Analoghi del GLP1 e protezione cardiovascolare

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Bologna, 27 giugno 2019

Conflitti di interessi

Negli ultimi due anni, E. Mannucci ha ricevuto:
compensi per consulenze da ***AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck, Mundipharma*** e ***Novo Nordisk***
compensi per relazioni a corsi/convegni da ***Abbott*** e ***Eli Lilly***
compensi da agenzie in simposi sponsorizzati da ***Abbott, Allergan, AstraZeneca, Boehringer Ingelheim, Bruno, Eli Lilly, Menarini, Merck, Mundipharma, Novo Nordisk, Sanofi*** e ***Takeda***

La struttura diretta da E. Mannucci ha ricevuto:
finanziamenti per attività di ricerca e/o educative da ***AstraZeneca, Bayer, Boehringer Ingelheim, Molteni*** e ***Novo Nordisk***
compensi per trial clinici da:
AstraZeneca, Eli Lilly, Genentech, Janssen, Novartis e ***Novo Nordisk.***

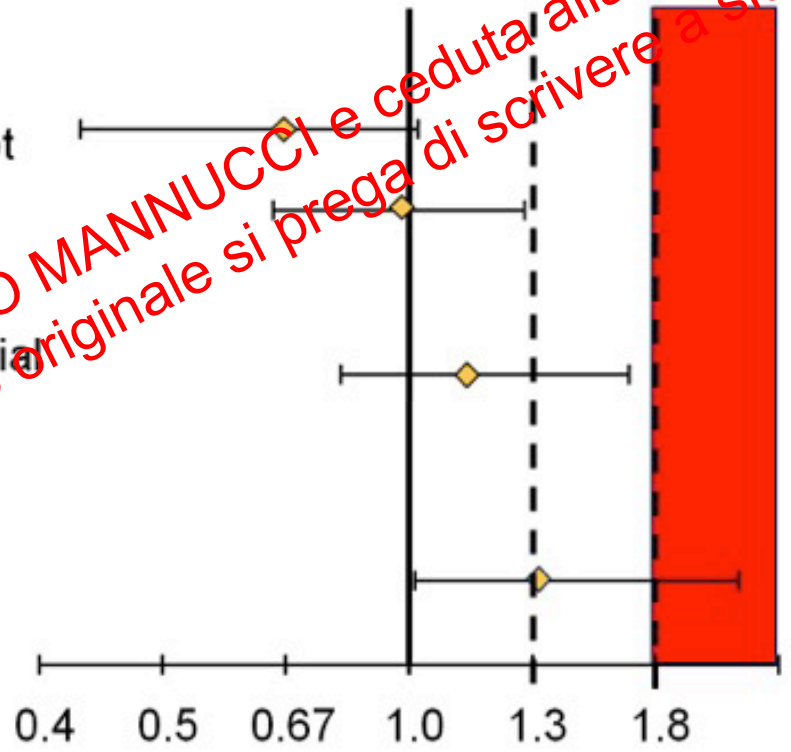
FDA Guidance for CV safety of new drugs for diabetes

- Perform meta-analyses of Phase II/III trials (or specific Phase III cardiovascular [CV] outcome studies), to assess the risk of major CV events

<1.3 – a post-marketing cardiovascular trial may not generally be necessary

<1.8 – conduct large safety trial post-approval

>1.8 – conduct large safety trial pre-approval



https://www.fda.gov/downloads/Drugs/.../Guidances/ucm071627.pdf

CV safety studies for diabetes drugs

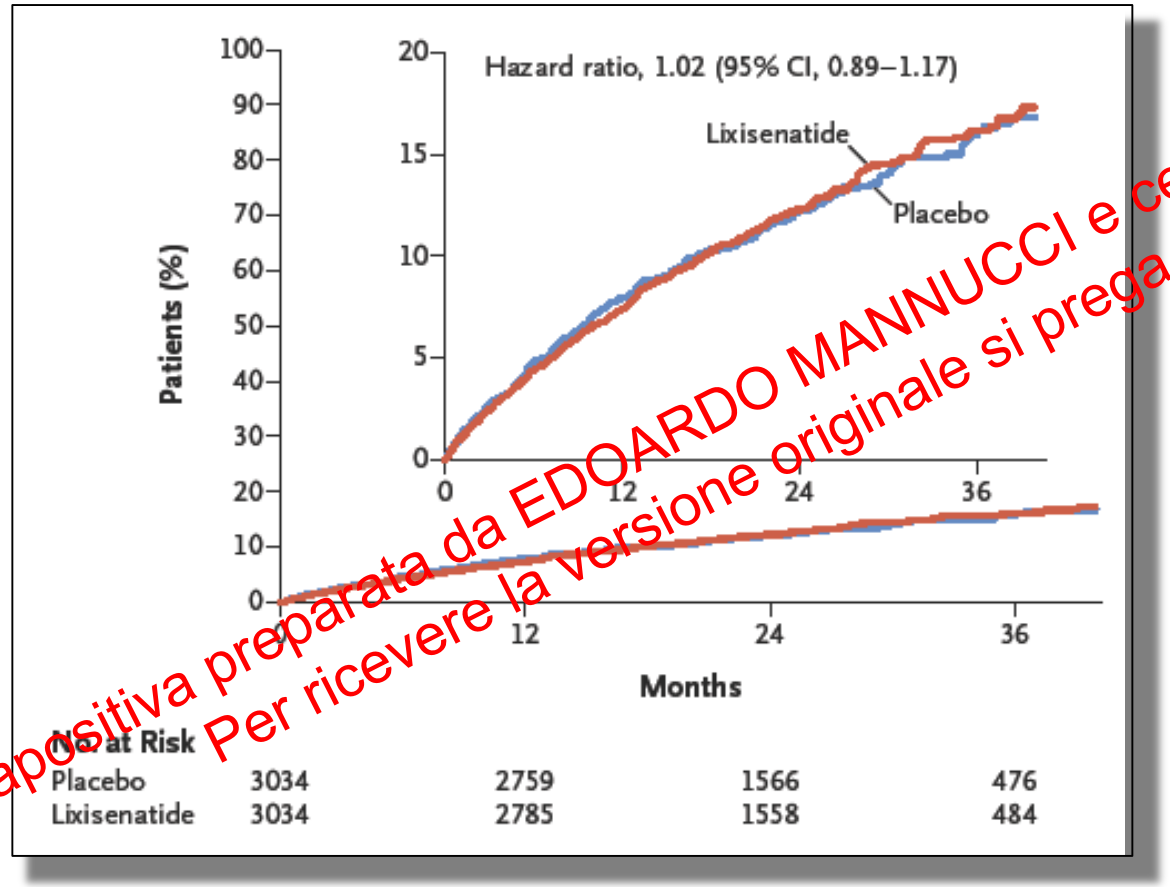
Methodological issues

- Designed for non-inferiority (event-driven, target 611 events)
- Enrolment of very high-risk patients
- Relatively short duration of follow-up
- Attempt at minimizing between-group differences in glucose control

Mannucci E, Mosenzon O, Avogaro A. *Diabetes Care*. 39 Suppl 2:S196-204, 2016.

Lixisenatide: effect on major cardiovascular events

Results of the ELIXA trial



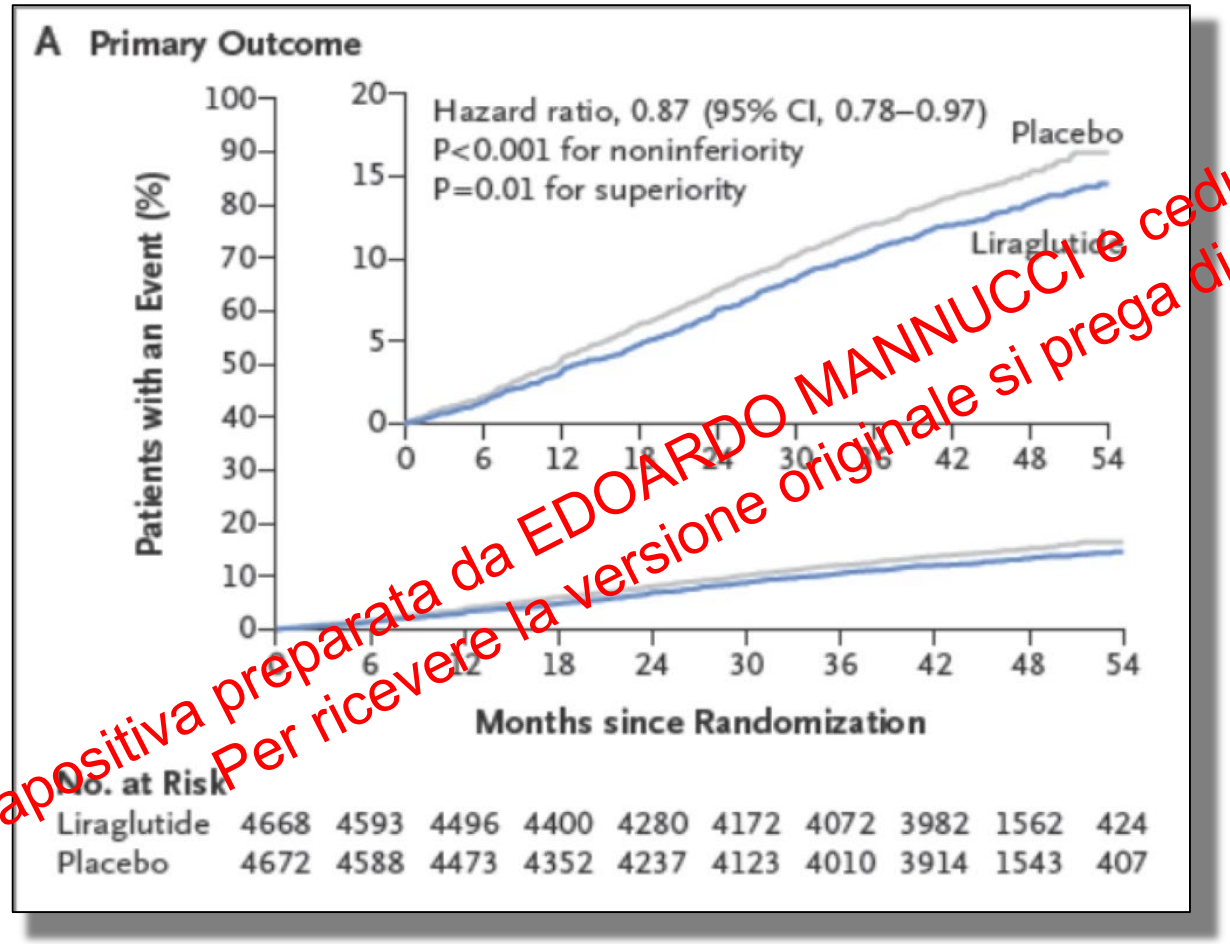
Principal endpoint:
4-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death, hospitalization for unstable angina)

