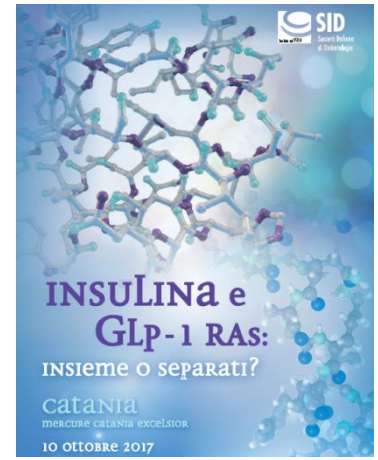


Vantaggi e limiti della terapia insulinica

Giorgio Sesti

Università “Magna Graecia” di Catanzaro

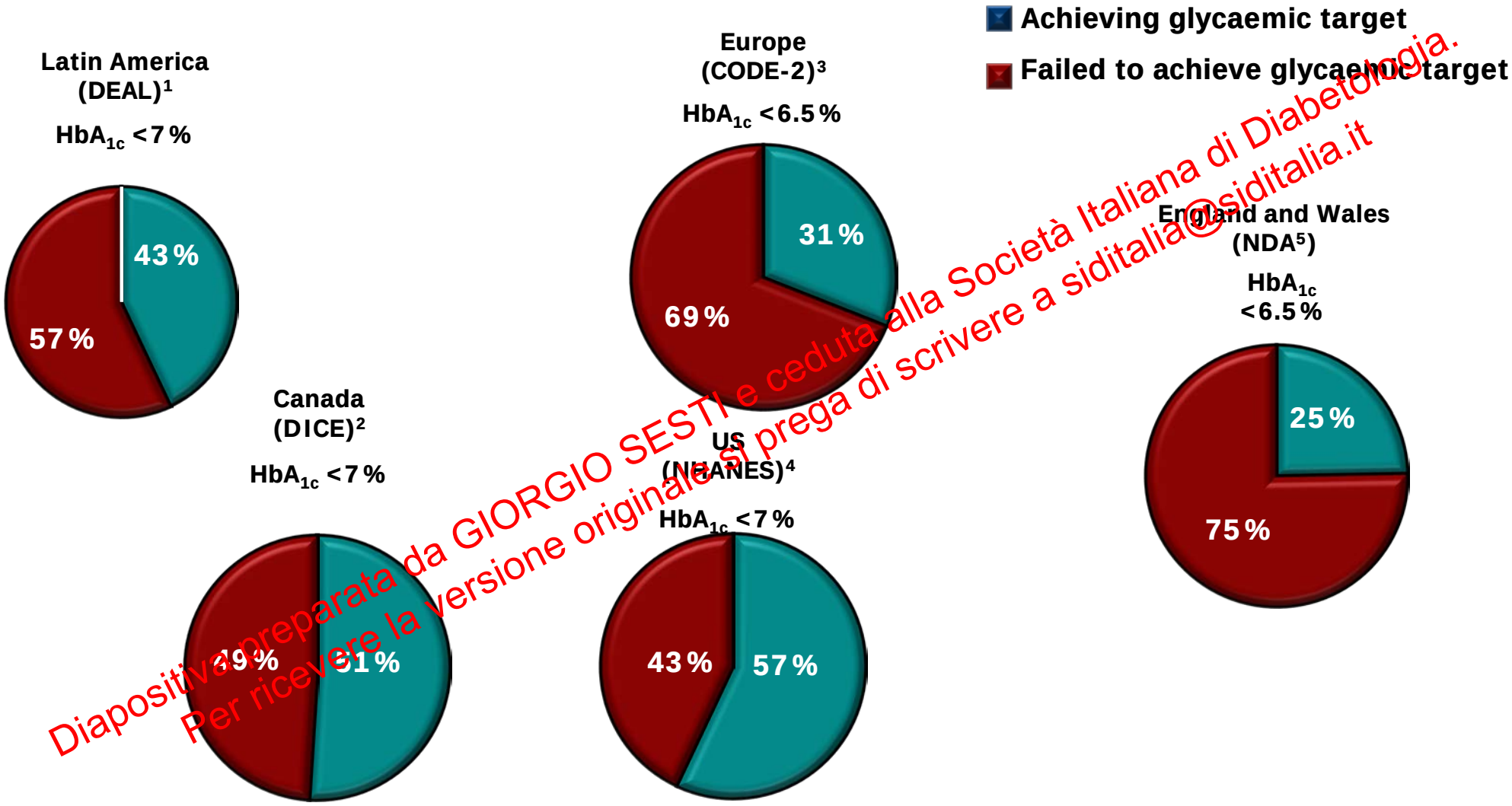
Potenziali conflitti di interesse

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

Novo Nordisk, MSD, Boehringer Ingelheim, Lilly, Janssen, Astra Zeneca, Theras Lifetech, Abbott e Novartis per attività di Relatore ad eventi.

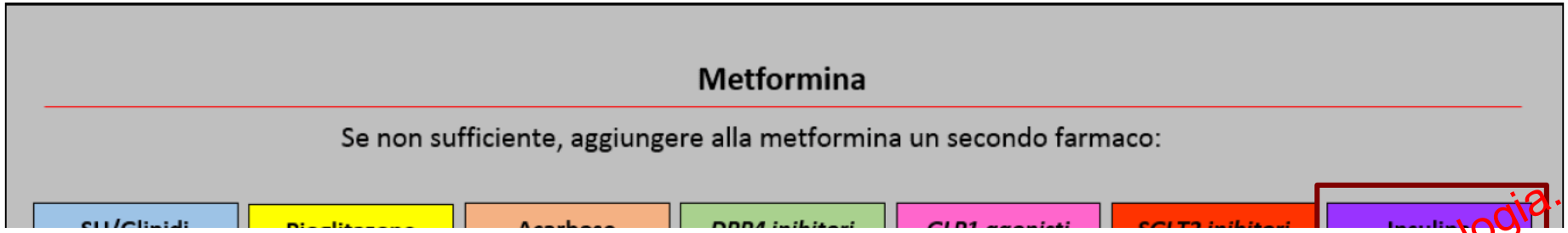
Servier, Mylan, Novo Nordisk, Boehringer Ingelheim, Lilly, Astra Zeneca, MSD Italy, Sanofi, Pfizer e Abbott per attività di Consulenza.

Diabetes is a progressive disease that requires reassessment to reach target



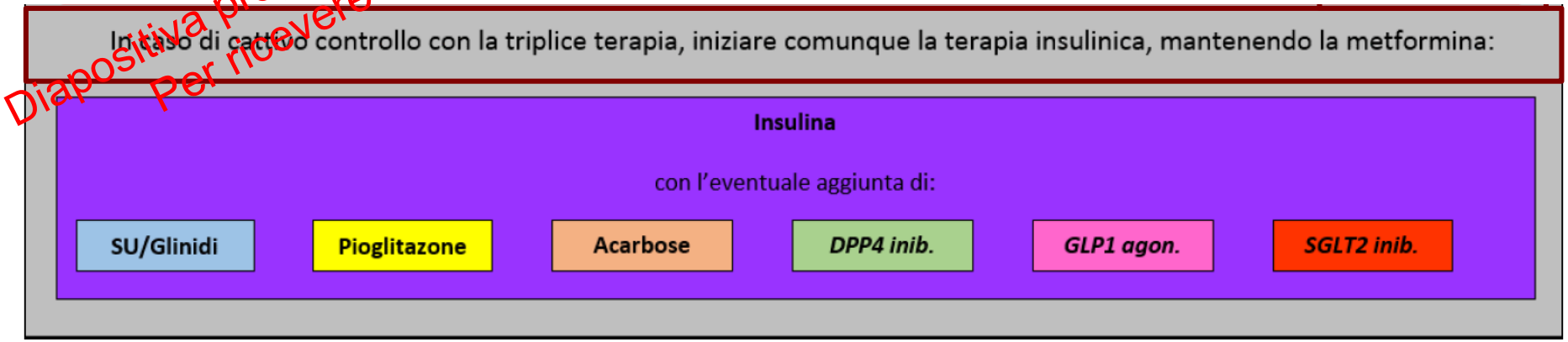
DEAL, Diabetes En America Latina; CODE-2, The Cost of Diabetes in Europe - Type II; DICE, Diabetes in Canada Evaluation; NDA, National Diabetes Audit; NHANES, National Health and Nutrition Examination Survey

1. Lopez Stewart et al. Rev Panam Salud Publica 2007;22:12–20; 2. Harris et al. Diabetes Res Clin Pract 2005;70:90–7;
3. Liebl et al. Diabetologia 2002;45:S23–8; 4. Hoerger et.al. Diabetes Care 2008;31:81–6; 5. HSCIC et al. National Diabetes Audit Report, 2011-12



In caso di marcato scompenso glicometabolico o presenza di sintomi specifici del diabete, anche nel paziente non precedentemente trattato con farmaci si può prendere in considerazione immediatamente la terapia combinata con metformina associata a un'altra molecola (**Livello della prova I, Forza della raccomandazione B**) o il trattamento con insulina associata o meno a metformina (**Livello della prova II, Forza della raccomandazione B**). Nel caso che sia presente chetoacidosi oppure sindrome iperosmolare non chetosica, la terapia insulinica è assolutamente necessaria (**Livello della prova I, Forza della Raccomandazione A**).

Quando il controllo della glicemia non è soddisfacente, anche in politerapia, è necessario iniziare la terapia insulinica mono o multiiniettiva. (**Livello della prova I, Forza della raccomandazione A**).



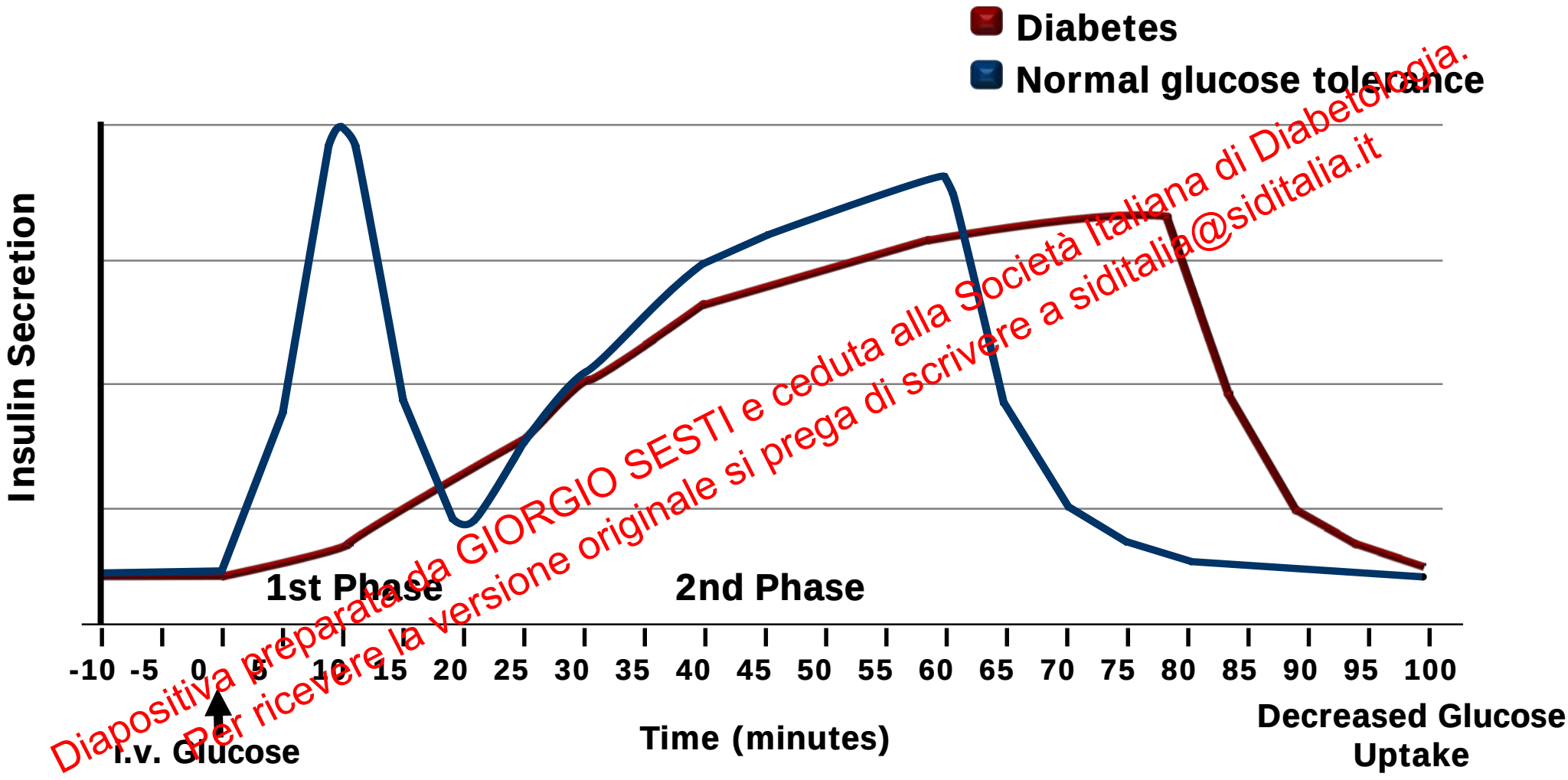
Insulin therapy in T2DM

ADVANTAGES

- **The primary defect in insulin secretion is reverted by insulin treatment**

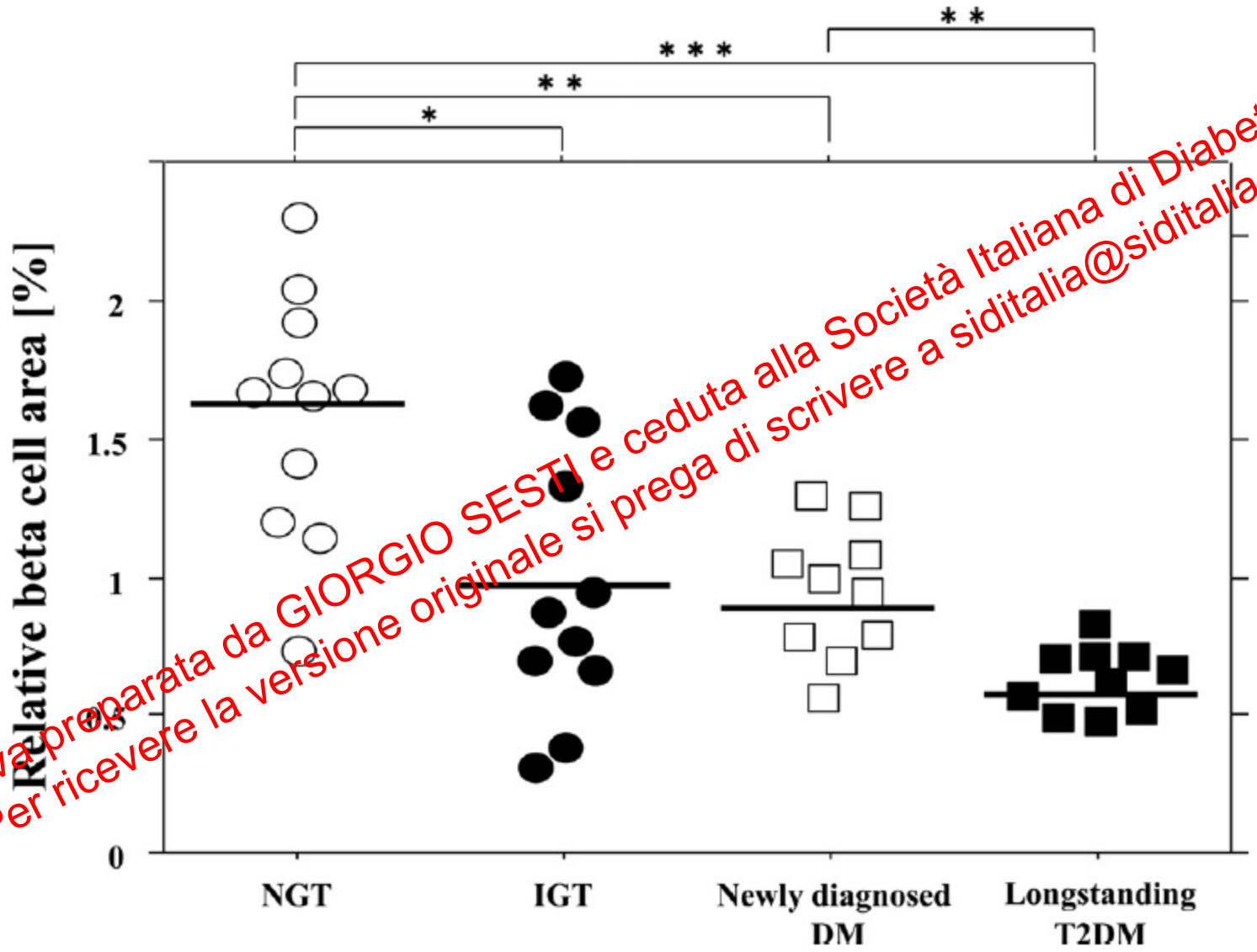
LIMITATIONS

Defects in insulin secretion



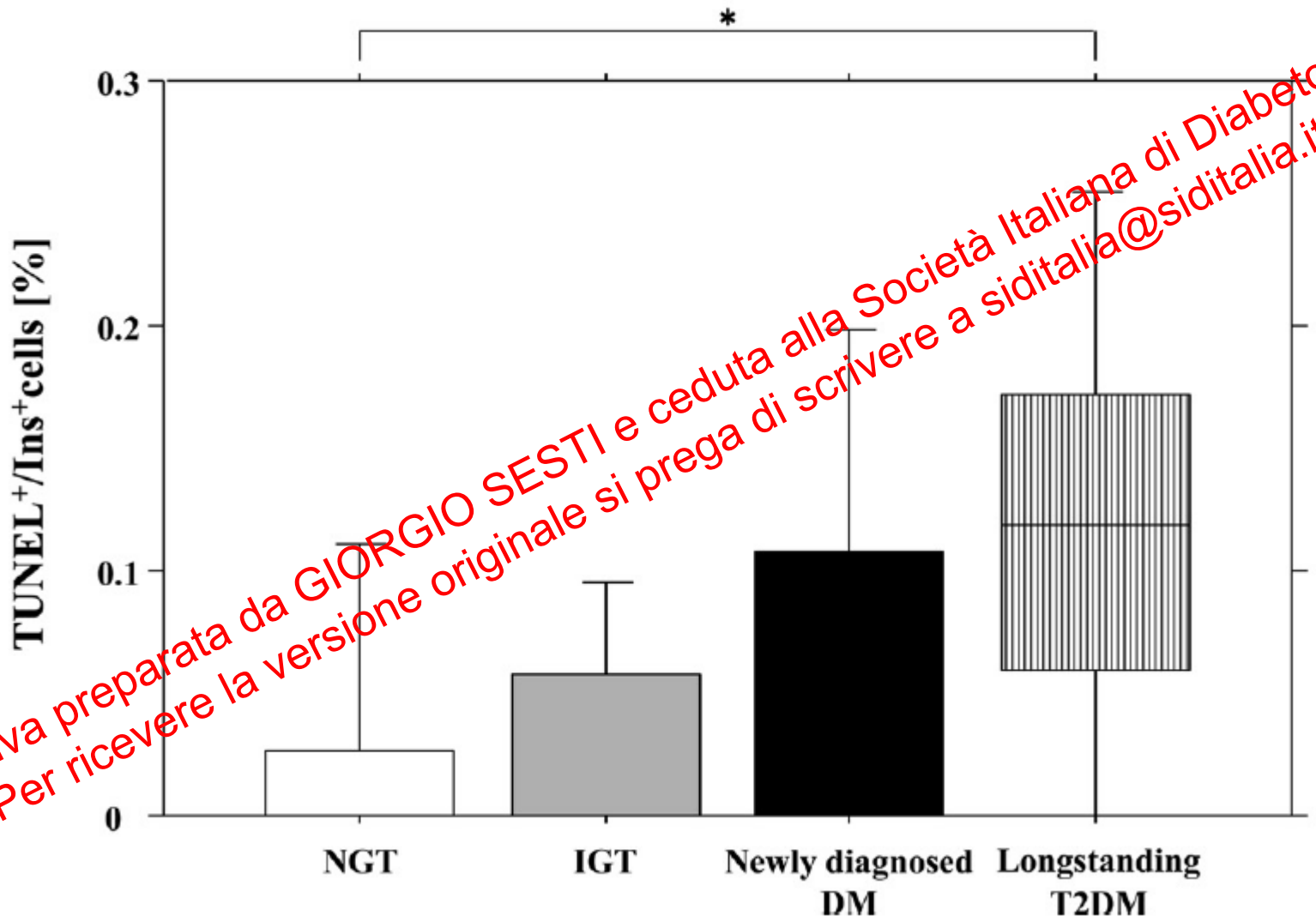
Adapted from Weyer C, et al. J Clin Invest. 1999;104:784-789; Ward WK, et al. Diabetes Care. 1984;7:491-502.

