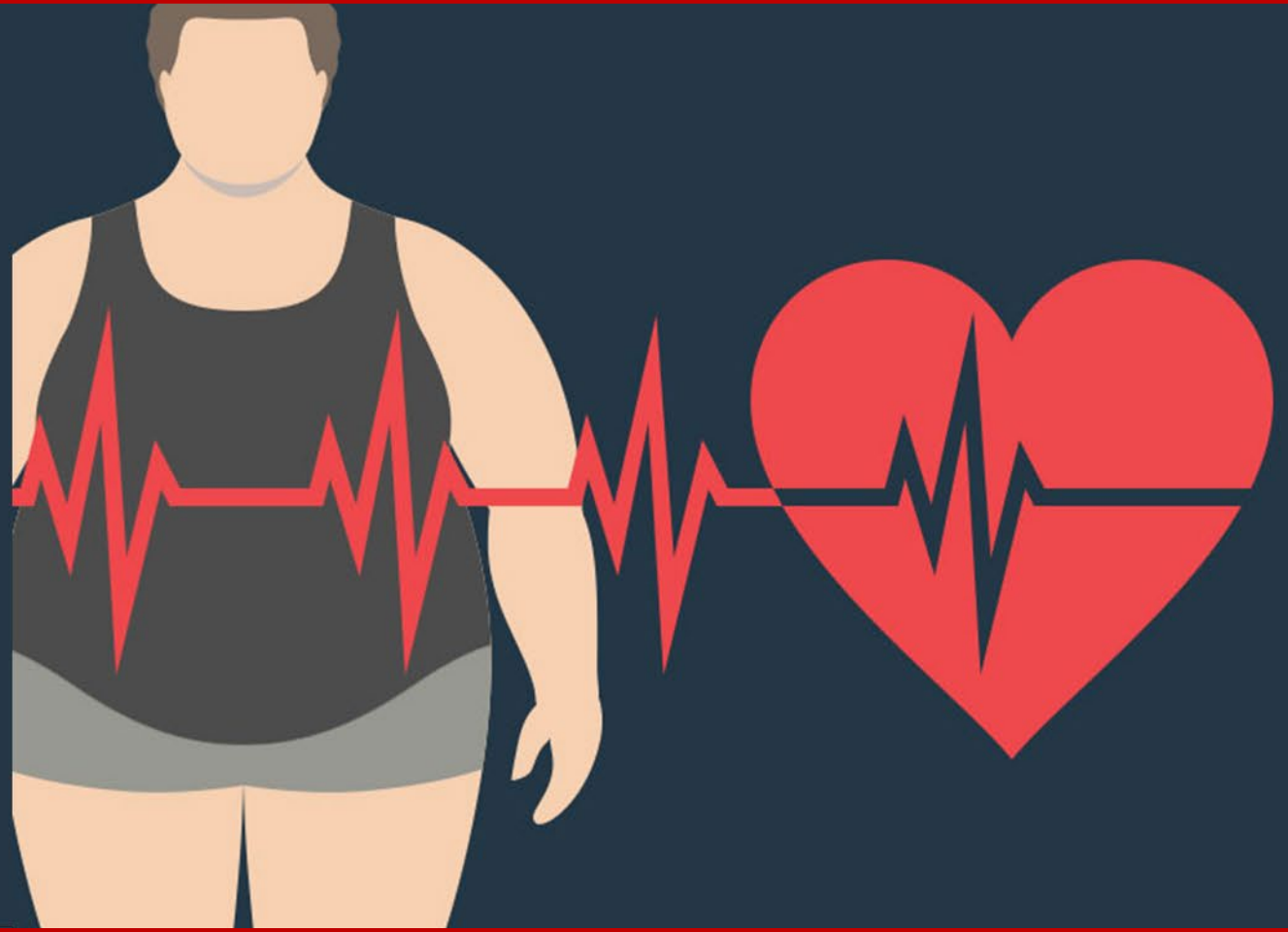
Beyond the insulin pump: unraveling diabetes tech dependency

Emanuele Feliziani, Maria Caterina Chios, Paolo Pozzilli

Diabetes Res Clin Pract, 2024

Obesity and type 1 diabetes

- Overweight/obesity affects a large number of patients with type 1 diabetes (T1D) across their lifetime, with rates ranging between 3% and 37%
- Patients with T1D and obesity are characterized by presence of insulin resistance, high insulin requirements for treatment, a greater cardio-metabolic risk and an **ENHANCED RISK OF DEVELOPING CHRONIC COMPLICATIONS** when compared to normal-weight subjects with T1D.



A summary of variables contributing to obesity in T1D

β-cell autoimmunity

Metabolic, psychosocial,
environmental stressors

Type 1 Diabetes

Intensive subcutaneous insulin therapy

Hypoglycaemic avoidance

Genetic susceptibility

Hormonal alterations

Anti influx of energy-dense food

Psychological factors

Sociodemographic disparities

Obesity in Type 1 Diabetes

Chronic low-grade inflammation

Lipotoxicity

Glucotoxicity

Mitochondrial dysfunction

Adipose tissue dysfunction

Endocrine alterations

Gut microbiome dysbiosis

Systemic complications

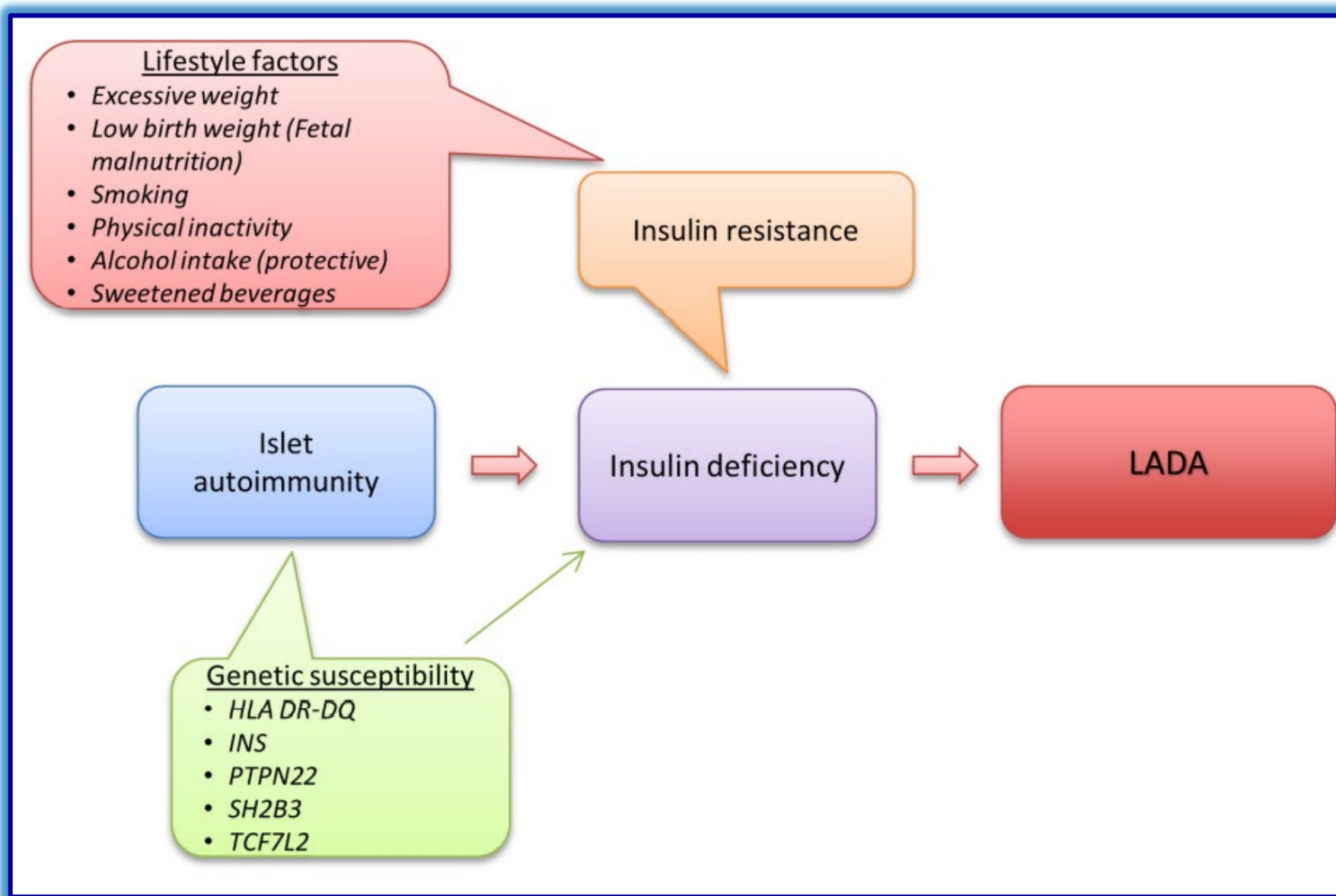
- Metabolic syndrome
- Insulin resistance
- Cardiovascular disease

