Possiamo puntare ancora di più sulla protezione vascolare?

Edoardo Mannucci

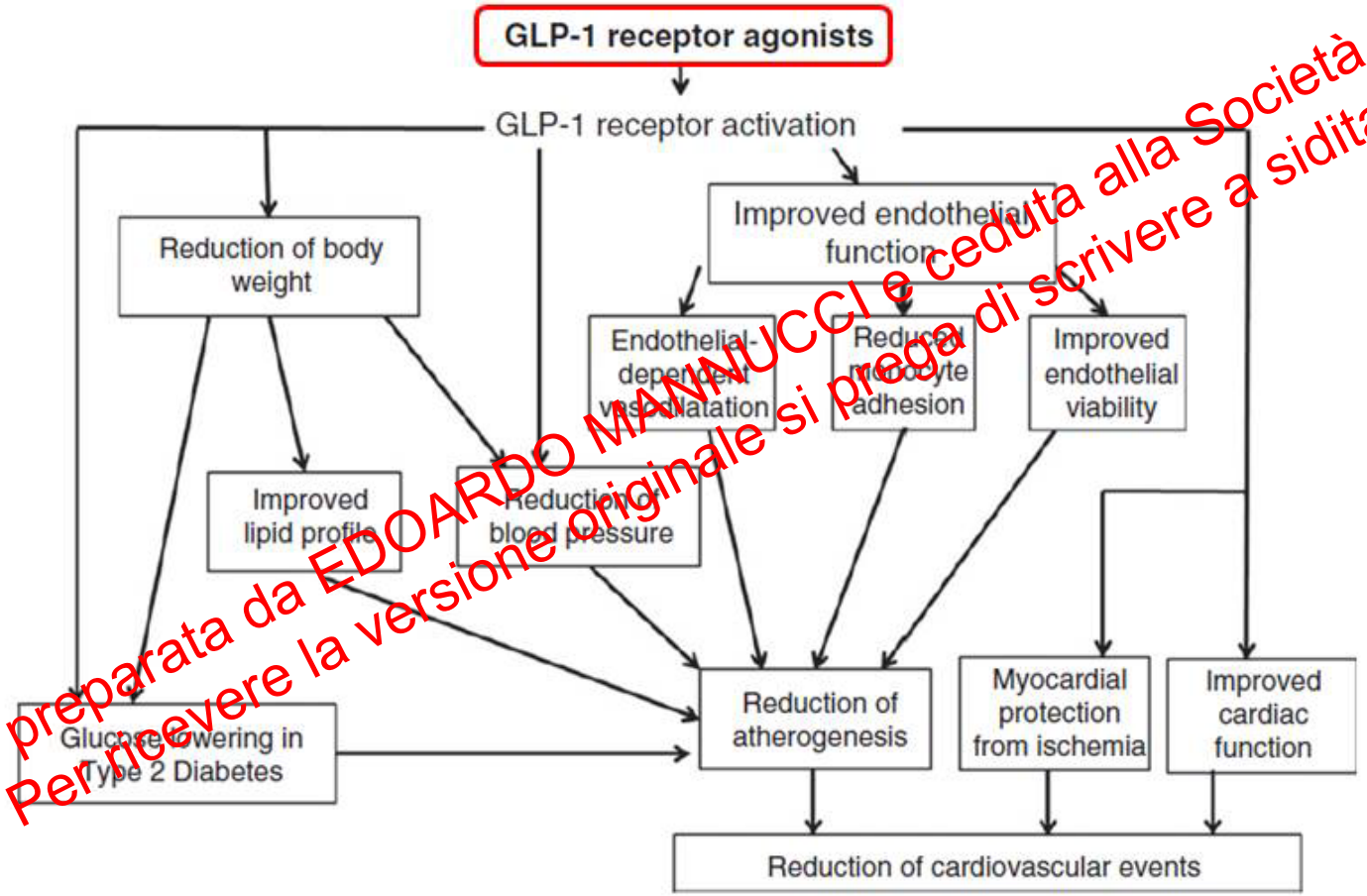
Bologna, 19 novembre 2019

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.***

GLP1 receptor agonists: cardiovascular actions



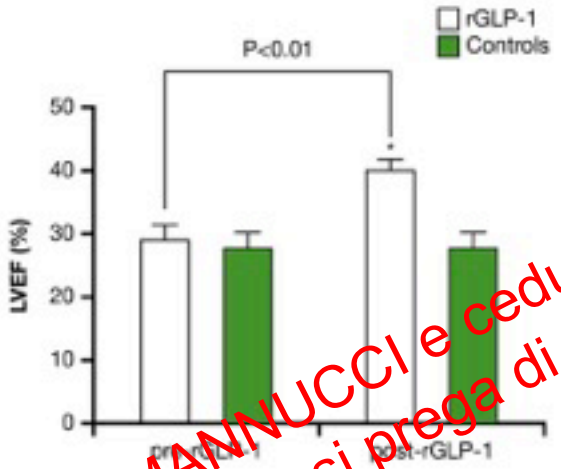
Mannucci E & Dicembrini I, *Curr Med Res Opin* 28:715-21, 2012

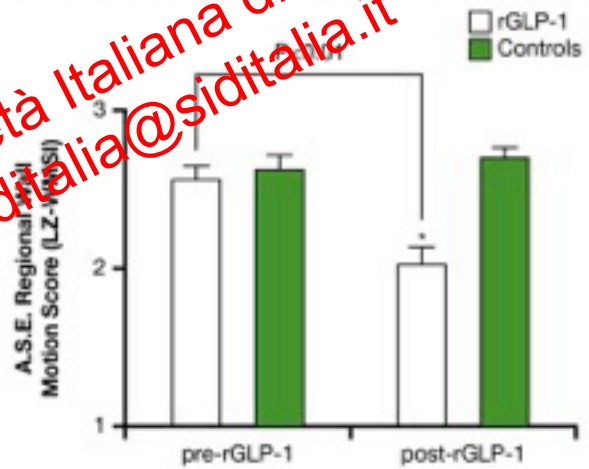
Myocardial effects of GLP-1: actions on ischemia

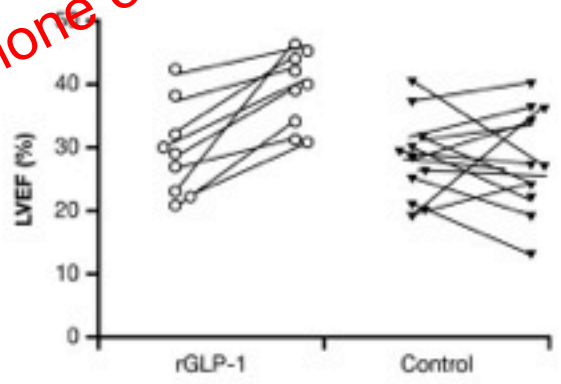
Pilot study, non-randomized

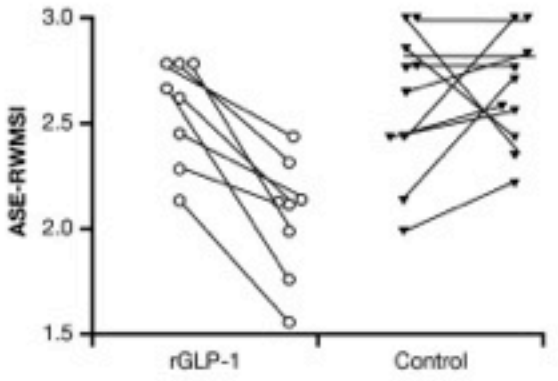
Patients with MI and PTCA, without DM.

72-h human GLP-1 infusion, started immediately after the revascularization procedure.









Nikolaidis LA *et al*, *Circulation* 109_962-5, 2004

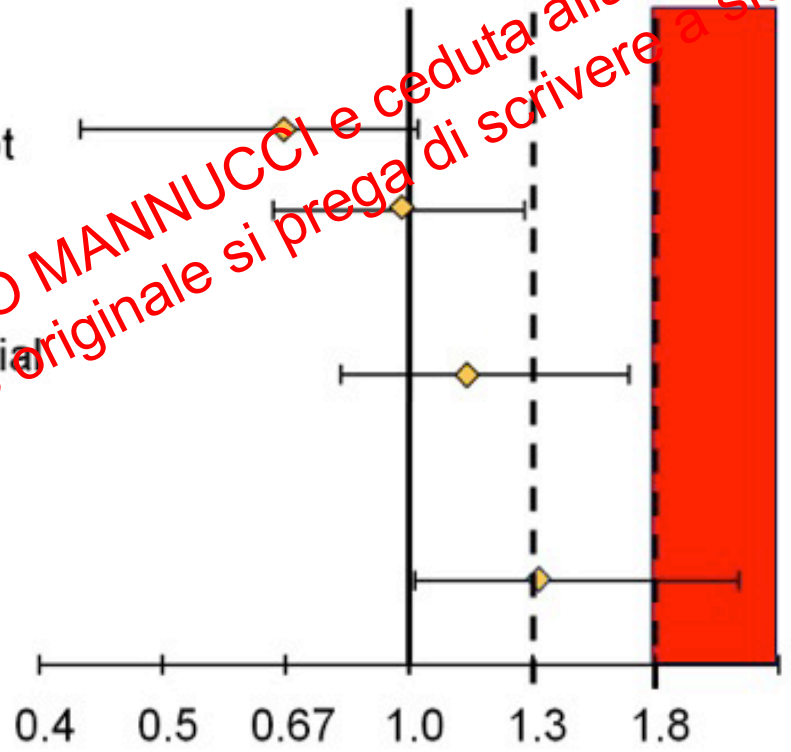
FDA Guidance for CV safety of new drugs for diabetes

