Diabete di tipo 1: Come sta cambiando l'epidemiologia e cosa ci dicono le linee guida

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DISCLOSURE STATEMENT

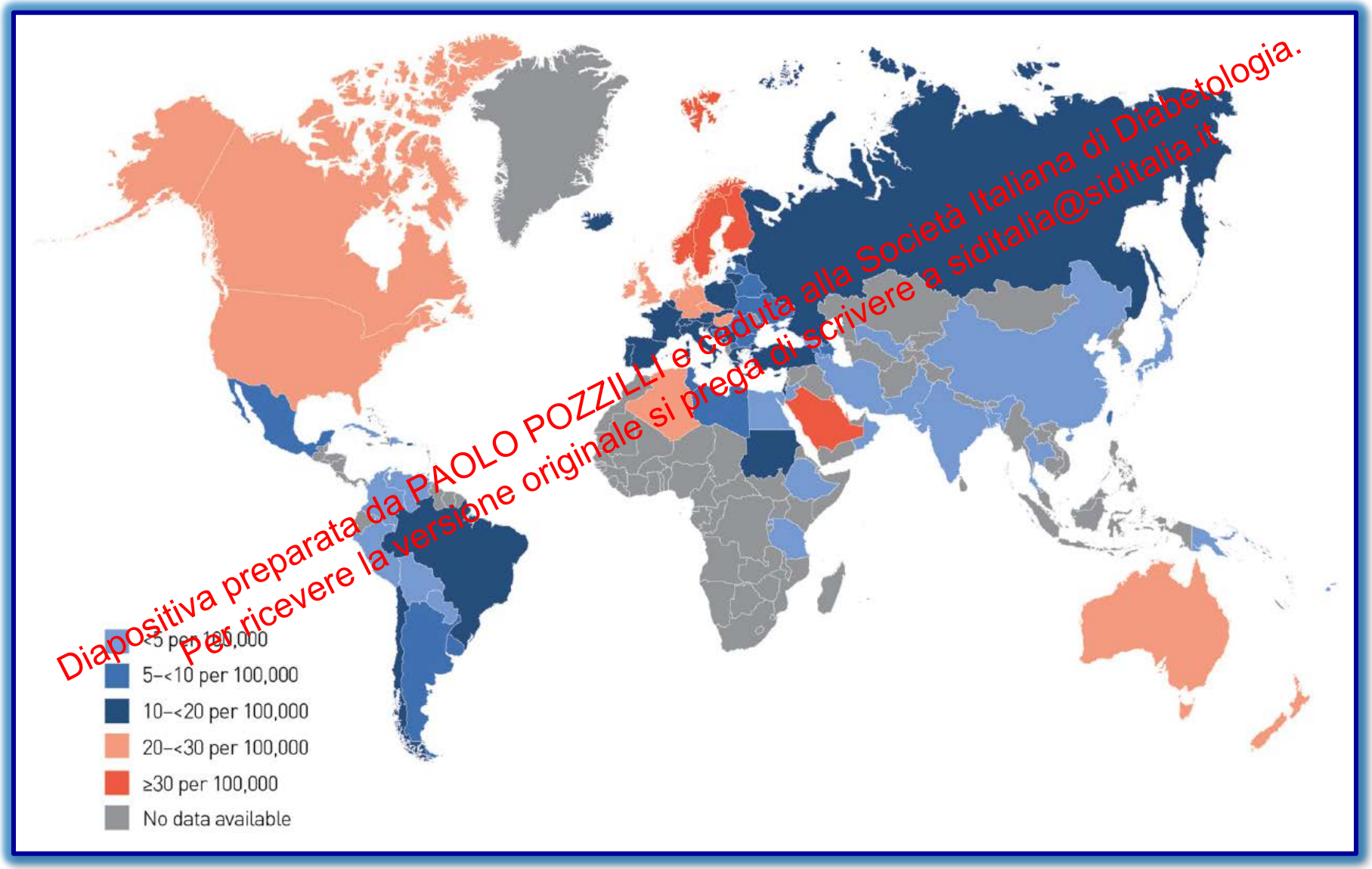
Speakers Name: Prof. Paolo Pozzilli

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

- ☒ Research Contracts
- ☒ Consulting
- ☐ Employment in the Industry
- ☐ Stockholder of a healthcare company
- ☐ Owner of a healthcare company
- ☐ Other(s)

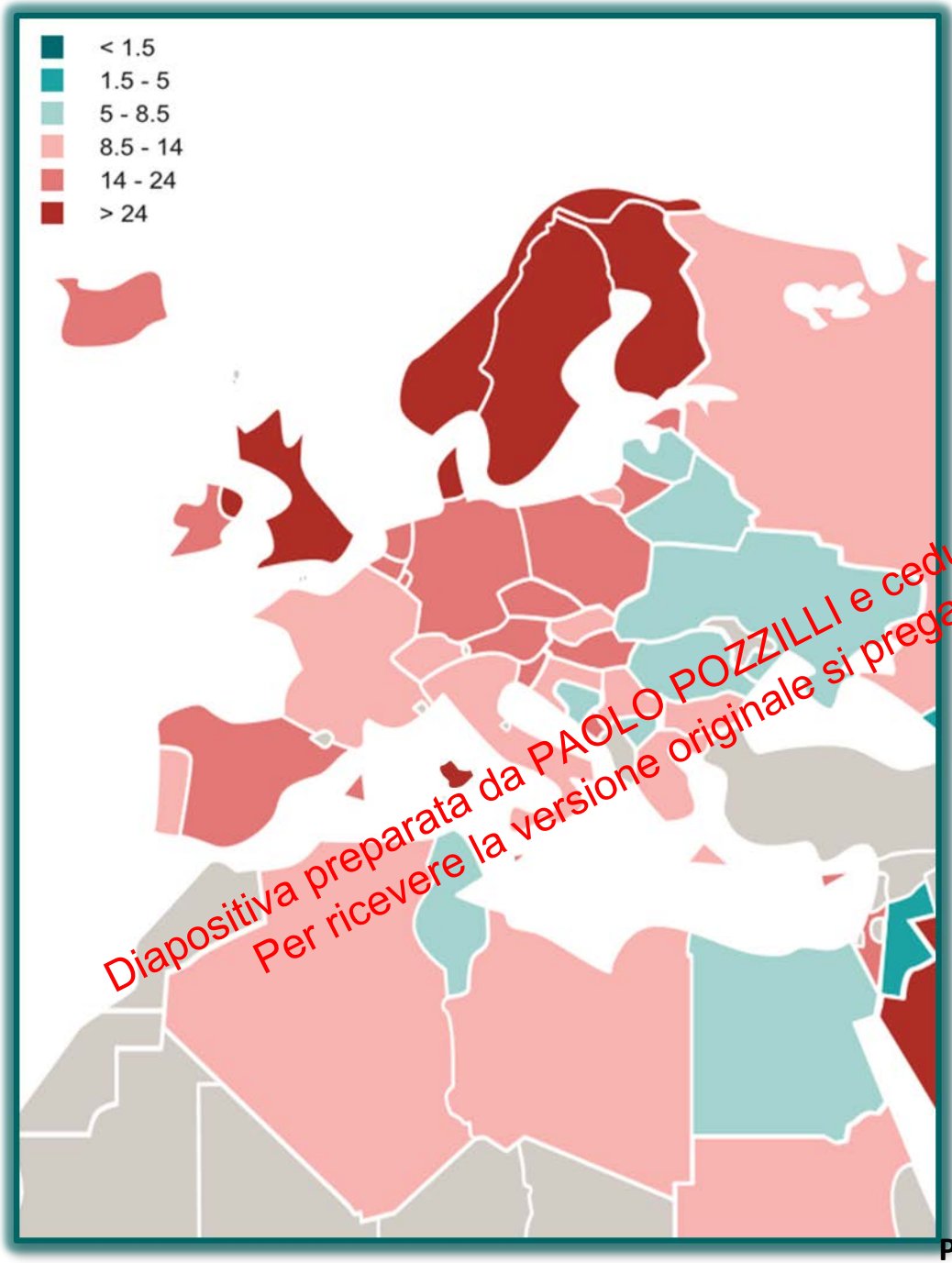
Eli Lilly, Sanofi, Merck Sharp & Dohme, AstraZeneca, Boehringer Ingelheim, GSK

Map of age-sex standardised incidence rates (per 100,000) from publications of T1D in children aged under 15 years



IDF ATLAS 9th edition, 2019

Geographical distribution of T1D in Europe



Rates are generally highest in European Caucasian populations, particularly in **Northern Europe**

One salient exception is located in one region of southern Europe, **Sardinia**.

The population of this Italian island, home to the most ancient human settlements in the Mediterranean area, possesses a well-preserved particular genetic composition that is unique in the European phylogenetic tree.

Patterson C. Diabetes Research and Clinical Practice 2014

Type 1 diabetes in Italy

Italy is one of the 43 countries of the IDF EUR region.

425 million people have diabetes in the world and more than 38 million people in the EUR Region; by 2045 this will rise to 66.7 million.