6068 T2DM patients with recent acute coronary syndrome, lixisenatide vs placebo 1:1.
Follow-up: 2.1 y

Pfeffer MA et al. *N Engl J Med* 373: 2247-57, 2015

Liraglutide: effect on major cardiovascular events

Results of the LEADER trial



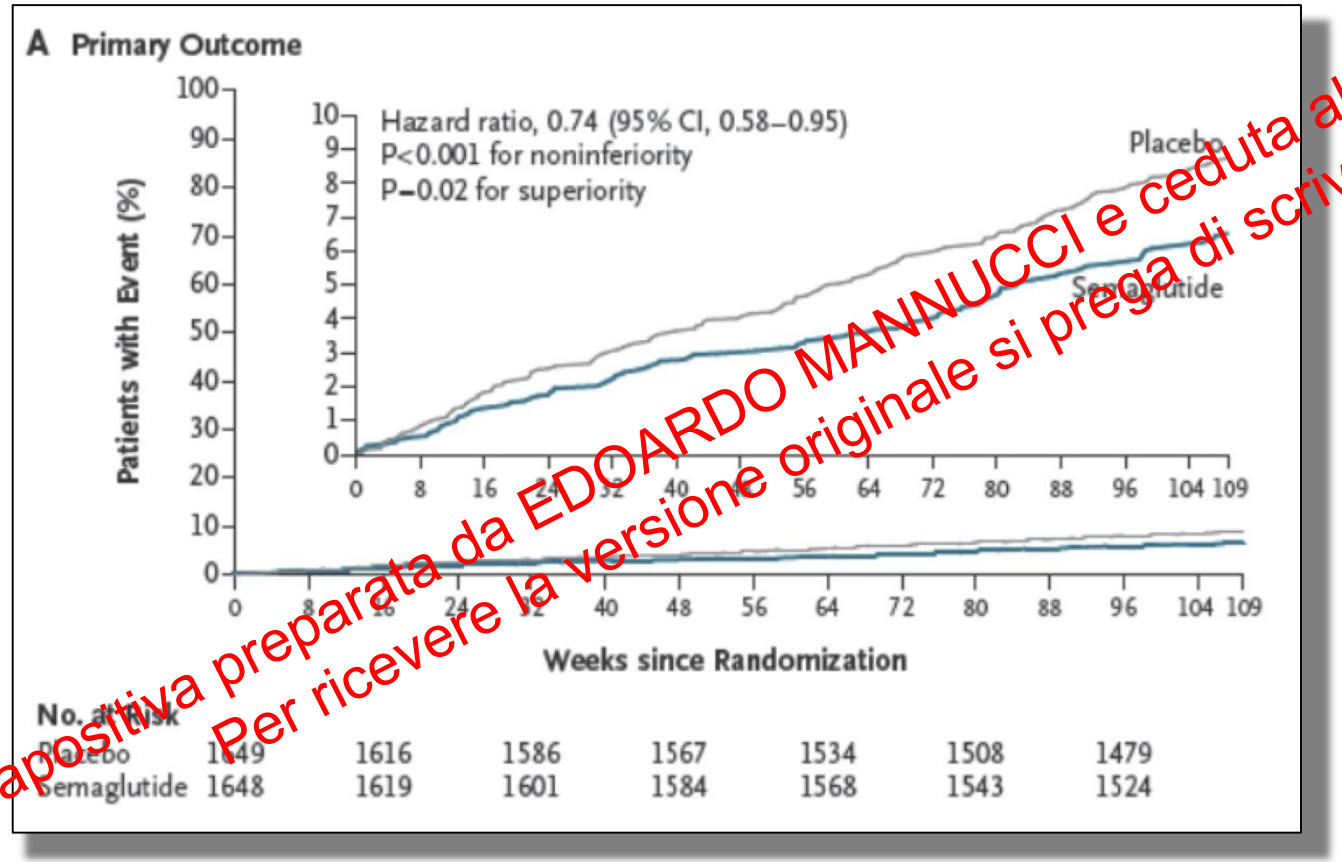
Principal endpoint:
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

9,340 T2DM patients with prior cardiovascular disease and/or high CV risk, Liraglutide vs placebo 1:1. Follow-up: 4 y

Marso SP et al. *N Engl J Med* 375: 311-22, 2016

Semaglutide: effect on major cardiovascular events

Results of the SUSTAIN-6 trial



Principal endpoint:
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

3,297 T2DM patients with prior cardiovascular disease and/or high CV risk, Semaglutide vs placebo 1:1.
Follow-up: 2 y

Marso SP et al. *N Engl J Med* 375: 1834-44, 2016

CV outcome trials with GLP1RAs

Comparison of baseline characteristics of enrolled patients

	ELIXA	LEADER	SUSTAIN-6
Mean age (y)	60	64	65
Mean duration of diabetes (y)	9	13	14
Women (%)	31	36	39
BMI (kg/m^2)	30.1	32.5	32.8
HbA1c (%)	7.7	8.7	8.7
eGFR<60 ml/min*m^2 (%)	NR	23	28

Pfeffer MA et al. *N Engl J Med* 373: 2247-57, 2015; Marso SP et al. *N Engl J Med* 375: 311-22, 2016; Marso SP et al. N Engl J Med 375: 1834-1844

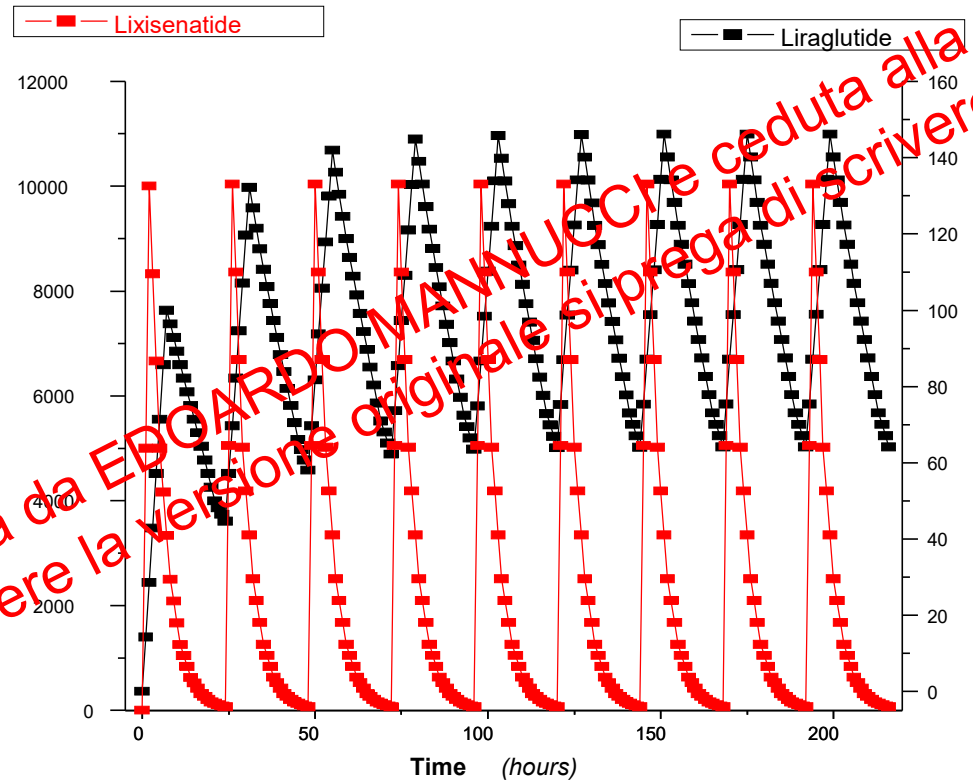
Effects of GLP1RAs on risk factors in CVOTs

	ELIXA	LEADER	SUSTAIN-6
HbA1c (%)	- 0.2	- 0.4	- 0.9
BW (kg)	- 0.6	- 2.3	- 3.6
sBP (mmHg)	- 0.8	- 1.2	- 1.9

Pfeffer MA et al. *N Engl J Med* 373: 2247-57, 2015;
Marso SP et al. *N Engl J Med* 375: 311-22, 2016;
Marso SP et al. *N Engl J Med* 375: 1834-44, 2016

