

# II DIABETE OGGI:

UNA MALATTIA SEMPRE PIÙ COMPLESSA

**Quando l'obesità coesiste  
con il diabete di tipo 1**

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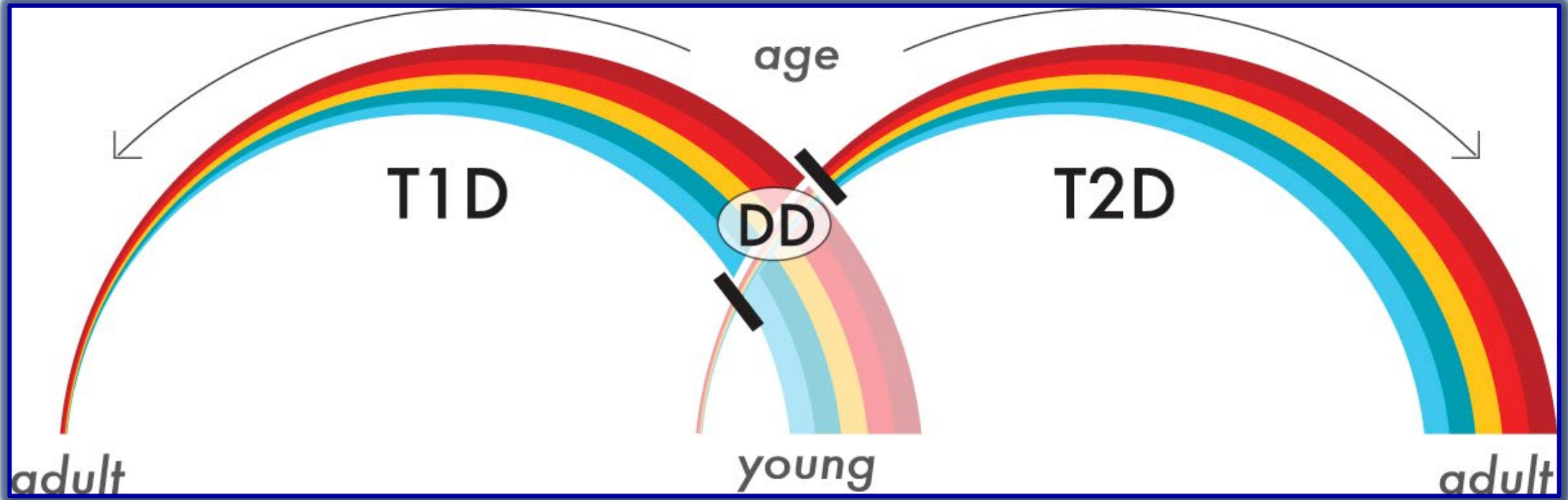
## DISCLOSURE STATEMENT

Speakers Name: Prof. Paolo Pozzilli

☒ I have the following potential conflicts of interest to report:

- **Advisory Board Member:** Dompè, Altheia
- **Consulting Fee:** Sanofi, Eli Lilly & Company.
- **Grant Recipient:** Amgen Inc, Sanofi, Dompè, Abbott, Novo Nordisk
- **Speaker:** Eli Lilly & Company, Dompè

## A new expression of diabetes: double diabetes



The incidence of both type 1 and type 2 diabetes has shown a rise, in parallel with a notable increase in the incidence of a new expression of the disease in children and adolescents, with the characteristics of a mixture of the two types of diabetes, and referred to as 'double diabetes'.

Insulin resistance and obesity, together with the presence of markers of pancreatic autoimmunity - namely, autoantibodies to islet cell antigens - typically define this condition.

Received: 6 December 2019

Revised: 4 March 2020

Accepted: 5 March 2020

DOI: 10.1111/dom.14022

## **COMMENTARY**

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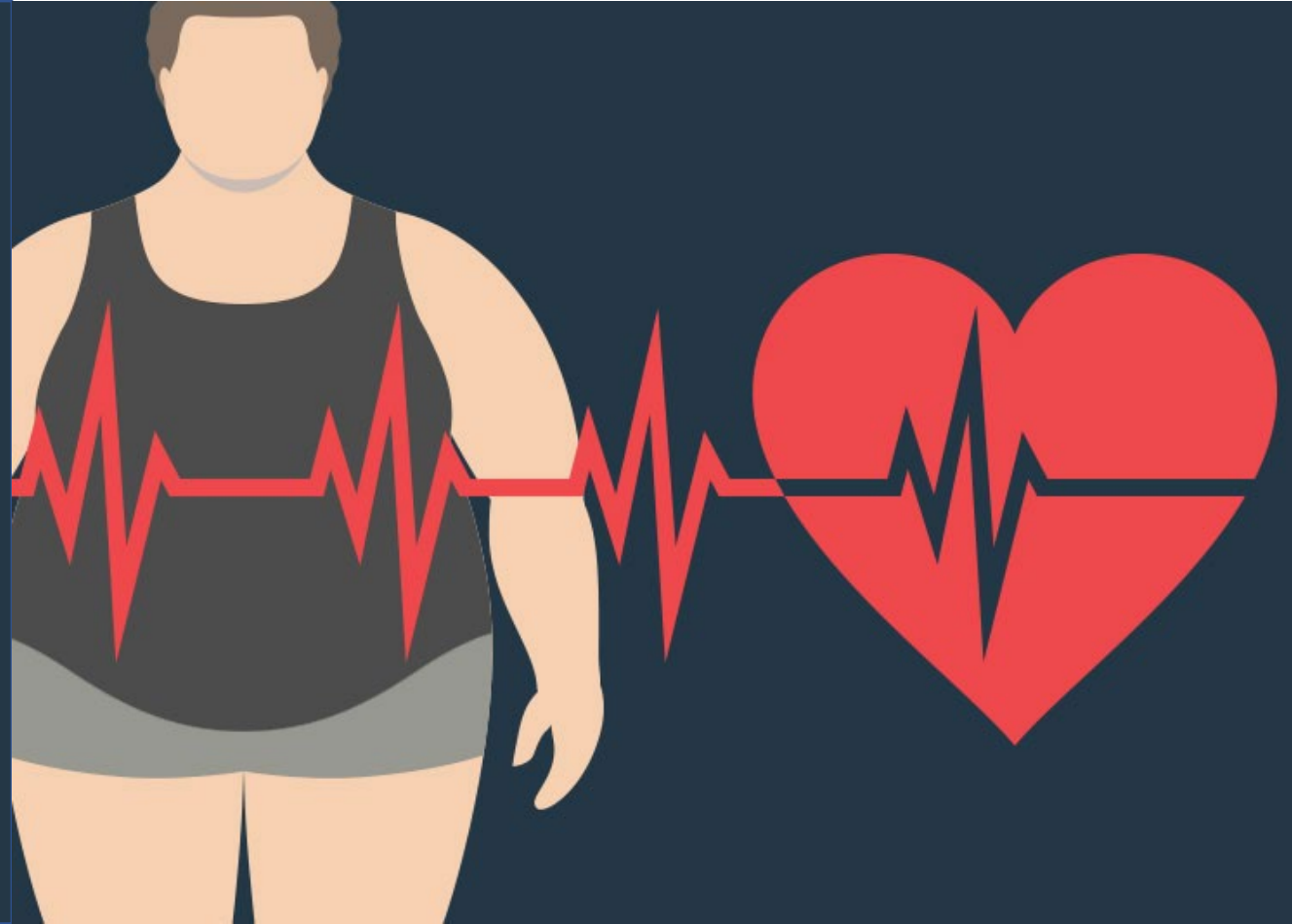
# **Impact of obesity on the increasing incidence of type 1 diabetes**

