SID Società Italiana di Diabetologia

BOLOGNA | 27 GIUGNO 2019

Terapia con analoghi del GLP-1: quando e perché

Analoghi del GLP-1 dopo la metformina

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TOR VERGATA
UNIVERSITÀ DEGLI STUDI DI ROMA

La dr./sa Simona Frontoni dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Novo-Nordisk
- Astrazeneca
- Takeda

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.).

Intensificazione trattamento

A quali valori di glicata si intensifica la terapia per il diabete?

a) ≥8.0%

b) ≥9.0%

c) ≥7.0%

d) ≥10.0%

The DISCOVER study

More Than a Half of Patients with T2DM Worldwide Undergo Treatment Intensification at HbA_{1c}≥8.0%

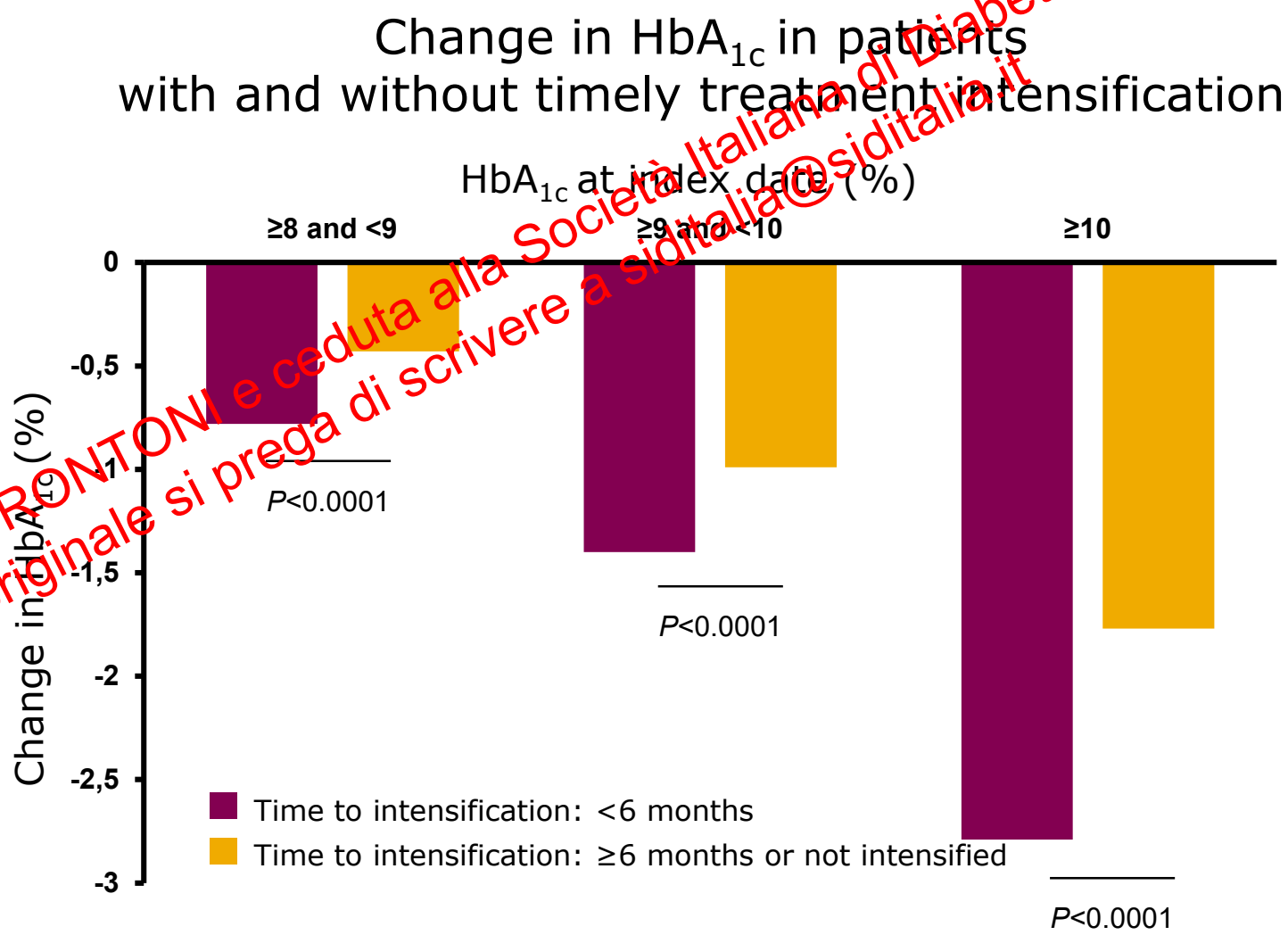
HbA_{1c} at the time of treatment intensification with a second-line agent in real-world clinical practice (N=15,992)

	Total (N = 15,992)	Africa (n = 812)	Americas (n = 2002)	South-East Asia (n = 3360)	Europe (n = 3279)	Eastern Mediterranean (n = 2182)	Western Pacific (n = 4157)
Time from diagnosis to initiation of second-line therapy, years							
Mean (SD)	5.6 (5.3)	6.9 (5.7)	6.2 (6.3)	4.6 (4.1)	6.6 (5.4)	5.8 (5.3)	5.1 (5.4)
Median (IQR)	4.1 (1.9–7.9)	5.7 (2.9–9.3)	4.4 (1.9–8.7)	3.4 (2.0–6.1)	5.4 (2.7–9.1)	4.2 (2.1–8.0)	3.4 (1.0–7.6)
Missing	397	0	62	1	154	2	176
HbA_{1c}, mmol/mol							
Mean (SD)	67.7 (18.6)	70.3 (20.2)	69.3 (20.6)	70.8 (18.5)	65.4 (17.1)	71.1 (17.2)	64.9 (18.6)
Median (IQR)	63.9 (55.2–76.0)	63.9 (51.2–79.2)	63.9 (55.2–79.2)	67.2 (58.5–81.4)	62.0 (55.0–72.0)	67.2 (59.6–79.2)	59.6 (53.0–71.6)
Missing	3208	345	471	1309	476	137	470
HbA_{1c}, %							
Mean (SD)	8.3 (1.7)	8.6 (1.9)	8.5 (1.9)	8.6 (1.7)	8.1 (1.6)	8.7 (1.6)	8.1 (1.7)
Median (IQR)	8.0 (7.0–9.4)	8.0 (7.4–9.4)	8.0 (7.2–9.4)	8.3 (7.5–9.6)	7.8 (7.2–8.7)	8.3 (7.6–9.4)	7.6 (7.0–8.7)
<7.0	2249 (17.6)	57 (12.2)	262 (17.1)	274 (13.4)	561 (18.7)	196 (9.6)	899 (24.4)
7.0 to <8.0	4039 (31.6)	162 (34.7)	460 (30.0)	530 (25.8)	1056 (35.2)	507 (24.8)	1324 (35.9)
8.0 to <9.0	2978 (23.3)	94 (20.1)	336 (21.9)	515 (25.1)	732 (24.4)	648 (31.7)	658 (17.8)
≥9.0	3513 (27.5)	154 (33.0)	473 (30.9)	732 (35.7)	654 (21.8)	694 (33.9)	806 (21.9)
Missing	3208	345	471	1309	476	137	470

Gomes MB, Diab Res Clin Pract 2019

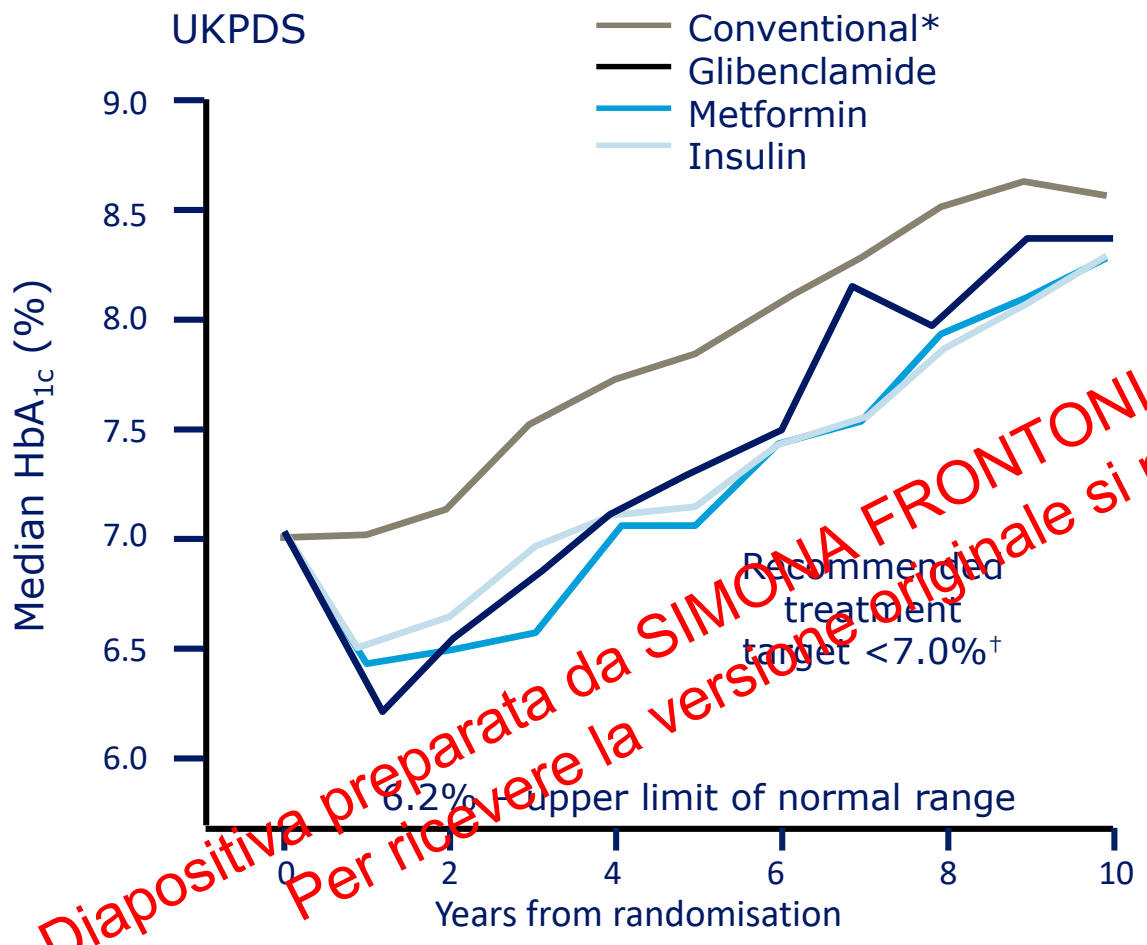
Early Treatment Intensification Was Associated with a Larger Reduction in HbA_{1c} Values Across All Baseline HbA_{1c} Categories
RWE data

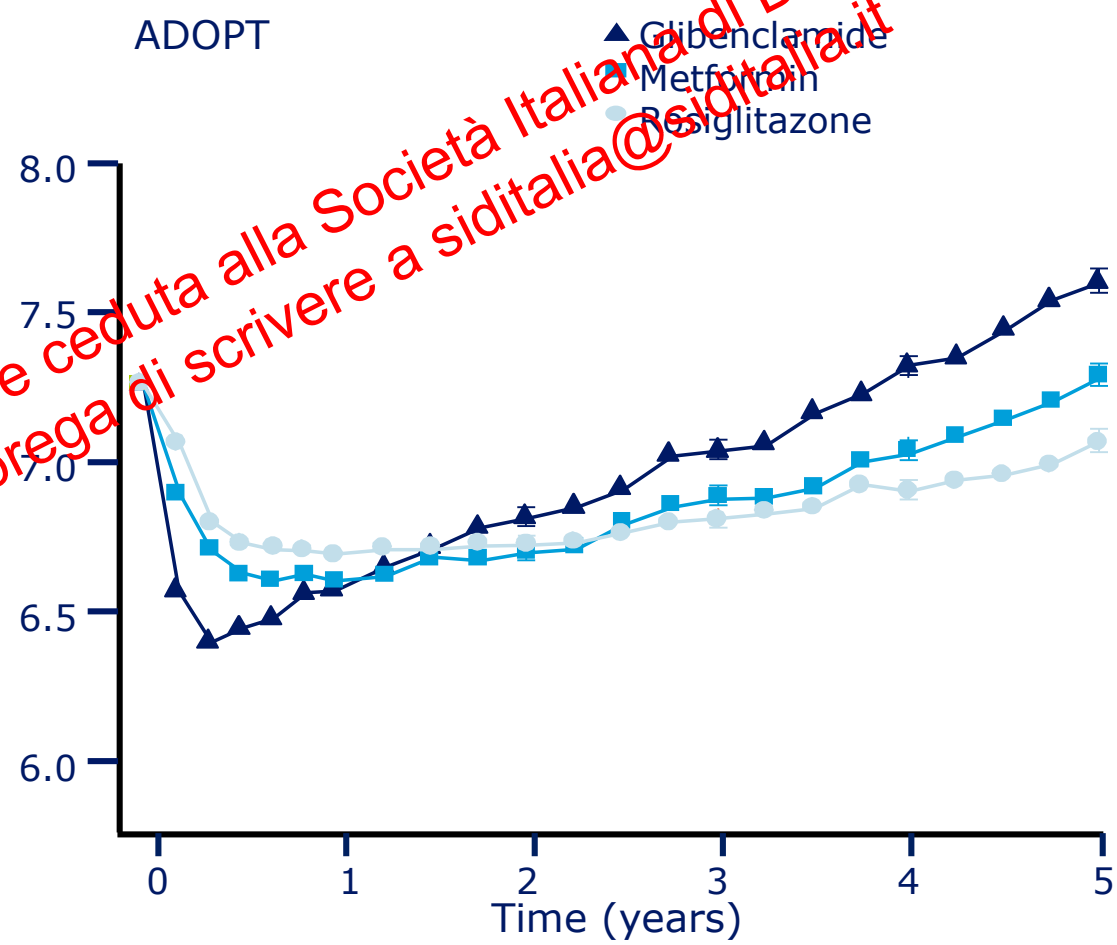
- Data from patients with T2DM in a large US insurance claims database (N=11,525) who have been using metformin with or without other oral antidiabetes drugs ≥3 months (index date)
- Patients with a shorter time to treatment intensification had larger reductions in HbA_{1c} between index date and 1 year of follow-up



