VANTAGGI E LIMITI DELLA TERAPIA INSULINICA

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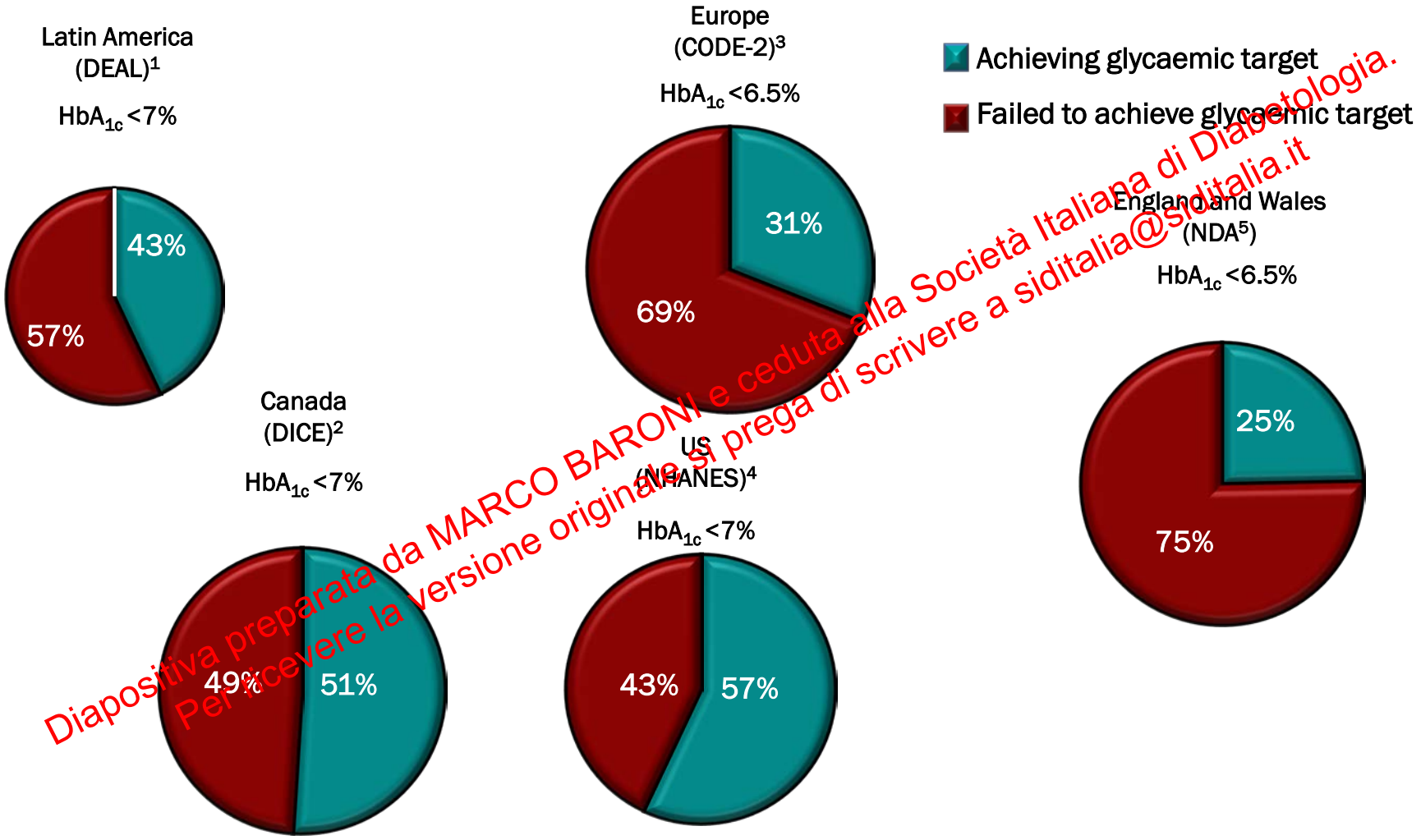
Dichiaro di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

Sanofi

Novo Nordisk

Abbott

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

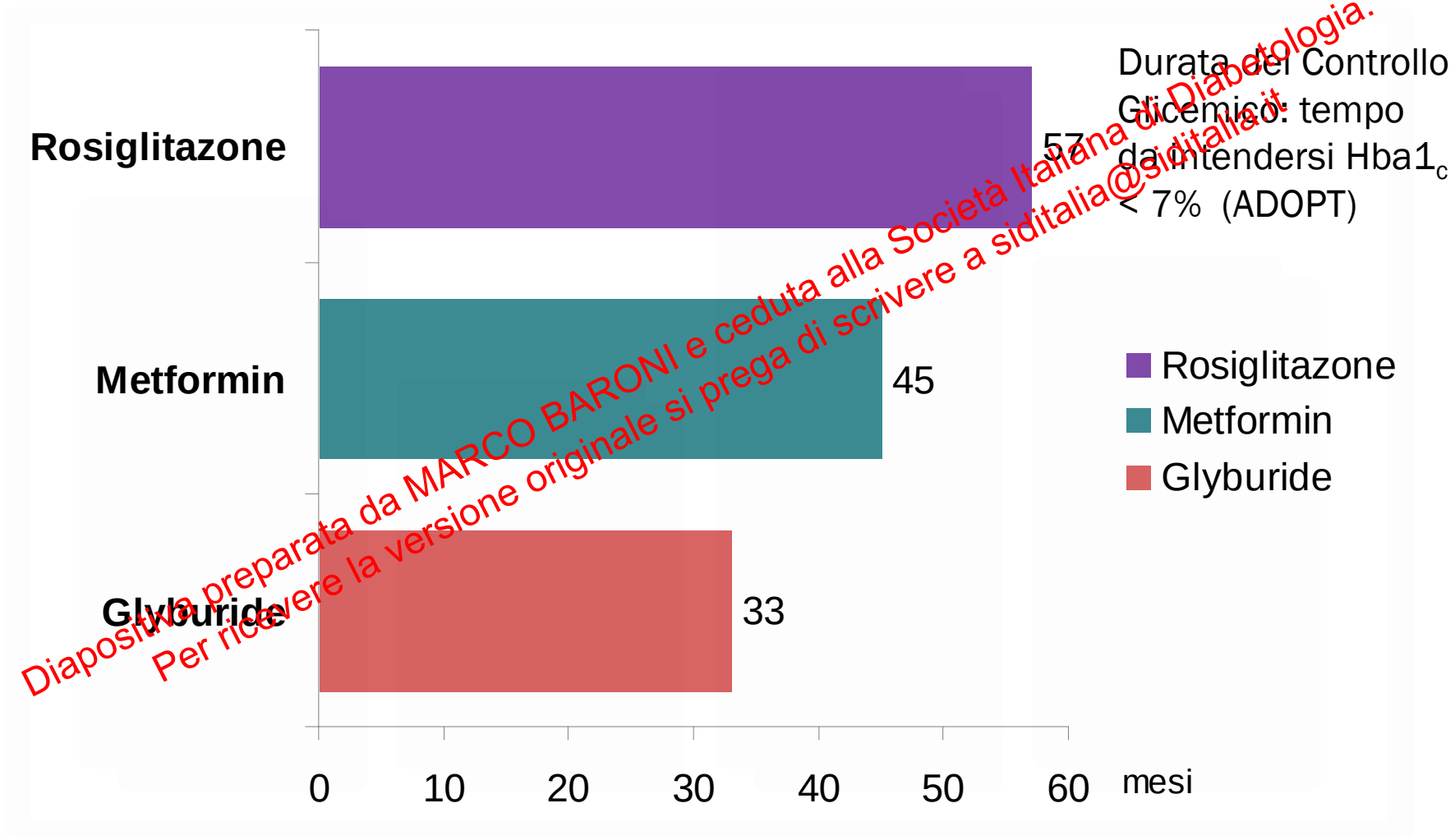
Controllo glicemico nei pazienti italiani con diabete tipo 2

Andamento per classi dell' HbA1c (normalizzata a 6,0)

Il 43.8% dei pazienti presenta valori <7.0%
mentre il 27.2% presenta valori >8%
Il 12% ha valori < 6%

Annali AMD 2012

Diabete di tipo 2:
durata dell'efficacia dei singoli farmaci



Kahn SE et al. NEJM 2006; 355: 2427–2443

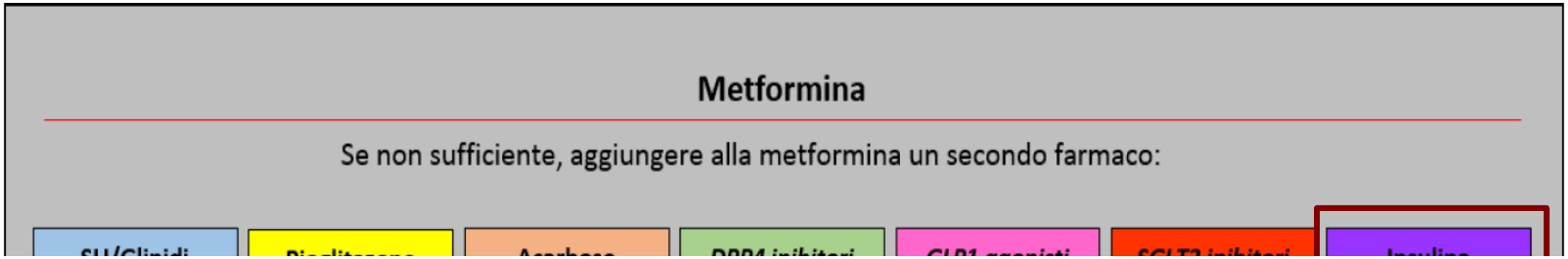
Early *vs* late glycemic intervention: UKPDS enrolled newly diagnosed patients

	UKPDS[1] (n=3867)	ADVANCE[2] (n=11,140)	ACCORD[3] (n=10,251)	VADT[4] (n=1791)
	Disease progression			
Duration of diabetes (years)	0*	8	10	11.5
FPG (mmol/L)	8.0	8.5	9.7	11.4
Mean age (years)	53	66	62	60
Microvascular	↓	↓	±	=
Macrovascular	↓	=	↑	=

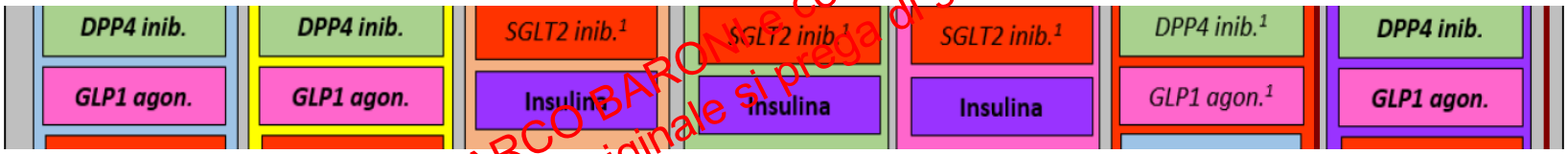
Intervento precoce ed individualizzazione della terapia

**Newly diagnosed patients with no previous history of CVD; FPG: fasting plasma glucose*

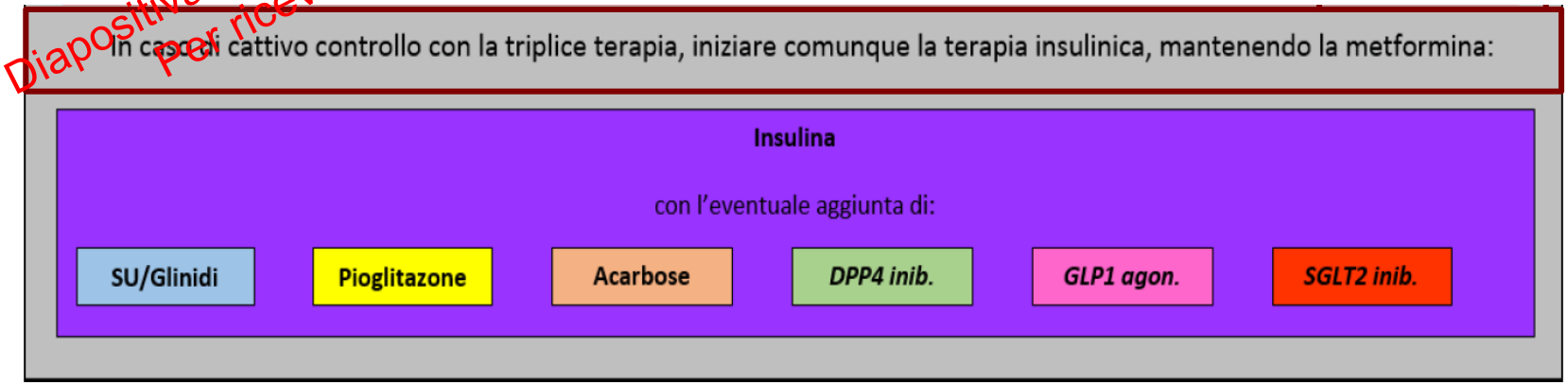
[1]UKPDS Group. ***Lancet*** 1998; 352:837. [2]ADVANCE Collaborative Group. ***N Engl J Med*** 2008; 358:2560
[3]ACCORD Study Group. ***N Engl J Med*** 2008; 358:2545. [4]Duckworth et al ***N Engl J Med*** 2009; 360:129



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

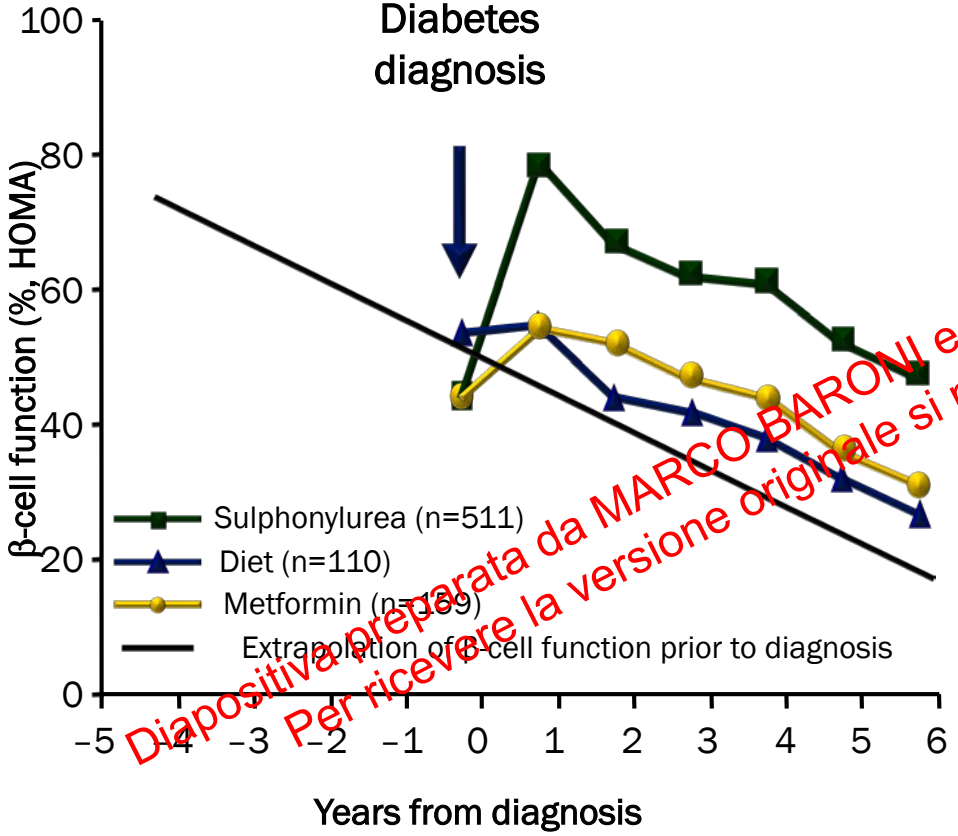
ADVANTAGES

- The defect in insulin secretion is a primary one. The primary defect in insulin secretion is reverted by insulin treatment

