UNIVERSITÀ DEGLI STUDI FIRENZE

BREAKING NEWS:
Le terapie innovative per il diabete

Edoardo Mannucci

Frascati, 11 gennaio 2020

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.***

SGLT-2i: effects on MACE

A meta-analysis of CVOTs

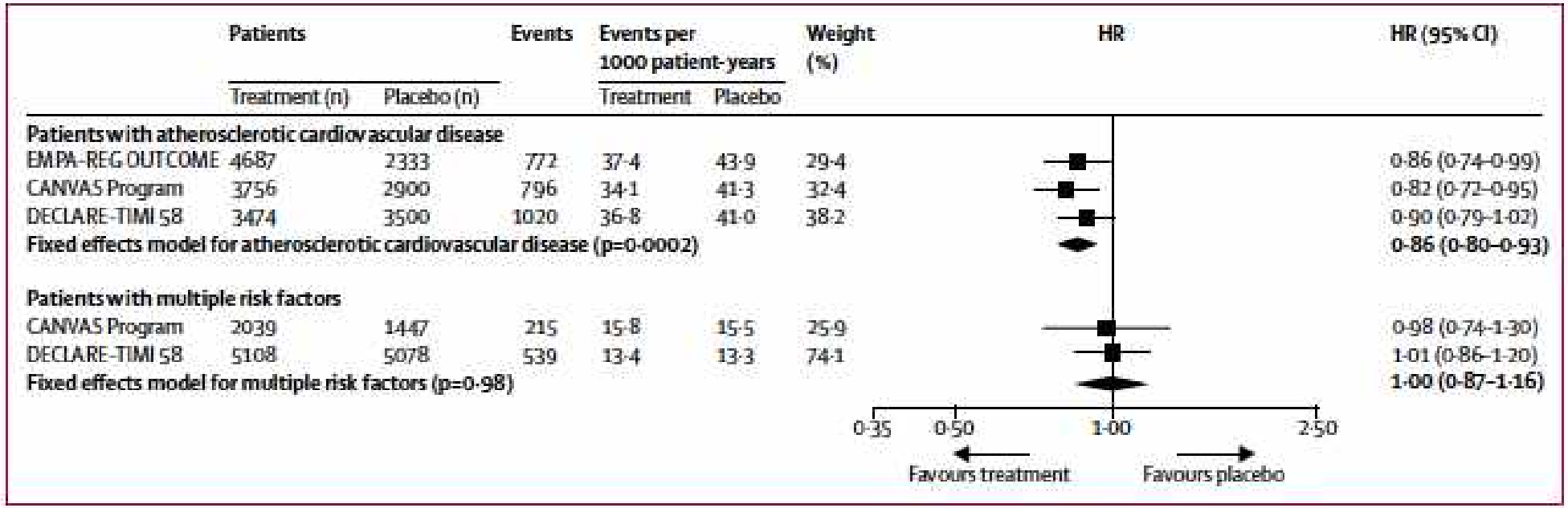
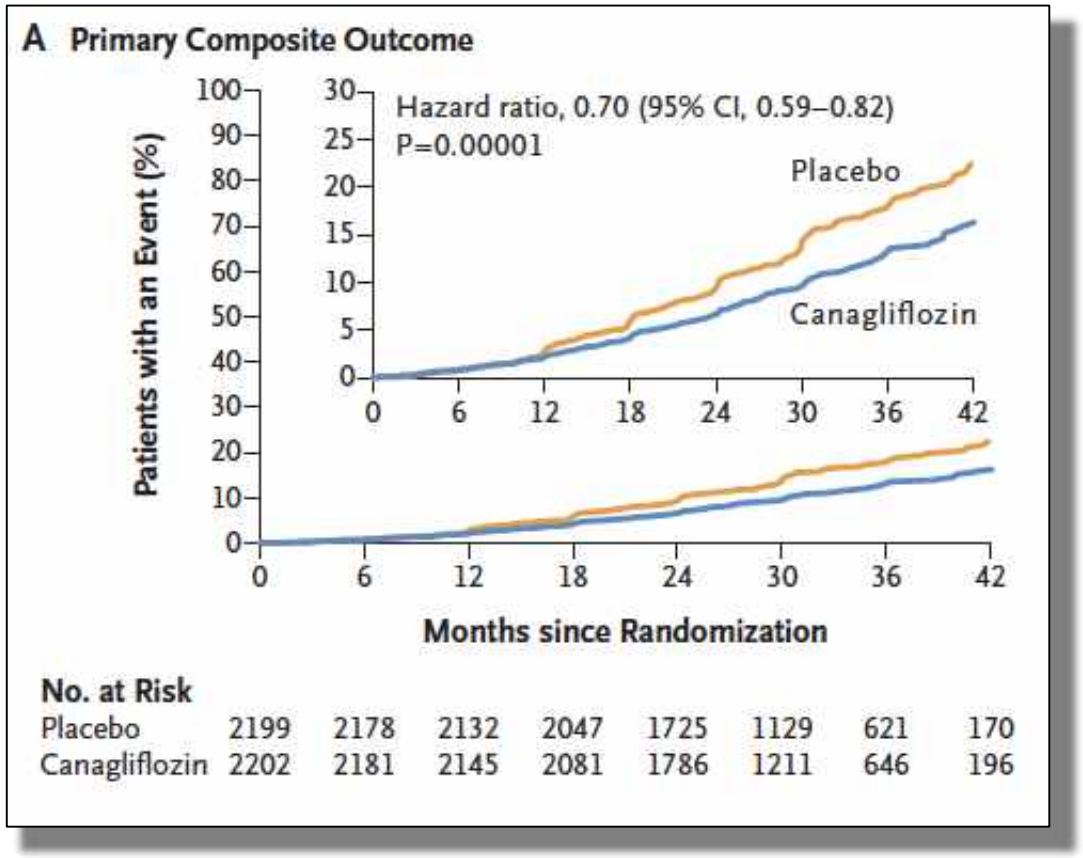


Figure 1: Meta-analysis of SGLT2i trials on the composite of myocardial infarction, stroke, and cardiovascular death (major adverse cardiovascular events) stratified by the presence of established atherosclerotic cardiovascular disease

Zelniker TA et al. *Lancet* 393: 31–39, 2019

Canagliflozin: effect on diabetic nephropathy

Results of the CREDENCE trial



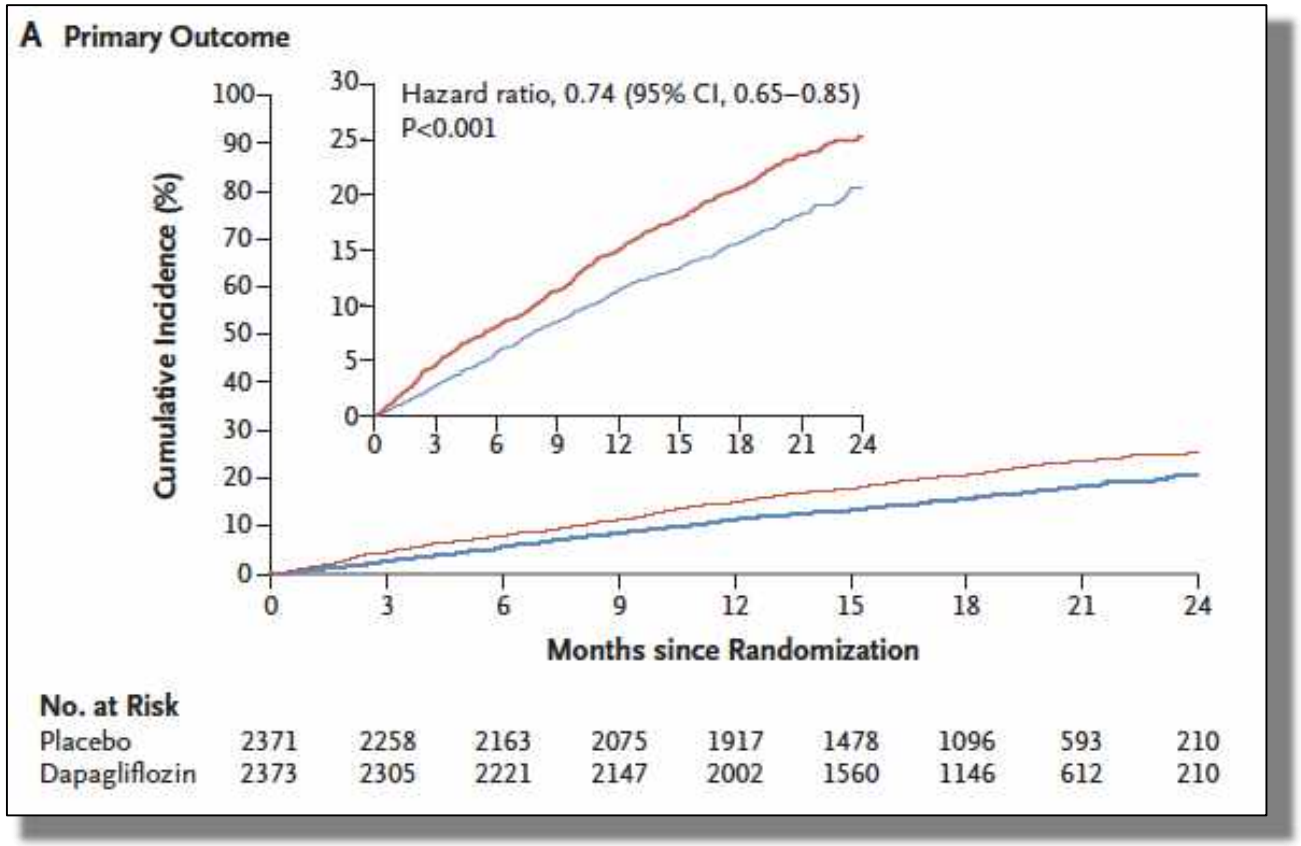
Principal endpoint:
Composite renal endpoint (doubling of creatinine, end-stage renal disease, and CV or renal death)