- 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

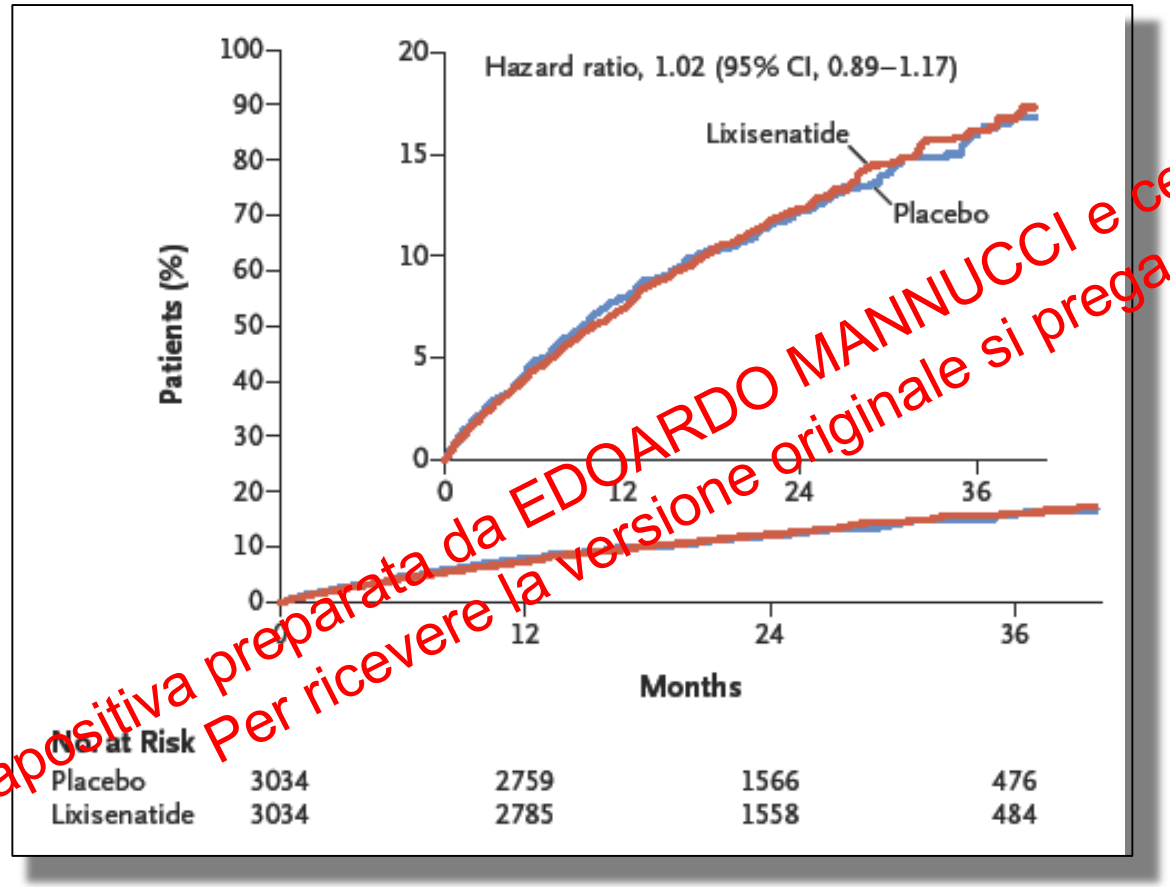
Methodological issues

- 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



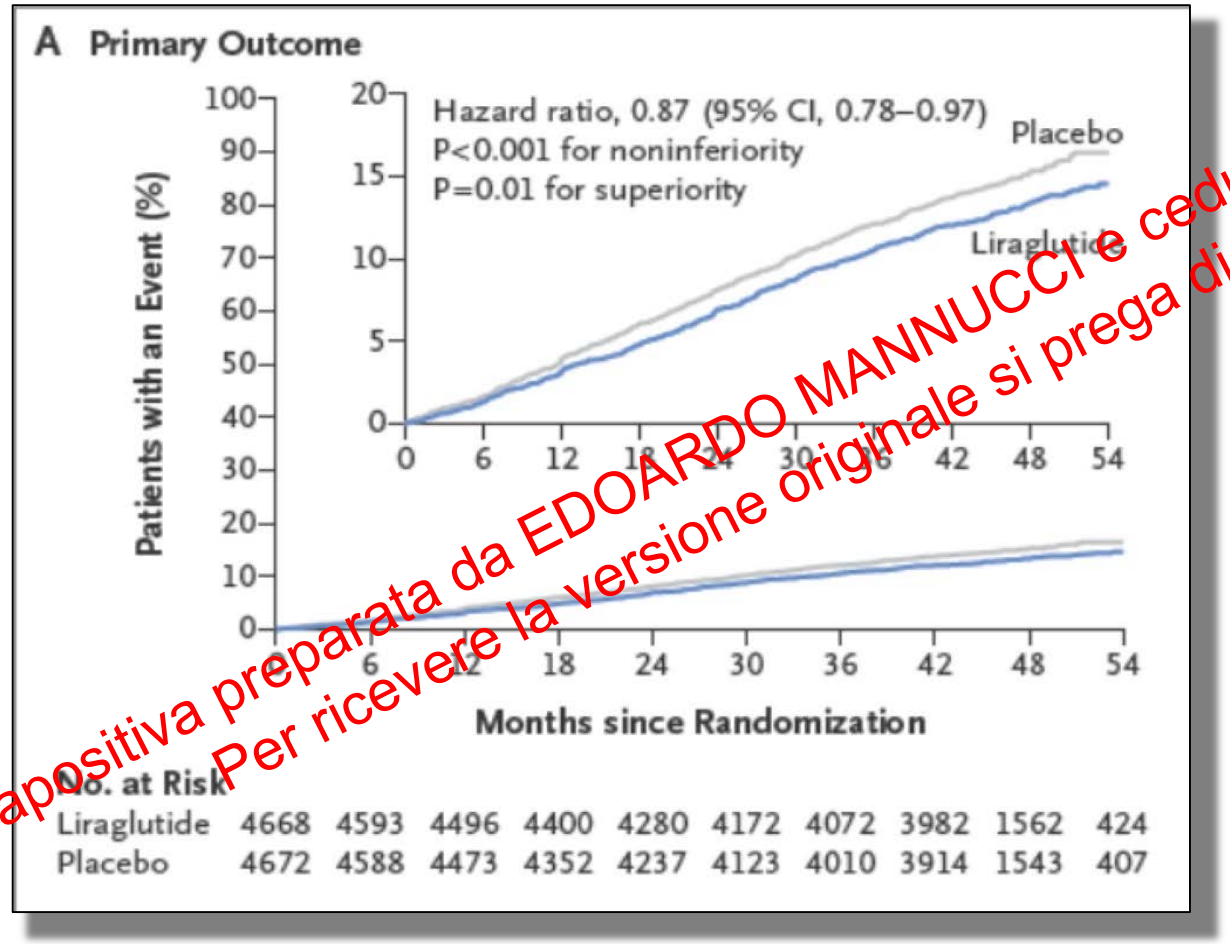
Principal endpoint:
4-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death, hospitalization for unstable angina)

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



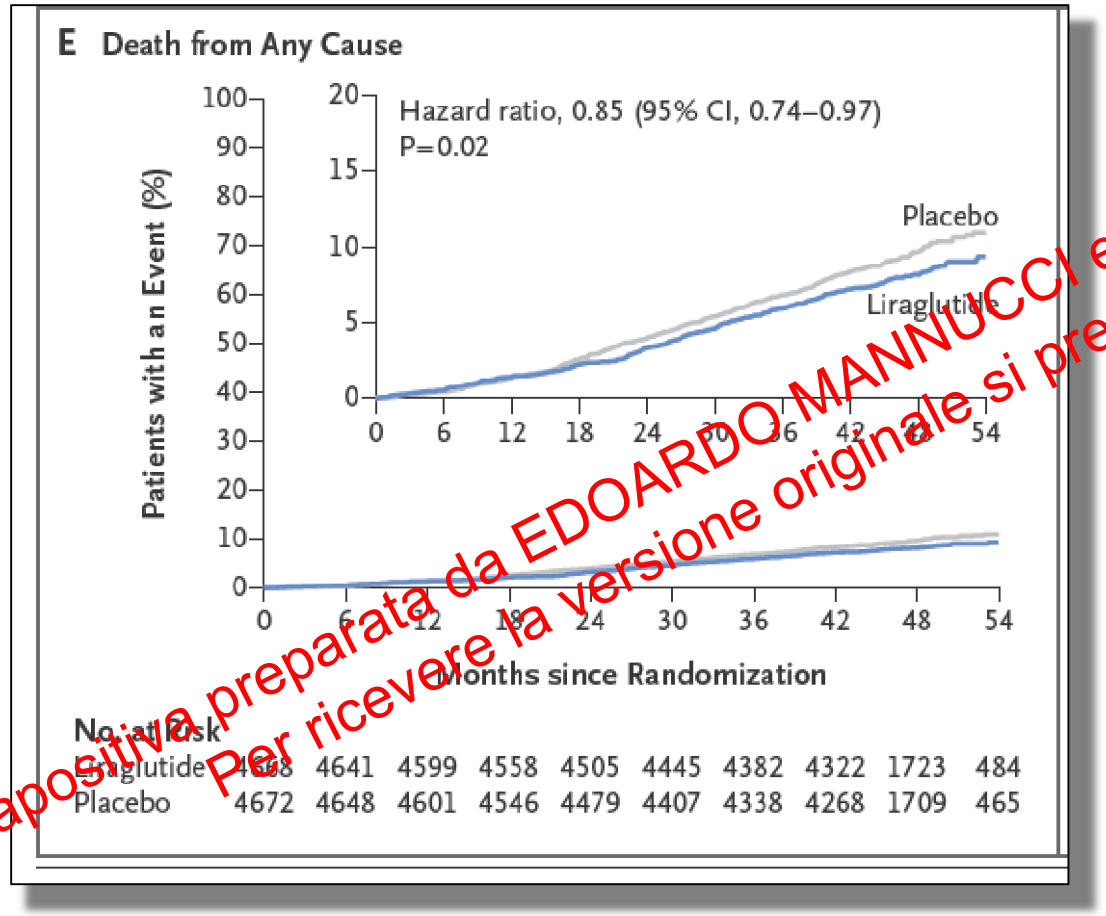
Principal endpoint:
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