Fu AZ, Sheehan JJ. Curr Med Res Opin 2017;33:853–858

Over time, glycaemic control deteriorates

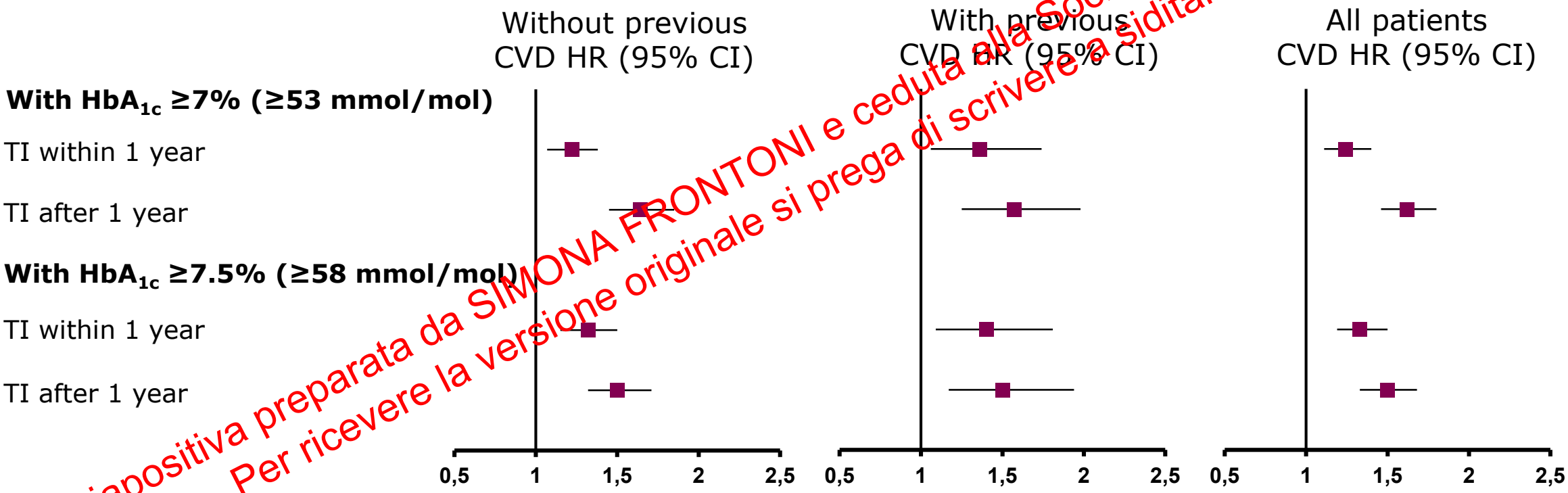




**Diet initially then sulphonylureas, insulin and/or metformin if FPG>15 mmol/L*
†ADA clinical practice recommendations. UKPDS 34, n=1704
UKPDS 34. Lancet 1998:352:854–865; Kahn et al. (ADOPT). N Engl J Med 2006;355:2427–2443

Treatment Intensification (TI) May Decrease the Risks of CV Events in Patients with T2DM

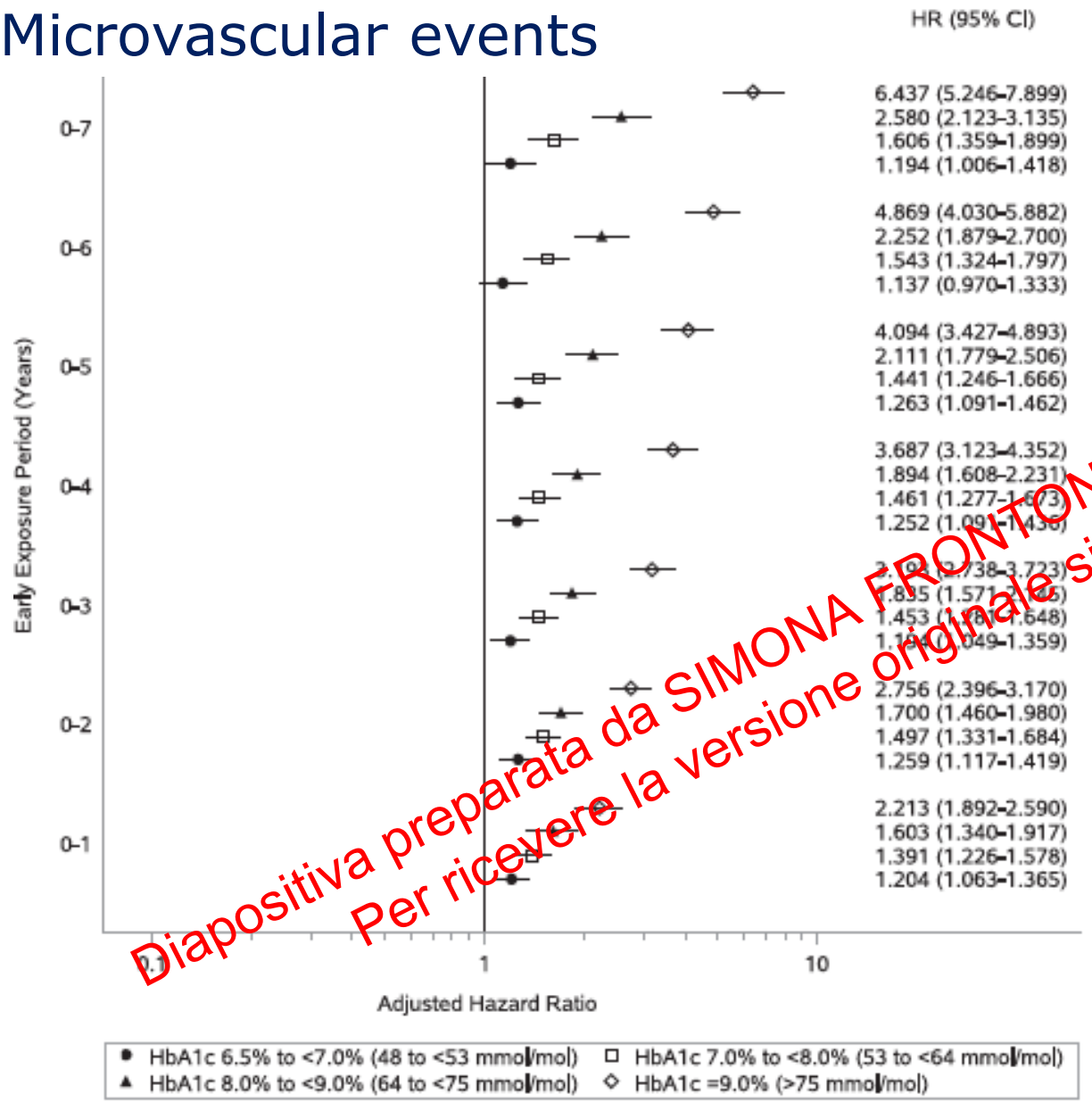
Risks of any CV event associated with delays in treatment intensification in interaction with poor glycaemic control during 1 year post-diagnosis



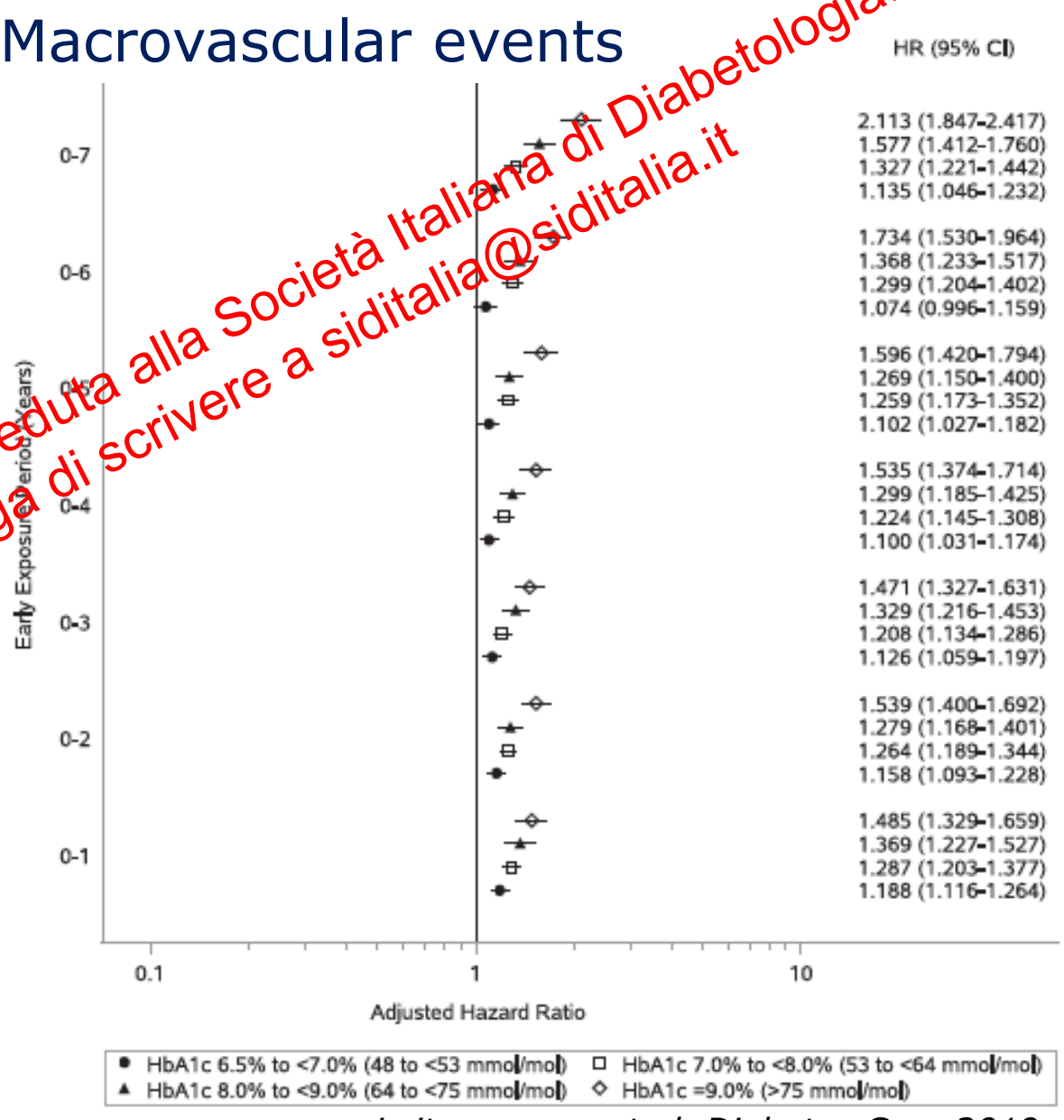
Paul SK, et al. Cardiovasc Diabetol 2015;14:100

The Legacy Effect in Type 2 Diabetes
Impact of Early Glycemic Control on Future Complications

