La malattia cardiovascolare e la rivoluzione dei CVOTs

Edoardo Mannucci

Diabetologia e Malattie Metaboliche, AOU Careggi
Endocrinologia, Università di Firenze

Conflitti di interesse

Negli ultimi due anni, E. Mannucci ha ricevuto compensi per relazioni e/o consulenze da

Boehringer Ingelheim, Eli Lilly, MSD, Novo Nordisk, Sanofi

La struttura di appartenenza di E. Mannucci ha ricevuto :

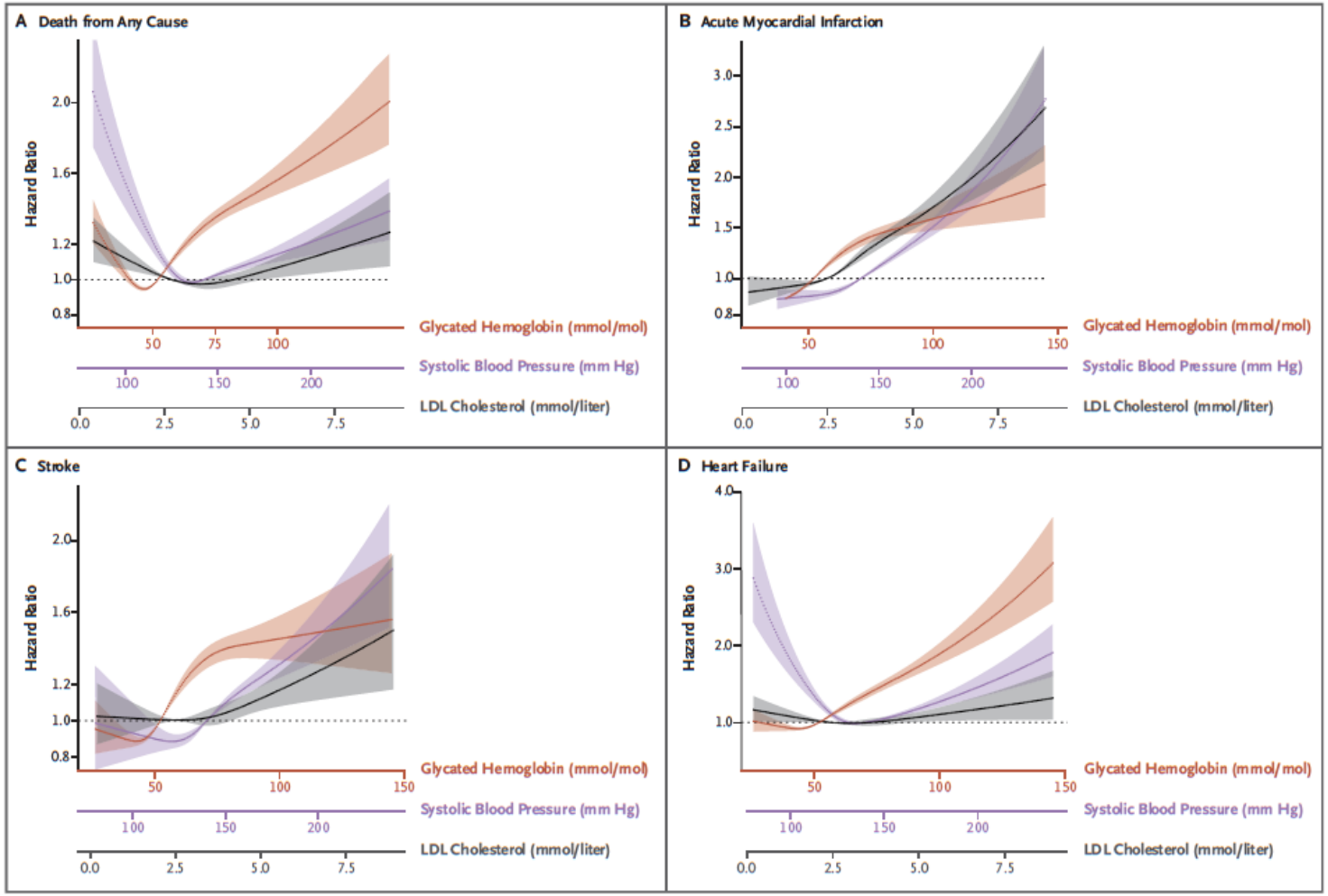
- Finanziamenti per ricerca indipendente non condizionata da ***Abbott***
- Compensi per studi clinici sponsorizzati da ***Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, Molteni, Novo Nordisk***

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Aidin Rawshani, M.D., Araz Rawshani, M.D., Ph.D., Stefan Franzén, Ph.D., Naveed Sattar, M.D., Ph.D., Björn Eliasson, M.D., Ph.D., Ann-Marie Svensson, Ph.D., Björn Zethelius, M.D., Ph.D., Mervete Miftaraj, M.Sc., Darren K. McGuire, M.D., M.H.Sc., Annika Rosengren, M.D., Ph.D., and Soffia Gudbjörnsdottir, M.D., Ph.D.



Matrched cohorts study

Cohorts:
- 271,174 patients with T2DM from the Swedish National Diabetes Register
- 1,335,870 matched subjects from the general population

Follow-up: 5.7 years

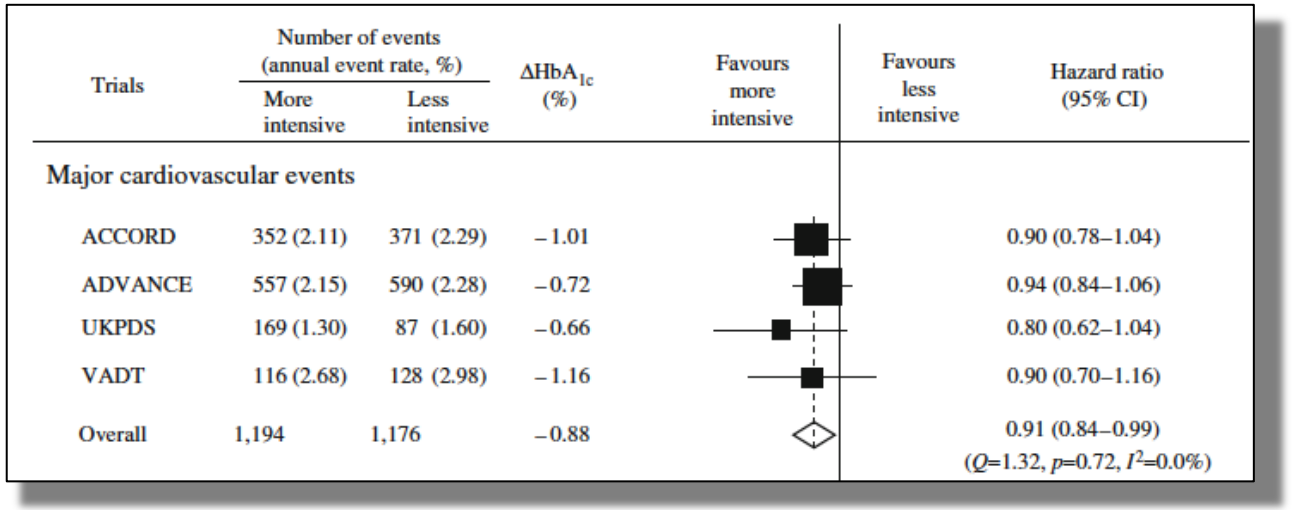
Rawshani A et al. *N Engl J Med* 379:633–644, 2018

Diabetologia (2009) 52:2288–2298
DOI 10.1007/s00125-009-1470-0

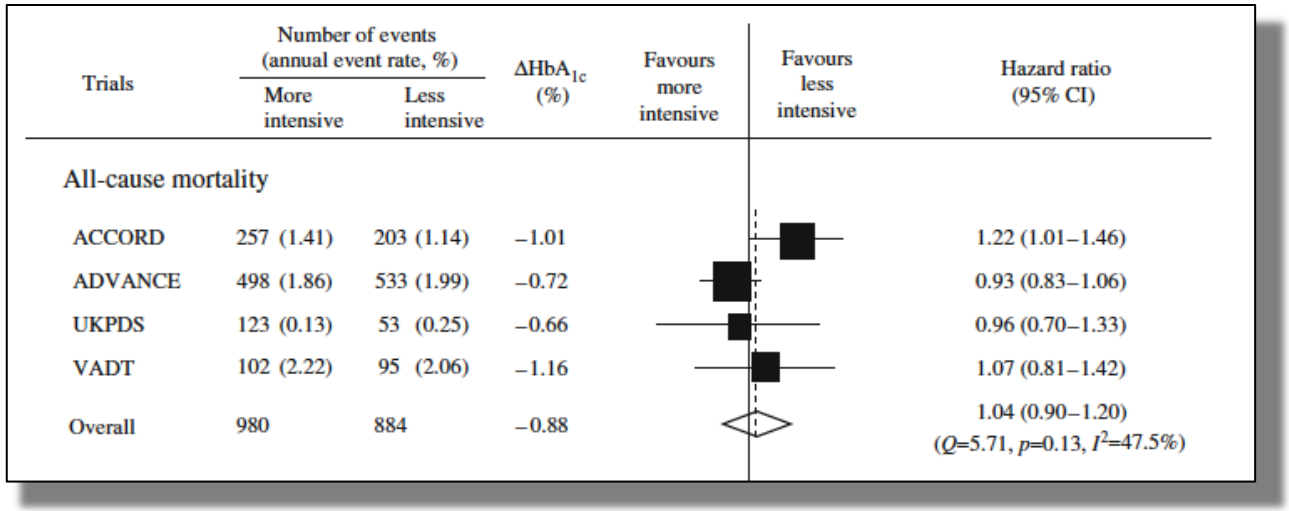
META-ANALYSIS

Intensive glucose control and macrovascular outcomes in type 2 diabetes

F. M. Turnbull · C. Abraira · R. J. Anderson · R. P. Byington · J. P. Chalmers · W. C. Duckworth · G. W. Evans · H. C. Gerstein · R. R. Holman · T. E. Moritz · B. C. Neal · T. Ninomiya · A. A. Patel · S. K. Paul · F. Travert · M. Woodward



