

Le sfide attuali per la gestione della terapia insulinica oggi

Paolo Fiorina MD PhD

University of Milan

Fatebenefratelli-Sacco-Melloni Hospitals, Milan

Sistema Socio Sanitario



Regione
Lombardia

ASST Fatebenefratelli-Sacco



HARVARD
MEDICAL SCHOOL

Diapositiva preparata da PAOLO FIORINA e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

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

- ...Menarini.....
- ...Lilly.....
- ...Astrazenca.....
- ...Novo

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

Diapositiva preparata da PAOLO FIORINA e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Outline

1. Introduction
2. Insulin therapy in T2D
3. Weekly Insulin
4. Conclusions

Diapositiva preparata da PAOLO FIORINA e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Outline

1. Introduction
2. Insulin therapy in T2D
3. Weekly Insulin
4. Conclusions

Diapositiva preparata da PAOLO FIORINA e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Role of Insulin Therapy in Diabetes Care

- Essential therapy for 150–200 million people worldwide
- Cornerstone of T1D management
- In the US: ~12.3% of adults with diabetes initiate insulin within 1 year of diagnosis

Is insulin important only for glucose regulation?

Non-glycemic Actions of Insulin

Lipid metabolism

- Inhibition of lipolysis ($\downarrow$ free fatty acids)
- Stimulation of lipogenesis ($\uparrow$ triglyceride synthesis)
- Inhibition of ketogenesis

Protein metabolism

- Stimulation of protein synthesis
- Inhibition of proteolysis

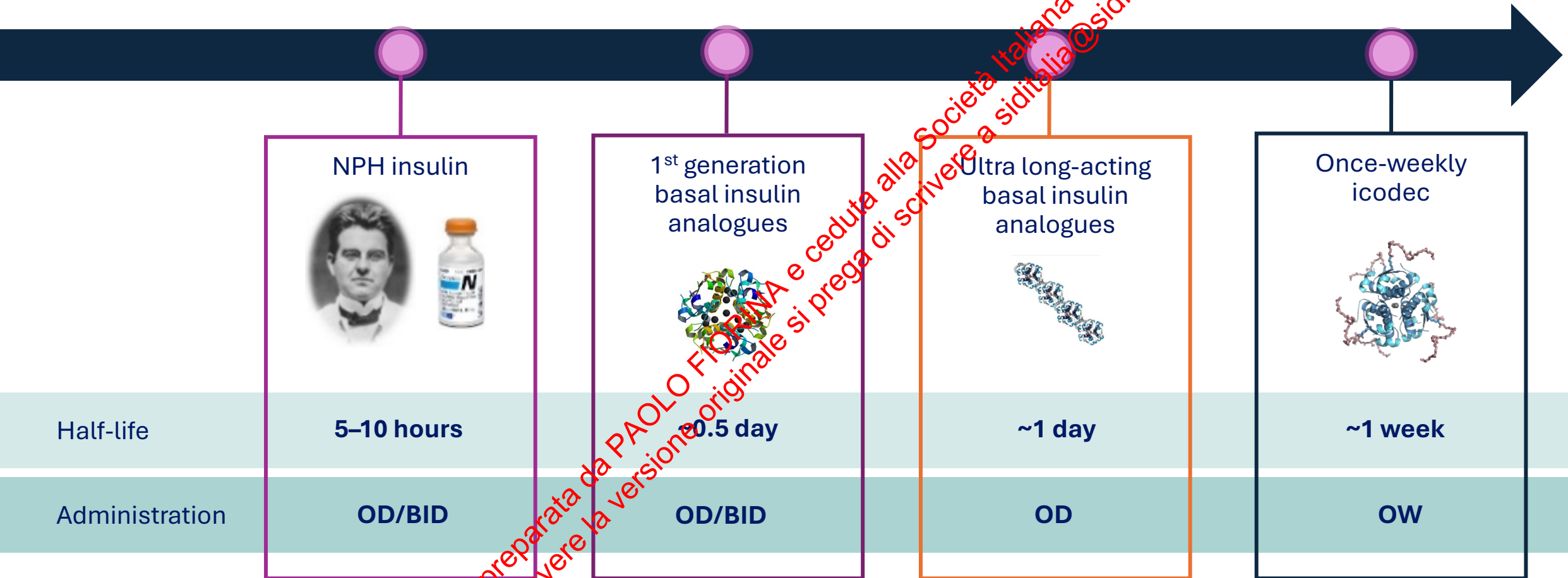
Effects on ions

- Stimulation of intracellular K^+ transport (useful in hyperkalemia)
- Increased uptake of phosphate and magnesium

Vascular and cellular effects

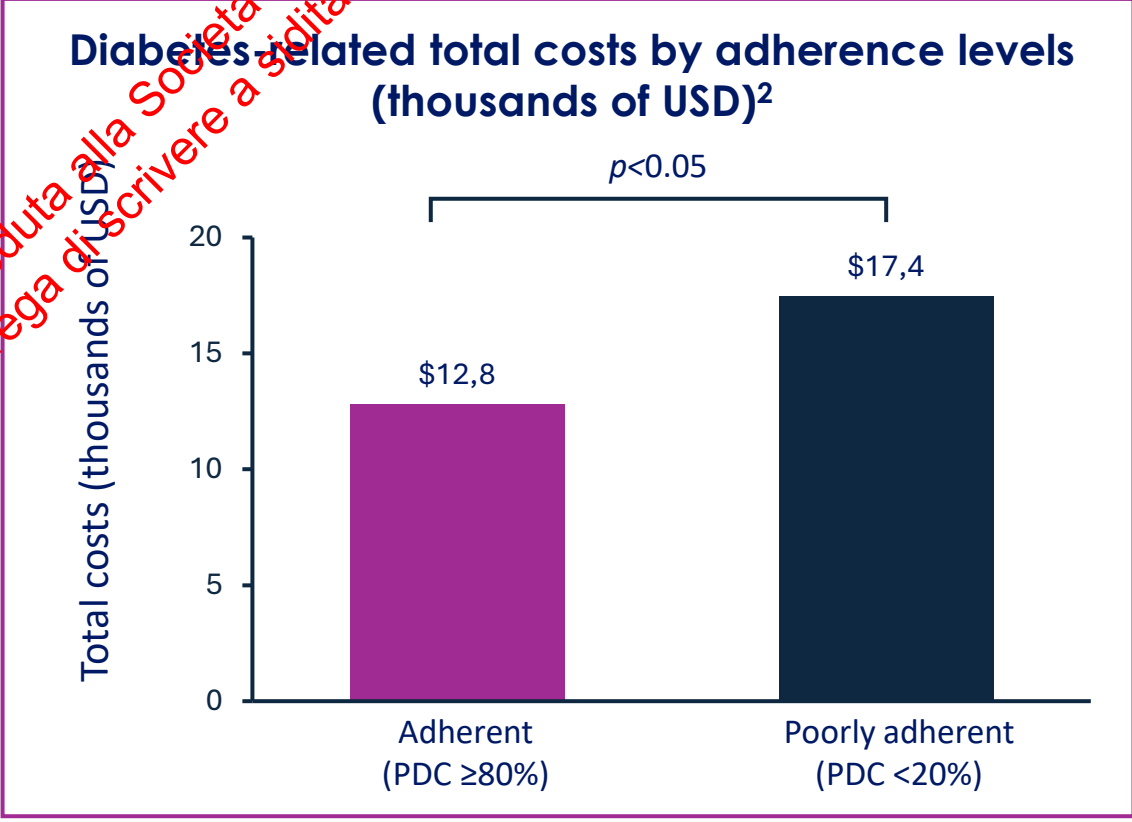
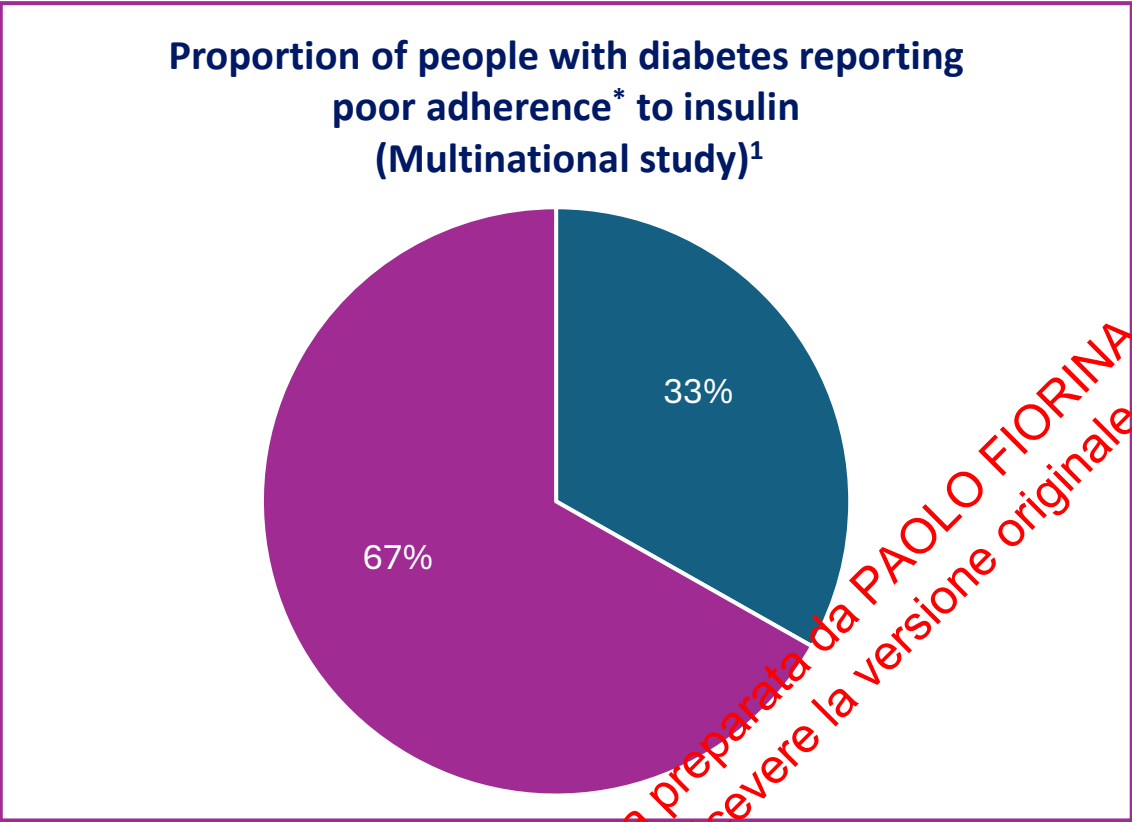
- Stimulation of NO synthesis $\rightarrow$ vasodilation
- General anabolic action (cell growth and differentiation)