There were 3.402.300 cases of diabetes in Italy in 2017.

Total adult population: 44.517.00

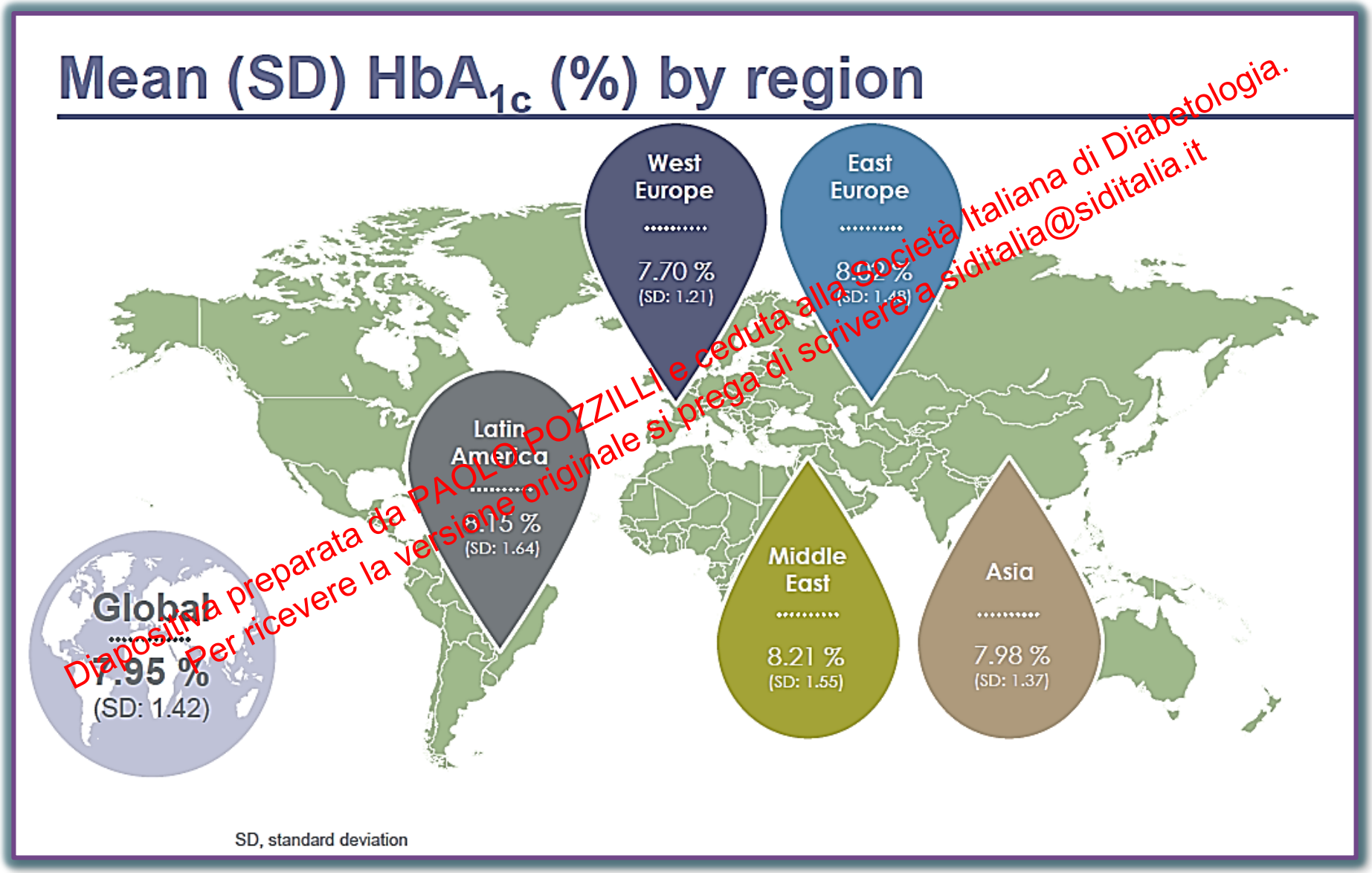
Prevalence of diabetes in adults: 7.6%

Total cases of diabetes in adults: 3.402.300

Total cases of type 1 diabetes in adults: 304.230

DATI ISTAT 2018; IDF 2018

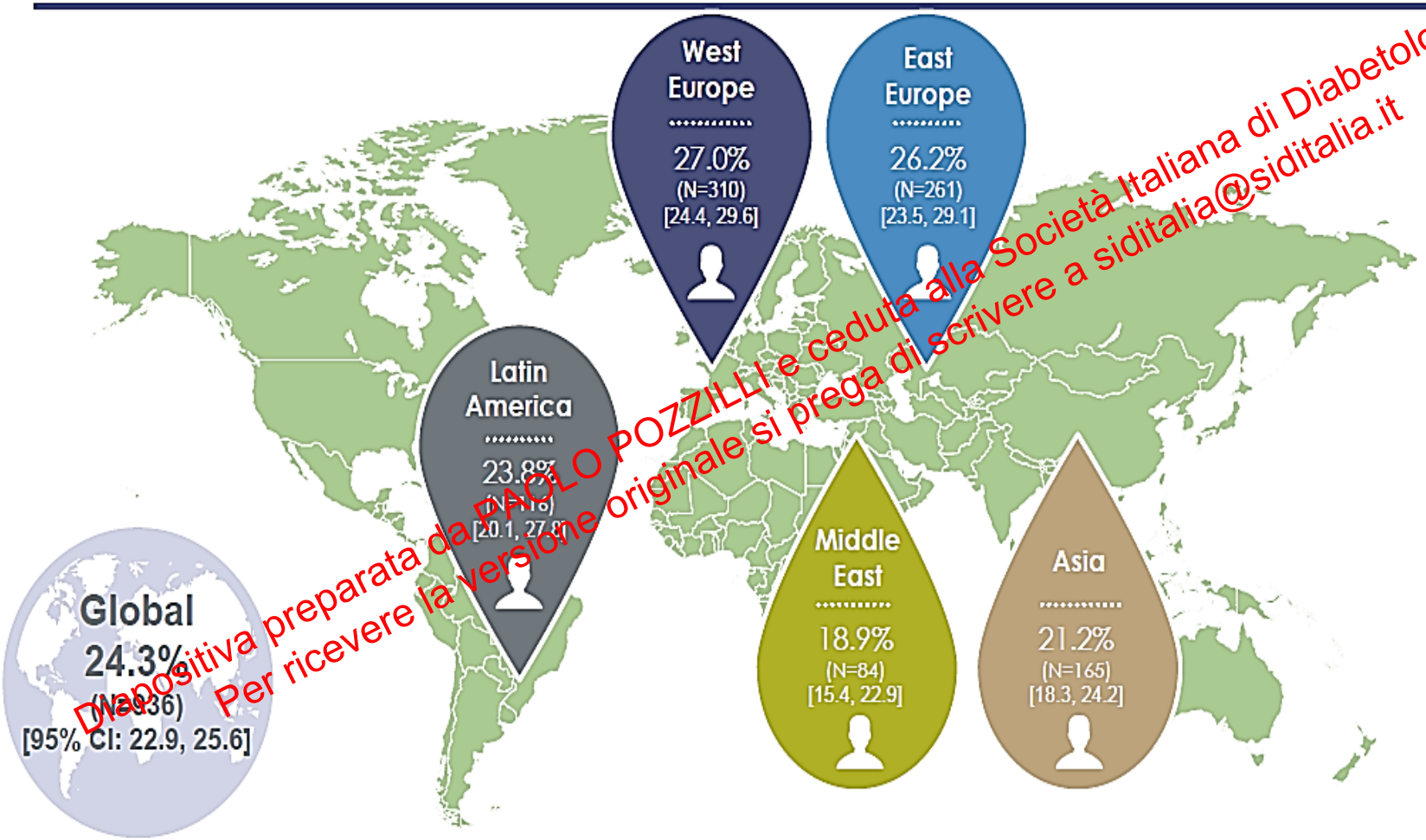
Regional differences in GLYCAEMIC CONTROL, hypoglycaemia and disease management in adults with T1DM: the SAGE STUDY



Renard E.,…, Pozzilli P. et al., EASD 2019

SAGE Study

Primary endpoint: Percentage of patients at glycaemic target HbA_{1c} <7 %



CI, confidence interval

Renard E.,…, Pozzilli P. et al., EASD 2019

Overweight and Obesity in Youth with Type 1 Diabetes

Numerous studies have now demonstrated that the prevalence of childhood overweight and obesity has risen during the past 30 years in children with T1D.

