Gli studi di meta-analisi

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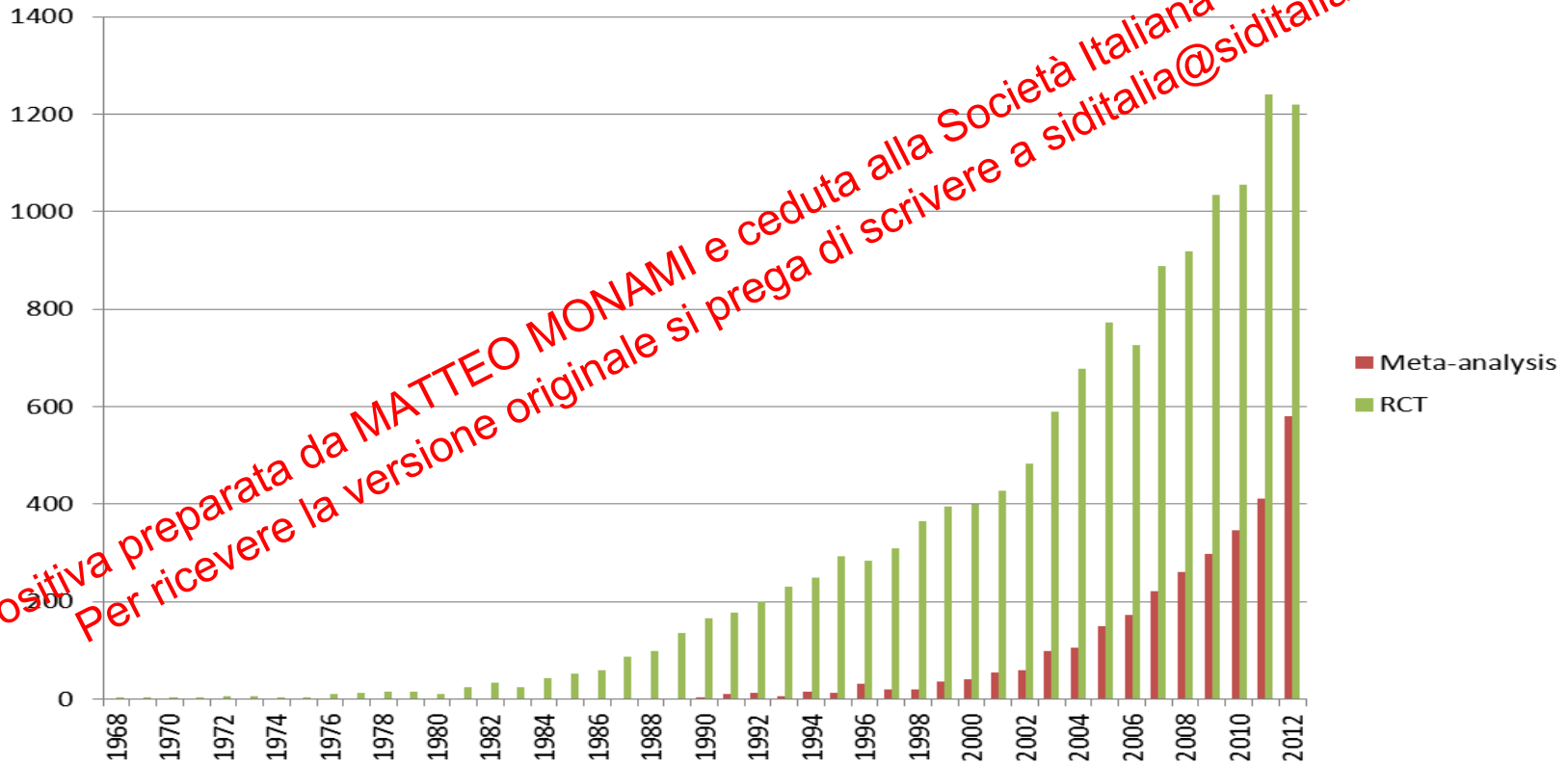
Disclosures

- Dr Monami has received consultancy and/or speaking fees from:
  - Merck Sharp & Dohme
  - AstraZeneca
  - Bristol-Myers Squibb
  - Eli Lilly
  - Novo Nordisk
  - Sanofi
  - Takeda
- In addition, the Diabetes Section directed by Dr Monami received research grants from AstraZeneca and BMS.

Meta-analysis and diabetes

A new pandemia?



Qualità degli studi primari e revisioni sistematiche: rating del livello delle evidenze

Ia ***Metaanalisi o review sistematiche basate su più studi di livelli Ib***

Ib Trial diagnostici o studi di esito di buona qualità

II Trial diagnostici or studi di esito di media qualità, numero insufficiente di pazienti, o altri trials (case–control, altri designi)

III Studi descrittivi, case report ed altri studi

IV Indicazioni di comitati, opinioni di esperti, e così di seguito (reviews non sistematiche etc.)

Rating della forza delle evidenze a supporto delle raccomandazioni nelle linee guida

A Supportati da almeno due studi di livello Ib o da una review di livelli Ia ("E' stato dimostrato")

B Supportate da almeno due studi indipendenti di livello II o estrapolazioni da studi di livelli I ("E' plausibile")

C Non supportati da adeguati studi di livello I o II ("indicazioni")

D Indicazioni di esperti ("non ci sono prove")

Summarize the Evidence

How to do?

1. **Narrative review:**

   It has the disadvantage to summarize available evidence without really synthetizing it in simple numbers

2. **Pooled analysis** (based on individual patient data, meaning that patients enrolled in different trials are analyzed together as if they have participated to the same trial)

   Retrospectively planned

   Prospectively planned:

Meta-analisi in cui gli studi, in genere studi clinici randomizzati, vengono individuati, valutati e inclusi nel protocollo della meta-analisi prima che siano noti i risultati degli studi stessi.

3. **Meta-analysis** of published data

What is a meta-analysis?

Potential strengths

Meta-analysis is the statistical combination of results from two or more separate studies.

1. Increase in power
2. Settle controversies arising from conflicting claims
3. Ability to answer questions not posed by individual studies

Meta-analysis

Potential strengths

1. **Increase in power**: the power of a meta-analysis is that of a single trial enrolling a total sample composed by all individual samples of the trials included in the meta-analysis
2. Settle controversies arising from conflicting claims
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Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes

Underpowered studies

	Chlorpropamide (n=619)	Glibenclamide (n=615)	Insulin (n=911)	OVERALL (n=2,145)	p
Myocardial Infarction	*0.87* (0.68-1.12)	*0.78* (0.60-1.01)	*0.87* (0.70-1.09)	**0.84** (0.71-1.00)	**0.052**
Stroke	*1.01* (0.65-1.58)	*1.38* (0.92-2.08)	*0.86* (0.57-1.81)	**1.11** (0.81-1.51)	0.52
All-cause mortality	*1.02* (0.82-1.27)	*0.91* (0.73-1.15)	*0.93* (0.76-1.14)	**0.94** (0.80-1.10)	0.44

UK Prospective Diabetes Study (UKPDS) Group.
The Lancet, Volume 352, Issue 9131, Pages 837 - 853

CV outcome studies in T2DM

Power calculations

	UKPDS*	ADVANCE	ACCORD	VADT
Number	3,867	11,140	10,251	1,791
Mean follow-up (y)	11	5	3	6
Incidence of MACE in ctrl (% pt*y)	1.7	2.1	2.3	4.9
Power for 10% reduction (%)	21	42	22	21
% reduction for 80% power	21	16	25	24

* MI

capacità di vedere differenze superiori al 10% tra i due gruppi in termini di MACE

Strengths

Underpowered studies

Effect of Intensive vs conventional treatment on the risk of microvascular and macrovascular complications

UKPDS 33 **VADT** **ADVANCE**

Cardiovascular endpoint, but prematurely terminated → **ACCORD**

Underpowered studies

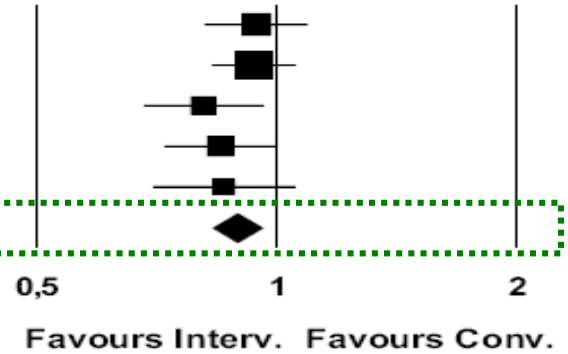
Prevention of cardiovascular disease through glycemic control in type 2 diabetes:

A meta-analysis of randomized clinical trials

Increase in power

A Cardiovascular events

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
ACCORD	0,944	0,811	1,099	-0,746	0,455
ADVANCE	0,937	0,830	1,059	-1,035	0,301
PROACTIVE	0,81	0,68	0,966	-2,346	0,019
UKPDS 33+34	0,852	0,723	1,003	-1,920	0,055
VADT	0,860	0,700	1,058	-1,425	0,154
OVERALL	0,893	0,832	0,957	-3,182	0,001



E. Mannucci*, M. Monami, C. Lamanna, F. Gori, N. Marchionni Nutrition, Metabolism & Cardiovascular Diseases (2009)

Meta-analysis

Potential strengths

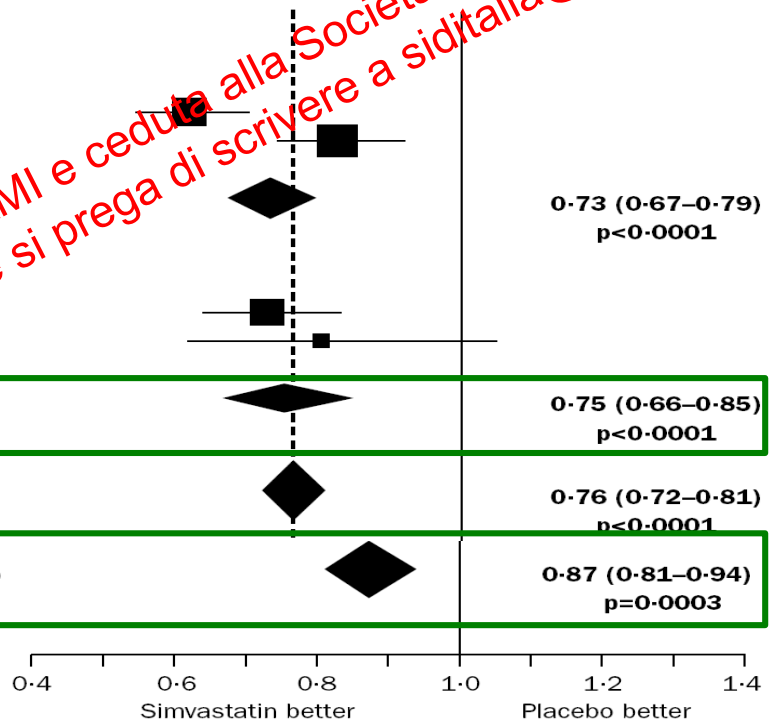
1. Increase in power: the power of a meta-analysis is that of a single trial enrolling a total sample composed by all individual samples of the trials included in the meta-analysis
2. **Settle controversies** arising from conflicting claims
3. Ability to answer questions not posed by individual studies

MRC/BHF Heart Protection study of cholesterol lowering with simvastatin in 20,536 high-risk individuals