Trials	Number of events (annual event rate, %) More intensive	Number of events (annual event rate, %) Less intensive	ΔHbA$_{1c}$ (%)	Favours more intensive	Favours less intensive	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%)



Trials	Number of events (annual event rate, %) More intensive	Number of events (annual event rate, %) Less intensive	ΔHbA$_{1c}$ (%)	Favours more intensive	Favours less intensive	Hazard ratio (95% CI)
All-cause mortality						
ACCORD	257 (1.41)	203 (1.14)	−1.01			1.22 (1.01–1.46)
ADVANCE	498 (1.86)	533 (1.99)	−0.72			0.93 (0.83–1.06)
UKPDS	123 (0.13)	53 (0.25)	−0.66			0.96 (0.70–1.33)
VADT	102 (2.22)	95 (2.06)	−1.16			1.07 (0.81–1.42)
Overall	980	884	−0.88			1.04 (0.90–1.20) (Q=5.71, p=0.13, I^2=47.5%)

Meta-analysis of patient-level data

RCTs on T2DM, with adjudication of cardiovascular outcomes, assessing the effects of intensification of diabetes therapy

Treatment: intensified glucose control
Comparator: conventional treatment
Outcome: MACE, mortality

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

ARTICLES

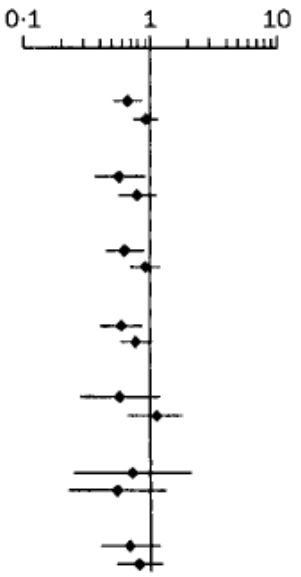
Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34)

*UK Prospective Diabetes Study (UKPDS) Group**

UKPDS trial – metformin substudy

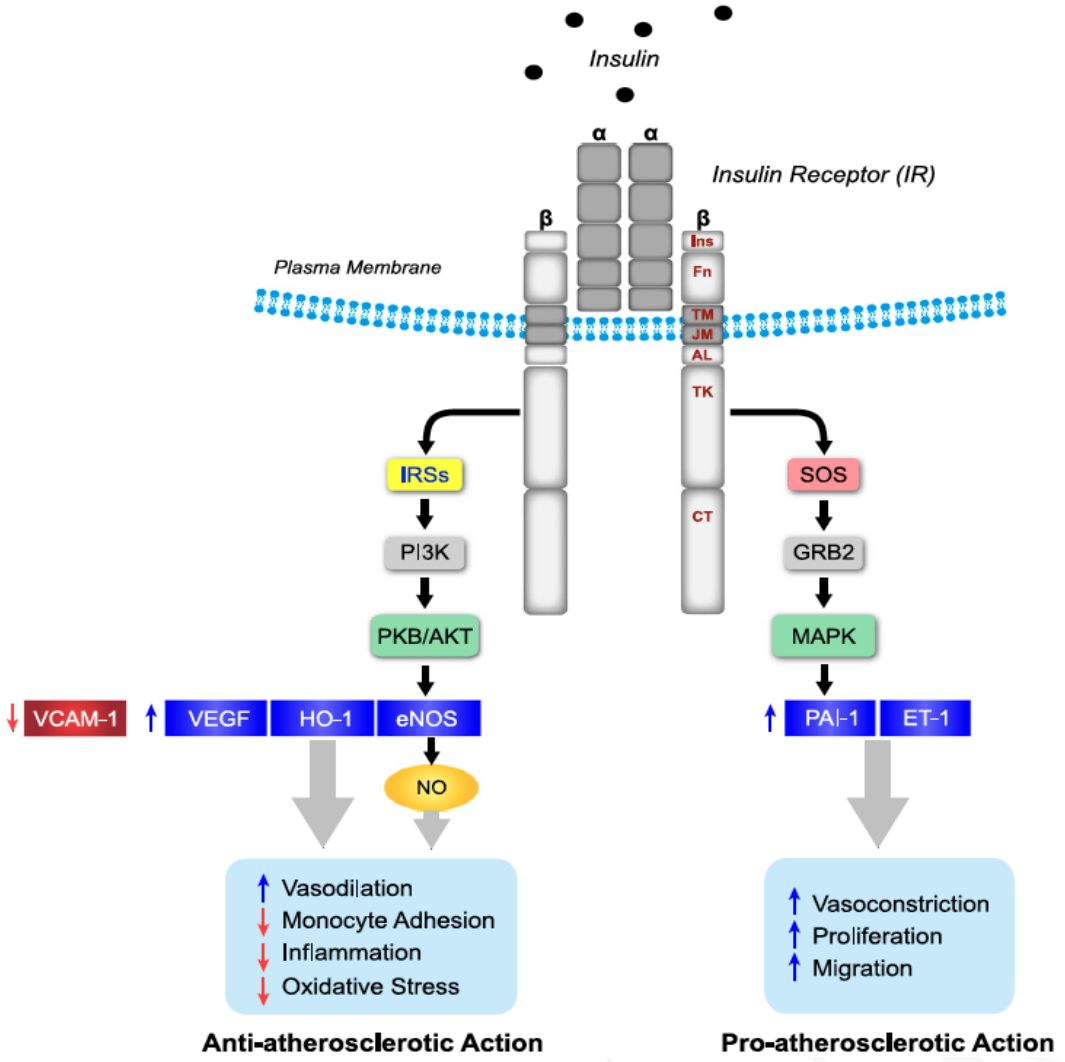
Treatment: intensified treatment with metformin
Comparator: conventional or intensified with insulin/SU
Principal outcome: composite of cardiovascular and microvascular events
Patients: 1704 newly-diagnosed overweight T2DM
Follow-up: 10 years

AGGREGATE ENDPOINT	p for metformin *vs* other intensive	Patients with aggregate endpoints		Absolute risk (events per 1000 patient-years)		Log-rank 2p	RR (95% CI) *vs* conventional
		Metformin or intensive	Conventional	Metformin or intensive	Conventional		
Any diabetes-related endpoint	p=0·0034						
Metformin		98	160	29·8	43·3	0·0023	0·68 (0·53–0·87)
Intensive		350	160	40·1	43·3	0·46	0·93 (0·77–1·12)
Diabetes-related death	p=0·11						
Metformin		28	55	7·5	12·7	0·017	0·58 (0·37–0·91)
Intensive		103	55	10·3	12·7	0·19	0·80 (0·58–1·11)
All-cause mortality	p=0·021						
Metformin		50	89	13·5	20·6	0·011	0·64 (0·45–0·91)
Intensive		190	89	18·9	20·6	0·49	0·92 (0·71–1·18)
Myocardial infarction	p=0·12						
Metformin		39	73	11·0	18·0	0·01	0·61 (0·41–0·89)
Intensive		139	73	14·4	18·0	0·11	0·79 (0·60–1·05)
Stroke	p=0·032						
Metformin		12	23	3·3	5·5	0·13	0·59 (0·29–1·18)
Intensive		60	23	6·2	5·5	0·60	1·14 (0·70–1·84)
Peripheral vascular disease	p=0·62						
Metformin		6	9	1·6	2·1	0·57	0·74 (0·26–2·09)
Intensive		12	9	1·2	2·1	0·18	0·56 (0·24–1·33)
Microvascular	p=0·39						
Metformin		24	38	6·7	9·2	0·19	0·71 (0·43–1·19)
Intensive		74	38	7·7	9·2	0·38	0·84 (0·57–1·24)



UKPDS Group. *Lancet* 352:854-53, 1998

Effects of insulin on atherogenesis



King GL et al. *Diabetes* 65:1462-71, 2016

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Basal Insulin and Cardiovascular and Other Outcomes in Dysglycemia

