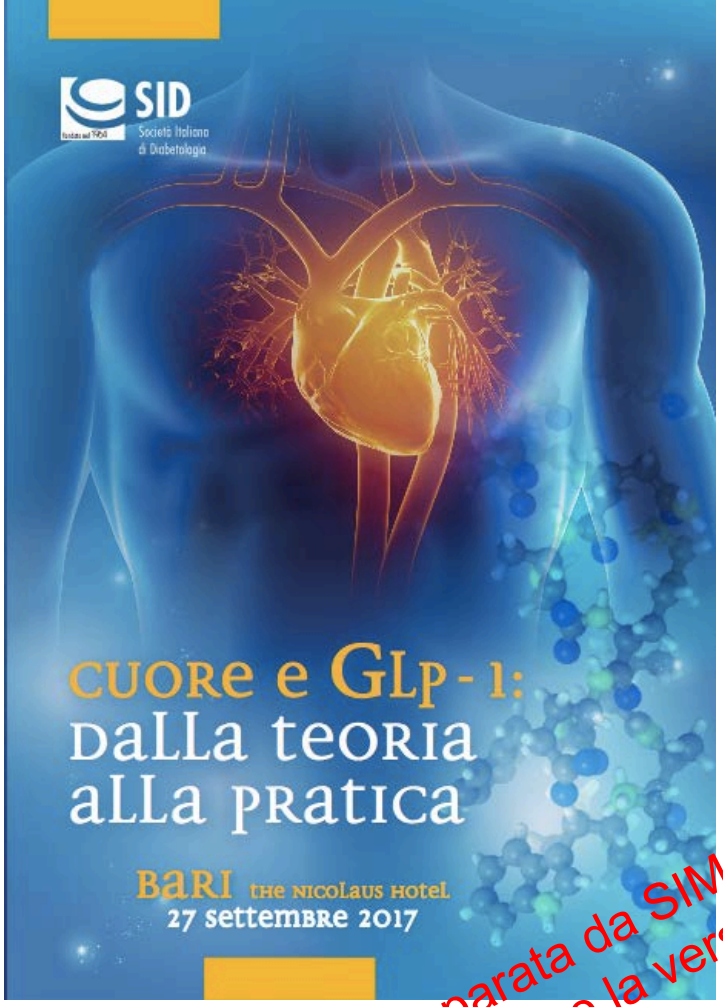

GLP1-RAs e rischio cardiovascolare

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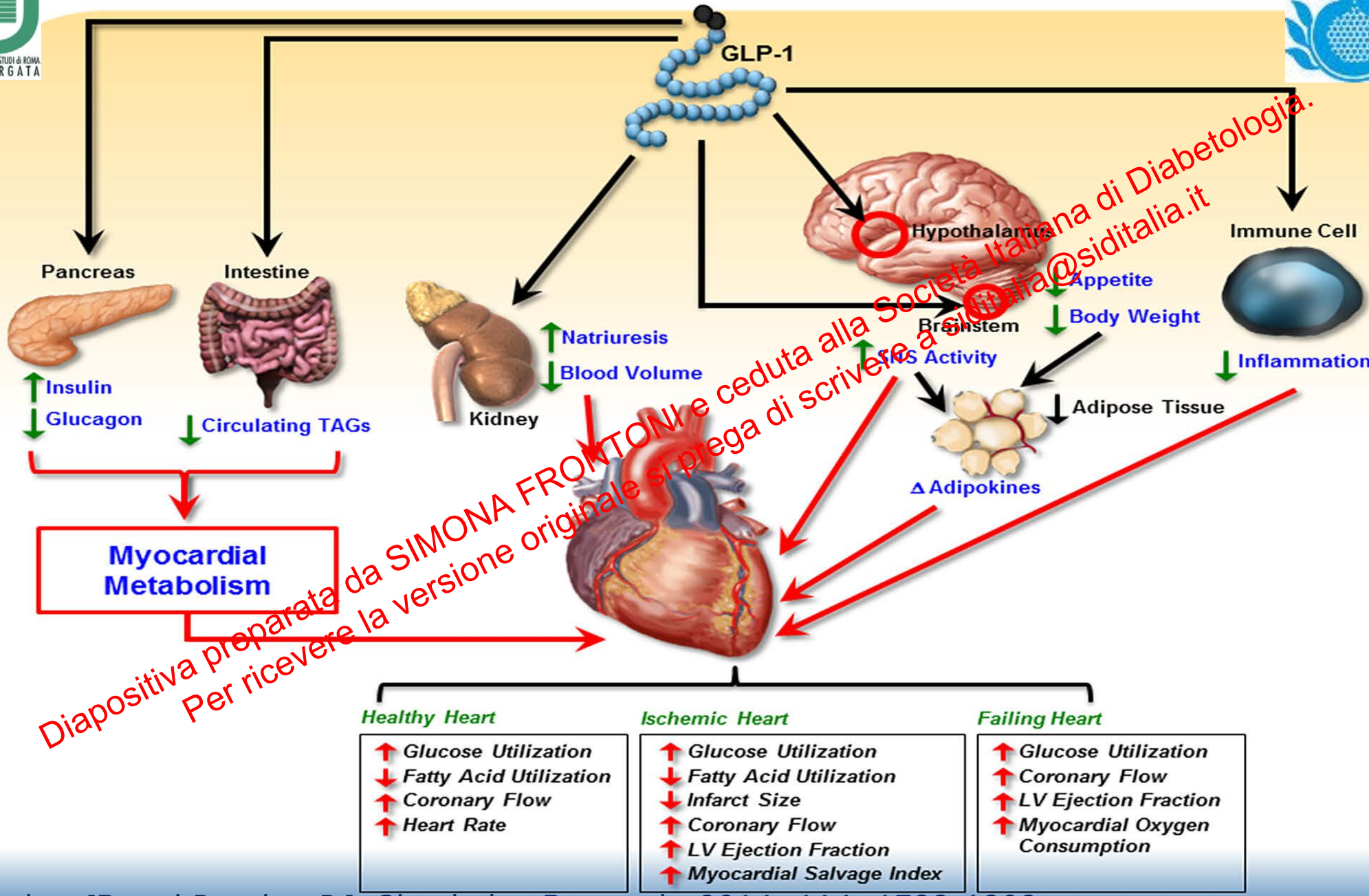
Disclosures

Astrazeneca, Boheringher Ingelheim, Bristol Myers Squibb, Janssen, Eli Lilly, MSD, Novartis, Novo Nordisk, Sanofi, Takeda

Potential indirect cardiovascular effects of GLP-1R agonists



Ussher JR and Drucker DJ. Circulation Research. 2014; 114: 1788-1803.

RCTs of GLP-1 RAs and CVD

Study	Drug	No.	Age	Duration diabetes	HbA1c
ELIXA	Lixisenatide	6068	60	9	7.7
LEADER	Liraglutide	9340	64	13	8.7
SUSTAIN 6	Semaglutide	3297	65	14	8.7
FREEDOM CVOT	Exenatide ER	4000	40+	???	???
EXSCEL	Exenatide LAR	14752	63	12	8
REWIND	Dulaglutide	9901	66	10	7.3
HARMONY CVOT	Albiglutide	???	???	???	???

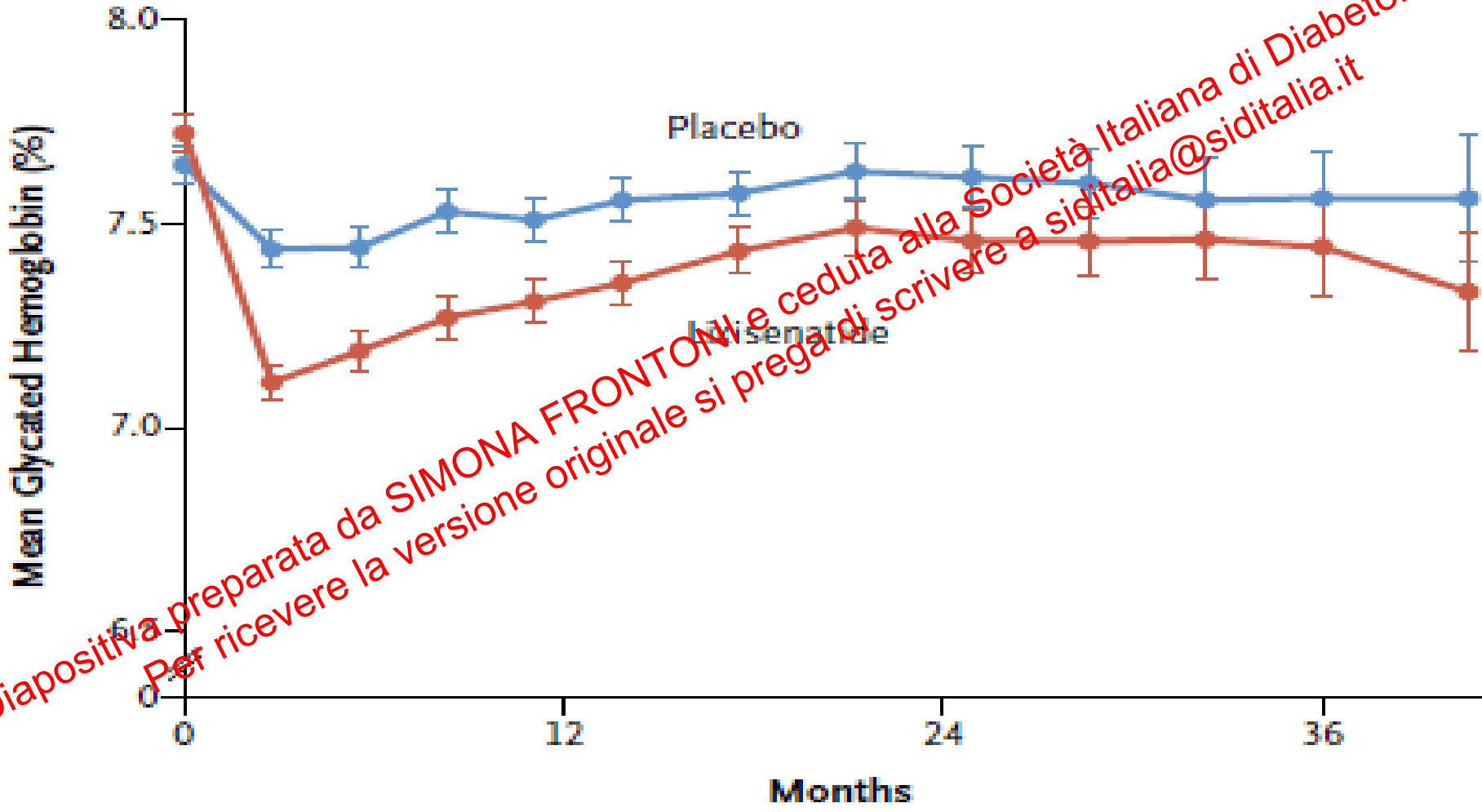
RCTs of GLP-1 RAs and CVD

Study	Drug	Median Follow-up (yrs)	Prior CVD (%)	Endpoints
ELIXA	Lixisenatide	2.0	100 (recent ACS)	MACE + UA
LEADER	Liraglutide	3.8	82	MACE
SUSTAIN 6	Semaglutide	2.1	71	MACE
FREEDOM CVOT	Exenatide QY	1.2	Most	MACE
EXSCEL	Exenatide OW	5	73	MACE
REWIND	Dulaglutide	???	31	MACE
HARMONY CVOT	Albiglutide	???	???	MACE

ELIXA

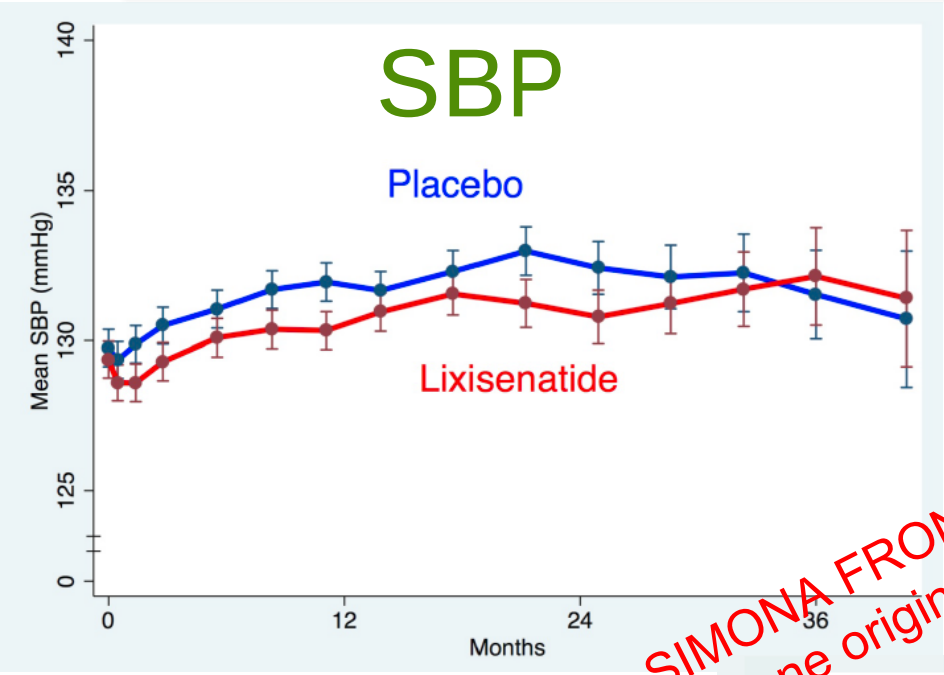
Lixisenatide vs. placebo on top of background treatment in subjects with recent ACS

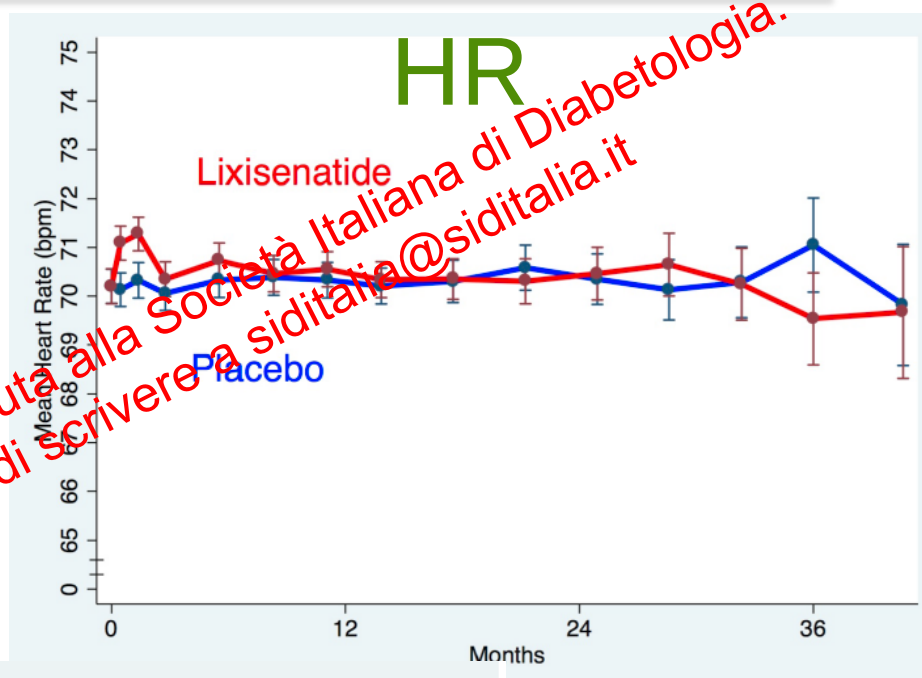
ELIXA – Time course of HbA1c

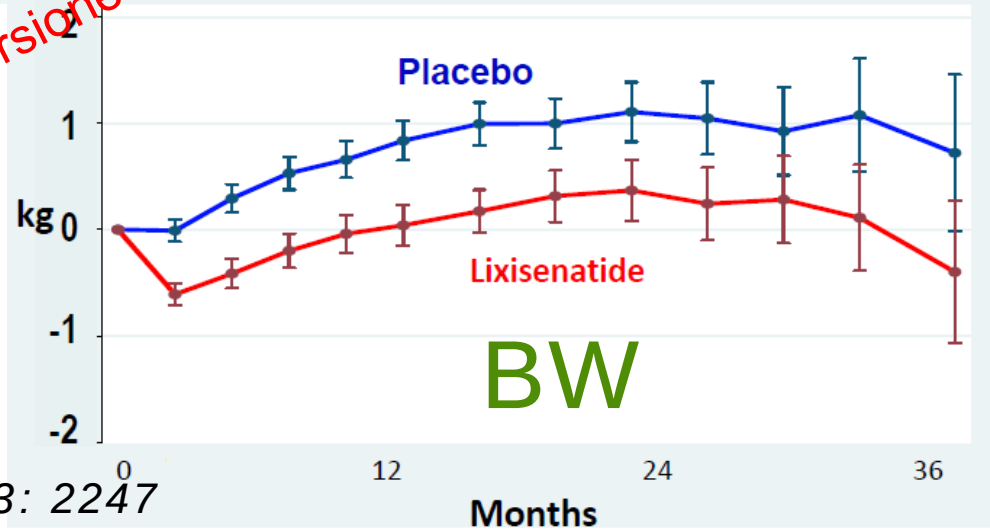


Pfeffer M et al – NEJM 2015; 373: 2247

ELIXA
time course of BW, SBP, HR

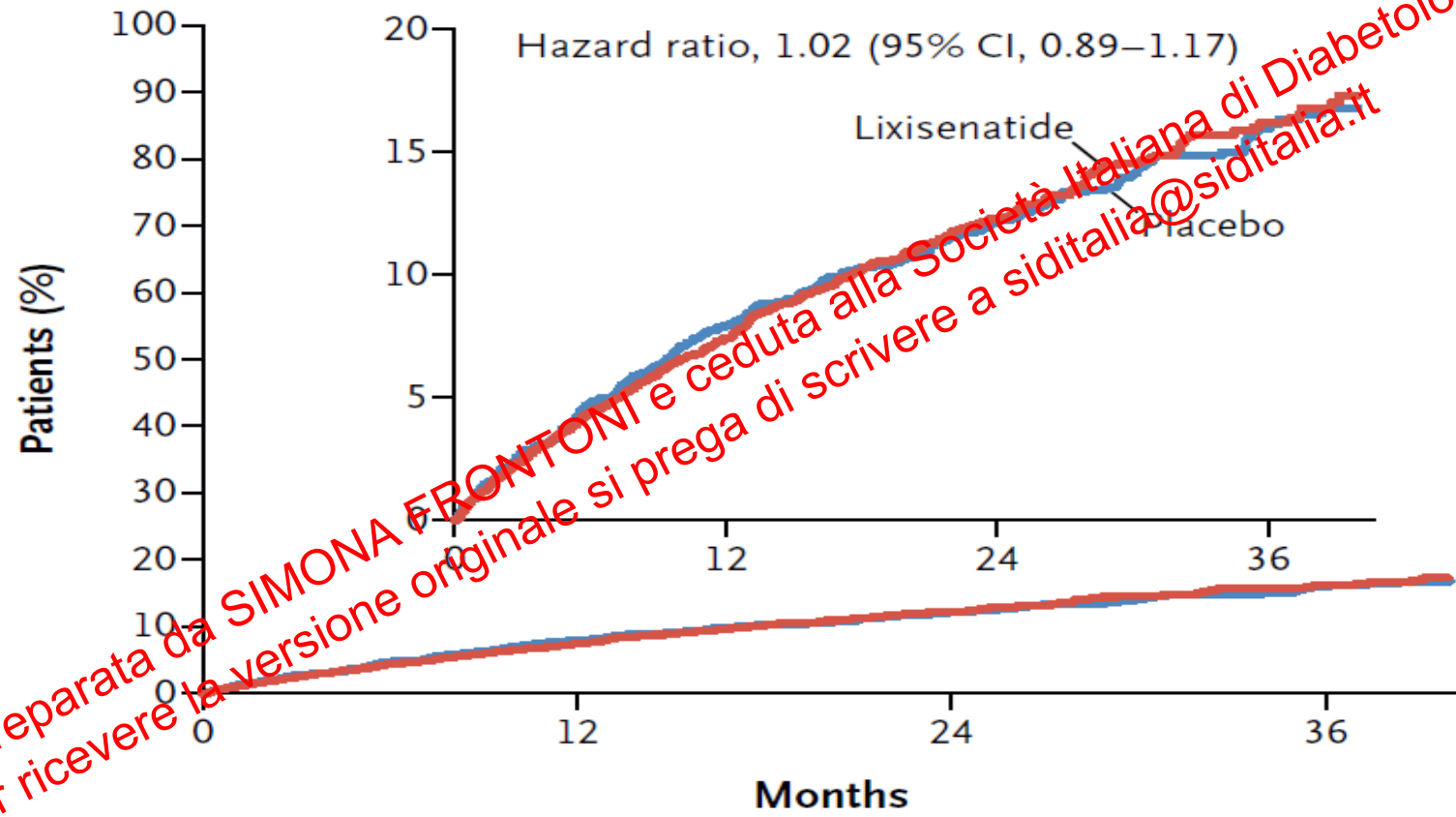






Pfeffer M et al – NEJM 2015; 373: 2247

ELIXA
primary endpoint (MACE + UA)



No. at Risk

Placebo	3034	2759	1566	476
Lixisenatide	3034	2785	1558	484

Pfeffer M et al – NEJM 2015; 373: 2247

ELIXA
Incidence and HR for CVD endpoints

Table 2. Incidence Rates and Hazard Ratios, with Adjustment for Geographic Region, for the Primary Composite End Point, Its Components, and Other Efficacy Outcomes.