LIMITATIONS

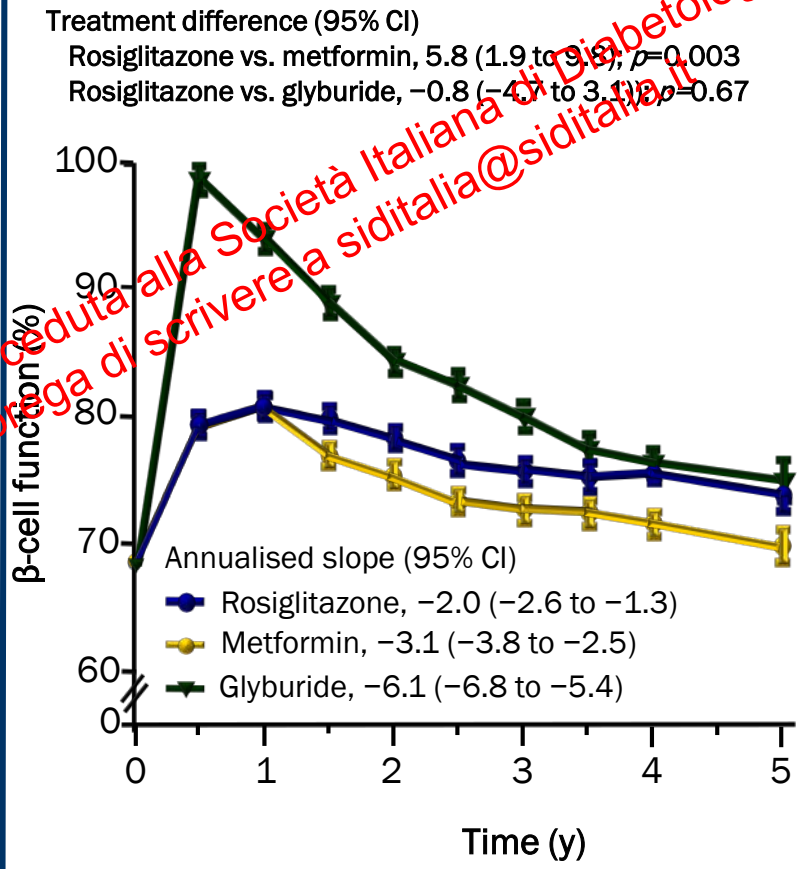
β-cell function progressively declines

UKPDS



UKPDS 16. Diabetes 1995;44:1249–58; Lebovitz 1999;7:139–53

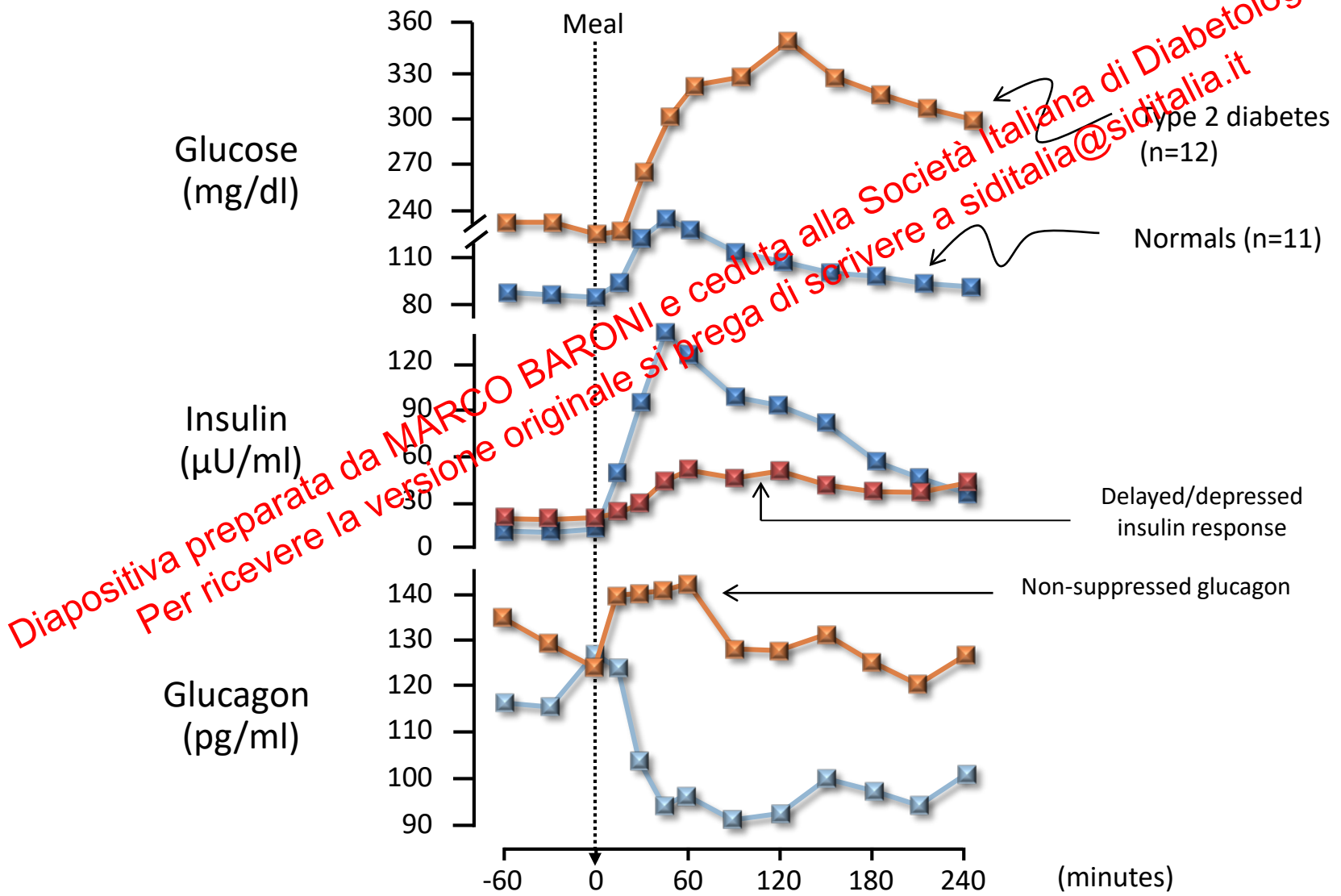
ADOPT



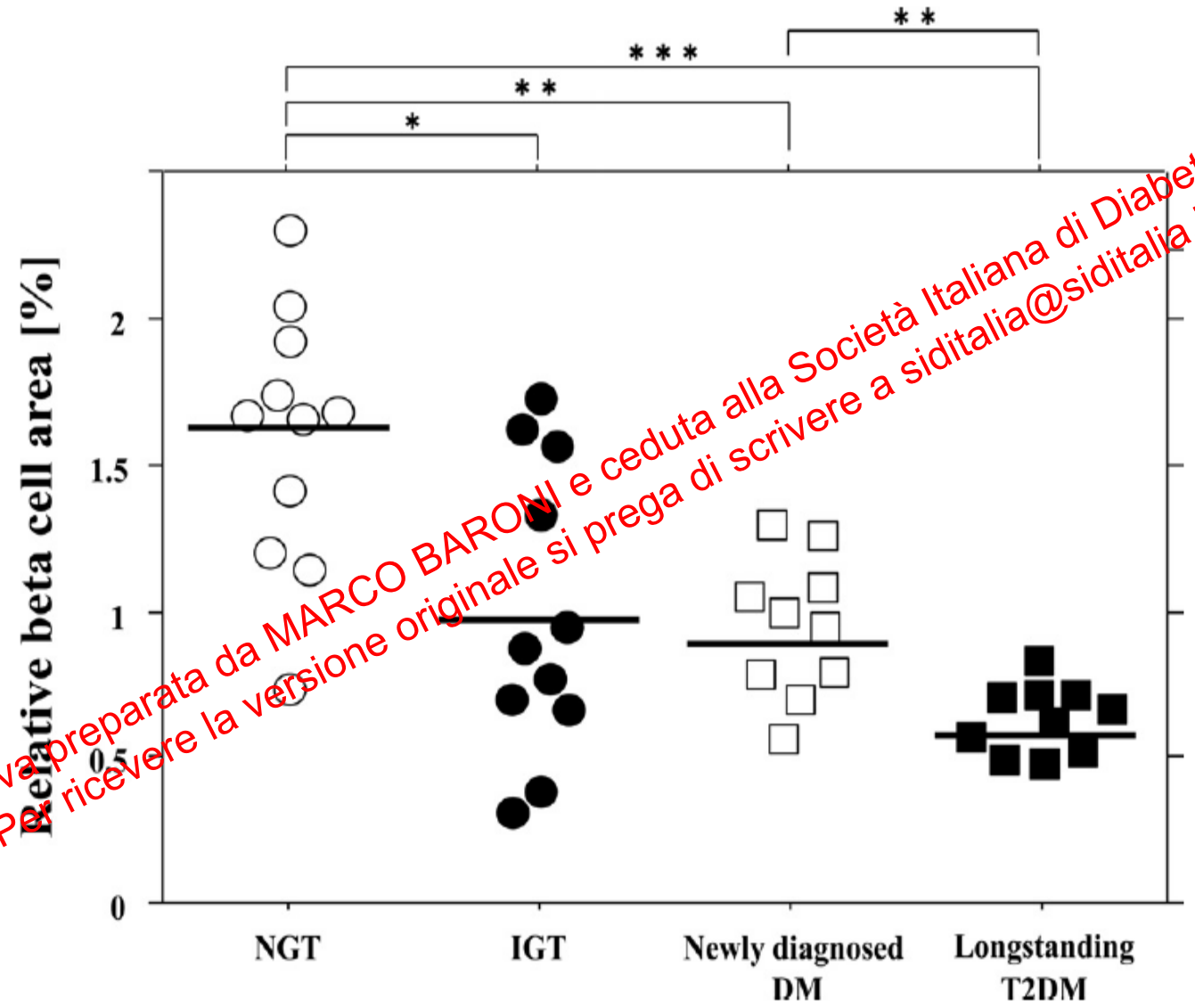
Kahn et al. N Engl J Med 2006;355:2427–43

Insulin and glucagon dynamics in response to meals are abnormal in type 2 diabetes

Adapted from Muller WA et al. ***N Engl J Med***. 1970;283:109

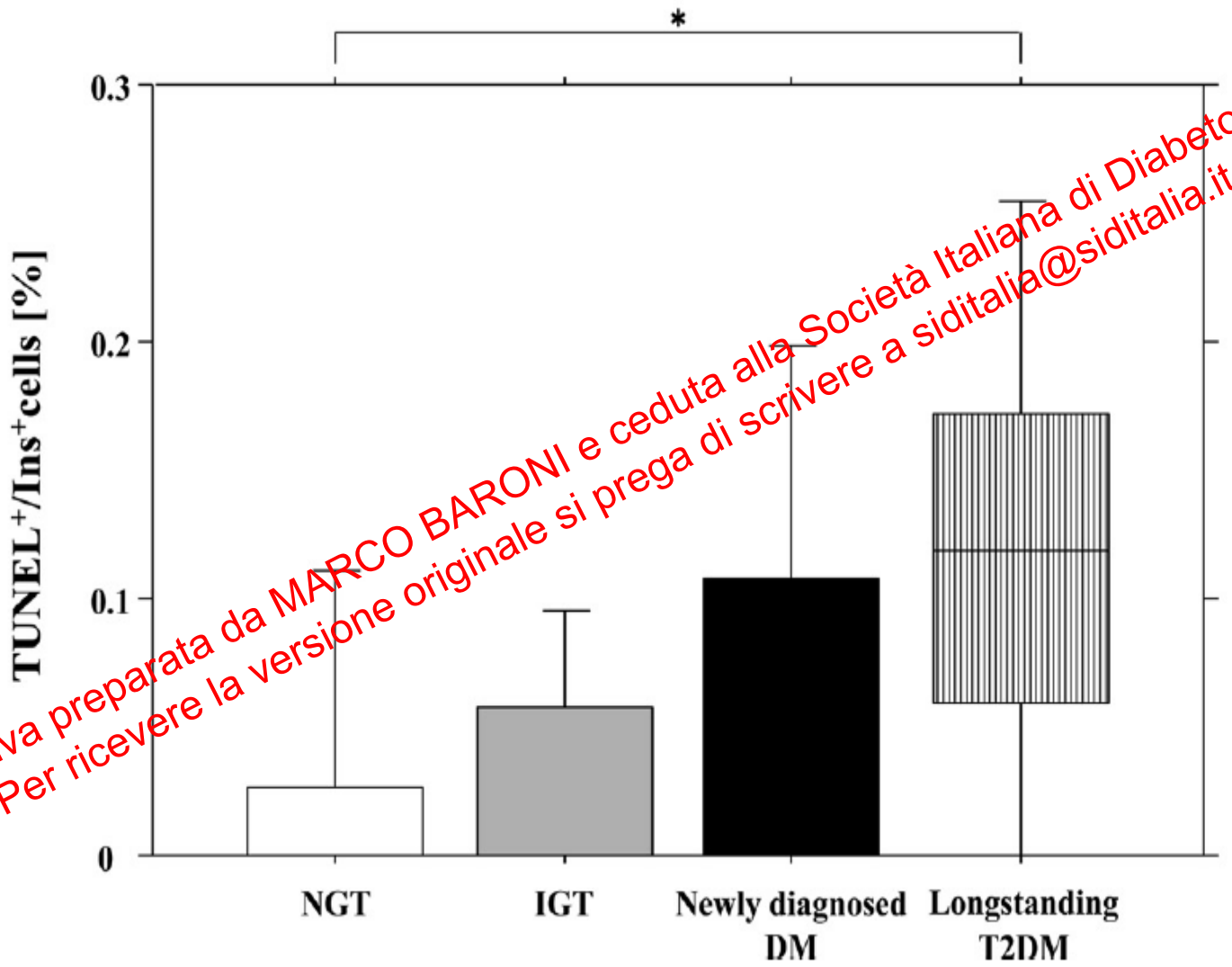


Relative β-cell area to entire pancreatic section in NGT, IGT, newly diagnosed DM and longstanding T2DM



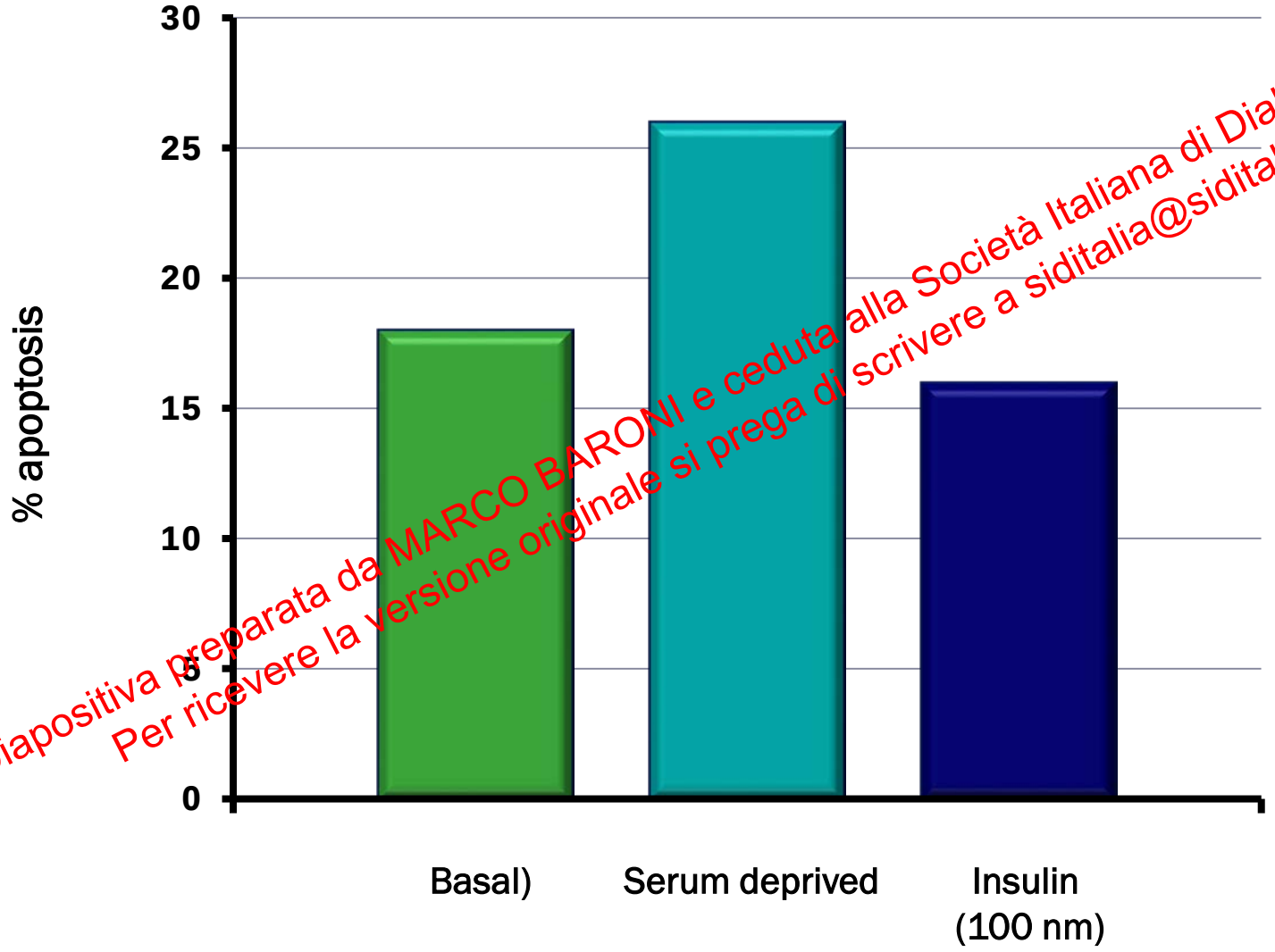
Yoneda S et al. J Clin Endocrinol Metab 98: 2053–2061, 2013

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



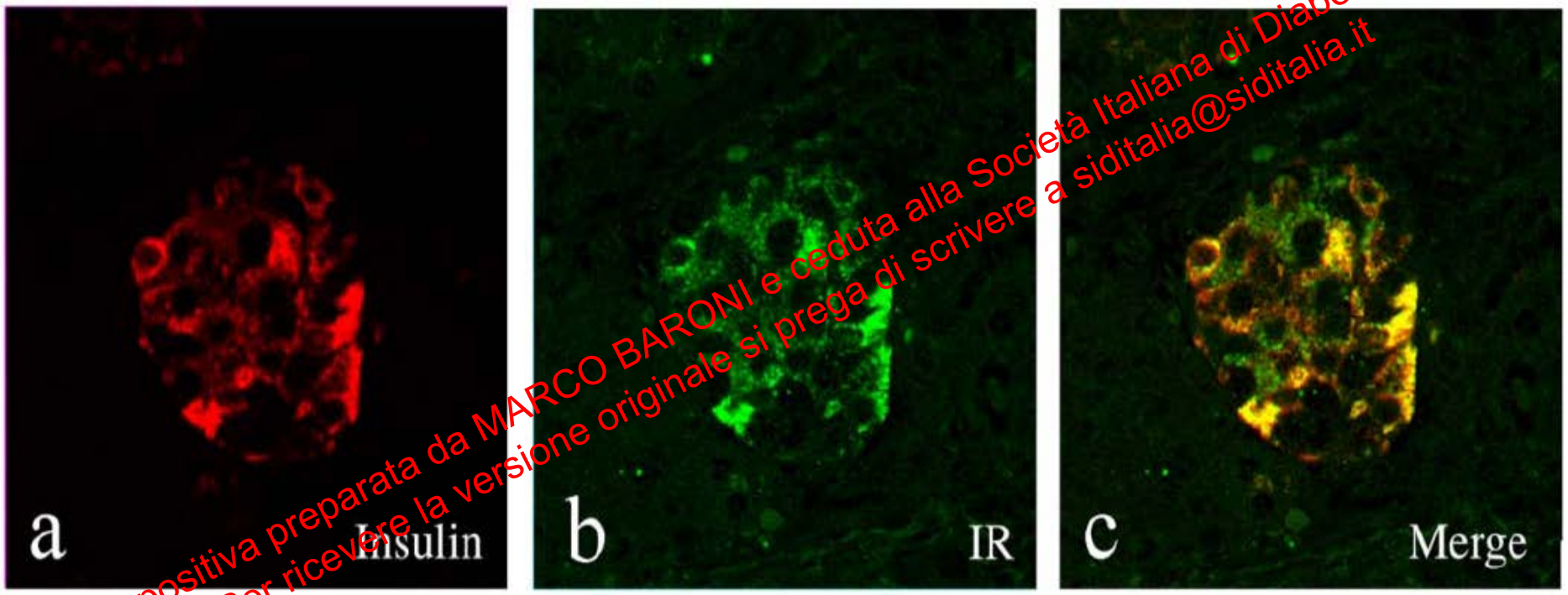
Yoneda S et al. J Clin Endocrinol Metab 98: 2053–2061, 2013