4,401 T2DM patients with albuminuria and eGFR 30-90 ml/min
Follow-up: 2.6 y

Perkovic V et al. *N Engl J Med* 380:2295-306, 2019

Dapagliflozin: effect on heart failure

Results of the DAPA-HF trial



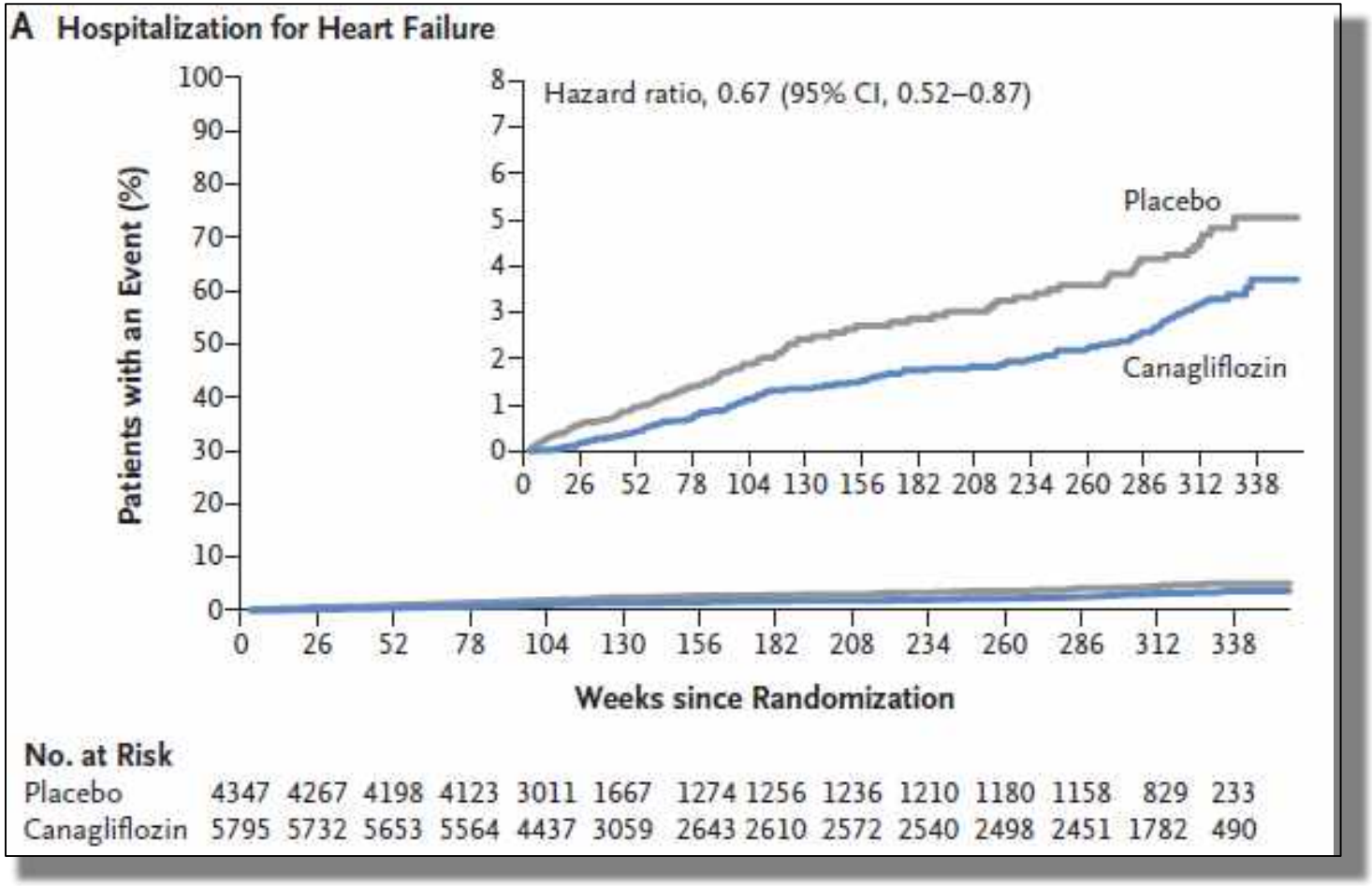
Principal endpoint:
Composite of hospitalization for heart failure and CV death

4,744 patients with heart failure (NYHA class II-IV) and EF<0.40
(with diabetes: 41.8%)
Follow-up: 18.2 months

McMurray JJV et al. *N Engl J Med* 381:1995-2008, 2019

Canagliflozin: effect on heart failure

Results of the CANVAS and CANVAS-R trial



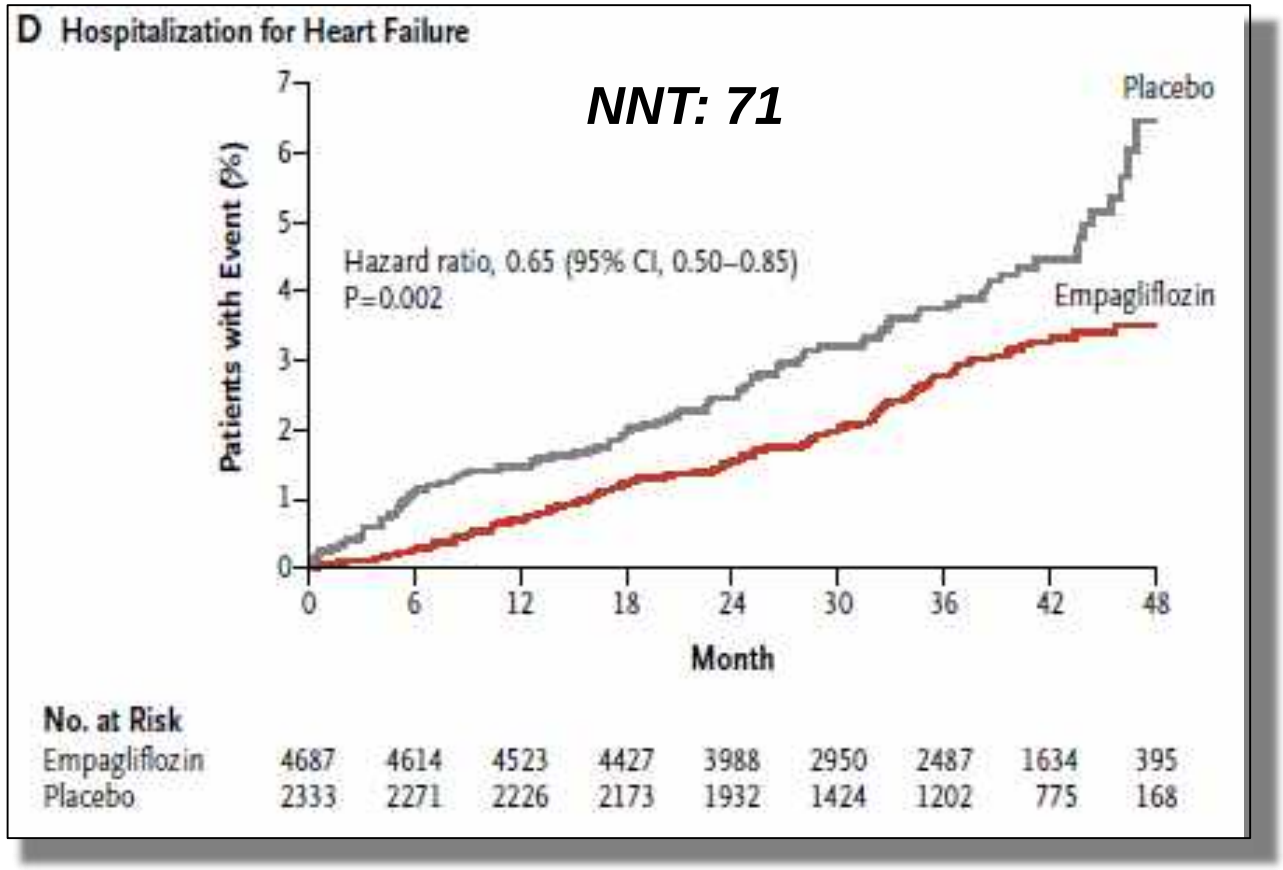
Principal endpoint:
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

10,142 T2DM patients with prior CVD or multiple risk factors, Canagliflozin vs placebo
Follow-up: 3.6 y

Neal et al. *N Engl J Med* 377: 644-57, 2017

Empagliflozin: effect on heart failure

Results of the EMPAREG-OUTCOME trial



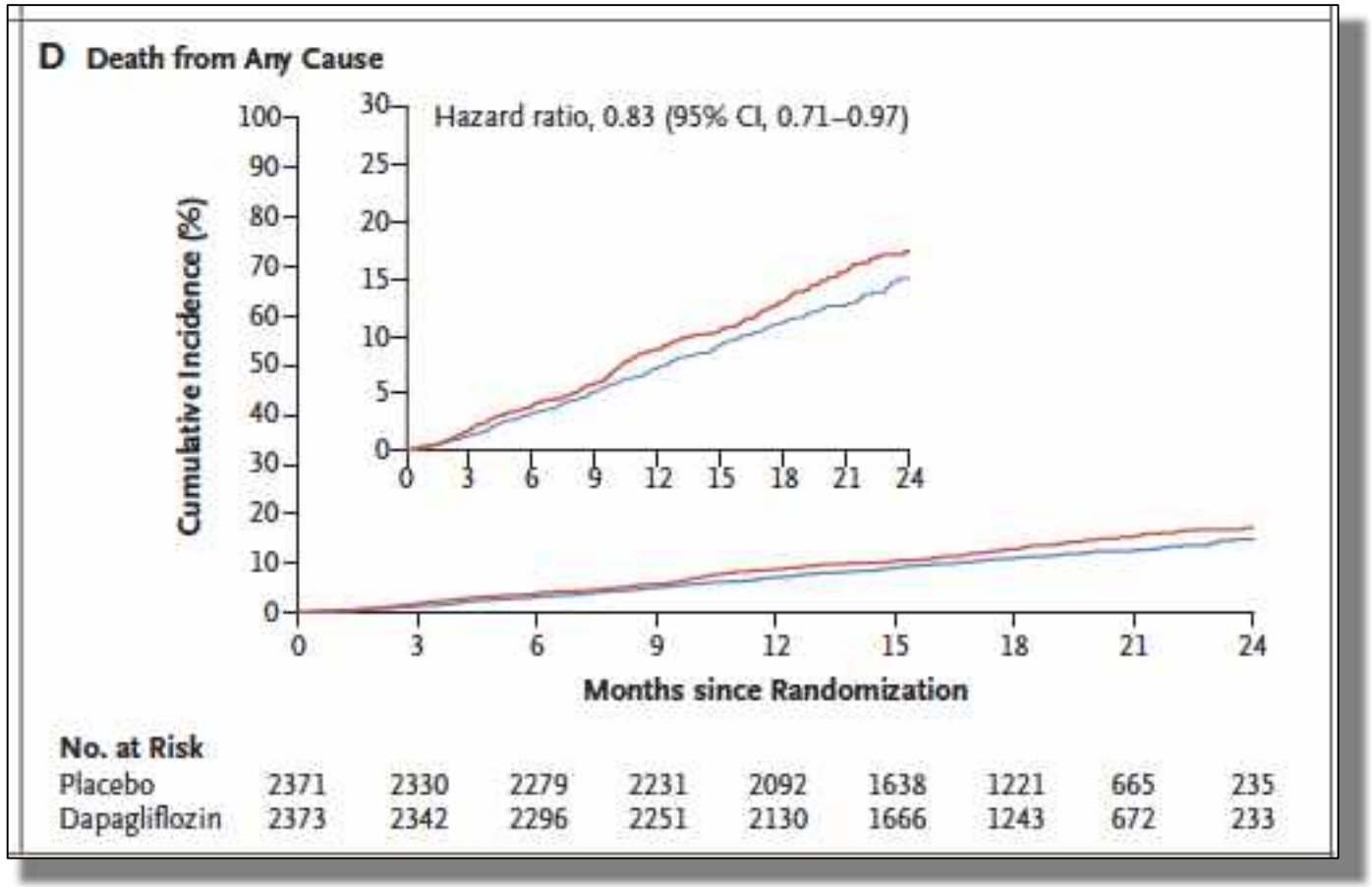
Principal endpoint:
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

9,340 T2DM patients with prior CVD, Empagliflozin vs placebo
Follow-up: 3 y

Zinman B et al. *N Engl J Med* 373: 2117-28, 2015

Dapagliflozin: effect on mortality

Results of the DAPA-HF trial



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Composite of hospitalization for heart failure and CV death

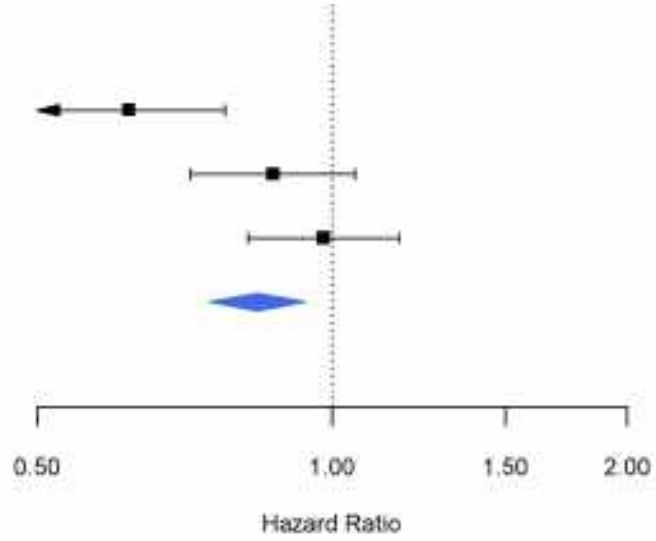
4,744 patients with heart failure (NYHA class II-IV) and EF<0.40 (with diabetes: 41.8%)
Follow-up: 18.2 months