A randomized placebo-controlled trial

MRC/BHF Heart Protection Study Collaborative Group*

Type of major vascular event	Simvastatin-allocated (10 269)	Placebo-allocated (10 267)	Event rate ratio (95% CI)
Coronary events			
Non-fatal MI	357 (3·5%)	574 (5·6%)	
Coronary death	587 (5·7%)	707 (6·9%)	
Subtotal: major coronary event	**898 (8·7%)**	**1212 (11·8%)**	**0·73 (0·67–0·79) p<0·0001**
Strokes			
Non-fatal stroke	366 (3·6%)	498 (4·9%)	
Fatal stroke	96 (0·9%)	119 (1·2%)	
Subtotal: any stroke	**444 (4·3%)**	**585 (5·7%)**	**0·75 (0·66–0·85) p<0·0001**
ANY MAJOR VASCULAR EVENT	**2033 (19·8%)**	**2585 (25·2%)**	**0·76 (0·72–0·81) p<0·0001**
ANY DEATH	**1328 (12·9%)**	**1507 (14·7%)**	**0·87 (0·81–0·94) p=0·0003**



Lancet 2002; **360:** 7–22

Pravastatin in elderly individuals at risk of vascular disease (PROSPER)

A randomized controlled trial

PROSPER study group[1]

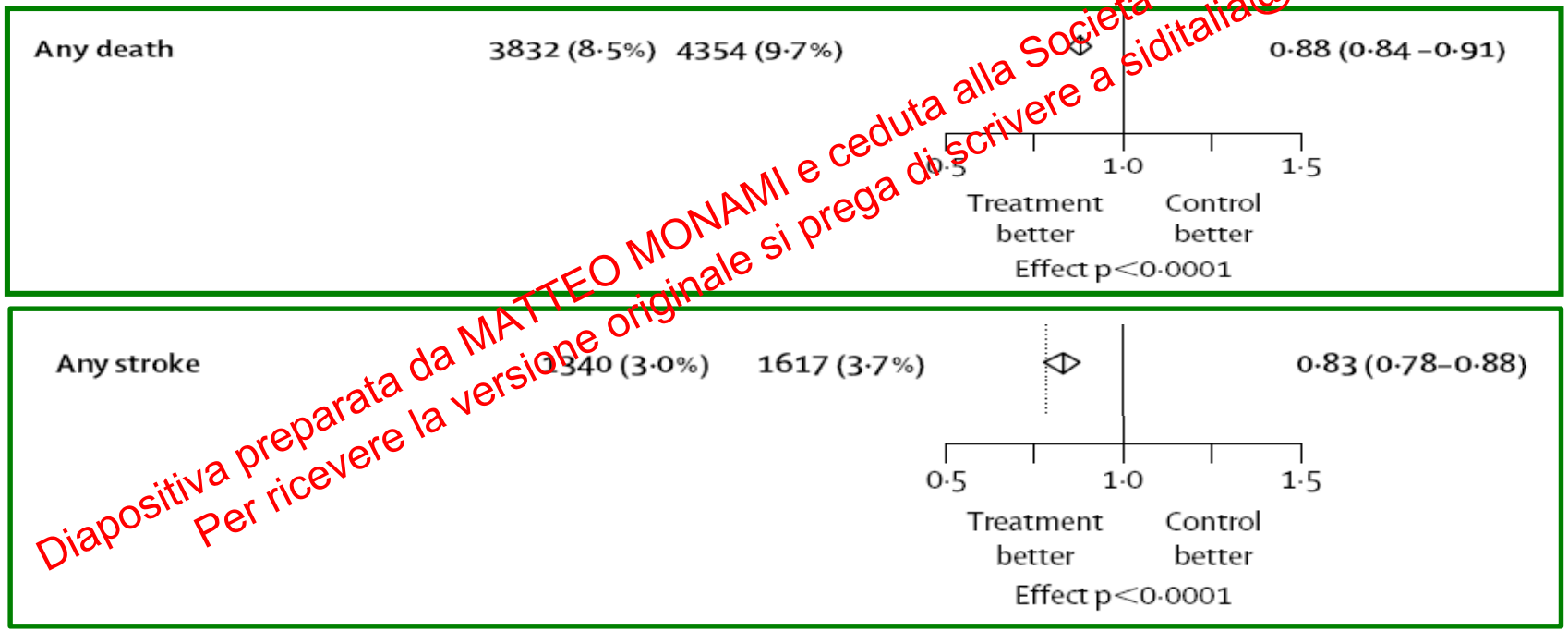
	Placebo (n, %) (n=2913)	Pravastatin (n, %) (n=2891)	Hazard ratio (95% CI)	p*
Primary endpoint				
Coronary heart disease death or non-fatal myocardial infarction or fatal or non-fatal stroke	473 (16·2)	408 (14·1)	0·85 (0·74–0·97)	0·014
Secondary endpoints				
Coronary heart disease death or non-fatal myocardial infarction	356 (12·2)	292 (10·1)	0·81 (0·69–0·94)	0·006
Fatal or non-fatal stroke	134 (4·5)	135 (4·7)	1·03 (0·81–1·31)	0·81
Deaths				
Coronary heart disease	122 (4·2)	94 (3·3)	0·76 (0·58–0·99)	0·043
Stroke	14 (0·5)	22 (0·8)	1·57 (0·80–3·08)	0·19
Vascular	157 (5·4)	135 (4·7)	0·85 (0·67–1·07)	0·16
Non-vascular	149 (5·1)	163 (5·6)	1·11 (0·89–1·38)	0·38
Cancer	91 (3·1)	115 (4·0)	1·28 (0·97–1·68)	0·082
Trauma or suicide	7 (0·2)	2 (0·1)	N/A	N/A
All causes	306 (10·5)	298 (10·3)	0·97 (0·83–1·14)	0·74

Lancet 2002; **360:** 1623–30.

Efficacy and safety of cholesterol-lowering treatment

Prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins

Cholesterol Treatment Trialists' (CTT) Collaborators



Lancet 2005; 366: 1267–78

Meta-analysis

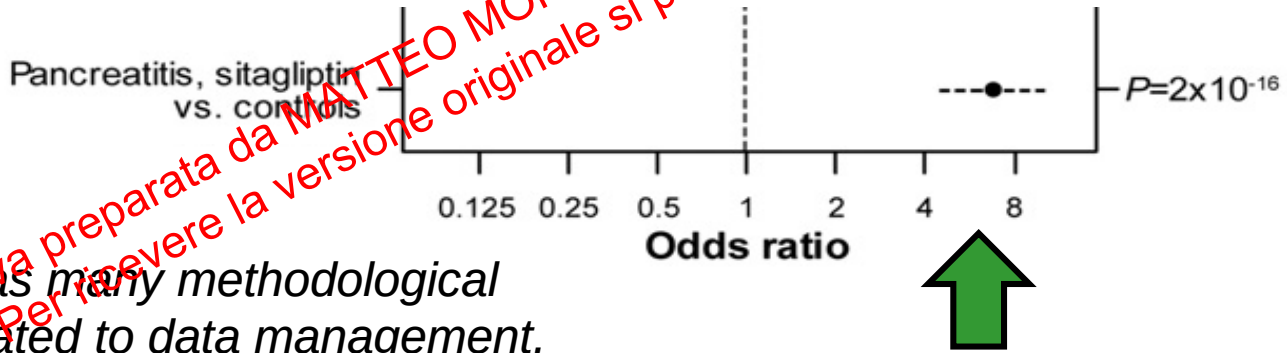
Potential strengths

1. Increase in power: the power of a meta-analysis is that of a single trial enrolling a total sample composed by all individual samples of the trials included in the meta-analysis
2. Settle controversies arising from conflicting claims
3. Ability to answer **questions not posed by individual studies**

Pancreatitis, Pancreatic, and Thyroid Cancer With GLP-1-Based Therapies

M. Elashoff, V.A. Matveyenko, B. Gier, R. Elashoff, P.C. Butler

PANCREATITIS				
Drug	Pancreatitis events	Control events	Odds ratio vs control drugs	*P*-value vs control drugs
Exenatide	971	1433	10.68	2×10^{-16}
Sitagliptin	131	306	6.74	2×10^{-16}
Controls	43	678	—	—



This study has many methodological problems related to data management, underreporting adverse events and confounding factors.

7-fold increased risk of pancreatitis

Gastroenterology 2011; 141:150-156

Dipeptidyl peptidase-4 inhibitors and pancreatitis risk

A meta-analysis of randomized clinical trials

- 109 trials with duration ≥12 weeks with available information
- Exposure: 45,239 patient–years
- Cases of acute pancreatitis: 36

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

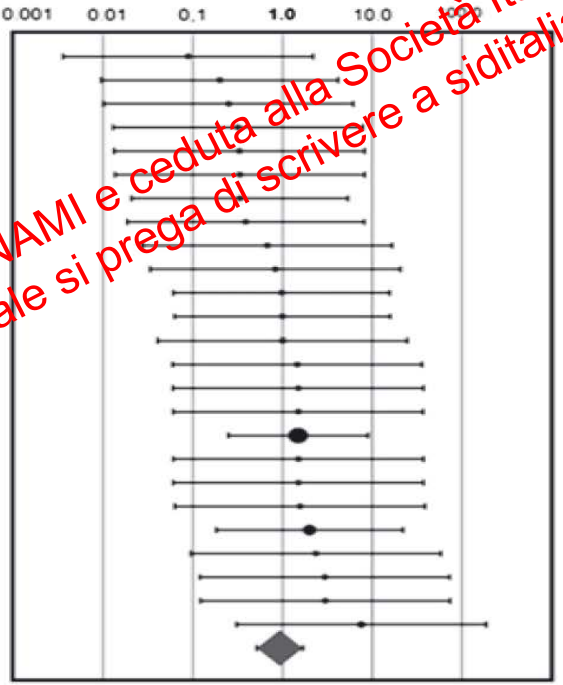
Diabetes, Obesity and Metabolism 2013.

DPP-4 inhibitors and pancreatitis risk

A meta-analysis of randomized clinical trials

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

First author (ref)	MH-OR (95% Confidence Intervals)			p	Relative weight (%)	DPP-4 inhibitors Events	DPP-4 inhibitors Patients	Comparators Events	Comparators Patients
Raz 2006 (41)	0,089	0,004	2,192	0,14	3,42	0	411	1	110
NCT00575588 (1)	0,200	0,010	4,178	0,30	3,81	0	428	2	430
NCT00722371 (1)	0,250	0,010	6,152	0,40	3,43	0	922	1	693
Scherbaum 2008 (65)	0,318	0,013	7,878	0,48	3,42	0	156	1	150
NCT00614939 (1)	0,329	0,013	8,202	0,50	3,40	0	85	1	85
NCT01289119 (1)	0,333	0,014	8,221	0,50	3,42	0	252	1	253
Pfutzner 2011 (21)	0,335	0,021	5,366	0,44	4,57	1	978	1	328
Bergenstal 2010 (52)	0,389	0,019	8,141	0,54	3,80	0	166	2	325
NCT00700817 (1)	0,677	0,027	16,675	0,81	3,43	0	219	1	446
NCT01204294 (1)	0,831	0,034	20,523	0,91	3,41	1	450	0	124
Williams-Herman 2010 (45)	0,980	0,061	15,708	0,99	4,57	1	551	1	540
NCT00482729 (1)	0,994	0,062	15,920	1,00	4,57	1	625	1	621
Rosenstock 2010 (10)	1,000	0,041	24,668	1,00	3,43	1	491	0	163
Hollander 2011 (26)	1,455	0,059	35,88	0,82	3,42	1	381	0	184
NCT00996658 (1)	1,496	0,060	37,080	0,81	3,41	1	186	0	92
DeFronzo 2012 (5)	1,496	0,061	36,796	0,81	3,43	1	1,038	0	517
Ferrannini 2009 (69)	1,498	0,066	8,914	0,66	10,97	3	1,396	2	1,393
Pan 2008 (53)	1,505	0,061	37,098	0,80	3,43	1	440	0	220
Rosenstock 2009 (6)	1,505	0,061	37,291	0,80	3,42	1	260	0	130
Garber 2008 (60)	1,562	0,063	38,554	0,79	3,42	1	305	0	158
NCT00954447 (1)	2,000	0,181	22,113	0,57	6,09	2	631	1	630
NCT00328172 (1)	2,345	0,095	58,033	0,60	3,42	1	170	0	132
Wainstein 2012 (50)	2,954	0,120	72,849	0,51	3,42	1	261	0	256
Seck 2010 (49)	2,985	0,121	73,416	0,50	3,43	1	588	0	584
Russell-Jones 2012 (51)	7,560	0,306	186,538	0,22	3,42	1	163	0	409
OVERALL	**0,933**	**0,515**	**1,688**	**0,817**	**100,00**	**20**	**11,553**	**16**	**8,973**



MH-OR: 0.93 (0.51–1.69)

Diabetes, Obesity and Metabolism 2013.

