Overview dei trial di outcome cardiovascolare nel diabete

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DUALITY OF INTEREST DISCLOSURE

Dr Mannucci has received speaking and/or consulting fees from:

Abbott, AstraZeneca, BMS, Boehringer Ingelheim, Eli Lilly, Janssen, Lifescan, Merck, Novartis, Novo Nordisk, Sanofi, Takeda

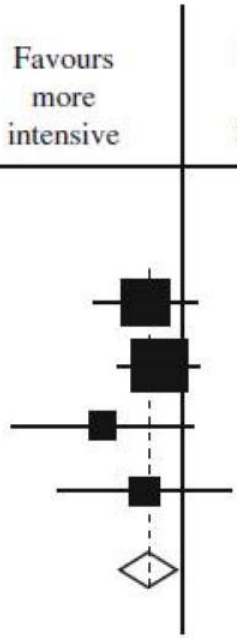
Dr Mannucci and his research unit received research grants from:

AstraZeneca, BMS, Boehringer Ingelheim, Eli Lilly, Janssen, Novartis, Novo Nordisk, Sanofi

Glycemic control and CVD

Meta-analysis of trials on T2DM

Trials	Number of events (annual event rate, %) More intensive	Number of events (annual event rate, %) Less intensive	ΔHbA_{1c} (%)	Hazard ratio (95% CI)
Major cardiovascular events				
ACCORD	352 (2.11)	371 (2.29)	−1.01	0.90 (0.78–1.04)
ADVANCE	557 (2.15)	590 (2.28)	−0.72	0.94 (0.84–1.06)
UKPDS	169 (1.30)	87 (1.60)	−0.66	0.80 (0.62–1.04)
VADT	116 (2.68)	128 (2.98)	−1.16	0.90 (0.70–1.16)
Overall	1,194	1,176	−0.88	0.91 (0.84–0.99) (Q=1.32, p=0.72, I^2=0.0%)



Turnbull et al., *Diabetologia* 2009; 52:2288-98,

Metformin and CVD

UKPDS 34

Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes

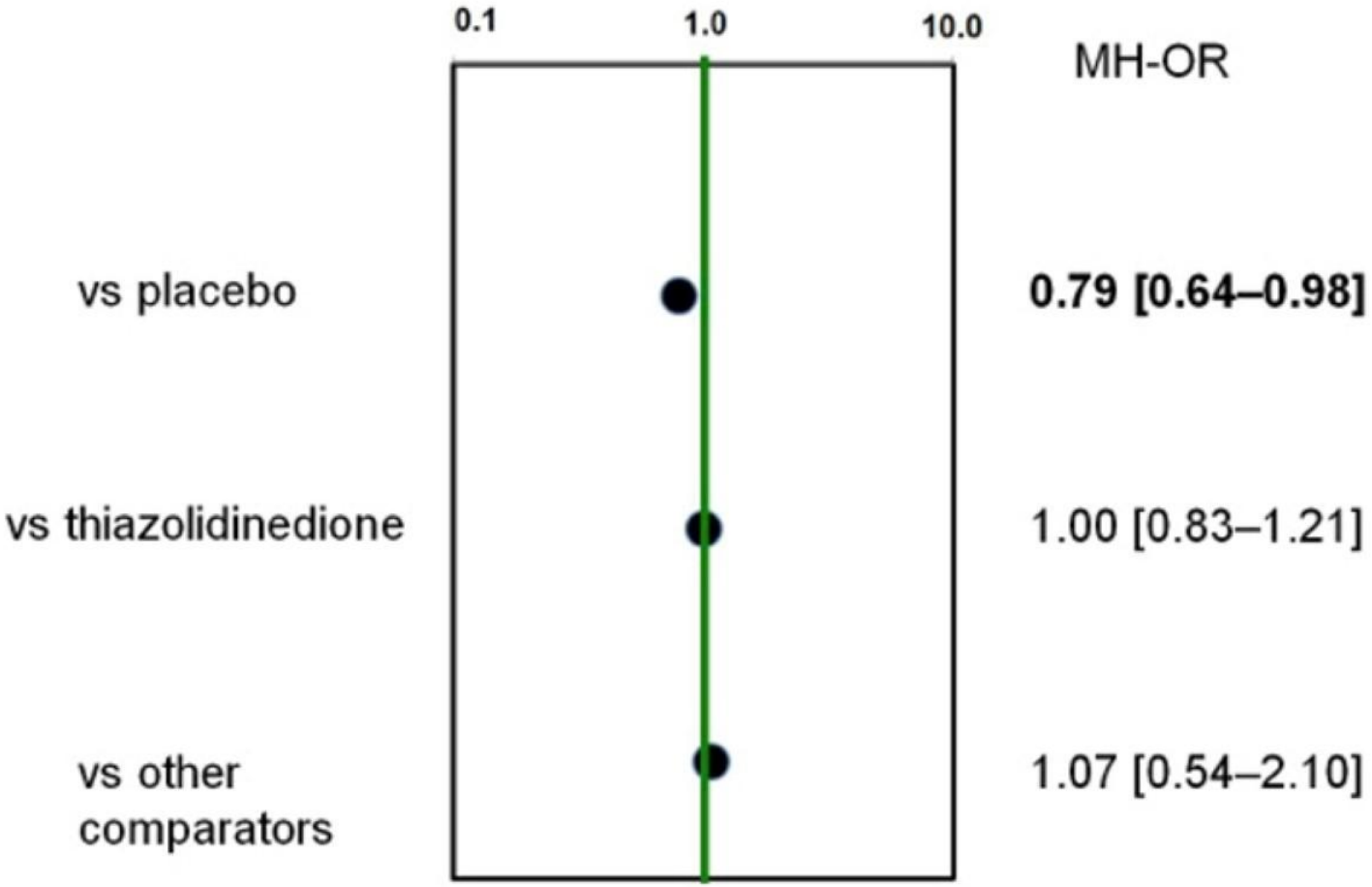
	Metformin (n=342)	Insulin/sulfonylurea (SU) (n=951)	Conventional (n=411)
Absolute risk (events per 1,000 patient-years)			
Myocardial infarction	11.0*	14.4	18.0
Stroke	3.3	6.2†	5.5
All-cause mortality	13.5*†	18.9	20.6

*P<0.05 vs conventional; †P<0.05 vs insulin/SU

UK Prospective Diabetes Group. *Lancet* 1998;352;854–65.

Metformin and MACE

Meta-analysis of available RCTs



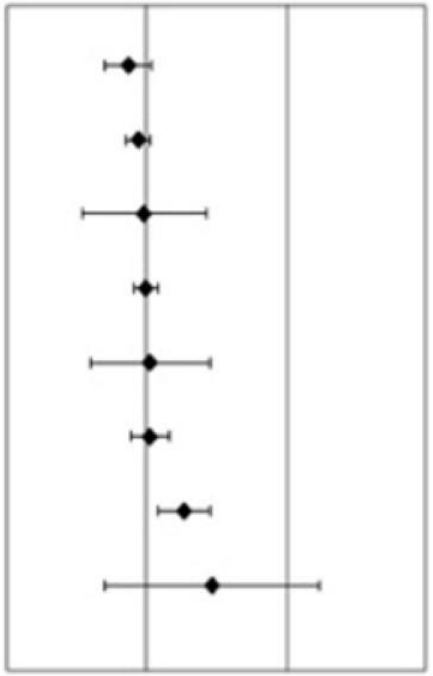
Lamanna C, Monami M, Marchionni N, Mannucci E.
Diabetes Obes Metab 2011;13:221–8.

SU and MACE

Meta-analysis of available RCTs

Major CV events:

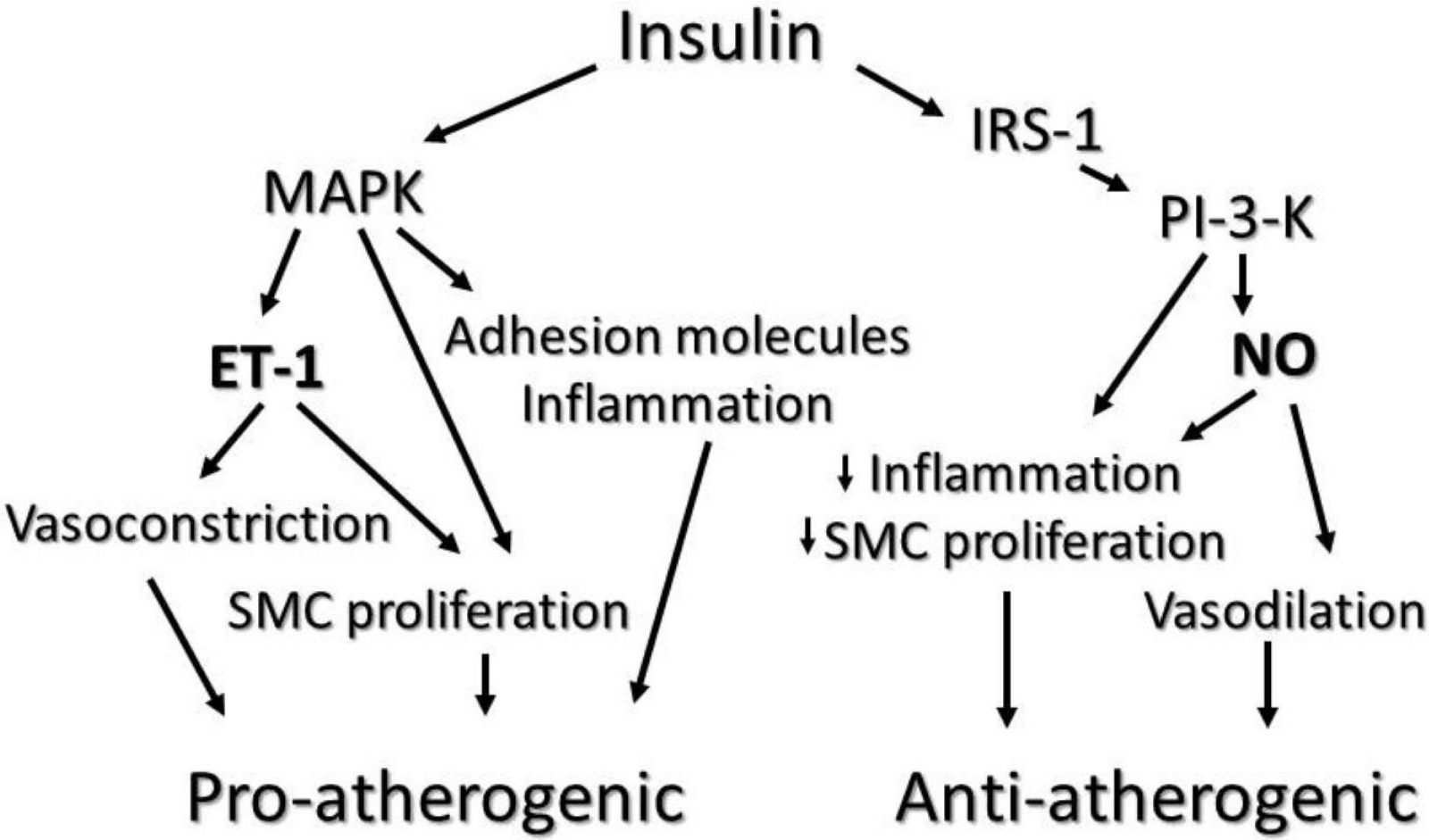
Comparators	# Trials	MH-OR	LL	UL	P	*Sulfonylureas* # Events	*Sulfonylureas* # Patients	*Comparator* # Events	*Comparator* # Patients
Rosiglitazone	6	0.74	0.50	1.10	0.140	209	3.490	251	3.714
Placebo/No therapy	2	0.87	0.71	1.07	0.190	279	1.306	225	969
Metformin	2	0.95	0.34	2.70	0.93	78	1.589	85	1.610
Insulin	2	0.98	0.80	1.20	0.830	278	1.252	209	929
GLP-1RA	2	1.05	0.39	2.84	0.920	8	380	9	515
Pioglitazone	8	1.05	0.77	1.44	0.740	86	3.173	80	3.195
DPP-4i	5	1.85	1.20	2.87	0.005	61	3.701	32	3.704
AGi	2	2.95	0.50	17.27	0.230	4	140	2	228