Microvascular events



Macrovascular events

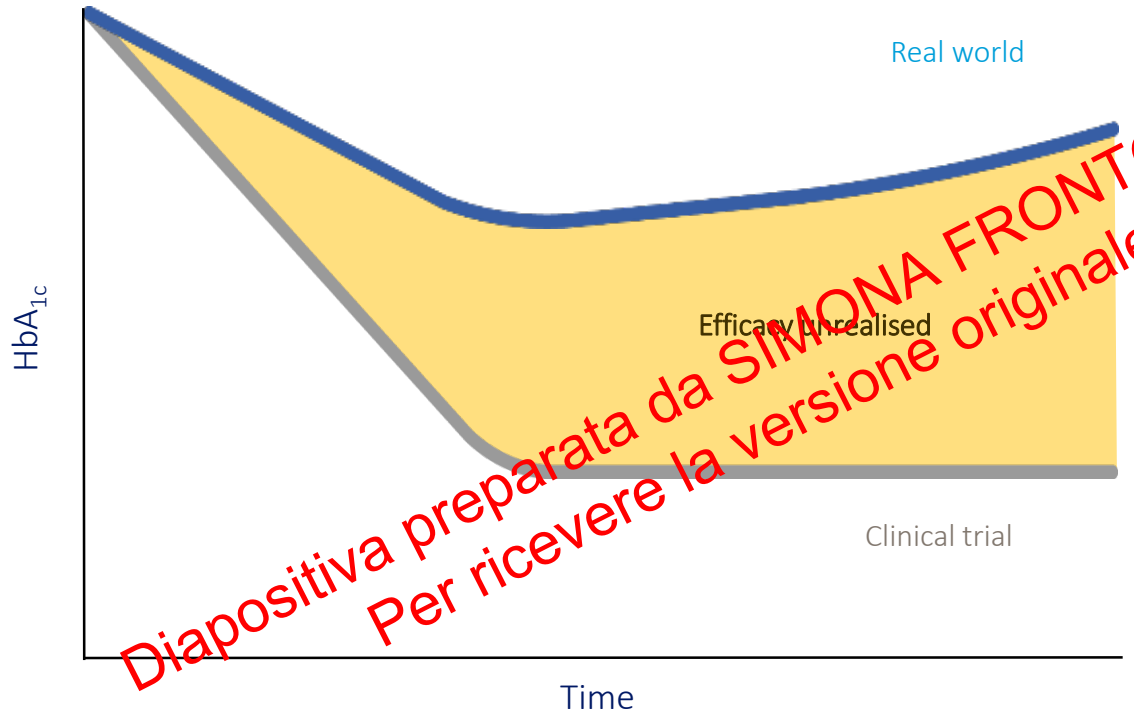


Laiteerapong et al. Diabetes Care 2019

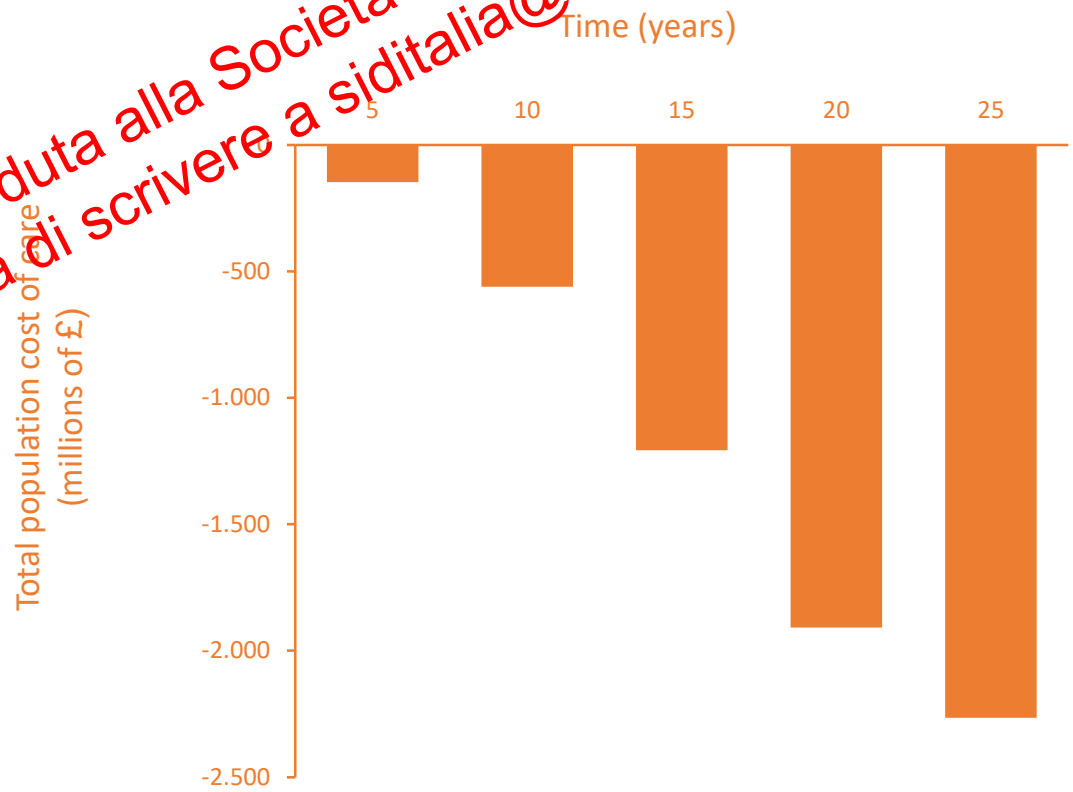
Avoiding complications reduces cost over time

There may be an efficacy gap between clinical trial results and real-world outcomes in T2D management

Conceptual schematic

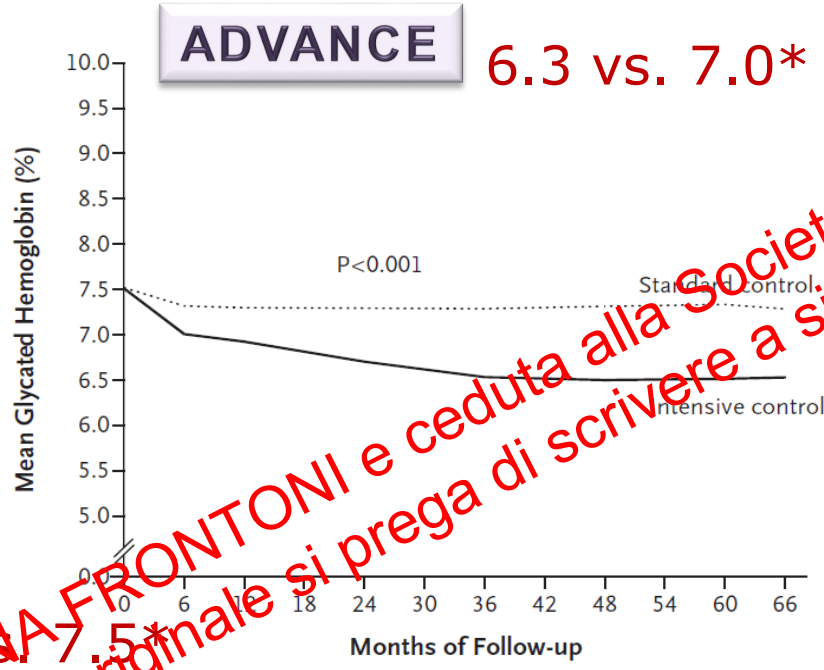


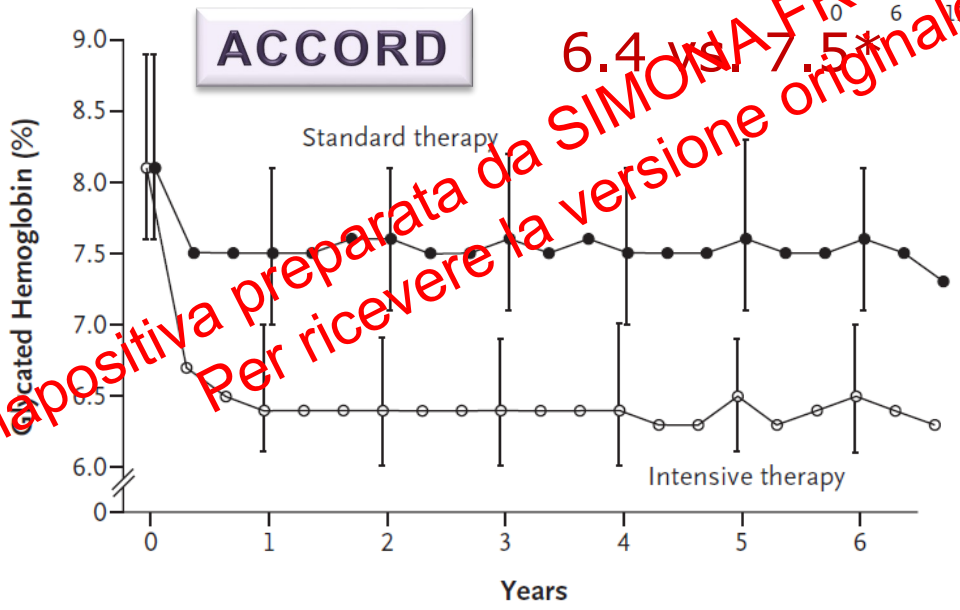
Estimated cost reductions over time for the total UK adult population with T2D from **avoided complications** for management of HbA_{1c} at <7.5%

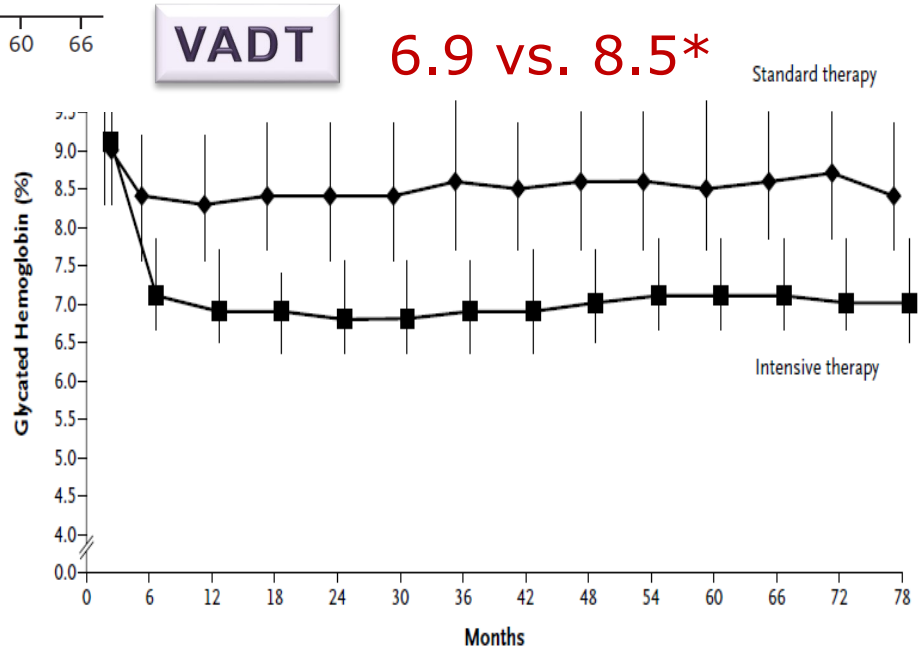


Baxter M, et al. Diabet Med. 2016;33:1575-1581. Edelman SV, Polonsky WH. Diabetes Care. 2017;40:1425-1432.