The ORIGIN Trial Investigators*

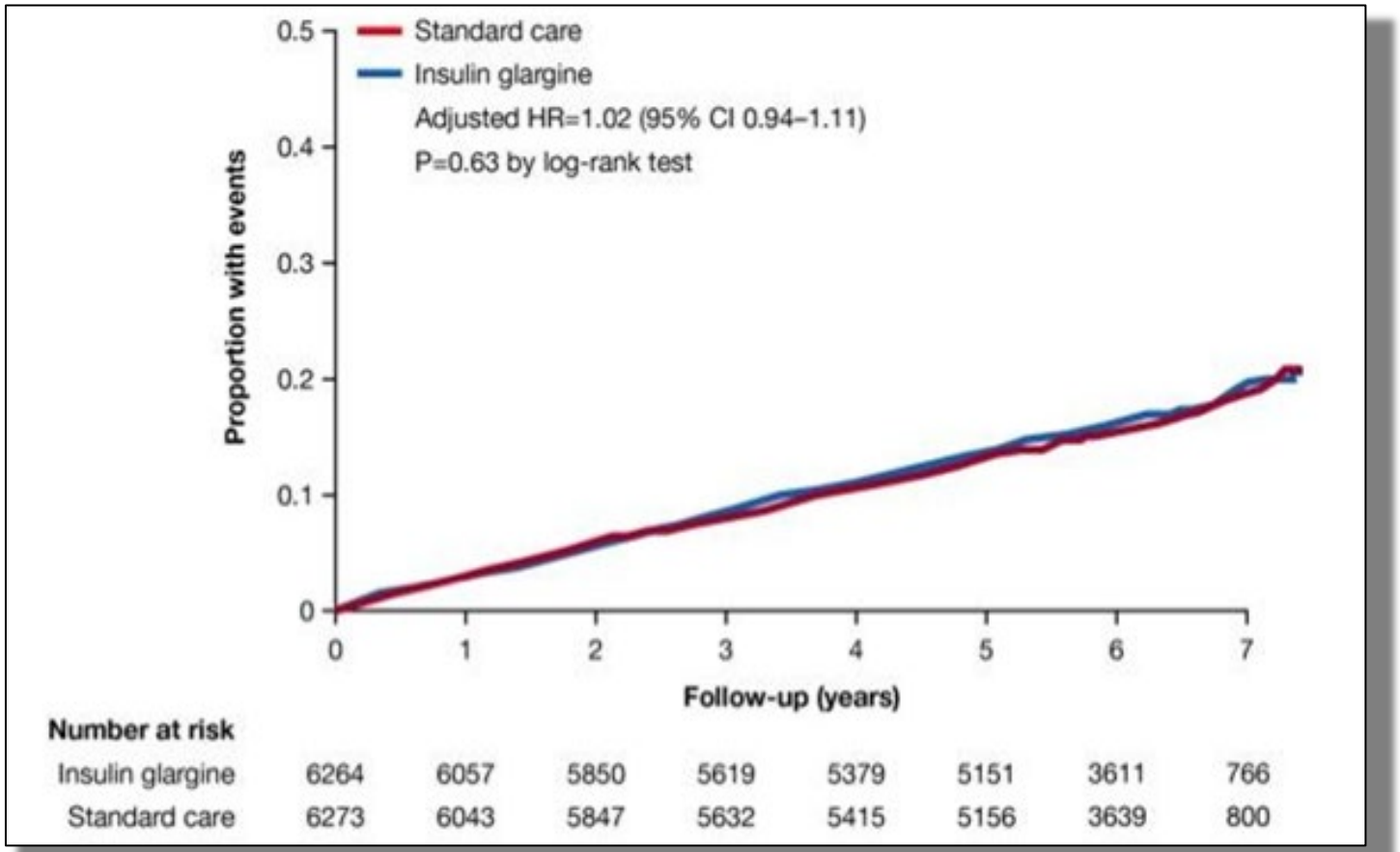
ORIGIN trial

Treatment: glargine insulin
Comparator: standard of care

Principal outcome: MACE (CV death, nonfatal MI, nonfatal stroke)

Patients: 12,537 patients with IFG, IGT, or newly diagnosed T2DM and CV risk factors

Follow-up: 6.2 year



ORIGIN trial investigators. *N Engl J Med* 367:319-28, 2012

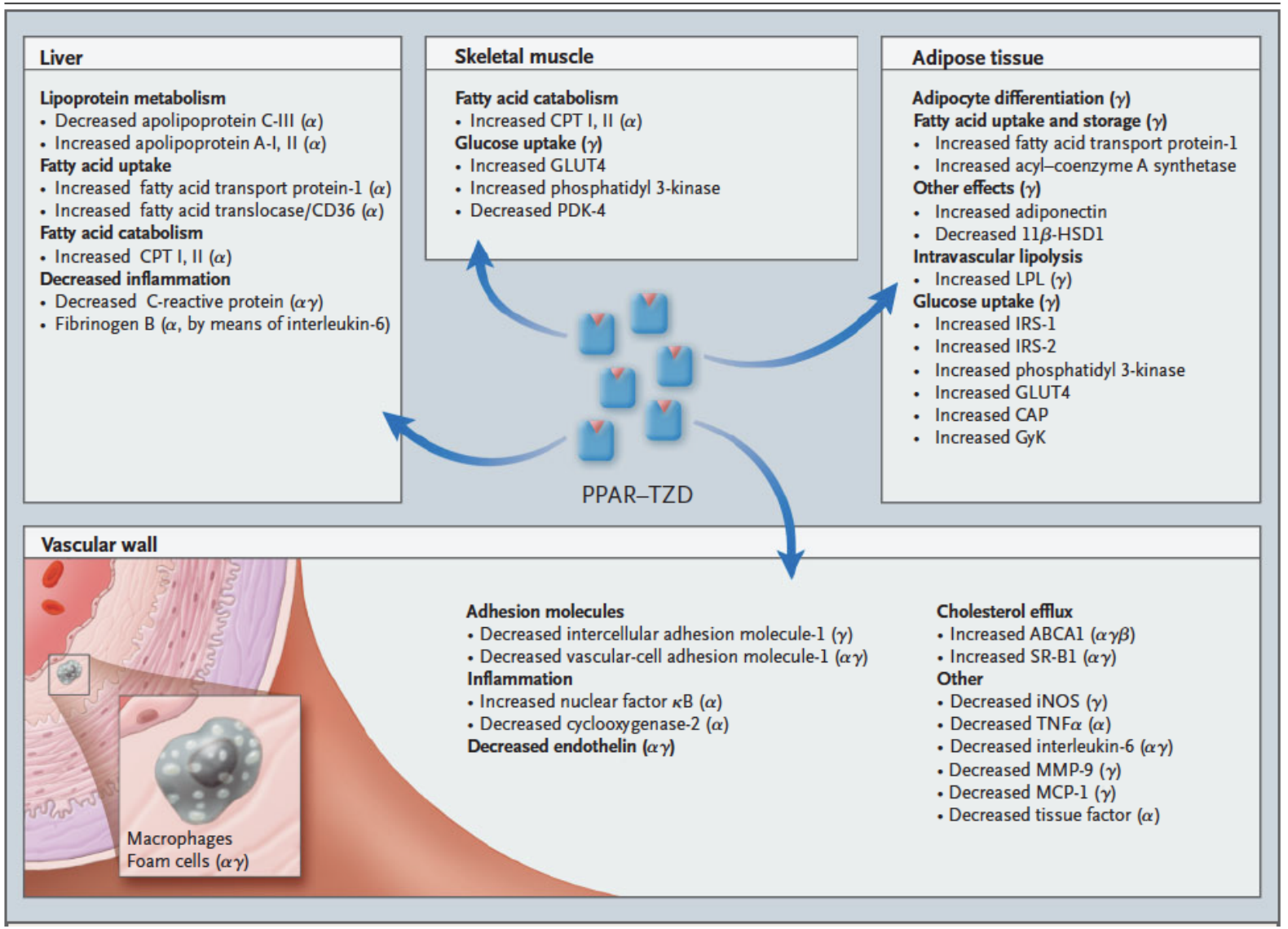
The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

DRUG THERAPY

Thiazolidinediones

Hannele Yki-Järvinen, M.D., F.R.C.P.



Yki-Jarvinen H. *N Engl J Med* 351:1106-18, 2004

ORIGINAL CONTRIBUTION JAMA-EXPRESS

Comparison of Pioglitazone vs Glimepiride on Progression of Coronary Atherosclerosis in Patients With Type 2 Diabetes

The PERISCOPE Randomized Controlled Trial

PERISCOPE trial

Treatment: Pioglitazone
Comparator: Glimepiride

Principal outcome: Change in atheroma volume

Patients: 543 patients with T2DM and coronary artery disease

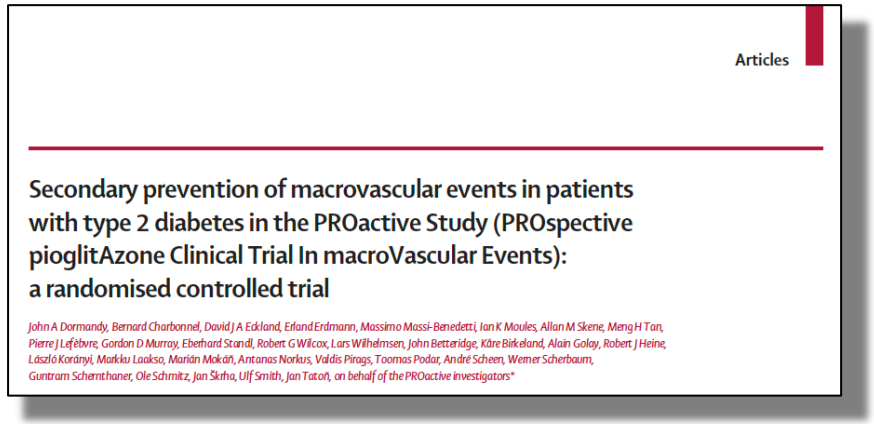
Follow-up: 18 months

Table 3. Baseline, Follow-up, and Change From Baseline in Intravascular Ultrasound End Points

	Glimepiride (n = 181)		Pioglitazone (n = 179)		
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	*P* Value[a]
Baseline Examination					
Percent atheroma volume, %[b]	40.3 (8.9)	40.3 (34.7 to 45.9)	40.6 (8.4)	40.3 (34.1 to 46.0)	.54
Maximum atheroma thickness, mm[c]	0.82 (0.26)	0.80 (0.64 to 0.98)	0.81 (0.25)	0.79 (0.61 to 1.00)	.94
Normalized total atheroma volume,[c] mm^3	219.8 (95.2)	197.8 (148.1 to 277.7)	207.5 (83.8)	190.9 (147.6 to 254.5)	.27
Atheroma volume in 10-mm most diseased segment,[c] mm^3	64.7 (31.5)	62.1 (40.9 to 86.6)	62.7 (28.1)	59.4 (43.6 to 78.7)	.59
Follow-up Examination					
Percent atheroma volume, %[b]	41.0 (9.0)	40.5 (35.2 to 46.9)	40.5 (8.5)	40.5 (33.6 to 46.3)	.73
Maximum atheroma thickness, mm[c]	0.83 (0.26)	0.81 (0.64 to 0.99)	0.80 (0.24)	0.76 (0.62 to 0.97)	.39
Normalized total atheroma volume,[c] mm^3	217.7 (95.3)	192.6 (150.9 to 278.3)	200.8 (81.6)	184.5 (144.6 to 248.4)	.13
Atheroma volume in 10-mm most diseased segment,[c] mm^3	62.4 (31.2)	57.8 (39.5 to 83.1)	60.0 (27.5)	57.9 (39.7 to 77.8)	.62
Nominal Change From Baseline					
	LS Mean (95% CI)	*P* Value Change From Baseline	LS Mean (95%CI)	*P* Value Change From Baseline	*P* Value[d]
Percent atheroma volume, %[b]	0.73 (0.33 to 1.12)	<.001	–0.16 (–0.57 to 0.25)	.44	.002
Maximum atheroma thickness, mm[c]	0.011 (–0.0002 to 0.022)	.054	–0.011 (–0.022 to 0.0004)	.06	.006
Normalized total atheroma volume,[c] mm^3	–1.5 (–4.50 to 1.54)	.34	–5.5 (–8.67 to –2.38)	<.001	.06
Atheroma volume in 10-mm most diseased segment,[c] mm^3	–2.1 (–3.33 to –0.84)	.001	–2.0 (–3.33 to –0.67)	.003	.93

Abbreviation: CI, confidence interval; IQR, interquartile range; LS, least squares.
[a] *P* values for baseline and average follow-up values were generated from a 2-way analysis of variance model with terms for treatment and pooled center.
[b] Primary efficacy parameter.
[c] Secondary efficacy parameter.
[d] *P* values from 2-way analysis of variance with terms for treatment and pooled center and baseline value as covariates.

