L'evoluzione della terapia del diabete tipo 2

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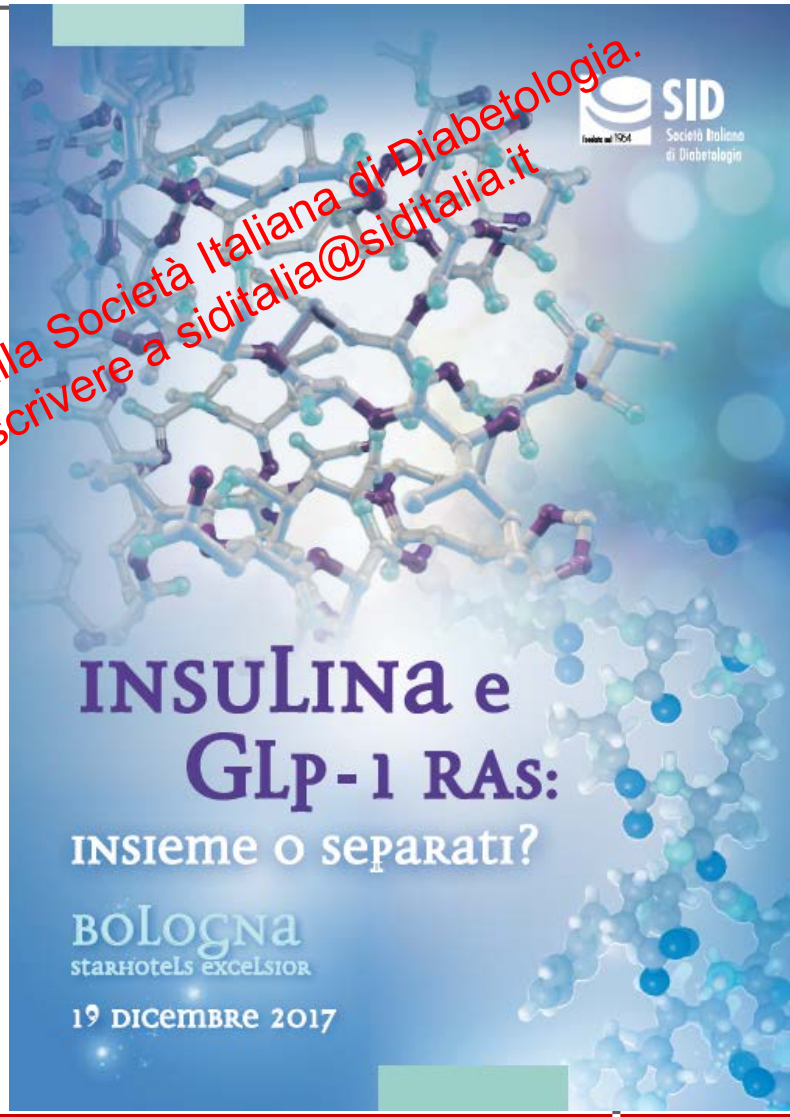


Disclosures

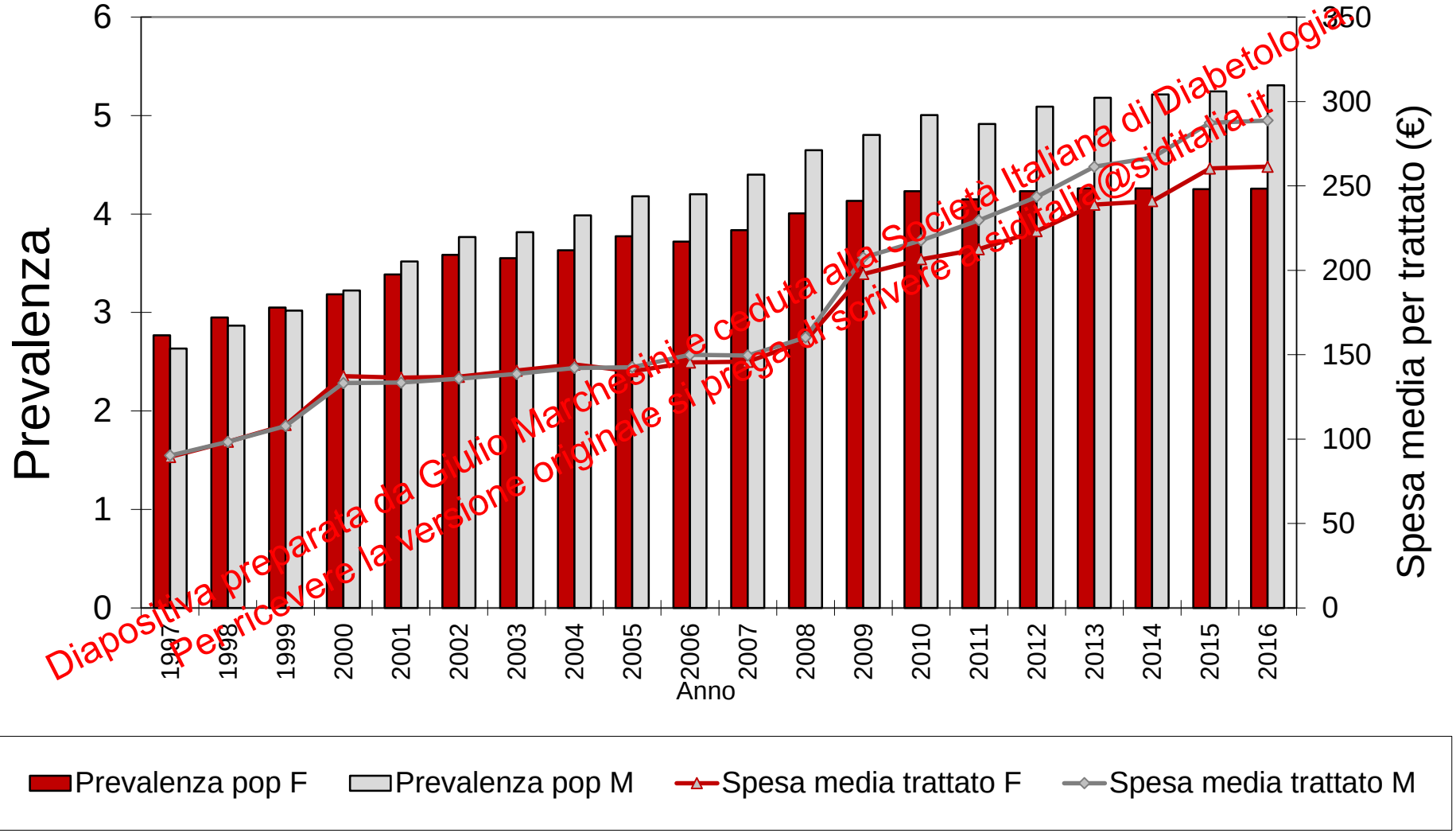
Giulio Marchesini

- **Advisory Board**: Lilly, Gilead
- **Honoraria**: Sanofi, Merck Sharp & Dohme, Novartis
- **Clinical Studies**: Boehringer Ingelheim, Janssen Cilag, Sanofi, Lilly, Novo Nordisk, Gilead, GENFIT, Glaxo

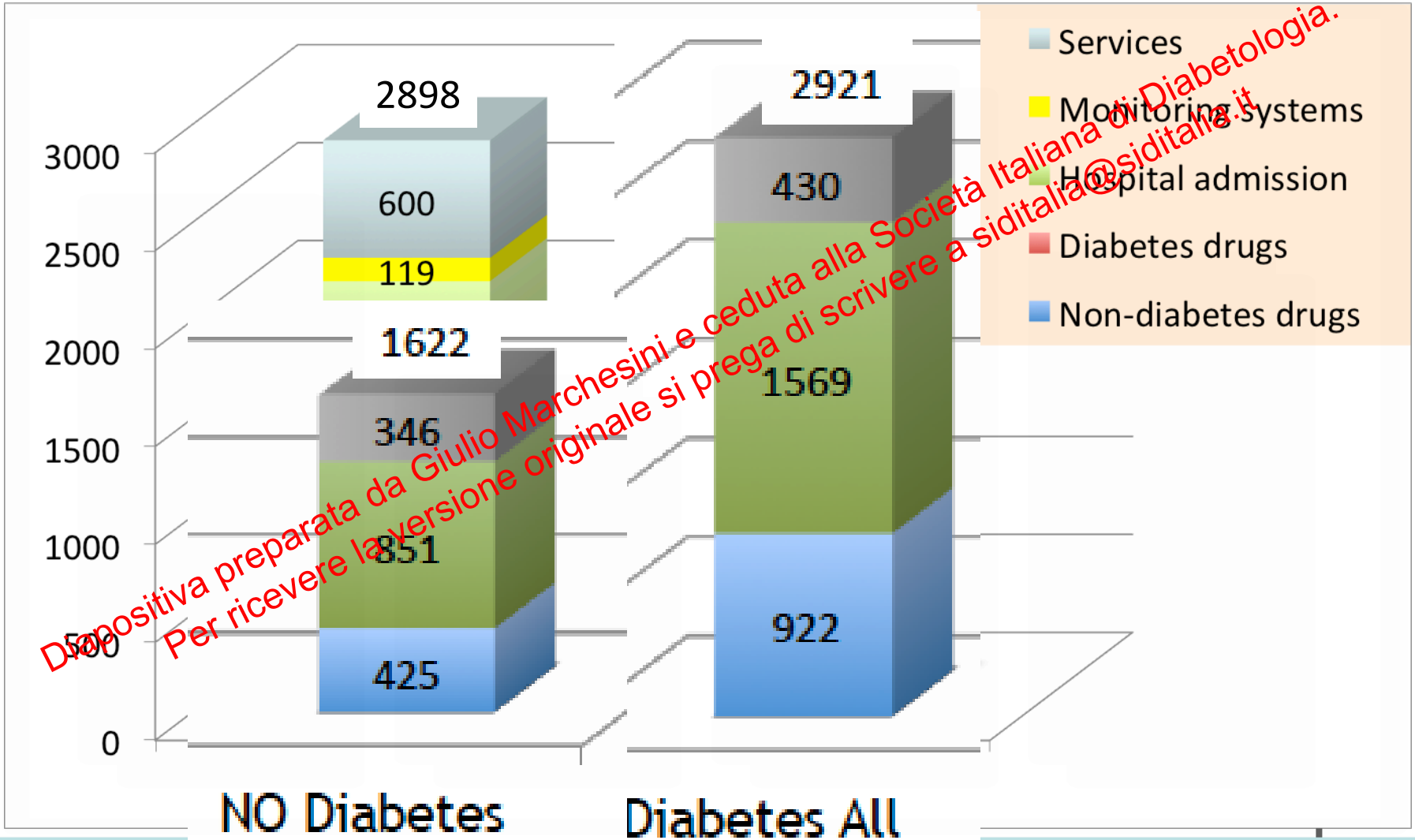
Draft della presentazione

- Stato attuale del trattamento
- Momenti topici nel cambiamento
  - Proactive
  - NHI regulatory action
  - GLP-1RAs – DPP-4Is
  - Grandi trial (Advance – Accord – VADT)
  - SGLT-2Is
  - Degludec
  - EMPA-REG Outcome
  - TECOS – EXAMINE – SAVOR-TIMI
  - Biosimilare di Glargine
  - Glargine 300
  - GLP-1RAs settimanali
  - GLP-1RAs+Insulina basale

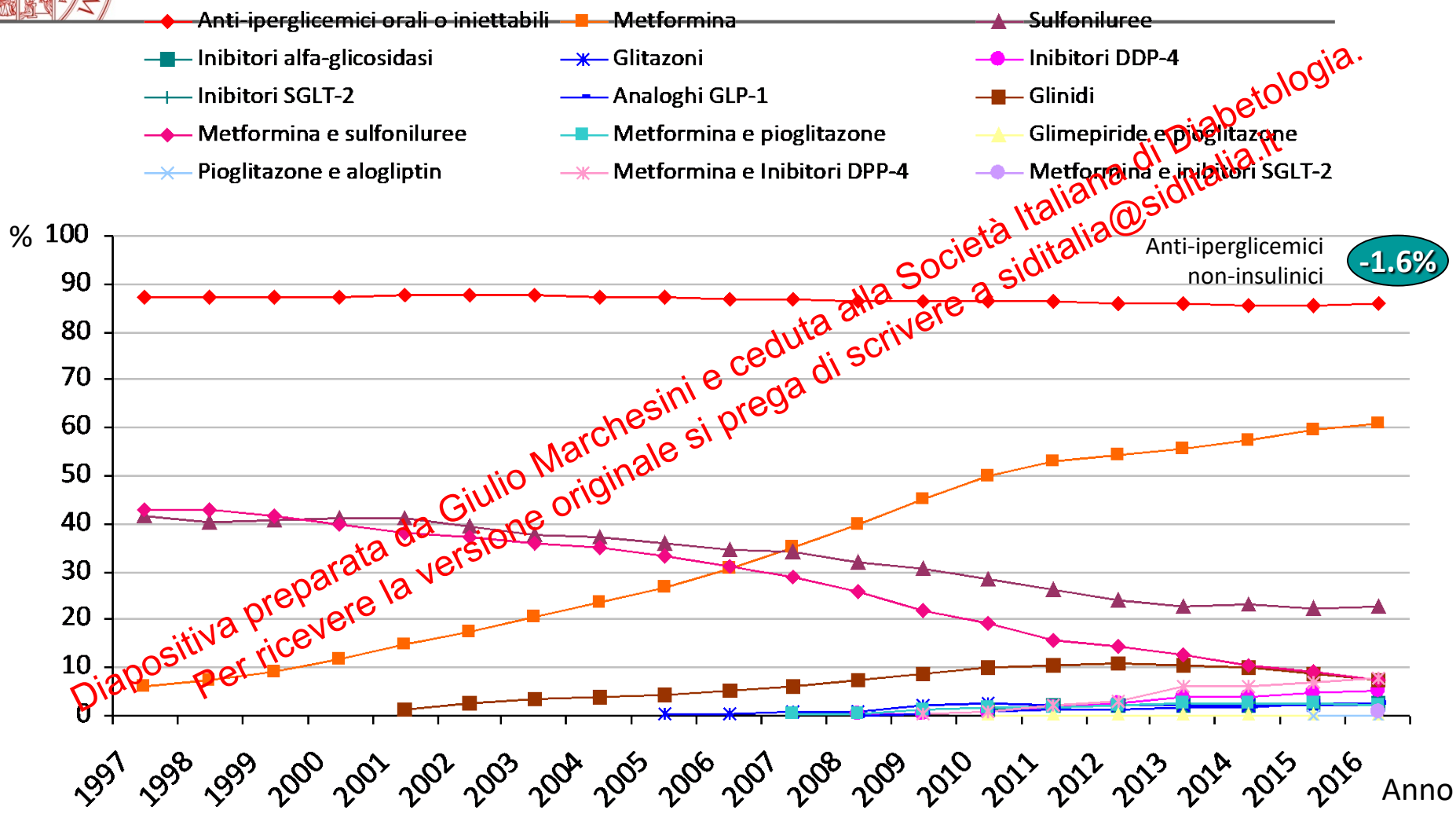
Trend di prevalenza e spesa negli anni



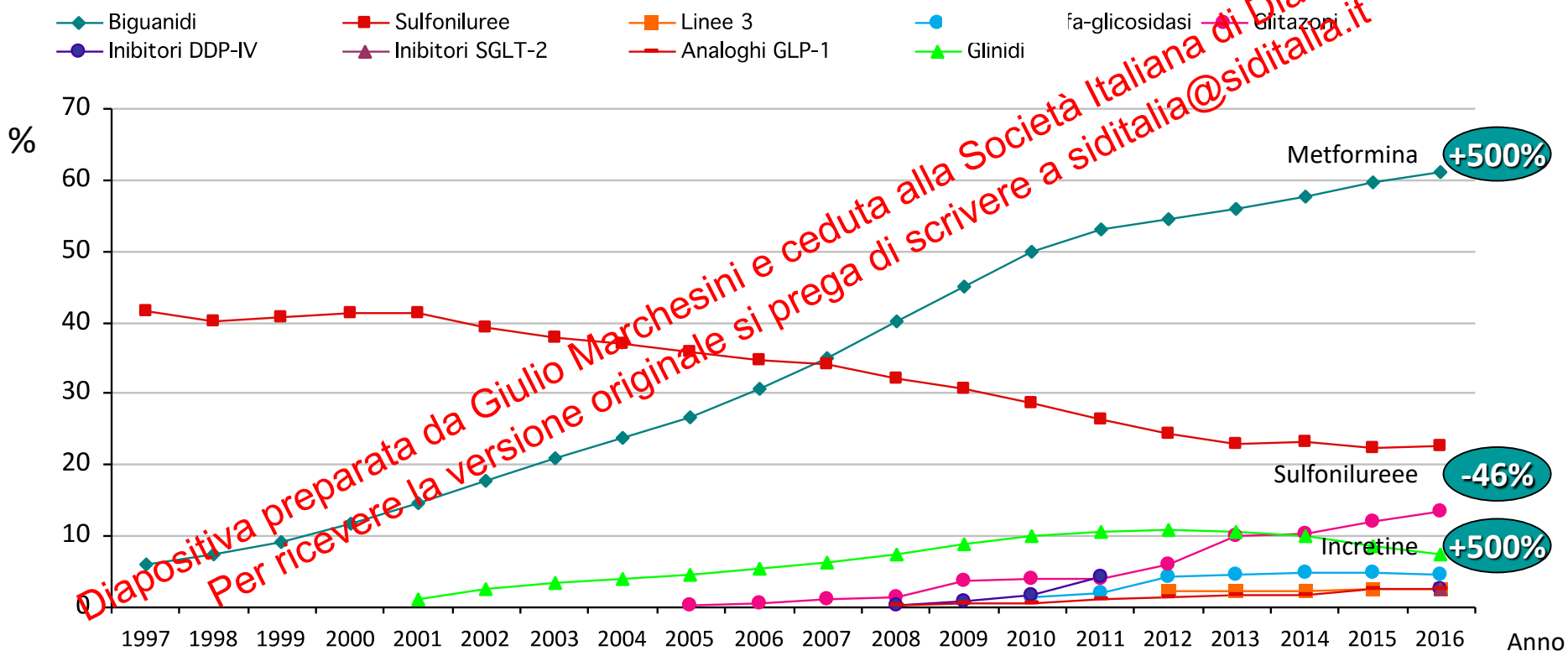
ARNO 2015
Costi diretti del diabete



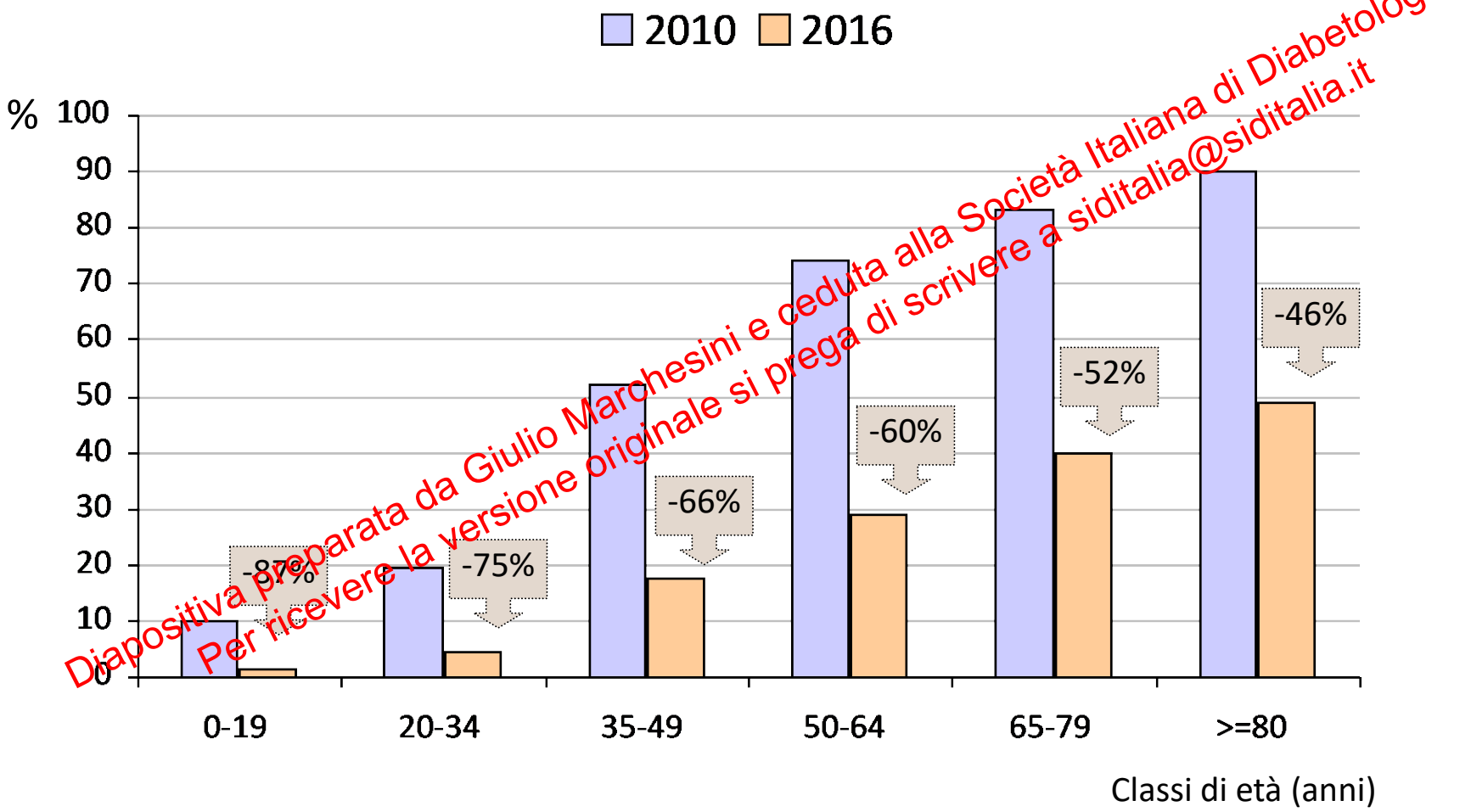
Andamento della terapia con anti-iperglicemici non-insulinici



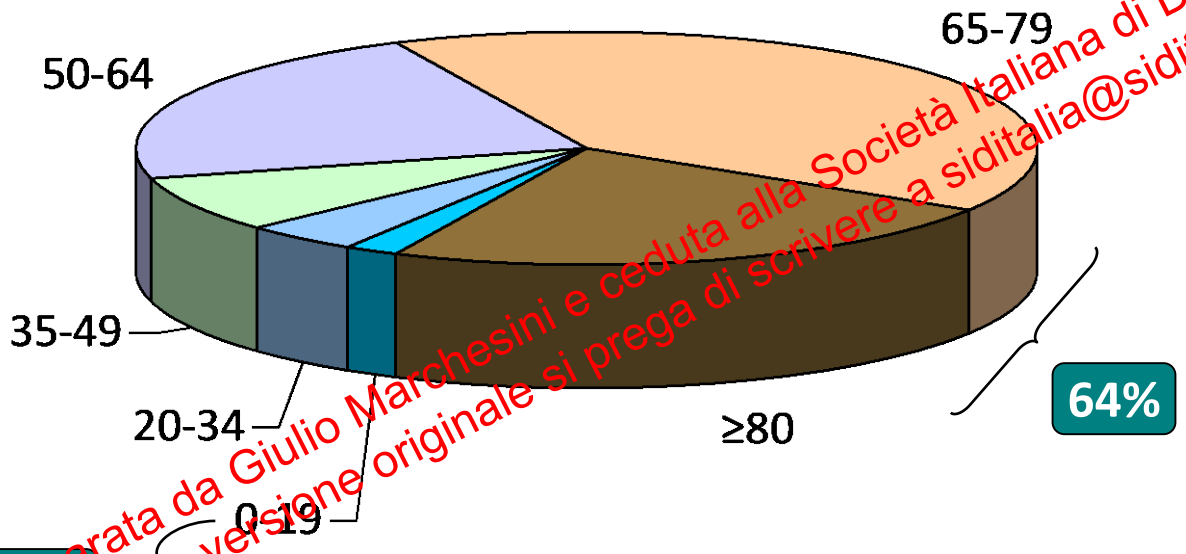
Andamento della terapia con anti-iperglicemici non-insulinici impiegati non in combinazione precostituita



