GLP-1 RAs e rischio cardiovascolare

Enzo Bonora
Endocrinologia, Diabetologia e Metabolismo
Università e Azienda Ospedaliera Universitaria
Integrata di Verona

Diabete: prevalenza delle complicanze croniche più severe

Dei 4 milioni di diabetici italiani:

- Circa 400.000 hanno avuto un infarto
- Circa 250.000 hanno avuto un ictus
- Circa 200.000 hanno un problema serio ai reni (eGFR <30 ml/min oppure macroalbuminuria)
- Circa 200.000 hanno un problema serio agli occhi (retinopatia proliferante o pregressa panfotocoagulazione o maculopatia)
- Circa 150.000 hanno un problema serio ai piedi

Diabete: incidenza delle complicanze croniche più severe

Nuovi eventi per anno nei 4 milioni di diabetici italiani:

- Scompenso cardiaco: circa 70.000
- Infarto: circa 50.000
- Ictus: circa 50.000
- Inizio terapia dialitica: circa 2.000
- Fotocoagulazione retinica: circa 15.000
- Amputazione: circa 10.000 (circa 3000 sono maggiori)

Una malattia che può rendere disabili e uccidere

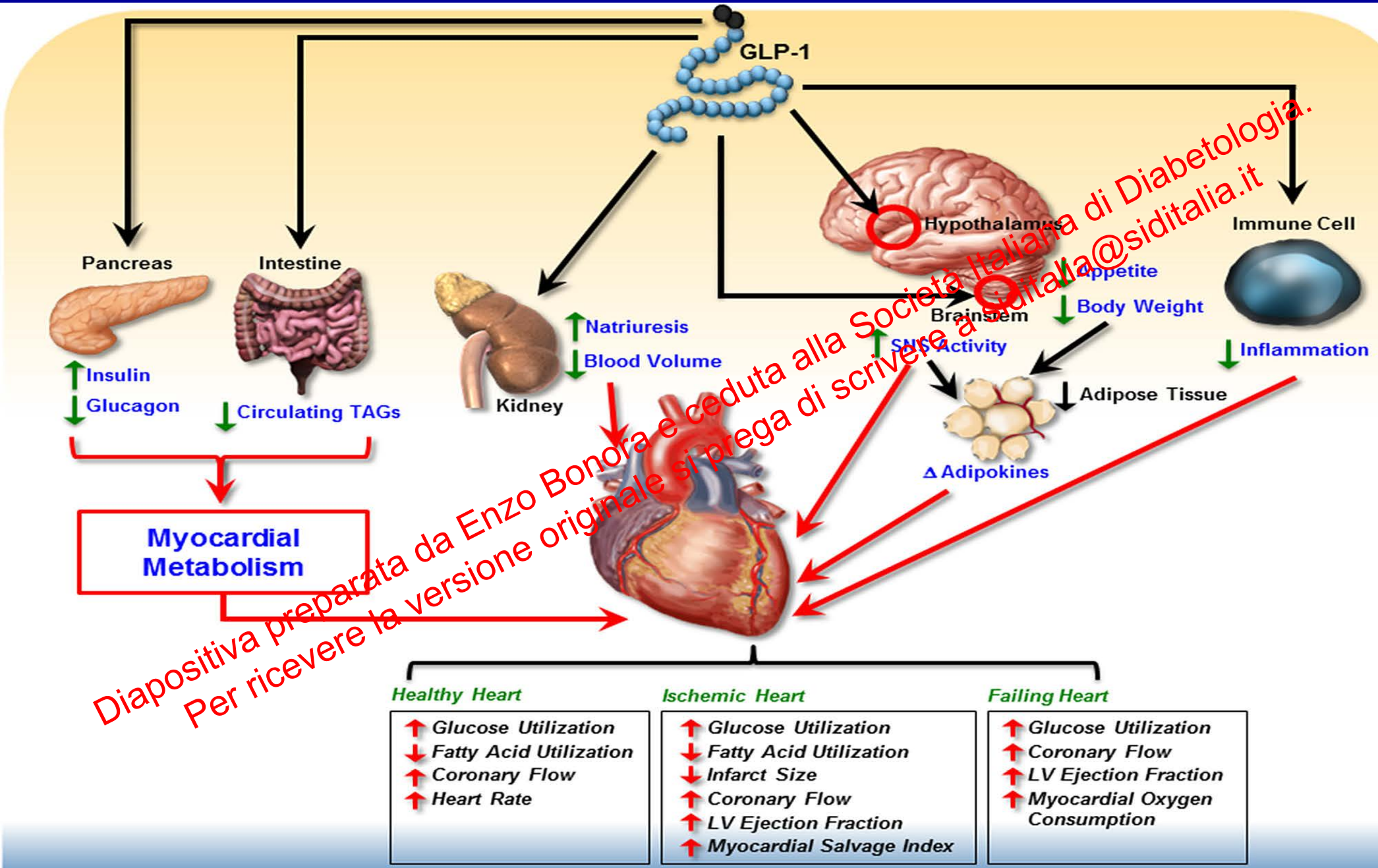
In Italia:

- Ogni 10 minuti una persona con diabete ha un infarto
- Ogni 10 minuti una persona con diabete sviluppa un deficit visivo importante
- Ogni 10 minuti una persona con diabete ha un ictus
- Ogni 52 minuti una persona subisce un'amputazione a causa del diabete
- Ogni 4 ore una persona con diabete comincia la terapia dialitica
- Ogni 5 minuti una persona muore a causa del diabete (circa120 mila per anno, pari al cancro)

Quesiti

1. Gli agonisti dei recettori GLP-1 possono contribuire a cambiare certi numeri sulla malattia cardiovascolare nel diabete?
2. In caso affermativo, su quali endpoint cardiovascolari?
3. In caso affermativo, si tratta di un effetto classe?
4. In caso affermativo, i benefici potenziali riguardano solo alcune categorie di soggetti con diabete oppure tutti?
5. In caso affermativo, esiste un corrispettivo nelle attuali linee guida?
6. In caso affermativo, esistono degli ostacoli alla applicazione delle stesse?

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

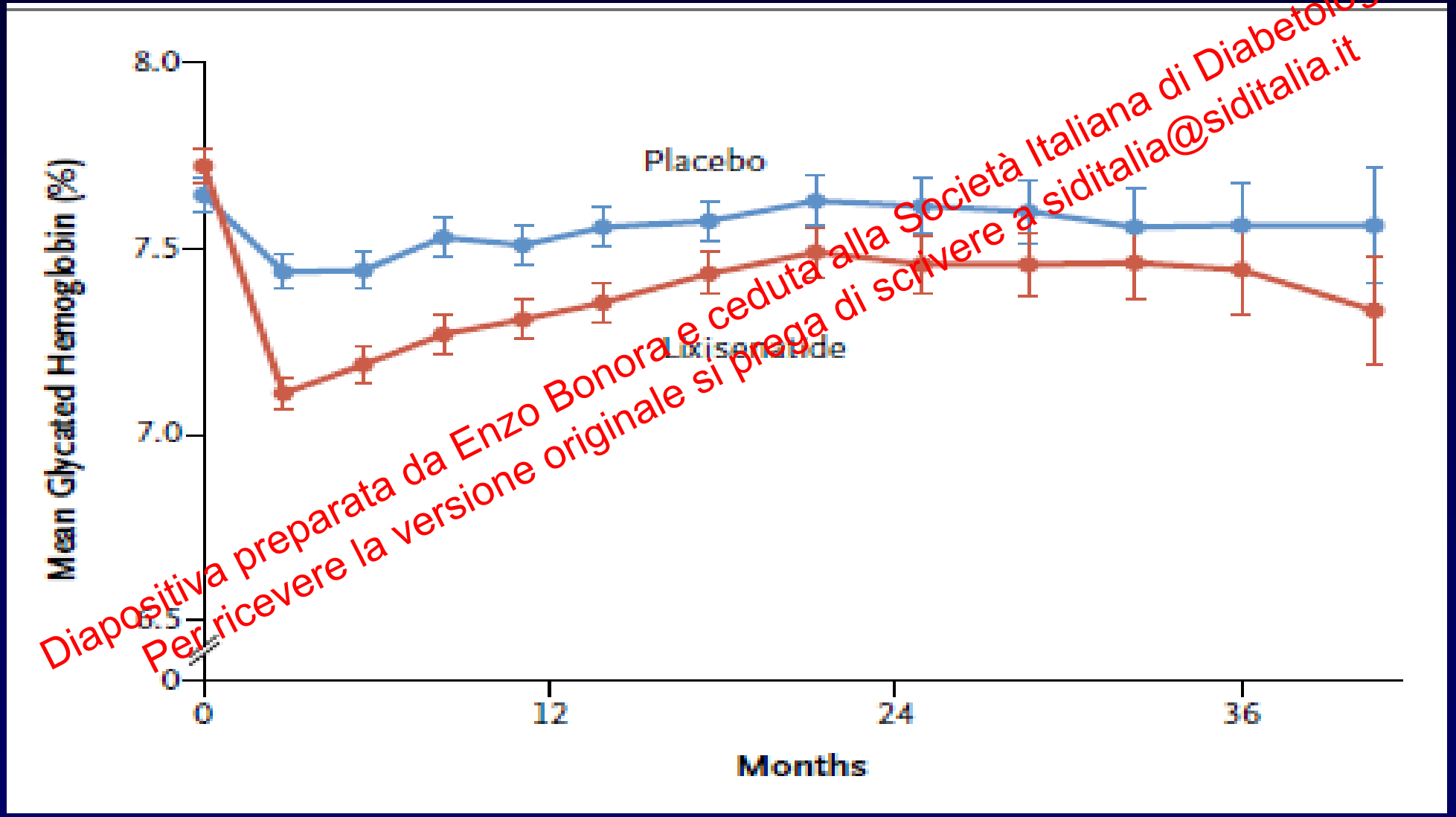
Study	Drug	Median Follow-up (yrs)	Prior CVD (%)	Endpoints
ELIXA	Lixisenatide	2.0	100 (recent ACS)	MACE + UA
LEADER	Liraglutide	3.8	82	MACE
SUSTAIN 6	Semaglutide	2.1	71	MACE
FREEDOM CVOT	Exenatide QY	1.2	Most	MACE
EXSCEL	Exenatide OW	5	73	MACE
REWIND	Dulaglutide	???	31	MACE
HARMONY CVOT	Albiglutide	???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

ELIXA

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

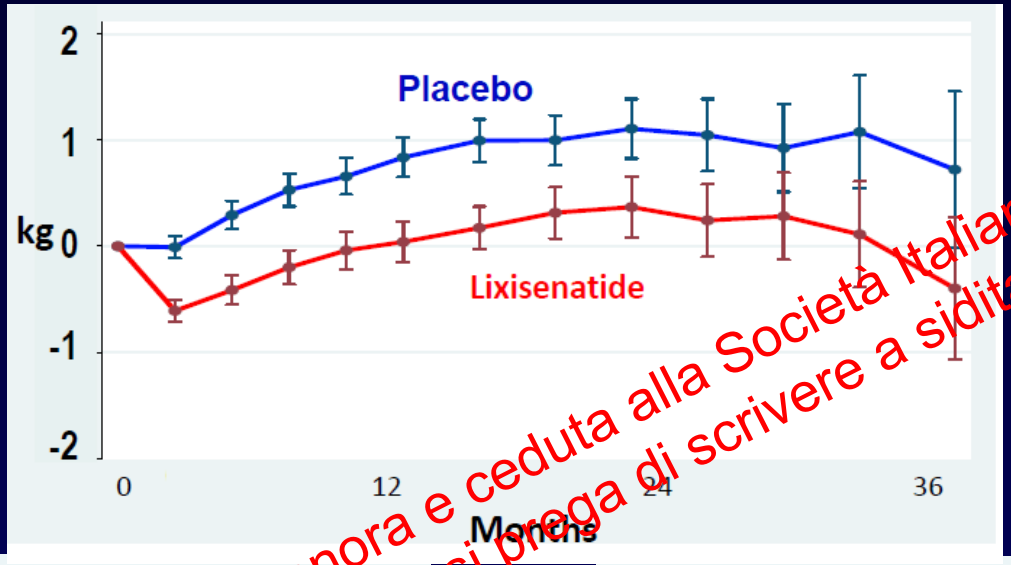
ELIXA – Time course of HbA1c

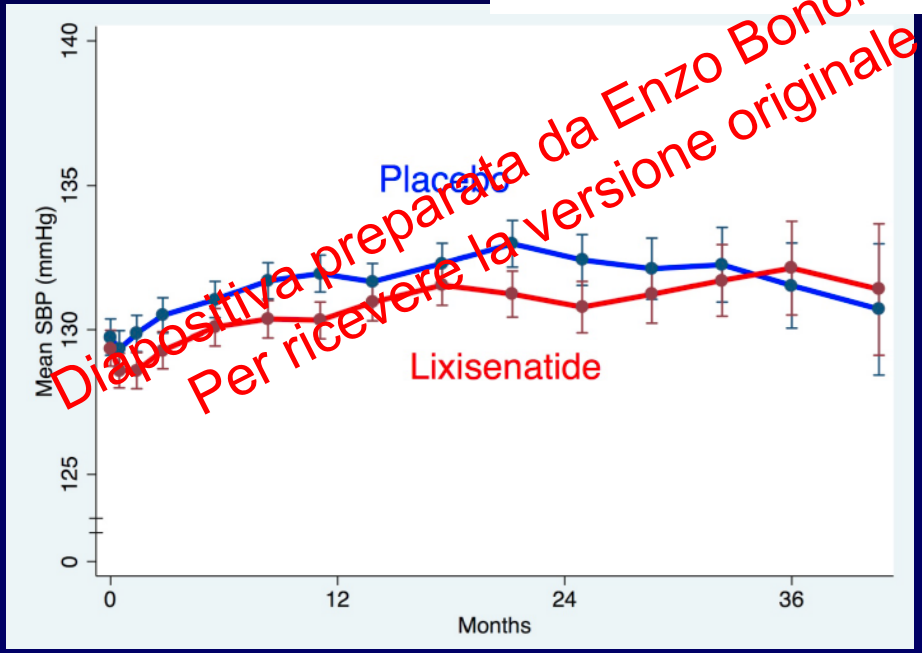
Pfeffer M et al – NEJM 215; 373: 2247

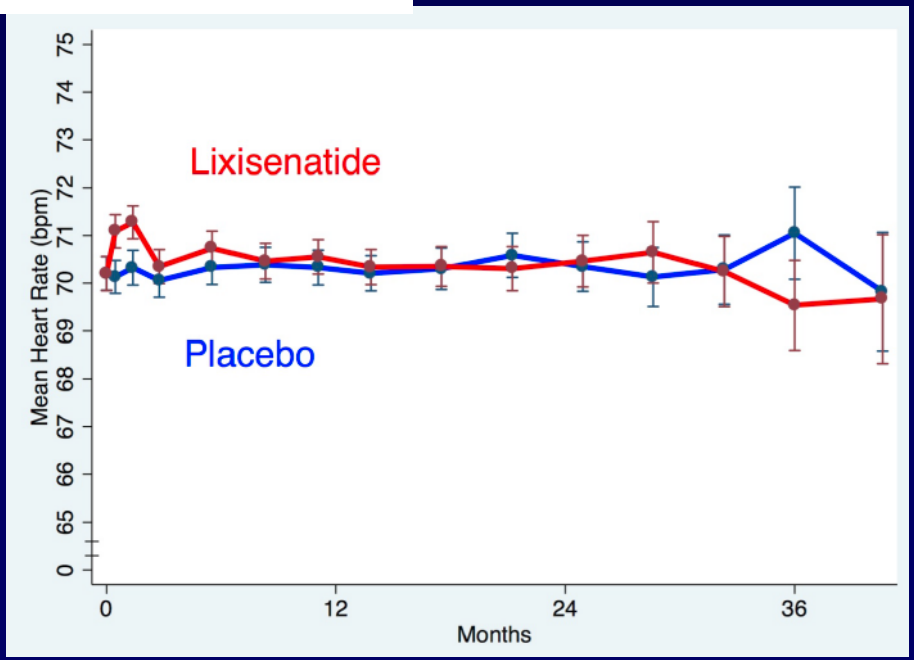


ELIXA – Time course of BW, sBP, HR

Pfeffer M et al – NEJM 215; 373: 2247

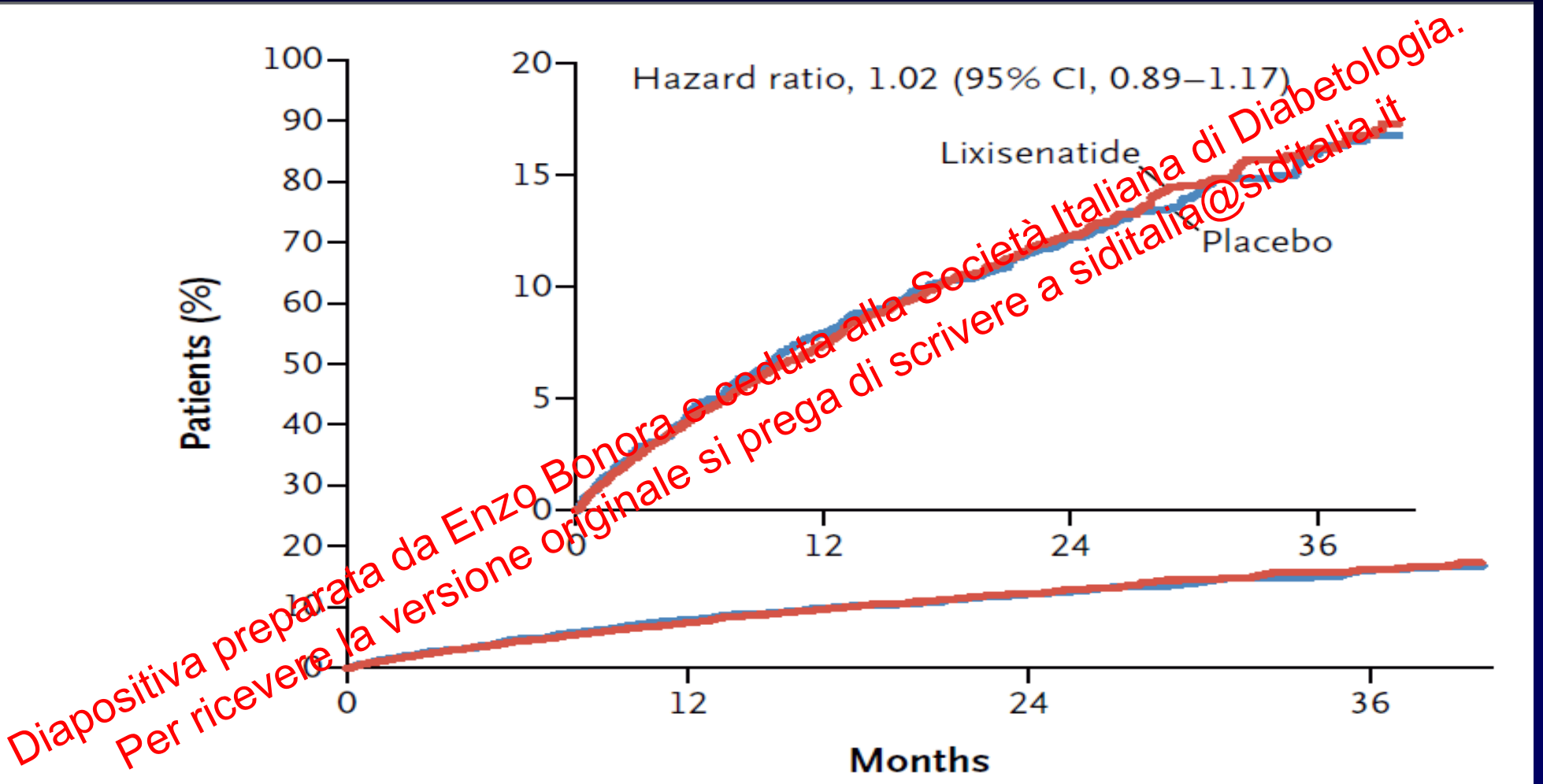






ELIXA – Primary Endpoint (MACE + UA)

Pfeffer M et al – NEJM 215; 373: 2247



No. at Risk

Placebo	3034	2759	1566	476
Lixisenatide	3034	2785	1558	484

ELIXA – Incidence and HR for CVD endpoints

Pfeffer M et al – NEJM 215; 373: 2247

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

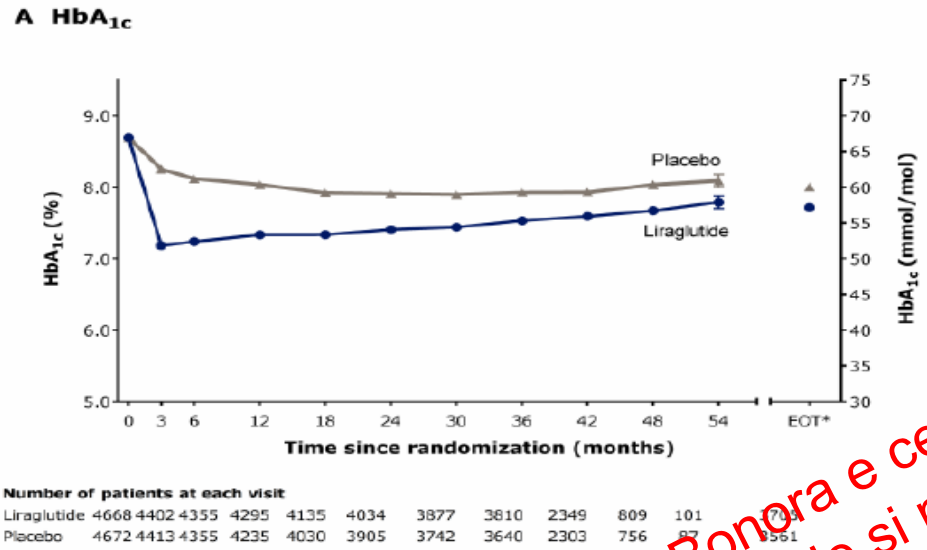
End Point	Placebo (N=3034)		Lixisenatide (N=3034)		Adjusted Hazard Ratio (95% CI)	P Value
	Patients with Event	No. of Events/ 100 Patient-Yr	Patients with Event	No. of Events/ 100 Patient-Yr		
Primary end point: death from cardiovascular causes, nonfatal stroke, nonfatal myocardial infarction, or unstable 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)	—	255/406 (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

LEADER

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

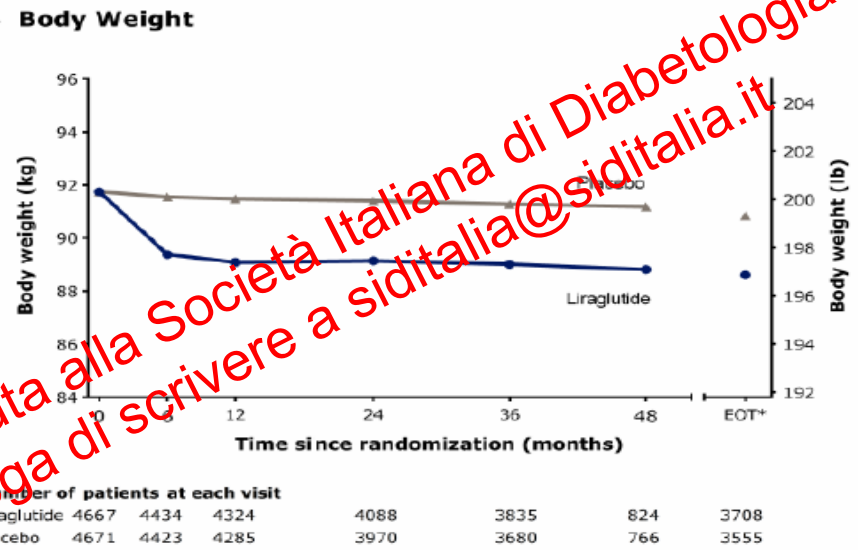
LEADER – Time course of HbA1c, BW, BP, HR

Marso SP et al – NEJM June 13, 2016



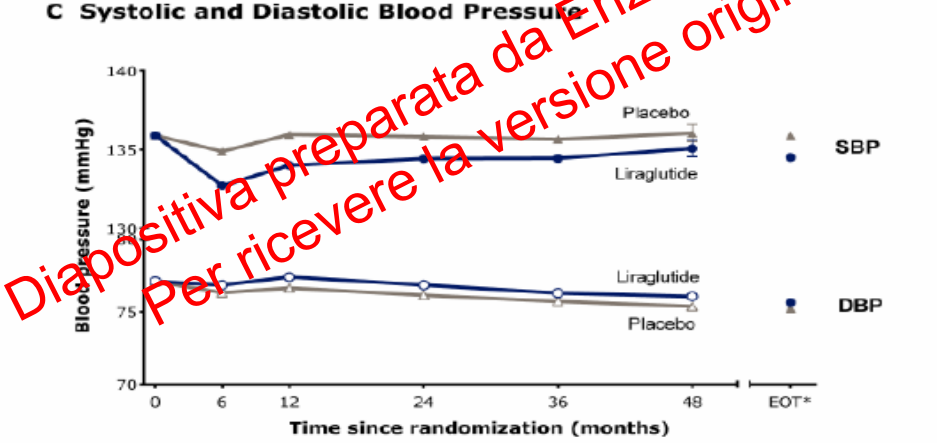
Number of patients at each visit

Liraglutide	4668	4402	4355	4295	4135	4034	3877	3810	2349	809	101	703
Placebo	4672	4413	4355	4235	4030	3905	3742	3640	2303	756	87	561