Relative β-cell area to entire pancreatic section in NGT, IGT, newly diagnosed DM and longstanding T2DM



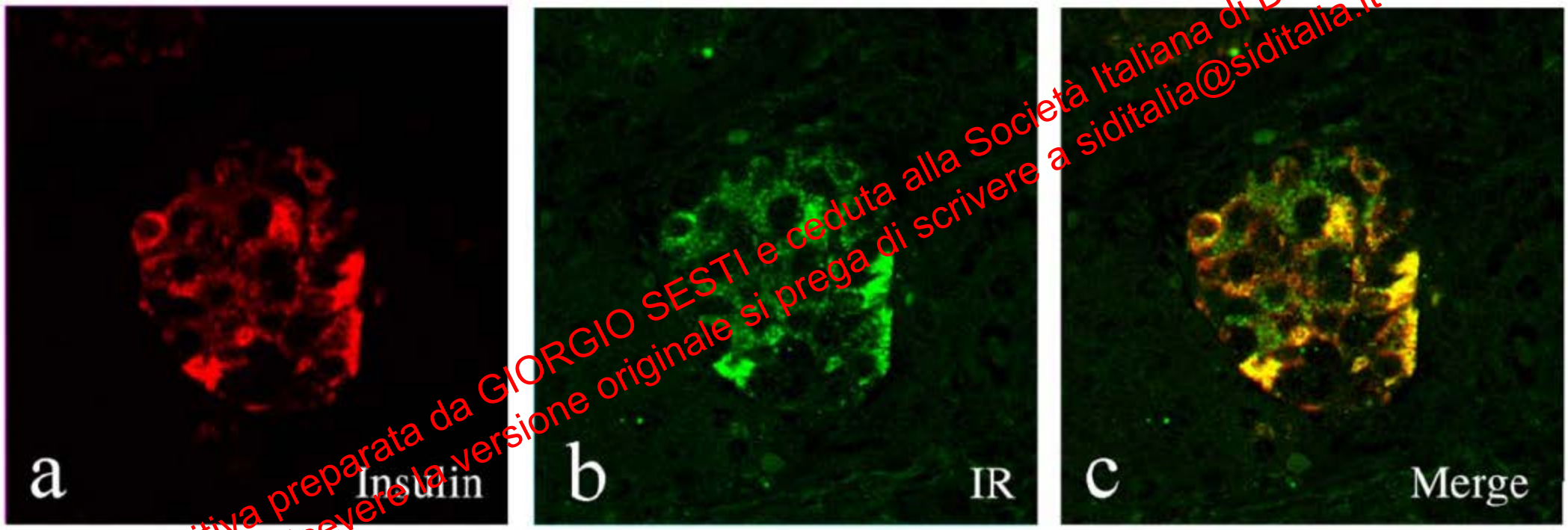
Yoneda S et al. J Clin Endocrinol Metab 98: 2053–2061, 2013

T2DM had a significantly increased β-cell apoptosis compared with the NGT



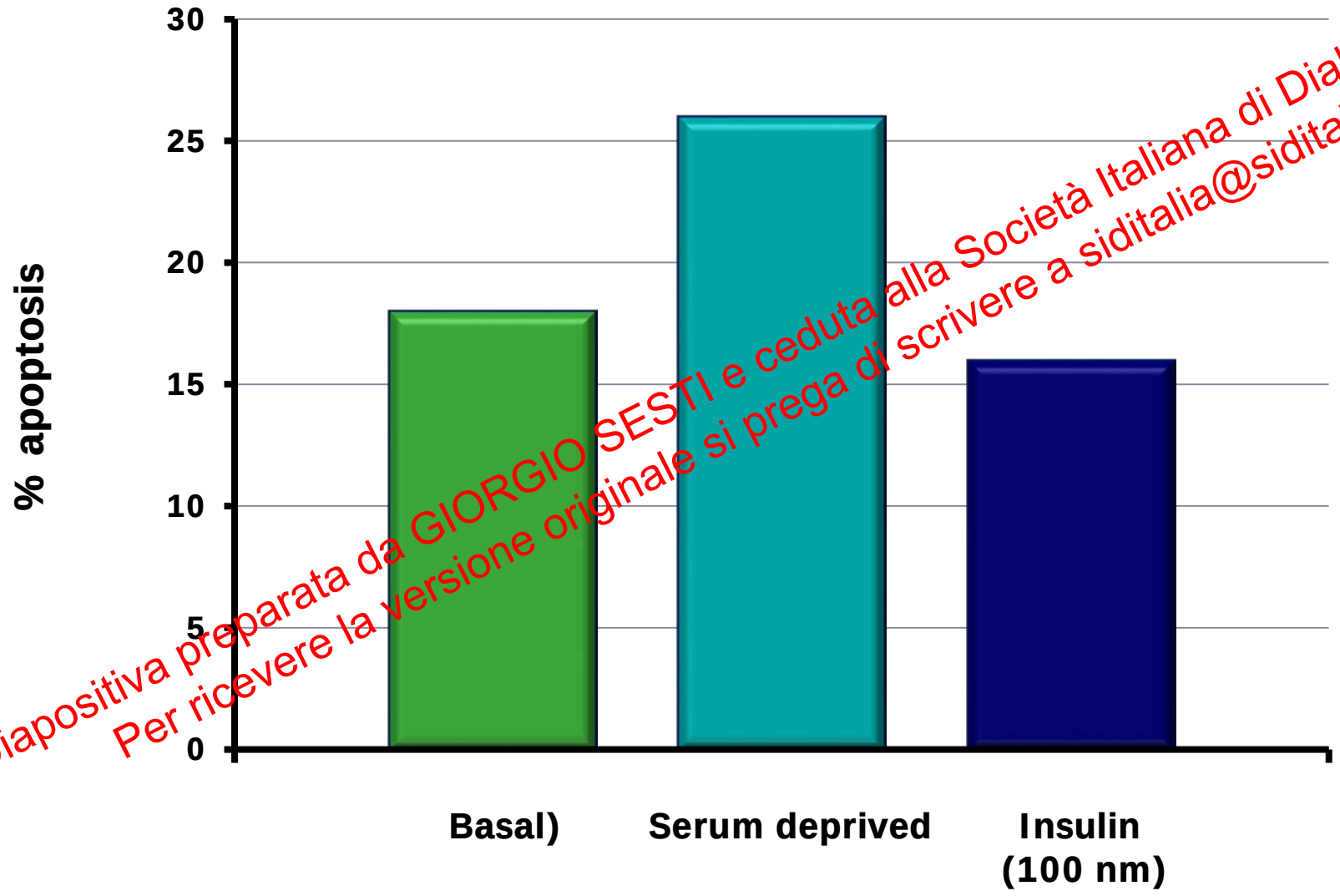
Yoneda S et al. J Clin Endocrinol Metab 98: 2053–2061, 2013

The insulin receptor is localized in insulin secretory vescicles in human pancreatic β-cells



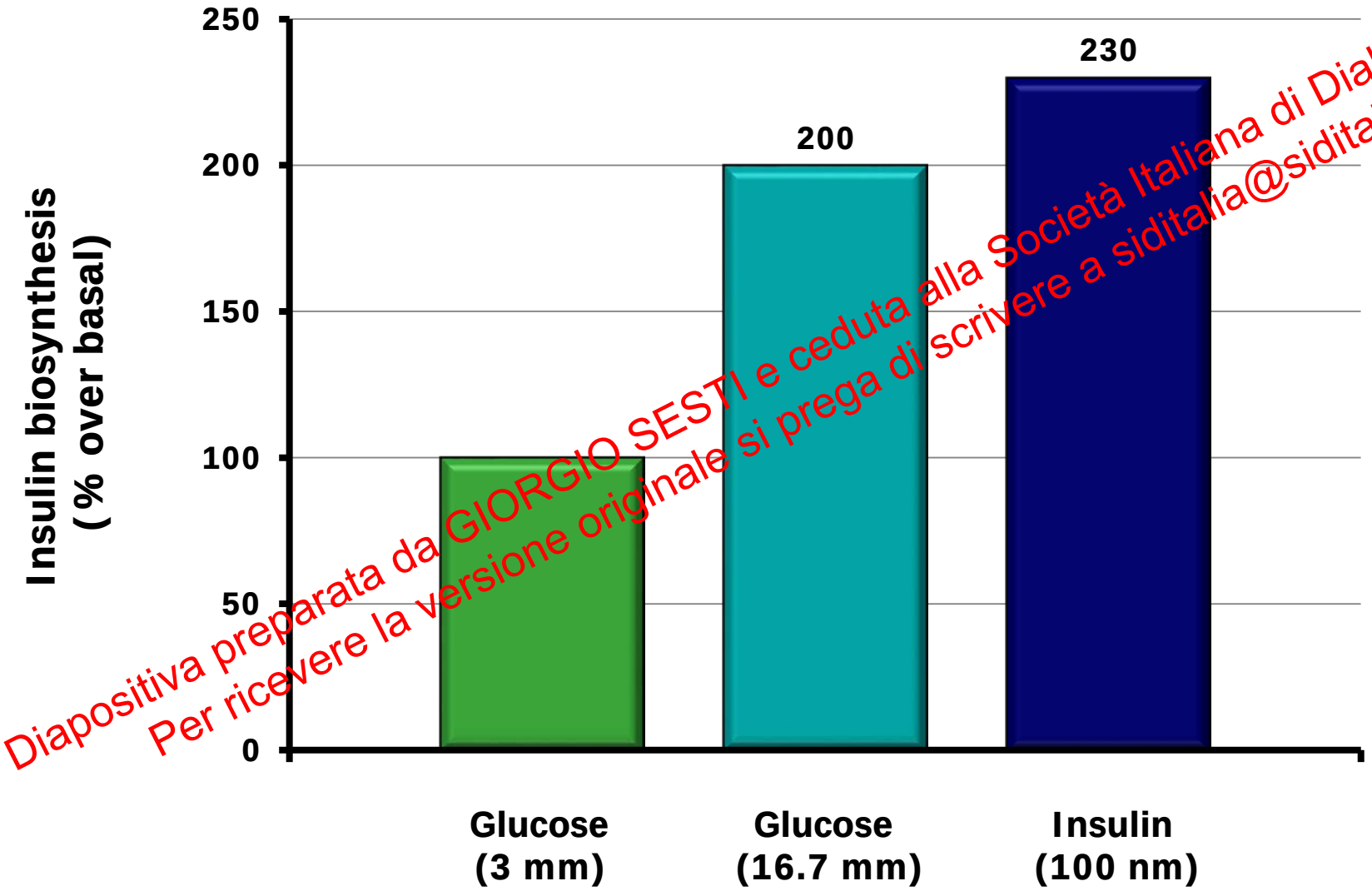
Hribal et al. FASEB J 17: 1340-1342, 2003

Insulin prevents apoptosis induced by serum deprivation for 24 h in human pancreatic islets



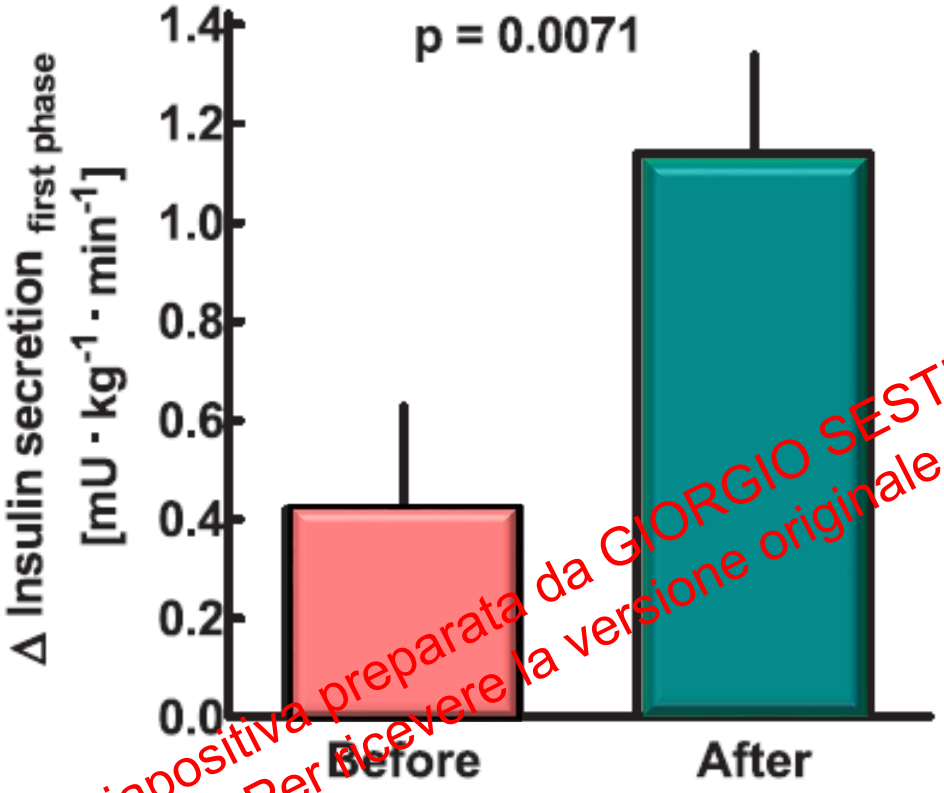
Modified from Federici M al. FASEB J 15: 22-24, 2001

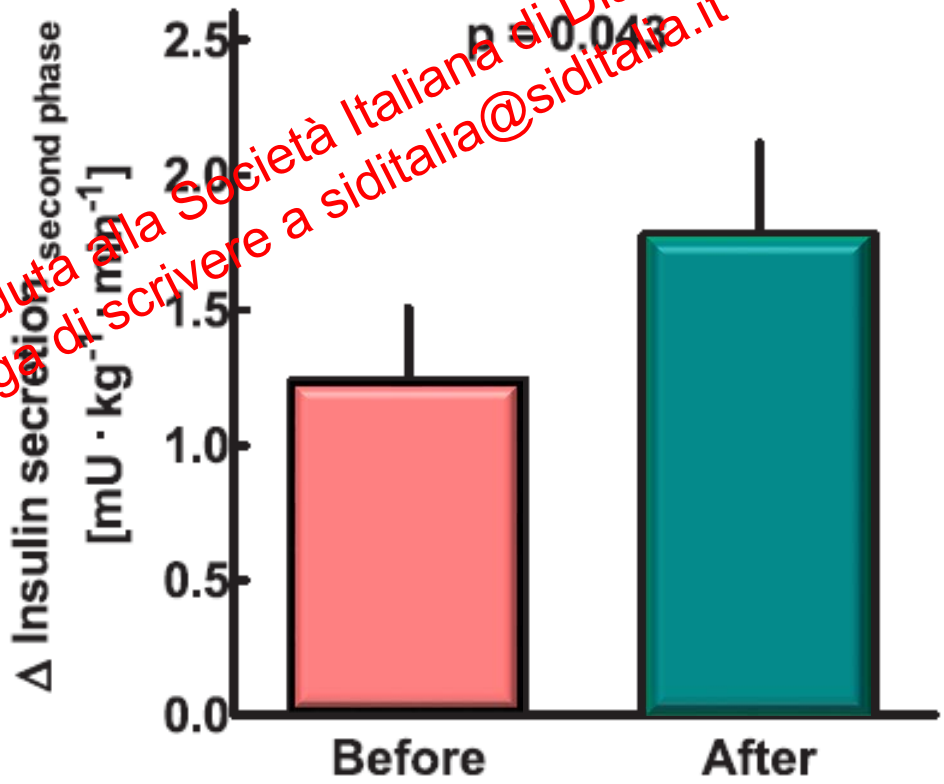
Insulin stimulates biosynthesis in human pancreatic islets



Modified from Andreozzi F et al. Endocrinology 145: 2845–2857, 2004

First-phase and second-phase insulin secretion in response to IVGTT in 14 patients with type 2 diabetes before and after 8 weeks of insulin glargine treatment add-on to metformin