Accelerates β-cell apoptosis

Obesity-associated insulin resistance

Requires higher doses of insulin

Autoimmune diabetes in adults (LADA) associated with overweight/obesity: a model based on current knowledge



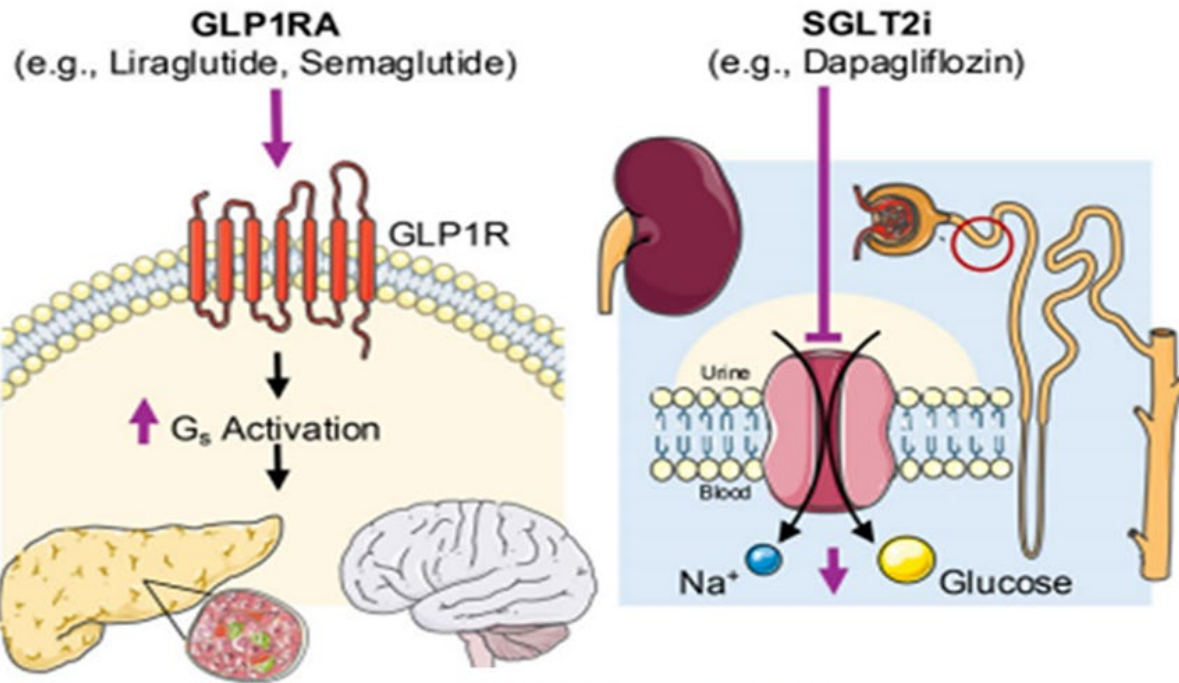
LADA may share several environmental risk factors with T2D including:

- Overweight;
- Physical inactivity;
- Alcohol consumption;
- Smoking.

The importance of targeting metabolic control for T1D management and treatment

- Metabolic interventions, through their direct and indirect impacts on β -cells, have shown promise in preserving β -cell function.
- These interventions can reduce glucose toxicity, alleviate oxidative stress and inflammation, enhance insulin sensitivity, and indirectly mitigate the autoimmune responses.
- By preserving β -cell function, individuals with T1D attain better glycaemic control, reduced complication risks and exhibit improved overall metabolic health.

Overview of metabolic interventions as adjuncts to insulin therapy for the treatment of T1D



Primary Target Tissue

β-Cells + CNS

Kidney

Benefits

Glucose-Stimulated Insulin Secretion
Satiety/Weight Loss
Insulin Sensitization
Improved Glycemic Control
Preserved β-Cell function?

Improved Glycemic Control
Improved Blood Pressure
Weight Loss
Lower Insulin Requirement

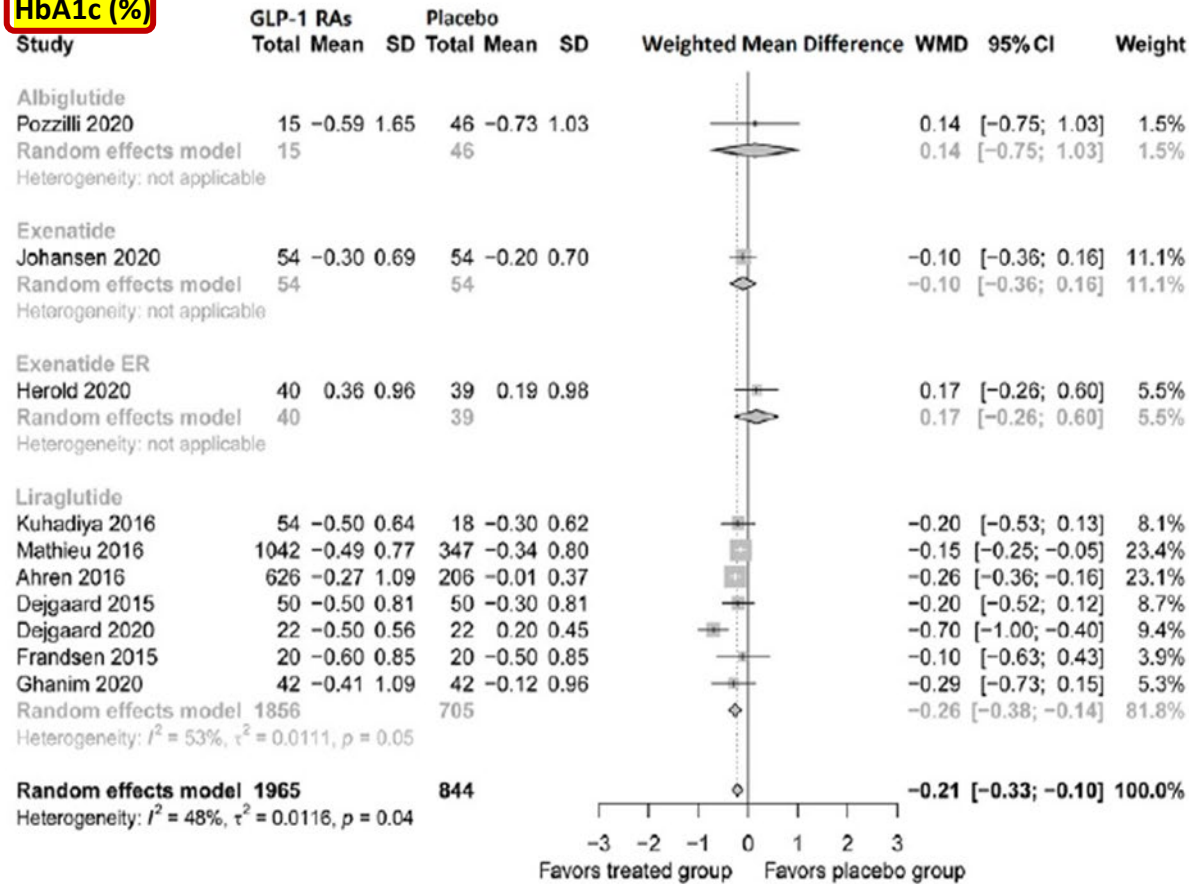
Limitations

Nausea
Vomiting
Increased Time-in-Hypoglycemia?
Risk of DKA?