Raffaella Buzzetti MD<sup>1</sup> | Simona Zampetti PhD<sup>1</sup> | Paolo Pozzilli MD<sup>2,3</sup> 

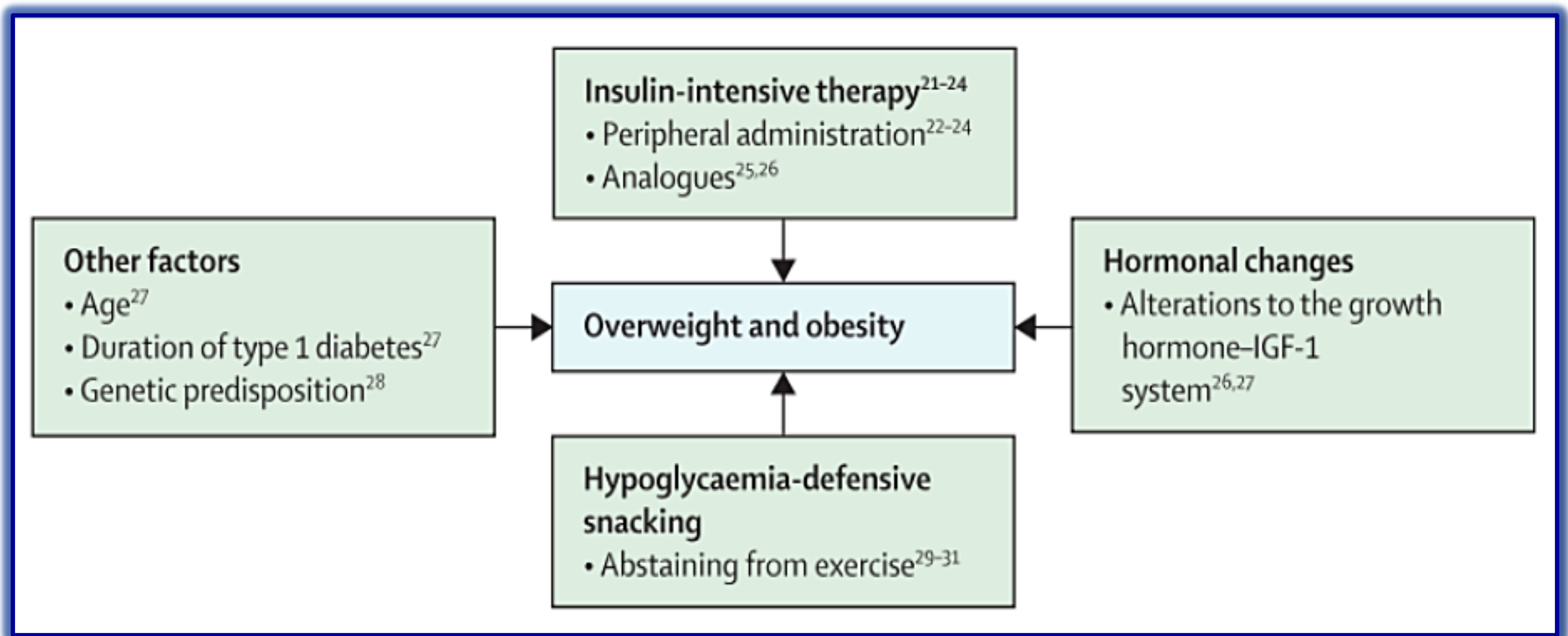
# Obesity and type 1 diabetes

Obesity affects large numbers of patients with type 1 diabetes (T1D) across their lifetime, with rates ranging between 2.8% and 37.1%

Patients with T1D and obesity are characterized by presence of insulin resistance, high insulin requirements, a greater cardio-metabolic risk and an enhanced risk of developing chronic complications when compared to normal-weight people with T1D.

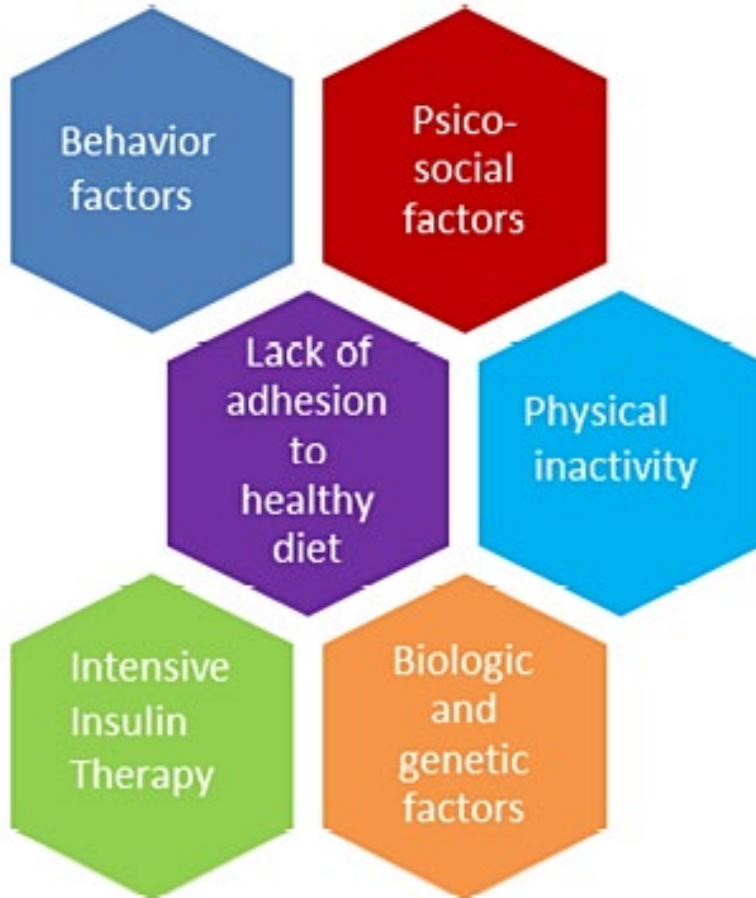
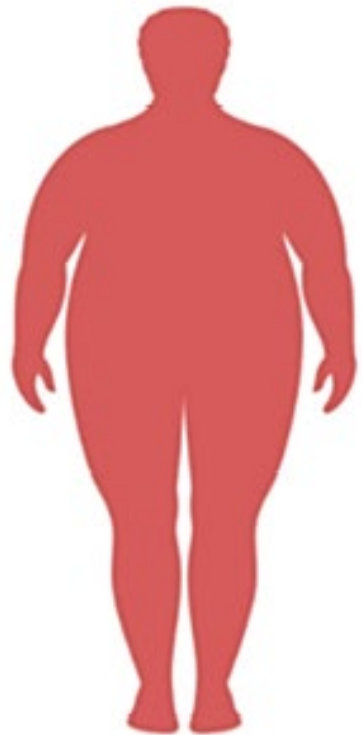