McMurray JJV et al. *N Engl J Med* 381:1995-2008, 2019

SGLT-2i: effects on cardiovascular mortality

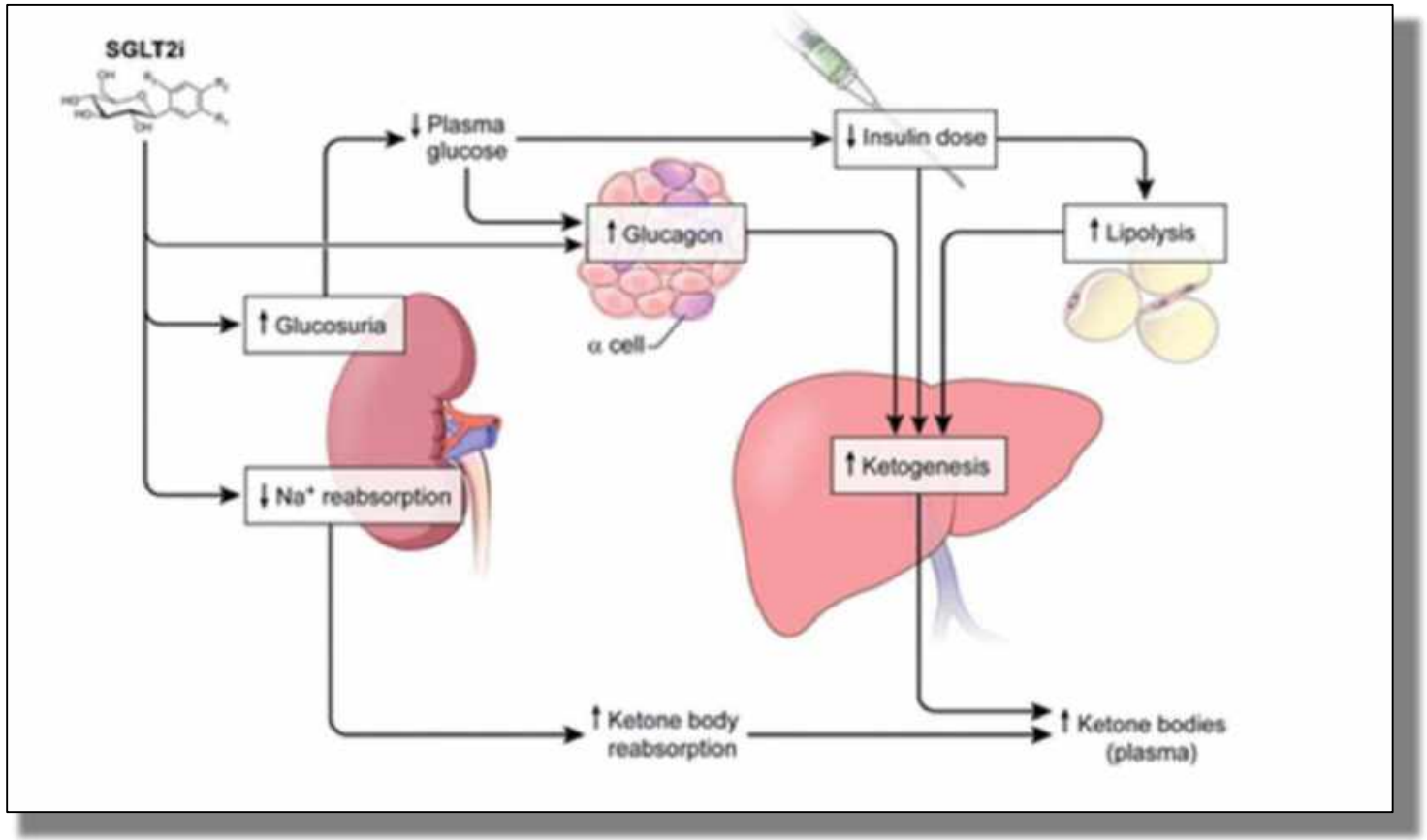
A meta-analysis of CVOTs

Trials	Patients	Events	Treatment Events per 100 ptyrs	Placebo Events per 100 ptyrs	Weights	HR [95% CI]
SGLT2i						
EMPA-REG OUTCOME	7020	309	1.2	2.0	25.1	0.62 [0.49, 0.77]
CANVAS Program	10142	453	1.2	1.3	34.3	0.87 [0.72, 1.06]
DECLARE-TIMI 58	17160	494	0.7	0.7	40.6	0.98 [0.82, 1.17]
Fixed Effects for CV Death (P-value=0.002)						0.84 [0.75, 0.94]



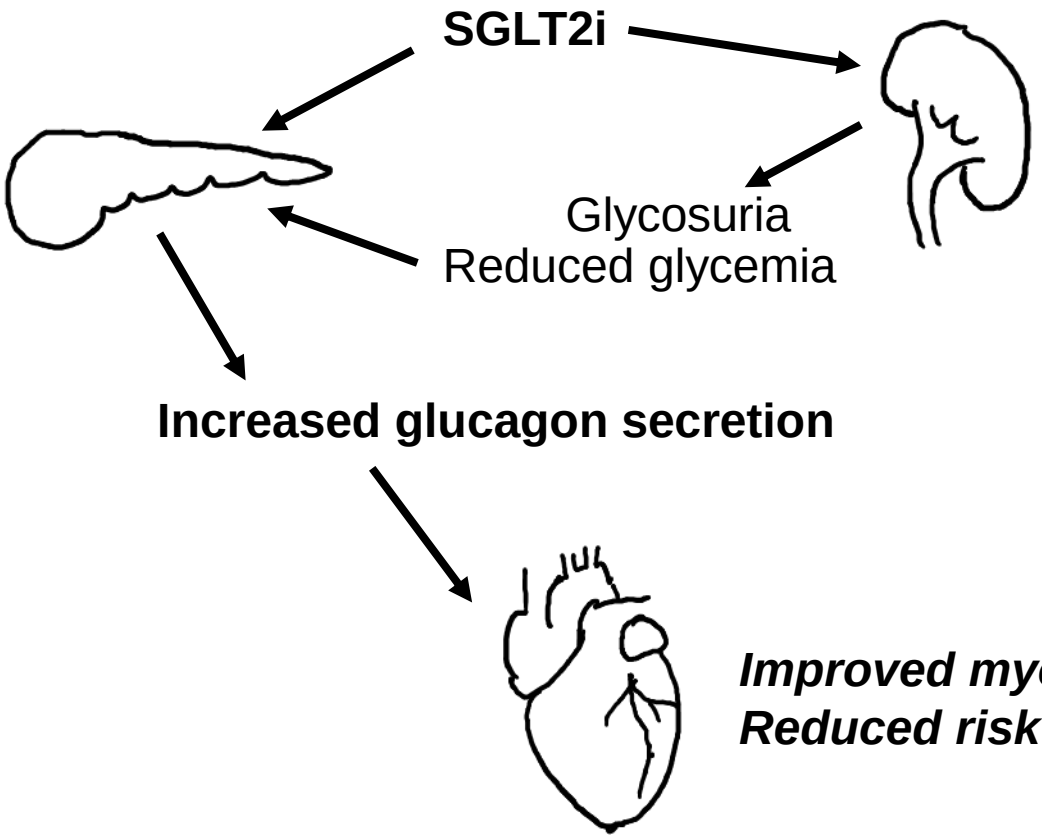
Zelniker TA et al. *Circulation* 23;139:2022-31, 2019

SGLT2i and CV risk: the «substrate shift» hypothesis



Taylor SI et al. *J Clin Endocrinol Metab* 100: 2849-52, 2015

SGLT2i and HF: the «glucagon» hypothesis

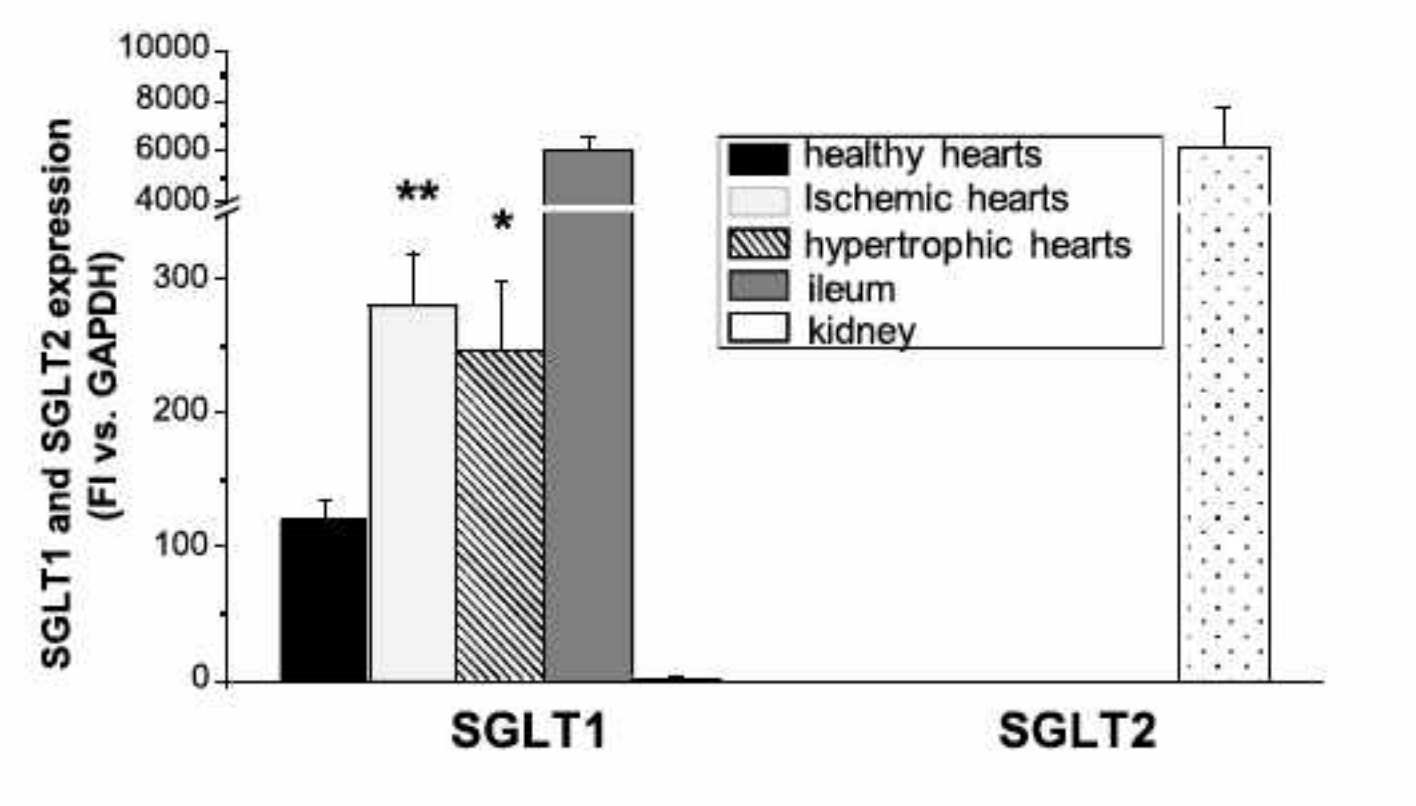


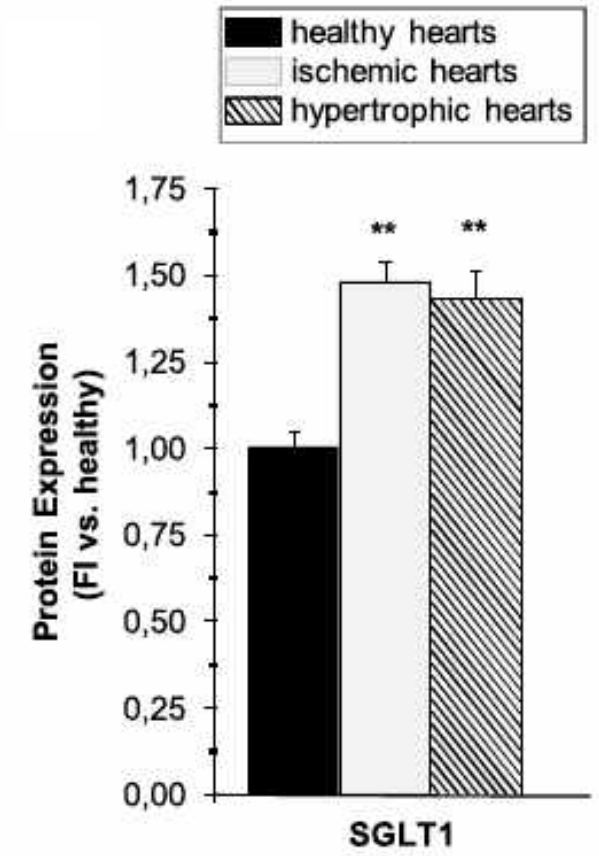
Improved myocardial function
Reduced risk of arrhythmia