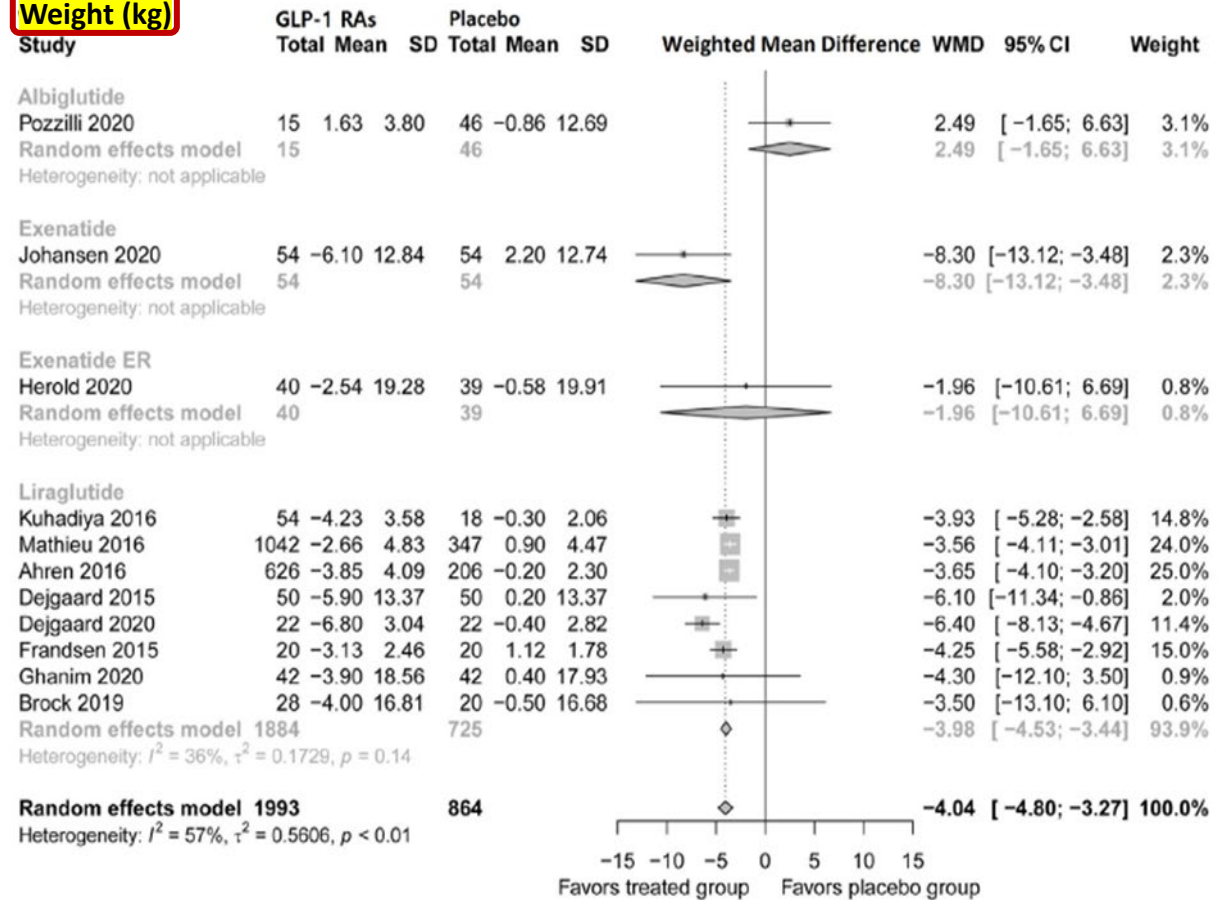
Risk of DKA
Increased Glucagon

Glucagon-like peptide-1 receptor agonists as add-on therapy to insulin for T1D

HbA1c (%)

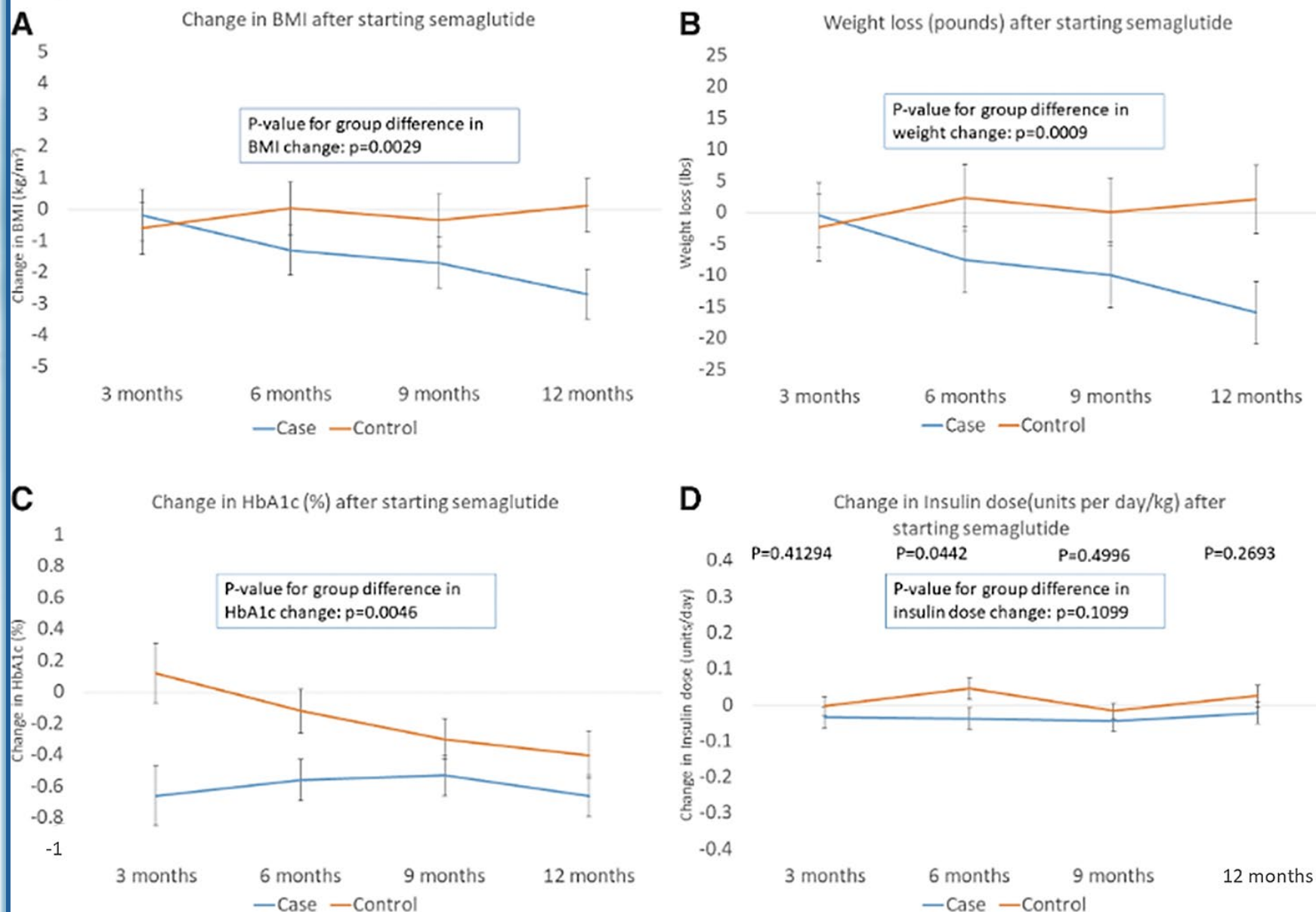


Weight (kg)



This meta-analysis of randomized clinical trials suggests moderate beneficial effects of GLP-1 RAs on the metabolic profile in patients with T1D, without an increased risk of serious adverse events.