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/sulphonylurea (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

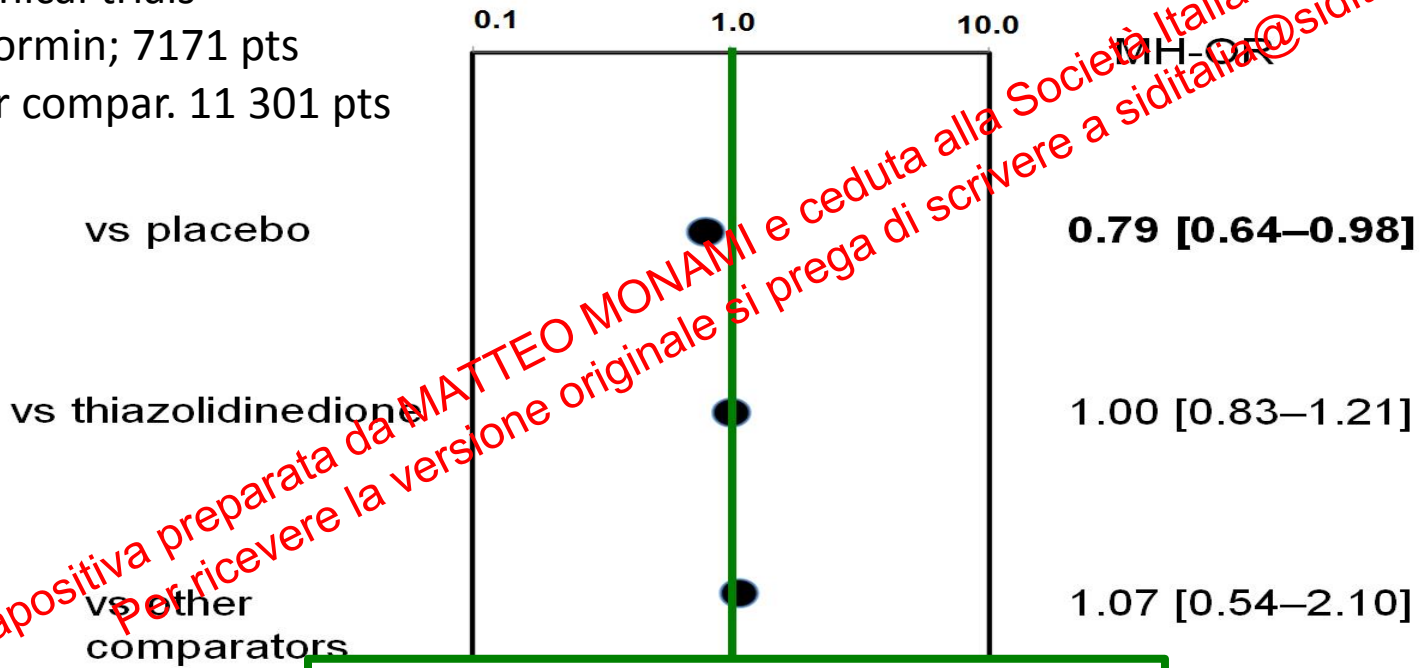
*P<0.05 vs conventional; †P<0.05 vs insulin/SU

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

Metformin and MACE

Meta-analysis of available RCTs

35 clinical trials
Metformin; 7171 pts
Other compar. 11 301 pts



Overall MH-OR 0.94[0.82-1.07], p = 0.34)

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

SU and CV risk

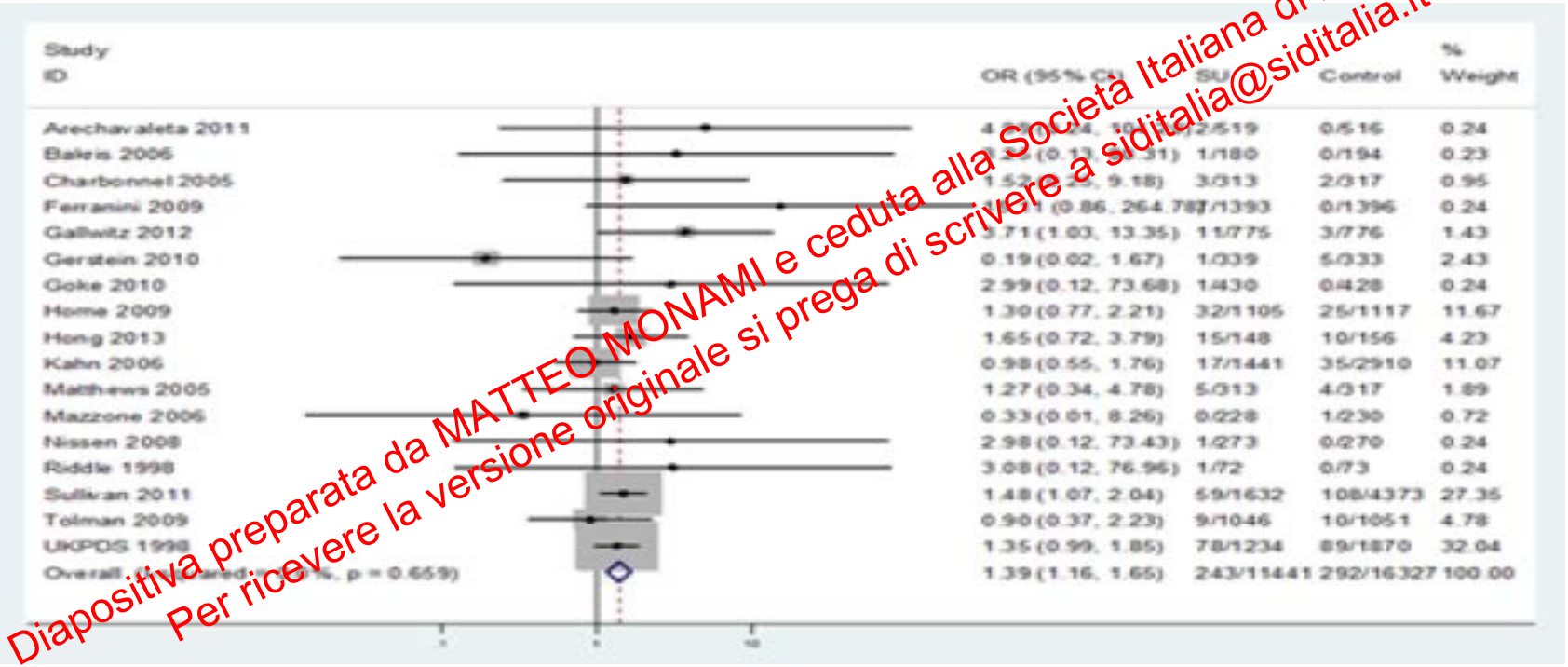
Meta-analysis of observational studies

	Case-control	Cohort	Total
MI	1.30 [1.09-1.54]	1.16 [0.97-1.38]	1.11 [1.00-1.24]
MACE	1.22 [0.59-2.51]	1.11 [1.05-1.17]	1.11 [1.05-1.18]
CV death	1.26 [1.18-1.34]	---	1.26 [1.18-1.34]

Phung OJ et al. *Diabet Med* 2013, 30: 1160-71

SU and stroke

Meta-analysis of available RCTs



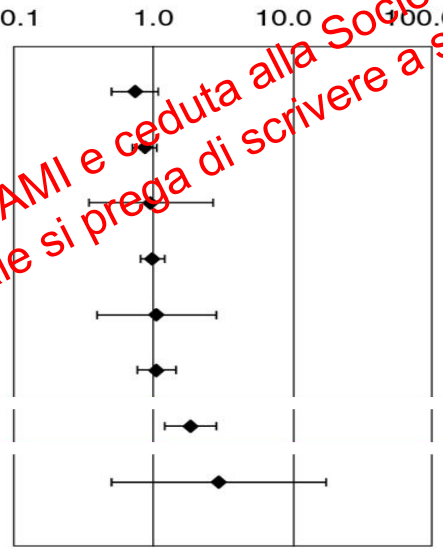
Liu R, Feng Z-P, Mannucci E, Sun H-S, et al. *Diabetes*. 2016, 65:2795-809.

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	3	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

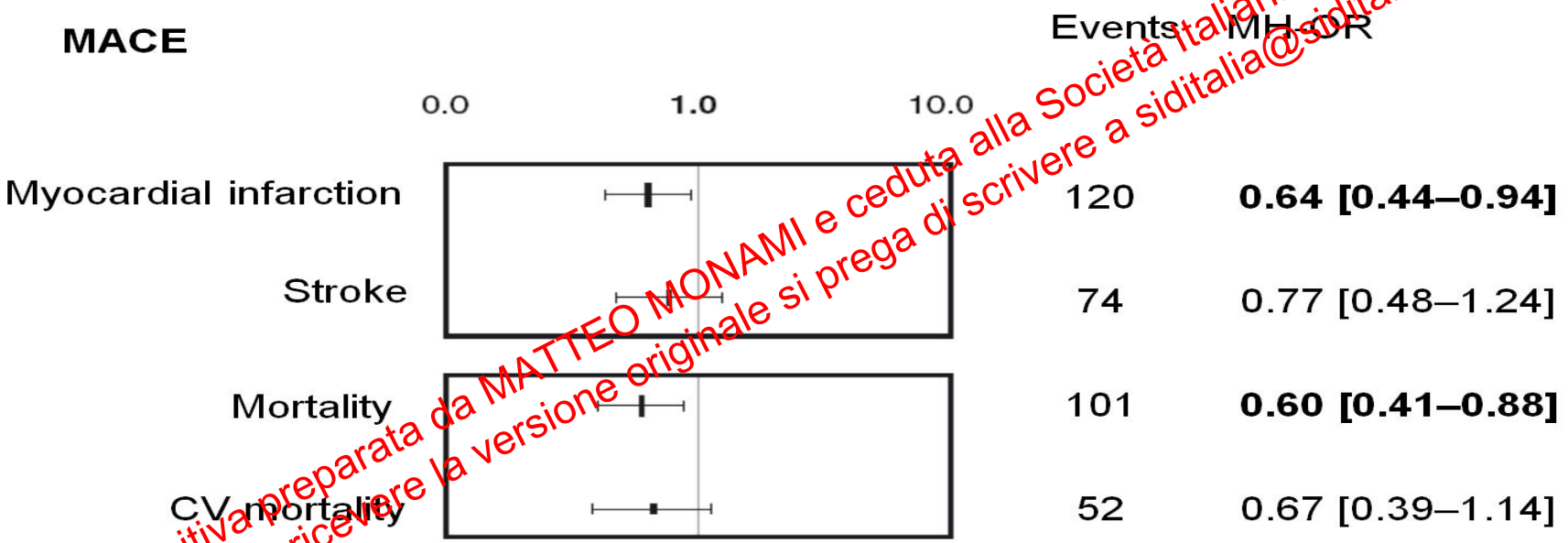


All-cause mortality: 1.22 [1.01–1.49] P=0.047

MH-OR, Mantel–Henzel odds ratio.
Adapted from: Monami M, *et al. Diabetes Obes Metab* 2013 (in press).