Nissen SE et al. *JAMA* 299:1561-73, 2008


Articles

Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial

John A Dormandy, Bernard Charbonnel, David J A Eckland, Erland Erdmann, Massimo Massi-Benedetti, Ian K Moules, Allan M Skene, Meng H Tan, Pierre J Lefèbvre, Gordon D Murray, Eberhard Standl, Robert G Wilcox, Lars Wilhelmsen, John Betteridge, Kåre Birkeland, Alain Golay, Robert J Heine, László Korányi, Markku Laakso, Marián Mokáň, Antanas Norkus, Valdis Pirags, Toomas Podar, André Scheen, Werner Scherbaum, Guntram Schernthaner, Ole Schmitz, Jan Skrha, Ulf Smith, Jan Taton, on behalf of the PROactive investigators*

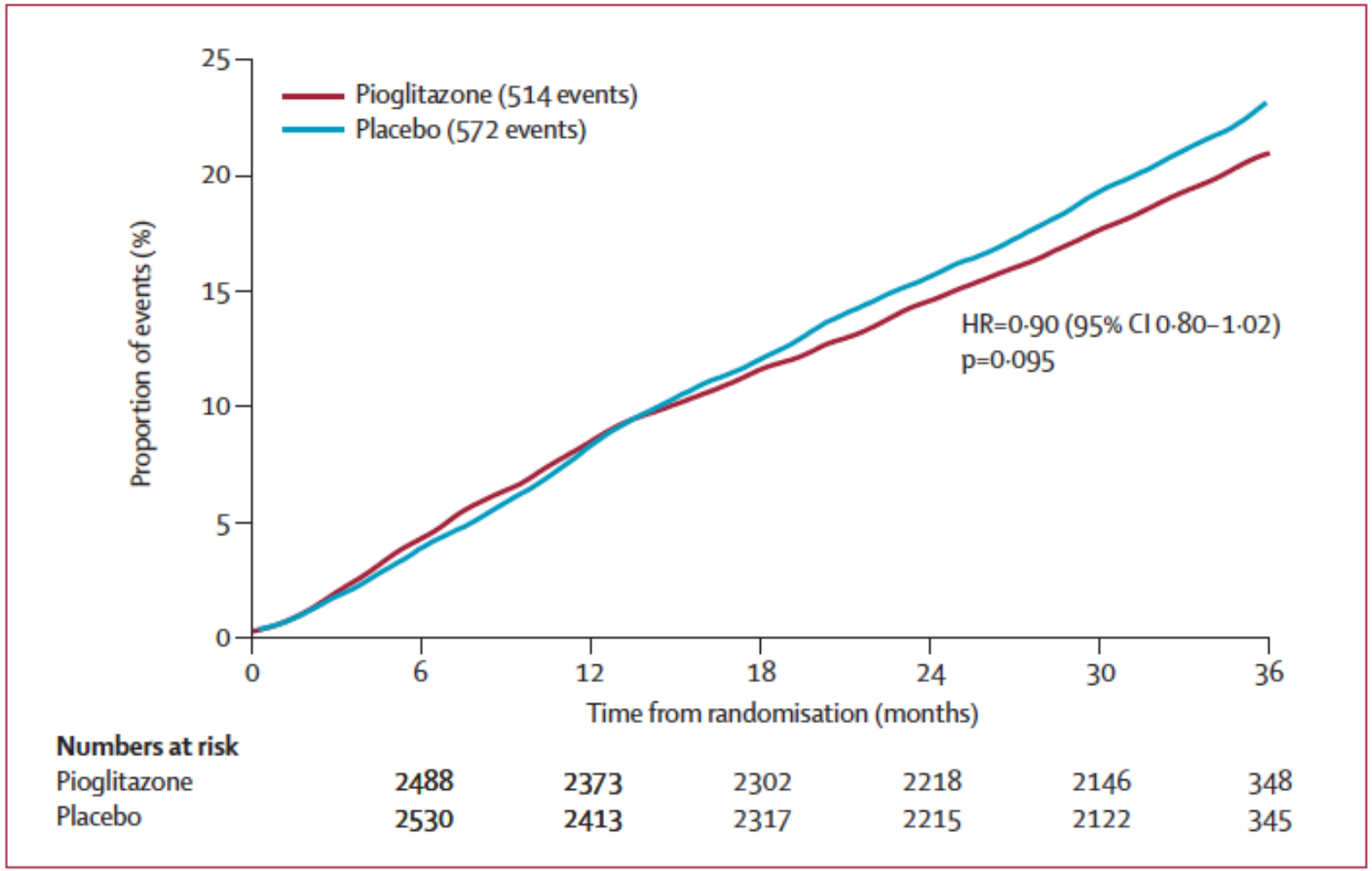
PROACTIVE trial

Treatment: Pioglitazone
Comparator: Placebo

Principal endpoint: All-casue mortality, nonfatal MI or stroke, any ACS, revascularizations, major amputations

Patients: 5238 patients with T2DM and established cardiovascular disease

Follow-up: 34.5 months



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

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 14, 2007 VOL. 356 NO. 24

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

Table 4. Rates of Myocardial Infarction and Death from Cardiovascular Causes.

Study	Rosiglitazone Group	Control Group	Odds Ratio (95% CI)	P Value
	no. of events/total no. (%)			
Myocardial infarction				
Small trials combined	44/10,285 (0.43)	22/6106 (0.36)	1.45 (0.88–2.39)	0.15
DREAM	15/2,635 (0.57)	9/2634 (0.34)	1.65 (0.74–3.68)	0.22
ADOPT	27/1,456 (1.85)	41/2895 (1.42)	1.33 (0.80–2.21)	0.27
Overall			1.43 (1.03–1.98)	0.03
Death from cardiovascular causes				
Small trials combined	25/6,845 (0.36)	7/3980 (0.18)	2.40 (1.17–4.91)	0.02
DREAM	12/2,635 (0.46)	10/2634 (0.38)	1.20 (0.52–2.78)	0.67
ADOPT	2/1,456 (0.14)	5/2895 (0.17)	0.80 (0.17–3.86)	0.78
Overall			1.64 (0.98–2.74)	0.06

Meta-analysis
RCTs on rosiglitazone >24 wk

Treatment: Rosiglitazone
Comparator: placebo/other drugs
Outcome: Myocardial infarction, CV mortality

Nissen S, Wolski K. *N Engl J Med.* 356:2457-71, 2007

Rosiglitazone and Cardiovascular Risk

TO THE EDITOR: The meta-analysis by Nissen and Wolski includes two large trials with primary end points that did not include cardiovascular events. In the Diabetes Reduction Assessment with Ramipiril and Rosiglitazone Medication (DREAM) trial,[1] the observation was stopped when diabetes developed in study patients. In the A Diabetes Outcome Prevention Trial (ADOPT),[2] observation was stopped when unsatisfactory glycemic levels occurred.

Since rosiglitazone provided better results than comparators in both trials, the mean follow-up in the rosiglitazone group was longer than that in the control group. These differences were not accounted for in the meta-analysis. For example, in the ADOPT trial, the yearly incidences of myocardial infarction in the rosiglitazone group and the control group were 0.46% and 0.39%, respectively, with an estimated increase in risk in the rosiglitazone group of 18%, rather than 33%, as reported in the meta-analysis. Data on mean follow-up in the DREAM trial were not reported. However, the reported number of patients at all points of follow-up was higher in the rosiglitazone group than in the placebo group. Therefore, the effect of rosiglitazone on cardiovascular end points in longer-term trials could have been overestimated.

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Methodological issues

- Statistical methods: use of Peto's OR vs MH-OR (fixed vs random)
- Differential duration of exposure bias (ADOPT)
- Selection of trials from one single (and ostensibly incomplete) source