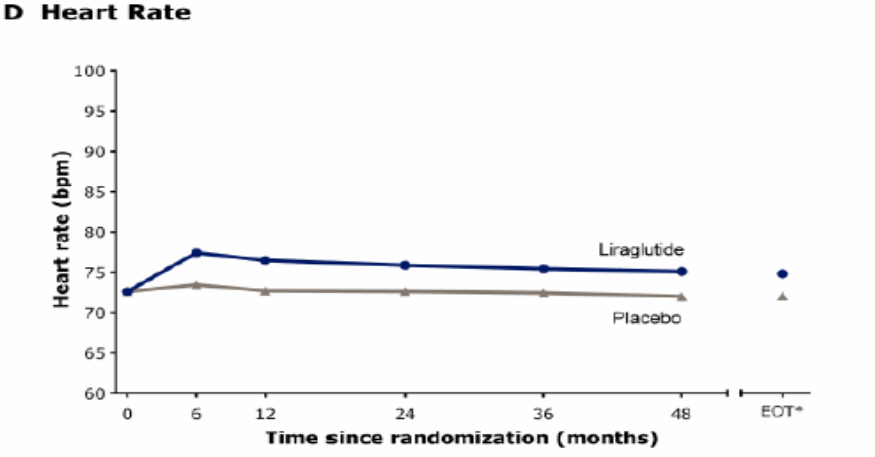
Number of patients at each visit

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

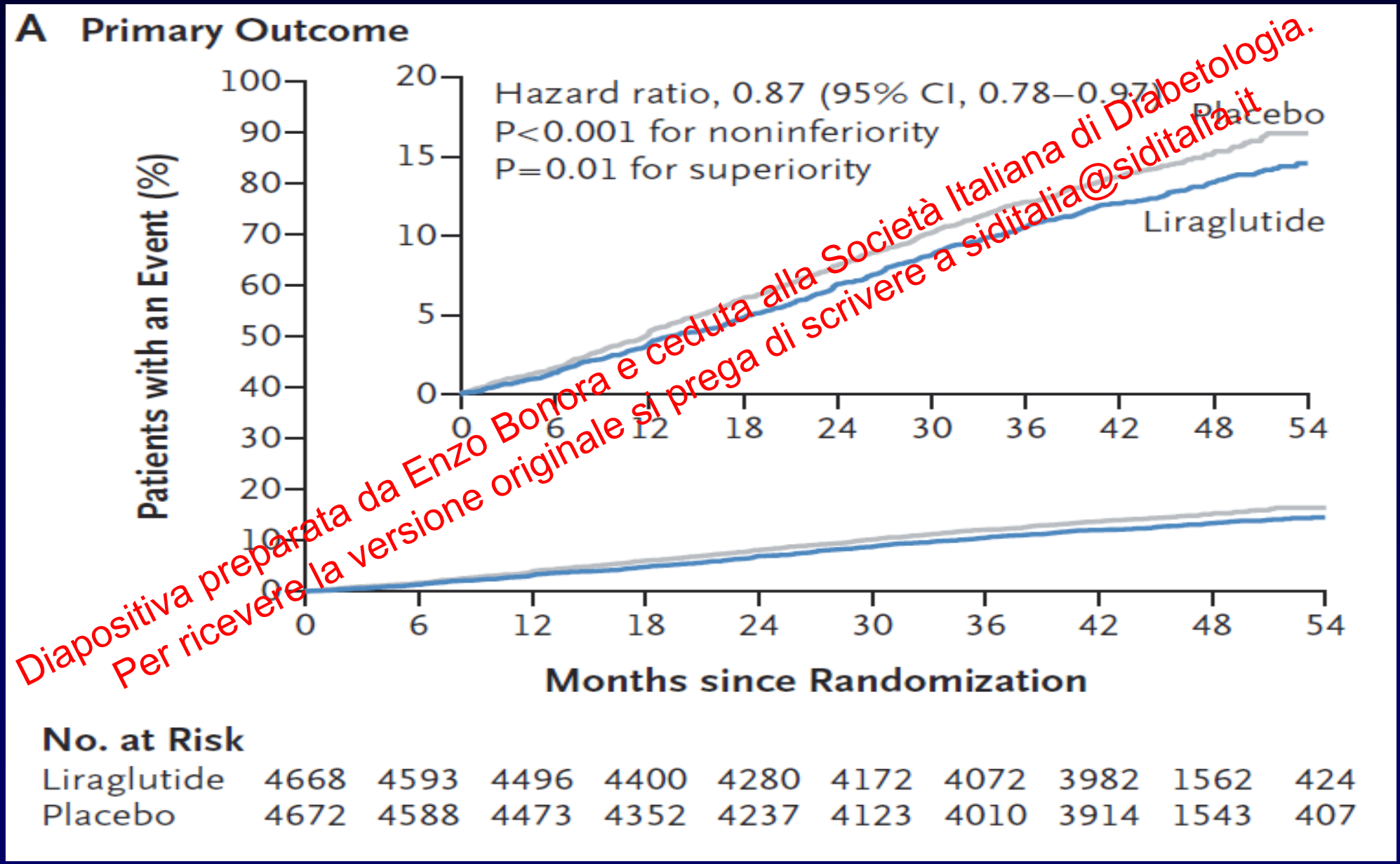


Number of patients at each visit

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

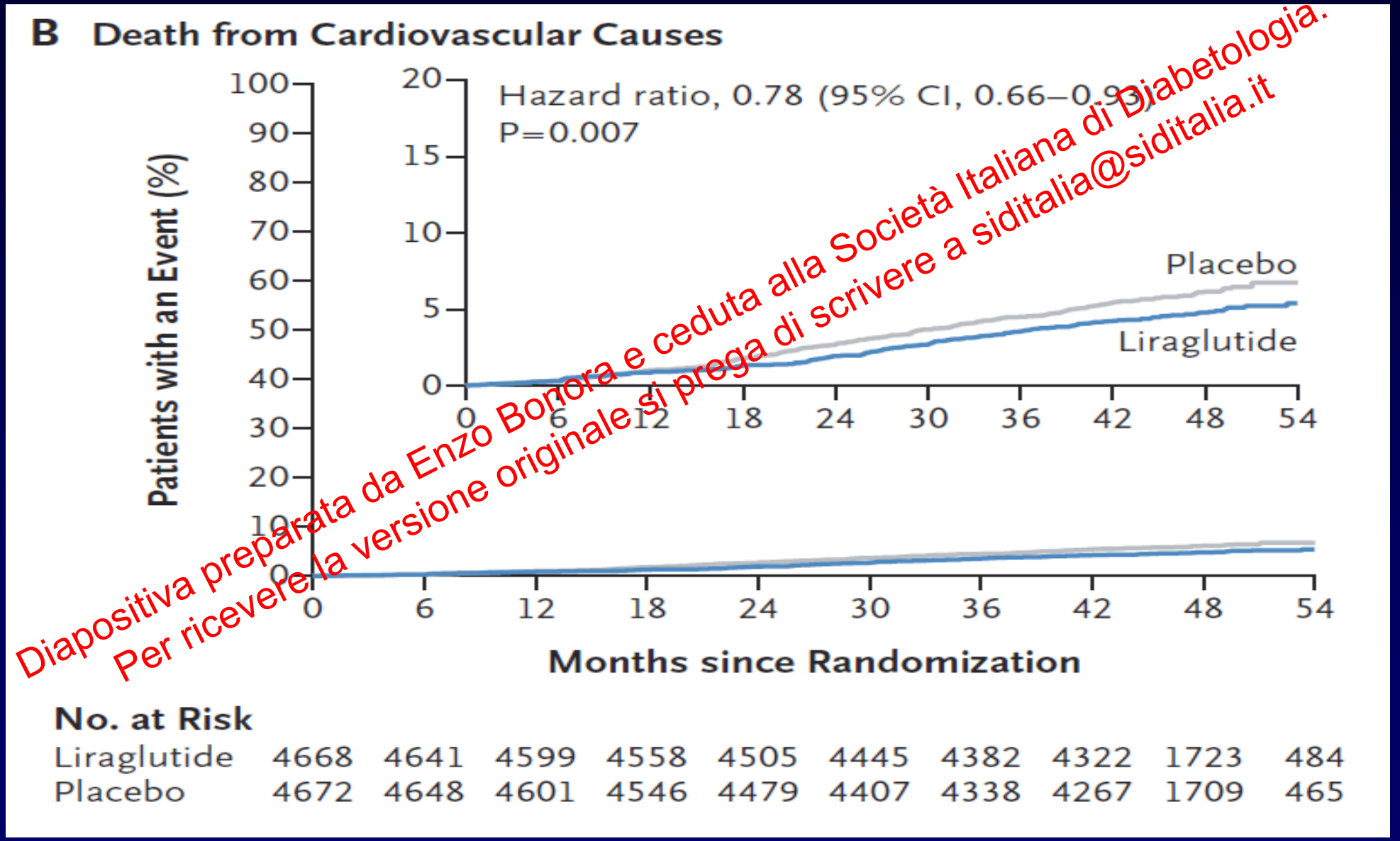
LEADER – Primary endpoint (MACE)

Marso SP et al – NEJM June 13, 2016



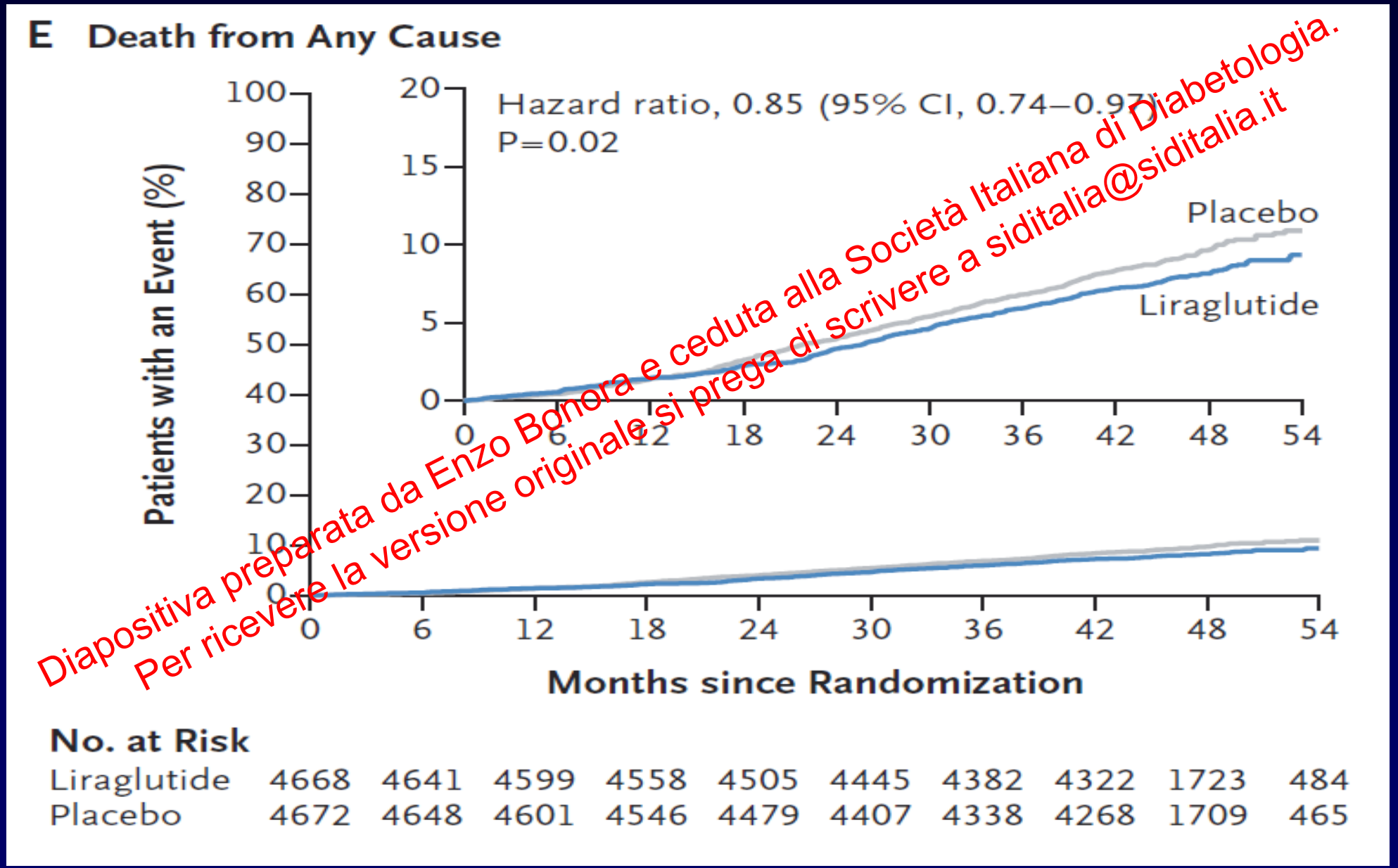
LEADER – Death from CVD

Marso SP et al – NEJM June 13, 2016



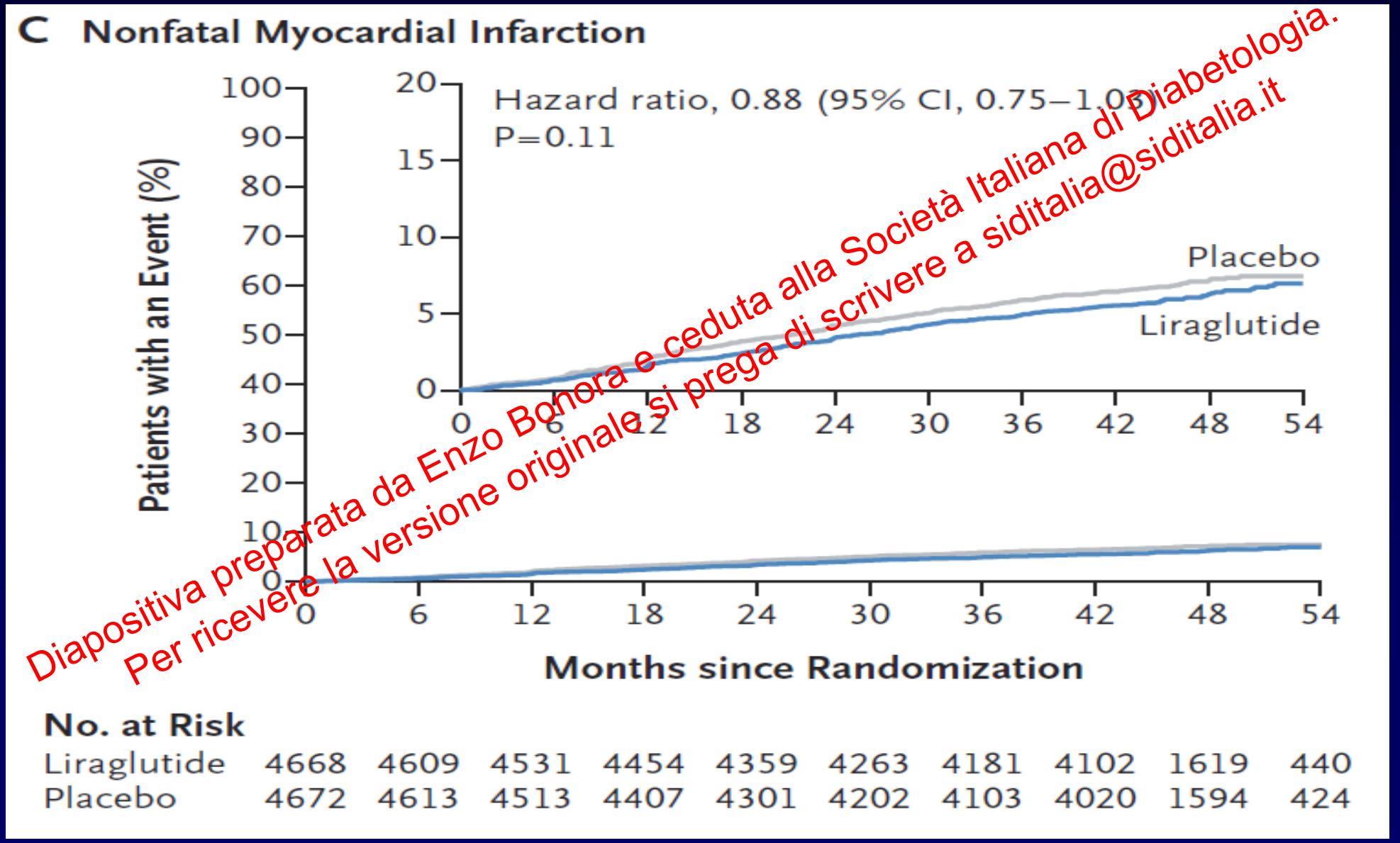
LEADER - Death from any cause

Marso SP et al – NEJM June 13, 2016



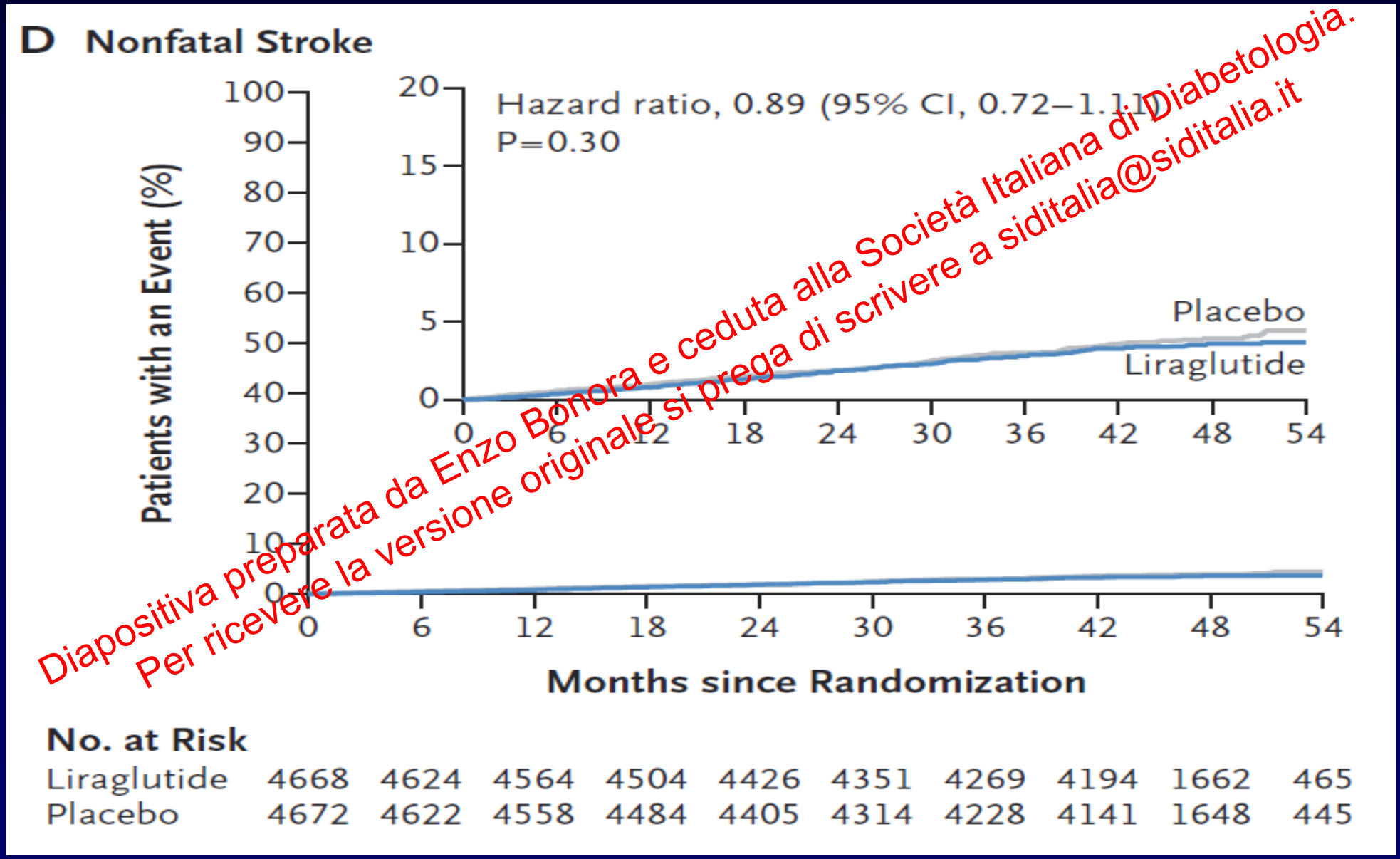
LEADER – Non-fatal MI

Marso SP et al – NEJM June 13, 2016



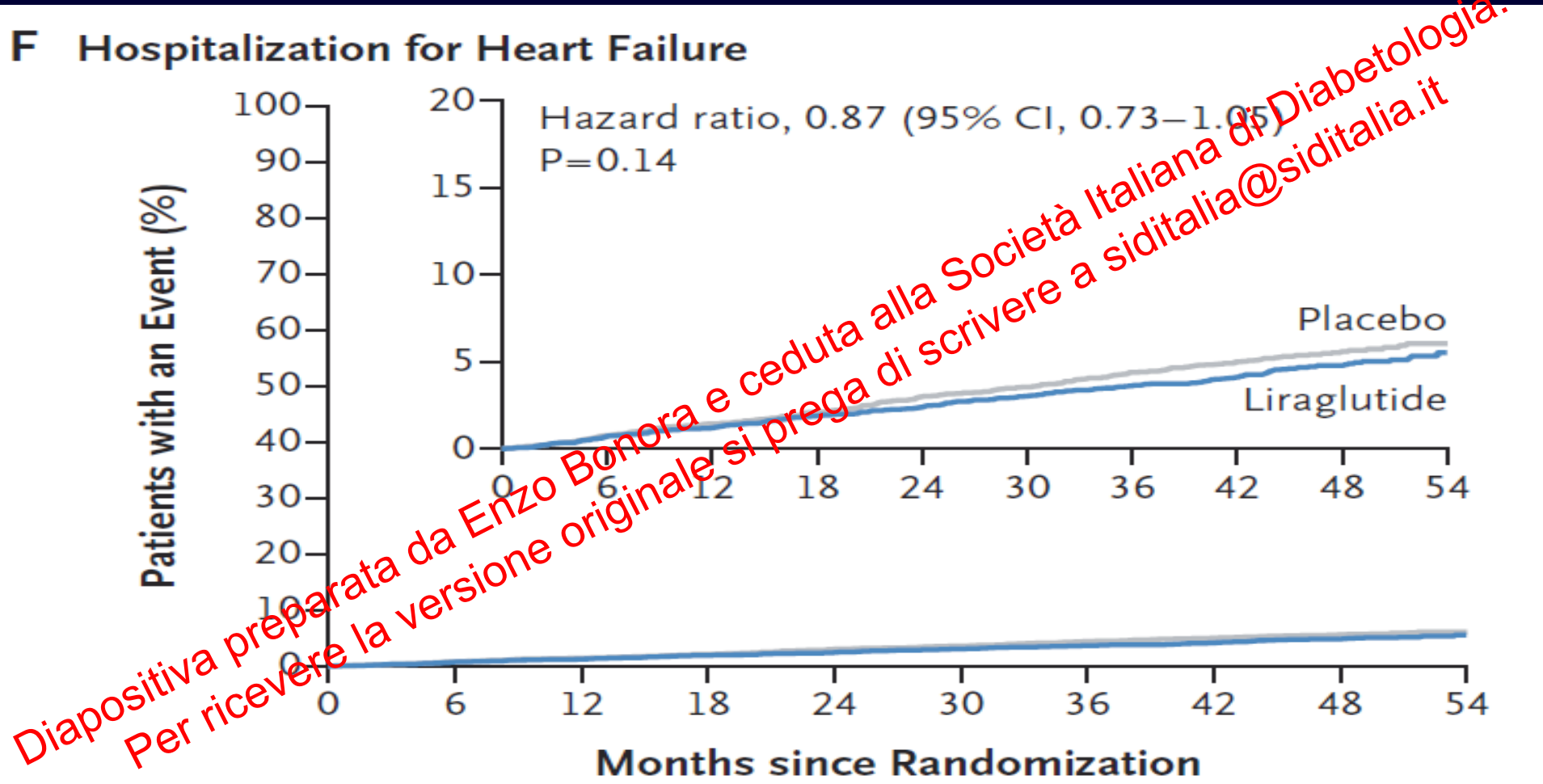
LEADER – Non-fatal stroke

Marso SP et al – NEJM June 13, 2016



LEADER – Heart failure (hospitalization)

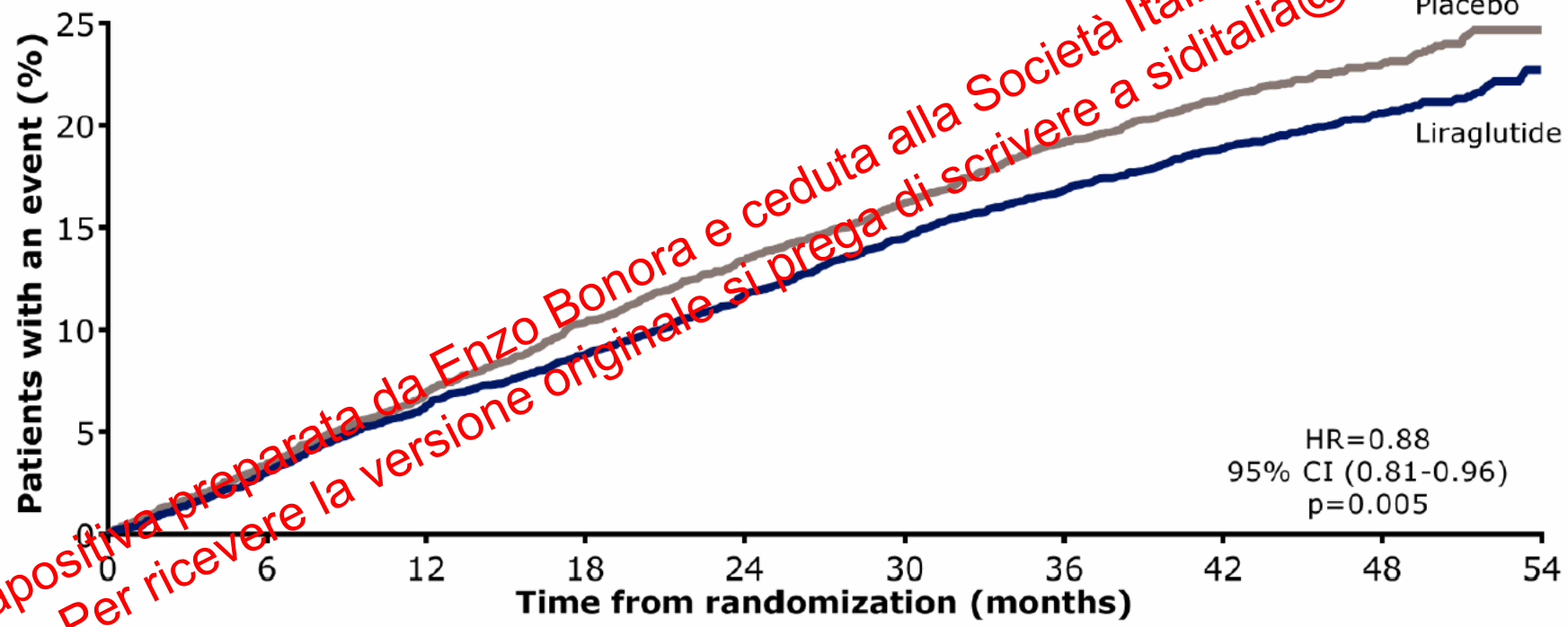
Marso SP et al – NEJM June 13, 2016



LEADER – Expanded composite CVD endpoint

Marso SP et al – NEJM June 13, 2016

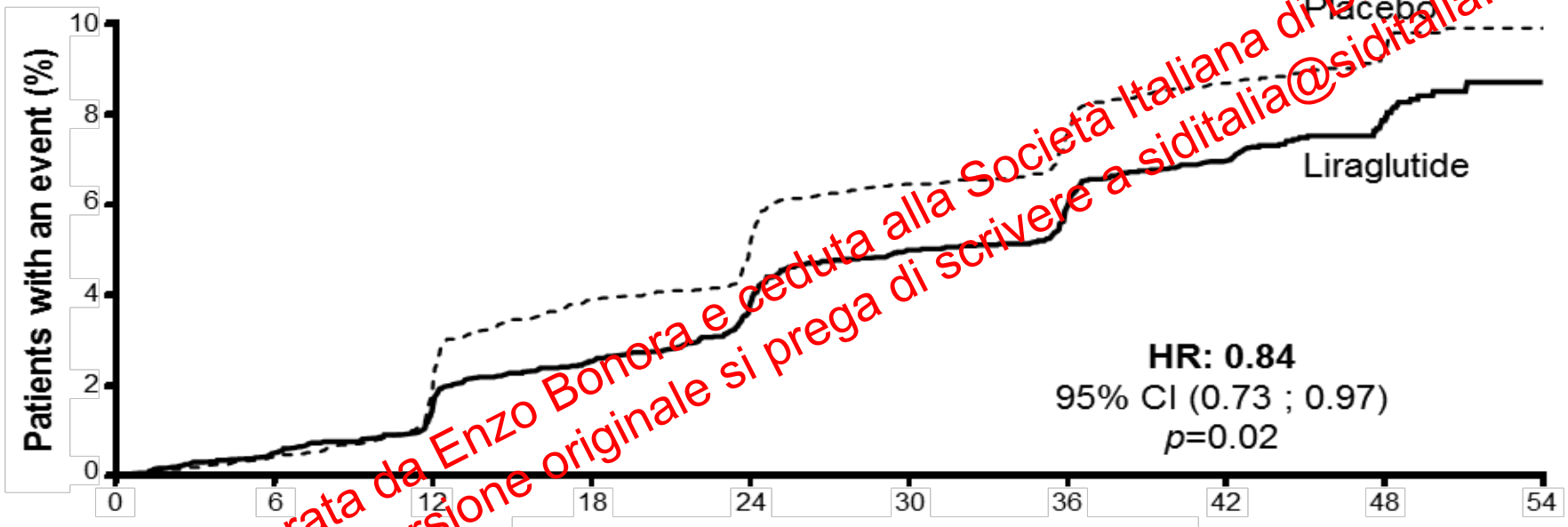
Figure S4. Time to first expanded composite cardiovascular outcome (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina pectoris or hospitalization for heart failure).