DPP-4 inhibitors and MACE

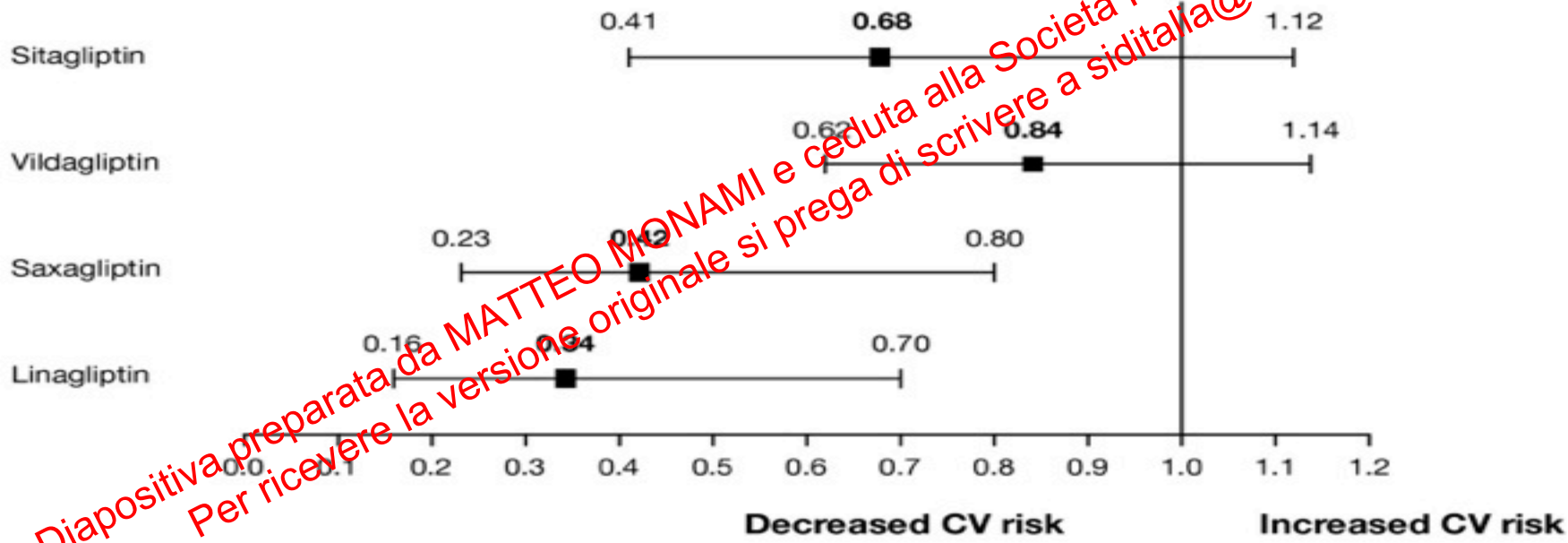
Meta-analysis of available RCTs



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

DPP-4 inhibitors and MACE

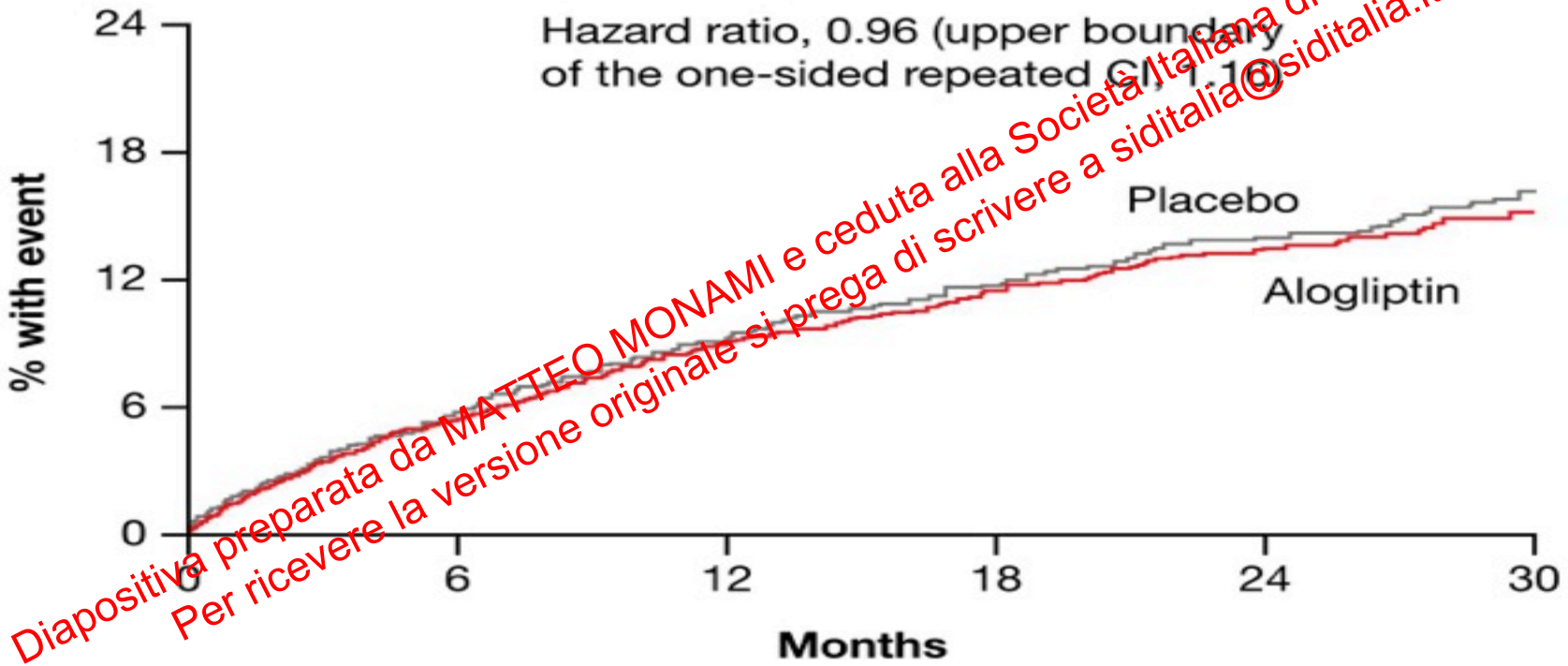
Pooled analyses of Phase II–III trials



1. Williams-Herman D, *et al. BMC Endocr Disord* 2010;10:7; 2. Schweizer A, *et al. Diabetes Obes Metab* 2010;12:485–94; 3. Frederich R, *et al. Postgrad Med* 2010;122:16–27; 4. Johansen O, *et al. Cardiovasc Diabetol* 2012;11:3.

Alogliptin and MACE

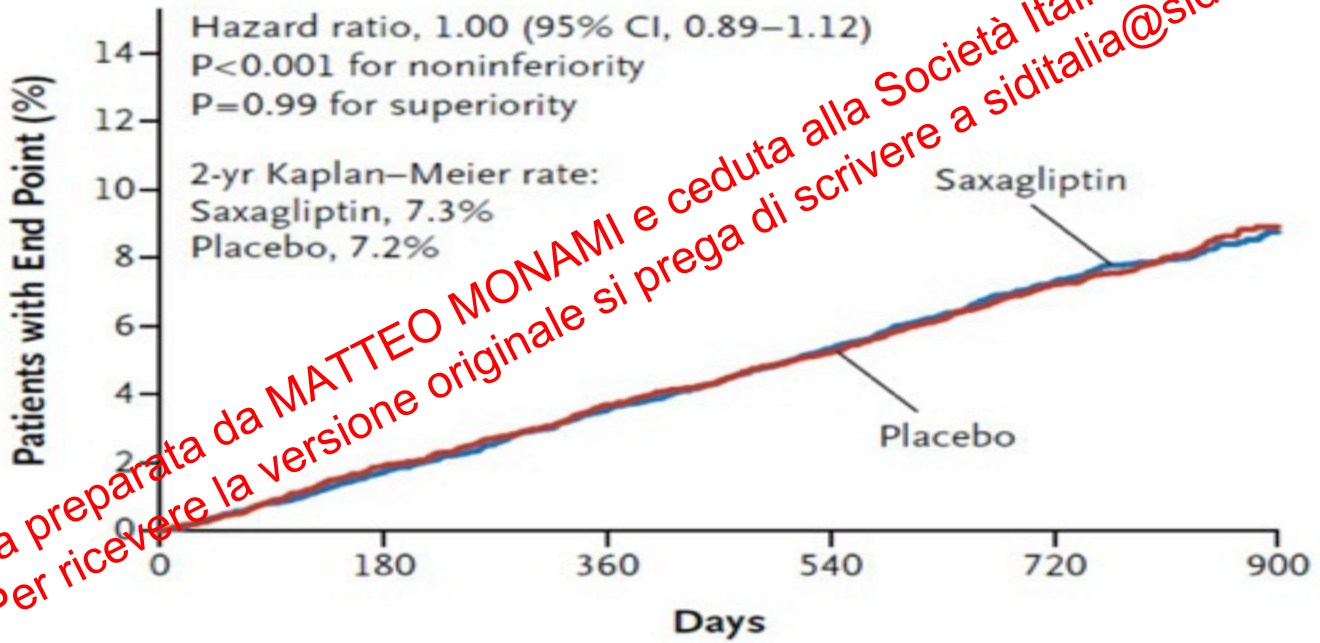
Results of the EXAMINE trial



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

Saxagliptin and MACE

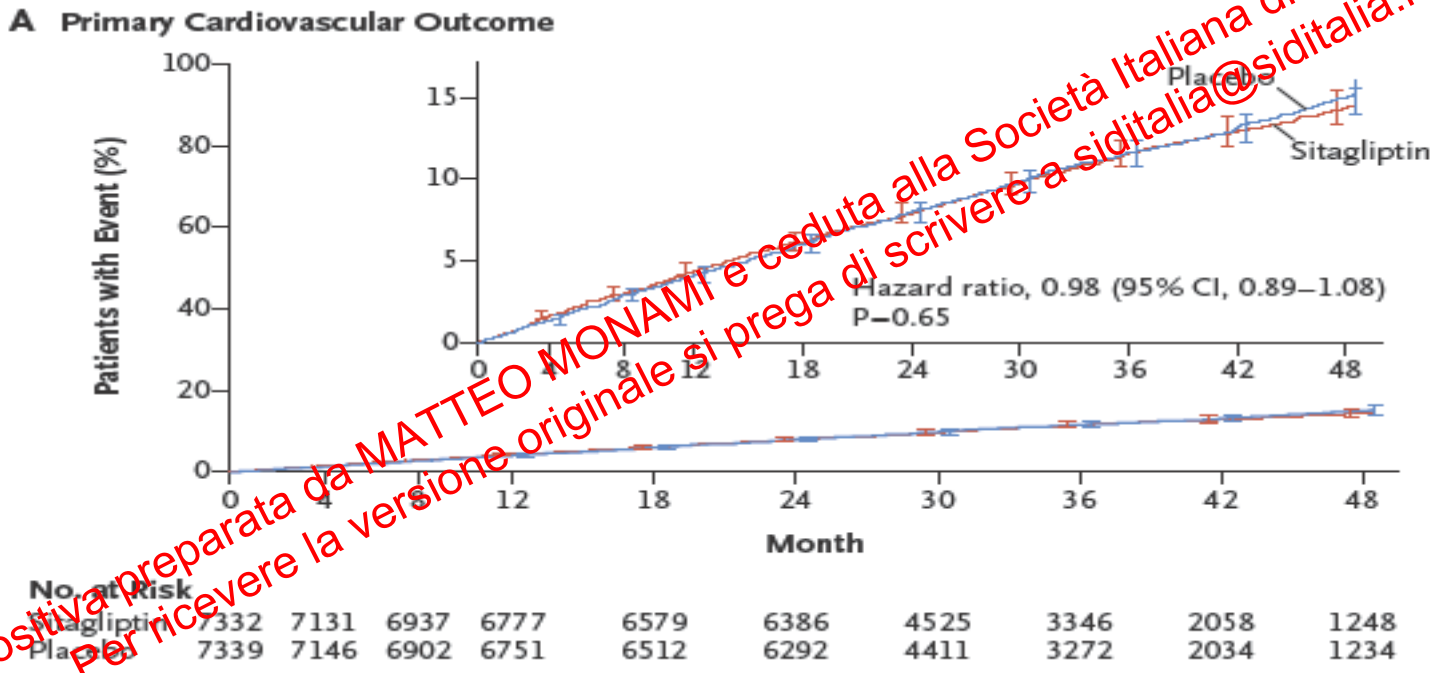
Results of the SAVOR trial: primary endpoint