Mannucci E, Monami M, Marchionni N. *N Engl J Med* 357:938-9, 2007

ELSEVIER

International Journal of Cardiology 143 (2010) 135–140

International Journal of Cardiology

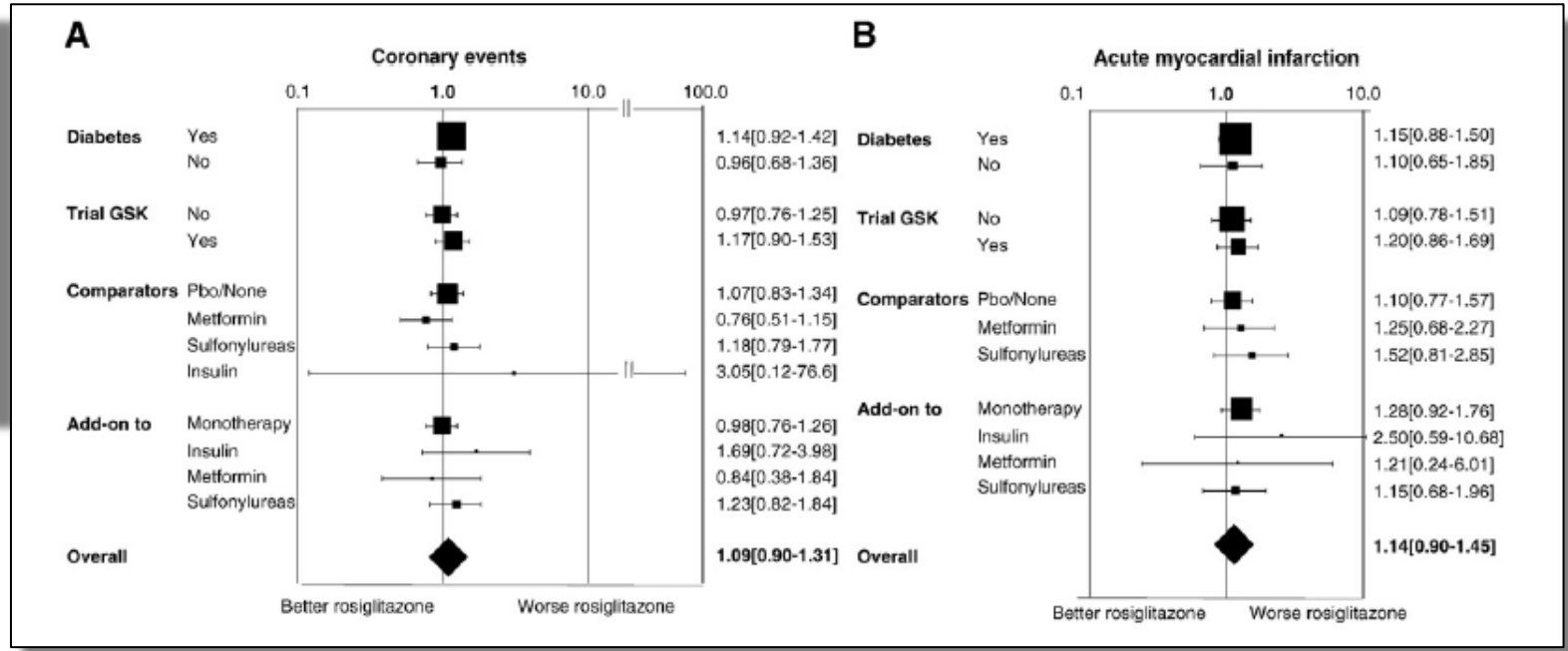
www.elsevier.com/locate/ijcard

Cardiac safety profile of rosiglitazone
A comprehensive meta-analysis of randomized clinical trials

Edoardo Mannucci [a,*], Matteo Monami [a], Mauro Di Bari [a], Caterina Lamanna [a], Francesca Gori [a], Gian Franco Gensini [b], Niccolò Marchionni [a]

[a] Sections of Geriatric Cardiology, Department of Cardiovascular Medicine, University of Florence and AOU Careggi, Florence
[b] Unit of Geriatric Medicine, Department of Cardiovascular Medicine, University of Florence and AOU Careggi, Florence

Received 2 August 2008; received in revised form 20 November 2008; accepted 29 January 2009
Available online 27 March 2009



Meta-analysis

RCTs on rosiglitazone >4 wk

Treatment: Rosiglitazone
Comparator: placebo/other drugs
Outcome: Myocardial infarction, CV mortality

Mannucci E et al. *Int J Cardiol.* 143:135-140, 2010

U.S. Food and Drug Administration
Protecting and Promoting Your Health

Drug Safety Communications

FDA Drug Safety Communication: FDA eliminates the Risk Evaluation and Mitigation Strategy (REMS) for rosiglitazone-containing diabetes medicines

This is an update to the FDA Drug Safety Communication: FDA requires removal of some prescribing and dispensing restrictions for rosiglitazone-containing diabetes medicines issued on November 25, 2013.

Safety Announcement

[12-16-2015] The U.S. Food and Drug Administration (FDA) is eliminating the Risk Evaluation and Mitigation Strategy (REMS) for rosiglitazone-containing type 2 diabetes medicines, which are approved as Avandia, Avandamet, Avandaryl, and generics. The REMS is no longer necessary to ensure that the benefits of rosiglitazone medicines outweigh their risks.

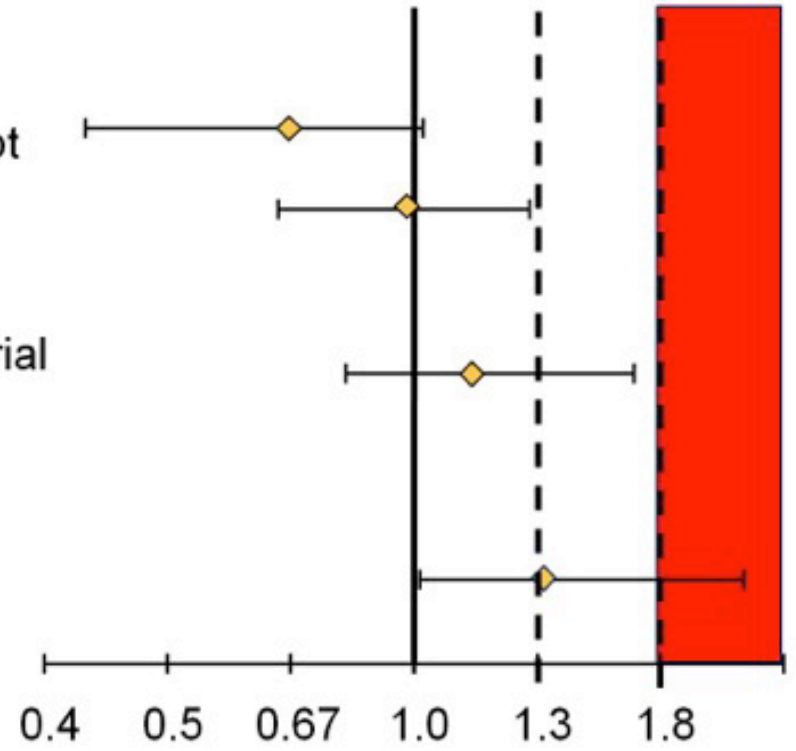
FDA Guidance for CV safety of new drugs for diabetes

- 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

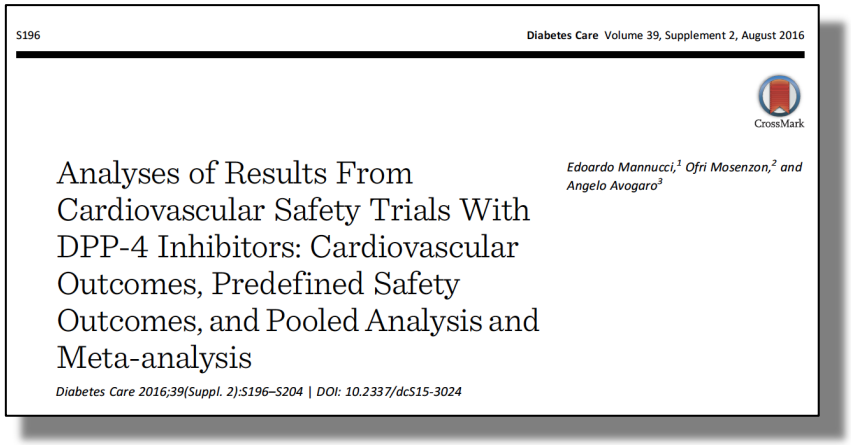
<1.8 – conduct large safety trial post-approval

>1.8 – conduct large safety trial pre-approval



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

Methodological issues of CVOTs in diabetes



S196 Diabetes Care Volume 39, Supplement 2, August 2016

Analyses of Results From Cardiovascular Safety Trials With DPP-4 Inhibitors: Cardiovascular Outcomes, Predefined Safety Outcomes, and Pooled Analysis and Meta-analysis

Edoardo Mannucci,[1] Ofri Mosenzon,[2] and Angelo Avogaro[3]

Diabetes Care 2016;39(Suppl. 2):S196–S204 | DOI: 10.2337/dcS15-3024

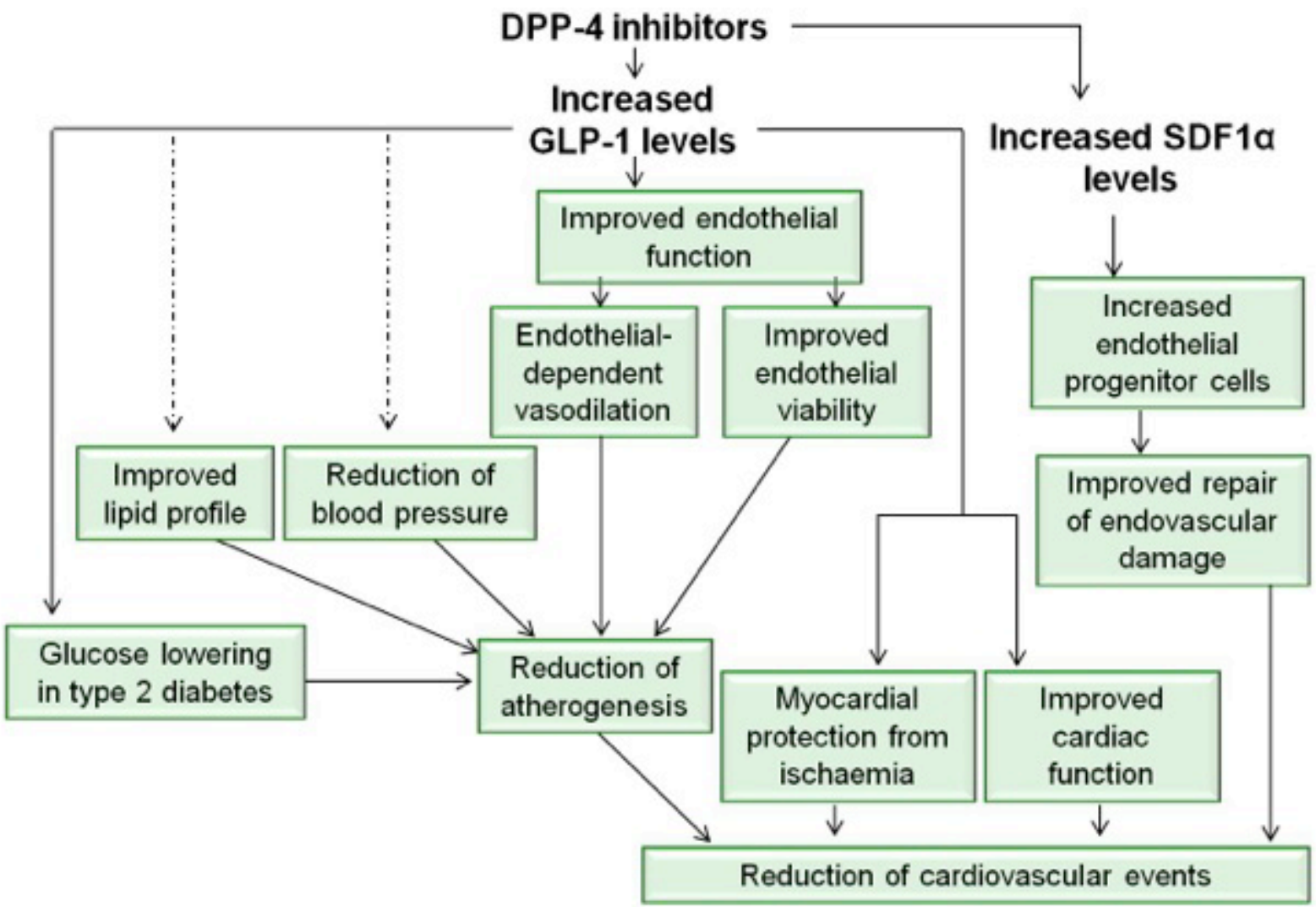
- Heterogeneity of the primary endpoint (MACE)
- Designed for non-inferiority (event-driven, target 611 events)
- Enrolment of very high-risk patients
- Relatively short duration of follow-up
- Attempt at minimizing between-group differences in glucose control