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

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

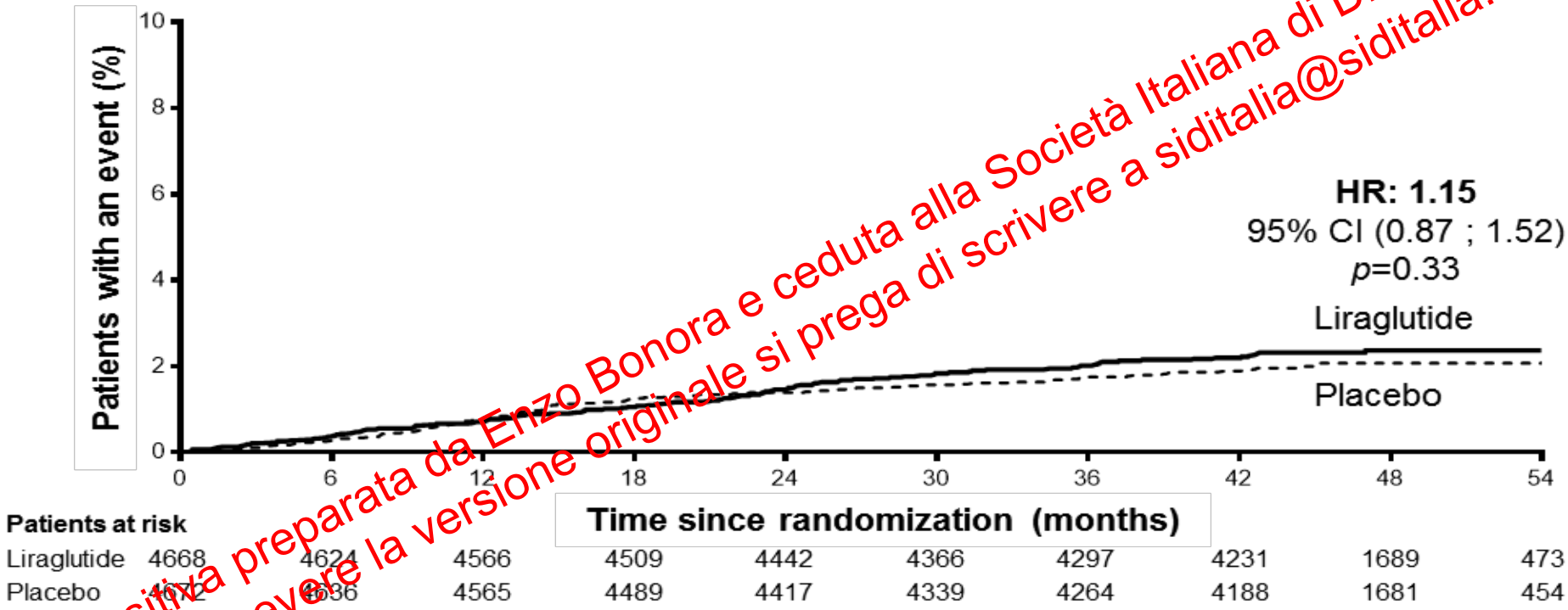
The cumulative incidences were estimated using the Kaplan–Meier method, and the HRs using the Cox proportional-hazards regression model. The data analyses are truncated at 54 months because less than 10% of the patients had an observation time beyond 54 months
CI: confidence interval; HR: hazard ratio

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

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

Time to first eye outcome

Photocoagulation or treatment with intravitreal agents, vitreous hemorrhage or blindness



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

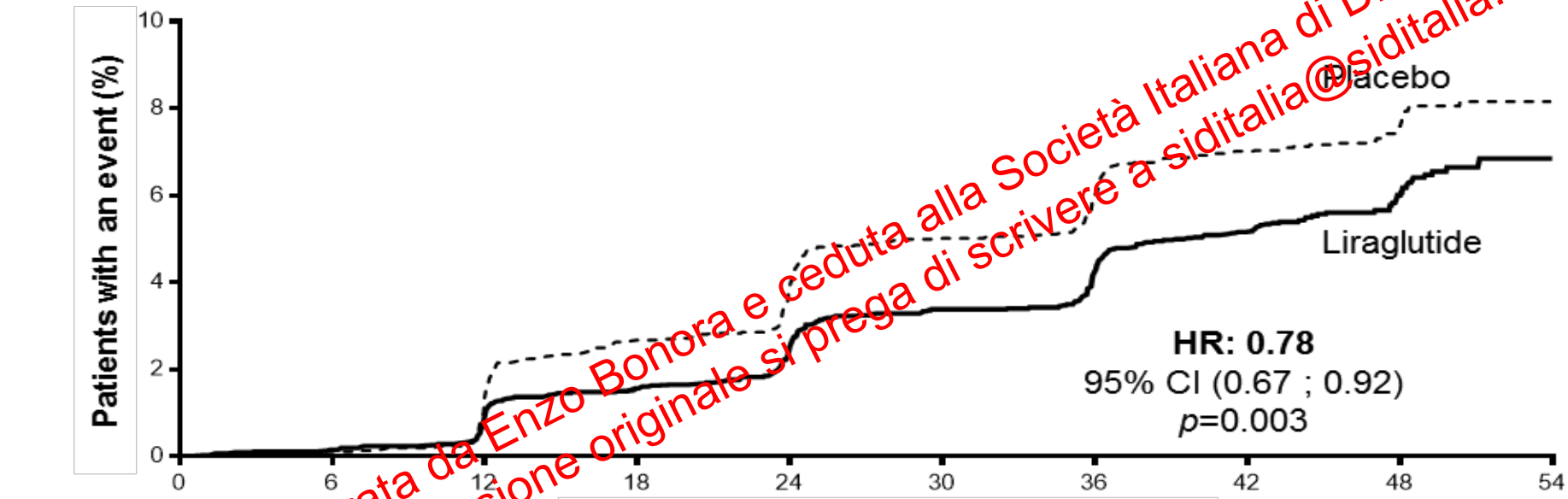
CI: confidence interval; HR: hazard ratio

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

Time to first renal outcome

Macroalbuminuria, doubling of serum creatinine*, ESRD, renal death



Patients at risk

Liraglutide	4668	4635	4561	4492	4400	4304	4210	4114	1632	454
Placebo	4672	4643	4540	4428	4316	4196	4094	3990	1613	433

*and eGFR ≤45 mL/min/1.73 m^2 per MDRD

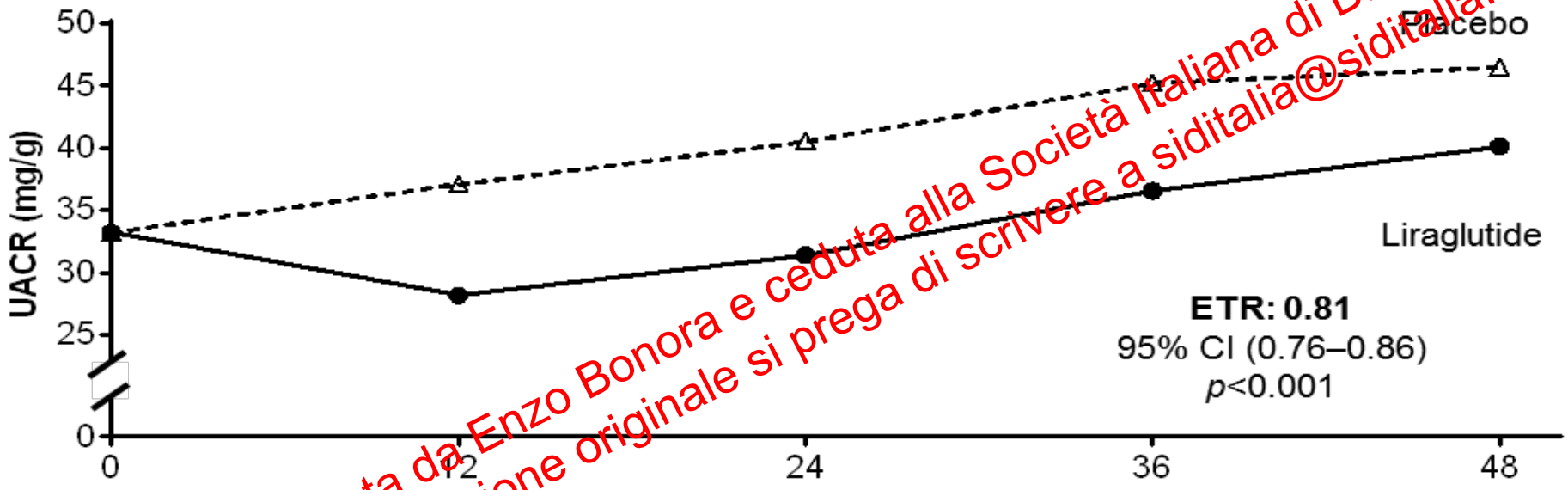
The cumulative incidences were estimated using the Kaplan–Meier method, and the HRs using the Cox proportional-hazards regression model. The data analyses are truncated at 54 months because less than 10% of the patients had an observation time beyond 54 months

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

Urinary albumin-to-creatinine ratio over time



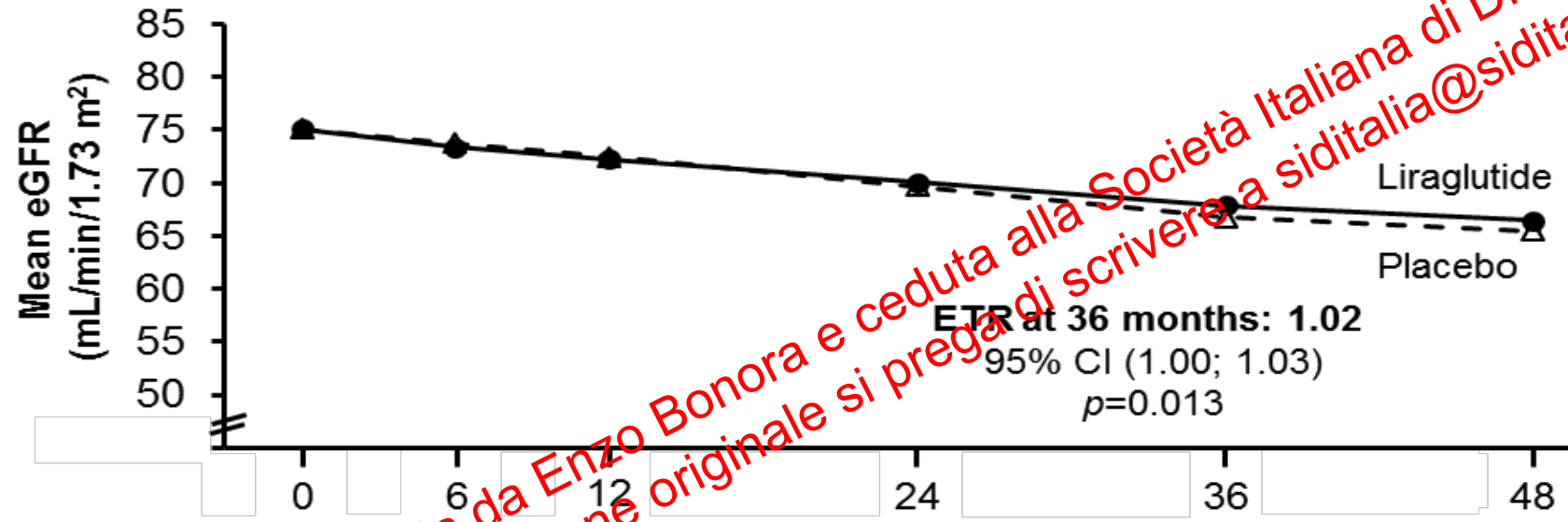
Number of patients					
Liraglutide	3775	3430	3247	3065	646
Placebo	3781	3468	3232	2956	591

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

Changes in eGFR (MDRD)



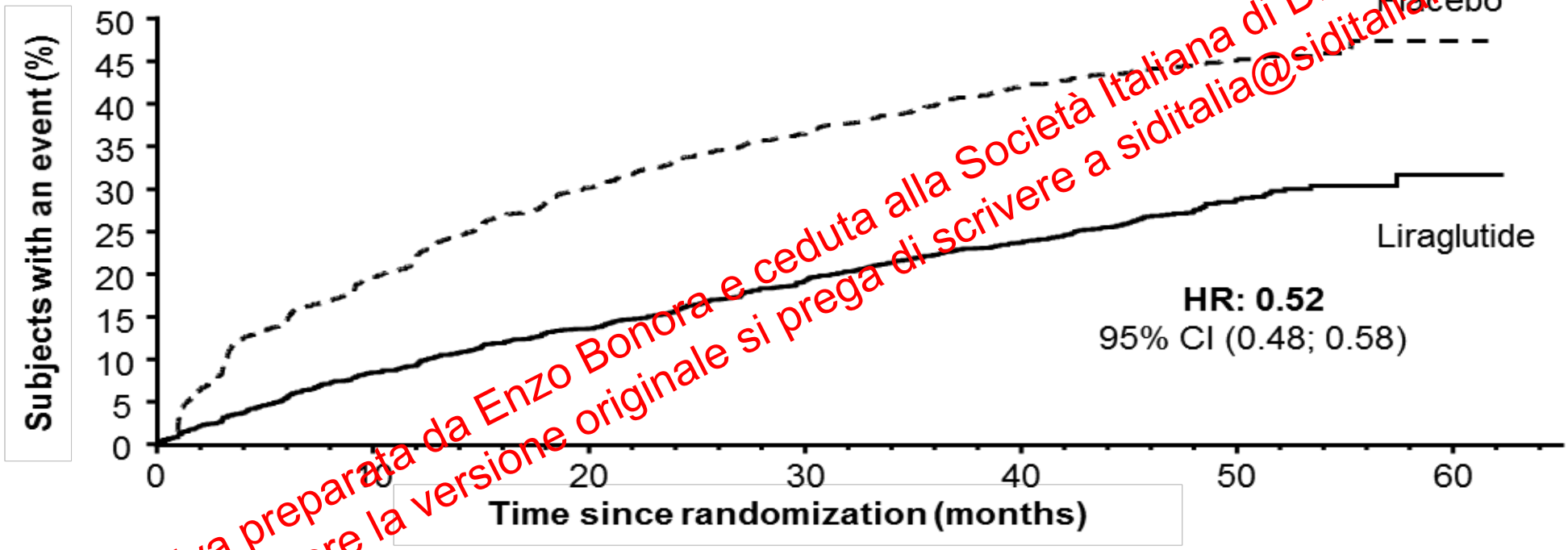
Estimated means ± standard error. Change from baseline to last assessment analyzed using a linear mixed model for log-transformed assessment accounting for repeated measures. Analyses truncated at 48 months as <10% of patients had a measurement at visit at 60 months

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

Time to insulin initiation – patients insulin-naïve at baseline



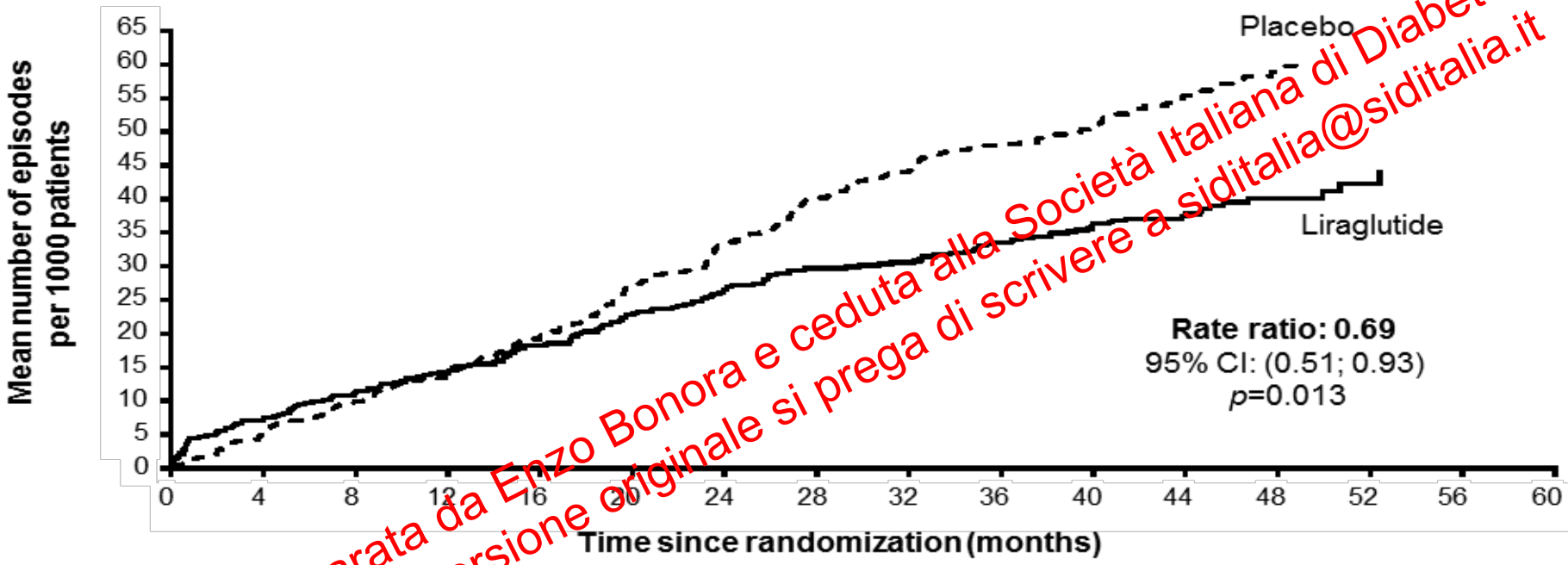
Subjects at risk							
Liraglutide	2633	2386	2238	2057	1906	448	3
Placebo	2548	2026	1728	1534	1374	336	7

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

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

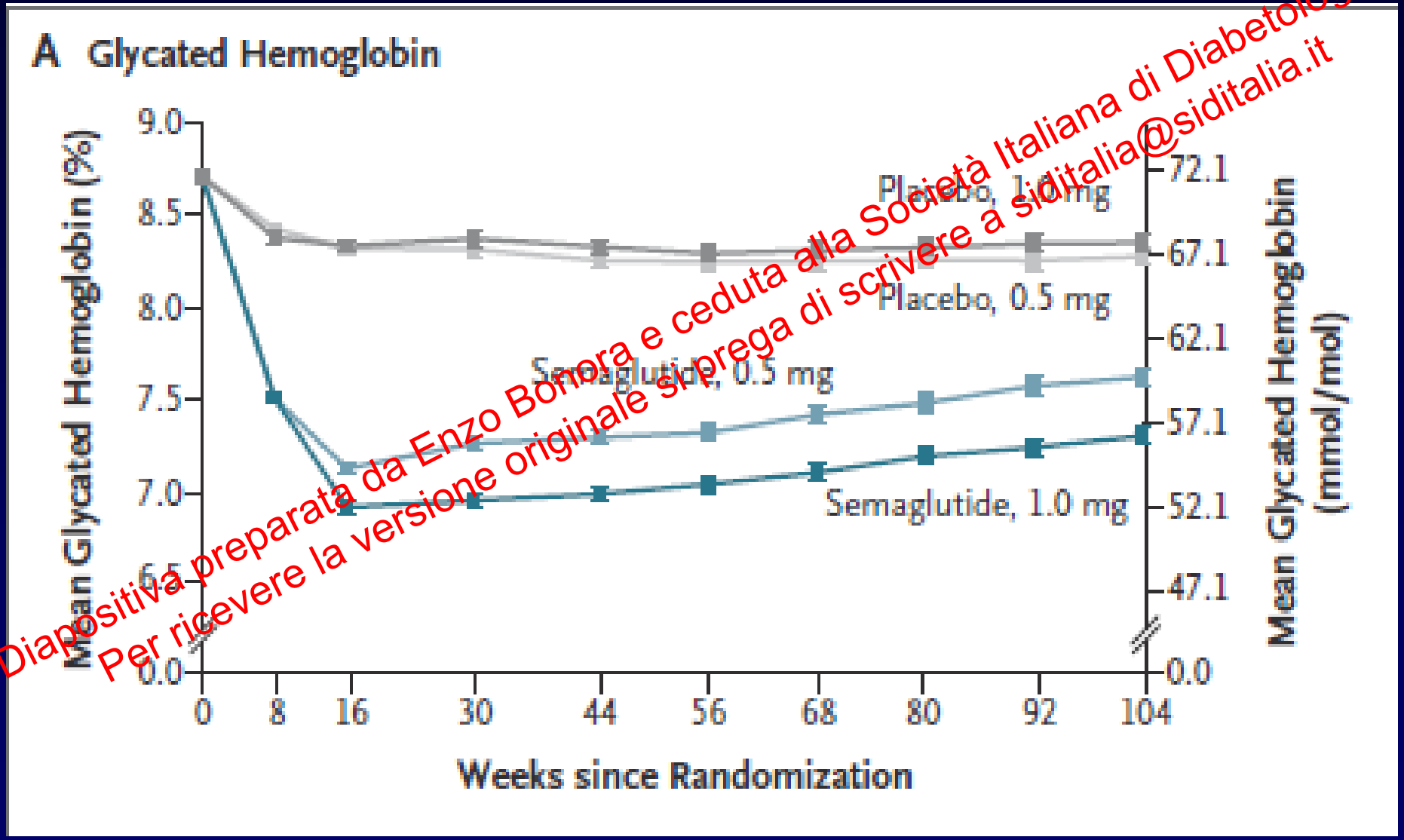
Presented at the American Diabetes Association 77th Scientific Sessions, Session 1-AC-SY13. June 11 2017, San Diego, CA, USA