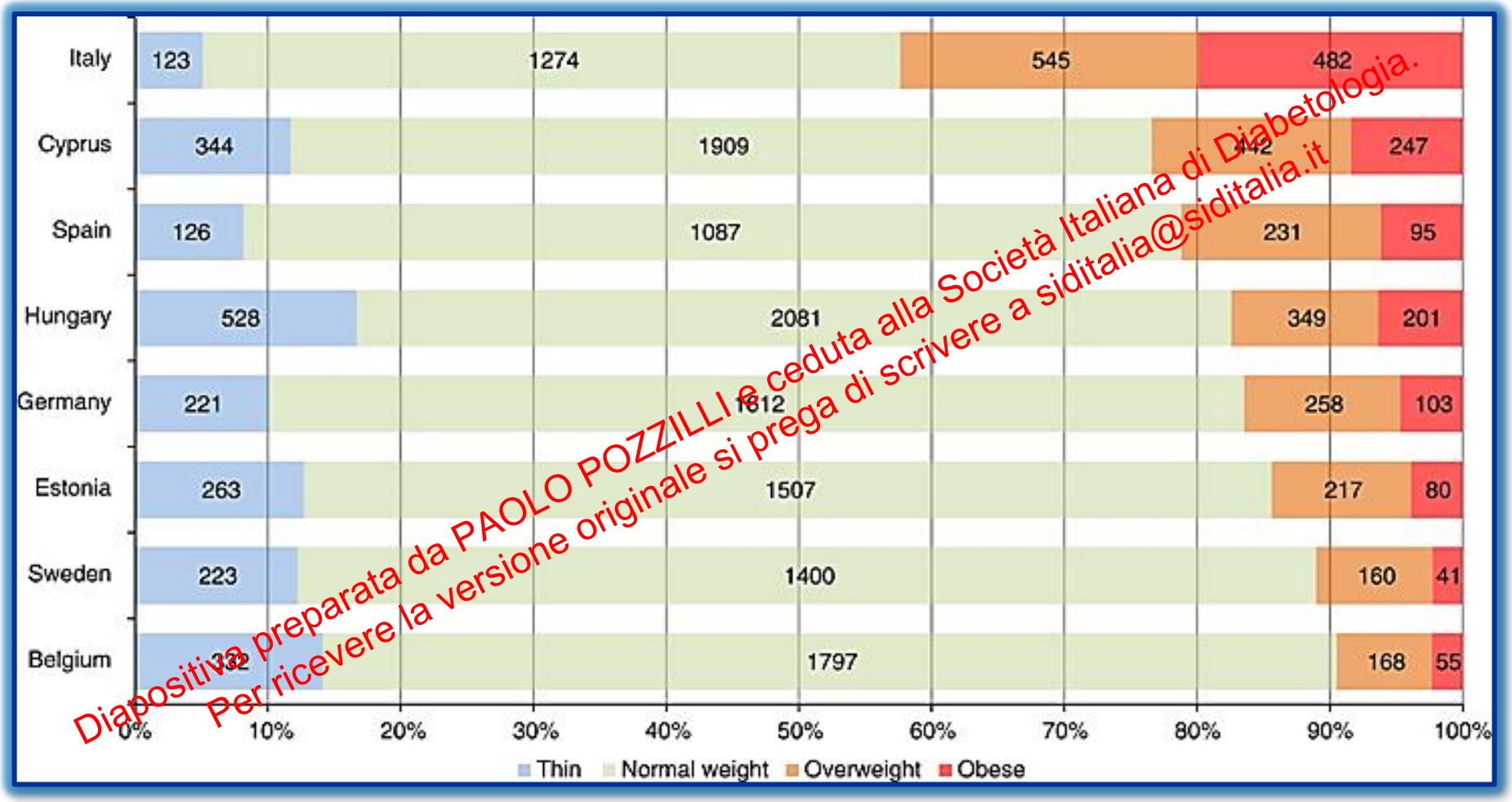
Worldwide prevalence of obesity has remarkably risen from <1% in 1975 to 7.8% and to 5.6% in 2016 for boys and girls, respectively

About 50% of patients with long-standing T1D are either overweight or obese, showing also higher waist and hip circumferences compared to healthy controls.

Such increase may be due to hyperinsulinisation and the effect of total calories intake, in response to threat or experience for hyperglycaemia.

Maffeis C., Pediatr Diabetes. 2018
NCD Risk Factor Collaboration (NCD-RisC), Lancet 2017