The mean diabetes duration was 4.6±3.0 years

Pennartz C et al. Diabetes Care 34:2048–2053, 2011

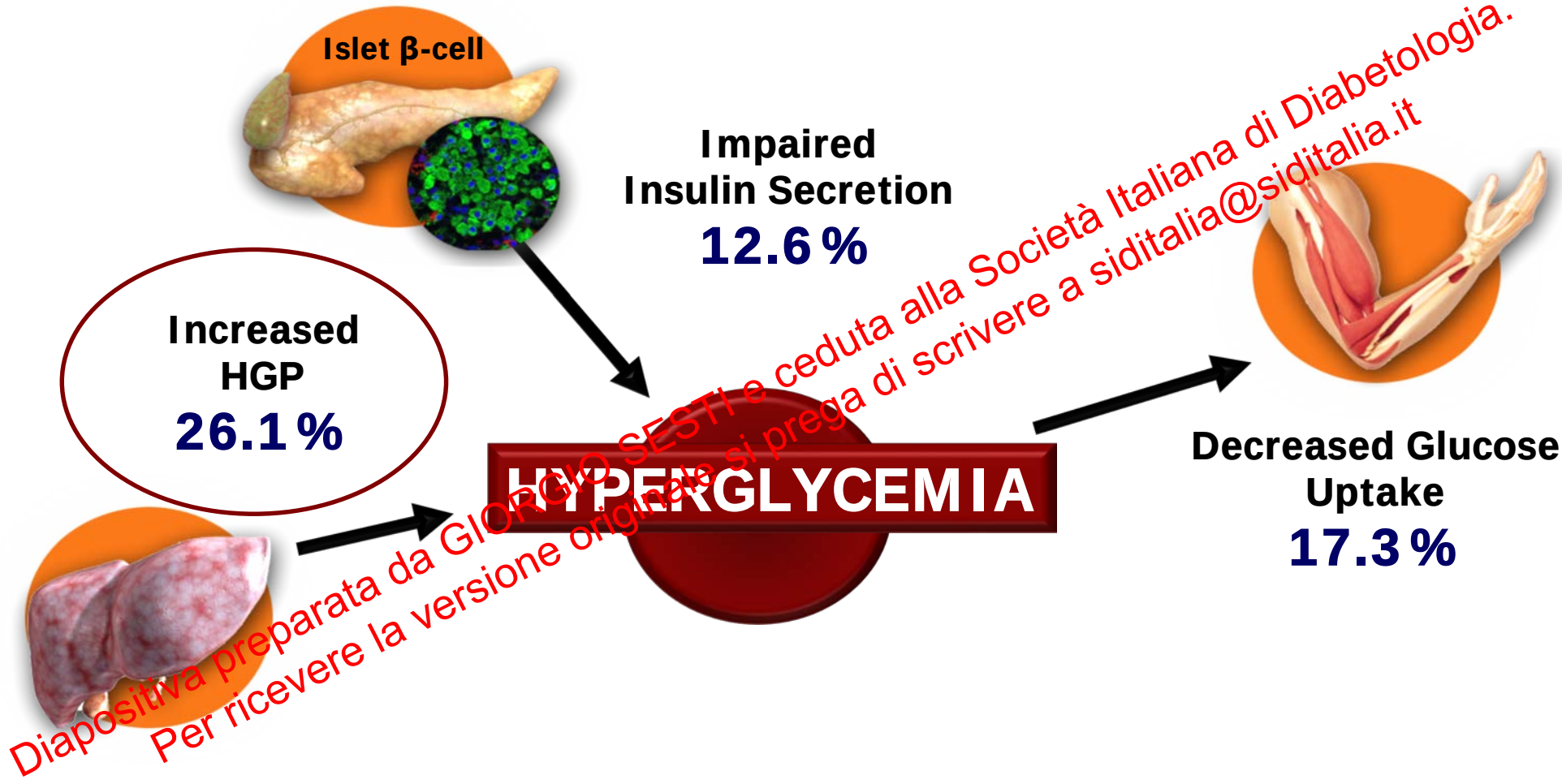
Insulin therapy in T2DM

ADVANTAGES

- The primary defect in insulin secretion is reverted by insulin treatment.
- **Insulin treatment reverted defects in hepatic glucose production.**

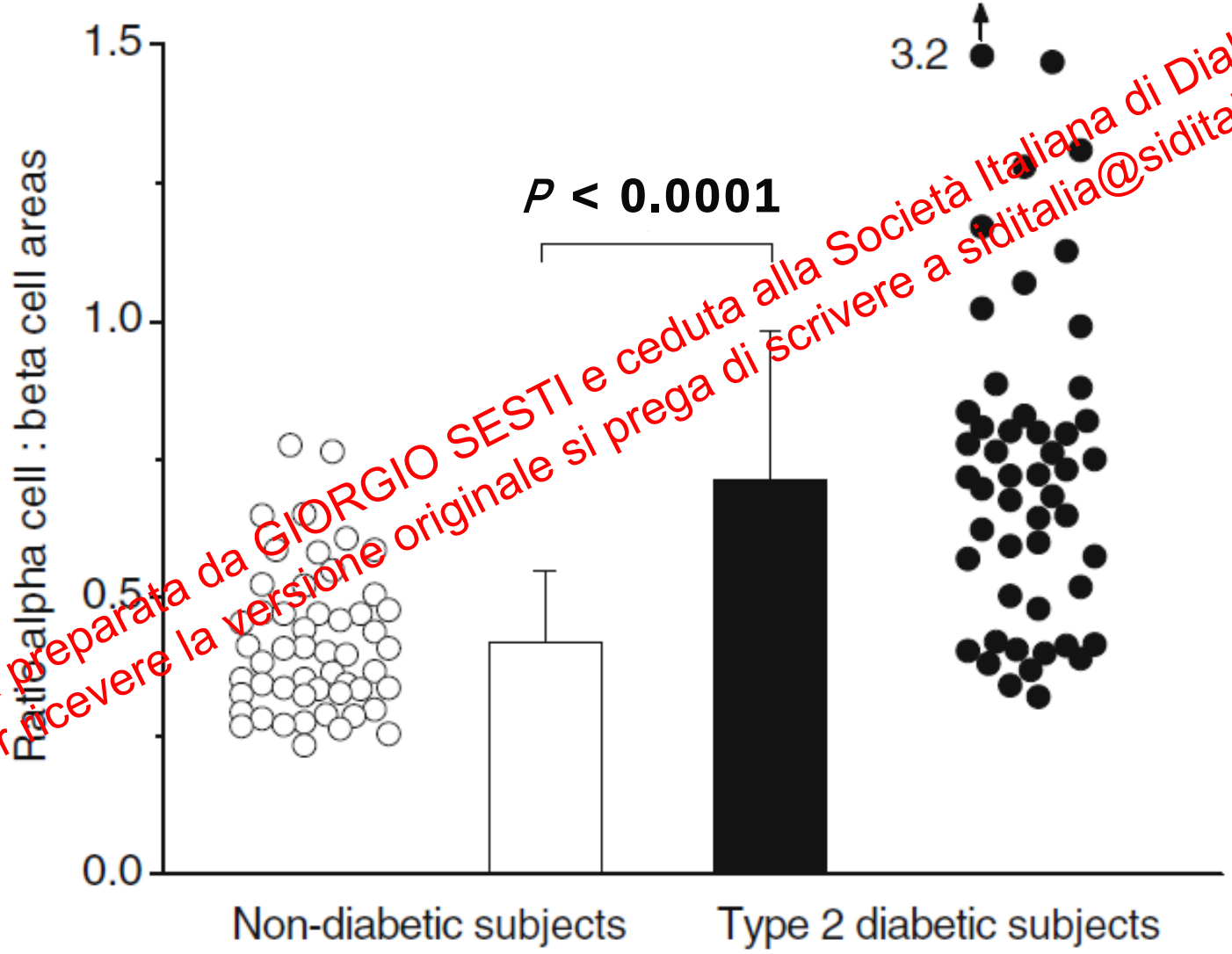
LIMITATIONS

Relative contributions of HGP, and glucose disposal to secondary failure to oral agents in Finnish diabetic patients



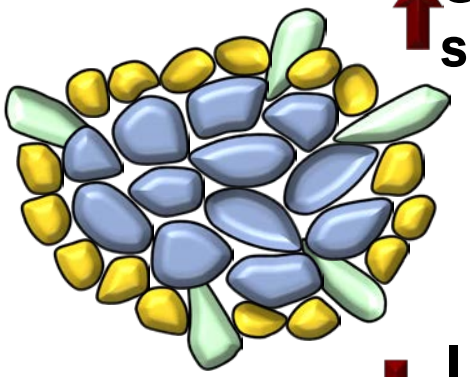
Groop L et al. Am J Med 87:183-190, 1989
Mod. da Gerich JE, Diabetes,Obesity and Metabolism 2:345-350, 2000

Ratio of alpha cell/beta cell areas in 52 non-diabetic subjects (ND) and 50 type 2 diabetic (T2D) subjects



Henquin JCet al. Diabetologia 54:1720–1725, 2011

Eccessive hepatic glucose production



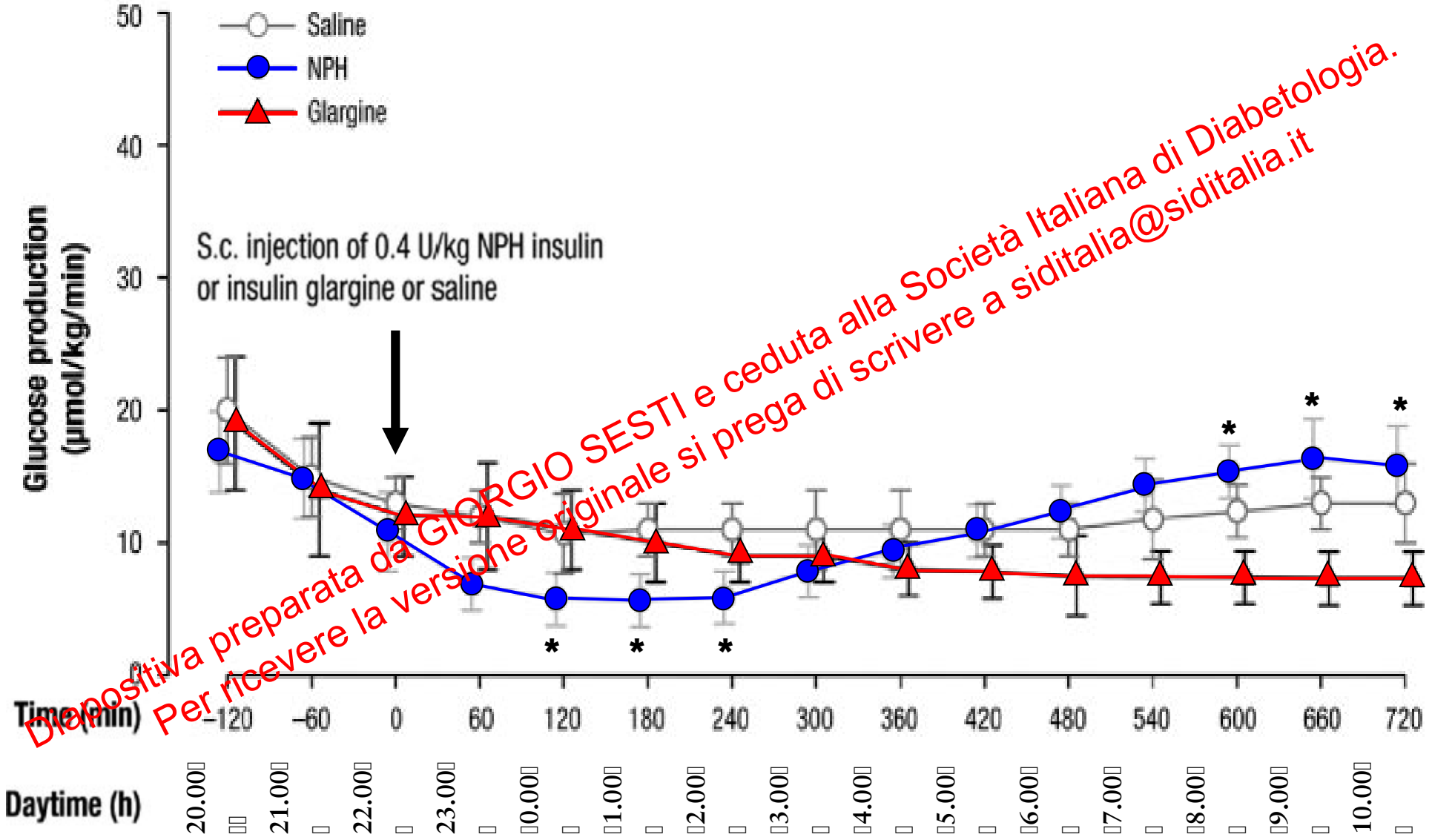
Glucagon secretion

Insulin secretion

Hepatic glucose production

Pancreatic cells: β-cell α-cell δ-cell

Nocturnal Hepatic Glucose Production after Bedtime Injection of Glargine or NPH Insulin in Patients with Type 2 Diabetes



Linn T et al. J Clin Endocrinol Metab 93: 3839–3846, 2008

Insulin therapy in T2DM

ADVANTAGES

- The primary defect in insulin secretion is reverted by insulin treatment
- Insulin treatment reverted defects in hepatic glucose production.
- **Insulin therapy is not associated with atherogenesis and increased risk of CV events.**

LIMITATIONS

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

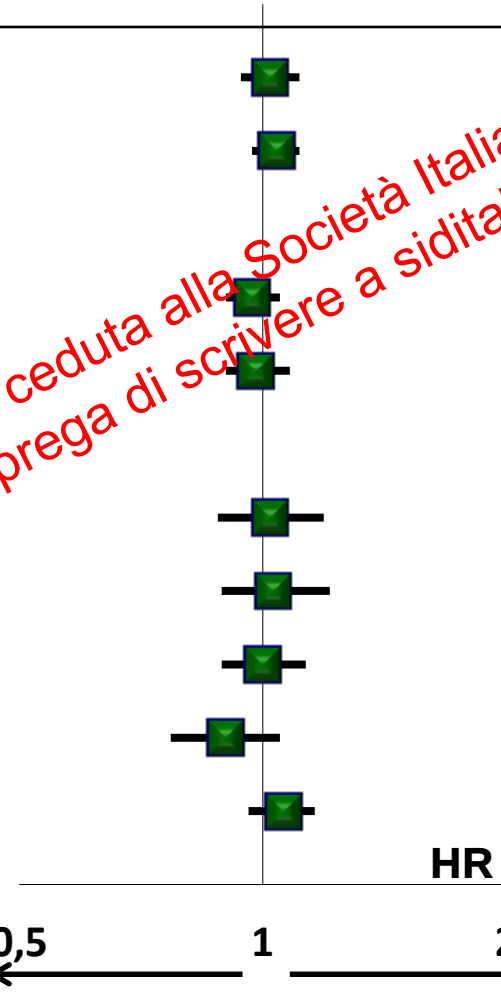
Basal Insulin and Cardiovascular and Other Outcomes in Dysglycemia

The ORIGIN Trial Investigators*

ORIGIN Trial Investigators, N Engl J Med 367: 319-28, 2012

Primary & Secondary Outcomes & their Components

	HR (95% CI)	P	Insulin /100 py	Standard /100 py
1st Coprimary	1.02 (0.94, 1.11)	0.63	2.94	2.85
2nd Coprimary	1.04 (0.97, 1.11)	0.27	5.52	5.28
Microvascular	0.97 (0.90, 1.05)	0.43	3.87	3.99
Death	0.98 (0.90, 1.08)	0.70	2.57	2.60
MI	1.02 (0.88, 1.19)	0.75	0.93	0.90
Stroke	1.03 (0.89, 1.21)	0.69	0.91	0.88
CV Death	1.00 (0.89, 1.13)	0.98	1.57	1.55
CHF Hospital	0.90 (0.77, 1.05)	0.16	0.85	0.95
Revascularized	1.06 (0.96, 1.16)	0.24	2.69	2.52



ORIGIN Trial Investigators, N Engl J Med 367: 319-28, 2012

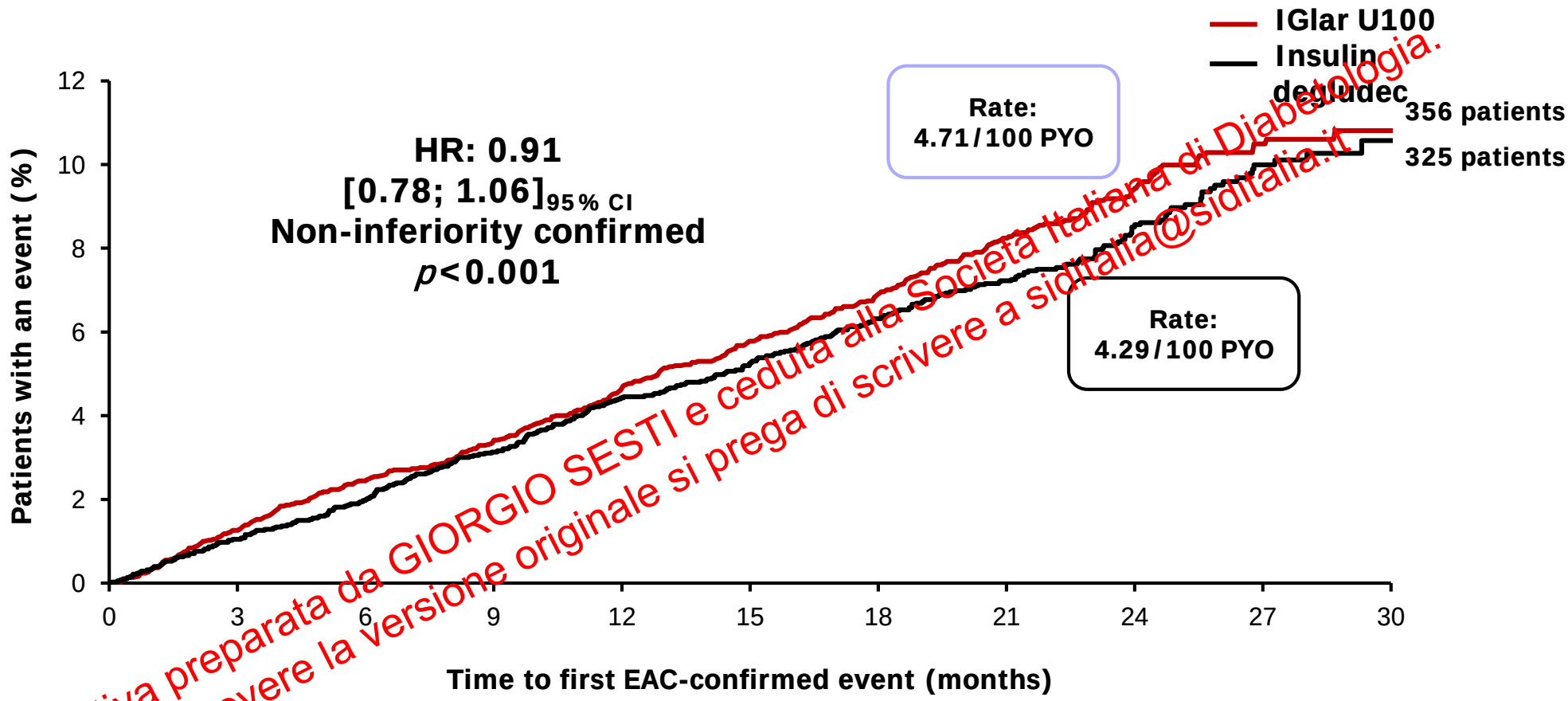
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy and Safety of Degludec versus Glargine in Type 2 Diabetes