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



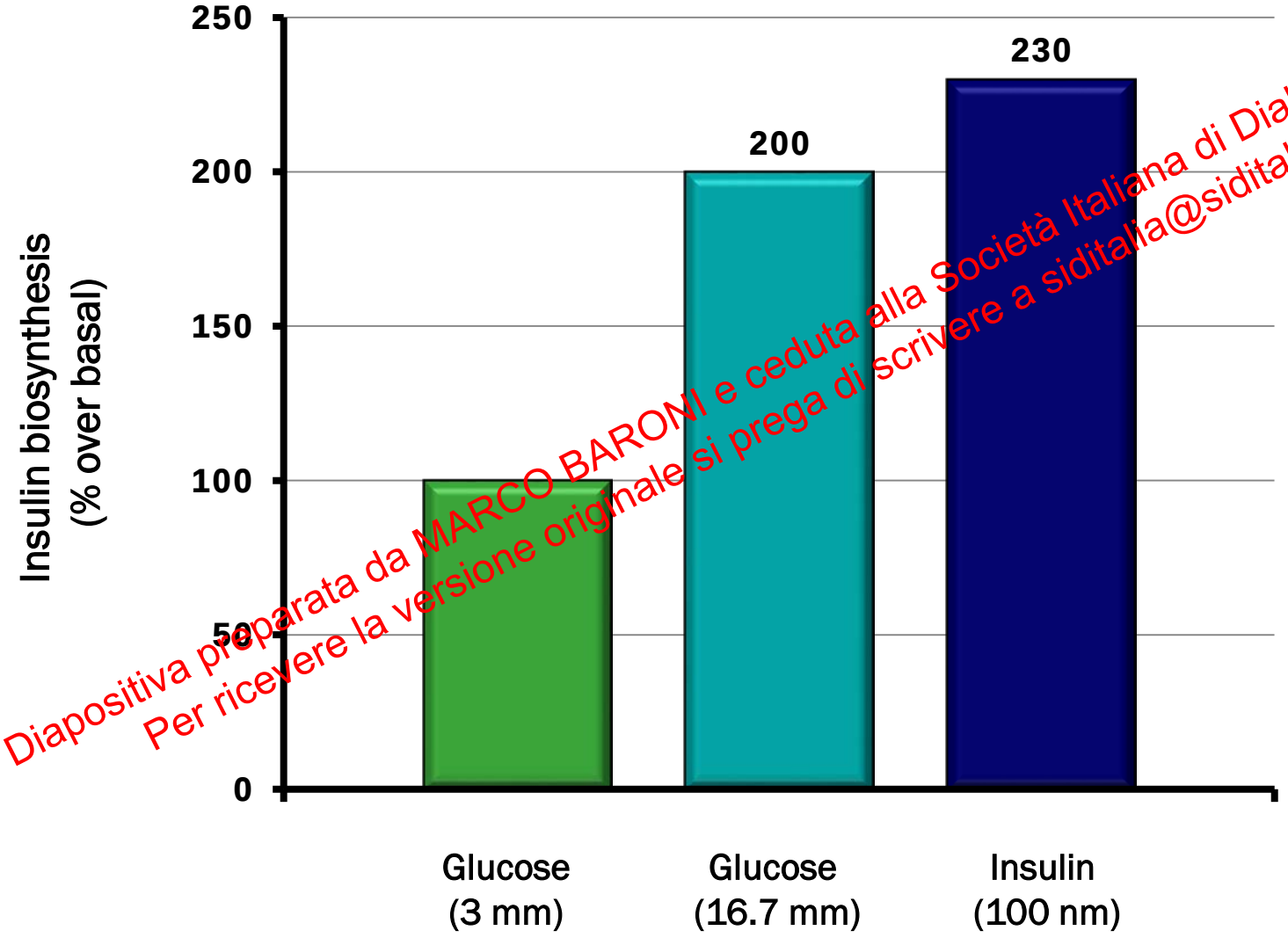
Modified from Federici M al. FASEB J 15: 22-24, 2001

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



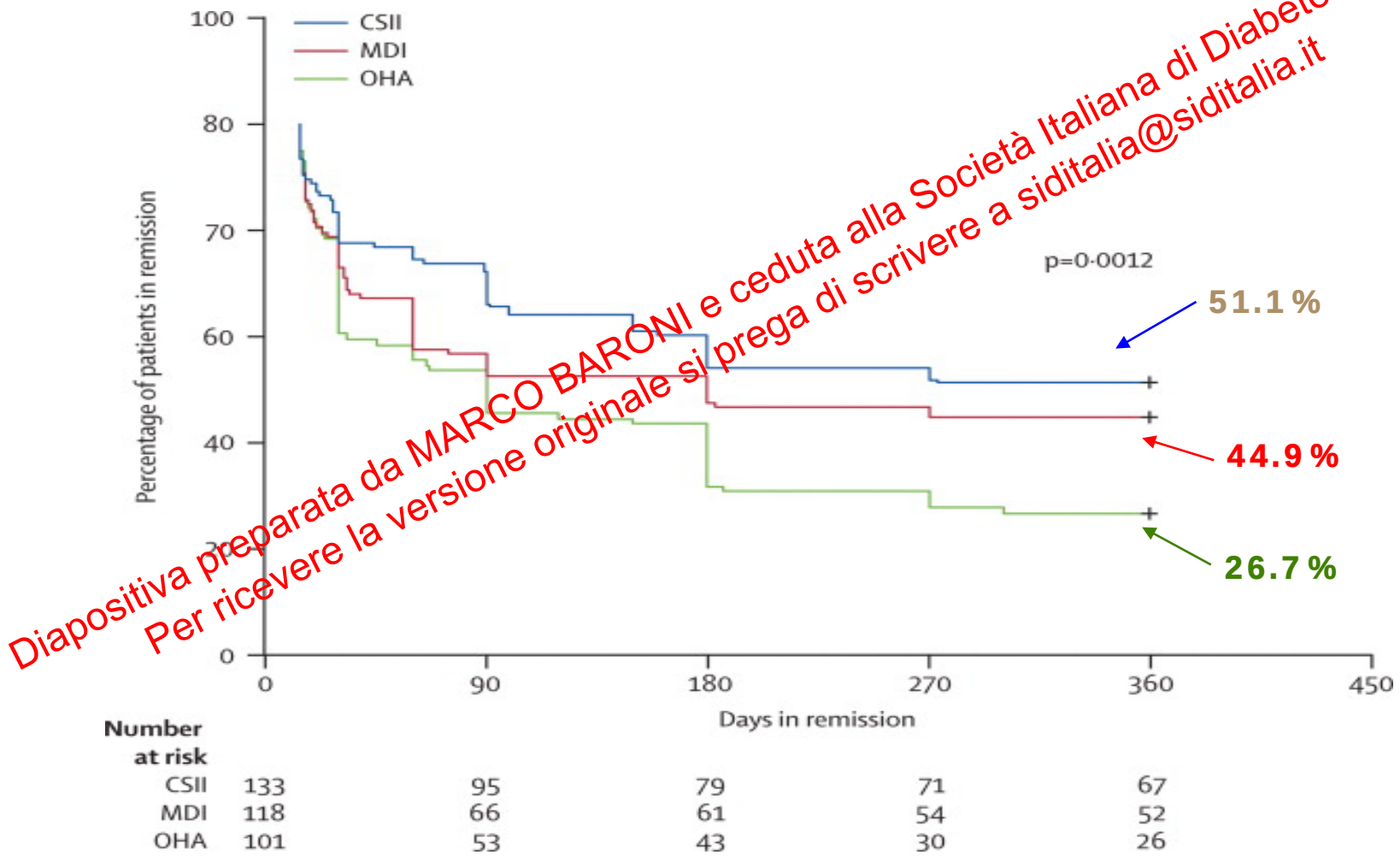
Hribal et al. FASEB J 17: 1340-1342, 2003

Insulin stimulates its biosynthesis in human pancreatic islets



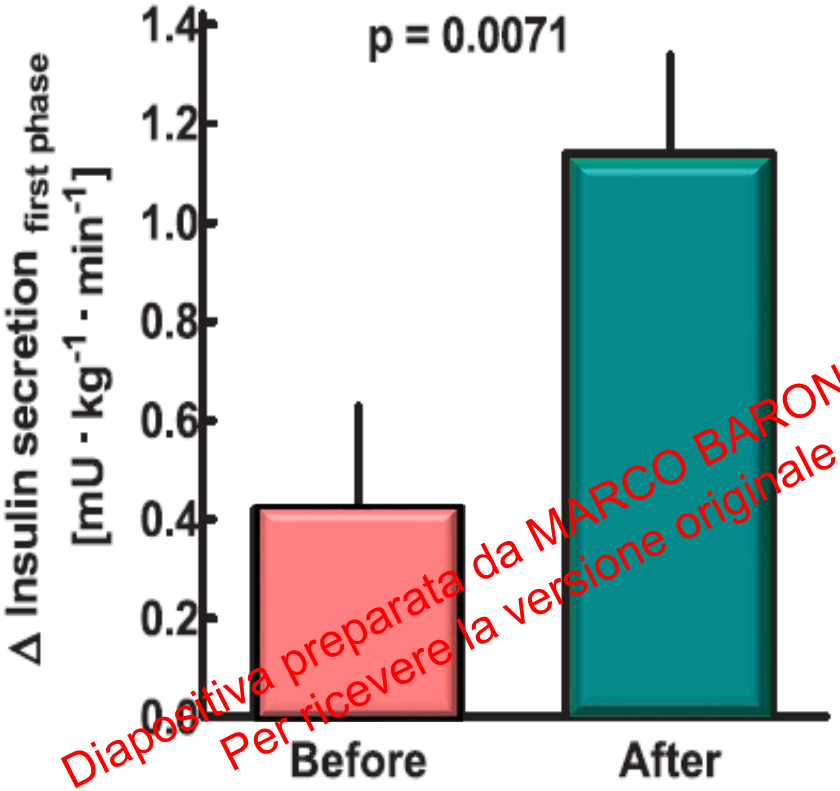
Modified from Andreozzi F et al. Endocrinology 145: 2845–2857, 2004

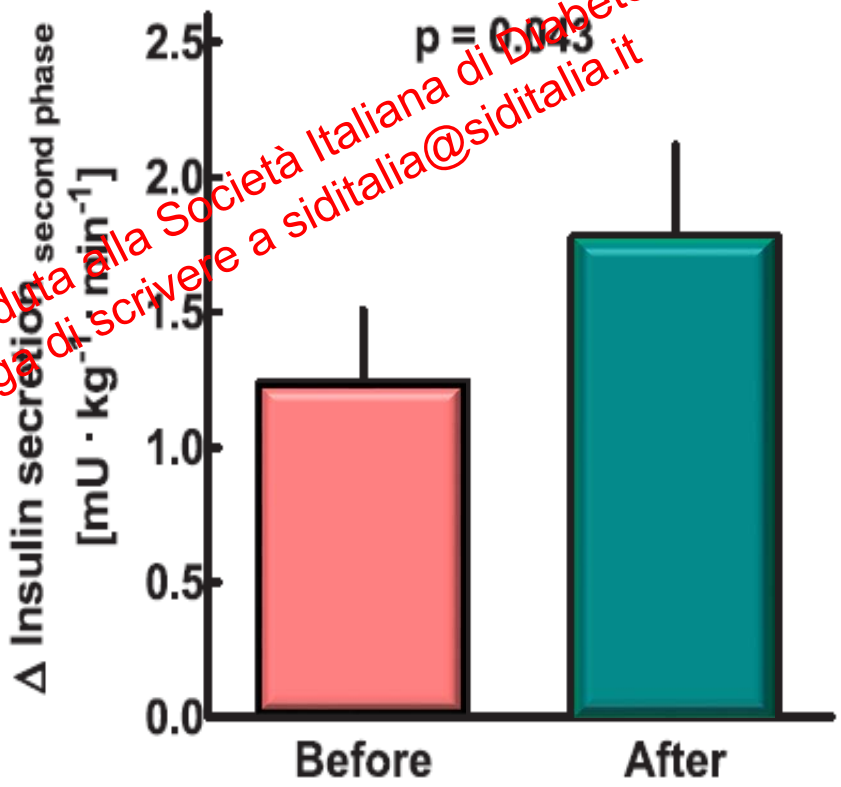
Effetto della terapia insulinica intensiva sulla funzione □-cellulare e sul controllo glicemico in diabetici tipo 2 di nuova diagnosi



Lancet 2008; 371: 1753-1760

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

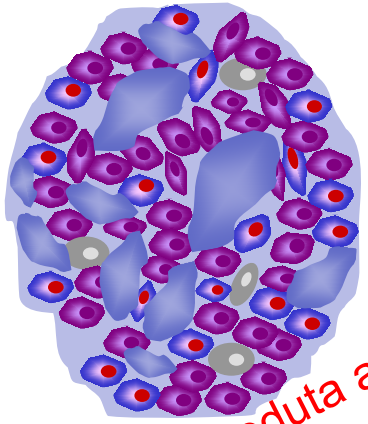
ADVANTAGES

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

LIMITATIONS

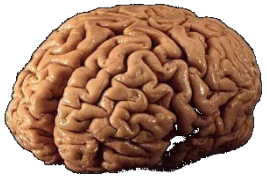
Key Pathogenetic Defects in T2DM: The Ominous Octet

INAPPROPRIATE GLUCAGON SECRETION

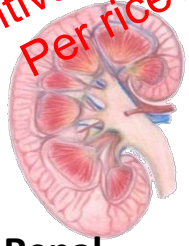


IMPAIRED INSULIN SECRETION

Altered Brain Signalling

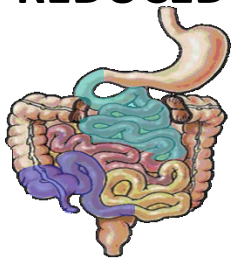


Altered Adipocyte Metabolism

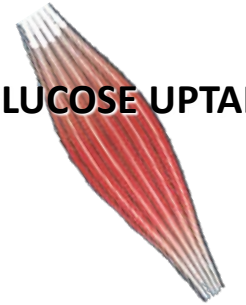


Increased Renal Glucose Reabsorption

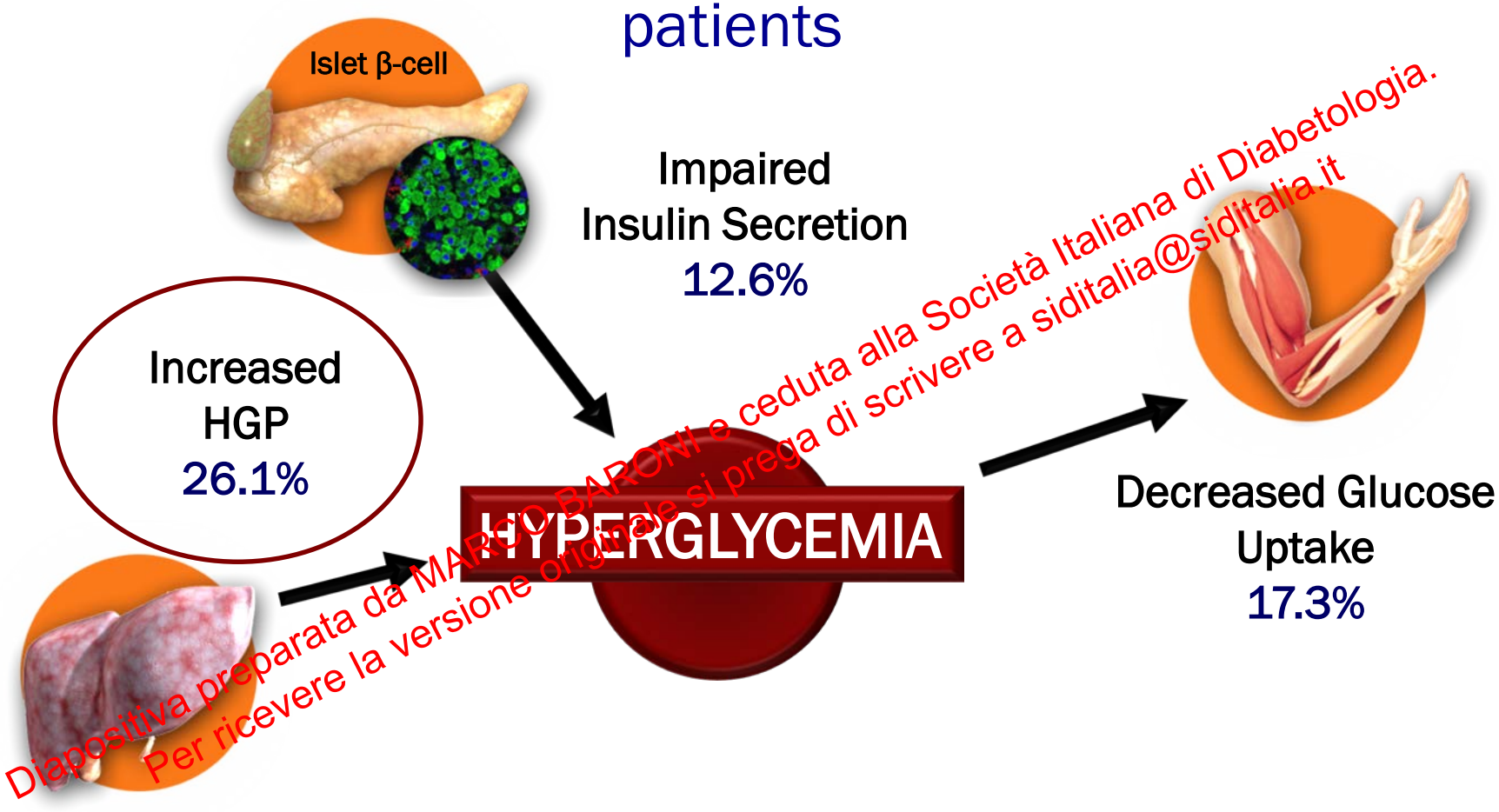
REDUCED GLP-1



REDUCED GLUCOSE UPTAKE

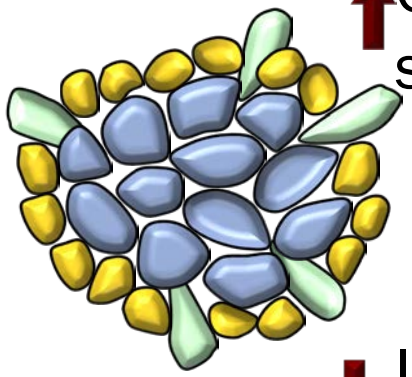


Relative contributions of HGP and glucose disposal to secondary failure to oral agents in Finnish diabetic patients