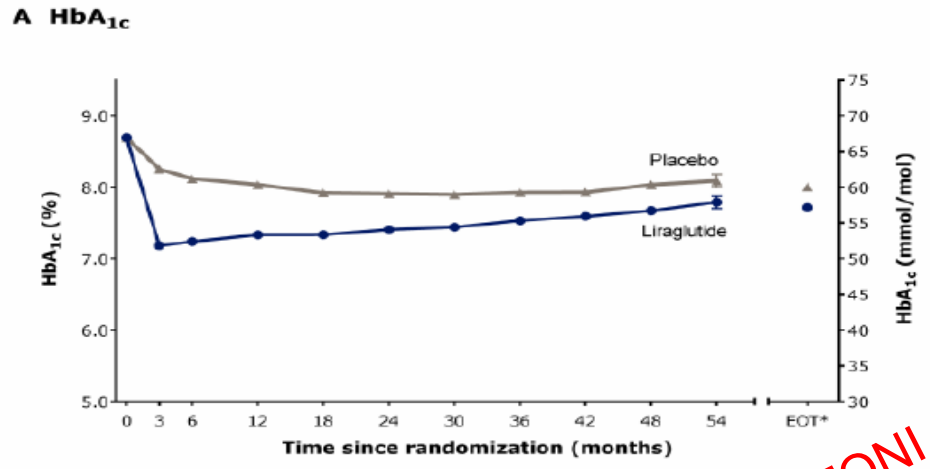
End Point	Placebo (N=3034)		Lixisenatide (N=3034)		Adjusted Hazard Ratio (95% CI)	P Value
	Patients with Event	No. of Events/ 100 Patient-Yr	Patients with Event	No. of Events/ 100 Patient-Yr		
Primary end point: death from cardiovascular causes, nonfatal stroke, nonfatal myocardial infarction, or unstable angina — no. (%)	399 (13.2)	6.3	406 (13.4)	6.4	1.02 (0.89–1.17)	0.81
Components of primary end point — no./total no. (%)						
Death from cardiovascular causes	93/399 (23.3)	—	88/406 (21.7)	—	—	—
Nonfatal myocardial infarction	247/399 (61.9)	—	256/406 (62.8)	—	—	—
Nonfatal stroke	49/399 (12.3)	—	54/406 (13.3)	—	—	—
Unstable angina	10/399 (2.5)	—	9/406 (2.2)	—	—	—
Patients with each primary end-point event — no. (%)*						
Death from cardiovascular causes	158 (5.2)	2.4	156 (5.1)	2.3	0.98 (0.78–1.22)	0.85
Myocardial infarction	261 (8.6)	4.1	270 (8.9)	4.2	1.03 (0.87–1.22)	0.71
Stroke	60 (2.0)	0.9	67 (2.2)	1.0	1.12 (0.79–1.58)	0.54
Unstable angina	10 (0.3)	0.1	11 (0.4)	0.2	1.11 (0.47–2.62)	0.81
Secondary end points — no. (%)						
Primary end-point event or hospitalization for heart failure	469 (15.5)	7.6	456 (15.0)	7.3	0.97 (0.85–1.10)	0.63
Primary end-point event, hospitalization for heart failure, or revascularization	659 (21.7)	11.2	661 (21.8)	11.1	1.00 (0.90–1.11)	0.96
Additional end points — no. (%)						
Hospitalization for heart failure	127 (4.2)	1.9	122 (4.0)	1.8	0.96 (0.75–1.23)	0.75
Death from any cause	223 (7.4)	3.3	211 (7.0)	3.1	0.94 (0.78–1.13)	0.50

Pfeffer M et al – NEJM 2015; 373: 2247

LEADER

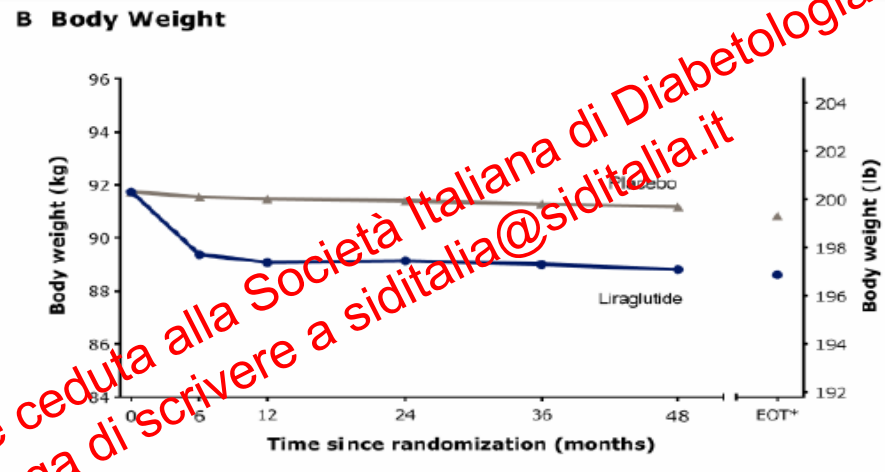
Liraglutide vs. placebo on the top of background treatment in subjects with previous CVD or CKD or high CVD risk

LEADER
time course of HbA1c, BW, BP, HR



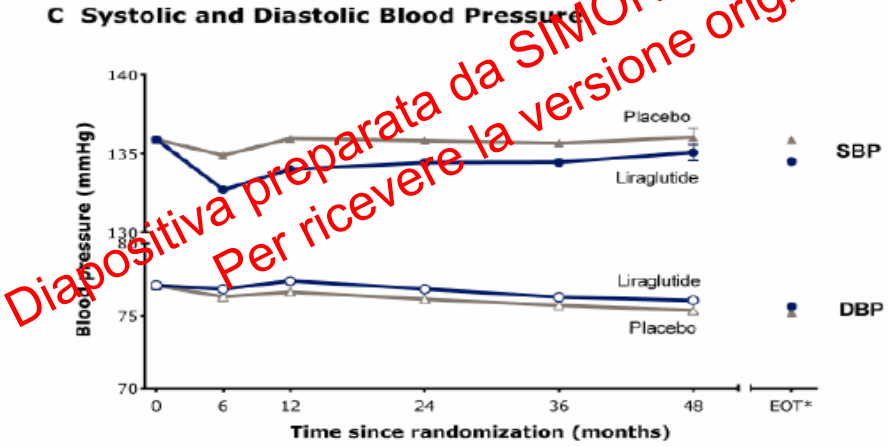
Number of patients at each visit

Liraglutide	4668	4402	4355	4295	4135	4034	3877	3810	2349	809	101	3705
Placebo	4672	4413	4355	4235	4030	3905	3742	3640	2303	756	87	3561



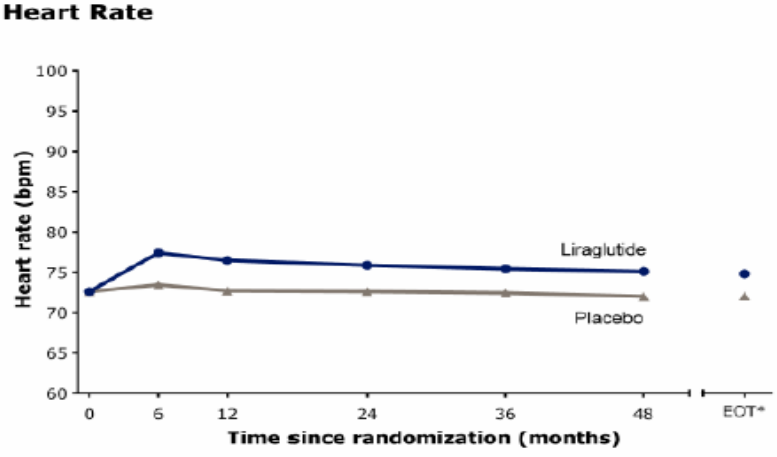
Number of patients at each visit

Liraglutide	4667	4434	4324	4088	3835	824	3708
Placebo	4671	4423	4285	3970	3680	766	3555



Number of patients at each visit

Liraglutide	4668	4445	4332	4107	3859	823	3722
Placebo	4672	4435	4295	3975	3699	767	3570

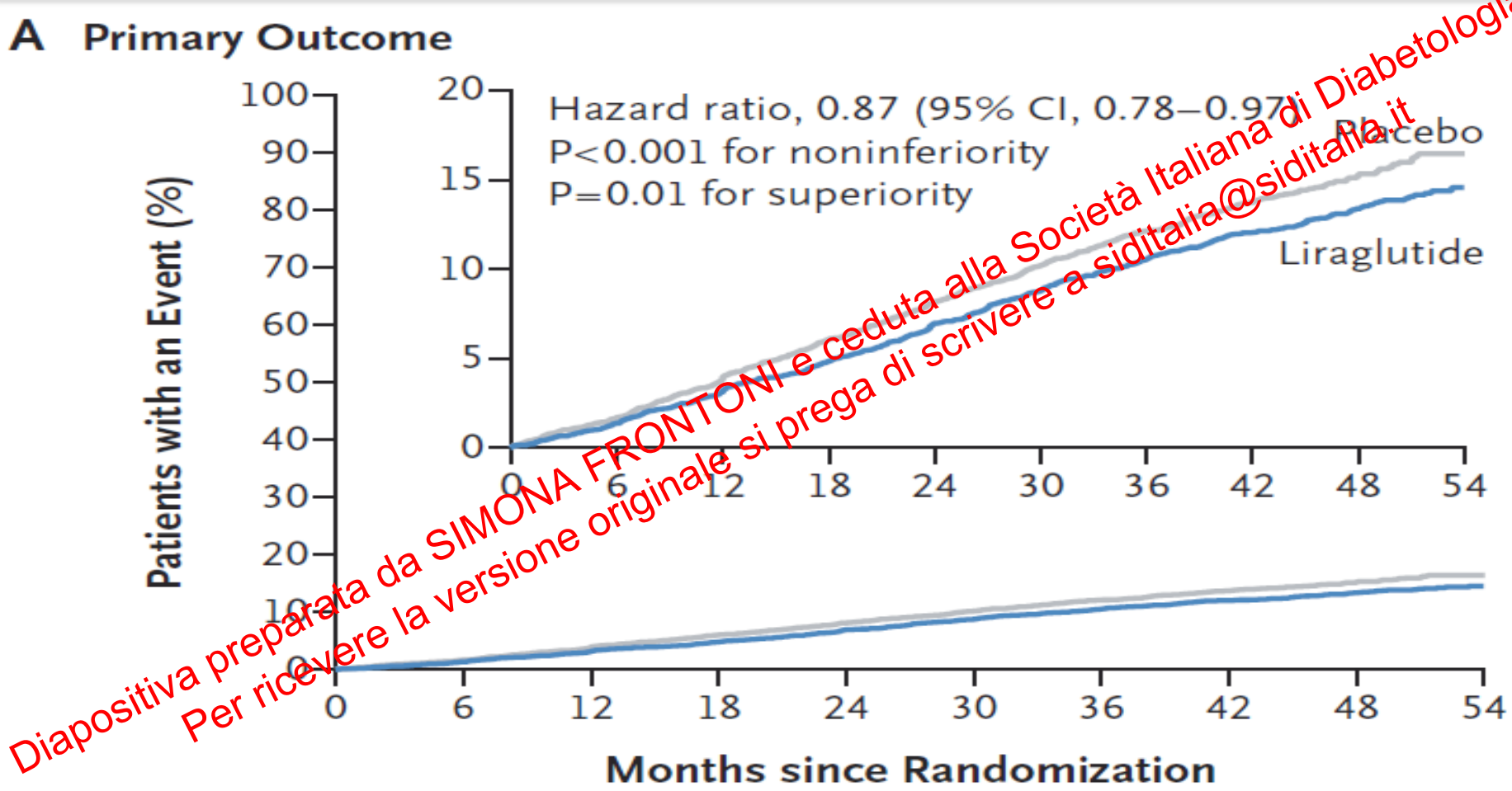


Number of patients at each visit

Liraglutide	4668	4442	4330	4099	3853	824	3722
Placebo	4672	4434	4294	3971	3695	767	3569

Marso SP et al – NEJM 2016

LEADER
primary endpoint (MACE)