GLP1 receptor agonists kinetics

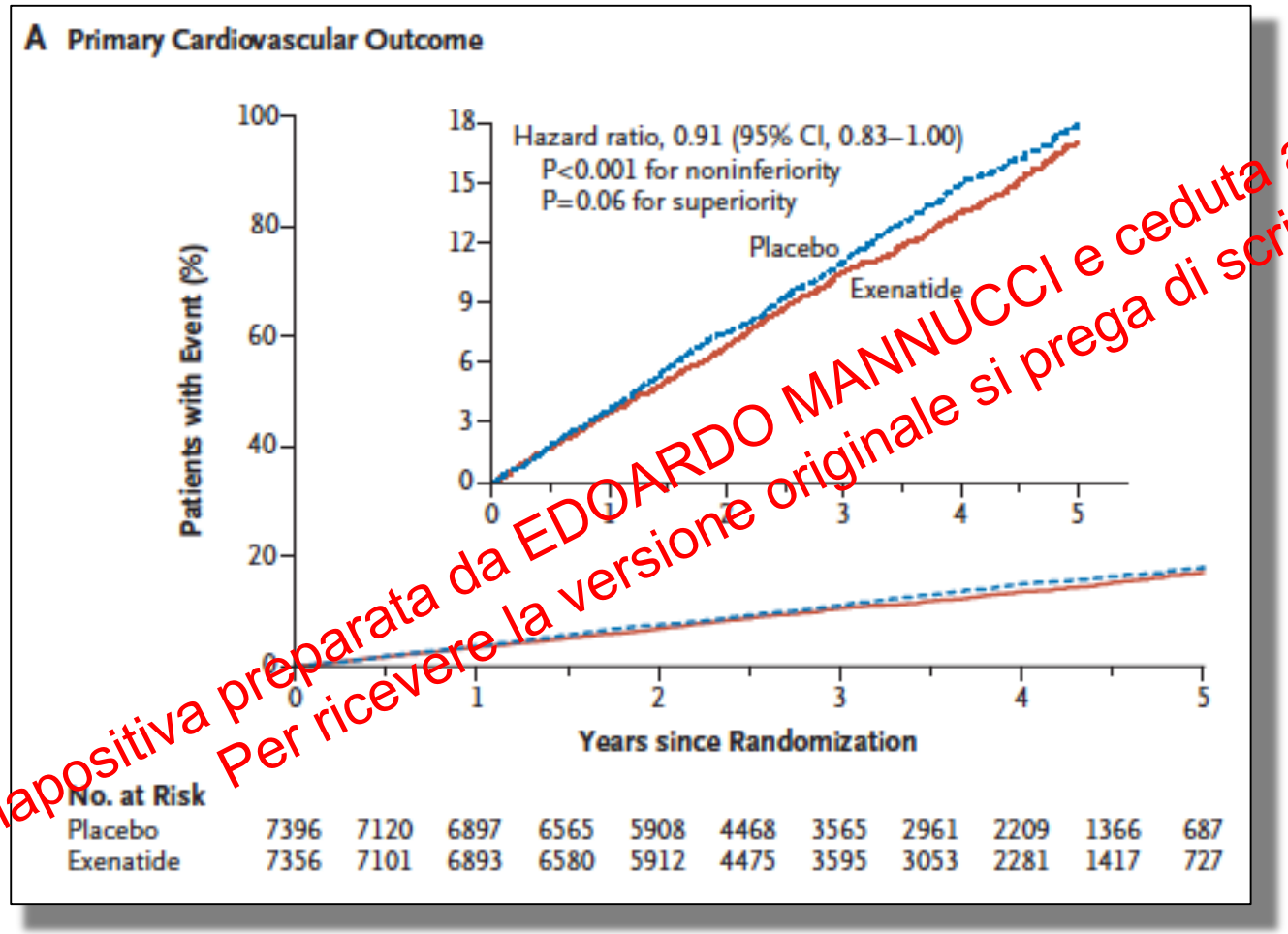
Liraglutide vs lixisenatide



Cantini G, Mannucci E, Luconi M. *Trends Endocrinol Metab* 27: 427-38, 2016.

Exenatide LAR: effect on major cardiovascular events

Results of the EXSCEL trial



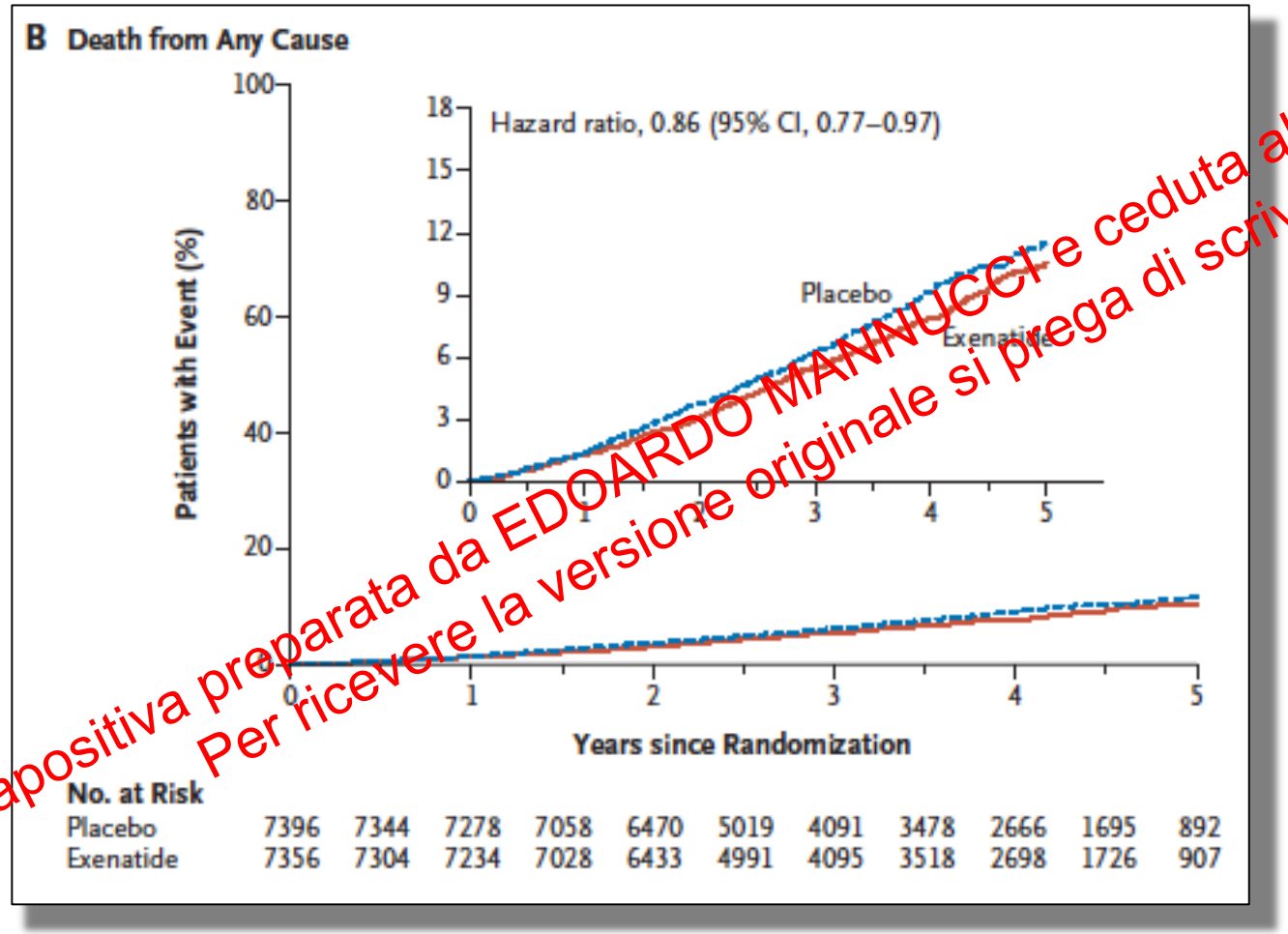
Principal endpoint:
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

14,752 T2DM patients with prior cardiovascular disease and/or high CV risk, exenatide LAR vs placebo 1:1. Follow-up: 3.2 y

Holman RR et al. *N Engl J Med* 377: 1228-39, 2016

Exenatide LAR: effect on all-cause mortality

Results of the EXSCEL trial



Principal endpoint:
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

14,752 T2DM patients with prior cardiovascular disease and/or high CV risk, exenatide LAR vs placebo 1:1. Follow-up: 3.2 y

Holman RR et al. *N Engl J Med* 377: 1228-39, 2016

Baseline characteristics in CV trials with long-acting GLP1RAs

Comparison between LEADER, SUSTAIN-6 and EXSCEL trials

Characteristics	LEADER (liraglutide)	SUSTAIN-6 (semaglutide)	EXSCEL (exenatide LAR)
Number	9,340	3,297	14,752
Age (y)	64.3	64.6	62.0
Duration of diabetes (y)	12.3	13.9	12.0
A1c (%)	8.7	8.7	8.0
Prior CVD (%)	81.2	60.5	73.1
eGFR<60 ml/min (%)	21.8	28.9	21.6

Liraglutide vs exenatide LAR: effect on HbA1c

RCT, add-on to SU and/or Met; DURATION-6

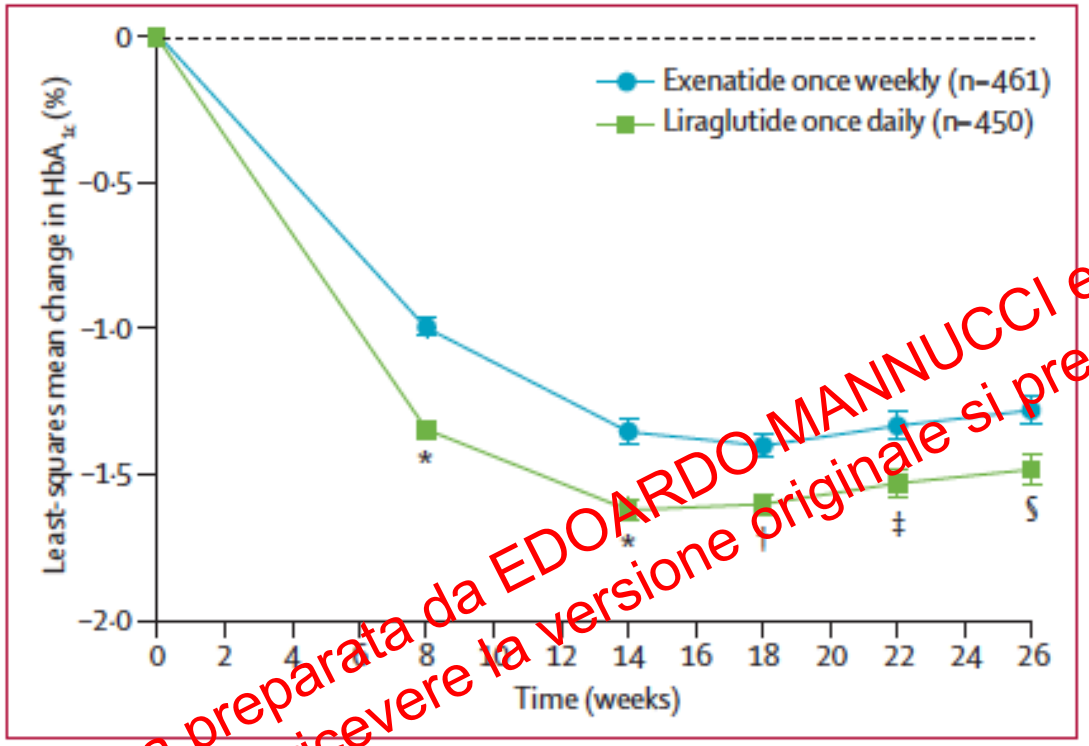


Figure 2: Change in glycaemic control from baseline to week 26
p values for treatment difference are presented for weeks 8, 14, 18, 22, and 26. 95% CIs for treatment differences were: week 8 (0·27–0·43), week 14 (0·16–0·37), week 18 (0·09–0·31), week 22 (0·08–0·32), and week 26 (0·08–0·33). HbA_{1c}=glycated haemaglobin. *p<0·0001. †p=0·0005. ‡p=0·0012. §p=0·0018.