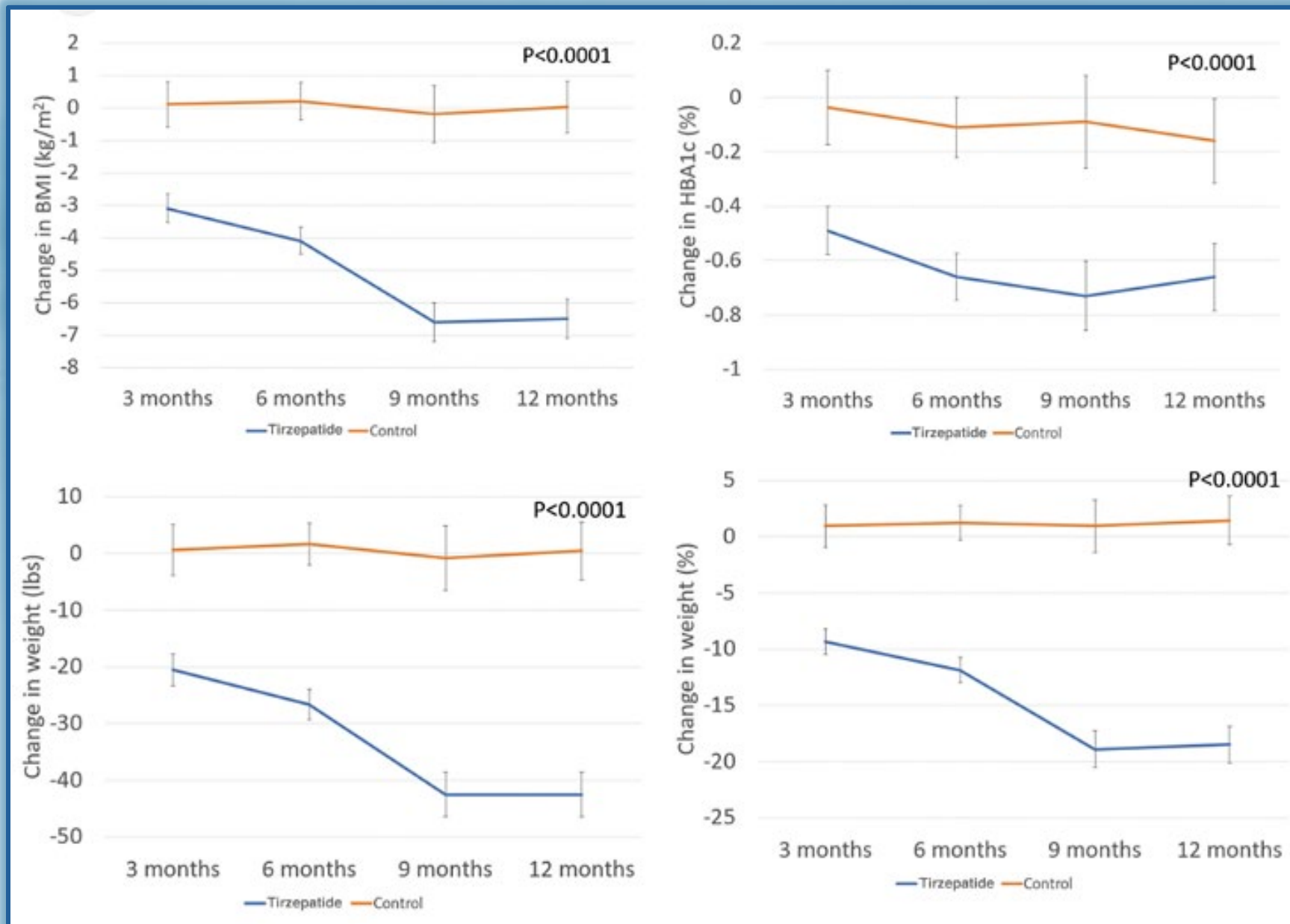
Efficacy of Semaglutide in Overweight and Obese Patients with T1D



The use of semaglutide in patients who are OW and/or OB with T1D is effective in lowering body weight and BMI and improving glycemic metrics in this pilot real-world study.

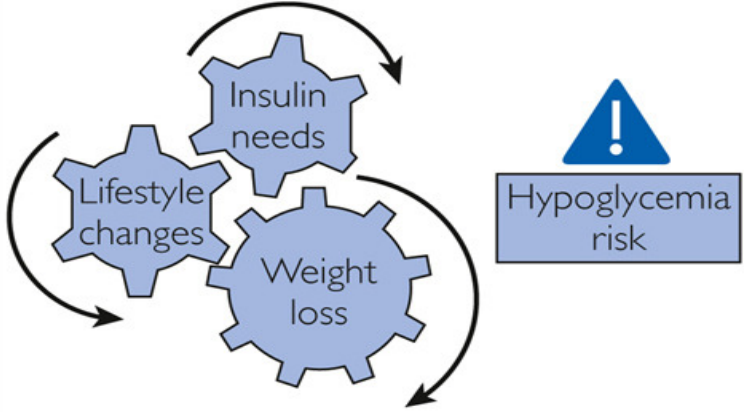
Prospective, large-randomized clinical trials with newer GLP-1 analogs like semaglutide and tirzepatide for subjects with T1D associated with OW and/or OB are strongly recommended.

Efficacy and Safety of Tirzepatide in Overweight and Obese Adult Patients with T1D

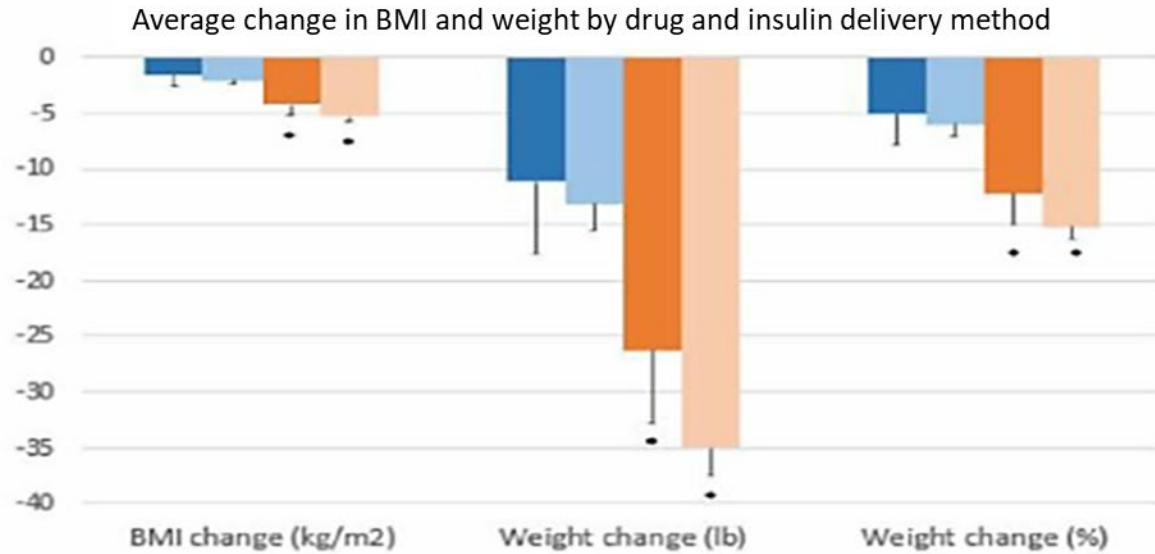


In this pilot (off label) study, tirzepatide facilitated an average 18.5% weight loss and improved glucose control in OW/OB patients with T1D at 1 year. For safe use of tirzepatide in patients with T1D, a large prospective randomized control trial in OW/OB patients with T1D is strongly recommended.