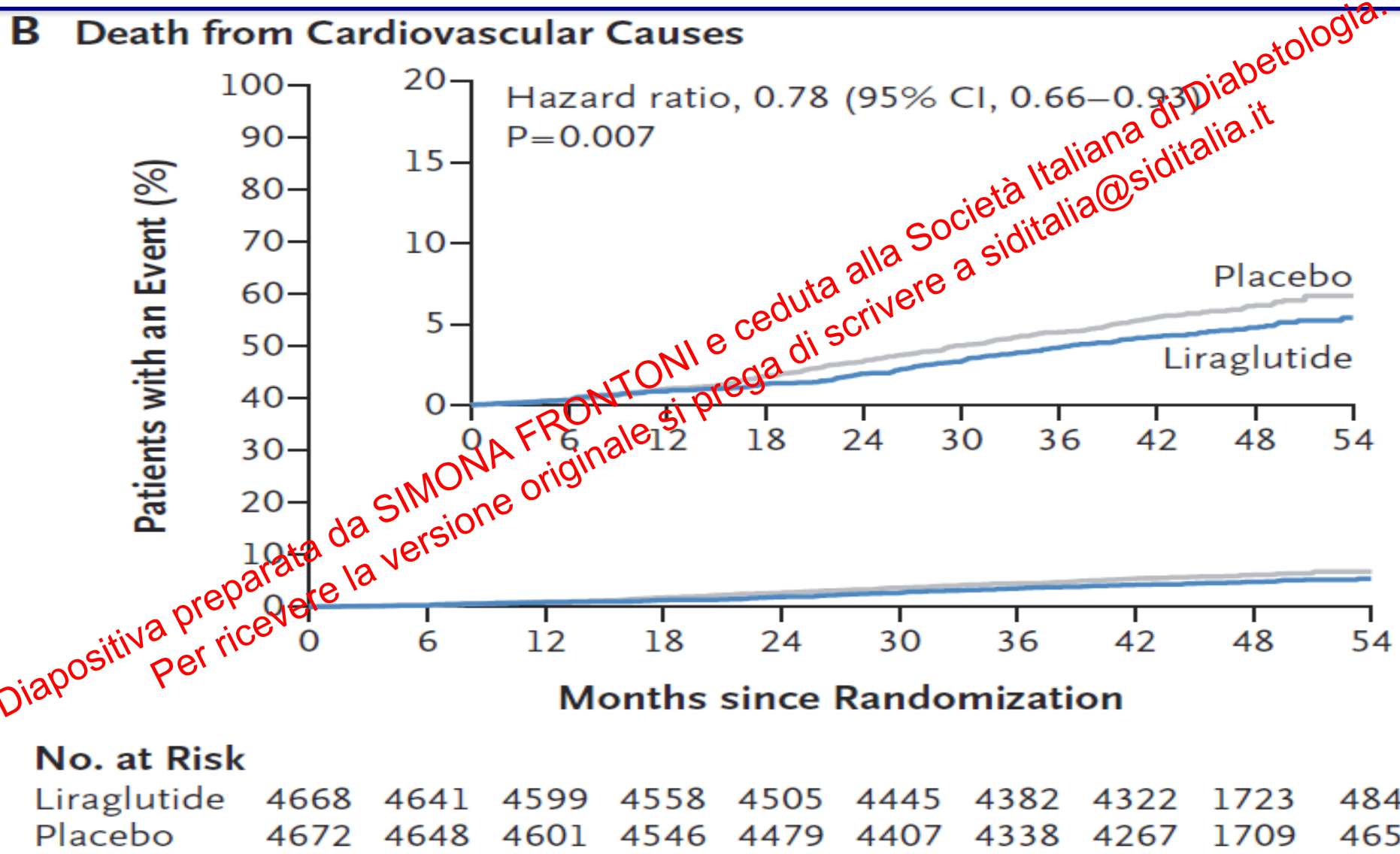


No. at Risk

Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

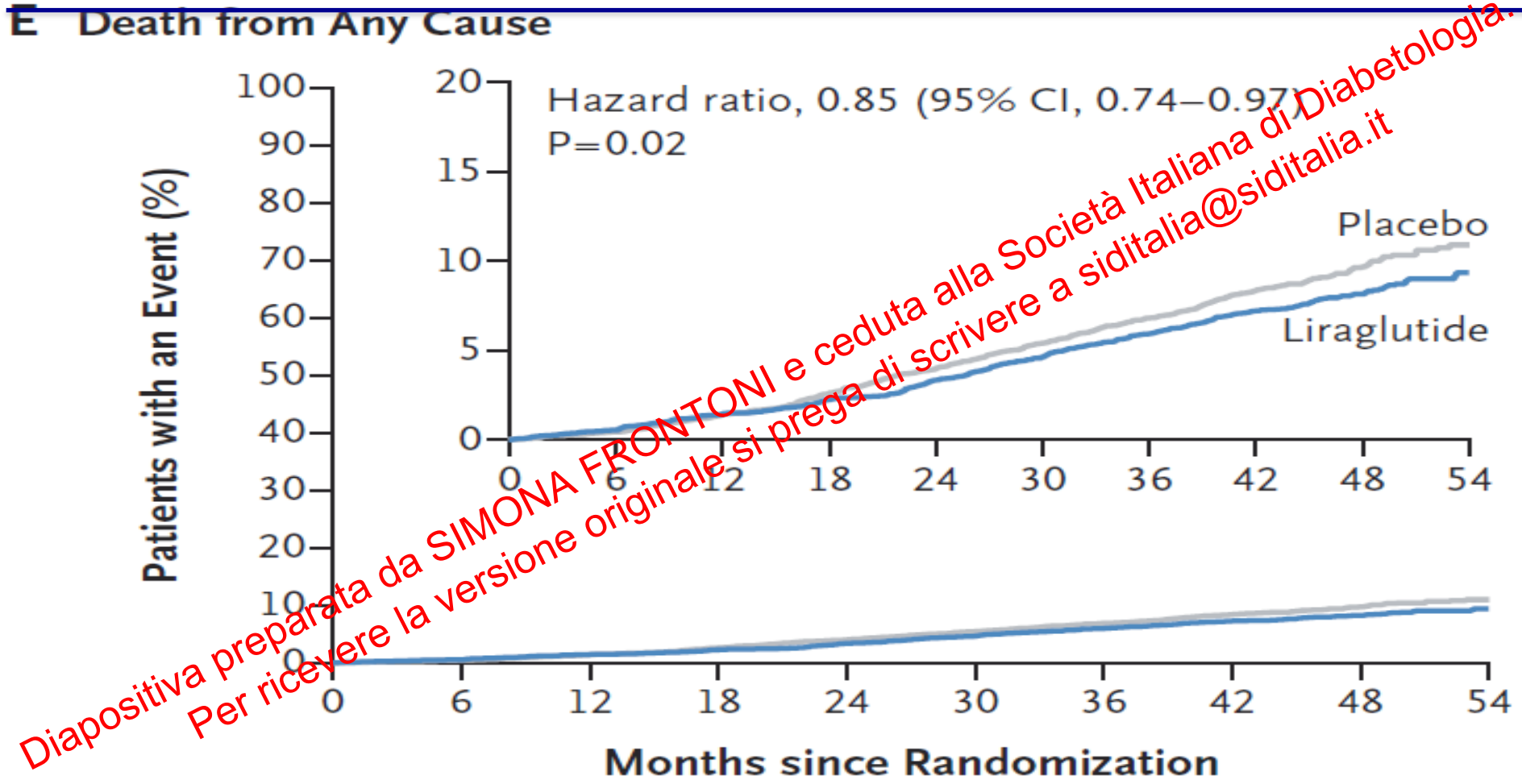
Marso SP et al – NEJM 2016

LEADER
death from CVD



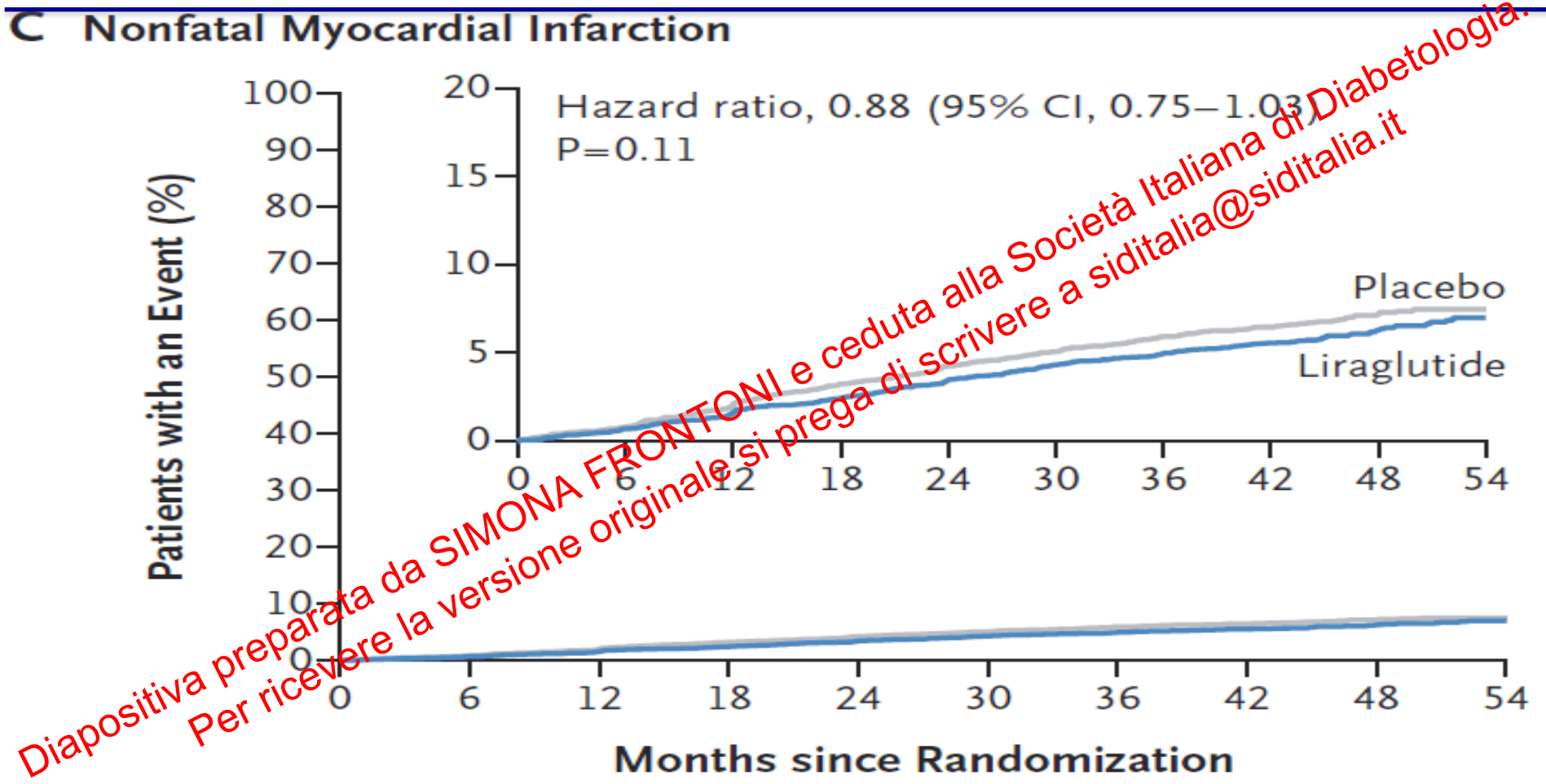
Marso SP et al – NEJM 2016

LEADER
death from any cause



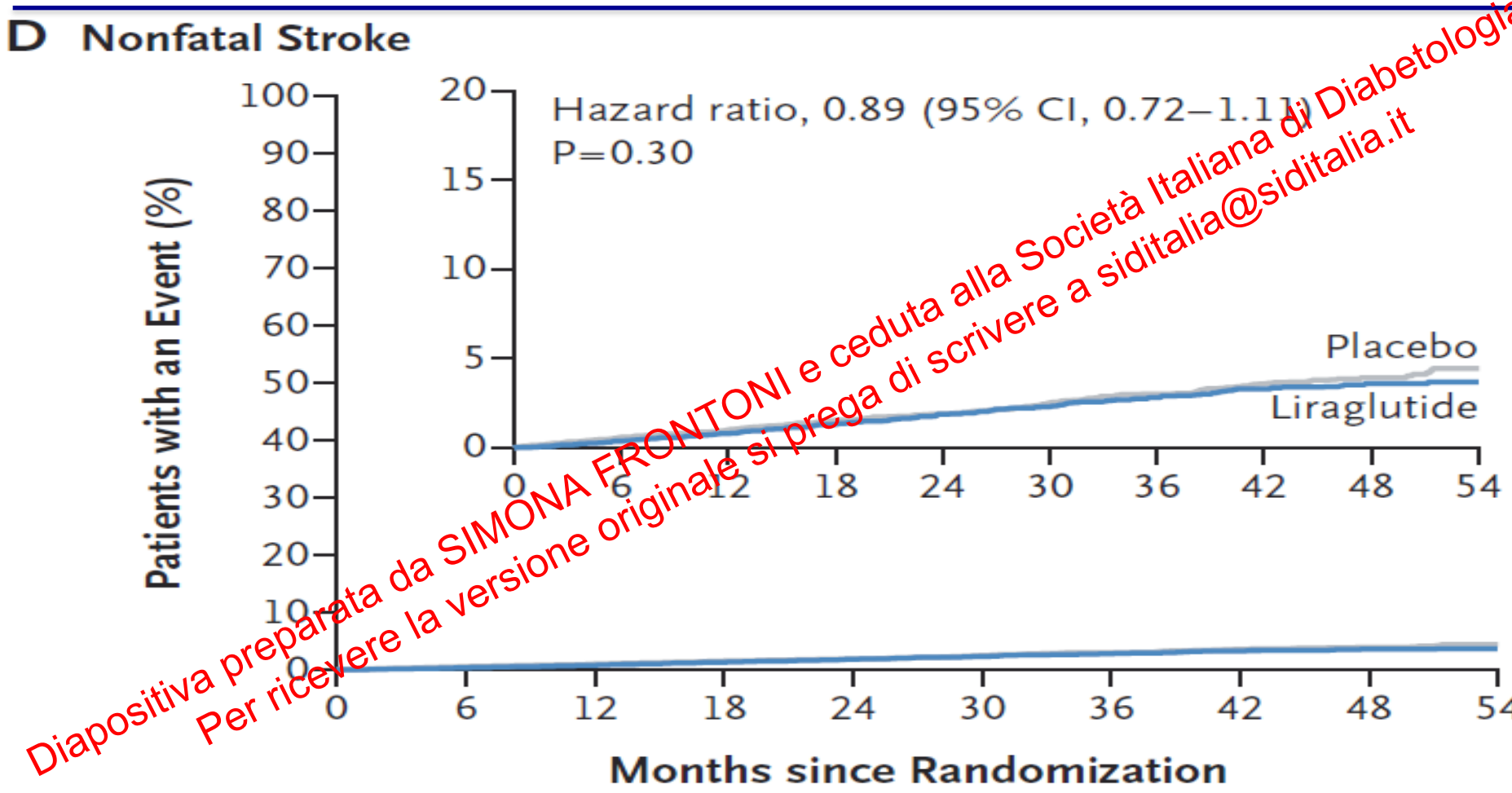
Marso SP et al – NEJM 2016

LEADER
non-fatal MI



Marso SP et al – NEJM 2016

LEADER
non-fatal stroke



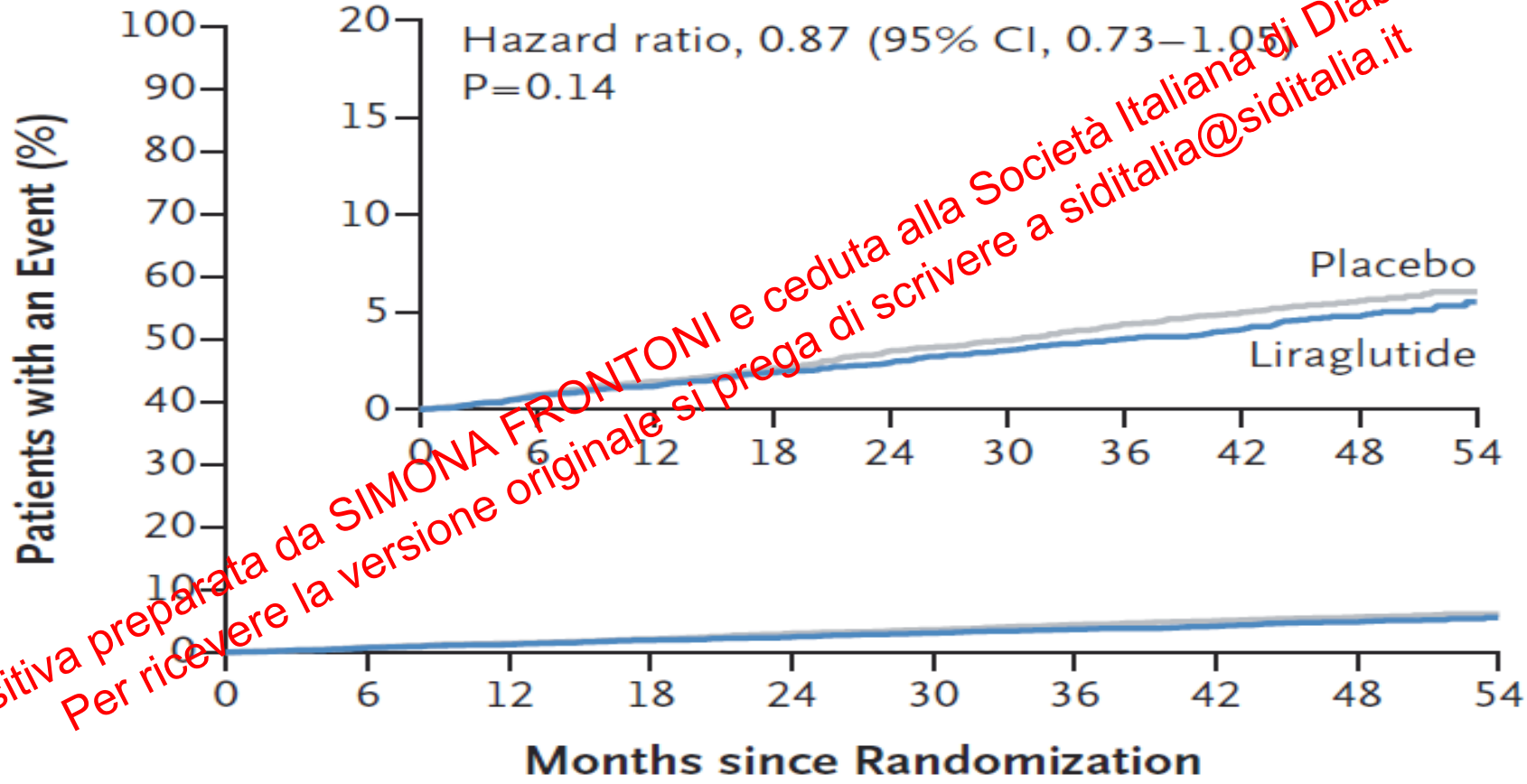
No. at Risk

Liraglutide	4668	4624	4564	4504	4426	4351	4269	4194	1662	465
Placebo	4672	4622	4558	4484	4405	4314	4228	4141	1648	445

Marso SP et al – NEJM 2016

LEADER
heart failure (hospitalization)

F Hospitalization for Heart Failure



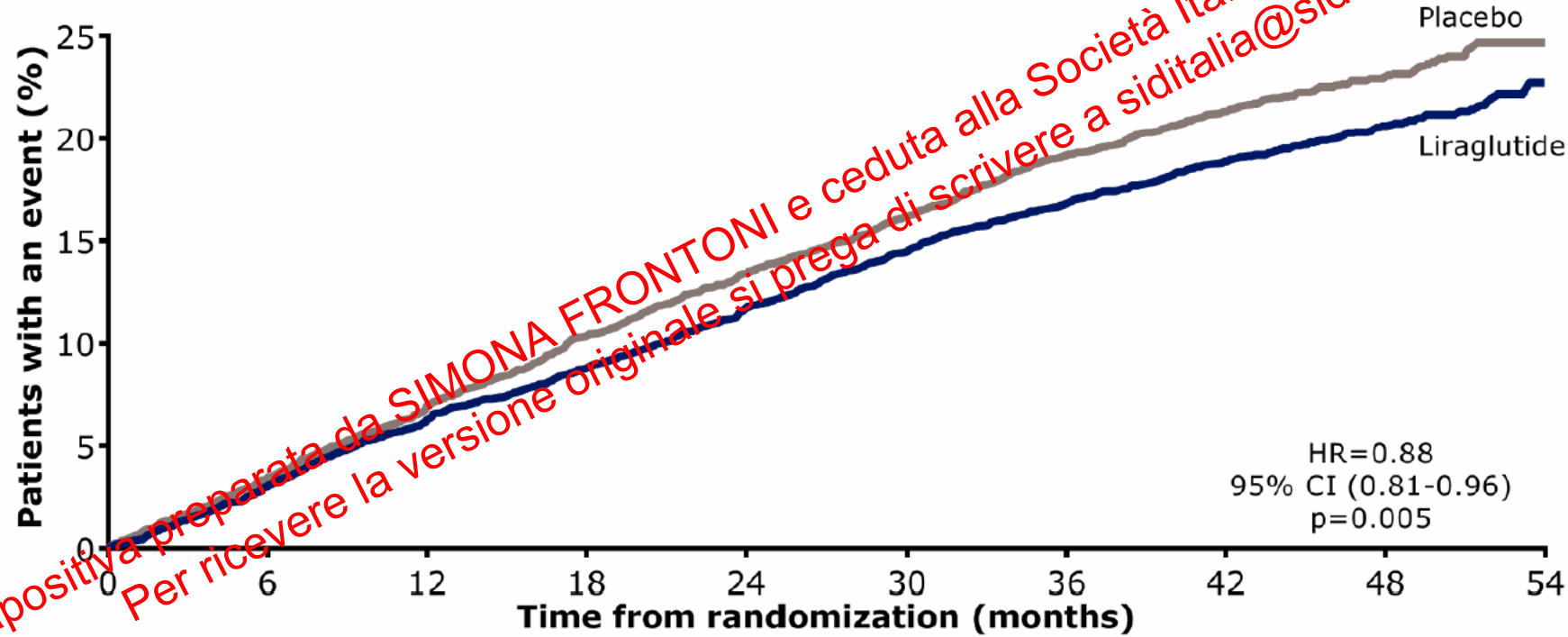
No. at Risk

Liraglutide	4668	4612	4550	4483	4414	4337	4258	4185	1662	467
Placebo	4672	4612	4540	4464	4372	4288	4187	4107	1647	442

Marso SP et al – NEJM 2016

LEADER
expanded composite CVD endpoint

Figure S4. Time to first expanded composite cardiovascular outcome (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina pectoris or hospitalization for heart failure).