All-cause mortality: **1.22 [1.01–1.49] P=0.047**

Monami M, Genovese S, Mannucci E.
Diabetes Obes Metab 2013; 15:938-53,

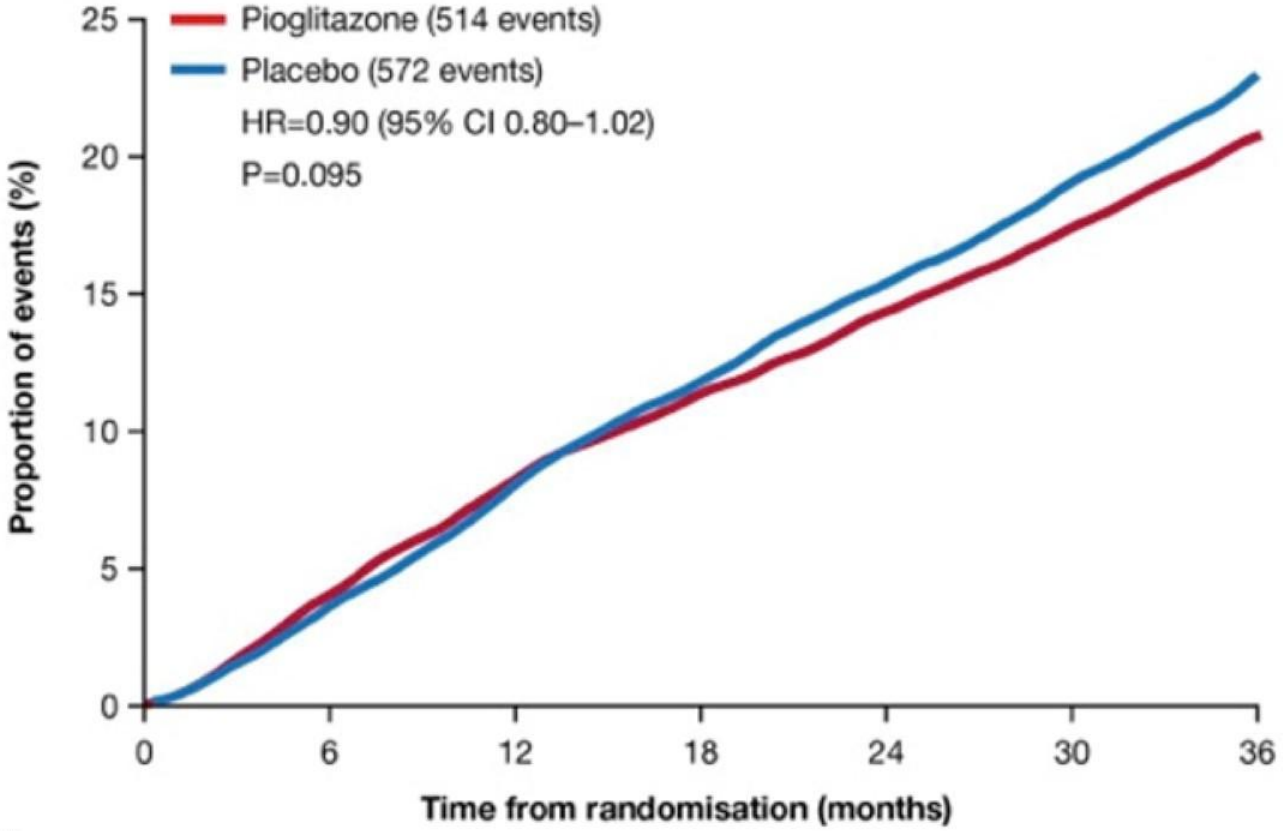
CV effects of insulin



Pioglitazone and CVD

The PROACTIVE trial

Primary endpoint



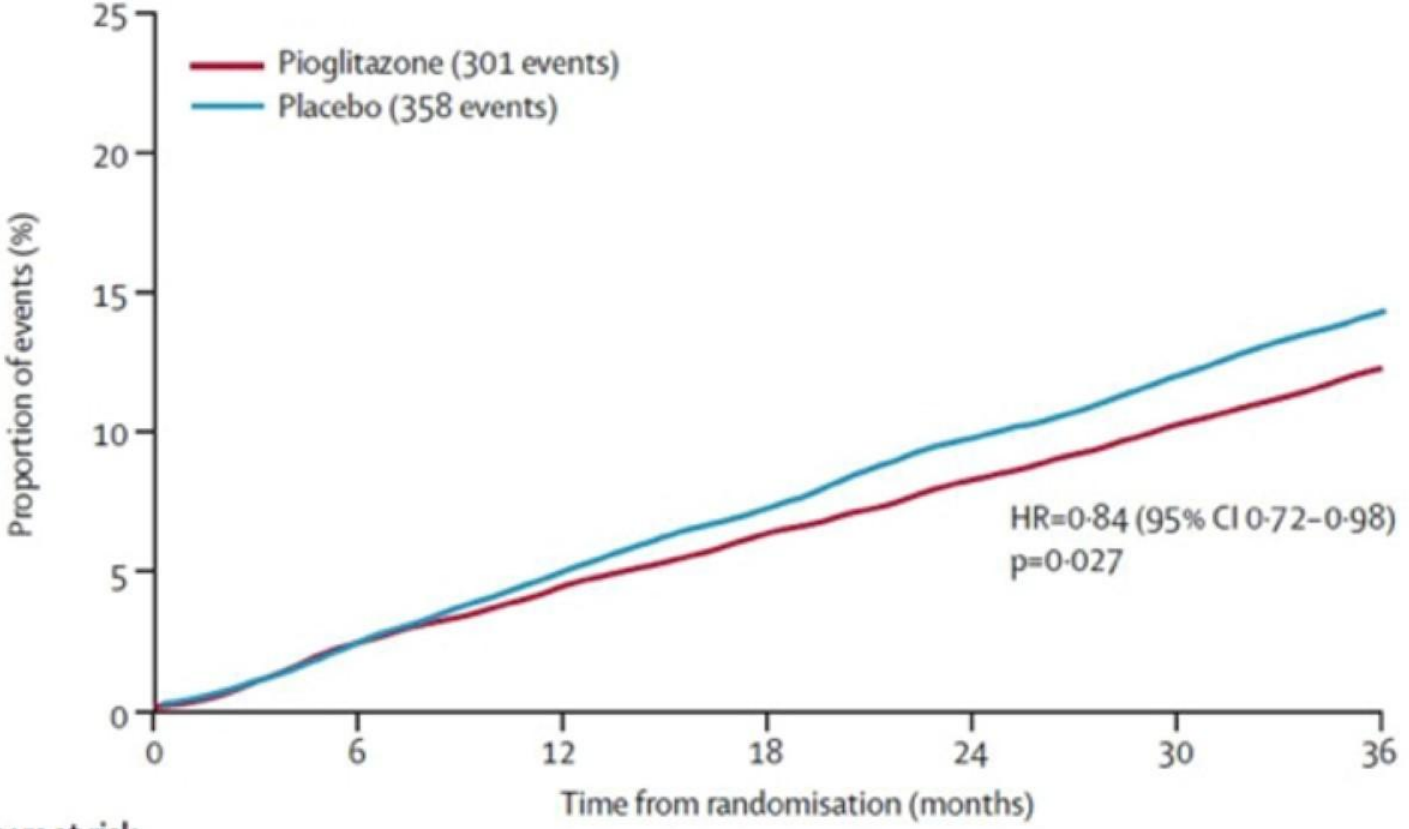
Number at risk						
Pioglitazone	2488	2373	2302	2218	2146	348
Placebo	2530	2413	2317	2215	2122	345

Dormandy J, *et al. Lancet* 2005;366:1279–89.

Pioglitazone and CVD

The PROACTIVE trial

Main secondary endpoint

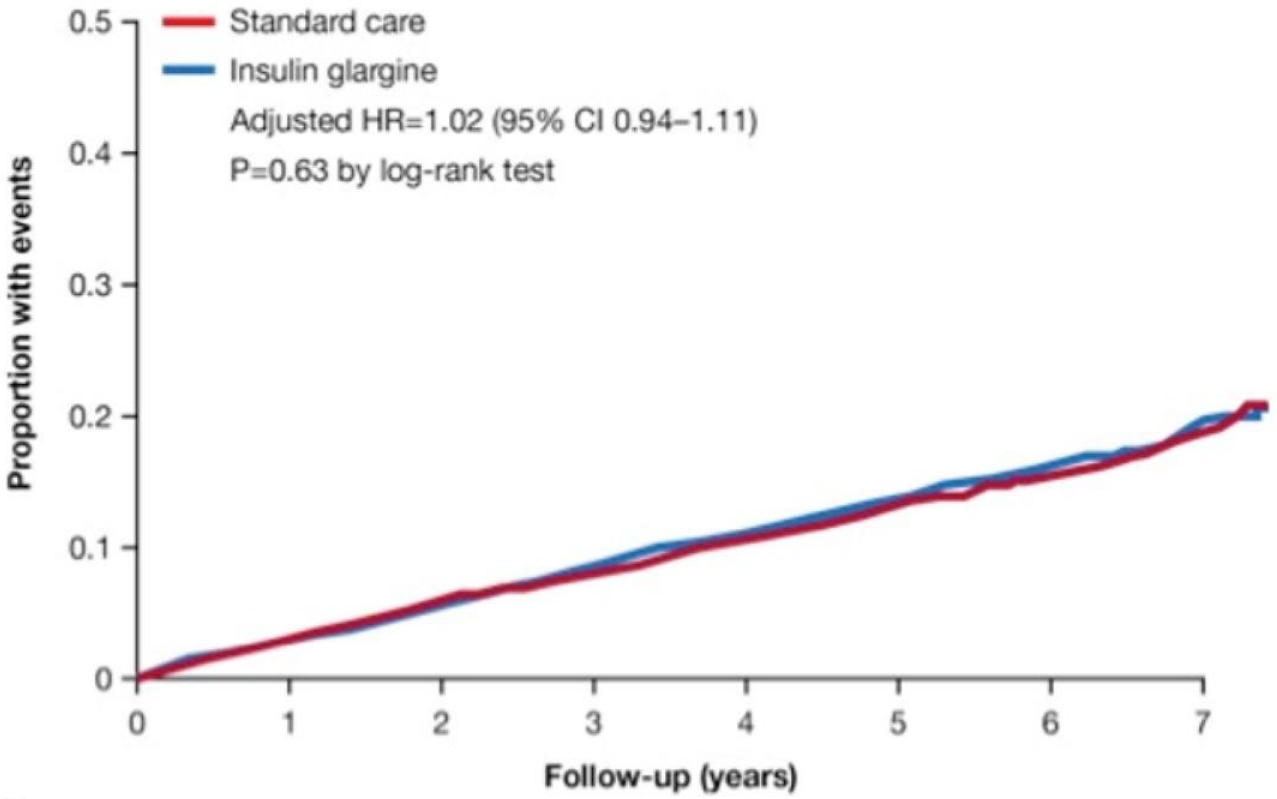


Numbers at risk						
Pioglitazone	2536	2487	2435	2381	2336	396
Placebo	2566	2504	2442	2371	2315	390

Dormandy J, *et al. Lancet* 2005;366:1279–89.