SUSTAIN 6

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

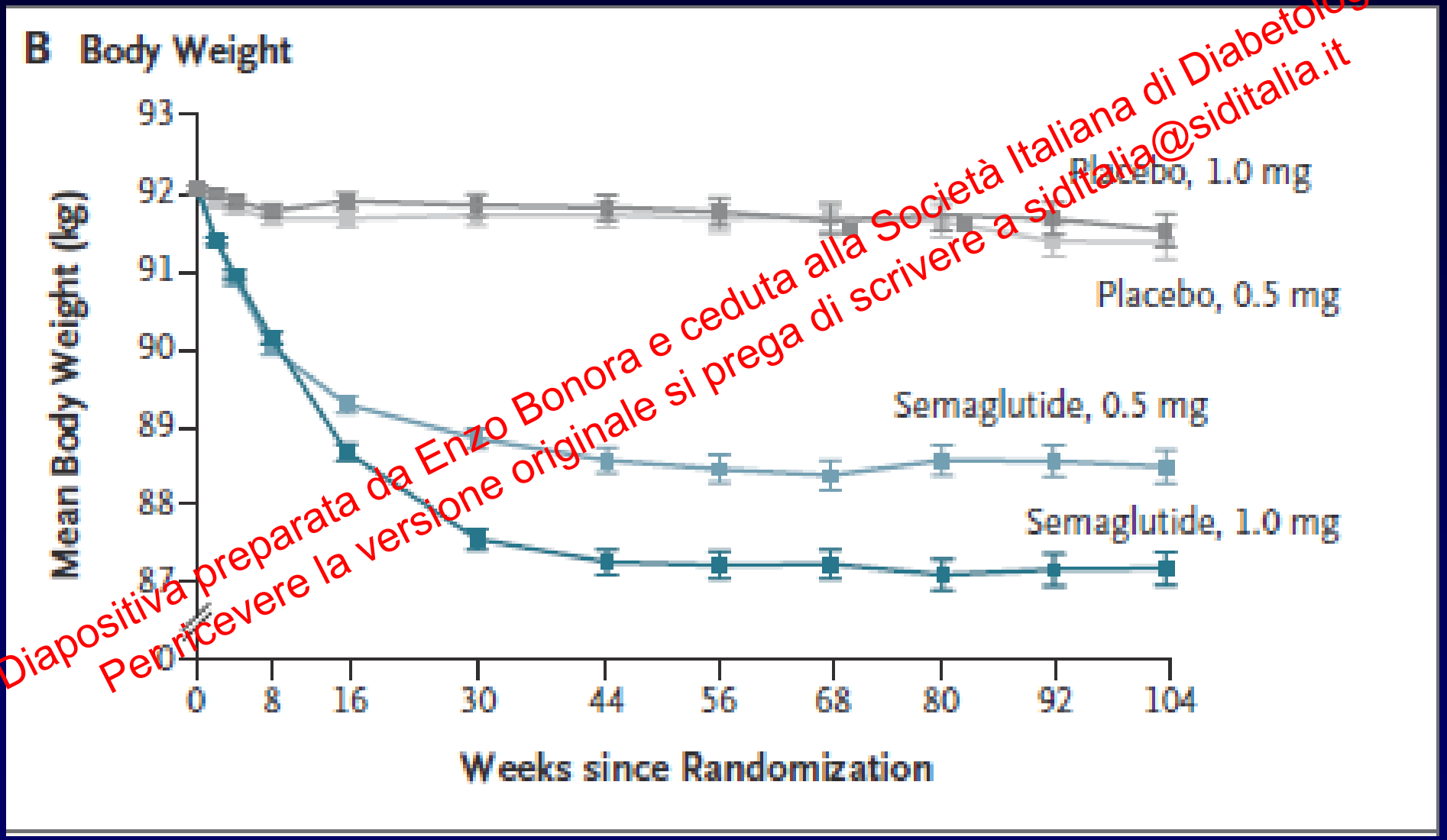
SUSTAIN 6 – Time course of HbA1c

Marso et al – NEJM 2016; 375: 1834



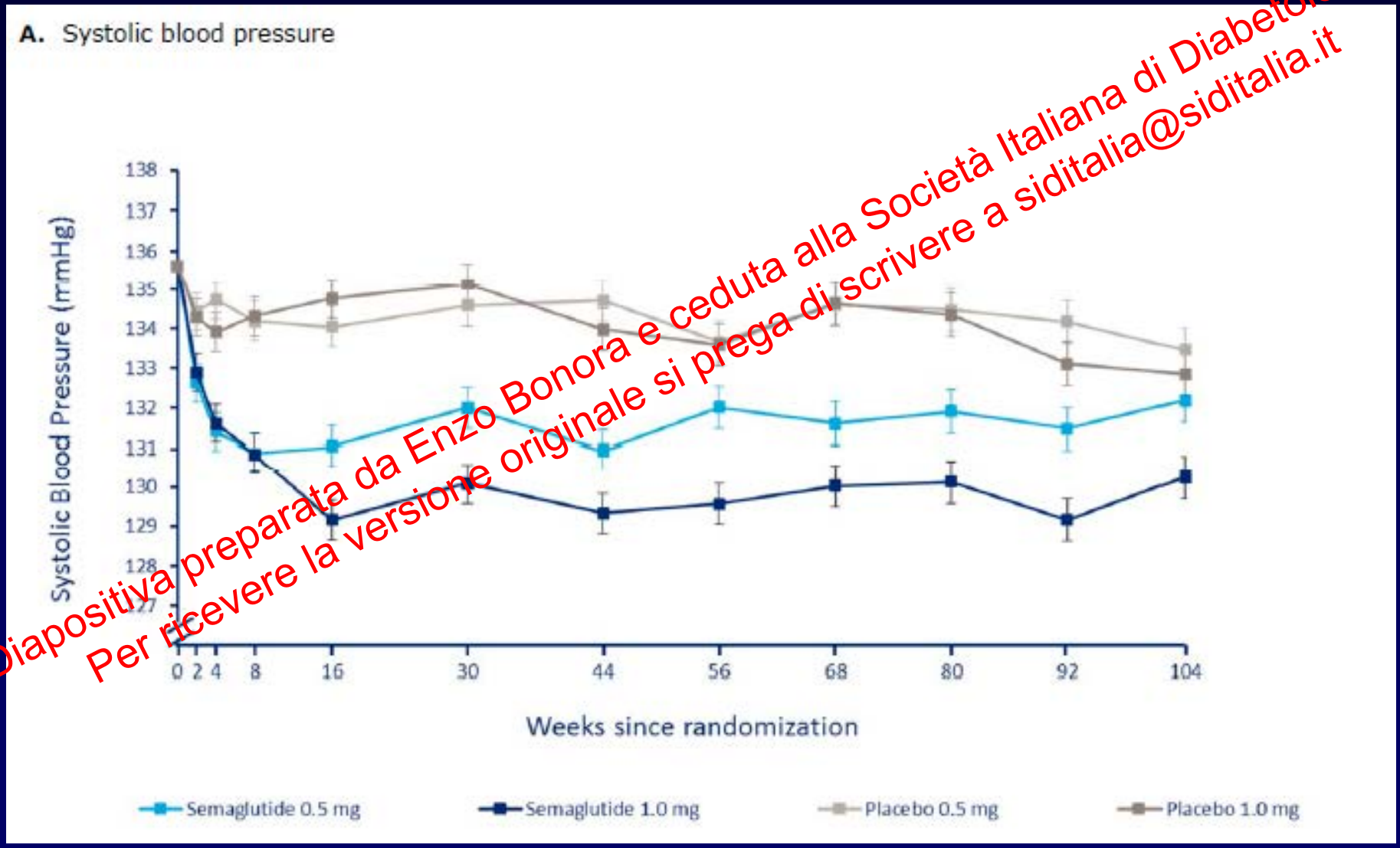
SUSTAIN 6 – Time course of BW

Marso et al – NEJM 2016; 375: 1834



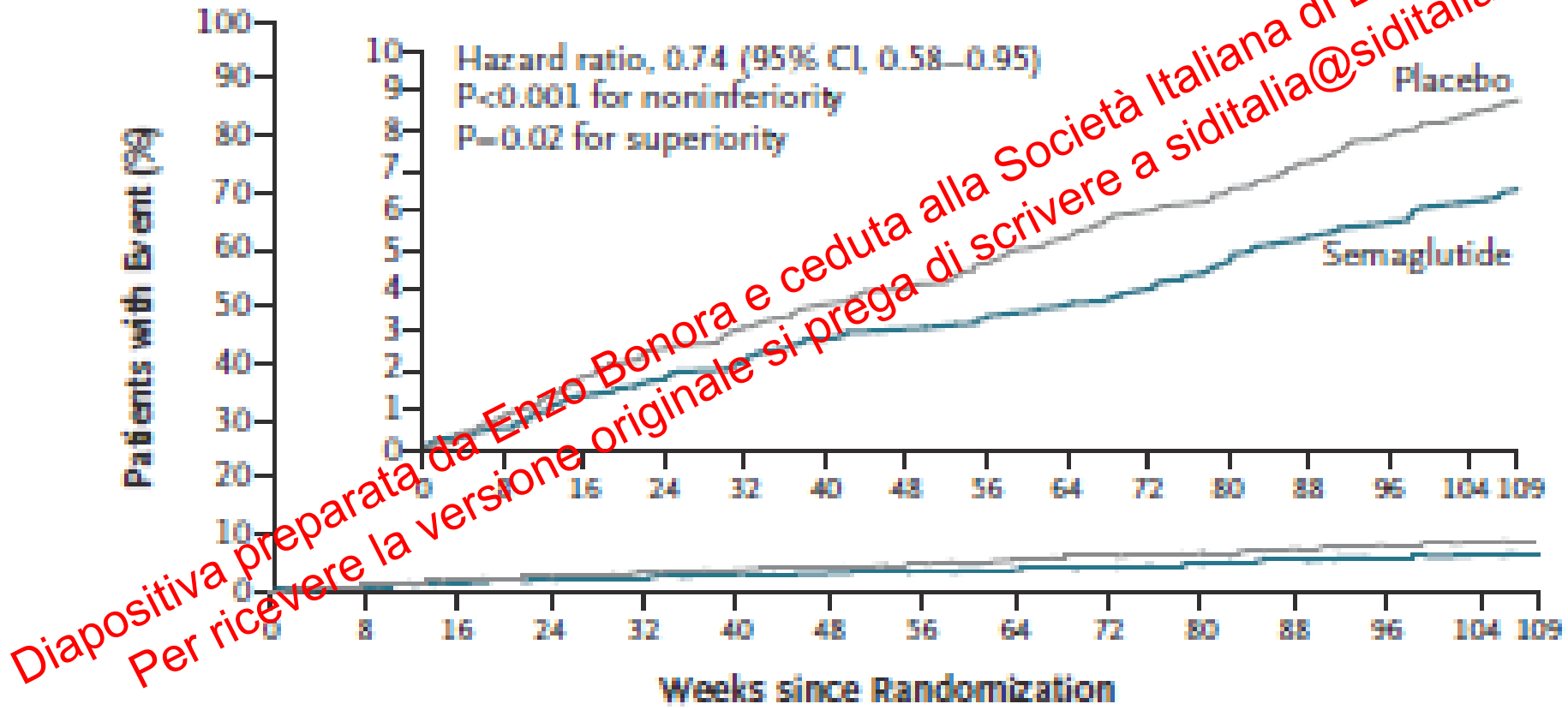
SUSTAIN 6 – Time course of sBP

Marso et al – NEJM 2016; 375: 1834



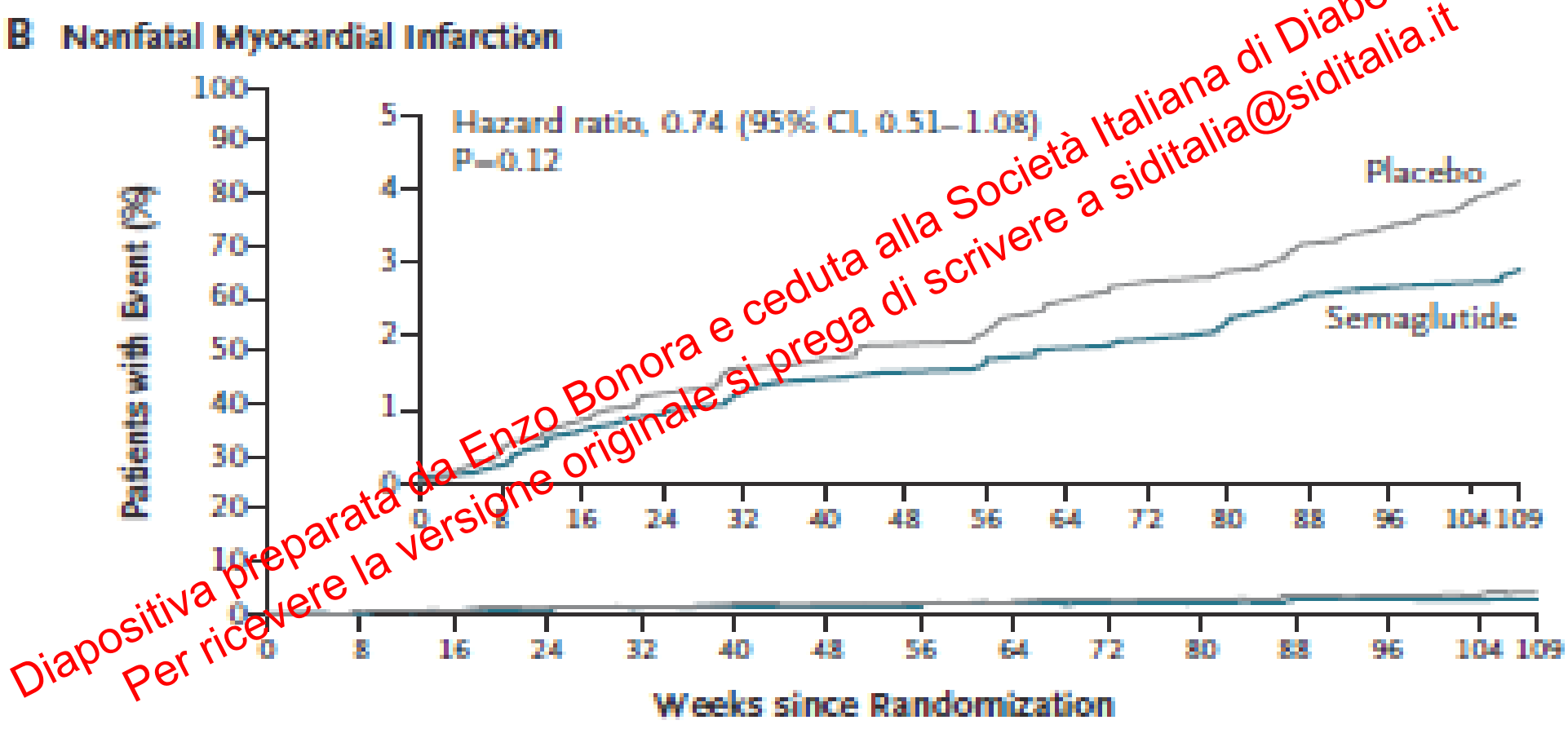
SUSTAIN 6 – Primary Outcome (MACE)

Marso et al – NEJM 2016; 375: 1834



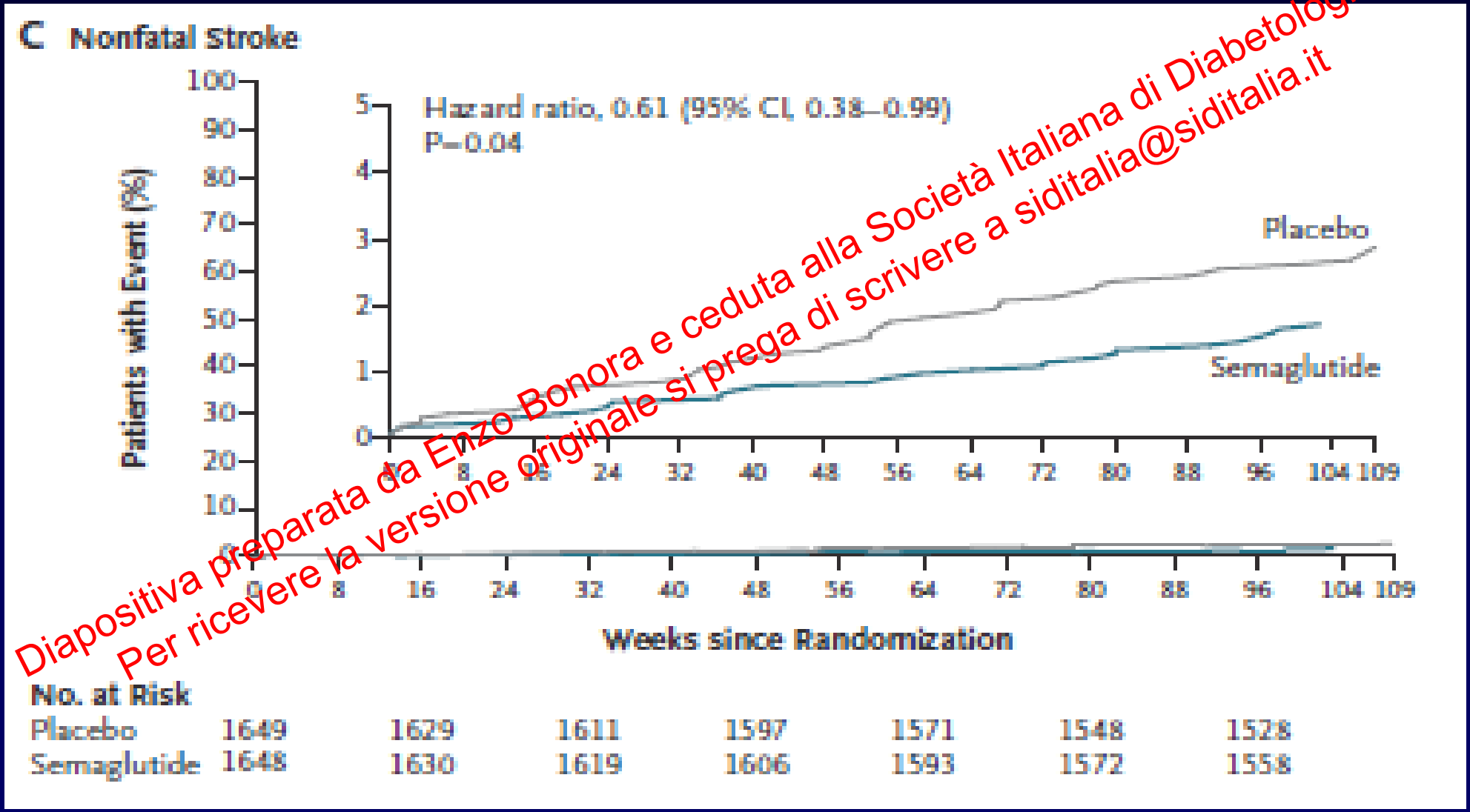
SUSTAIN 6 – Non-fatal MI

Marso et al – NEJM 2016; 375: 1834



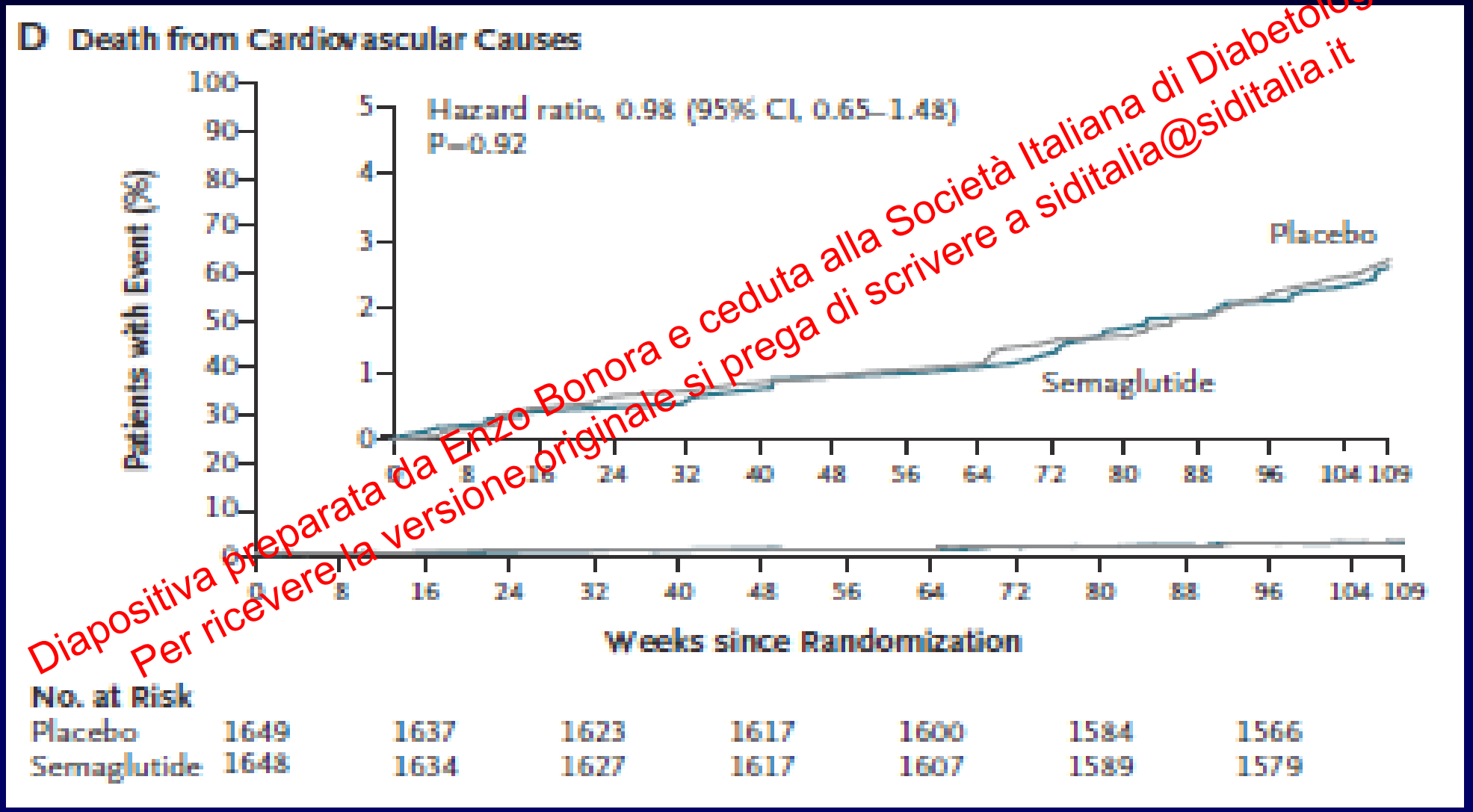
SUSTAIN 6 – Non-fatal stroke

Marso et al – NEJM 2016; 375: 1834



SUSTAIN 6 – Cardiovascular death

Marso et al – NEJM 2016; 375: 1834



SUSTAIN 6 – Primary and secondary outcomes

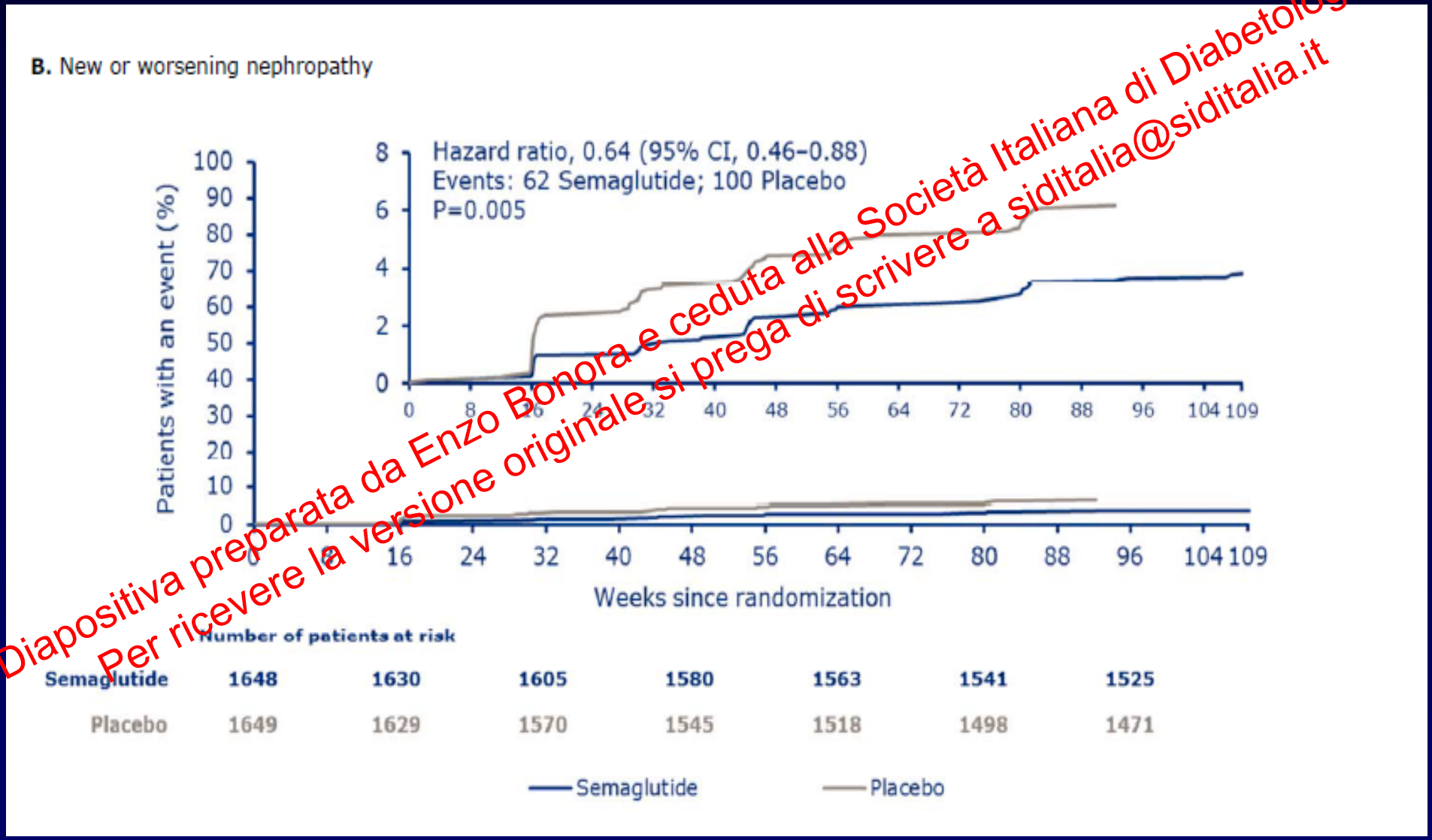
Marso et al – NEJM 2016; 375: 1834

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

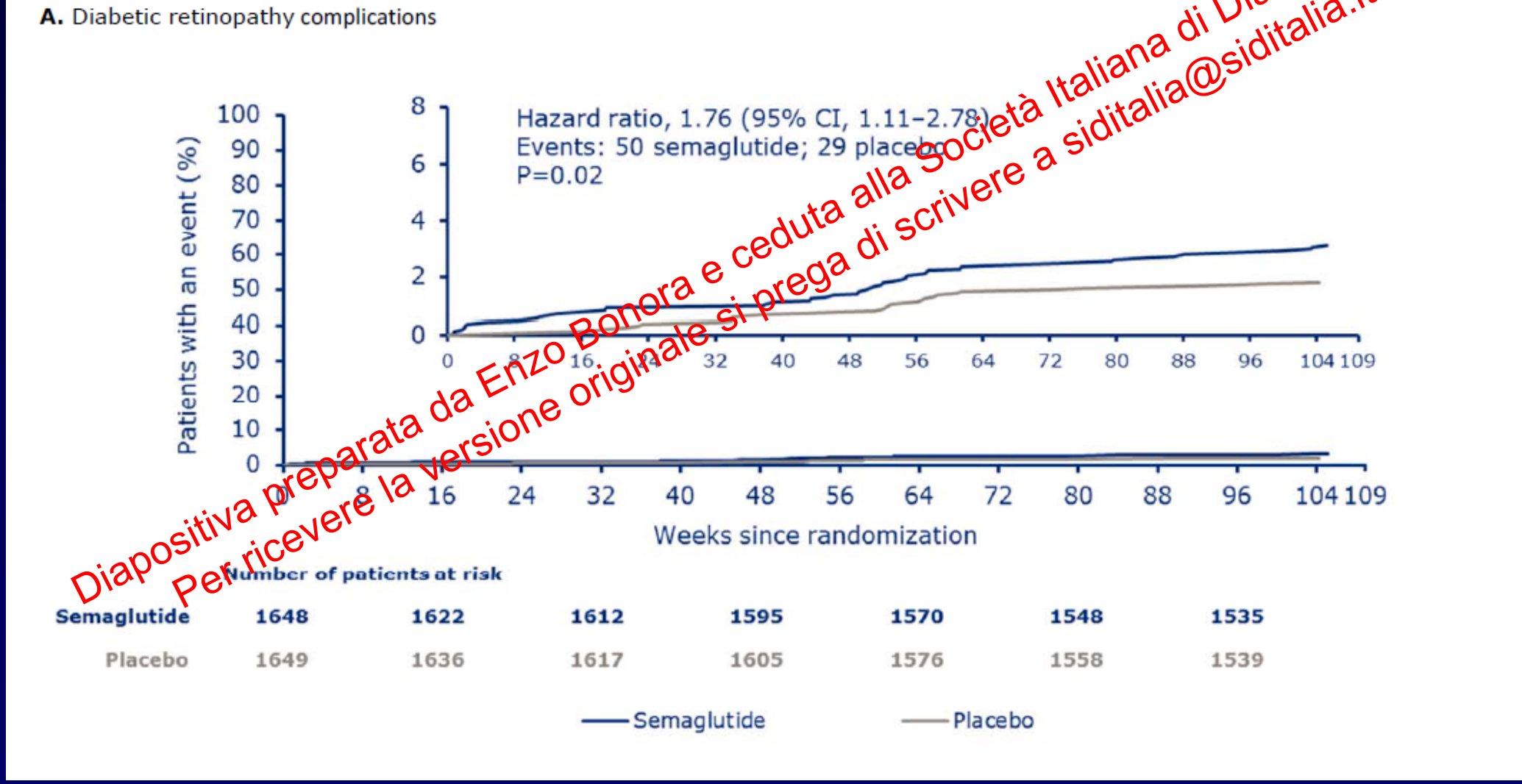
SUSTAIN 6 – New or worsening nephropathy

Marso et al – NEJM 2016; 375: 1834



SUSTAIN 6 – Retinopathy complication

Marso 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

PRESS RELEASE – March 2017

Bydureon EXSCEL trial meets primary safety objective in type 2 diabetes patients at wide range of cardiovascular risk

Based on a composite measure of major adverse CV events (MACE), Bydureon did not increase cardiovascular (CV) risk and showed a consistent safety profile. Fewer CV events were observed in the Bydureon arm, however, the efficacy objective of reduction in CV risk did not reach statistical significance.