Andamento nella frequenza d'uso dei sulfoniluree+glinidi in relazione alle classi di età

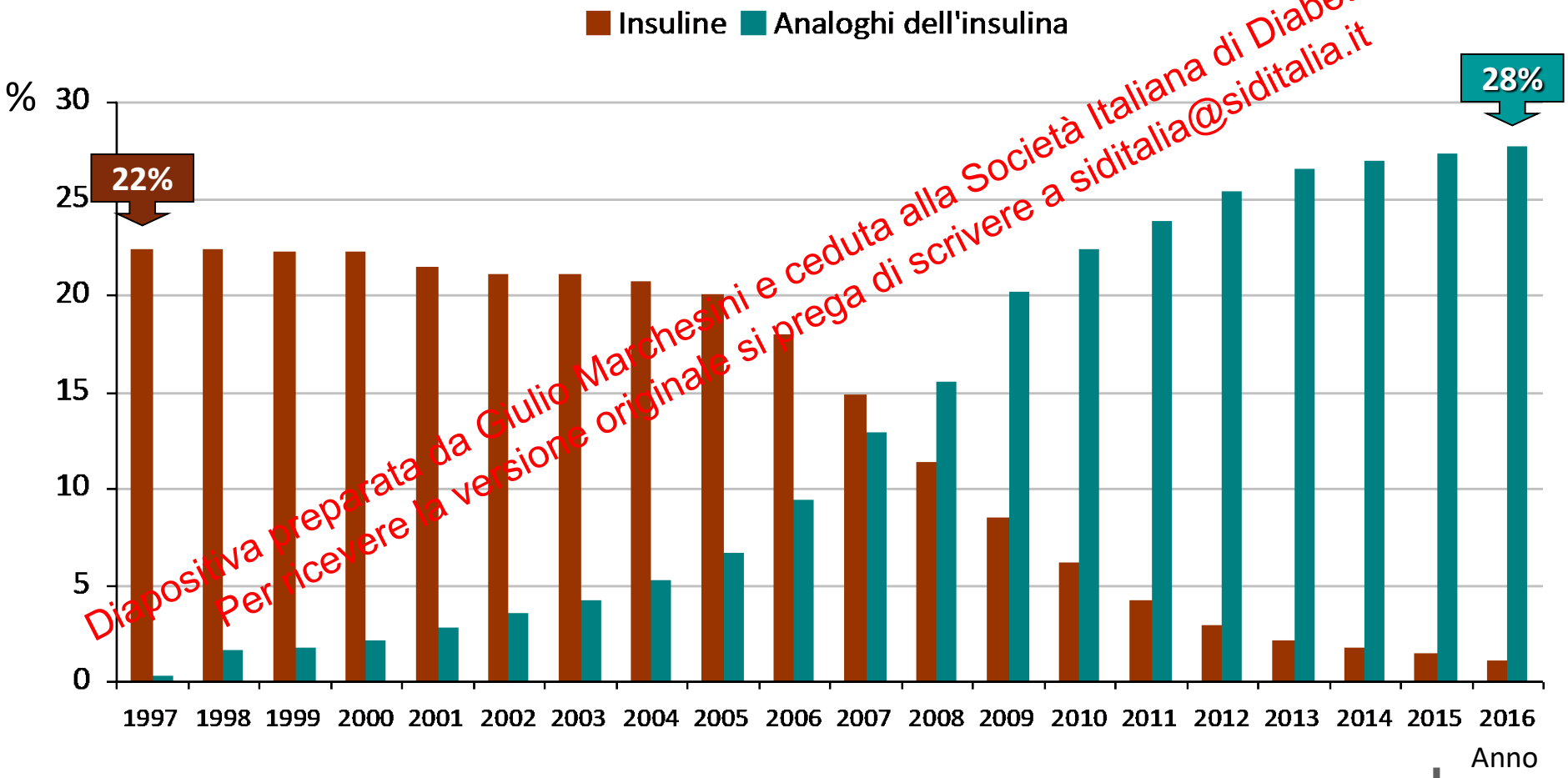


Trattamento insulinico in relazione all'età



Fra tutti i pazienti in terapia insulinica (26%), il 64% ha più di 65 anni.
Solo il 6% ha meno di 35 anni.

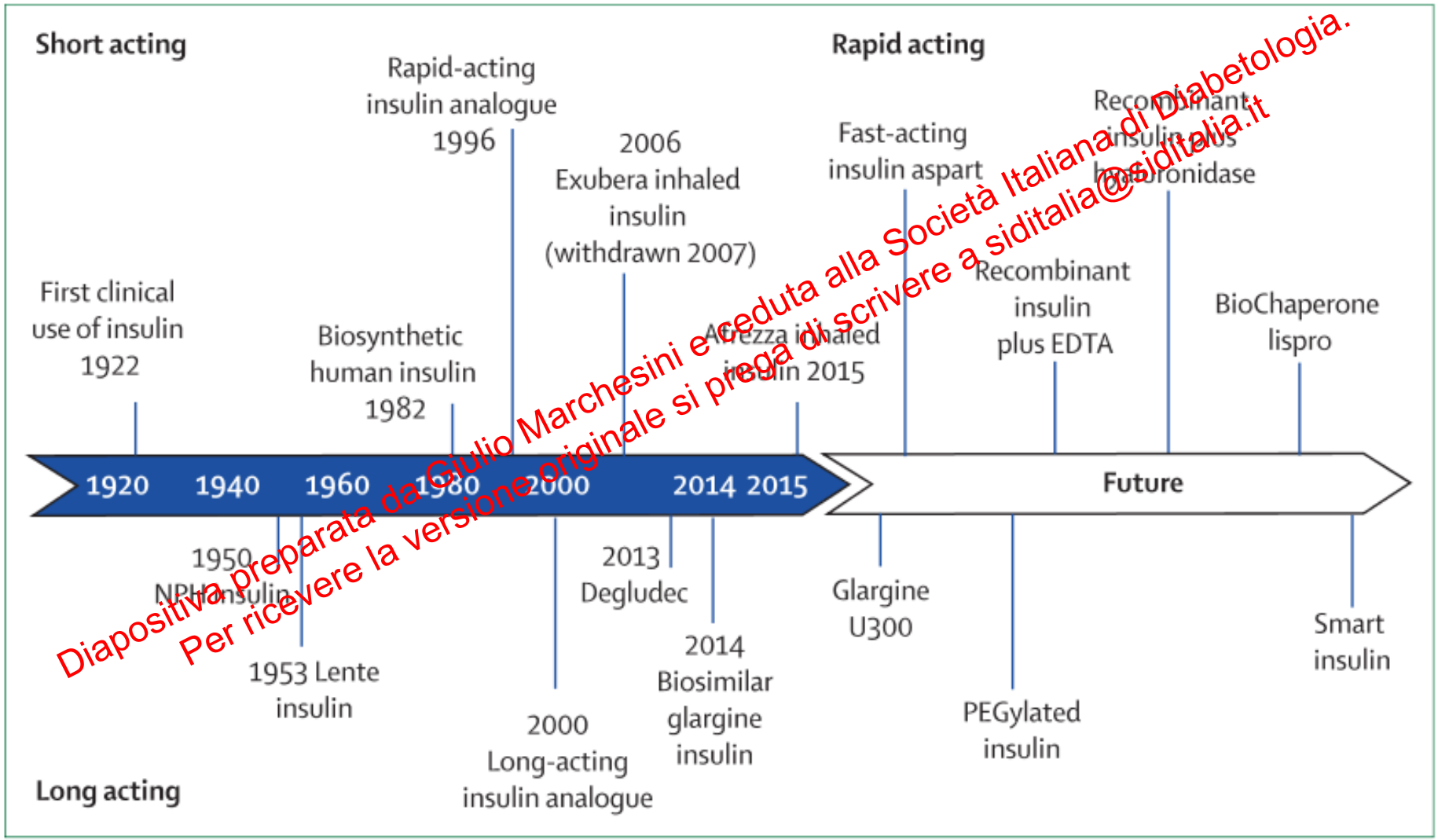
Impiego dell'insulina umana (DNA-r) e degli analoghi dell'insulina nel corso degli anni



La scala dei farmaci del diabete

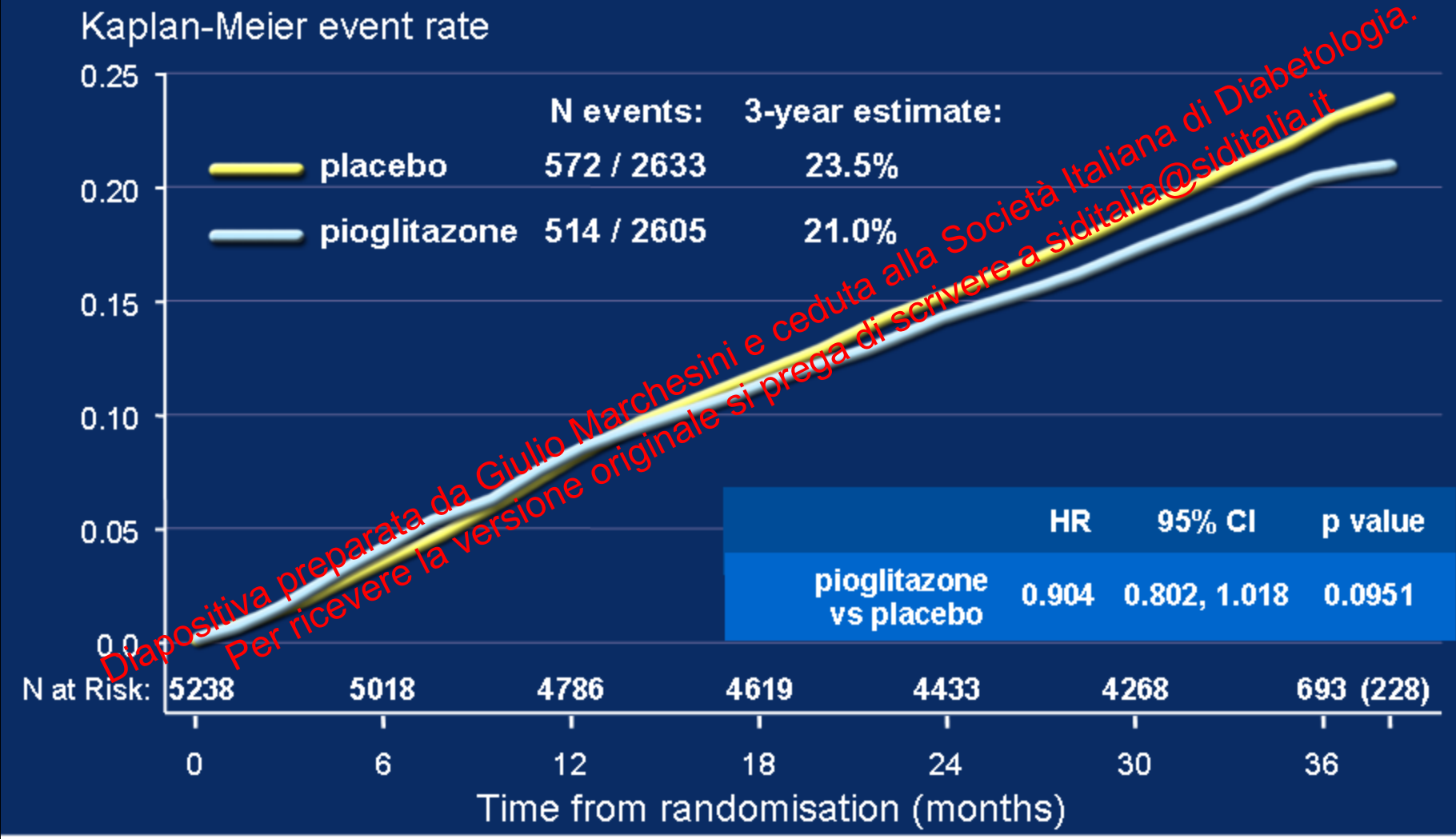
Cahn, Lancet Diabetes Endocrinol 2015

La scala dei farmaci del diabete

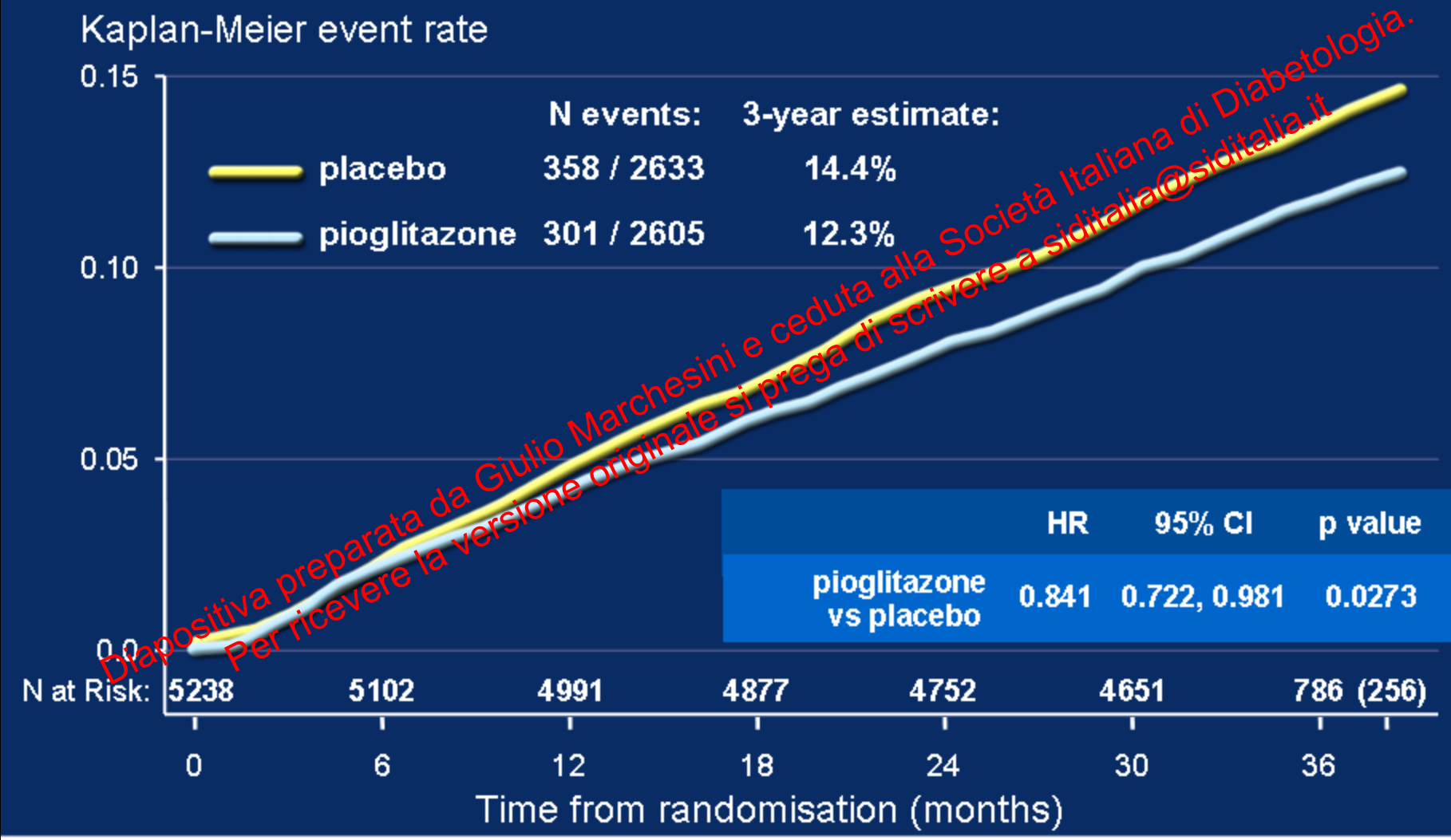


Cahn, Lancet Diabetes Endocrinol 2015

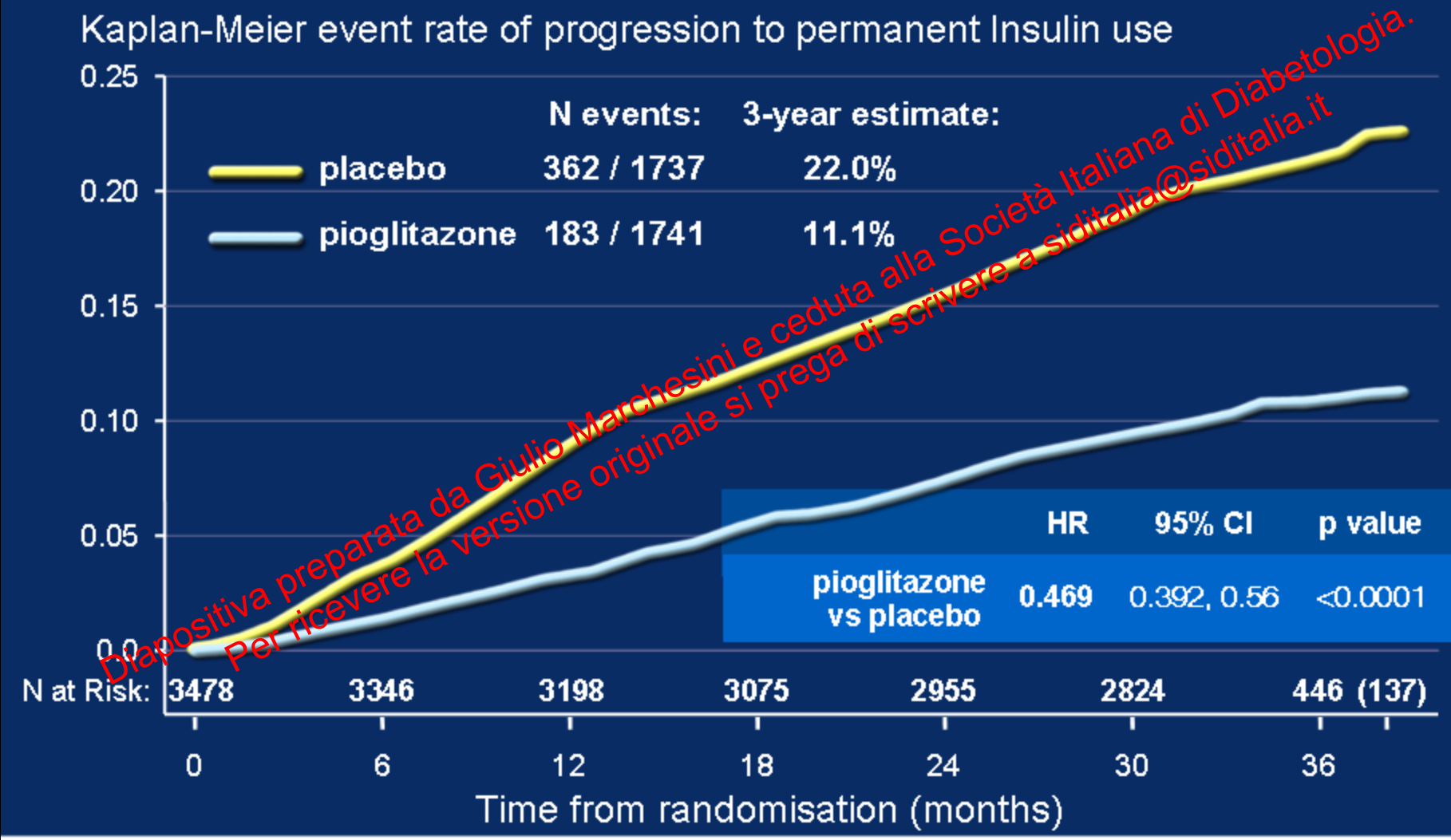
Time to Primary Composite Endpoint



Time to Death, MI (Excluding Silent) or Stroke

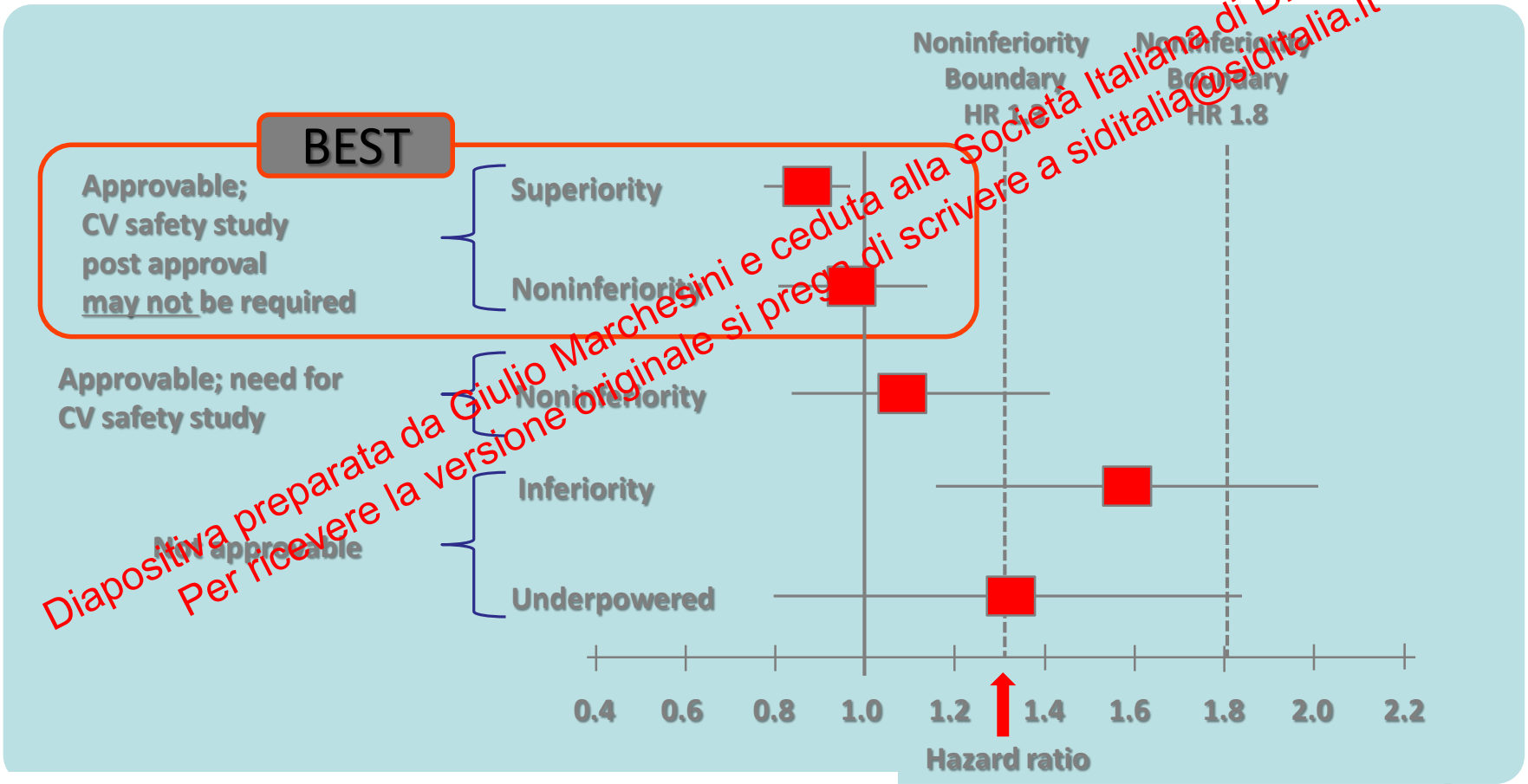


Time to Permanent Insulin Use



Statistical Criteria for Approval[1]

Five hypothetical examples of possible HRs, and regulatory consequences



FDA = Food and Drug Administration; HR = hazard ratio; CV = cardiovascular.