The past and present of basal insulin innovation



One-third of people with diabetes are poorly adherent to insulin therapy

Adherent
Poorly adherent



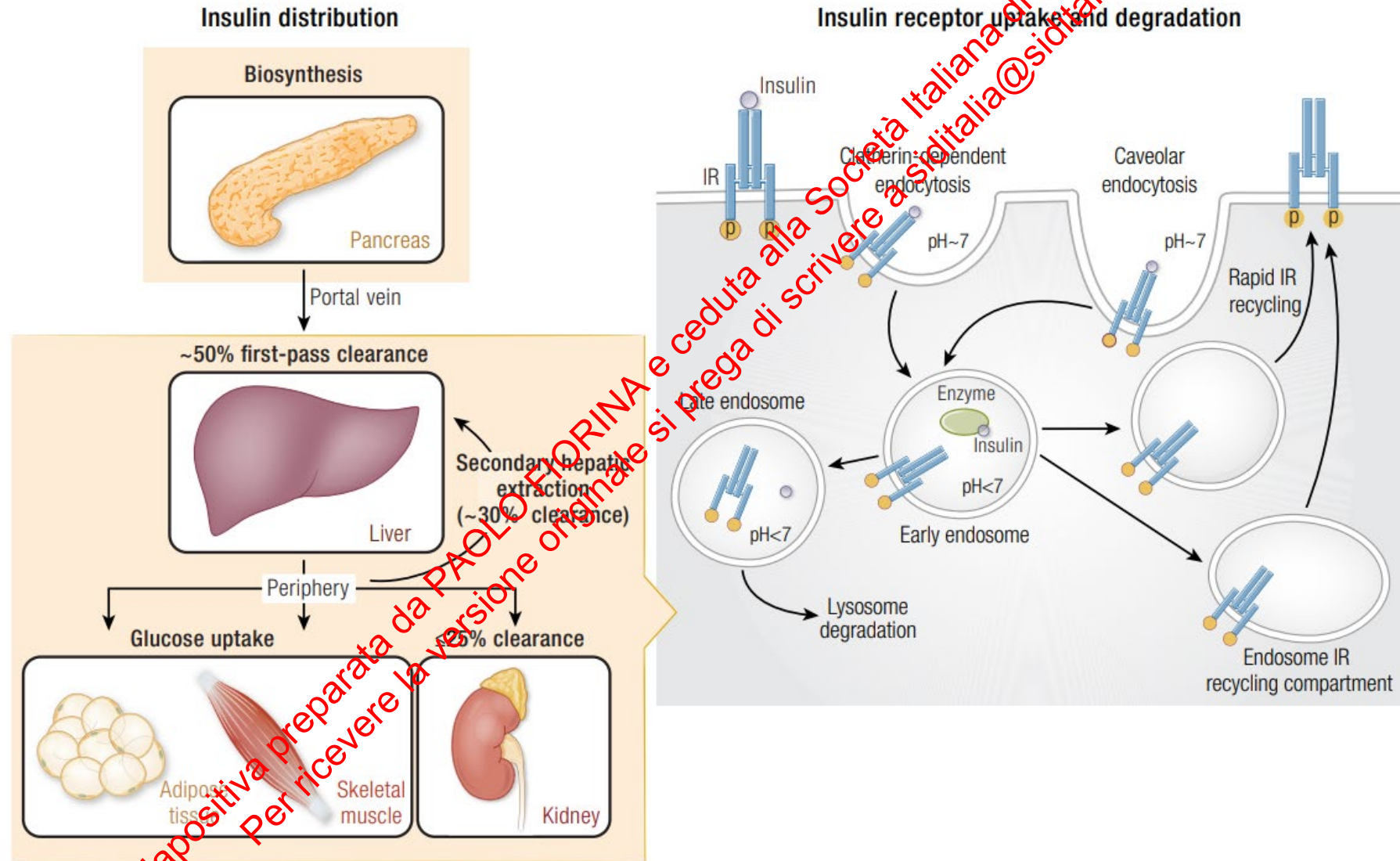
*Patient reporting insulin omission/non-adherence at least one day in the last month. PDC, proportion of days covered.

1. Peyrot M et al. *Diabet Med.* 2012;29(5):682-689; 2. Donnelly LA et al. *QJM.* 2007;100(6):345-350.

PDC, proportion of days covered; USD, United States dollar.

1. Donnelly LA et al. *QJM.* 2007;100(6):345-350; 2. Boye KS et al. *Patient Prefer Adherence.* 2016;10:1573-1581.

Challenges with insulin therapy



Challenges with insulin therapy

- Peripheral vs. portal delivery ***Hyperinsulation, weight gain, fasting hyperglycemia***
- SubQ vs. plasma ***Lag-time, post-prandial hypo/hyperglycemia, lipodystrophy***
- Lack of stability ***Glycemic variability, Suboptimal titration***
- No glucose feedback ***«reactive» management of hyperglycemia with insulin***
- Impact on daily life ***Reduction of QoL, missed doses, adherence & compliance***

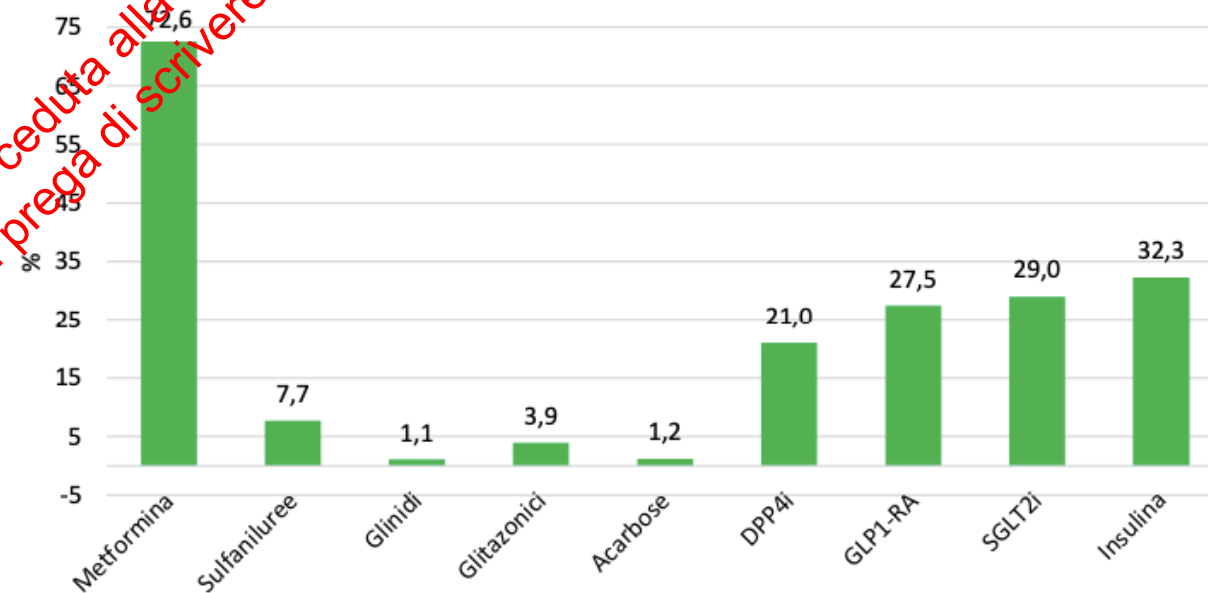
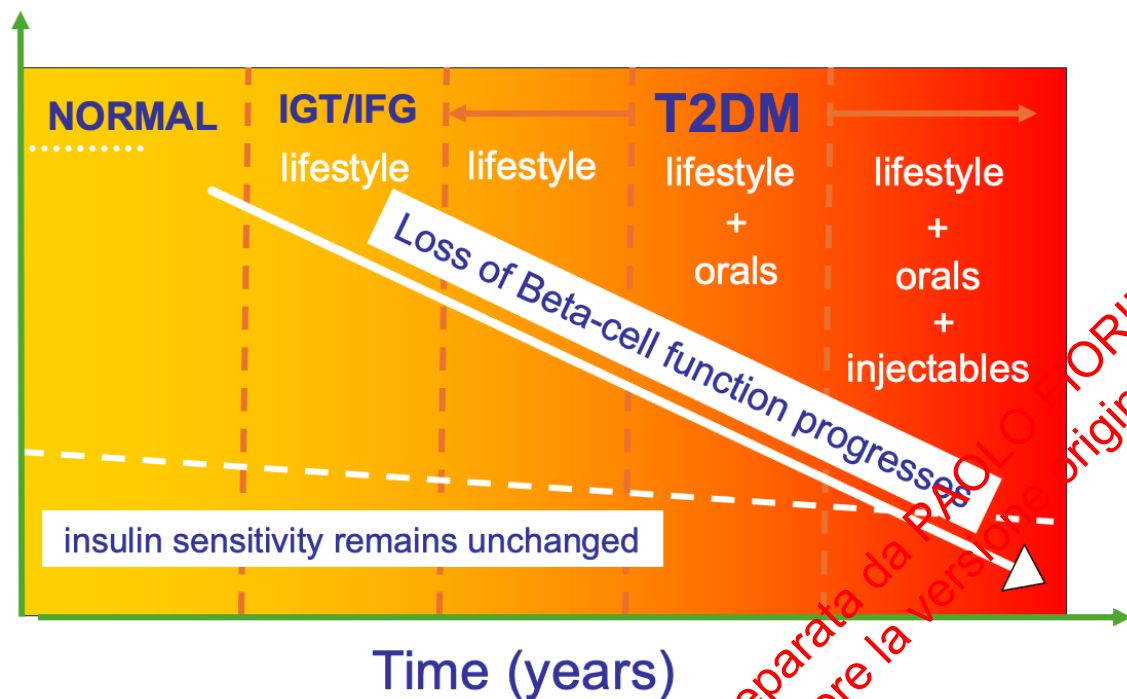
Diapositiva preparata da PAOLO FIORINA e ceduta alla Societa Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Outline