# Drivers of overweight and obesity in people living with T1D



**The drivers of weight gain in people with T1D are several and complex.**

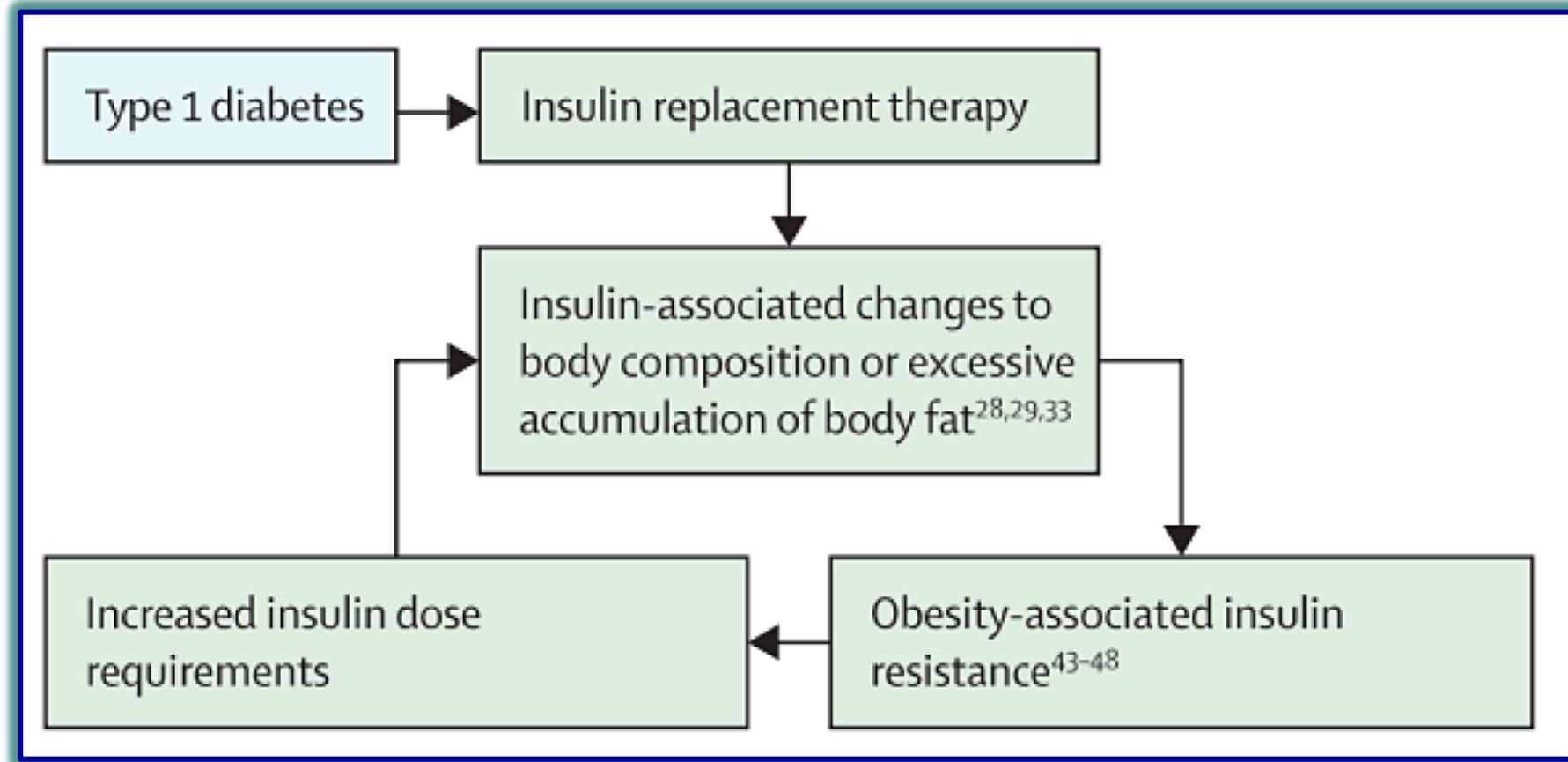
# Causes of Increasing Prevalence of Obesity in T1D



**The trigger** of the increasing prevalence of obesity in T1D **is the obesogenic environment.**

Obesity is a complex multifactorial chronic disease; besides unhealthy habits, other exogenous factors such as the presence of altered eating behaviour, eating disorders, short sleep duration, chronic stress and other psychosocial factors are implicated in its aetiology.