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

Liraglutide: effect on all-cause mortality

Results of the LEADER trial



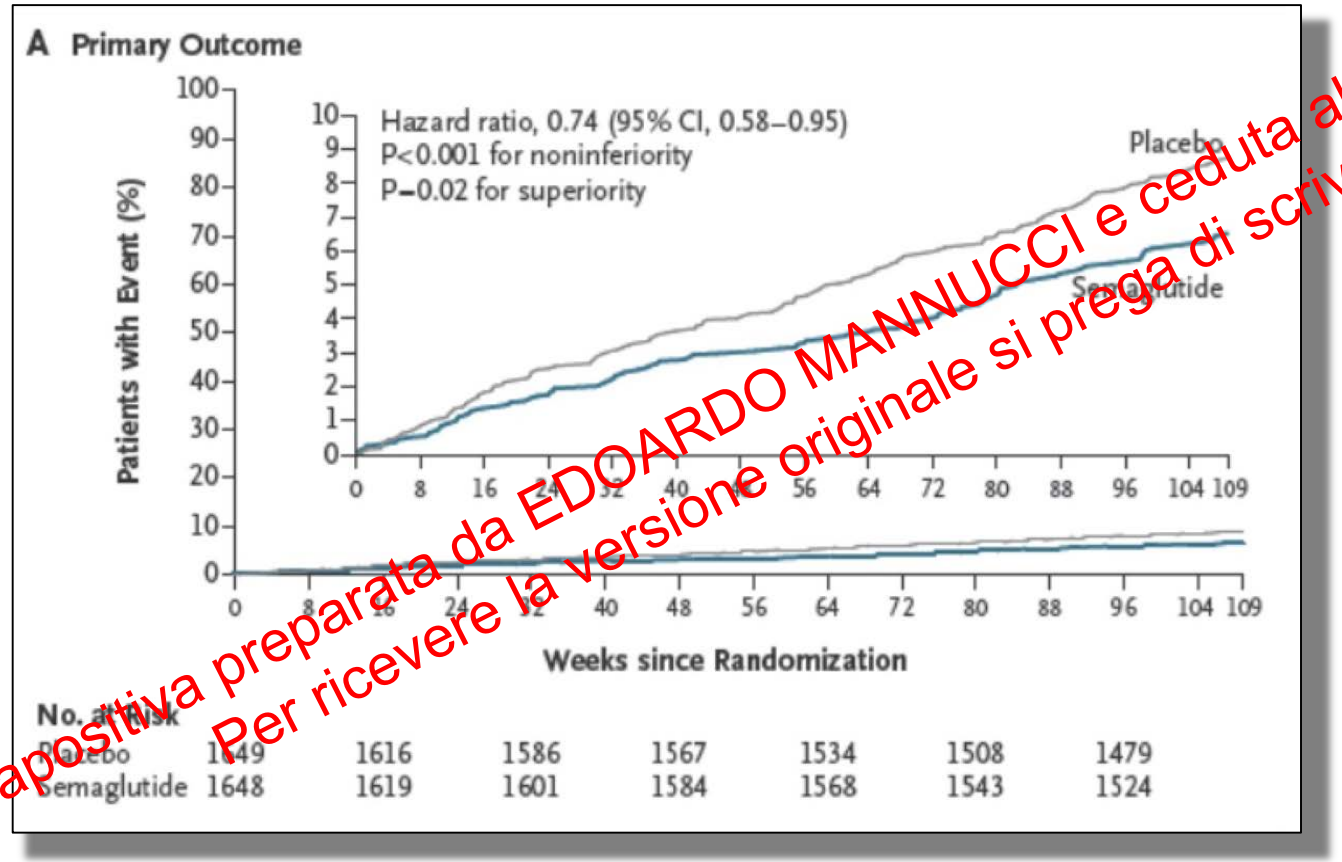
Secondary endpoint:
All-cause mortality

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



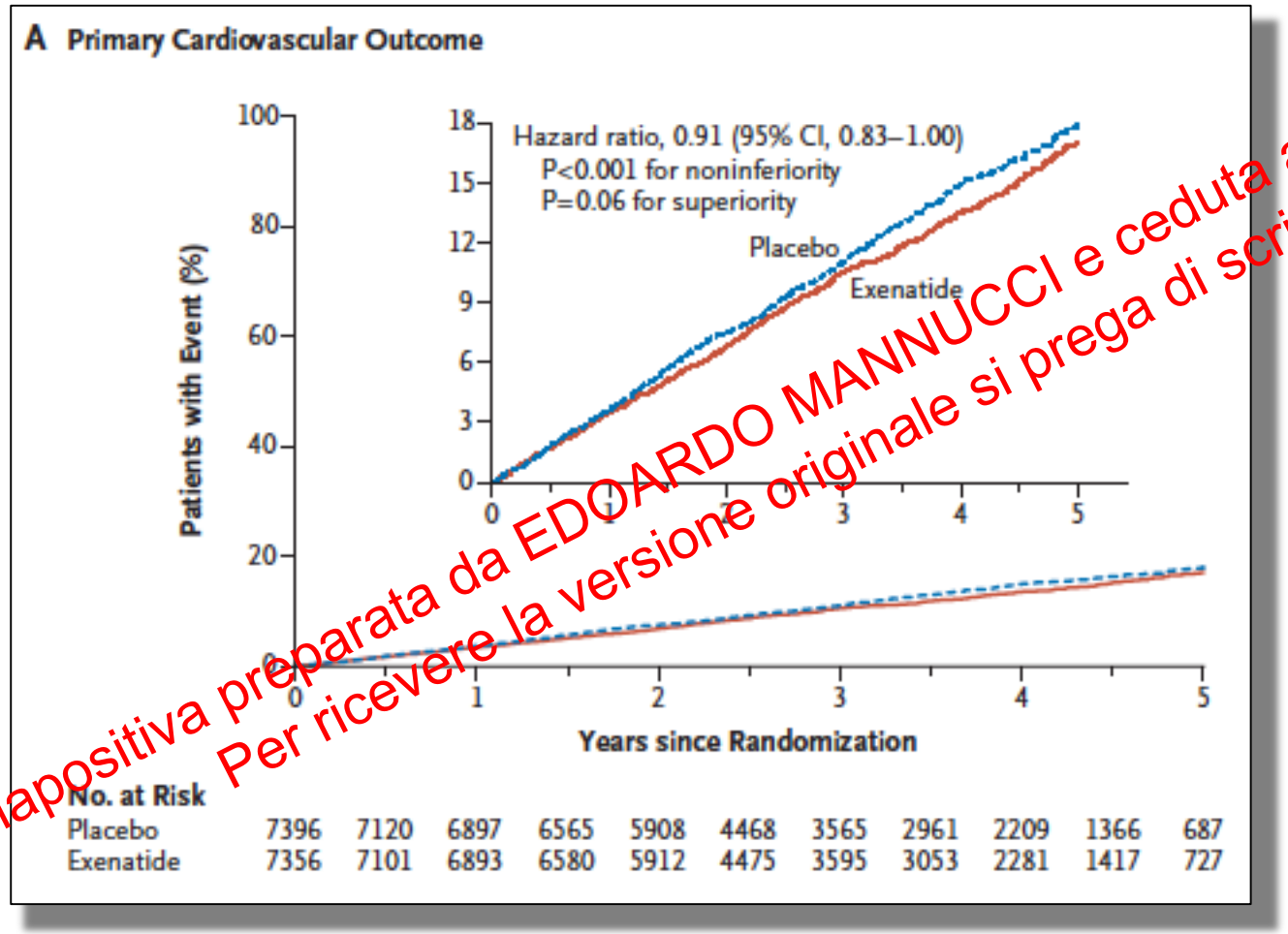
Principal endpoint:
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

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

Exenatide LAR: effect on major cardiovascular events

Results of the EXSCEL trial



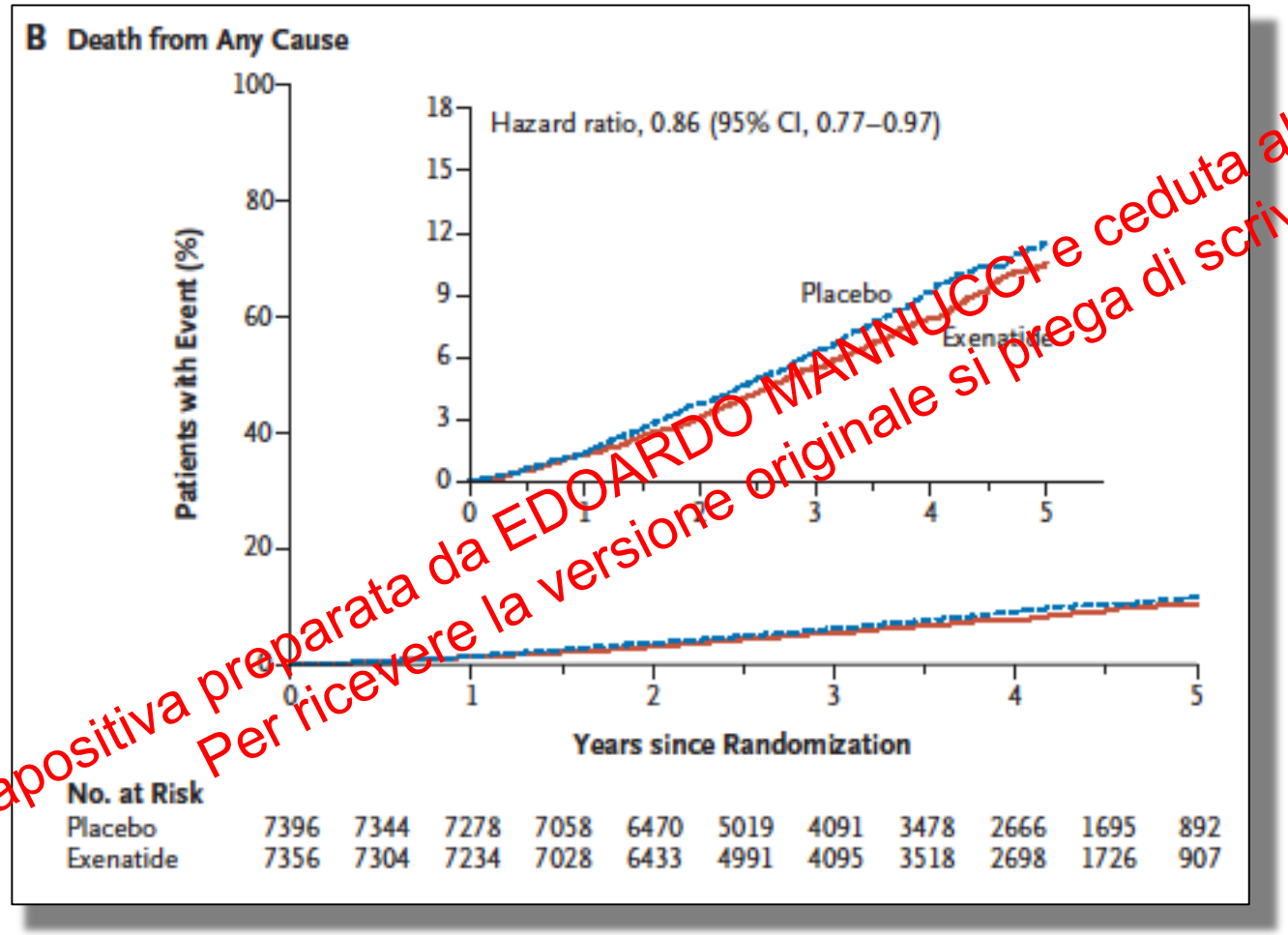
Principal endpoint:
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