Ceriello A, Genovese S, Mannucci E, Gronda E. *Lancet Diabetes Endocrinol* 3:92, 2015

Effect of ischemia on myocardial SGLT-1 expression

Samples of human hearts

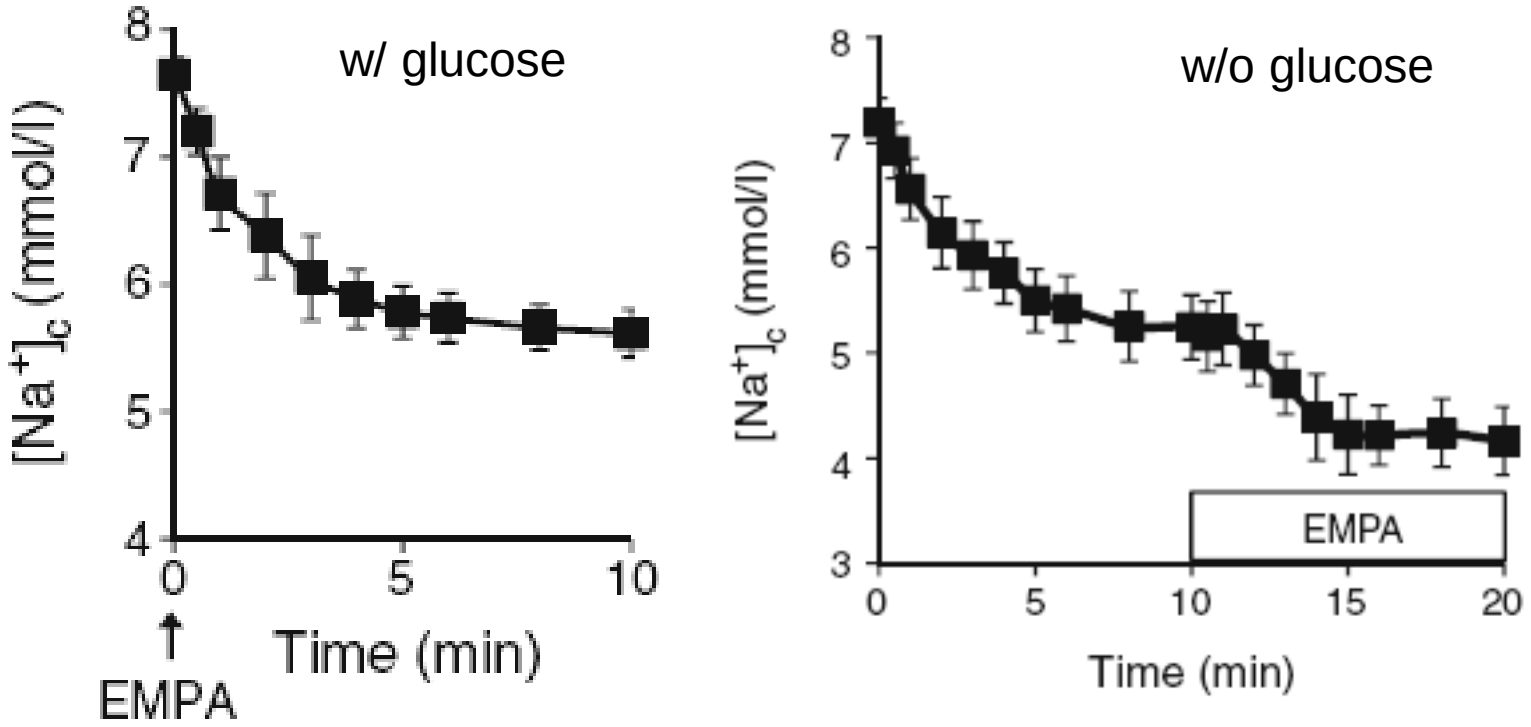




Di Franco A et al., *Int J Cardiol* 243:86-90, 2017

Effect of empagliflozin on intracellular Na

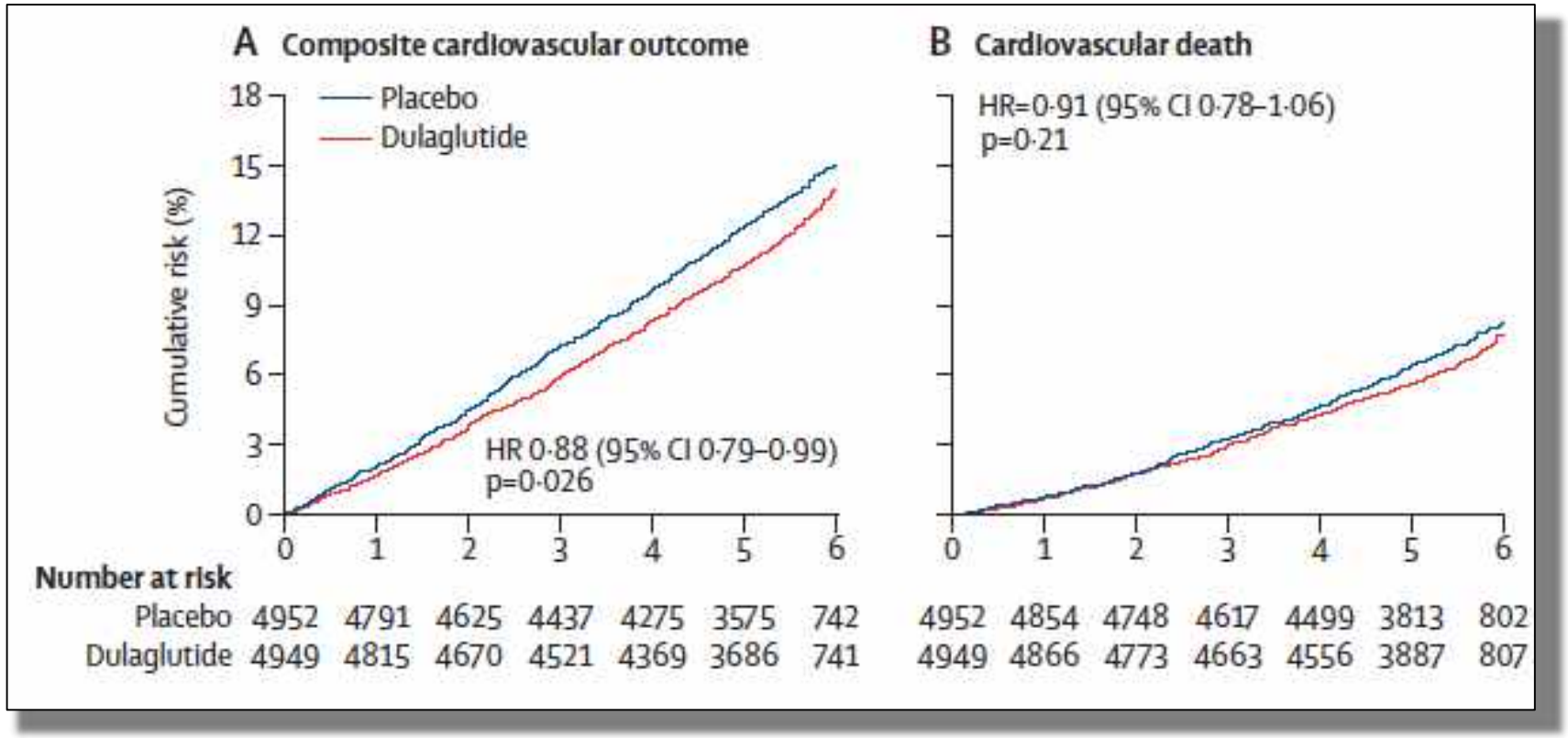
Isolated myocardiocytes from healthy rats



Baartscheer A et al. *Diabetologia* 2017; 50:568-73

Dulaglutide: effect on MACE

Results of the REWIND trial



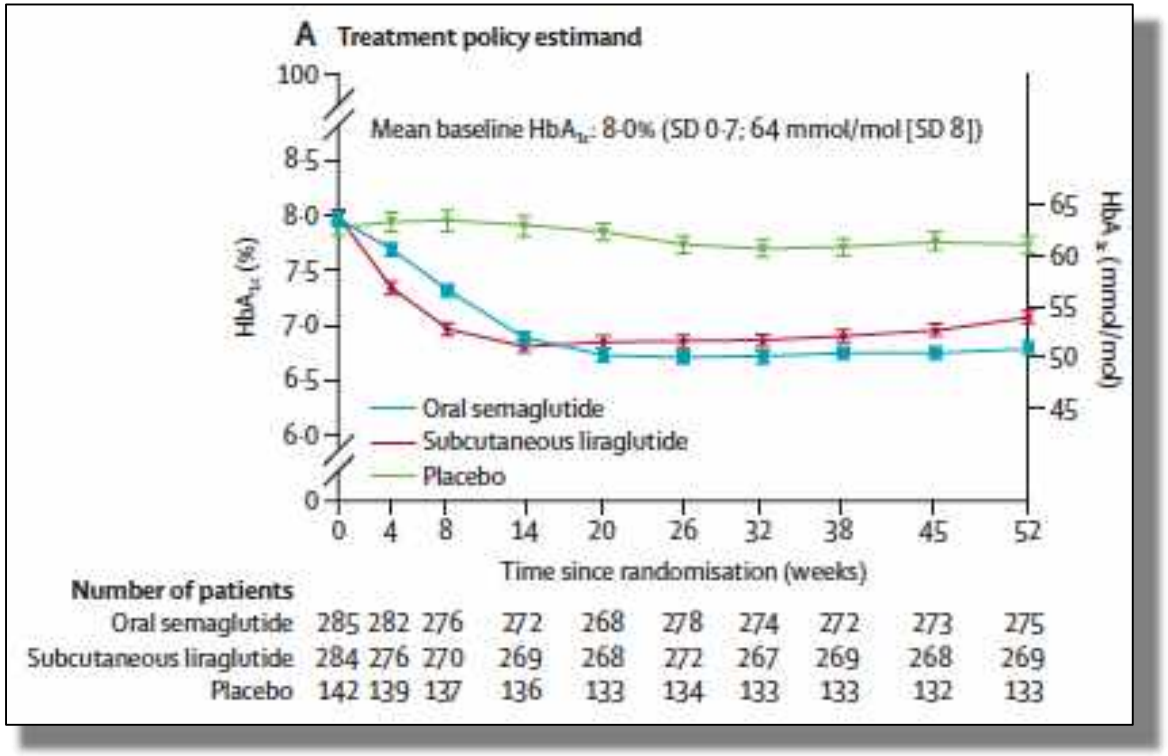
Principal endpoint:
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