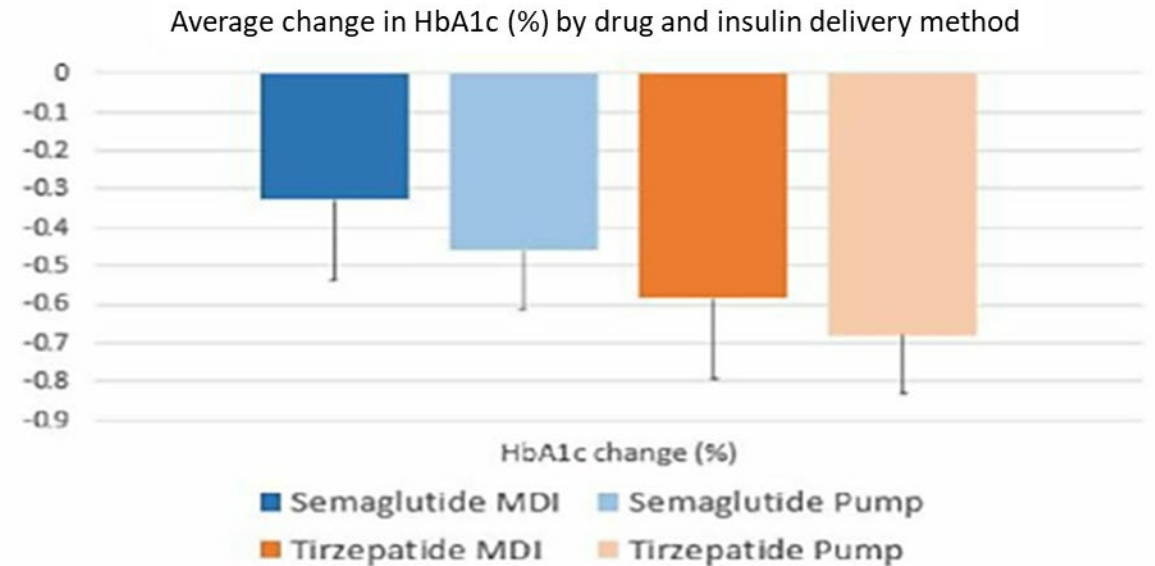
Effect of Tirzepatide on Body Weight and Diabetes Control in Adults With T1D and Overweight or Obesity

Background	Methods	
The treatment of overweight and obesity in individuals with type 1 diabetes poses a clinical challenge. 	 Retrospective chart review of 51 adults with type 1 diabetes using tirzepatide for overweight or obesity for at least 3 months. <th>Results</th>	Results
	Over a median follow-up time of 8 months, we observed:  ☒ Weight loss 8.5%  ☒ HbA1c ↓ 0.9%  ☒ Daily insulin requirements ↓ 36% Basal ↓ 36% Meal ↓ 31% *With most changes occurring within 6 months of therapy initiation  ☒ Improvement in cardiometabolic parameters  ☒ No increased hypoglycemia  ☒ No diabetes ketoacidosis	
Objective	Conclusions	
To determine the effect of tirzepatide on weight, diabetes control, and insulin requirements, and its safety profile in adults with type 1 diabetes and overweight or obesity.	In adults with type 1 diabetes, tirzepatide leads to substantial weight loss, better diabetes control, and decreased insulin requirements, without worsening hypoglycemia.	

Change in BMI, Weight and HbA1c by Drug and Insulin Delivery Method



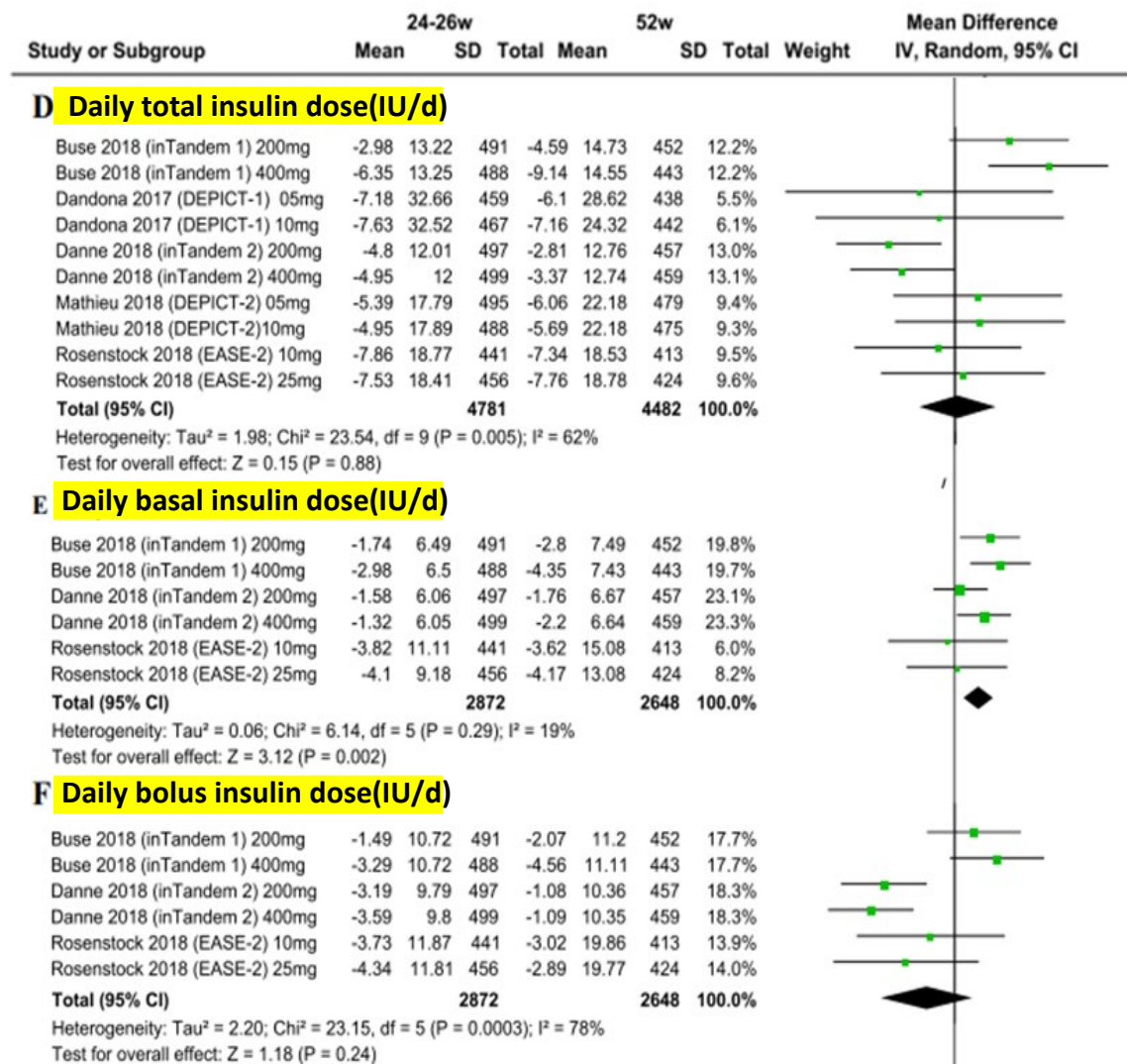
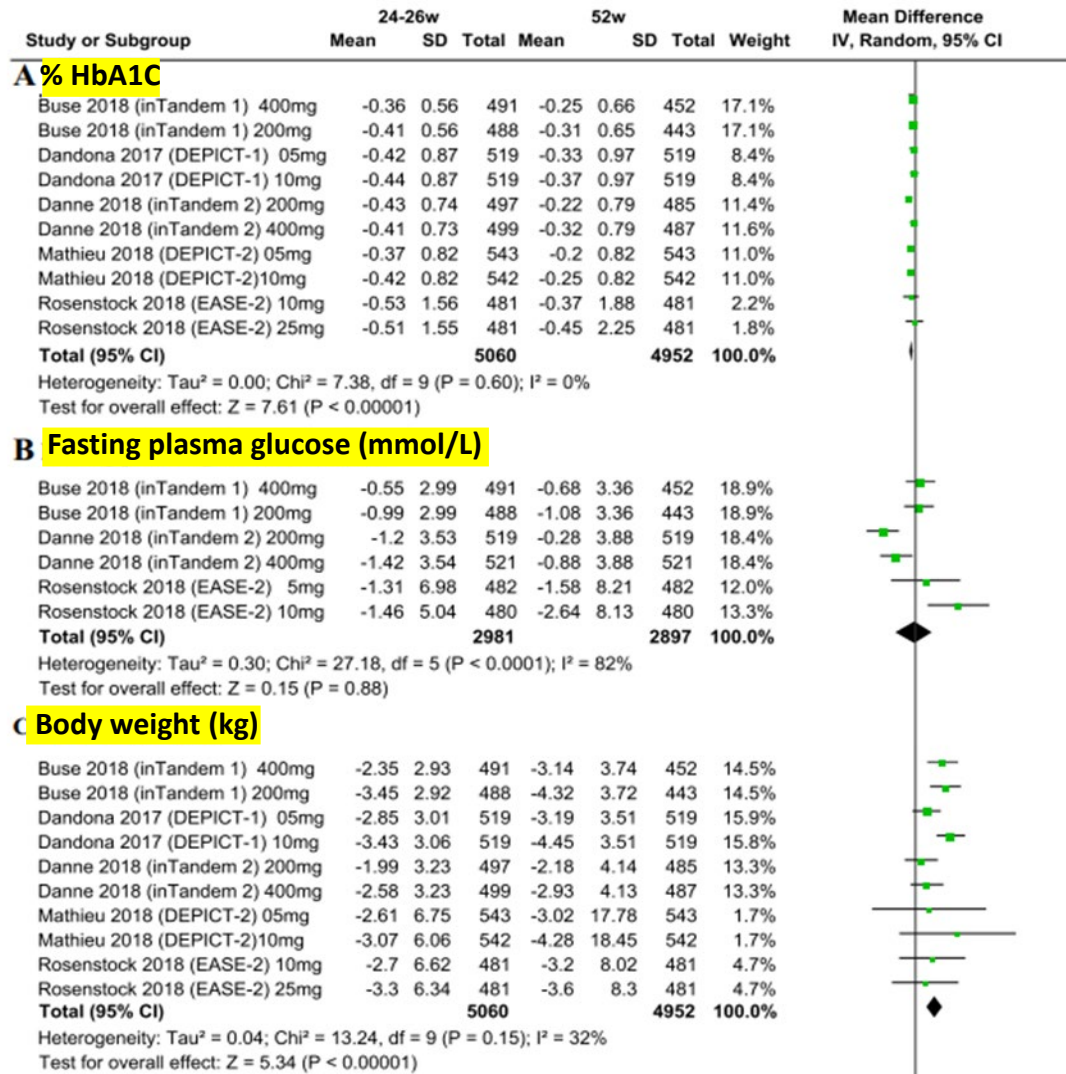
* p<0.05 compared to semaglutide group