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

Excessive hepatic glucose production



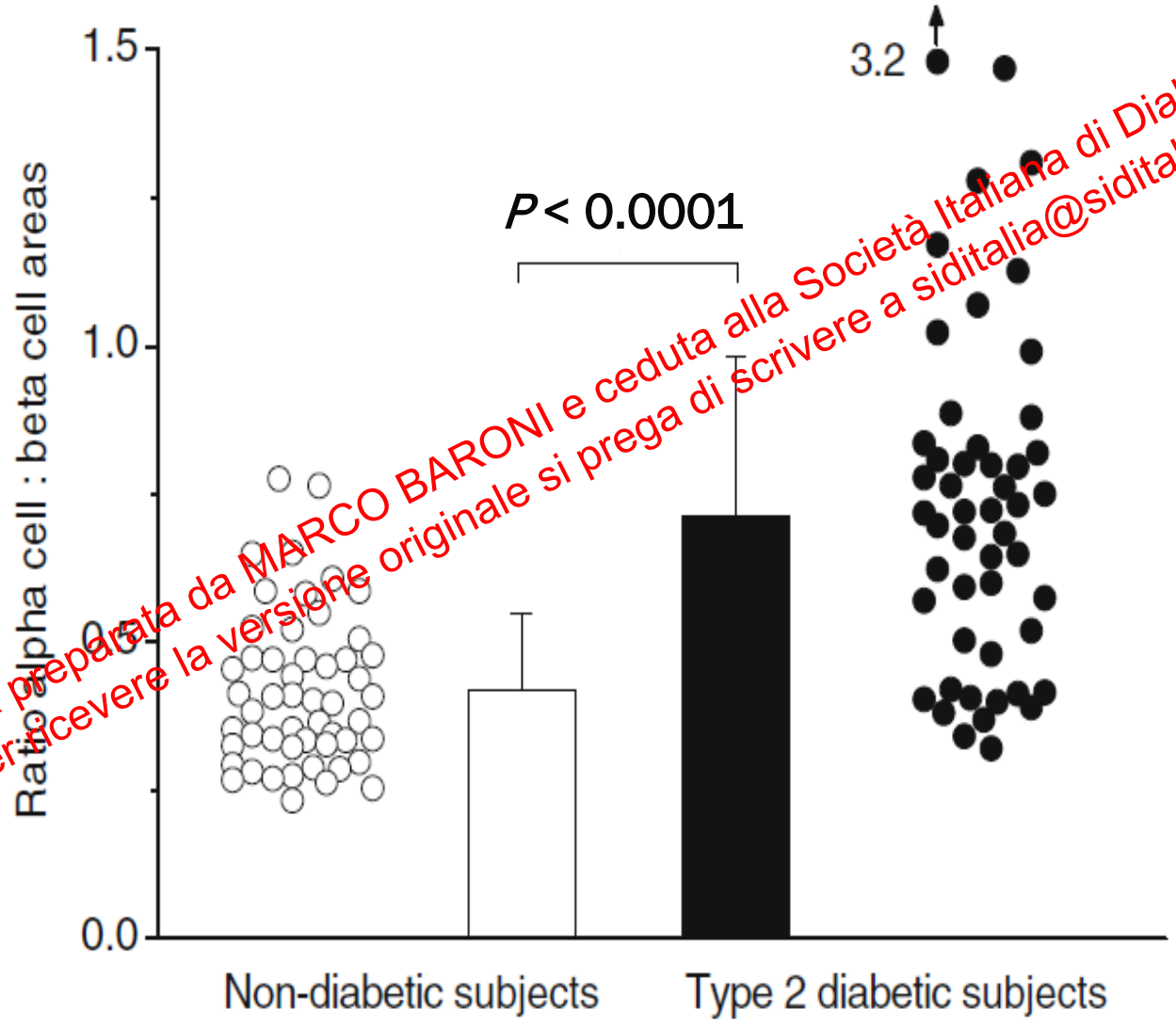
↑ Glucagon secretion

↓ Insulin secretion

↑ Hepatic glucose production

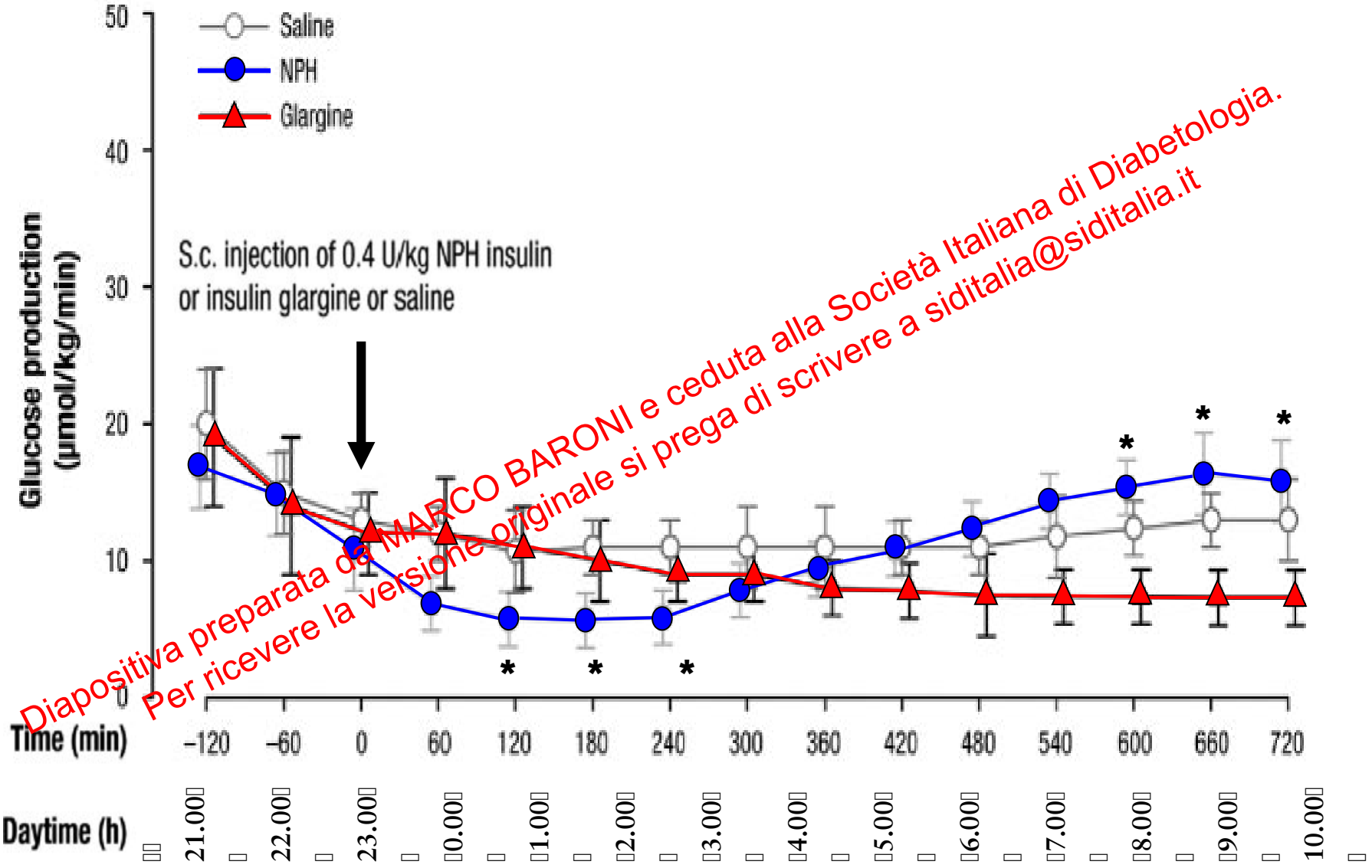
Pancreatic cells: β-cell α-cell δ-cell

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



Henquin JC et al. Diabetologia 54:1720–1725, 2011

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

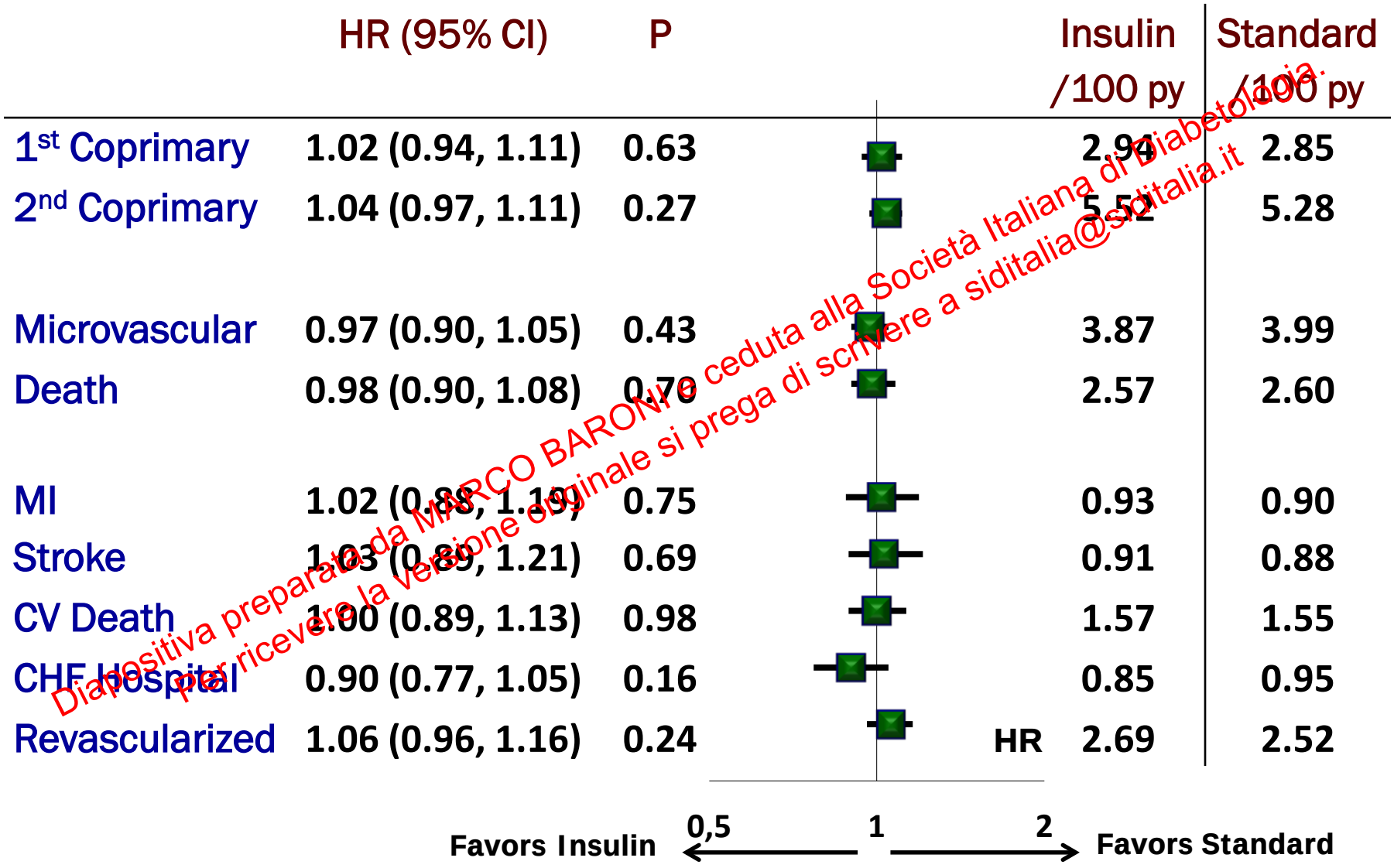
ORIGINAL ARTICLE

Basal Insulin and Cardiovascular and Other Outcomes in Dysglycemia

The ORIGIN Trial Investigators*

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

ORIGIN
Primary & Secondary Outcomes & their Components



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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

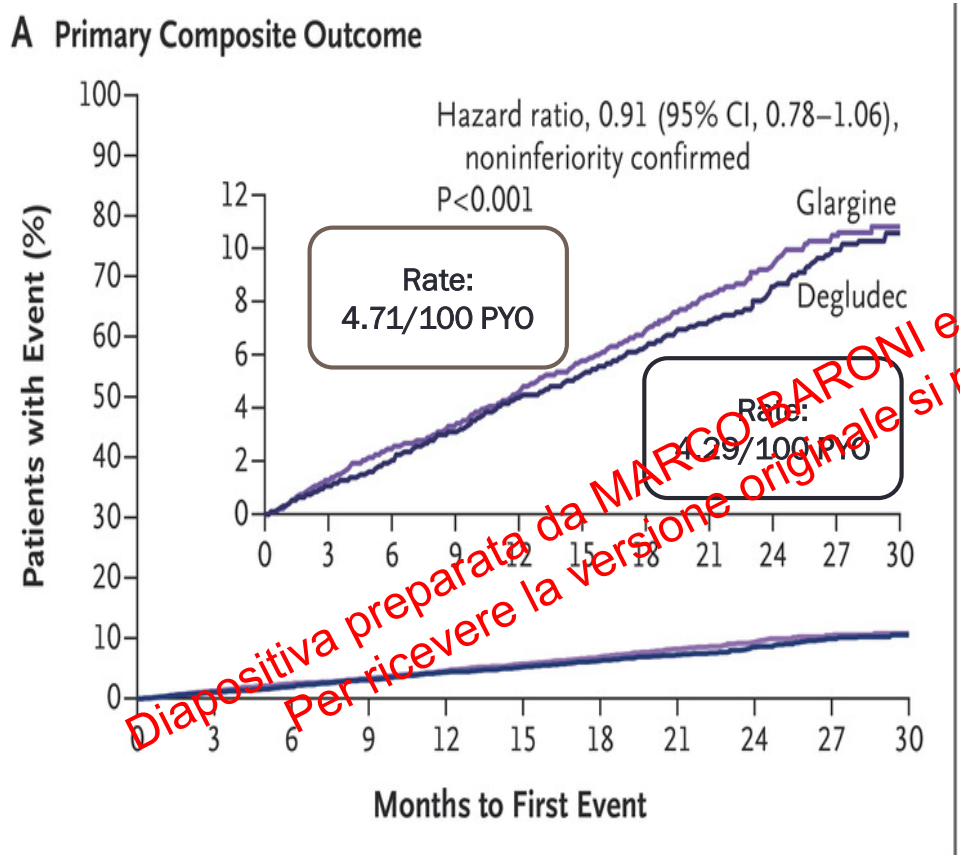
Efficacy and Safety of Degludec versus Glargine in Type 2 Diabetes

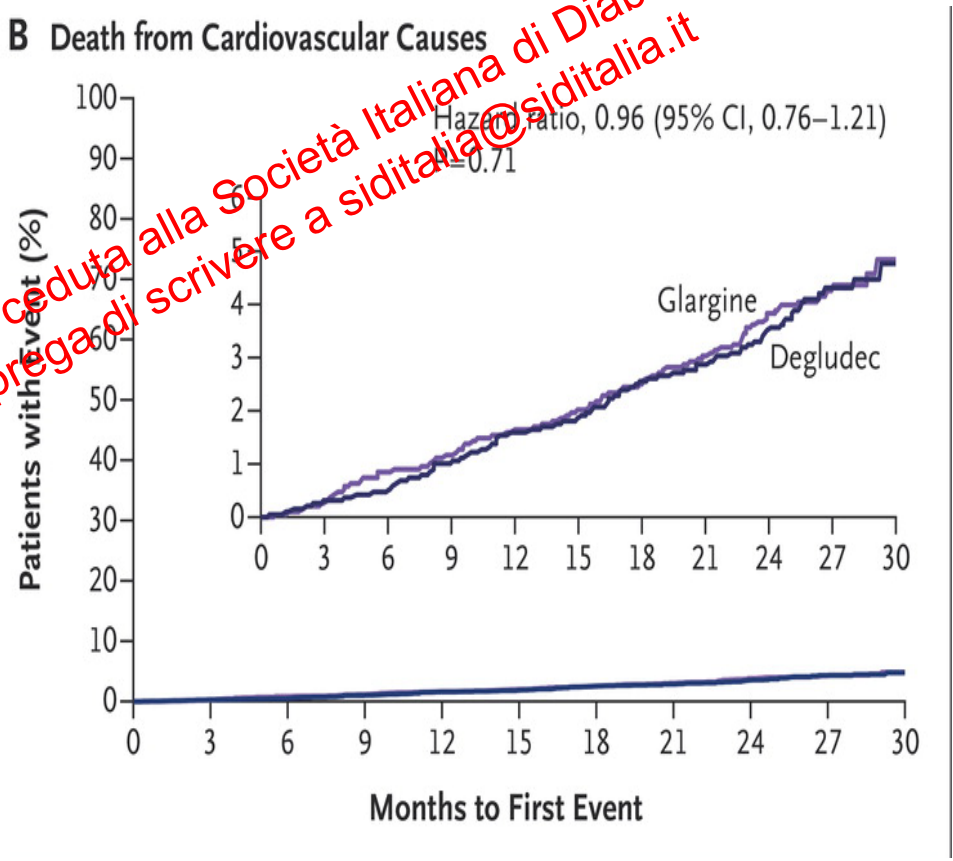
Steven P. Marso, M.D., Darren K. McGuire, M.D., Bernard Zinman, M.D., Neil R. Poulter, F.Med.Sci., Scott S. Emerson, M.D., Ph.D., Thomas R. Pieber, M.D., Richard E. Pratley, M.D., Poul-Martin Haahr, M.D., Martin Lange, M.D., Ph.D., Kirstine Brown-Frandsen, M.D., Alan Moses, M.D., Simon Skibsted, M.D.,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

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

DEVOTE

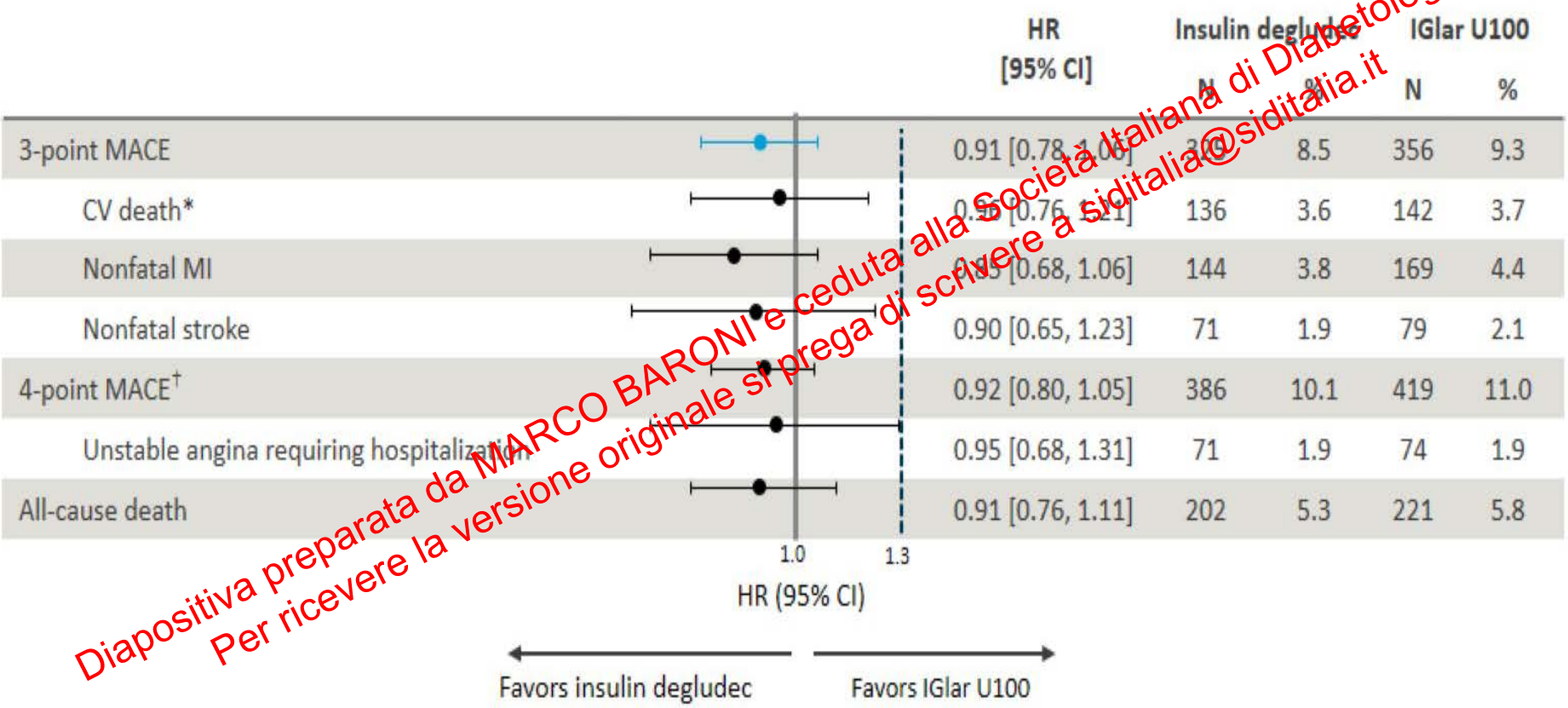
Kaplan–Meier Analysis of the Composite Primary Outcome





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

Devote Primary Endpoints: 3-Point MACE, 4-Point MACE, and All-Cause Mortality



	HR [95% CI]	Insulin degludec N	Insulin degludec %	IGlar U100 N	IGlar U100 %
3-point MACE	0.91 [0.78, 1.06]	3[illegible]	8.5	356	9.3
CV death*	0.[illegible] [0.76, 1.21]	136	3.6	142	3.7
Nonfatal MI	0.85 [0.68, 1.06]	144	3.8	169	4.4
Nonfatal stroke	0.90 [0.65, 1.23]	71	1.9	79	2.1
4-point MACE†	0.92 [0.80, 1.05]	386	10.1	419	11.0
Unstable angina requiring hospitalization	0.95 [0.68, 1.31]	71	1.9	74	1.9
All-cause death	0.91 [0.76, 1.11]	202	5.3	221	5.8

CV death includes undetermined cause of death; †4-point MACE defined as cardiovascular death, nonfatal MI, nonfatal stroke, or unstable angina requiring hospitalization.