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

Sitagliptin and MACE

Results of theTECOS trial



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

Limitations of meta-analyses

- Diagnostic criteria for the event not specified (or not specified uniformly)
- No specific screening/diagnostic procedures
- No adjudication of events in many studies
- Short duration of studies
- Small number of events (for rare adverse events)
- Selection of relatively healthy populations

SAVOR-TIMI 53

Comparison with meta-analysis of early trials

	SAVOR	Early trials
Number of patients	16,492	41,959
Number of events	1,422	495
Duration of follow-up (years)	2.1 (median)	~1.0 (mean)
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

3.7%*yr

1.2%*yr

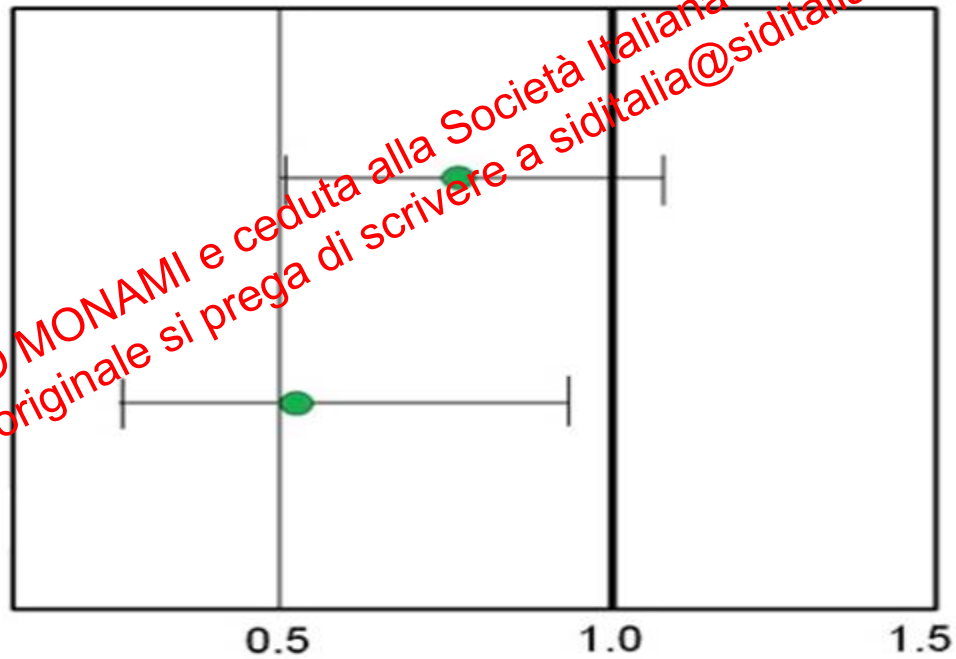
Scirica BM, *et al. N Engl J Med* 2013
Monami M, *et al. Diabetes Obes Metab* 2013;15:112–20.

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

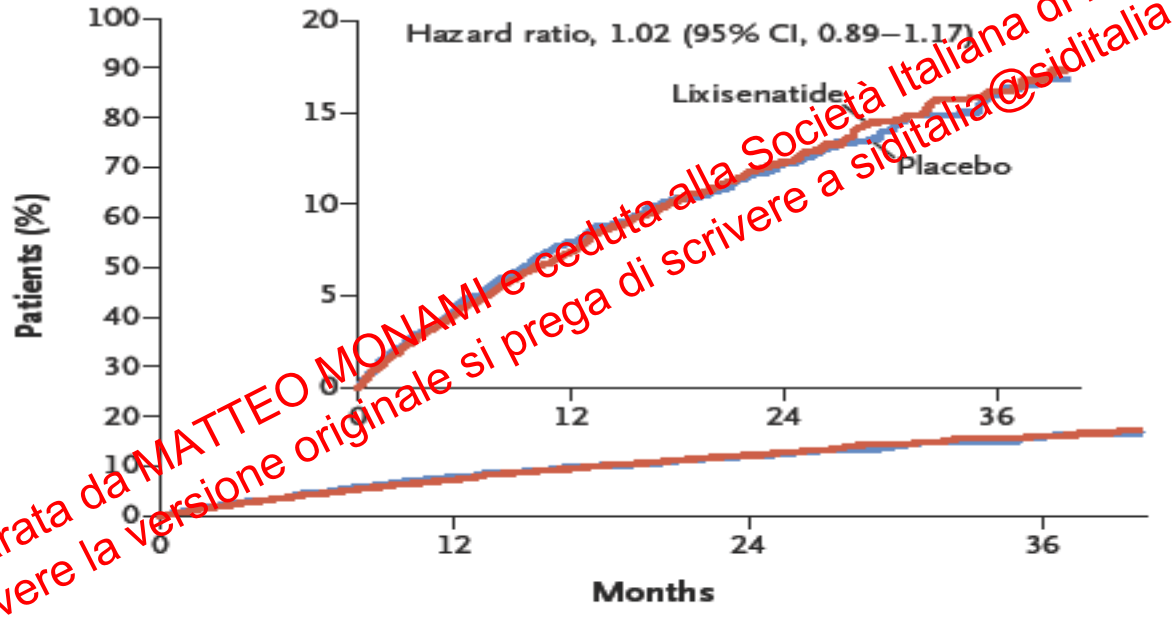
vs. placebo
N= 12 RCTs
MH-OR: 0.51[0.27;0.93]; p=0.029