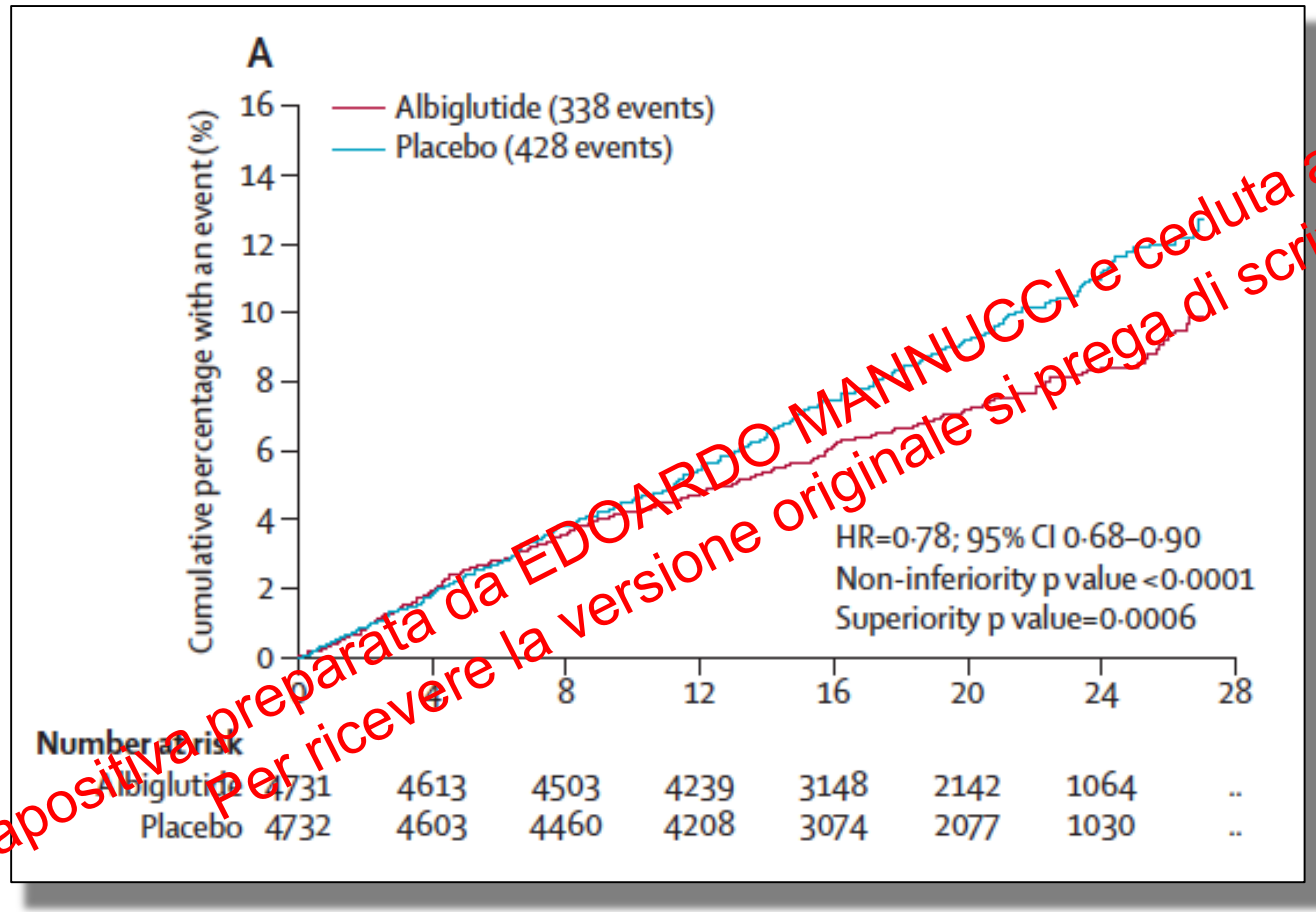
Principal endpoint:
A1c at 26 wk

911 T2DM patients inadequately controlled with oral drugs, Exenatide LAR 2 mg/wk vs Liraglutide 1.8 mg/day
Follow-up: 26 wk

Buse JB et al. *Lancet* 381: 117-24, 2013

Albiglutide: effect on MACE

Results of the HARMONY OUTCOMES trial

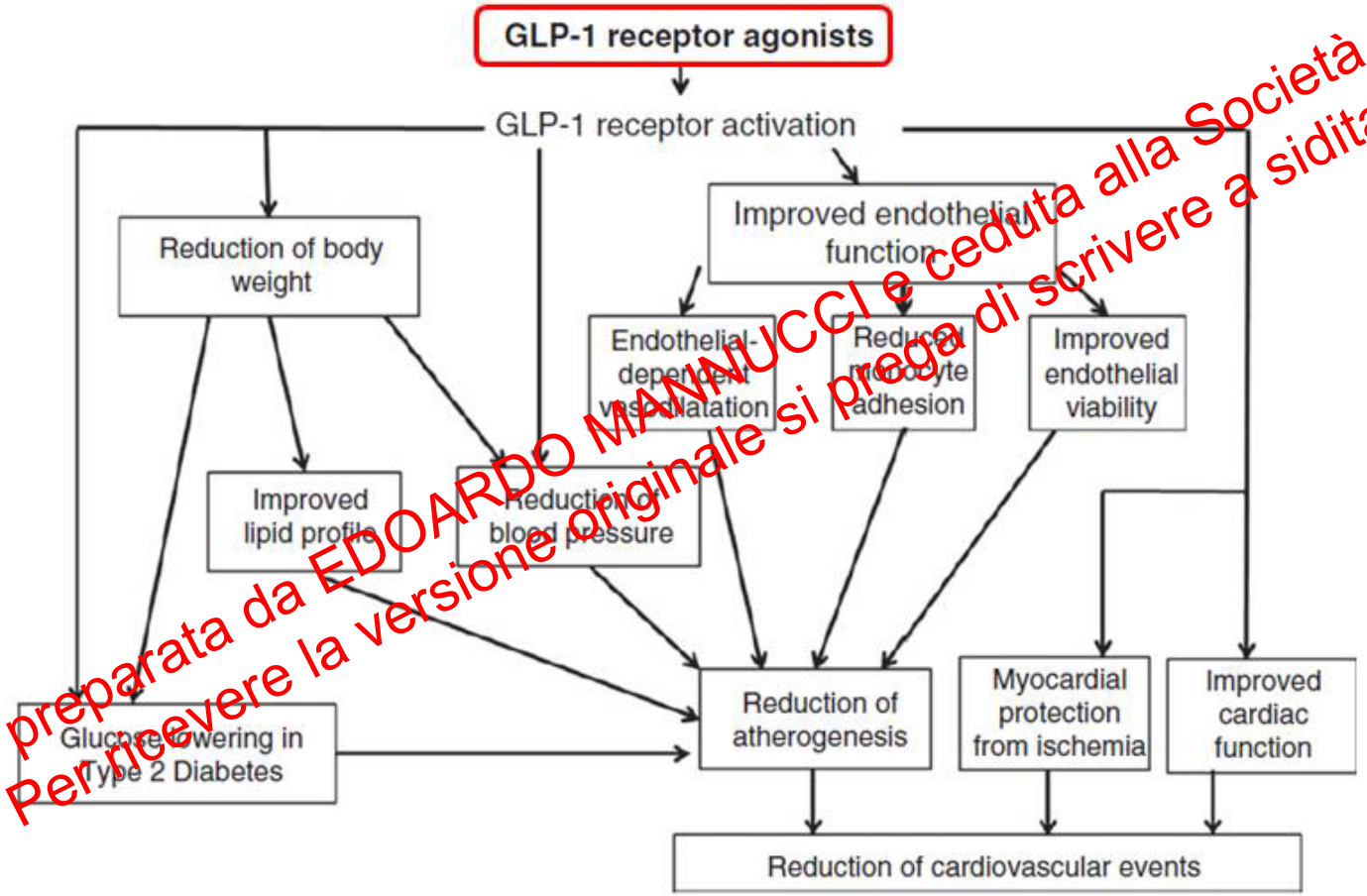


Principal endpoint:
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

9,463 T2DM patients with prior cardiovascular disease and/or high CV risk, albiglutide vs placebo 1:1.
Follow-up: 1.6 y