Insulin and CVD

The ORIGIN trial



Number at risk

Insulin glargine	6264	6057	5850	5619	5379	5151	3611	766
Standard care	6273	6043	5847	5632	5415	5156	3639	800

ORIGIN trial investigators. *N Engl J Med* 2012;367:319–28.

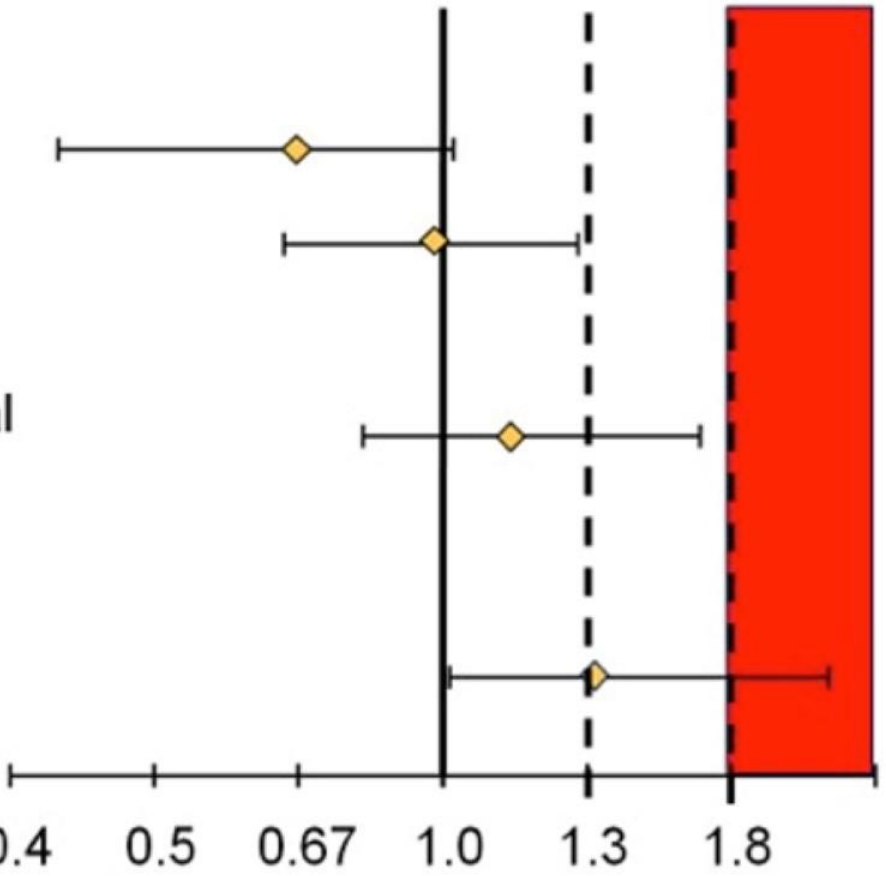
FDA Guidance on diabetes drugs

- 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

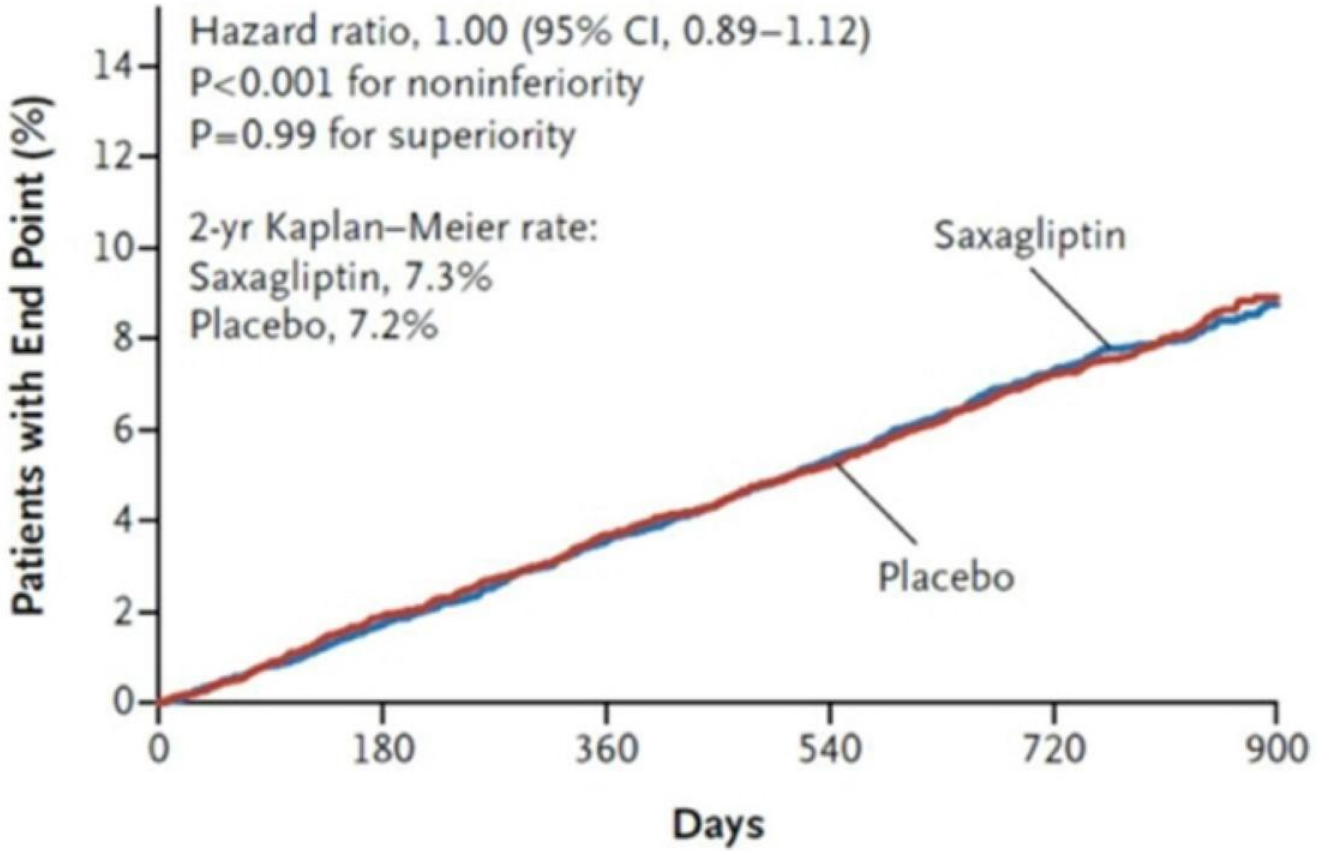
>1.8 – conduct large safety trial pre-approval



Food and Drug Administration, 2008. Available from: http://www.fda.gov/downloads/Drugs/guidanceComplianceRegulatoryInformation/guidances/ucm071627.pdf. Last accessed July 2013.

Saxagliptin and MACE

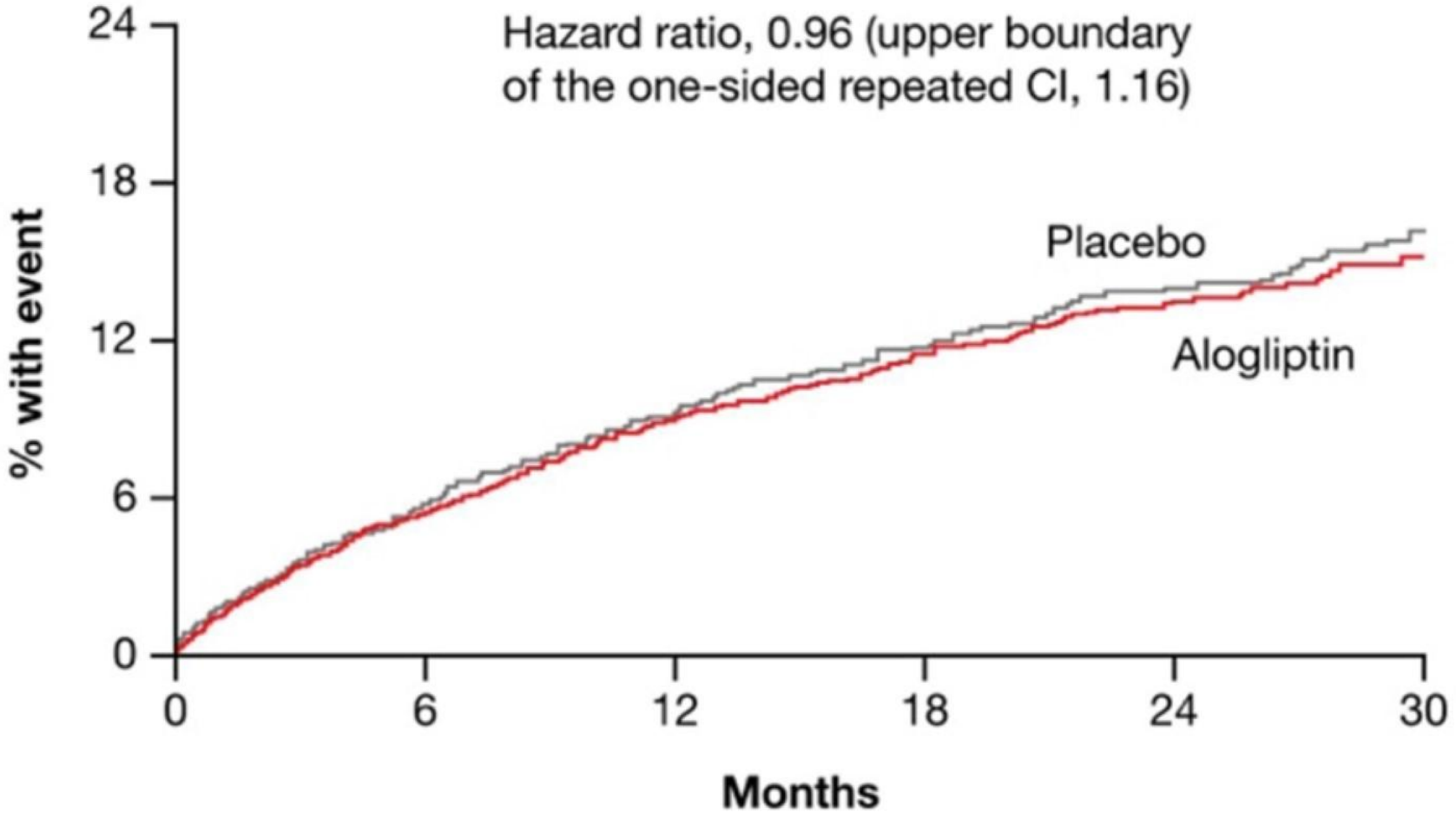
Results of the SAVOR trial: primary endpoint