Treatment Intensification Trials





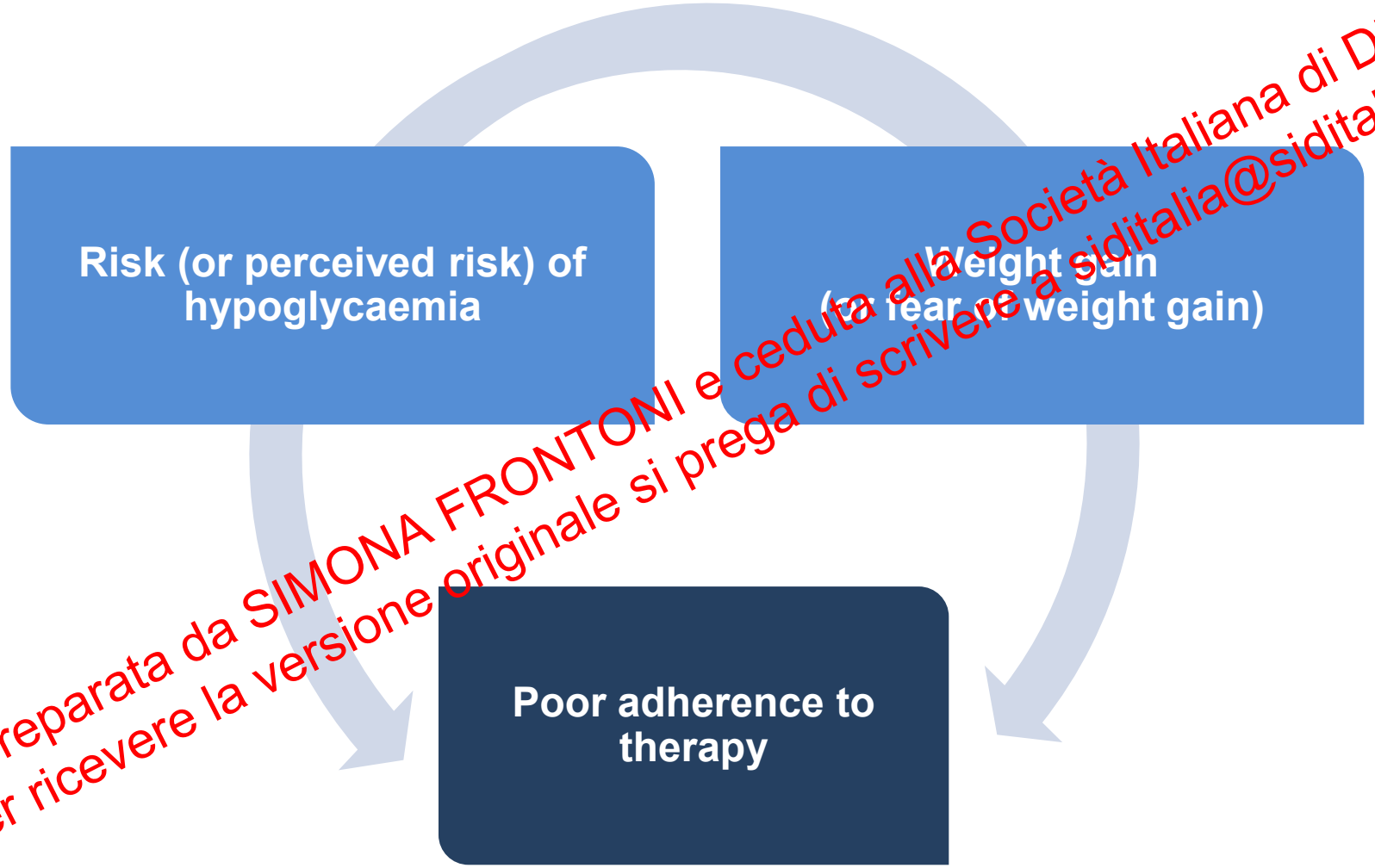


CV Outcome Studies with Intensive Glucose Lowering

Study	N	Follow-up (yr)	HbA_{1c} (%) difference between arms	Primary endpoint	Primary endpoint HR (95% CI)	All-cause mortality HR (95% CI)	Weight gain (kg)	Major hypoglycemia (%)
ACCORD	10,251	3.5	1.1	MACE	0.90 (0.78-1.04)	1.22 (1.01-1.46)	3.5 vs. 0.4	16.2 vs. 5.1
ADVANCE	11,140	5.0	0.8	MACE	0.94 (0.84-1.06)	0.93 (0.83-1.06)	0.0 vs. -1.0	2.7 vs. 1.5
VADT	1,791	5.6	1.5	MACE + HF, vascular surgery, new, ischemic amputation	0.88 (0.74-1.05)	1.07 (0.81-1.42)	7.8 vs. 3.4	21.2 vs. 9.9

Adapted from Giorgino F et al., Diabetes Care 39 Suppl 2:S187-95, 2016

Weight gain and hypoglycaemia influence patient adherence



Khunti K, et al. Diabetes Obes Metab 2010;12:474-484.

Intensificazione trattamento

Quali tra i seguenti fattori influenza gli effetti di un trattamento intensivo del diabete?

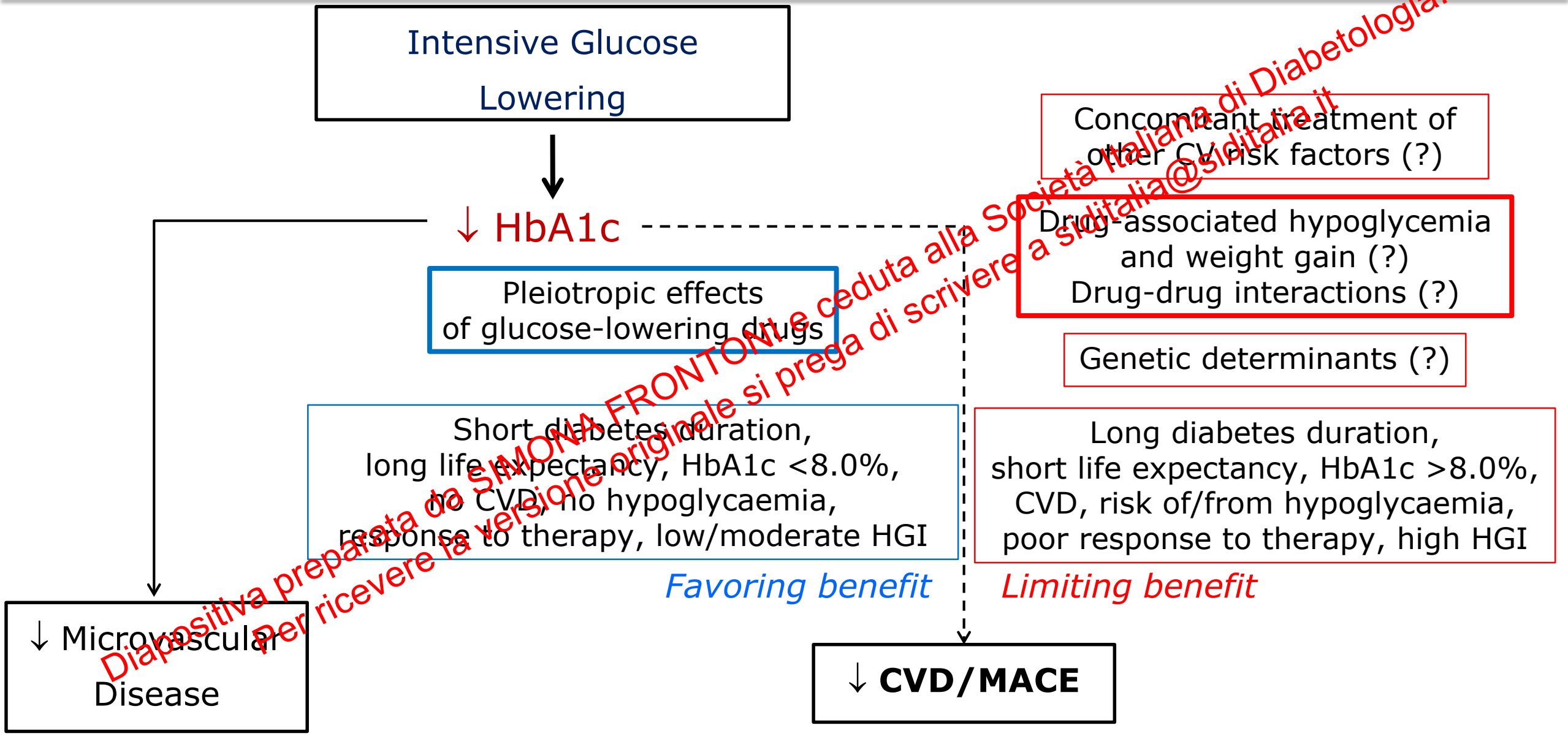
a) durata malattia

b) aspettativa di vita

c) CVD

d) tutte le precedenti

A new concept of intensification



Adapted from Giorgino F, Home PD, and Tuomilehto J, Diabetes Care 2016

Various Parameters Impact T2D Pathophysiology

THE OMINOUS OCTET

Adapted from DeFronzo RA. Diabetes 2009;58:773–95 and DeFronzo RA et al. Nat Rev Dis Primers 2015;1:15019.

GLP-1RAs Have Multifactorial Effects

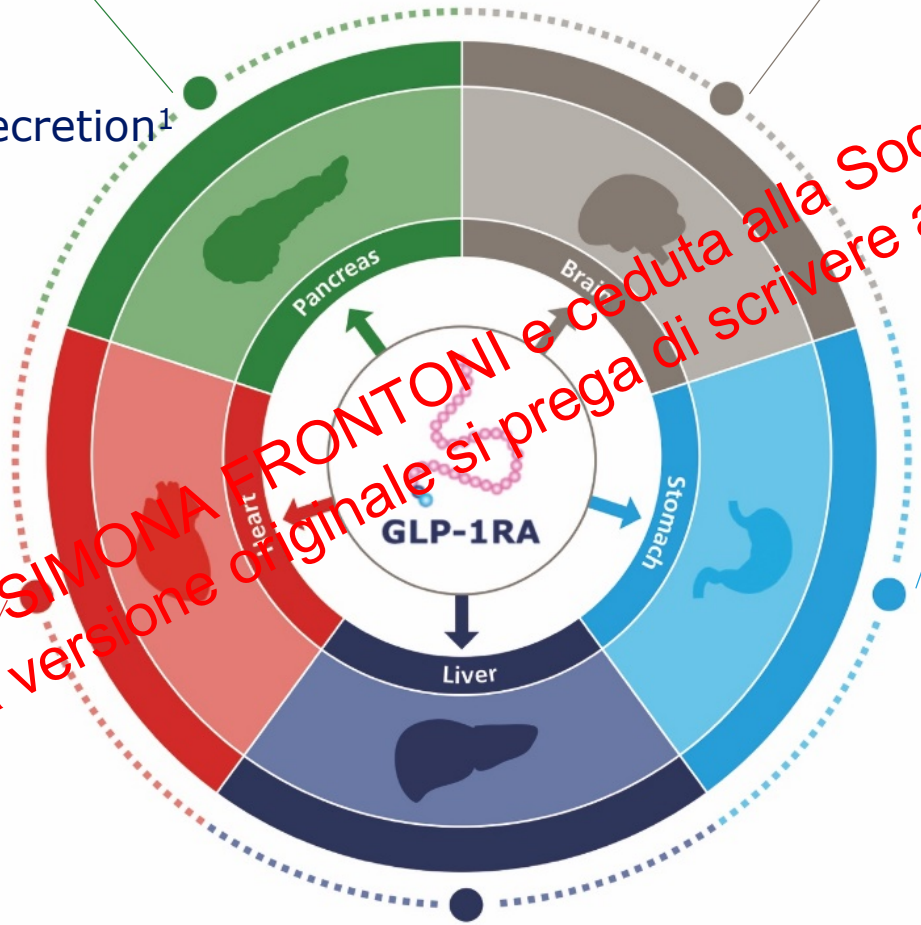
PHARMACOLOGICAL EFFECTS OF GLP-1RAs

Pancreas

- ↑ Beta-cell function[1]
- ↑ Insulin biosynthesis[1]
- ↑ Glucose-dependent insulin secretion[1]
- ↓ Glucose-dependent glucagon secretion[1]

Brain

- ↓ Body weight[5]
- ↓ Food intake[6]
- ↑ Satiety[7,8]



Stomach

- ↓ Gastric emptying[9]

Heart

- ↓ Cardiovascular risk[2]
- ↓ Fatty acid metabolism[3]
- ↑ Cardiac function[3]
- ↓ Systolic blood pressure[3]
- ↓ Inflammation[4]