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



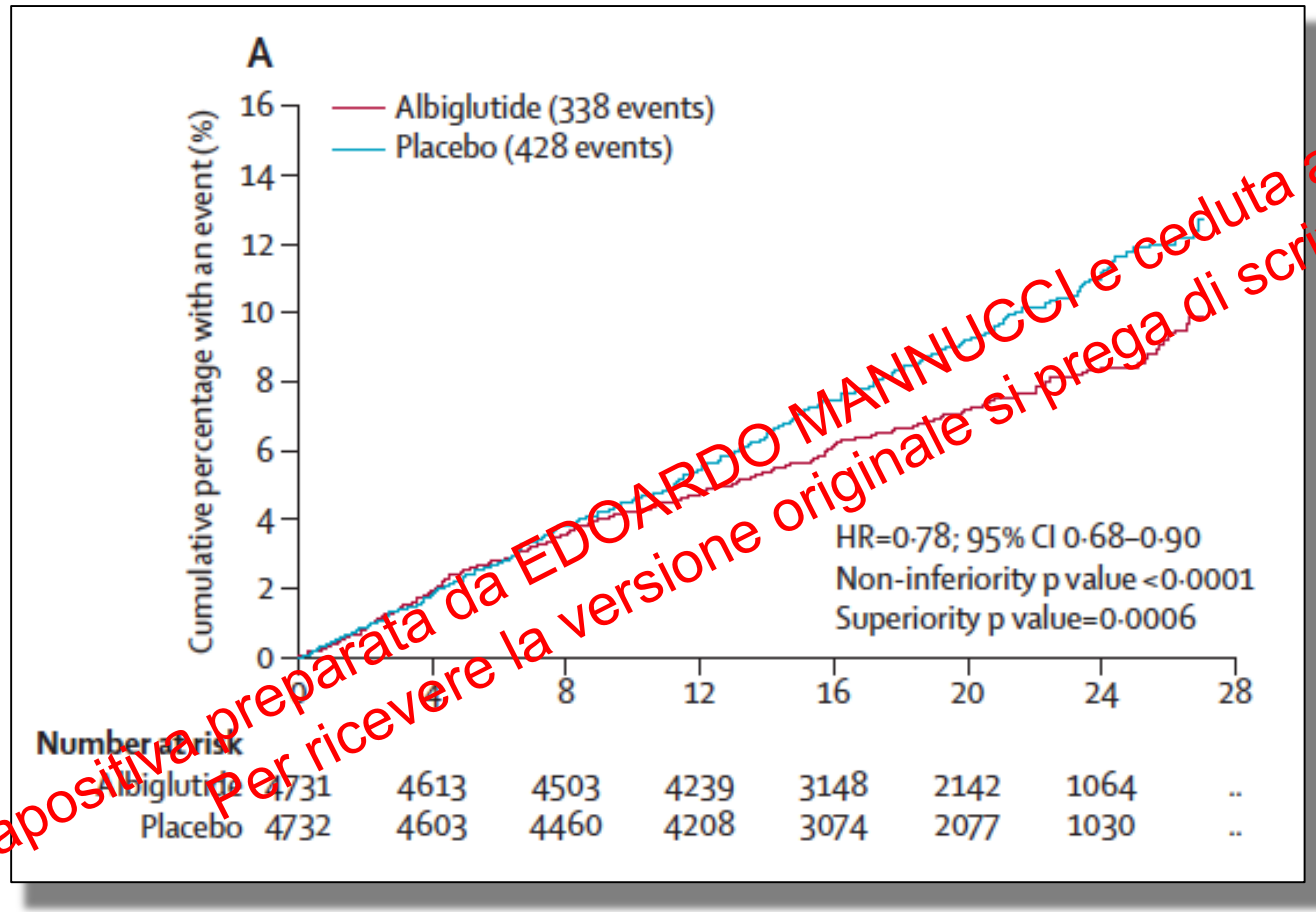
Principal endpoint:
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

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

Albiglutide: effect on MACE

Results of the HARMONY OUTCOMES trial



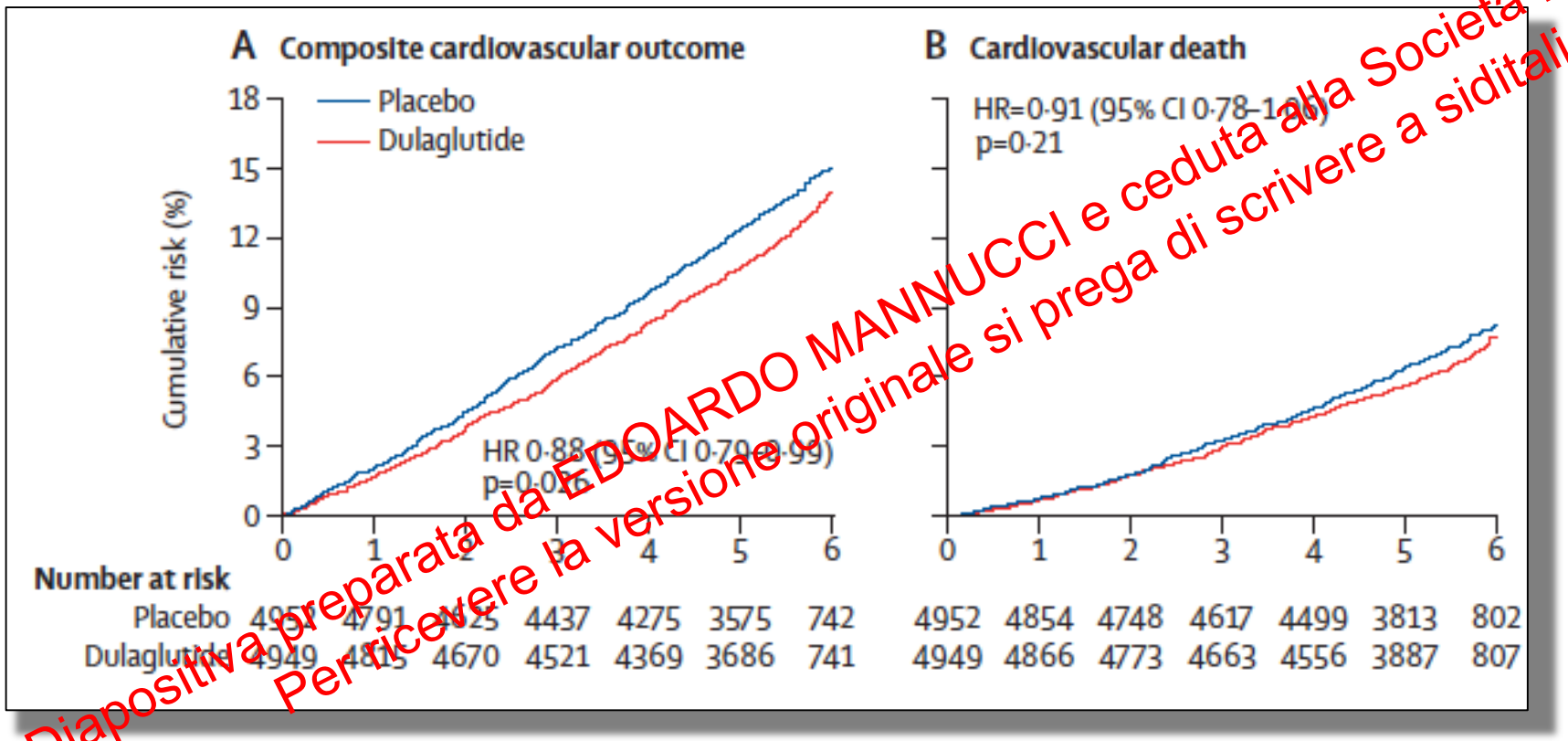
Principal endpoint:
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

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

Dulaglutide: effect on MACE

Results of the REWIND trial



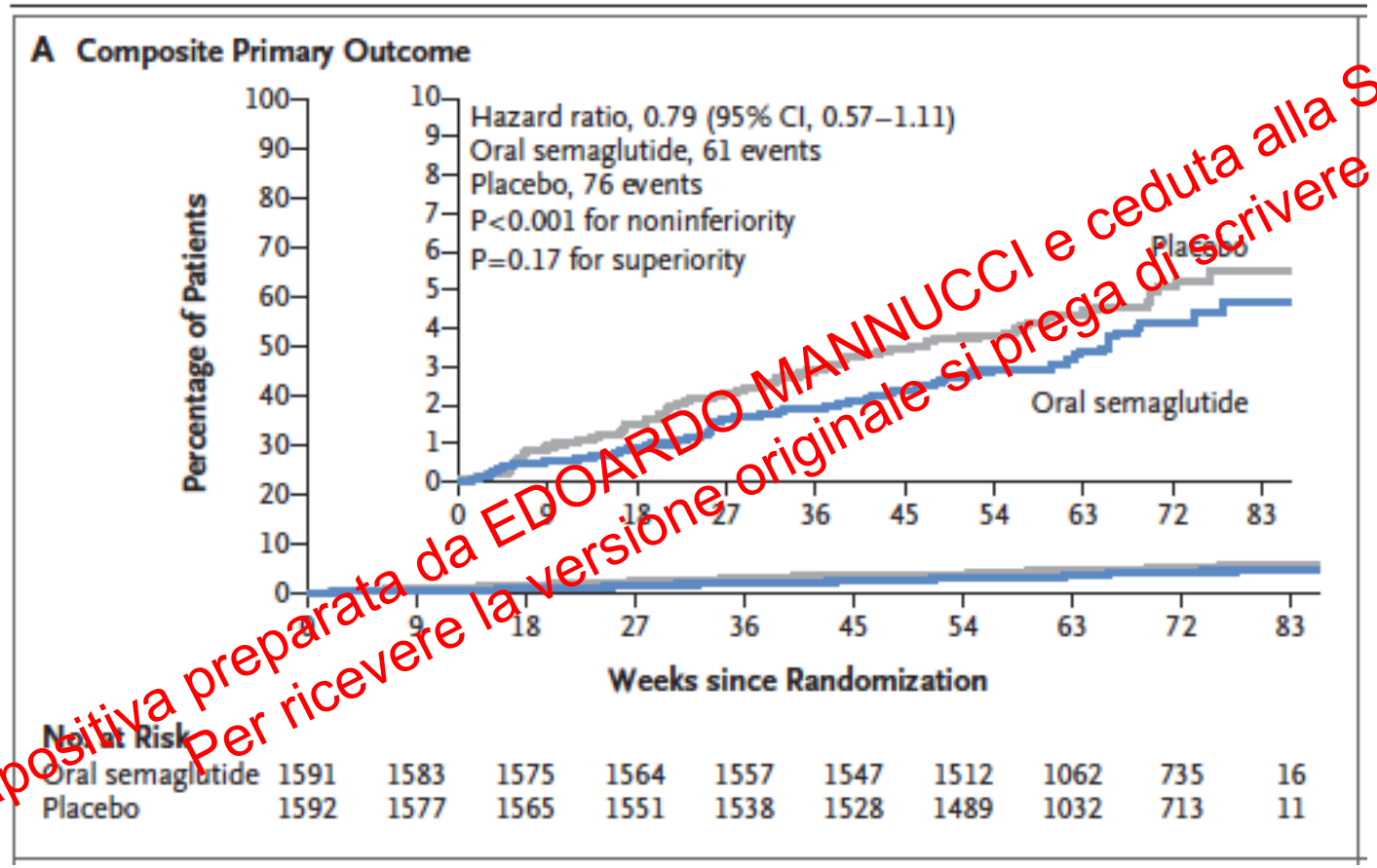
Principal endpoint:
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