Scirica BM, *et al*. *N Engl J Med* 2013 (in press)

Alogliptin and MACE

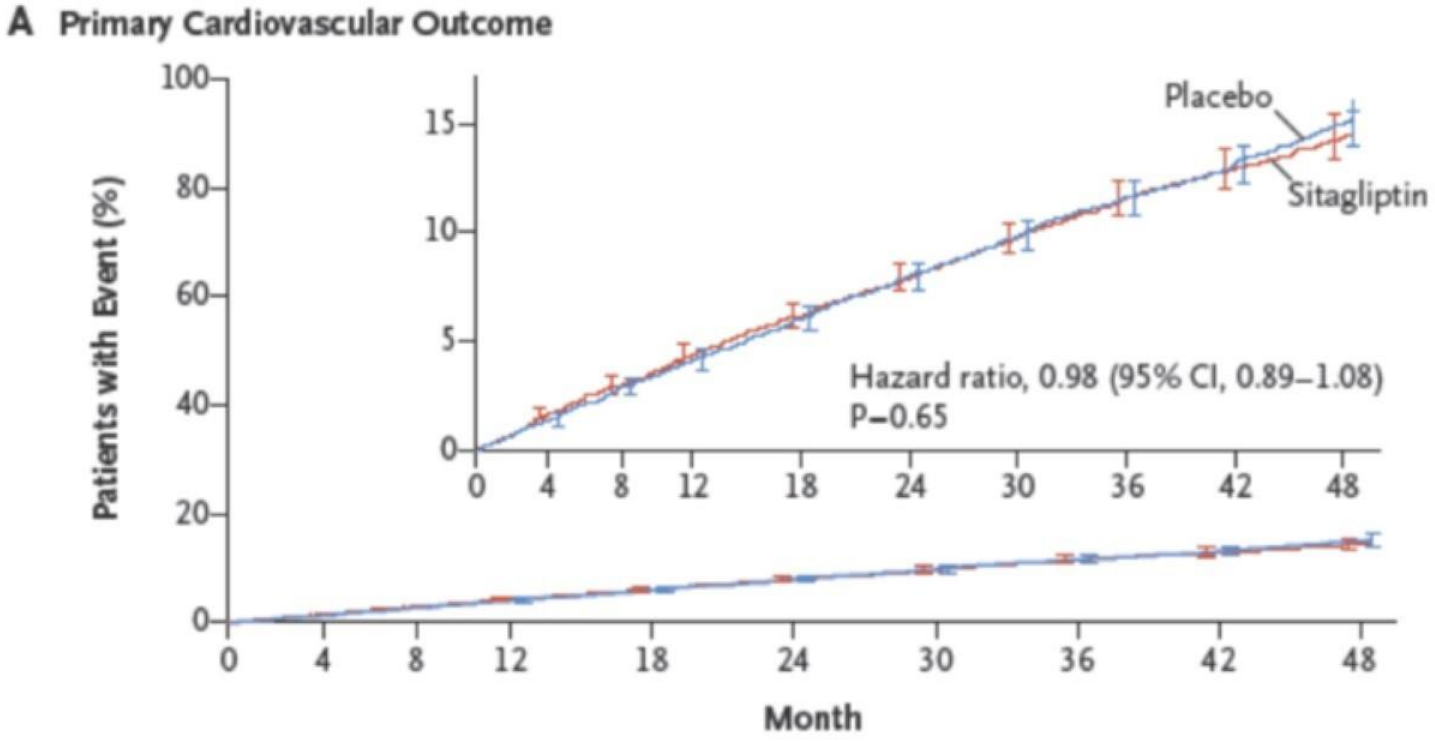
Results of the EXAMINE trial



White WB, *et al*. *N Engl J Med* 2013;DOI: 10.1056/NEJMoa1305889.

Sitagliptin and MACE

Results of theTECOS trial

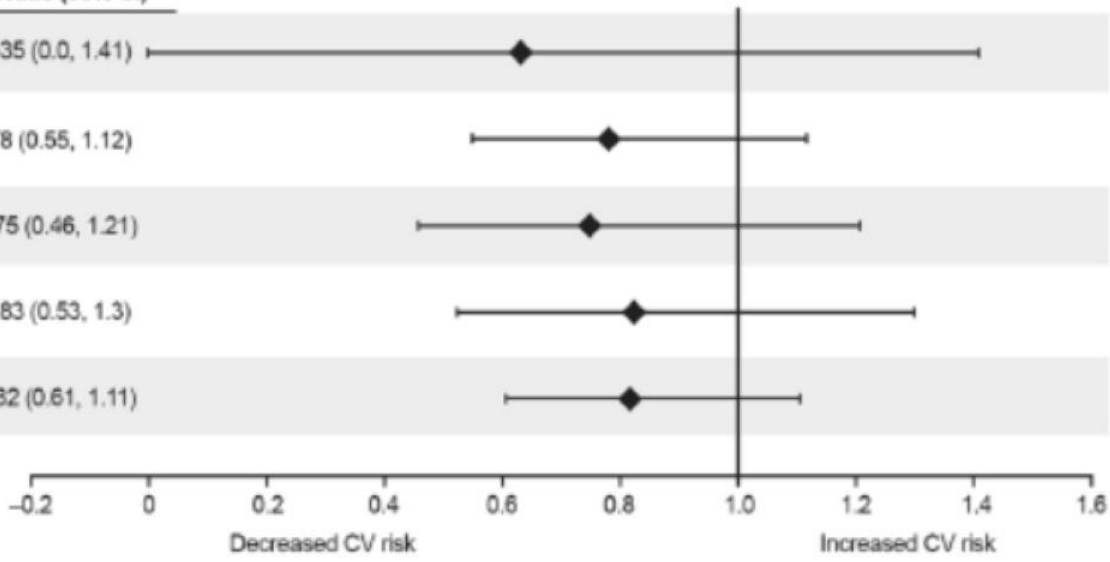


Green JB, et al. *N Engl J Med* 2015; 373:232.

DPP4i and MACE

Pooled phase 2-3 trials

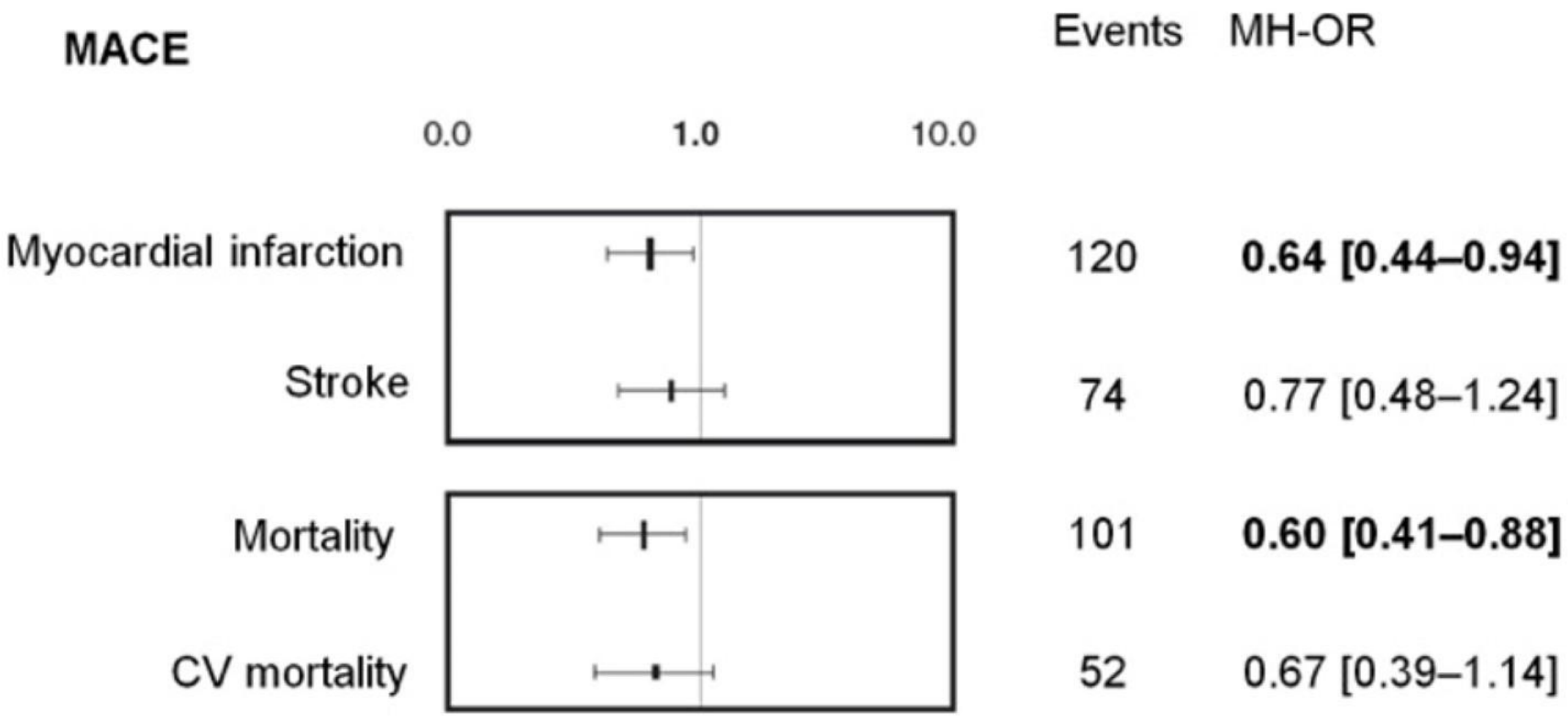
Drug [reference]	Primary statistical method	Number of patients	Risk ratio (95% CI)
Alogliptin [26]	Cox proportional hazards	6028	0.635 (0.0, 1.41)
Linagliptin [21]	Cox HR estimate	9459	0.78 (0.55, 1.12)
Saxagliptin [24]	Cox HR estimate	9156	0.75 (0.46, 1.21)
Sitagliptin [23]	Adjusted incidence rate ratio using Exact method for Poisson processes	14611	0.83 (0.53, 1.3)
Vildagliptin[a] [25]	Mantel–Haenszel RR	17446	0.82 (0.61, 1.11)



Mannucci E, Monami M. *Adv Ther,* 2016.

DPP-4 inhibitors and MACE

Meta-analysis of available RCTs



Monami M, Ahrén B, Dicembrini I, Mannucci E. *Diabetes Obes Metab* 2013;15:112–20.