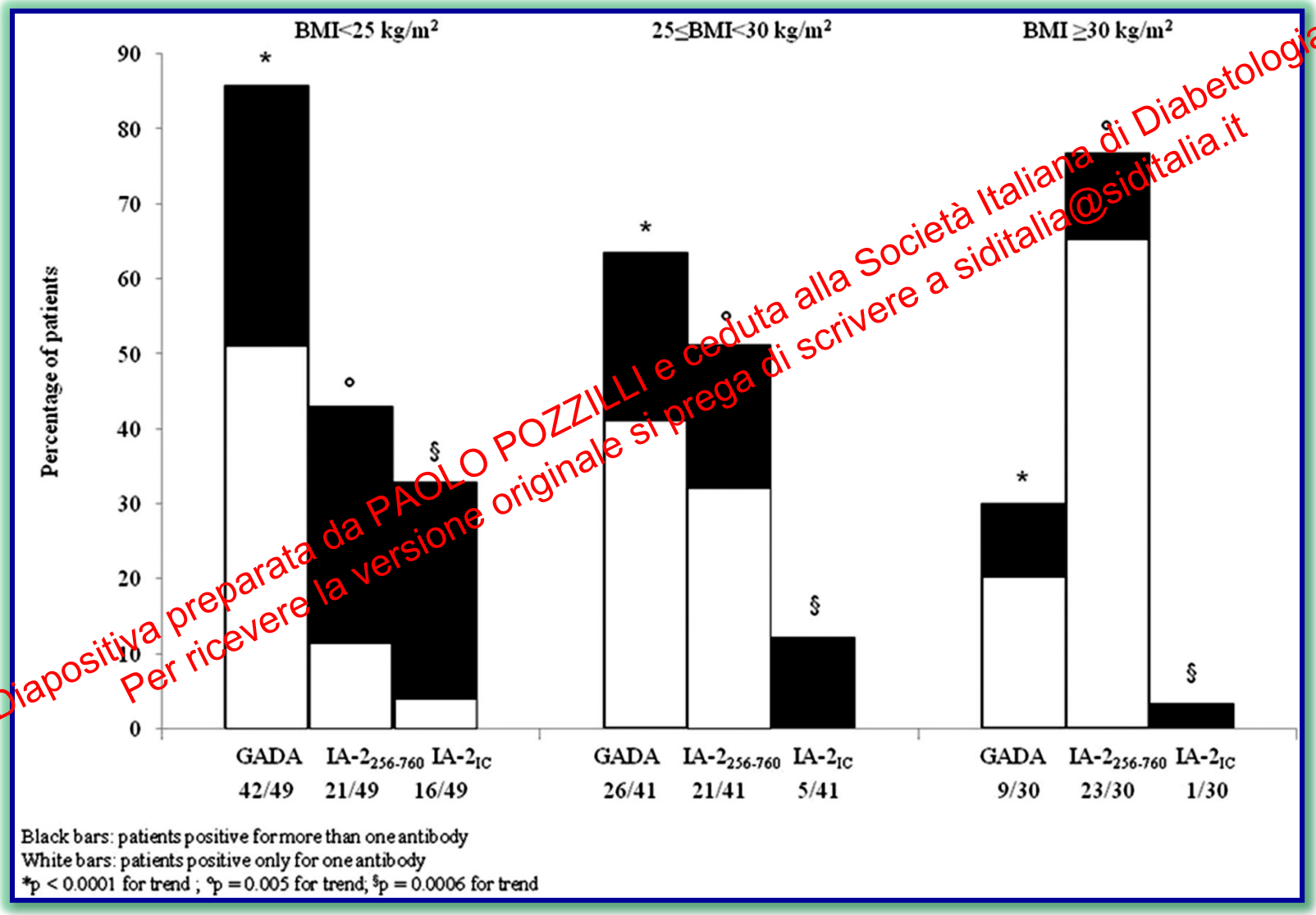
BODY WEIGHT and Type 1 diabetes



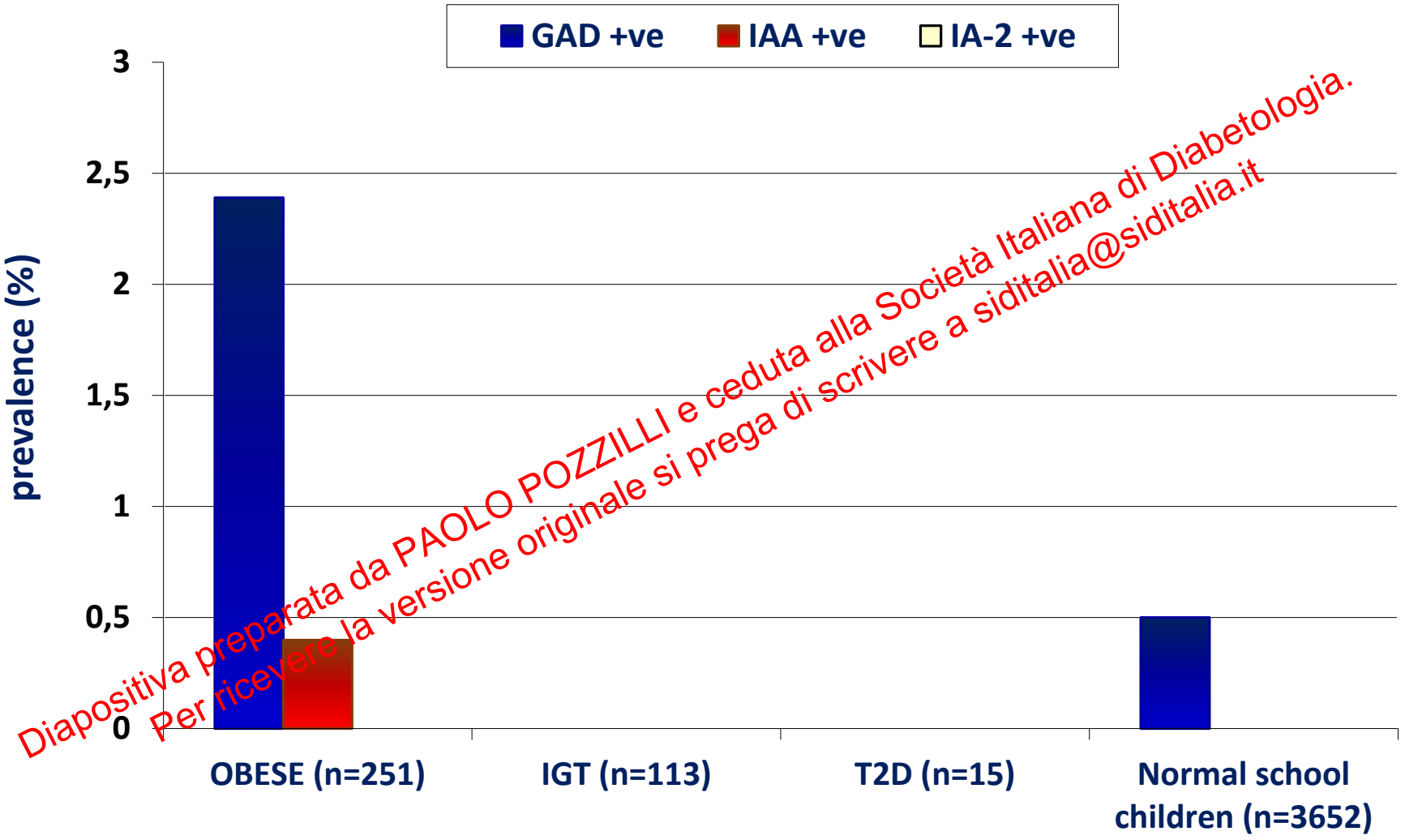
Prevalence of weight categories according to Cole and Lobstein by study region (boys and girls combined; number of subjects displayed in bars)