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



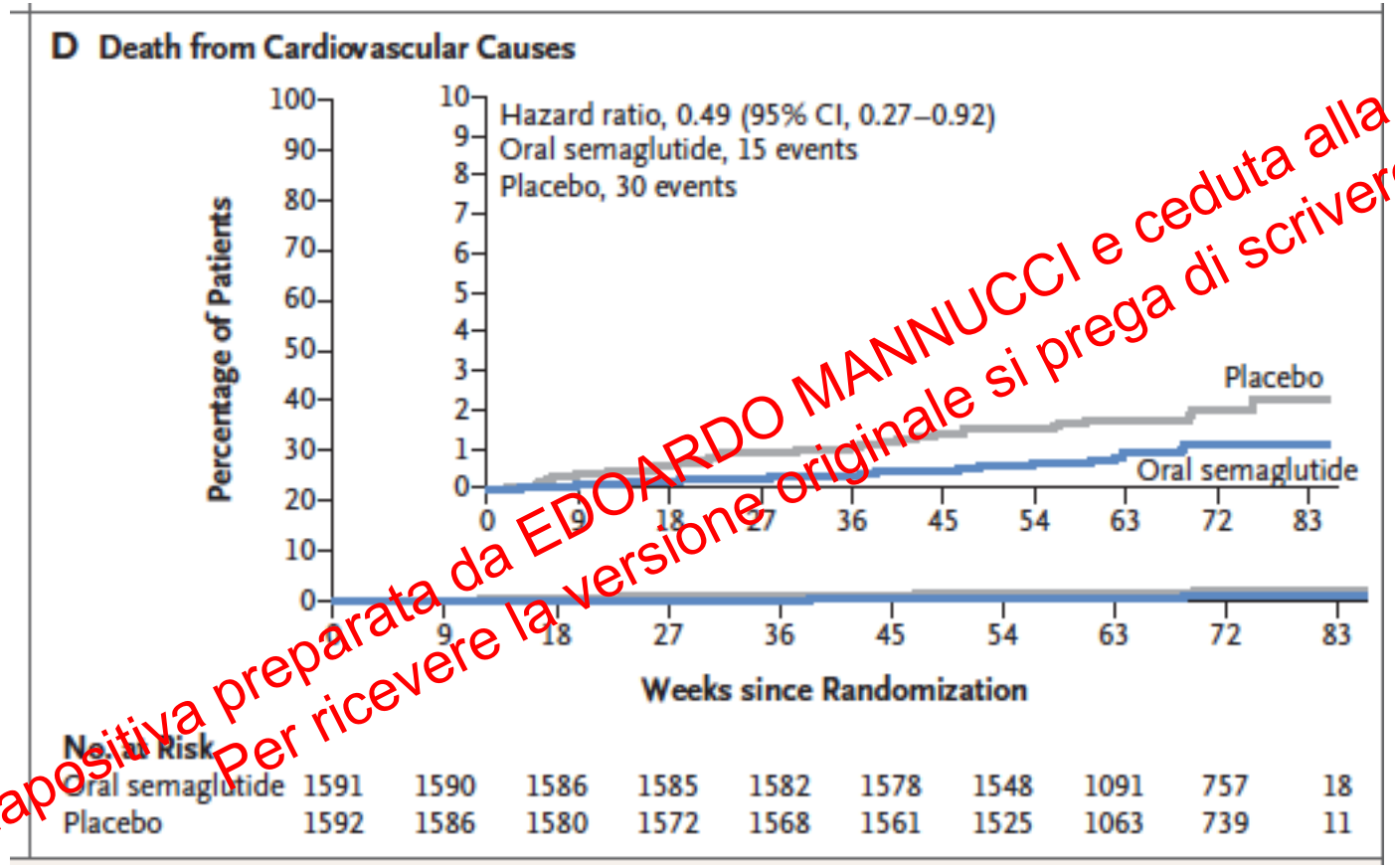
Principal endpoint:
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

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

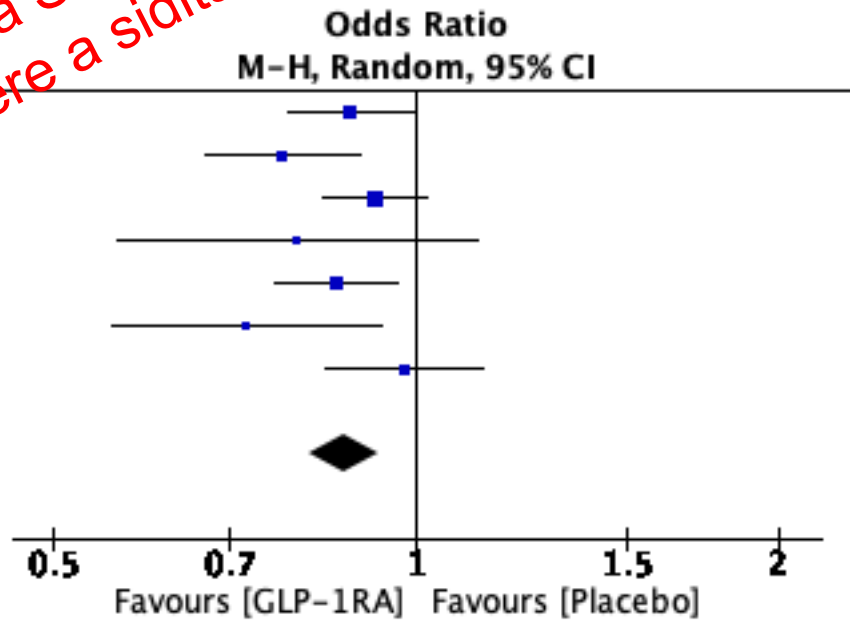
GLP1RA: effects on cardiovascular events

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: $Z = 4.16$ ($P < 0.0001$)



Mannucci E et al al. *Diabetes Obes Metab* 2019

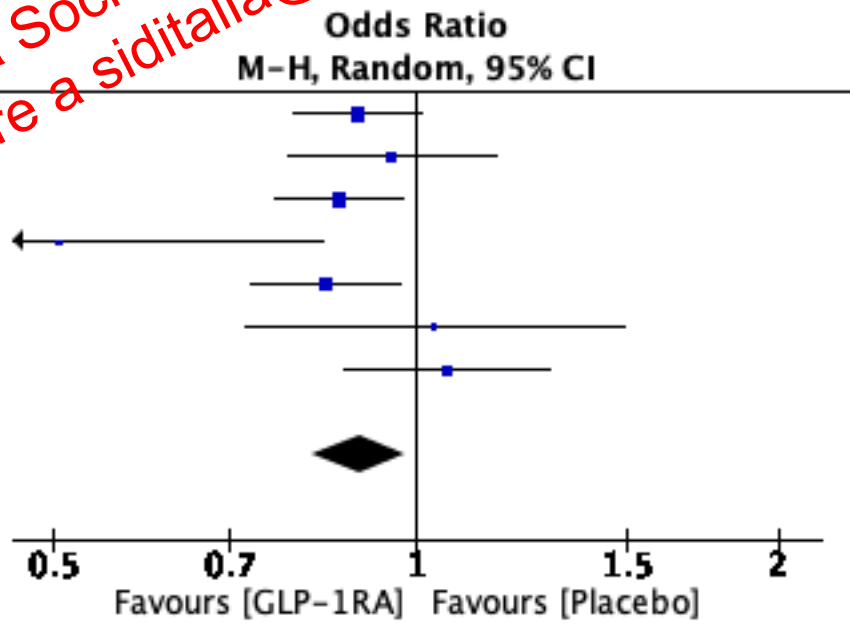
GLP1RA: effects on all-cause mortality

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	1649	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); $I^2 = 40\%$

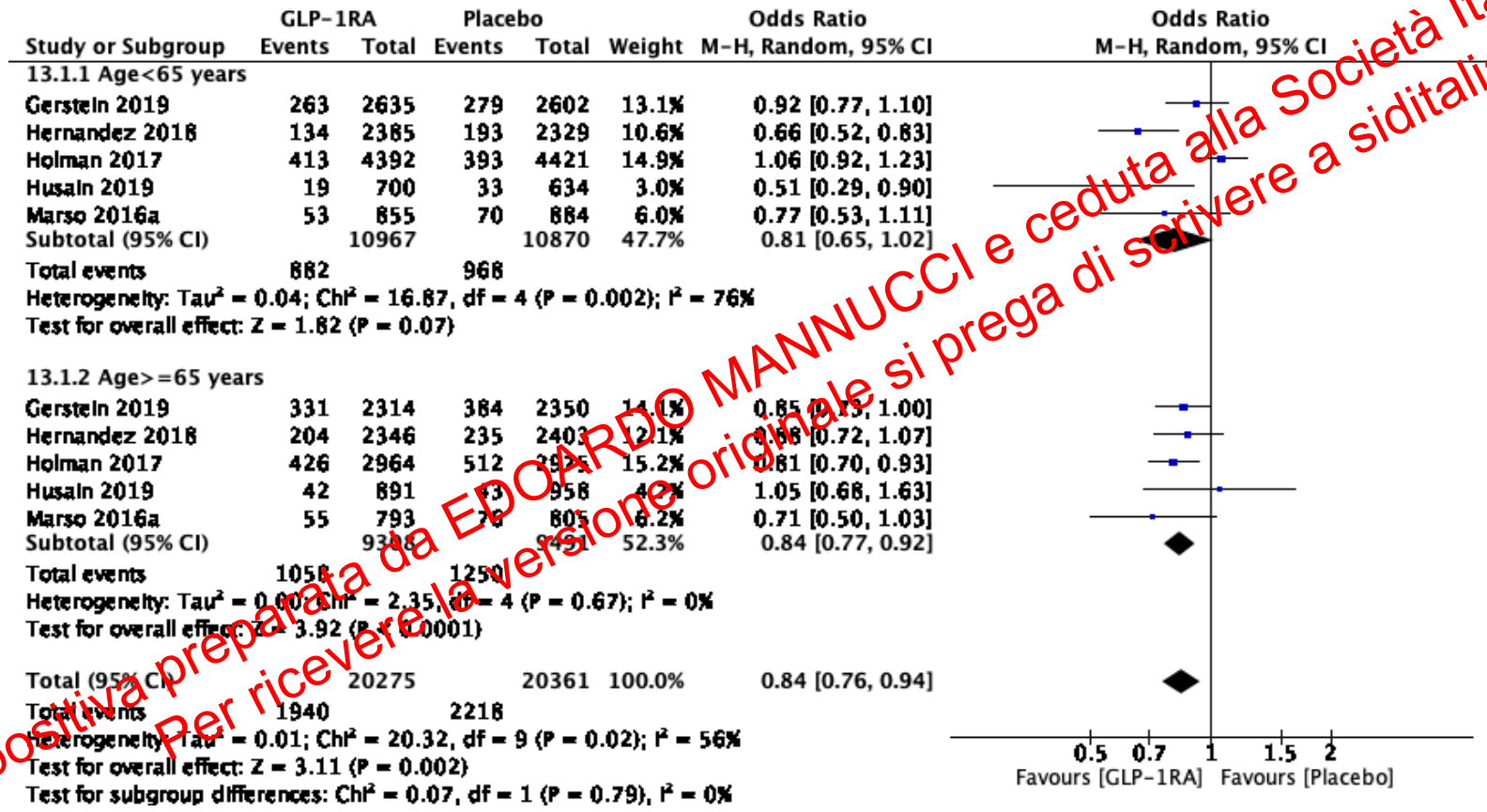
Test for overall effect: Z = 2.37 (P = 0.02)