Effectiveness of Semaglutide and Tirzepatide in Overweight and Obese Adults with T1D

Weight loss of 9.1% and 21.4% and improved glucose control in semaglutide and tirzepatide users, respectively, after 1 year of off-label use were observed. As off-label use of these drugs is increasing in patients with T1D, larger, prospective safety and efficacy trials are needed.

SGLT- 2 inhibitors as an add-on therapy to insulin for T1D: Meta-analysis of randomized controlled trials



SGLT2i as an add-on therapy to insulin improved glycaemic control and body weight and decreased the required dose of insulin without increasing the risk of hypoglycemia. After 6 months the benefits of SGLT2is on glycaemic control may weaken and the risks of DKA increased.

SGLT2 Inhibitors in the Management of T1D: Ongoing Clinical Trials

- **Dapagliflozin in Physical Exercise in Type 1 Diabetes (NCT04049110)**
- **Dapagliflozin Plus Pioglitazone in T1DM (NCT03878459)**
- **Ketone Monitoring in T1D: Effect of SGLT2i During Usual Care and With Insulin Deficiency (NCT05541484)**
- **Triple Therapy in T1DM (NCT03899402)**
- **Study to Explore the Effect of Dapagliflozin and Stress in Adolescent and Adults subjects With Type 1 Diabetes (T1D) (Dapa-Stress) (NCT04234867)**
- **Adolescent Type 1 Diabetes Treatment With SGLT2i for hyperglycEMia and hyPerfilTration Trial (ATTEMPT) (NCT04333823)**
- **Combination Adjunctive Therapy to Address Multiple Metabolic Imbalances in Type 1 Diabetes (SOTA) (NCT05696366)**

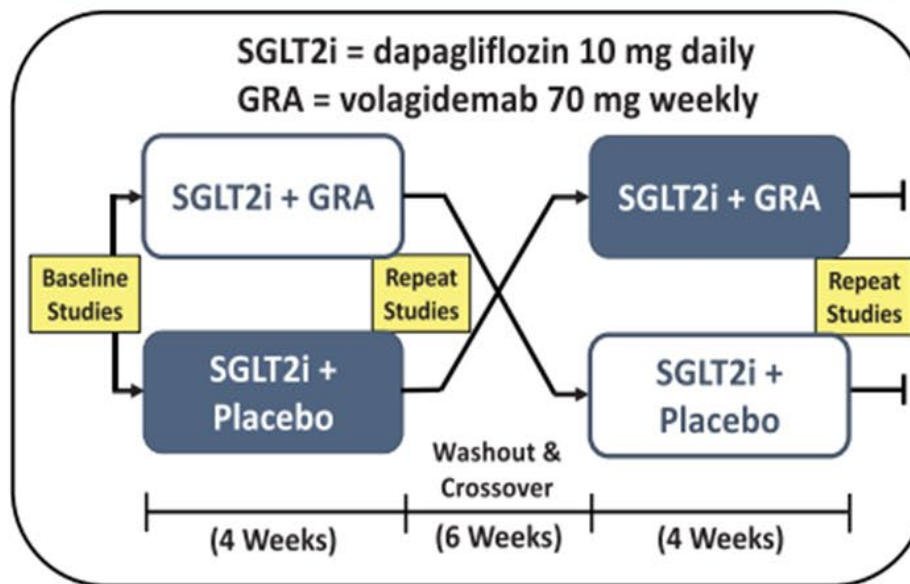
Combination of SGLT-2 Inhibitor and GLP-1RA Therapy in T1D: A Randomized Clinical Trial

Hypothesis

Combining an SGLT2 inhibitor with a GRA will:

1. Improve glycemia
2. Reduce insulin use
3. Reduce ketogenesis during insulinopenia

Study Design (n=12)