AstraZeneca today announced top-line results from the Phase IIIbMV EXSCEL (**EX**enatide **S**tudy of **C**ardiovascular **E**vent **L**owering) trial. The trial compared the effect of once-weekly *Bydureon* (exenatide extended-release) versus placebo, when added to usual type 2 diabetes care, on the risk of **MACE**, a composite endpoint of CV death, non-fatal myocardial infarction or non-fatal stroke, in adults with **type 2 diabetes (T2D) at a wide range of CV risk.**

The EXSCEL trial met its primary safety objective of non-inferiority for **MACE**. These results address the US Food and Drug Administration (FDA) requirement that medicines to treat T2DM are not associated with an increase in CV risk. Fewer CV events were observed in the *Bydureon* arm of the trial, however, the efficacy objective of a superior reduction in MACE did not reach statistical significance. Data were consistent with the known safety profile of *Bydureon*.

The EXSCEL trial is the largest and most inclusive patient population of any CV outcomes trial of the glucagon-like peptide-1 (GLP-1) receptor agonist class conducted to date, having included more than **14,000 patients** from 35 countries.

A full evaluation of the EXSCEL data is ongoing. The results will be presented at the European Association for the Study of Diabetes (EASD) annual meeting on Thursday, 14 September 2017 in Lisbon, Portugal.

REWIND

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

Design and Baseline Characteristics of Participants in the Researching cardiovascular Events with a Weekly INcretin in Diabetes (REWIND) Trial of Dulaglutide's Cardiovascular Effects

REWIND Trial Investigators*

Gerstein H et al
DOM 2017

Abstract

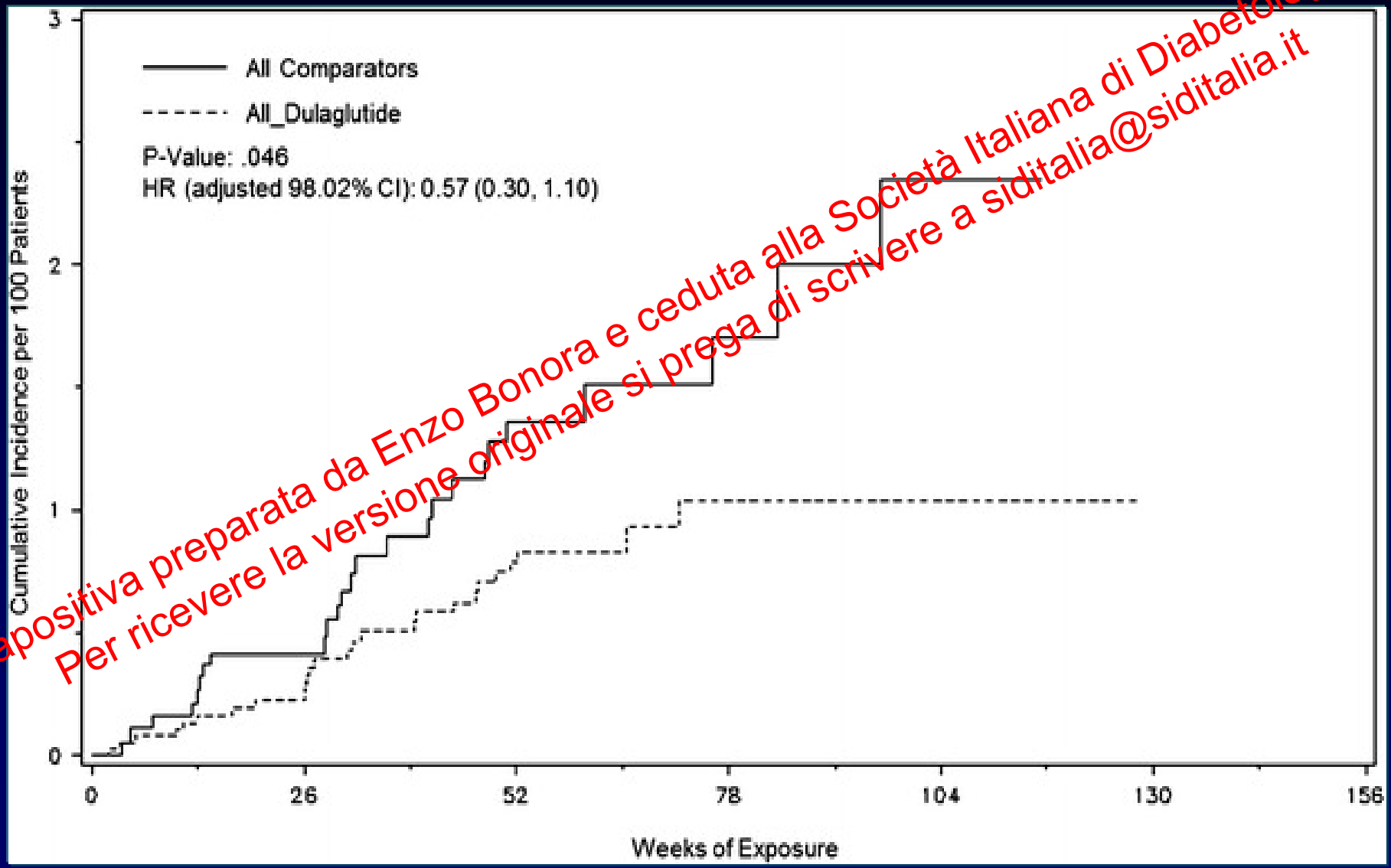
Background: Dulaglutide, a synthetic once-weekly, injectable human glucagon-like peptide 1 (GLP1) analogue lowers blood glucose, body weight, appetite, and blood pressure. Its effect on cardiovascular outcomes is unknown.

Methods: People with type 2 diabetes, aged 50 or older, a HbA1c ≤9.5%, and either a previous cardiovascular (CV) event, evidence of CV disease or ≥ 2 CV risk factors were randomly allocated to a weekly subcutaneous injection of either dulaglutide (1.5 mg) or placebo and followed within the Researching cardiovascular Events with a Weekly INcretin in Diabetes (REWIND) trial every 3 to 6 months. The primary cardiovascular outcome is the first occurrence of the composite of cardiovascular death or non-fatal MI or nonfatal stroke. Secondary outcomes include each component of the primary composite cardiovascular outcome, a composite clinical microvascular outcome comprising retinal or renal disease, hospitalization for unstable angina, heart failure requiring hospitalization or an urgent heart failure visit, and all-cause mortality. Follow-up will continue until the accrual of 1200 confirmed primary outcomes.

Results: Recruitment of 9901 participants (mean age 66, 46% women) occurred in 370 sites located in 24 countries over a period of 2 years. The mean duration of diabetes was 10 years, mean baseline HbA1c was 7.3 %, and 31% had prior cardiovascular disease.

Conclusion: The REWIND trial's international scope, high proportion of women, high proportion of people without prior cardiovascular disease, and inclusion of participants whose mean baseline HbA1c was 7.3% suggests that its cardiovascular and safety findings will be directly relevant to the typical middle-aged patient seen in general practice throughout the world.

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 meta-analysis.

Lancet Diabetes Endocrinol. 2015 Sep;3(9):697-703.

BACKGROUND:
Albiglutide is a glucagon-like peptide-1 receptor agonist, a new class of drugs used to treat type 2 diabetes. We did a prospective meta-analysis of the cardiovascular safety of albiglutide as stipulated by the US Food and Drug Administration recommendations for the assessment of new treatments for diabetes.

METHODS:
We did a meta-analysis of eight phase 3 trials and one phase 2b trial in which patients were randomly assigned to albiglutide, placebo, or active comparators (glimepiride, insulin glargine, insulin lispro, liraglutide, pioglitazone, or sitagliptin). The safety population included **5107 patients**, of whom 2524 took albiglutide (4870 person-years) and 2583 took comparators (5213 person-years). Possible major cardiovascular events were recorded prospectively and adjudicated by an independent endpoint committee masked to treatment allocation. The primary endpoint was a composite of first occurrence of major adverse cardiovascular events (ie, cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke, **MACE) or hospital admission for unstable angina**. Secondary endpoints were major adverse cardiovascular events alone, all-cause mortality, silent myocardial infarction, hospital admission for heart failure, chest pain, other angina, and subdural or extradural haemorrhage. The occurrence of all other adverse events classified by the investigators as cardiovascular events were documented, but these were not adjudicated.

FINDINGS:
The primary endpoint was not significantly different between albiglutide and all comparators (58 events vs 58 events; hazard ratio [HR] 1·00, 95% CI 0·68-1·49, p=0·0019 for non-inferiority). Major adverse cardiovascular event alone was also not significantly different (52 events vs 53; HR, 0·99; 95% CI, 0·65-1·49). When albiglutide was compared separately with placebo or active comparators, we noted no significant differences. We detected no significant differences in the other secondary endpoints. More patients had atrial fibrillation or atrial flutter in the albiglutide group (35 [1·4%] of 2524 patients; 8·6 events per 1000 patient-years) than in the all-comparators group (16 [0·6%] of 2583 patients; 3·4 events per 1000 patient-years).

INTERPRETATION:
Cardiovascular events were not significantly more likely to occur with albiglutide than with all comparators. Because the upper bound of the 95% CI for major adverse cardiovascular event plus hospital admission for unstable angina was greater than 1.3, a dedicated study with a cardiovascular endpoint is underway to confirm the safety of albiglutide

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).*

Risposte a quesiti

1. Gli agonisti dei recettori GLP-1 possono contribuire a cambiare certi numeri sulla malattia cardiovascolare nel diabete? **Certamente sì.**

2. In caso affermativo, su quali endpoint cardiovascolari? **Morte cardiovascolare, infarto, ictus.**

3. In caso affermativo, si tratta di un effetto classe? **No, perché non tutti i farmaci della classe hanno mostrato dei benefici cardiovascolari, ma solo liraglutide e semaglutide.**

4. In caso affermativo, i benefici potenziali riguardano solo alcune categorie di soggetti con diabete oppure tutti? **I benefici sono evidenti soprattutto nei soggetti con pregressa malattia cardiovascolare.**

5. In caso affermativo, esiste un corrispettivo nelle attuali linee guida? **Certo, nel position statement della SID di circa un anno fa.**

6. In caso affermativo, esistono degli ostacoli alla applicazione delle stesse? **I criteri attuali di rimborsabilità in Italia non costituiscono un ostacolo nella maggior parte dei casi.**

E adesso che si fa?
Si cambia?

I farmaci iniettabili prescritti per la cura del diabete

Osservatorio ARNO Diabete CINECA-SID - 2014

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

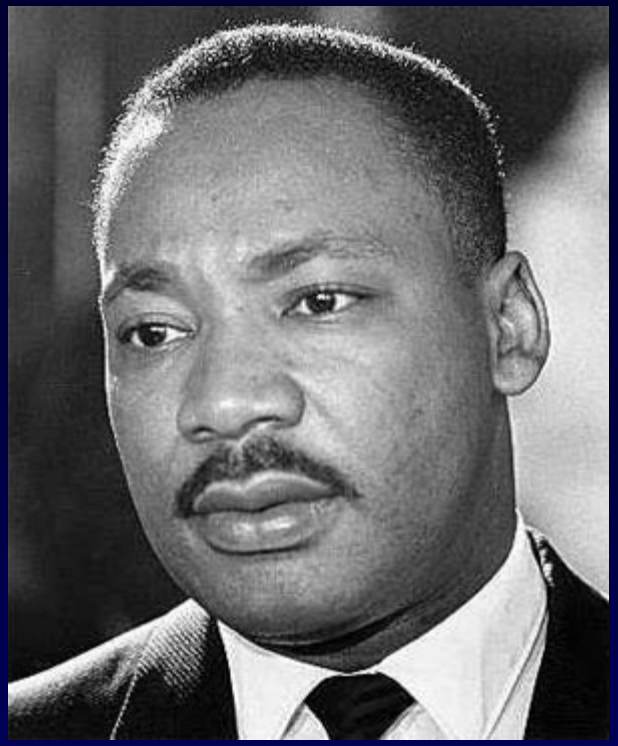
Agonisti recettore GLP-1 ancora meno del 2% dopo 7 anni dal lancio

I farmaci antidiabetici più prescritti

Osservatorio ARNO Diabete CINECA-SID - 2014

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



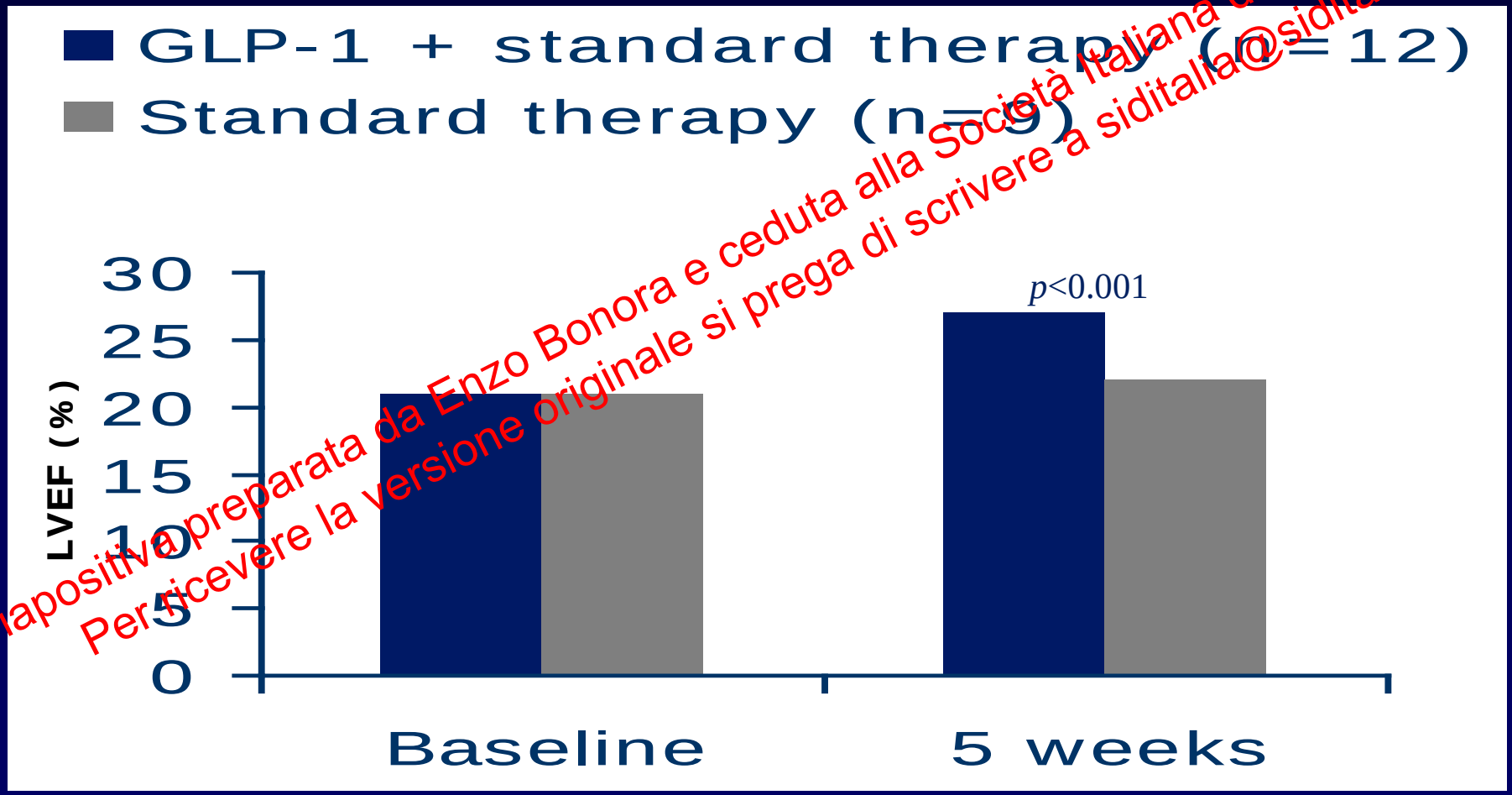
“Può darsi che non siate responsabili per la situazione in cui vi trovate ma lo diventerete se non farete nulla per cambiarla”

Martin Luther King

Grazie per l’attenzione

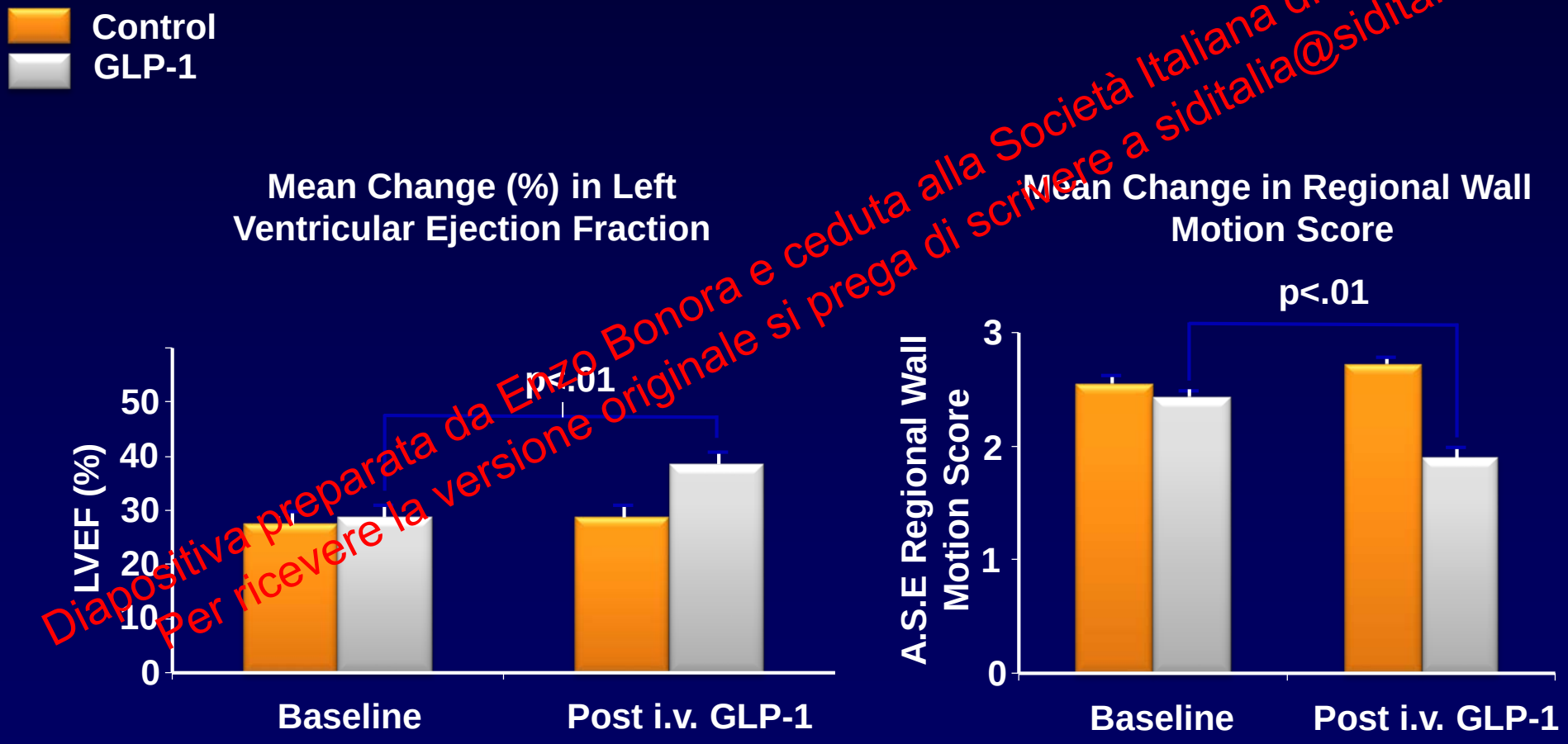
GLP-1 infusion improves left ventricular function in patients with congestive heart failure

Sokos et al - J Cardiac Failure 2006; 12:694–99



Cardiac Effects of GLP-1 in Patients with AMI and Left Ventricular Dysfunction

Nikolaidis et al - Circulation 2004;109: 962



GLP-1 Receptor Agonists

Prandial (short and “long acting”)

- Exanatide (BID)
- Lixisenatide (daily)

Non prandial (long, very long and very very long acting)

- Liraglutide (daily)
- Exenatide LAR (weekly, yearly)
- Dulaglutide (weekly)
- Albiglutide (weekly)
- Semaglutide (weekly)

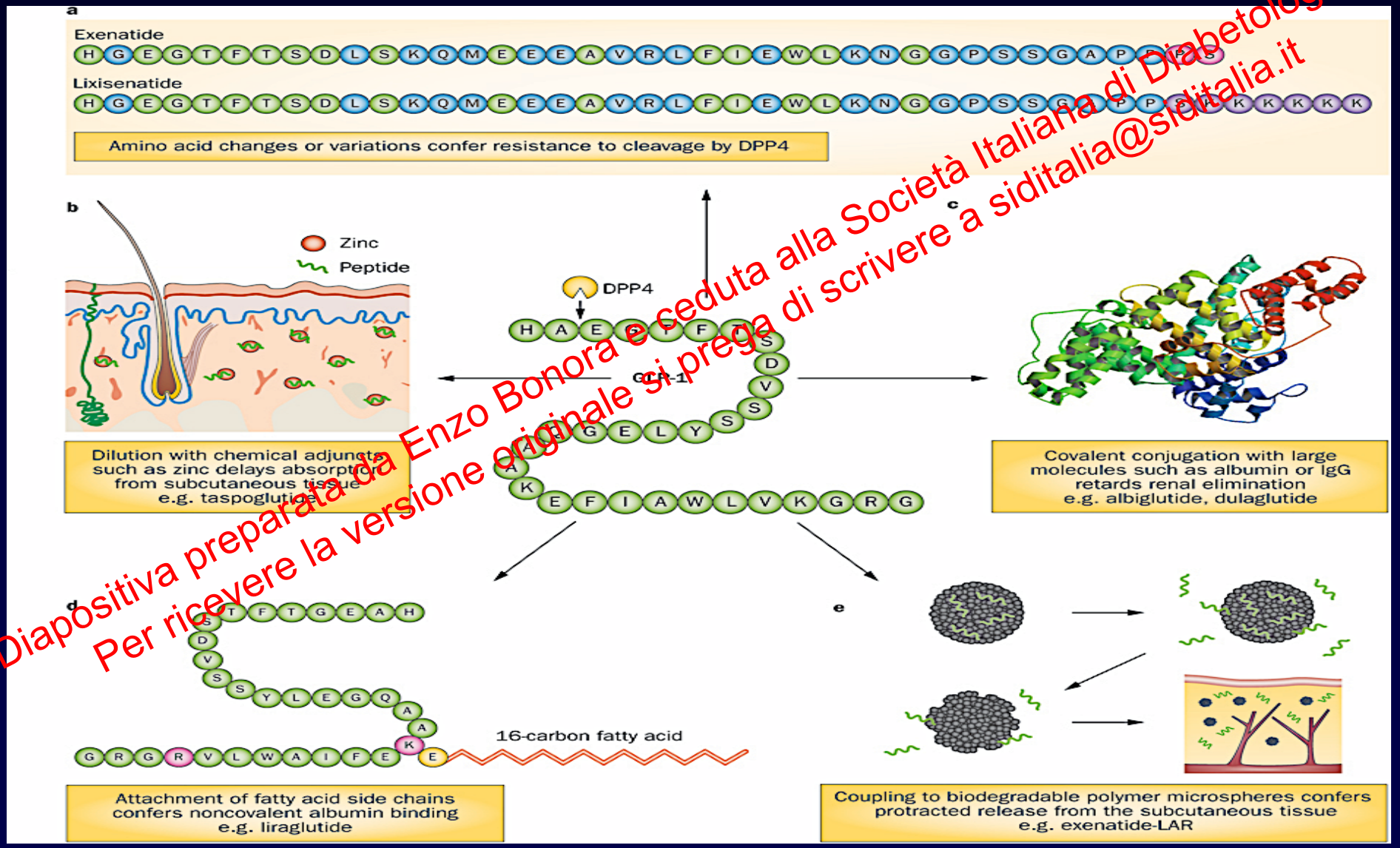
Comparison of Prandial (Short-acting) vs. Non-prandial (Long-acting) GLP-1 RA