Steven P. Marso, M.D., Warren K. McGuire, M.D., Bernard Zinman, M.D., Neil R. Poulter, F.Med.Sci., Scott S. Emerson, M.D., Ph.D., Thomas R. Pieber, M.D., Richard E. Pratley, M.D., Poul-Martin Haahr, M.D., Martin Lange, M.D., Ph.D., Kirstine Brown-Frandsen, M.D., Alan Moses, M.D., Simon Skibsted, M.D., Ph.D., Kajsa Kvist, Ph.D., and John B. Buse, M.D., Ph.D., for the DEVOTE Study Group*

Time to first 3-point MACE



Insulin degludec (N)	3818	3765	3721	3699	3611	3563	3504	2851	1767	811	217
IGlar U100 (N)	3819	3758	3703	3655	3595	3530	3472	2832	1742	811	205

Full analysis set; Cox regression analysis accounting for treatment. Analysis includes events between randomization date and follow-up date. Patients without an event are censored at the time of last contact (phone or visit)
EAC, Event Adjudication Committee; N, number of patients at risk; PYO, patient-years of observation

Marso SP et al. N Engl J Med. 377(8):723-732, 2017

Insulin therapy in T2DM

ADVANTAGES

- The primary defect in insulin secretion is reverted by insulin treatment
- Insulin treatment reverted defects in hepatic glucose production.
- Insulin therapy is not associated with atherogenesis and increased risk of CV events.
- **Basal insulin is easy to use : one insulin, once daily injection, one glucose target (FPG), and easy dose titration (FPG).**

LIMITATIONS

Titration algorithm: insulin degludec and insulin glargine

Pre-breakfast/pre-main evening meal plasma glucose[a]		Adjustment
mmol/L	mg/dL	U
<3.1[b]	<56[b]	−4 (If dose >45 U, reduce by 10%)
3.1–3.9[b]	56–70[b]	−2 (If dose >45 U, reduce by of 5%)
4.0–4.9	71–89	0
5.0–6.9	90–125	+2
7.0–7.9	126–143	+4
8.0–8.9	144–161	+6
≥9.0	≥162	+8

[a] Mean of 3 consecutive days' measurements for up titration
[b] Unless there is obvious explanation for the low value, such as a missed meal

Meneghini L et al. Diabetes Care 36:858–864, 2013

Insulin therapy in T2DM

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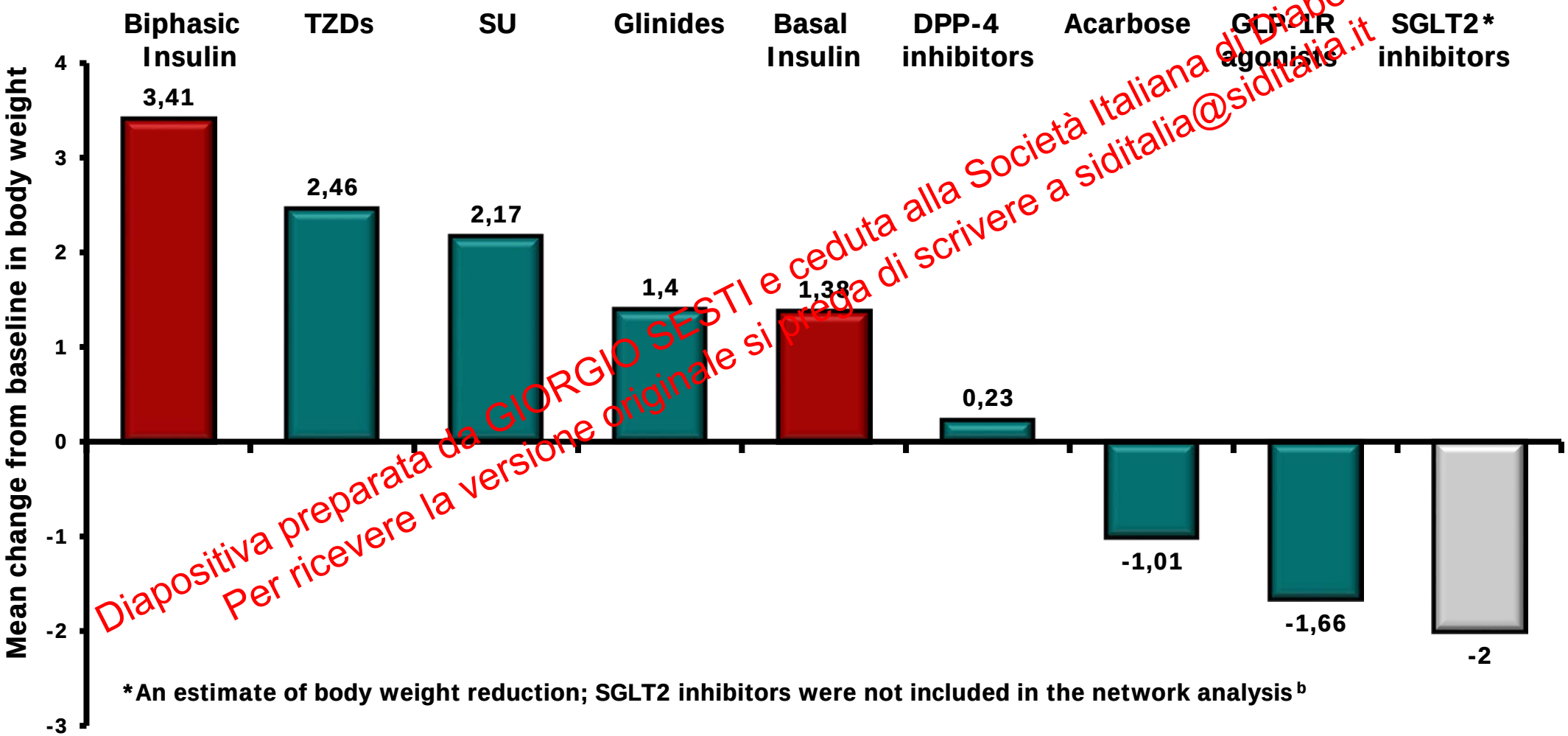
LIMITATIONS

- Treatment with insulin is associated with body weight gain.

Network meta-analysis of pairwise comparisons of randomised controlled trials evaluating the use of anti-hyperglycaemic agents in addition to metformin vs. placebo: Mean change from baseline in body weight



*An estimate of body weight reduction; SGLT2 inhibitors were not included in the network analysis [b]

DPP-4, dipeptidyl peptidase-4; SGLT2, sodium glucose cotransporter-2; TZDs, thiazolidinediones; GLP-1R, glucagon-like peptide 1 receptor; SU, sulphonylurea

Liu S-C et al. Diabetes Obes and Metab 2012; 14: 810-820
[b] Fujita Y et al. J Diabetes Investing 2014; 5: 265-275

Insulin therapy in T2DM

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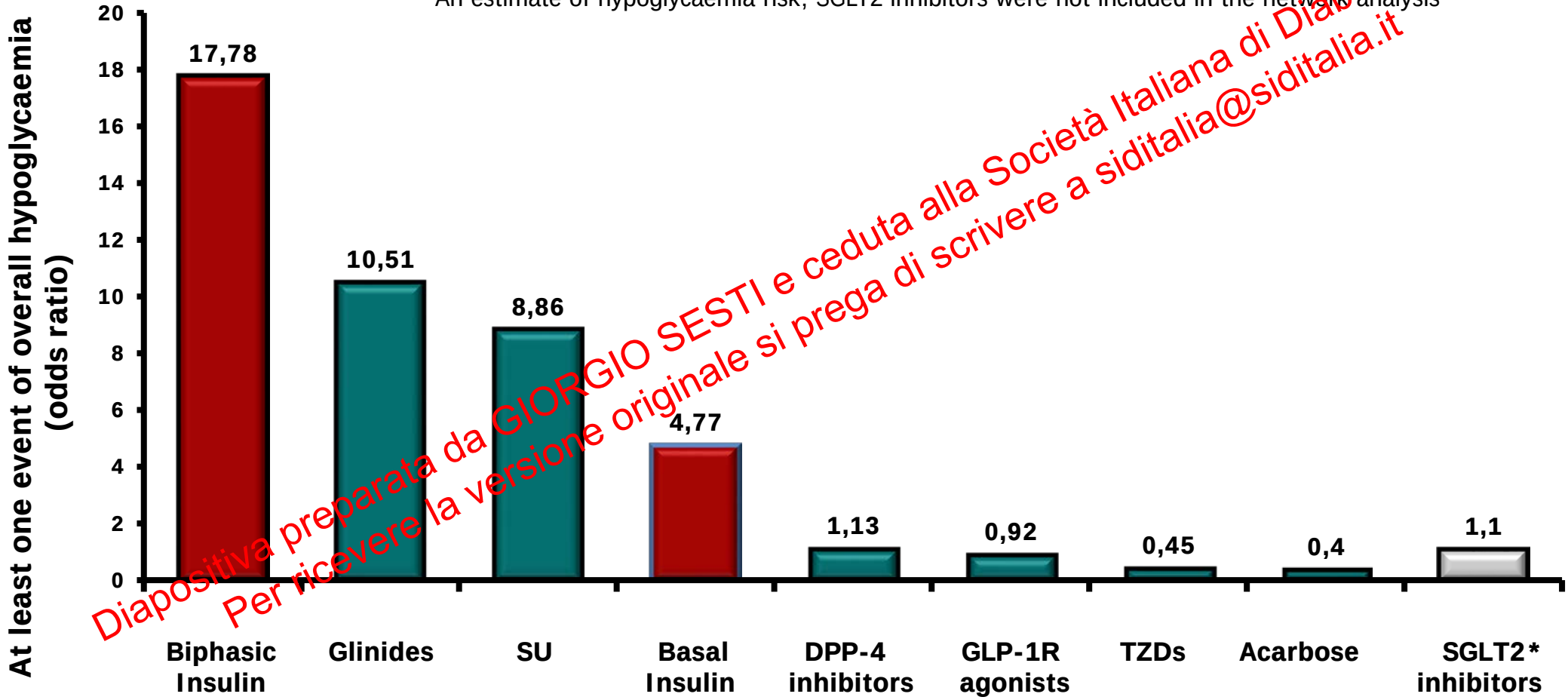
LIMITATIONS

- **Treatment with insulin is associated with body weight gain.**
- **Treatment with insulin is associated with increased risk for hypoglycemia.**

Network meta-analysis of pairwise comparisons of randomised controlled trials evaluating the use of anti-hyperglycaemic agents in addition to metformin vs. placebo: At least one event of overall hypoglycaemia (odds ratio)

*An estimate of hypoglycaemia risk; SGLT2 inhibitors were not included in the network analysis [b]



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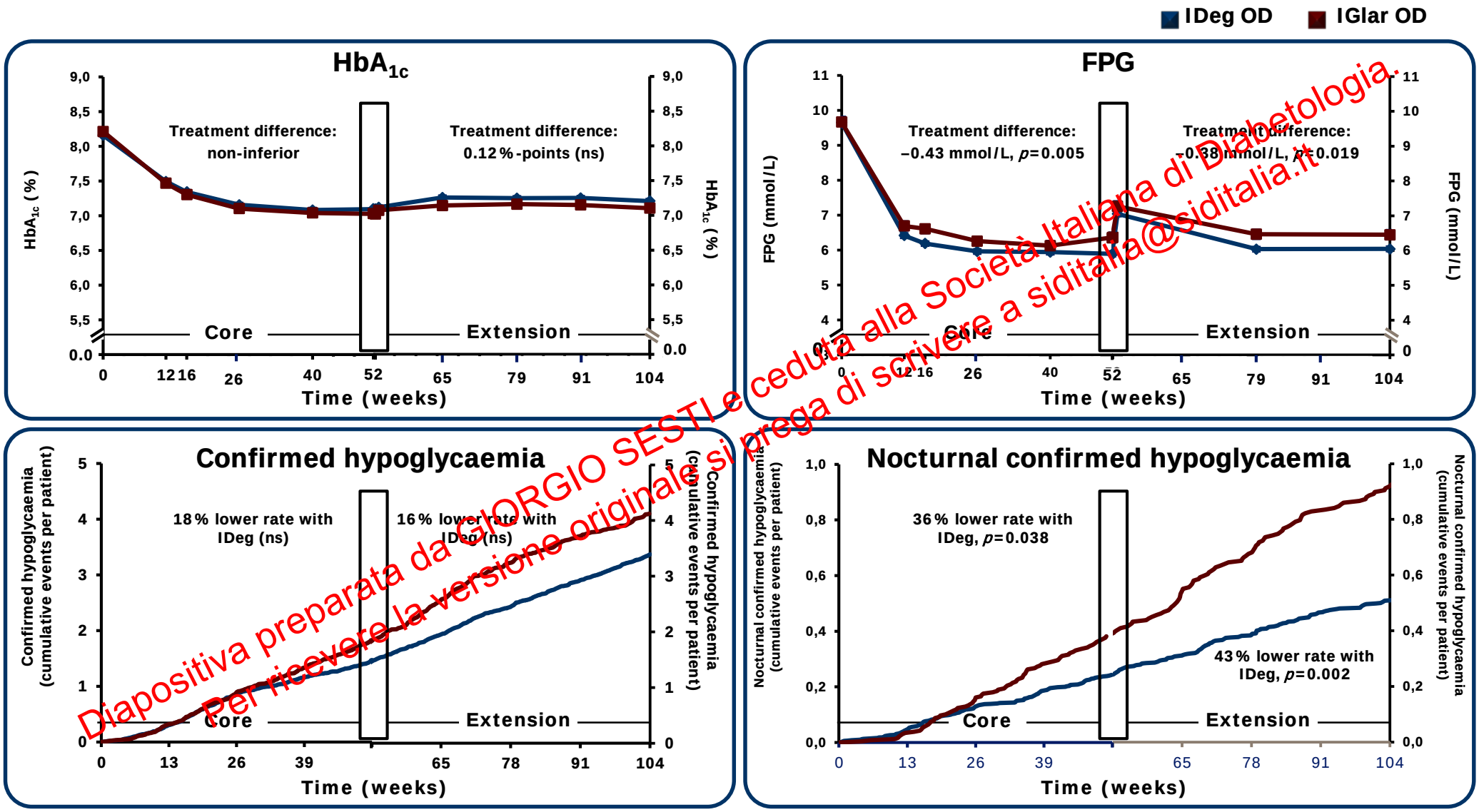
[b] Fujita Y et al. J Diabetes Investing 2014; 5: 265-275

Insulin-naïve T2D: study design

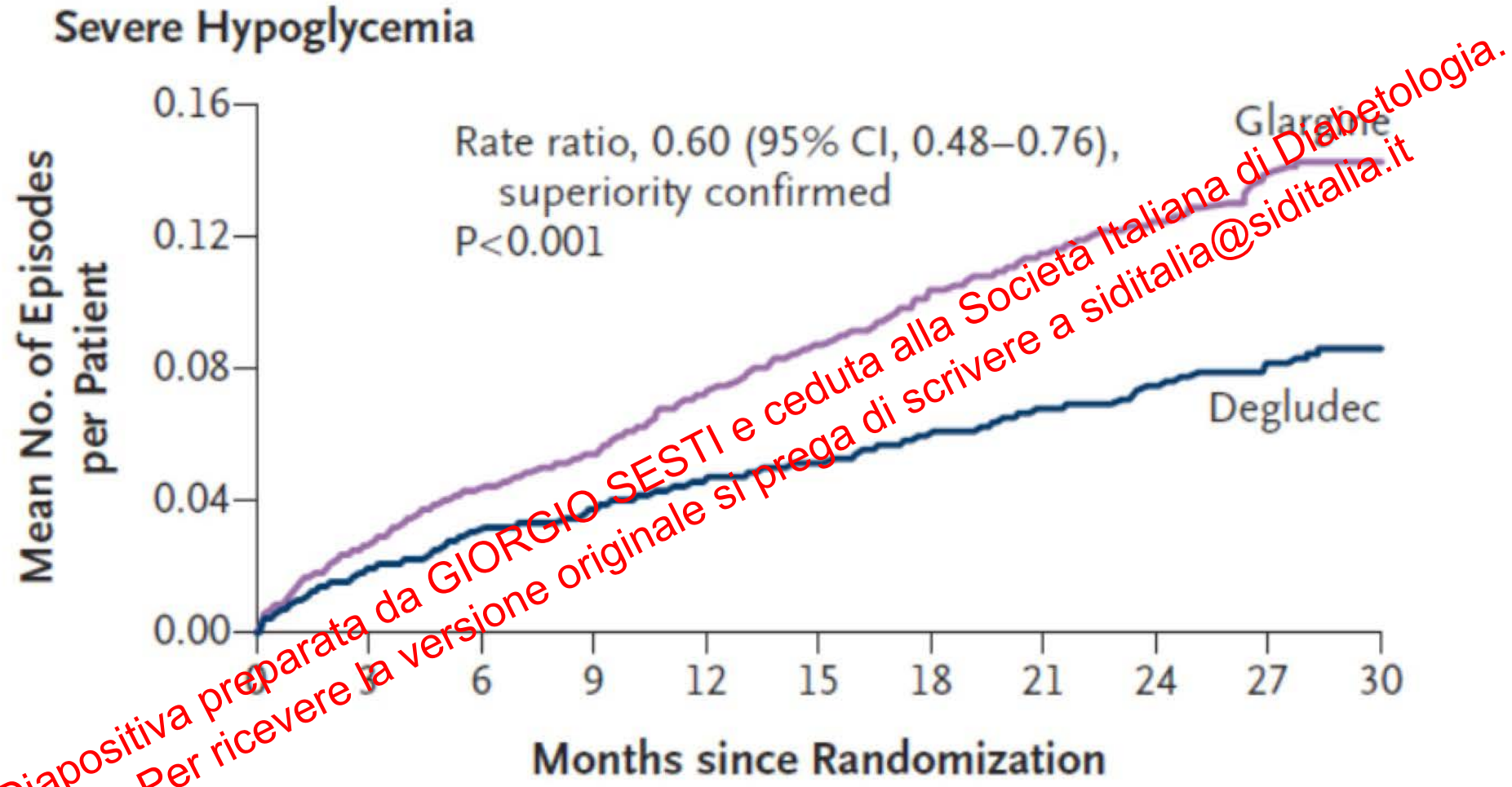
BEGIN ONCE LONG – 2 years



Black box denotes both treatment arms switching to NPH for 1 week then resuming IDeg or IGlar to allow for antibody measurement