Mannucci E et al al. *Diabetes Obes Metab* 2019

GLP1RA and MACE: effect of age

Metanalysis of RCTs>52 wk with CV endpoint

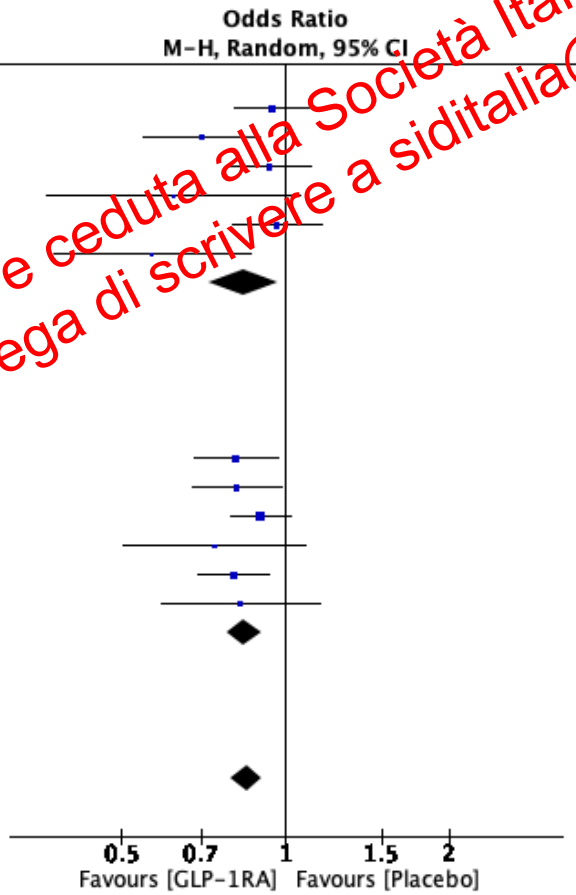


Mannucci E et al al. *Diabetes Obes Metab* 2019

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), $I^2 = 0\%$						

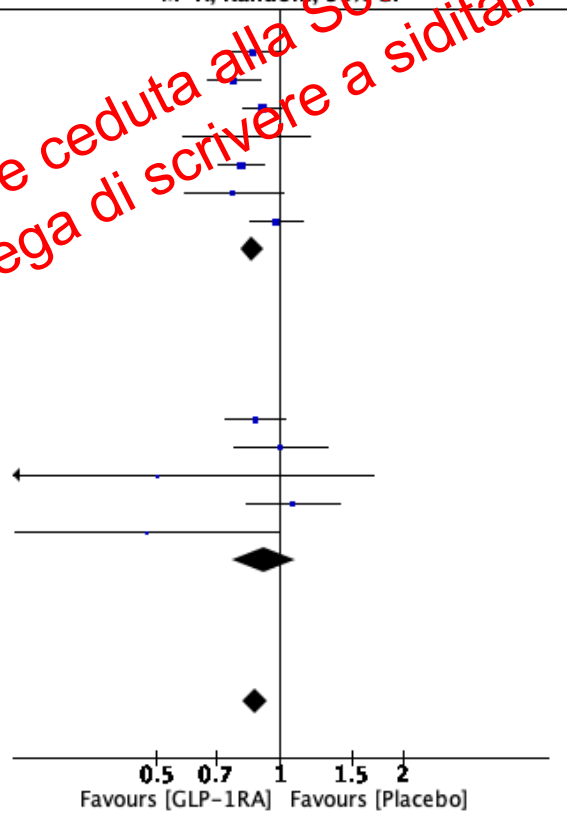


Mannucci E et al al. *Diabetes Obes Metab* 2019

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)		6947		7061	22.7%	0.92 [0.77, 1.10]
Total events	537		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%						



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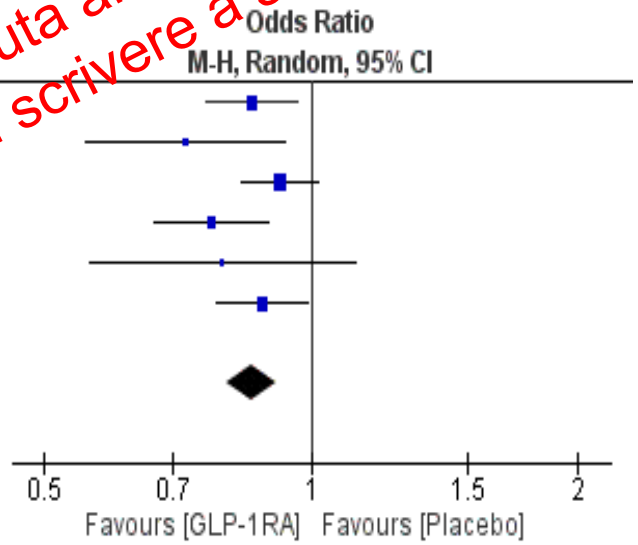
GLP1RA and MACE: long-acting molecules

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	Year
SUSTAIN-6	608	4668	694	4672	23.1%	0.86 [0.76, 0.97]	2016
LEADER	108	1648	146	1649	5.8%	0.72 [0.56, 0.94]	2016
EXSCEL	839	7356	905	7396	29.2%	0.92 [0.84, 1.02]	2017
HARMONY OUTCOMES	338	4731	428	4732	15.8%	0.73 [0.67, 0.80]	2018
PIONEER-6	61	1591	76	1592	3.4%	0.80 [0.56, 1.12]	2019
REWIND	594	4949	666	4952	22.7%	0.88 [0.78, 0.99]	2019
Total (95% CI)		**24943**		**25093**	**100.0%**	**0.86 [0.80, 0.91]**	
Total events	2548		2913				

Heterogeneity: Tau² = 0.00; Chi² = 6.01, df = 5 (P = 0.30); I² = 17%

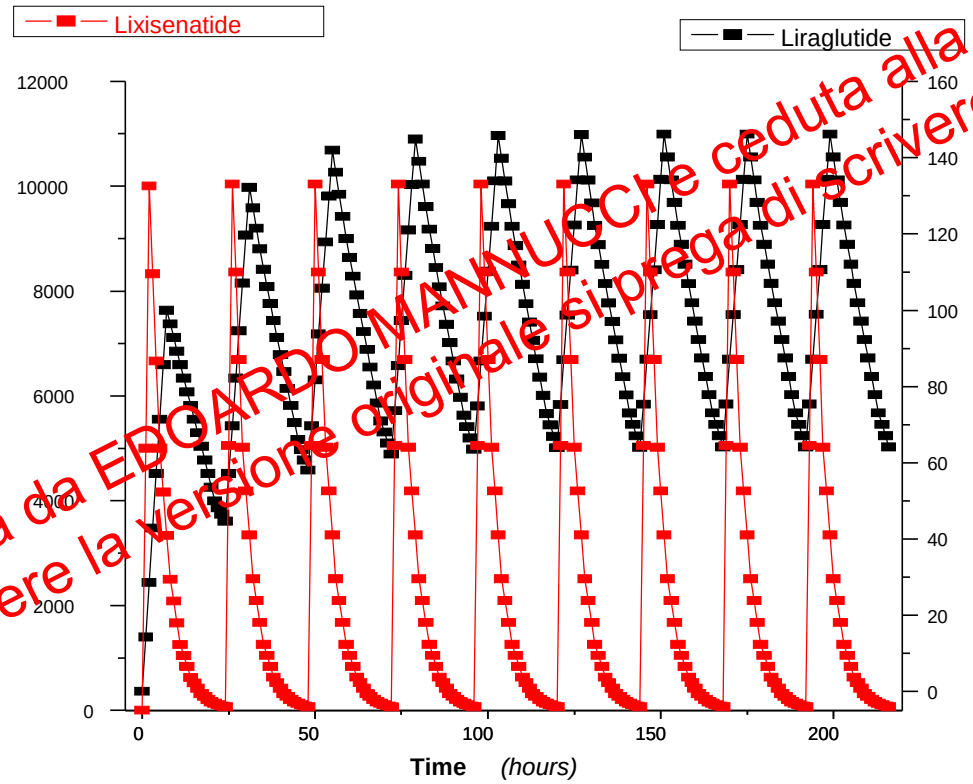
Test for overall effect: Z = 4.69 (P < 0.00001)