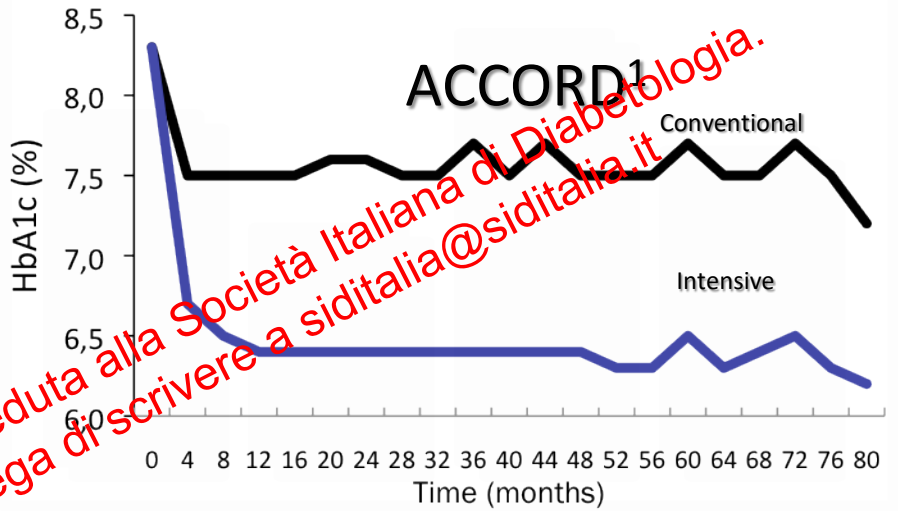
Comparison of CV Outcome Study Design

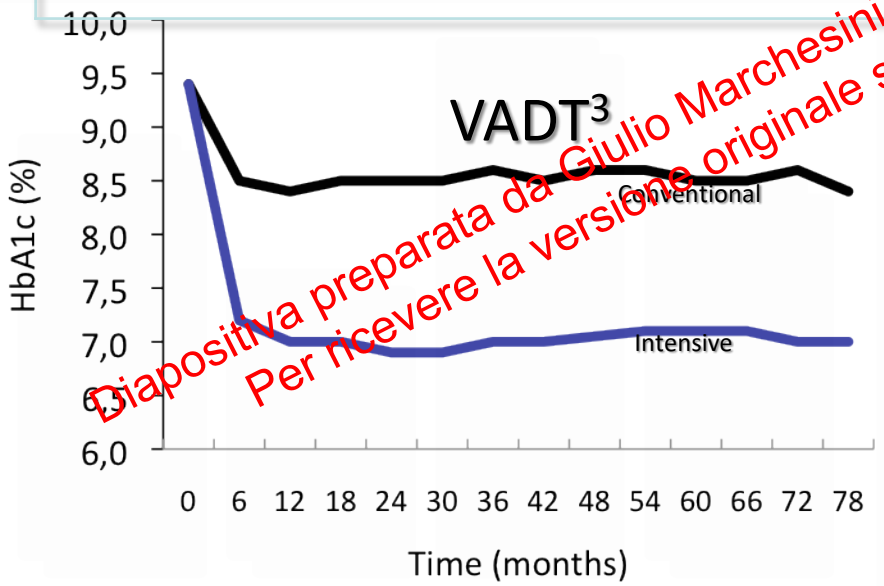
	SAVOR-TIMI (Saxagliptin) [1]	EXAMINE (Alogliptin) [2]	TECOS (Sitagliptin) [3]
Recruitment Period	Sept 2010 → Jan 2012	2009 → 2012	Dec 2008 → July 2012
Primary Endpoint	Composite of CV death, nonfatal MI, nonfatal stroke	Composite of CV death, nonfatal myocardial infarction, and nonfatal stroke	Composite of CV death, nonfatal MI, nonfatal stroke, or unstable angina requiring hospitalization
Analysis Population/ # of events	ITT for both NI and superiority Powered for 1040 events	NI, then superiority Type of analysis not mentioned in design paper Powered for 650 events	PP for NI; ITT for superiority Powered for 1300 events
Completion Date	Q3 2013	Q4 2013	Q4 2014

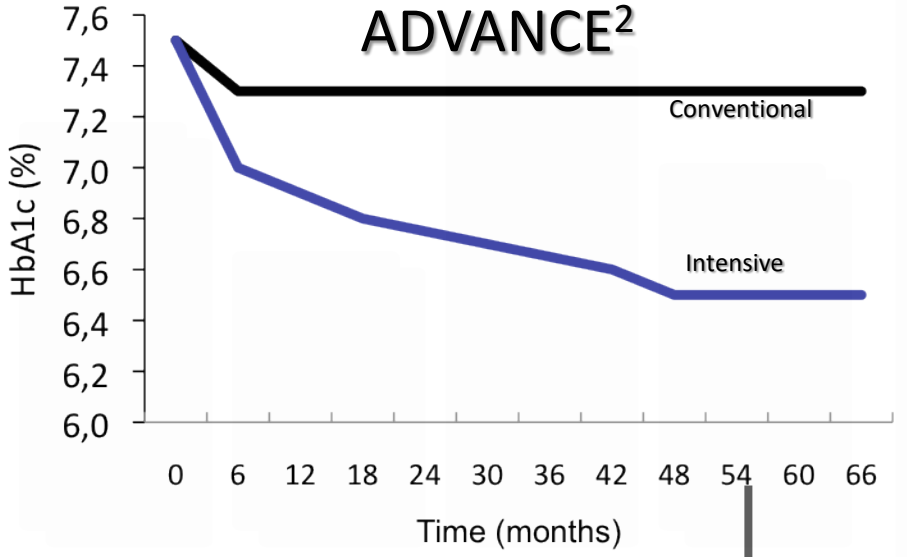
1-Scirica BM et al, Am Heart J 2011; 2-White W. et al Am Heart J 2011; 3-Clinicaltrials.gov accessed, 2013

ACCORD, ADVANCE & VADT – Effect of intensive treatment on glycaemic control

	ACCORD[1]	ADVANCE[2]	VADT[3]
A1c at entry (%)	8.1	7.2	9.4
Target A1c	<6.0	≤6.5	<6.0
Method to goal	Monthly contact Target A1c after 4–6 months	Predefined titration Target A1c after 36 months	Started on max dose Target A1c after 3 months





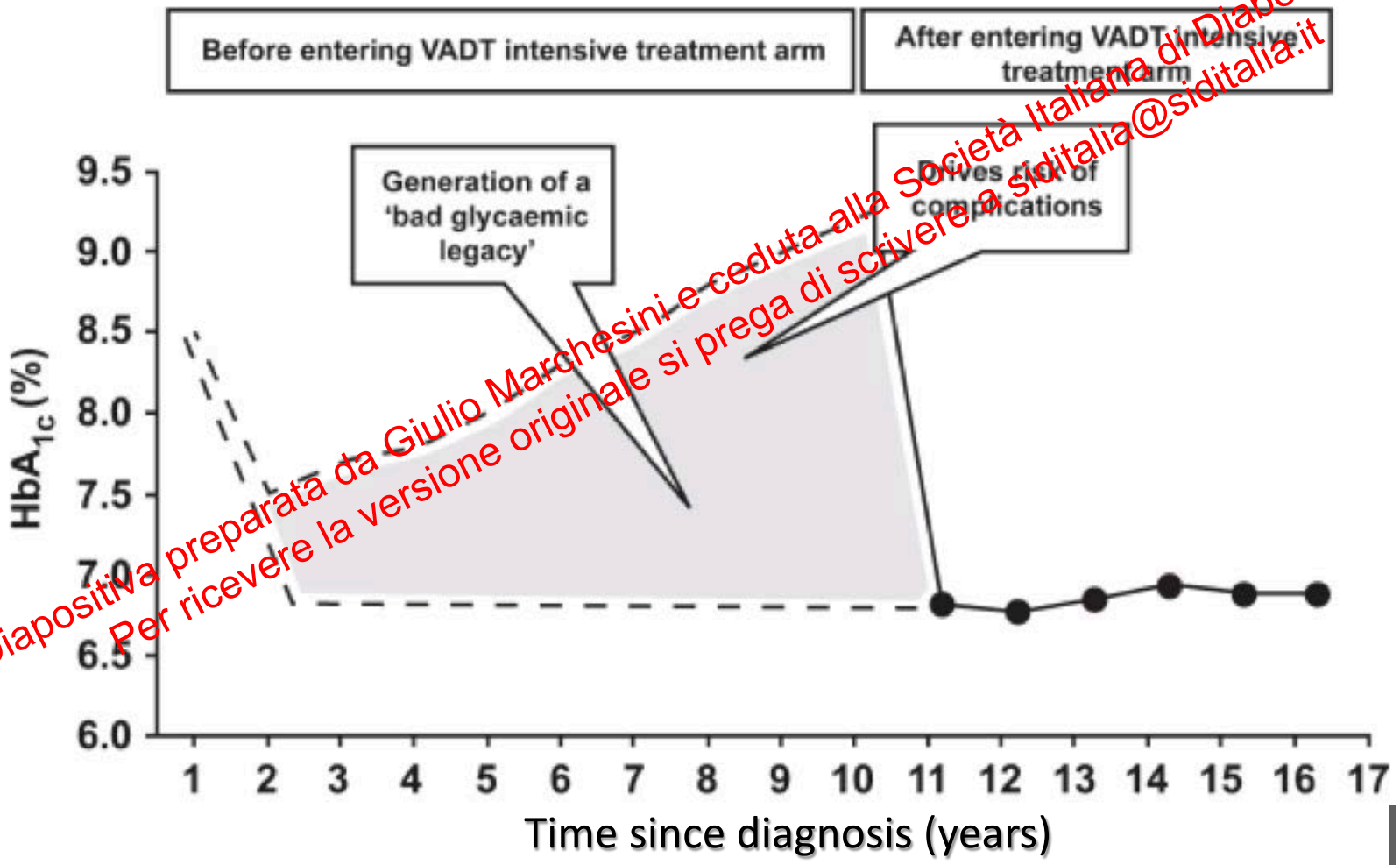


1. The ACCORD Study Group. *N Engl J Med* 2008
2. The ADVANCE Collaborative Group. *N Engl J Med* 2008
3. Duckworth W *et al. N Engl J Med* 2009

Tailoring treatment to the individual in type 2 diabetes practical guidance from the *Global Partnership for Effective Diabetes Management*

S. Del Prato,[1] J. LaSalle,[2] S. Matthaei,[3] C. J. Bailey,[4] on behalf of the *Global Partnership for Effective Diabetes Management**

Linked Comment: Aschner *et al*. *Int J Clin Pract* 2010; 64: 305–15.



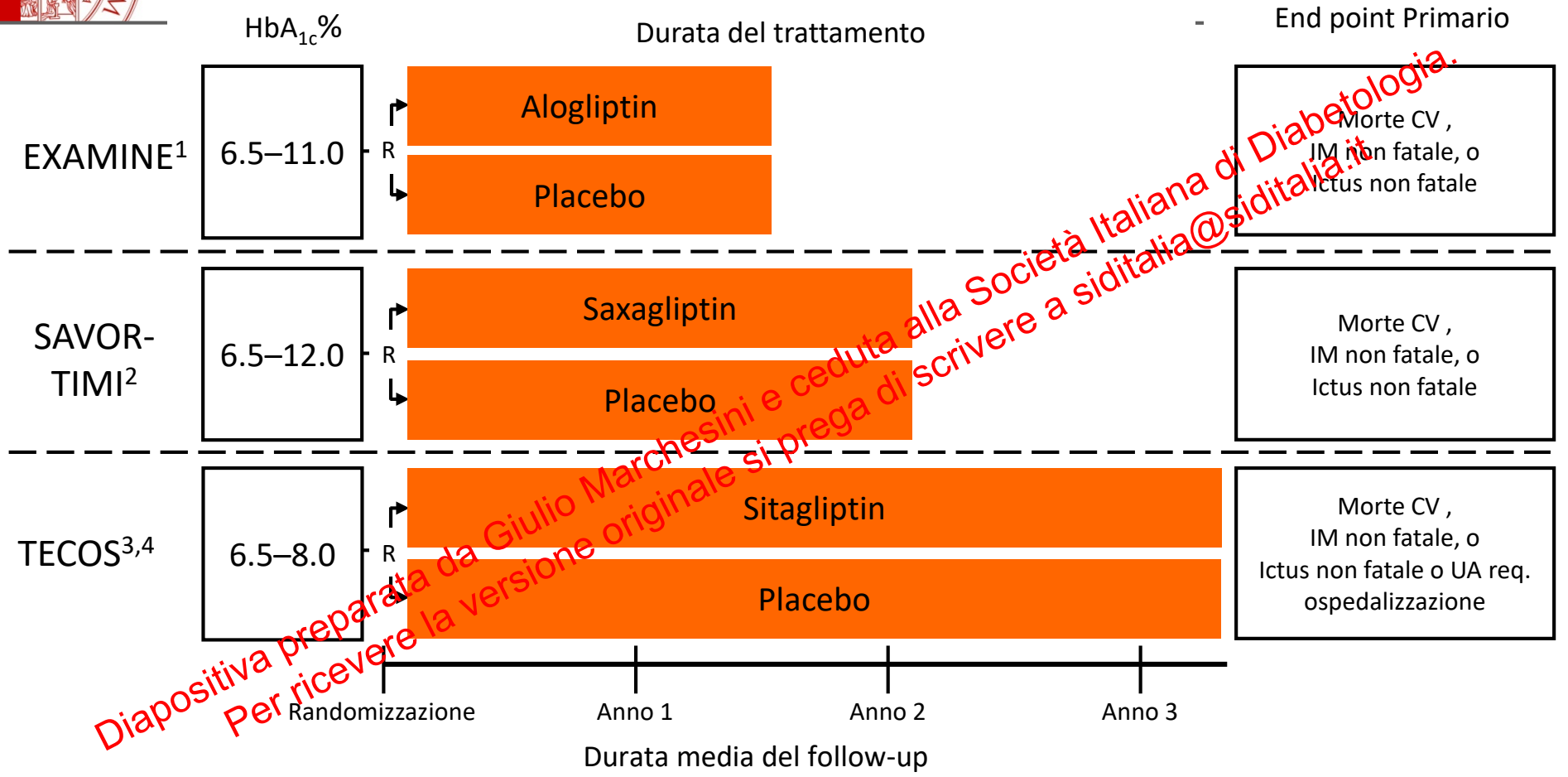
Del Prato, Diabetologia 2009

Analisi di risultato

Factors associated with the probability to achieve hemoglobin A1c <7% at 3-4 month assessment or later for the three drugs in the AIFA monitoring database, identified by logistic regression analysis in the population enrolled by centers with follow-up > 80%.

	Exenatide		Sitagliptin		Vildagliptin	
	No. events/ No. at risk^	OR (95% CI)	No. events/ No. at risk^	OR (95% CI)	No. events/ No. at risk^	OR (95% CI)
Hemoglobin A1c at baseline (%)	1864/7651	0.51 [0.49-0.54]	3779/10824	0.47 [0.45-0.49]	1681/4504	0.51 [0.47-0.55]
Age (years/10)	1864/7651	1.00 [0.95-1.06]°	3779/10824	1.00 [0.96-1.04]°	1681/4504	0.99 [0.93-1.05]°
Diabetes duration (years/10)	1864/7651	1.00 [0.98-1.02]°	3779/10824	0.79 [0.75-0.84]	1681/4504	0.71 [0.65-0.79]
Treatment duration (months)	1864/7651	1.03 [1.02-1.04]	3779/10824	1.01 [1.00-1.02]	1681/4504	0.99 [0.98-1.00]
Body mass index at baseline (kg/m^2/5)	1864/7651	1.01 [1.00- 1.01]°	3779/10824	0.99 [0.98- 1.00]°	1681/4504	1.00 [0.99- 1.01]°
Associated treatment						
Metformin (yes/no)	1012/3325	1.48 [1.33-1.65]	2529/6560	1.41 [1.30-1.53]	1475/3758	1.46 [1.23-1.73]
Sulfonylureas (yes/no)	102/486	0.67[0.44- 1.02]°	155/500	1.04 [0.86-1.25]°	146/605	1.20 [0.85-1.70]°
Metformin + Sulfonylureas (yes/no)	750/3837	0.73 [0.65-0.81]	934/3292	0.70 [0.64-0.77]	-----	-----*
Glitazones (yes/no)	-----	-----*	136/409	0.99 [0.80- 1.21]°	59/141	1.20 [0.85- 1.70]°

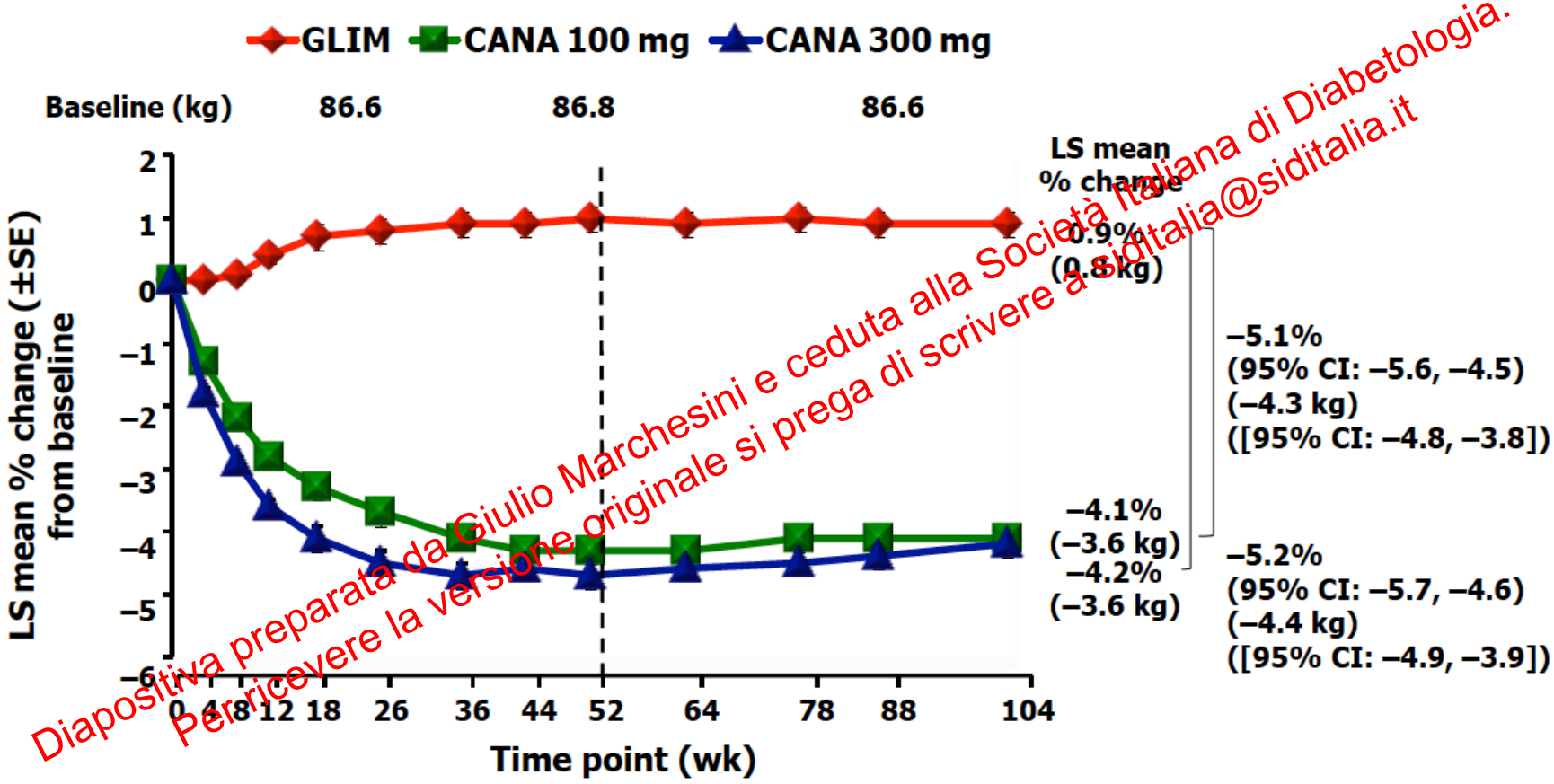
EXAMINE, SAVOR-TIMI e TECOS



EXAMINE = Examination of Cardiovascular Outcomes: Alogliptin vs Standard of Care in Patients With Type 2 Diabetes Mellitus and Acute Coronary Syndrome;SAVOR-TIMI = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus Trial-Thrombolysis in Myocardial Infarction; TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin. CV = cardiovascular; MI = myocardial infarction; UA = unstable angina.

White WB et al. *N Engl J Med.* 2013;369:1327–1335. Scirica BM et al. *N Engl J Med* 2013;369:1317–1326. Green JB et al. *Am Heart J.* 2013;166:983–989.e7. 4. Bethel MA et al. *Diabetes Obes Metab*. 2015; 10.1111/dom.12441.

Canaglifozin – Effects on body weight

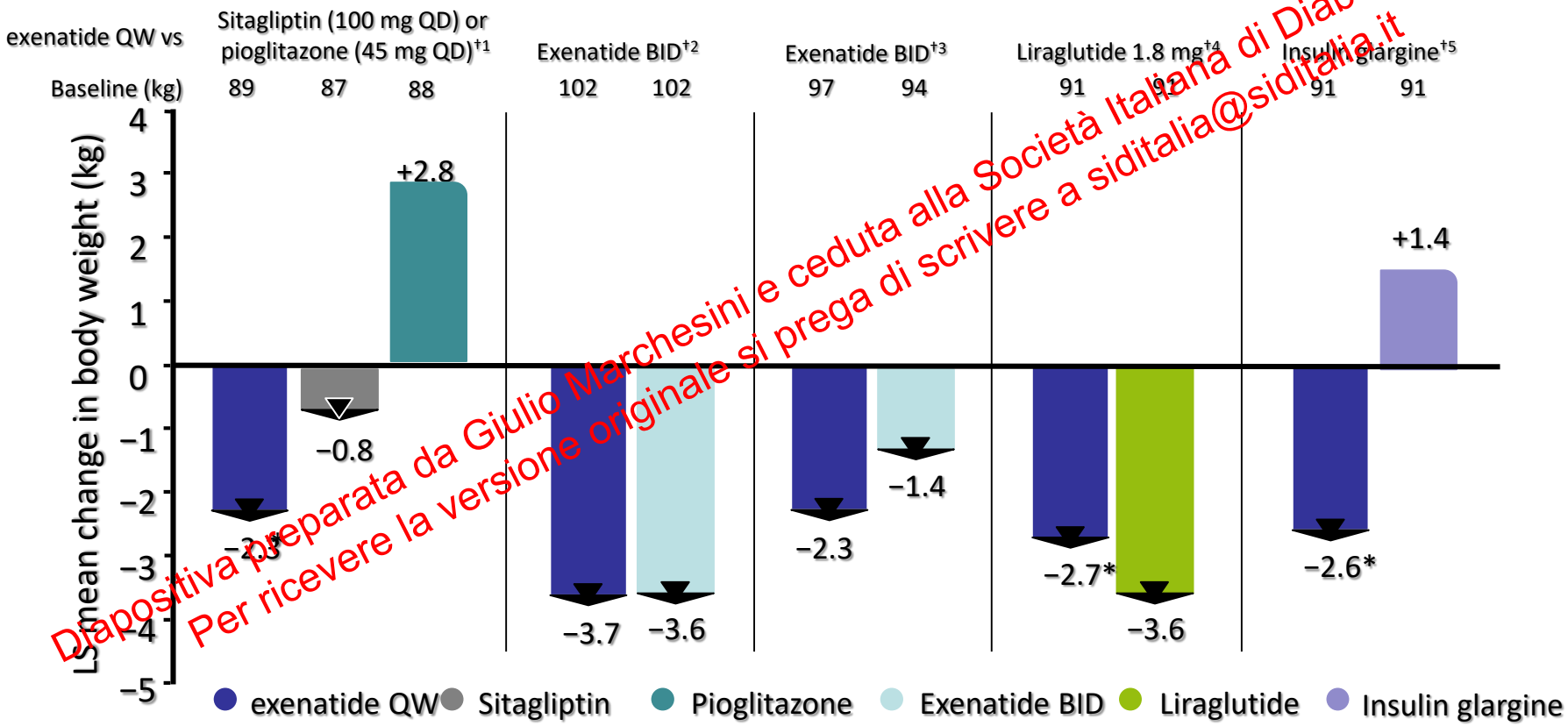


*N = 1,450 (Baseline); N = 1,425 (Week 4); N = 1,436 (Week 8); N = 1,438 (Weeks 12, 18, 26, 36, 44, 52, 64, 78, 88, and 104).