Zinman et al. Diab Care 35:2464–71, 2012; Rodbard et al. Diabetic Med 30:1298–304, 2013

Devote Secondary Endpoints: Rates of severe hypoglycaemia



Full analysis set; Mean number of confirmed severe hypoglycemic episodes. The number of events is analyzed using a negative binomial regression model using a log link and the logarithm of the observation time (100 years) as offset

Marso SP et al. N Engl J Med. 377(8):723-732, 2017

Insulin therapy in T2DM

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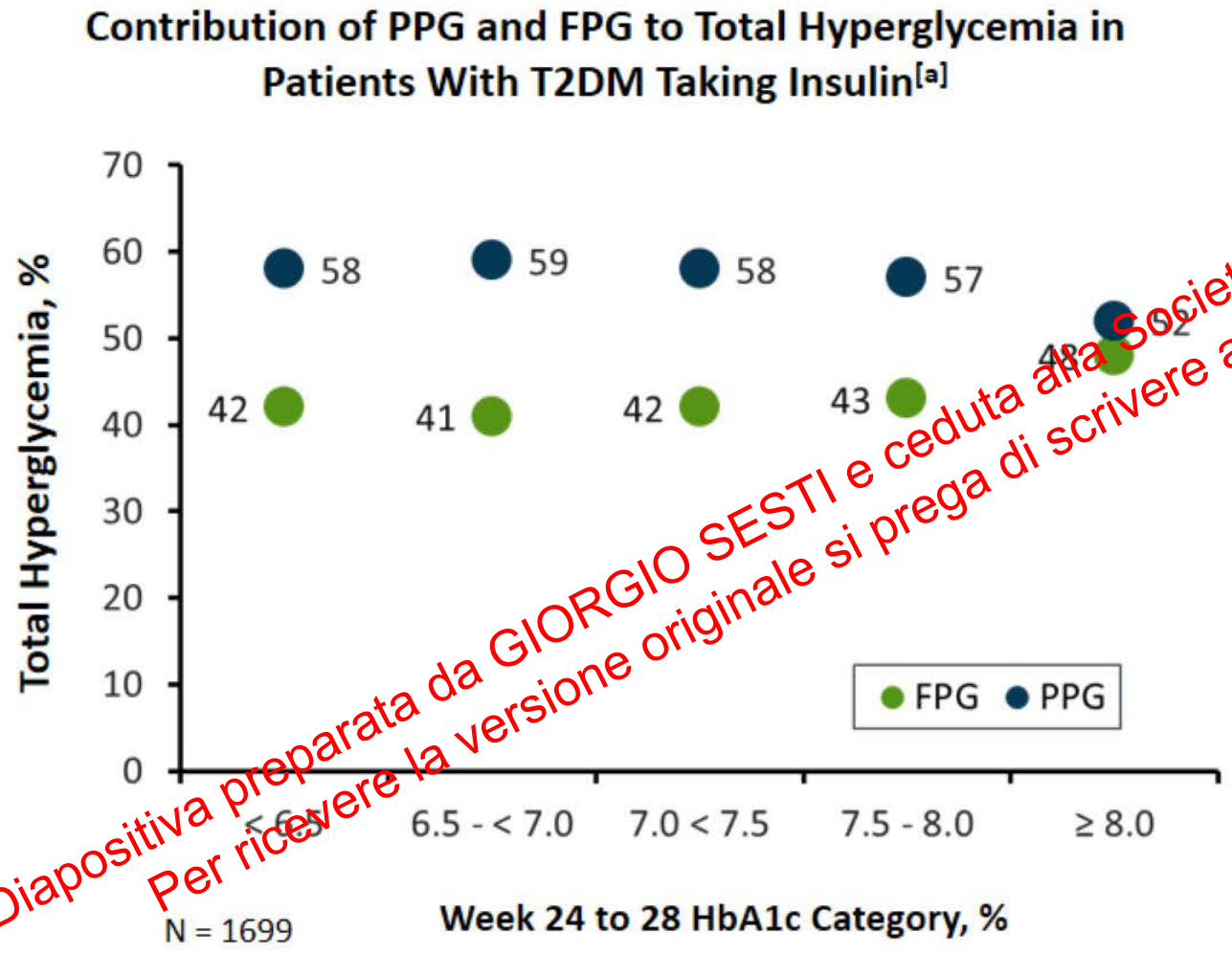
LIMITATIONS

- Treatment with insulin is associated with body weight gain.
- Treatment with insulin is associated with increased risk for hypoglycemia.
- Insulin therapy needs to control both FPG and post-prandial PG.

Insulin therapy needs to control both FPG and post-prandial PG



- Many patients with T2DM do not reach target HbA1c with basal insulin alone[a]
- They do not appreciate the contribution that PPG makes to poor glycemic control, and don't check levels[a-c]

a. Riddle M, et al. *Diabetes Care.* 2011;34:2508-2514.
b. Monnier L, et al. *Diabetes Care.* 2003;26:881-885.
c. Woerle HJ, et al. *Diabetes Res Clin Pract.* 2007;77:280-285.

Insulin therapy in T2DM

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- **Treatment with insulin is associated with increased risk for hypoglycemia.**
- **Insulin therapy needs to control both FPG and post-prandial PG.**
- **Insulin treatment may be refused by the patient barriers.**

Patient barriers to use of basal insulin

- Fear / stigma of needles.
- Perception that initiating injectable therapy signals failure.
- Fear of hypoglycemia.
- Fear of weight gain.
- Concern about frequency, complexity, and difficulty of self-injecting.
- Hard to live normal life while managing diabetes.
- Concern about the need for frequent glucose monitoring.
- Apprehension about side effects and incorrect dosing.
- Confusion as to how to titrate insulin during the day.
- Perception that it is an indication of imminent deterioration or death.

Insulin therapy in T2DM

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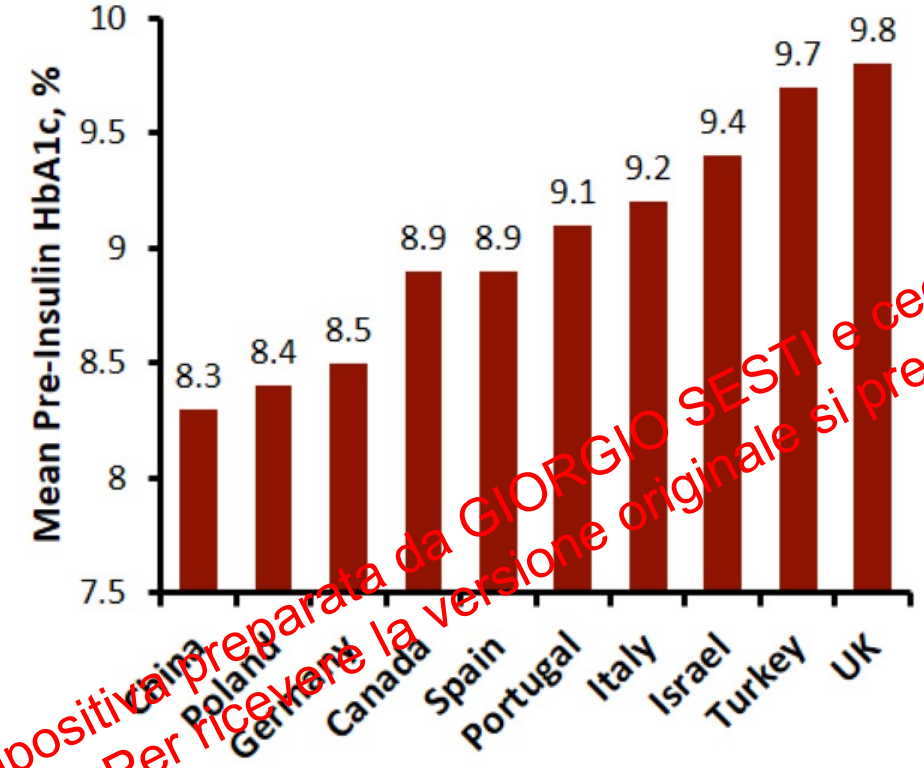
- **Insulin therapy needs to control both FPG and post-prandial PG.**
- **Insulin treatment may be refused by the patient barriers.**
- **Insulin treatment is associated with clinical inertia.**

Clinical Inertia With Insulin Therapy

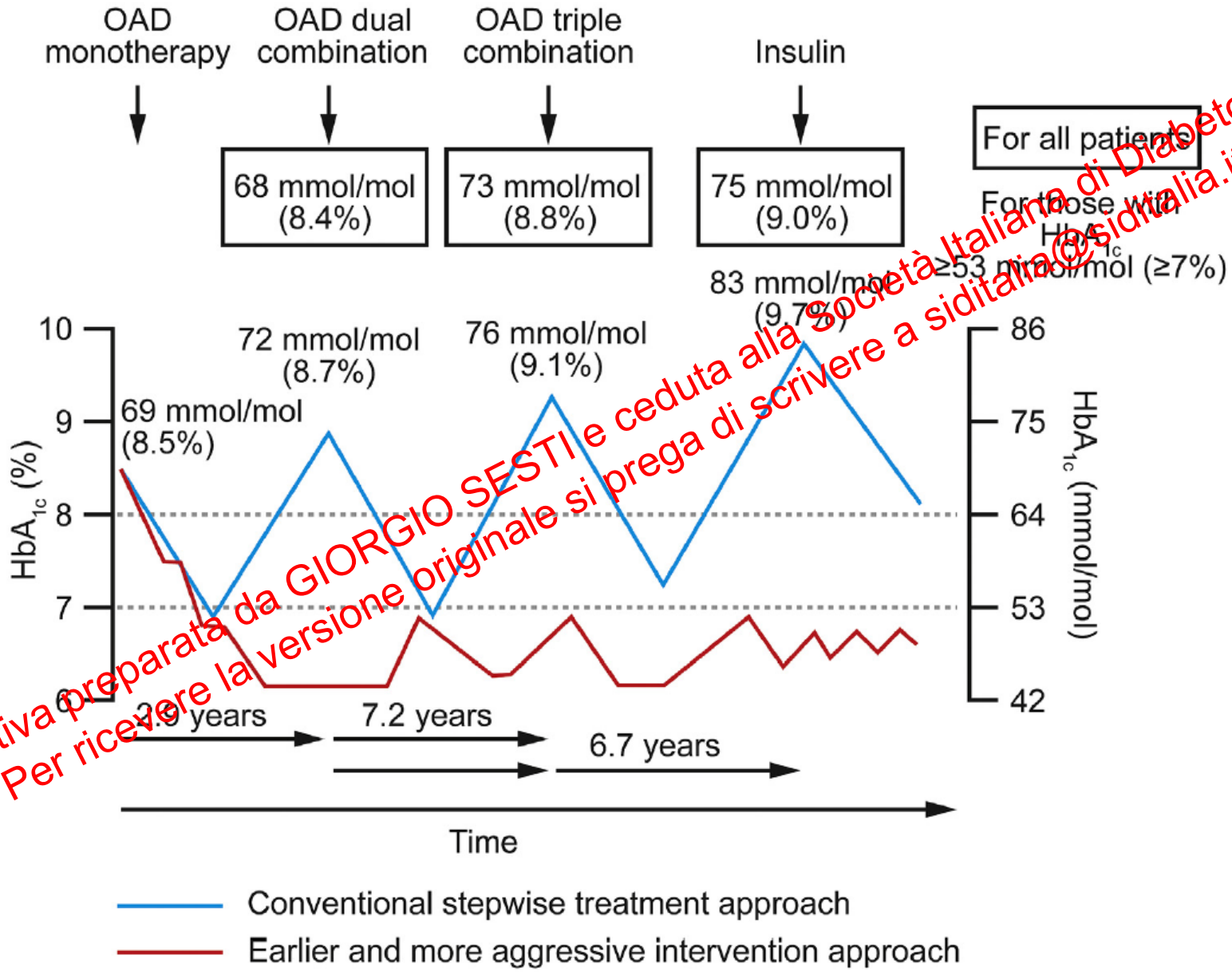


SOLVE™ Study of Patients Being Treated With 1 or More OADs Initiated on Once-Daily Levemir, (n= 17,734)

- Clinical Inertia: failure to advance antihyperglycemic therapy when required[a]
- Guidelines recommend HbA1c targets ~7.0%[b]
- SOLVE™ study found that pre-insulin mean HbA1c ranged from 8.3% to 9.8%[c]
- Insulin was started later than guidelines recommend in all countries[c]

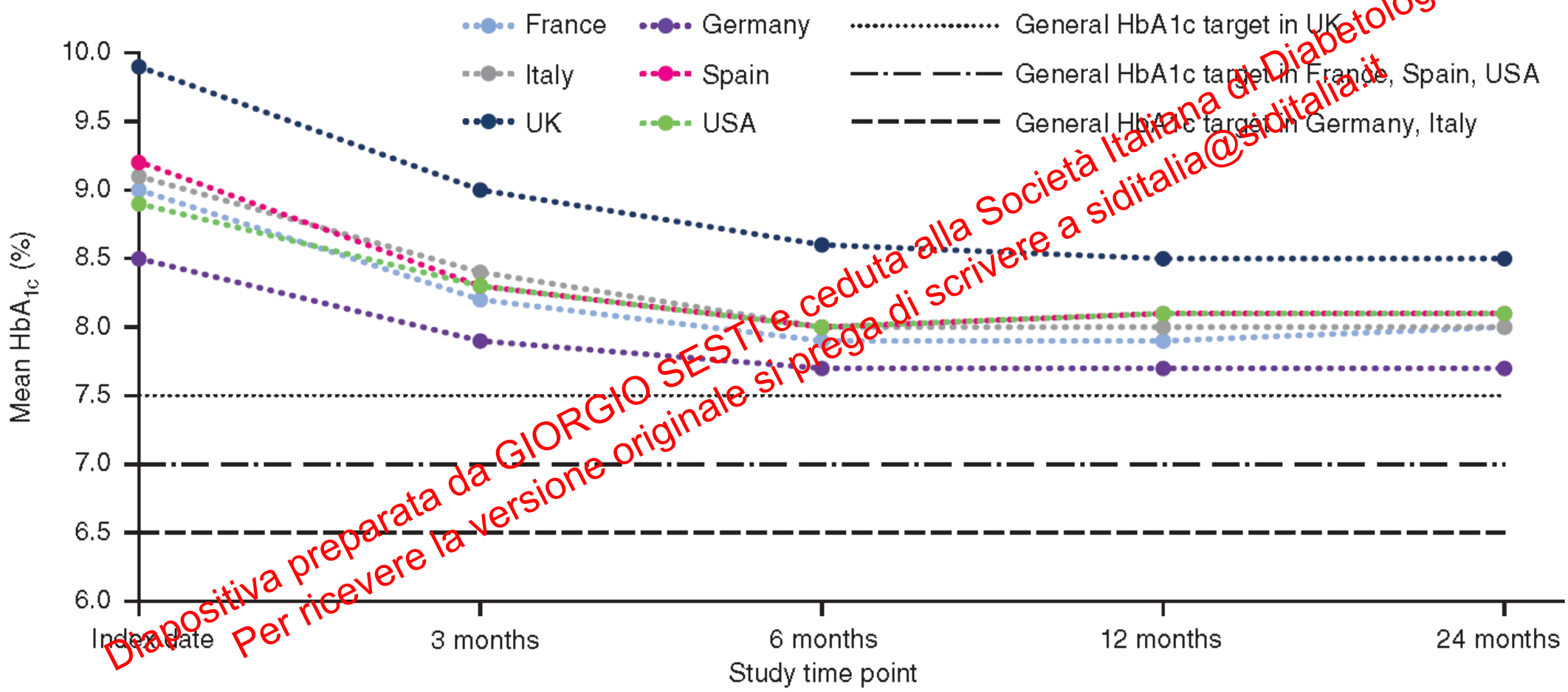
a. Khunti K, et al. *Diabetes Care.* 2013;36:3411-3417; b. Inzucchi SE, et al. *Diabetes Care.* 2015;38:140-149;
c. Khunti K, et al. *Diabetes Obes Metab.* 2012;14:654-661.