SAVOR-TIMI 53

Comparison with meta-analysis of early trials

	SAVOR *	Meta-analysis **
Number of patients	16,492	41,959
Number of events	1,222	495
Duration of follow-up (years)	2.1 (median)	~1.0 (mean)
Incidence of MACE (/100 py)	3.5	1.1
Mean age (years)	65	55
Mean duration of diabetes (years)	12	5
Mean BMI (kg/m^2)	31.1	31.1
Mean HbA_{1C} (%)	8.0	8.2
Insulin-treated (%)	43	<5
Previous CV (%)	75	~30

Why did the SAVOR trial have such different results from the meta-analyses?

* Scirica BM, *et al. N Engl J Med* 2013

** Monami M, *et al. Diabetes Obes Metab* 2013;15:112–20.

Saxagliptin and MACE

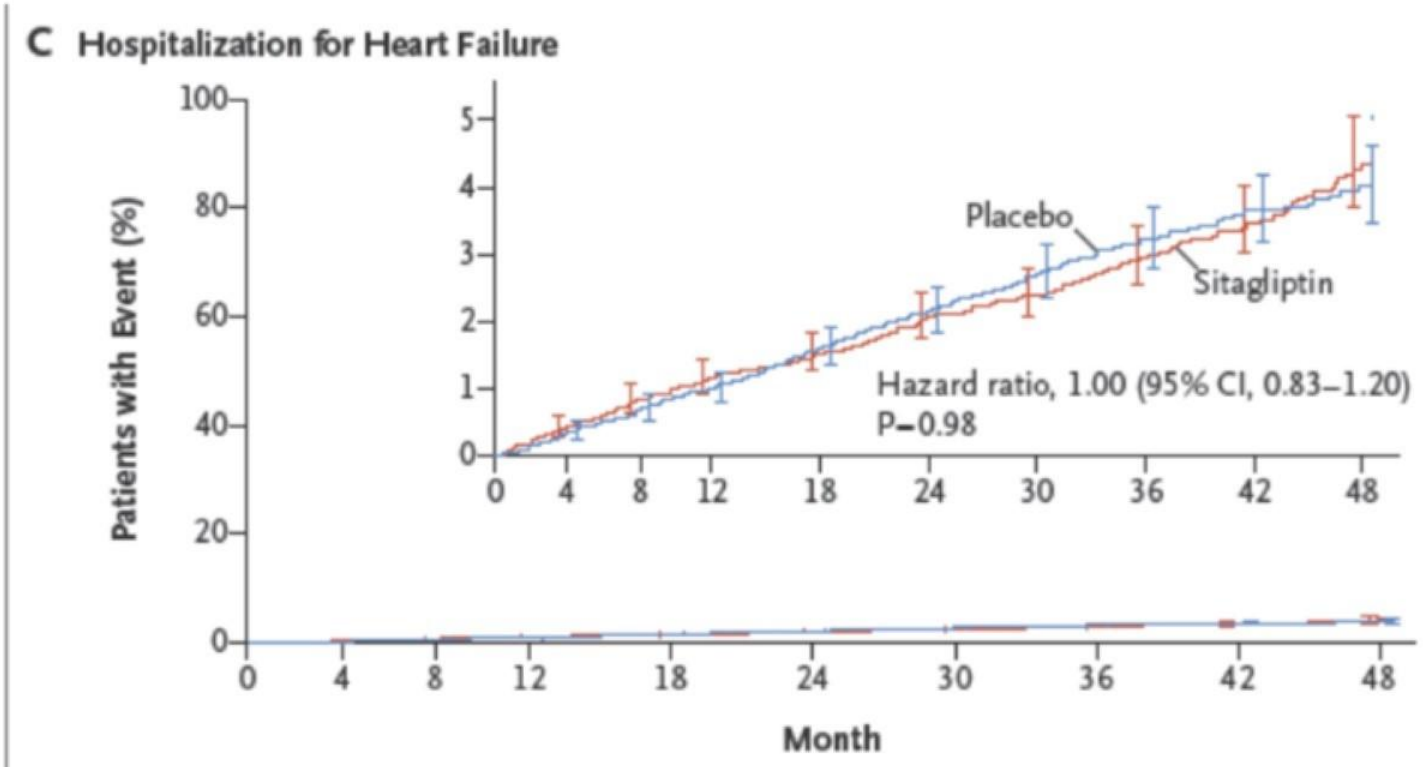
Results of the SAVOR trial: secondary endpoint

End Point	Saxagliptin (N=8280)	Placebo (N=8212)	Hazard Ratio (95% CI)	P Value
	no. (%)			
Cardiovascular death, myocardial infarction, or stroke: primary efficacy end point	613 (7.3)	609 (7.2)	1.00 (0.89–1.12)	0.99
Cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, heart failure, or coronary revascularization: secondary efficacy end point	1059 (12.8)	1034 (12.4)	1.02 (0.94–1.11)	0.66
Death from any cause	420 (4.9)	378 (4.2)	1.11 (0.96–1.27)	0.15
Death from cardiovascular causes	269 (3.2)	260 (2.9)	1.03 (0.87–1.22)	0.72
Myocardial infarction	265 (3.2)	278 (3.4)	0.95 (0.80–1.12)	0.52
Ischemic stroke	157 (1.9)	141 (1.7)	1.11 (0.88–1.39)	0.38
Hospitalization for unstable angina	97 (1.2)	81 (1.0)	1.19 (0.89–1.60)	0.24
Hospitalization for heart failure			1.27 (1.07–1.51)	0.007
Hospitalization for coronary revascularization	423 (5.2)	459 (5.6)	0.91 (0.80–1.04)	0.18

Scirica BM, *et al. N Engl J Med* 2013 (in press)

Sitagliptin and HF

Results from TECOS: secondary endpoint



No. at Risk

Sitagliptin	7332	7189	7036	6917	6780	6619	4728	3515	2175	1324
Placebo	7339	7204	7025	6903	6712	6549	4599	3443	2131	1315

Green JB, et al. *N Engl J Med* 2015; 373:232.

SGLT2 and MACE

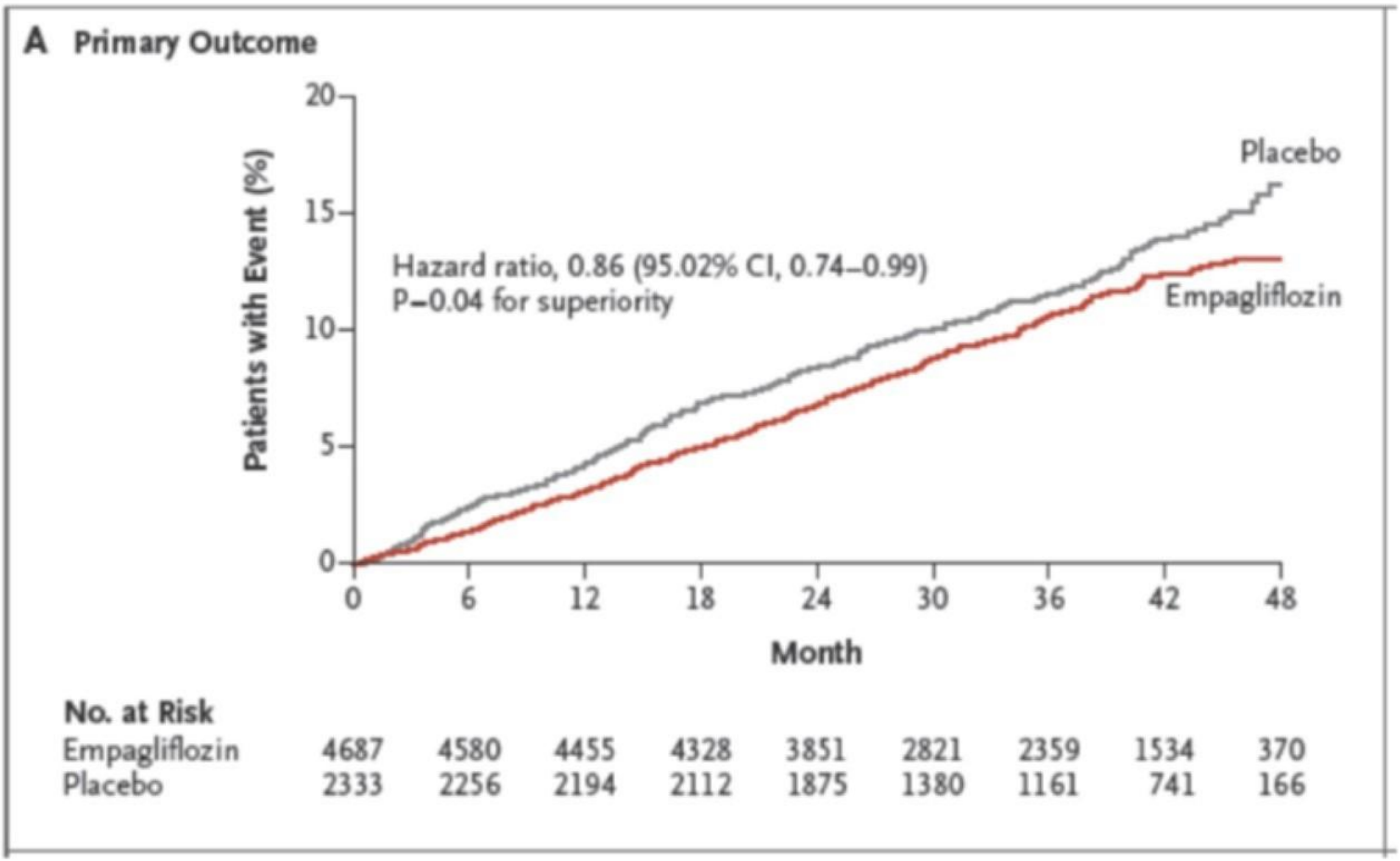
Pooled analisys of phase III non-CV trials