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

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LIMITATIONS

- Treatment with insulin is associated with body weight gain.

Type 2 diabetes –weight gain over time is associated with insulin and oral antidiabetic therapies

These major trials have shown weight gain over time:

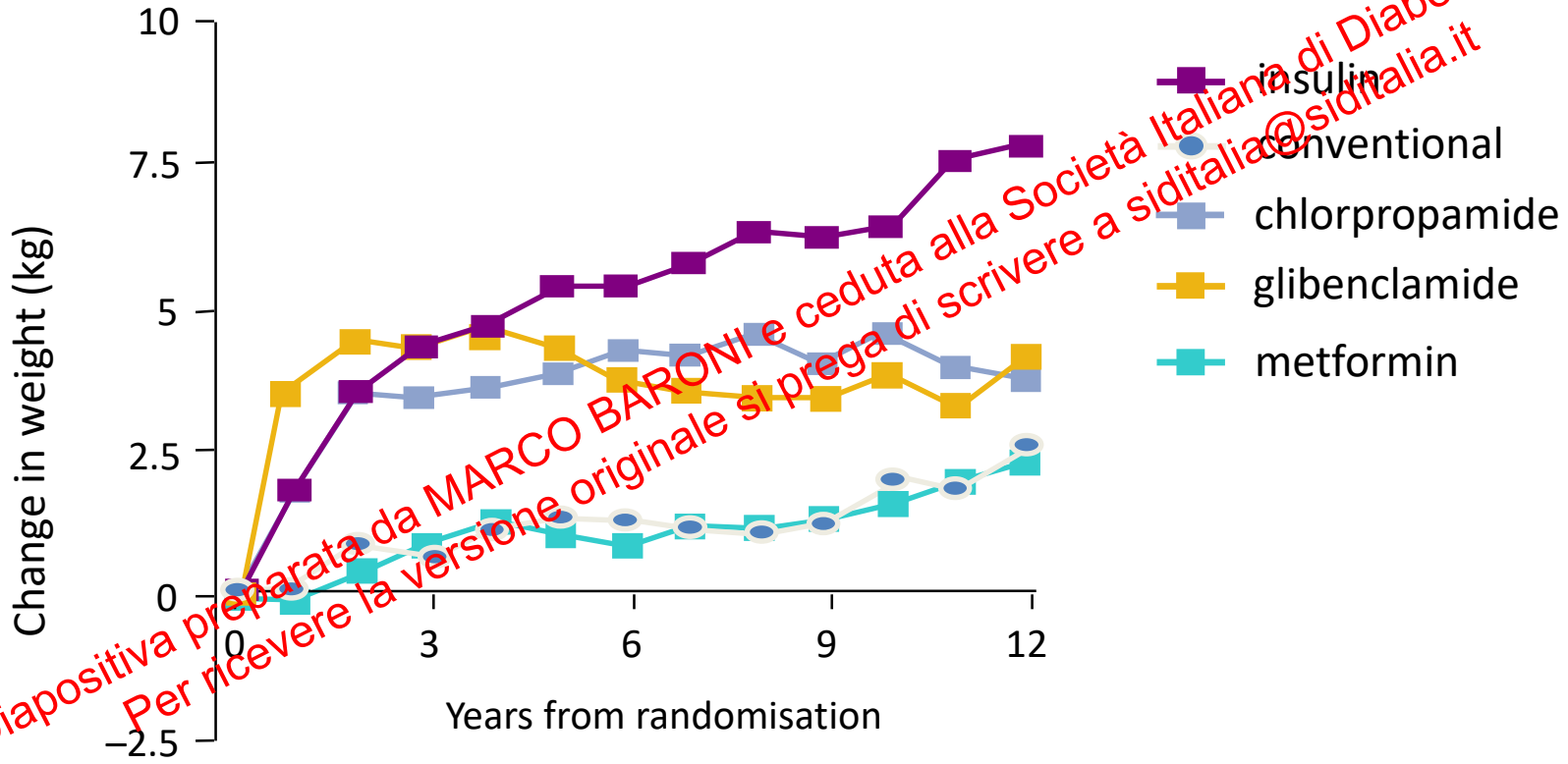
- UKPDS, significant mean increase of 3.1 kg in weight in the intensive treatment (sulphonylurea or insulin) group compared with the conventional treatment (diet and exercise) group[1]

- Action to Control Cardiovascular Risk in Diabetes (ACCORD), where patients receiving intensive therapy (targeting an HbA_{1c} <6%, often through the use of insulin and multiple agents) gained an average of 3.5 kg, with nearly 30% gaining >10 kg[3]

- In A Diabetes Outcome Progression Trial (ADOPT), patients receiving glibenclamide gained an average of 1.6 kg over a median treatment duration of 3.3 years[4]

1. UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:837–53; 2. UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:854–65;
3. Members of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group. *N Engl J Med* 2008;358:2545–59;
4. Kahn SE, Haffner SM, Heise MA, *et al.* for the ADOPT Study Group. *N Engl J Med* 2006;355:2427–43.

In the UKPDS, insulin-treated patients with type 2 diabetes gained the most weight



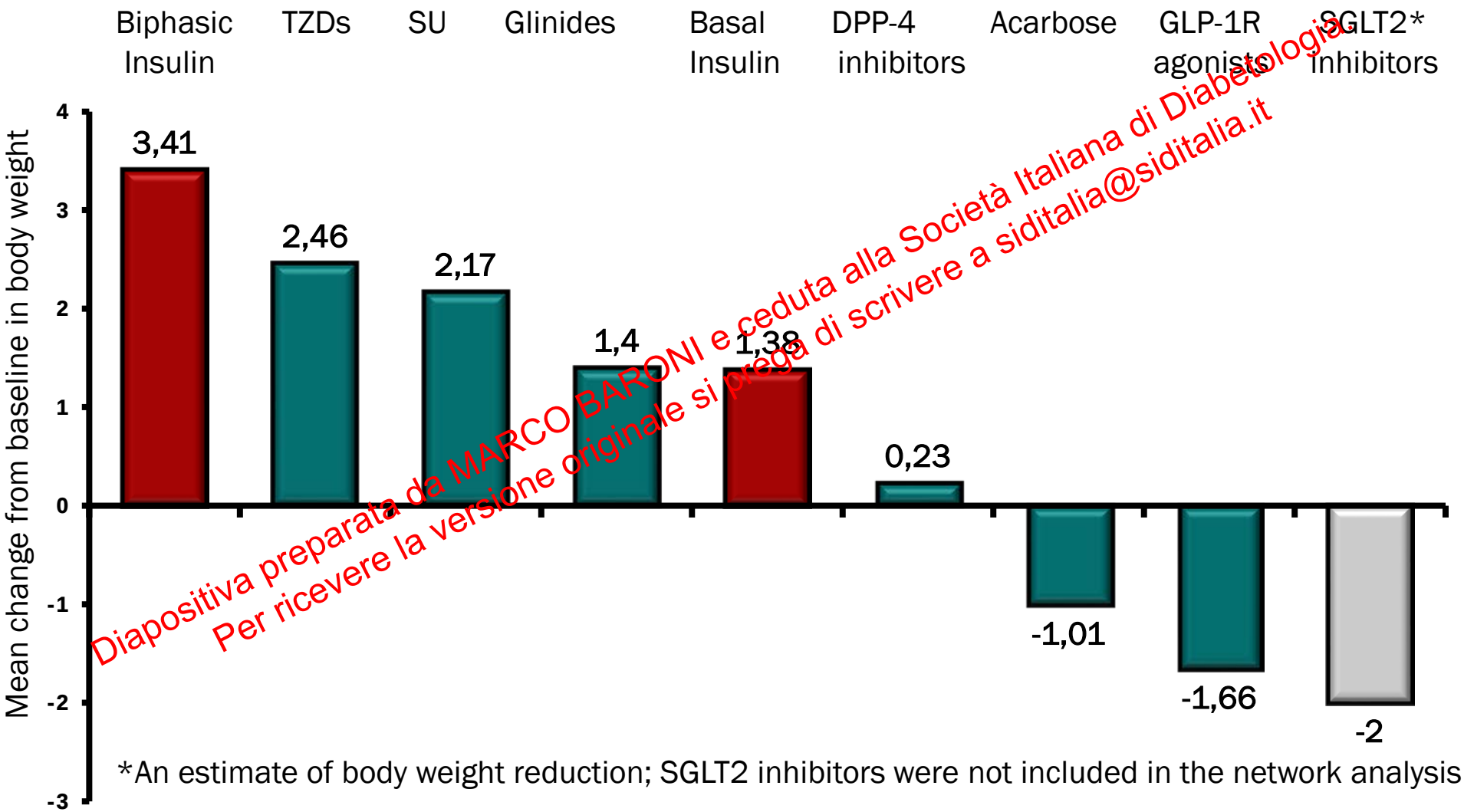
While patients on all therapies gained weight, patients receiving insulin gained the most (up to 8 kg after 12 years of insulin therapy)

UKPDS 34. ***Lancet*** **1998:352:854–865.**

Insulin and weight

- Reduced glycosuria
- Anabolic action of insulin
- Fluid retention
- Hypoglycaemia and increased calorie consumption
- Excess insulin administration

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

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

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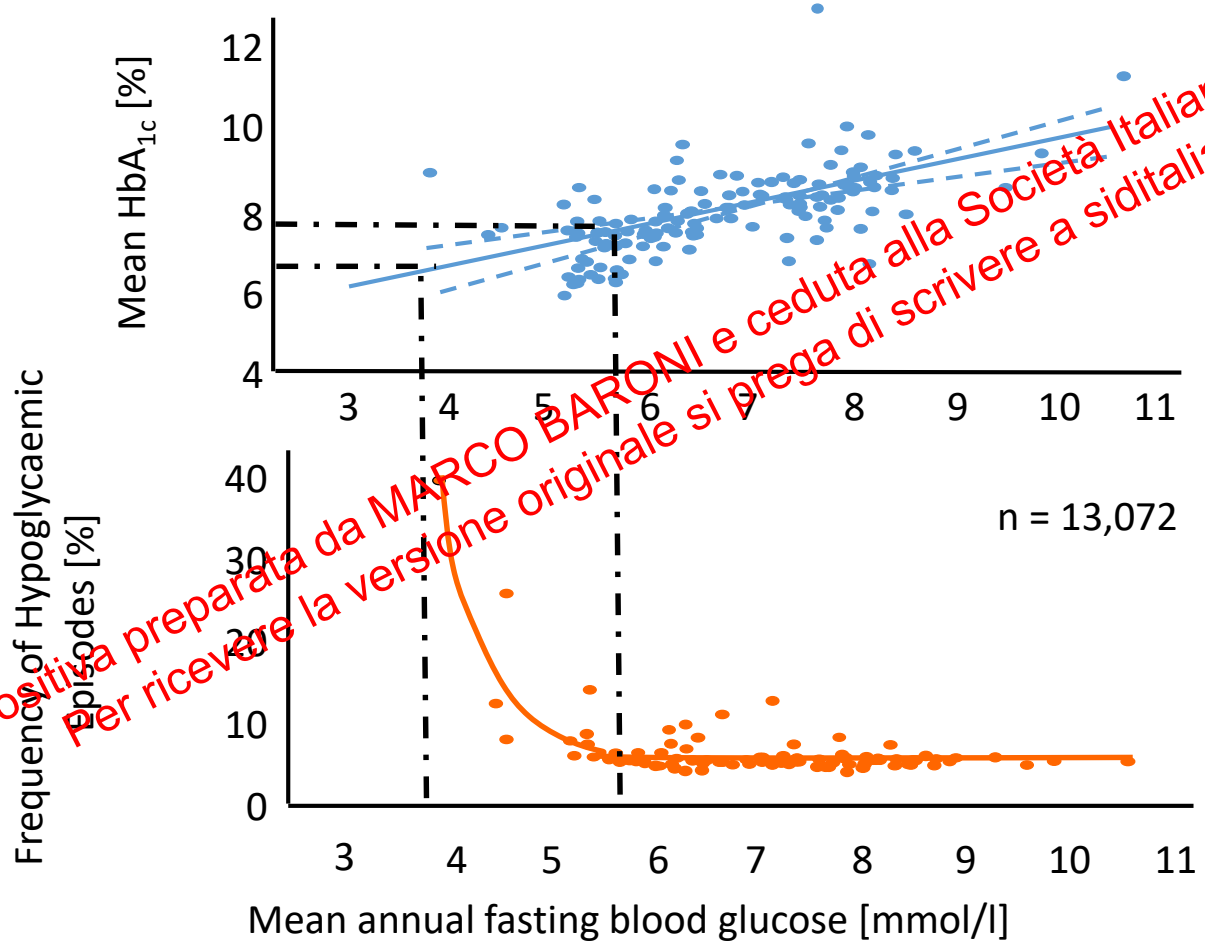
- The primary defect in insulin secretion is reverted by insulin treatment
- Insulin treatment reverted defects in hepatic glucose production.
- Insulin therapy is not associated with atherogenesis and increased risk of CV events.
- Basal insulin is easy to use : one insulin, once daily injection, one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

LIMITATIONS

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

Hypoglycaemia limits further reduction of FPG with basal insulin

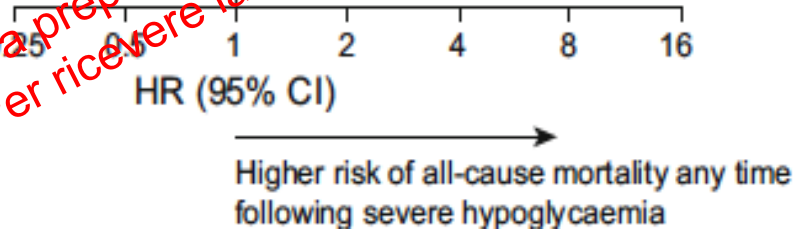


Yki-Jarvinen *et al. Ann Int Med* 1999

DEVOTE 3: temporal relationships between severe hypoglycaemia, cardiovascular outcomes and mortality

Published online: 15 September 2017

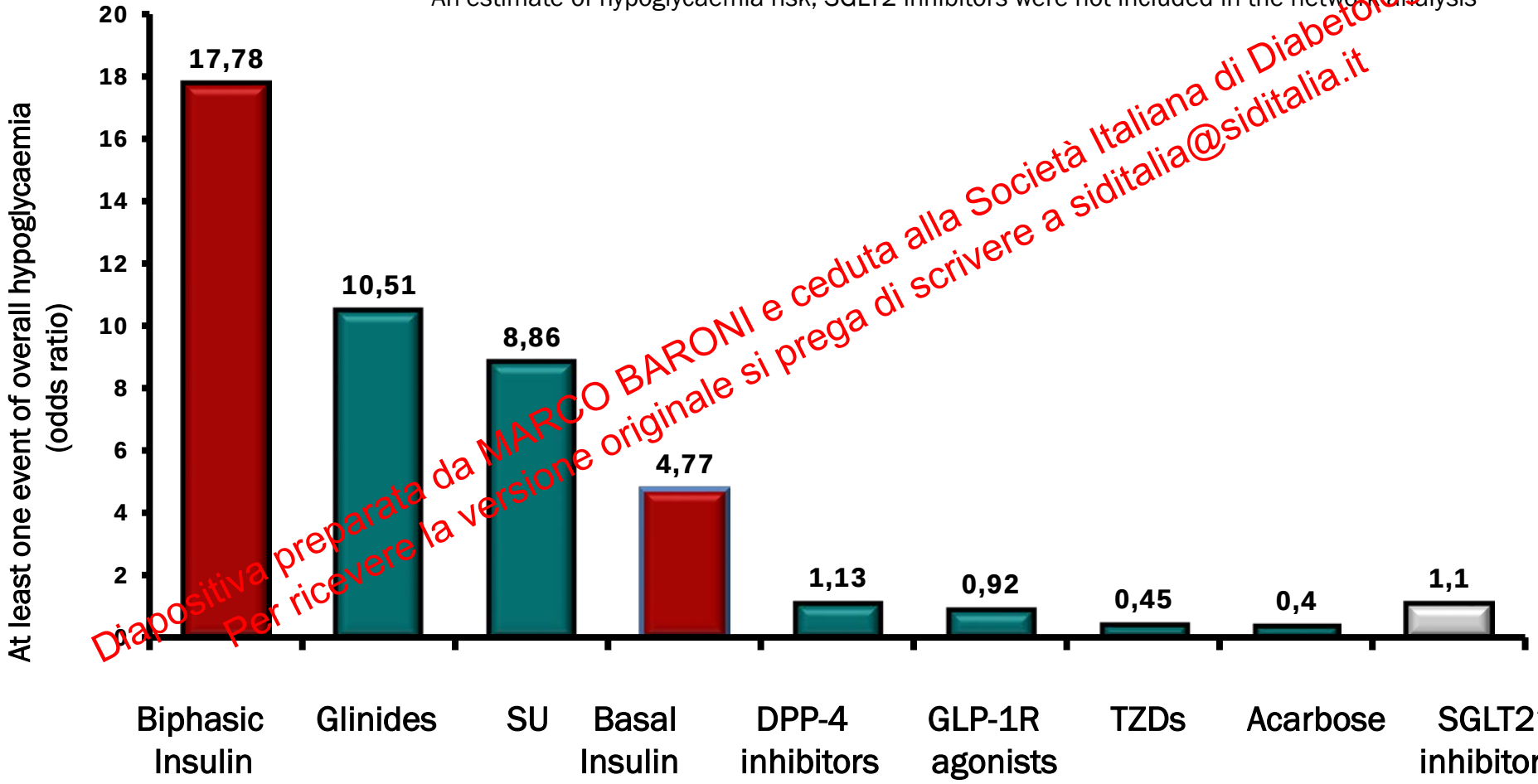
Window (days)	HR (95% CI)	All-cause mortality with prior severe hypoglycaemia in window		All-cause mortality without prior severe hypoglycaemia in window	
		n	Rate	*n*	Rate
Any time	2.51 (1.76, 3.50)	38	7.32	385	2.64
365 days	2.78 (1.92, 4.04)	30	7.78	393	2.67
180 days	3.13 (1.99, 4.90)	20	8.56	403	2.71
90 days	3.28 (1.85, 5.83)	12	8.95	411	2.74
60 days	2.74 (1.30, 5.79)	7	7.40	416	2.77
30 days	3.66 (1.51, 8.84)	5	9.84	418	2.77
15 days	4.20 (1.35, 13.09)	3	11.23	420	2.78



Thomas R. Pieber et al Diabetologia 2017

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)