Median time to intensification and mean HbA1c at intensification in patients with T2DM currently treated with one or two OADs with intensification to two OADs or insulin, respectively



Paul, SK et al. Cardiovasc. Diabetol. 14: 100, 2015

Glycaemic control in patients with T2DM initiating basal insulin in Europe and the USA



Mauricio D et al. Diabetes Obes Metab 19:1155–1164, 2017

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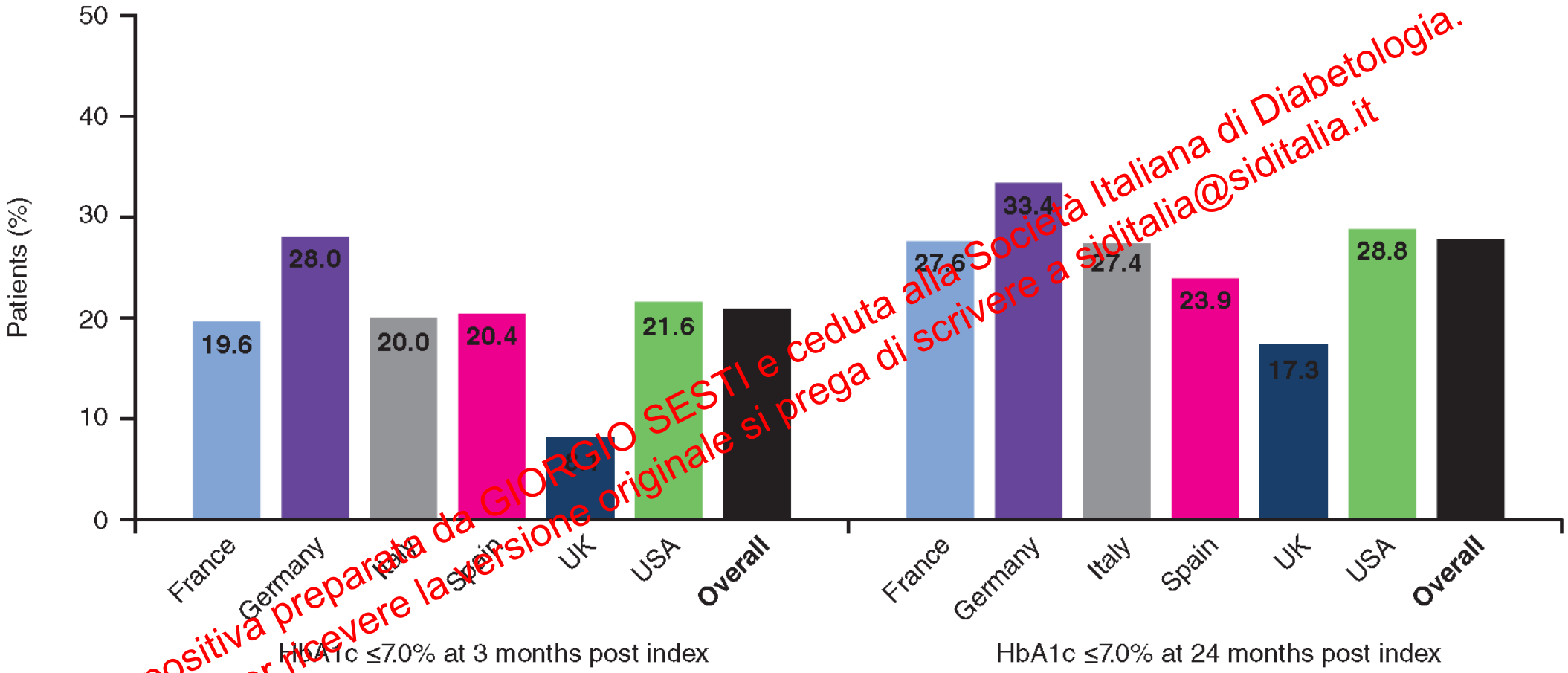
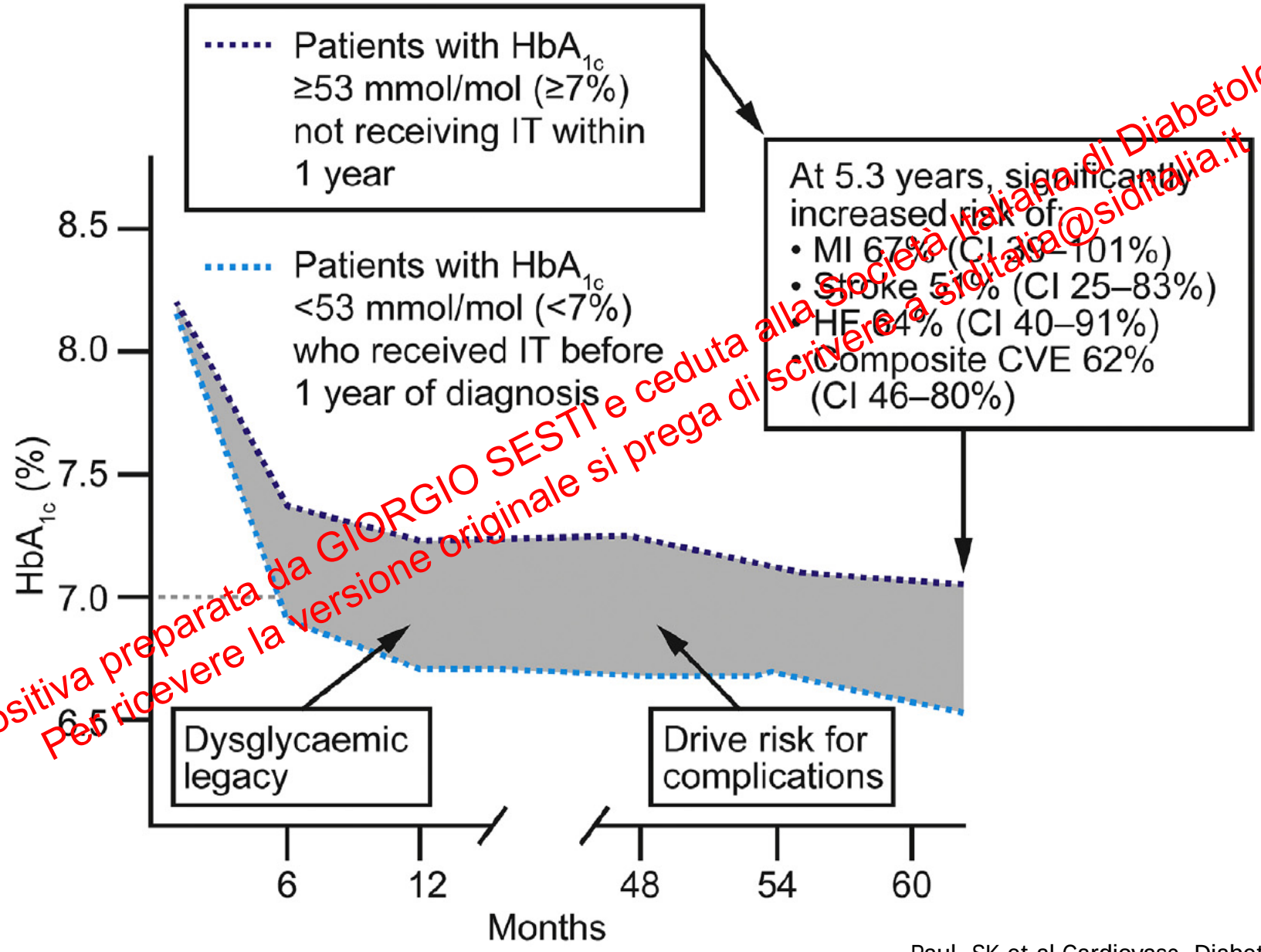


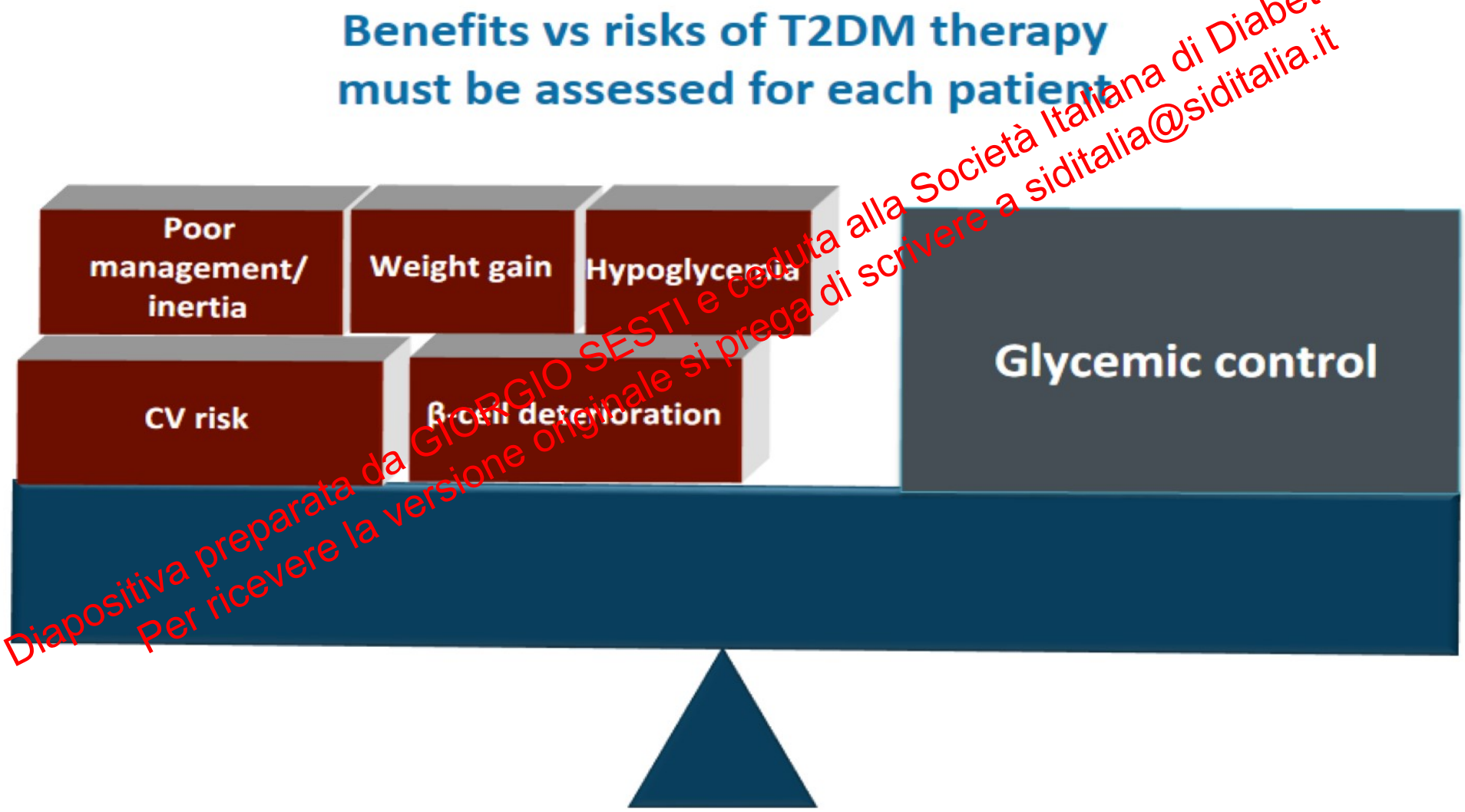
Mauricio D et al. Diabetes Obes Metab 19:1155–1164, 2017

Consequences of delayed intervention in patients with T2DM



Paul, SK et al.Cardiovasc. Diabetol. 14: 100, 2015

Need for personalized care



THANK YOU !

Now it’s time for discussion.

Dangers of Delayed Insulin Initiation

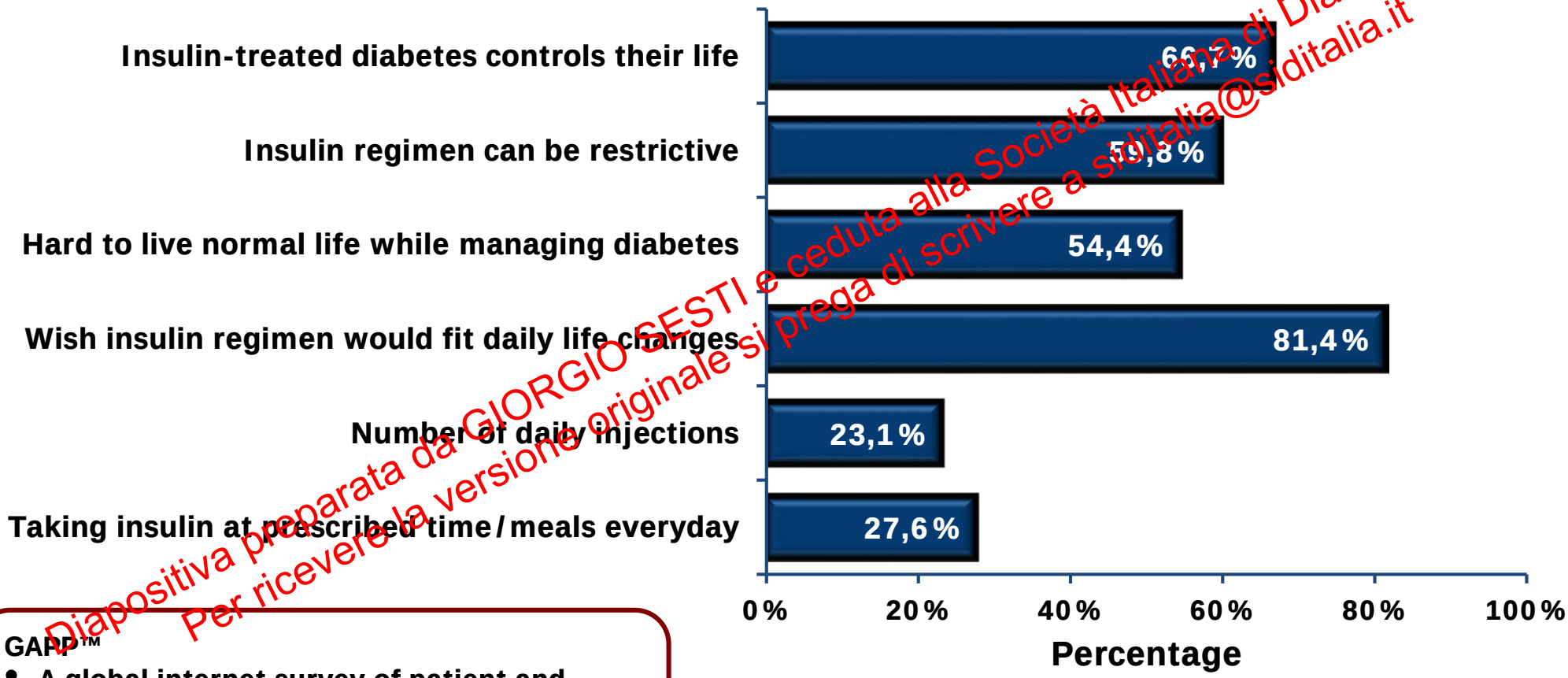
- The availability of increasing numbers of non-insulin, oral antidiabetic agents has fostered a reluctance to use insulin among physicians and patients both[a]
- A European retrospective analysis showed that between 2005 and 2010, the time from T2DM diagnosis to insulin initiation increased by approximately 2 years[b]
- During the same period, the percentage of patients with at least 1 macrovascular complication also increased[b]

a. Lovre D, et al. *J Diabet Comp*. 2015;29:295-301.
b. Kostev K, et al. *Prim Care Diabetes*. 2013;7:229-233.

Triggers to Initiate Insulin in Primary Care

- Patients uncontrolled on triple therapy
- Patients with long-standing diabetes that is poorly controlled
- Any patient not at HbA1c target despite intensive treatment

Patient-cited issues with insulin treatment



GAPP™

- A global internet survey of patient and physician beliefs regarding insulin therapy
- n=1530 insulin treated patients with diabetes

Peyrot et al. Diabetic Med 29:682–9, 2012

Antihyperglycemic therapy in type 2 diabetes: general recommendations

Start with Monotherapy unless:

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy **Metformin** **Lifestyle Management**

EFFICACY*	high
HYPO RISK	low risk
WEIGHT	neutral/loss
SIDE EFFECTS	GI/lactic acidosis
COSTS*	low

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Dual Therapy **Metformin +** **Lifestyle Management**

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Triple Therapy **Metformin +** **Lifestyle Management**

Sulfonylurea +	Thiazolidinedione +	DPP-4 inhibitor +	SGLT2 inhibitor +	GLP-1 receptor agonist +	Insulin (basal) +
TZD	SU	SU	SU	SU	TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or SGLT2-i	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin[§]	or GLP-1-RA	or Insulin[§]	or GLP-1-RA
or Insulin[§]	or Insulin[§]		or Insulin[§]		

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

Combination Injectable Therapy **(See Figure 8.2)**

Standards of Medical Care in Diabetes—2017, Diabetes Care, 40:S1-S135, 2017

- **In certain patients, glucose control remains poor despite the use of three antihyperglycemic drugs in combination.**

- **With long-standing diabetes, a significant diminution in pancreatic insulin secretory capacity dominates the clinical picture.**

- **In any patient not achieving an agreed HbA1c target despite intensive therapy, basal insulin should be considered an essential component of the treatment strategy.**

Adapted from Inzucchi SE et al. Diabetes Care 38:140–149, 2015

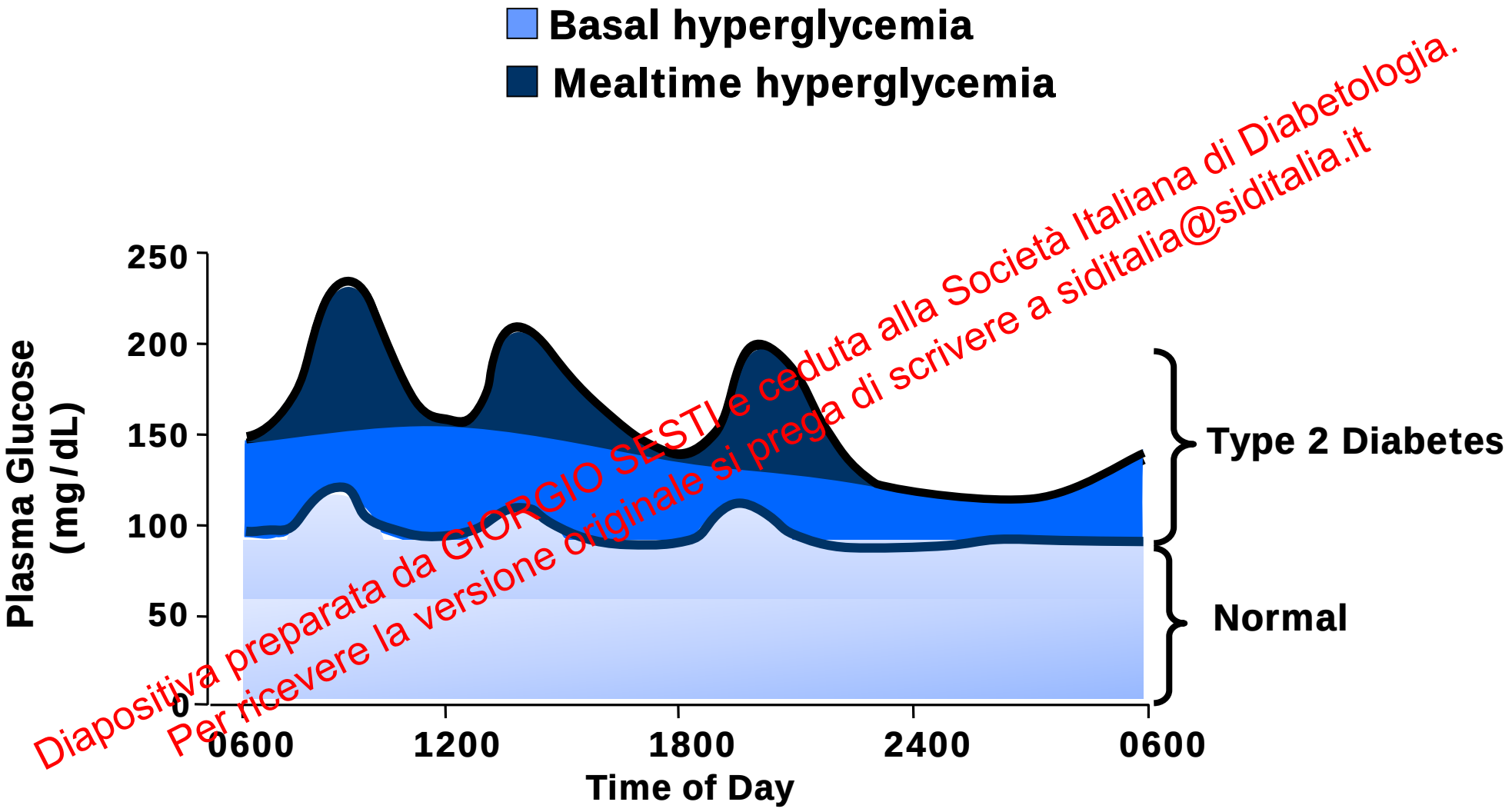
Clinical inertia in people with type 2 diabetes
A retrospective cohort study of 81,573 people with type 2 diabetes in the U.K. Clinical Practice Research Datalink