DURATION trials

Change in body weight from baseline

†Exenatide QW is not indicated for the management of obesity, and weight change was a secondary endpoint in clinical trials.

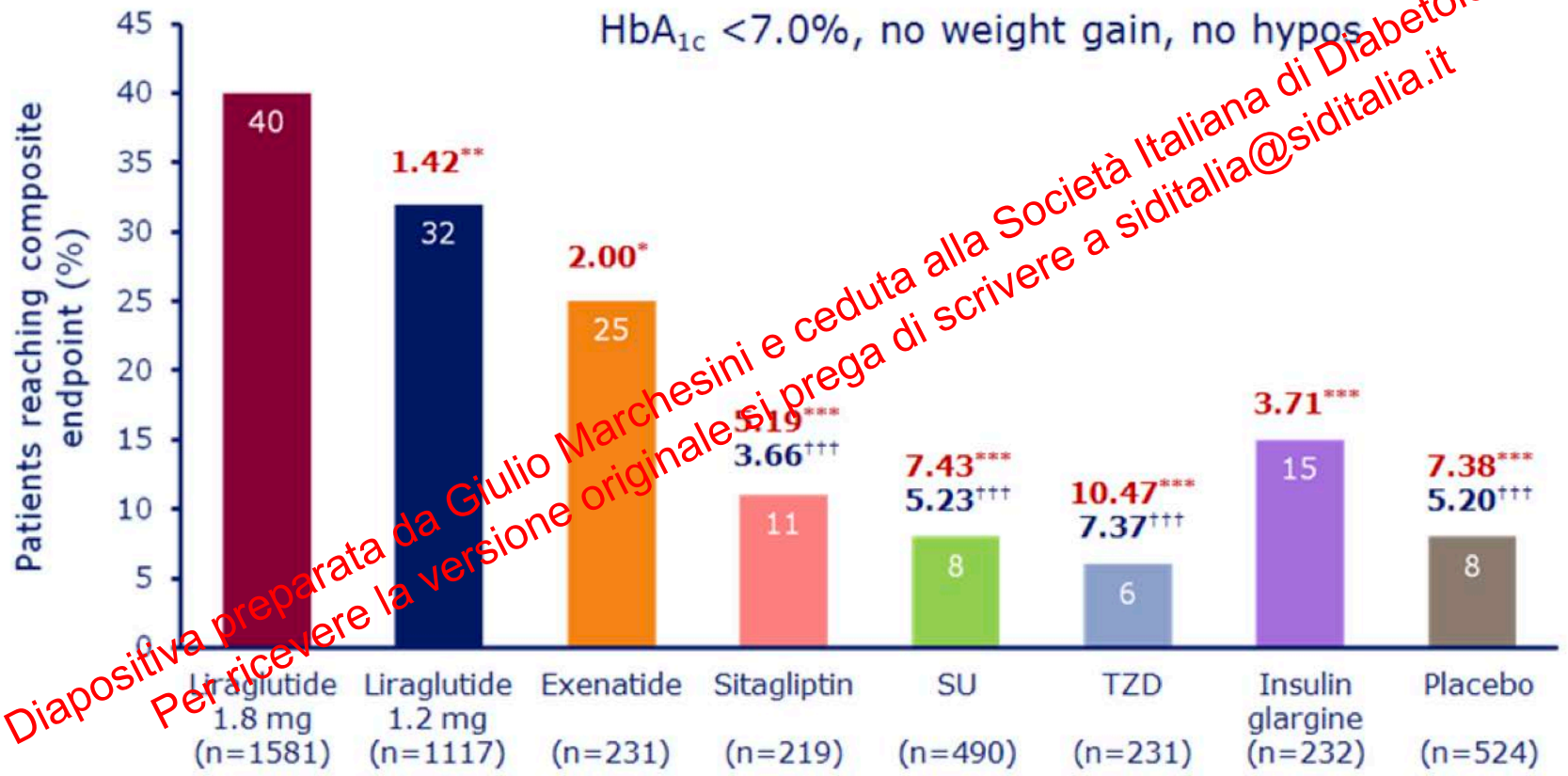


Data from 24–30 Weeks. *$P<0.05$ vs each comparator; †ITT population.

1. Bergenstal RM, et al. *Lancet*. 2010;376:431-439; 2. Drucker DJ, et al. *Lancet*. 2008;372:1240-1250; 3. Blevins T, et al. *J Clin Endocrin Metab*. 2011;96:1301-1310; 4. Buse JB, et al. *Lancet*. 2013;381(9861):117-124; 5. Diamant M, et al. *Lancet*. 2010;375:2234-2243.

Composite endpoint

Hba1c <7% + No weight gain + No confirmed hypos



Odds-ratio of achieving composite endpoint with liraglutide 1.8 mg is superior, with *p<0.01; **p<0.001, ***p<0.0001
Odds-ratio of achieving composite endpoint with liraglutide 1.2 mg is superior, with †††p<0.0001

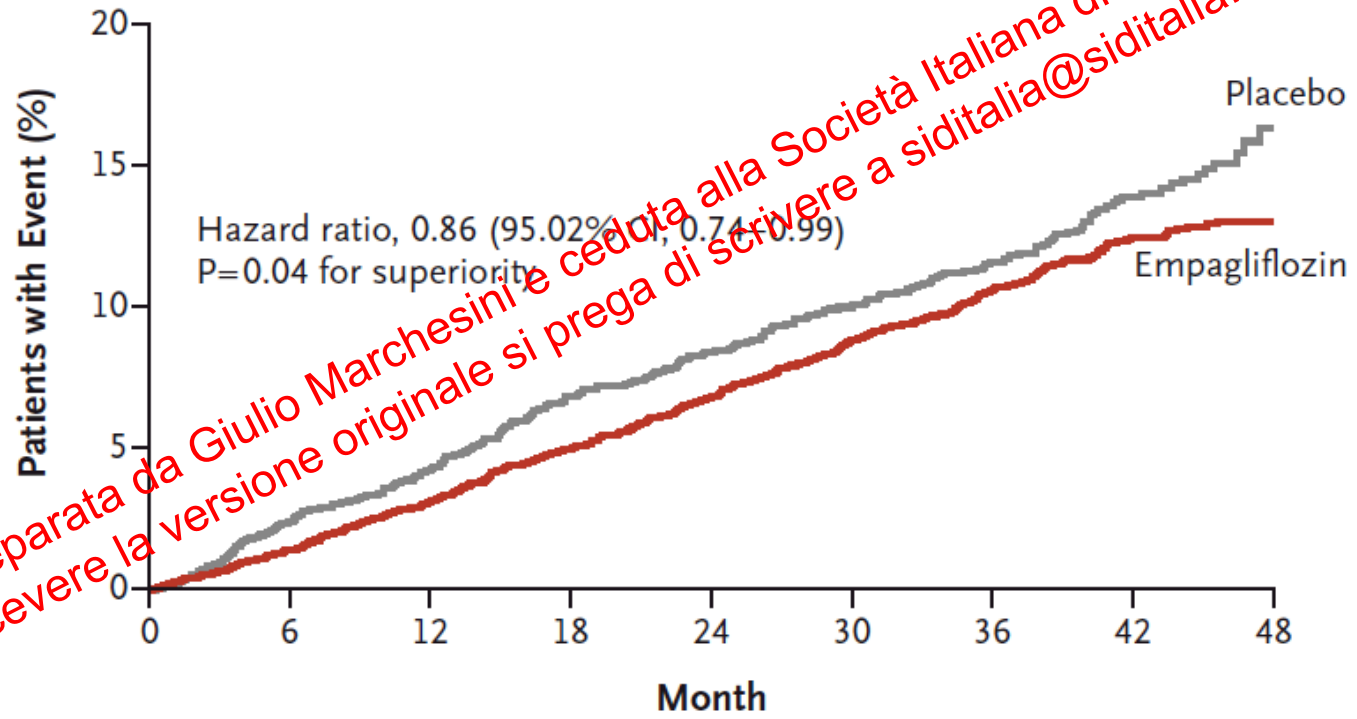
*p<0.01 vs. liraglutide 1.8 mg

Zinman *et al. Diabetes* 2009;58(Suppl. 1):A143–4

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

A Primary Outcome

Death from CV causes, nonfatal MI, or nonfatal stroke



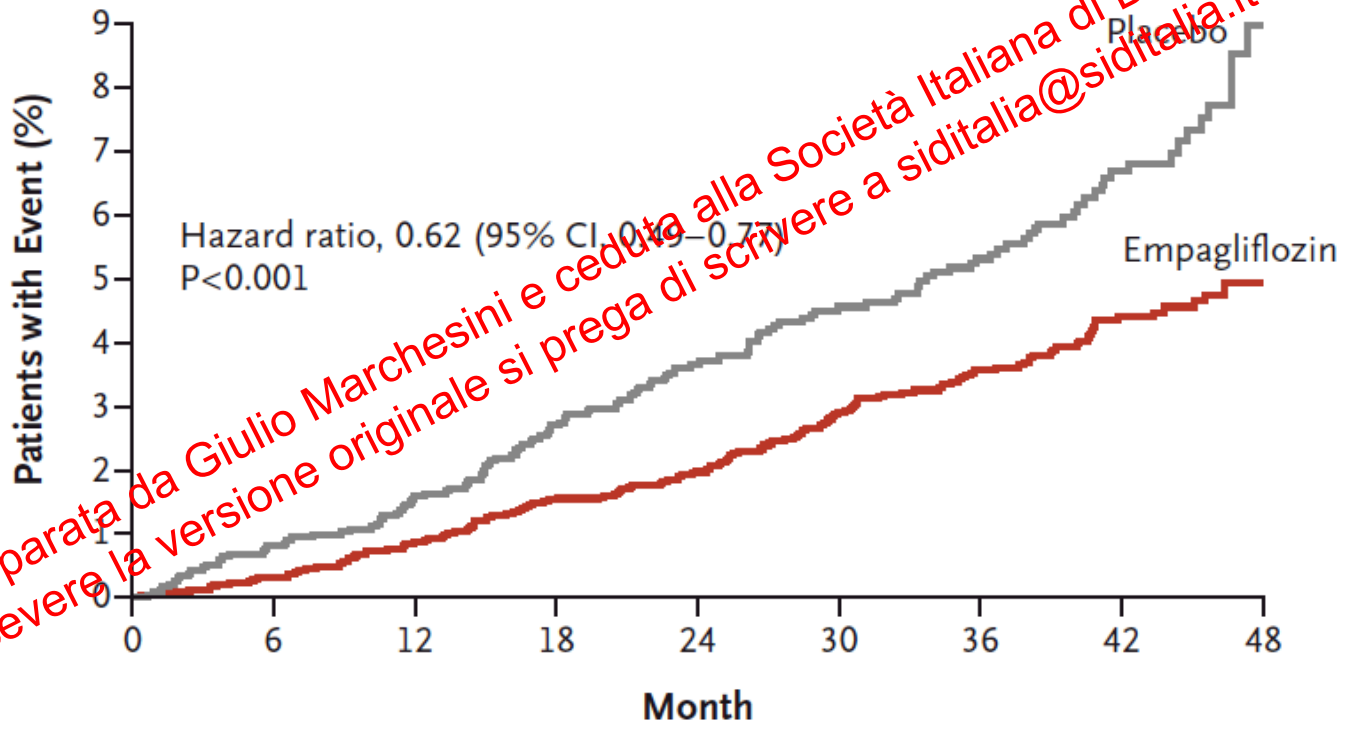
No. at Risk

Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

Zinman, N Engl J Med 2015

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

B Death from Cardiovascular Causes

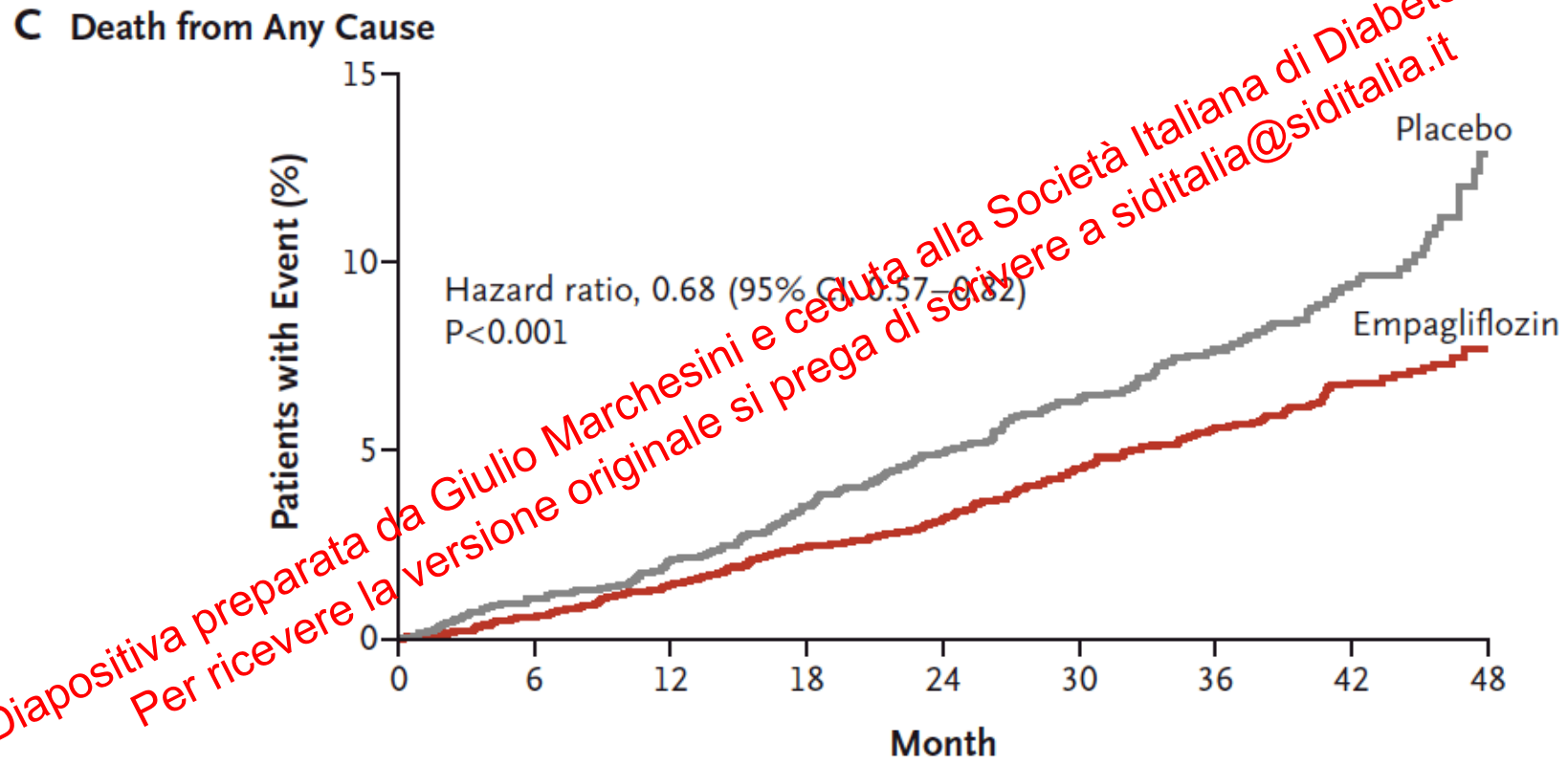


No. at Risk

Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Zinman, N Engl J Med 2015

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes



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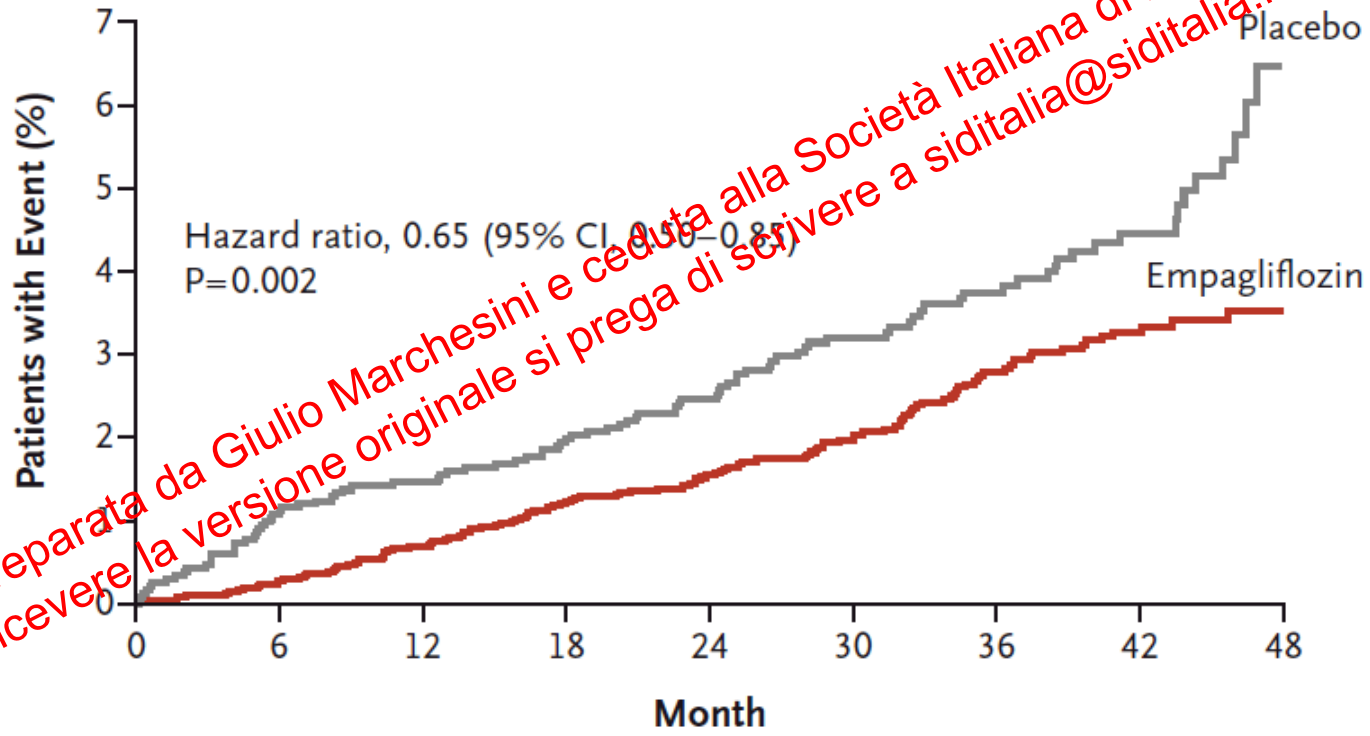
Zinman, N Engl J Med 2015

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

D Hospitalization for Heart Failure



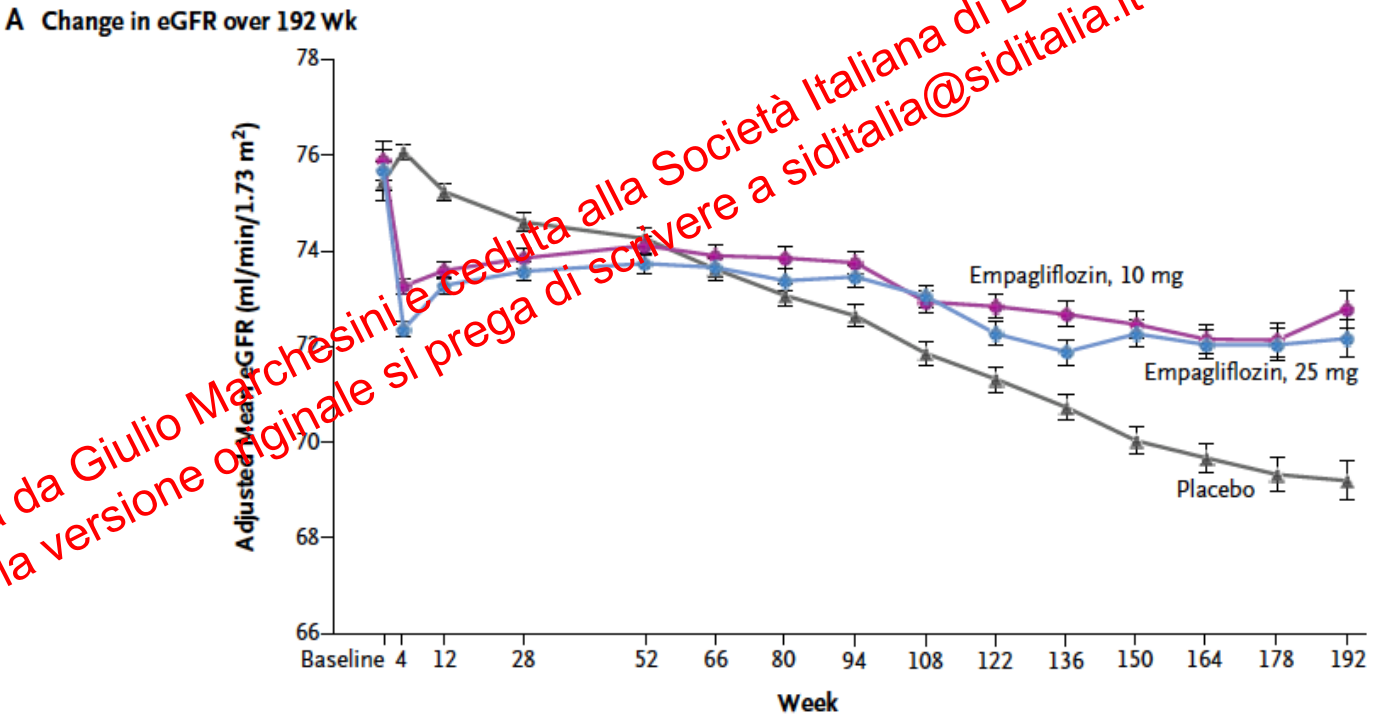
No. at Risk

Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

Zinman, N Engl J Med 2015

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

In the recent EMPA-REG OUTCOME trial, the primary goal was to assess cardiovascular outcomes. Here we report the results of a prespecified secondary objective of that trial, which was to examine the effects of empagliflozin on micro-vascular outcomes and, in particular, progression of kidney disease in patients with T2DM at high risk for cardiovascular events.