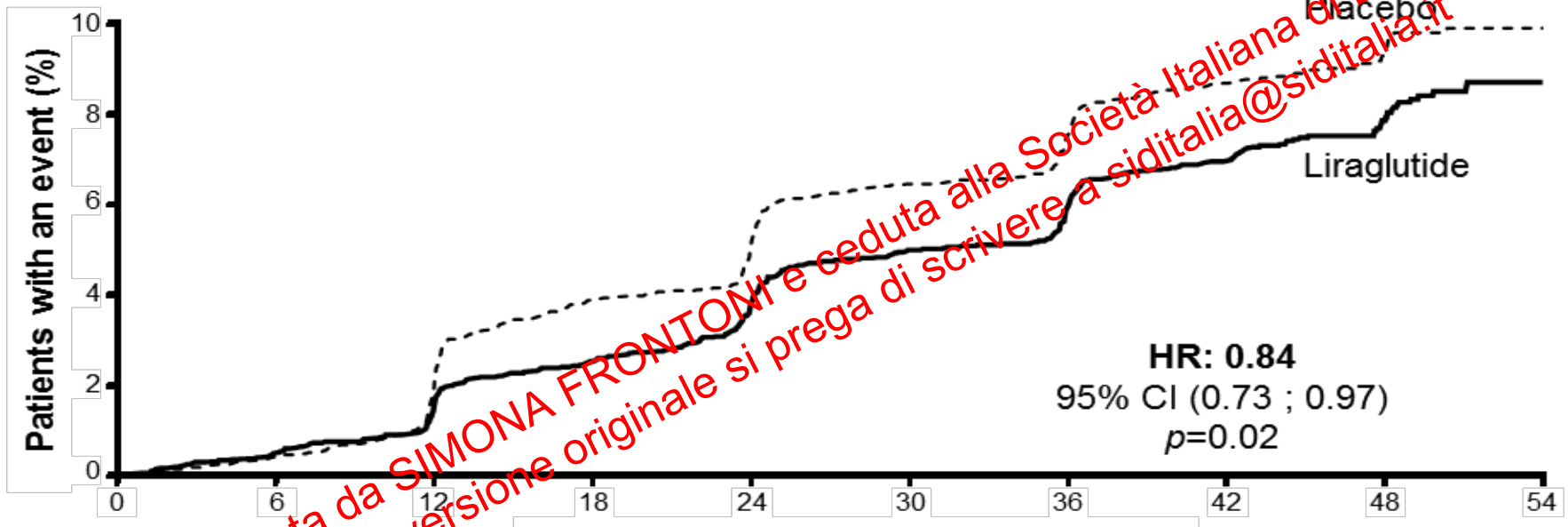


Patients at risk

Liraglutide	4668	4515	4356	4221	4063	3914	3793	3682	1452	395
Placebo	4672	4506	4336	4157	4002	3857	3697	3581	1410	366

Marso SP et al – NEJM 2016

LEADER
time to first microvascular outcome



Patients at risk

Liraglutide	4668	4618	4530	4446	4344	4234	4137	4038	1603	444
Placebo	4672	4631	4504	4373	4260	4134	4030	3921	1589	422

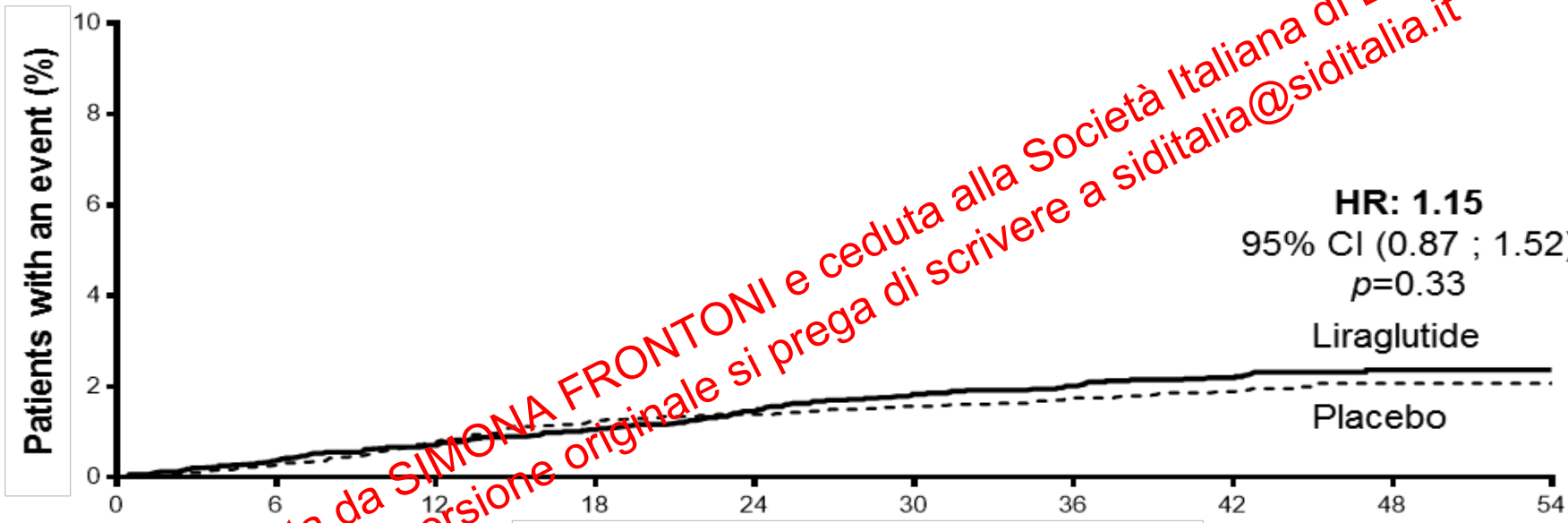
The cumulative incidences were estimated using the Kaplan–Meier method, and the HRs using the Cox proportional-hazards regression model. The data analyses are truncated at 54 months because less than 10% of the patients had an observation time beyond 54 months
CI: confidence interval; HR: hazard ratio

LEADER
Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

Presented at 52nd EASD Annual Meeting, 14 September 2016, Munich, Germany

LEADER
time to first eye outcome

Photocoagulation or treatment with intravitreal agents, vitreous hemorrhage or blindness



Patients at risk

Liraglutide	4668	4624	4566	4509	4442	4366	4297	4231	1689	473
Placebo	4672	4636	4565	4489	4417	4339	4264	4188	1681	454

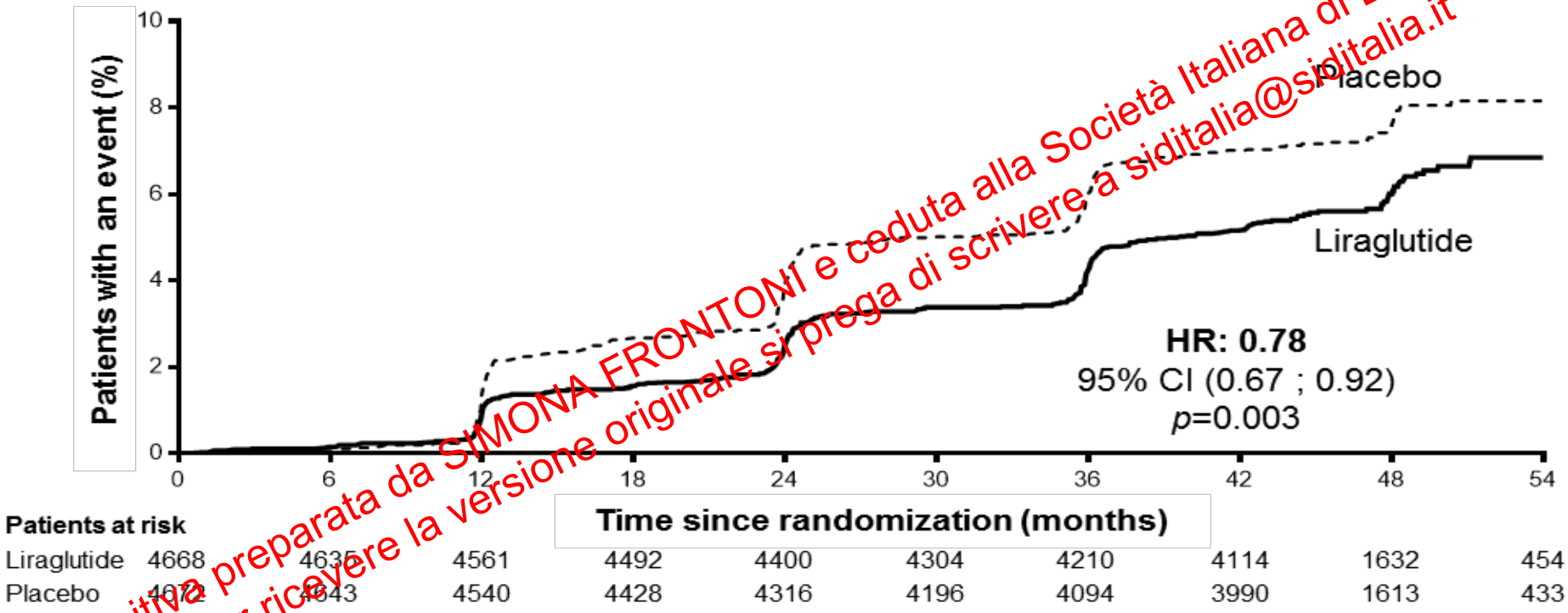
The cumulative incidences were estimated using the Kaplan–Meier method, and the HRs using the Cox proportional-hazards regression model. The data analyses are truncated at 54 months because less than 10% of the patients had an observation time beyond 54 months
CI: confidence interval; HR: hazard ratio

LEADER
Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA

LEADER
time to first renal outcome

Macroalbuminuria, doubling of serum creatinine, ESRD, renal death



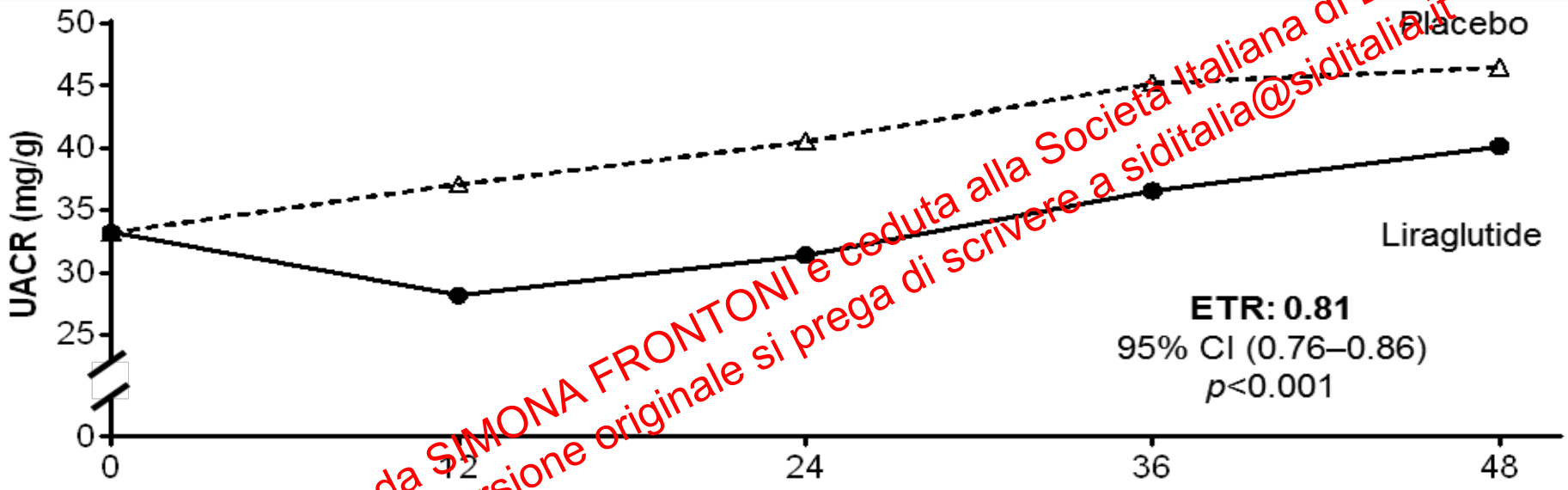
*and eGFR ≤45 mL/min/1.73 m^2 per MDRD
The cumulative incidences were estimated using the Kaplan–Meier method, and the HRs using the Cox proportional-hazards regression model. The data analyses are truncated at 54 months because less than 10% of the patients had an observation time beyond 54 months
CI: confidence interval; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease;
HR: hazard ratio; MDRD: modification of diet in renal disease

LEADER
Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

Presented at 52nd EASD Annual Meeting, 14 September 2016, Munich, Germany

LEADER

Urinary albumin-to-creatinine ratio over time



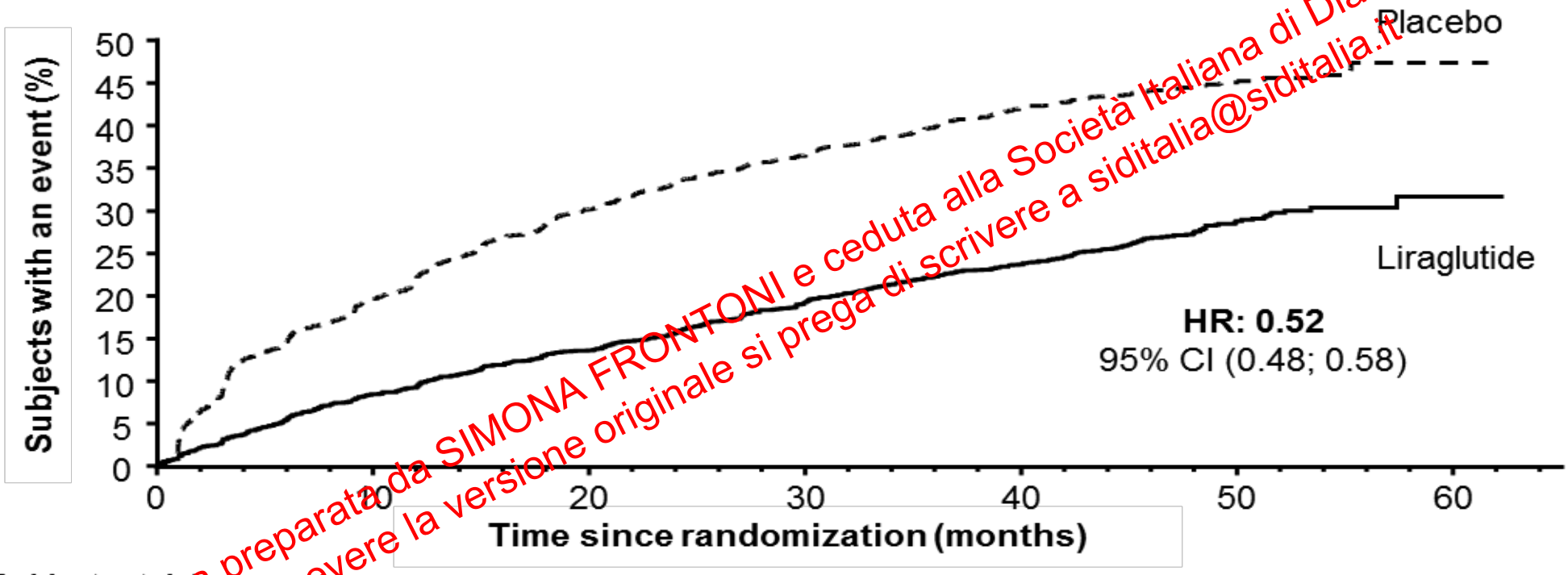
Number of patients					
Liraglutide	3775	3430	3247	3065	646
Placebo	3761	3468	3232	2956	591

Values below LLOQ not included (app. 20% of total)
Full analysis set. Estimated geometric means
CI: confidence interval; ETR: estimated treatment ratio; LLOQ: lower limit of quantification; UACR: urinary albumin:creatinine ratio

LEADER
Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

Presented at 52nd EASD Annual Meeting, 14 September 2016, Munich, Germany

LEADER
time to insulin initiation
patients insulin-naïve at baseline



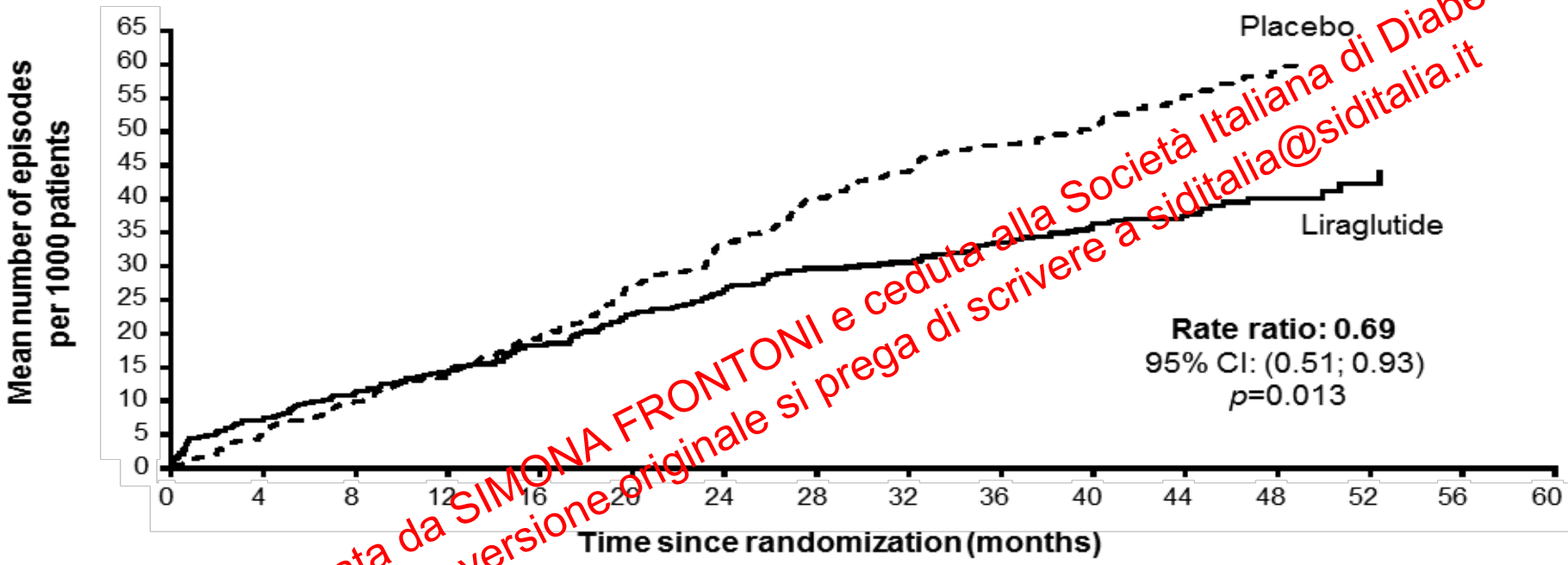
Subjects at risk							
Liraglutide	2633	2386	2238	2057	1906	448	3
Placebo	2548	2026	1728	1534	1374	336	7

LEADER
Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

Kaplan–Meier plot of time to insulin initiation in patients who were insulin-naïve at baseline; Cox proportional-hazards regression model adjusted for treatment; patients without an event are censored at time of last contact (phone or visit)
CI: confidence interval; HR: hazard ratio

Presented at the American Diabetes Association 77th Scientific Sessions, Session 1-AC-SY13. June 11 2017, San Diego, CA, USA

LEADER
severe hypoglycemia over time



	Liraglutide	Placebo
Number of patients with severe hypoglycemia (%)	114 (2.4)	153 (3.4)