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

Lixisenatide and MACE

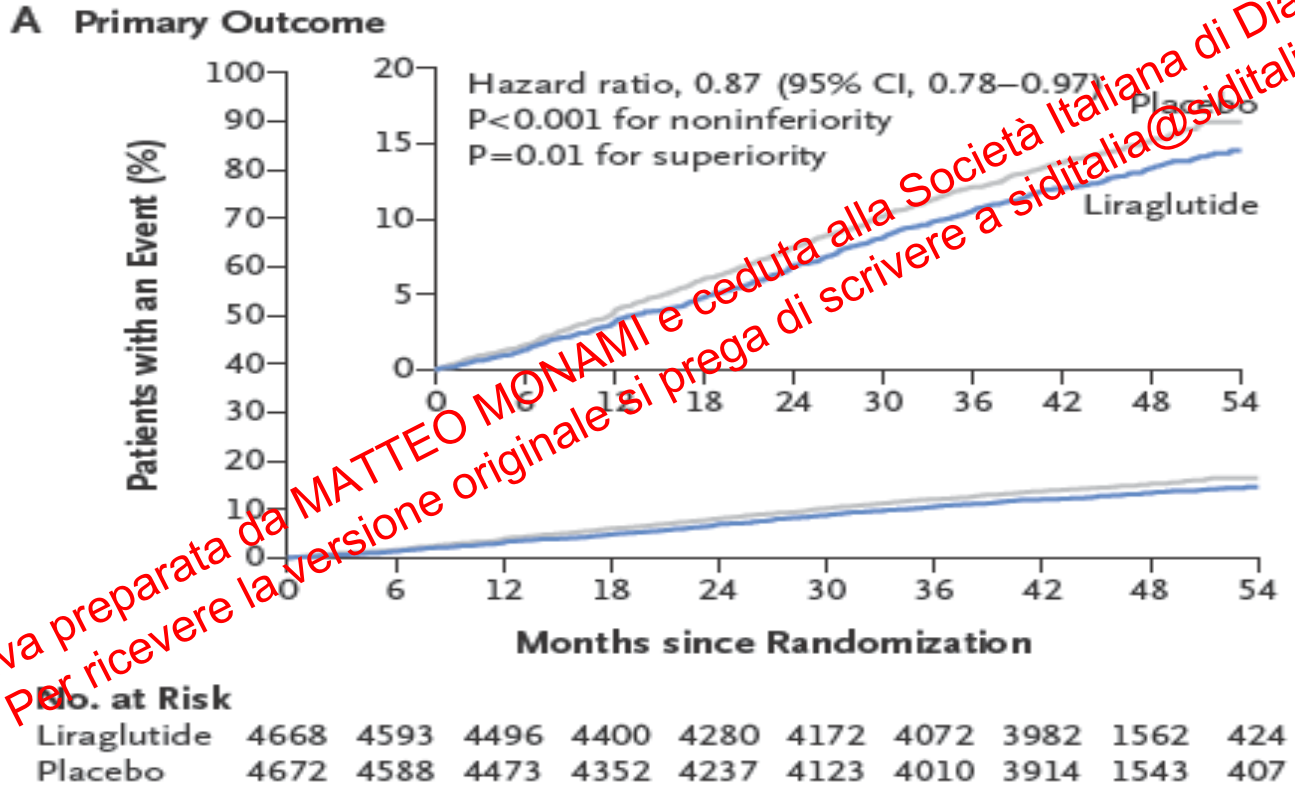
ELIXA trial – primary endpoint



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

Liraglutide and CV risk

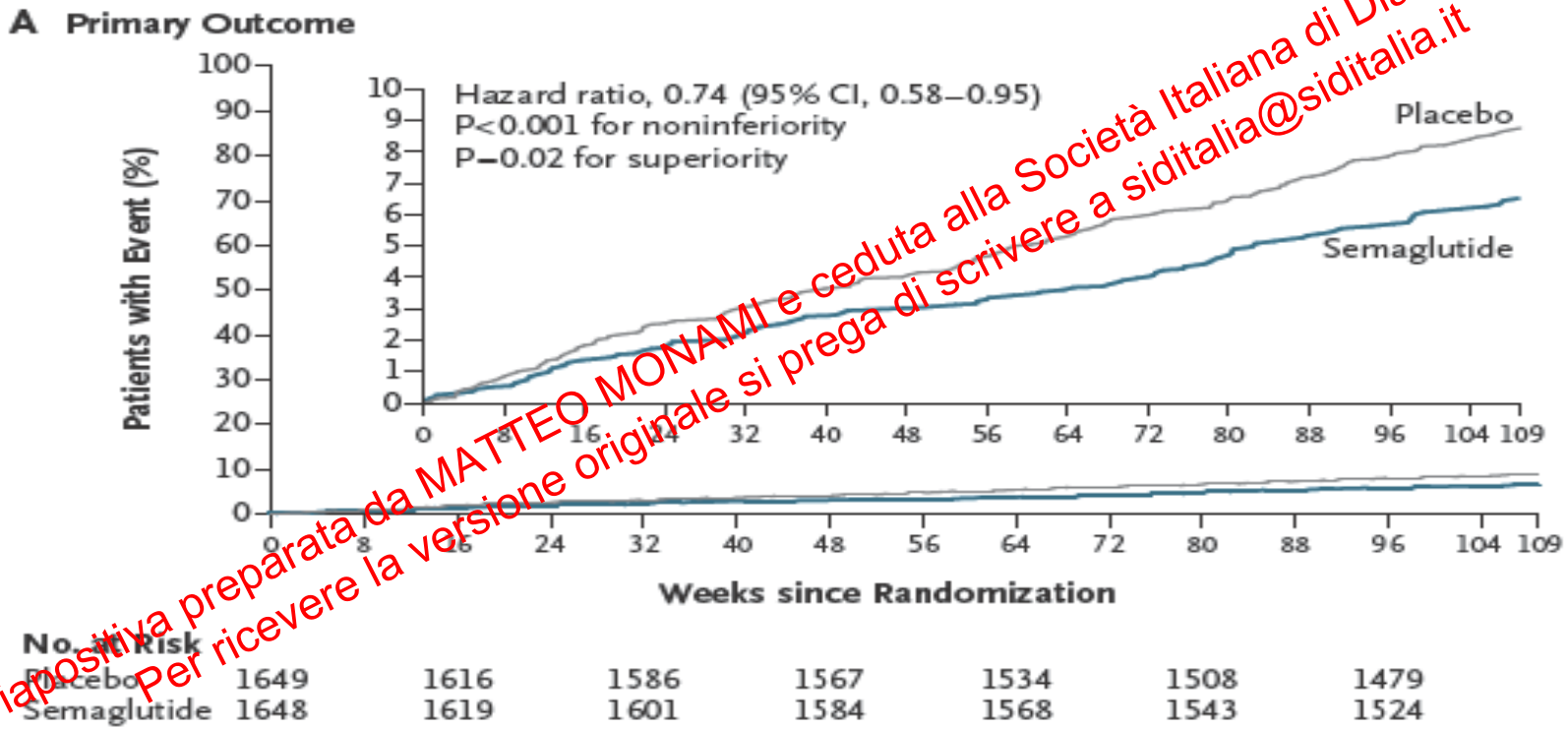
LEADER trial



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

Semaglutide and CV risk

SUSTAIN-6 trial



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

Liraglutide and MACE

LEADER trial

Table 1. Primary and Secondary Outcomes.*

Outcome	Liraglutide (N=4668)	Incidence Rate	Placebo (N=4672)	Incidence Rate	Hazard Ratio (95% CI)	P Value
	no. of patients (%)	*no. of events/ 100 patient-yr*	*no. of patients (%)*	*no. of events/ 100 patient-yr*		
Primary composite outcome†	608 (13.0)	4.4	694 (14.9)	3.9	0.87 (0.78–0.97)	0.01
Expanded composite outcome‡	948 (20.3)	5.3	1062 (22.7)	6.0	0.88 (0.81–0.96)	0.005
Death from any cause	381 (8.2)	2.1	447 (9.6)	2.5	0.85 (0.74–0.97)	0.02
Death from cardiovascular causes	219 (4.7)	1.2	278 (6.0)	1.6	0.78 (0.66–0.93)	0.007
Death from noncardiovascular causes	162 (3.5)	0.9	169 (3.6)	1.0	0.95 (0.77–1.18)	0.66
Myocardial infarction§	292 (6.3)	1.6	339 (7.3)	1.9	0.86 (0.73–1.00)	0.046
Fatal§	21 (0.4)	0.1	28 (0.6)	0.2	0.60 (0.33–1.10)	0.10
Nonfatal	281 (6.0)	1.6	317 (6.8)	1.8	0.88 (0.75–1.03)	0.11
Silent§	62 (1.3)	0.3	76 (1.6)	0.4	0.86 (0.61–1.20)	0.37
Stroke§	173 (3.7)	1.0	199 (4.3)	1.1	0.86 (0.71–1.06)	0.16
Fatal§	16 (0.3)	0.1	25 (0.5)	0.1	0.64 (0.34–1.19)	0.16
Nonfatal	159 (3.4)	0.9	177 (3.8)	1.0	0.89 (0.72–1.11)	0.30

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

Semaglutide and MACE

SUSTAIN-6 trial

Table 2. Primary and Secondary Cardiovascular and Microvascular Outcomes.

Outcome	Semaglutide (N=1648)		Placebo (N=1669)		Hazard Ratio (95% CI)*	P Value
	no. (%)	*no./100 person-yr*	*no. (%)*	*no./100 person-yr*		
Primary composite outcome†	108 (6.6)	3.24	146 (8.9)	4.44	0.74 (0.58–0.95)	<0.001 for noninferiority; 0.02 for superiority
Expanded composite outcome‡	199 (12.1)	6.17	264 (16.0)	8.36	0.74 (0.62–0.89)	0.002
All-cause death, nonfatal myocardial infarction, or nonfatal stroke	122 (7.4)	3.66	158 (9.6)	4.81	0.77 (0.61–0.97)	0.03
Death						
From any cause	62 (3.8)	1.82	60 (3.6)	1.76	1.05 (0.74–1.50)	0.79
From cardiovascular cause	44 (2.7)	1.29	46 (2.8)	1.35	0.98 (0.65–1.48)	0.92
Nonfatal myocardial infarction	47 (2.9)	1.40	64 (3.9)	1.92	0.74 (0.51–1.08)	0.12
Nonfatal stroke	27 (1.6)	0.80	44 (2.7)	1.31	0.61 (0.38–0.99)	0.04

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

The fragility index

The fragility index is a measure of the robustness (or fragility) of the results of a clinical trial. The fragility index is a number indicating how many patients would be required to convert a trial from being statistically significant to not significant ($p \geq 0.05$).

It describes the number of non-events that need to become events in order to render a trial result non-significant (i.e. $p>0.05$).

The intent of the fragility index is to be used in conjunction with the P value, 95% confidence interval, and various measures describing benefit or risk (relative risk reduction, absolute risk reduction, etc).

P-values are calculated using a Fisher's exact test.

The fragility index

There is no specific fragility index that is accepted as being a "good" (robust) or "bad" (fragile) value. In the manuscript introducing the concept, a convenience sample of 399 randomized controlled trials with statistically significant results were analyzed from five high-impact journals. This study found the following results, which serves to describe the landscape of fragility index among clinical trials that in general are considered high-quality or "robust" studies:

The median fragility index was **8** (IQR **3** to **18**)
10% of trials had a fragility index of zero
When loss to follow-up was reported, 52.9% of trials had a larger fragility index compared to the number of patients lost to follow-up

In the cases where a Fisher's exact test produces a non-significant P value (without "converting" a patient from a non-event to an event), the fragility index is reported as '0' and clearly emphasizes the lack of robustness of the trial data.

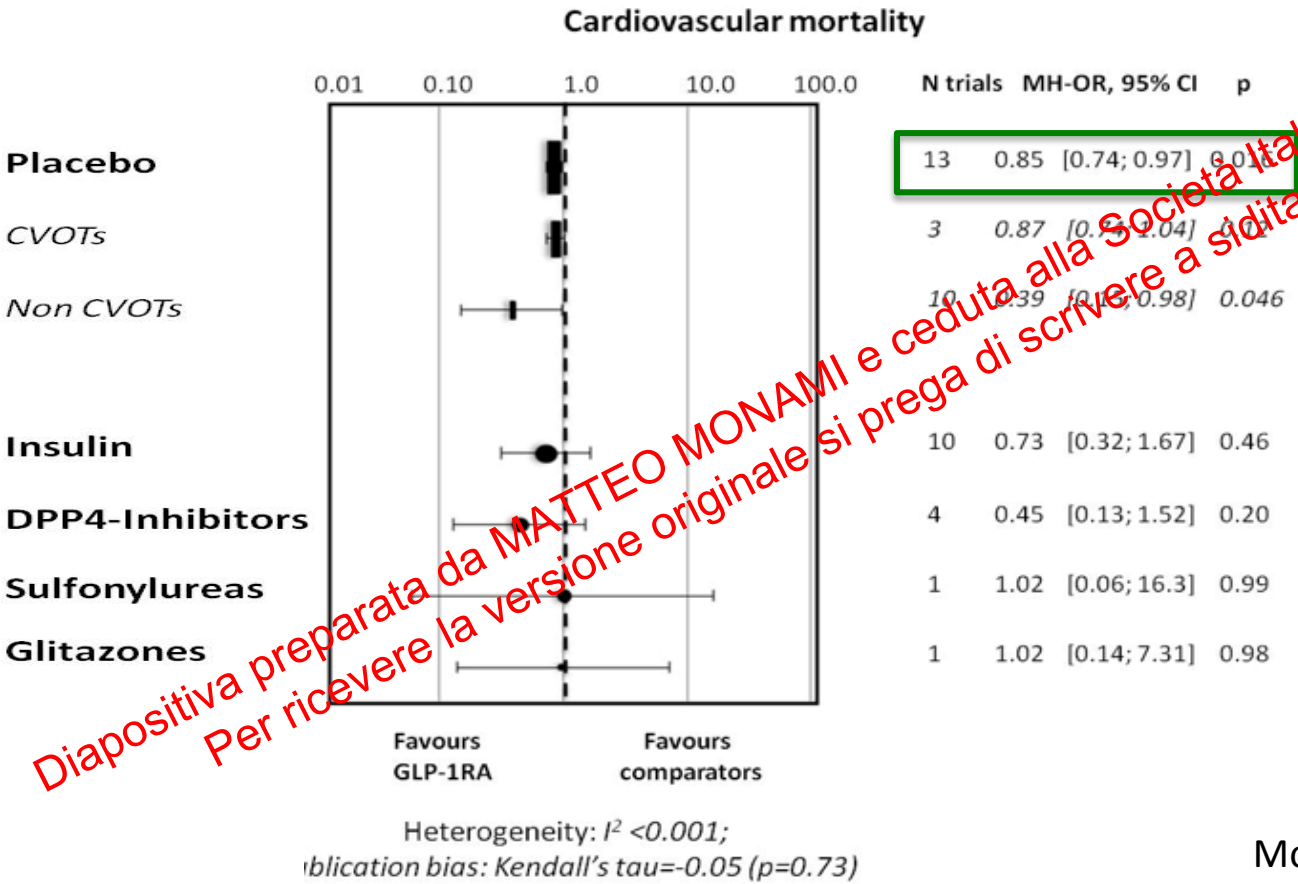
RCTs and the fragility index

Trial	Interv	Compar	HR	p	Fragility	p corr.
LEADER	**4668**	**4672**				
MACE	608	694	0.87	0.01	**19**	0.050
CVD	219	278	0.78	0.007	15	0.051
Nonfatal stroke	159	177	0.89	0.30	-18	0.046
Nonfatal MI	292	339	0.86	0.046	1	0.052
Retinopathy	106	92	1.15	0.33	-40 15	0.049 0.047
Nephropathy	268	337	0.78	0.003	21	0.052

RCTs and the fragility index

Trial	Interv	Compar	HR	p	Fragility	p corr.
SUSTAIN	**1648**	**1649**				
MACE	108	146	0.74	0.016	7	0.053
CVD	44	46	0.98	0.92	-16	0.044
Nonfatal stroke	27	44	0.61	0.039	1	0.054
Nonfatal MI	47	64	0.74	0.12	-4	0.049
Retinopathy	50	29	1.76	0.017	4	0.059
Nephropathy	62	100	0.64	0.003	12	0.051