# The vicious cycle of insulin-associated weight gain

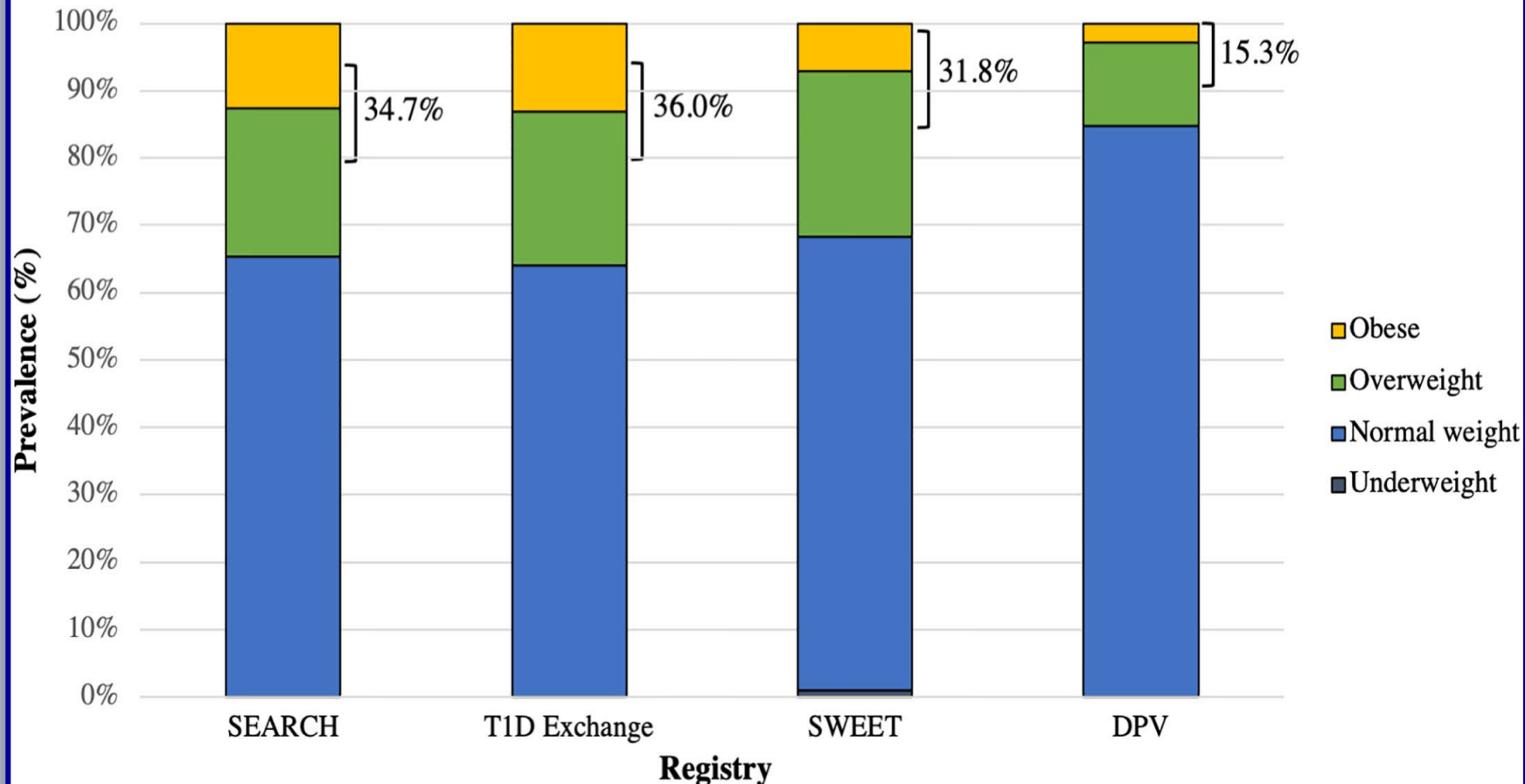


Insulin replacement therapy is believed to be one of the biggest contributors to weight gain in T1D patients.

Weight gain associated with intensive insulin therapy increases insulin resistance, leading to increased insulin dose requirement, which promotes further insulin-associated weight gain.

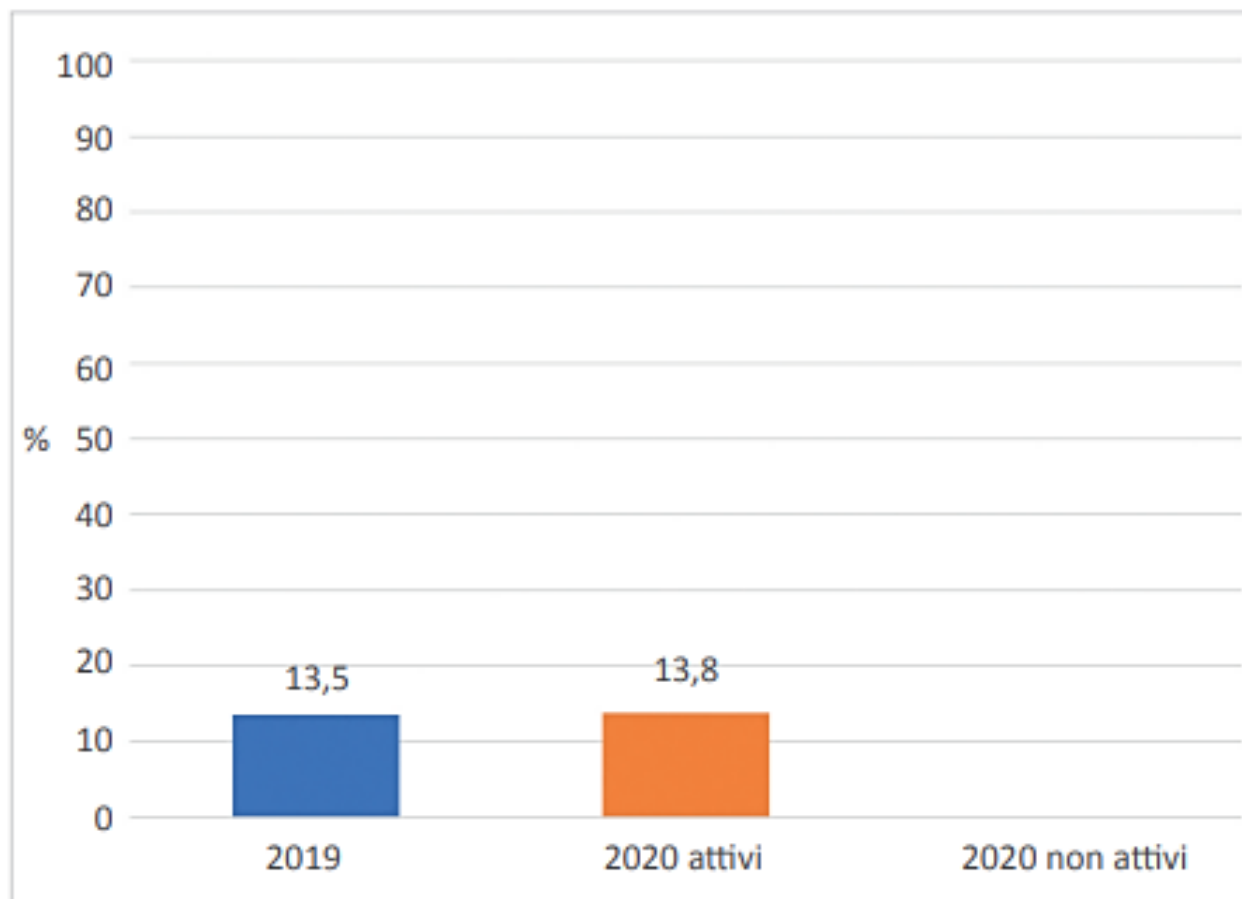
# Obesity in Children and Adolescents With Type 1 Diabetes

**Prevalence of Normal Weight, Overweight, and Obesity in Pediatric Type 1 Diabetes Across Four Registries**



With the increasing incidence of both T1D and obesity, the prevalence of overweight and obesity in youths with T1D at diagnosis has also increased.

Unlike T2D, where obesity is a known risk factor, children with new-onset T1D in the past were not overweight at diagnosis and traditionally thought to be thin.