Ahrens W et al., International Journal of Obesity 2014

Islet autoantibody in OBESE T1D

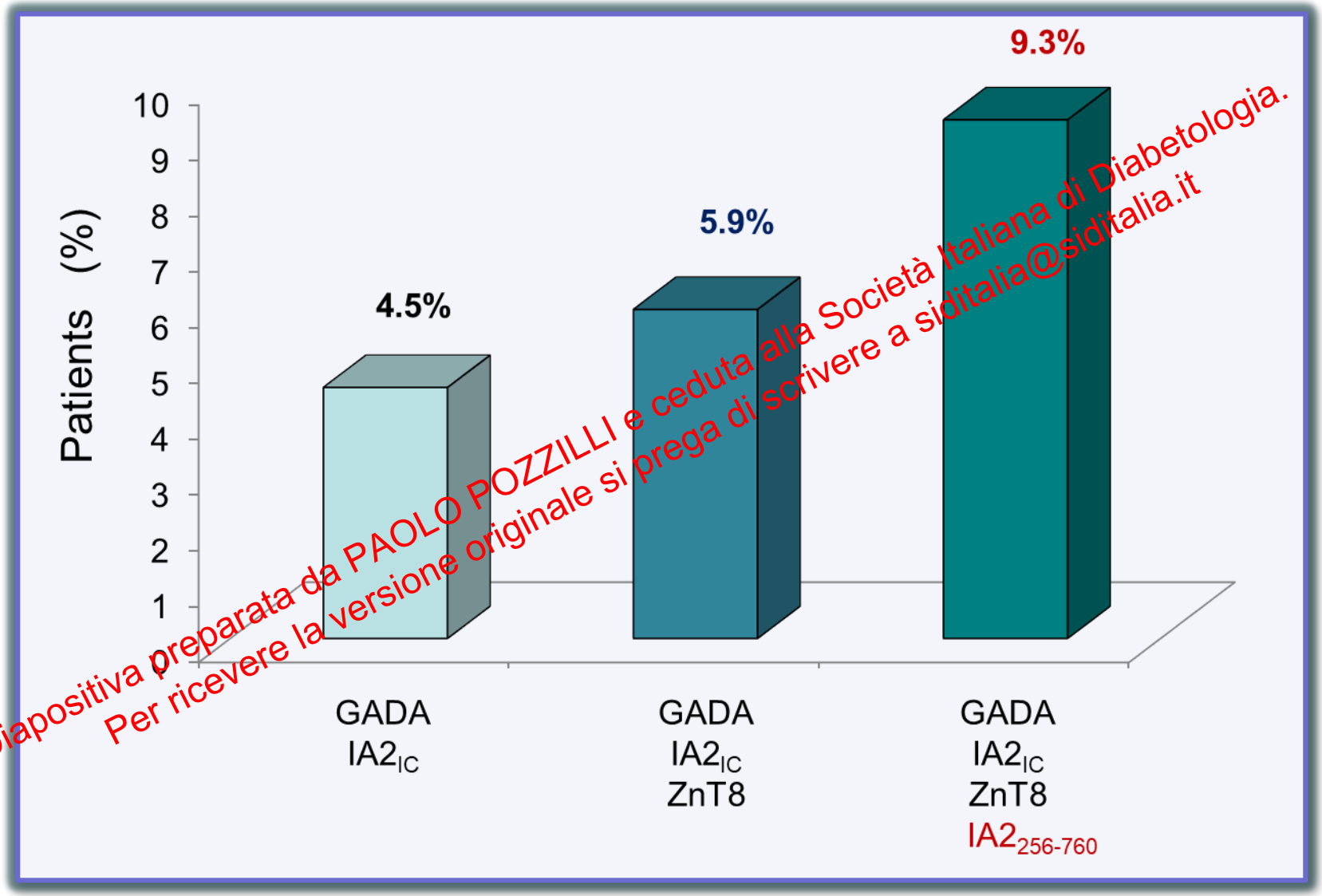


Buzzetti et al. Diabetes Care 2015



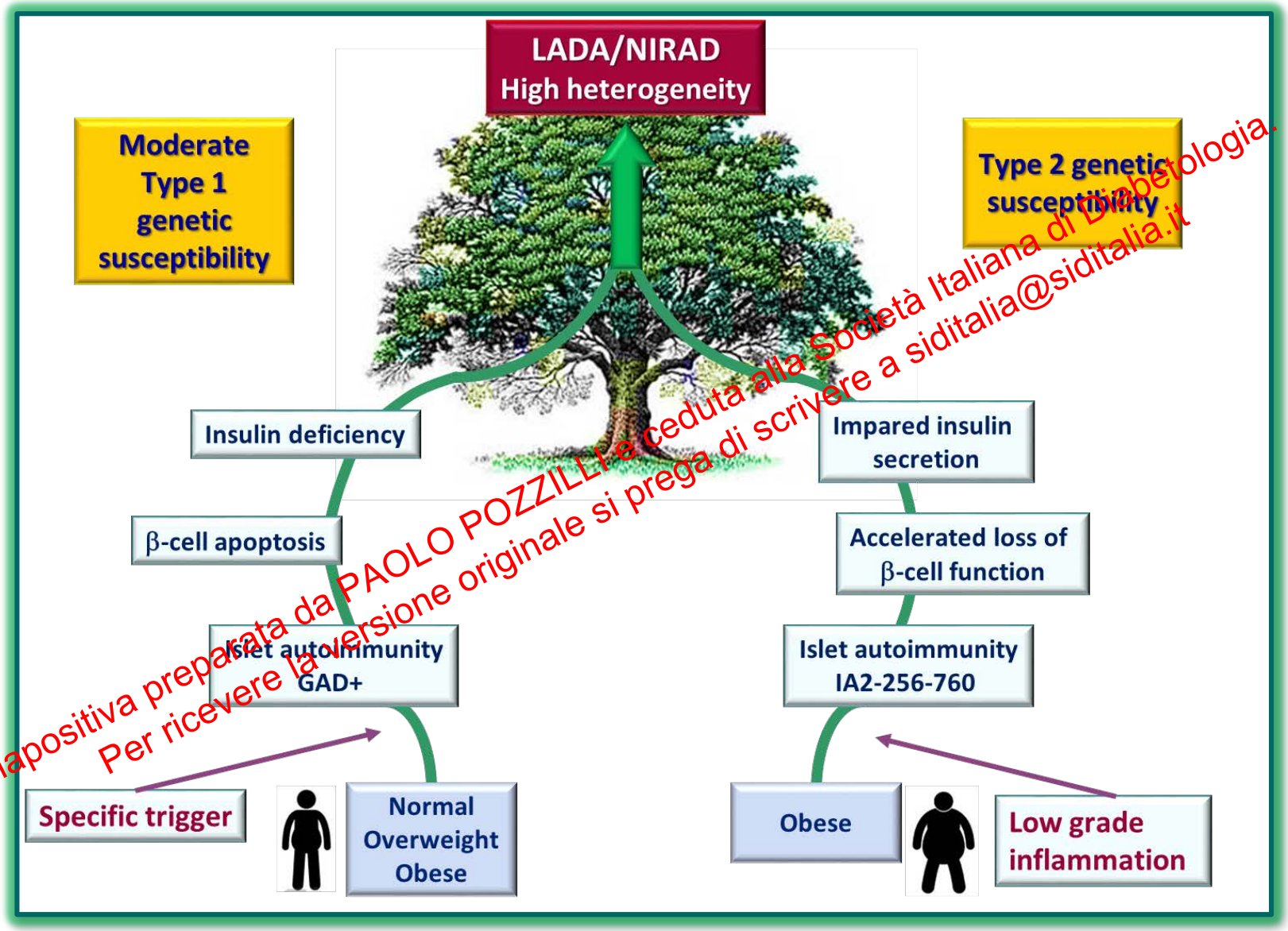
Pozzilli P, et al. Diabetes Care. 2011

Autoantibody positivity in T2DM patients



Buzzetti R et al, Diabetes Care 2007; Lampasona V et al, Diabetes 2010; Tiberti C et al, Diabetes 2008

Eterogeneità del diabete tipo 1 e il caso LADA/NIRAD



Latent Autoimmune Diabetes in Adults= LADA
Non Insulin Requiring Autoimmune Diabetes= NIRAD

Buzzetti R et al Nature Endocrine Reviews 2017

Unmet Needs in Type 1 Diabetes

- Other than insulin only Dapgliflozin is currently approved for treatment for T1D
- Drugs already in use for T2D and many new drugs are under clinical development for T1D
- The extensive heterogeneity of autoimmune diabetes makes it difficult to determine an *a priori* algorithm for treatment
- The control of blood levels of glucose should not be the sole aim of T1D treatment
- Need of a multifactorial approach to treatment that takes into account the complexity of the patient in terms of comorbidities
- Preservation of beta-cell function

Quali sono le opportunità terapeutiche per questi pazienti?

Terapia Insulinica

Insulino-sensibilizzanti (metformina)

Agonisti recettoriali GLP-1

DPP-4 inibitori

SGLT inibitori

Miglioramento del compenso glicemico….

Riduzione dell'insulino-resistenza, calo ponderale

Azione protettiva sulla β-cellula, calo ponderale

Azione protettiva sulla β-cellula

Riduzione della variabilità glicemica, calo ponderale

Buzzetti R, et al. Nat Rev Endocrinol. 2017 Nov;13(11):674-686.

NOVEL STUDIES

Focus on SGLT-2 inhibitors

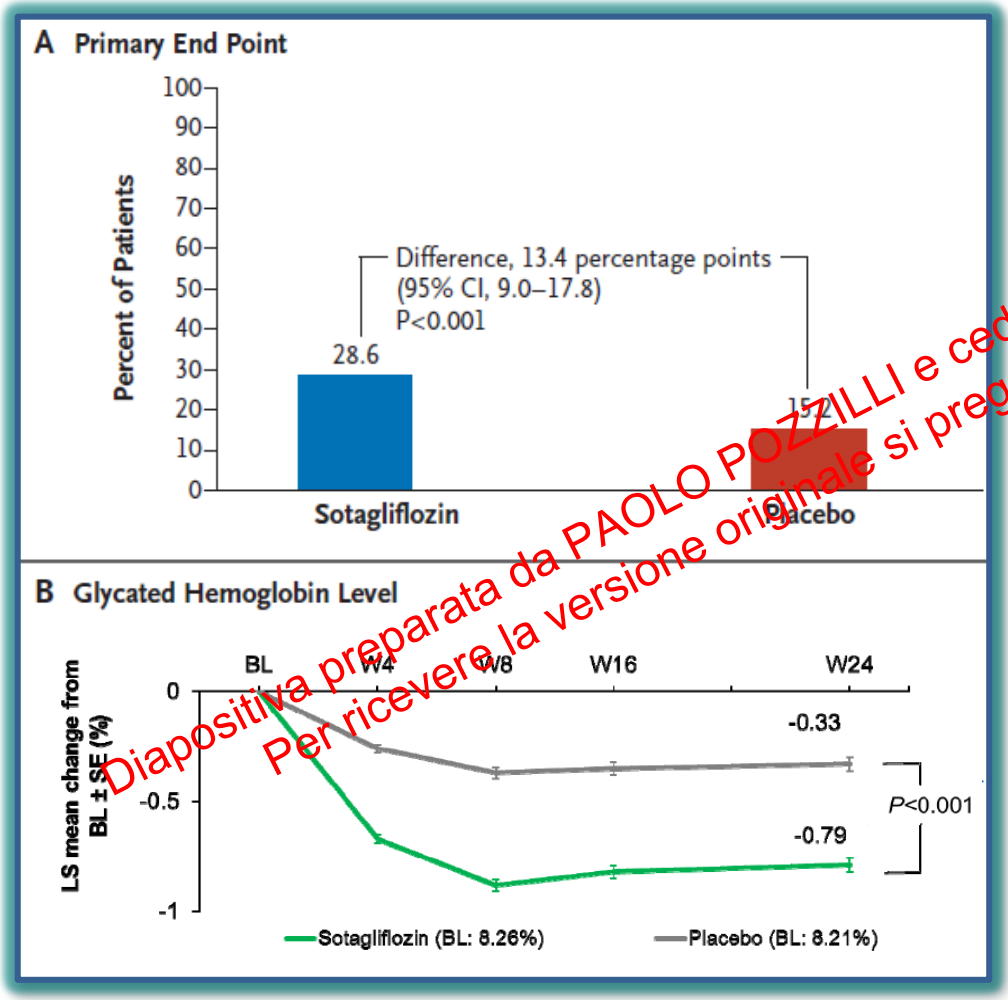
inTANDEM-1, inTANDEM-2, inTANDEM-3,

DEPICT-1, DEPICT-2 and EASE-2 and EASE-3

trials with a total of 6330 T1D patients

InTANDEM-3 Trial

Effects of Sotagliflozin added to Insulin in Patients with type 1 diabetes

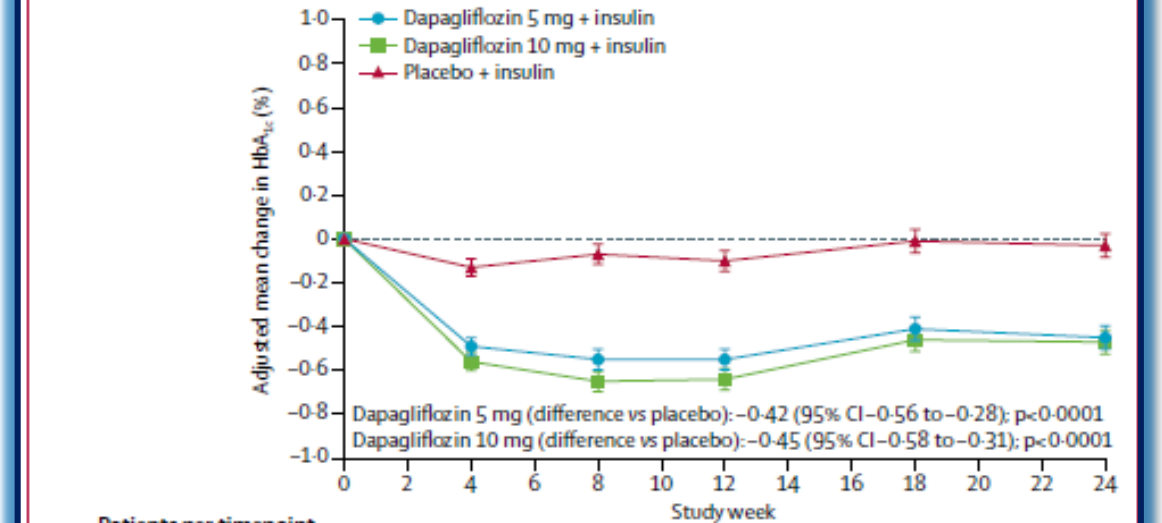


Among patients with type 1 diabetes who were receiving insulin, the proportion of patients who achieved a glycated hemoglobin level lower than 7.0% with no severe hypoglycemia or diabetic ketoacidosis was larger in the group that received sotagliflozin than in the placebo group.