Mannucci E et al al. *Diabetes Obes Metab* 2019

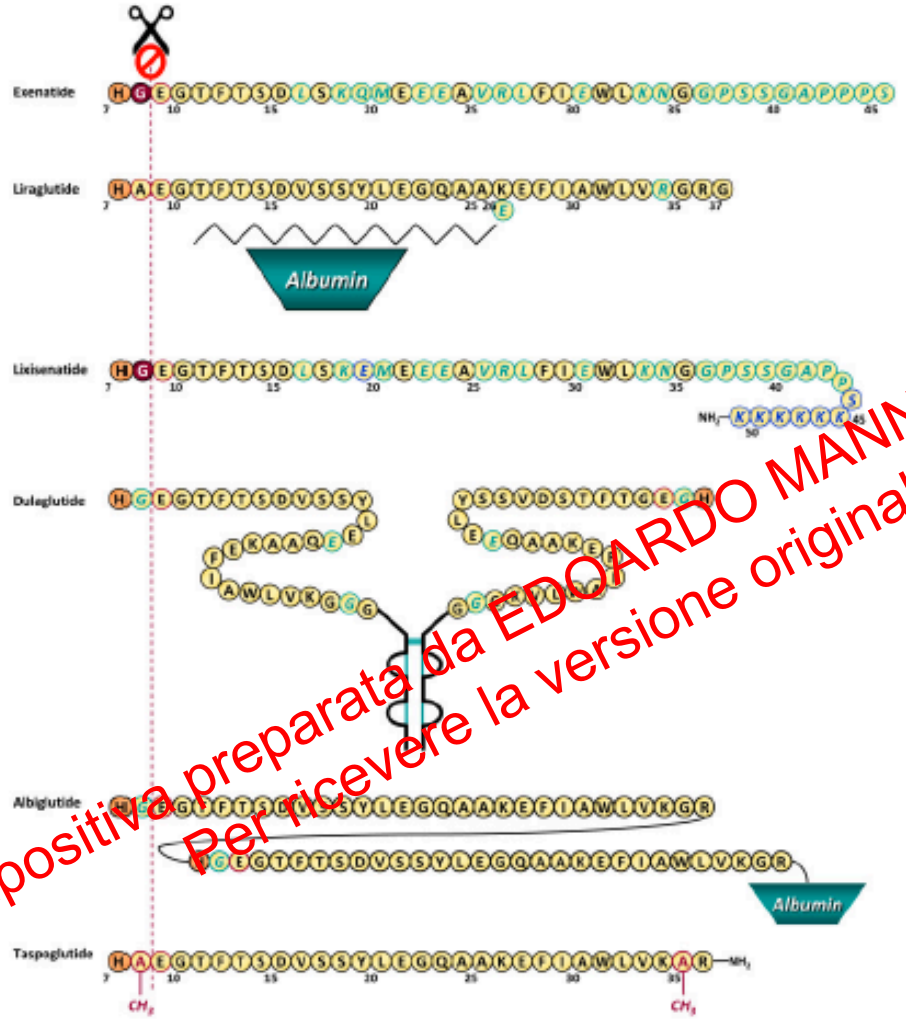
GLP1 receptor agonists kinetics

Liraglutide vs lixisenatide



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

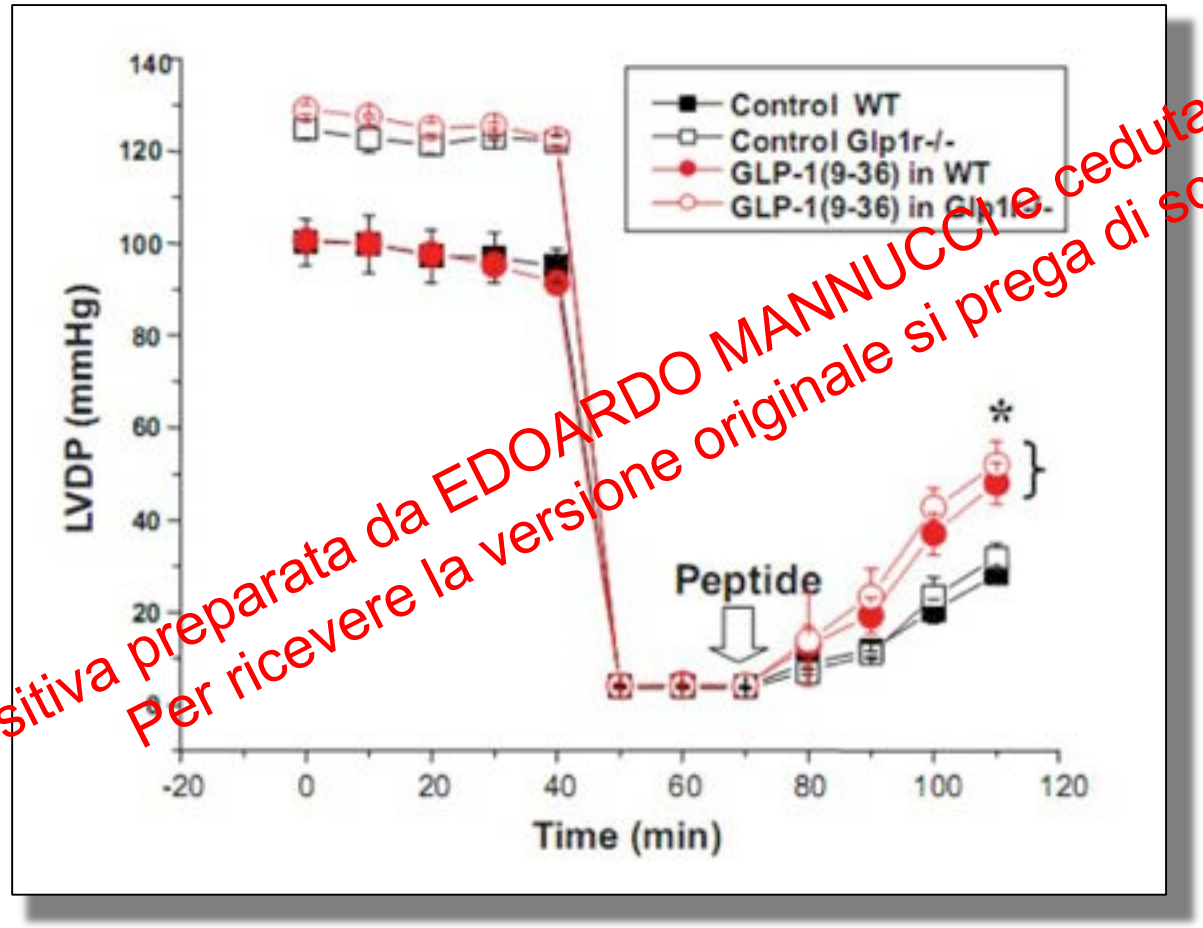
GLP1 receptor agonists



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

Myocardial effects of GLP-1 (9-36)

Recovery after ischemia-reperfusion in rats

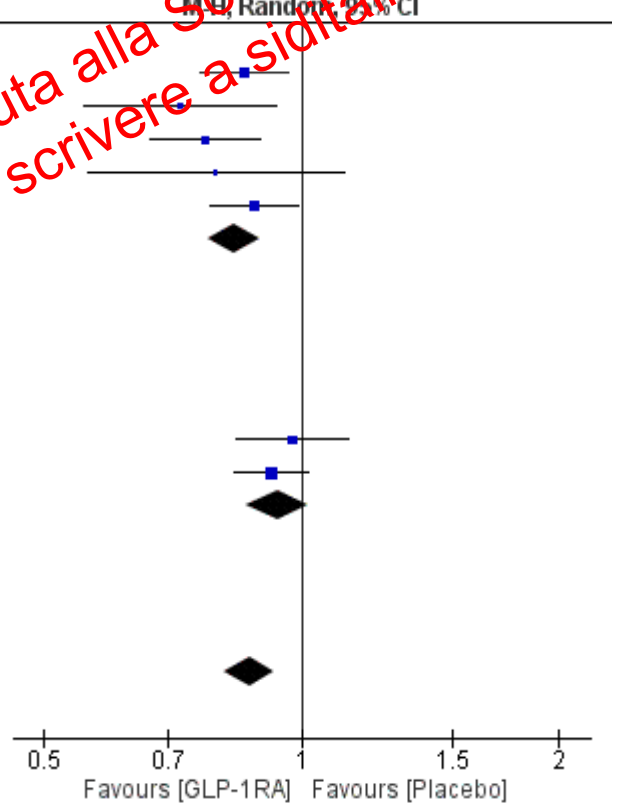


Ban et al. *Circulation* 17: 2340-50, 2008.

GLP1RA and MACE: human GLP1-like vs exenatide-like

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	Year
10.1.1 Human GLP-1 like GLP-1RA							
LEADER	608	4668	694	4672	19.6%	0.86 [0.76, 0.97]	2016
SUSTAIN-6	108	1648	146	1649	5.7%	0.72 [0.56, 0.94]	2016
HARMONY OUTCOMES	338	4731	428	4732	14.2%	0.77 [0.67, 0.90]	2018
PIONEER-6	61	1591	76	1592	3.4%	0.80 [0.56, 1.12]	2019
REWIND	594	4949	663	4952	19.4%	0.88 [0.78, 0.99]	2019
Subtotal (95% CI)		**17587**		**17597**	**62.3%**	**0.85 [0.78, 0.93]**	
Total events	1709		2007				
Heterogeneity: Tau² = 0.00; Chi² = 3.35, df = 4 (P = 0.50); I² = 0%							
Test for overall effect: Z = 5.16 (P < 0.00001)							
10.1.2 Exendin like GLP-1RA							
ELIXA	389	3034	397	3034	14.0%	0.98 [0.84, 1.13]	2015
EXSCEL	839	7356	905	7396	23.7%	0.92 [0.84, 1.02]	2017
Subtotal (95% CI)		**10390**		**10430**	**37.7%**	**0.94 [0.86, 1.02]**	
Total events	1228		1302				
Heterogeneity: Tau² = 0.00; Chi² = 0.38, df = 1 (P = 0.54); I² = 0%							
Test for overall effect: Z = 1.47 (P = 0.14)							
Total (95% CI)		**27977**		**28027**	**100.0%**	**0.87 [0.81, 0.93]**	
Total events	2937		3309				
Heterogeneity: Tau² = 0.00; Chi² = 8.35, df = 6 (P = 0.21); I² = 28%							
Test for overall effect: Z = 4.16 (P < 0.0001)							
Test for subgroup differences: Chi² = 4.63, df = 1 (P = 0.03), I² = 78.4%							



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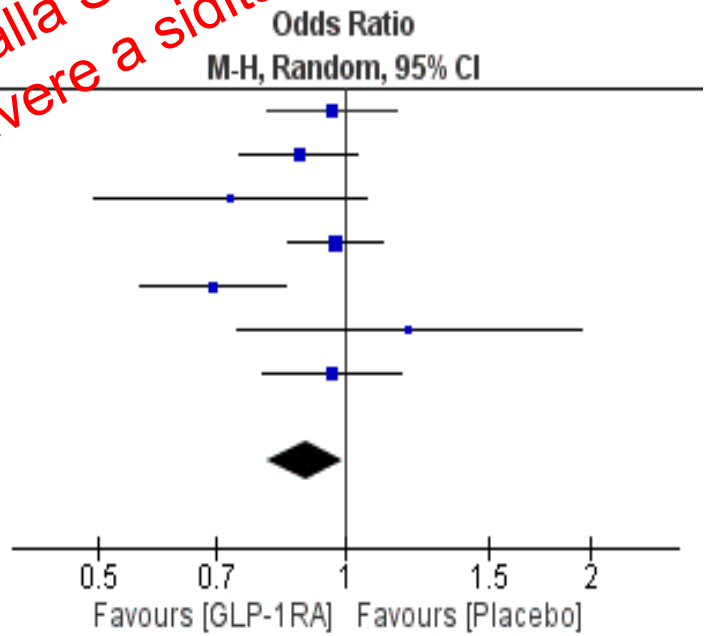
GLP1RA and MACE: nonfatal myocardial infarction