1. Introduction
2. Insulin therapy in T2D
3. Weekly Insulin
4. Conclusions

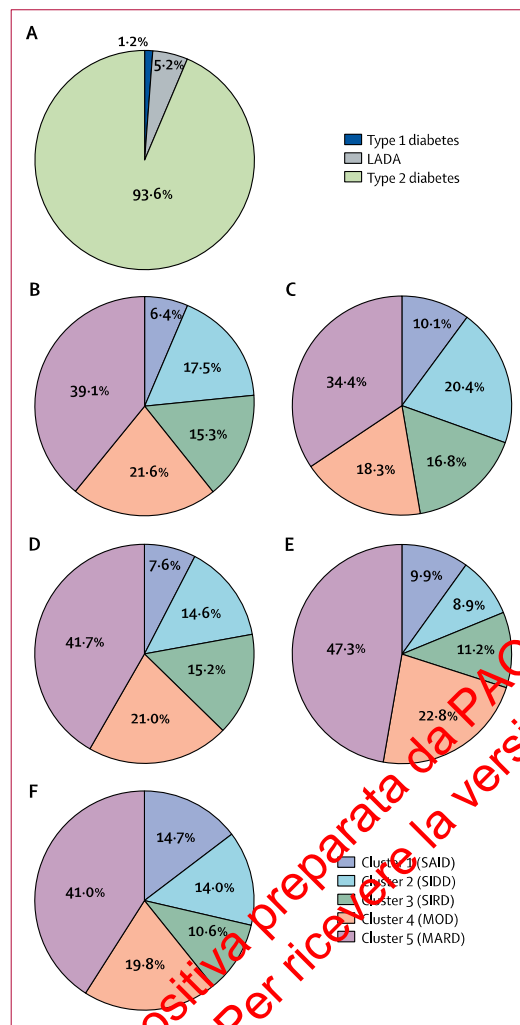
Diapositiva preparata da PAOLO FIORINA e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Natural history of T2D based on UKPDS

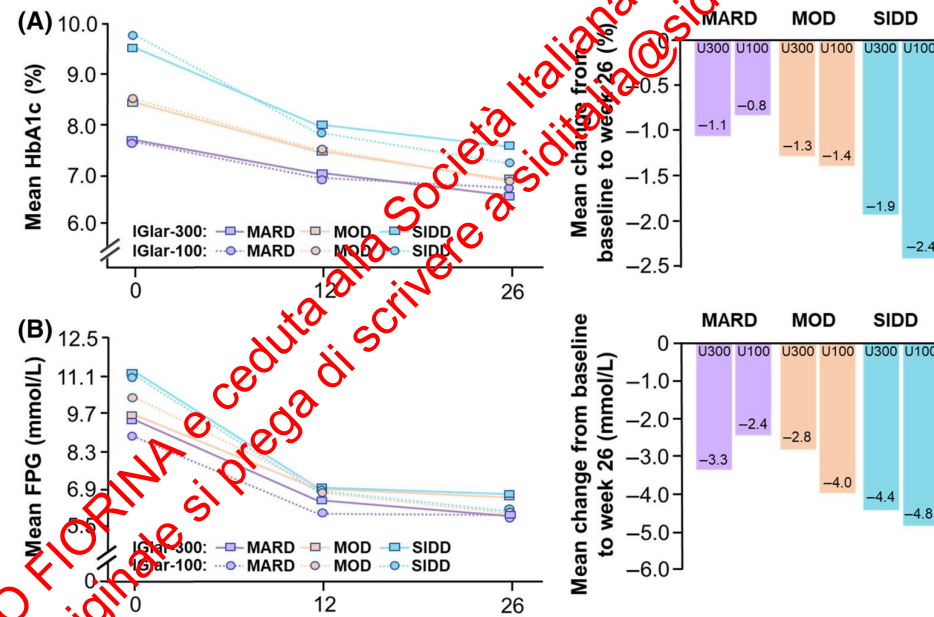


IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance.

Subgroups of adult-onset diabetes and insulin use



Lancet Diabetes Endocrinol 2018



- SAID, Severe autoimmune Diabetes
- SIDD, Severe insulin-deficient diabetes
- SIRD, Severe insulin-resistant diabetes
- MOD, Mild obesity-related diabetes
- MARD, Mild age-related diabetes

Landgraf W et al., Diabetes Obes Metab 2024

Basal insulin recommended as the initial insulin option for treatment intensification in T2D

ADA/EASD consensus report 2022

! Consider immediate start of insulin

- Severe hyperglycaemia
- Acute glycaemic dysregulation
- When T1D suspected

- Maintain cardiorenal protective agents
- Maintain metformin, SGLT-2i and GLP-1RA to avoid weight gain and limit insulin dose and hypoglycaemia risk
- Consider using combination products of basal insulin/GLP-1RA

! If not already on GLP-1RA, consider use of GLP-1RA

Consider adding insulin when personalised HbA_{1c} targets are not met with strategies described in holistic approach

Start using basal insulin*

(10U or 0.1–0.2 U/kg per day) at bedtime or more flexibility with timing for longer-acting analogues

Titrate to FPG target but avoid overbasalisation of insulin

(consider introduction of CGM)

When FPG is on target but HbA_{1c} or TIR is not

If not already on GLP-1RA, consider use of GLP-1RA

Add mealtime insulin under form of:

Basal plus

(Progressive addition of boluses)

MDI (Multiple daily injections)

Premix insulins



! When not familiar with insulin use or when targets not reached, consider shared care with specialist team

Intensify along the way and preferentially at each step

- Healthy behaviour
- Nutritional therapy
- DSMES: with additional focus on injection technique, hypoglycaemia, weight

*NPH insulin or preferably analogue to reduce nocturnal hypoglycaemia risk. CGM, continuous glucose monitoring; DSMES, diabetes self-management education and support; FPG, fasting plasma glucose; GLP-1RA, glucagon-like peptide 1 receptor agonist; SGLT-2i, sodium-glucose cotransporter 2 inhibitor; TIR, time-in-range.