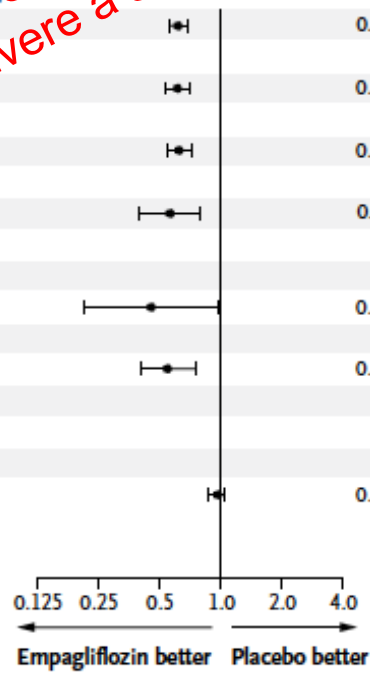


No. at Risk															
Placebo	2323	2295	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448
Empagliflozin, 10 mg	2322	2290	2264	2235	2162	2114	2012	2064	1839	1540	1314	1180	1024	785	513
Empagliflozin, 25 mg	2322	2288	2269	2216	2156	2111	2006	2067	1871	1563	1340	1207	1063	838	524
No. in Follow-up Analysis															
Total	7020	7020	6996	6931	6864	6765	6696	6651	6068	5114	4443	3961	3488	2707	1703

Wanner, N Engl J Med 2016

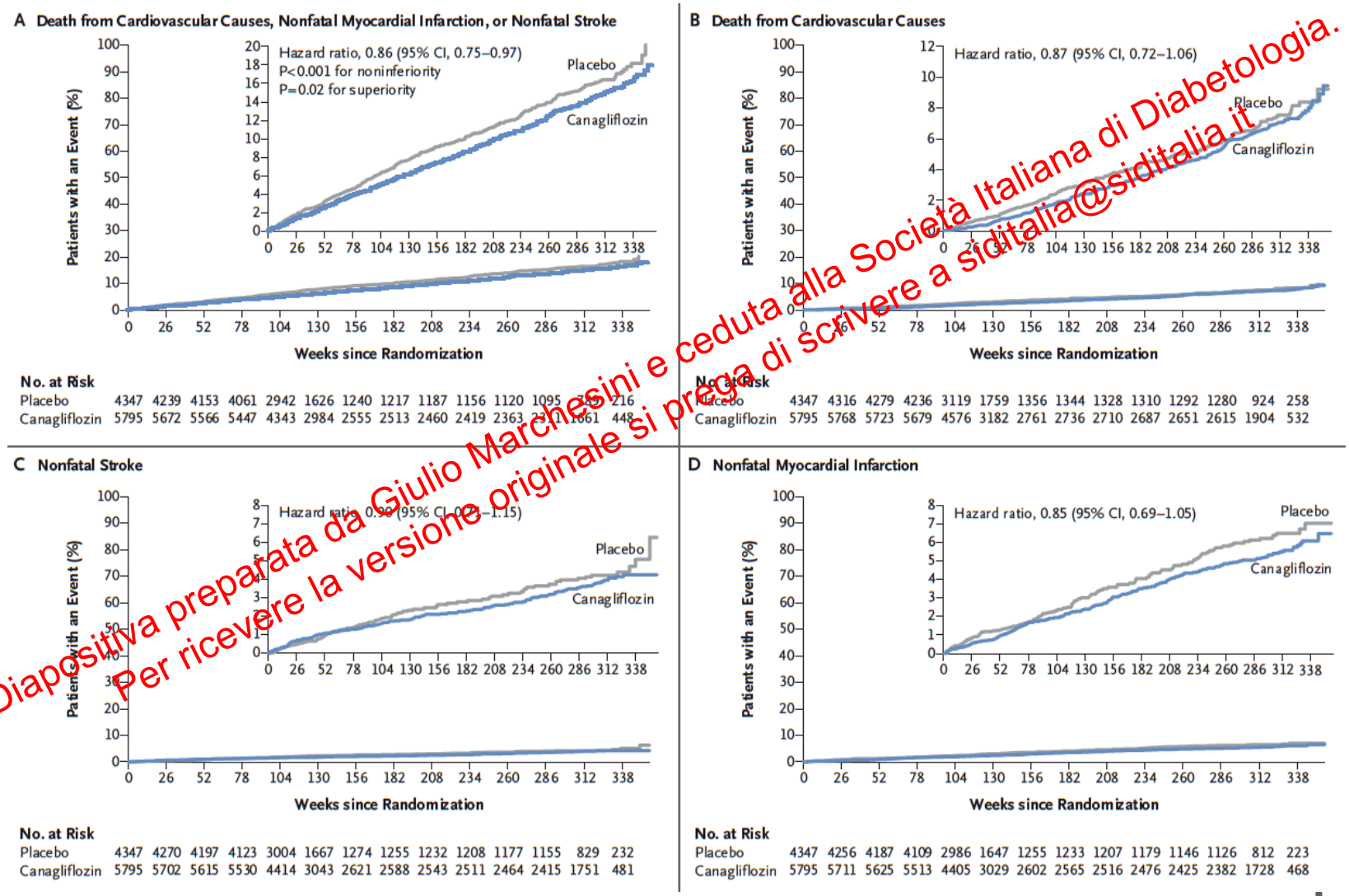
Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Renal Outcome Measure	Empagliflozin: no. with event/ no. analyzed (%)	Empagliflozin: rate/1000 patient-yr	Placebo: no. with event/ no. analyzed (%)	Placebo: rate/1000 patient-yr	Hazard Ratio (95% CI)	P Value
Incident or worsening nephropathy or cardiovascular death	675/4170 (16.2)	60.7	497/2102 (23.6)	85.9	0.61 (0.55–0.69)	<0.001
Incident or worsening nephropathy	525/4124 (12.7)	47.8	388/2061 (18.8)	68.0	0.61 (0.53–0.70)	<0.001
Progression to macroalbuminuria	459/4091 (11.2)	41.8	330/2035 (16.2)	64.9	0.62 (0.54–0.72)	<0.001
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2	70/4645 (1.5)	5.5	60/2323 (2.6)	9.7	0.56 (0.39–0.79)	<0.001
Initiation of renal-replacement therapy	13/4687 (0.3)	1.0	14/2333 (0.6)	2.1	0.45 (0.21–0.97)	0.04
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2, initiation of renal-replacement therapy, or death from renal disease	81/4645 (1.7)	6.3	71/2323 (3.1)	11.5	0.54 (0.40–0.75)	<0.001
Incident albuminuria in patients with a normal albumin level at baseline	1430/2779 (51.5)	252.5	703/1374 (51.2)	266.0	0.95 (0.87–1.04)	0.25



Wanner, N Engl J Med 2016

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes



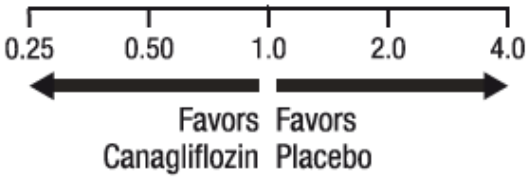
Neal, N Engl J Med 2017

Canagliflozin for Primary and Secondary Prevention of Cardiovascular Events

Results From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study)

● Secondary prevention □ Primary prevention ◇ Overall population

	Number of participants	Patients per 1000 patient-years: Canagliflozin	Patients per 1000 patient-years: Placebo	Hazard ratio (95% CI)	Interaction *P* value
CV death, nonfatal MI, or nonfatal stroke	796	34.1	41.3	0.82 (0.72–0.95)	0.18
	215	15.8	15.5	0.98 (0.74–1.30)	
	1011	26.9	31.5	0.86 (0.75–0.97)*	
CV death	362	14.8	16.8	0.86 (0.70–1.06)	0.44
	91	6.5	6.2	0.93 (0.60–1.43)	
	453	11.6	12.8	0.87 (0.72–1.06)	
Nonfatal MI	304	12.5	16.0	0.79 (0.63–0.99)	0.10
	70	5.5	4.4	1.21 (0.73–2.00)	
	374	11.1	11.6	0.85 (0.69–1.05)	
Nonfatal stroke	209	8.8	10.4	0.88 (0.67–1.16)	0.83
	66	4.5	5.0	0.97 (0.59–1.61)	
	274	7.1	8.4	0.90 (0.71–1.15)	
Hospitalization for any cause	2586	142.5	161.3	0.91 (0.84–0.99)	0.23
	980	84.4	86.3	1.01 (0.88–1.15)	
	3486	118.7	131.1	0.94 (0.88–1.00)	
Hospitalization for heart failure	198	7.3	11.3	0.68 (0.51–0.90)	0.91
	45	2.6	4.2	0.64 (0.35–1.15)	
	243	5.5	8.7	0.67 (0.52–0.87)	

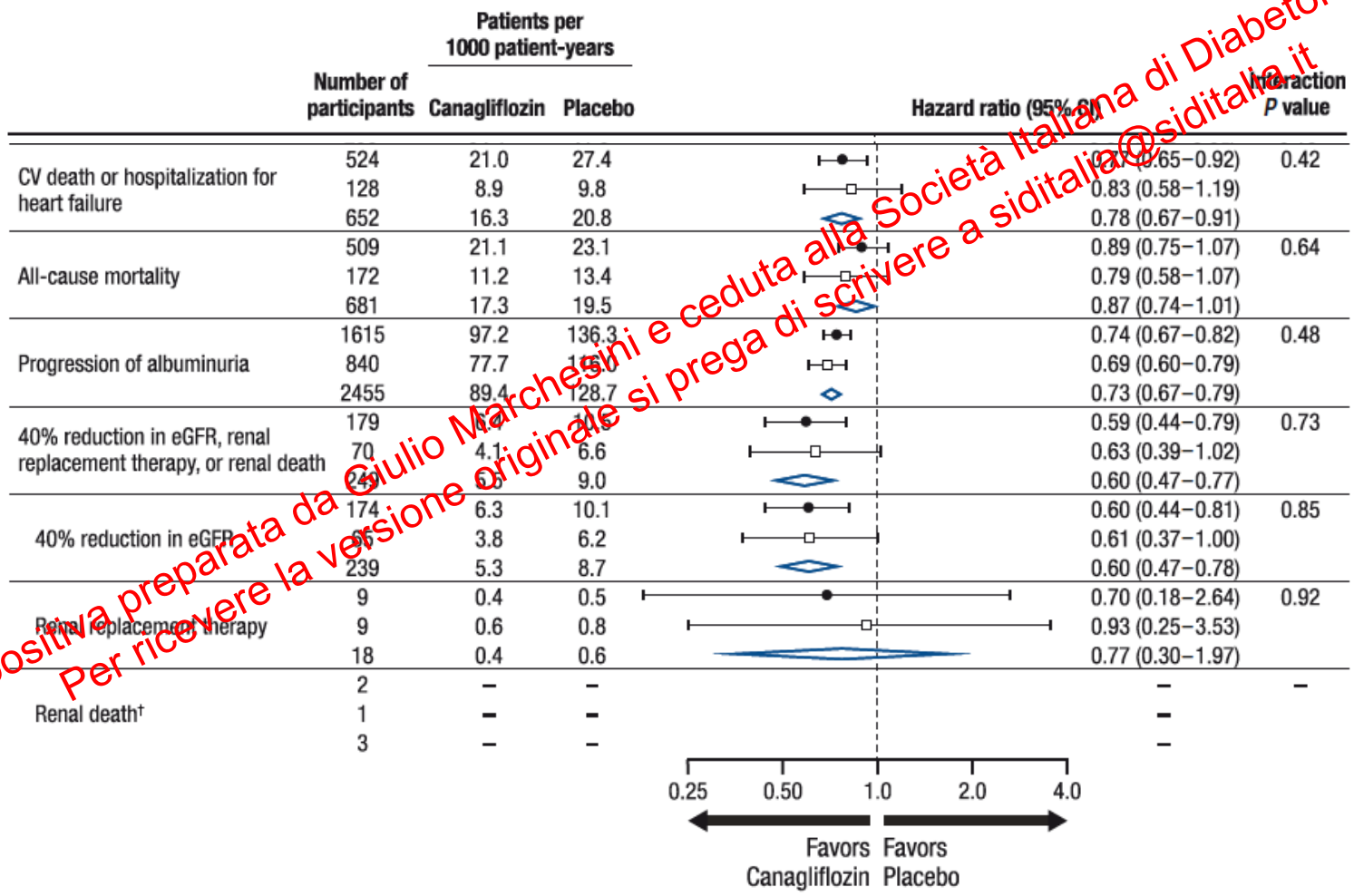


Mahaffey, Circulation (in press)

Canagliflozin for Primary and Secondary Prevention of Cardiovascular Events

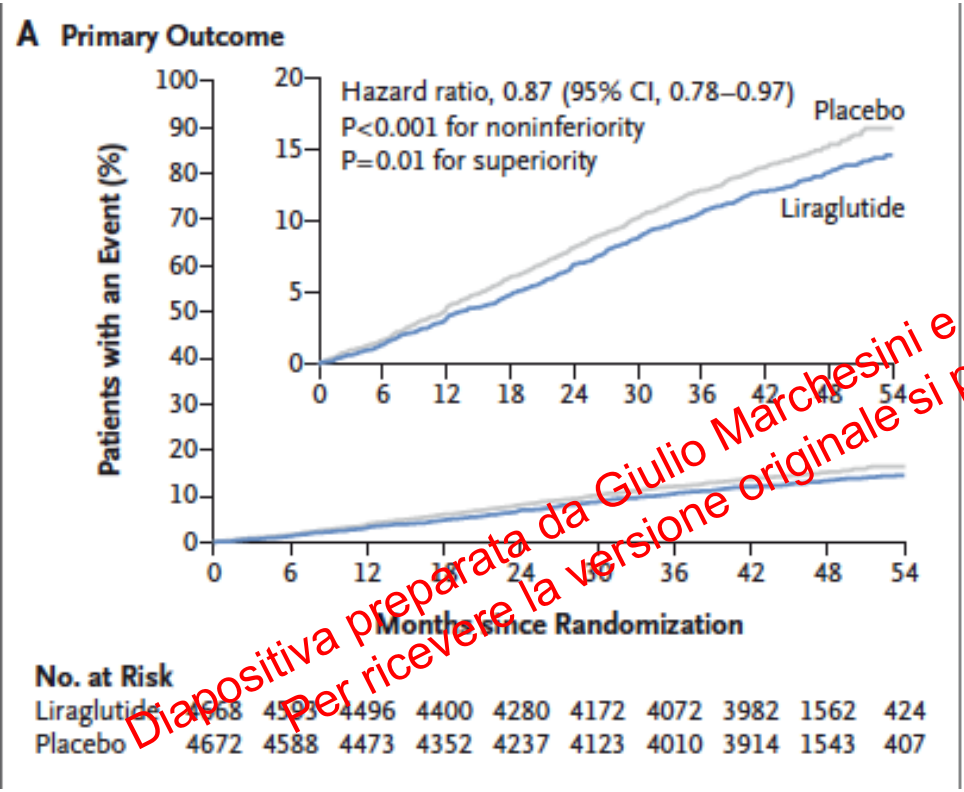
Results From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study)

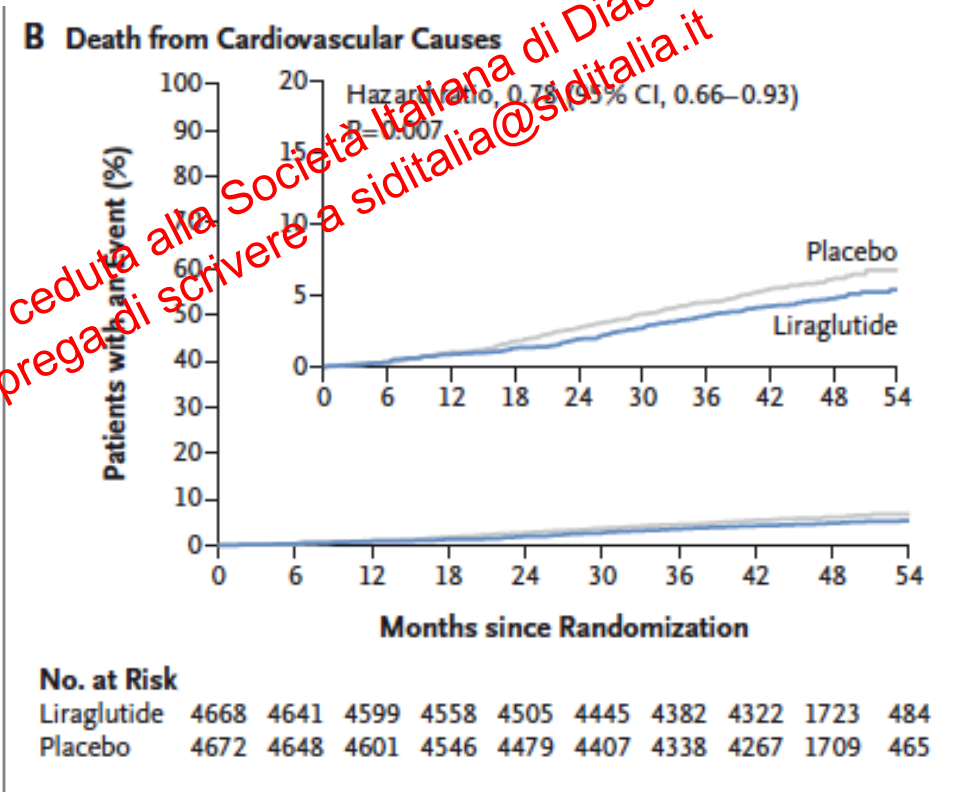
● Secondary prevention □ Primary prevention ◇ Overall population



Mahaffey, Circulation (in press)

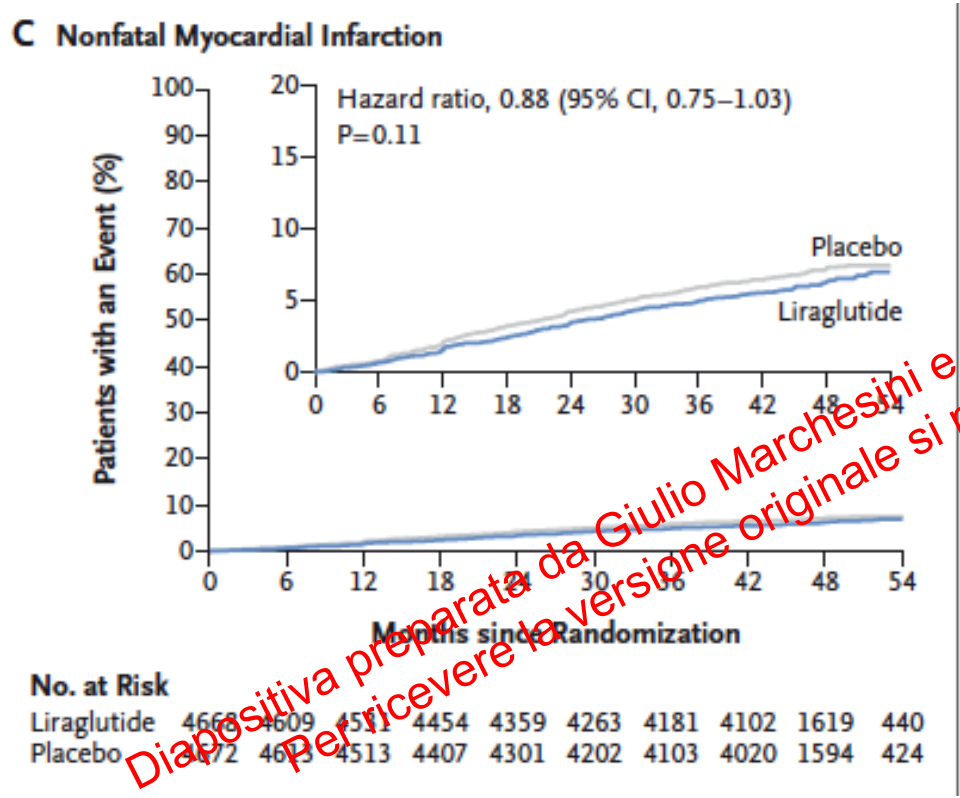
Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

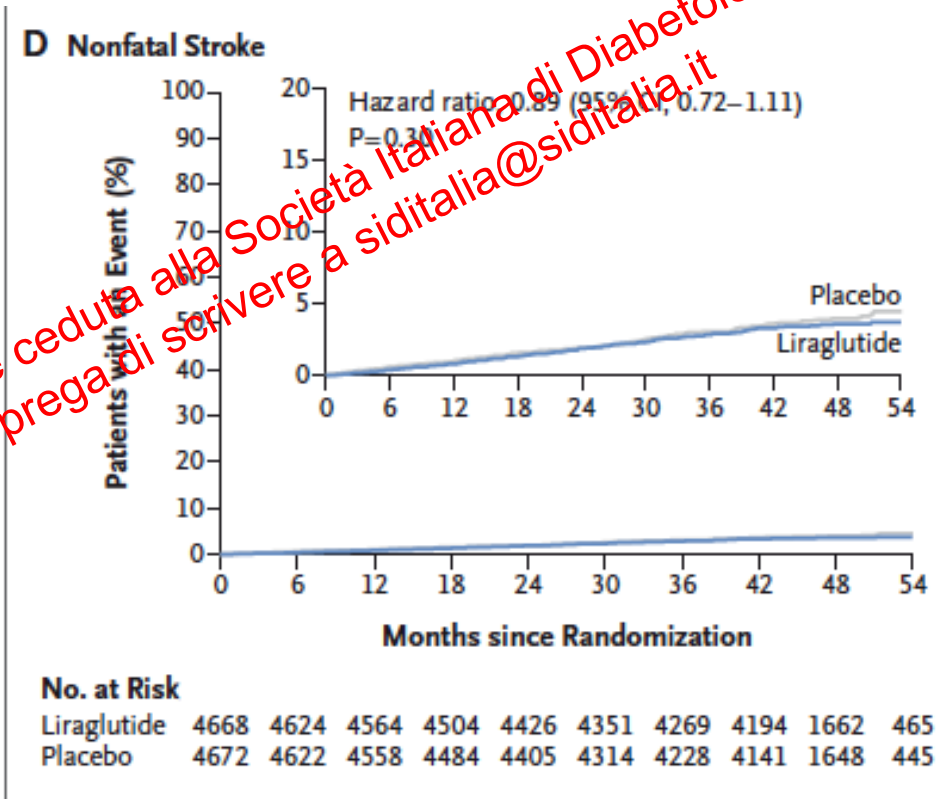




Primary composite outcome: first occurrence of death from cardiovascular causes, nonfatal (including silent) myocardial infarction, or nonfatal stroke.