Median time to insulin intensification in people with type 2 diabetes

HbA1c (%)	Treatment with 2 OADs	Treatment with 3 OADs
≥7,5	>7.2 years	>6.1 years
≥8,0	>6.0 years	>6.0 years

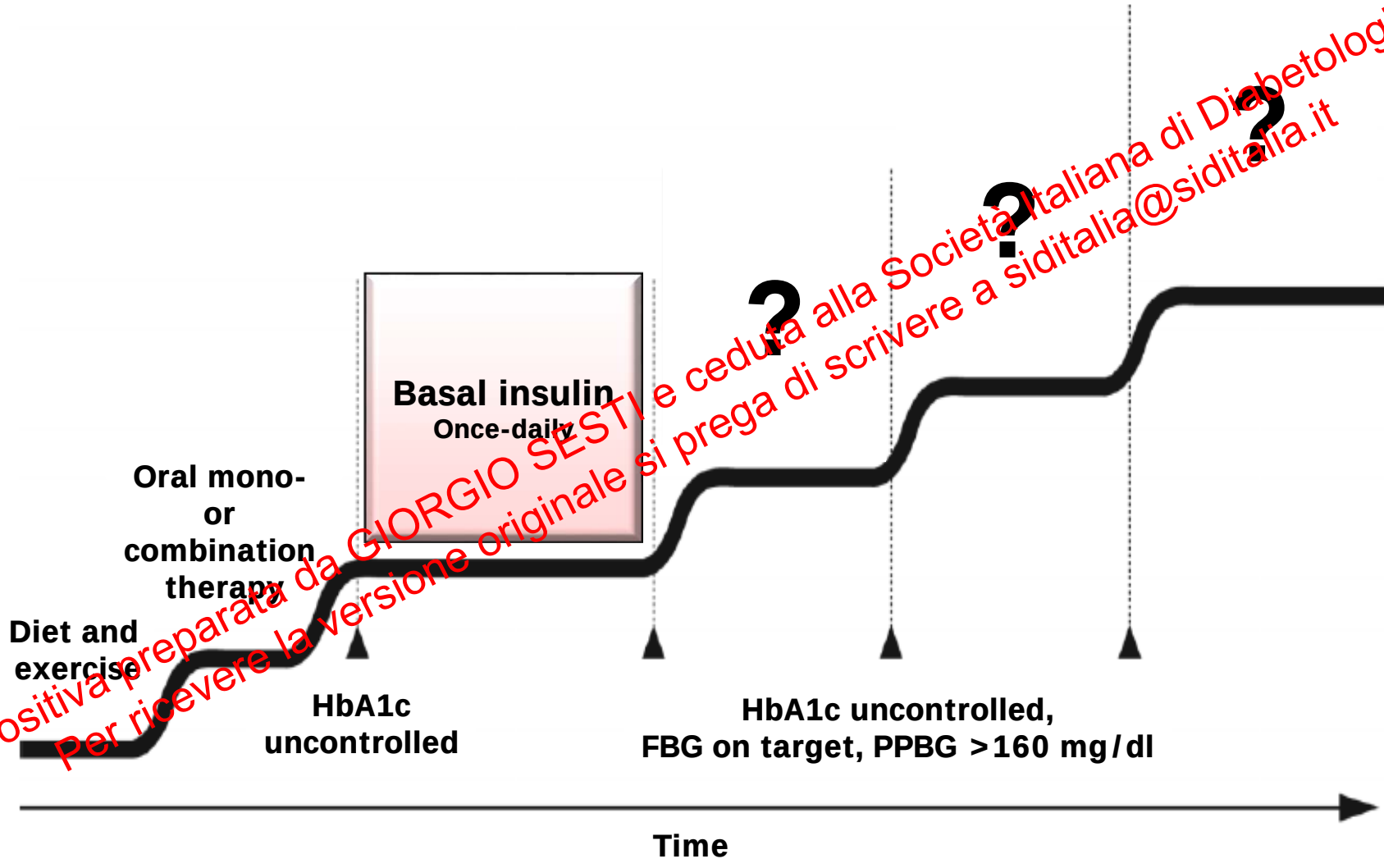
Khunti et al. Diabetes Care 36:3411-7, 2013

Basal vs Mealtime Hyperglycemia in Type 2 DM

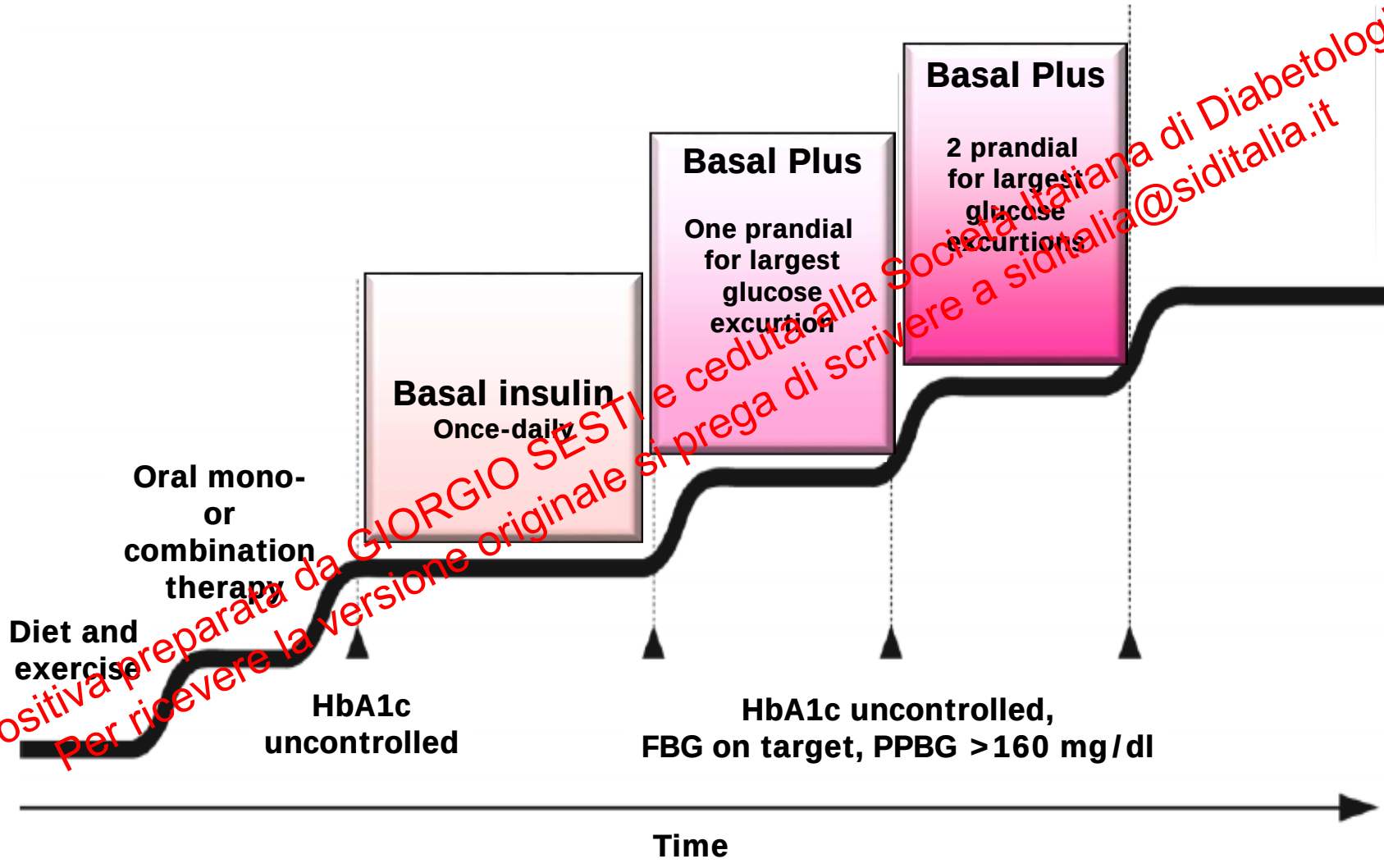


Riddle MC Diabetes Care 13:676-686, 1990

What next?



Modified from Raccah d et al. Diabetes Metab Res Rev 23: 257-264, 2007



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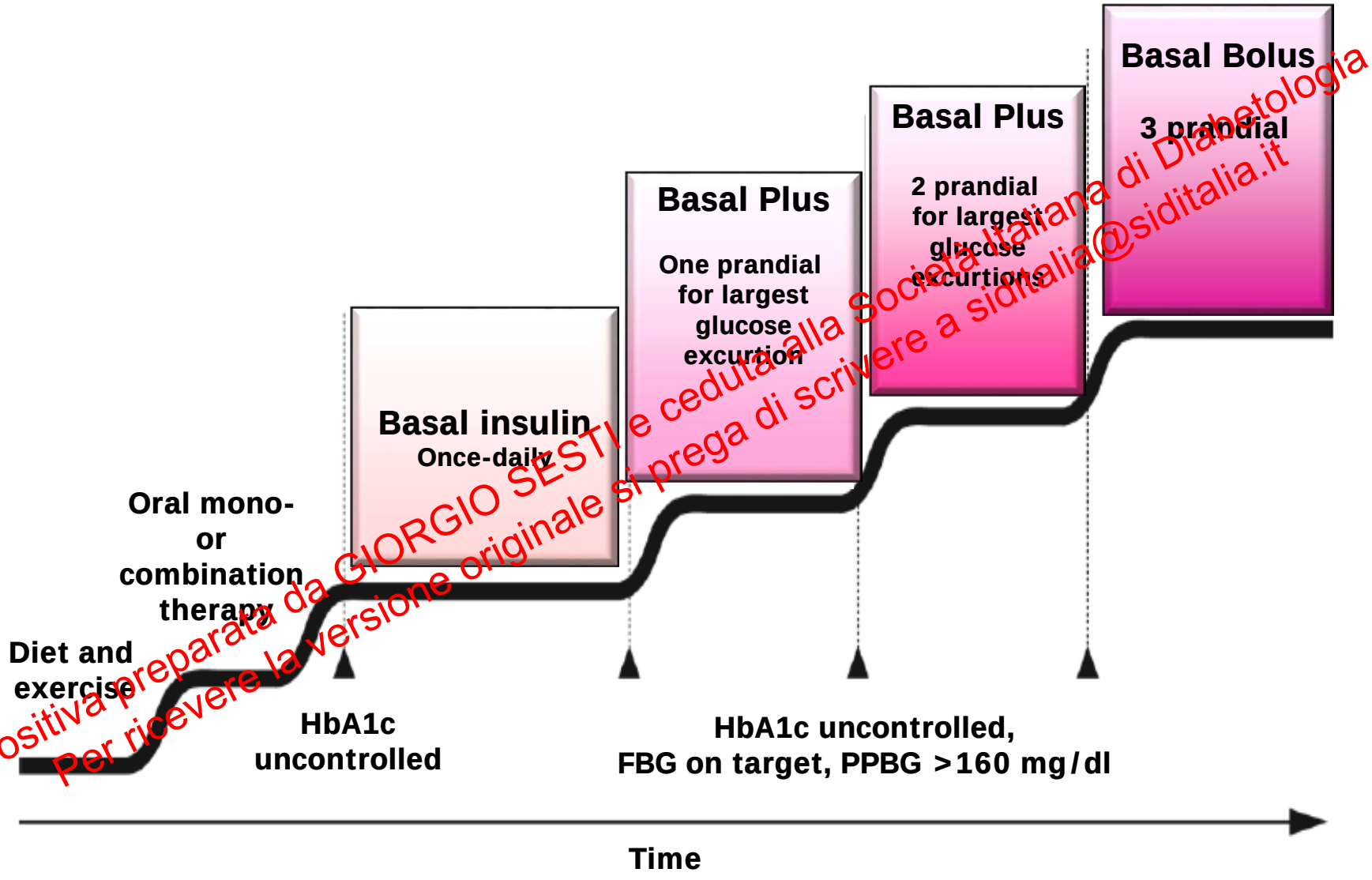
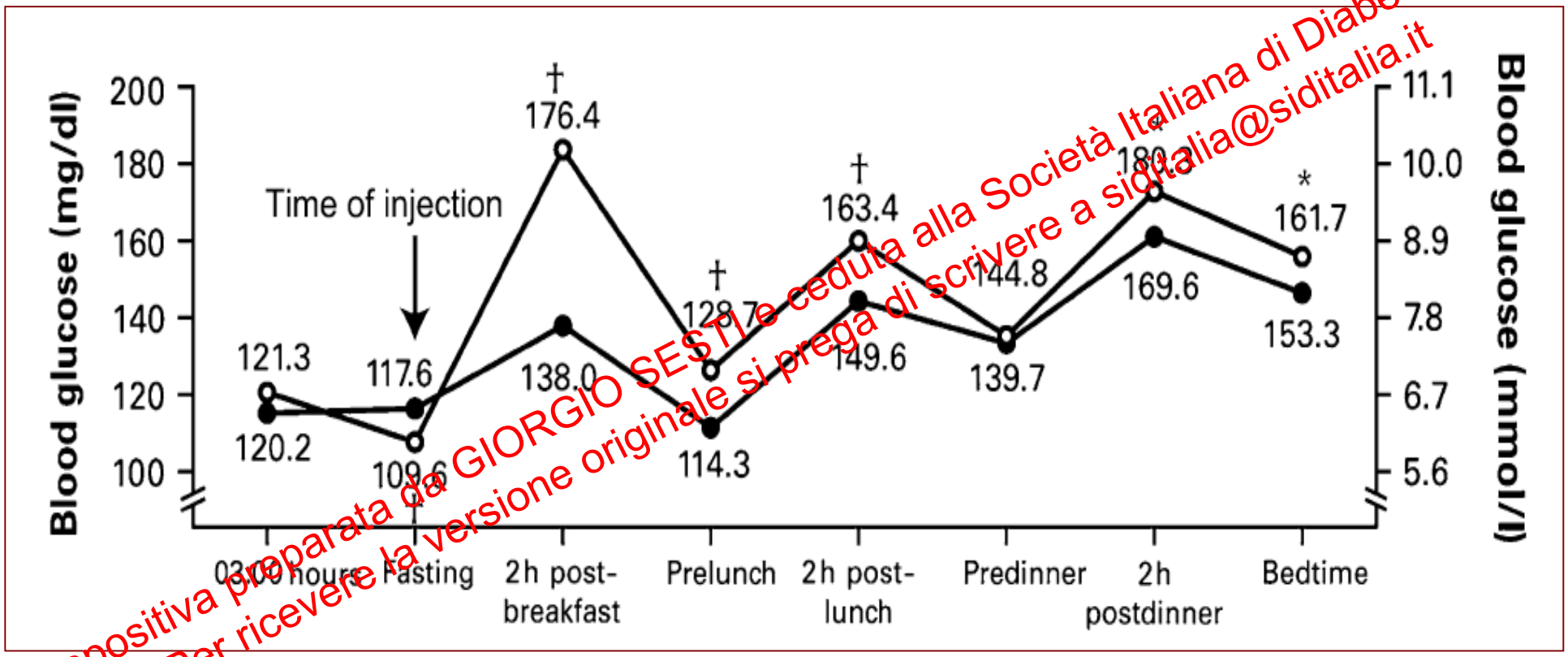


Modified from Raccah d et al. Diabetes Metab Res Rev 23: 257-264, 2007

Basal Plus: One prandial for largest glucose excurtion

OPAL: blood glucose profile of patients with type 2 diabete inadequately controlled with OADs+Glargine



Lankisch M et al. Diabetes Obes Metab 10: 1178-1185, 2008

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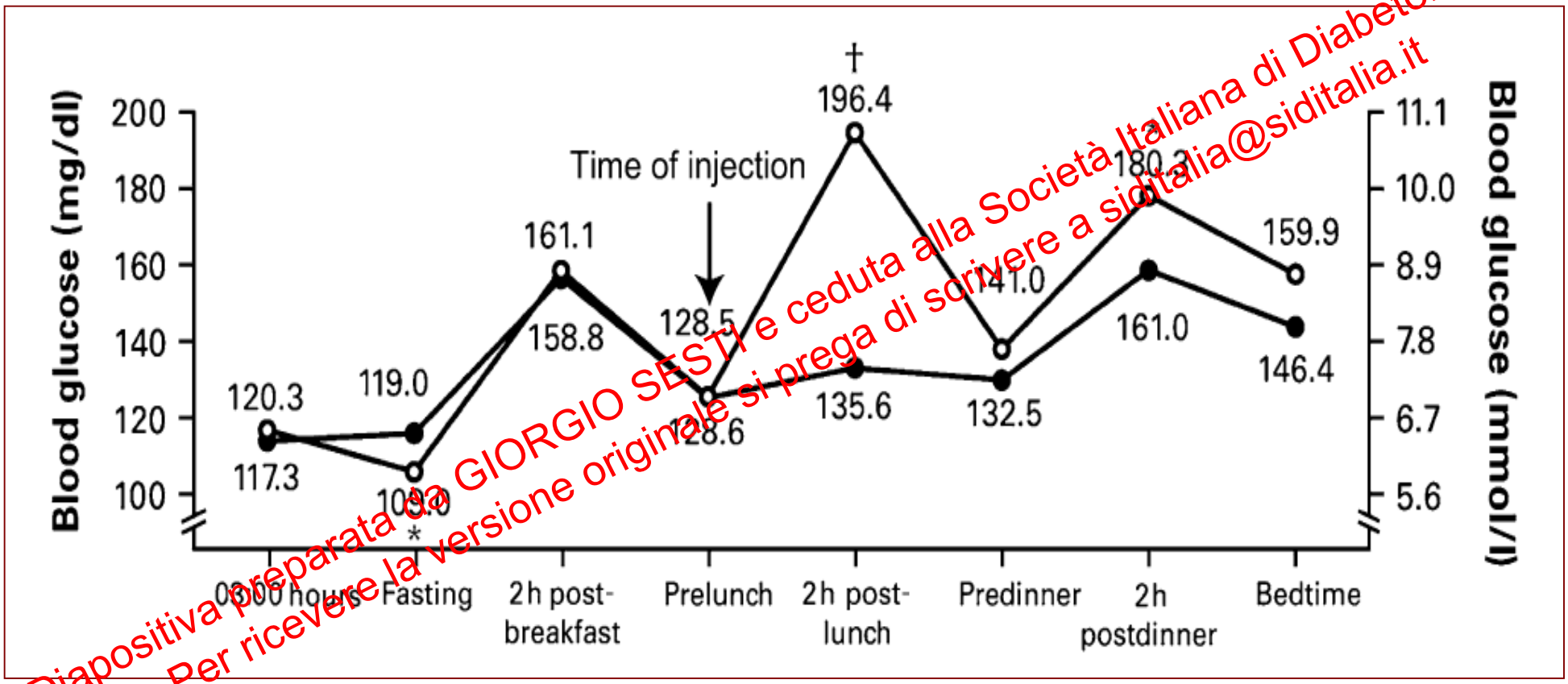