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	Year
ELIXA	247	3034	255	3034	17.1%	0.97 [0.80, 1.18]	2016
LEADER	281	4668	317	4672	18.7%	0.88 [0.75, 1.04]	2016
SUSTAIN-6	47	1648	64	1649	6.5%	0.73 [0.50, 1.07]	2016
EXSCEL	466	7356	480	7396	23.1%	0.97 [0.85, 1.11]	2017
HARMONY OUTCOMES	160	4731	228	4731	15.1%	0.69 [0.56, 0.85]	2018
PIONEER-6	37	1591	31	1592	4.1%	1.20 [0.74, 1.94]	2019
REWIND	205	4949	212	4954	15.9%	0.97 [0.79, 1.18]	2019
Total (95% CI)		**27977**		**28027**	**100.0%**	**0.90 [0.80, 1.00]**	
Total events	1443		1587				

Heterogeneity: Tau² = 0.01; Chi² = 11.33, df = 6 (P = 0.08); I² = 47%

Test for overall effect: Z = 1.97 (P = 0.05)



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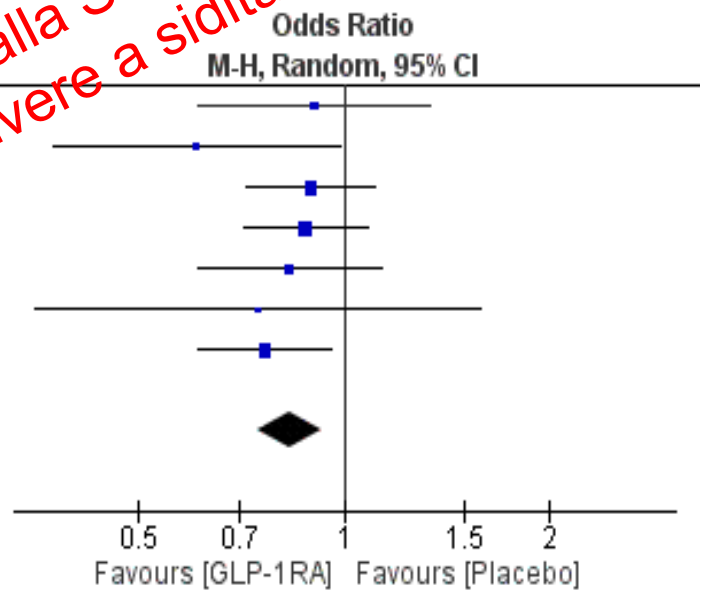
GLP1RA and MACE: nonfatal stroke

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	Year
ELIXA	49	3034	54	3034	7.6%	0.91 [0.61, 1.34]	2015
SUSTAIN-6	27	1648	44	1649	4.9%	0.61 [0.37, 0.99]	2016
LEADER	159	4668	177	4672	24.3%	0.90 [0.72, 1.13]	2016
EXSCEL	169	7356	193	7396	26.5%	0.88 [0.72, 1.08]	2017
HARMONY OUTCOMES	76	4731	91	4732	11.3%	0.83 [0.61, 1.13]	2018
PIONEER-6	12	1591	16	1592	2.0%	0.75 [0.35, 1.59]	2019
REWIND	135	4949	175	4952	23.3%	0.77 [0.61, 0.96]	2019
Total (95% CI)		27977		28027	**100.0%**	**0.83 [0.75, 0.93]**	
Total events	627		750				

Heterogeneity: Tau² = 0.00; Chi² = 3.08, df = 6 (P = 0.80); I² = 0%

Test for overall effect: Z = 3.31 (P = 0.0009)



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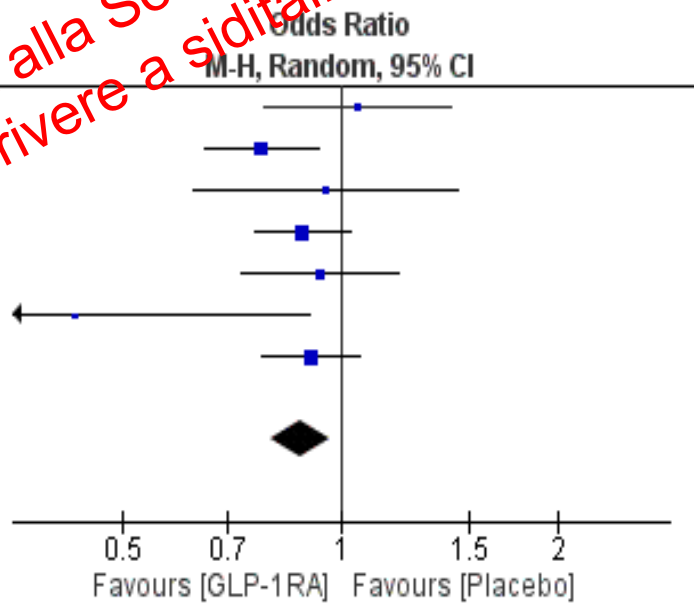
GLP1RA and MACE: cardiovascular mortality

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	Year
ELIXA	93	3034	88	3034	9.2%	1.06 [0.79, 1.42]	2015
LEADER	219	4668	278	4672	20.4%	0.78 [0.65, 0.93]	2016
SUSTAIN-6	44	1648	46	1649	4.9%	0.96 [0.63, 1.45]	2016
EXSCEL	340	7356	383	7396	26.8%	0.89 [0.76, 1.03]	2017
HARMONY OUTCOMES	122	4731	130	4732	13.3%	0.94 [0.73, 1.20]	2018
PIONEER-6	10	1591	23	1592	1.6%	0.43 [0.20, 0.91]	2019
REWIND	317	4949	346	4952	25.1%	0.91 [0.78, 1.07]	2019
Total (95% CI)		27977		28027	100.0%	**0.88 [0.80, 0.97]**	
Total events	1145		1294				

Heterogeneity: Tau² = 0.00; Chi² = 7.35, df = 6 (P = 0.29); I² = 18%

Test for overall effect: Z = 2.56 (P = 0.01)



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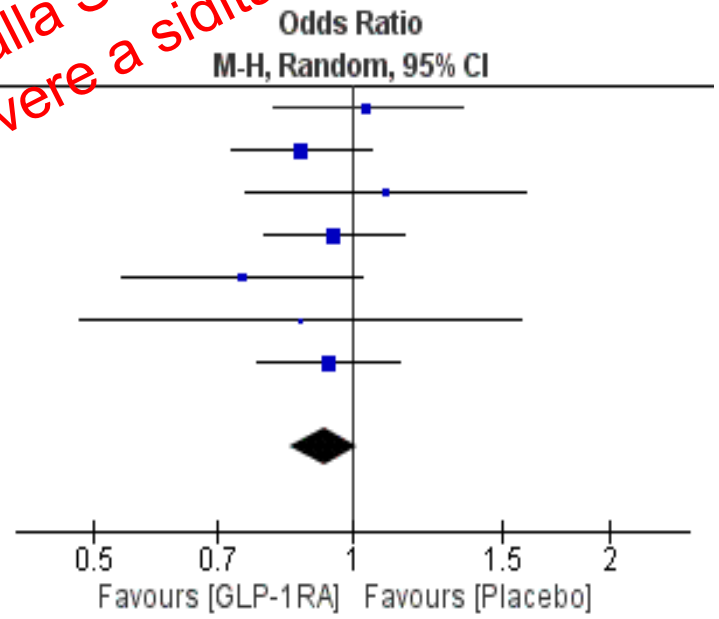
GLP1RA and hospitalization for heart failure

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	Year
ELIXA	127	3034	122	3034	13.0%	1.04 [0.81, 1.34]	2015
LEADER	218	4668	248	4672	24.0%	0.87 [0.73, 1.05]	2016
SUSTAIN-6	59	1648	54	1649	5.9%	1.10 [0.75, 1.60]	2016
EXSCEL	219	7356	231	7396	23.7%	0.96 [0.79, 1.15]	2017
HARMONY OUTCOMES	66	4731	88	4732	8.1%	0.75 [0.54, 1.03]	2018
PIONEER-6	21	1591	24	1592	2.4%	0.87 [0.48, 1.58]	2019
REWIND	213	4949	226	4952	22.8%	0.94 [0.78, 1.14]	2019
Total (95% CI)		27977		28027	100.0%	**0.93 [0.85, 1.02]**	
Total events	923		993				

Heterogeneity: Tau² = 0.00; Chi² = 3.33, df = 6 (P = 0.70); I² = 0%

Test for overall effect: Z = 1.59 (P = 0.11)



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GLP1RA and MACE

Metanalysis of RCTs>52 wk with CV endpoint

Certainty assessment							Summary of findings				
Number of participants (studies)	Bias risk	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect, OR (95% CI)	Anticipated absolute effects	
							With placebo	With GLP-1RA		Risk with placebo	Risk difference with GLP-1RAs
MACE											
56 004 (seven RCTs)	Not serious	Not serious	Not serious	Not serious	None	⨁⨁⨁⨁ high	3309/28027 (11.8)	2937/27977 (10.5)	0.87 (0.81 to 0.93)	118 per 1.000	14 fewer per 1.000 (from 20 fewer to seven fewer)
Non-fatal myocardial infarction											
56 004 (seven RCTs)	Not serious	Serious[a]	Not serious	Serious[b]	none	⨁⨁◯◯ low	1587/28027 (5.7)	1443/27977 (5.2)	0.9 (0.8 to 1.0)	57 per 1.000	Five fewer per 1.000 (from 11 fewer to 0 fewer)
Non-fatal stroke											
56 004 (seven RCTs)	Not serious	Not serious	Not serious	Not serious	None	⨁⨁⨁⨁ high	750/28027 (2.7)	627/27977 (2.2)	0.83 (0.75 to 0.93)	27 per 1.000	Four fewer per 1.000 (from seven fewer to two fewer)
Cardiovascular mortality											
56 004 (seven RCTs)	Not serious	Not serious	Not serious	Not serious	None	⨁⨁⨁⨁ high	1294/28027 (4.6)	1145/27977 (4.1)	0.88 (0.80 to 0.97)	46 per 1.000	Five fewer per 1.000 (from nine fewer to one fewer)

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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 effect on stroke is wider than that on myocardial infarction
- 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)