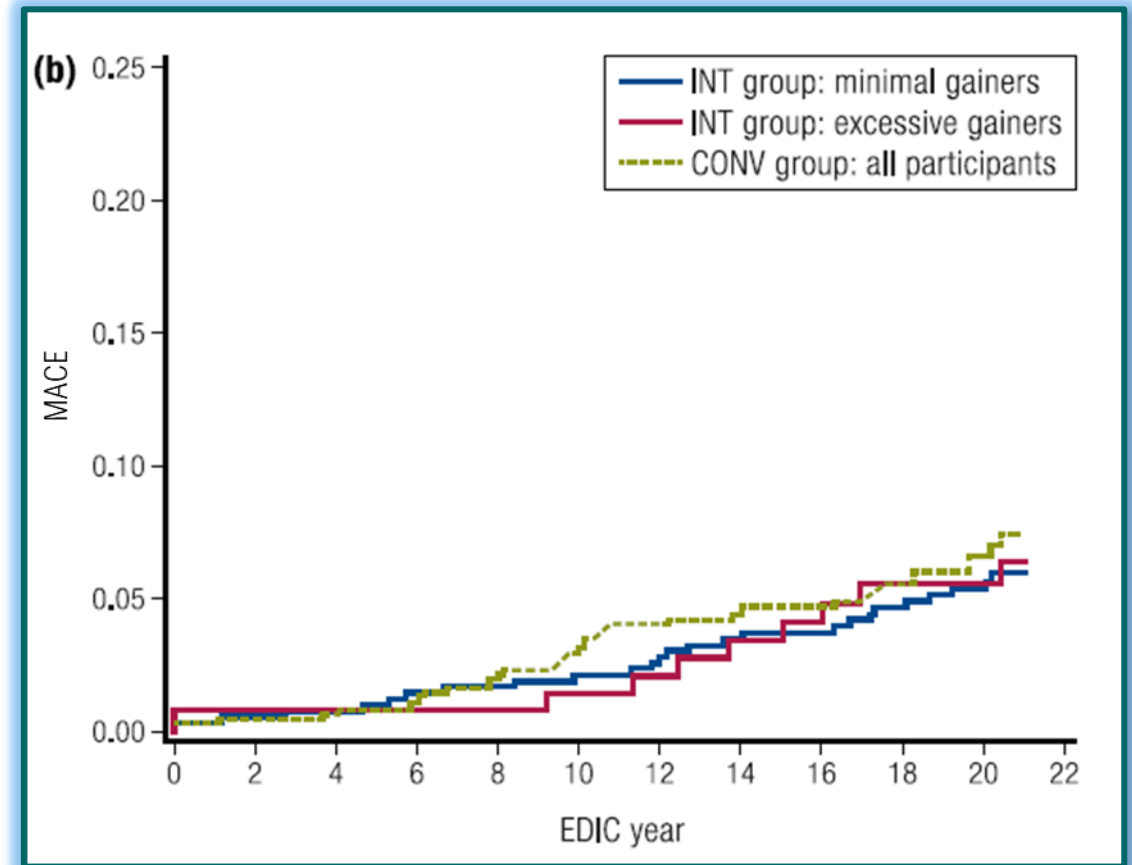
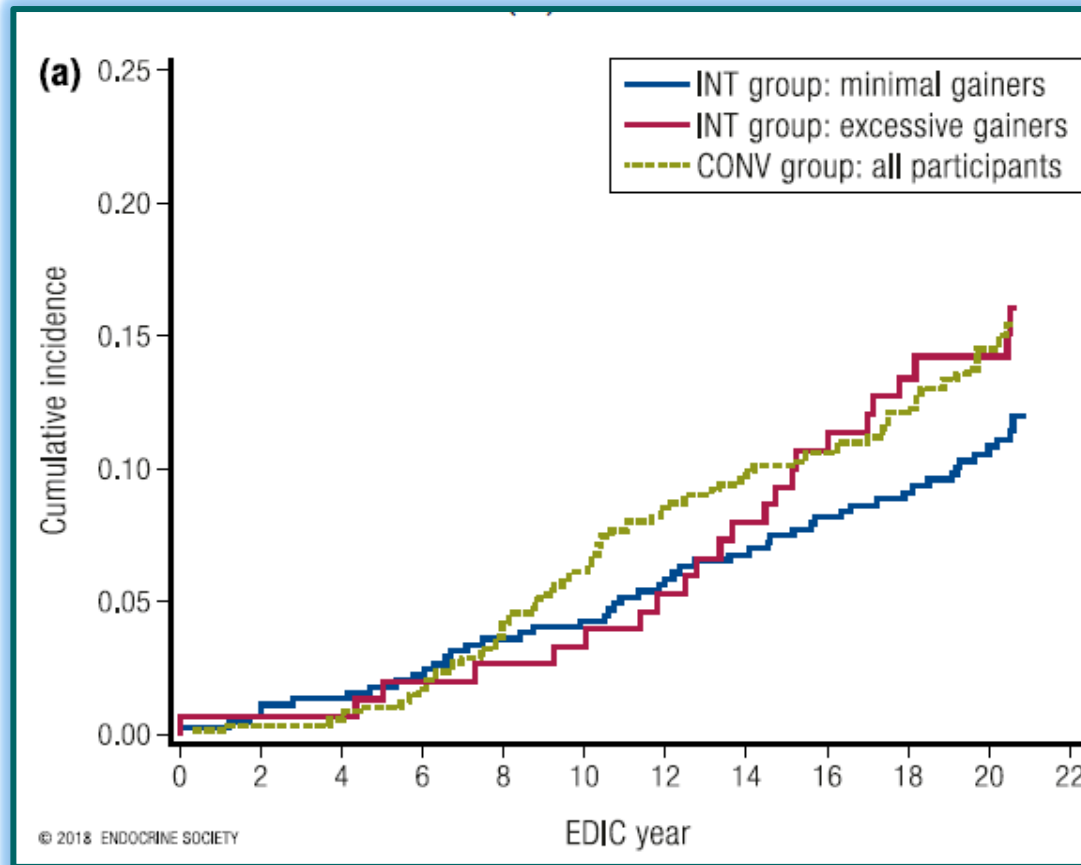
**Soggetti con BMI  $\geq 30$  Kg/m<sup>2</sup>**

Complessivamente, il 13,5% della popolazione con DM1 è risulta obesa nel 2019. Nel 2020, la percentuale è risultata analoga.