1. Davies MJ et al. *Diabetes Care*. 2022;45(11):2753-2786. 2. Davies MJ et al. *Diabetologia*. 2022;65:1925-1966.

Basal Insulin is a key option in the treatment of T2D

- In T2D basal insulin is deficient – basal insulin is necessary to suppress endogenous glucose production & lipolysis
- Efficacious, everybody is a responder provided optimal titration
- Anabolic effects (protein synthesis), pro-endothelial, anti-atherosclerotic effects
- Best treatment for recovery of B-cell & insulin sensitivity
- No contra-indications, no side effects (natural hormone)

Diapositiva preparata da PAOLO FIORINA e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Titration of basal insulin in practice

Prefer simplicity, safety, empowerment of patients

Measure fasting PG every morning, after 3 days take the median:

Median PG > 110 mg/dl, add 2U

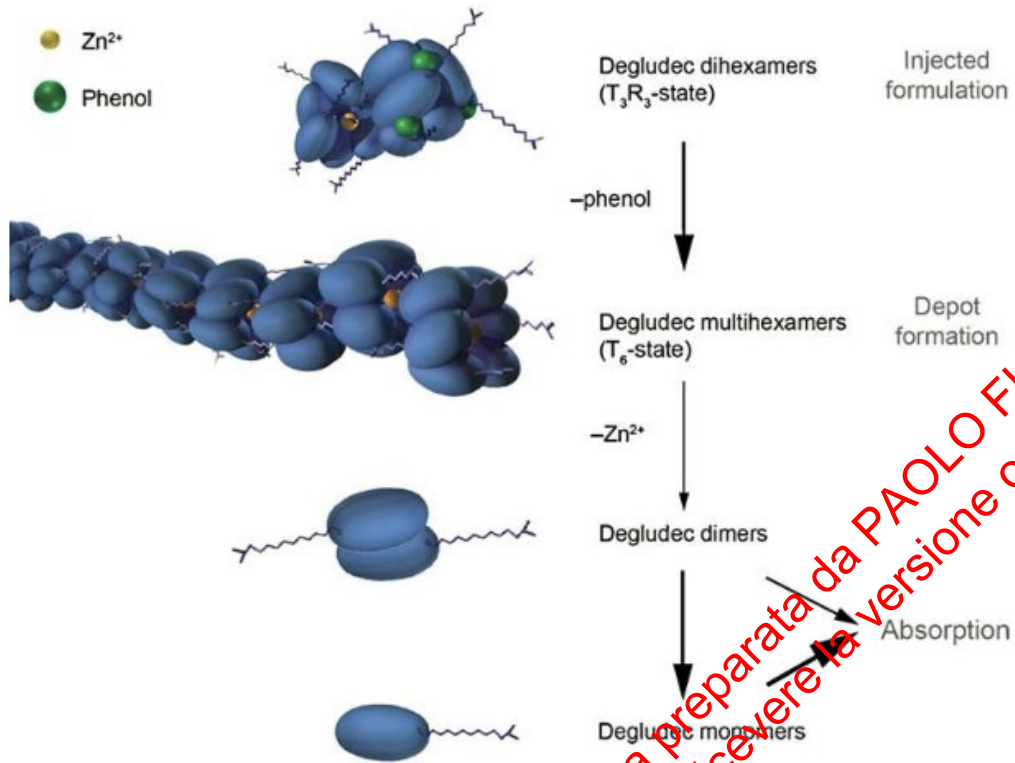
Median PG = 110 mg/dl, keep same dose

Median PG < 110 mg/dl, decrease 2U

Diapositiva preparata da PAOLO FIORINA e ceduta alla Societa Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