Drug	HR (95% CI)
Empagliflozin	0.48 [0.27-0.86]
Dapagliflozin	0.81 [0.58-1.15]
Canagliflozin	0.73 [0.23-2.29]

www.ema.europa.eu

Empagliflozin and MACE

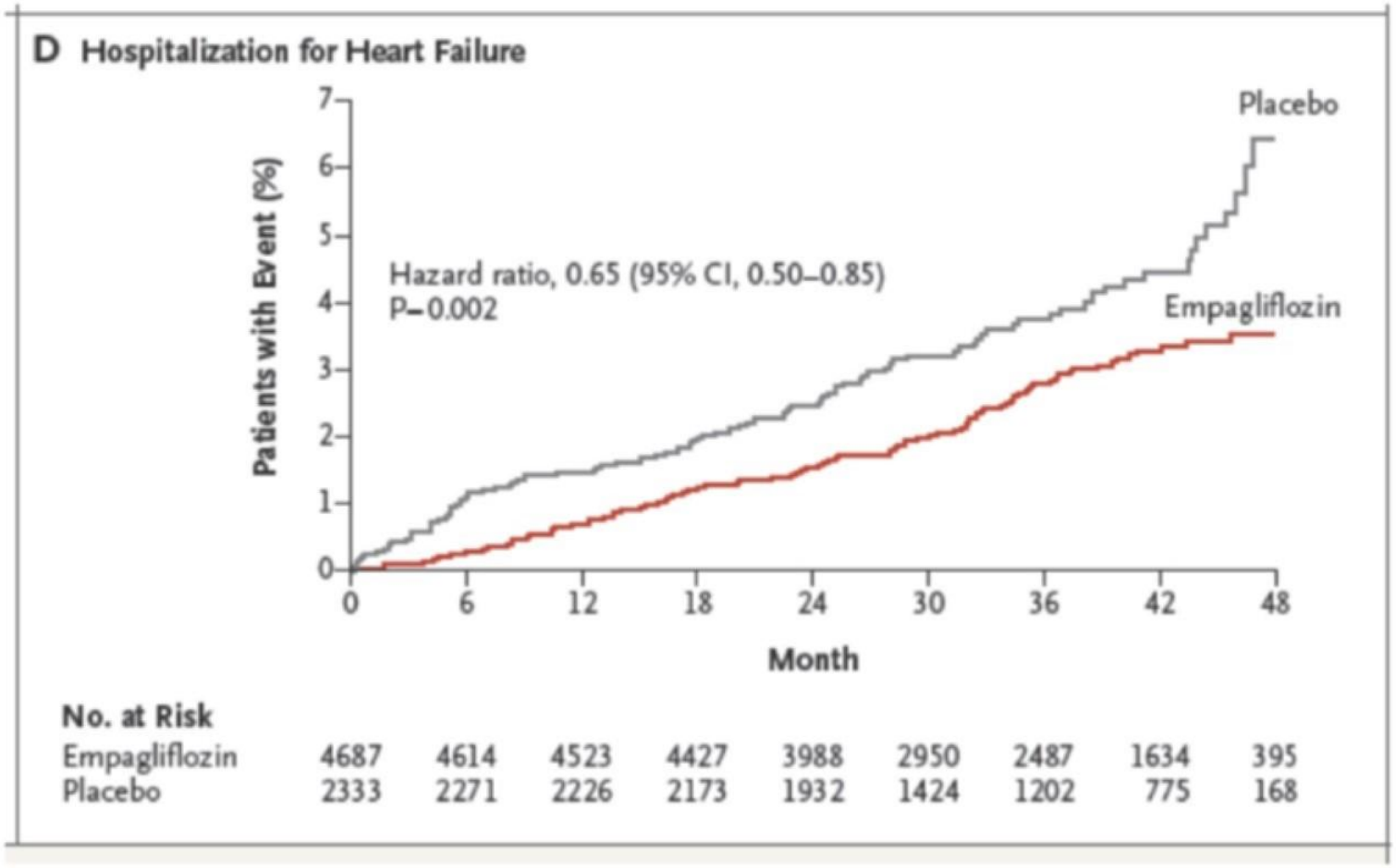
EMPA-REG OUTCOME trial: primary endpoint



Zinman et al., *N Engl J Med* 2015.

Empagliflozin and MACE

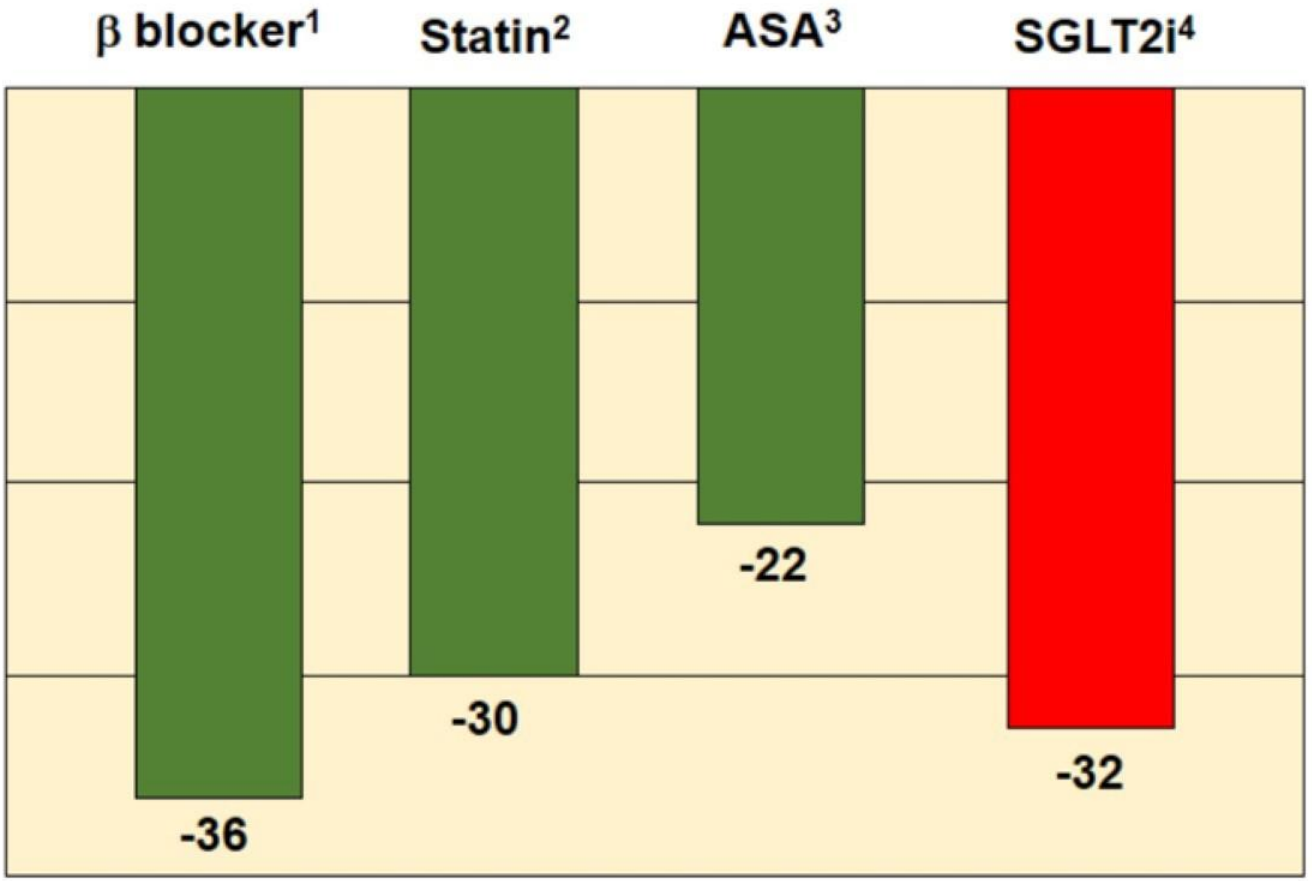
EMPA-REG OUTCOME trial: heart failure



Zinman et al., *N Engl J Med* 2015.

All-cause mortality in MI

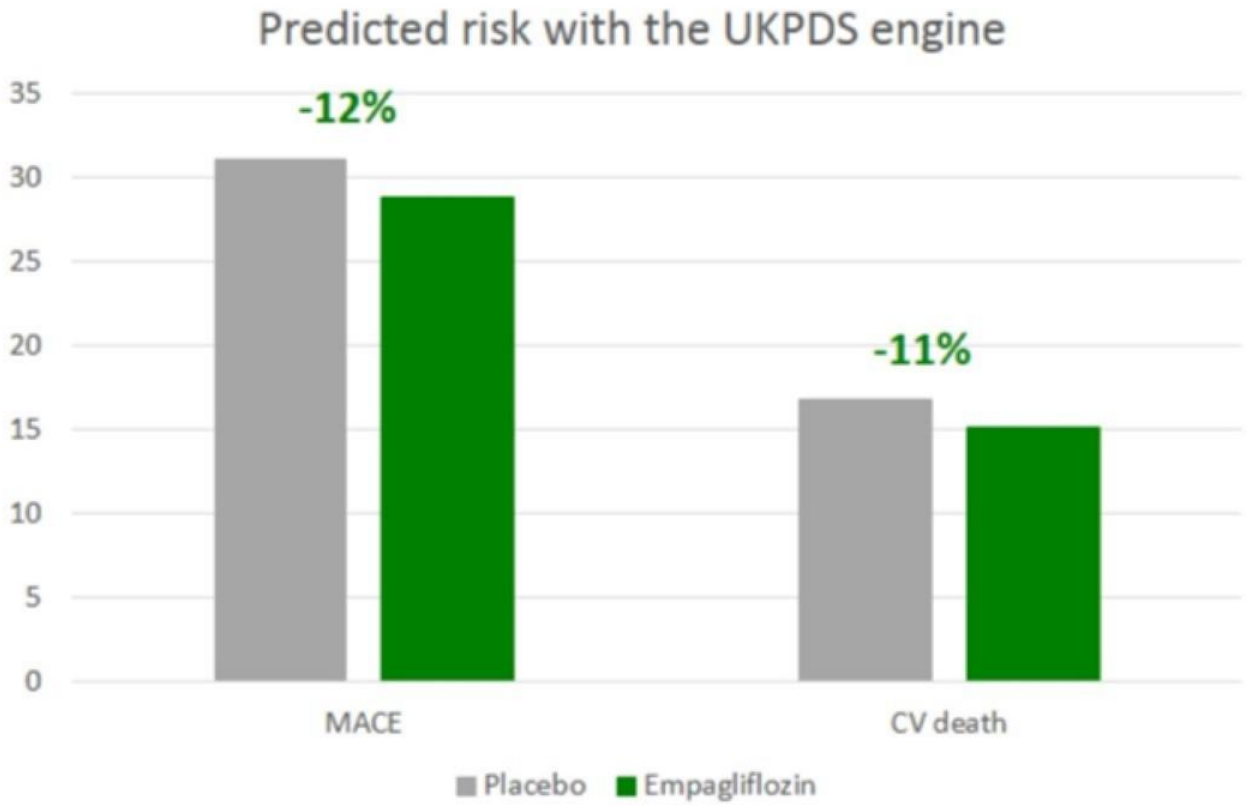
Effects of different treatments



1. Metoprolol in Hialmarson et al., Lancet 1986; 2. Simvastatin in 4S;
3. ASA in acute phase of ISIS-2; 4 empagliflozin in EMPA-REG OUTCOME

Risk factors and events

EMPAREG OUTCOME Study



Actually observed figures: MACE **-14%**, CV mortality **-38%**

Luconi M, Raimondi L, Di Franco A, Mannucci E.
Nutr Metab Cardiovasc Dis 2016; Epub ahead of print

Hypothesis on mechanisms

CV protection in EMPAREG OUTCOME Study

Table 2 Putative hypothesized mechanisms underlying the reduced cardiovascular mortality observed in the EMPAREG-OUTCOME-study.

Type of mechanism	Mechanism
Systemic, metabolic	↑Ketone bodies
	↑Sodium excretion
	↓Extracellular sodium in myocardium
	↑Hematocrit
	↓Blood pressure
	↓Body weight
	↑Diuresis
	RAS activation
Systemic, endocrine	↑Renal production of erythropoietin
	↑Sympathoadrenergic activity
	↑Glucagon
Direct myocardial effect	Inhibition of cardiomyocyte SGLT1R resulting in:
	↓Depolarization
	↓Sodium/calcium overload
	↓Glucose uptake and glucotoxicity
	↓ROS production

All mechanisms discussed in the present review are listed, according to their nature. The mechanisms assessed in the EMPAREG-OUTCOME study are indicated in bold.