Hernandez AF et al. *Lancet* 392: 1519–29, 2018

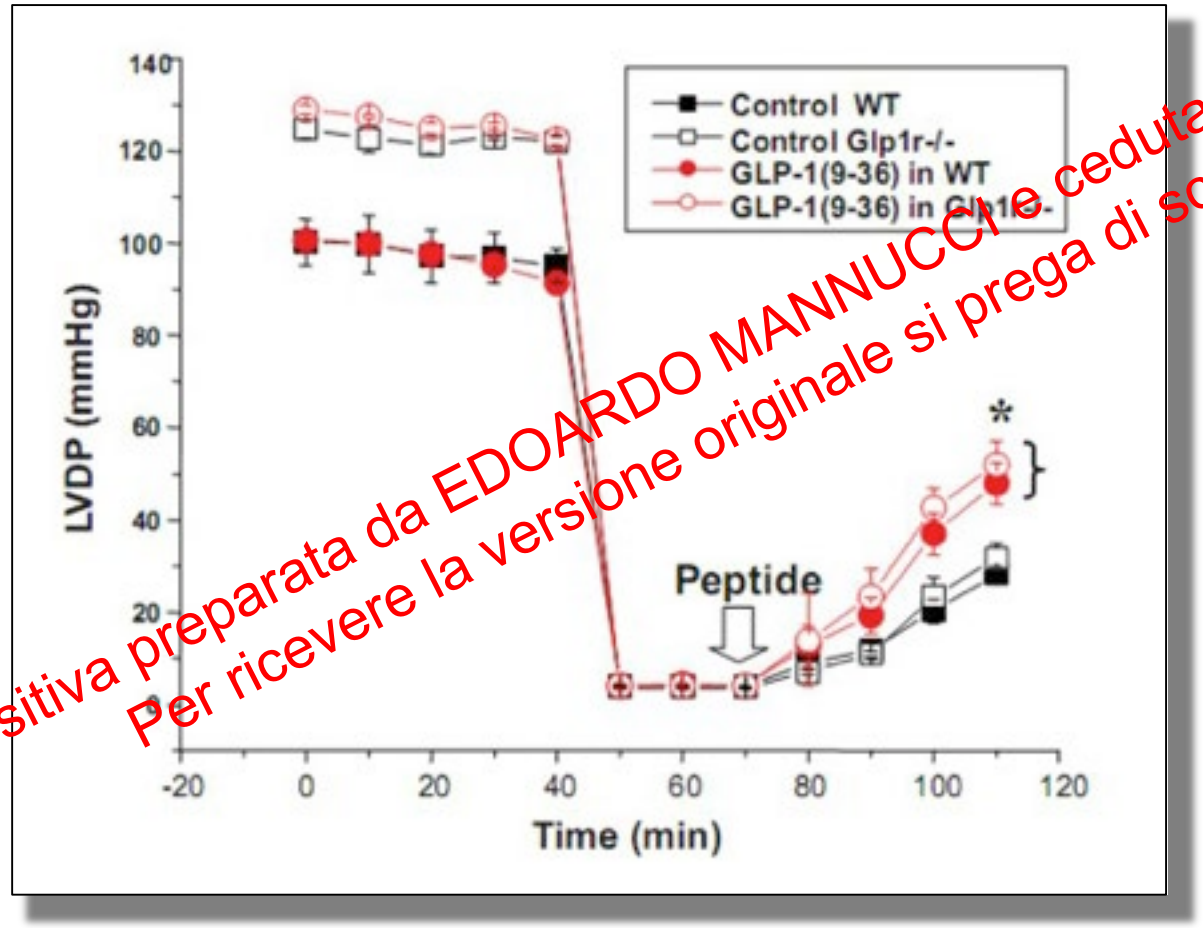
GLP1 receptor agonists: cardiovascular actions



Mannucci E & Dicembrini I, *Curr Med Res Opin* 28:715-21, 2012

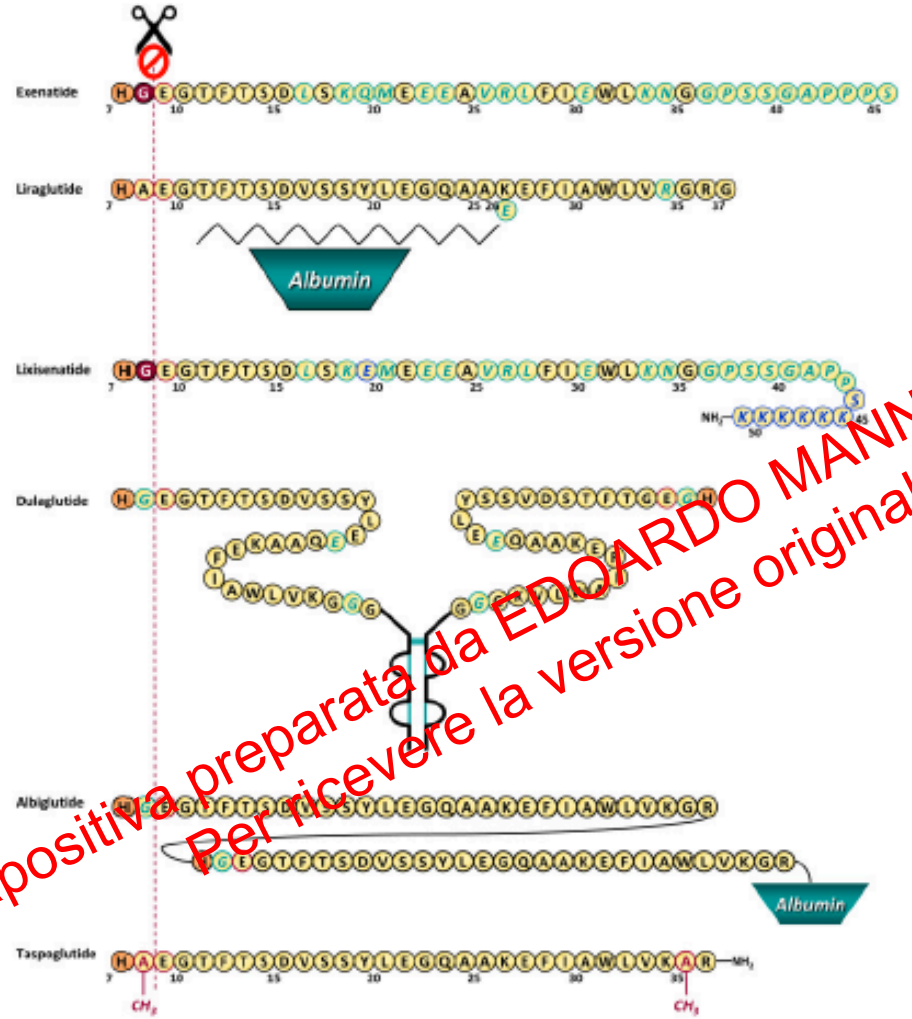
Myocardial effects of GLP-1 (9-36)

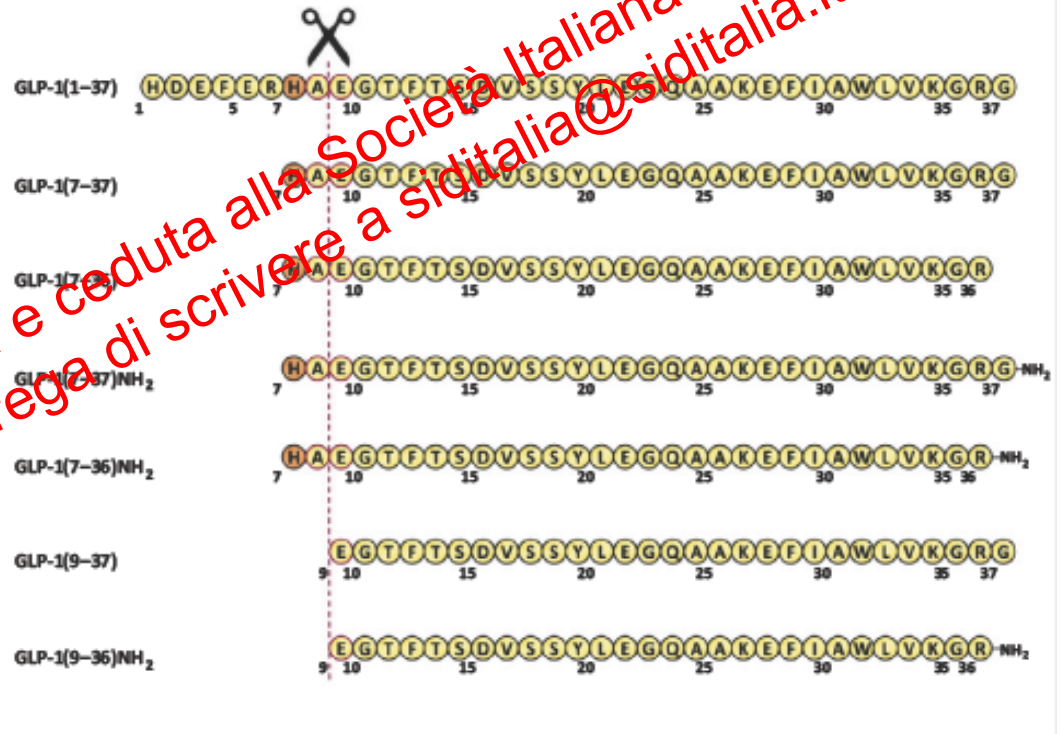
Recovery after ischemia-reperfusion in rats



Ban et al. *Circulation* 17: 2340-50, 2008.