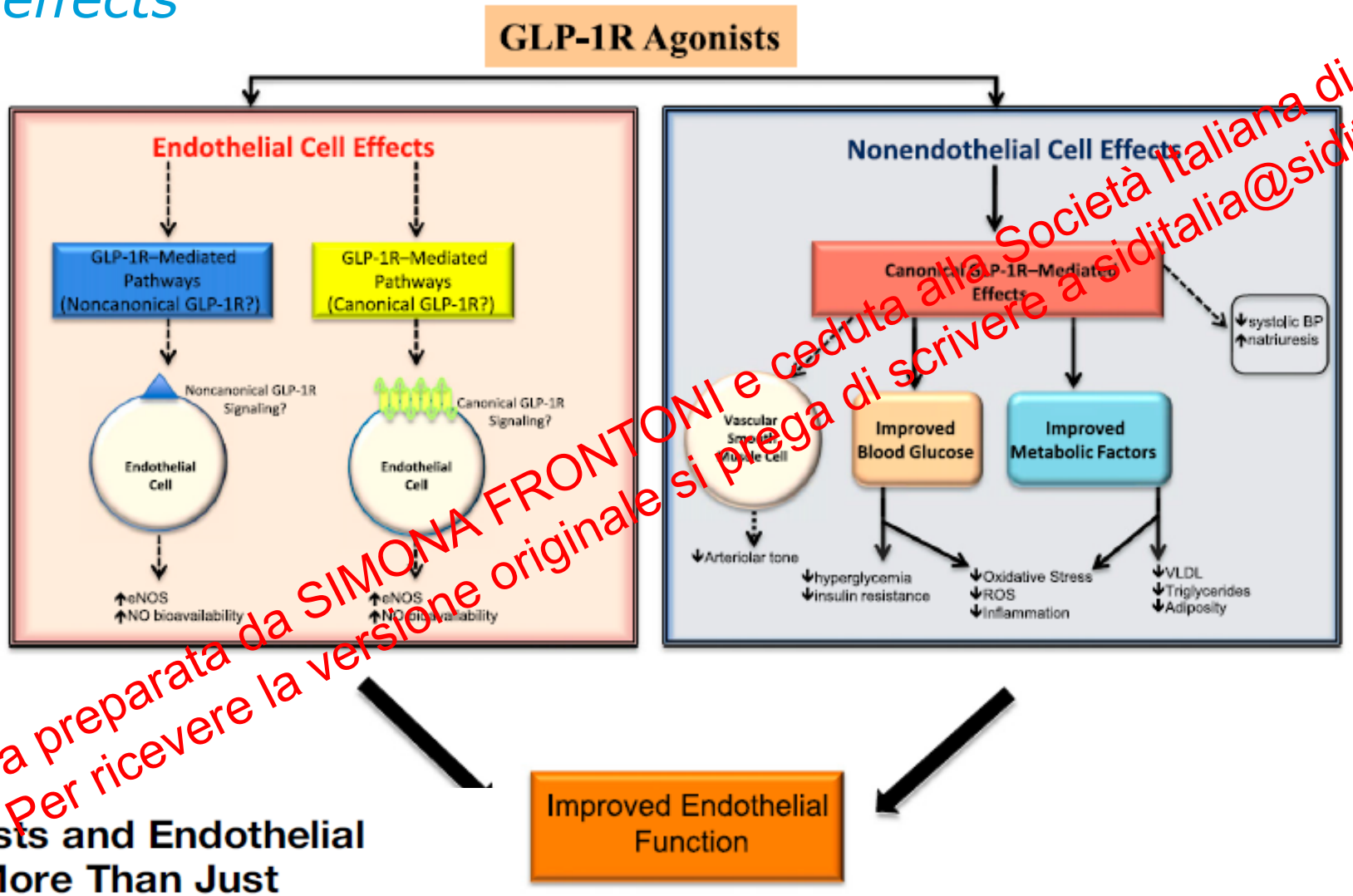
Liver

- ↓ Endogenous glucose production[10]
- ↑ Hepatic insulin sensitivity[10]
- ↓ *De novo* lipogenesis[10]
- ↓ Lipotoxicity[10]
- ↓ Steatosis[11]

Adapted from Campbell JE, Drucker DJ. Cell Metab 2013;17:819–37 and Pratley RE, Gilbert M. Rev Diabet Stud 2008;5:73–94.

GLP-1RAs Have Multifactorial Effects

Endothelial effects



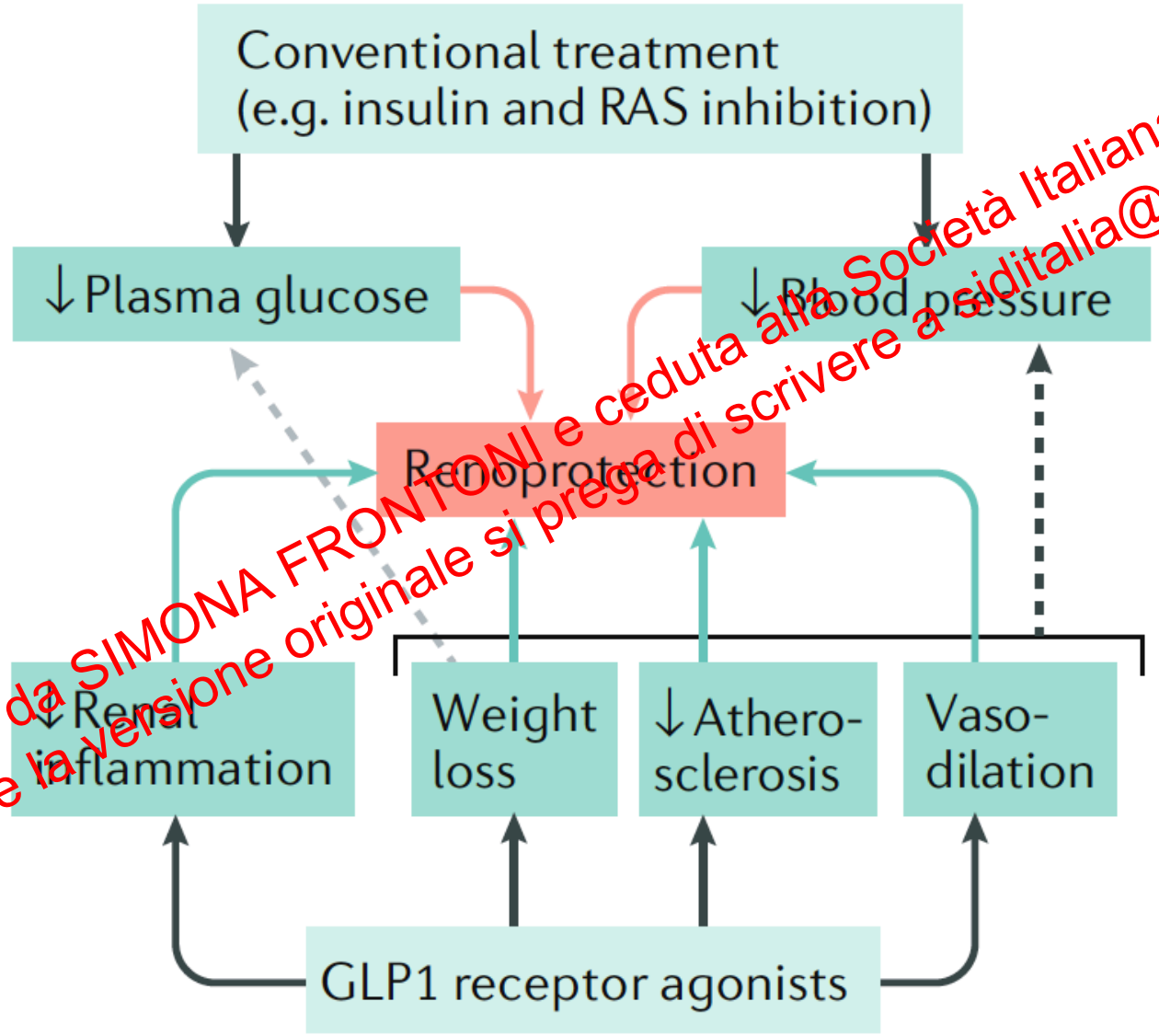
GLP-1R Agonists and Endothelial Dysfunction: More Than Just Glucose Lowering?

Diabetes 2015;64:2319–2321 | DOI: 10.2337/db15-0366

ion. Potential signaling pathways in endothelial and nonendothelial cells and tissues improving endothelial function are shown. Hashed lines represent potential pathways; ve oxygen species.

GLP-1RAs Have Multifactorial Effects

Renal effects

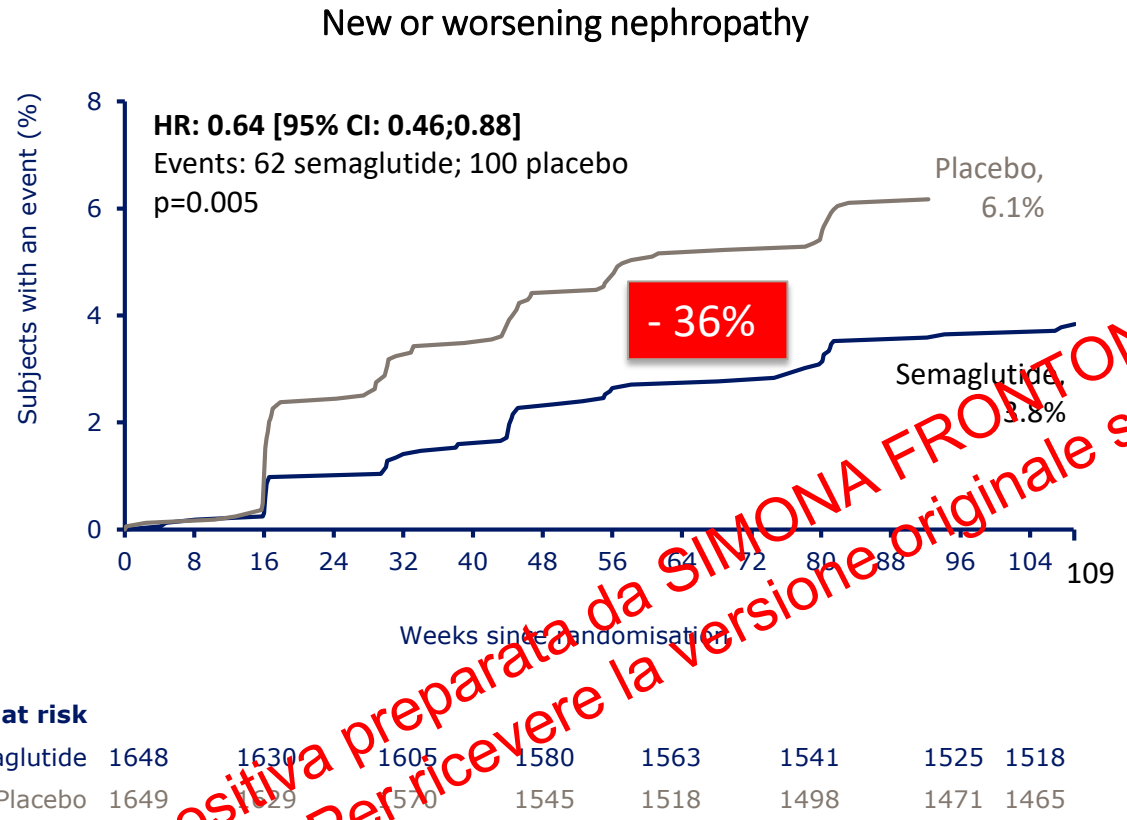


nature Reviews | NePhroLoGy, Nov 2018

GLP-1RAs Have Multifactorial Effects

SUSTAIN 6

Nephropathy outcomes



Nephropathy outcomes	Semaglutide N (%)	Semaglutide Incidence rate per 100 PYR	Placebo N (%)	Placebo Incidence rate per 100 PYR	HR (95% CI)	P value
New or worsening nephropathy	62 (3.8)	1.86	100 (6.1)	3.06	0.64 (0.46; 0.88)	0.005
Persistent macroalbuminuria	44 (2.7)	1.31	81 (4.9)	2.47	0.54 (0.37; 0.77)	0.001
Persistent doubling of serum Cr level and CrCl per MDRD <45 ml/min/1.73 m^2	18 (1.1)	0.53	14 (0.8)	0.41	1.28 (0.64; 2.58)	0.48
Need for continuous renal-replacement therapy	11 (0.7)	0.32	12 (0.7)	0.35	0.91 (0.40; 2.07)	0.83

Kaplan–Meier plot for time from randomisation to first EAC-confirmed new or worsening nephropathy (A) or EAC-confirmed diabetic retinopathy complication (B) using 'in-trial' data from subjects in the full analysis set. HR is from a proportional hazard model. CI, confidence interval; Cr, creatinine; CrCl, creatinine clearance; EAC, (external) event adjudication committee; HR, hazard ratio; MDRD, modification of diet in renal disease.

Marso SP et al. N Engl J Med 2016;375:1834–44.