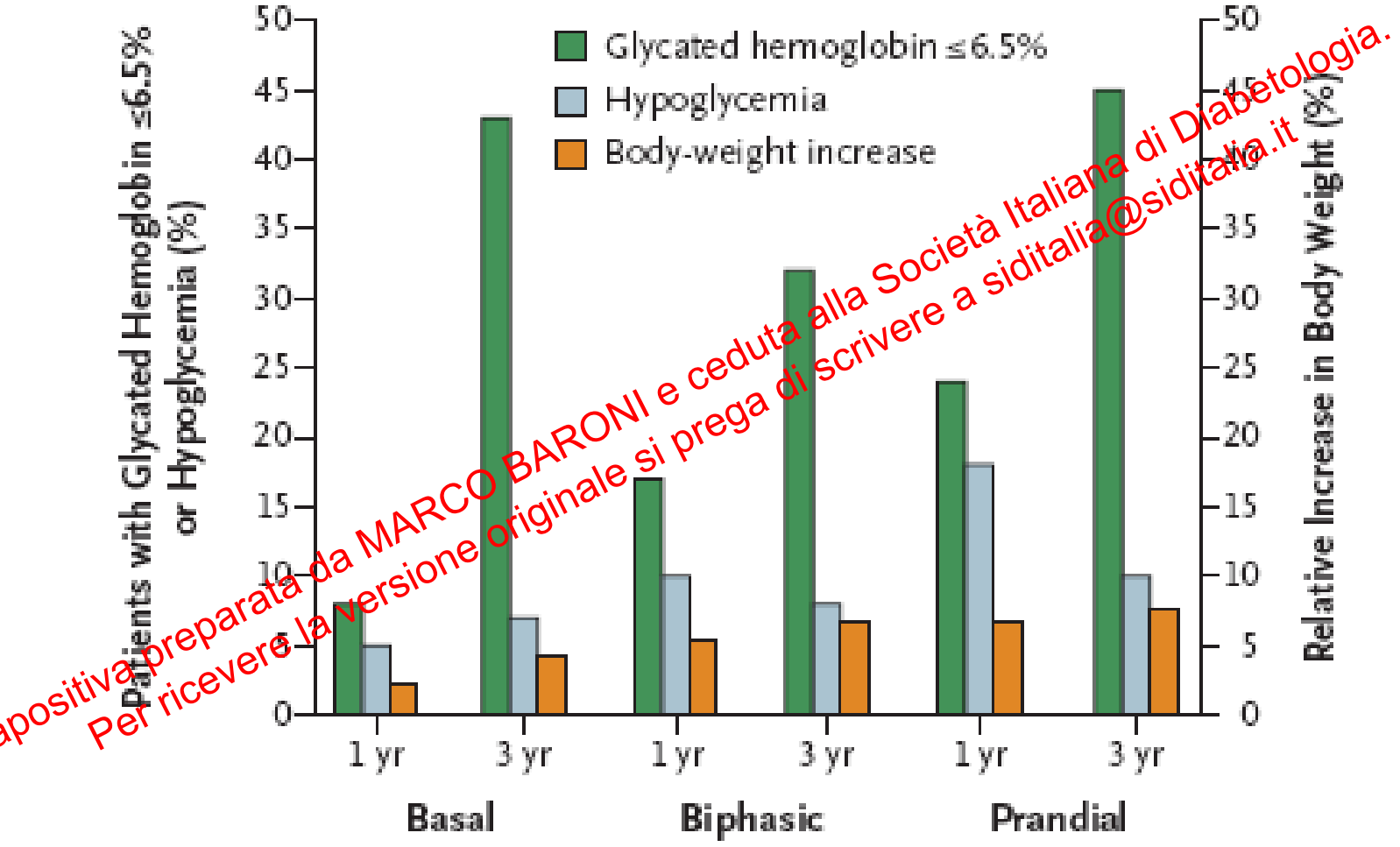
*An estimate of hypoglycaemia risk; SGLT2 inhibitors were not included in the network analysis [b]



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

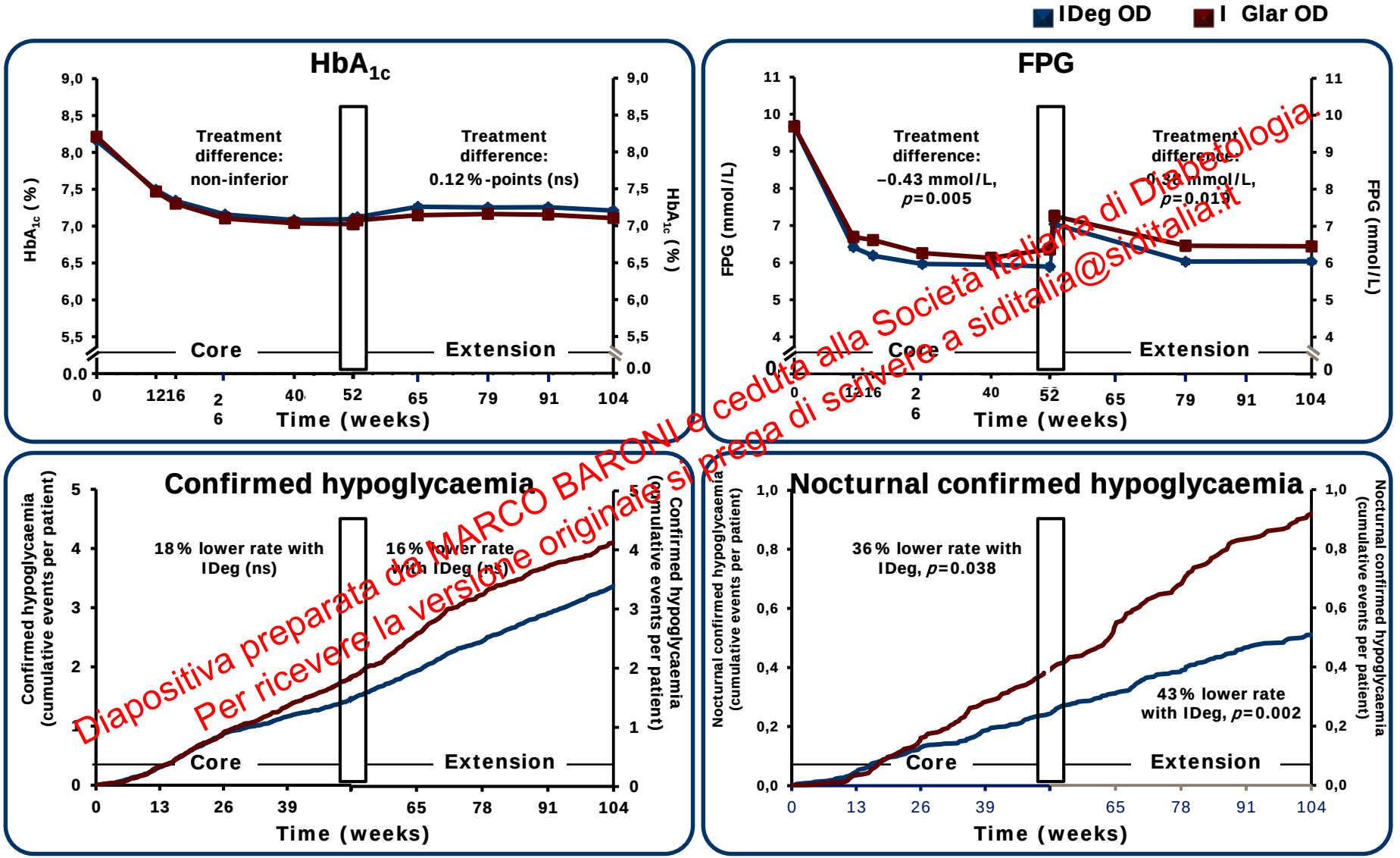
4T Study: Glycated Hemoglobin Level, Hypoglycemia, and Increase in Body Weight at 1 Year and 3 Years



	Basal		Biphasic		Prandial	
	1 yr	3 yr	1 yr	3 yr	1 yr	3 yr
Units insulin/kg body weight/day	0.49	1.03	0.53	0.78	0.61	0.94

N Engl J Med 361;18, 2009

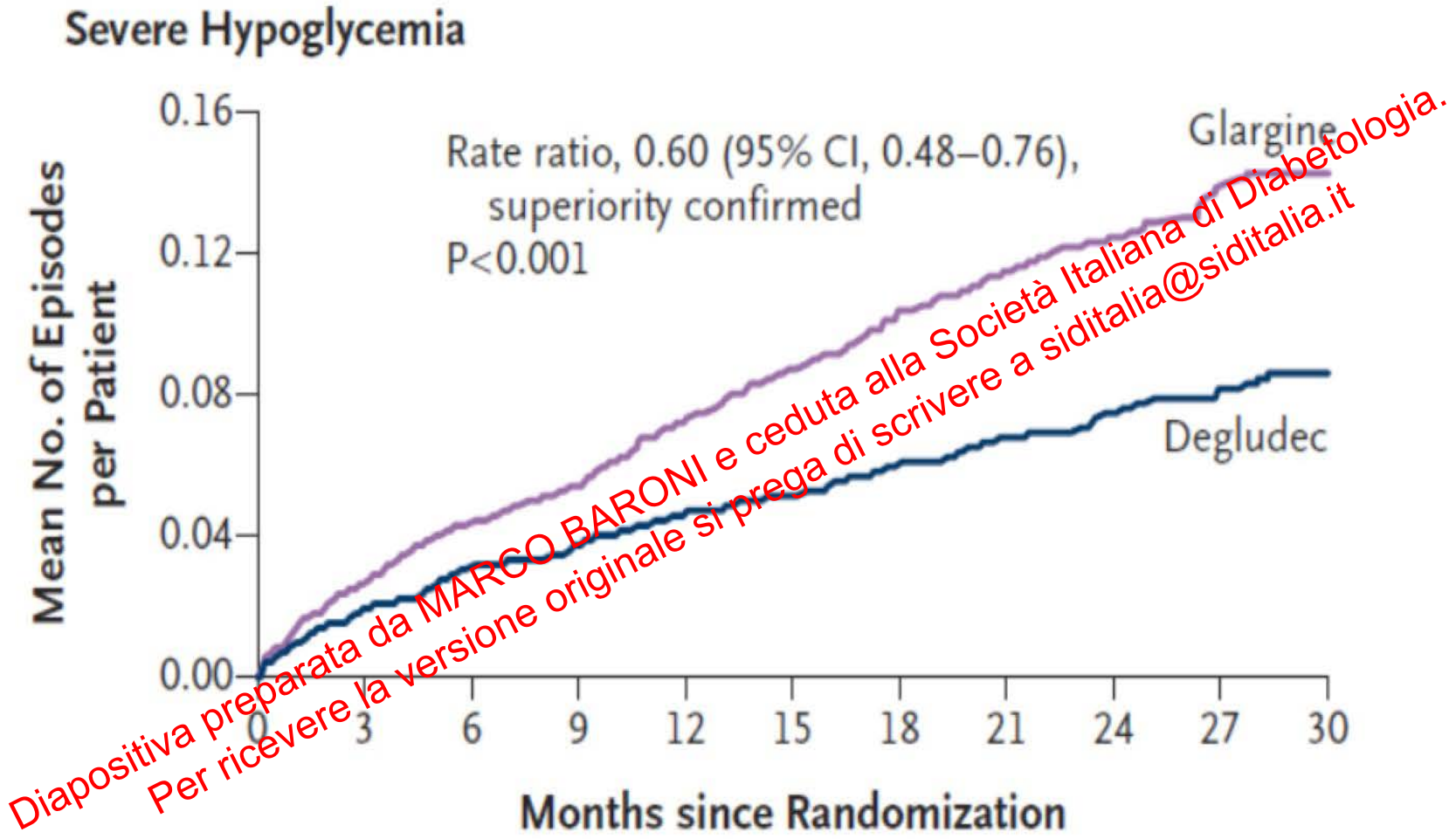
Insulin-naïve T2D: study design
BEGIN ONCE LONG – 2 years



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

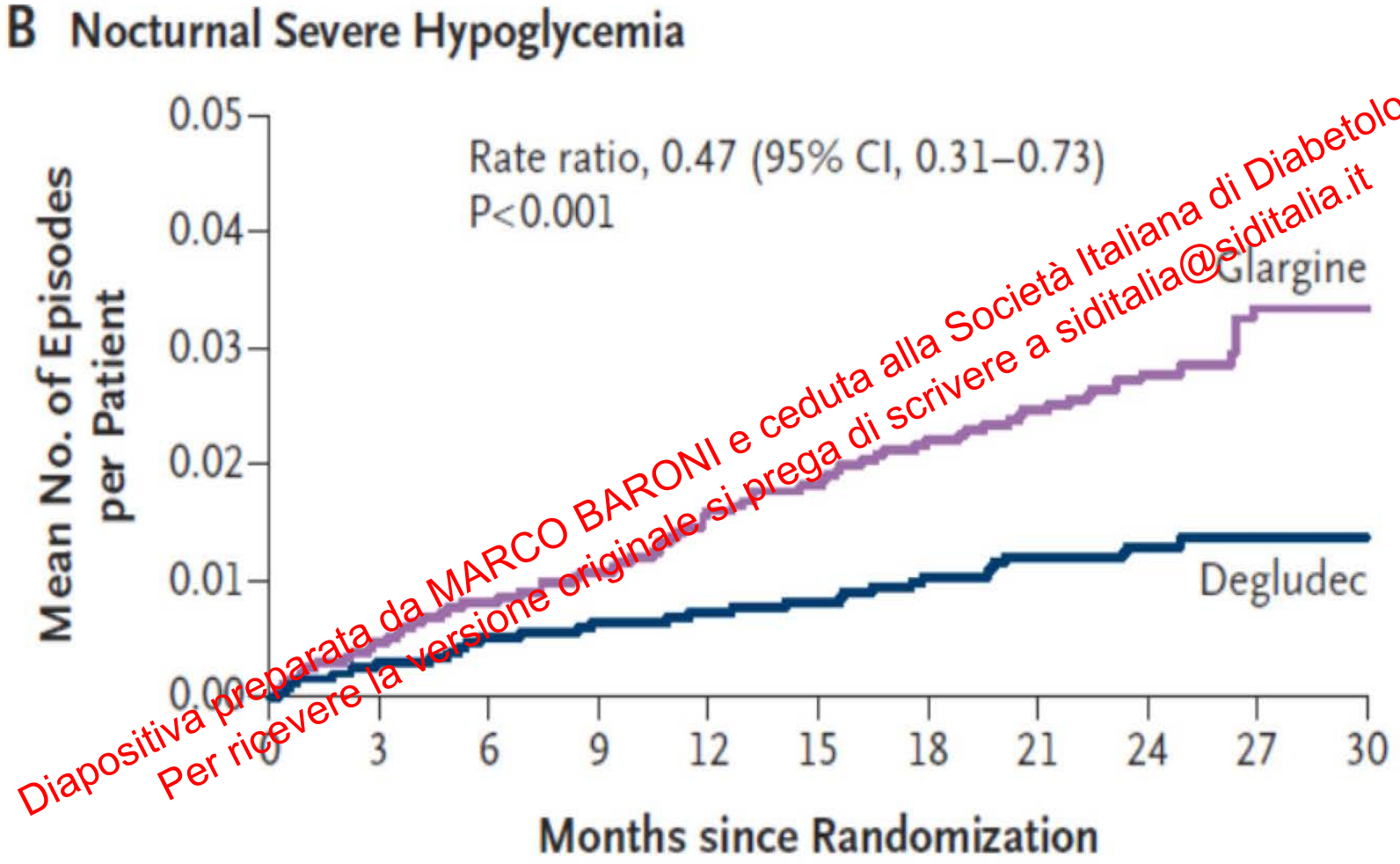
Devote Secondary Endpoints: Rates of severe hypoglycaemia



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

Devote Secondary Endpoints: Rates of nocturnal severe hypoglycaemia



Full analysis set; Nocturnal hypoglycemia: EAC-confirmed severe hypoglycemic episode with an investigator-reported onset between 00:01 and 05:59.

Mean number of nocturnal EAC-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