Meier JJ - Nat Rev Endocrinol 2012; 8:728-742

Parameters	Prandial GLP-1 receptor agonists	Non-prandial GLP-1 receptor agonists
Compounds	Exenatide BID Lixisenatide	Liraglutide Exenatide LAR Dulaglutide Albiglutide
Half-life	2–5 hours	12h–several days
Effects		
Fasting blood glucose levels	Modest reduction	Strong reduction
Postprandial hyperglycaemia	Strong reduction	Modest Reduction
Fasting insulin secretion	Modest stimulation	Strong stimulation
Postprandial insulin secretion	Reduction	Modest stimulation
Glucagon secretion	Reduction	Reduction
Gastric emptying rate	Deceleration	No effect
Blood pressure	Reduction	Reduction
Heart rate	No effect or small increase (0–2 bpm)	Moderate increase (2–5 bpm)
Body weight reduction	1–5kg	2–5kg
Induction of nausea	20–50% attenuates slowly (weeks to many months)	20–40% attenuates quickly (~4–8weeks)

Strategies to develop GLP1-receptor agonists

Meier JJ – Nat Rev Endocrinol 2012; 8: 728-742



Effetti di exenatide sui fattori di rischio cardiovascolare

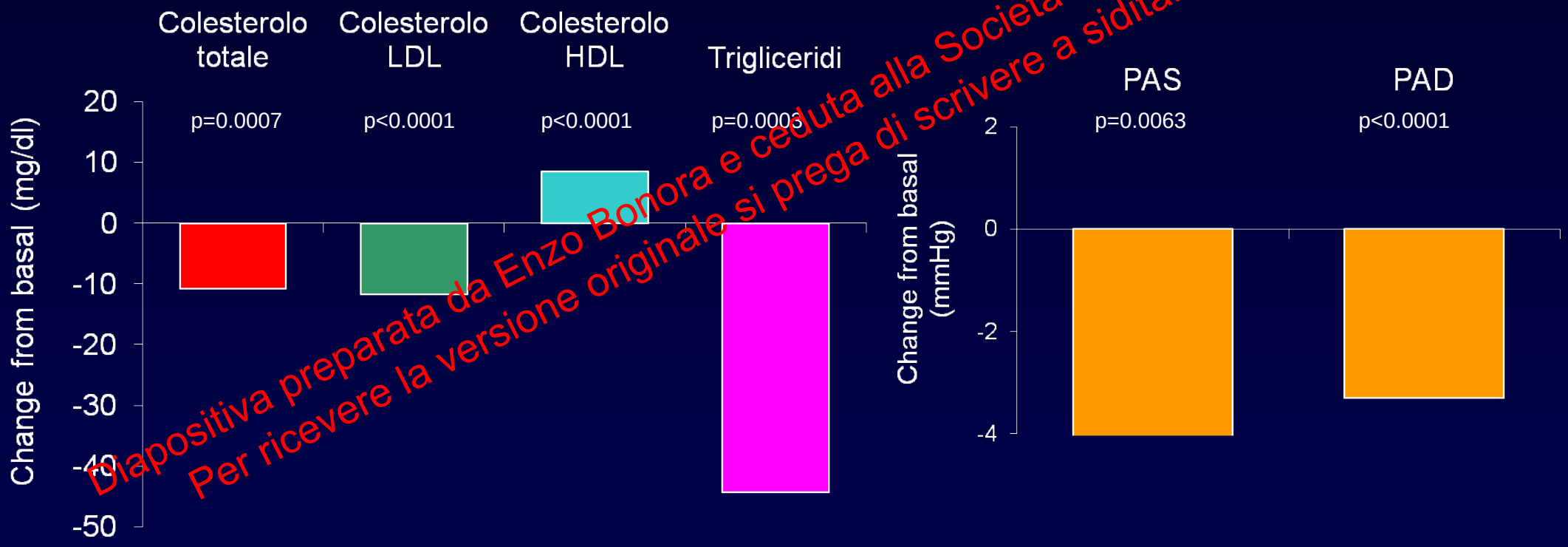
Klonoff et al. Curr Med Res Opinion. 2008;24:275

Miglioramenti nei fattori di rischio cardiovascolare con 3,5 anni di trattamento a base di exenatide (n = 151)

Fattore di rischio cardiovascolare	Basale (media ± SEM)	Variazione rispetto al basale (media ± SEM)	Variazione % media	IC 95%	Valore p
Trigliceridi (mg/dl)	225.1 ± 11.6	–44.4 ± 12.1	–12	Da -68,3 a -20,5	0.0003
Colesterolo totale (mg/dl)	184.4 ± 3.0	–10.8 ± 3.1	–5	Da -17,0 a -4,6	0.0007
HDL-C (mg/dl)	38.6 ± 0.8	8.5 ± 0.6	+24	Da 7,2 a 9,7	<0.0001
LDL-C (mg/dl)	113.7 ± 2.7	–11.8 ± 2.9	–6	Da -17,5 a -6,1	<0.0001
Pressione arteriosa sistolica (mmHg)	129.3 ± 1.0	–3.5 ± 1.2	–2	Da -5,9 a -1,0	0.0063
Pressione arteriosa diastolica (mmHg)	79.2 ± 0.6	–3.3 ± 0.8	–4	Da -4,9 a -1,7	<0.0001

Exenatide improves cardiovascular risk factors in T2DM

Klonoff DC - Curr Med Res Opin 2008; 24:275-286



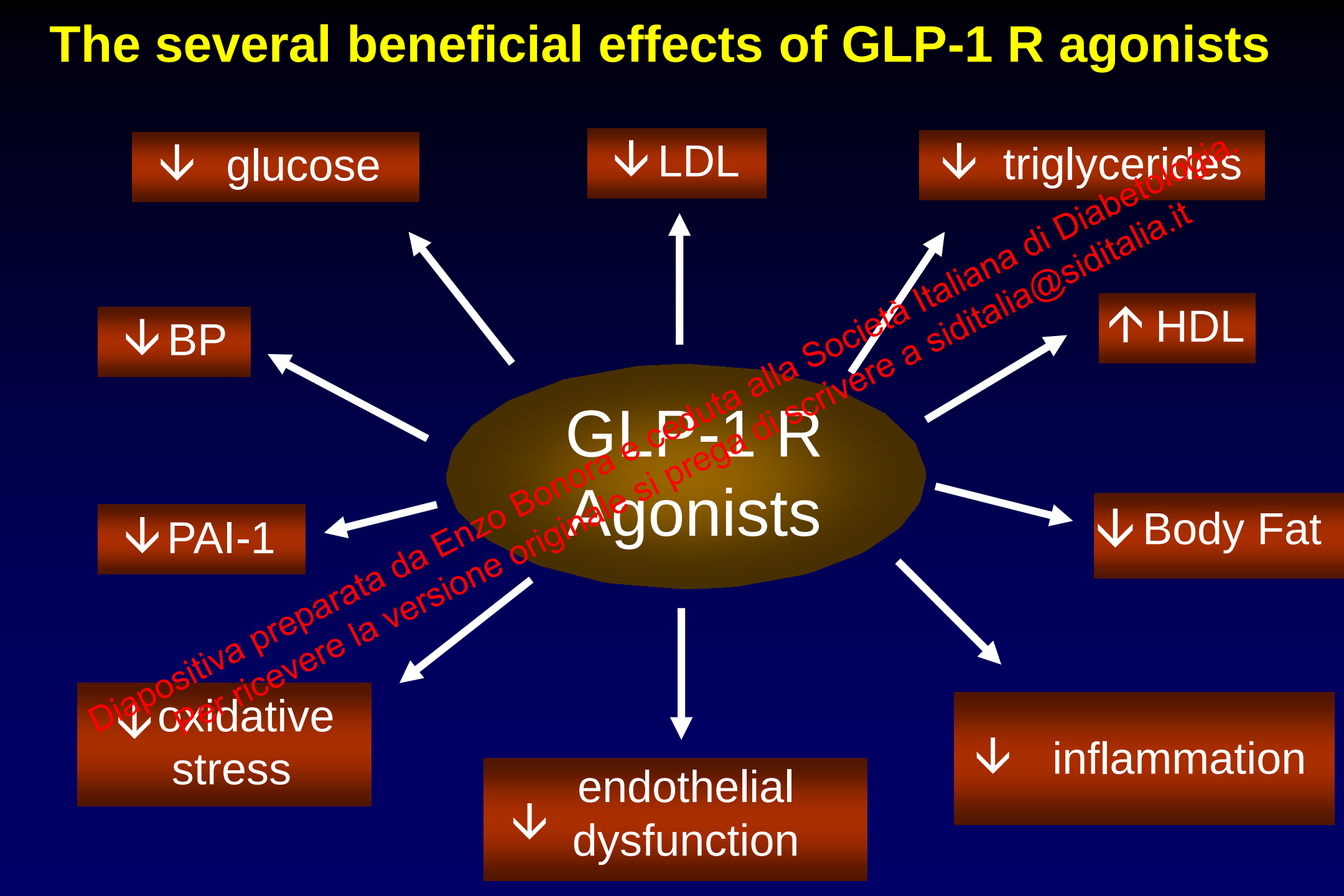
N=151; follow-up 3.5 anni

Effect of 14 wk liraglutide treatment on cardiometabolic risk factors in T2DM subjects

Visbøll et al - Diabetes Care 2007; 30:1608

	DIFFERENCE vs PLACEBO	Statistical Significance
Triglyceride	-22%	P<0,01
PAI-1	-29%	P<0,02
BNP	-30%	P<0,05
SBP	- 8 mmHg	P<0,01

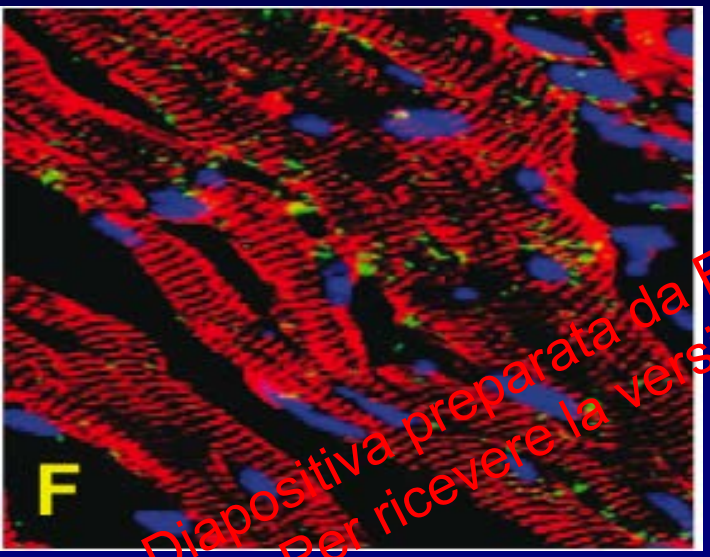
The several beneficial effects of GLP-1 R agonists



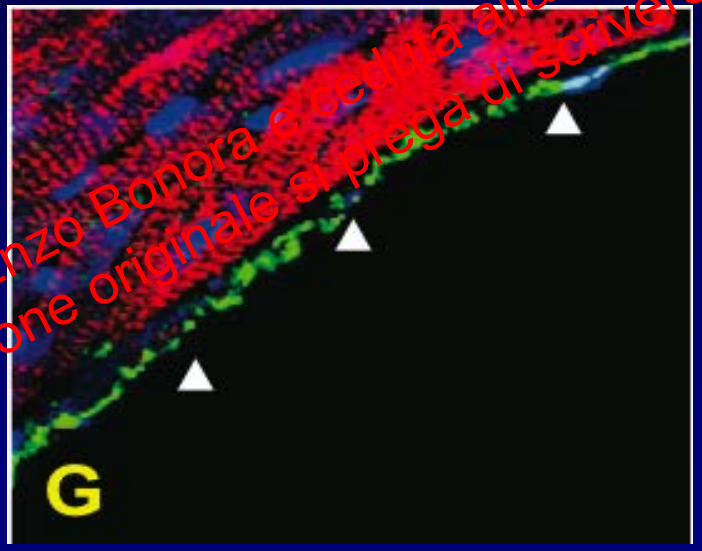
Expression of GLP1-Receptor in the Mouse Heart

Ban K et al. - Circulation 2008

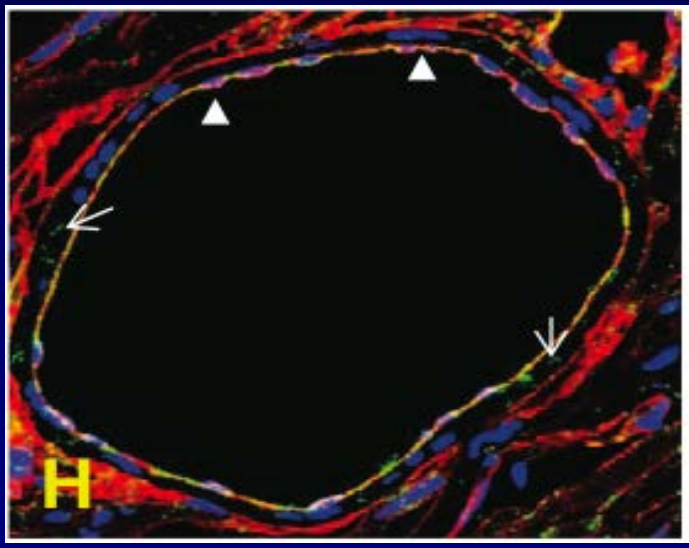
Cardiomyocytes



Endocardium



Coronary Arteries



Human coronary artery endothelial cells (HCAEC) express the GLP-1 receptor

Nystrom et al. – Am. J. Physiol. 2004

Exendin-4 riduce l’area di infarto nei ratti

Sønne et al - Reg Pept 2008

Modello dell’ischaemia e riperfusione
Exendina-4 somministrata al termine della fase ischemica

Controllo

Exendin-4

Tessuto infartuato (grigio)

Tessuto muscolare (rosso)

Effect of Exenatide on experimental ischemia in a pig model

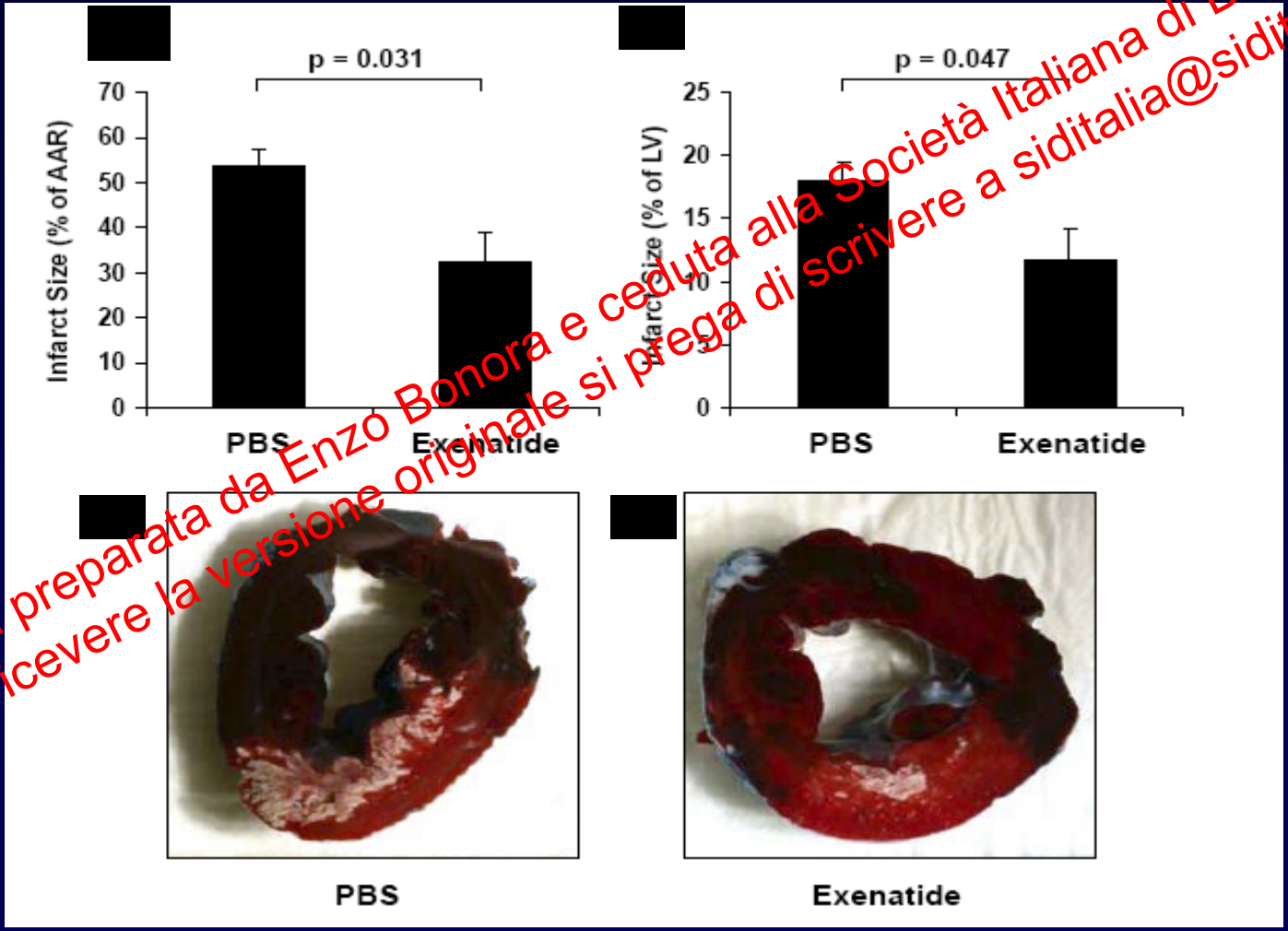
Timmers L. et al - JACC 2009

Infarction area as a % of area at risk

Infarction area as a % of left ventriculus

Infarction area in white

Area at risk in red



Riduzione con exenatide nella dimensione finale dell'infarto in pazienti affetti da infarto miocardico con sopraslivellamento del tratto ST (STEMI) e ischemia di breve durata

Lonborg et al. Circ Cardiovasc Interv. 2012;5:288-95

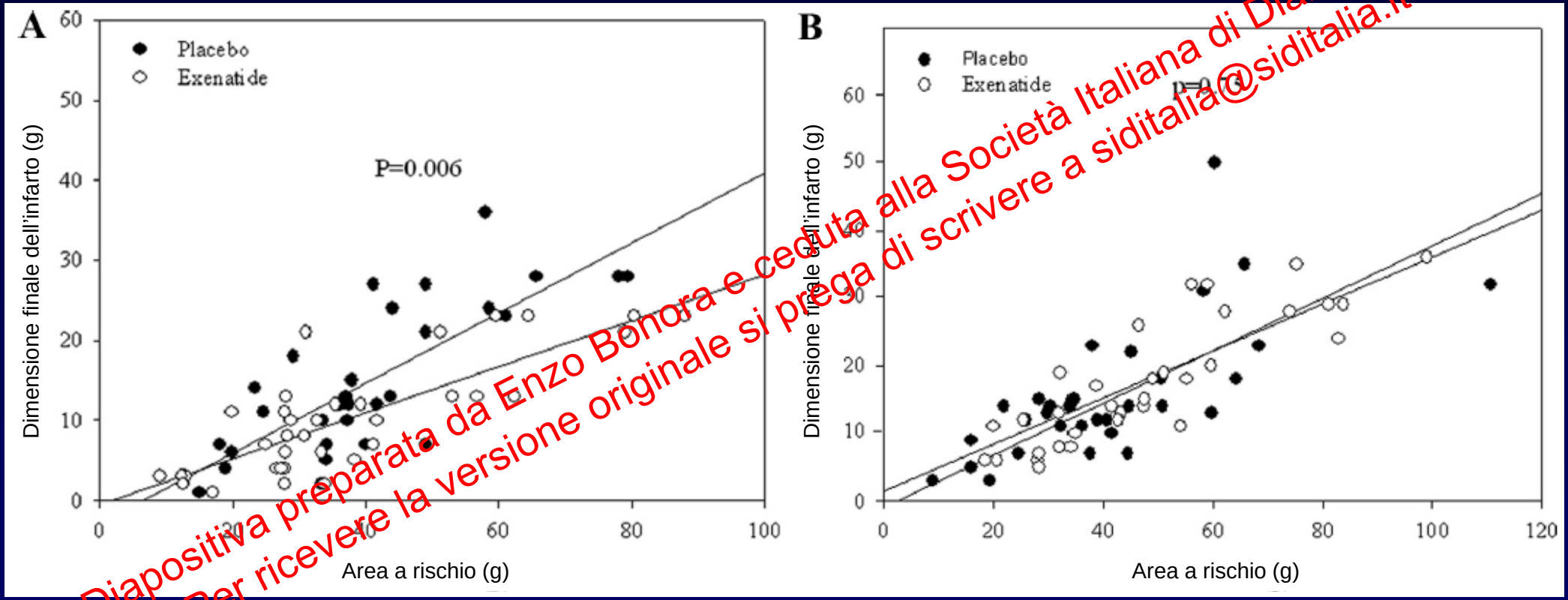
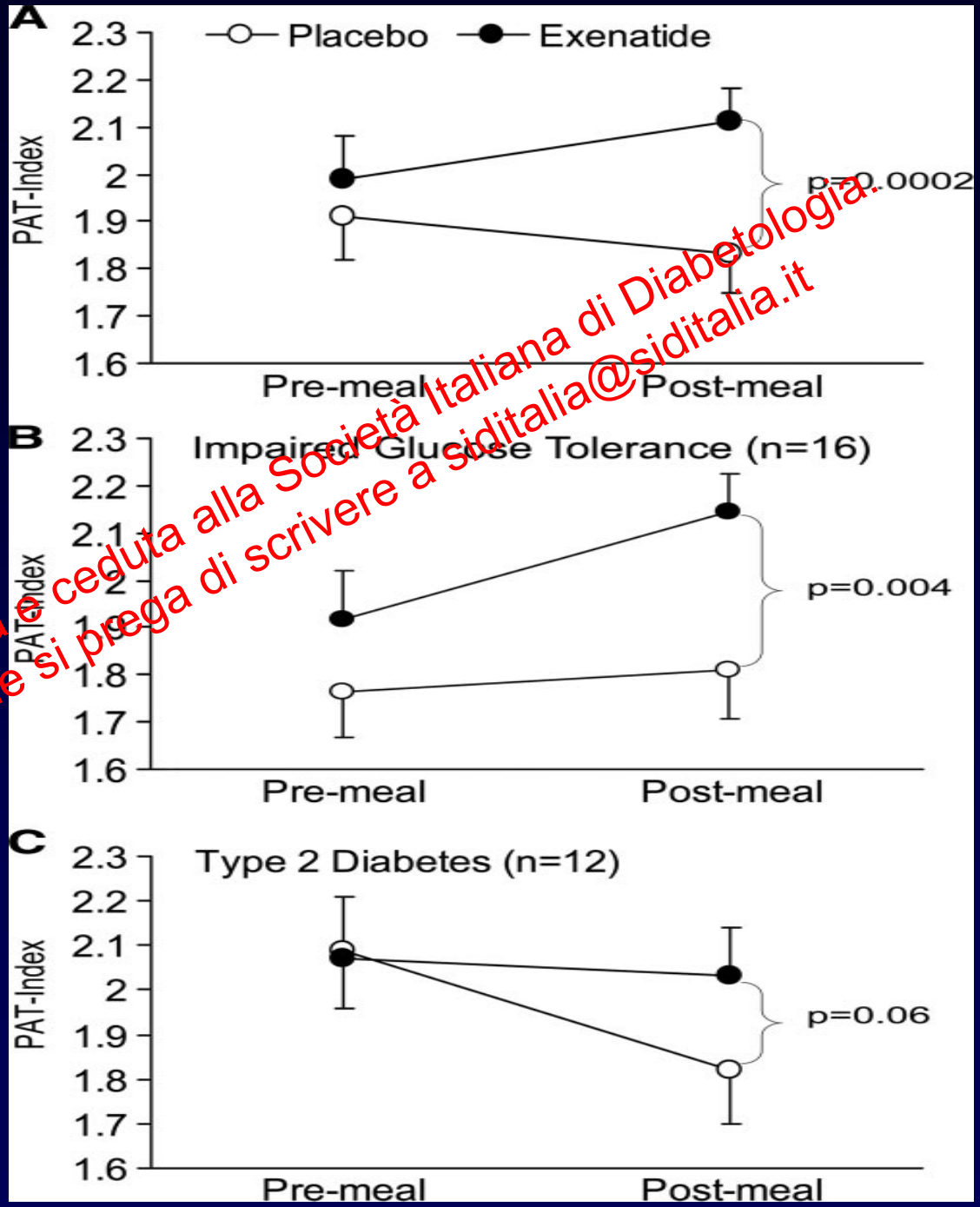


Diagramma della dimensione dell'infarto in relazione all'area a rischio per pazienti con ritardo nel trattamento ≤132 minuti (A) e >132 minuti (B).