Utilizzo dei farmaci per il diabete

Nello studio ARNO, la percentuale di utilizzo dei GLP1-RA è:

a) 10%

b) 2.4%

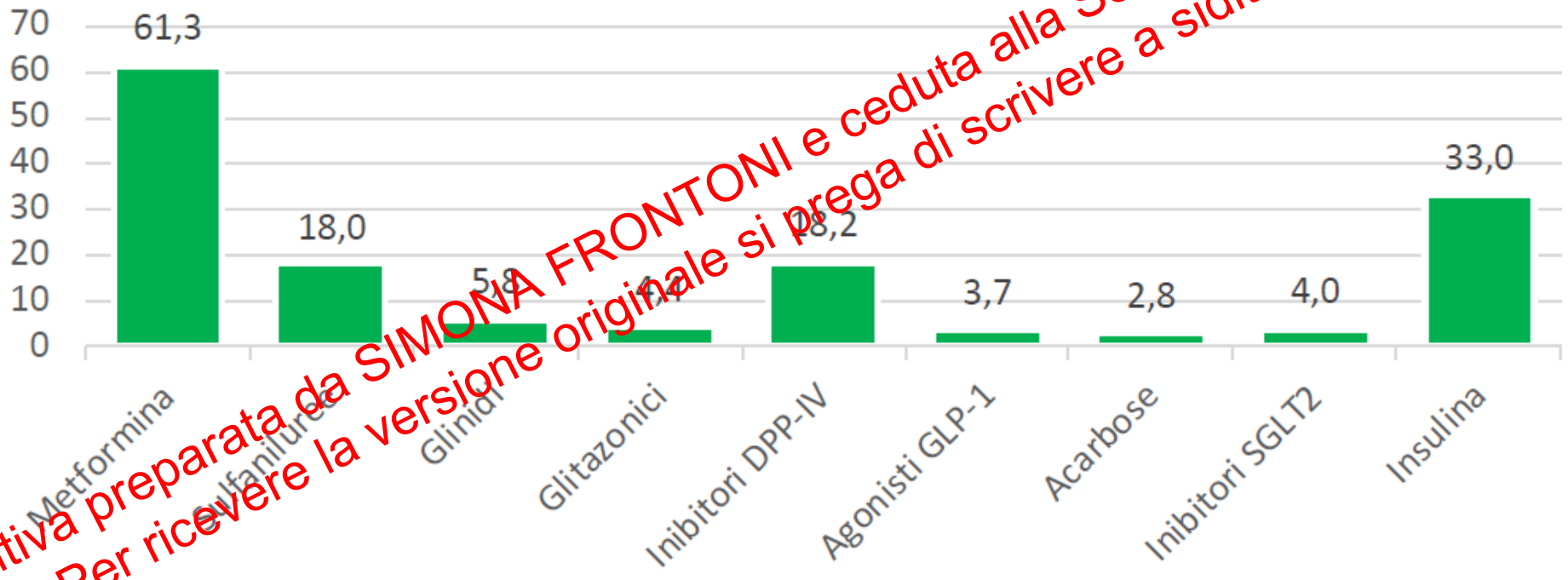
c) 4.8%

d) 9.6%

ARNO
Soggetti trattati coi vari farmaci anti-iperglicemici

Descrizione	Trattati (n=516.073)	% Trattati*	% spesa sul totale	Spesa media per trattato €	Spesa media pro capite € (n=640.846)
Iperglicemici orali o iniettabili	446.320	86,5	50	150	104,5
Metformina	321.009	62,2	9,4	39,3	19,7
Sulfoniluree	99.127	19,2	3,8	51,8	8
Glinidi (Repaglinide)	45.942	8,9	2,8	80	5,8
Metformina e sulfoniluree	42.527	8,2	1,9	59,2	3,9
Metformina e Inibitori DPP-4	35.942	7	10	371,5	20,8
Inibitori DDP-4	25.991	5	7	358,2	14,5
Inibitori alfa-glicosidasi (Acarbosio)	19.210	3,7	1,2	84,6	2,5
Metformina e pioglitazone	14.245	2,8	3	285,6	6,3
Analoghi GLP-1	12.447	2,4	7,2	778,5	15,1
Glitazoni (Pioglitazone)	9.582	1,9	1	141,9	2,1
Inibitori SGLT-2	7.236	1,4	1,4	257,1	2,9
Metformina e inibitori SGLT-2	4.425	0,9	0,8	230,8	1,6
Glimepiride e pioglitazone	1.361	0,3	0,3	310,2	0,7
Pioglitazone e alogliptin	1.009	0,2	0,2	270,9	0,4
Insuline umane	5.345	1	0,7	162,9	1,4
Insuline ad azione rapida	4.174	0,8	0,5	155,4	1
Insuline ad azione intermedia	1.314	0,3	0,1	105,6	0,2
Insuline ad azione intermedia e azione rapida miscelate	736	0,1	0,1	113,7	0,1
Analoghi dell'Insulina	134.409	26	49,4	491,8	103,2
Analoghi ad azione rapida	100.132	19,4	27,6	369,4	57,7
Analoghi ad azione intermedia e azione rapida miscelati	12.547	2,4	2,6	273,2	5,3
Analoghi ad azione intermedia	6.656	1,3	1	199,9	2,1
Analoghi ad azione lenta	105.998	20,5	18,2	229,8	38
Totale	516.073	-	100,0	259,5	209

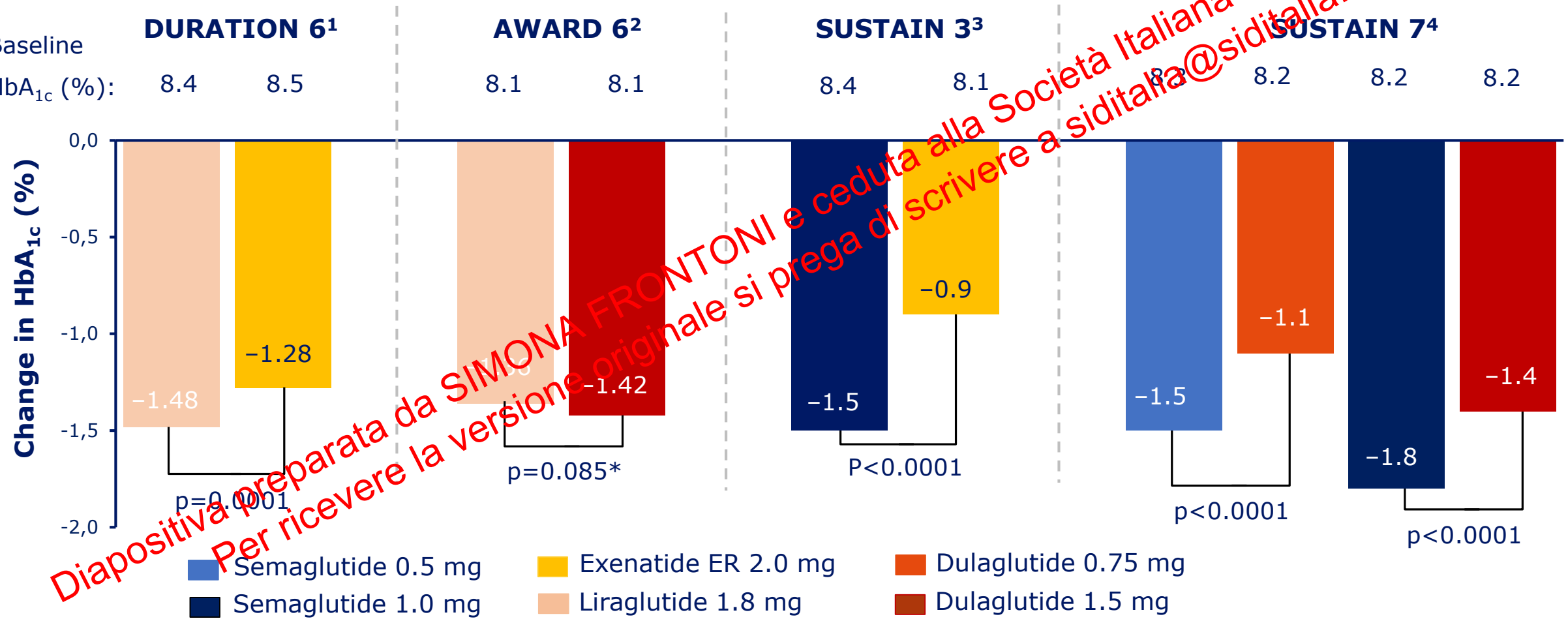
Distribuzione dei pazienti con DM2 per classe di farmaco ipoglicemizzante (%)



Annali 2018

GLP1-RAs: reduction of HbA_{1c}

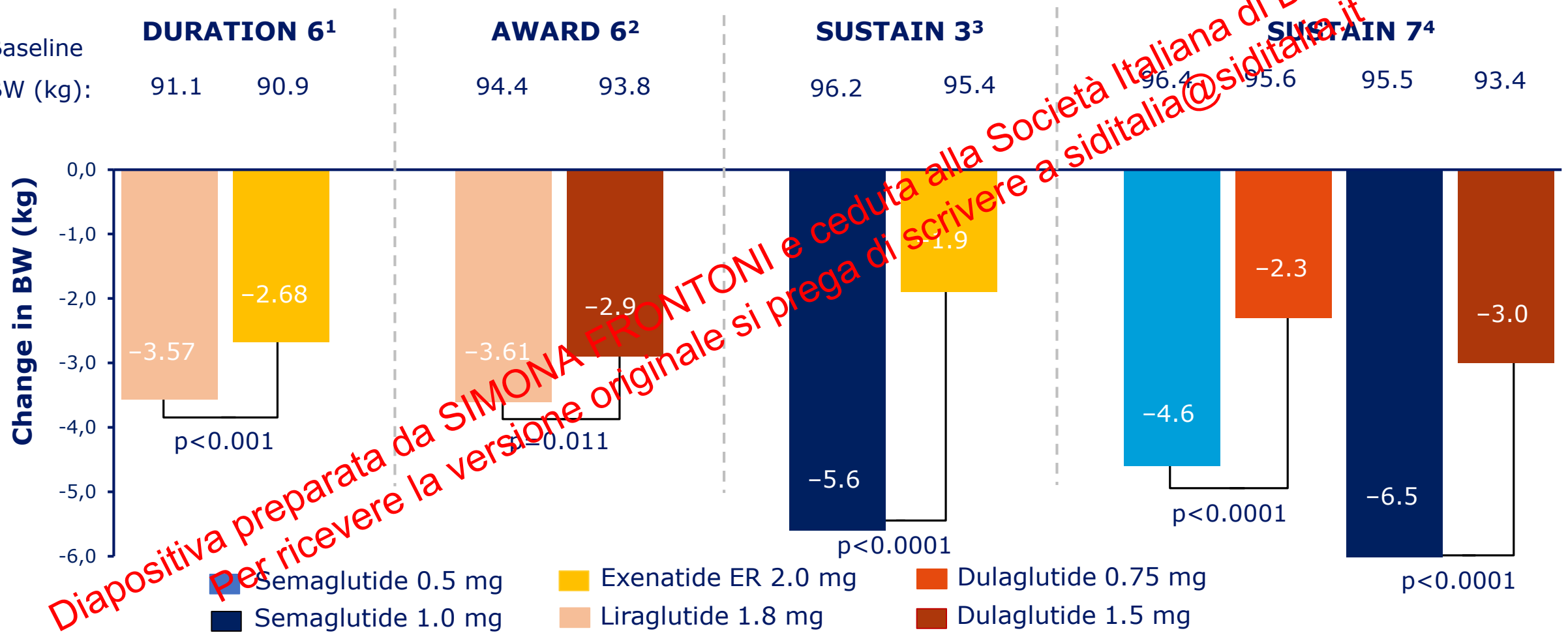
RESULTS FROM COMPARATIVE TRIALS



*Treatment difference (nominal 95% CI) = −0.06 (−0.19;0.07), p<0.0001 for non inferiority vs liraglutide. 1. Buse JB et al. Lancet 2013;381:117–24; 2. Dungan KM et al. Lancet 2014;384:1349–57; 3. Ahmann AJ et al. Diabetes Care 2018;41:258–66; 4. Pratley RE et al. Lancet Diabetes Endocrinol 2018;6:275–86.