Luconi M, Raimondi L, Di Franco A, Mannucci E.
Nutr Metab Cardiovasc Dis 2016; Epub ahead of print

GLP1-RA and MACE

Meta-analysis of available RCTs

All trials

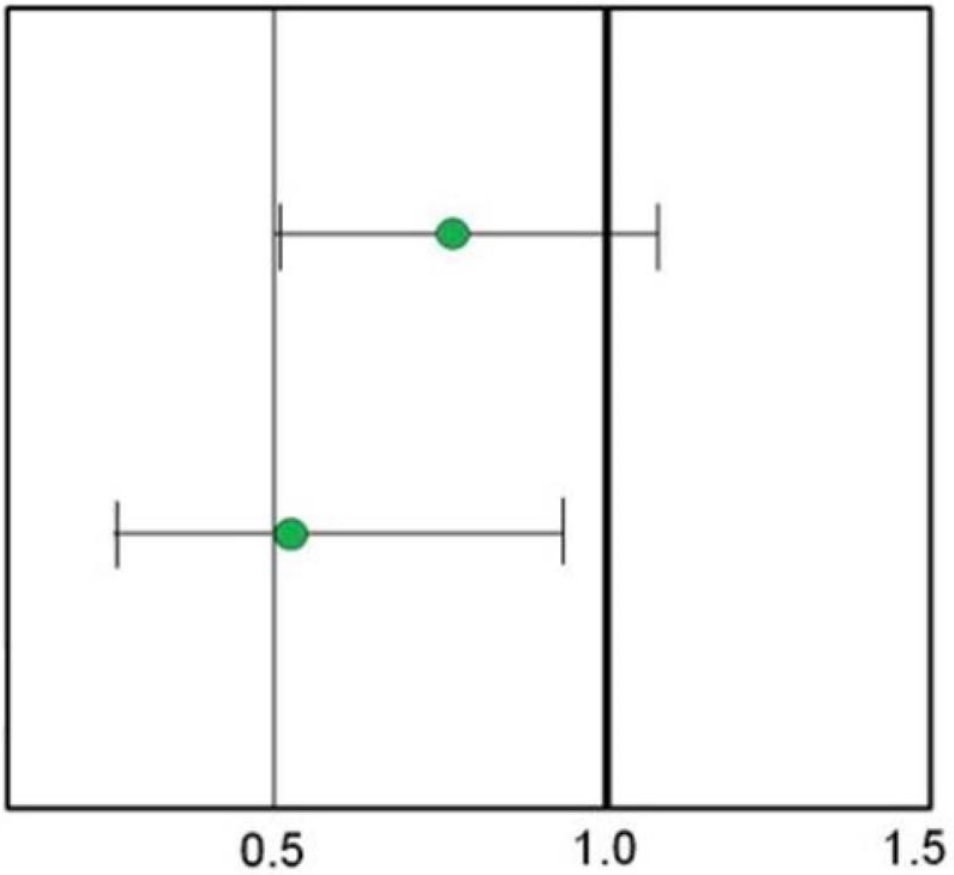
N= 25 RCTs

MH-OR: 0.78[0.54;1.13]; p=0.18

vs. placebo

N= 12 RCTs

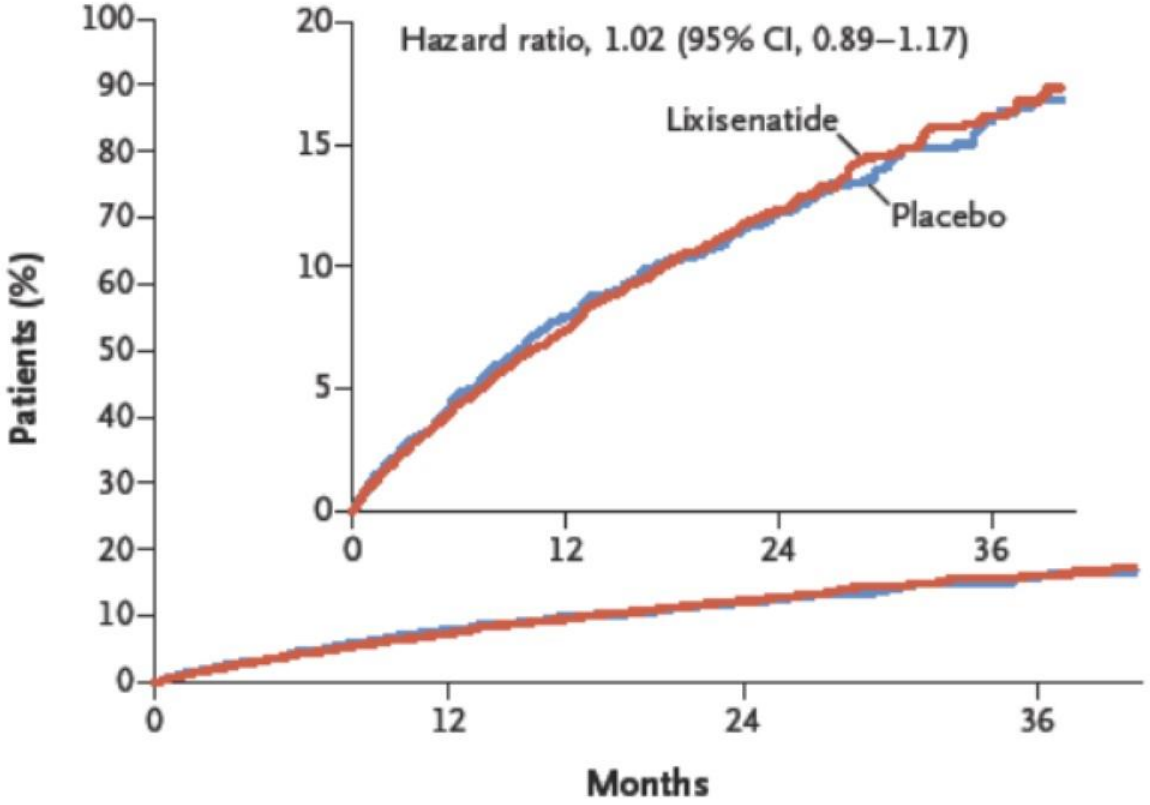
MH-OR: 0.51[0.27;0.93]; p=0.029



Monami M, Dicembrini I, Nardini C, Fiordelli I; Mannucci E.
Diabetes Obes Metab. 2014 Jan;16(1):38-47