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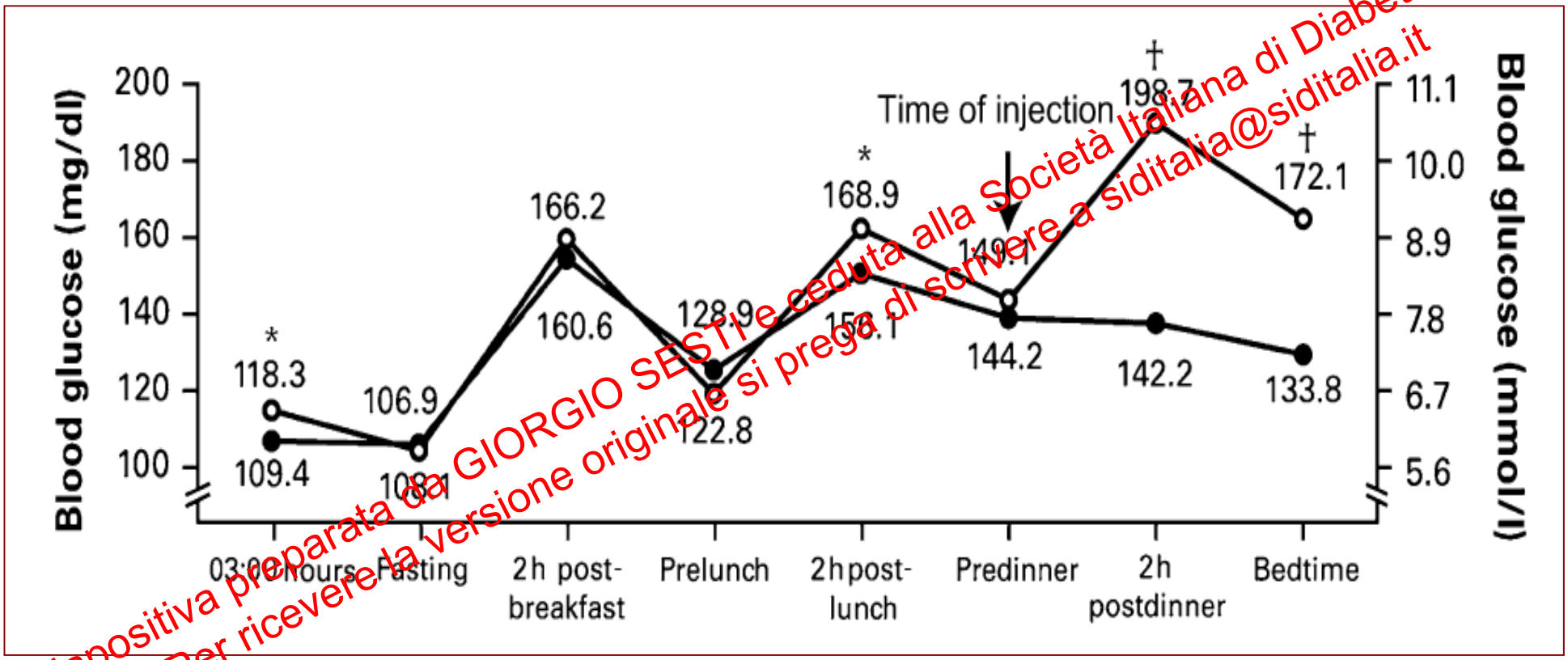
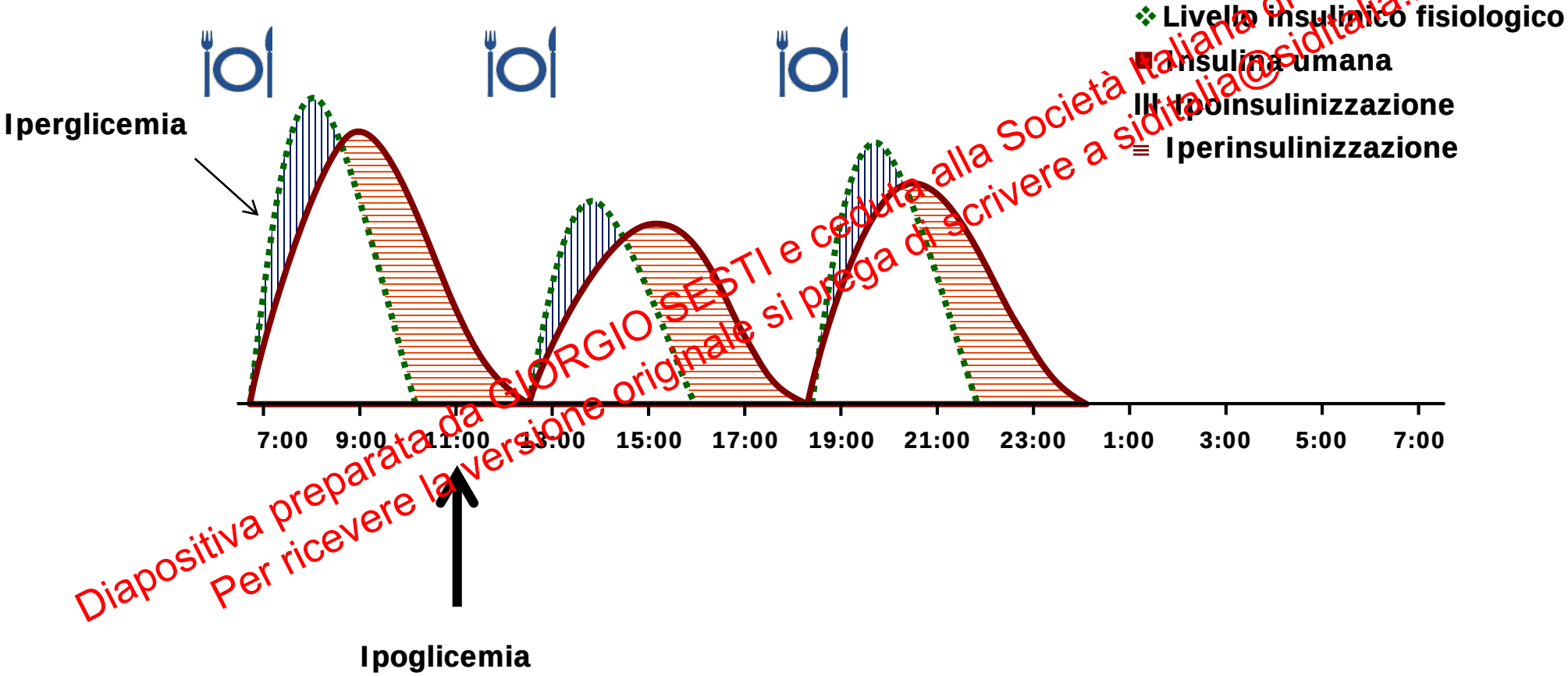


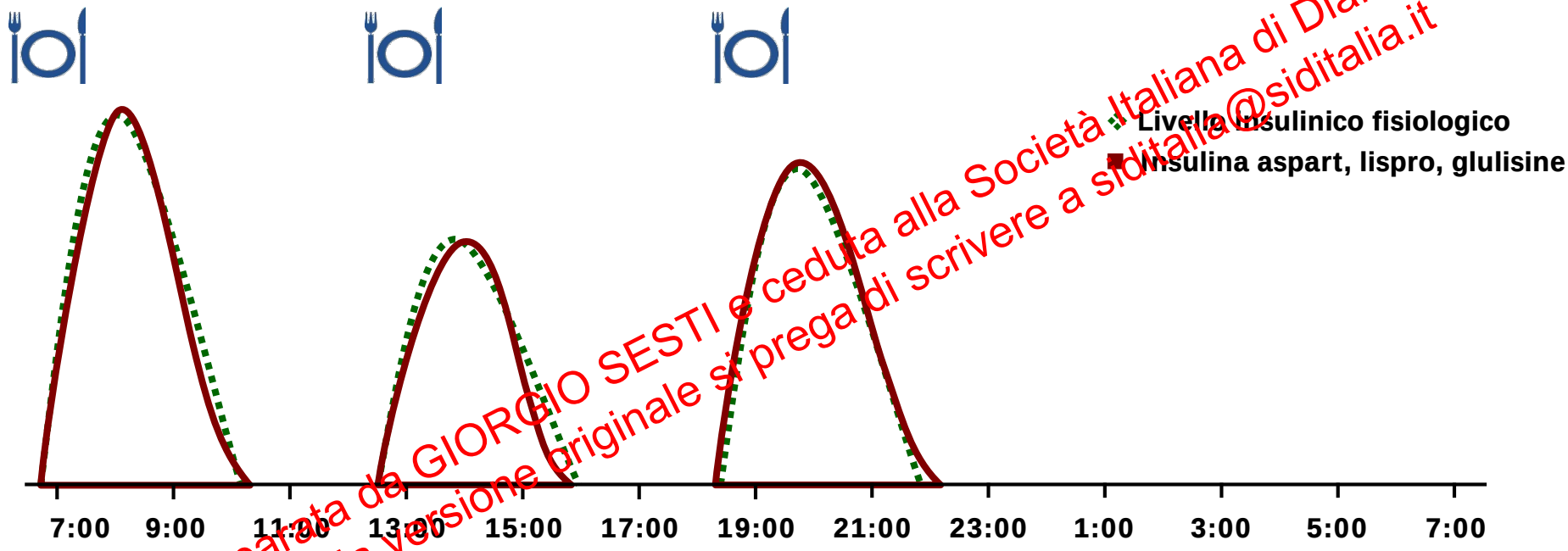
Lankisch M et al. Diabetes Obes Metab 10: 1178-1185, 2008

Limiti dell'insulina umana regolare

- **Elevate escursioni della glicemia postprandiale**
- **Aumentato rischio d'ipoglicemia**
- **Tempistica di somministrazione (30 min prima del pasto)**



Profilo farmacocinetico degli analoghi rapidi dell'insulina



- **Contenimento delle escursioni della glicemia postprandiale**
- **Diminuzione del rischio d'ipoglicemia**
- **Tempistica di somministrazione più flessibile**

Arguments in favor of timely insulin use in T2DM

- **The defect in insulin secretion is a primary one.**
- **Insulin treatment reverted defects in insulin secretion and hepatic glucose production.**
- **Treatment with insulin has high efficacy and is indicated in certain clinical condition (pregnancy, hospitalized patients, critically ill patients) .**
- **Increase in body weight and the risk for hypoglycemia may be minimized.**

IN T2 DM, USE INSULIN...

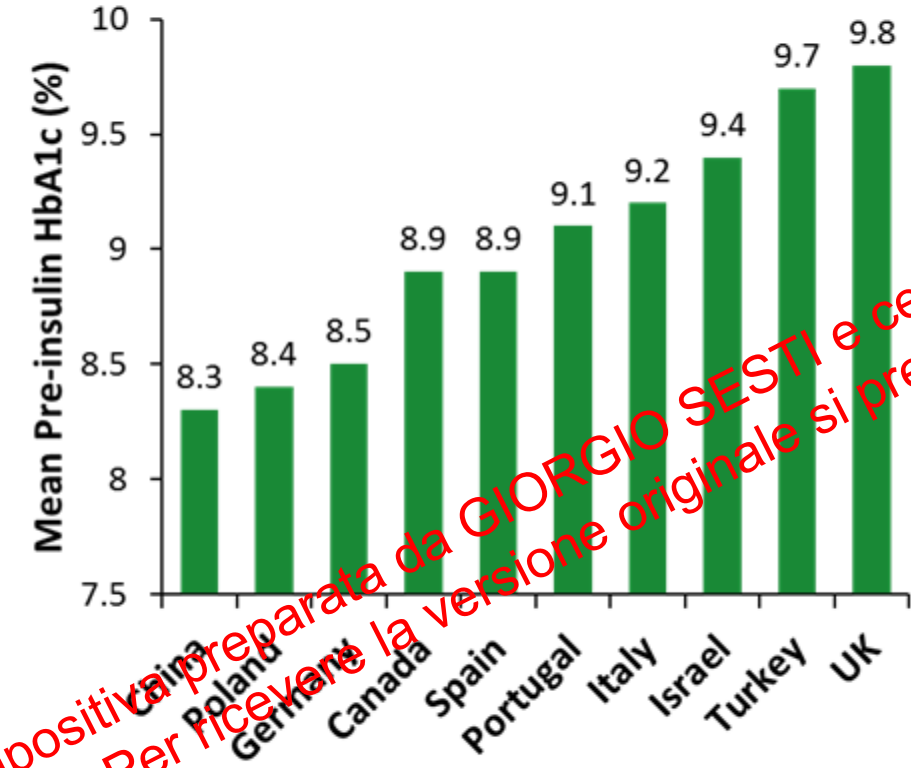
...according to the rule of the

5 More

IN T2 DM, USE INSULIN…

- **MORE TIMELY**
  - *(As soon as other agents fail to maintain the appropriate target)*
- **MORE PHYSIOLOGICALLY**
  - *(Prefer basal insulin first, add prandial later as needed – do not mix…)*
- **MORE MINDFULLY**
  - *(Define the target and treat to it)*
- **MORE EASILY**
  - *(One Shot, One Finger Prick, Easy to «develop» into a multiple injections regimen)*
- **MORE SAFELY**
  - *(minimize hypoglycaemia and weight gain)*

Initiation of Insulin Therapy Is Often Delayed

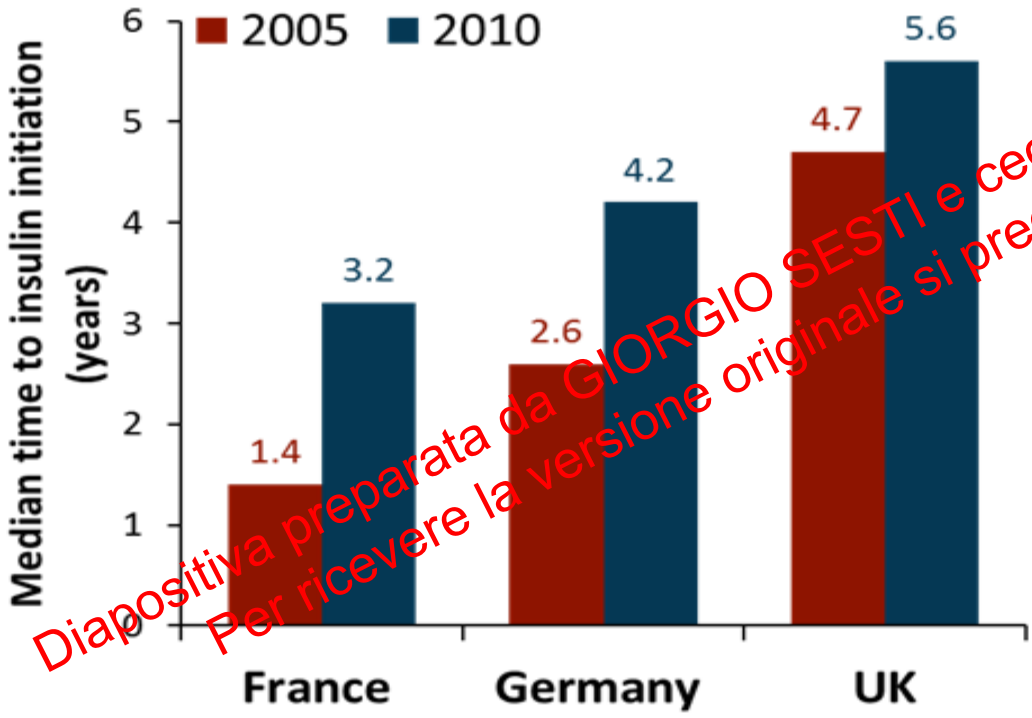


- SOLVE™ study found that pre-insulin mean HbA1c ranged from 8.3% to 9.8%
- Insulin was started later than guidelines recommend in all countries
- Lack of support for patients and physicians is a key problem outside clinical trial settings
- Other reasons for delays include fear of hypoglycemia, weight gain, and needles

Khunti K, et al. *Diabetes Obes Metab.* 2012;14:1129-1136.
Khunti K, et al. *Diabetes Care.* 2013;36:3411-3417.
Petznick AM. *J Am Osteopath Assoc.* 2013;113 (Suppl 2):S6-S16.
Peyrot M, et al. *Diabetes Obes Metab.* 2012;14:1081-1087.

Delays in Starting Insulin Seem to Be Increasing

Retrospective cohort study of routine diabetes care by GPs in France, Germany, and the UK



Kostev K, et al. *Diabetologia*. 2011;54(Suppl 1):P374.

Reasons for delays include:

- Increasing numbers of people with T2DM put pressure on healthcare systems
- The choice of antihyperglycemic agents is growing, possibly leading to confusion among physicians about the best treatment option
- Physicians are not always comfortable with insulin

Petznick AM. *J Am Osteopath Assoc*. 2013;113(Suppl 2):S6-S16.
Polonsky WH, et al. *Diab Care*. 2005;28:2543-2545.