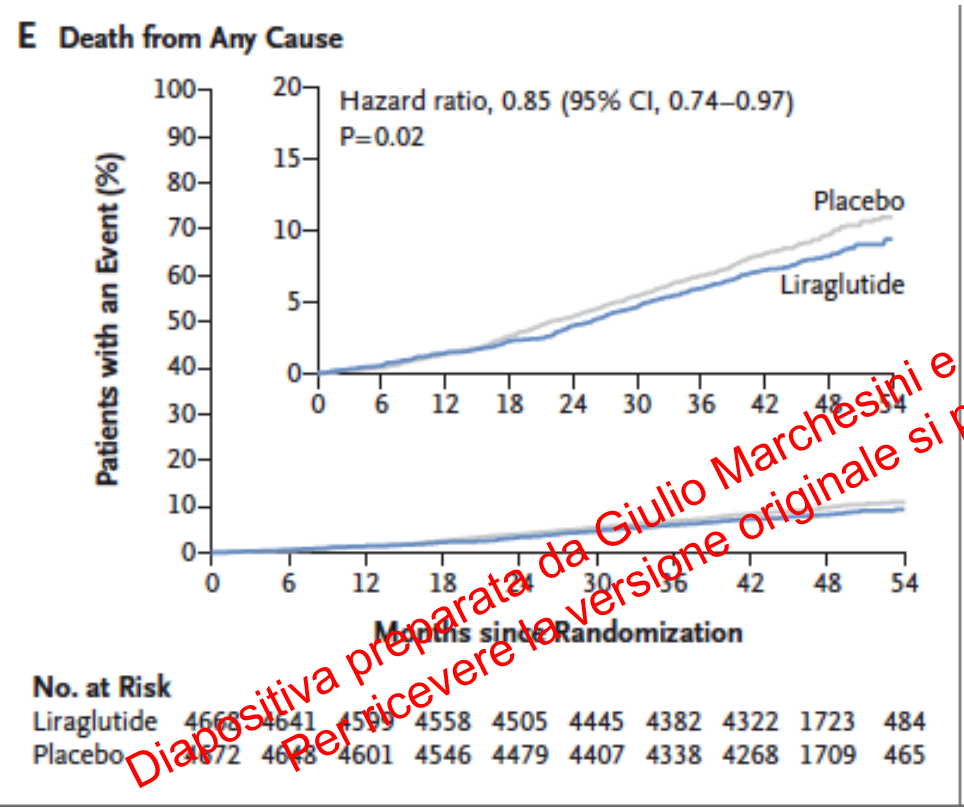
Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

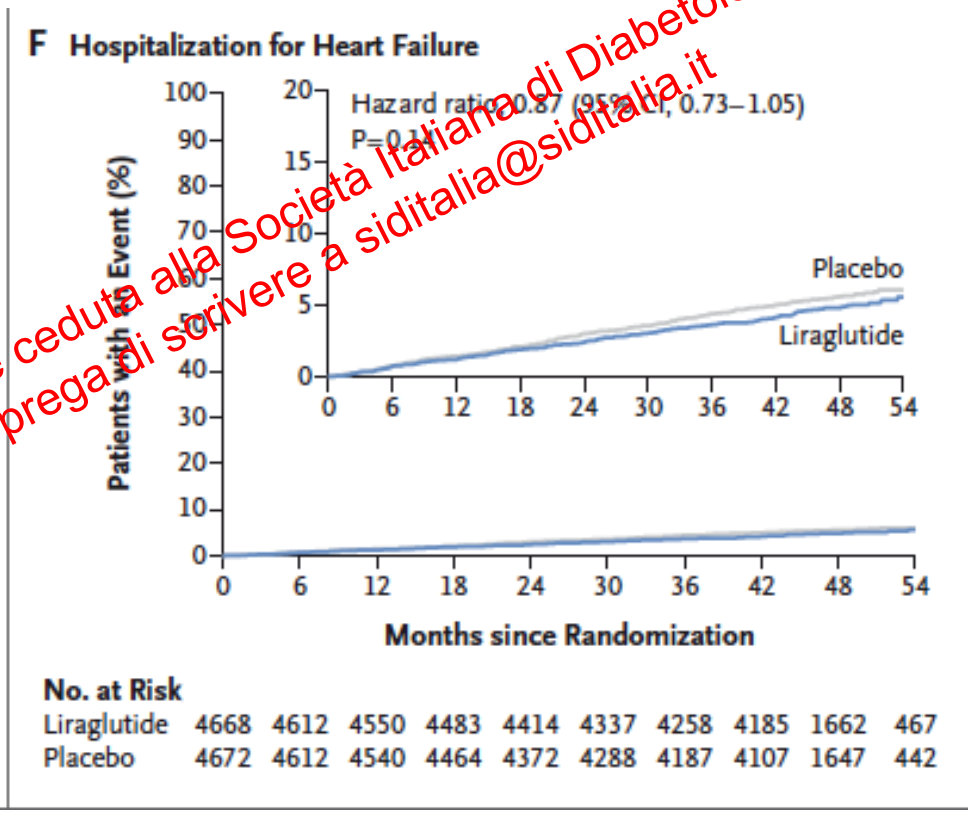




Exploratory outcomes: composite cardiovascular outcome (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina pectoris or heart failure), death from any cause, a composite renal and retinal microvascular outcome

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

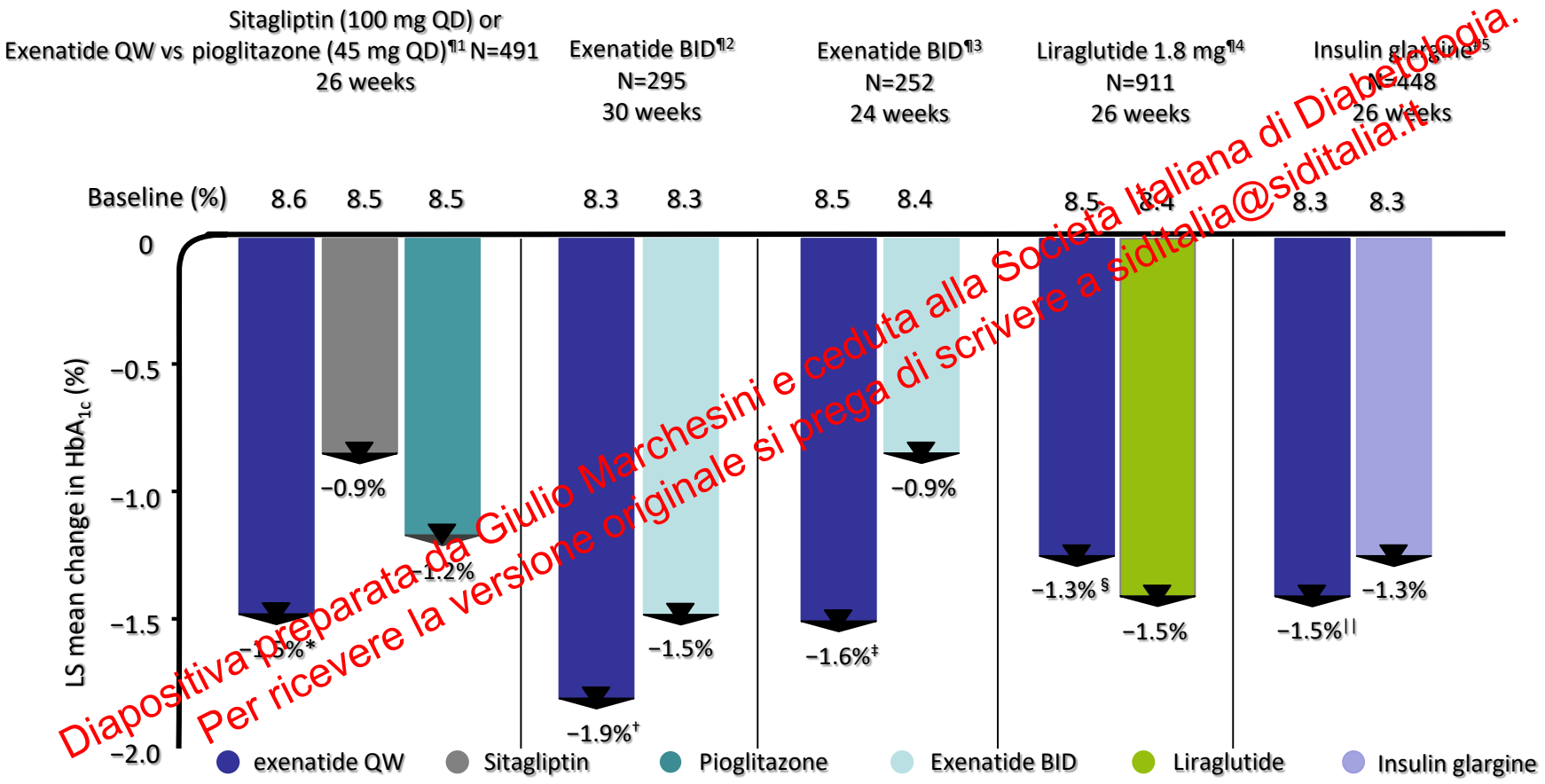




Exploratory outcomes: composite cardiovascular outcome (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina pectoris or heart failure), death from any cause, a composite renal and retinal microvascular outcome

DURATION trials

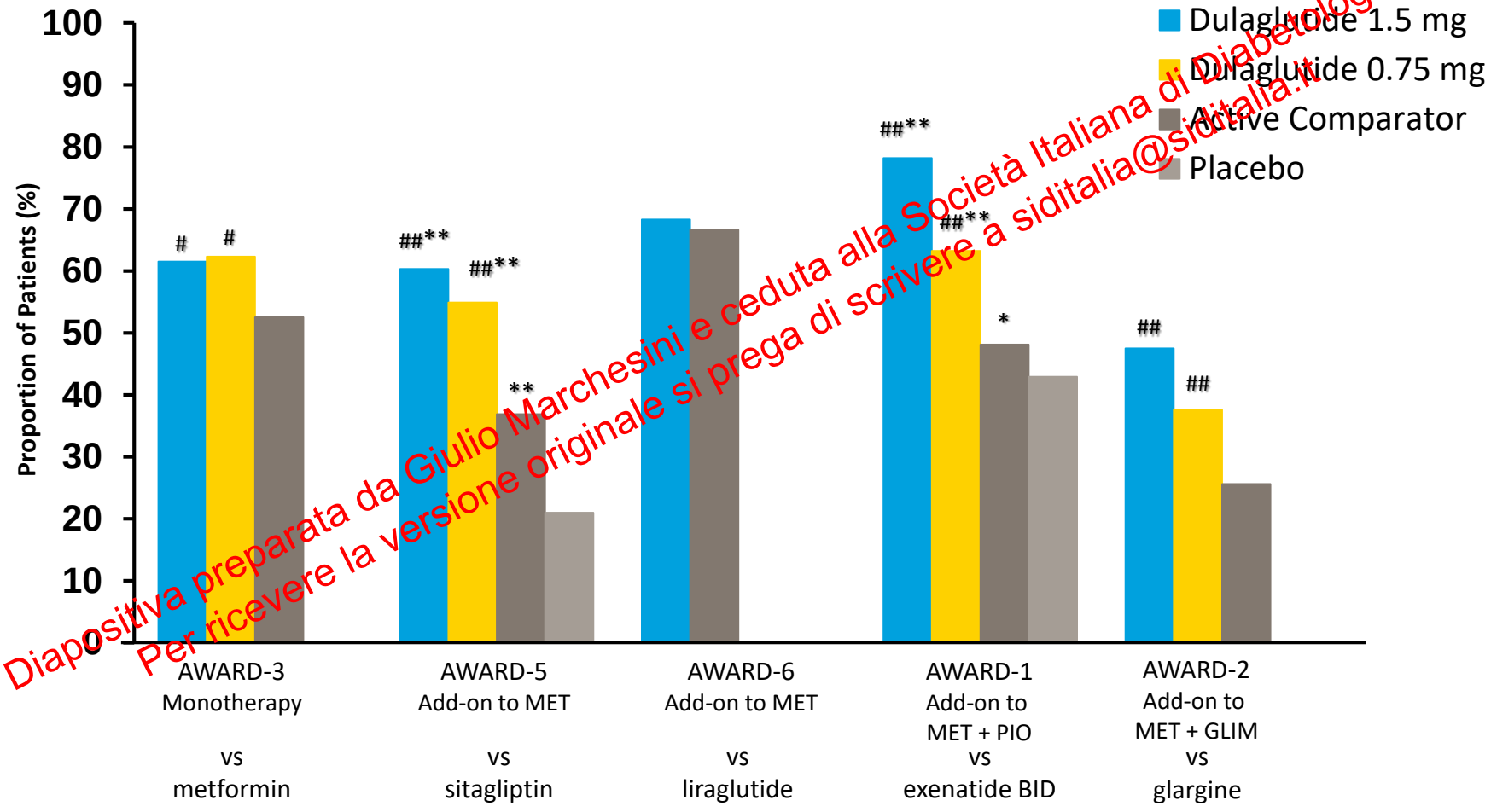
HbA_{1c} reductions of −1.3% to −1.9%



Data from 24–30 Weeks. *P<0.05 vs both; †P<0.01; ‡P<0.0001; §P=0.02; ||P=0.017; ¶ITT population; #Modified ITT population.

1. Bergenstal RM, et al. *Lancet*. 2010;376:431-439; 2. Drucker DJ, et al. *Lancet*. 2008;372:1240-1250; 3. Blevins T, et al. *J Clin Endocrin Metab*. 2011;96:1301-1310; 4. Buse JB, et al. *Lancet*. 2013;381(9861):117-124; 5. Diamant M, et al. *Lancet*. 2010;375:2234-2243.

Proportion of Patients Achieving HbA1c <7.0% and No Hypoglycemia at Week 26

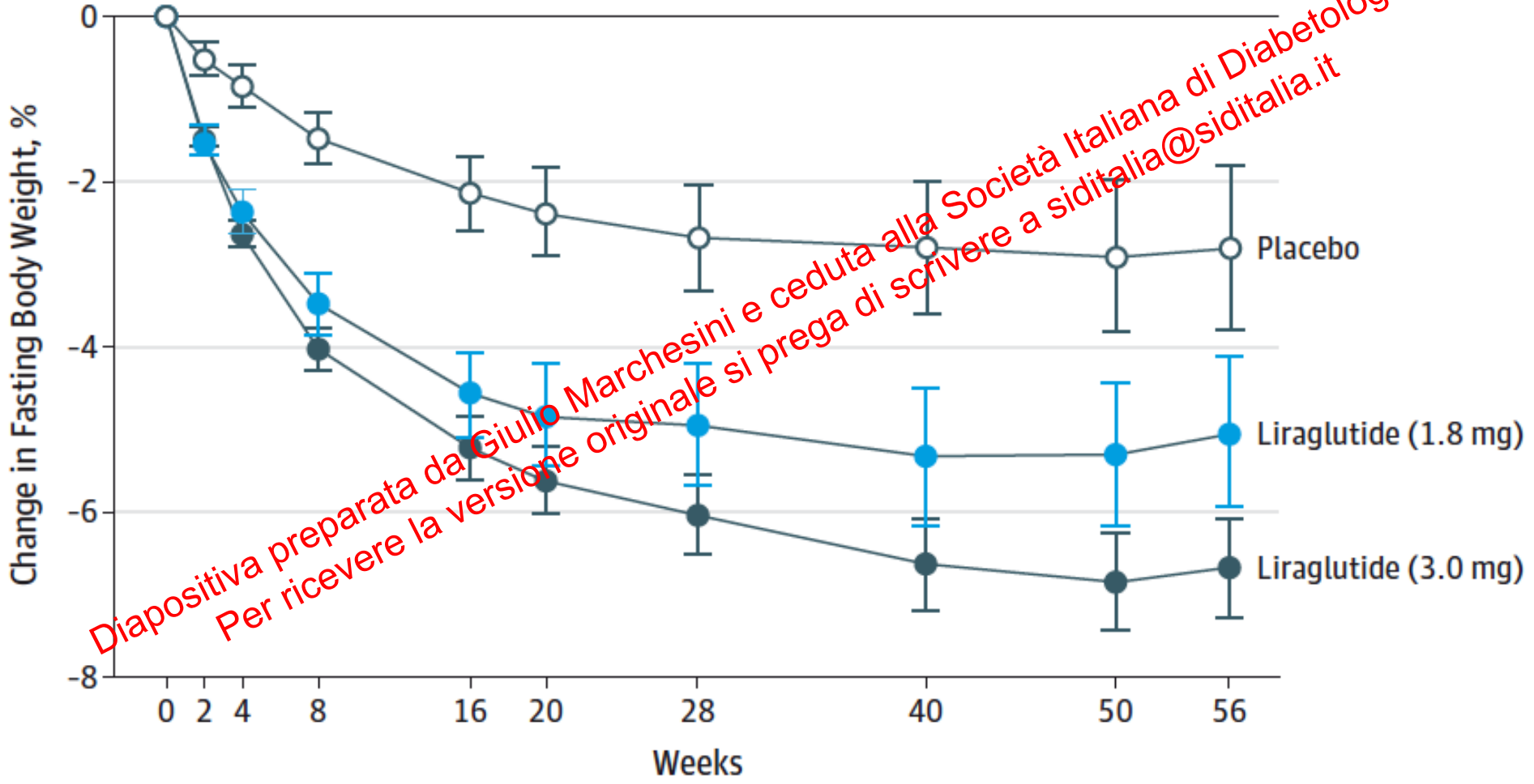


#p<.05 and ##p<.001 vs active comparator
*p<.05 and **p<.001 vs placebo

Dungan et al. *Diabetes Obes Metab* 2015;(Ahead of print)

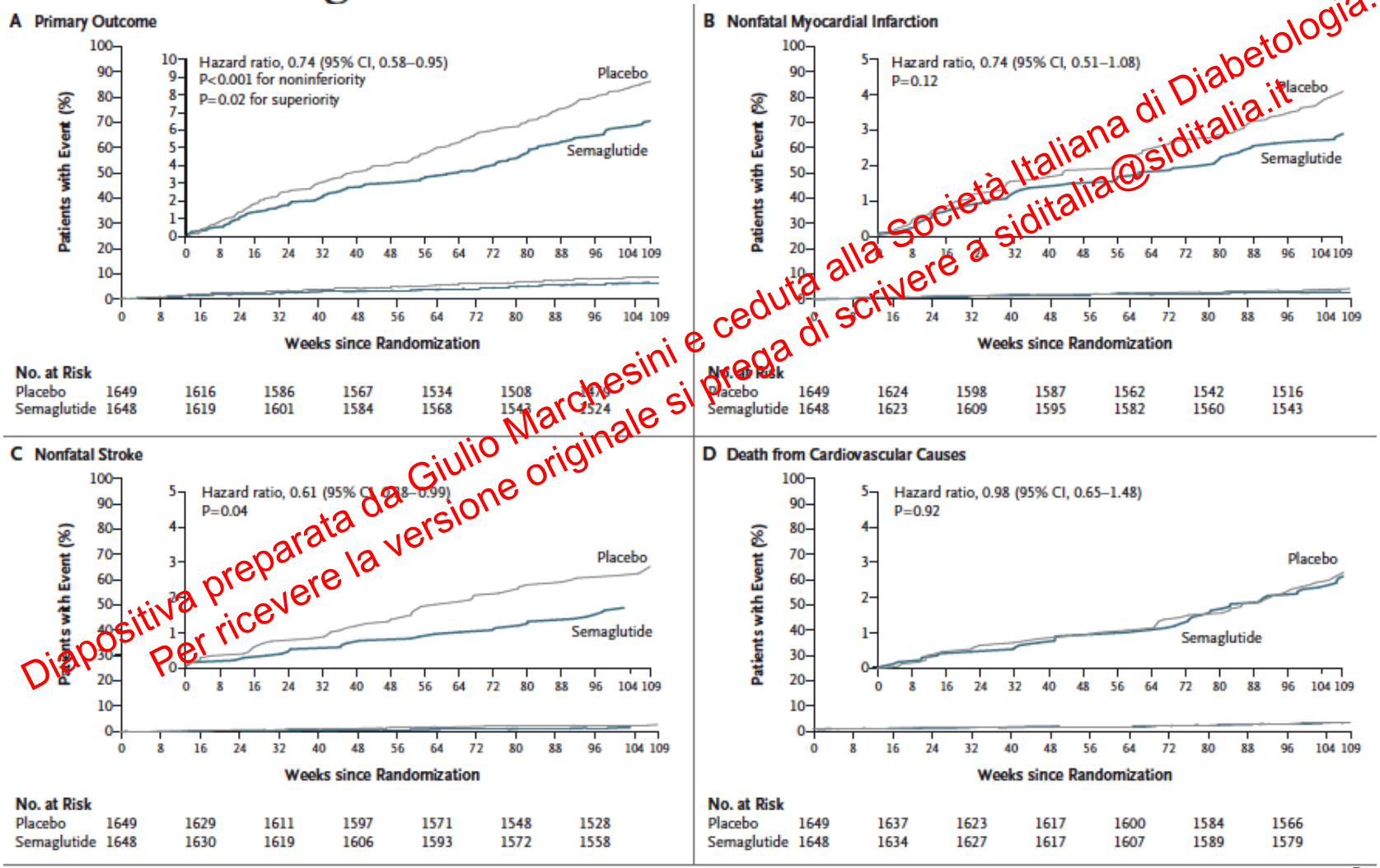
Efficacy of Liraglutide for Weight Loss Among Patients With Type 2 Diabetes

The SCALE Diabetes Randomized Clinical Trial



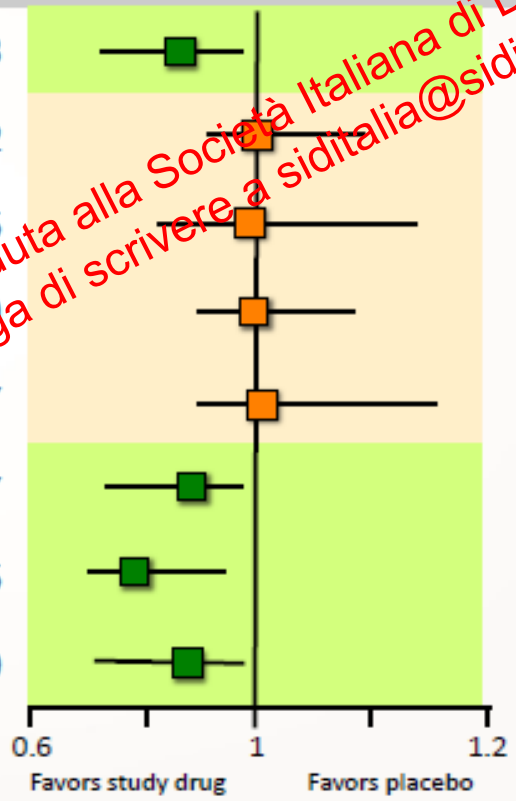
Davies, JAMA 2016

Semaglutide and Cardiovascular Outcomes



Effetto dei farmaci ipoglicemizzanti sul MACE-3 nel DM2

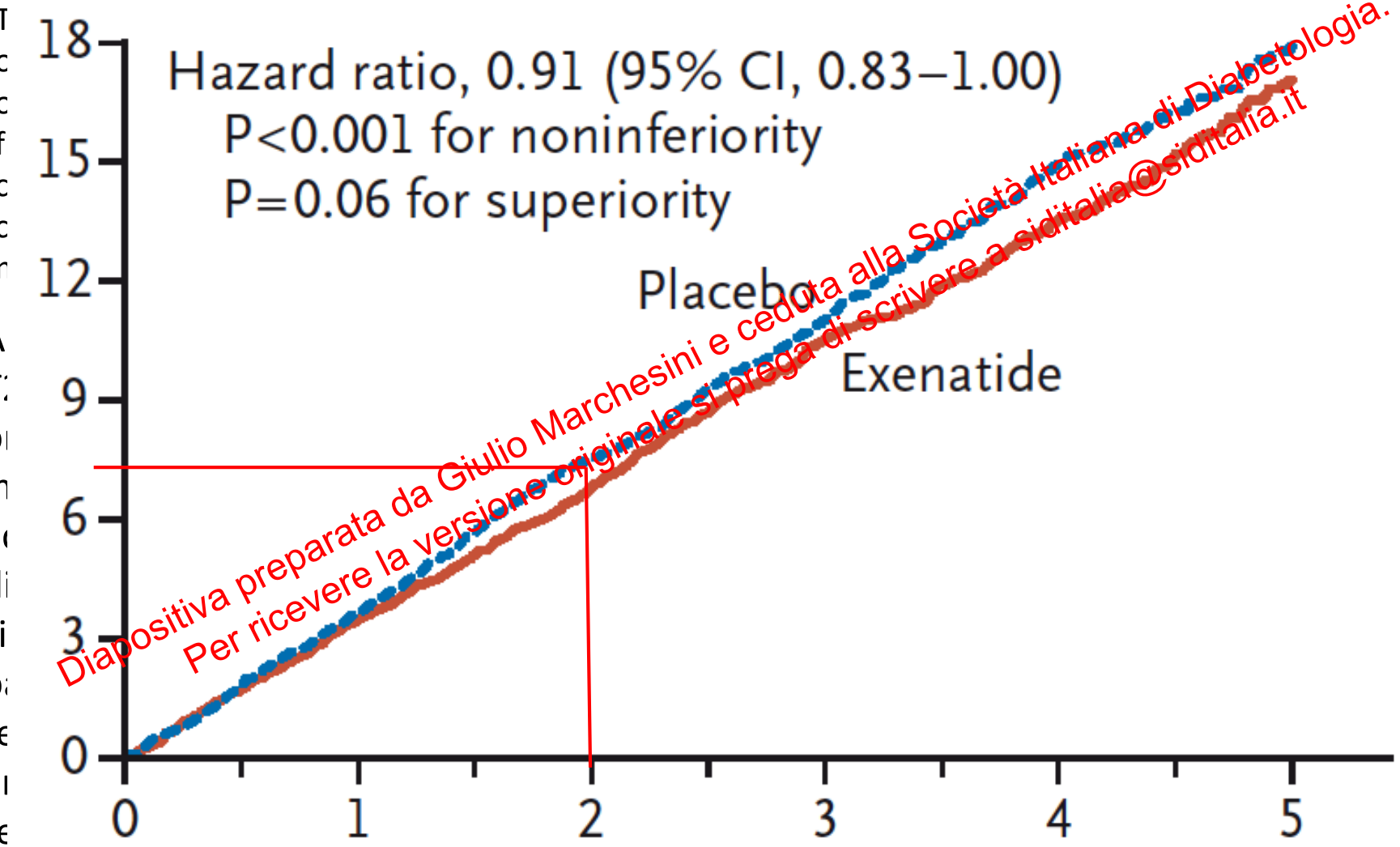
Study	Glucose-lowering drug	HR	95% CI	P-value
PROACTIVE	Pioglitazone	0.84	0.72-0.98	0.027
SAVOR	Saxagliptin	1.00	0.89-1.12	NS
EXAMINE	Alogliptin	0.96	0.80-1.15	NS
TECOS	Sitagliptin	0.99	0.89-1.10	NS
ELIXA	Lixisenatide	1.02	0.89-1.17	NS
LEADER	Liraglutide	0.87	0.78-0.97	0.010
SUSTAIN-6	Semaglutide	0.74	0.58-0.95	0.020
EMPA-REG	Empagliflozin	0.86	0.74-0.99	0.038