Lixisenatide and MACE

ELIXA trial – primary endpoint

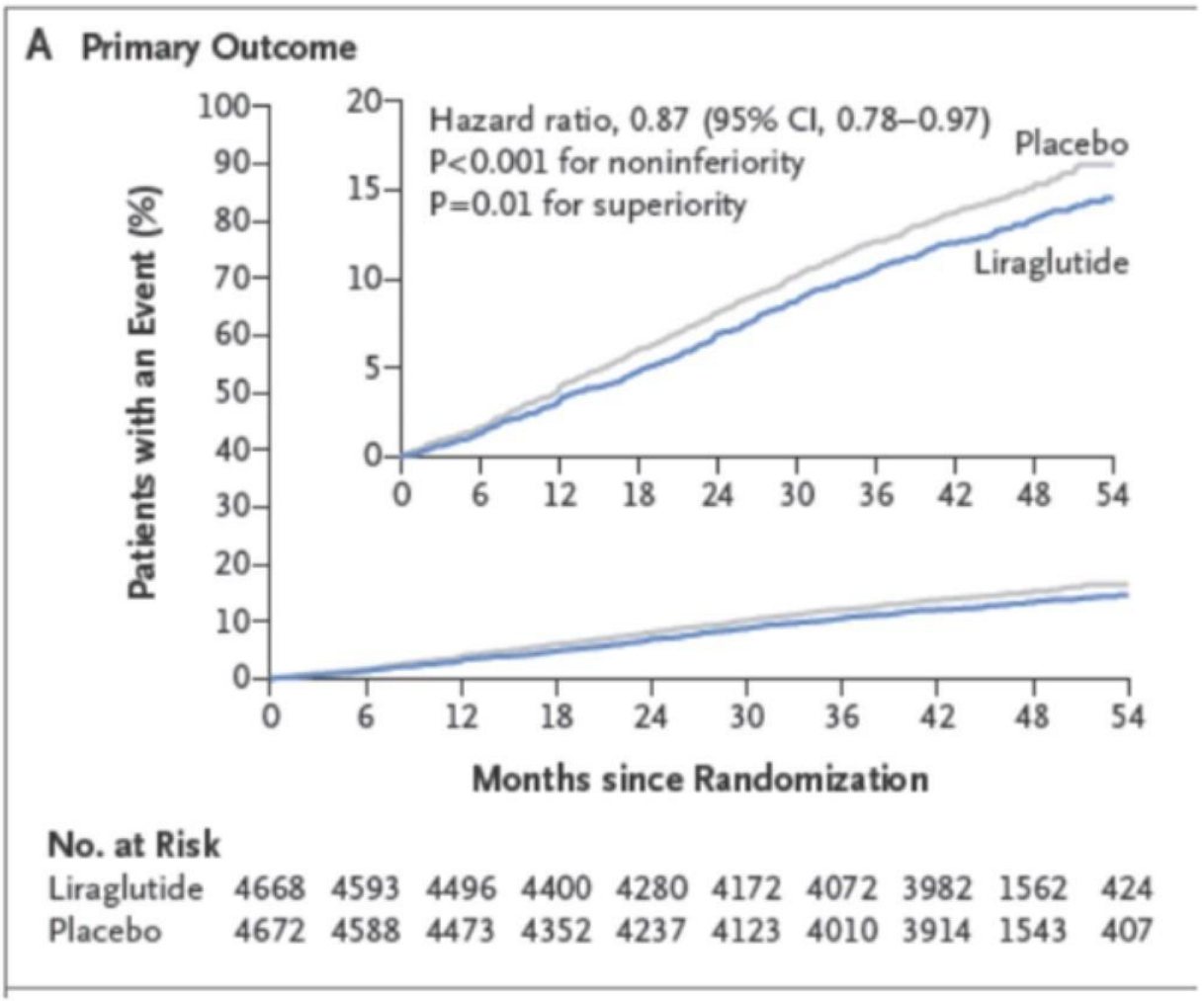


No. at Risk				
Placebo	3034	2759	1566	476
Lixisenatide	3034	2785	1558	484

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

Liraglutide and CV risk

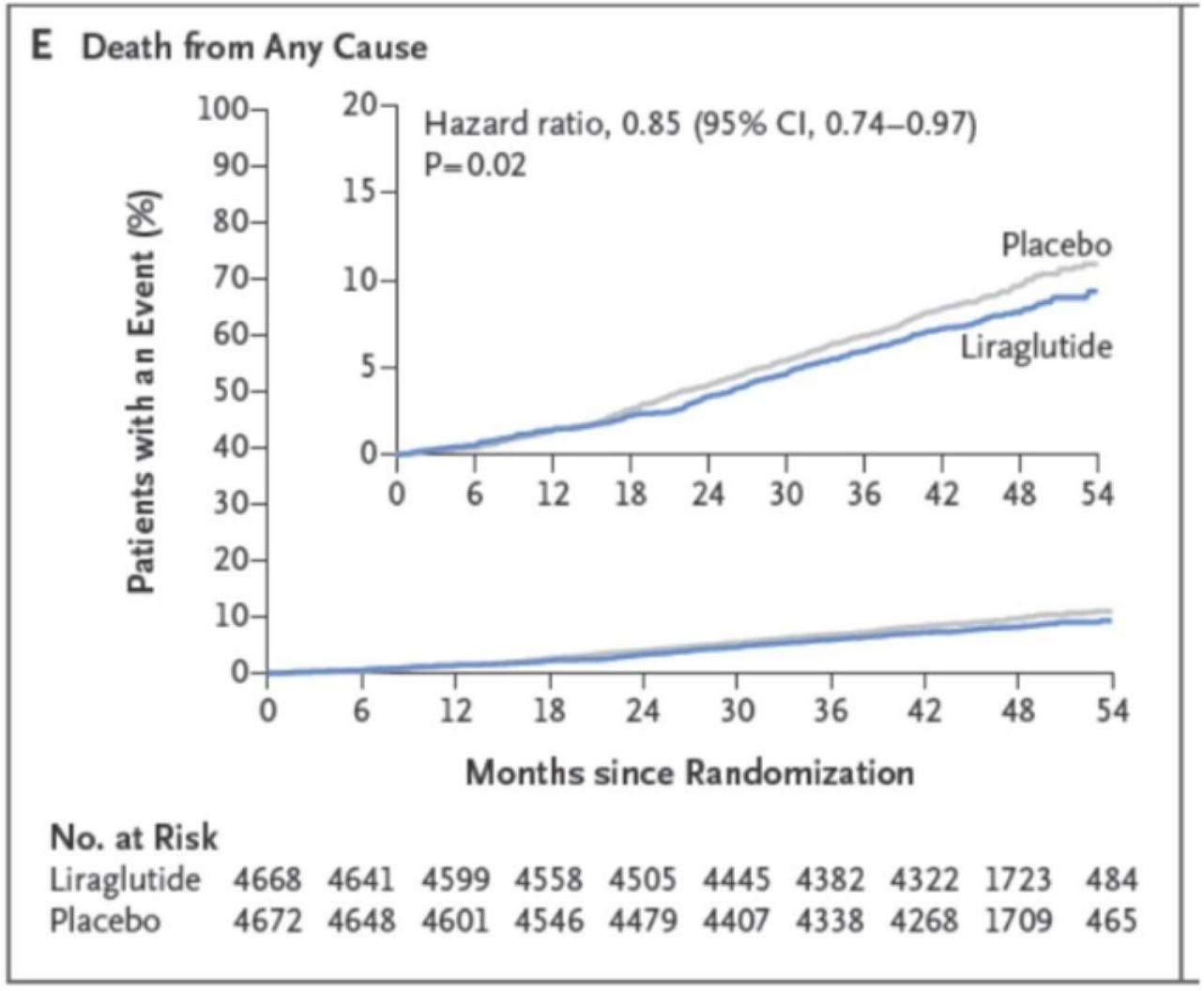
LEADER trial



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

Liraglutide and mortality

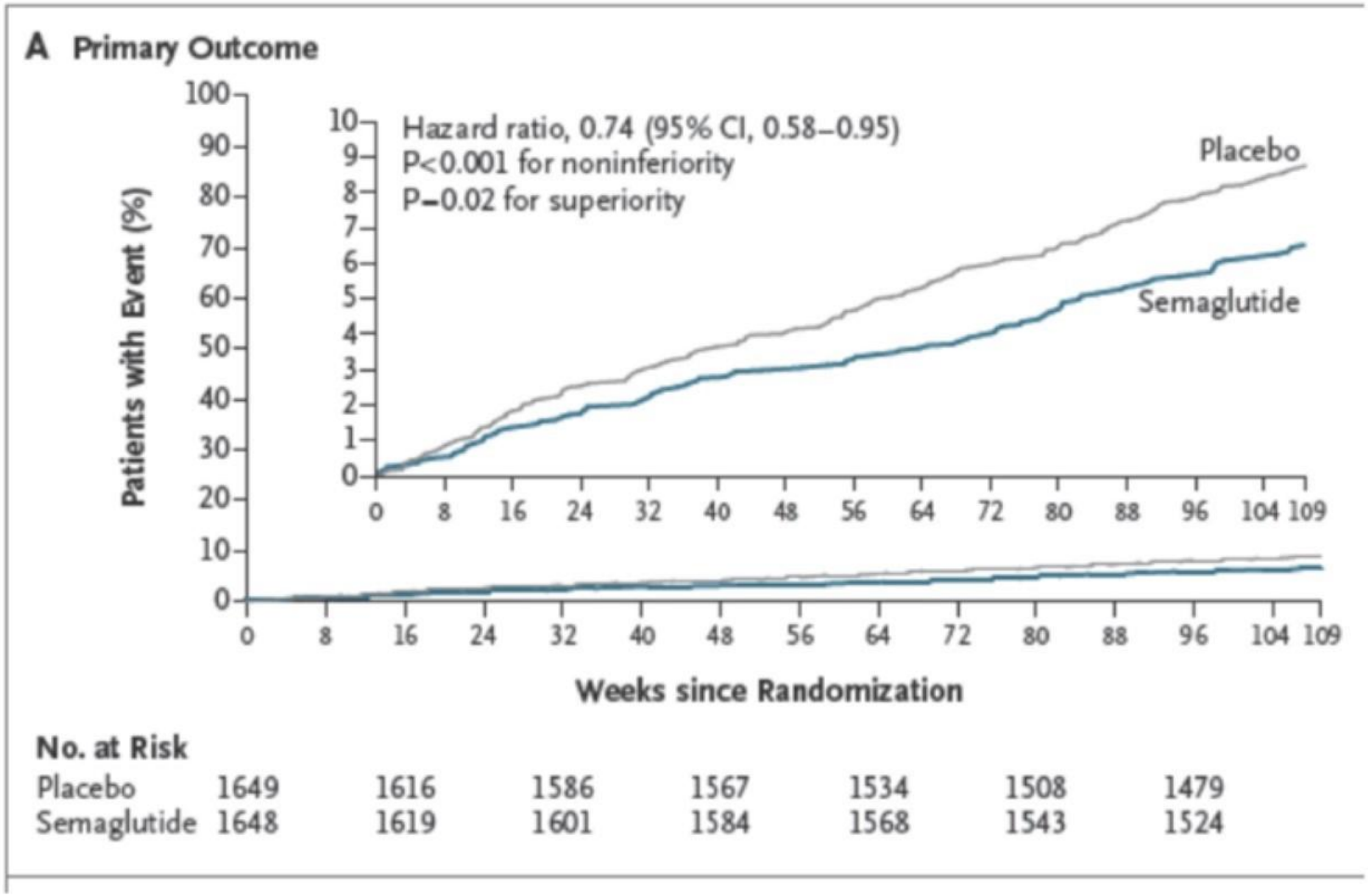
LEADER trial



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

Semaglutide and CV risk

SUSTAIN-6 trial

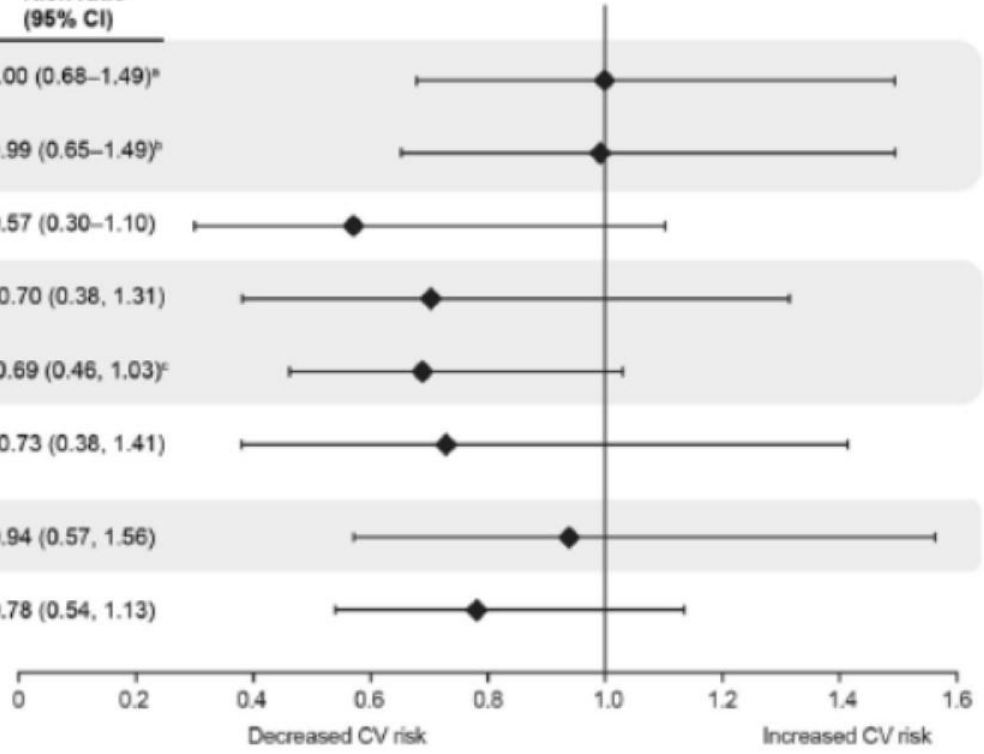


Marso SP, et al. *N Engl J Med*. 2016,

GLP1RA and MACE

Pooled phase 2-3 trials

Drug [Reference]	Type of analysis	Primary statistical analysis	Number of patients	Risk ratio (95% CI)
Albiglutide [53]	Pooled analysis	Cox proportional hazards	5107	1.00 (0.68–1.49)[a] 0.99 (0.65–1.49)[b]
Dulaglutide [54]	Pooled analysis	Cox proportional hazards	6010	0.57 (0.30–1.10)
Exenatide twice daily [51]	Pooled analysis	Mantel–Haenszel RR	3945	0.70 (0.38, 1.31) 0.69 (0.46, 1.03)[c]
Liraglutide [50]	Pooled analysis	Incidence ratios estimated by Cochran–Mantel–Haenszel	6638	0.73 (0.38, 1.41)
Taspoglutide [52]	Pooled analysis	Peto fixed-effects OR	7056	0.94 (0.57, 1.56)
GLP-1 receptor agonists [12]	Meta-analysis	Mantel–Haenszel OR	12475	0.78 (0.54, 1.13)



Mannucci E, Monami M. *Adv Ther,* 2016.

Conclusions

Glucose-lowering drugs have different (divergent) effects on cardiovascular morbidity and mortality

Pioglitazone, empagliflozin, liraglutide and semaglutide reduce cardiovascular morbidity and/or mortality in patients with diabetes and prior CV events

Available data are insufficient to discriminate molecule-specific and class effects on CV events and mortality

We no have no evidence on the cardiovascular effects of different drugs in primary prevention – and no reason to believe that there should be any difference from secondary prevention