La terapia con exenatide è stata associata a una riduzione del 30% nella dimensione finale dell'infarto in pazienti con breve ritardo nel trattamento, mentre non è stato osservato alcun effetto cardioprotettivo nei pazienti con lungo ritardo nel trattamento.

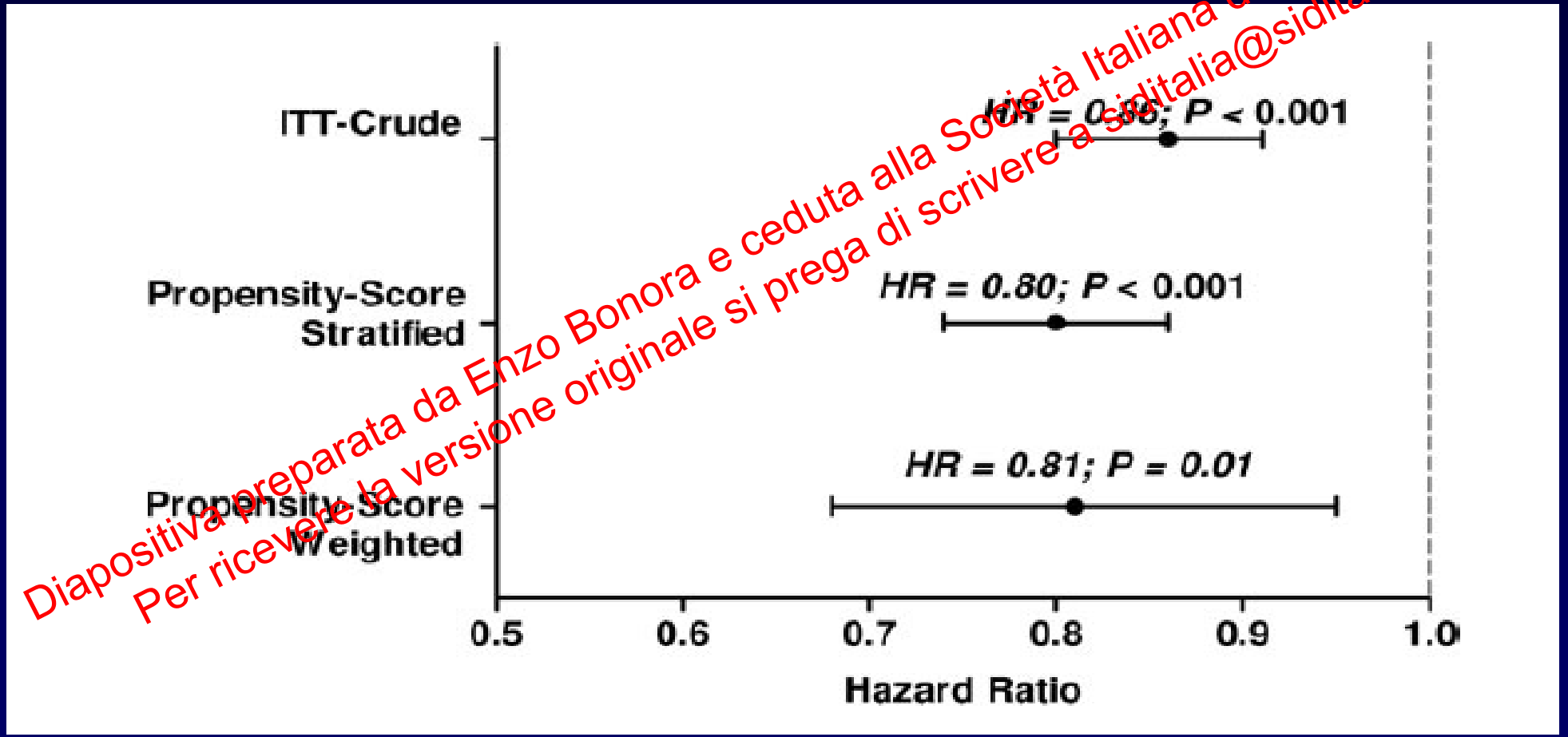
Effect of acute exenatide vs. saline on endothelial function (peripheral arterial tonometry) before and after meal in IGT/T2DM

Koska J et al
Diabetes Care 33: 1028, 2010



Risk of CVD in T2DM Treated with Exenatide vs. Other Anti-Diabetic Agents
A retrospective analysis of the LifeLink database

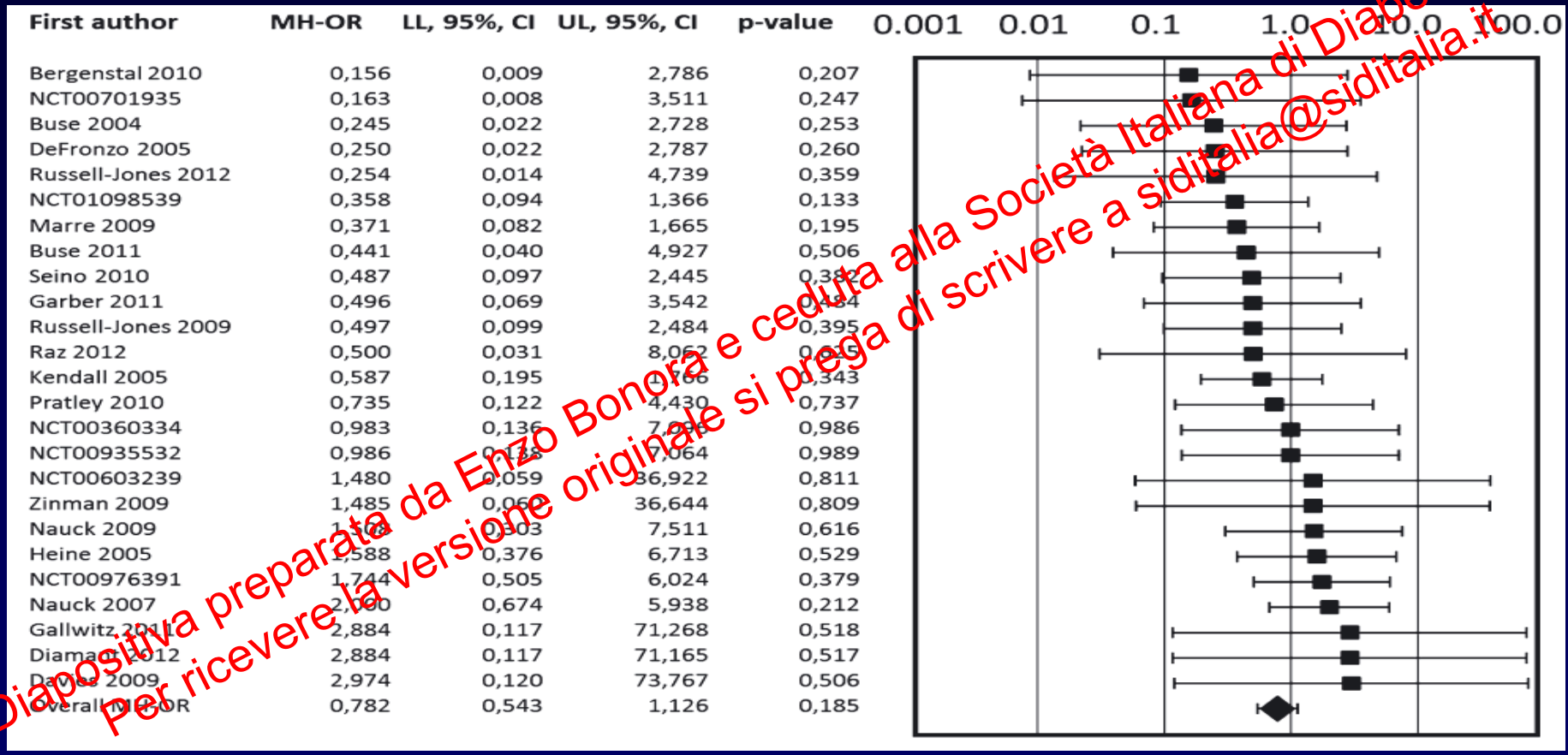
Best et al – Diabetes Care 2011; 34: 90-95



First new prescription: Exenatide (n=21,754) - Other agents (n=361,771)

Meta-analysis of effects on MACE in phase 2-3 studies with GLP-1 RAs vs. comparator

Monami et al. Diabetes, Obesity and Metabolism 16: 38–47, 2014



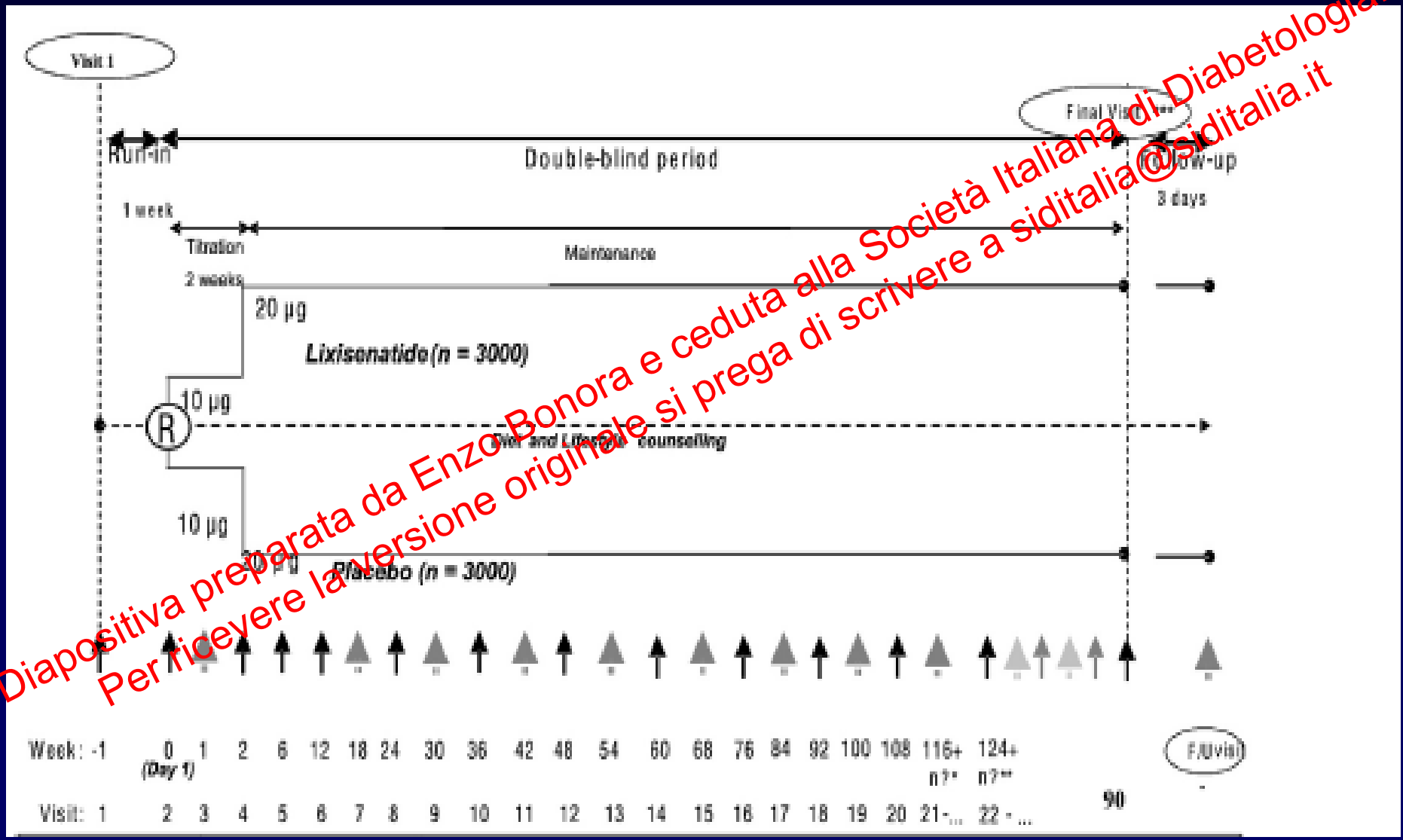
First author	MH-OR	LL, 95%, CI	UL, 95%, CI	p-value
Bergenstal 2010	0,156	0,009	2,786	0,207
NCT00701935	0,163	0,008	3,511	0,247
Buse 2004	0,245	0,022	2,728	0,253
DeFronzo 2005	0,250	0,022	2,787	0,260
Russell-Jones 2012	0,254	0,014	4,739	0,359
NCT01098539	0,358	0,094	1,366	0,133
Marre 2009	0,371	0,082	1,665	0,195
Buse 2011	0,441	0,040	4,927	0,506
Seino 2010	0,487	0,097	2,445	0,383
Garber 2011	0,496	0,069	3,542	0,484
Russell-Jones 2009	0,497	0,099	2,484	0,395
Raz 2012	0,500	0,031	8,062	0,635
Kendall 2005	0,587	0,195	1,766	0,343
Pratley 2010	0,735	0,122	4,430	0,737
NCT00360334	0,983	0,136	7,096	0,986
NCT00935532	0,986	0,138	7,064	0,989
NCT00603239	1,480	0,059	36,922	0,811
Zinman 2009	1,485	0,060	36,644	0,809
Nauck 2009	1,564	0,303	7,511	0,616
Heine 2005	1,588	0,376	6,713	0,529
NCT00976391	1,744	0,505	6,024	0,379
Nauck 2007	2,000	0,674	5,938	0,212
Gallwitz 2011	2,884	0,117	71,268	0,518
Diamant 2012	2,884	0,117	71,165	0,517
Davies 2009	2,974	0,120	73,767	0,506
Overall MH-OR	0,782	0,543	1,126	0,185

Figure 1. Mantel–Haenszel odds ratio with 95% confidence interval [MH-OR (95%, CI)] for major cardiovascular events for each individual trial with at least one event

GLP-1 RA were associated with a significant reduction in the incidence of MACE in comparisons with placebo and pioglitazone, with a nonsignificant trend towards reduction in DPP4i-controlled studies.

ELIXA – Experimental design

Pfeffer M et al – NEJM 215; 373: 2247



ELIXA – Baseline characteristics

Pfeffer M et al – NEJM 215; 373: 2247

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Placebo (N=3034)	Lixisenatide (N=3034)
Age — yr	60.6±9.6	59.9±9.7
Age ≥65 yr — no. (%)	1040 (34.3)	1003 (33.1)
Female sex — no. (%)	938 (30.9)	923 (30.4)
Duration of diabetes — yr	9.4±8.3	9.2±8.2
Glycated hemoglobin — %	7.6±1.3	7.7±1.3
Retinopathy — no. (%)	331 (10.9)	320 (10.5)
Neuropathy — no. (%)	498 (16.4)	512 (16.9)
Body weight — kg	85.1±19.6	84.6±19.2
Body-mass index†	30.2±5.8	30.1±5.6
Race — no. (%)‡		
Asian	367 (12.1)	404 (13.3)
Black	103 (3.4)	118 (3.9)
Other	246 (8.1)	254 (8.4)
White	2318 (76.4)	2258 (74.4)

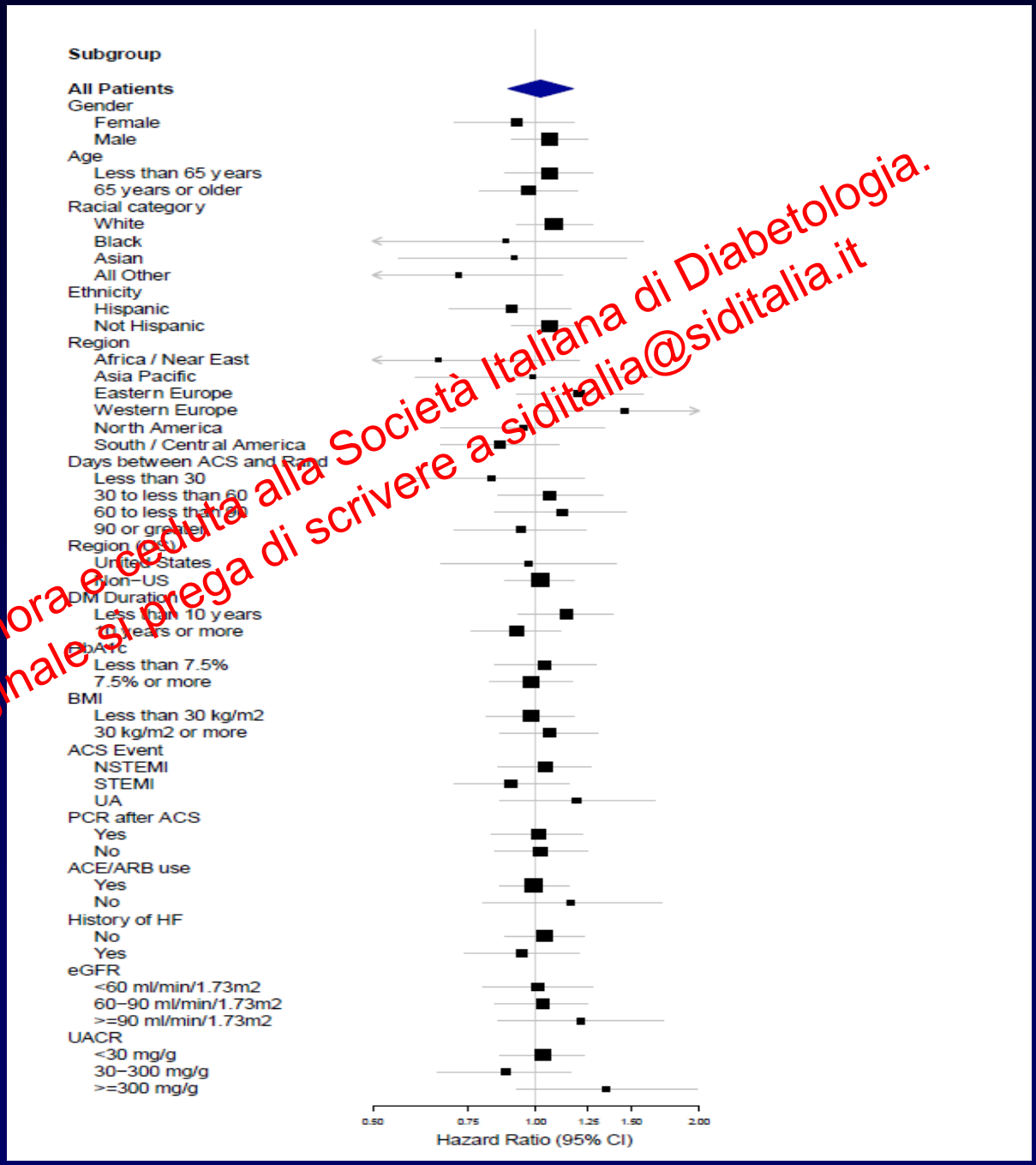
ELIXA – Baseline characteristics

Pfeffer M et al – NEJM 215; 373: 2247

Table 1. Characteristics of the Patients at Baseline.*		
Current smoking — no. (%)	354 (11.7)	356 (11.7)
Systolic blood pressure — mm Hg	130±17	130±17
Heart rate — beats/min	70.2±9.9	70.2±10.1
HDL cholesterol — mg/dl	42.9±10.9	43.0±10.8
LDL cholesterol — mg/dl	78.2±35.2	78.8±35.4
eGFR — ml/min/1.73 m^2	75.2±21.4	76.7±21.3
Qualifying ACS event — no. (%)		
NSTEMI	1183 (39.0)	1165 (38.4)
STEMI	1317 (43.4)	1349 (44.5)
Unstable angina	528 (17.4)	514 (16.9)
Unclassified	6 (0.2)	6 (0.2)
Days from ACS to randomization	72.2±43.9	71.8±43.4
Urinary albumin:creatinine ratio¶		
Median	10.5	10.2
Interquartile range	6.0–33.6	6.0–29.6

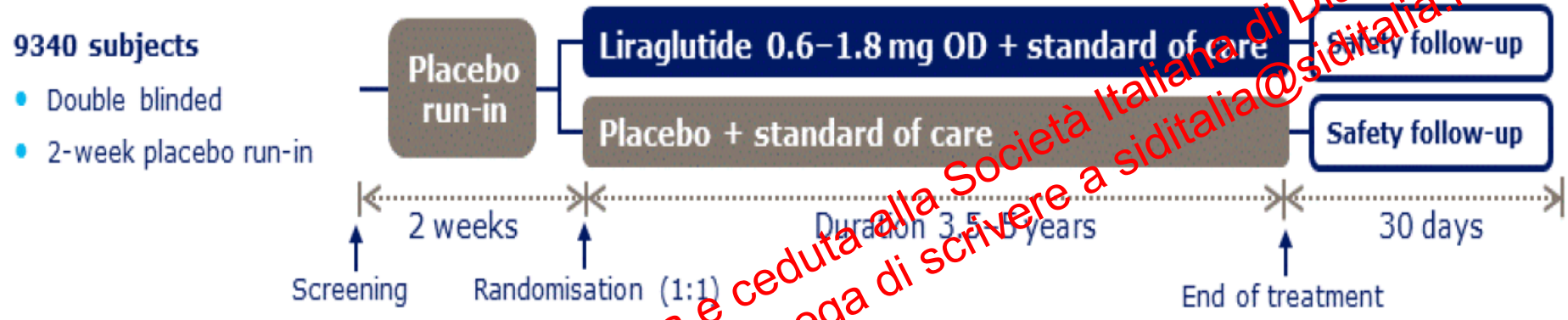
ELIXA
HR for primary endpoint Sensitivity analysis

Pfeffer M et al – NEJM 215; 373: 2247



LEADER – Experimental design

Marso SP et al – NEJM June 13, 2016



Key inclusion criteria

- T2DM, HbA_{1c} ≥7.0%
- Antidiabetic drug naïve; OADs and/or basal/premix insulin
- Age ≥50 years and established CV disease or chronic renal failure

or

- Age ≥60 years and risk factors for CV disease

Primary objective

To assess the effect of treatment with liraglutide compared with placebo on the incidence of CV events in adults with T2DM that are at high risk for CV events

Primary endpoint

- Time from randomisation to first occurrence of a composite CV outcome (CV death, non-fatal MI, or non-fatal stroke)

Key secondary endpoints

- Time from randomisation to first occurrence of an expanded composite CV outcome (CV death, non-fatal MI, non-fatal stroke, revascularisation, unstable angina or hosp. for heart failure)
- Time from randomisation to all cause death
- Time from randomisation to each individual component of the expanded composite CV outcome

LEADER Baseline characteristics

Marso SP et al – NEJM June 13, 2016

	Liraglutide (N=4,668)	Placebo (N=4,672)
Male sex	3011 (64.5)	2992 (64.0)
Age, years	64.2 ±7.2	64.4 ± 7.2
Diabetes duration, years	12.8 ± 8.0	12.9 ± 8.1
Geographic region		
Europe	1639 (35.1)	1657 (35.5)
North America	1401 (30.0)	1446 (31.0)
Asia	360 (7.7)	351 (7.5)
Rest of the world	1268 (27.2)	1218 (26.1)
Glycated hemoglobin, %	8.7 ± 1.5	8.7 ± 1.5
BMI, kg/m^2	32.5 ± 6.3	32.5 ± 6.3
Body weight, kg	91.9 ± 21.2	91.6 ± 20.8
Systolic blood pressure, mm Hg	135.9 ± 17.8	135.9 ± 17.7
Diastolic blood pressure, mm Hg	77.2 ± 10.3	77.0 ± 10.1
Heart failure[a]	835 (17.9)	832 (17.8)
Established CVD (age ≥50)	3831 (82.1)	3767 (80.6)
Prior myocardial infarction	1464 (31.4)	1400 (30.0)
Prior stroke or transient ischemic attack	730 (15.6)	777 (16.6)
Prior revascularization	1835 (39.3)	1803 (38.6)
>50% stenosis of coronary, carotid, or lower extremity arteries	1188 (25.4)	1191 (25.5)
Documented symptomatic CHD[b]	412 (8.8)	406 (8.7)
Documented asymptomatic cardiac ischemia[c]	1241 (26.6)	1231 (26.3)
Heart failure NYHA II – III	653 (14.0)	652 (14.0)
Chronic kidney disease[d]	1185 (25.4)	1122 (24.0)
CVD risk factors (age ≥60)	837 (17.9)	905 (19.4)
Microalbuminuria or proteinuria	501 (10.7)	558 (11.9)
Hypertension and left ventricular hypertrophy	248 (5.3)	251 (5.4)
Left ventricular systolic or diastolic dysfunction	203 (4.3)	191 (4.1)
Ankle-brachial index <0.9	110 (2.4)	116 (2.5)
Renal function		
Normal (eGFR ≥90)	1620 (34.7)	1655 (35.4)
Mild impairment (eGFR 60–89)	1932 (41.4)	1975 (42.3)
Moderate impairment (eGFR 30–59)	999 (21.4)	935 (20.0)
Severe impairment (eGFR <30)	117 (2.5)	107 (2.3)