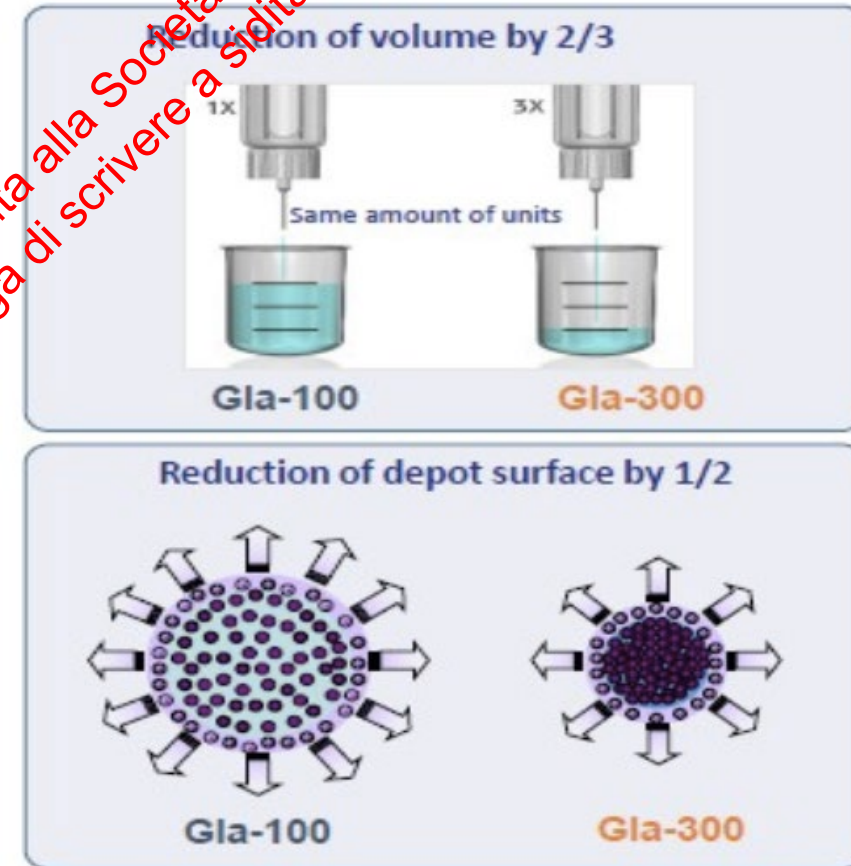
Next-generation basal insulins

DEGLUDEC



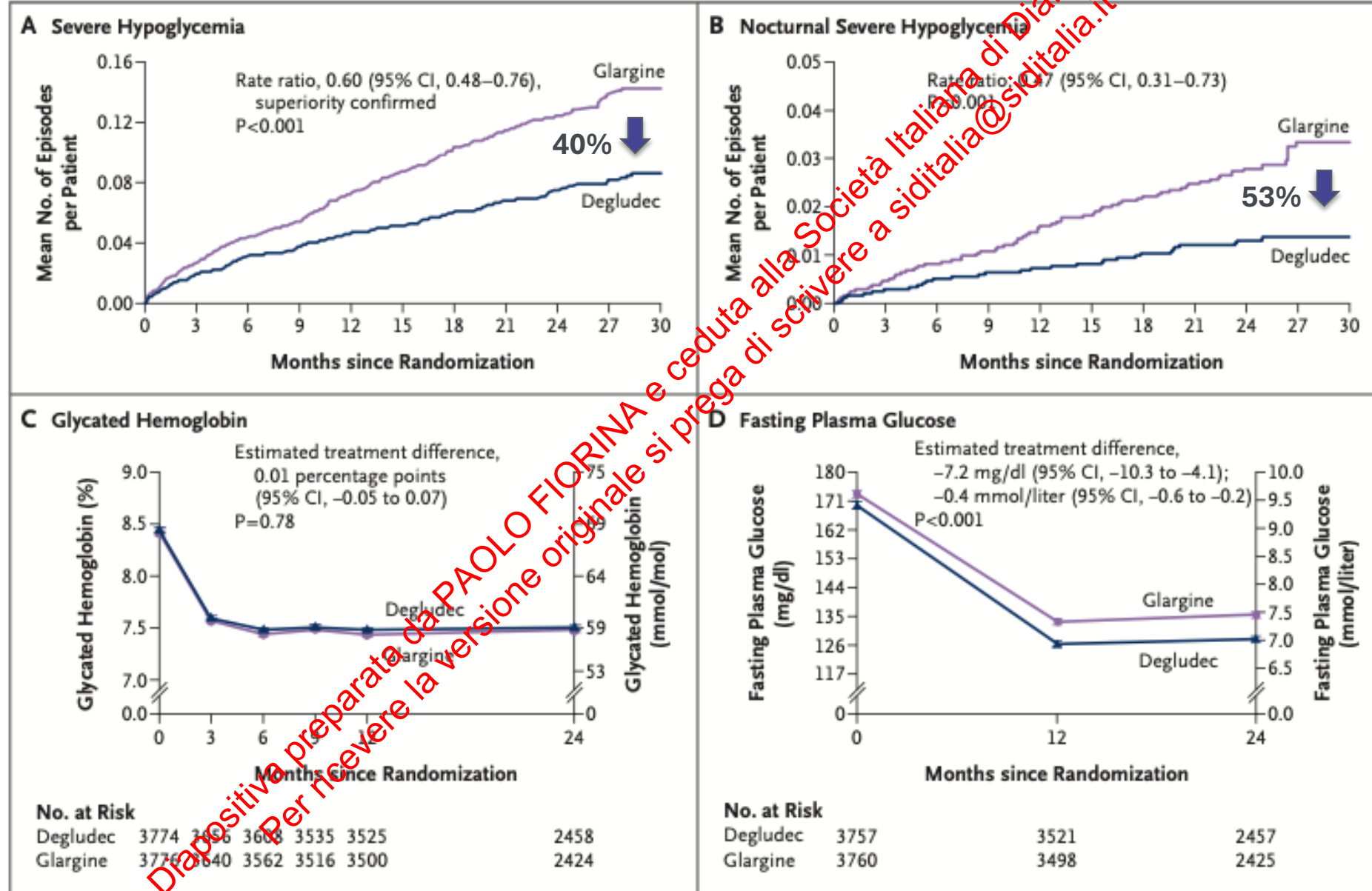
Jonassen et al., Pharm Res 2012

GLARGINE U-300

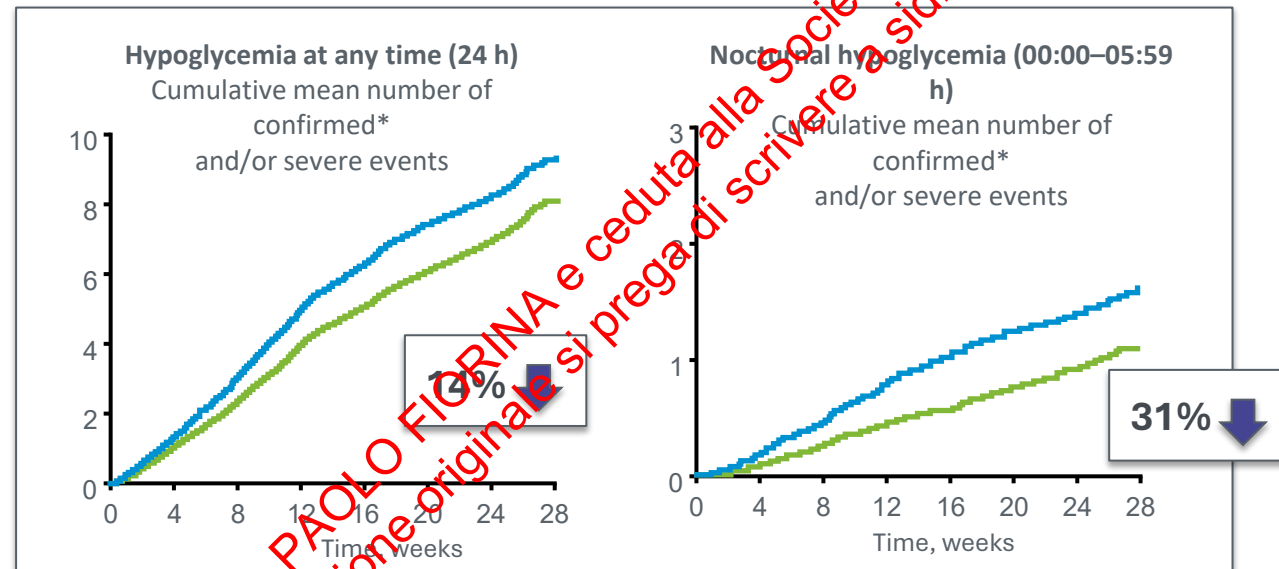


Owens D et al., Diabetes Metab Res Rev 2014

Efficacy and safety of Degludec versus Glargine 100 in T2D



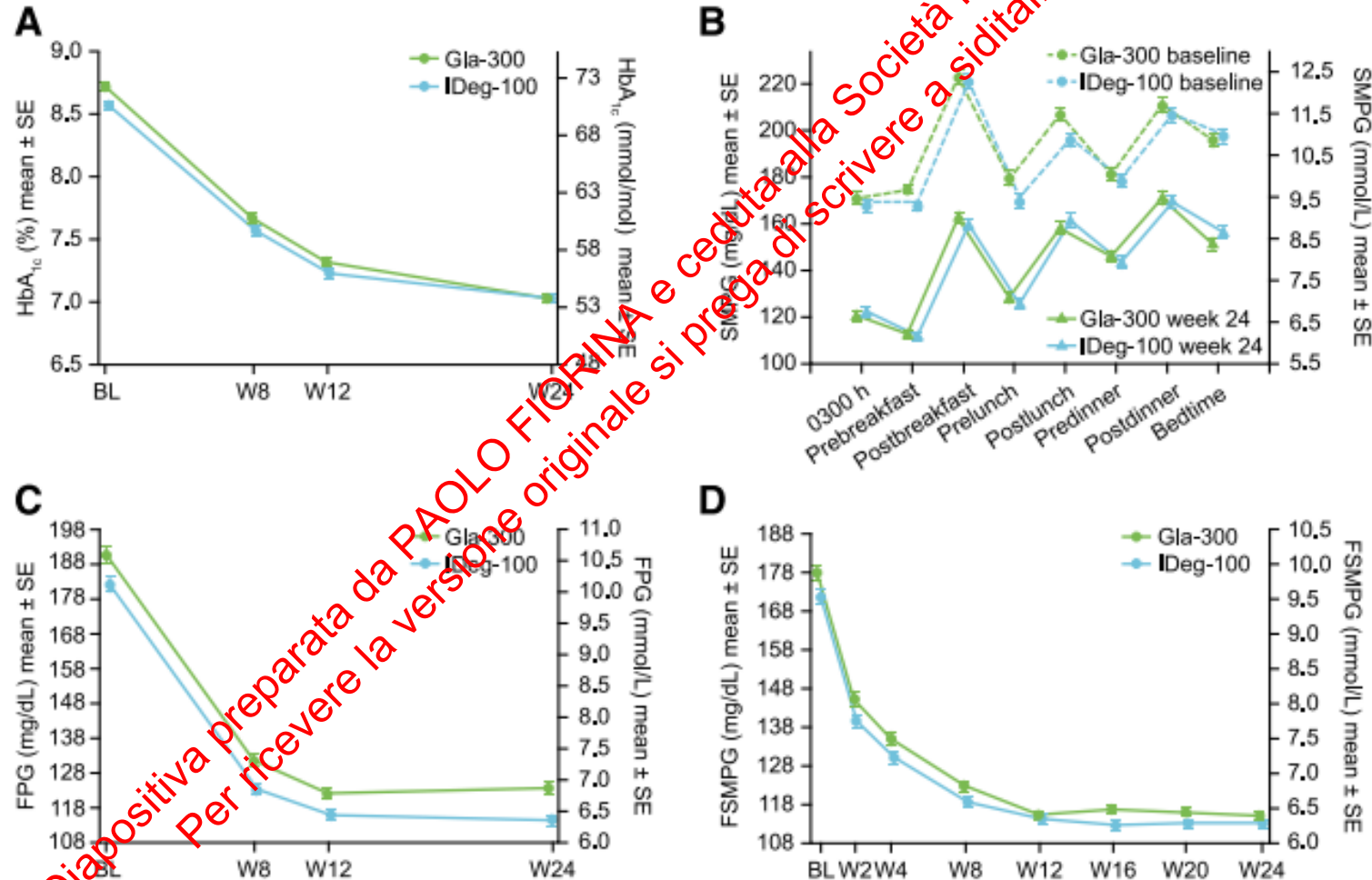
Less Hypoglycemia with Gla-300 vs Gla-100



Riddle MC, et al. Diabetes Care. 2014;37(10):2755–2762; Yki-Järvinen H, et al. Diabetes Care. 2014;37(12):3235–3243; Bolli GB, et al. Diabetes Obes Metab. 2015;17(4):386–394; Terauchi Y, et al. Diabetes Obes Metab. 2016 Apr;18(4):366–374 (main article and Supplementary Table 2); Home PD, et al. Diabetes Care. 2015;38(12):2217–2225; Matsuhisa M, et al. Diabetes Obes Metab. 2016;18(4):375–383 (main article and Supplementary Table 1), Ritzel R. et al., Diabetes, Obesity and Metabolism 2015

Similarities between insulin Glargine 300 and insulin Degludec

The Randomized Head-to-Head BRIGHT Trial



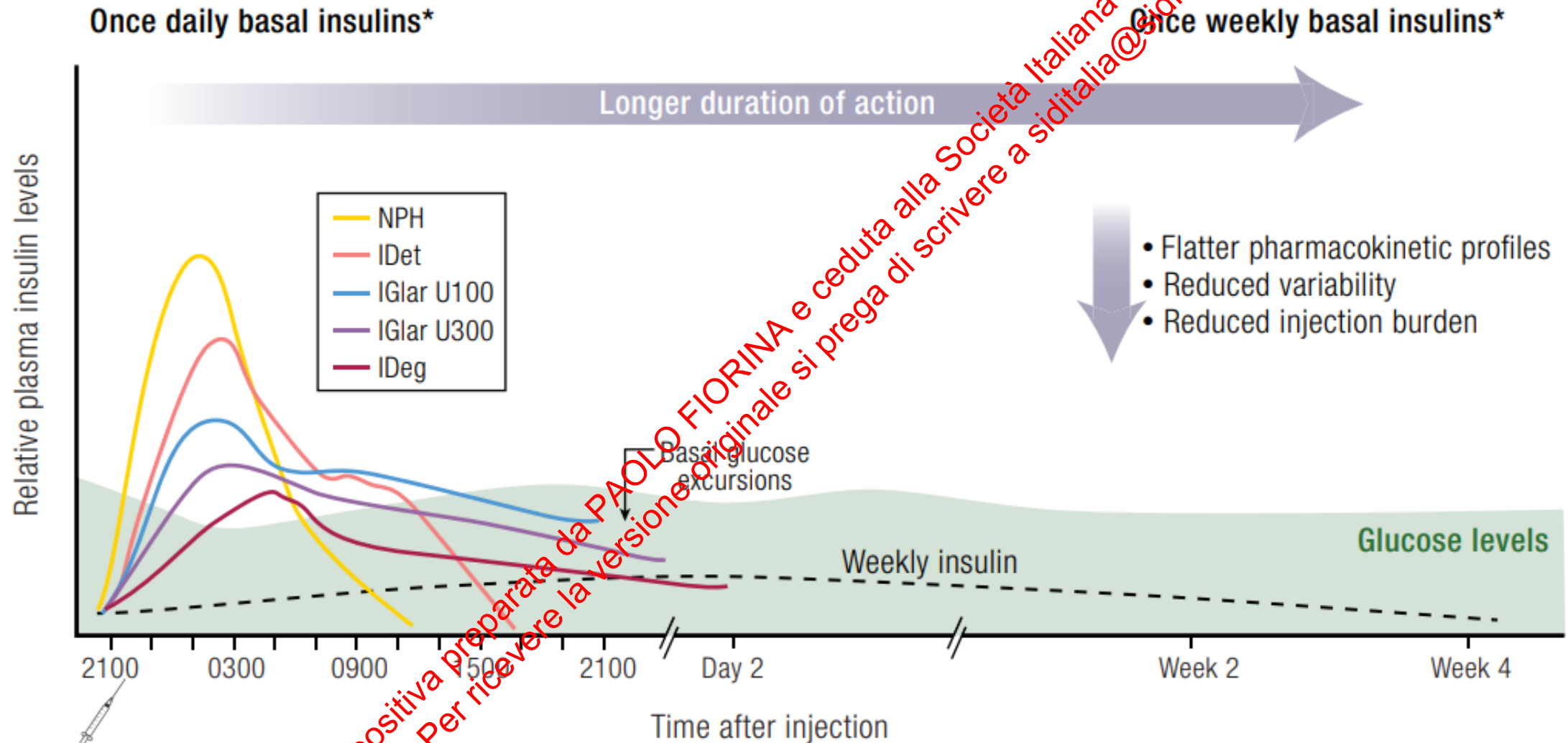
Diapositiva preparata da PAOLO FIORINA e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Outline