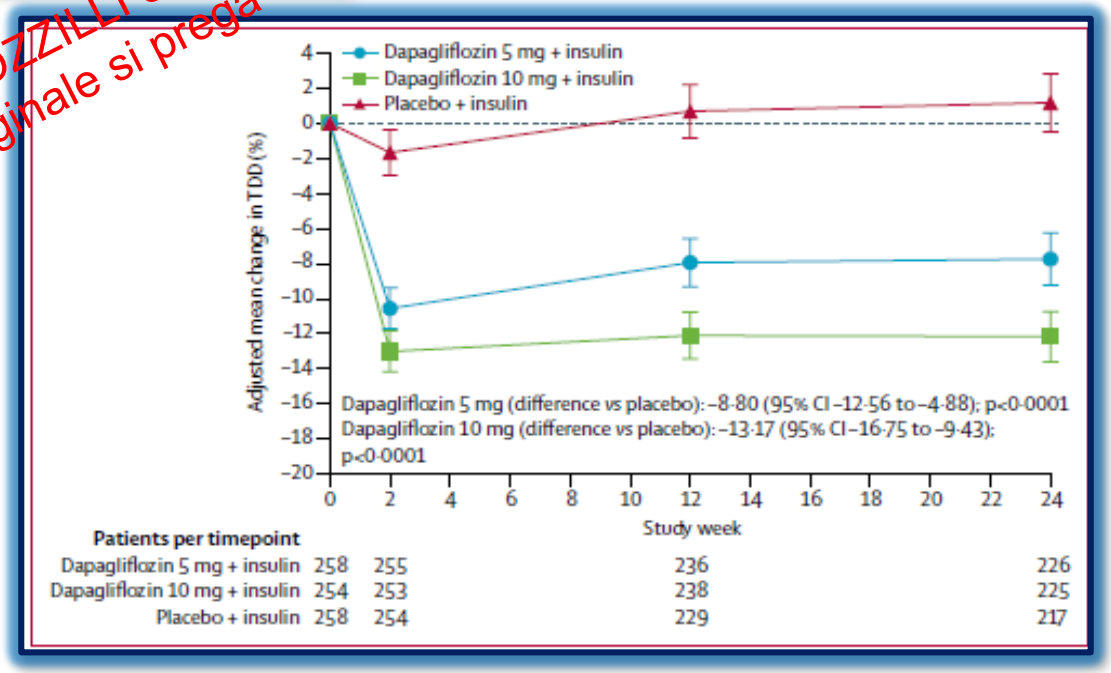
Garg SK,…,Pozzilli P et al, NEJM 2017

DEPICT-1 trial

Dapagliflozin in T1D: a 24 week results of a multicentred double blind phase III randomized control trial

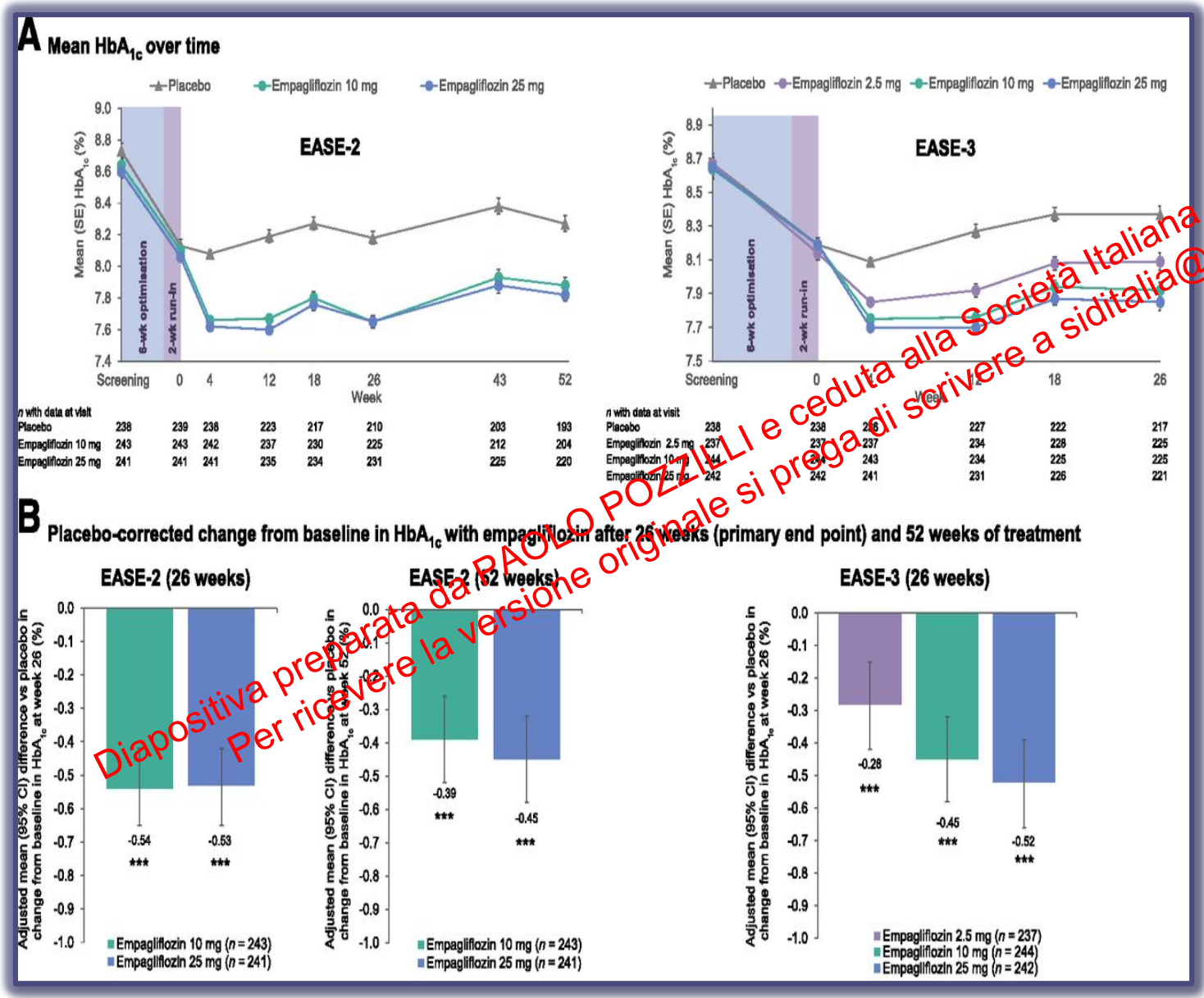


Compared with placebo, dapagliflozin at both doses produced significant and clinically relevant reduction from baseline to week 24 in HbA1c and in total daily insulin dose (p< 0.0001).



Dandona P. et al, Lancet Diabetes Endocrinol 2017

Empagliflozin as Adjunctive to insulin therapy in Type 1 diabetes: The EASE trials



The empagliflozin T1D program was a comprehensive evaluation of the benefit-risk profile of this SGLT2i as adjunctive therapy to insulin. After 26-week placebo-controlled randomized treatment phase, the >0.5% HbA1c reduction with empagliflozin 10 and 25 mg has a clinically meaningful effect over intensified insulin.

Rosenstock J et al., Diabetes Care 2018

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Dapagliflozin in Type 1 diabetes

EMA's human medicines committee (CHMP) has recommended for the first time an adjunct treatment to insulin in the form of a tablet for certain patients with type 1 diabetes mellitus

The CHMP is now recommending to extend the indication of dapagliflozin to certain patients with type 1 diabetes mellitus, when their insulin alone does not provide adequate control of their blood glucose levels despite optimal insulin therapy. Patients considered for this treatment should fulfil certain requirements and should not have a body mass index (BMI) below 27 kg/m^2.

EMA 01/02/2019

THE LANCET
Diabetes & Endocrinology

NEWS | VOLUME 7, ISSUE 10, P750-751, OCTOBER 01, 2019

NICE guidance on dapagliflozin with insulin for type 1 diabetes

On August 28, 2019, the National Institute for Health and Care Excellence (NICE) published guidance recommending dapagliflozin (a sodium-glucose co-transporter-2 inhibitor) for treating type 1 diabetes in adults with a BMI of at least 27 kg/m^2 when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy.