LEADER
Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

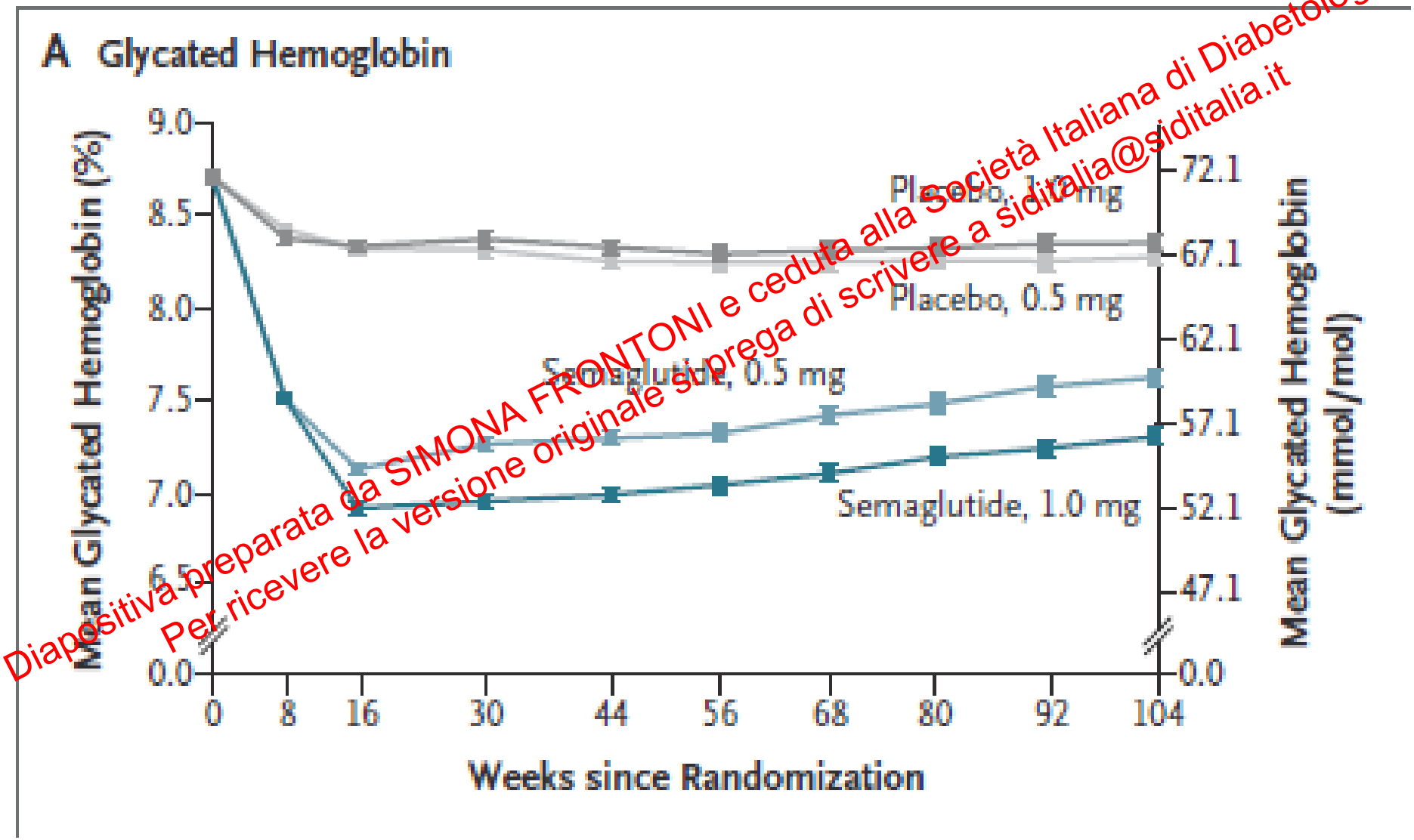
Full analysis set. Mean number of severe hypoglycemic episodes. Number of events analyzed using a negative binomial regression model using a log link and the logarithm of the observation time (100 years) as offset. Treatment, sex, region and antidiabetic therapy at baseline included as fixed effects and age at baseline included as covariates
CI: confidence interval

Presented at the American Diabetes Association 77th Scientific Sessions, Session 1-AC-SY13. June 11 2017, San Diego, CA, USA

SUSTAIN 6

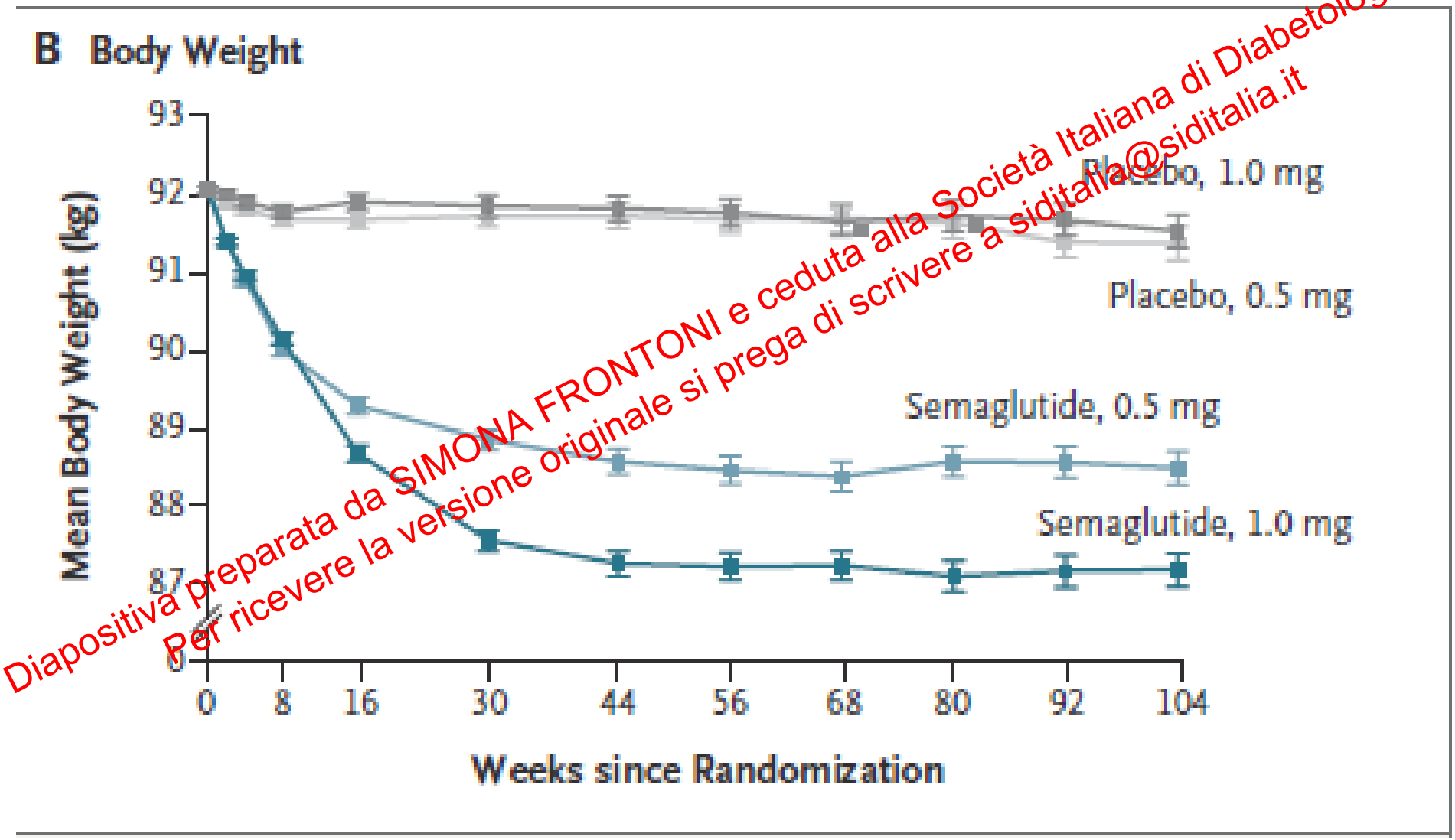
Semaglutide vs. placebo on top of background treatment in subjects with previous CVD or high CVD risk

SUSTAIN 6
time course of HbA1c



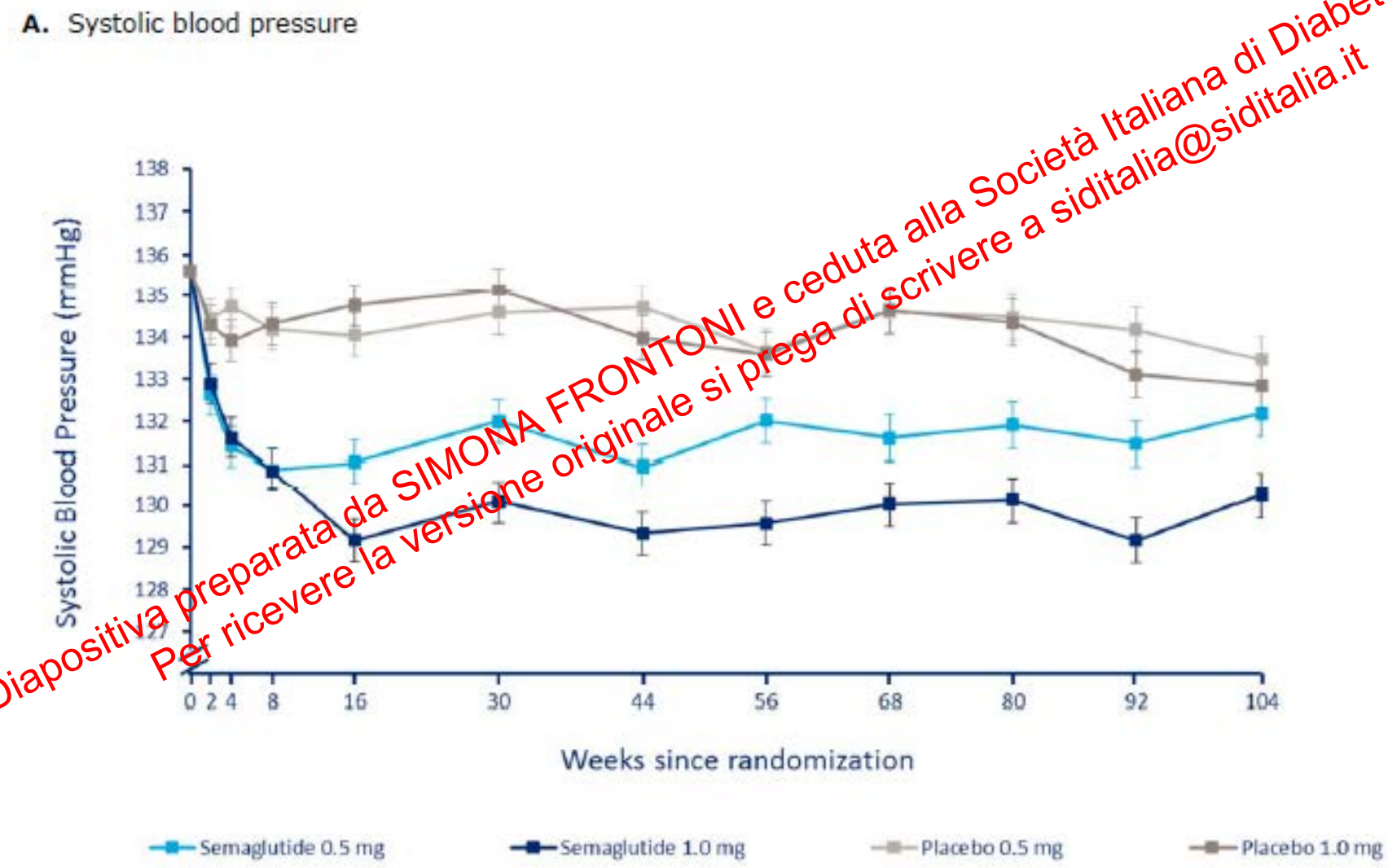
Marso SP et al – NEJM 2016; 375: 1834

SUSTAIN 6
time course of BW



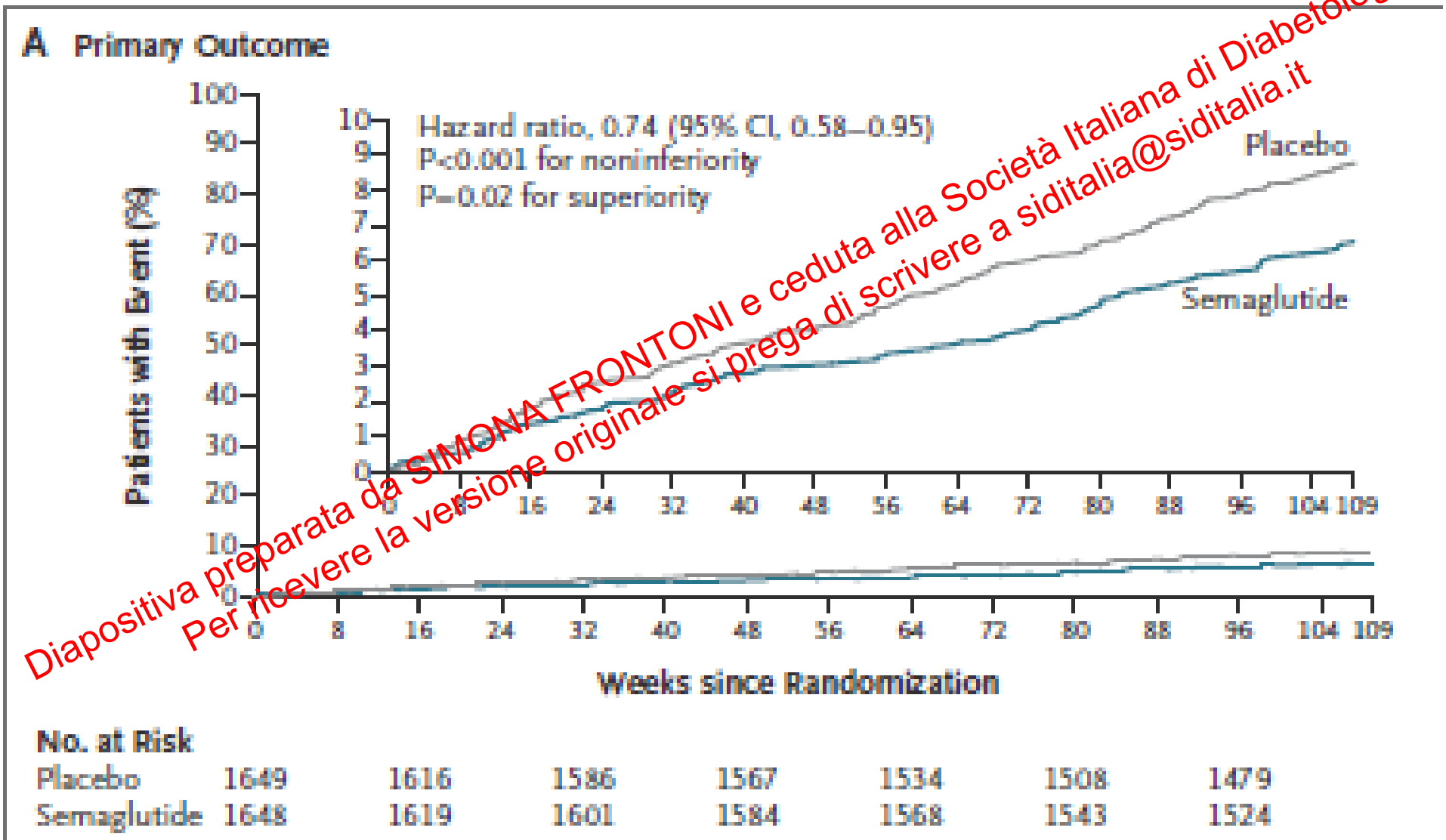
Marso SP et al – NEJM 2016; 375: 1834

SUSTAIN 6
time course of SBP



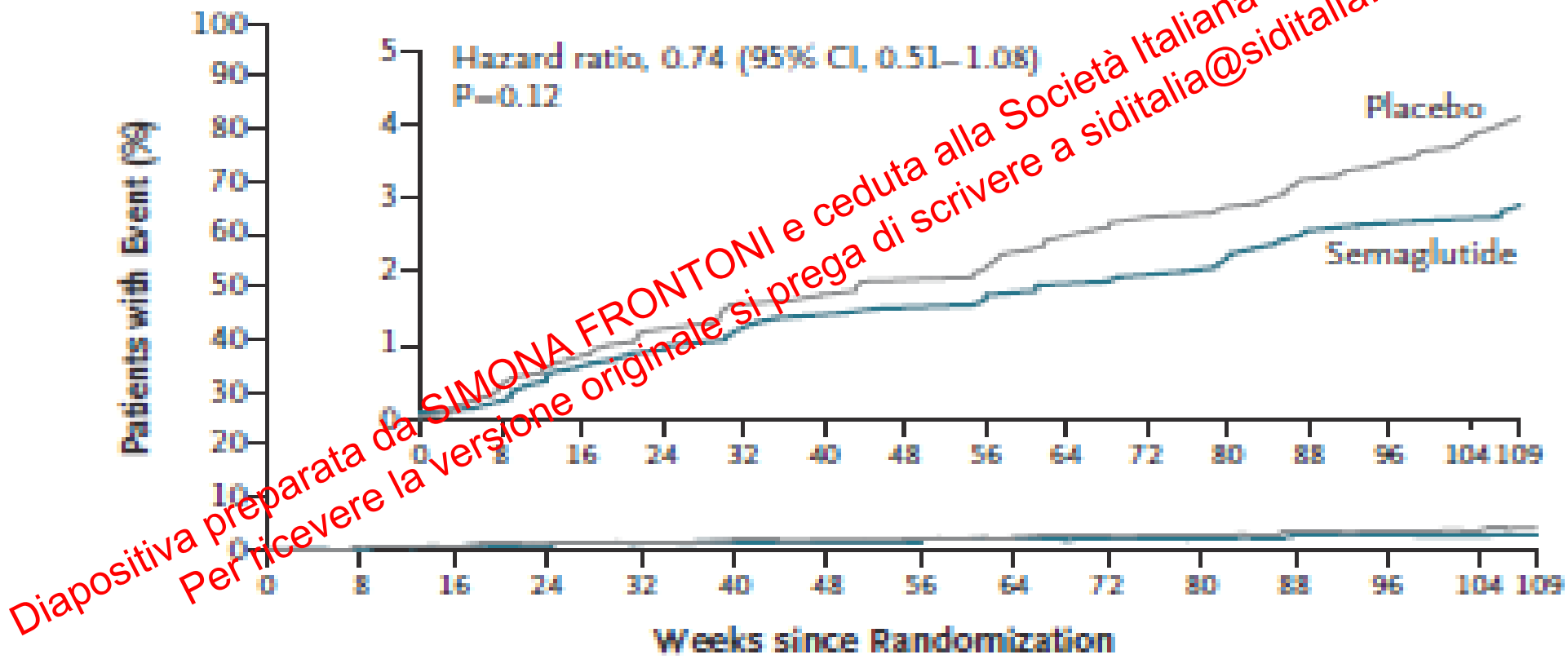
Marso SP et al – NEJM 2016; 375: 1834

SUSTAIN 6
primary outcome (MACE)