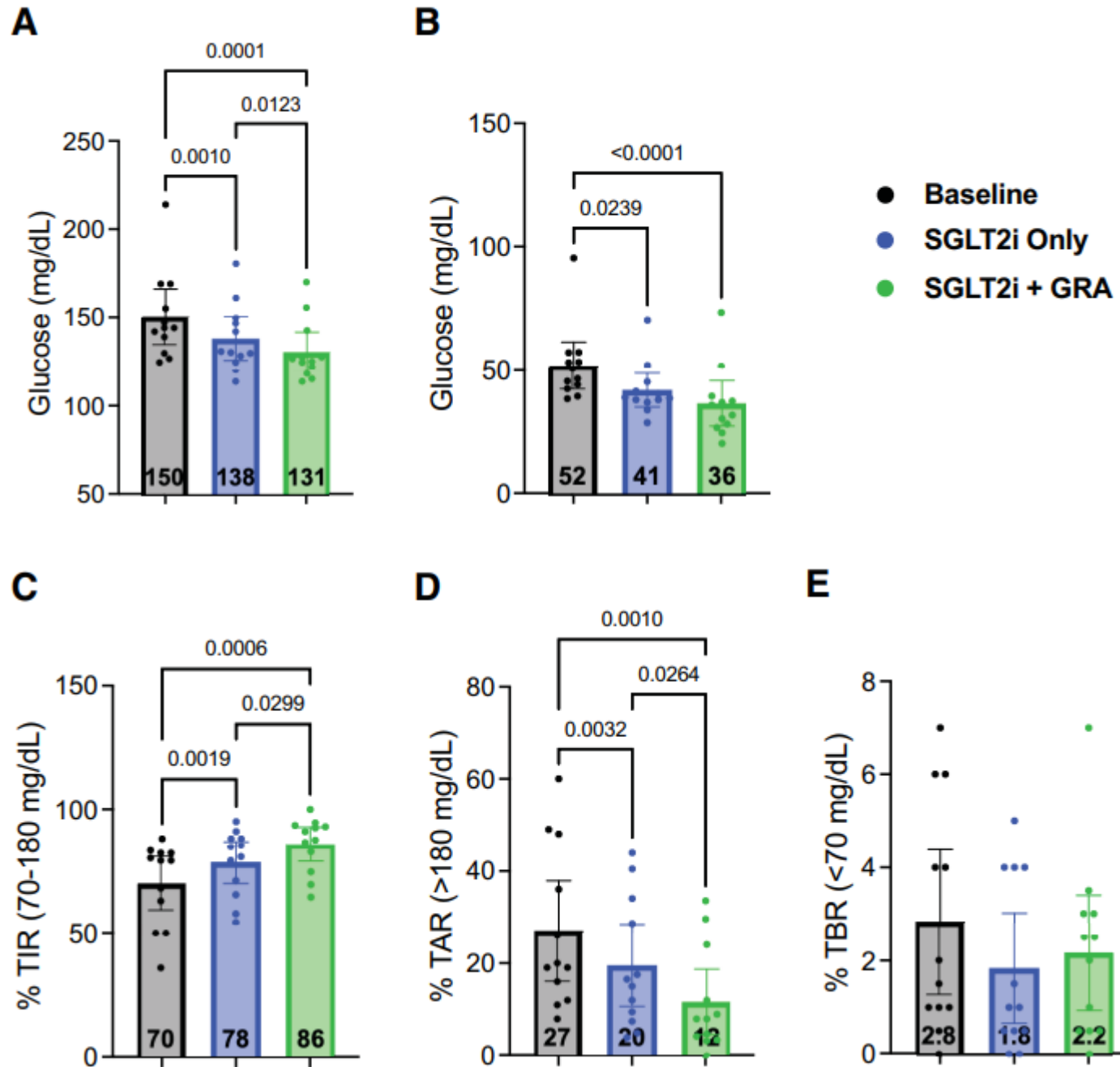


Results

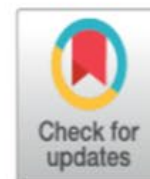
With combination therapy:

- Average glucose ↓ 19 mg/dL
- Time in range ↑ 16%
- No increased hypoglycemia
- Total insulin use ↓ 27%
- Ketones in insulinopenia ↓ 17%

Conclusion: Combination SGLT2 inhibitor + GRA is a promising adjunctive therapy strategy for type 1 diabetes



Glucagon antagonism enhances the therapeutic effects of SGLT2 inhibition in T1D. Combination therapy improves glycemic control, reduces insulin dosing, and suggests a strategy to unlock the benefits of SGLT2 inhibitors while mitigating the risk of diabetic ketoacidosis.

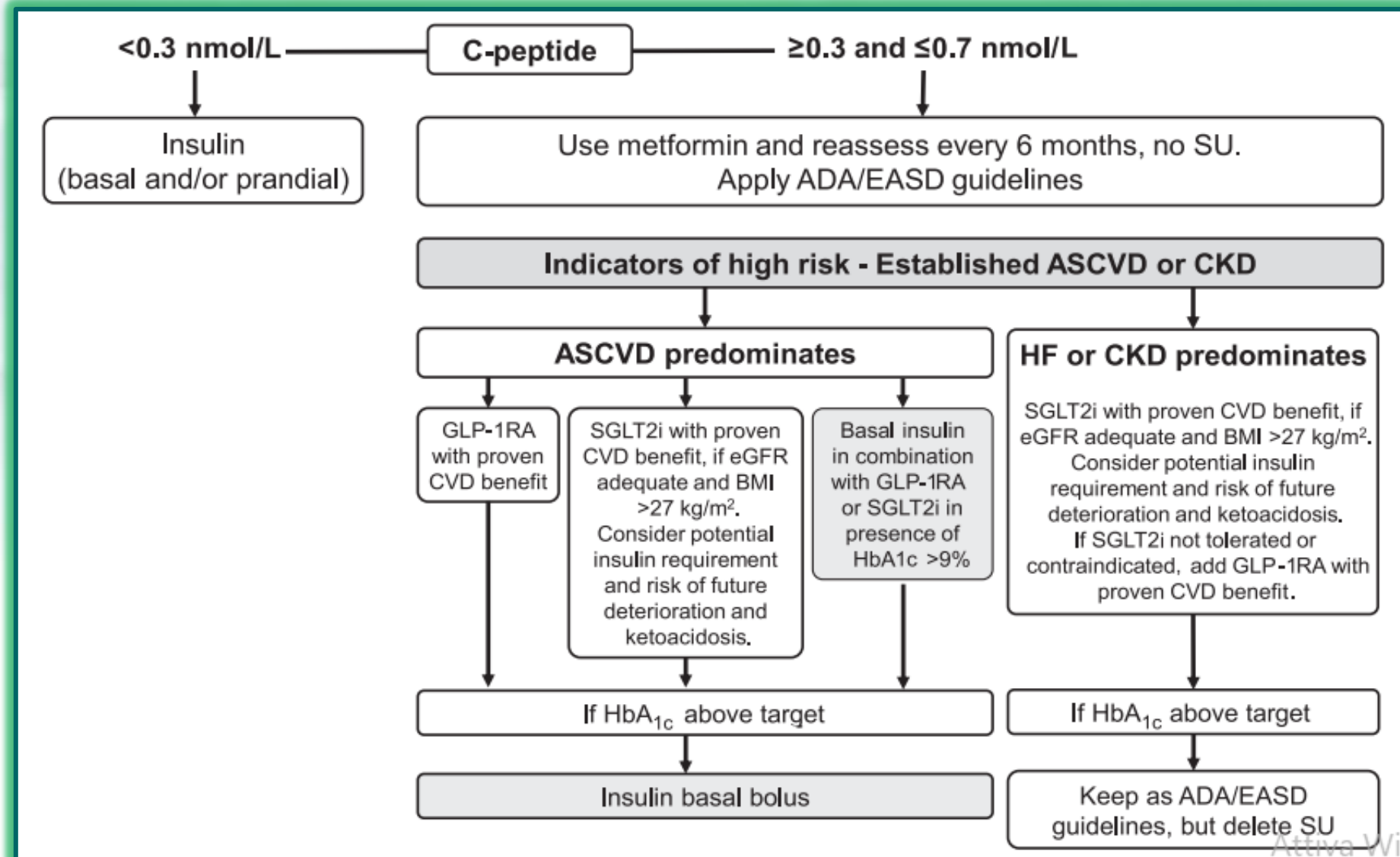


Management of Latent Autoimmune Diabetes in Adults: A Consensus Statement From an International Expert Panel