GLP1 receptor agonists

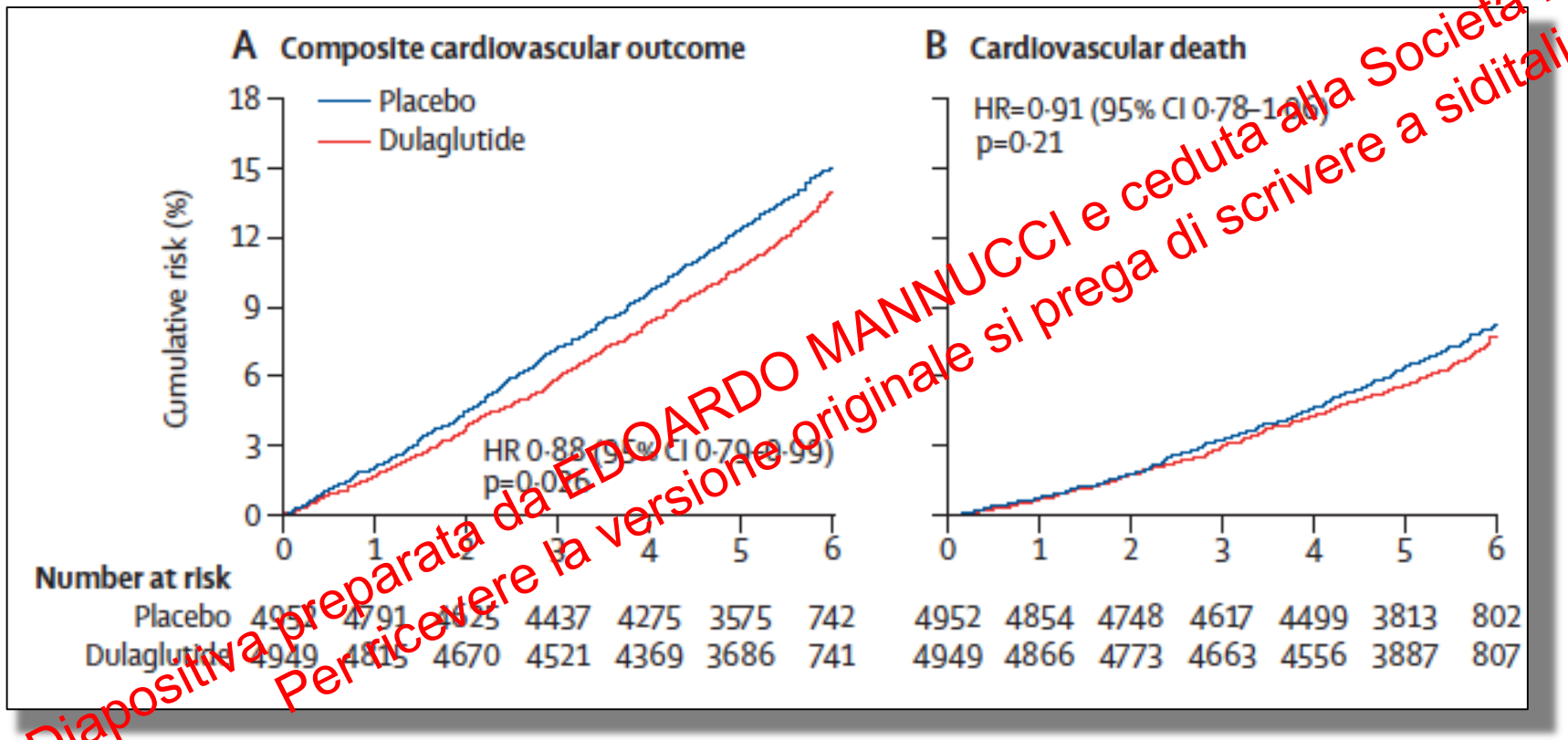




Cantini G, Mannucci E, Luconi M. *Trends Endocrinol Metab* 27: 427-38, 2016.

Dulaglutide: effect on MACE

Results of the REWIND trial



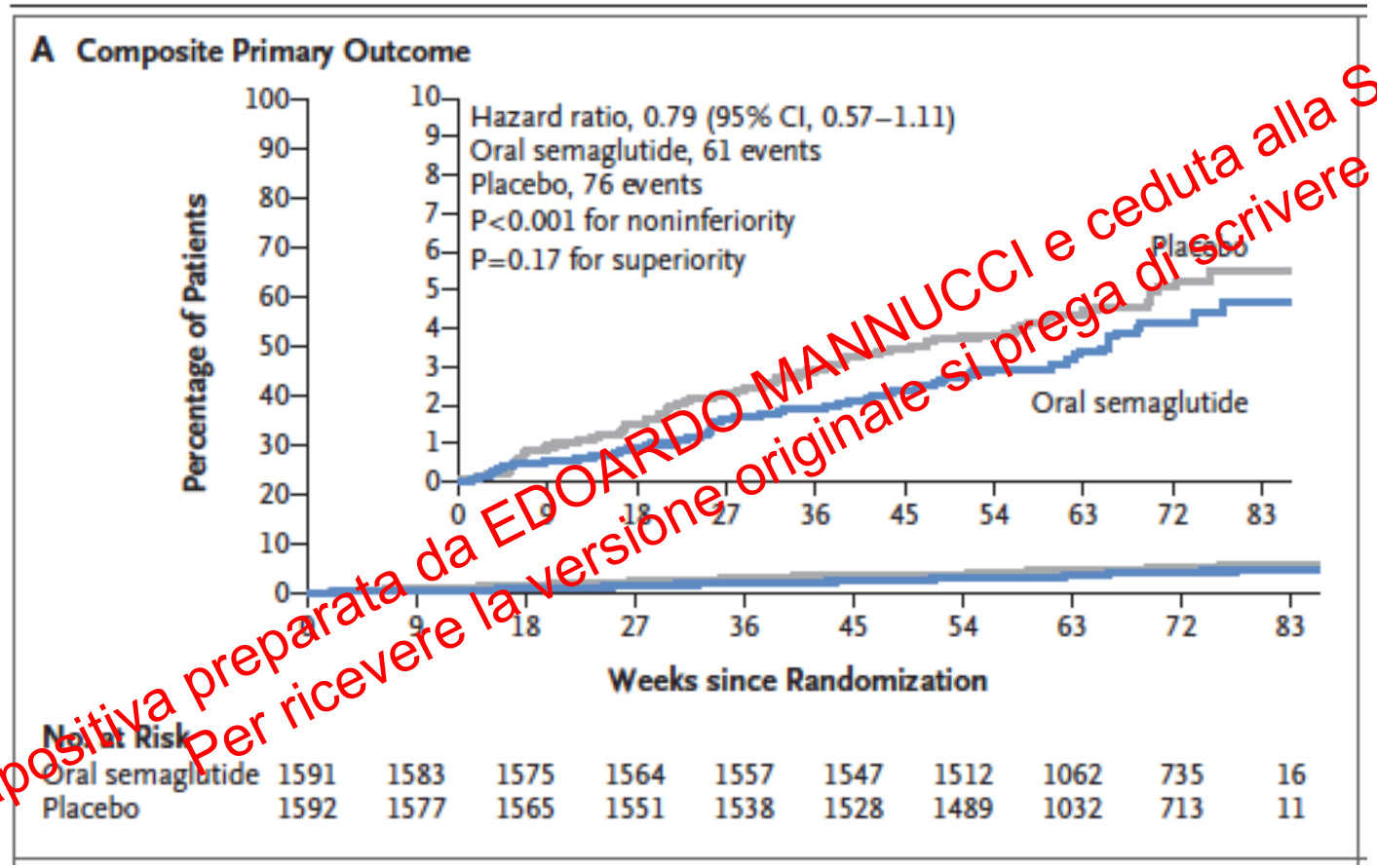
Principal endpoint:
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

9,901 T2DM patients with prior cardiovascular disease and/or high CV risk, dulaglutide vs placebo 1:1. Follow-up: 5.6 y

Gerstein HC et al. *Lancet* 2019

Oral semaglutide: effect on MACE

Results of the PIONEER-6 trial



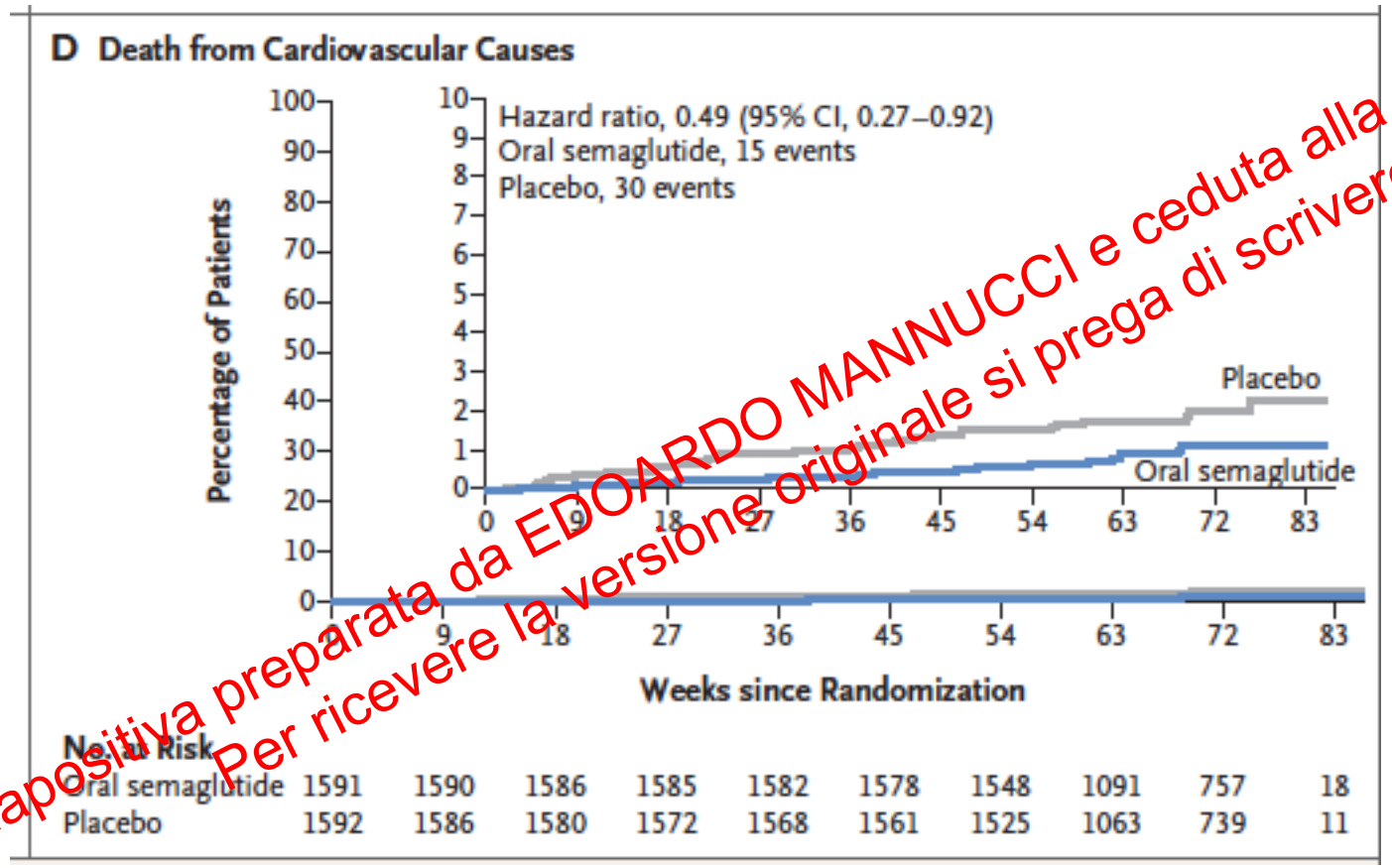
Principal endpoint:
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