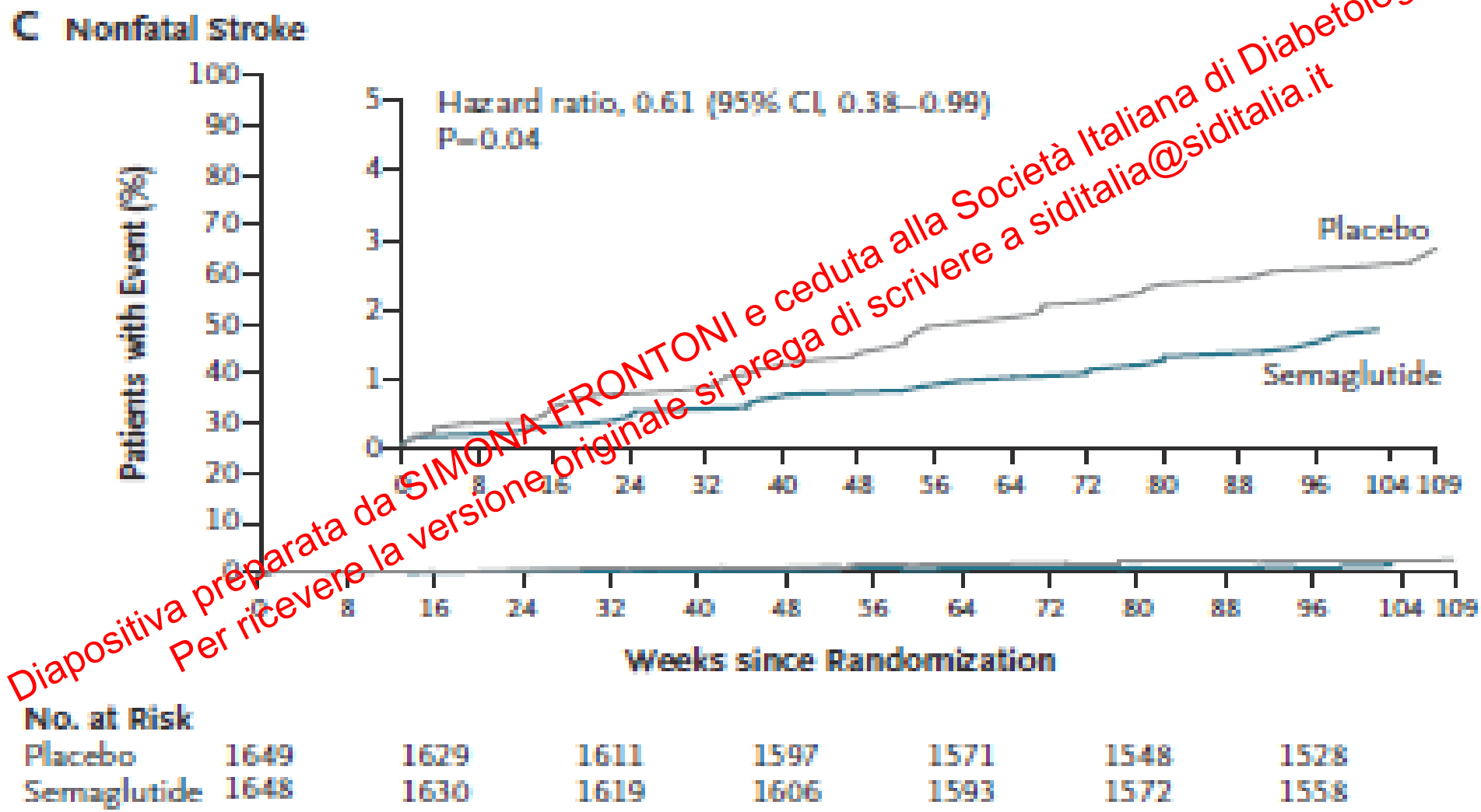
Marso SP et al – NEJM 2016; 375: 1834

SUSTAIN 6
non-fatal MI



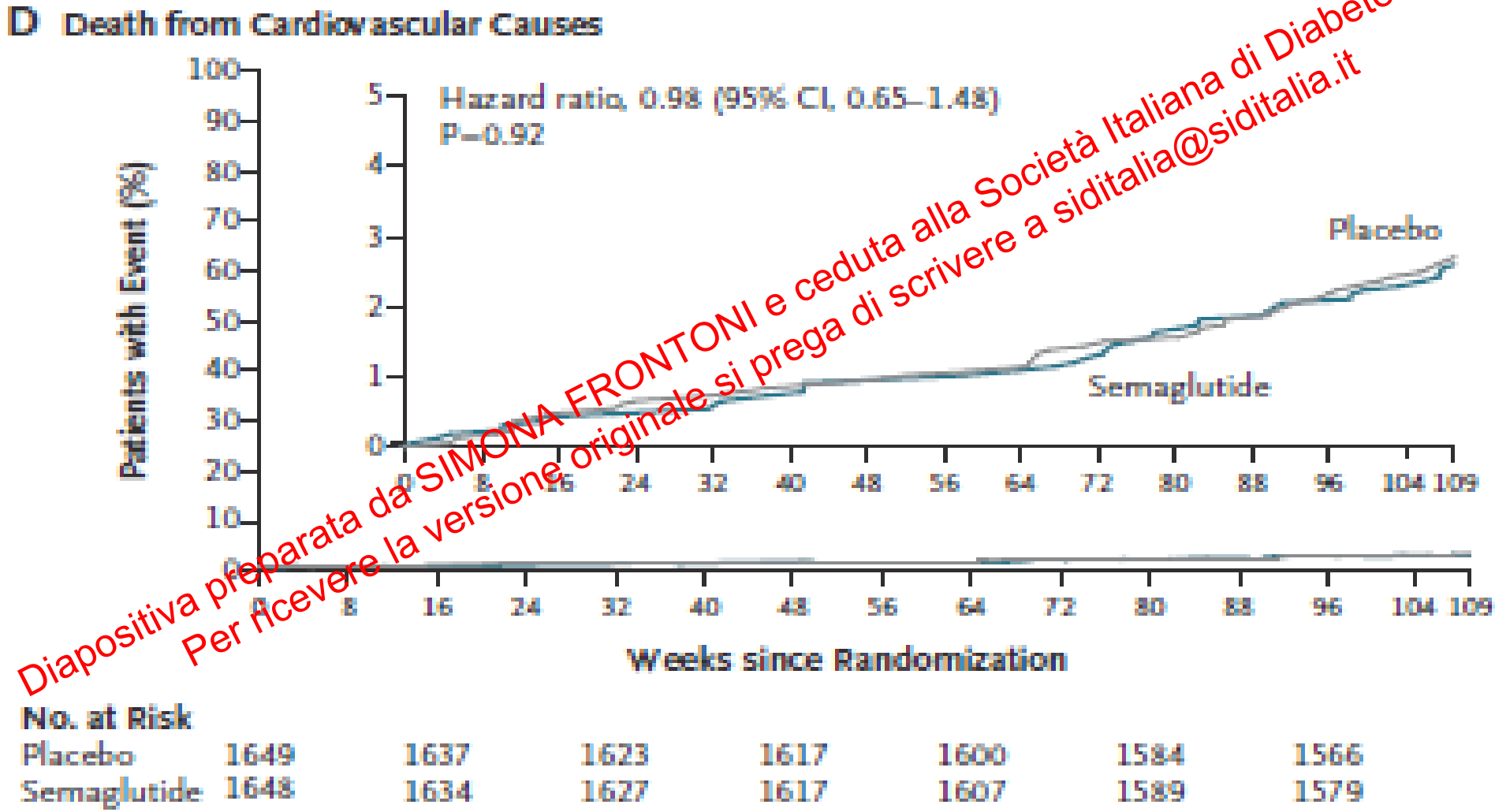
Marso SP et al – NEJM 2016; 375: 1834

SUSTAIN 6
non-fatal stroke



Marso SP et al – NEJM 2016; 375: 1834

SUSTAIN 6
cardiovascular death



Marso SP et al – NEJM 2016; 375: 1834

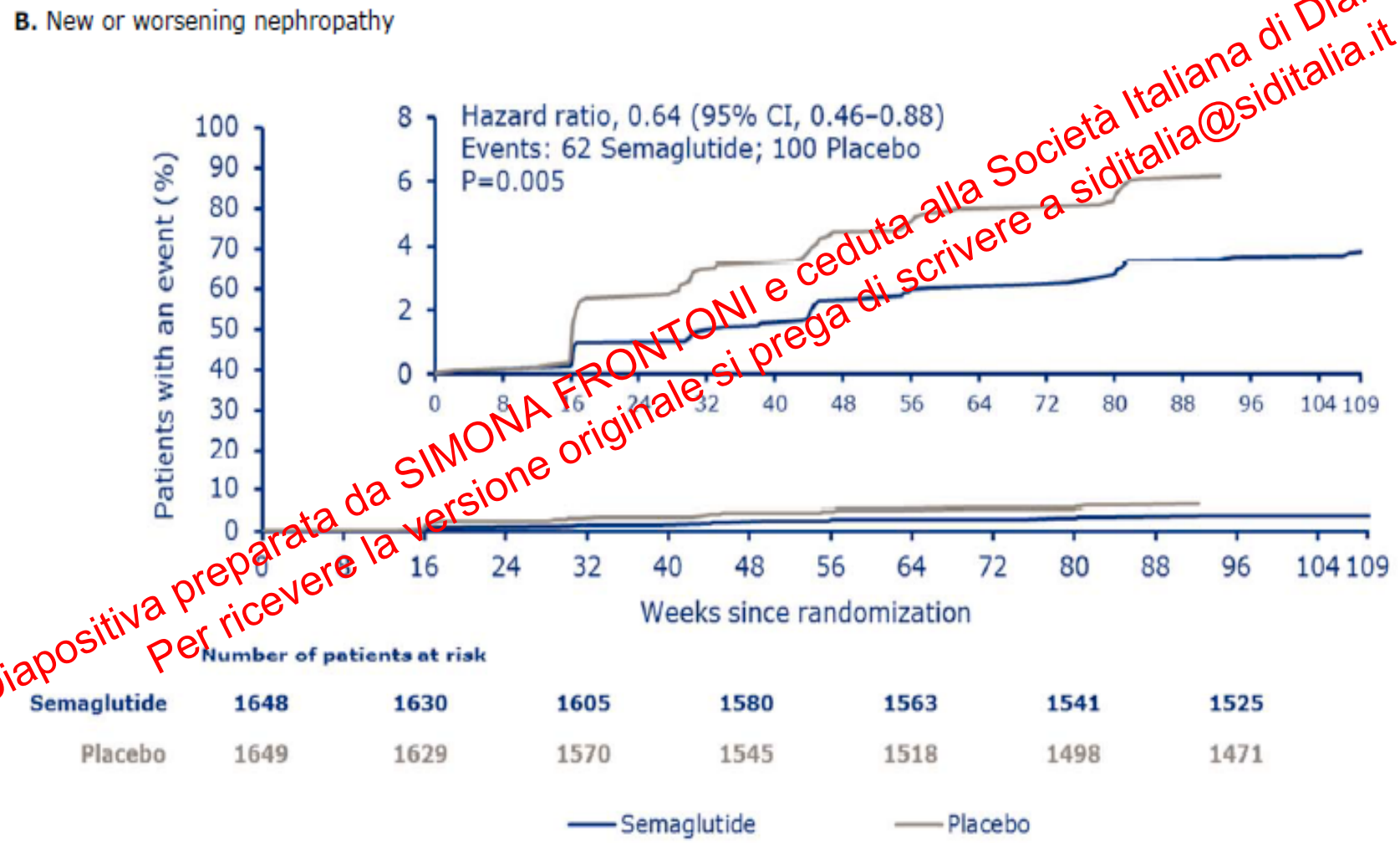
SUSTAIN 6
primary and secondary outcome

Table 2. Primary and Secondary Cardiovascular and Microvascular Outcomes.

Outcome	Semaglutide (N=1648)		Placebo (N=1649)		Hazard Ratio (95% CI)	P Value
	no. (%)	*no./100 person-yr*	*no. (%)*	*no./100 person-yr*		
Primary composite outcome†	108 (6.6)	3.24	146 (8.9)	4.44	0.74 (0.58–0.95)	<0.001 for noninferiority; 0.02 for superiority
Expanded composite outcome‡	199 (12.1)	6.17	264 (16.0)	8.36	0.74 (0.62–0.89)	0.002
All-cause death, nonfatal myocardial infarction, or nonfatal stroke	122 (7.4)	3.66	158 (9.6)	4.81	0.77 (0.61–0.97)	0.03
Death						
From any cause	62 (3.8)	1.82	60 (3.6)	1.76	1.05 (0.74–1.50)	0.79
From cardiovascular cause	44 (2.7)	1.29	46 (2.8)	1.35	0.98 (0.65–1.48)	0.92
Nonfatal myocardial infarction	47 (2.9)	1.40	64 (3.9)	1.92	0.74 (0.51–1.08)	0.12
Nonfatal stroke	27 (1.6)	0.80	44 (2.7)	1.31	0.61 (0.38–0.99)	0.04
Hospitalization for unstable angina pectoris	22 (1.3)	0.65	27 (1.6)	0.80	0.82 (0.47–1.44)	0.49
Revascularization	83 (5.0)	2.50	126 (7.6)	3.85	0.65 (0.50–0.86)	0.003
Hospitalization for heart failure	59 (3.6)	1.76	54 (3.3)	1.61	1.11 (0.77–1.61)	0.57
Retinopathy complications§	50 (3.0)	1.49	29 (1.8)	0.86	1.76 (1.11–2.78)	0.02
New or worsening nephropathy¶	62 (3.8)	1.86	100 (6.1)	3.06	0.64 (0.46–0.88)	0.005

Marso SP et al – NEJM 2016; 375: 1834

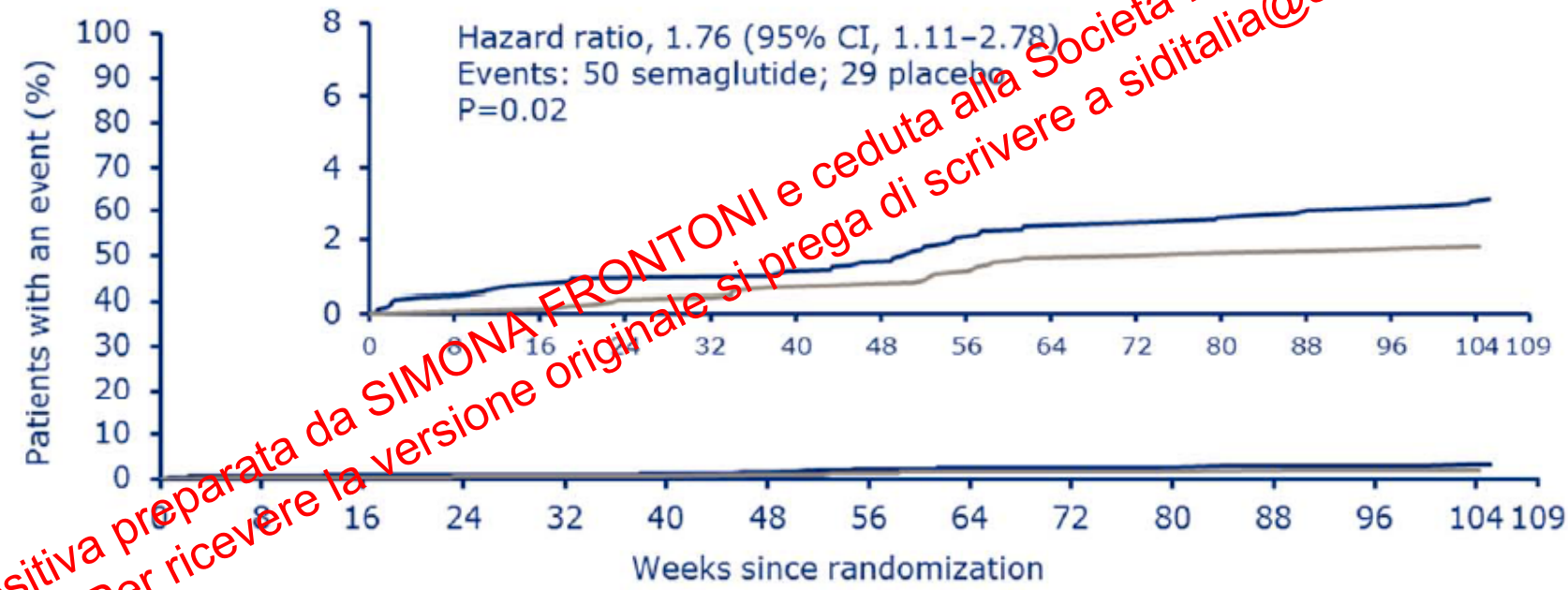
SUSTAIN 6
new or worsening nephropathy



Marso SP et al – NEJM 2016; 375: 1834

SUSTAIN 6
retinopathy complications

A. Diabetic retinopathy complications



Number of patients at risk

Semaglutide	**1648**	**1622**	**1612**	**1595**	**1570**	**1548**	**1535**
Placebo	1649	1636	1617	1605	1576	1558	1539

Semaglutide — Placebo

Marso SP et al – NEJM 2016; 375: 1834

FREEDOM CVO

Exenatide Once Yearly vs. placebo on top of background treatment in subjects with previous CVD or high CVD risk

PRESS RELEASE – May 2016

Intarcia Announces Successful Cardiovascular Safety Results in Phase 3 FREEDOM-CVO Trial for ITCA 650, an Investigational Therapy for T2DM

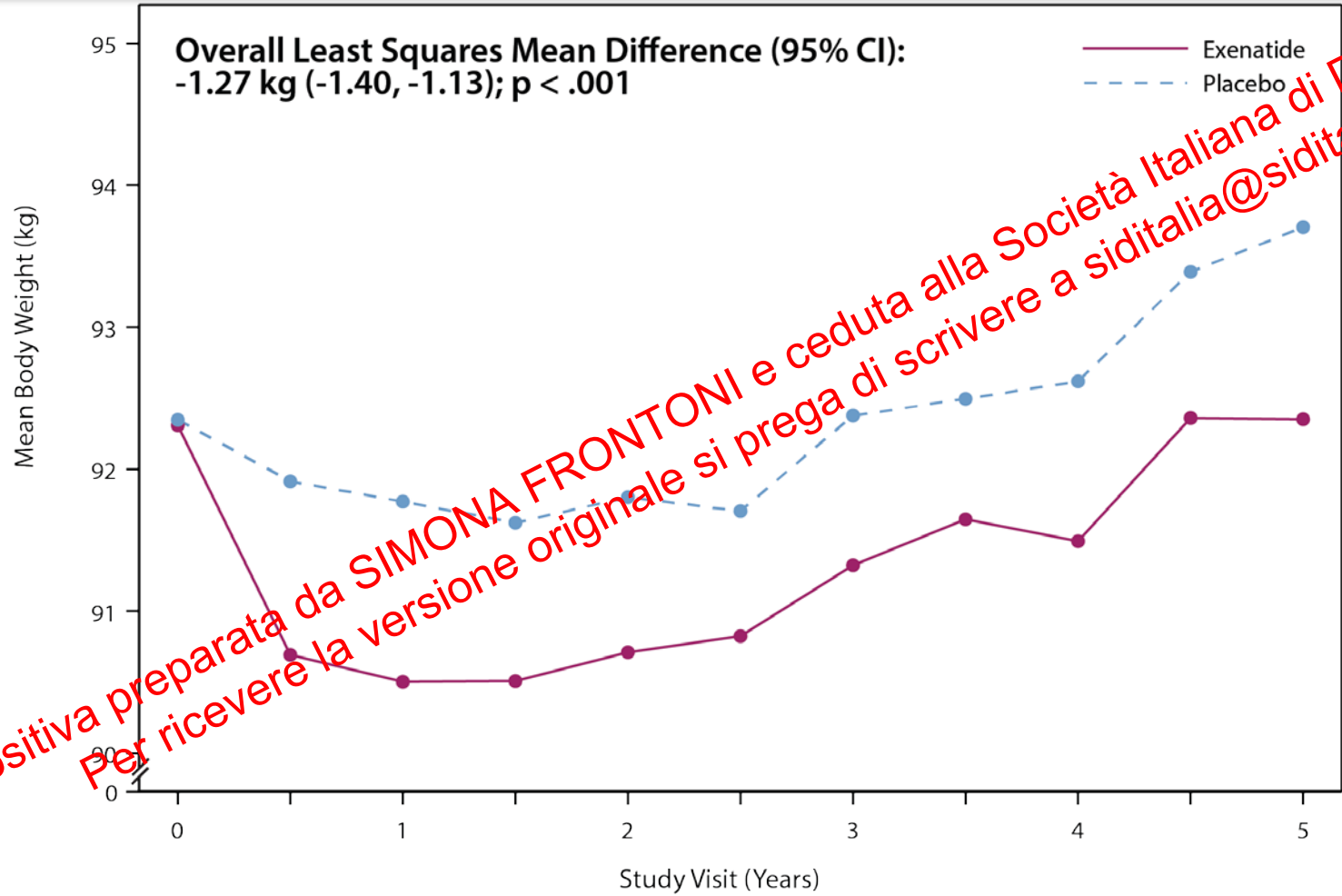
FREEDOM-CVO Phase 3 safety trial in more than 4,000 patients meets its primary and secondary endpoints by demonstrating FDA required non-inferiority for pre-approval cardiovascular (CV) safety. Final data to be published and presented at major future medical meeting.