EXSCEL EXENATIDE HR 0.91 95 % IC 0,83-1 P < 0.001 per non inferiorita , p 0.06 per superiorita

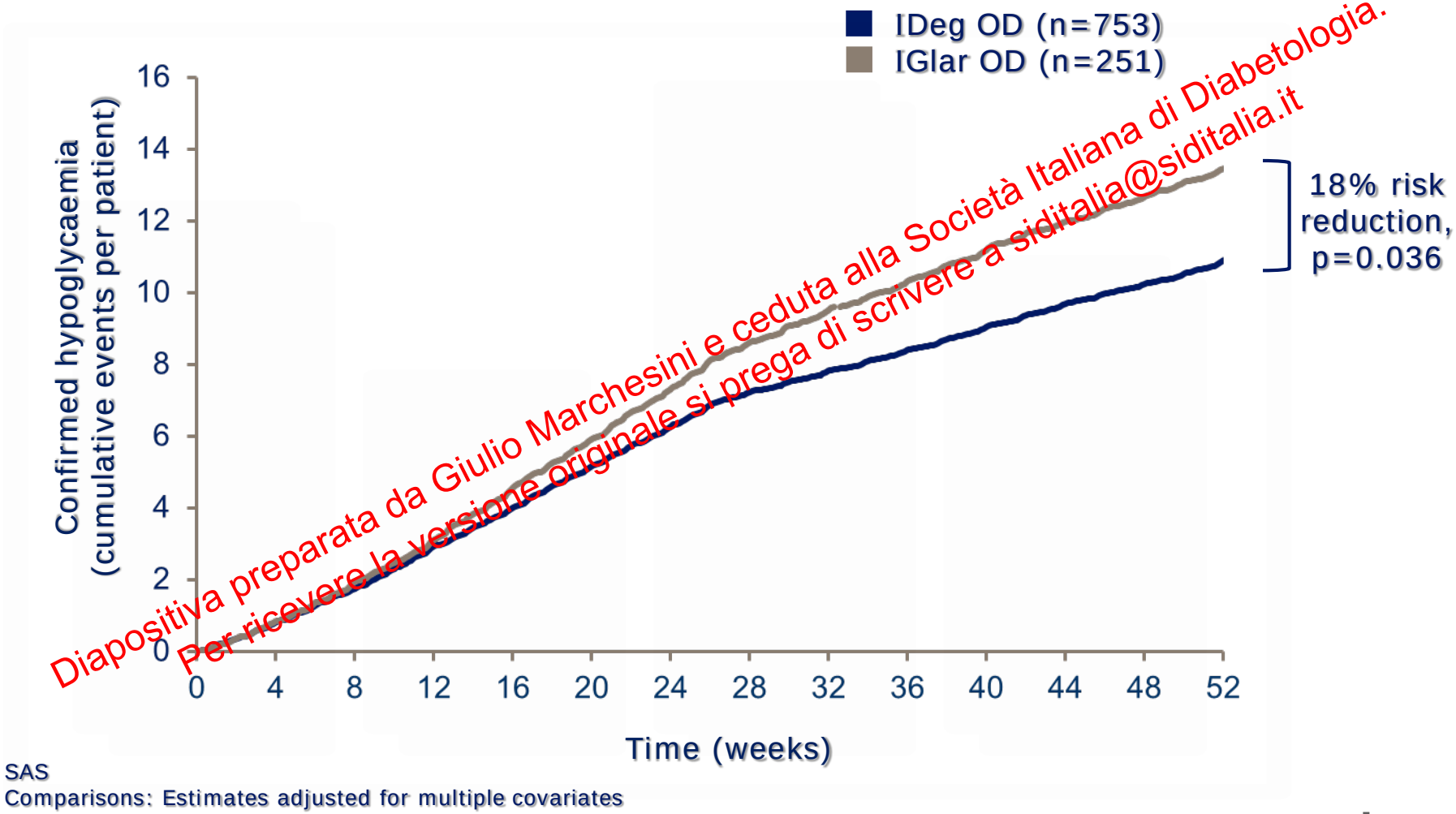
CANVAS HR 0,86 95 % IC 0.52-0,87 p 0,001 non inf eriorita , p0.02 per superiorita

Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes



Holman, N Engl J Med 2017

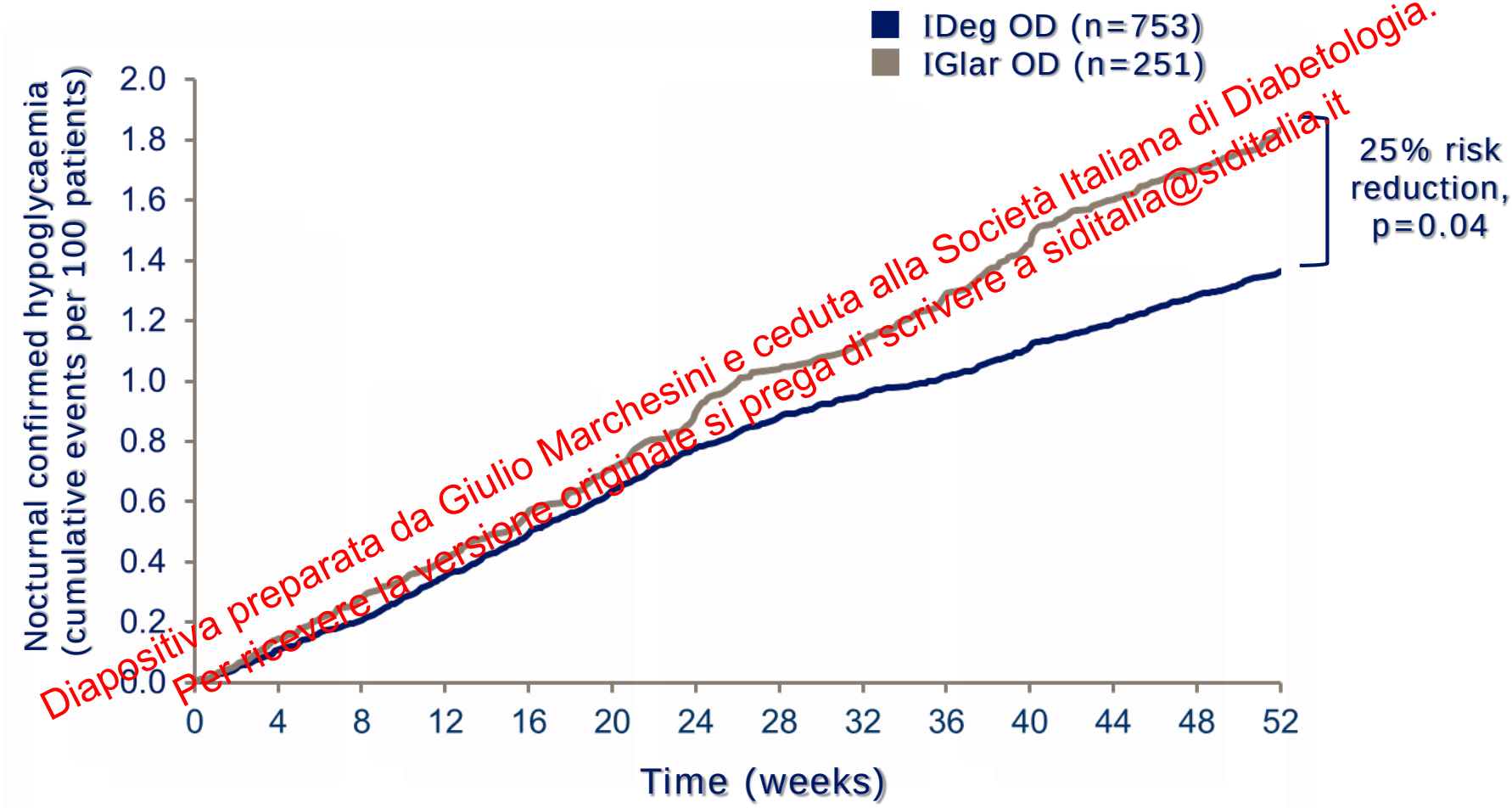
Confirmed hypoglycaemia



SAS
Comparisons: Estimates adjusted for multiple covariates

Garber A *et al. Lancet* 2012;379:1498-507

Nocturnal confirmed hypoglycaemia

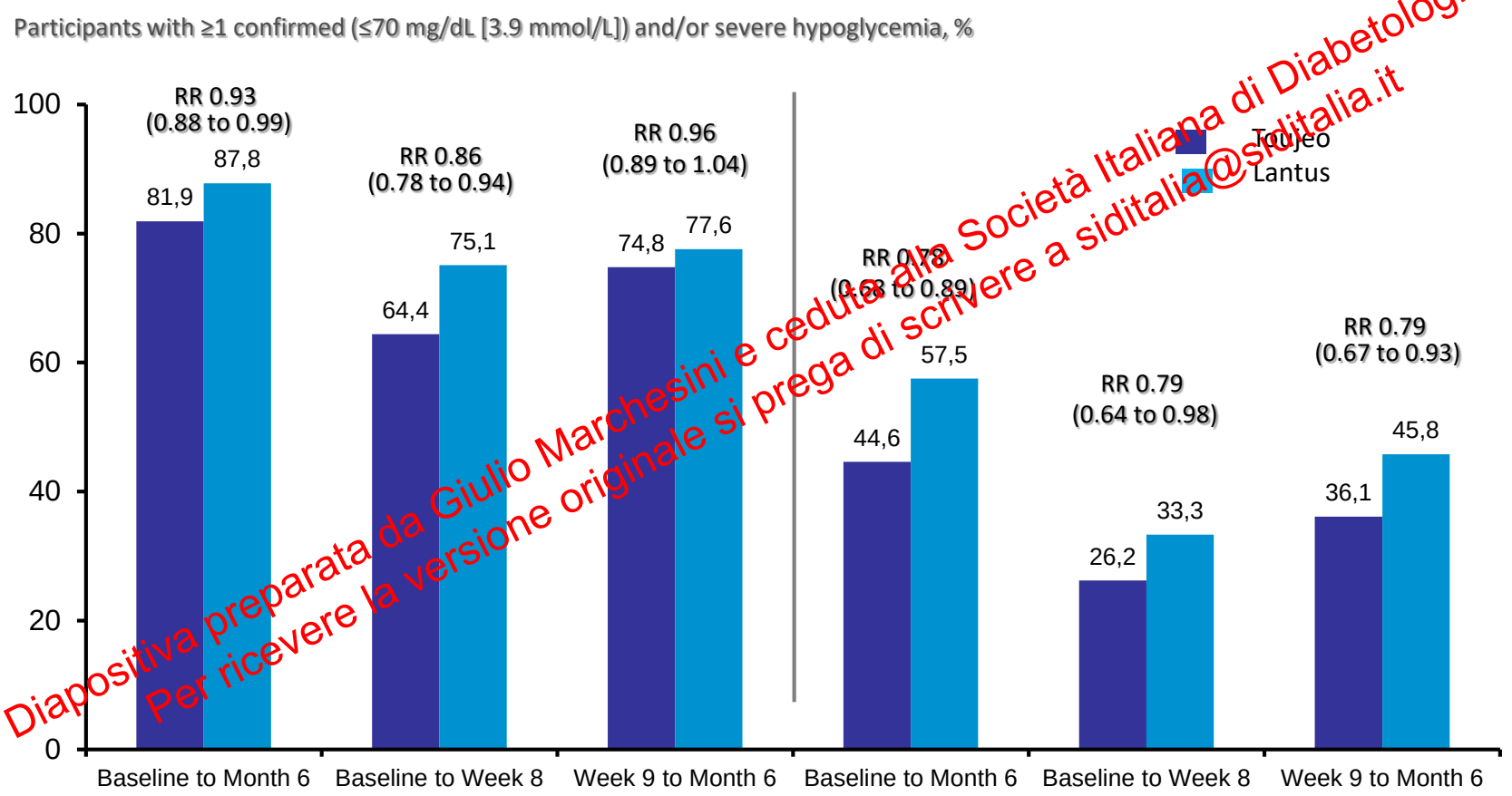


SAS
Comparisons: Estimates adjusted for multiple covariates

Garber A *et al. Lancet* 2012;379:1498-507

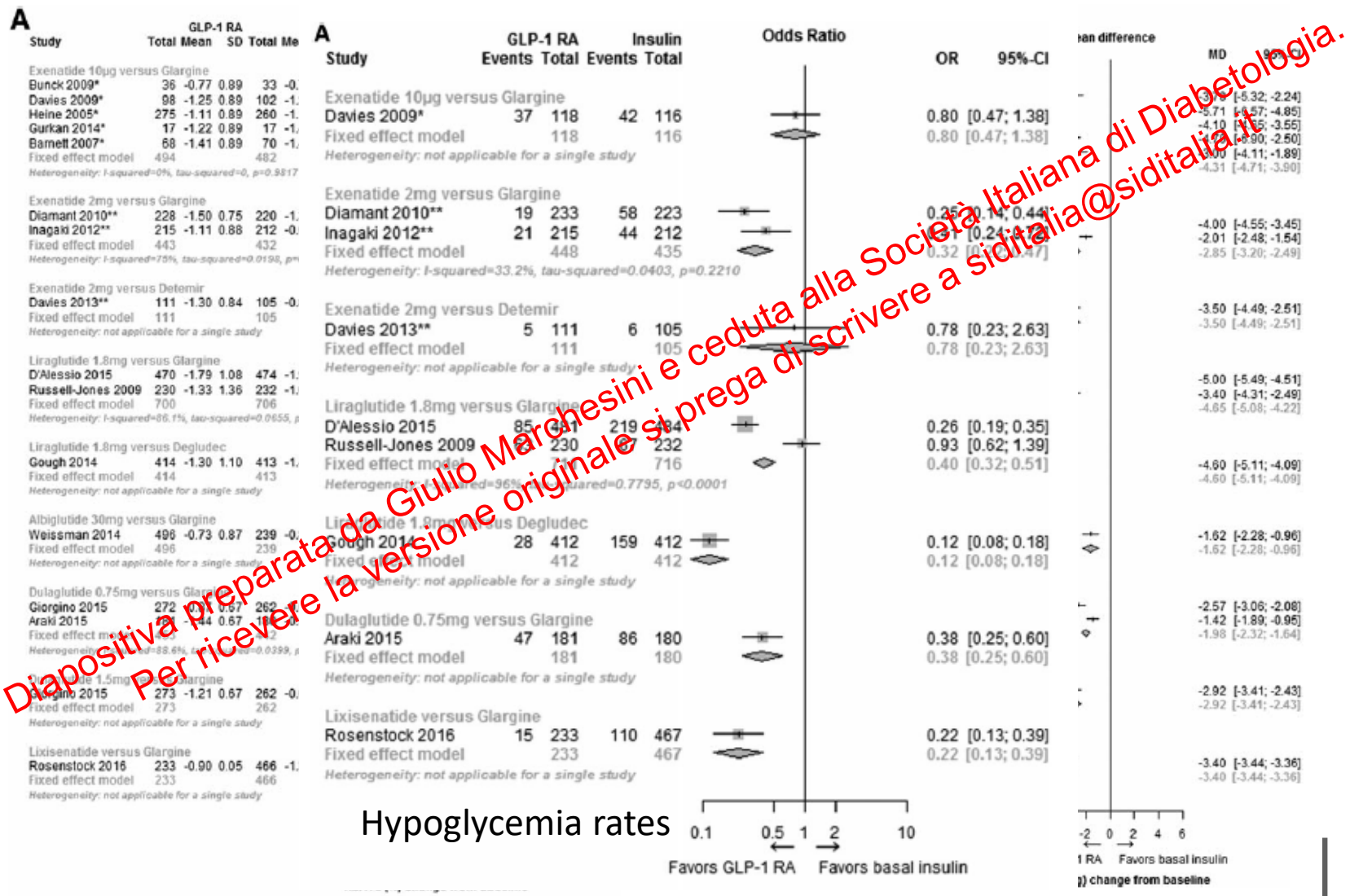
Toujeo reduced confirmed and/or severe hypoglycemia in the maintenance period as well as during the first 8 weeks*

Hypoglycemia at any time (24 h) | Nocturnal hypoglycemia (00:00–05:59 h)



*Gla-300 vs Gla-100 significant reduction, except for hypoglycemia at any time from Week 9 to Month 6
Safety population
Relative risk (95% CI)
Riddle MC et al. Diabetes Care. 2014;37:2755-62

Glucagon-like peptide-1 receptor agonists compared with basal insulins for the treatment of type 2 diabetes mellitus: a systematic review and meta-analysis



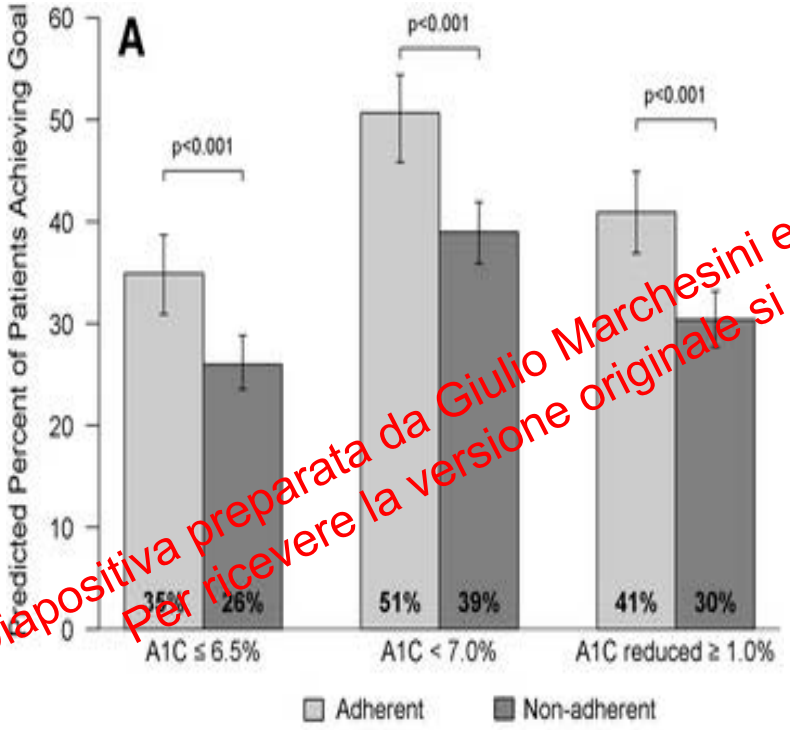
Hypoglycemia rates

Singh, Diabetes Obes Metab 2016

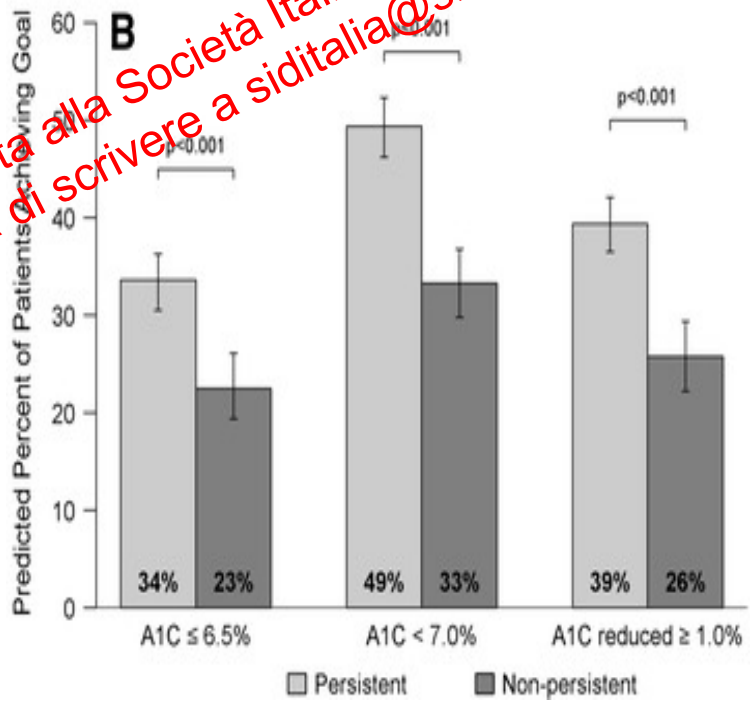
Impatto di aderenza e persistenza sul controllo glicemico

(Analisi retrospettiva su luglio 2009-settembre 2013 con 1^prescrizione liraglutide n=1321)