1. Introduction
2. Insulin therapy in T2D
- 3. Weekly Insulin**
4. Conclusions

Diapositiva preparata da PAOLO FIORINA e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

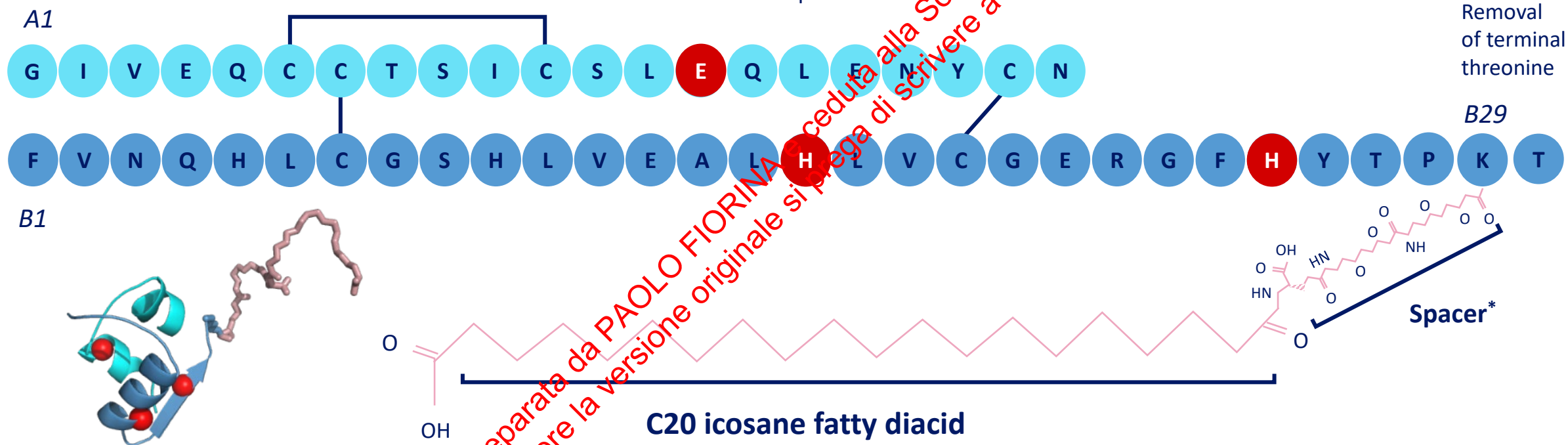
The basis for weekly insulin therapy



Icodec

Three amino acid substitutions

- Molecular stability
- Reduced enzymatic degradation
- Slow receptor-mediated clearance



Insulin Icodec

First once-weekly insulin analogue

Approved in Europe (EMA) in March 2024 for T2D

Administration: SC injection (thigh, abdomen, upper arm)

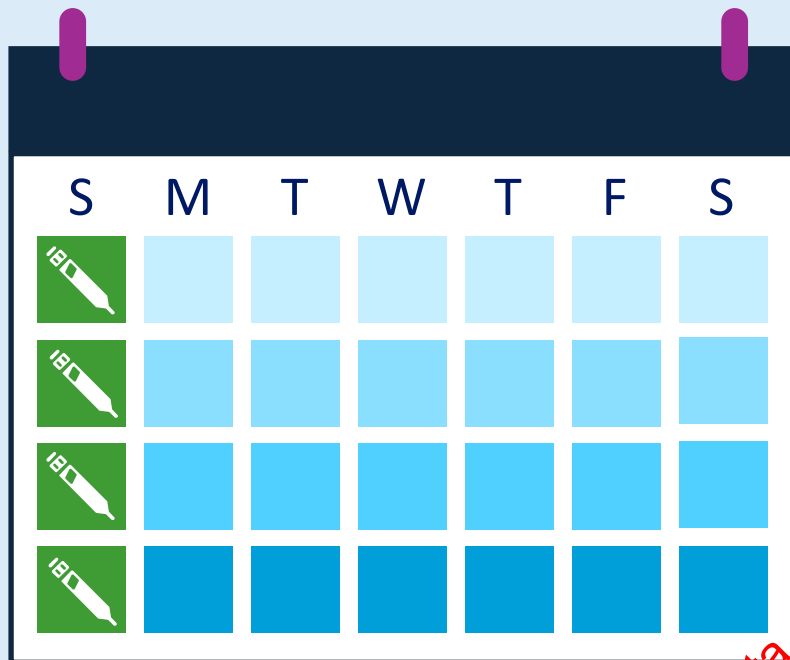
Formulations: pens 1 mL, 1.5 mL, 3 mL; 700 IU/mL concentration

Starting dose (insulin-naïve): 70 IU/week + 10 IU/day

Switching from basal insulin: 1:1 weekly conversion, with +50–100% loading dose at first injection

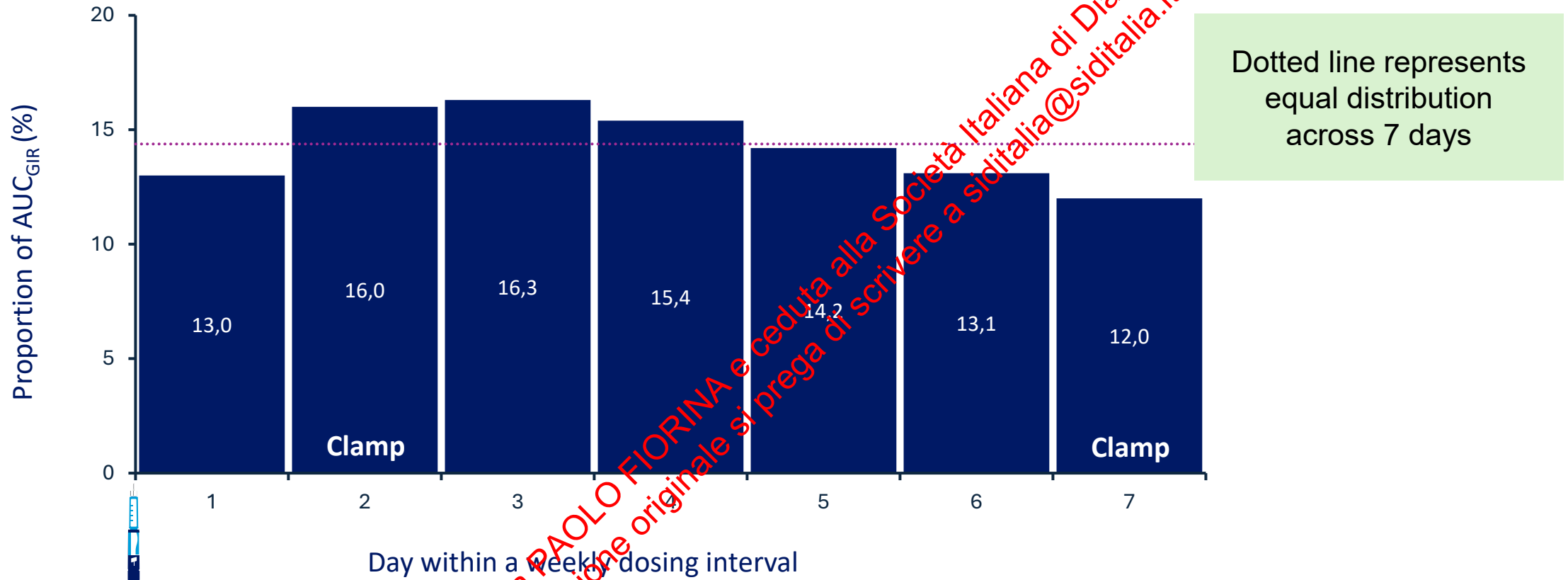
Diapositiva preparata da PAOLO FIORINA e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Recognised Attributes of Once-weekly Medications