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 HbA1c

Results of the PIONEER-4 trial



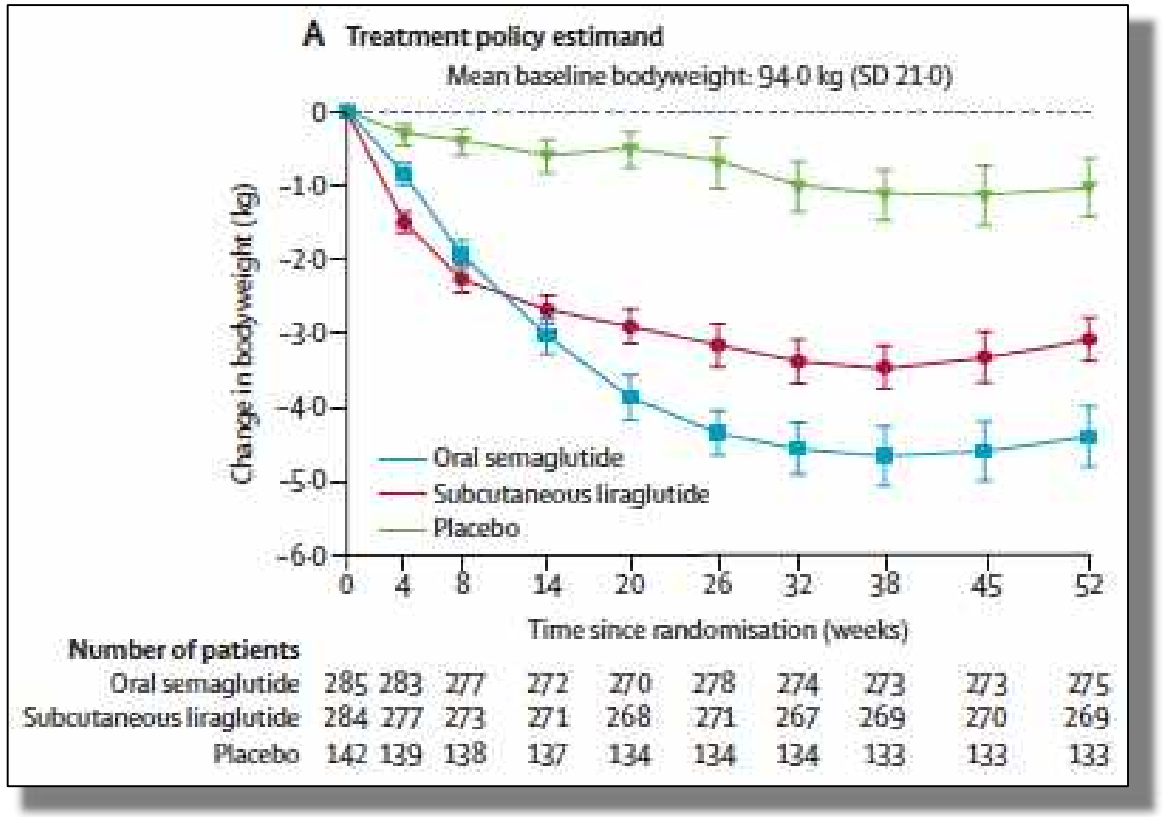
Principal endpoint:
HbA1c at 26 weeks

711 T2DM patients inadequately controlled with metformin
Oral semaglutide 8 mg, liraglutide 1.8 mg, or placebo.
Follow-up: 52 y

Pratley R et al. *Lancet* 394:39-50, 2019

Oral semaglutide: effect on body weight

Results of the PIONEER-4 trial



Principal endpoint:
HbA1c at 26 weeks

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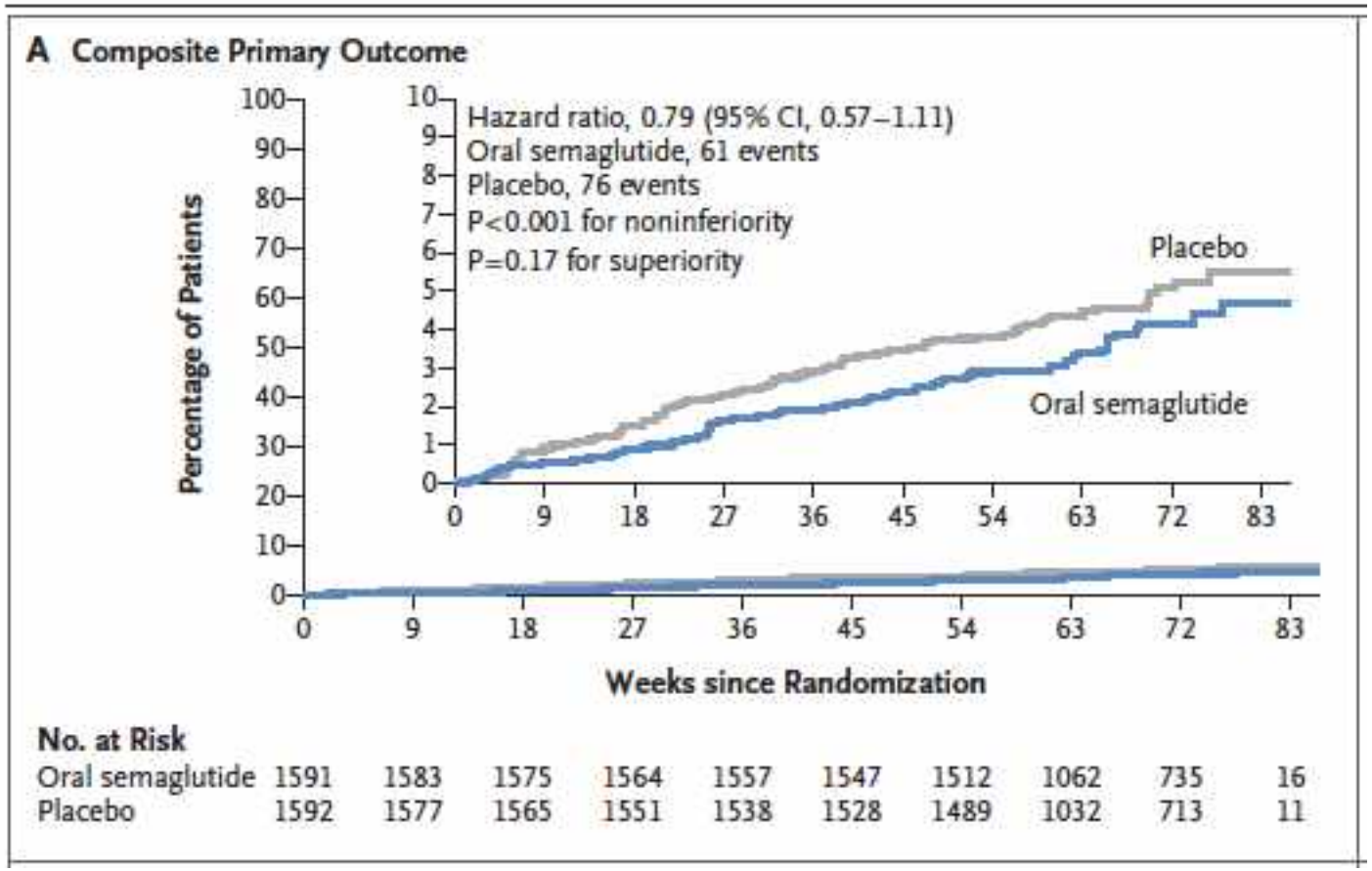
Oral semaglutide 8 mg, liraglutide 1.8 mg, or placebo.
Follow-up: 52 y

Pratley R et al. *Lancet* 394:39-50, 2019

Oral semaglutide: effect on MACE

Results of the PIONEER-6 trial



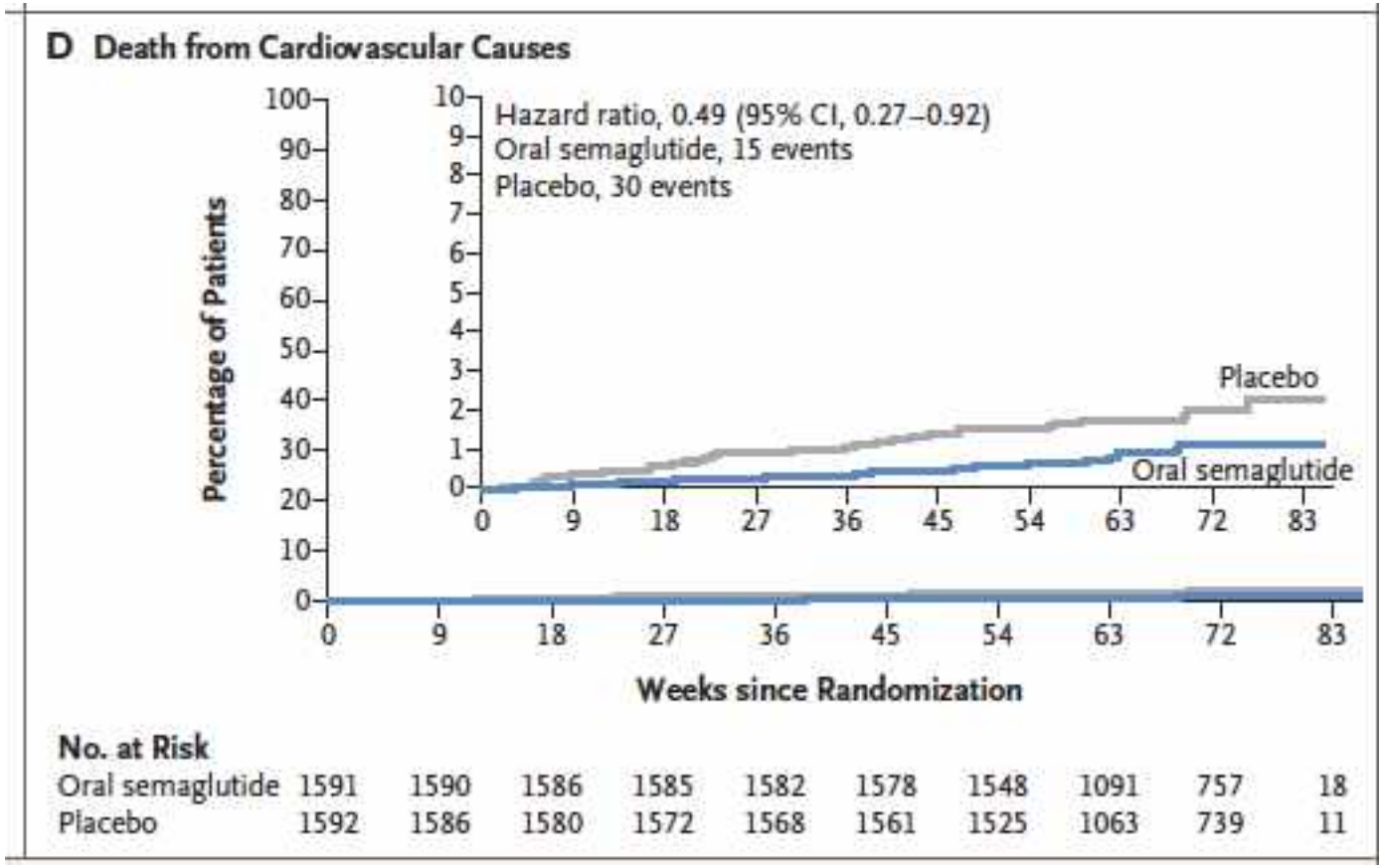
Principal endpoint:
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

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

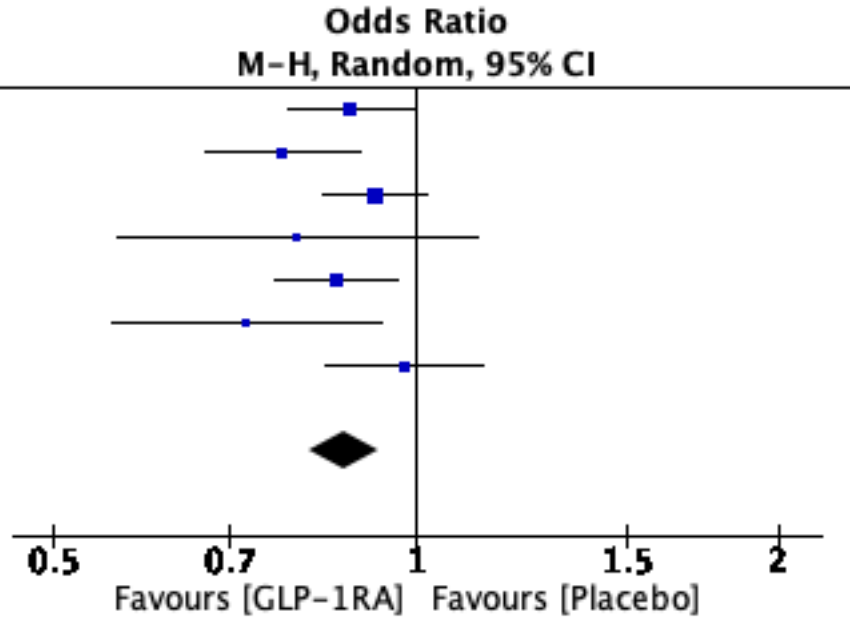
GLP1RA: effects on cardiovascular events