GLP1-RAs: reduction of body weight

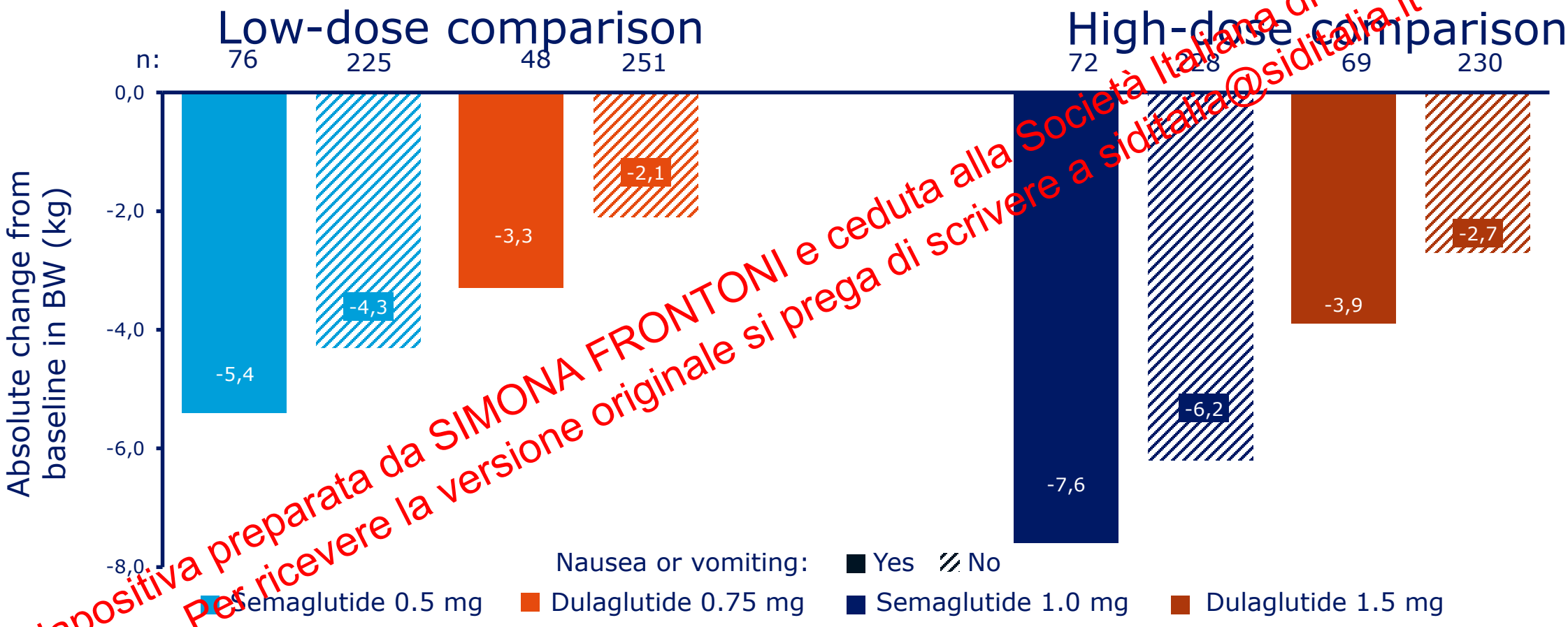
RESULTS FROM COMPARATIVE TRIALS



1. Buse JB et al. Lancet 2013;381:117–24; 2. Dungan KM et al. Lancet 2014;384:1349–57; 3. Ahmann AJ et al. Diabetes Care 2018;41:258–66; 4. Pratley RE et al. Lancet Diabetes Endocrinol 2018;6:275–86

Changes in Body Weight by Nausea or Vomiting

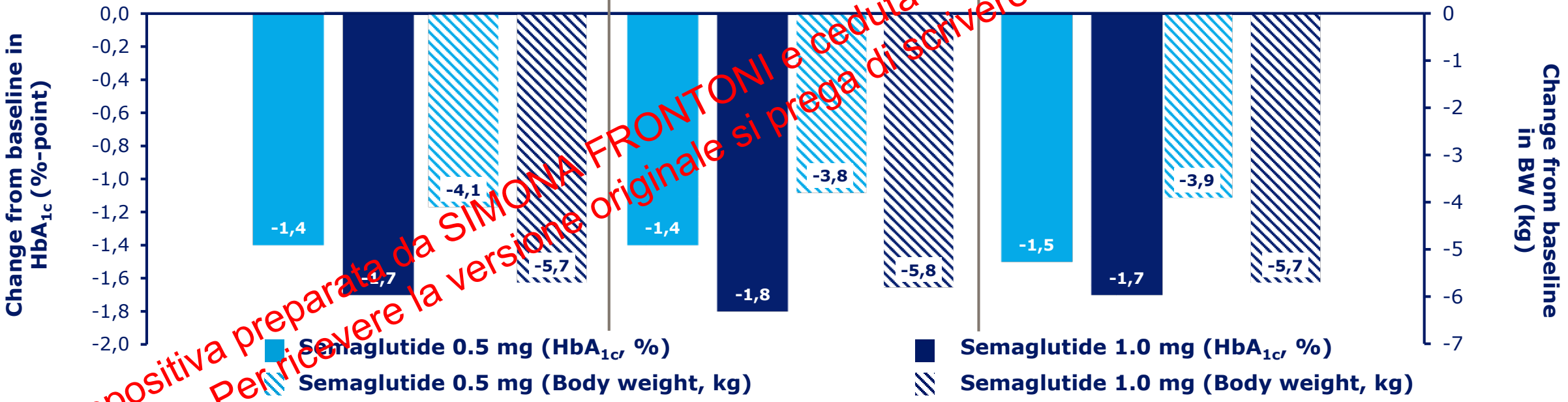
SUSTAIN 7



Data are 'on-treatment without rescue medication' estimated changes from baseline at week 40 from all randomised patients exposed to at least one dose of trial product (full analysis set). Missing data were imputed from a mixed model for repeated measurements with treatment, region and stratum as fixed factors and baseline value as covariate, all nested within visit. BW, body weight.
Lingvay I et al. EASD 2018

Change in HbA_{1c} and weight by diabetes duration

Diabetes duration	≤5 years				>5 to ≤10 years				>10 years			
Change from baseline:	HbA_{1c} (%)		Body weight (kg)		HbA_{1c} (%)		Body weight (kg)		HbA_{1c} (%)		Body weight (kg)	
N	533	641	533	641	423	565	423	565	376	528	376	528
Baseline	8.1	8.1	95.9	95.9	8.2	8.2	93.5	93.5	8.3	8.3	89.8	89.8
End of treatment	6.6	6.4	91.8	90.1	6.8	6.4	89.6	87.7	6.8	6.5	85.8	84.1

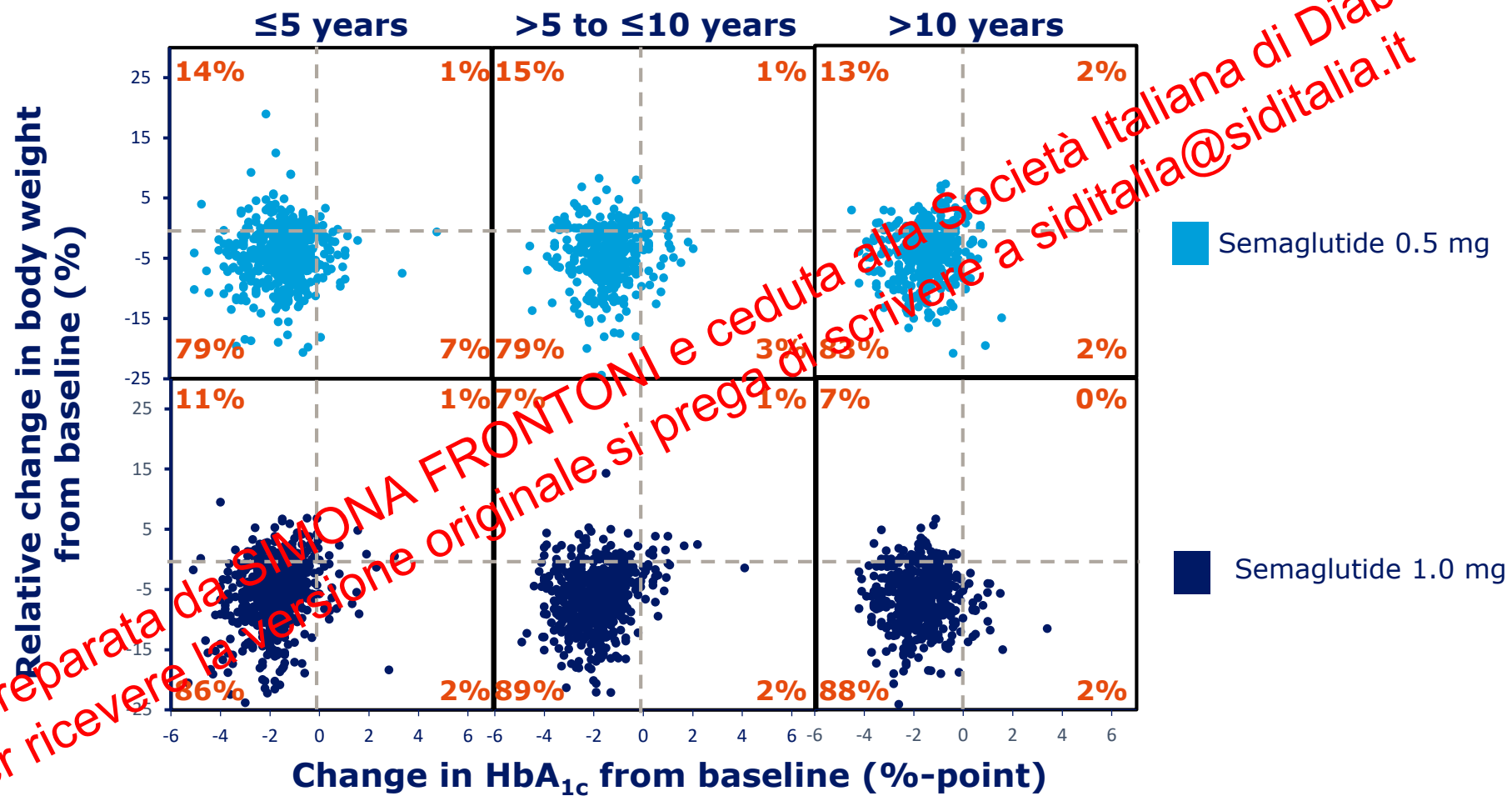


Data presented are estimated change from baseline to week 30 or week 40 based on a meta-analysis of data from the six trials. BW, body weight; N, number of subjects in the full analysis set.

Rosenstock J et al. Presented at the 78th Scientific Sessions of the American Diabetes Association, 22–26 June, 2018, Orlando, Florida, USA: Poster Presentation 1081-P.

Changes in HbA_{1c} vs body weight by diabetes duration

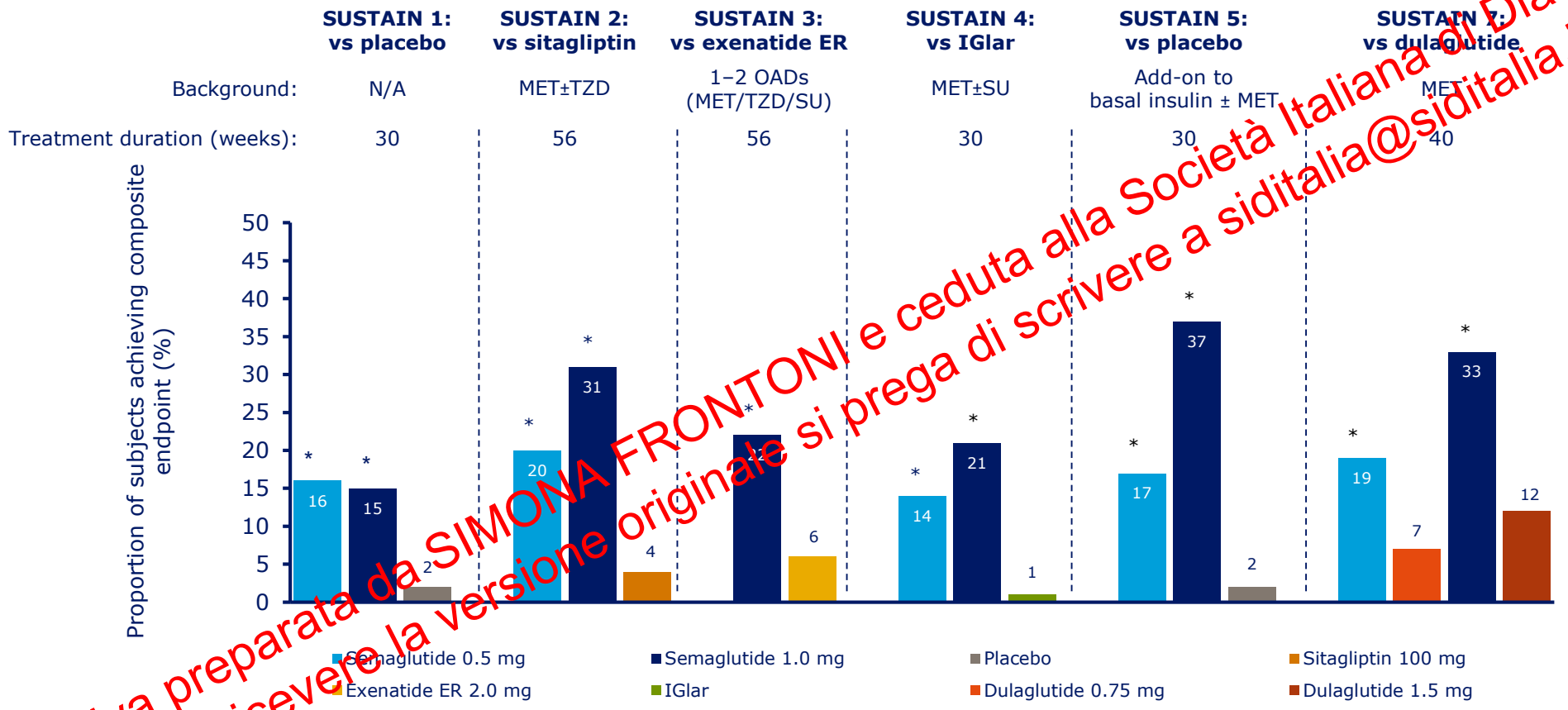
SUSTAIN 1–5 and 7



Data presented are based on observed on-treatment without rescue medication data, with MMRM predictions for missing HbA_{1c} and body weight values, from the six trials.
MMRM, Mixed Model Repeat Measurements.
Rosenstock J et al. Presented at the 78th Scientific Sessions of the American Diabetes Association, 22–26 June, 2018, Orlando, Florida, USA: Poster Presentation 1081-P.