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

CMRO
Current Medical Research & Opinion Vol. 28, No. 5, 2012, 715–721
0300-7995
Article ST-0476.R1/678940
doi:10.1185/03007995.2012.678940

Brief review

Incretin-based therapies and cardiovascular risk



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

original article

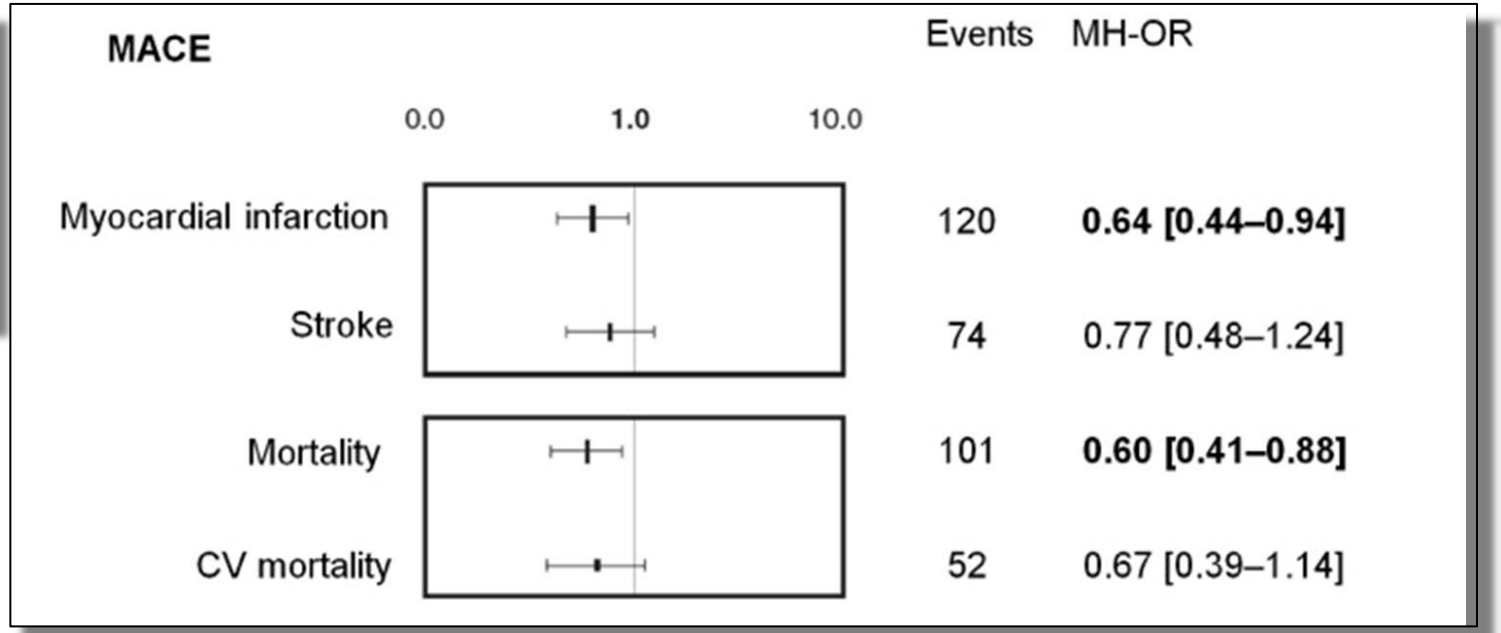
Diabetes, Obesity and Metabolism 15: 112–120, 2013.

ORIGINAL ARTICLE

Dipeptidyl peptidase-4 inhibitors and cardiovascular risk: a meta-analysis of randomized clinical trials

M. Monami[1], B. Ahrén[2], I. Dicembrini[3] & E. Mannucci[4]

[1] Section of Geriatric Cardiology and Medicine, Careggi Teaching Hospital, Florence, Italy
[2] Department of Clinical Sciences Lund, Lund University, Lund, Sweden
[3] Obesity Agency, Careggi Teaching Hospital, Florence, Italy
[4] Diabetes Agency, Careggi Teaching Hospital, Florence, Italy



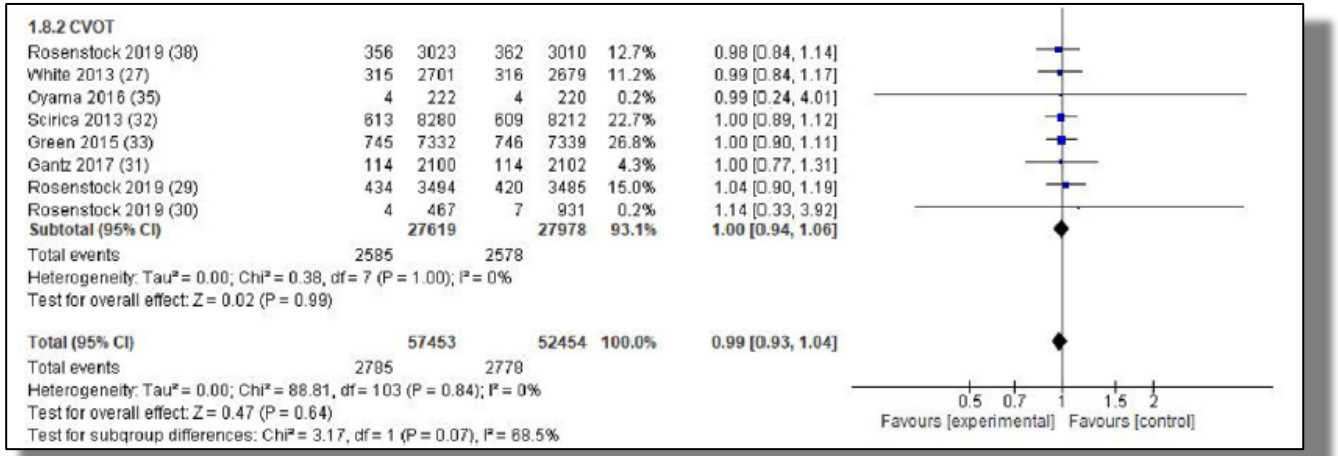
Meta-analysis
RCTs on DPP4i >24 wk
(mainly phase II-III trials)

Treatment: DPP4 inhibitors
Comparator: placebo/other drugs
Outcome: CV events, mortality

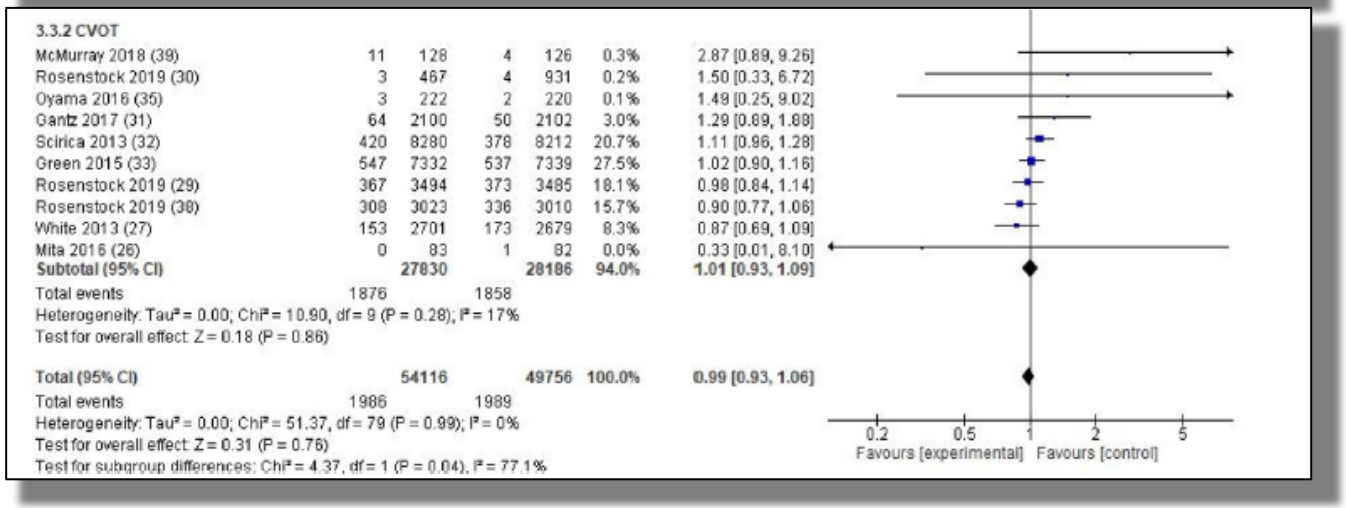
Monami M et al. *Diabetes Obes Metab* 15:112-20, 2013