- **Greater convenience**
 - **Better medication adherence**
 - **Improved health-related quality of life**
 - **Less overwhelming sense of treatment**
 - **Easier for individuals in need of medical assistance**
- ✓ $t_{1/2}$ = 196 hours (~7 days)
 - ✓ Steady state after 3–4 weekly injections

Modelled Glucose-lowering Effect of icodec



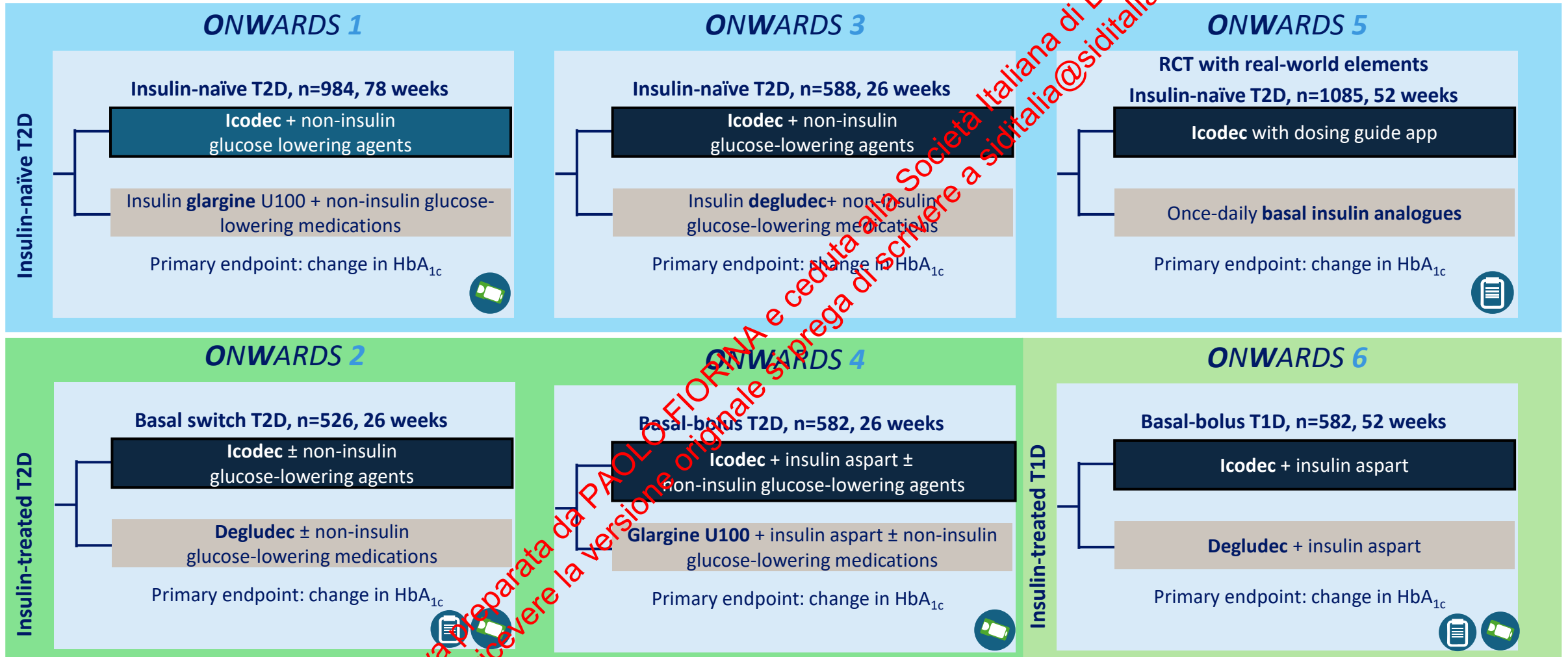
Close to even distribution of total glucose-lowering effect of insulin icodec over seven days

Modelled distribution of total glucose-lowering effect (AUC_{GIR}) of icodec within a dosing interval of one week at close to steady state. All three dose levels are combined. Individuals completing both glucose clamps and with pharmacokinetic data at steady state are included (n=32). Data are arithmetic mean.

AUC, area under the curve; GIR, glucose infusion rate; n, number of subjects.

1. Nishimura E et al. *BMJ Open Diab Res Care*. 2021;9(1).

ONWARDS Programme



CGM, continuous glucose monitoring; n, number of subjects; PROs, patient reported outcomes; RCT, randomised controlled trial.

1. Philis-Tsimikas A et al. Diabetes Obes Metab. 2022

ONWARDS Programme: Topline Results



*insulin degludec or insulin glargine U100/U300. Clinically significant hypoglycaemia (level 2): blood glucose <3.0 mmol/L (<54 mg/dL) confirmed by blood glucose meter. Severe hypoglycaemia (level 3): hypoglycaemia with severe cognitive impairment requiring external assistance for recovery. OD, once-daily; RCT, randomized clinical trial.

1. Rosenstock J et al. *N Engl J Med*. 2020;383:2107–2116; 2. Lingway I et al. *JAMA*. 2023;10.1001/jama.2023.11313; 3. Lingway I et al. 2023 ADA Scientific Sessions. 178-OR; 4. Bajaj H. 2023 ADA Scientific Sessions. 803-P. 5. Philis-Tsimikas A et al. *Lancet Diabetes Endocrinol*. 2023;11(6):414-425. 6. Mathieu C et al. *Lancet*. 2023;401(10392):1929-40; 7. Russell-Jones D et al. 2023. EASD 59th Annual Meeting.

Titration Algorithm

Icodec in insulin-naïve T2D

Pre-breakfast SMBG		Glargine U100 dose adjustment	Icodec dose adjustment
Up-titration	Mean of SMBG values >130 mg/dL	+3 U	+20 U
Target	Mean of SMBG values 80–130 mg/dL	0 U	0 U
Down-titration	Lowest SMBG value <80 mg/dL	–3 U	–20 U

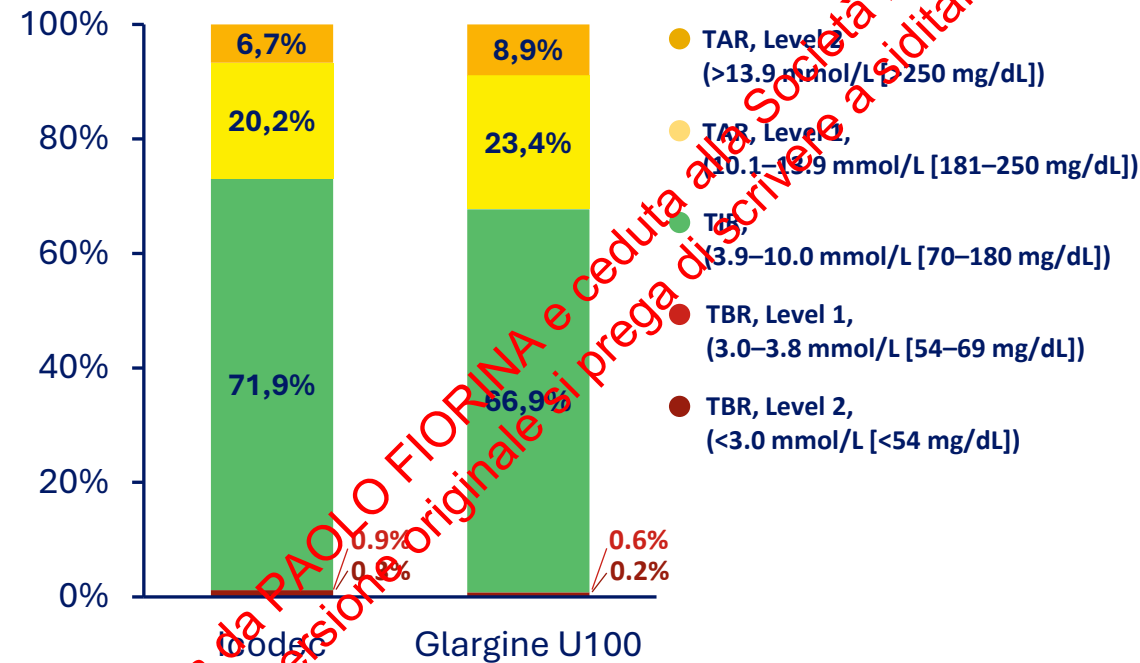
Dose adjustment was based on three pre-breakfast SMBG values, measured two days prior to and on the day of titration. If any of the three pre-breakfast SMBG values were below the lower limit of the target range, titration was based on the lowest recorded value. If all three SMBG values were above the lower limit of the target range, titration was based on the mean of the three measurements. Both insulins were titrated once-weekly.

SMBG, self-measured blood glucose; U, unit(s).