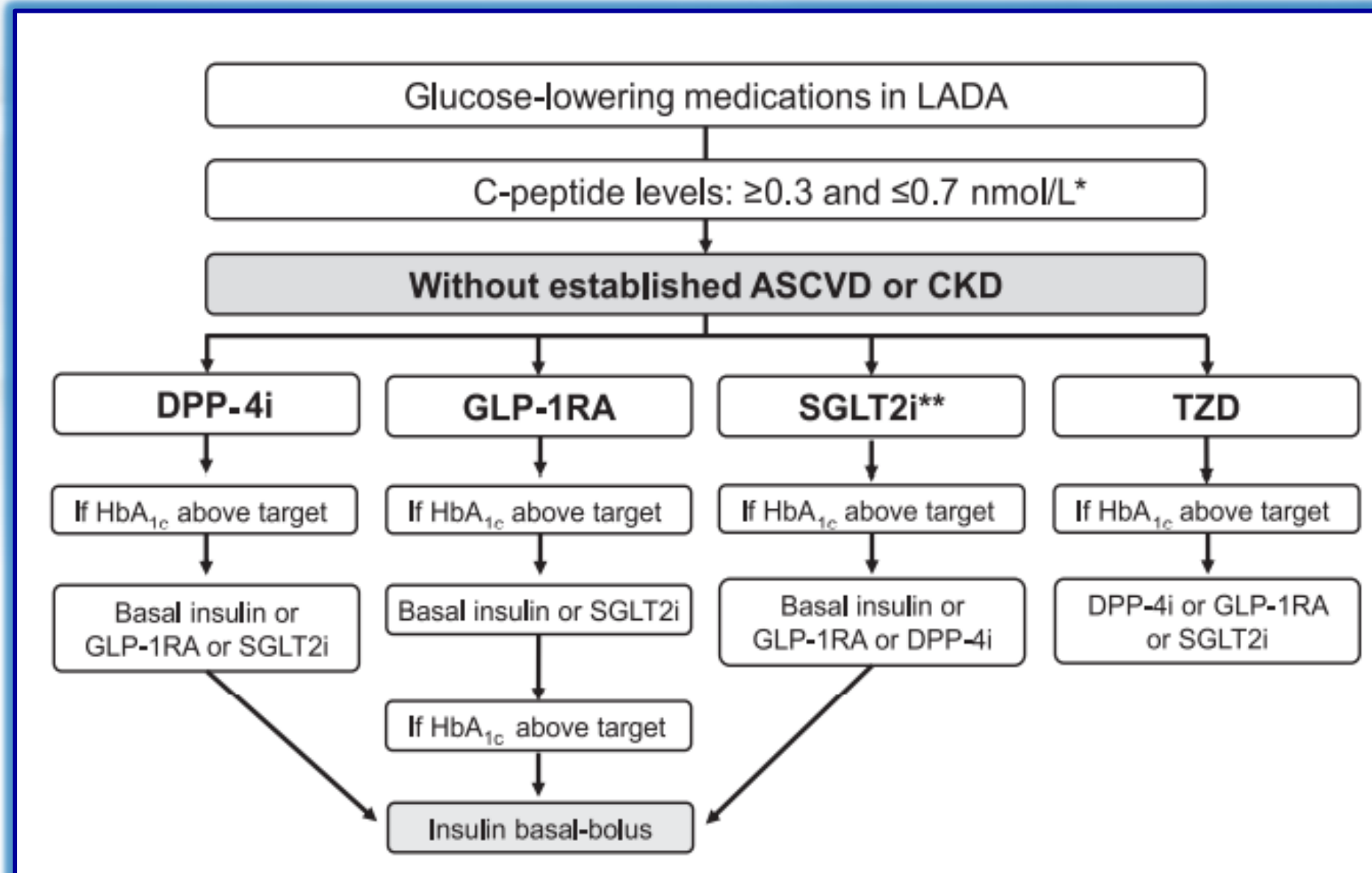
Raffaella Buzzetti,¹ Tiinamaija Tuomi,^{2,3} Didac Mauricio,⁴ Massimo Pietropaolo,⁵ Zhiguang Zhou,⁶ Paolo Pozzilli,^{7,8} and Richard David Leslie⁸

Diabetes 2020;69:1–11 | <https://doi.org/10.2337/dbi20-0017>

Algorithm for glucose-lowering medications in LADA patients with C-peptide < 0.3 nmol/L or with C-peptide ≥ 0.3 and ≤ 0.7 nmol/L

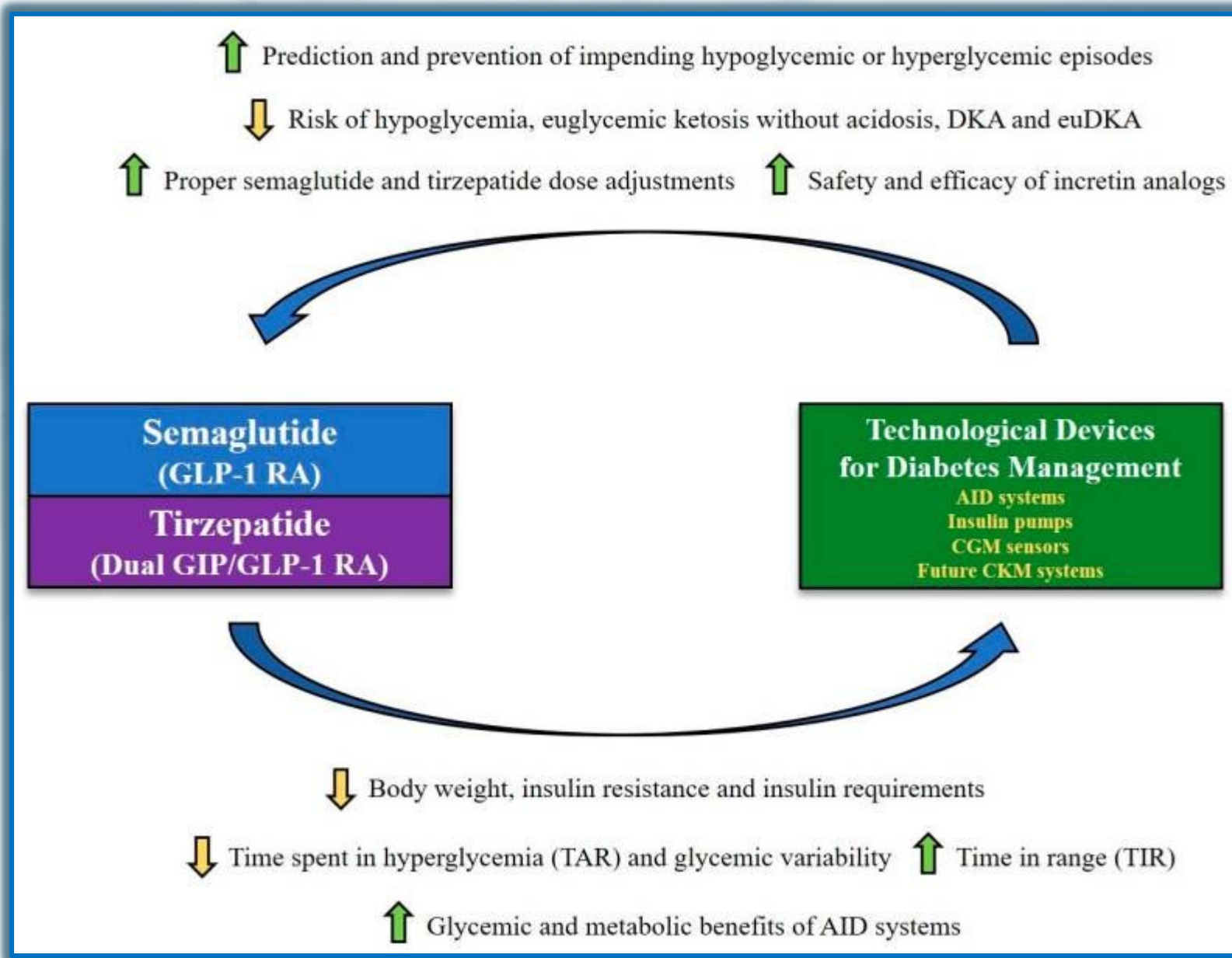


Algorithm for glucose-lowering medications in LADA patients with C-peptide levels ≥ 0.3 and ≤ 0.7 nmol/L without established ASCVD



Unveiling the Therapeutic Potential of the Second-Generation Incretin Analogs Semaglutide and Tirzepatide in T1D and Latent Autoimmune Diabetes in Adults

Potential synergistic benefits of second-generation incretin analogs (semaglutide and tirzepatide) and advanced technological devices used for diabetes management in patients with T1D, double diabetes and LADA.



Conclusions

- In conclusion, the adoption of metabolic-based interventions alongside insulin therapy holds strong promise for advancing T1D treatment by addressing the significant limitations of traditional insulin monotherapy.
- These adjunctive therapies for the increased obesity in T1D offer novel pathways to improve glucose control and reduce insulin dose, while also holding potential to delay or even preserving residual β -cell function.
- The use of GLP-1RAs and SGLT-2i will become an additional treatment to insulin in overweight/obese T1D improving metabolic control and modify disease trajectories.