## Consequences of overlapping T1D and obesity complications

| T1D complications                                                                         | Obesity complications                                                                                                                                              | Consequences of overlapping                                                                    |
|-------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| Macrovascular: atherosclerosis, thrombosis<br>atherogenic lipid profile<br>Hyperglycaemia | Dyslipidemia Increased coronary artery calcium index<br>Increased thickness of intima-media<br>Insulin resistance Abdominal obesity Hyperlipidemia<br>Hypertension | Hypertension Increased risk of premature cardiovascular diseases Strokes<br>Metabolic syndrome |
| Hyperglycaemia                                                                            | Adipose tissue dysfunction Elevated alanine<br>aminotransferase                                                                                                    | NAFLD-> CVD events, polyneuropathy, incidence of<br>chronic kidney diseases                    |
| Impaired glucose tolerance Hyperinsulinemia                                               | Dyslipidemia Insulin resistance Psychological comorbidities                                                                                                        | PCOS: problems with fertility or higher risk for the<br>development of endometrial cancer      |
| Increased risk of nephropathy and<br>albuminuria                                          | High blood cholesterol<br>Albuminuria                                                                                                                              | Kidney diseases, including end-stage renal disease                                             |

# Weight gain impacts cardiovascular event rates after 14 years of follow-up in the EDIC trial



At year 14 of EDIC, the cardiovascular event curves began to diverge in the intensive insulin therapy group only through the 20-year follow-up.

A Cox proportional hazard model showed that after year 14, the cardiovascular events in the intensive insulin therapy group (INT) with the most weight gain were significantly higher than the minimal weight gain group.

# Preventing and treating excessive weight gain in people living with T1D

## Diet and exercise

- Risk of hypoglycaemia might influence defensive snacking and exercise absenteeism
- Weight regain is likely with wavering commitment to treatment



## Pharmaceuticals

- Restricted by market authorisations
- Require chronic use
- High cost and inadequate reimbursement
- Issues with tolerability
- SGLT inhibitors associated with diabetic ketoacidosis risk
- GLP-1 receptor agonists require additional injections



## Bariatric surgery

- Increased risk of hypoglycaemia and diabetic ketoacidosis
- Under-researched



Many weight management strategies for people living with diabetes have been implemented for T2D.

Whether or not these same strategies are effective for people living with T1D is unknown.

All approaches to weight loss present specific difficulties for people living with T1D: Hypoglycaemia when fasting, cutting carbohydrates, or during exercise.

# A review of potential adjuvant pharmacological therapies to insulin in obese patients with T1D

| Name of the drug               | Mechanism of action                                                                                                                                        | The benefits for obese patients with T1DM                                                                                                         | Side effects                                                                                                             |
|--------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|
| <b>Metformin</b>               | <ul style="list-style-type: none"> <li>Reducing gluconeogenesis in the liver, promoting glucose uptake in peripheral tissues</li> </ul>                    | <ul style="list-style-type: none"> <li>Reducing cardiovascular risk, improving insulin sensitivity, reducing weight, BMI and adiposity</li> </ul> | <ul style="list-style-type: none"> <li>Increased prevalence of minor gastrointestinal side effects</li> </ul>            |
| <b>GLP-1 receptor agonists</b> | <ul style="list-style-type: none"> <li>Increasing the secretion of insulin and decreasing the release of glucagon in a glucose-dependent manner</li> </ul> | <ul style="list-style-type: none"> <li>Reducing HbA1c, BMI, fasting and postprandial blood glucose levels and insulin dose</li> </ul>             | <ul style="list-style-type: none"> <li>Increased prevalence of gastrointestinal side effects</li> </ul>                  |
| <b>DPP-4 inhibitors</b>        | <ul style="list-style-type: none"> <li>Inhibition of GLP-1 degradation</li> </ul>                                                                          | <ul style="list-style-type: none"> <li>No significant effect on the reduction of HbA1c, body weight, BMI or insulin dose</li> </ul>               | <ul style="list-style-type: none"> <li>Unknown</li> </ul>                                                                |
| <b>Pramlintide</b>             | <ul style="list-style-type: none"> <li>Decreasing postprandial glucagon output, delaying gastric emptying, promoting satiety</li> </ul>                    | <ul style="list-style-type: none"> <li>Improving glycaemic control, reducing insulin dose and body weight</li> </ul>                              | <ul style="list-style-type: none"> <li>Transient hypoglycemia, gastrointestinal side effects</li> </ul>                  |
| <b>SGLT-2 inhibitors</b>       | <ul style="list-style-type: none"> <li>Inhibiting glucose reabsorption in proximal tubule of nephron</li> </ul>                                            | <ul style="list-style-type: none"> <li>Reduction in HbA1c level, body weight and total daily insulin dose</li> </ul>                              | <ul style="list-style-type: none"> <li>Euglycemic diabetic ketoacidosis, urinary tract and genital infections</li> </ul> |

# GLP-1 RA liraglutide as adjunct therapy in people living with T1D

|                                                                | ADJUNCT-ONE <sup>73</sup> (n=1398; 52 week follow-up; randomisation 3:1) |                         |                        | ADJUNCT-TWO <sup>74</sup> (n=835; 26 week follow-up; randomisation 3:1) |                         |                         |                    |
|----------------------------------------------------------------|--------------------------------------------------------------------------|-------------------------|------------------------|-------------------------------------------------------------------------|-------------------------|-------------------------|--------------------|
|                                                                | Liraglutide 1.8 mg                                                       | Liraglutide 1.2 mg      | Liraglutide 0.6 mg     | Liraglutide 1.8 mg                                                      | Liraglutide 1.2 mg      | Liraglutide 0.6 mg      | Placebo            |
| Mean effect on body weight, kg                                 | -4.90 (-5.70 to -4.20)                                                   | -3.60 (-4.30 to -2.80)  | -2.20 (-2.90 to -1.50) | -5.10 vs baseline*                                                      | -4.00 vs baseline*      | -2.50 vs baseline*      | -0.20 vs baseline* |
| Mean effect on HbA <sub>1c</sub>                               | -0.20% (-0.32 to -0.07)                                                  | -0.15% (-0.27 to -0.03) | -0.09% (-0.21 to 0.03) | -0.35% (-0.50 to -0.20)                                                 | -0.23% (-0.38 to -0.08) | -0.24% (-0.39 to -0.10) | NA                 |
| Estimated treatment ratio for effect on insulin dosage         | 0.92 (0.88 to 0.96)                                                      | 0.95 (0.91 to 0.99)     | 1.00 (0.96 to 1.04)    | 0.90% (0.86 to 0.93)                                                    | 0.93% (0.90 to 0.96)    | 0.95% (0.92 to 0.99)    | NA                 |
| Estimated treatment ratio for symptomatic hypoglycaemic events | 1.31 (1.07 to 1.59)                                                      | 1.27 (1.03 to 1.55)     | 1.17 (0.97 to 1.43)    | NS                                                                      | 1.33 (1.07 to 1.67)     | NS                      | NA                 |