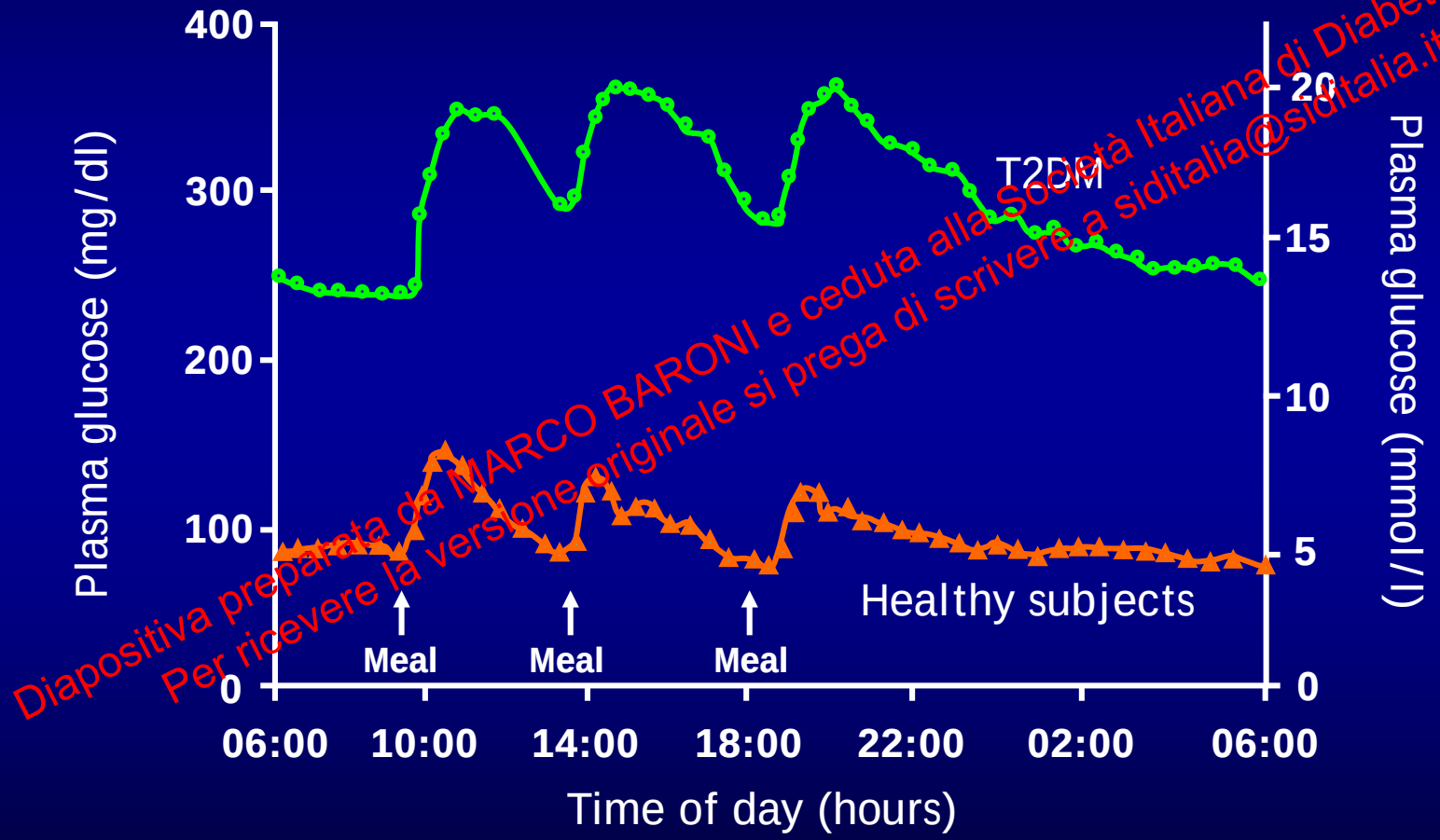
ADVANTAGES

- 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

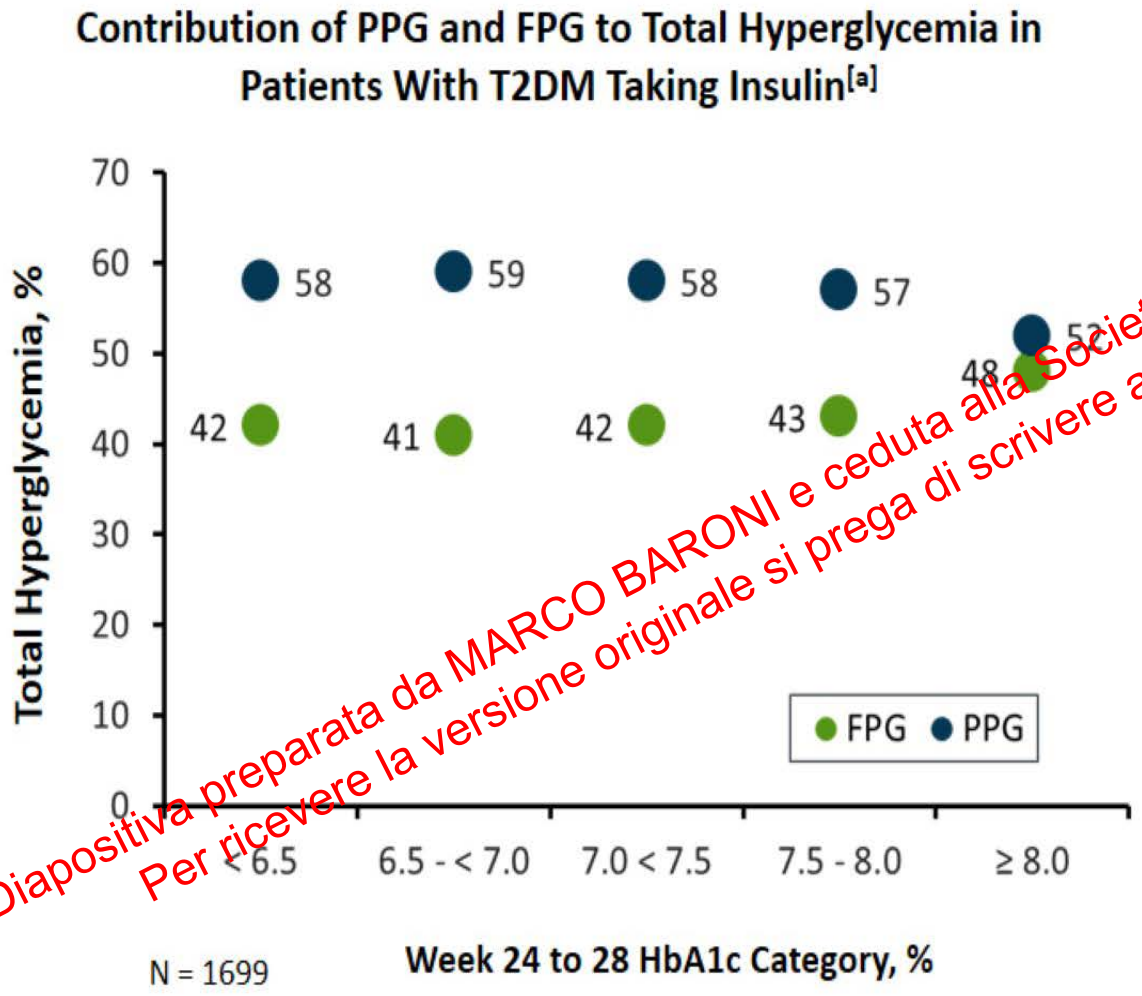
- Treatment with insulin is associated with body weight gain.
- Treatment with insulin is associated with increased risk for hypoglycemia.
- **Insulin therapy needs to control both FPG and post-prandial PG.**

24-hour plasma glucose profile in T2DM and healthy subjects



Comparison of 24-hour plasma glucose levels in healthy subjects vs patients with diabetes ($p<0.001$).
Adapted from Hirsch I et al Clin Diab 2005;23:78-86

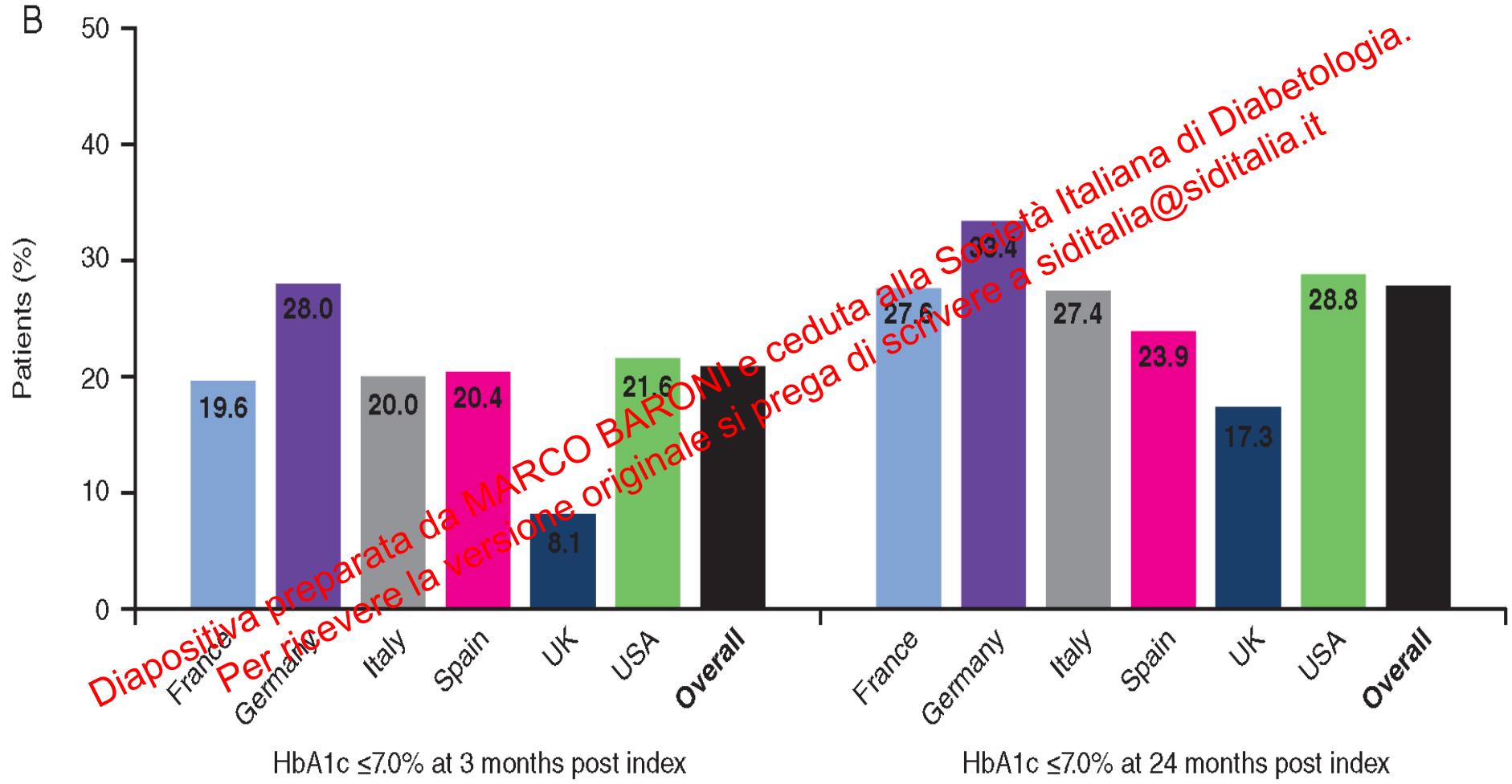
Insulin therapy needs to control both FPG and post-prandial PG



- 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.

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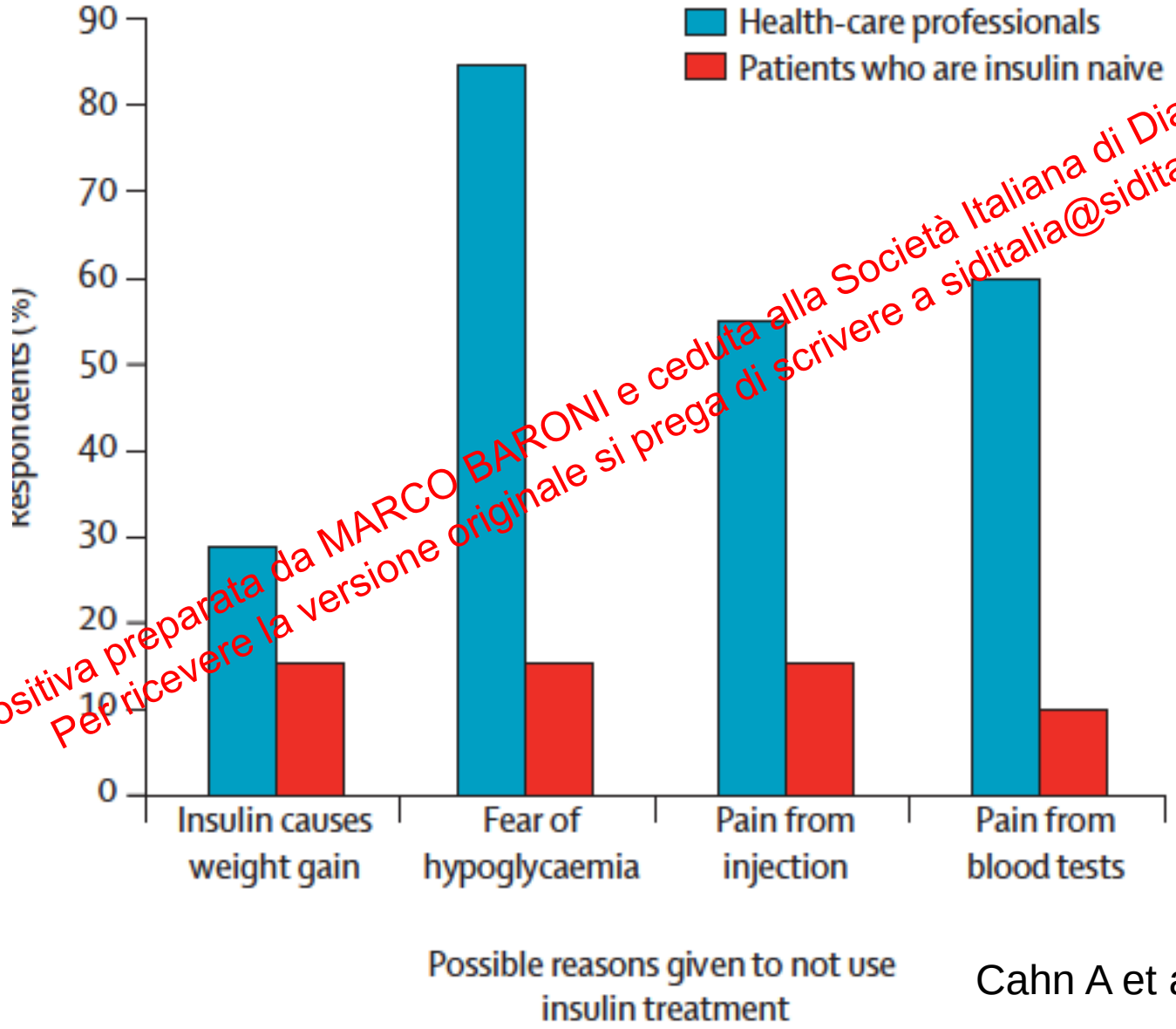
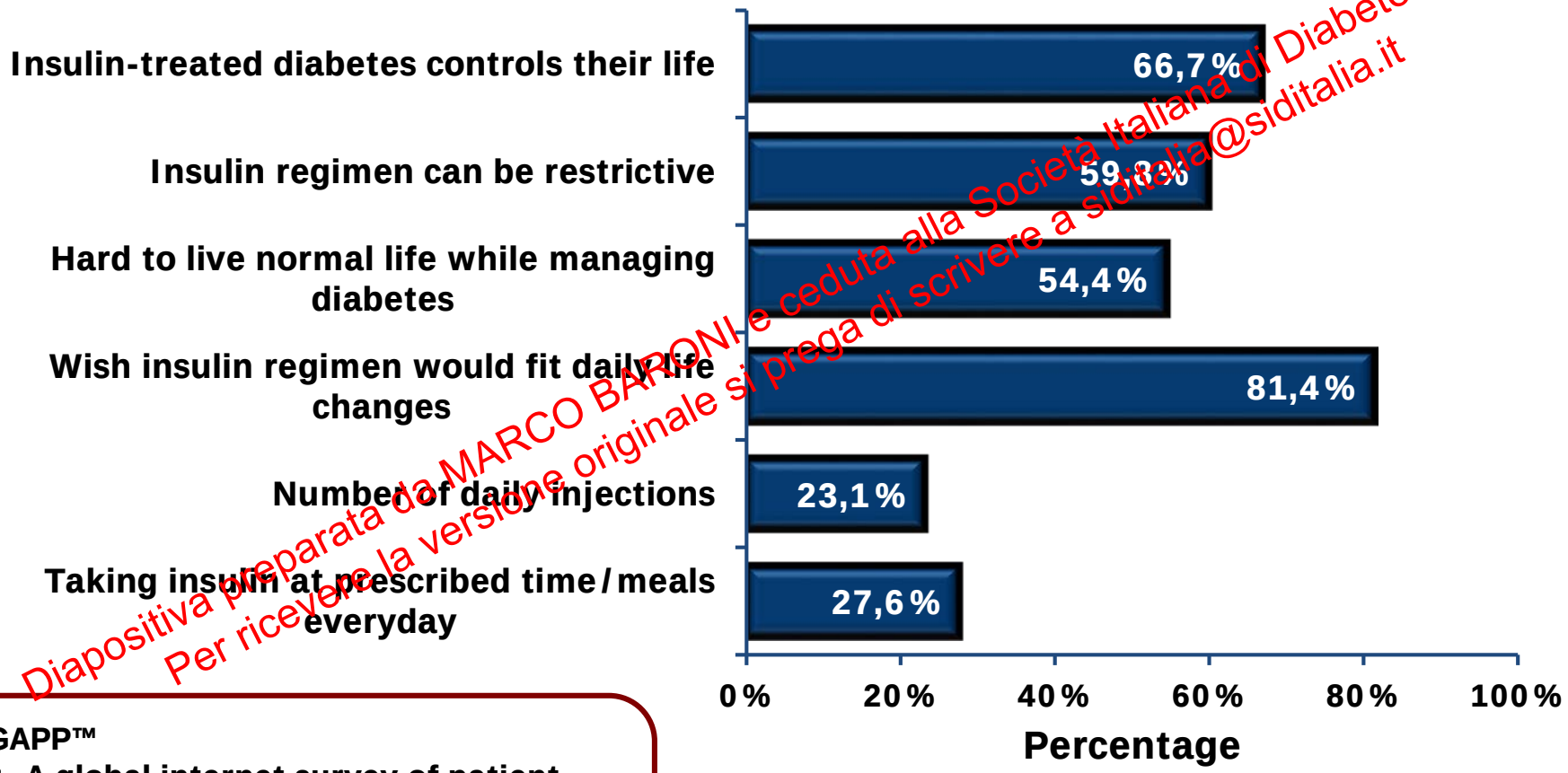
- Treatment with insulin is associated with increased risk for hypoglycemia.
- Insulin therapy needs to control both FPG and post-prandial PG.
- **Insulin treatment may be refused by the patient barriers.**

Reasons why health-care professionals and patients might refrain from starting insulin



Cahn A et al. Lancet 2015

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

Insulin therapy in T2DM

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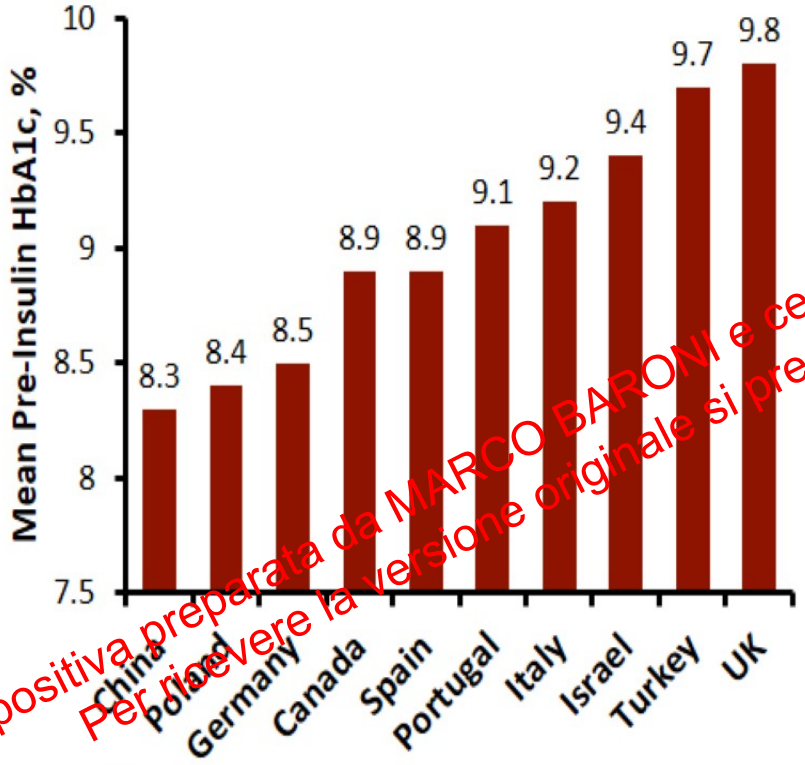
- Insulin therapy needs to control both FPG and post-prandial PG.
- Insulin treatment may be refused by the patient barriers.
- **Insulin treatment is associated with clinical inertia.**