The FREEDOM-CVO Safety Trial is the fourth and final Phase 3 clinical trial of the FREEDOM program. It is a global, placebo-controlled cardiovascular outcomes study designed to meet the pre-approval safety assessment requirements set out in the U.S. Food and Drug Administration's Guidance for Industry to evaluate cardiovascular risk for new therapies to treat type 2 diabetes. FREEDOM-CVO evaluated the safety of ITCA 650 at 60 micrograms per day vs. placebo in just over **4,000 patients** on a variety of approved standard of care anti-diabetes therapies. The duration of study was dependent on event-based outcomes, and lasted just under 3 years, reaching the target number of cardiovascular events in the fourth quarter of 2015. The average treatment duration in FREEDOM-CVO was **1.2 years**. Age eligibility for the study was 40 years and older. Inclusion criteria stipulated patients must have HbA1c > 6.5%, **a history of coronary, cerebrovascular or peripheral artery disease, or multiple CV risk factors**. The primary objective was to conduct a meta-analysis across FREEDOM-CVO and other phase 3 studies to demonstrate that the upper limit of the 95% confidence interval of the hazard ratio of major adverse cardiac events (MACE) in adult patients on Standard of Care for type 2 diabetes receiving either ITCA 650 or placebo, does not exceed 1.8. There were a total of 160 strict **MACE** events observed in the FREEDOM-CVO trial. The overall safety and tolerability data for ITCA 650 was consistent with the three phase 3 trials that have already been presented and what is documented in the published literature for exenatide and other GLP-1 receptor agonist therapies.

EXSCEL

Exenatide once weekly vs. placebo on top of background treatment in subjects with previous CVD or high CVD risk

EXSCEL
between group BW differences over time

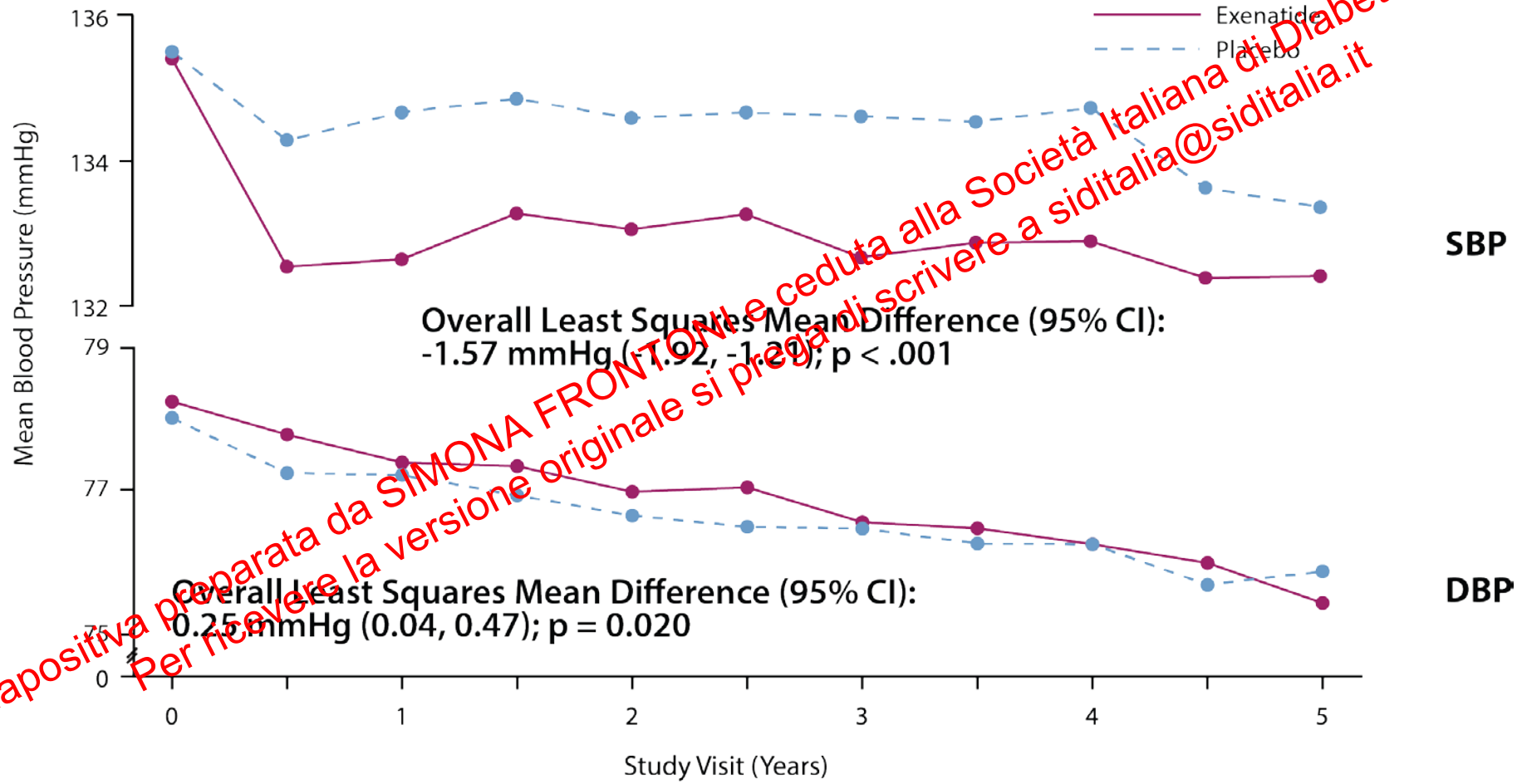


Number of Patients:

Exenatide	7334	6783	6452	6108	5777	4501	3464	2867	2387	1581	960
Placebo	7372	6798	6378	6022	5678	4381	3365	2761	2227	1451	793

Holman RR et al – NEJM 2017; sept. 14

EXSCEL
between group BP differences over time

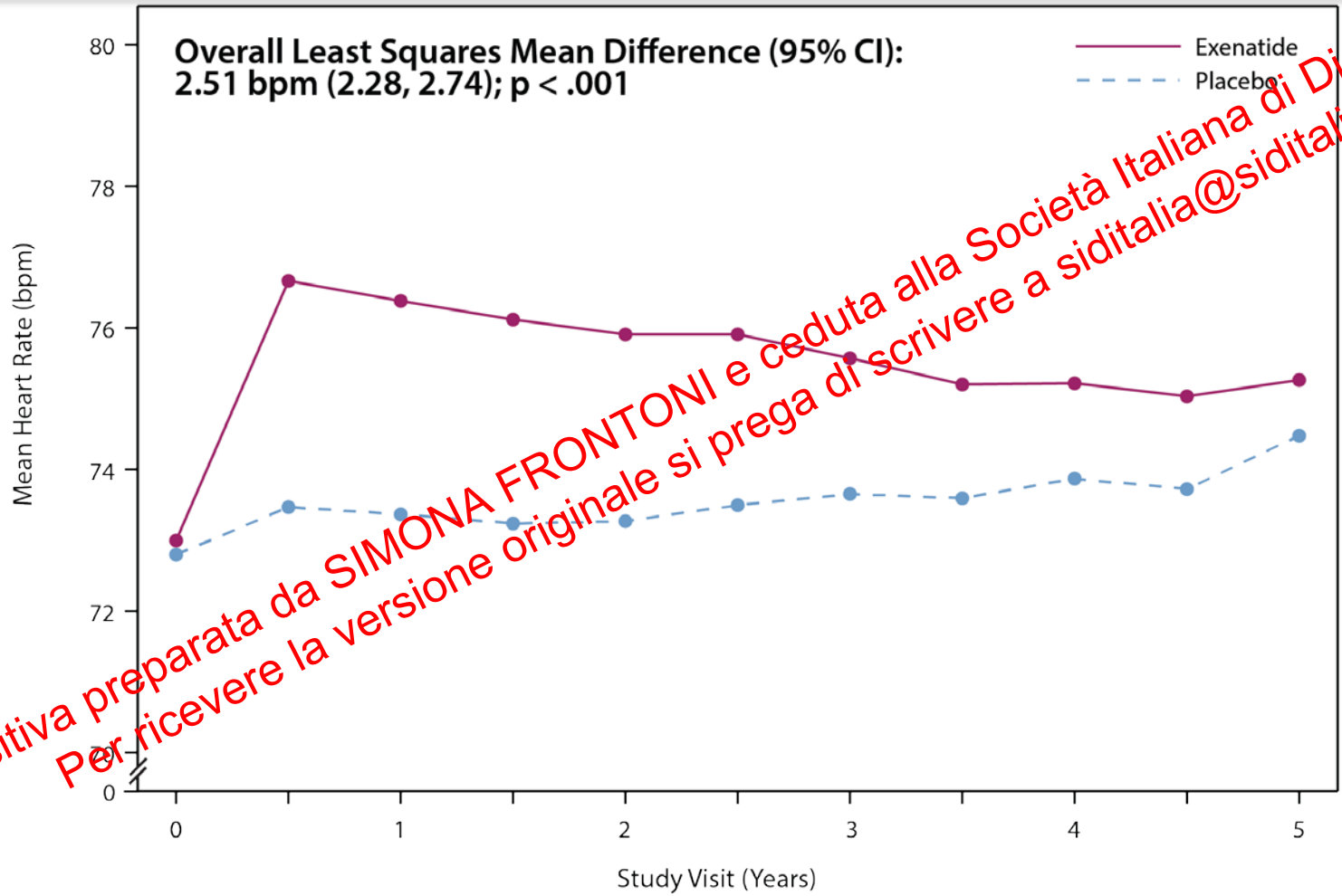


Number of Patients:

Exenatide	7346	6841	6502	6165	5818	4547	3489	2878	2396	1590	968
Placebo	7381	6853	6420	6074	5732	4419	3390	2785	2244	1464	804

Holman RR et al – NEJM 2017; sept. 14

EXSCEL
between group HR differences over time



Number of Patients:

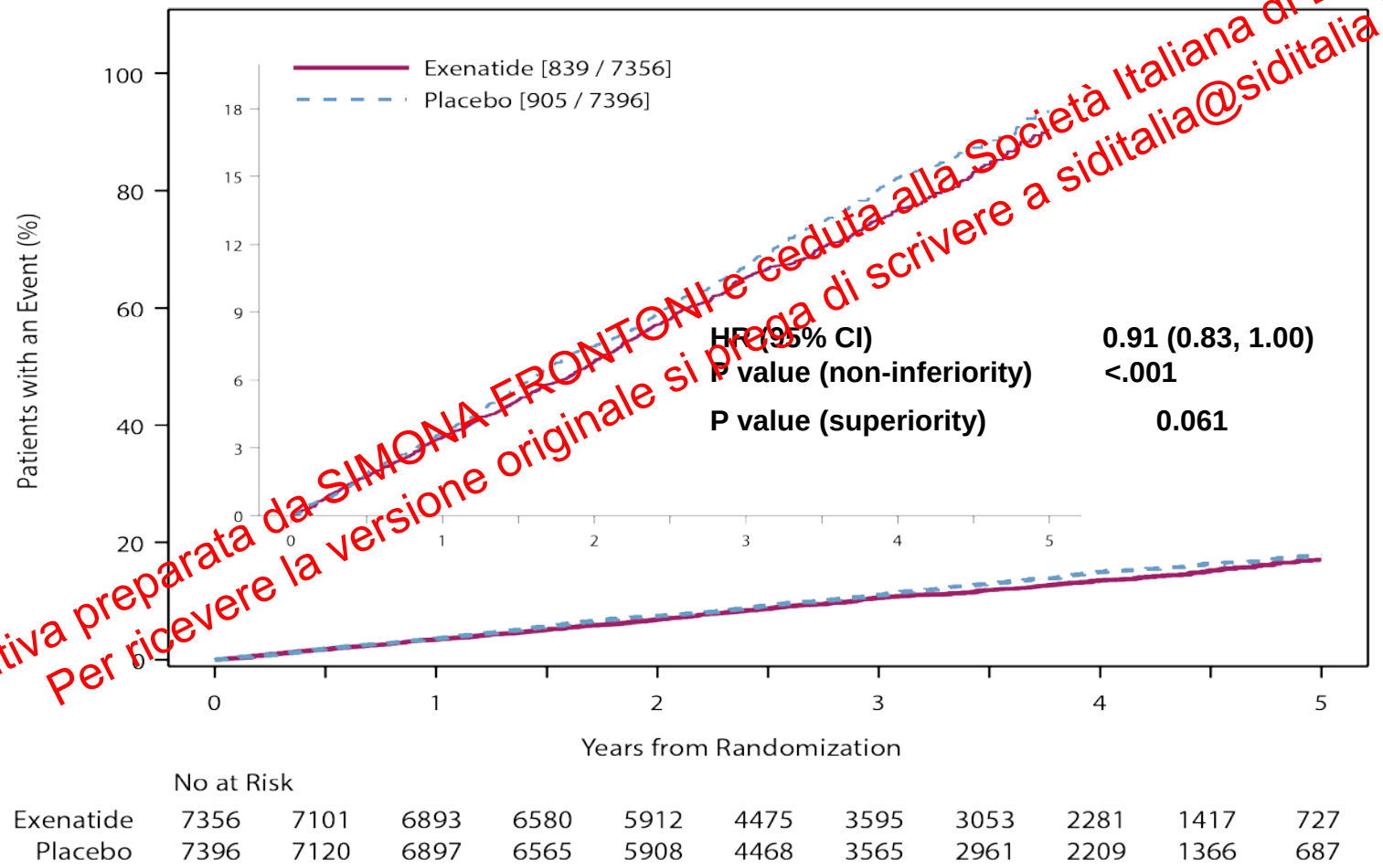
Exenatide	7320	6804	6460	6119	5780	4508	3462	2861	2378	1580	961
Placebo	7351	6818	6389	6048	5700	4381	3364	2765	2230	1454	794

Holman RR et al – NEJM 2017; sept. 14

EXSCEL

primary composite cardiovascular outcome

Intention-to-Treat Analysis for Non-inferiority & Superiority



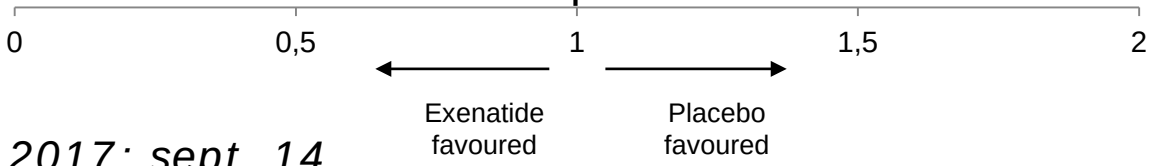
Holman RR et al – NEJM 2017; sept. 14

EXSCEL

primary composite cardiovascular outcome

Intention-to-Treat Analysis

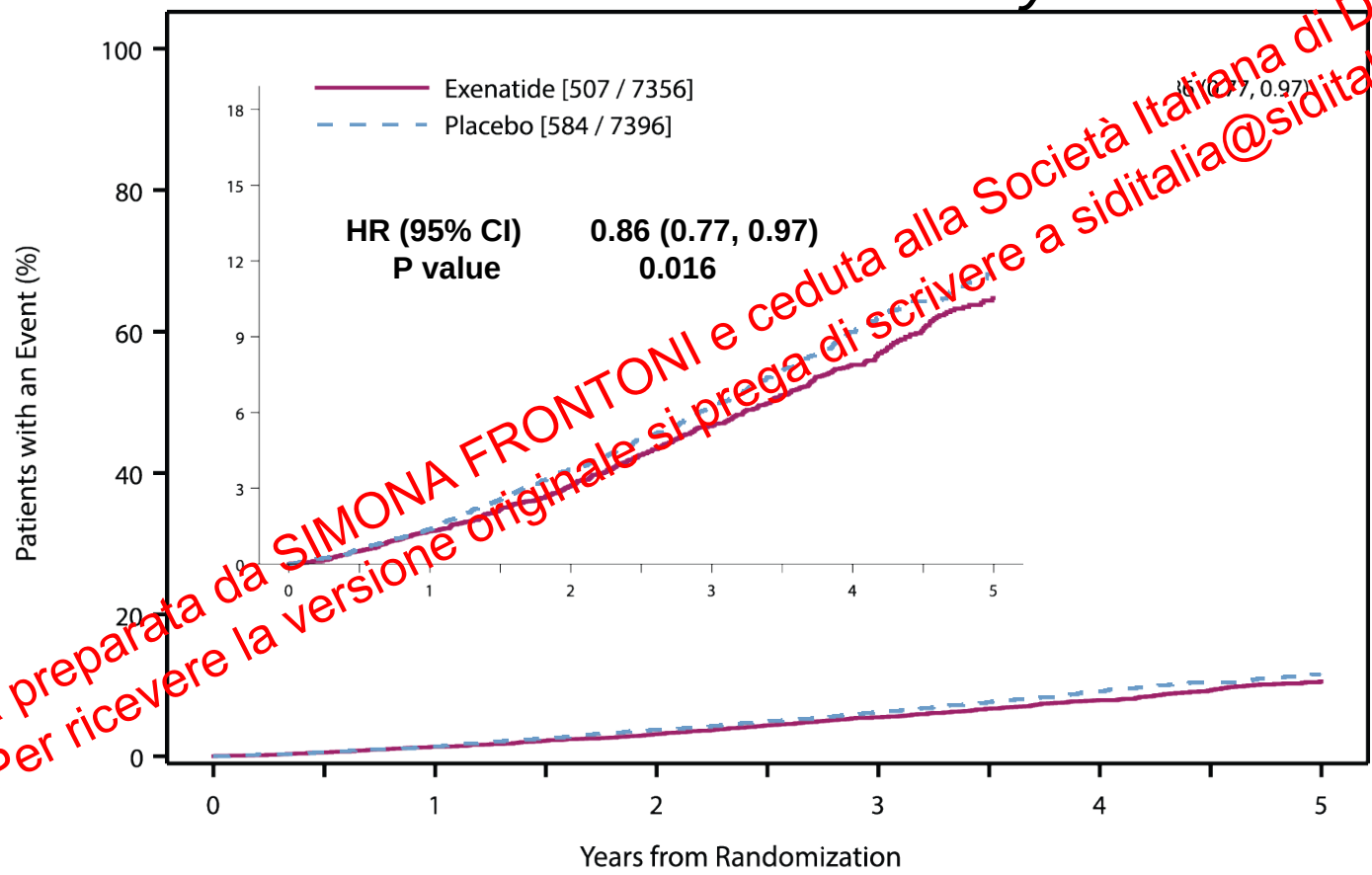
	Exenatide N=7356	Placebo N=7396	Hazard Ratio	95% CI	P value
MACE	839 (11.4%) 3.7 per 100 pt-yrs	905 (12.2%) 4.0 per 100 pt-yrs	0.91	0.83, 1.00	**<.001 (non-inferiority)** **0.061 (superiority)**
CV-death	229 (3.1%)	258 (3.5%)	0.88	0.73, 1.05	
Non-fatal MI	455 (6.2%)	470 (6.4%)	0.95	0.84, 1.09	**0.628 (homogeneity among components)**
Non-fatal stroke	155 (2.1%)	177 (2.4%)	0.86	0.70, 1.07	



Holman RR et al – NEJM 2017; sept. 14

EXSCEL
all-cause mortality

Intention-to-Treat Analysis



Holman RR et al – NEJM 2017; sept. 14

EXSCEL
Summary of results

EXSCEL met its primary safety hypothesis

– MACE-3 HR 0.91 (0.83, 1.00), p<0.001 for non-inferiority

EXSCEL did not meet its primary efficacy hypothesis

– MACE-3 HR 0.91 (0.83, 1.00), p=0.061 for superiority

Secondary outcomes were consistent with the primary outcome

– All-Cause Mortality: HR 0.86 (95% CI 0.77, 0.97), p=0.016

•Cardiovascular Death: HR 0.88 (95% CI 0.76, 1.02), p=0.096

•Fatal or Non-Fatal Myocardial Infarction: HR 0.97 (95% CI 0.85, 1.10), p=0.622

•Fatal or Non-Fatal Stroke: HR 0.85 (95% CI 0.70, 1.03), p=0.095

•Hospitalisation for Acute Coronary Syndrome: HR 1.05 (95% CI 0.94, 1.18), p=0.402