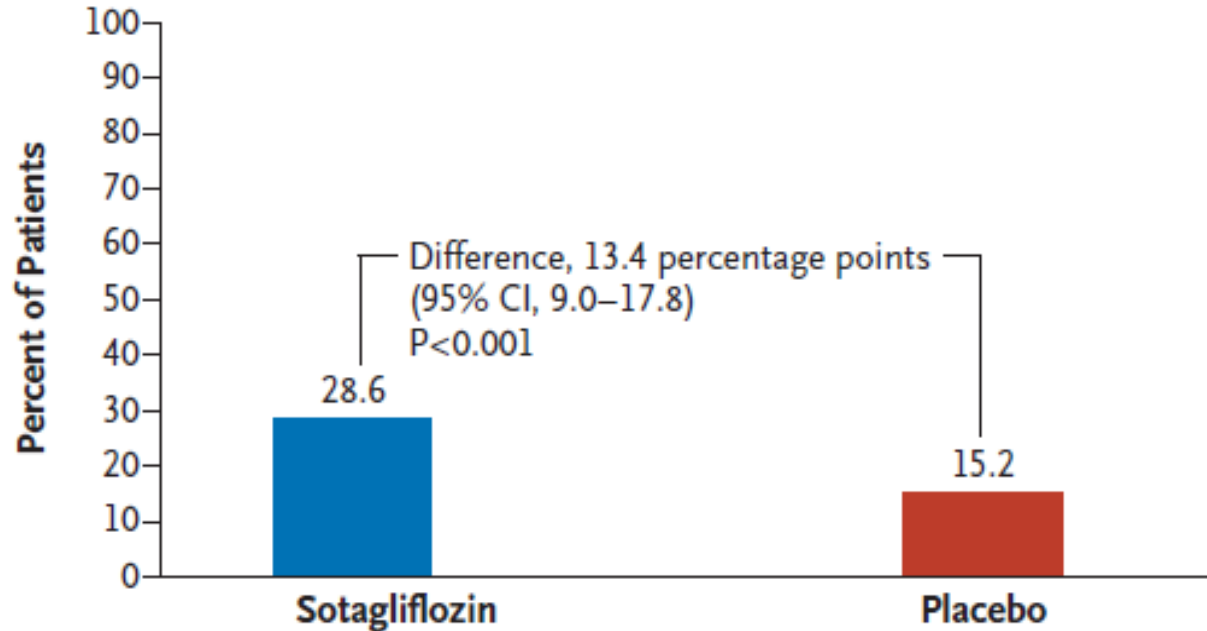
Data are mean (95% CI) or estimated treatment ratio (95% CI) for comparison against placebo, unless otherwise stated. NA=not applicable. NS=not significant versus placebo (actual p value not reported). Symptomatic hypoglycaemic events are typical symptoms of hypoglycaemia plus a measured plasma glucose concentration  $\leq 70$  mg/dL. \*p<0.0001.

## SGLT-2 inhibitors as adjunct therapy in people living with T1D

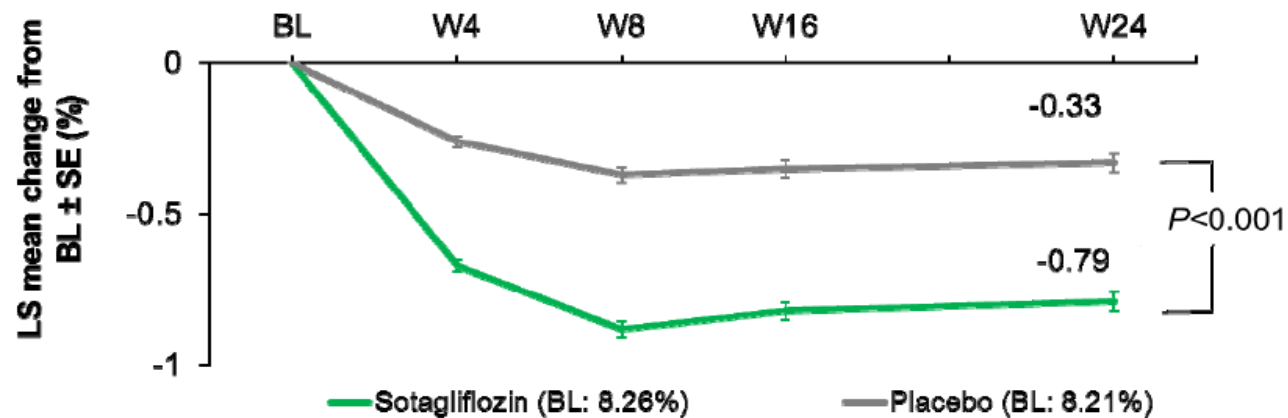
|                                        | Pooled analysis of DEPICT-1 and DEPICT-2 studies <sup>78</sup> |                                    |         | Phase 3 trial <sup>79</sup> (n=175)               | Pooled analysis of Tandem1 <sup>80</sup> and Tandem2 <sup>81</sup> (n=1575) |                                                    |         |
|----------------------------------------|----------------------------------------------------------------|------------------------------------|---------|---------------------------------------------------|-----------------------------------------------------------------------------|----------------------------------------------------|---------|
|                                        | Dapagliflozin 5 mg/day<br>(n=548)*                             | Dapagliflozin 10 mg/day<br>(n=566) | Placebo | Ipragliflozin 50 mg/day                           | Sotagliflozin 200 mg/day                                                    | Sotagliflozin 400 mg/day                           | Placebo |
| Effect on bodyweight                   | -3.11% (-3.61 to -2.62)                                        | -3.71% (-4.20 to -3.22)            | NA      | -2.87 kg (-3.58 to -2.16)                         | -2.17% (-2.54 to -1.80)                                                     | -3.02% (-3.39 to -2.65)                            | NA      |
| Effect on HbA <sub>1c</sub>            | -0.41% (-0.48 to -0.31)                                        | -0.43% (-0.52 to -0.34)            | NA      | -0.36% (-0.57 to -0.14)                           | -0.36% (-0.44 to -0.29)                                                     | -0.38% (-0.45 to -0.31)                            | NA      |
| Effect on insulin dosage               | -9.57% (-12.01 to -7.07)                                       | -11.75% (-14.13 to -9.30)          | NA      | -7.35 IU (-9.09 to -5.61)                         | 7.10 % (SE 1.30); p<0.001 vs placebo at 52 weeks                            | -10.33 % (SE 1.30); p<0.001 vs placebo at 52 weeks | NA      |
| Adverse events: diabetic ketoacidosis† | 2.00%                                                          | 1.90%                              | 0.60%   | No diabetic ketoacidosis reported in either group | 2.90 %                                                                      | 3.80 %                                             | 0.20 %  |

Data are mean (95% CI) for comparison with placebo at 24 weeks, unless otherwise stated. Dapagliflozin is an SGLT2 inhibitor approved for use in Europe and Japan. Ipragliflozin is an SGLT2 inhibitor approved for use in Japan. Sotagliflozin is a dual SGLT1/2 inhibitor approved by the European Medicines Agency. NA=not applicable. IU=international units. \*p<0.0001. †Other adverse events were not reported consistently between studies.