Proportion of subjects achieving composite endpoint

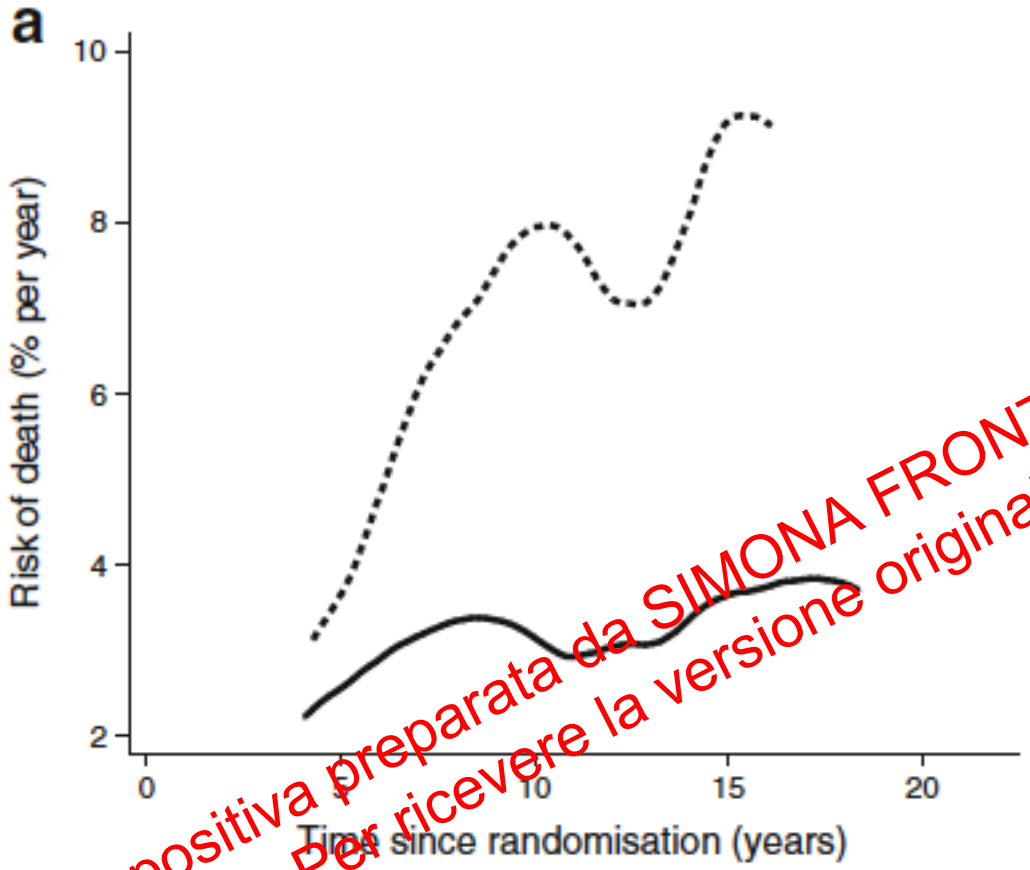
REDUCTION IN HbA_{1c} ≥1%, WEIGHT LOSS ≥5%, AND REDUCTION IN SBP ≥5 mmHg

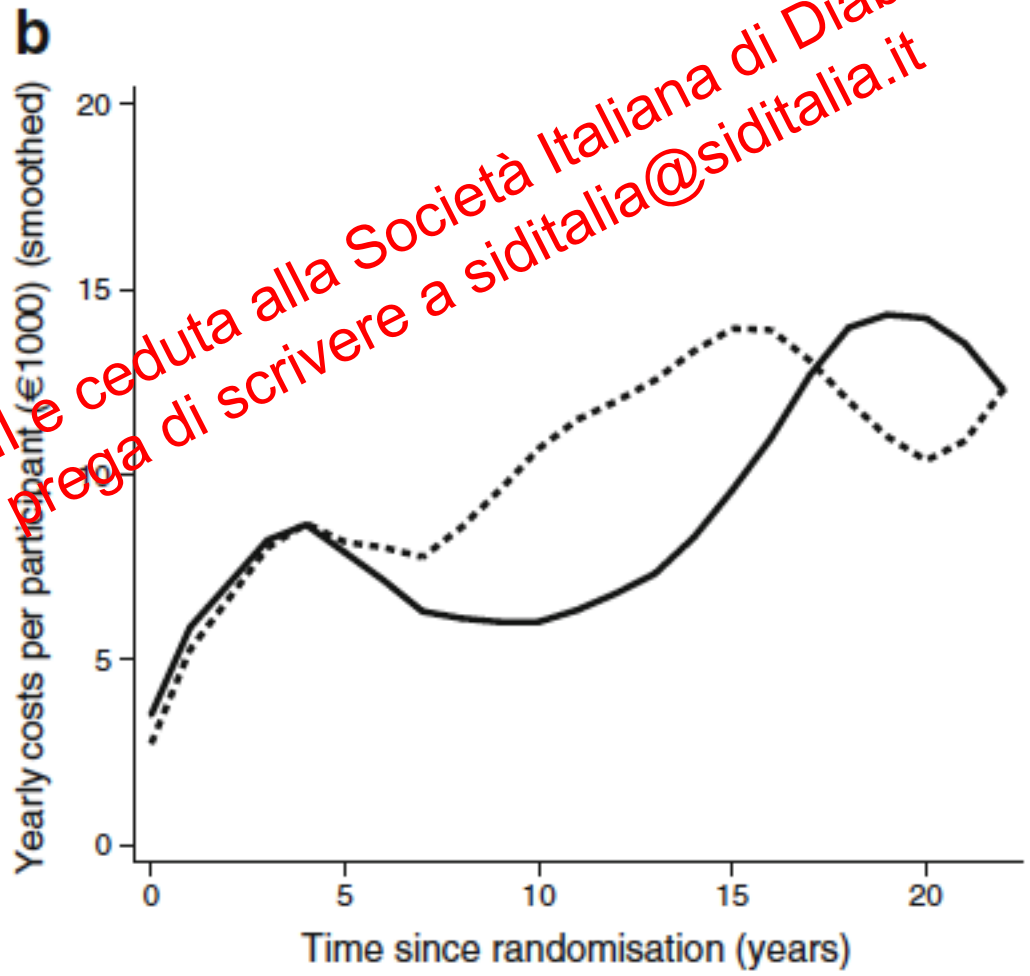


**Indicates significance (p<0.001) between semaglutide (0.5 mg or 1.0 mg) and comparator. Comparison for SUSTAIN 7 is semaglutide 0.5 mg vs dulaglutide 0.75 mg and semaglutide 1.0 mg vs dulaglutide 1.5 mg. 'On-treatment without rescue medication' data are presented. Logistic regression with treatment, trial-specific stratification, and country as fixed factors and baseline HbA_{1c}, body weight and SBP as covariate. Missing values for each component are imputed using an MMRM with trial-specific stratification and country as fixed factors and baseline value as covariate, all nested within visit. Exenatide ER, exenatide extended release; IGlar, insulin glargine; MET, metformin; MMRM, mixed model for repeated measurements; N/A, not applicable; OAD, oral antidiabetic drug; SBP, systolic blood pressure; SU, sulphonylurea; TZD, thiazolidinedione.*

Dungan K et al. Presented at the 78th Scientific Sessions of the American Diabetes Association, 22–26 June, 2018, Orlando, Florida, USA: Oral Presentation (129 OR).

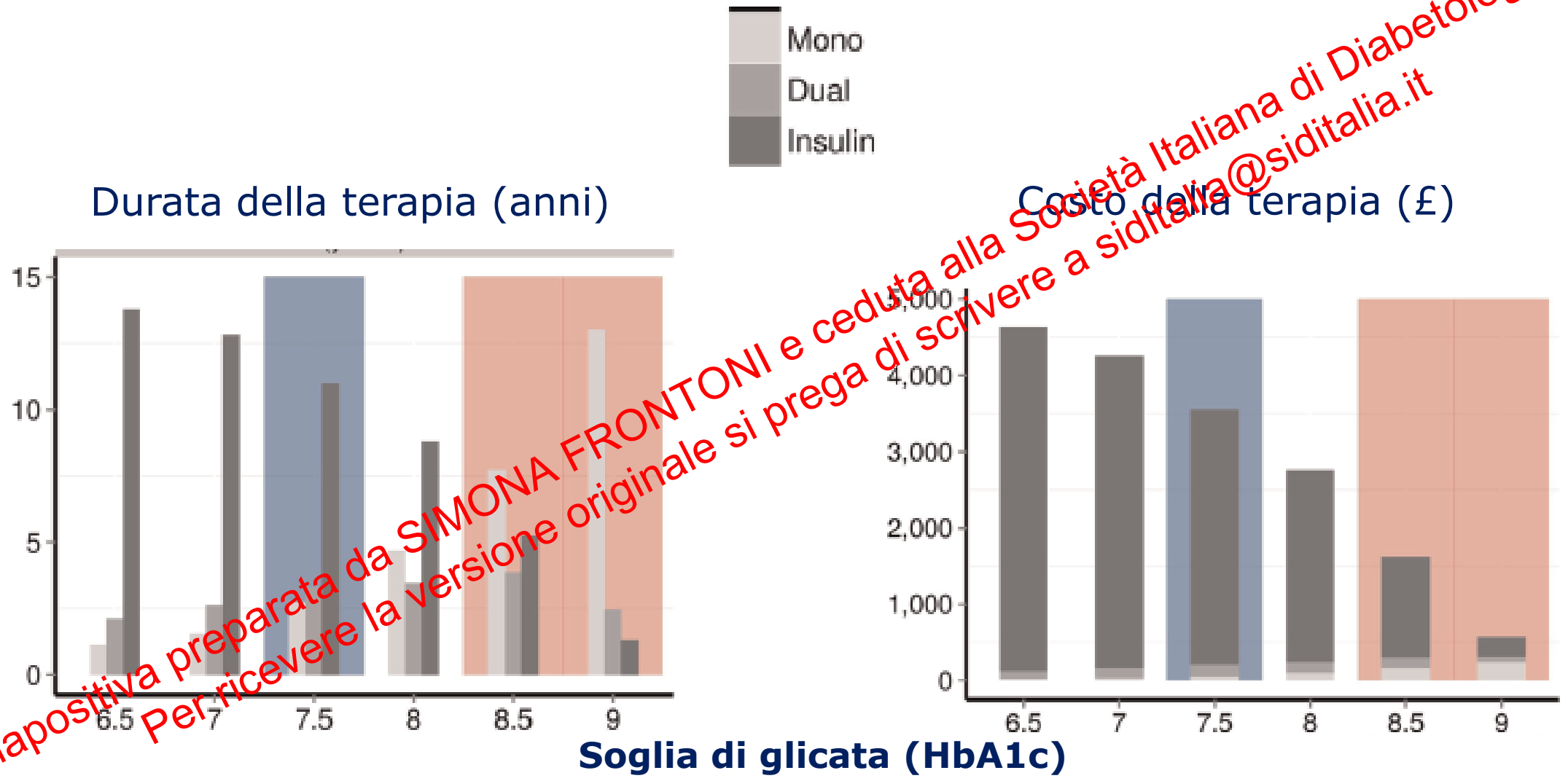
Analisi costi Steno 2





Gaede J, Diabetologia 2019

Costi attuali e attesi, secondo gli obiettivi NICE



McEwan P, Med Decis Making 2015

Conclusioni

- Un controllo glicemico intensivo APPROPRIATO permette di ottenere il mantenimento a lungo termine del controllo metabolico e di prevenire le complicanze micro e macrovascolari del diabete.

- L'uso di farmaci che riducono la glicemia in maniera efficace e sicura e contestualmente sono in grado di migliorare il rischio CV globale, modificando la traiettoria temporale della macroangiopatia, dovrebbe essere anticipato il più possibile.

- Gli analoghi del GLP-1 rappresentano un nuova opzione terapeutica anche per il trattamento precoce e per la prevenzione della progressione della nefropatia diabetica.

- Un'appropriata analisi dei costi documenta un risparmio a breve e lungo termine del trattamento intensivo precoce, con i nuovi farmaci a nostra disposizione