3,183 T2DM patients with prior cardiovascular disease (87%) and/or high CV risk, oral semaglutide vs placebo 1:1.
Follow-up: 1.3 y

Husain M et al. *N Engl J Med* 2019

Oral semaglutide: effect on CV mortality

Results of the PIONEER-6 trial



Principal endpoint:
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

3,183 T2DM patients with prior cardiovascular disease (87%) and/or high CV risk, oral semaglutide vs placebo 1:1.
Follow-up: 1.3 y

Husain M et al. *N Engl J Med* 2019

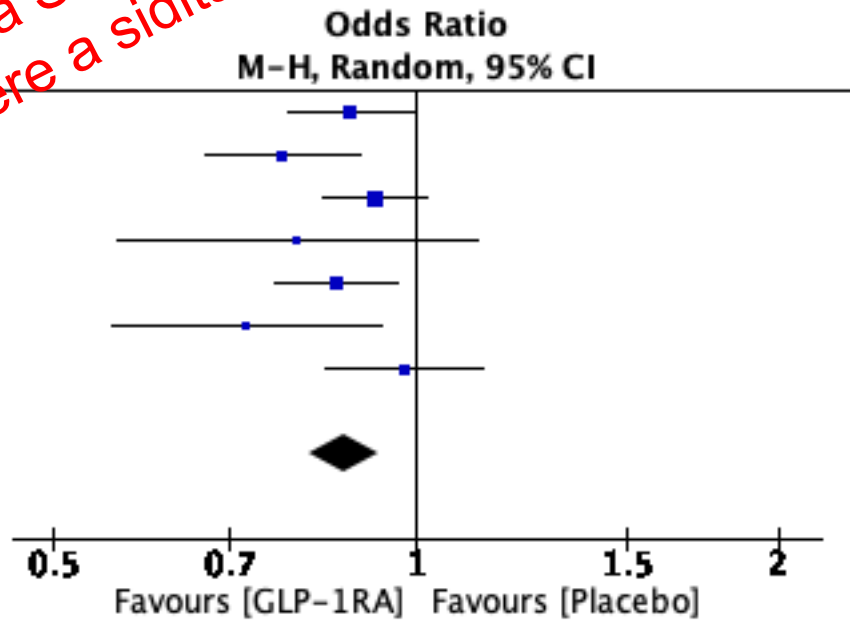
GLP1RA: effects on cardiovascular events

Metanalysis of RCTs>52 wk with CV endpoint

Study or Subgroup	GLP-1RA Events	GLP-1RA Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
Gerstein 2019	594	4949	663	4952	19.4%	0.88 [0.78, 0.99]
Hernandez 2018	338	4731	428	4732	14.2%	0.77 [0.67, 0.90]
Holman 2017	839	7356	905	7396	23.7%	0.92 [0.84, 1.02]
Husain 2019	61	1591	76	1592	3.4%	0.80 [0.56, 1.12]
Marso 2016	608	4668	694	4672	19.6%	0.86 [0.76, 0.97]
Marso 2016a	108	1648	146	1649	5.7%	0.72 [0.56, 0.94]
Pfeffer 2015	389	3034	397	3034	14.0%	0.98 [0.84, 1.13]
Total (95% CI)		27977		28027	100.0%	0.87 [0.81, 0.93]
Total events	2937		3309			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 8.35$, $df = 6$ ($P = 0.21$); $I^2 = 28\%$

Test for overall effect: $Z = 4.16$ ($P < 0.0001$)



Dicembrini I et al. *Manuscript in preparation*

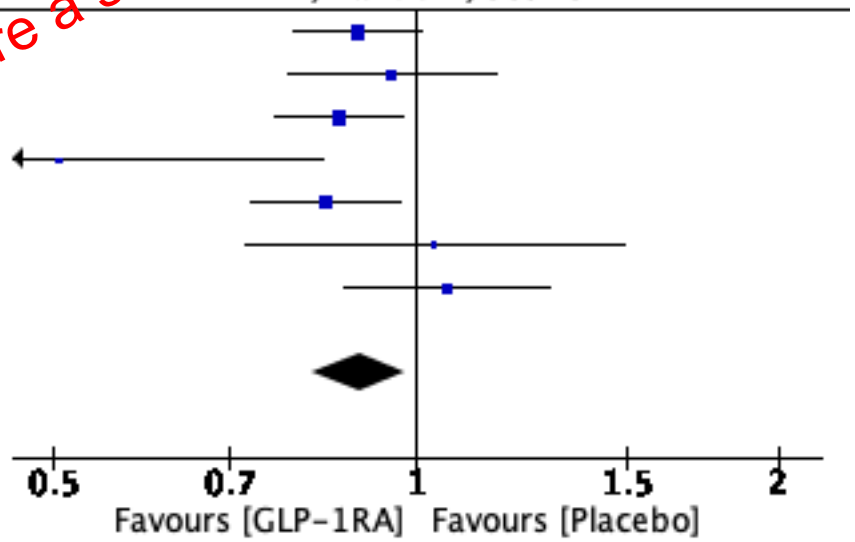
GLP1RA: effects on all-cause mortality

Metanalysis of RCTs>52 wk with CV endpoint

Study or Subgroup	GLP-1RA Events	GLP-1RA Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
Gerstein 2019	536	4949	592	4952	22.5%	0.89 [0.79, 1.01]
Hernandez 2018	196	4731	205	4732	13.3%	0.95 [0.78, 1.17]
Holman 2017	507	7356	584	7396	22.5%	0.86 [0.75, 0.98]
Husain 2019	23	1591	45	1592	2.9%	0.50 [0.30, 0.84]
Marso 2016	381	4668	447	4672	19.7%	0.84 [0.73, 0.97]
Marso 2016a	62	1648	60	1648	5.3%	1.04 [0.72, 1.49]
Pfeffer 2015	223	3034	211	3034	13.8%	1.06 [0.87, 1.29]
Total (95% CI)		27977		28027	100.0%	0.90 [0.82, 0.98]
Total events	1928		2344			

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 9.53$, df = 6 (P = 0.13); $I^2 = 40\%$

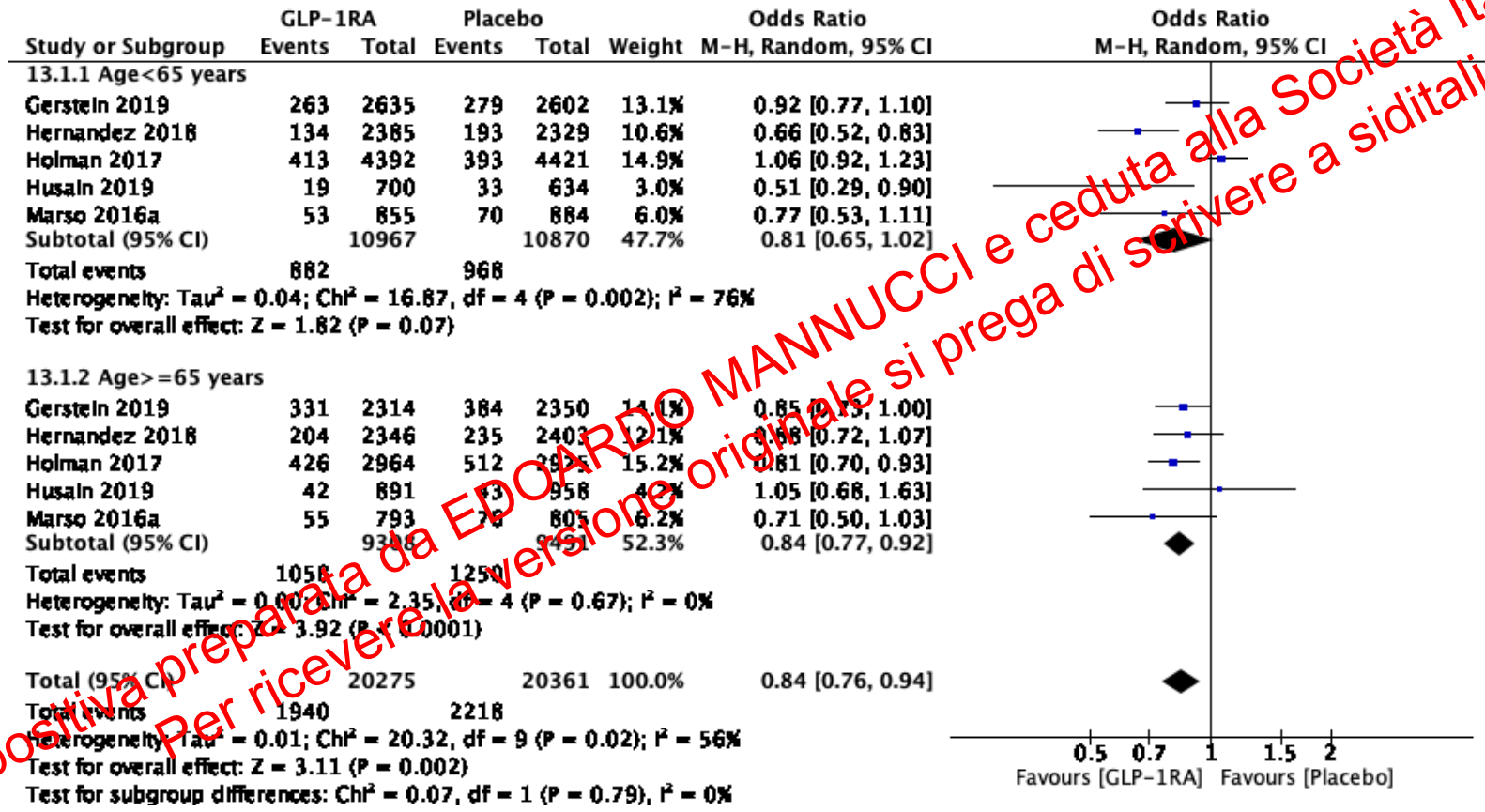
Test for overall effect: Z = 2.37 (P = 0.02)