•Hospitalisation for Heart Failure: HR 0.94 (95% CI 0.78, 1.13), p=0.485

REWIND

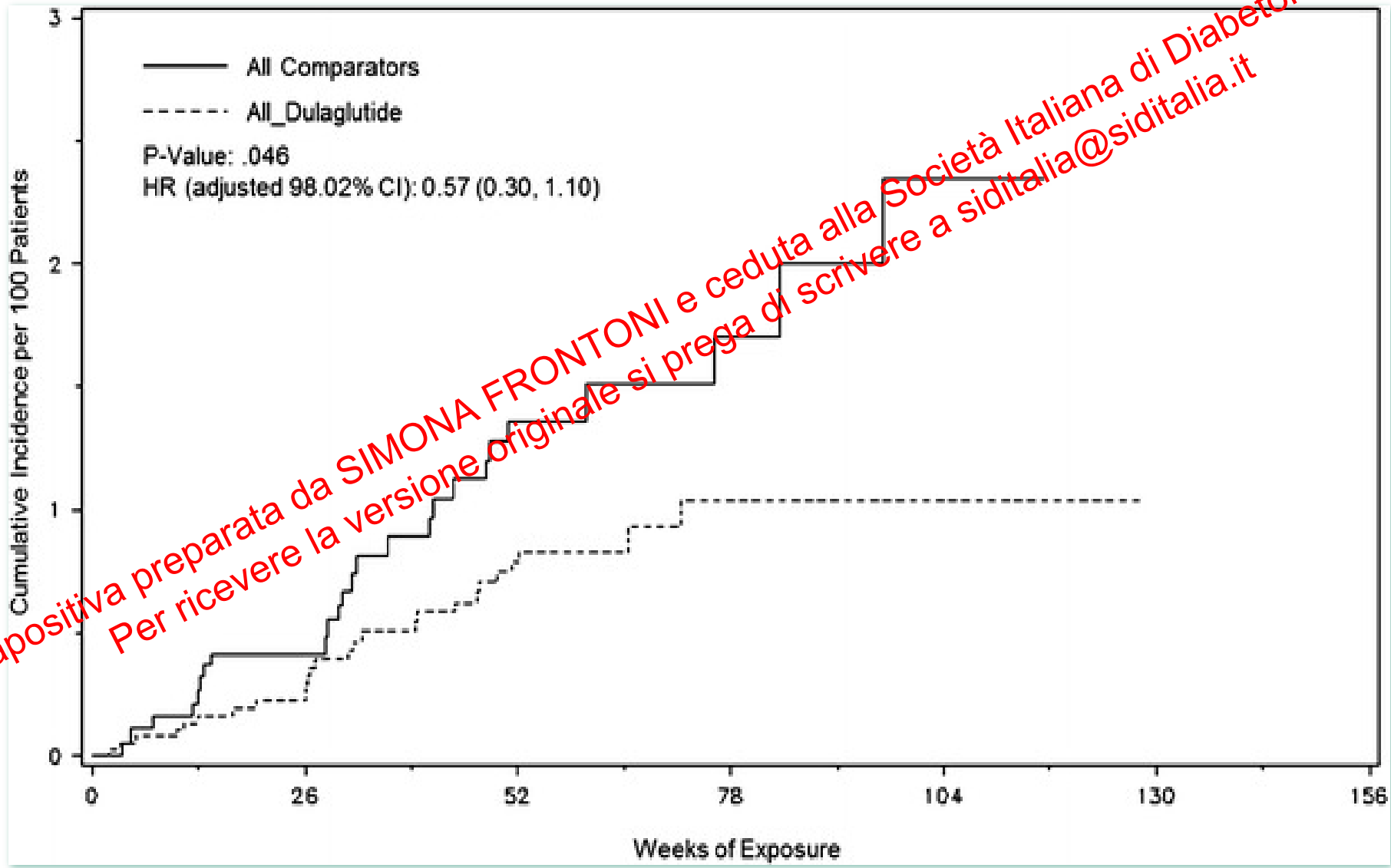
Dulaglutide vs. placebo on top of background treatment in subjects with previous CVD or high CVD risk

REWIND
Baseline characteristics

- 9901 participants, in 2 years
- mean age 66 yrs
- 46% women
- mean duration of diabetes 10 yrs
- mean baseline HbA1c 7.3%
- 31% prior cardiovascular disease

Gerstein H et al – DOM 2017

Dulaglutide
phase II/III trials: CV safety



Harmony CVOT

Albiglutide vs. placebo on top of background treatment in subjects with previous CVD or high CVD risk

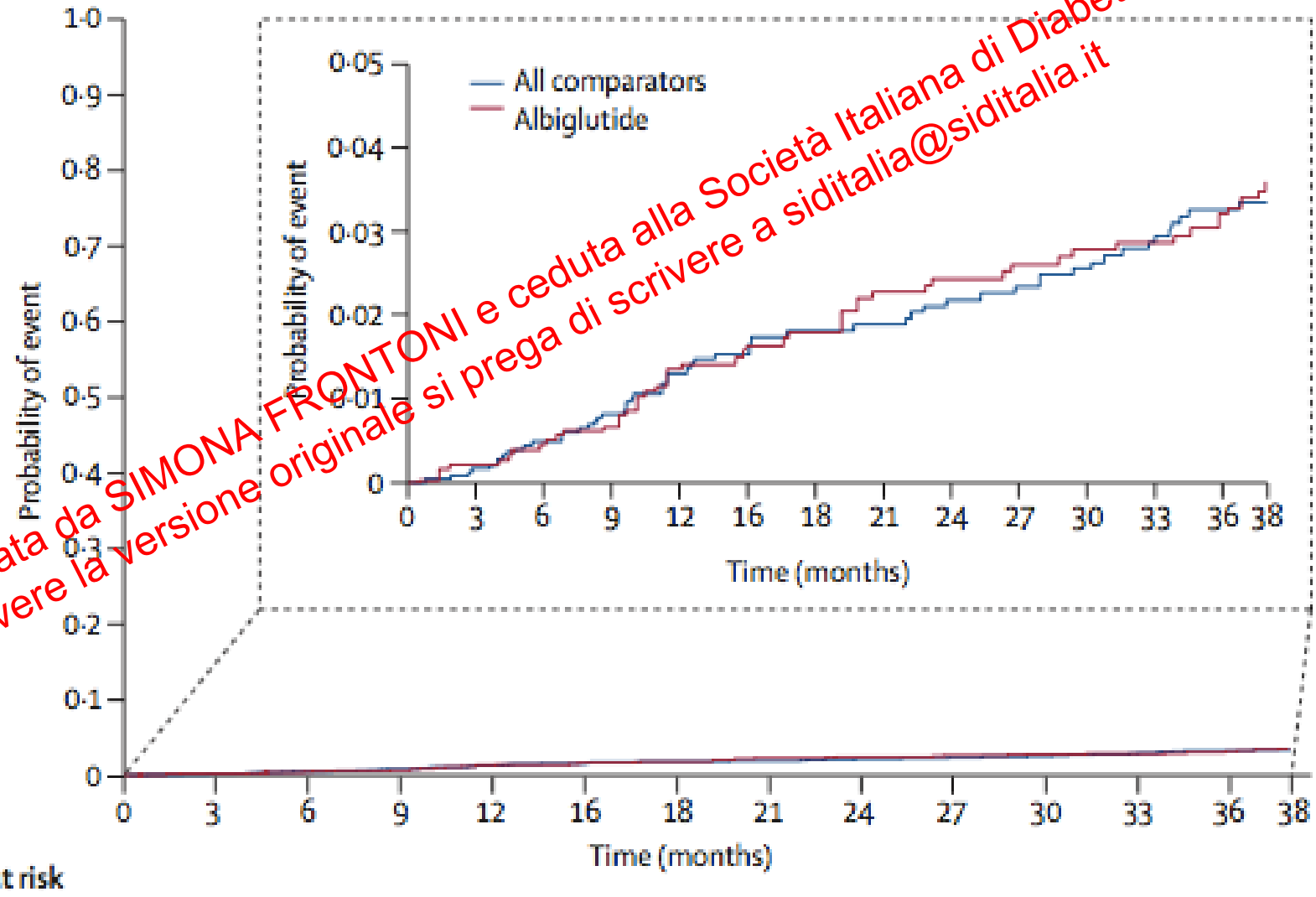
Cardiovascular safety of albiglutide in the Harmony programme

A prospective meta-analysis of 8 phase 3 and 1 phase 2b trials

	Albiglutide (n=2524)	All comparators (n=2583)
Sex		
Men	1326 (53%)	1364 (53%)
Women	1198 (47%)	1219 (47%)
Age at randomisation (years)	55·8 (10)	56·0 (10)
Ethnic origin		
Non-Hispanic white	1109 (44%)	1181 (46%)
Hispanic	584 (23%)	691 (27%)
Asian	423 (17%)	349 (14%)
Non-Hispanic African American	354 (14%)	313 (12%)
Other	54 (2%)	49 (2%)
Weight (kg)	90·5 (20·9)	91·1 (21·1)
BMI (kg/m^2)	32·3 (5·9)	32·4 (5·7)
Diabetes duration (years)	8·3 (6·3)	8·2 (6·2)
HbA_{1c} (%)	8·2% (0·91%)	8·2% (0·88%)

Fisher M et al – Lancet Diabetes Endocrinol 2015

Time to first MACE or hospital admission for unstable angina with albiglutide versus all comparators



Fisher M et al – Lancet Diabetes Endocrinol 2015

GSK
5 Crescent Drive
Philadelphia PA
19112

www.gsk.com

TANZEUM (albiglutide) Discontinuation — Q&A

On July 26, 2017, GSK announced plans to discontinue the manufacturing and sale of TANZEUM (albiglutide) (30 mg and 50 mg for injection) by July 2018.

This was a difficult decision for all of us at GSK. Given the availability of multiple treatment options for patients with type 2 diabetes, it has become harder and harder to make the impact we anticipated for patients. We believe patients can be well served by other companies that offer alternative treatments and also have ongoing investments in patient education and support services.

Che dicono le linee guida?

SID
Società Italiana di Diabetologia

POSITION STATEMENT

Farmaci ipoglicemizzanti, malattie cardiovascolari e renali

Box 1 *- Al momento attuale i farmaci ipoglicemizzanti che posseggono documentati benefici cardiovascolari sono metformina (prevenzione primaria), empagliflozin, liraglutide e pioglitazone (prevenzione secondaria).*

Box 2 *- L'associazione di empagliflozin e liraglutide potrebbe essere un eccellente opzione terapeutica per i pazienti con pregressa malattia cardiovascolare, ma sono necessarie ulteriori evidenze al riguardo.*

Box 3 *- In pazienti con pregressa malattia cardiovascolare la terapia ipoglicemizzante dovrebbe includere empagliflozin oppure liraglutide anche in persone in buon controllo glicemico con la terapia in corso.*

Box 4 *- Sembra prudente non considerare necessariamente estendibile ad un'intera classe quanto osservato con una singola molecola ma sembra ragionevole considerare possibile un effetto classe a meno che non ci siano evidenze che lo neghino. Nel caso specifico, l'effetto classe degli agonisti del recettore di GLP-1 è negato dalla valutazione complessiva dei risultati degli studi ELIXA e LEADER, senza che questo escluda che benefici cardiovascolari potrebbero essere osservati negli studi in corso con exenatide (EXSCEL), dulaglutide (REWIND) e semaglutide (SUSTAIN 6). L'effetto classe degli inibitori di SGLT-2 non può essere stabilito con certezza fino a che non saranno disponibili i risultati degli studi in corso con canagliflozin (CANVAS) e dapagliflozin (DECLARE).*

THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION VOLUME 40 | SUPPLEMENT 1

Diabetes Care

WWW.DIABETES.ORG/DIABETESCARE JANUARY 2017

- In patients with long-standing suboptimally controlled type 2 diabetes and established atherosclerotic cardiovascular disease, empagliflozin or liraglutide should be considered as they have been shown to reduce cardiovascular and all-cause mortality when added to standard care. Ongoing studies are investigating the cardiovascular benefits of other agents in these drug classes. B

1 INDICATIONS AND USAGE

VICTOZA is indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus,
- to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease *[see Clinical Studies (14.2)]*.

RCP, Riassunto delle Caratteristiche del Prodotto – sito FDA aggiornato ad 08/2017

Nuovo RCP

4.1 Indicazioni terapeutiche

Victoza è indicato per il trattamento di adulti affetti da diabete mellito tipo 2 non adeguatamente controllato in aggiunta alla dieta e all'esercizio fisico

- come monoterapia quando l'uso di metformina è considerato inappropriato a causa di intolleranza o controindicazioni
- in aggiunta ad altri medicinali per il trattamento del diabete.

Per i risultati degli studi clinici rispetto alle combinazioni, agli effetti sul controllo glicemico e agli eventi cardiovascolari e alle popolazioni studiate, vedere i paragrafi 4.4, 4.5 e 5.1.

RCP, Riassunto delle Caratteristiche del Prodotto – sito EMA aggiornato al 14/09/2017

Conclusioni

- Gli agonisti dei recettori GLP-1 hanno dimostrato di non esercitare effetti malefici sul rischio CV
- Alcuni di essi (liraglutide e semaglutide) hanno dimostrato, anzi, di ridurre morte cardiovascolare, infarto, ictus
- Il beneficio cardiovascolare è evidente soprattutto nei soggetti con pregressa malattia cardiovascolare
- Il position statement della SID (1 anno fa) e l'ultimo dell'ADA raccomandano empagliflozin e liraglutide in pazienti con pregressa malattia cardiovascolare

I farmaci iniettabili prescritti per la cura del diabete

Farmaci	Percentuale rispetto al totale dei pazienti trattati con farmaci antidiabetici
Agonisti recettore GLP-1	1,7
Insulina umana regolare	1,2
Insulina umana NPH	0,3
Insulina umana premiscelata	0,2
Analogo prandiale	18,9
Analogo intermedio	1,7
Analogo basale	18,6
Analogo premiscelato	3,0

Agonisti recettore GLP-1 ancora meno del 2% dopo 7 anni dal lancio

Osservatorio ARNO Diabete CINECA-SID - 2014

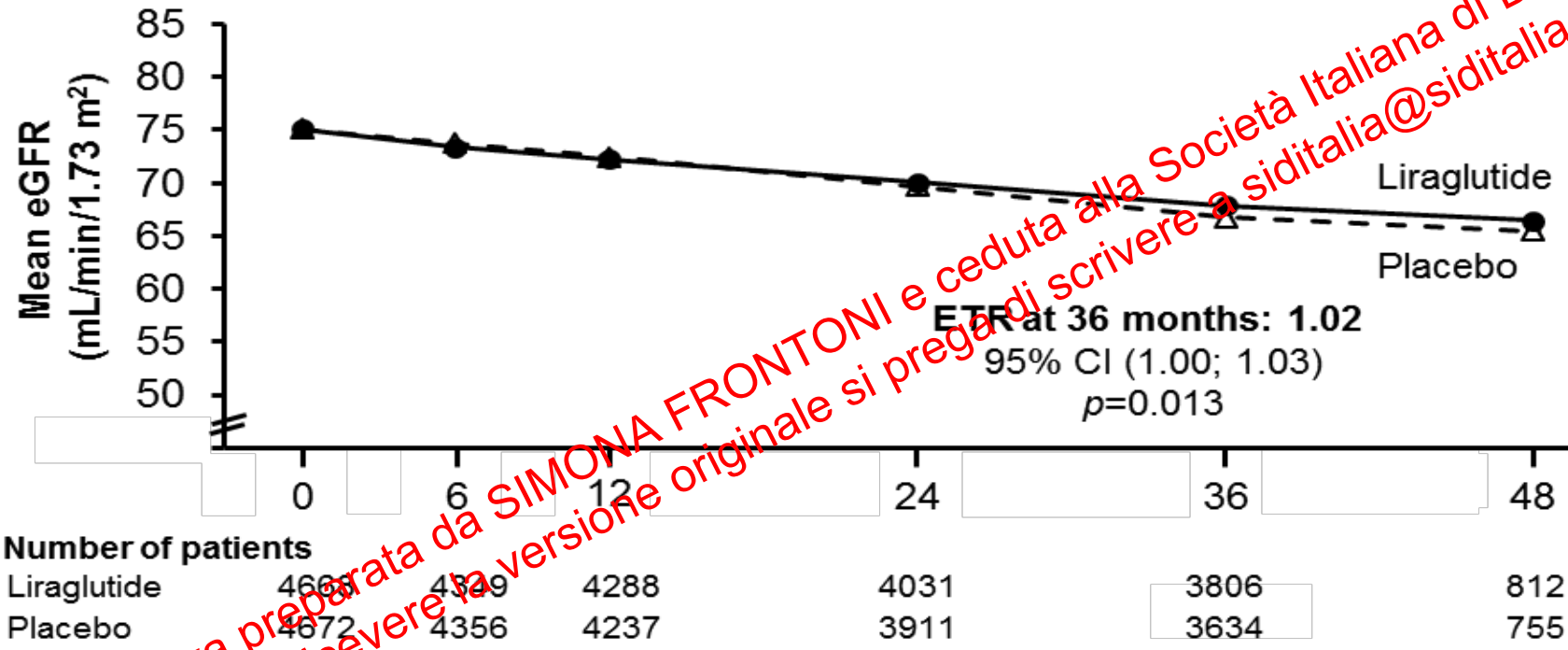
I farmaci per la cura del diabete più prescritti

Principio attivo	Percentuale sul totale (%)	Principio attivo	Percentuale sul totale (%)
Metformina	60,8	Pioglitazone	2,1
Insulina glargina	14,6	Vildagliptin/metformina	1,8
Gliclazide	11,0	Insulina lispro protamina	1,7
Gliblenclamide/metformina	10,8	Insulina aspart premiscelata	1,7
Repaglinide	10,3	Insulina lispro premiscelata	1,3
Insulina lispro rapida	8,5	Liraglutide	1,2
Glimepiride	8,5	Insulina umana rapida	1,2
Insulina aspart rapida	7,3	Glibenclamide	0,8
Insulina detemir	3,9	Vildagliptin	0,7
Sitagliptin/metformina	3,3	Linagliptin	0,6
Insulina glulisina	3,2	Linagliptin/metformina	0,6
Acarbosio	3,0	Saxagliptin	0,5
Pioglitazone e metformina	2,5	Exenatide	0,4
Sitagliptin	2,5	Insulina umana NPH	0,3

Nuovi farmaci ancora poco prescritti

Osservatorio ARNO Diabete CINECA-SID - 2014

LEADER
changes in eGFR (MDRD)



Estimated means ± standard error. Change from baseline to last assessment analyzed using a linear mixed model for log-transformed assessment accounting for repeated measures. Analyses truncated at 48 months as <10% of patients had a measurement at visit at 60 months

CI: confidence interval; eGFR: estimated glomerular filtration rate; ETR: estimated treatment ratio; MDRD: Modification of Diet in Renal Disease

LEADER
Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

Presented at 52nd EASD Annual Meeting, 14 September 2016, Munich, Germany