### A Primary End Point



### B Glycated Hemoglobin Level

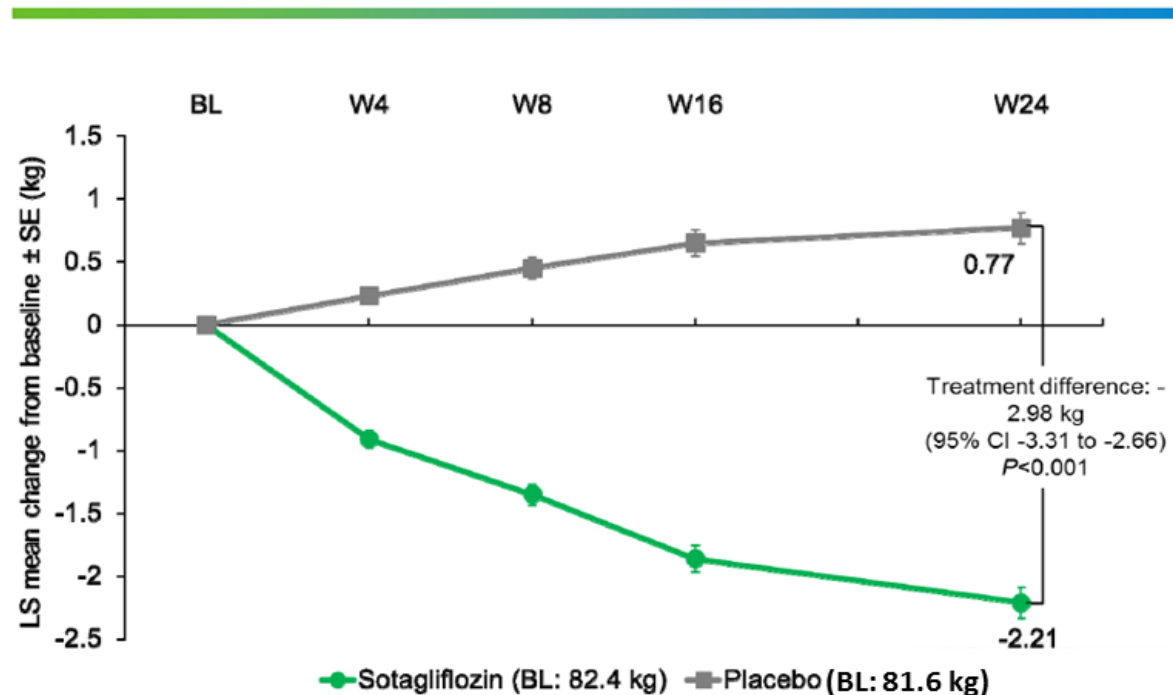


**In TANDEM-3 Trial  
Sotagliflozin in T1D  
with mean BMI 28.6**

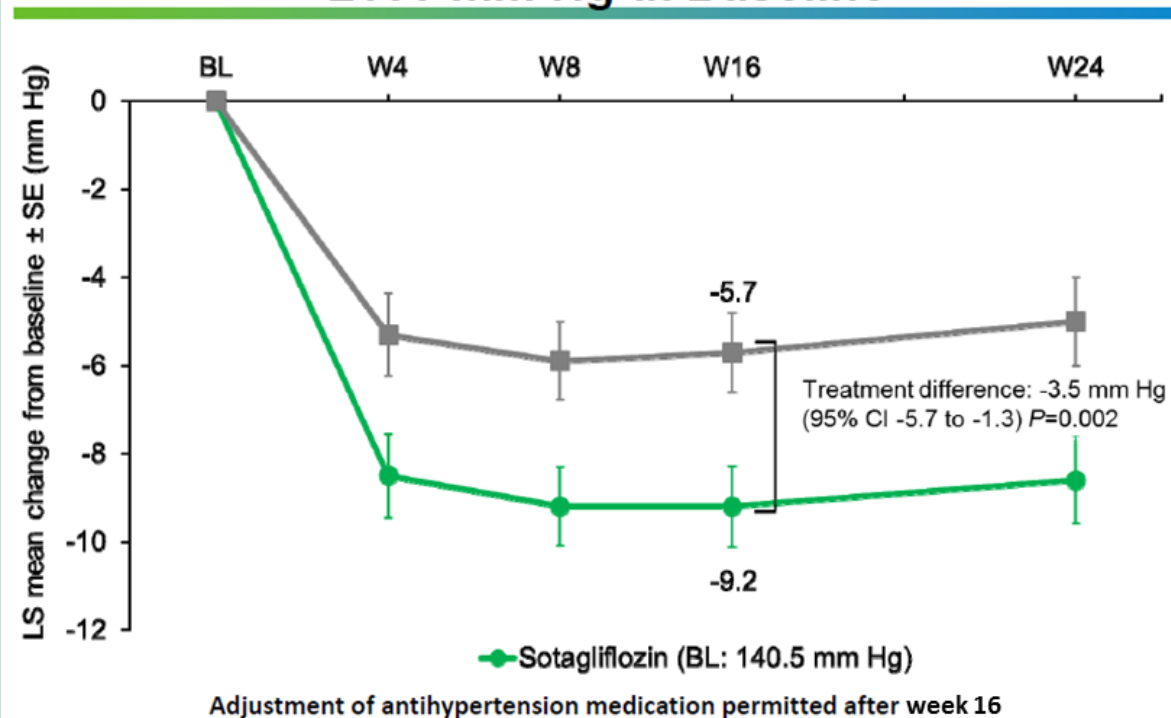
Among patients with type 1 diabetes who were receiving insulin, the proportion of patients who achieved a glycated hemoglobin level lower than 7.0% with no severe hypoglycemia or diabetic ketoacidosis was larger in the group that received sotagliflozin than in the placebo group.

## In TANDEM-3 Trial Sotagliflozin in T1D with mean BMI 28.6

### Body Weight



### Systolic Blood Pressure in Patients With SBP $\geq 130$ mm Hg at Baseline



# Conclusions

Genetic risk and environmental factors may lead to coexisting features of type 1 and 2 diabetes, with added implications for both pathogenesis and long-term health: Double Diabetes.

Overweight and obesity are increasingly common in youth and adults with T1D, perhaps a consequence of changing cultural practices surrounding diet, nutrition and exercise over the past several decades.

In the setting of widespread use of intensive insulin therapy, poor dietary choices and over-treatment of hyperglycemia may both contribute to weight gain.

There is limited evidence for a beneficial effect of currently available adjuvant therapies apart from lifestyle adjustments and SGLT2 inhibitors (off label). These all need further investigation for both the delay of T1D and the prevention of complications in those patients with double diabetes.