Aderenza



Persistenza

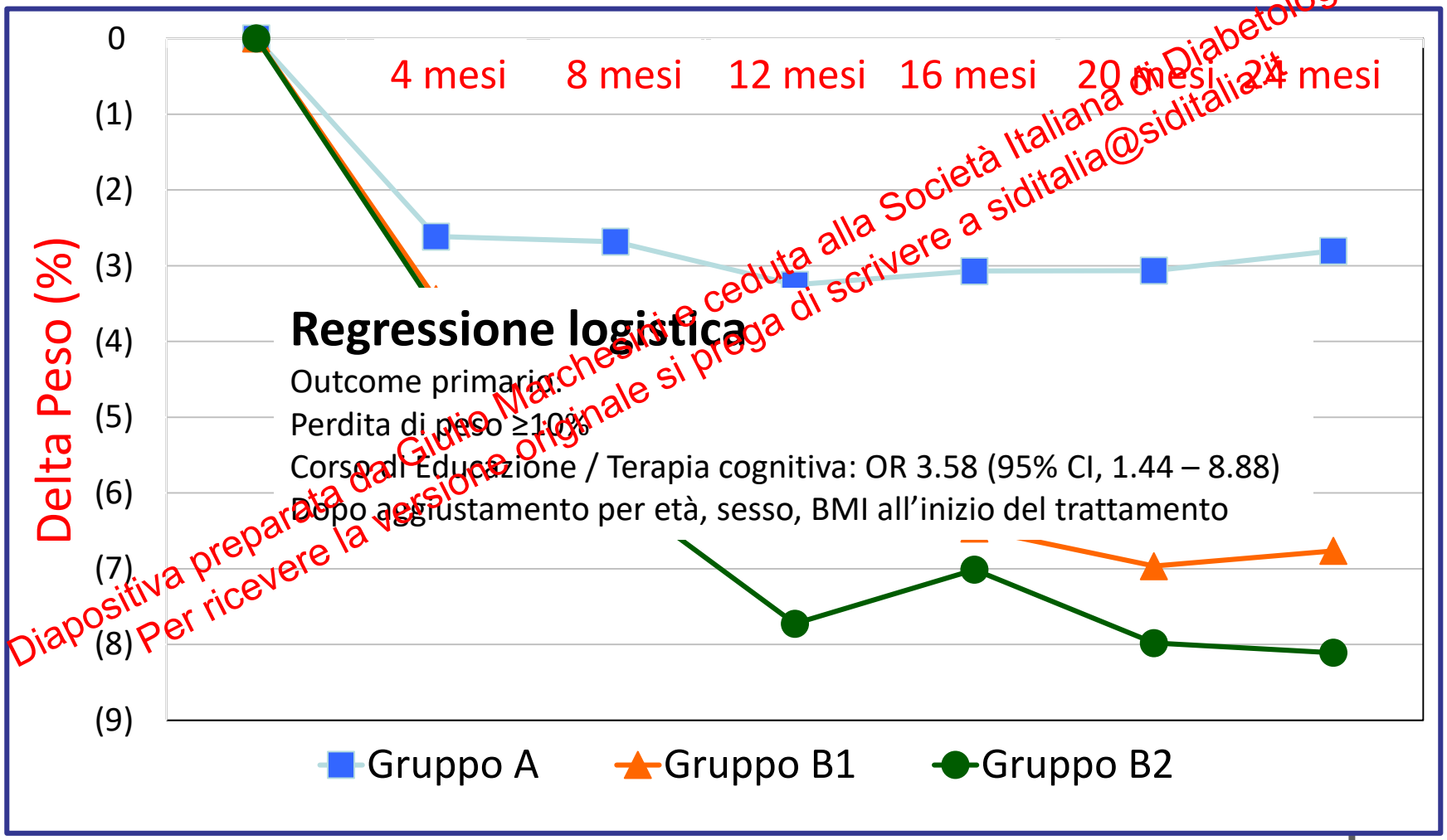


Aderenza = PDC ≥ 0.80

Non persistenza = gap in terapia > 90 giorni

Buysmann EK et al. Adv Ther;32(4):341-55

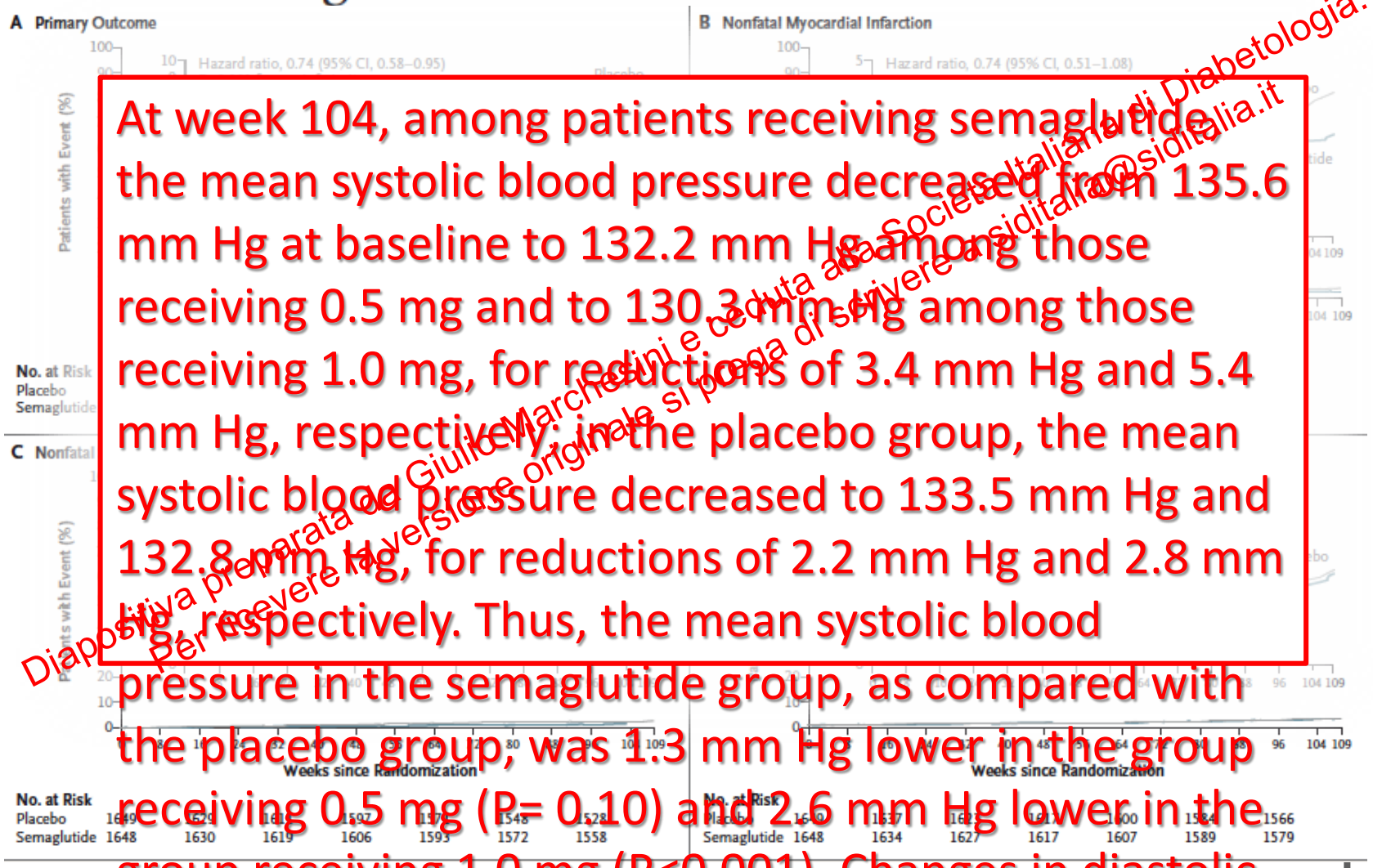
GLP-1 ed interventi sullo stile di vita



Caratteristiche dei pazienti ACCORD, VADT, ADVANCE

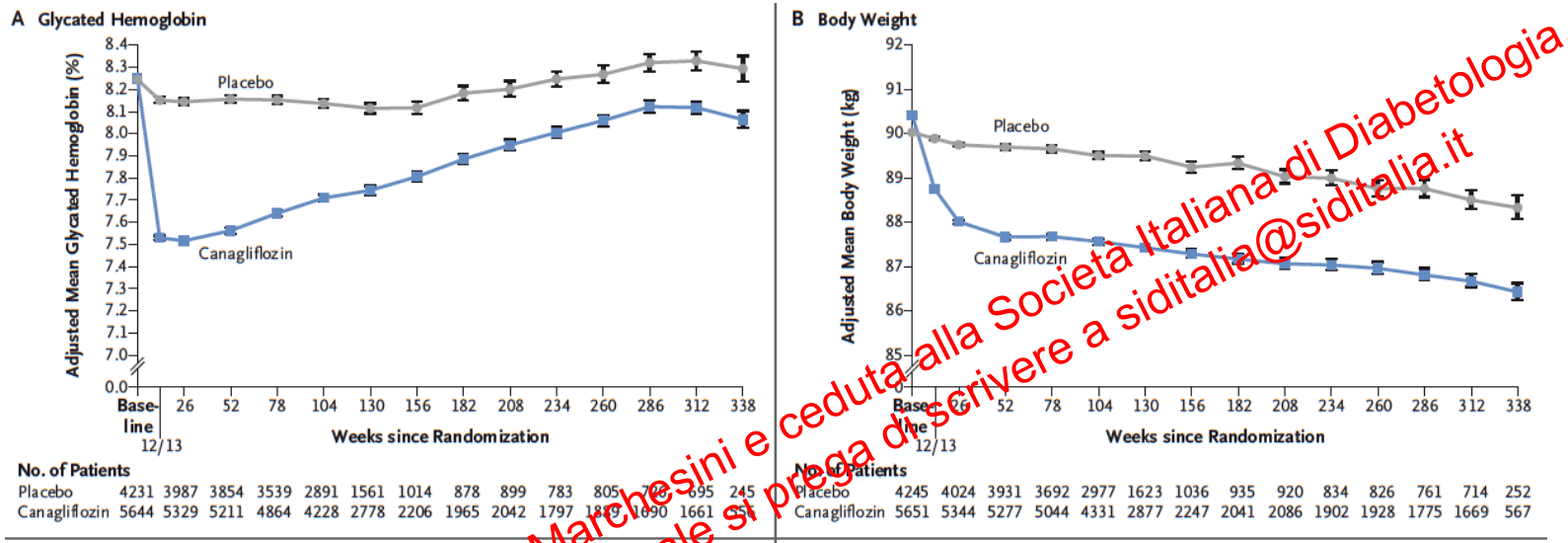
	ACCORD	VADT	ADVANCE	UKPDS
N. Casi	10251	1791	11400	vari
Età (anni)	62.1	60.4	66.0	53
BMI (kg/m2)	32.3	31.3	28	27.5
HbA1c (%)	8.3	9.4	7.2	7.1
PA sis (mmHg)	136	132	145	135
PA dia (mmHg)	75	76	81	82
Durata DM (anni)	10	11.5	8	---
Ter. insulinica	35%	52%	1.5%	---
Pregr CVD	35%	40%	32%	No eventi entro 1 anno, angina, scompenso, IRC, ipertensione severa

Semaglutide and Cardiovascular Outcomes



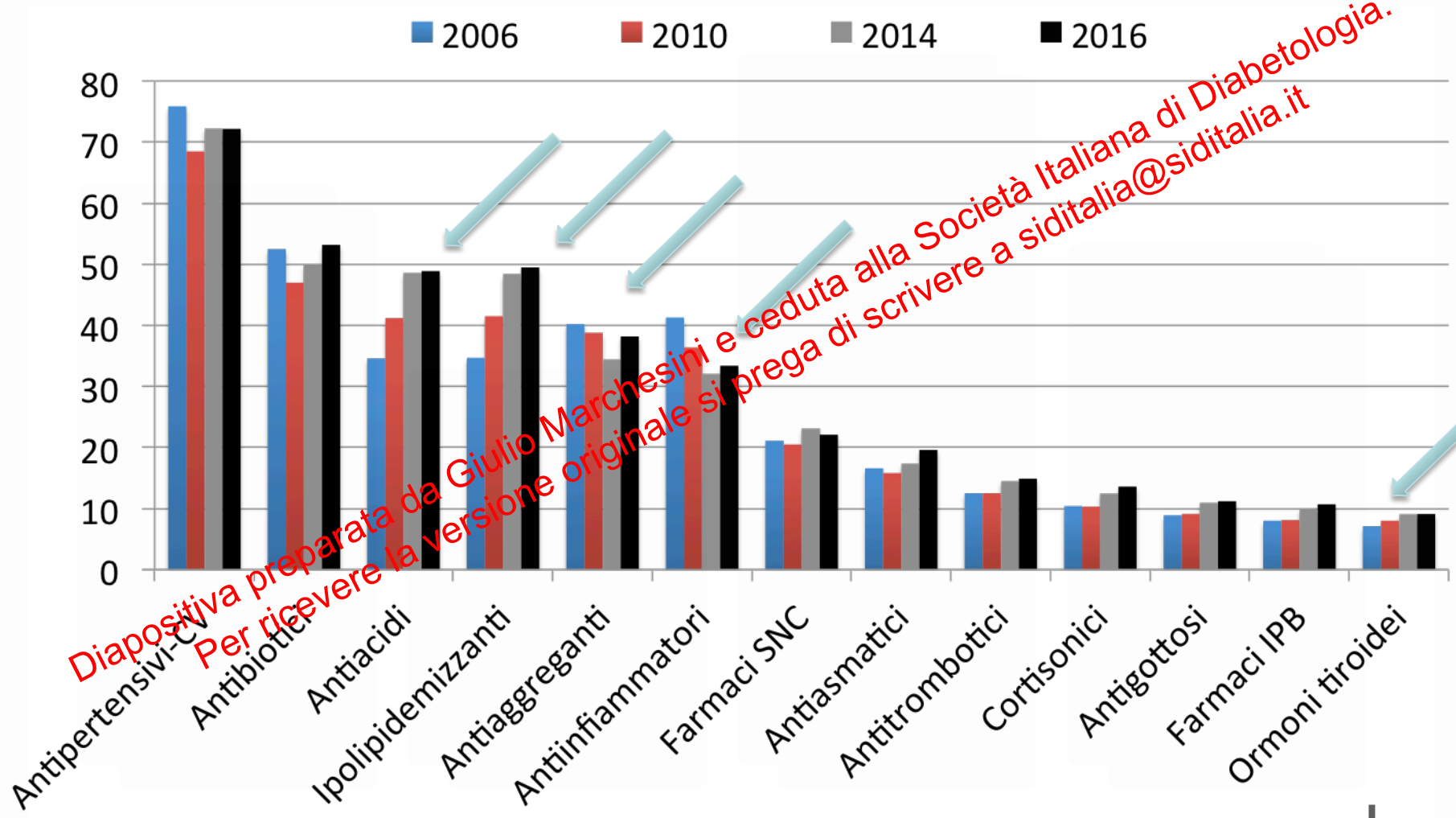
At week 104, among patients receiving semaglutide, the mean systolic blood pressure decreased from 135.6 mm Hg at baseline to 132.2 mm Hg among those receiving 0.5 mg and to 130.3 mm Hg among those receiving 1.0 mg, for reductions of 3.4 mm Hg and 5.4 mm Hg, respectively; in the placebo group, the mean systolic blood pressure decreased to 133.5 mm Hg and 132.8 mm Hg, for reductions of 2.2 mm Hg and 2.8 mm Hg, respectively. Thus, the mean systolic blood pressure in the semaglutide group, as compared with the placebo group, was 1.3 mm Hg lower in the group receiving 0.5 mg (P= 0.10) and 2.6 mm Hg lower in the group receiving 1.0 mg (P<0.001). Changes in diastolic blood pressure were similar in the treatment groups

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes



Neal, N Engl J Med 2017

ARNO 2015
Trattamento con altri farmaci



Efficacy of Liraglutide for Weight Loss Among Patients With Type 2 Diabetes

The SCALE Diabetes Randomized Clinical Trial

End Point	Change From Baseline to Week 56 or Percentage At Week 56			Estimate (95% CI)				
	Liraglutide				Liraglutide			
	3.0 mg (n = 411)	1.8 mg (n = 204)	Placebo (n = 211)	Estimate Type	3.0 mg vs Placebo	*P* Value	1.8 mg vs Placebo	*P* Value
Waist circumference, mean (SD), cm[b]	-6.1 (6.5)	-4.8 (5.6)	-2.7 (5.4)	Treatment difference	-3.22 (-4.10 to -2.23)	<.001	-2.06 (-3.20 to -0.92)	<.001
Body mass index, mean (SD)[b,c]	-2.2 (2.1)	-1.7 (2.1)	-0.8 (1.7)	Treatment difference	-1.50 (-1.83 to -1.18)	<.001	-0.95 (-1.33 to -0.57)	<.001
HbA_{1c}, mean (SD), % change[b]	-1.3 (0.9)	-1.1 (1.0)	-0.3 (0.9)	Treatment difference	-0.93 (-1.08 to -0.78)	<.001	-0.74 (-0.91 to -0.57)	<.001
Blood pressure, mean (SD), mm Hg[b]								
Systolic	-2.8 (13.5)	-3.5 (12.7)	-0.4 (13.4)	Treatment difference	-2.59 (-4.56 to -0.62)	.01	-2.68 (-4.98 to -0.38)	.02
Diastolic	-0.9 (8.7)	-1.1 (9.4)	-0.5 (9.1)	Treatment difference	-0.36 (-1.69 to 0.96)	.59	-0.19 (-1.74 to 1.36)	.81

Davies, JAMA 2016

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

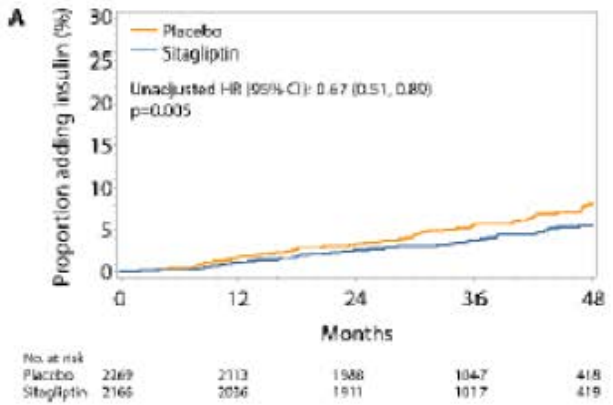
- The primary composite outcome was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction (including silent), or nonfatal stroke.
- Prespecified secondary outcomes included the first occurrence of an expanded composite cardiovascular outcome (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, revascularization [coronary or peripheral], and hospitalization for unstable angina or heart failure), an additional composite outcome (death from all causes, nonfatal myocardial infarction, or nonfatal stroke), the individual components of the composite outcomes, retinopathy complications, and new or worsening nephropathy.
- Each outcome, except for peripheral revascularization, was

CVD-REAL Nordic
Dapagliflozin compared to DPP4i

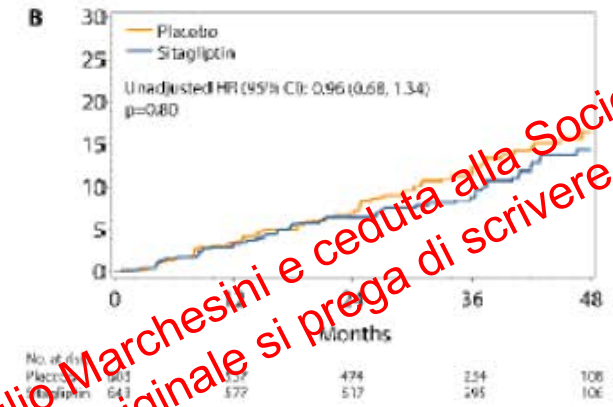
	Dapagliflozin N=8582		DPP-4 inhibitor N=25,746		Weighted average estimates N=34,328		
	No of events	Rate/100 P-Y	No of events	Rate/100 P-Y	Hazard ratio	95% CI	P-value
Hospitalization for HF	77	0.95	375	1.47	**0.63**	**0.50–0.81**	**<0.001**
MACE	83	1.83	372	2.57	**0.71**	**0.56–0.90**	**0.004**
Non-fatal AMI	40	0.88	170	1.17	0.75	0.53–1.06	0.102
Non-fatal stroke	37	0.81	147	1.01	0.80	0.56–1.15	0.222
CV mortality	18	0.39	77	0.53	0.74	0.44–1.23	0.241
All-cause death	106	1.04	471	1.45	**0.73**	**0.59–0.90**	**0.003**
HKD	52	0.64	417	1.64	**0.38**	**0.29–0.51**	**<0.001**
HKD or HHF	124	1.54	756	2.99	**0.50**	**0.42–0.61**	**<0.001**

Time to insulin in TECOS study

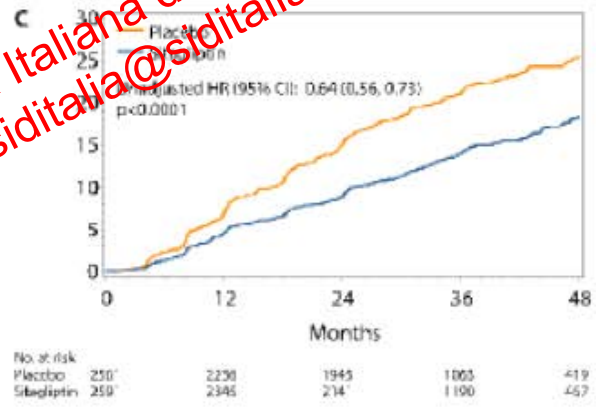
Metformin monotherapy at baseline



Sulfonylurea monotherapy at baseline



Combined monotherapy at baseline

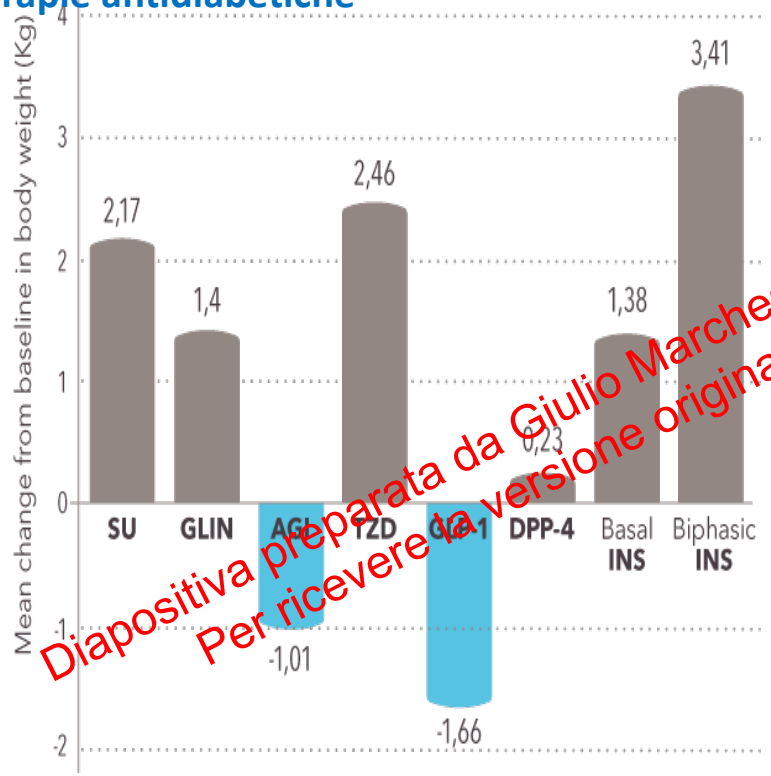


	Events, n (%)		Event rate per 100 pt-yrs		Hazard ratio (95% CI)	p-value
	Placebo	Sitagliptin	Placebo	Sitagliptin		
MET monotherapy (n=4435)	125 (5.5%)	83 (3.8%)	2.0	1.3	0.67 (0.51, 0.89)	0.005
SU monotherapy (n=1249)	68 (11.3%)	69 (10.7%)	4.2	4.0	0.96 (0.68, 1.34)	0.80
MET + SU (n=5154)	522 (20.4%)	363 (14.0%)	7.8	5.1	0.64 (0.56, 0.73)	<0.0001

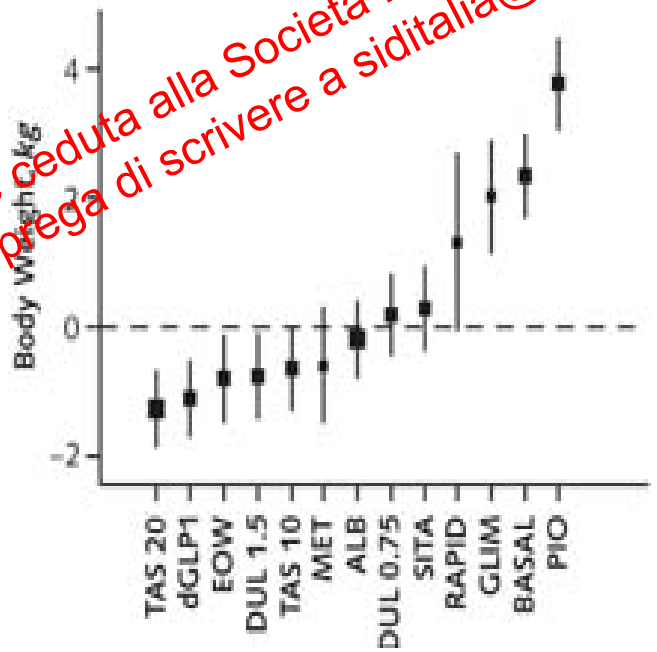
MA Bethel et al, ADA meeting 1183P 2017

Sovrappeso: quale farmaco scelgo?

Differenze di effetto sul peso delle terapie antidiabetiche [1]



Dulaglutide ha un'efficacia allineata alla classe dei GLP-1 RAs[2]



1. Modified from Liu SC, Tu YK, Chien MN, Chien KL. Diabetes Obes Metab. 2012 Sep;14(9):810-20.

2. Da Zaccardi F et al. *Ann Intern Med.* 2016;164(2):102-113

Studi di outcome cardiovascolare con GLP-1R agonisti e DPP-4 inibitori

Farmaco	Sponsor	Acronimo del trial	Data di completamento prevista	Risultati riportati
Agonisti recettore GLP-1				
Lixisenatide	Sanofi	ELIXA	Feb. 2015	Giu 2015
Semaglutide	Novo Nordisk	SUSTAIN 6	Gen 2016[a]	Set. 2016
Liraglutide	Novo Nordisk	LEADER	Nov 2015[a]	Giu 2016
Exenatide	AstraZeneca	EXSCEL	Mar 2017[a]	
Dulaglutide	Lilly	REWIND	Apr 2019[a]	
Inibitori DDP-4				
Saxagliptin	AstraZeneca	SAVOR-TIMI 53	Mag 2013	Set. 2013
Alogliptin	Takeda	EXAMINE	Giu 2013	Set. 2013
Sitagliptin	Merck	TECOS	Mar 2015	Giu 2015
Linagliptin	BI/Lilly	CARMELINA	Gen 2018[a]	
Linagliptin	BI/Lilly	CAROLINA	Set 2018[a]	