Italian guidelines for the treatment of T2DM
Evidence base for 2021 edition

MACE

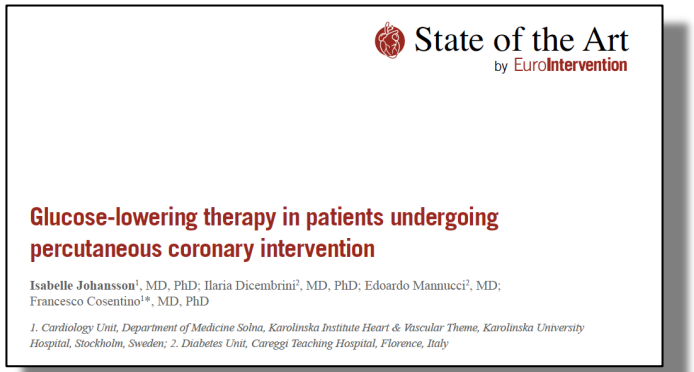


Mortality



DPP4 inhibitors

Mannucci E et al. for SID-AMD T2DM Guideline Panel. *Nutr Metab Cardiovasc Dis* 31:1027-34, 2021


State of the Art
by EuroIntervention

Glucose-lowering therapy in patients undergoing percutaneous coronary intervention

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Results of CV outcome trials with GLP1R agonists

	CV OUTCOMES TRIALS IN T2DM						
	ELIXA	LEADER	SUSTAIN-6	EXSCEL	Harmony Outcomes	REWIND	PIONEER 6
Number of patients	6,068	9,340	3,297	14,752	9,463	9,901	3,182
Drug (dose)	Lixisenatide vs placebo 10-20 ug sc	Liraglutide vs placebo 1.8 mg sc	Semaglutide vs placebo 0.5 mg or 1.0 mg sc	Exenatide vs placebo 2 mg sc weekly	Albiglutide vs placebo 30 to 50 mg sc weekly	Dulaglutide vs placebo 1.5 mg sc weekly	Oral semaglutide vs placebo 14 mg
Inclusion criteria							
T2DM	100%	100%	100%	100%	100%	100%	100%
Cardiovascular	CVD	CVD or CKD or RF	CVD or CKD or RF	CVD, CHD or RF	CVD or RF	CVD or RF	CVD or CKD or RF
Renal	eGFR ≥30	N/A	N/A	eGFR ≥30	eGFR ≥30	eGFR ≥15	eGFR ≥30
Cardiovascular outcomes (HR)							
Follow-up (years)	2.1	3.8	2.1	3.2	1.6	5.4	1.3
MACE	1.02 (0.89-1.17)	0.87 (0.78-0.97)	0.74 (0.58-0.95)	0.91 (0.83-1.00)	0.78 (0.68-0.90)	0.88 (0.79-0.99)	0.79 (0.57-1.11)
Death (any cause)	0.94 (0.78-1.13)	0.85 (0.74-0.97)	1.05 (0.74-1.50)	0.86 (0.77-0.97)	0.95 (0.79-1.16)	0.90 (0.80-1.01)	0.51 (0.31-0.84)
Death (CV)	0.98 (0.78-1.22)	0.78 (0.66-0.93)	0.98 (0.65-1.48)	0.88 (0.76-1.02)	0.93 (0.73-1.19)	0.91 (0.78-1.06)	0.49 (0.27-0.92)
HHF	0.96 (0.75-1.23)	0.87 (0.73-1.05)	1.11 (0.77-1.61)	0.94 (0.78-1.13)	N/A	0.93 (0.77-1.12)	0.86 (0.48-1.55)
Renal outcomes (HR)							
Composite renal	N/A	N/A	1.28 (0.64-2.58)	N/A	N/A	0.85 (0.77-0.93)[b]	N/A
Loss of renal function	N/A	0.78 (0.67-0.92)[a]	1.28 (0.46-0.88)	N/A	N/A	N/A	N/A
ESRD	N/A	N/A	0.91 (0.40-2.07)	N/A	N/A	N/A	N/A
Acute kidney injury	N/A	N/A	N/A	N/A	0.87 (0.75-1.02)	N/A	N/A

Cosentino F, et al. *Eurointervention* 17:e618-30, 2021

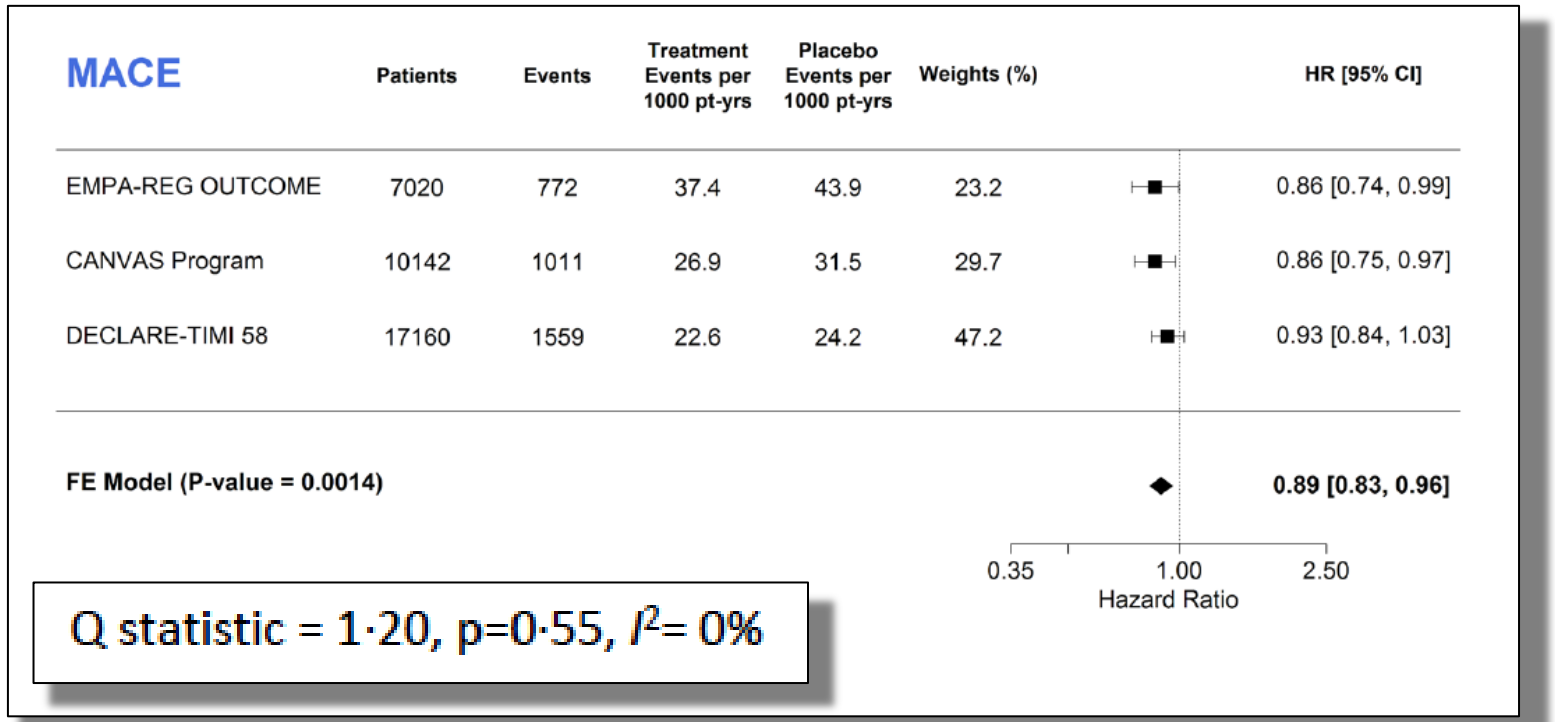
Articles

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

Thomas A Zelniker, Stephen D Wiviott, Itamar Raz, Kyungah Im, Erica L Goodrich, Marc P Bonaca, Ofri Mosenzon, Eri T Kato, Avivit Cahn, Remo H M Furtado, Deepak L Bhatt, Lawrence A Leiter, Darren K McGuire, John P H Wilding, Marc S Sabatine

Meta-analysis

Studies: CVOTs with SGLT2i in T2DM
Treatment: SGLT2i
Comparison: placebo
Outcome: major cardiovascular events (MACE)



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

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BRIEF REPORT

WILEY

Sodium-glucose co-transporter-2 inhibitors and all-cause mortality: A meta-analysis of randomized controlled trials

Giovanni Antonio Silverii MD[1] | Matteo Monami PhD[2] | Edoardo Mannucci MD[1]

Meta-analysis

Studies: RCTs on SGLT2i >12wk and >100 patients per arm
Treatment: SGLT2 inhibitors
Comparator: placebo, other drugs
Outcome: All.cause mortality

SGLT2 inhibitors	Number of trials (*n*)	Weighted event rates*		At a median 104 wk	
		SGLT2 inhibitor	Control	RRR (95% CI)*	NNT (CI)*
All	21 (70 364)	6.5%	7.5%	13% (8 to 18)	103 (76 to 160)
Empagliflozin	8 (15 485)	6.2%	7.6%	19% (8 to 28)	71 (47 to 158)
Ertugliflozin	3 (10 182)	7.1%	7.6%	7% (−8 to 19)	Not significant
Canagliflozin	4 (16 707)	6.2%	7.1%	12% (2 to 23)	116 (63 to 758)
Dapagliflozin	6 (27 990)	6.5%	7.6%	14% (6 to 21)	95 (64 to 237)

SGLT2 = sodium–glucose cotransporter-2; other abbreviations defined in Glossary.
*Weighted event rates, RRR, NNT, and CI calculated from control event rates and odds ratios in article.