GLP-1RA and metanalysis



13 placebo-controlled RCTs

Monami et al, Int J Cardiol 2017

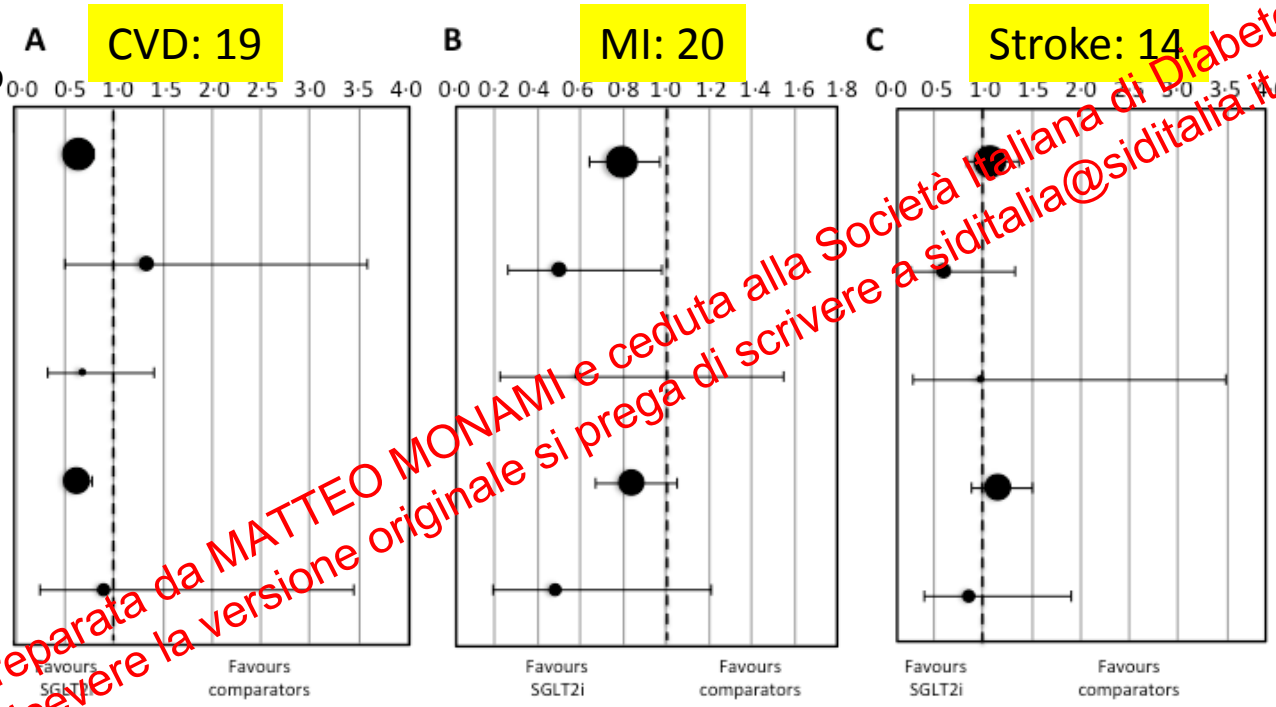
RCTs and the fragility index

Trial	Interv	Compar	HR	p	Fragility	p corr.
EMPAREG	**4687**	**2333**				
MACE	490	282	0.86	0.04	**21**	0.052
CVD	172	137	0.62	<0.001	19	0.050
Nonfatal stroke	150	60	1.24	0.16	+14 -70	0.037 0.047
Nonfatal MI	213	121	0.87	0.12	-20	0.049

*4170 vs 2102

SGLT-2i and metanalysis

N=23 RCT vs placebo



	MH-OR [95% CI]	p	MH-OR [95% CI]	p	MH-OR [95% C	p
All Trials:	*0·64[0·52-0·79]*	*<0·001*	*0·79[0·64-0·97]*	*0·024*	*1·07[0·83-1·37]*	0.25
Dapagliflozin	*1·32[0·49-3·59]*	*0·58*	*0·50[0·26-0·98]*	*0·044*	*0·50[0·26-1·32]*	*0·20*
Canagliflozin	*0·67[0·32-1·41]*	*0·29*	*0·59[0·22-1·55]*	*0·28*	*0·98[0·28-3·49]*	*0·98*
Empaglflozin*	*0·62[0·49-0·77]*	*<0·001*	*0·84[0·67-1·05]*	*0·13*	*1·15[0·88-1·50]*	*0·32*
Empaglflozin**	*0·90[0·24-3·44]*	*0·88*	*0·48[0·19-1·21]*	*0·12*	*0·86[0·39-1·90]*	*0·72*

Monami et al, ActaD 2017

Rosiglitazone and myocardial infarction

Study	Rosiglitazone group	Control group	Odds ratio (95% CI)	P-value
		Number of events/total number (%)		
Myocardial infarction				
Small trials combined	44/10.285 (0.43)	22/6.106 (0.36)	1.45 (0.88–2.39)	0.15
DREAM	15/2.635 (0.57)	9/2.634 (0.34)	1.65 (0.74–3.68)	0.22
ADOPT	27/1.456 (1.85)	41/2.895 (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)	7/3.980 (0.18)	2.40 (1.17–4.91)	0.02
DREAM	12/2.635 (0.46)	10/2.634 (0.38)	1.20 (0.52–2.78)	0.67
ADOPT	2/1.456 (0.14)	5/2.895 (0.17)	0.80 (0.17–3.86)	0.78
Overall			**1.64 (0.98–2.74)**	**0.06**

Adapted from: Nissen S. Wolski K. *N Engl J Med* 2007;356:2457–71.

Rosiglitazone: FDA warning black box

FOR IMMEDIATE RELEASE
November 14, 2007

Media Inquiries:
Susan Cruzan, 301-827-6242
Consumer Inquiries:
888-INFO-FDA

FDA Adds Boxed Warning for Heart-related Risks to Anti-Diabetes Drug Avandia
Agency says drug to remain on market, while safety assessment continues

The U.S. Food and Drug Administration announced today that the manufacturer of Avandia (rosiglitazone), a drug used to treat type 2 diabetes, has agreed to add new information to the existing boxed warning in the drug's labeling about potential increased risk for heart attacks.

People with type 2 diabetes who have underlying heart disease or who are at high risk of heart attack should talk with their health care provider about the revised warning as they evaluate treatment options. FDA advises health care providers to closely monitor patients who take Avandia for cardiovascular risks.

"FDA has moved expeditiously to review the cardiovascular risks of this drug so that we could inform patients and doctors at the earliest possible time of our findings," said Janet Woodcock, M.D., FDA's deputy commissioner for scientific and medical programs, chief medical officer, and acting director of the Center for Drug Evaluation and Research. "FDA remains committed to making sure that doctors and patients have the latest information about the risks and benefits of medicines."

Avandia, manufactured by GlaxoSmithKline (GSK), Philadelphia, Pa., was approved in 1999 as an adjunct to diet and exercise to improve control of blood sugar levels. Avandia is approved to be used as a single therapy or used in combination with metformin and sulfonylureas, other oral anti-diabetes treatments.

During the past year, FDA has carefully weighed several complex sources of data, some which show conflicting results related to the risk of chest pain, heart attacks and heart-related deaths, and deaths from any cause in patients treated with Avandia.

At this time, FDA has concluded that there isn't enough evidence to indicate that the risks of heart attacks or death are different between Avandia and some other oral type 2 diabetes treatments. Therefore, FDA has requested that GSK conduct a new long-term study to evaluate the potential cardiovascular risk of Avandia, compared to an active control agent. GSK has agreed to conduct the study and FDA will ensure it is initiated promptly.

The revision of Avandia's existing boxed warning – FDA's strongest form of warning – includes the following statement:

A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 total patients), most of which compared Avandia to placebo, showed Avandia to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration 41 months; 14,067 patients), comparing Avandia to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemi are inconclusive.

Rosiglitazone and cardiovascular risk

- Inclusion of trials with non-cardiovascular endpoints
- Questionable statistical methods: overestimation (Peto's analysis)
- Selection of trials (duration >24 wk. GSK-sponsored)
- Different duration of follow-up in rosiglitazone/comparator groups

"The *time limit* of 24 wks is largely too short to select trials showing a possible effect of rosiglitazone on atherosclerosis. and at the same time it is too long to collect all the RCTs providing informations about a possible effect of the drug on myocardial oxygen consumption…"
"…in the DREAM and ADOPT trials. the *duration of follow-up* in patients treated with rosiglitazone is longer. meaning that the proportion of CV adverse events is higher. determining a bias against rosiglitazone. which would need to be corrected".