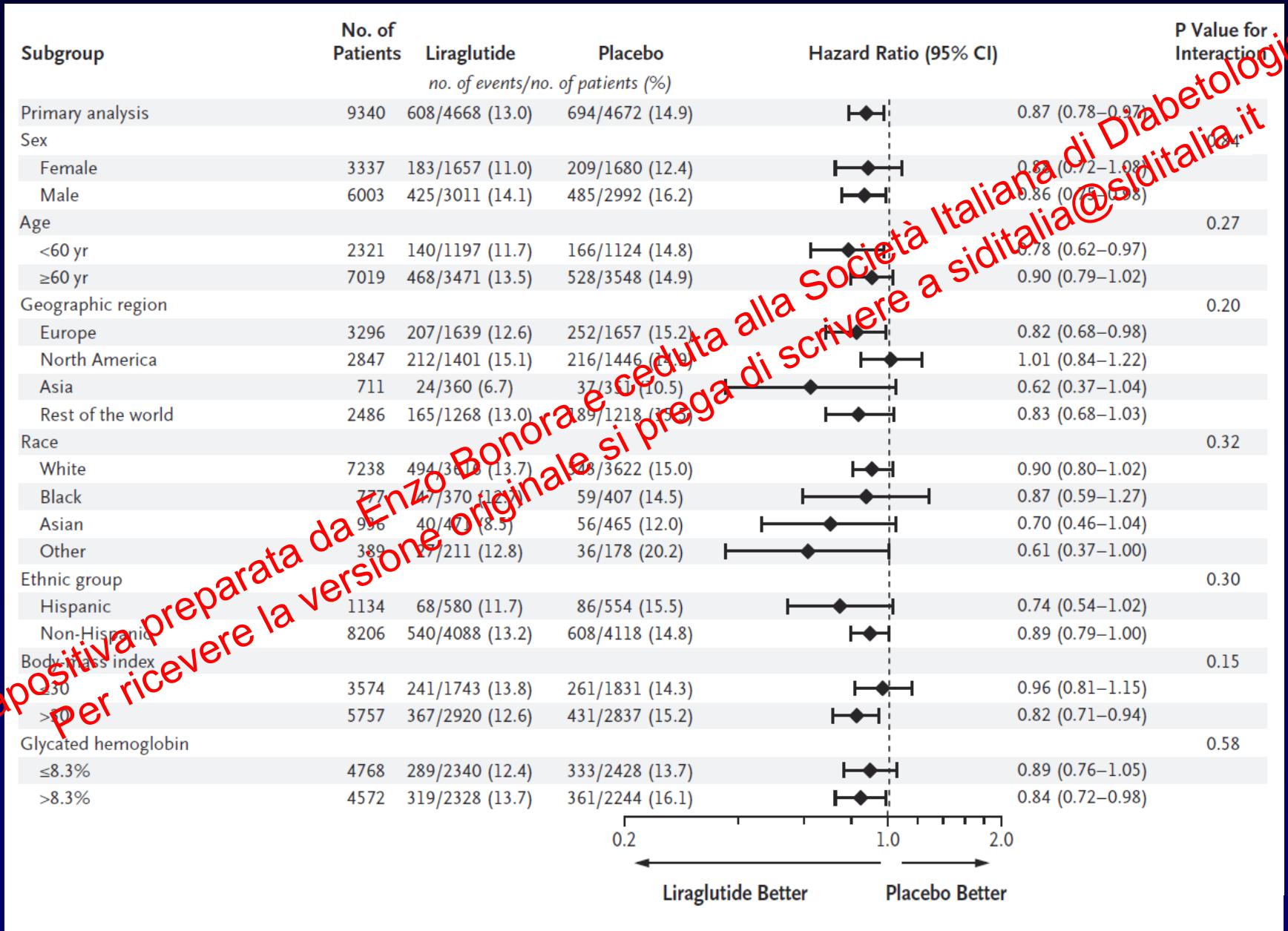
LEADER - Liraglutide vs. Placebo on CVD (primary and secondary endpoints)

Marso SP et al – NEJM June 13, 2016

Outcome	Liraglutide (N=4668)	Incidence Rate	Placebo (N=4672)	Incidence Rate	Hazard Ratio (95% CI)	P Value
	no. of patients (%)	*no. of events/ 100 patient-yr*	*no. of patients (%)*	*no. of events/ 100 patient-yr*		
Primary composite outcome†	608 (13.0)	3.4	694 (14.9)	3.9	0.87 (0.78–0.97)	0.01
Expanded composite outcome‡	948 (20.3)	5.3	1062 (22.7)	6.0	0.88 (0.81–0.96)	0.005
Death from any cause	381 (8.2)	2.1	447 (9.6)	2.5	0.85 (0.74–0.97)	0.02
Death from cardiovascular causes	219 (4.7)	1.2	278 (6.0)	1.6	0.78 (0.66–0.93)	0.007
Death from noncardiovascular causes	162 (3.5)	0.9	169 (3.6)	1.0	0.95 (0.77–1.18)	0.66
Myocardial infarction§	292 (6.3)	1.6	339 (7.3)	1.9	0.86 (0.73–1.00)	0.046
Fatal§	17 (0.4)	0.1	28 (0.6)	0.2	0.60 (0.33–1.10)	0.10
Nonfatal	281 (6.0)	1.6	317 (6.8)	1.8	0.88 (0.75–1.03)	0.11
Silent§	62 (1.3)	0.3	76 (1.6)	0.4	0.86 (0.61–1.20)	0.37
Stroke§	173 (3.7)	1.0	199 (4.3)	1.1	0.86 (0.71–1.06)	0.16
Fatal§	16 (0.3)	0.1	25 (0.5)	0.1	0.64 (0.34–1.19)	0.16
Nonfatal	159 (3.4)	0.9	177 (3.8)	1.0	0.89 (0.72–1.11)	0.30
Transient ischemic attack§	48 (1.0)	0.3	60 (1.3)	0.3	0.79 (0.54–1.16)	0.23
Coronary revascularization	405 (8.7)	2.3	441 (9.4)	2.5	0.91 (0.80–1.04)	0.18
Hospitalization for unstable angina pectoris	122 (2.6)	0.7	124 (2.7)	0.7	0.98 (0.76–1.26)	0.87
Hospitalization for heart failure	218 (4.7)	1.2	248 (5.3)	1.4	0.87 (0.73–1.05)	0.14
Microvascular event	355 (7.6)	2.0	416 (8.9)	2.3	0.84 (0.73–0.97)	0.02
Retinopathy	106 (2.3)	0.6	92 (2.0)	0.5	1.15 (0.87–1.52)	0.33
Nephropathy	268 (5.7)	1.5	337 (7.2)	1.9	0.78 (0.67–0.92)	0.003

LEADER - Primary endpoint (sensitivity analysis)

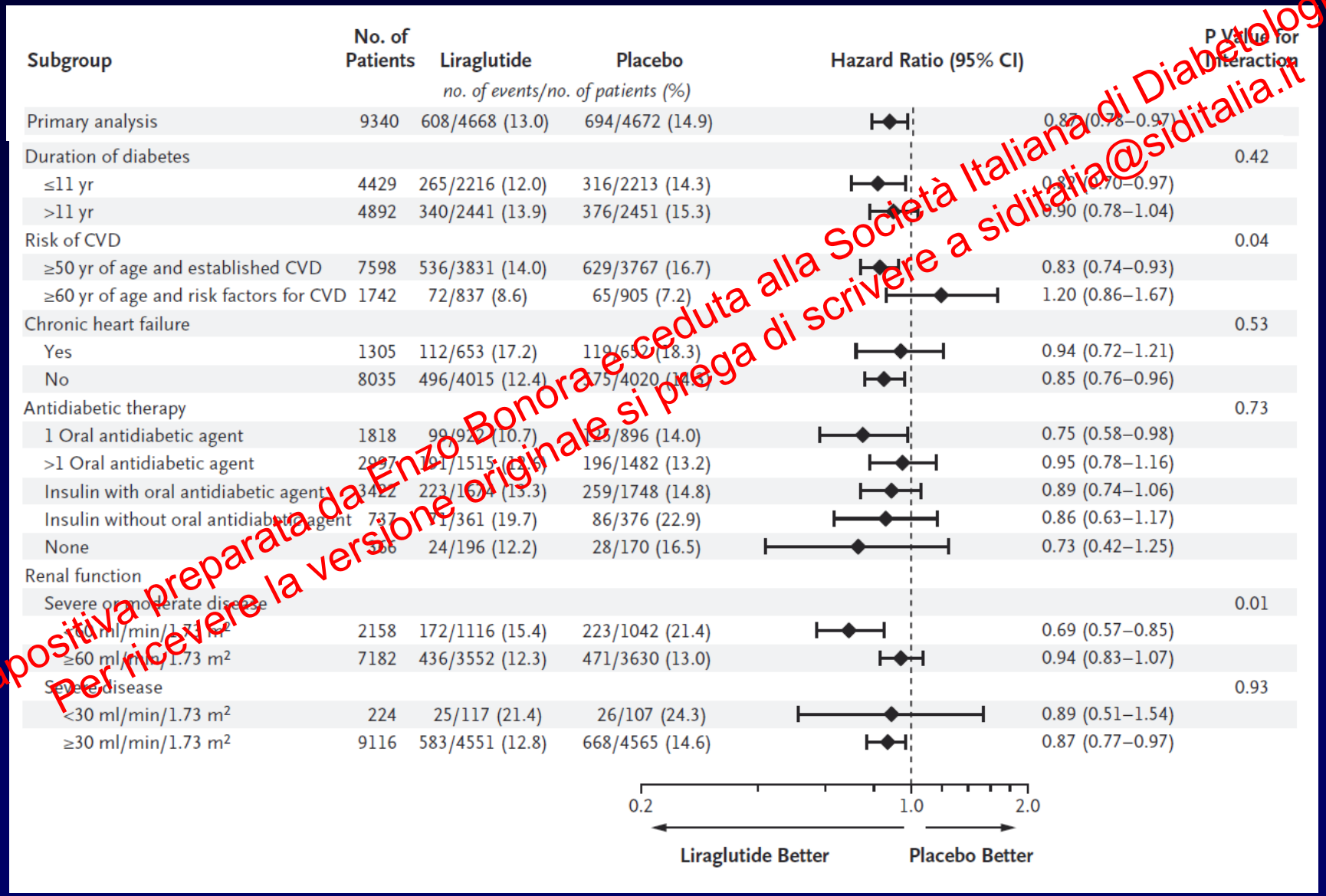
Marso SP et al – NEJM June 13, 2016



Subgroup	No. of Patients	Liraglutide	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
		no. of events/no. of patients (%)			
Primary analysis	9340	608/4668 (13.0)	694/4672 (14.9)	0.87 (0.78–0.97)	
Sex					0.64
Female	3337	183/1657 (11.0)	209/1680 (12.4)	0.87 (0.72–1.08)	
Male	6003	425/3011 (14.1)	485/2992 (16.2)	0.86 (0.75–0.98)	
Age					0.27
<60 yr	2321	140/1197 (11.7)	166/1124 (14.8)	0.78 (0.62–0.97)	
≥60 yr	7019	468/3471 (13.5)	528/3548 (14.9)	0.90 (0.79–1.02)	
Geographic region					0.20
Europe	3296	207/1639 (12.6)	252/1657 (15.2)	0.82 (0.68–0.98)	
North America	2847	212/1401 (15.1)	216/1446 (14.9)	1.01 (0.84–1.22)	
Asia	711	24/360 (6.7)	37/351 (10.5)	0.62 (0.37–1.04)	
Rest of the world	2486	165/1268 (13.0)	189/1218 (15.5)	0.83 (0.68–1.03)	
Race					0.32
White	7238	494/3616 (13.7)	548/3622 (15.0)	0.90 (0.80–1.02)	
Black	777	47/370 (12.7)	59/407 (14.5)	0.87 (0.59–1.27)	
Asian	996	40/471 (8.5)	56/465 (12.0)	0.70 (0.46–1.04)	
Other	389	27/211 (12.8)	36/178 (20.2)	0.61 (0.37–1.00)	
Ethnic group					0.30
Hispanic	1134	68/580 (11.7)	86/554 (15.5)	0.74 (0.54–1.02)	
Non-Hispanic	8206	540/4088 (13.2)	608/4118 (14.8)	0.89 (0.79–1.00)	
Body mass index					0.15
≤30	3574	241/1743 (13.8)	261/1831 (14.3)	0.96 (0.81–1.15)	
>30	5757	367/2920 (12.6)	431/2837 (15.2)	0.82 (0.71–0.94)	
Glycated hemoglobin					0.58
≤8.3%	4768	289/2340 (12.4)	333/2428 (13.7)	0.89 (0.76–1.05)	
>8.3%	4572	319/2328 (13.7)	361/2244 (16.1)	0.84 (0.72–0.98)	

LEADER - Primary endpoint (sensitivity analysis)

Marso SP et al – NEJM June 13, 2016



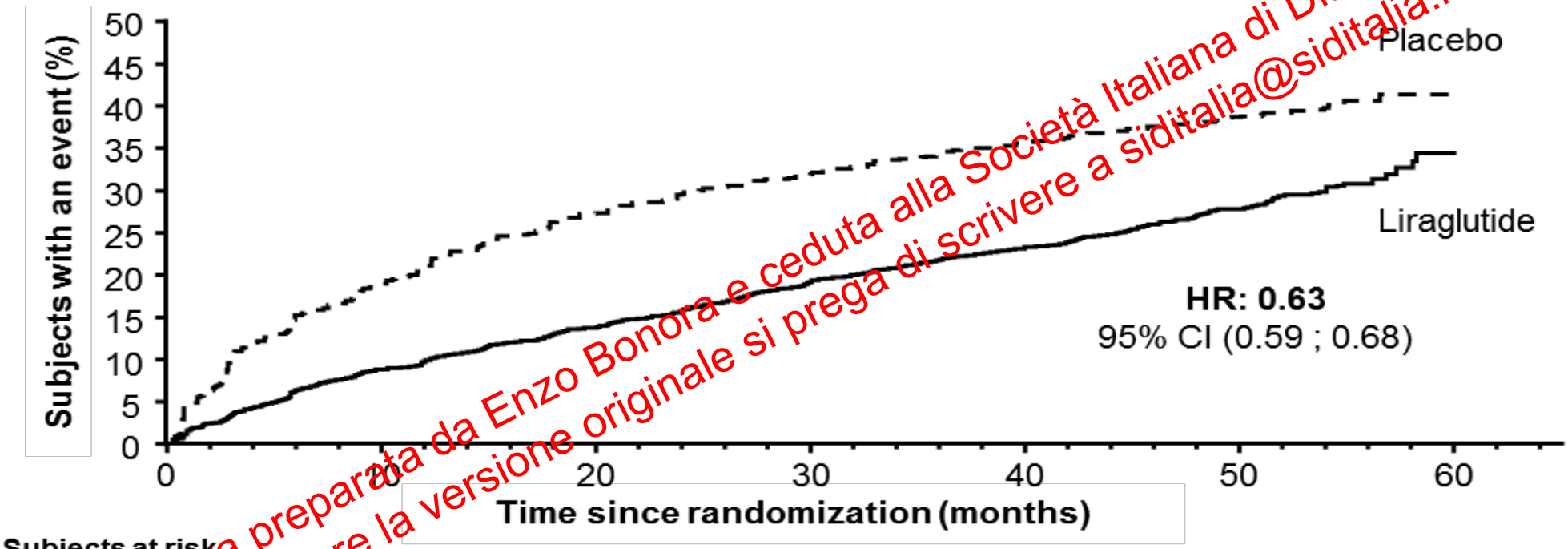
LEADER – Primary endpoint by baseline eGFR

Table S3. Sensitivity analysis of the primary composite outcome by baseline renal status

	Liraglutide	Placebo	Hazard Ratio	95% CI
eGFR ≥60 ml/min/1.73 m^2	436 (12.3)	471 (13.0)	0.94	0.83-1.07
eGFR 30-59 ml/min/1.73 m^2	147 (14.7)	197 (21.1)	0.67	0.54-0.83
eGFR <30 ml/min/1.73 m^2	25 (21.4)	26 (24.3)	0.89	0.51-1.54

Interaction p-value between treatment and factor: 0.027.

Time to first initiation of insulin or any new OAD



Subjects at risk

Liraglutide	4668	4068	3786	3452	3183	705	5
Placebo	4672	3575	3111	2803	2548	541	9

Time to first event analyzed using a Cox regression with treatment group as fixed factor. Only events that occurred between randomization date and follow-up date were used for defining first event. Subjects without an event were censored at time of last contact (phone or visit)
CI: confidence interval; HR: hazard ratio; OAD: oral antidiabetic drug

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

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

Time to narrow renal composite outcome

Doubling of serum creatinine*, ESRD or renal death in patients with stage 3 CKD†

Subjects at risk						
Liraglutide	999	981	962	908	866	210
Placebo	935	917	875	821	765	165

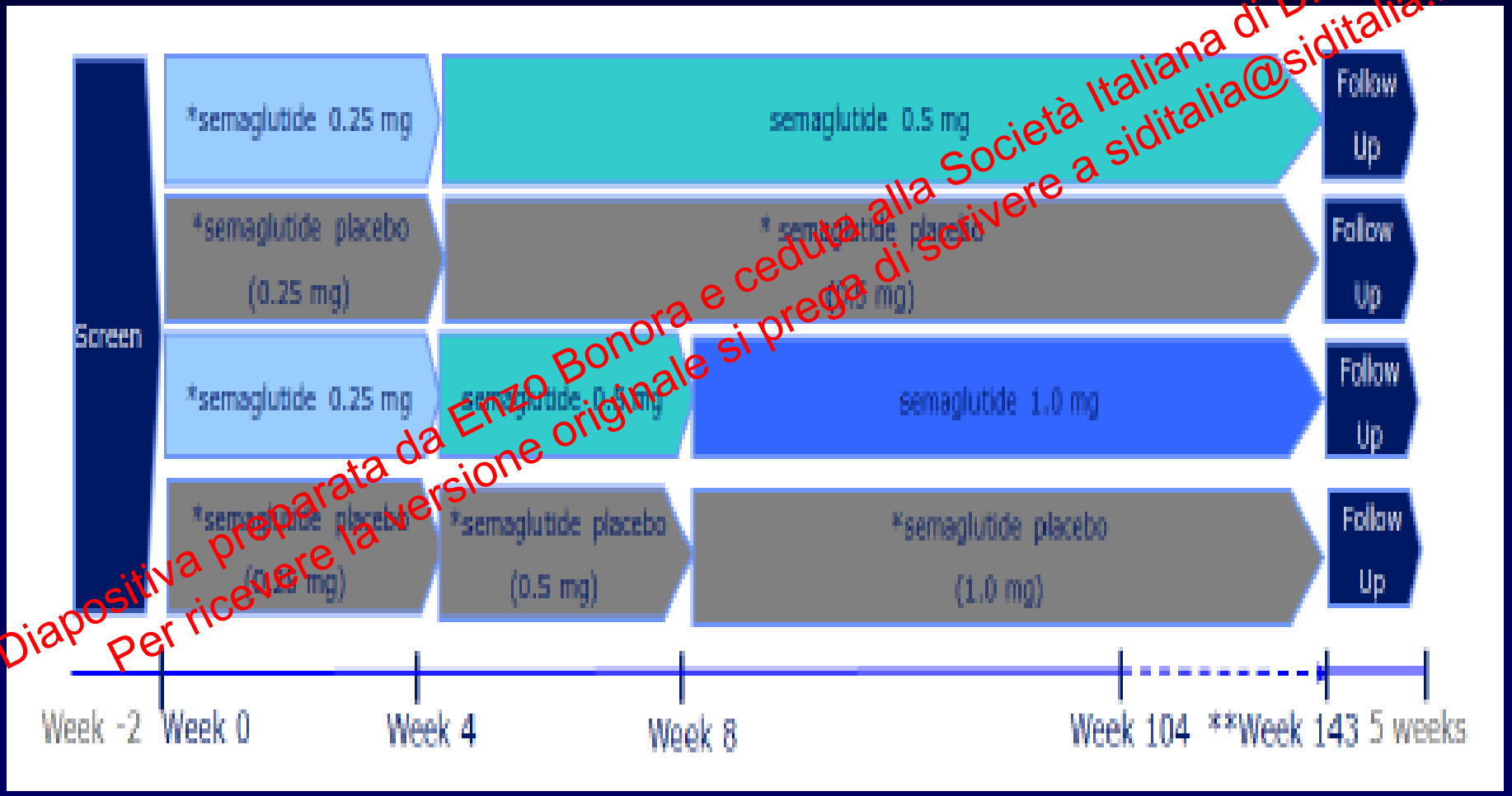
LEADER
Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

Doubling of serum creatinine and eGFR ≤45 mL/min/1.73 m^2 per MDRD; † Defined as eGFR 30 to <60 mL/min/1.73 m^2
CKD: chronic kidney failure; CI: confidence interval; EAC: event adjudication committee; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; HR: hazard ratio; MDRD: modification of diet in renal disease

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

SUSTAIN 6 – Experimental design

Marso et al – NEJM 2016; 375: 1834



SUSTAIN 6 – Baseline characteristics

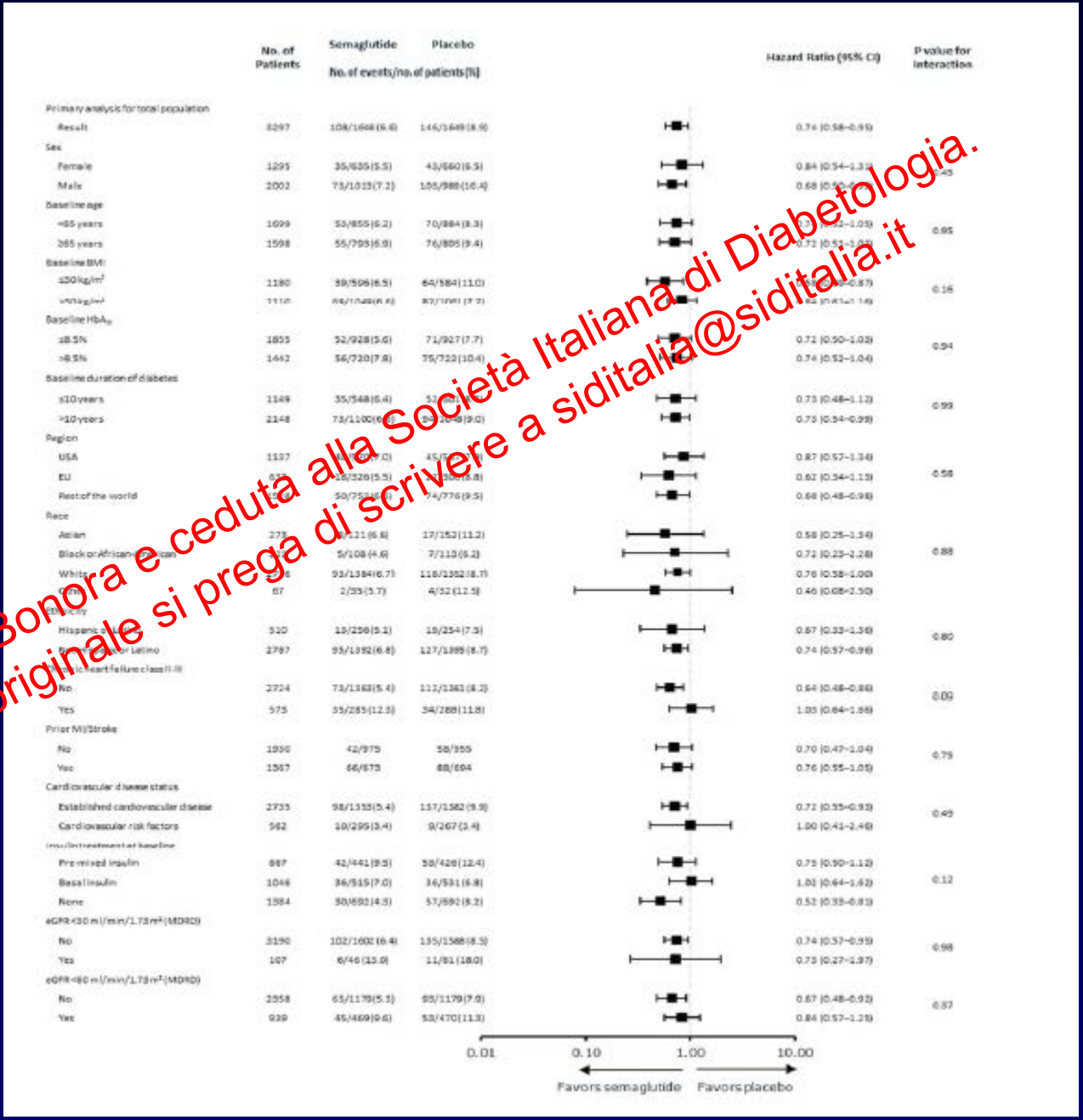
Marso et al – NEJM 2016; 375: 1834

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Semaglutide (N=1648)		Placebo (N=1649)		Total (N=3297)
	0.5 mg (N=826)	1.0 mg (N=822)	0.5 mg (N=824)	1.0 mg (N=825)	
Age — yr	64.6±7.3	64.7±7.1	64.8±7.6	64.4±7.5	64.6±7.4
Male sex — no. (%)	495 (59.9)	518 (63.0)	482 (58.5)	507 (61.5)	2002 (60.7)
Body weight — kg	91.8±20.3	92.9±22.1	91.8±20.3	91.9±20.8	92.1±20.6
Type 2 diabetes					
Duration — yr	14.3±8.2	14.1±8.2	14.0±8.5	13.2±7.4	13.9±8.1
Glycated hemoglobin — %	8.7±1.4	8.7±1.5	8.7±1.5	8.7±1.5	8.7±1.5
Cardiovascular risk factors					
Systolic blood pressure — mm Hg	136.1±18.0	135.8±17.0	135.8±16.2	134.8±17.5	135.6±17.2
Diastolic blood pressure — mm Hg	77.1±9.8	76.9±10.2	77.5±9.9	76.7±10.2	77.0±10.0
Low-density lipoprotein cholesterol — mg/dl†	81.6±47.1	83.3±41.2	80.9±48.1	83.6±45.9	82.3±45.6
Never smoked — no. (%)	390 (47.2)	364 (44.3)	391 (47.5)	348 (42.2)	1493 (45.3)
History of cardiovascular disease — no. (%)					
Ischemic heart disease	493 (59.7)	495 (60.2)	510 (61.9)	496 (60.1)	1994 (60.5)
Myocardial infarction	266 (32.2)	264 (32.1)	267 (32.4)	275 (33.3)	1072 (32.5)
Heart failure	201 (24.3)	180 (21.9)	190 (23.1)	206 (25.0)	777 (23.6)
Ischemic stroke	89 (10.8)	89 (10.8)	96 (11.7)	109 (13.2)	383 (11.6)
Hemorrhagic stroke	28 (3.4)	24 (2.9)	27 (3.3)	29 (3.5)	108 (3.3)
Hypertension	772 (93.5)	771 (93.8)	756 (91.7)	760 (92.1)	3059 (92.8)

SUSTAIN 6 Primary outcomes Sensitivity analysis

Marso et al – NEJM 2016; 375: 1834



EXSCEL papers

Exenatide Study of Cardiovascular Events

Rationale and design: Holman et al - Am Heart J 2015

Baseline characteristics: Mentz et al - Am Heart J 2017

Dulaglutide – Phase II/III trials: CV safety