Silverii et al. *Diabetes Obes Metab* 23:1052-6, 2021

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

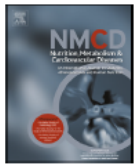
All mechanisms discussed in the present review are listed, according to their nature. The mechanisms assessed in the EMPAREG-OUTCOME study are indicated in bold.

Nutrition, Metabolism & Cardiovascular Diseases (2016) 26, 1071–1078

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd



Review

Which is the main molecular target responsible for the cardiovascular benefits in the EMPA-REG OUTCOME trial? A journey through the kidney, the heart and other interesting places

M. Luconi [a], L. Raimondi [b], A. Di Franco [a], E. Mannucci [a,c,*]

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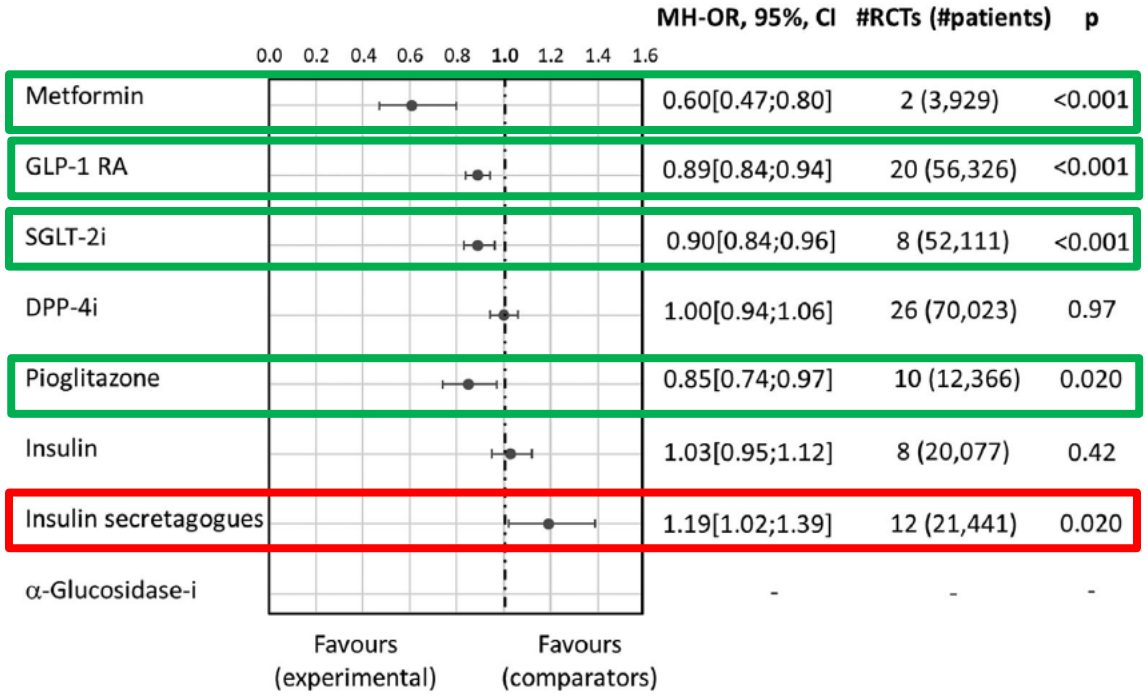
Available online 10 September 2016

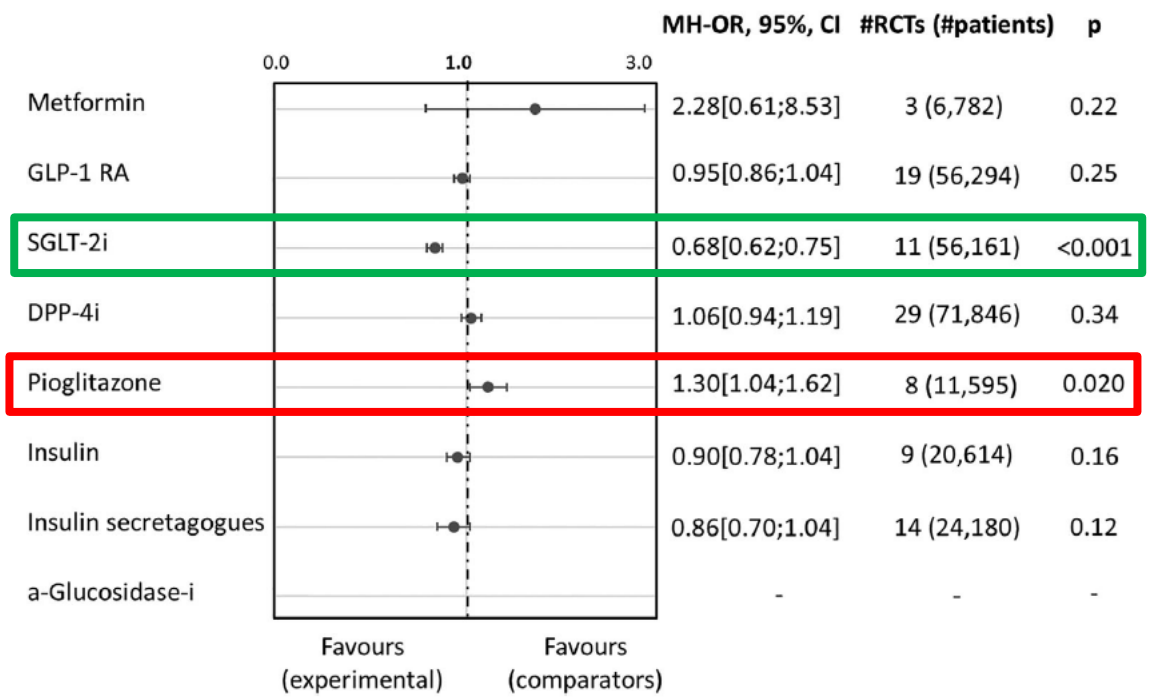
Luconi M, et al. *Nutr Metab Cardiovasc Dis* 26:1071-8, 2016

Italian guidelines for the treatment of T2DM
Evidence base for 2023 update

Major Cardiovascular Events



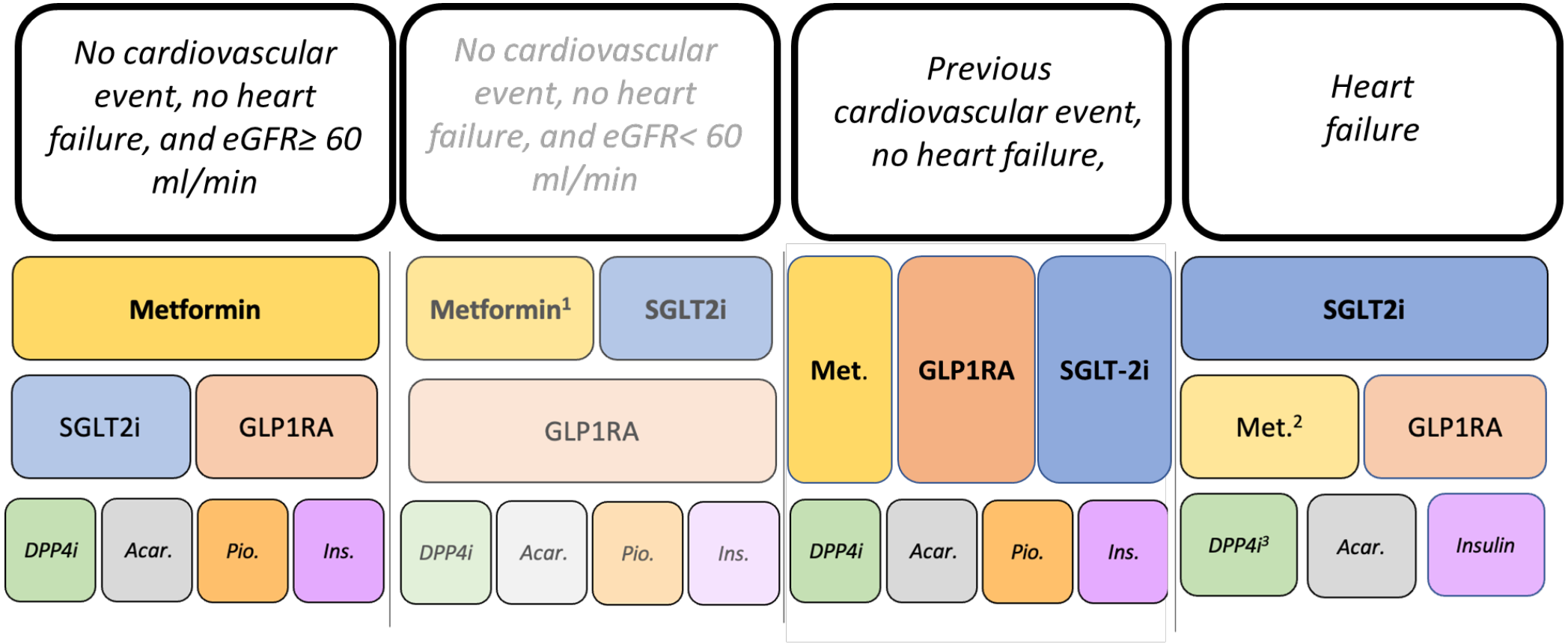
Hospitalizations for heart failure



Mannucci E et al. for SID-AMD T2DM Guideline Panel. *Diabetes Obes Metab* 25:444-53, 2023

Italian guidelines for the treatment of T2DM, 2023

Drug therapy



[1,2] *If metformin is not contraindicated.*

[3] *With the exception of saxagliptin which is not indicated for patients with heart failure.*

The recommendation for patients with eGFR< 60ml/min is weak (few studies on this population) and therefore is written with a lighter type

We recommend to deprescribe sulfonylureas and glinides.

Mannucci E et al. for SID-AMD guideline panel. *Acta Diabetol*, 2023