However, the guidance applies only if:

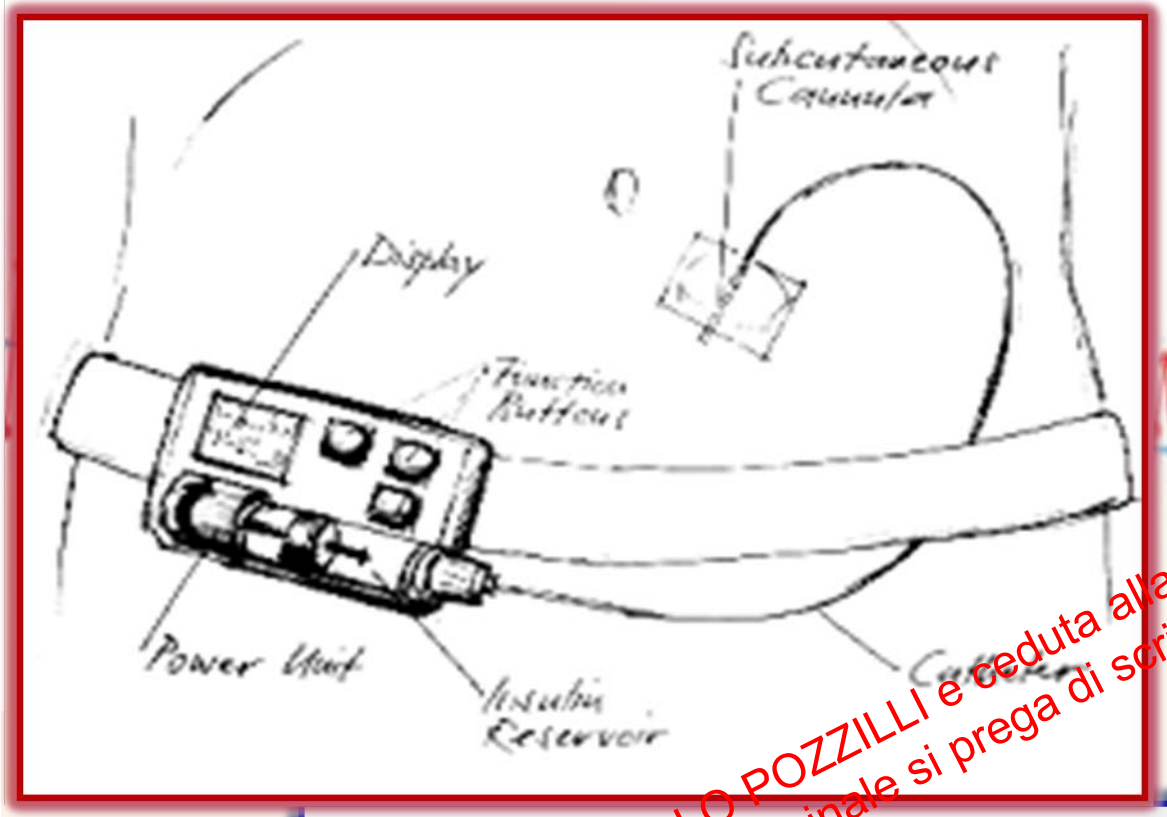
patients are on insulin doses of more than 0·5 units per kg bodyweight per day;

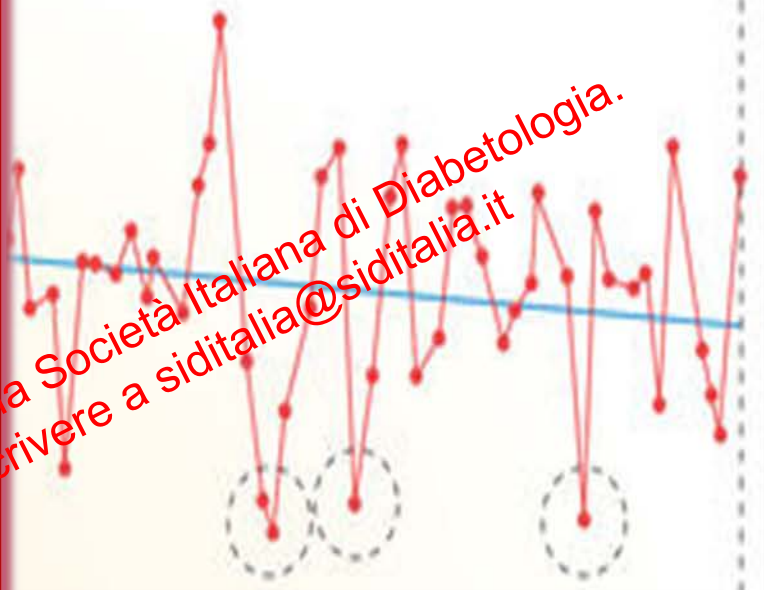
they have completed a structured education programme that includes information about diabetic ketoacidosis (DKA) such as recognising its risk factors, signs, and symptoms, how and when to monitor blood ketones, and what actions to take;

treatment is started and supervised by a consultant physician specialising in endocrinology and diabetes.

The structured education course, in line with the NICE quality standard for diabetes, 2 should be evidence based and quality assured, and be delivered by trained educators

Adler AI et al., The Lancet 2019





Continuous subcutaneous insulin infusion (CSII) for management of type 1 diabetes

State of the art

- In adults with type 1 diabetes, HbA1c decreased more with CSII than MDI.
- The **rt-CGM** has reached a lower level of HbA1c compared to the **Self Monitoring of Blood Glucose (SMBG)**, without any difference in severe hypoglycemia.
- In type 1 diabetes CSII + rt-CGM decreased the HbA1c levels more than MDI + SMBG.
- Mobile apps can be versatile and useful tools for successful self-management of type 1 diabetes.

A 2-Year Pilot Trial of CSII vs. MDI with the addition of nicotinamide to both groups in patients with newly diagnosed type 1 diabetes (IMDIAB 8)

Compared with baseline values, an increase of baseline C-peptide of 38% for the CSII group and 27% for the MDI group was observed; however, the difference between the groups was not significant.

The insulin requirement for the entire duration of the study, but not at entry and 3 months, was significantly higher in CSII compared with ISIT patients (0.62 ± 0.4 IU/kg/day vs. 0.3 ± 0.4 IU/kg/day, respectively, $p < 0.01$).

Implementation of CSII as well as ISIT at diagnosis of Type 1 diabetes and continuation for 2 years thereafter achieved similar and optimal metabolic control, but more insulin was required with the CSII group.

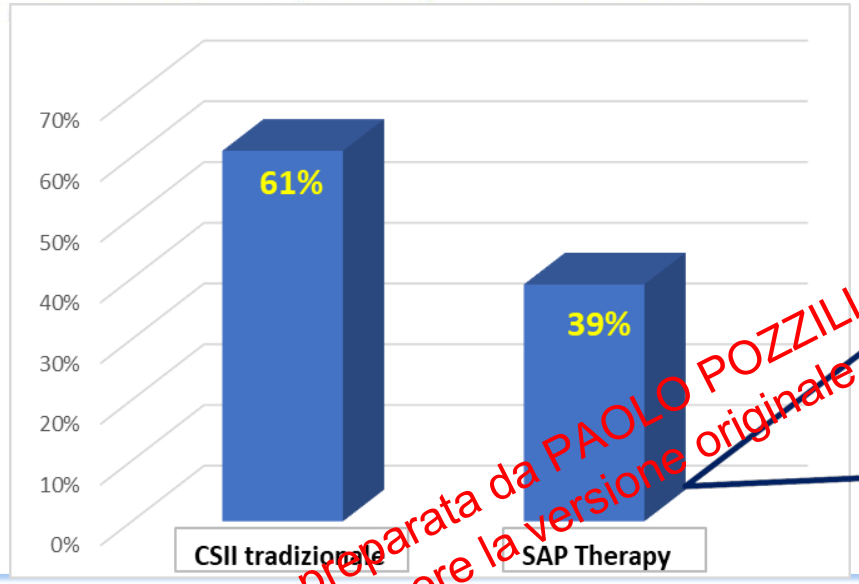
Both types of intensive insulin therapy combined with nicotinamide are able to preserve C-peptide secretion or even increase baseline levels for up to 2 years after diagnosis.

Pozzilli P et al., Diabetes, Technology & Therapeutics 2003

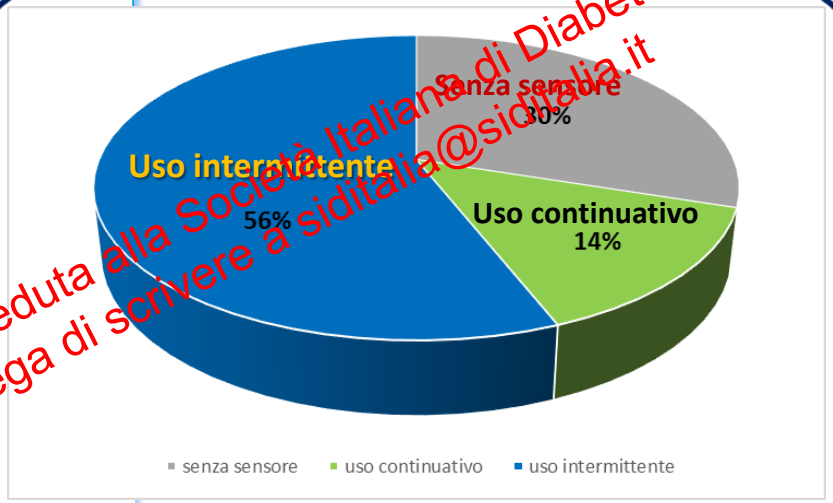
Numeri alla mano

Prevalenza dei pazienti in CSII therapy

La terapia insulinica sottocutanea continua (CSII) in Italia.