Metanalysis of RCTs>52 wk with CV endpoint

	GLP-1RA		Placebo			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	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

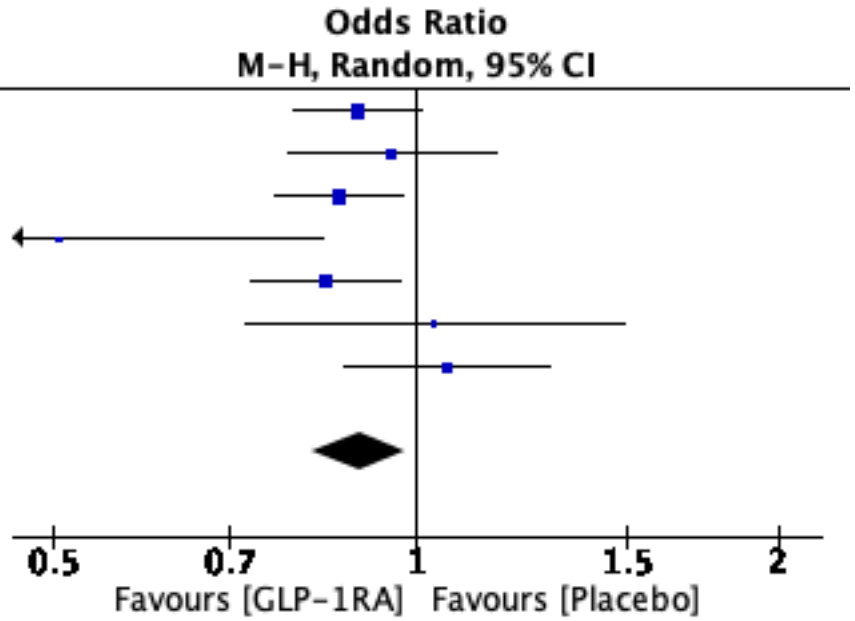
GLP1RA: effects on all-cause mortality

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 [0.76, 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		2144			

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 9.93$, $df = 6$ ($P = 0.13$); $I^2 = 40\%$

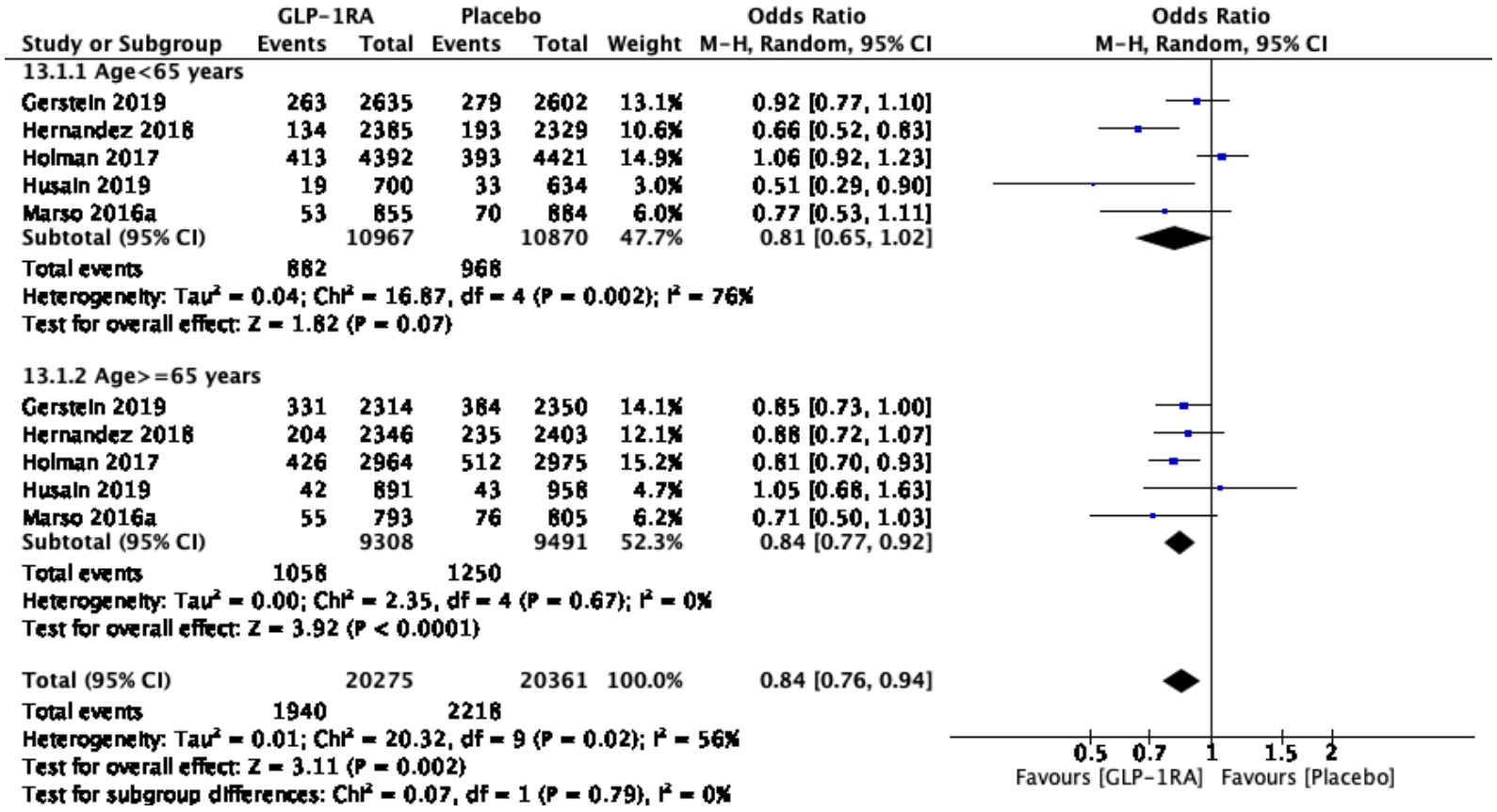
Test for overall effect: $Z = 2.37$ ($P = 0.02$)



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

GLP1RA and MACE: effect of age

Metanalysis of RCTs>52 wk with CV endpoint

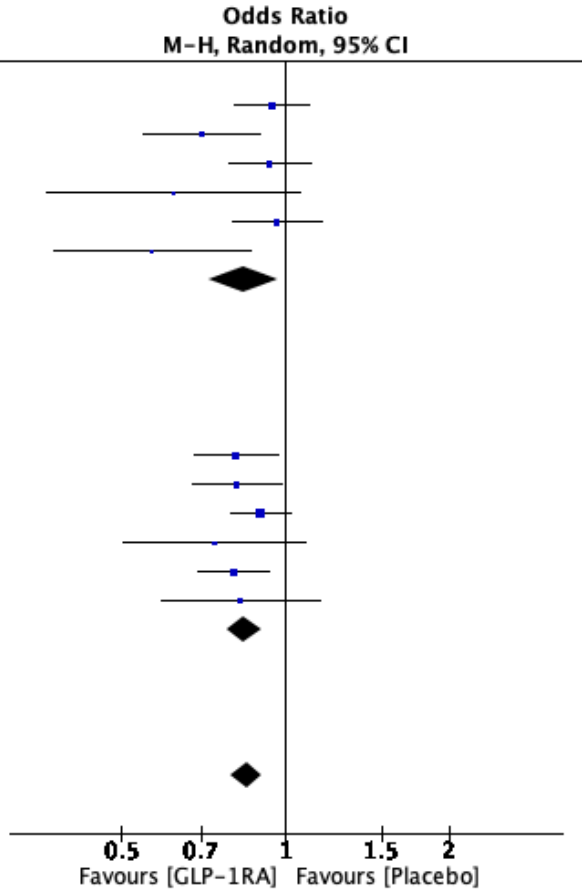


Mannucci E et al al. *Diabetes Obes Metab* 2019

GLP1RA and MACE: effect of obesity

Metanalysis of RCTs>52 wk with CV endpoint

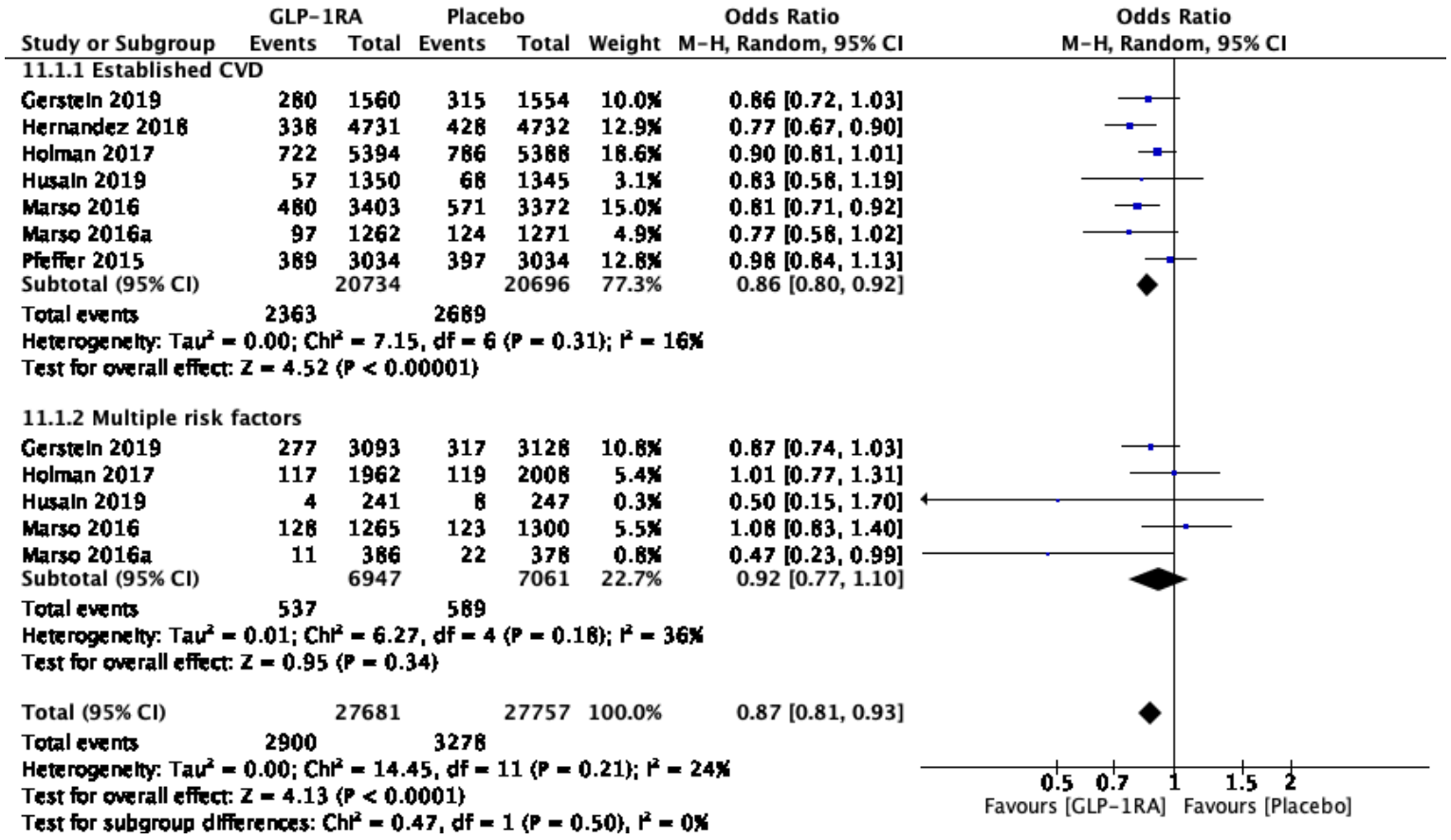
Study or Subgroup	GLP-1RA Events	GLP-1RA Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
14.1.1 <= 30 Kg/m2						
Gerstein 2019	340	2667	355	2650	12.3%	0.94 [0.81, 1.11]
Hernandez 2018	116	1788	164	1825	6.2%	0.70 [0.55, 0.90]
Holman 2017	275	2659	297	2704	10.9%	0.93 [0.79, 1.11]
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: Tau² = 0.02; Chi² = 11.15, df = 5 (P = 0.05); I² = 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	2886	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: Tau² = 0.00; Chi² = 2.24, df = 5 (P = 0.81); I² = 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: Tau² = 0.00; Chi² = 14.07, df = 11 (P = 0.23); I² = 22%						
Test for overall effect: Z = 4.82 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² = 0%						