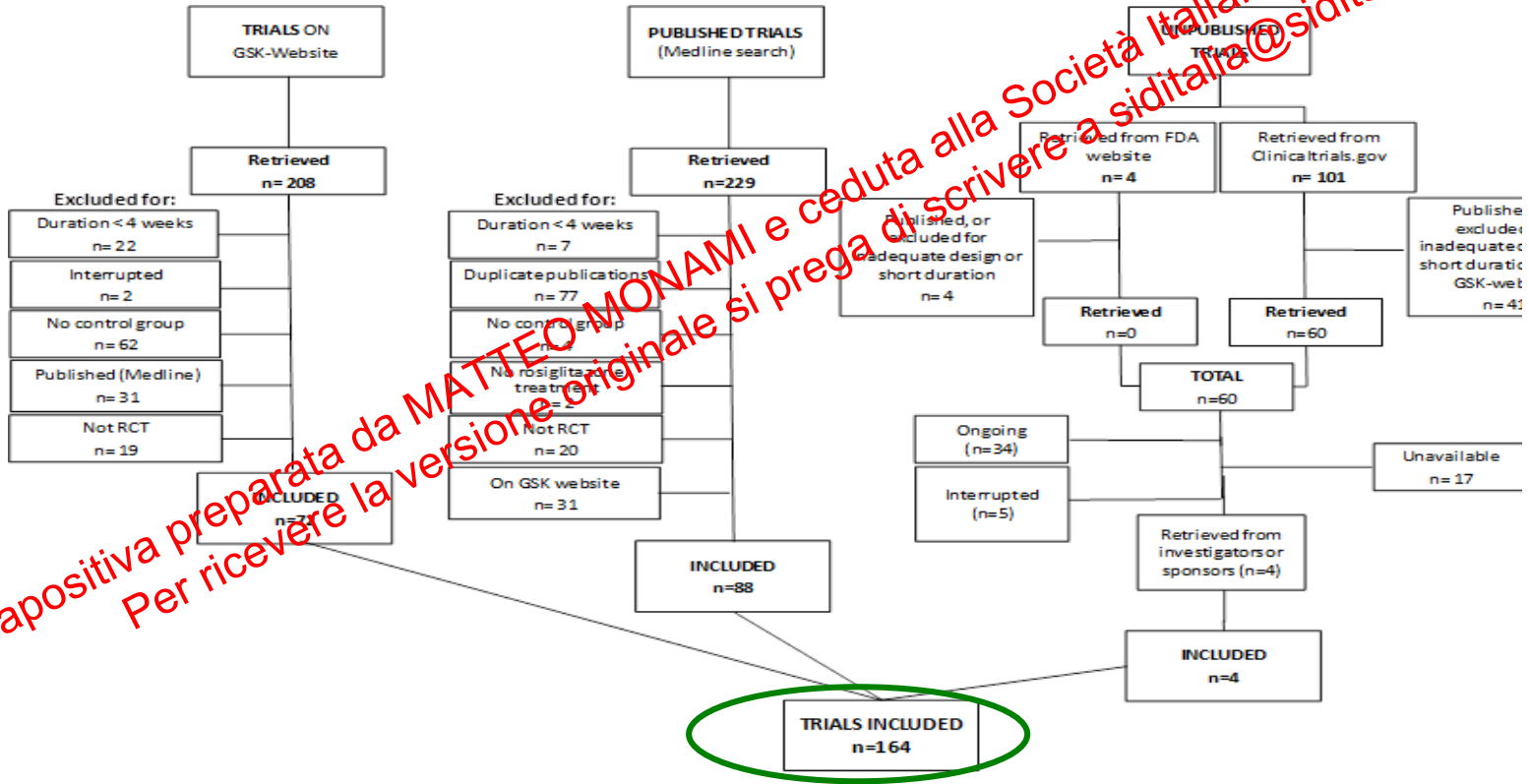
Adapted from: *Monami M,* et al NEJM

AUGUST 30, 2007

Cardiac safety profile of rosiglitazone

A comprehensive meta-analysis of randomized clinical trials

E. Mannucci et al. / International Journal of Cardiology 143 (2010) 135–140



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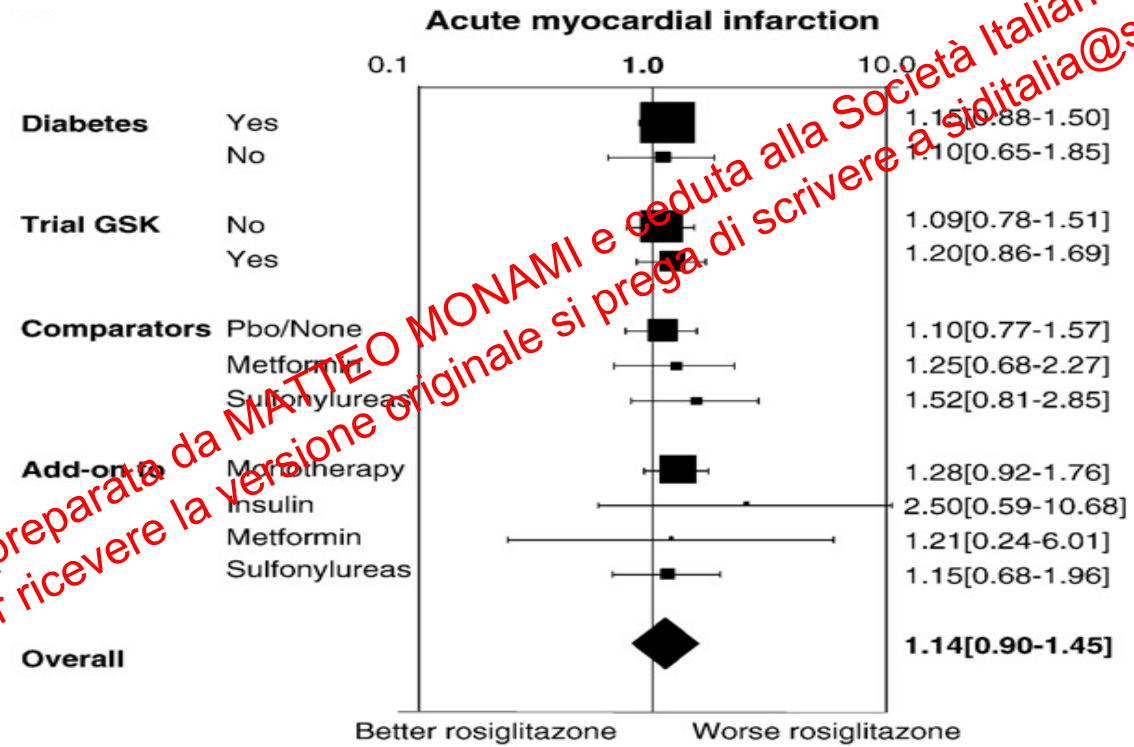

Nissen's: 1.43

Rosiglitazone: FDA 2013

BMJ

BMJ 2013;346:f3769 doi: 10.1136/bmj.f3769 (Published 10 June 2013)

NEWS

FDA panel advises easing restrictions on rosiglitazone

Miriam E Tucker

Bethesda, Maryland

Conduzione di una meta-analisi

Matteo Monami
SODc Diabetologia
AOU Careggi, Firenze

CIN and vitamin E use

Contrast-induced nephropathy (CIN) is usually defined by a fixed (**0.5 mg/dL** or 44 gmol/L) or a proportionate (**25%**) rise in serum creatinine (SCr) levels after contrast exposure.

RCT e metanalisi su:

Acetilcisteina

Vitamina C

Statine

Bicarbonato, ecc.

RCT su Vitamina E

Weisbord SD et all. Clin J Am Soc Nephrol 2008; 3(5): 1274-81.
Chen SL et all. Int J Cardiol 2008; 126(3): 407-13.

COSE DA FARE

1. Prospero registration
2. Search (medline/clinicaltrials.gov): *“vitamin diabetes contrast nephropathy”*
3. Flow chart
4. Database
5. Analysis
6. Manuscript

COSE DA FARE

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			14	13	11	1	3	

COSE DA FARE

1. PROSPERO website registration

https://www.crd.york.ac.uk/PROSPERO/myprospero.php

a) Descrizione della problematica
b) Definizione chiara degli obiettivi della meta-analisi
c) Formulazione delle ipotesi da testare
d) Definizione degli eventuali sotto-gruppi da considerare
e) Definizione della strategia statistica
f) Altro

COSE DA FARE

1. Prospero registration
2. Search

a) Published studies: Medline/Embase/Cochrane

b) Unpublished studies: www.clinicaltrials.gov

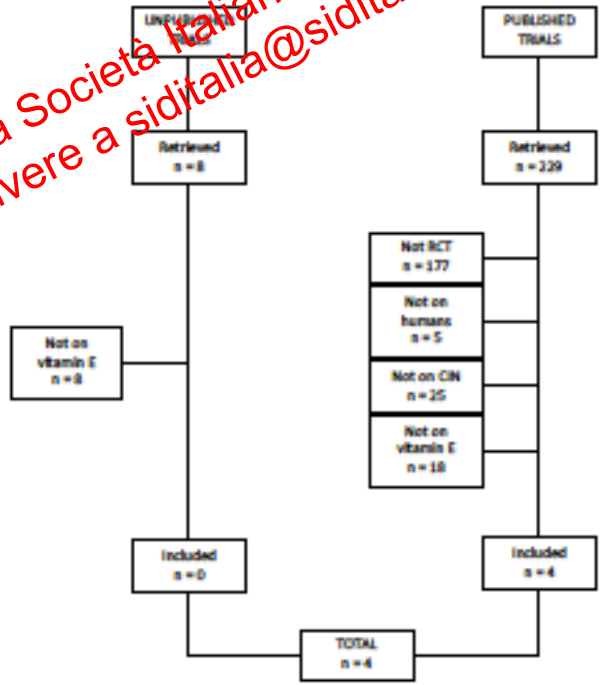
Key-words: *vitamin* and *contrast* and *nephropathy*

Limits: *meta-analysis* and *RCT*

COSE DA FARE

1. Prospero registration
2. Search (Medline/Embase/Cochrane/clin
3. Flow chart

Figure 1. Trial flow summary



COSE DA FARE

1. Prospero registration
2. Search (medline/clinicaltrials.gov): *"vitamin diabetes contrast nephropathy"*
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N	Study	N Drug	Comparator	N comp	Duration	PS/CO	SC/MC	Random	Allocation	Blinding	Dropouts	ITT	Age	HbA1c	FPG	BMI	Serum creat	eGFR-.....
1																		
...																		

CIN_Drug	CIN_Comp	Creat_Endp_Drug	DS	Creat_Endp_Comp	DS	DeathD	DeathC	CVDeathD	CVDrathC

COSE DA FARE

1. Prospero registration
2. Search (medline/clinicaltrials.gov): *"vitamin diabetes contrast nephropathy"*
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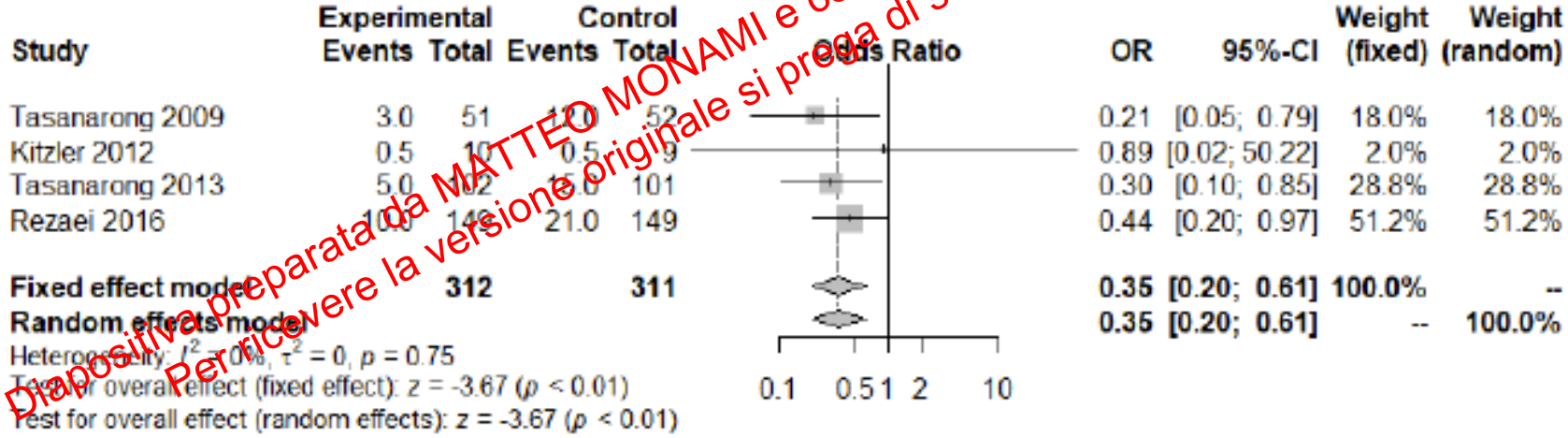
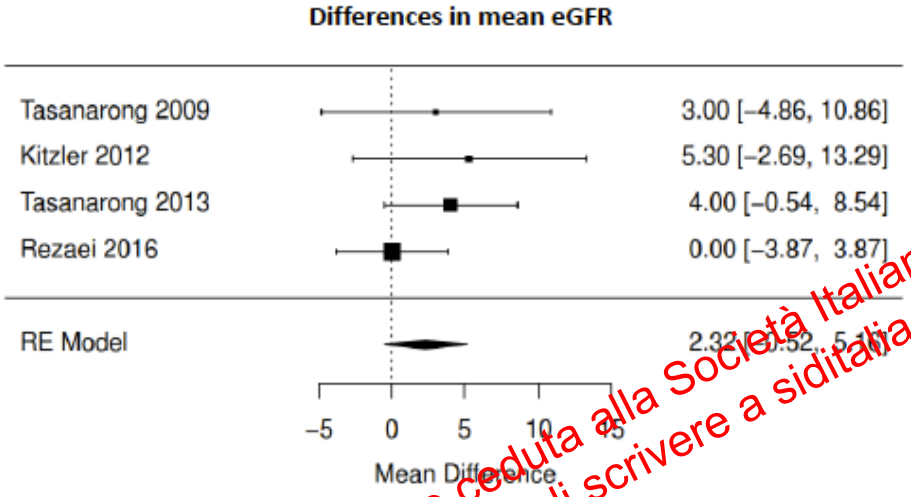
Figure 2. Forest plot of individual studies.

A

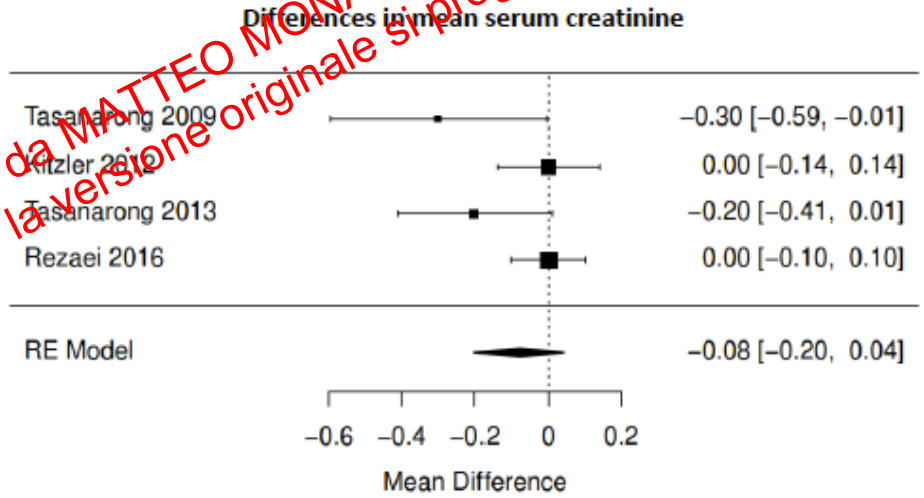
Analyses of MH-OR (95% CI) for CIN in placebo-controlled trials.



B



C



COSE DA FARE

1. Prospero registration
2. Search (medline/clinicaltrials.gov): *"vitamin diabetes contrast nephropathy"*
3. Flow chart
4. Database
5. Analysis
6. Manuscript

Tocopherol and contrast-induced nephropathy: a meta-analysis of randomized controlled trials.

M Monami[a], A Cignarelli[b], S Pinto[c], L D'Onofrio[d], A Milluzzo[e], R Miccoli[f], G Perrino[f], E Mannucci[a] on behalf of the Young Academy Group[1].

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Manuscript submitted

The Young Academy Group

ACKNOWLEDGEMENTS

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Manuscript submitted