Tipo di strumento utilizzato



Utilizzo effettivo del sensore in pazienti in SAP Therapy

Gruppo di Studio Italiano sulla Diffusione della CSII, G It Diabetol Metab 2015;35:121-129

DATI ISTAT 2018:

-**3,4 milioni il numero di diabetici in Italia**

-più di **300.000 i pazienti con DMT1**

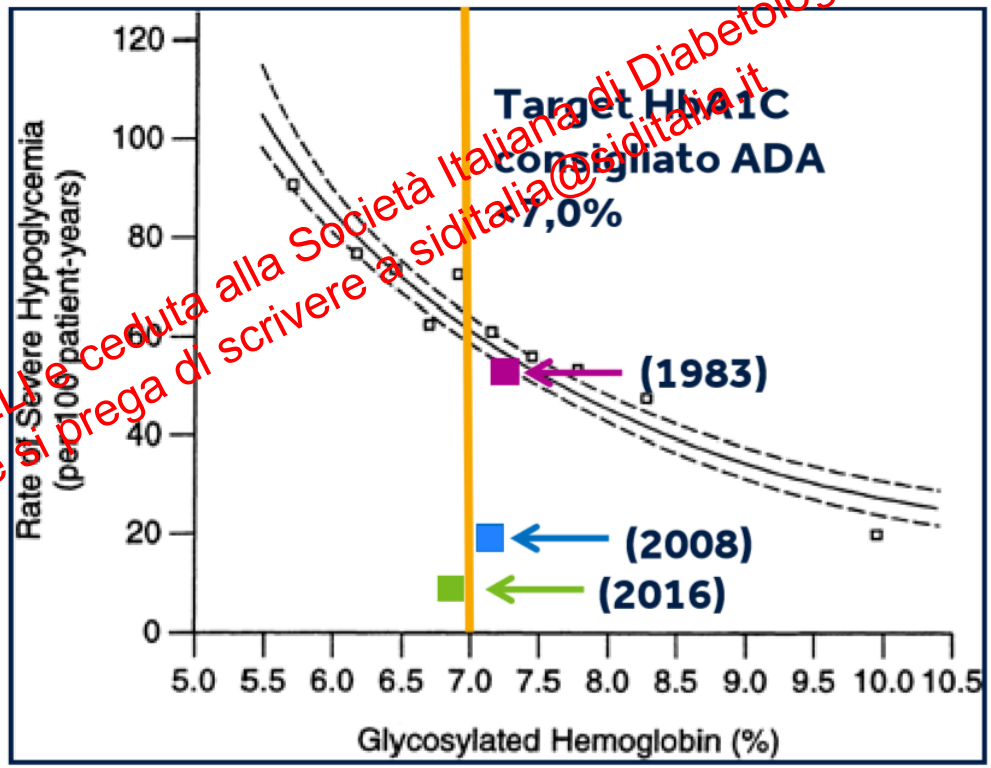
Di cui solo **27.000 (<10%)** è **in terapia con CSII**

HbA1c media con incidenza di tasso di ipoglicemia grave
STUDI CLINICI CHIAVE*

- DCCT[1] (adolescenti e adulti) Percentuale di ipo grave: 62,0 per 100 anni-pz., HbA1C: 9,0% → 7,2%

- JDRF CGM[2] (adulti, 1 soggetto escluso) Percentuale di ipo grave: 20,0 per 100 anni-pz., HbA1C: 7,6% → 7,1%

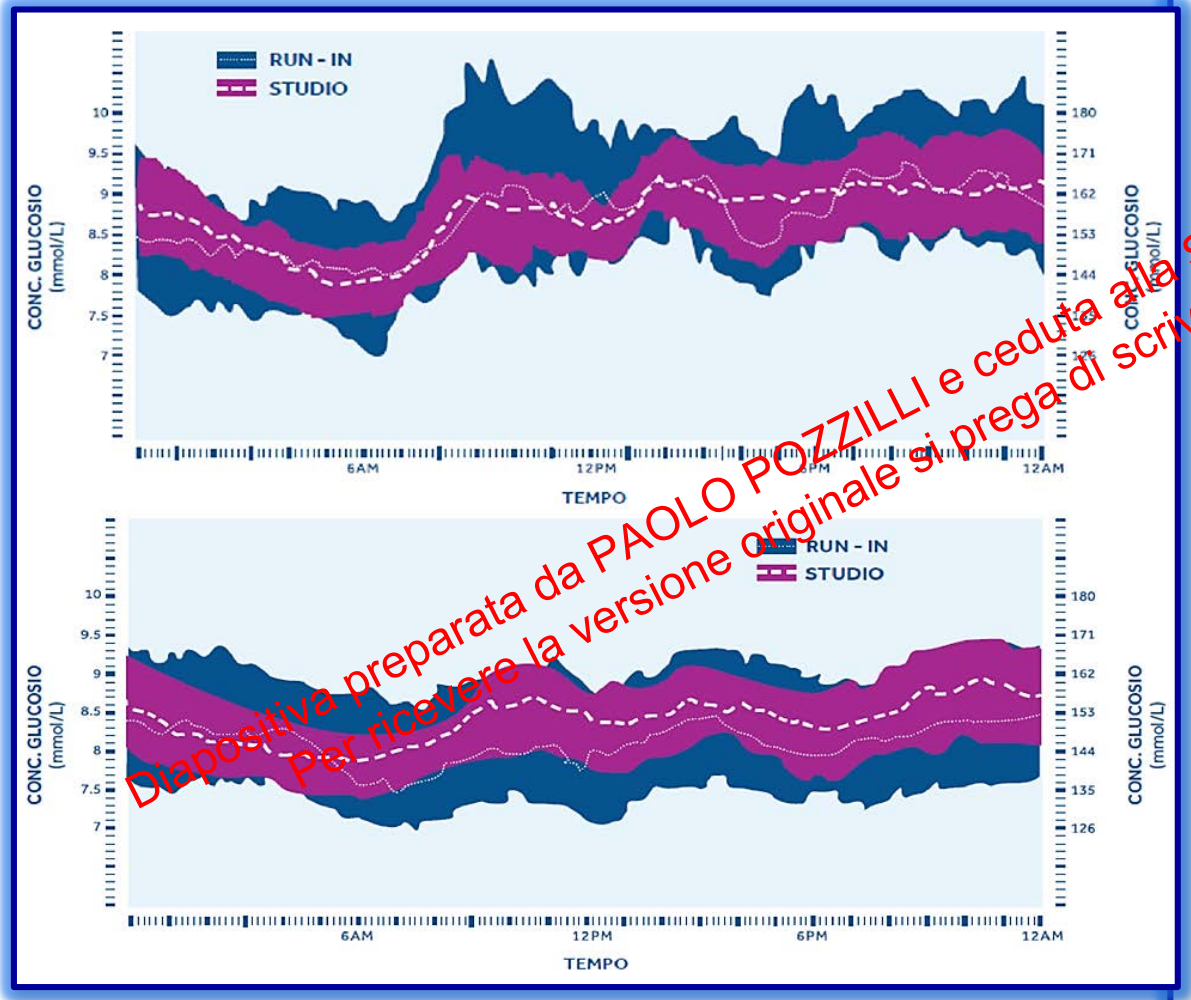
- Studio pivotal[3] (adolescenti e adulti) Percentuale di ipo grave: 0,0 per 100 anni-pz., HBA1C: 7,7% → 6,9%



1. DCCT Research Group. N Engl J Med. 1993;329:977-986.
2. Tamborlane,W. et al. New Engl J Med. 2008;359:1464-1476.
3. Bergenstal RM, et al. JAMA. 2016;316(13):1407-1408.

PIVOTAL Trial

Popolazione adolescente e adulta



RESULTS

- **ADOLESCENTS (14-21 yrs):**
  - ✓ Used the system for a median 75.8% of the time.
  - ✓ HbA1c levels decreased from **7.7%** to **7.1%** (P<0.001)
  - ✓ The proportion of overall in-target (71–180mg/dL) sensor glucose (SG) values increased from **60.4%** to **67.2%** (P<0.001)
- **ADULTS (22-75 yrs):**
  - ✓ Used the system for a median 88.0% of the time.
  - ✓ HbA1c levels decreased from **7.3%** to **6.8%** (P<0.001)
  - ✓ The proportion of overall in-target (71–180mg/dL) sensor glucose (SG) values increased from **68.8%** to **73.8%** (P<0.001)

Satish K. Garg et al., Diabetes Technology & Therapeutics Volume 19, Number 3, 2017

Conclusions I

- The use of CSII in the diagnosis of T1D could offer a new, effective treatment to rapidly increase metabolic control and protect residual beta-cell function.

- The use of modern technologies (CGM and CSII) in the management of diabetes represents an example of personalized therapy, where the evaluation and use should be both appropriate and targeted.

Conclusions II

SGLT2i therapy is a promising option for adjunctive therapy in the treatment of T1D.

Studies in this population have already demonstrated that use of SGLT2 inhibitors confers significant benefits, including improved glycemic control, increased time in range, improved quality of life and weight loss.

The major restriction on the wide use of these agents in T1D is represented by euglycemic diabetic ketoacidosis (DKA)

However, the incidence of DKA in T1D patients treated with SGLT-2i remains generally low.

Strategies for mitigating DKA risk are vital to the adoption and safe use of SGLT inhibitors in all diabetes populations, particularly those requiring insulin.