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

GLP1RA and MACE: primary vs secondary prevention

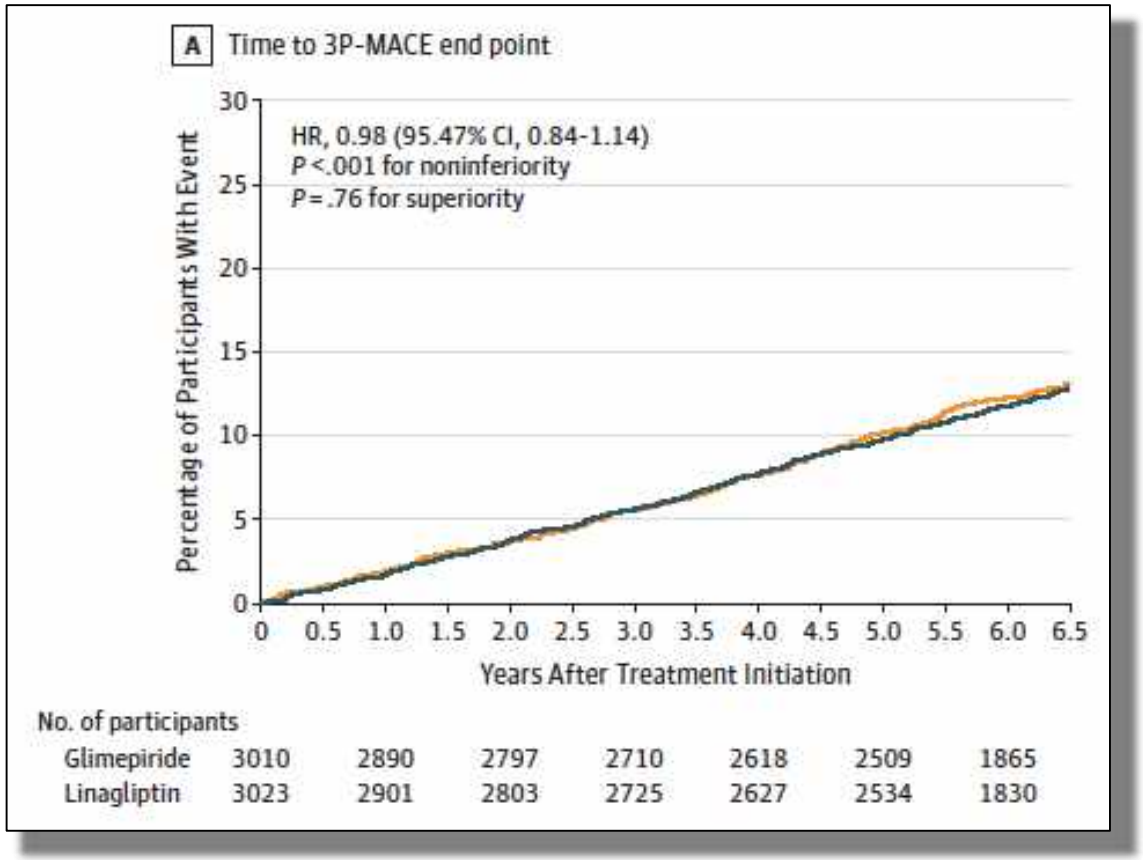
Metanalysis of RCTs>52 wk with CV endpoint



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

Linagliptin: effect on MACE

Results of the CAROLINA 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

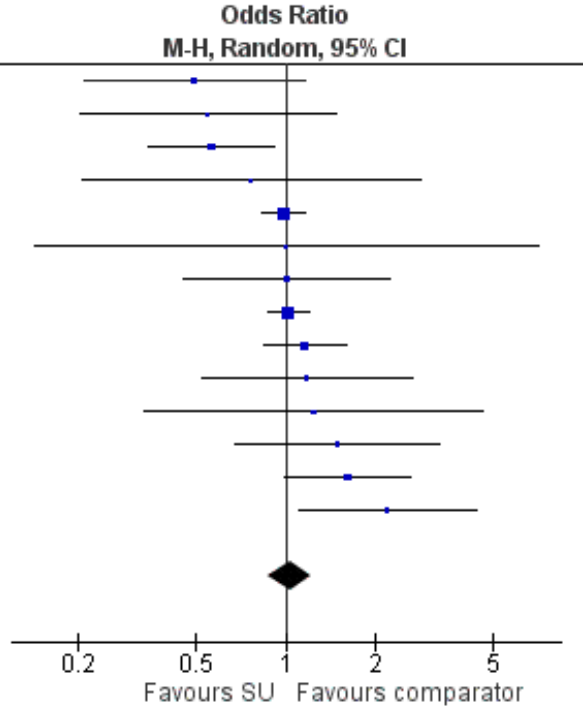
Sulfonylureas: effect on MACE

Metanalysis of RCTs

Study or Subgroup	SU Events	SU Total	Comparator Events	Comparator Total	Weight	Odds Ratio M-H, Random, 95% CI
Foley 2009	8	546	16	546	3.3%	0.49 [0.21, 1.16]
Ferrannini 2009	6	1393	11	1396	2.5%	0.54 [0.20, 1.48]
ADOPT	26	1441	46	1454	8.3%	0.56 [0.35, 0.91]
Filozof 2012	4	513	5	494	1.5%	0.77 [0.21, 2.88]
UKPDS	299	1234	443	1807	21.9%	0.98 [0.83, 1.17]
CHICAGO	2	228	2	230	0.7%	1.01 [0.14, 7.22]
Giles 2010	13	149	13	151	3.7%	1.01 [0.45, 2.27]
CAROLINA	362	3010	356	3023	22.7%	1.02 [0.88, 1.20]
TOSCA.IT	83	1493	74	1535	13.7%	1.16 [0.84, 1.60]
PERISCOPE	13	273	11	270	3.6%	1.18 [0.52, 2.68]
Goke 2013	5	430	4	428	1.5%	1.25 [0.33, 4.68]
Del Prato 2014	11	874	14	1665	3.8%	1.50 [0.68, 3.33]
SPREAD-DIMCAD	52	148	39	156	8.0%	1.63 [0.99, 2.67]
Gallwitz 2012	26	775	12	775	4.8%	2.21 [1.11, 4.41]
Total (95% CI)		**12507**		**13930**	**100.0%**	**1.04 [0.88, 1.22]**
Total events	910		1046			

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 20.33$, df = 13 (P = 0.09); $I^2 = 36\%$

Test for overall effect: Z = 0.41 (P = 0.68)



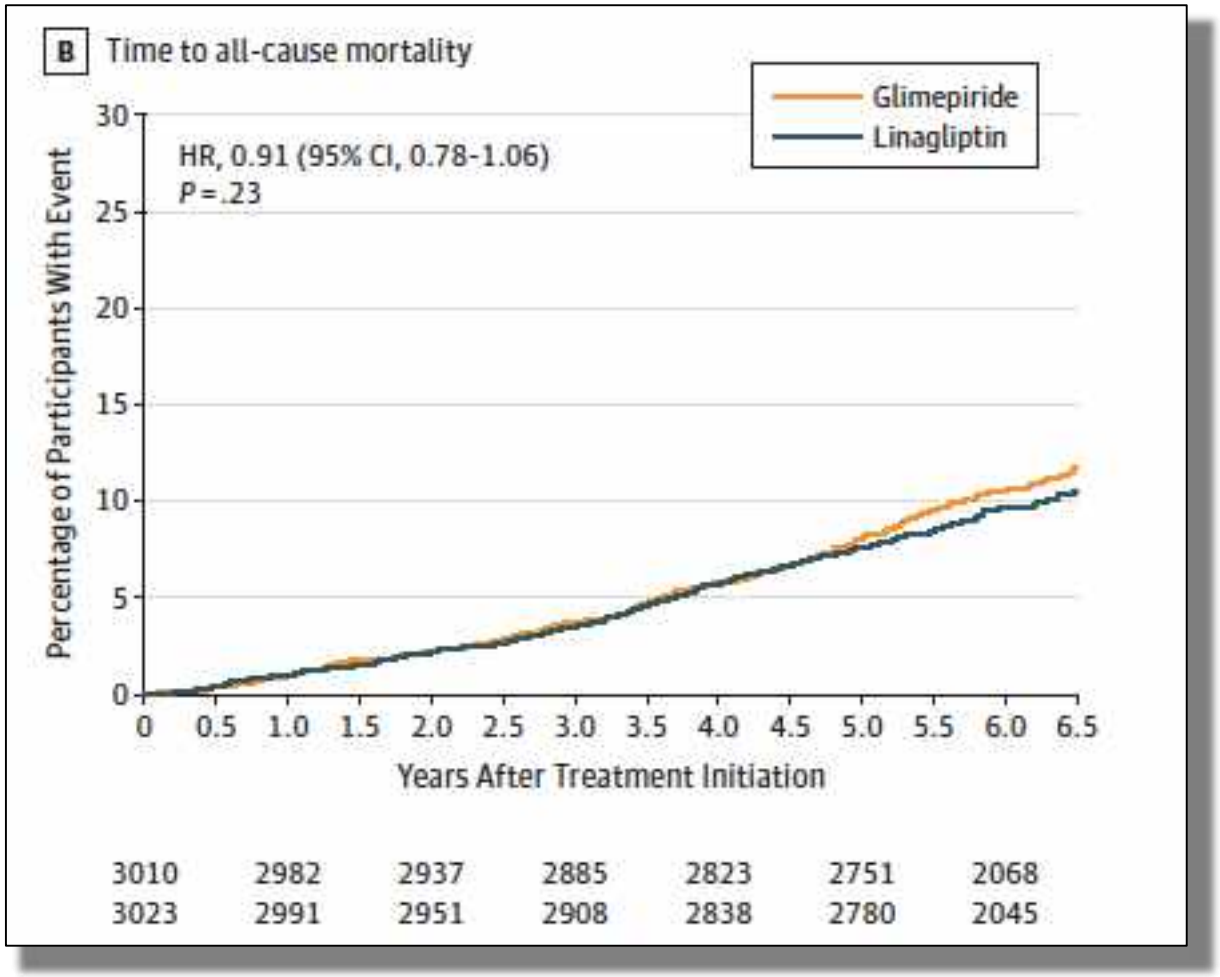
Principal endpoint:
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

Trials >52 wk, >100 pts, comparing SU/glinide with a non-SU/glinide drug, in T2DM, with MACE within primary endpoint or as pre-defined secondary endpoint with adjudication