Clinical Inertia With Insulin Therapy

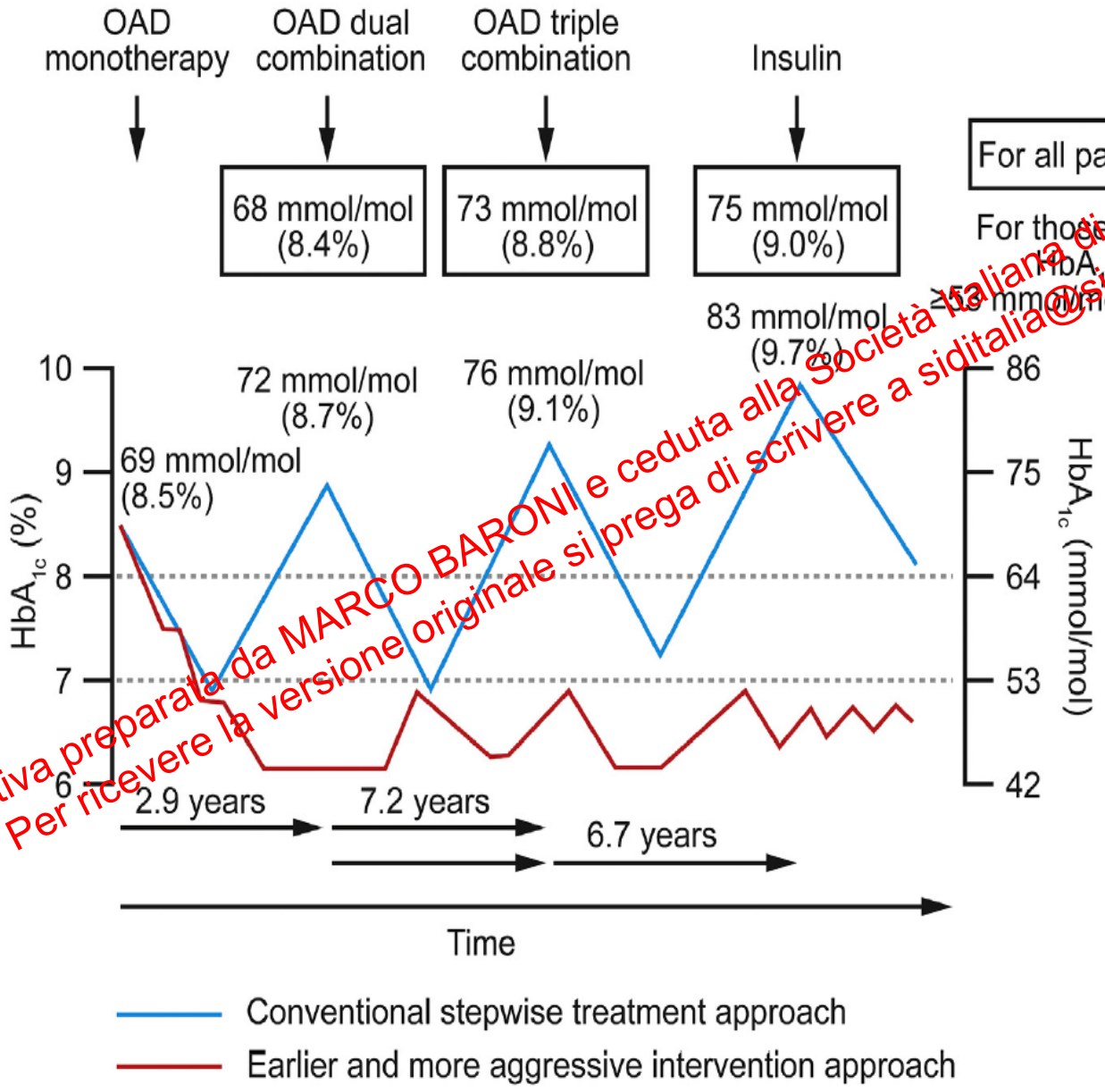


SOLVE™ Study of Patients Being Treated With 1 or More OADs Initiated on Once-Daily Levemir, (n= 17,734)

- 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]

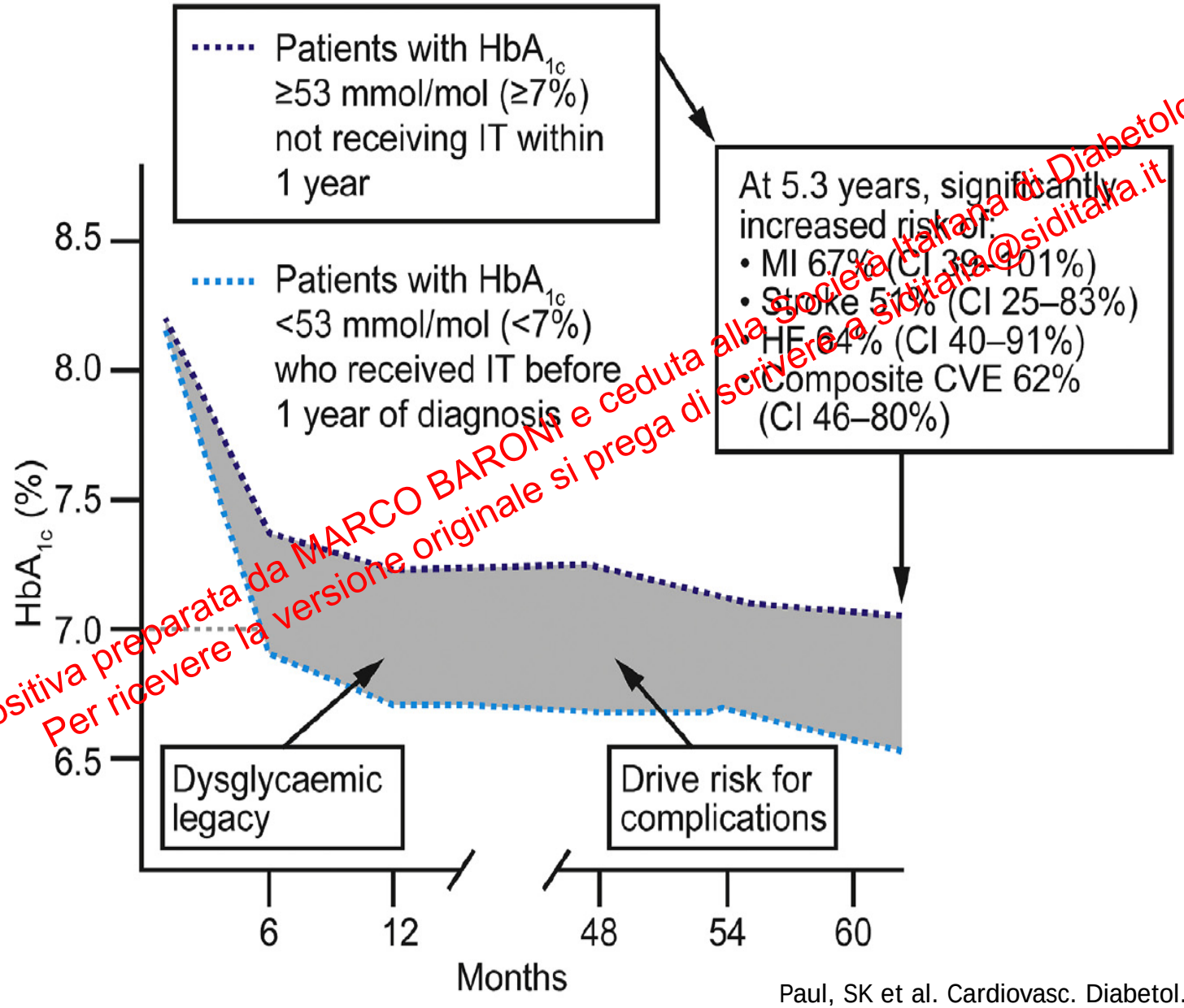
a. Khunti K, et al. *Diabetes Care.* 2013;36:3411-3417; b. Inzucchi SE, et al. *Diabetes Care.* 2015;38:140-149; c. Khunti K, et al. *Diabetes Obes Metab.* 2012;14:654-661.

Median time to intensification and mean HbA1c at intensification in patients with T2DM currently treated with 1-2 OADs with intensification to 3 OADs or insulin



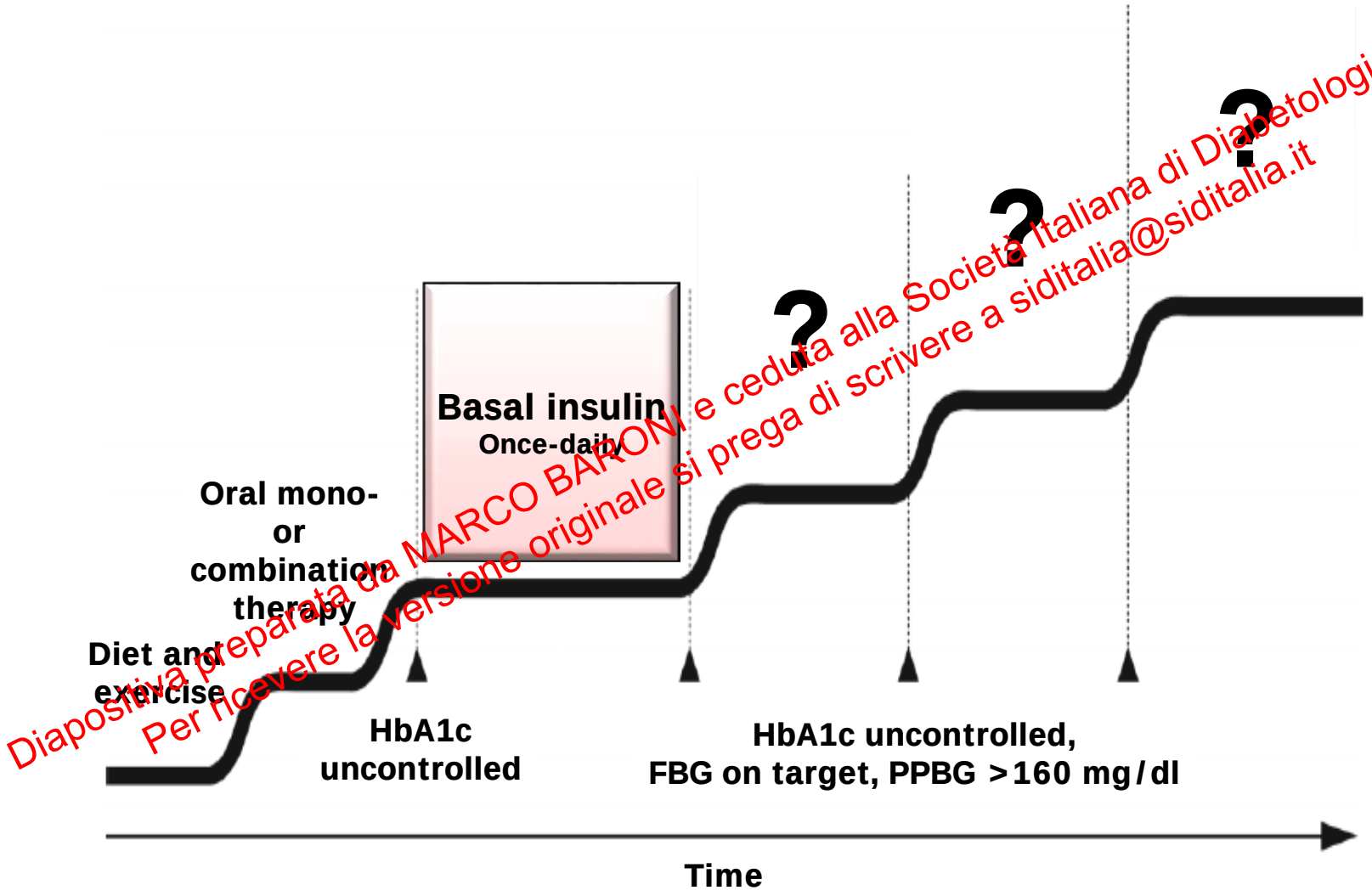
Khunti et al. Diabetes Care 36:3411-7, 2013

Consequences of delayed intervention in patients with T2DM

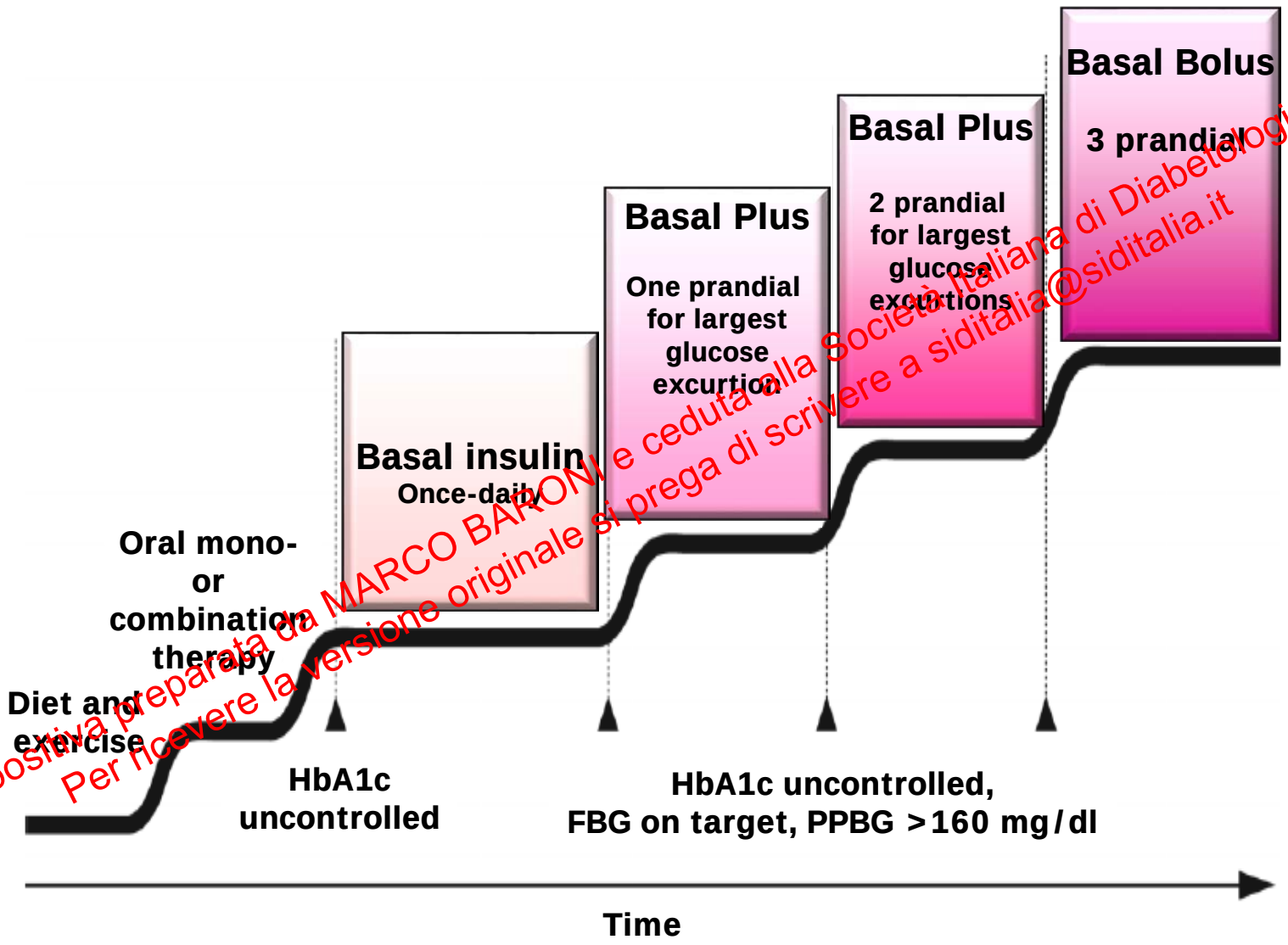


Paul, SK et al. Cardiovasc. Diabetol. 14: 100, 2015

What next?



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



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

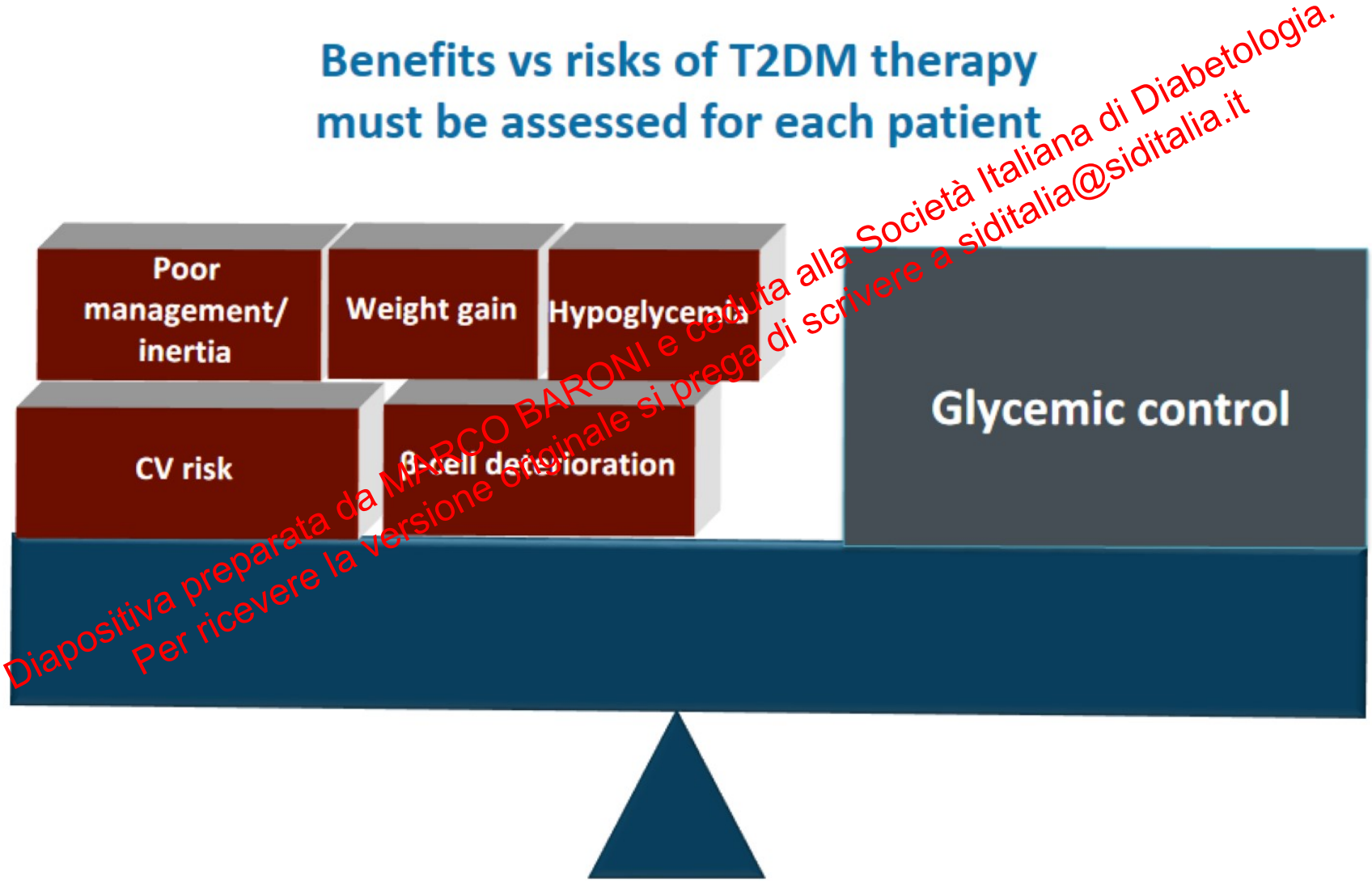
Arguments in favor of timely insulin use in T2DM

- The defect in insulin secretion is a primary one.
- Insulin treatment reverted defects in insulin secretion and hepatic glucose production.
- Early insulin initiation is associated with reduced CVD risk
- 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.

What are the real unmet needs in insulin therapy

- Early recognition of failure of oral therapy
- Strong positive recommendation of benefits of insulin treatment to patients
- Reassurance concerning potential negative consequences in therapy
- Intense support to optimise insulin dosage
- Regular expert clinic review to identify problems with insulin therapy

Need for personalized care



Grazie