Dicembrini I et al. *Manuscript in preparation*

GLP1RA and MACE: effect of gender

Metanalysis of RCTs>52 wk with CV endpoint

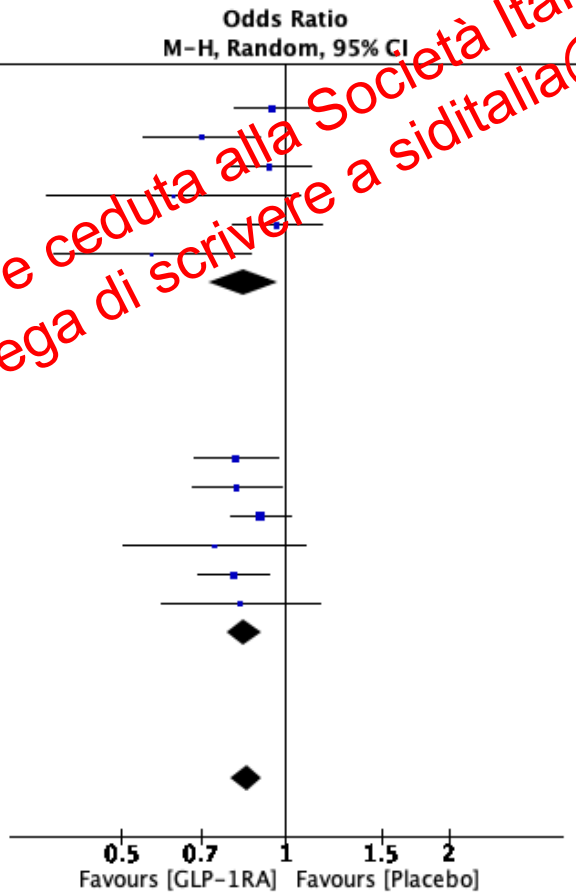


Dicembrini I et al. *Manuscript in preparation*

GLP1RA and MACE: effect of obesity

Metanalysis of RCTs>52 wk with CV endpoint

Study or Subgroup	GLP-1RA Events	GLP-1RA Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
14.1.1 <= 30 Kg/m2						
Gerstein 2019	340	2667	355	2650	12.3%	0.94 [0.81, 1.11]
Hernandez 2018	116	1788	164	1825	6.2%	0.70 [0.55, 0.90]
Holman 2017	275	2659	297	2704	10.9%	0.93 [0.79, 1.11]
Husain 2019	23	650	35	629	1.5%	0.62 [0.36, 1.07]
Marso 2016	241	1743	261	1831	9.6%	0.97 [0.80, 1.17]
Marso 2016a	39	596	64	584	2.4%	0.57 [0.38, 0.86]
Subtotal (95% CI)		10103		10223	42.9%	0.84 [0.72, 0.97]
Total events	1034		1176			
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 11.15$, df = 5 (P = 0.05); $I^2 = 55\%$						
Test for overall effect: Z = 2.36 (P = 0.02)						
14.1.2 BMI> 30 Kg/m2						
Gerstein 2019	254	2281	308	2302	10.6%	0.81 [0.68, 0.97]
Hernandez 2018	219	2914	262	2666	9.7%	0.81 [0.67, 0.98]
Holman 2017	546	4628	596	4611	16.9%	0.90 [0.80, 1.02]
Husain 2019	47	1064	64	1092	2.8%	0.74 [0.50, 1.09]
Marso 2016	367	2920	431	2837	13.4%	0.80 [0.69, 0.93]
Marso 2016a	68	1049	82	1061	3.7%	0.83 [0.59, 1.16]
Subtotal (95% CI)		14856		14789	57.1%	0.84 [0.78, 0.90]
Total events	1501		1743			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.24$, df = 5 (P = 0.81); $I^2 = 0\%$						
Test for overall effect: Z = 4.72 (P < 0.00001)						
Total (95% CI)		24959		25012	100.0%	0.85 [0.79, 0.91]
Total events	2535		2919			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 14.07$, df = 11 (P = 0.23); $I^2 = 22\%$						
Test for overall effect: Z = 4.82 (P < 0.00001)						
Test for subgroup differences: $Chi^2 = 0.00$, df = 1 (P = 0.99), $I^2 = 0\%$						

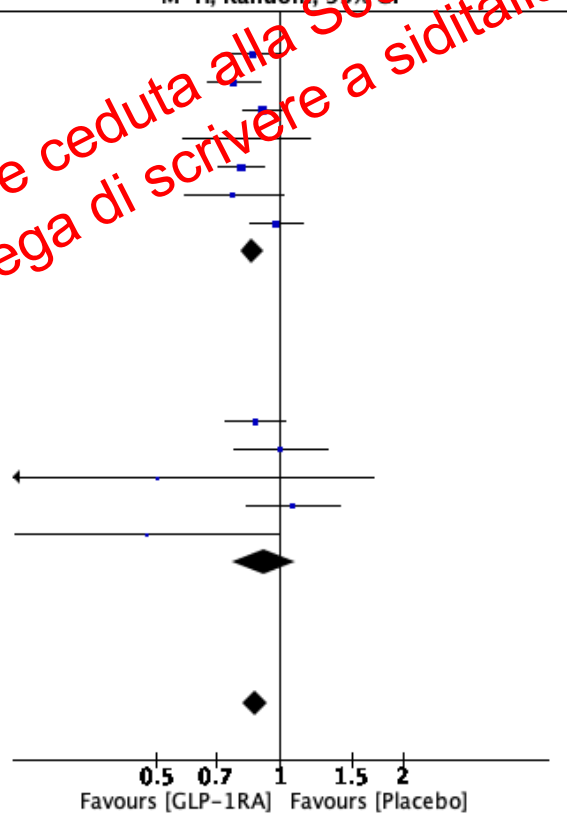


Dicembrini I et al. *Manuscript in preparation*

GLP1RA and MACE: primary vs secondary prevention

Metanalysis of RCTs>52 wk with CV endpoint

Study or Subgroup	GLP-1RA Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
11.1.1 Established CVD						
Gerstein 2019	280	1560	315	1554	10.0%	0.86 [0.72, 1.03]
Hernandez 2018	338	4731	428	4732	12.9%	0.77 [0.67, 0.90]
Holman 2017	722	5394	786	5388	18.6%	0.90 [0.81, 1.01]
Husain 2019	57	1350	68	1345	3.1%	0.83 [0.58, 1.19]
Marso 2016	480	3403	571	3372	15.0%	0.81 [0.71, 0.92]
Marso 2016a	97	1262	124	1271	4.9%	0.77 [0.58, 1.02]
Pfeffer 2015	389	3034	397	3034	12.8%	0.98 [0.84, 1.13]
Subtotal (95% CI)		20734		20696	77.3%	0.86 [0.80, 0.92]
Total events	2363		2689			
Heterogeneity: Tau² = 0.00; Chi² = 7.15, df = 6 (P = 0.31); I² = 16%						
Test for overall effect: Z = 4.52 (P < 0.00001)						
11.1.2 Multiple risk factors						
Gerstein 2019	277	3093	317	3126	10.6%	0.87 [0.74, 1.03]
Holman 2017	117	1962	119	2003	5.4%	1.01 [0.77, 1.31]
Husain 2019	4	241	6	247	0.3%	0.50 [0.15, 1.70]
Marso 2016	118	1265	123	1300	5.5%	1.08 [0.83, 1.40]
Marso 2016a	11	356	22	378	0.8%	0.47 [0.23, 0.99]
Subtotal (95% CI)		6917		7061	22.7%	0.92 [0.77, 1.10]
Total events	527		589			
Heterogeneity: Tau² = 0.01; Chi² = 6.27, df = 4 (P = 0.18); I² = 36%						
Test for overall effect: Z = 0.95 (P = 0.34)						
Total (95% CI)		27681		27757	100.0%	0.87 [0.81, 0.93]
Total events	2900		3278			
Heterogeneity: Tau² = 0.00; Chi² = 14.45, df = 11 (P = 0.21); I² = 24%						
Test for overall effect: Z = 4.13 (P < 0.0001)						
Test for subgroup differences: Chi² = 0.47, df = 1 (P = 0.50), I² = 0%						



Dicembrini I et al. *Manuscript in preparation*

CV effects of GLP1 RA: primary vs secondary prevention

	Baseline risk
LEADER - II	4.77
SUSTAIN - II	5.16
EXSCEL - II	6.08
HARMONY (II)	5.87
LEADER - I	2.05
SUSTAIN - I	1.57
EXSCEL - I	2.47

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CV outcome studies with GLP1RAs

Conclusions

- Although designed for safety, CVOTs have shown that long-acting GLP1RAs reduce CV morbidity and mortality in high-risk patients
- The effects on low-risk subjects is still uncertain, and possibly smaller than in high risk patients
- Differences across trials could be due to differences in trial characterstics and/or differences in the profile of action of individual molecules (including effects on traditional risk factors, direct cardiovascular effects, and effects possibly mediated by recetors other than GLP1R)