Mannucci E et al. *Manuscript in preparation*

Linagliptin: effect on mortality

Results of the CAROLINA trial



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Follow-up: 1.3 y

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

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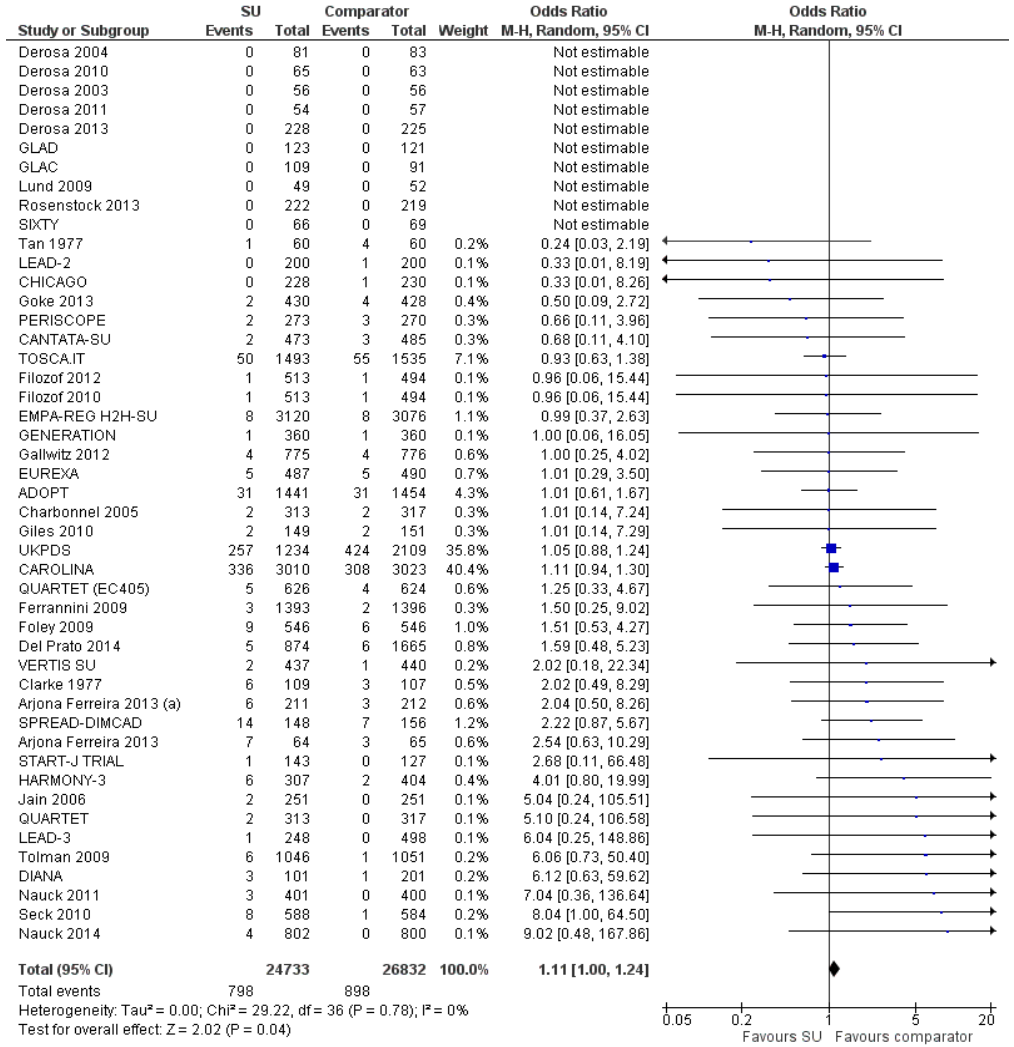
Metanalysis of RCTs



Study or Subgroup	SU Events	SU Total	Comparator Events	Comparator Total	Weight	Odds Ratio M-H, Random, 95% CI
Derosa 2004	0	81	0	83		Not estimable
Derosa 2010	0	65	0	63		Not estimable
Derosa 2003	0	56	0	56		Not estimable
Derosa 2011	0	54	0	57		Not estimable
Derosa 2013	0	228	0	225		Not estimable
GLAD	0	123	0	121		Not estimable
GLAC	0	109	0	91		Not estimable
Lund 2009	0	49	0	52		Not estimable
Rosenstock 2013	0	222	0	219		Not estimable
SIXTY	0	66	0	69		Not estimable
Tan 1977	1	60	4	60	0.2%	0.24 [0.03, 2.19]
LEAD-2	0	200	1	200	0.1%	0.33 [0.01, 8.19]
CHICAGO	0	228	1	230	0.1%	0.33 [0.01, 8.26]
Goke 2013	2	430	4	428	0.4%	0.50 [0.09, 2.72]
PERISCOPE	2	273	3	270	0.3%	0.66 [0.11, 3.96]
CANTATA-SU	2	473	3	485	0.3%	0.68 [0.11, 4.10]
TOSCA.IT	50	1493	55	1535	7.1%	0.93 [0.63, 1.38]
Filozof 2012	1	513	1	494	0.1%	0.96 [0.06, 15.44]
Filozof 2010	1	513	1	494	0.1%	0.96 [0.06, 15.44]
EMPA-REG H2H-SU	8	3120	8	3076	1.1%	0.99 [0.37, 2.63]
GENERATION	1	360	1	360	0.1%	1.00 [0.06, 16.05]
Gallwitz 2012	4	775	4	776	0.6%	1.00 [0.25, 4.02]
EUREXA	5	487	5	490	0.7%	1.01 [0.29, 3.50]
ADOPT	31	1441	31	1454	4.3%	1.01 [0.61, 1.67]
Charbonnel 2005	2	313	2	317	0.3%	1.01 [0.14, 7.24]
Giles 2010	2	149	2	151	0.3%	1.01 [0.14, 7.29]
UKPDS	257	1234	424	2109	35.8%	1.05 [0.88, 1.24]
CAROLINA	336	3010	308	3023	40.4%	1.11 [0.94, 1.30]
QUARTET (EC405)	5	626	4	624	0.6%	1.25 [0.33, 4.67]
Ferrannini 2009	3	1393	2	1396	0.3%	1.50 [0.25, 9.02]
Foley 2009	9	546	6	546	1.0%	1.51 [0.53, 4.27]
Del Prato 2014	5	874	6	1665	0.8%	1.59 [0.48, 5.23]
VERTIS SU	2	437	1	440	0.2%	2.02 [0.18, 22.34]
Clarke 1977	6	109	3	107	0.5%	2.02 [0.49, 8.29]
Arjona Ferreira 2013 (a)	6	211	3	212	0.6%	2.04 [0.50, 8.26]
SPREAD-DIMCAD	14	148	7	156	1.2%	2.22 [0.87, 5.67]
Arjona Ferreira 2013	7	64	3	65	0.6%	2.54 [0.63, 10.29]
START-J TRIAL	1	143	0	127	0.1%	2.68 [0.11, 66.48]
HARMONY-3	6	307	2	404	0.4%	4.01 [0.80, 19.99]
Jain 2006	2	251	0	251	0.1%	5.04 [0.24, 105.51]
QUARTET	2	313	0	317	0.1%	5.10 [0.24, 106.58]
LEAD-3	1	248	0	498	0.1%	6.04 [0.25, 148.86]
Tolman 2009	6	1046	1	1051	0.2%	6.06 [0.73, 50.40]
DIANA	3	101	1	201	0.2%	6.12 [0.63, 59.62]
Nauck 2011	3	401	0	400	0.1%	7.04 [0.36, 136.64]
Seck 2010	8	588	1	584	0.2%	8.04 [1.00, 64.50]
Nauck 2014	4	802	0	800	0.1%	9.02 [0.48, 167.86]
Total (95% CI)		**24733**		**26832**	**100.0%**	**1.11 [1.00, 1.24]**
Total events	798		898			

Heterogeneity: Tau² = 0.00; Chi² = 29.22, df = 36 (P = 0.78); I² = 0%
Test for overall effect: Z = 2.02 (P = 0.04)

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

Trials >52 wk, >100 pts, comparing SU/glinide with a non-SU/glinide drug, in T2DM

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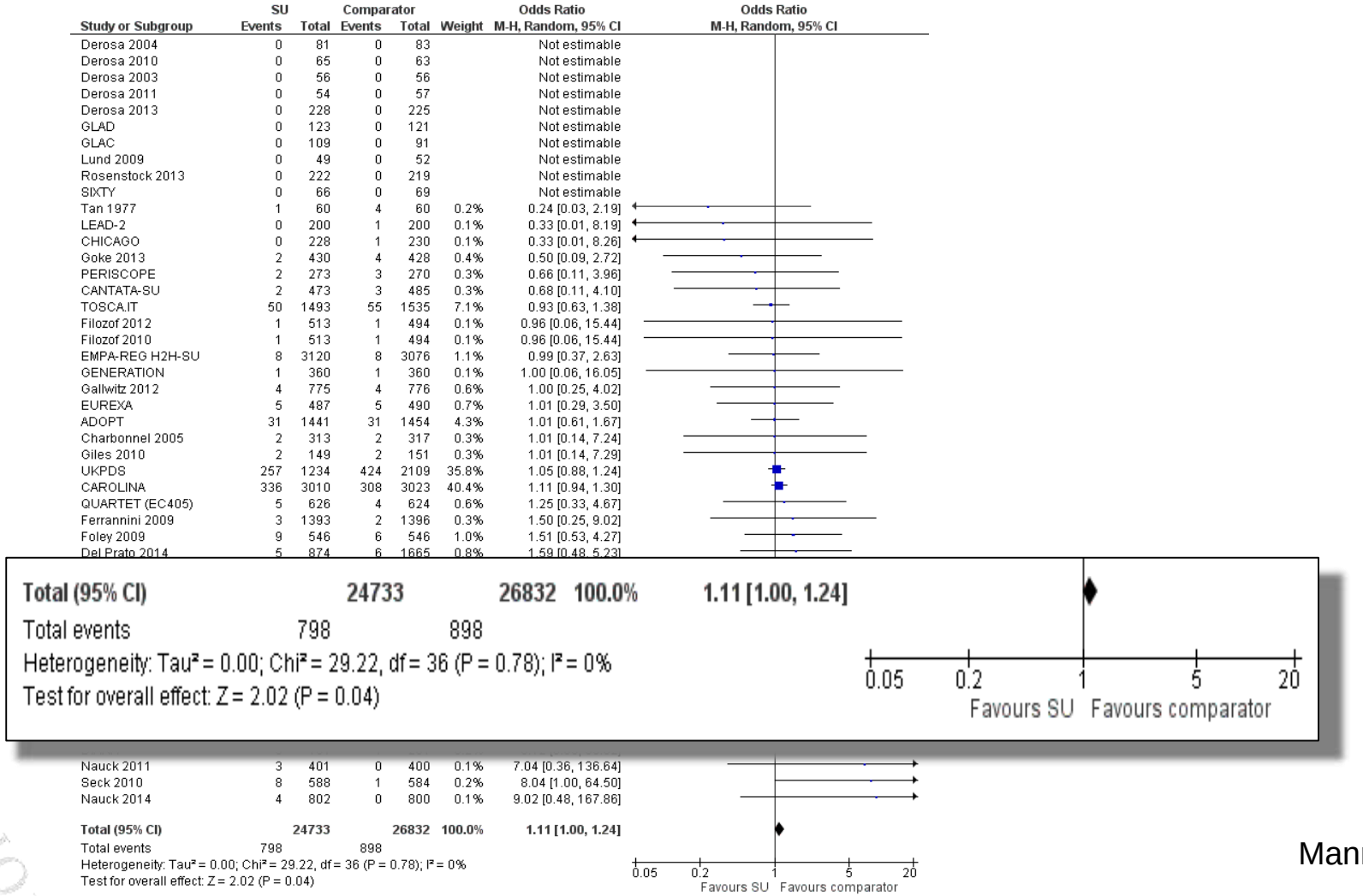
Sulfonylureas: effect on all-cause mortality

Metanalysis of RCTs



Total (95% CI) 24733 26832 100.0% 1.11 [1.00, 1.24]
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Heterogeneity: Tau² = 0.00; Chi² = 29.22, df = 36 (P = 0.78); I² = 0%
Test for overall effect: Z = 2.02 (P = 0.04)
0.05 0.2 1 5 20
Favours SU Favours comparator

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