1. Appendix to: Rosenstock J, et al. *N Engl J Med* 2023;10.1056/NEJMoa2303208.

CGM Parameters during Week 48 to 52

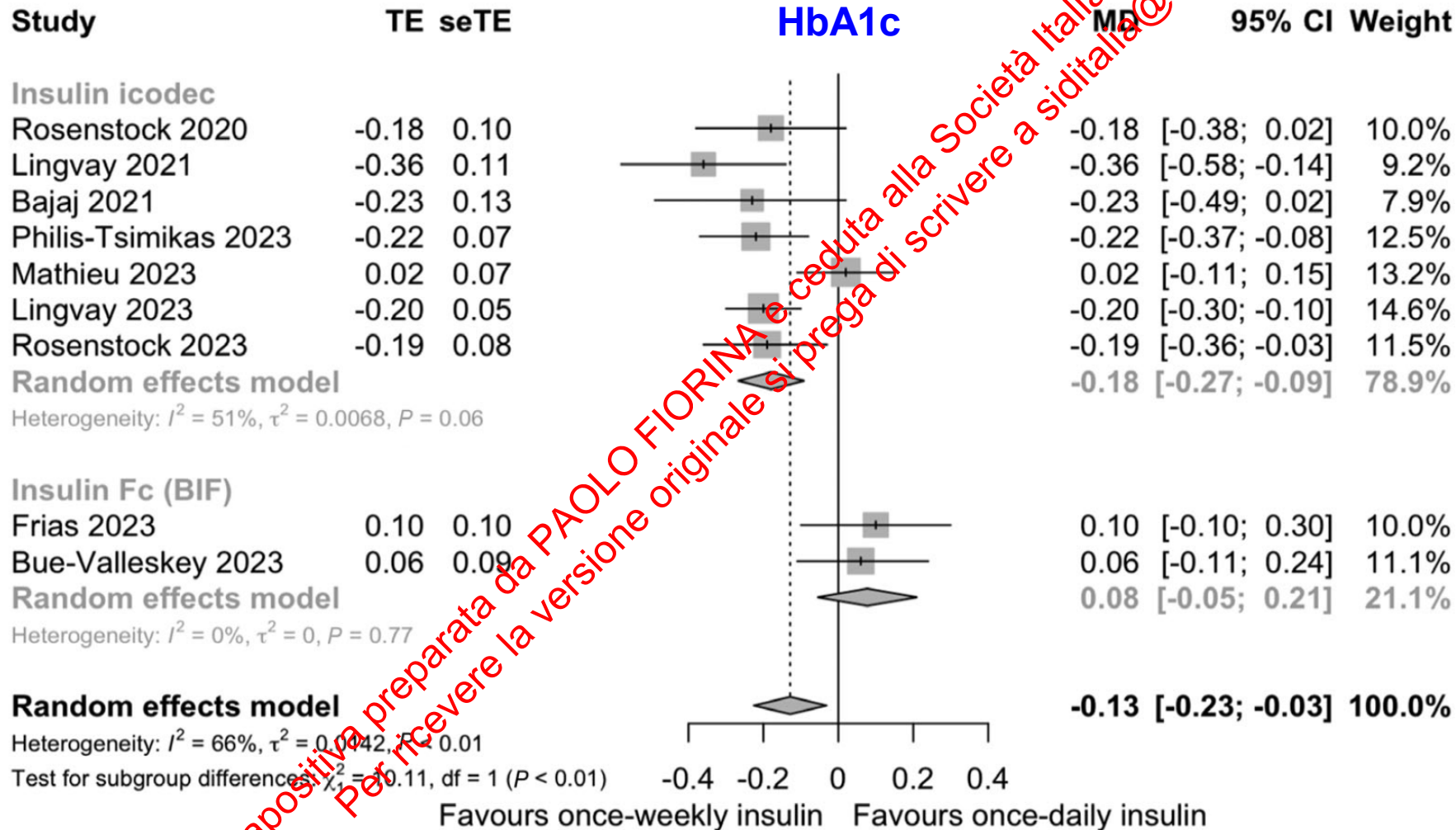
Icodec in insulin-naïve T2D



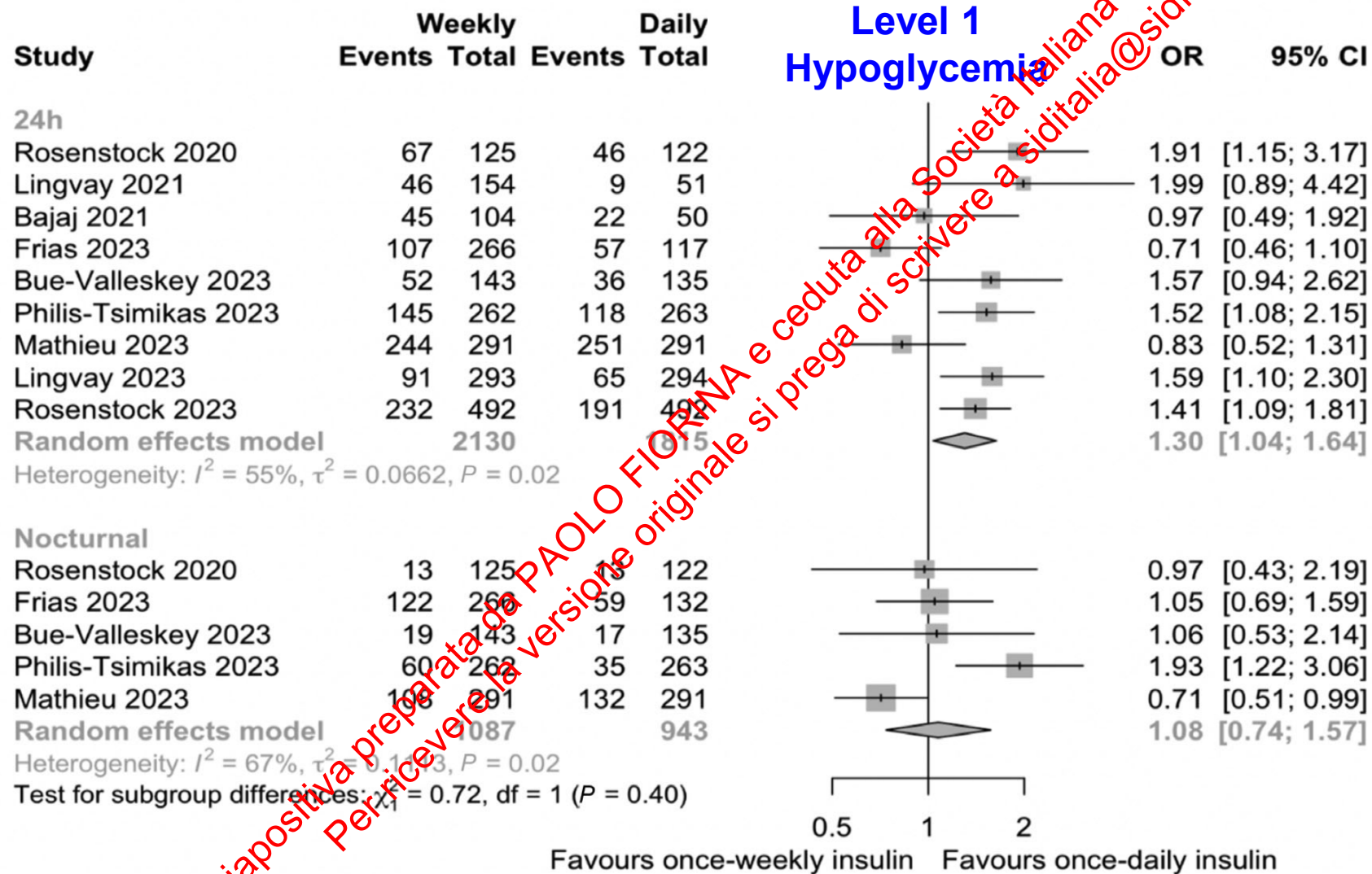
CGM, continuous glucose monitor; CI, confidence interval; ETD, estimated treatment difference; ETR, estimated treatment ratio; TAR, time-above-range; TBR, time-below-range; TIR, time-in-range.

1. Rosenstock J, et al. *N Engl J Med* 2023;10:1056/NEJMoa2303208; 2. Rosenstock J et al. 2023 ADA Scientific Sessions. 179-OR.

Efficacy and Safety of Once-weekly insulin in T2D



Efficacy and Safety of Once-weekly insulin analogues in T2D



Outline

1. Introduction
2. Insulin therapy in T2D
3. Weekly Insulin
4. Conclusions

Diapositiva preparata da PAOLO FIORINA e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Conclusions

- ✓ Traditional basal insulin, administered once daily, remains a cornerstone in the management of T2D
- ✓ Emerging weekly insulin formulations represent a significant innovation aimed at reducing injection burden, improving patient adherence, and maintaining stable glycemic control over a longer period
- ✓ Weekly insulin use requires careful initiation, slower dose titration, and further long-term studies to confirm safety, efficacy, and suitability across diverse patient populations

Diapositiva preparata da PAOLO FIORINA e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Acknowledgements

www.casadiabete.it



UNIVERSITÀ
DEGLI STUDI
DI MILANO

Sistema Socio Sanitario



Regione
Lombardia

ASST Fatebenefratelli Sacco