Glucagon-Like Peptide 1 Receptor Agonists in ambito cardiovascolare

Matteo Monami

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GLP1-RA and MACE

Meta-analysis of available RCTs

All trials

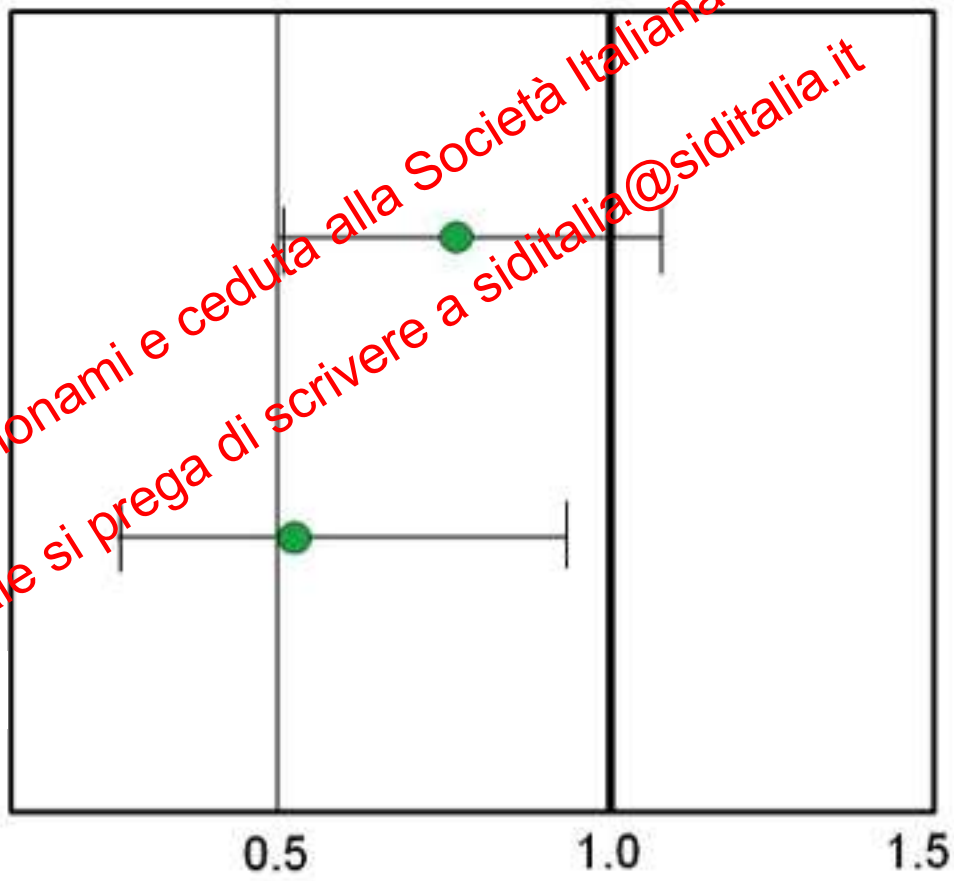
N= 25 RCTs

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

vs. placebo

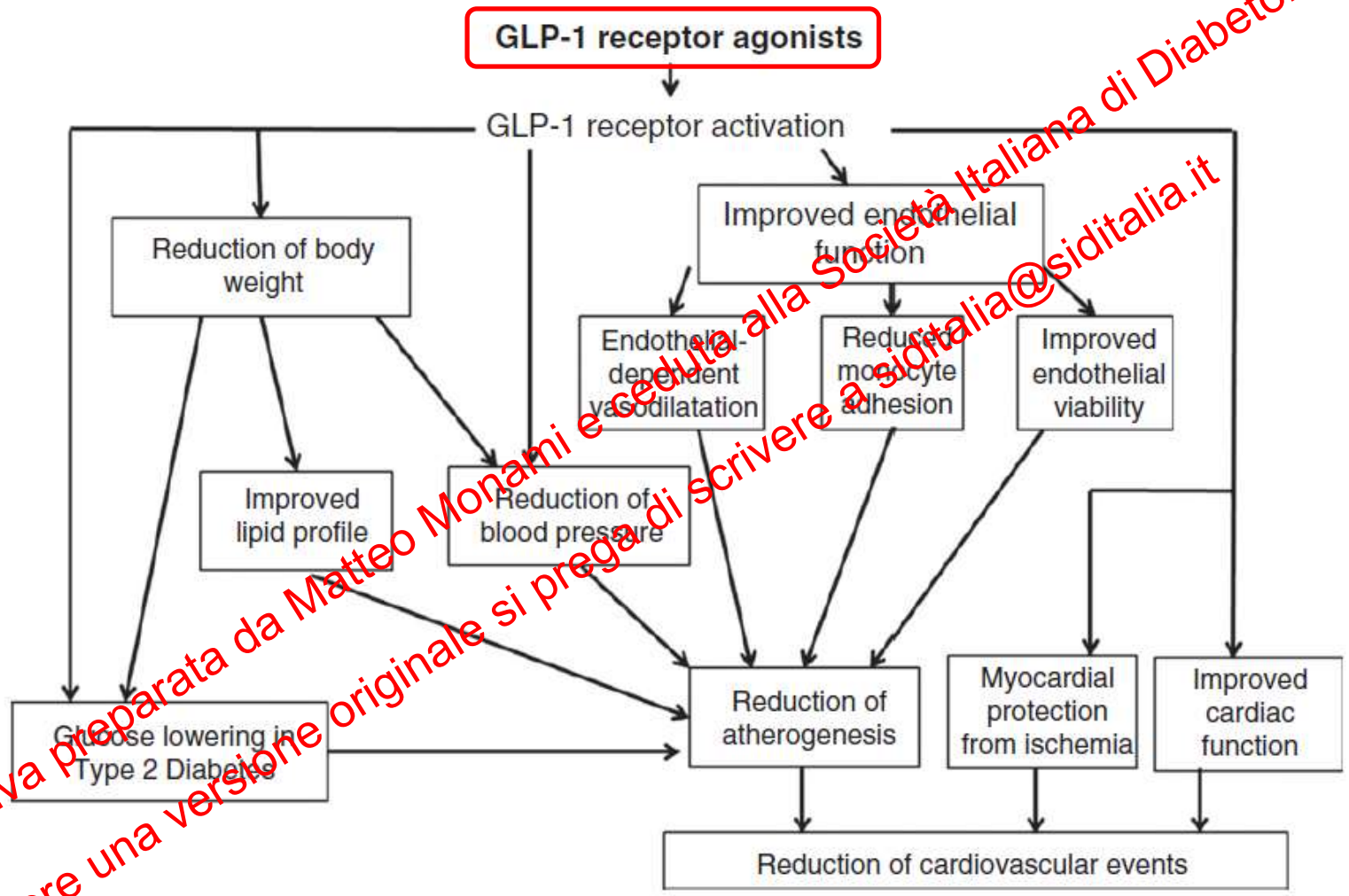
N= 12 RCTs

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



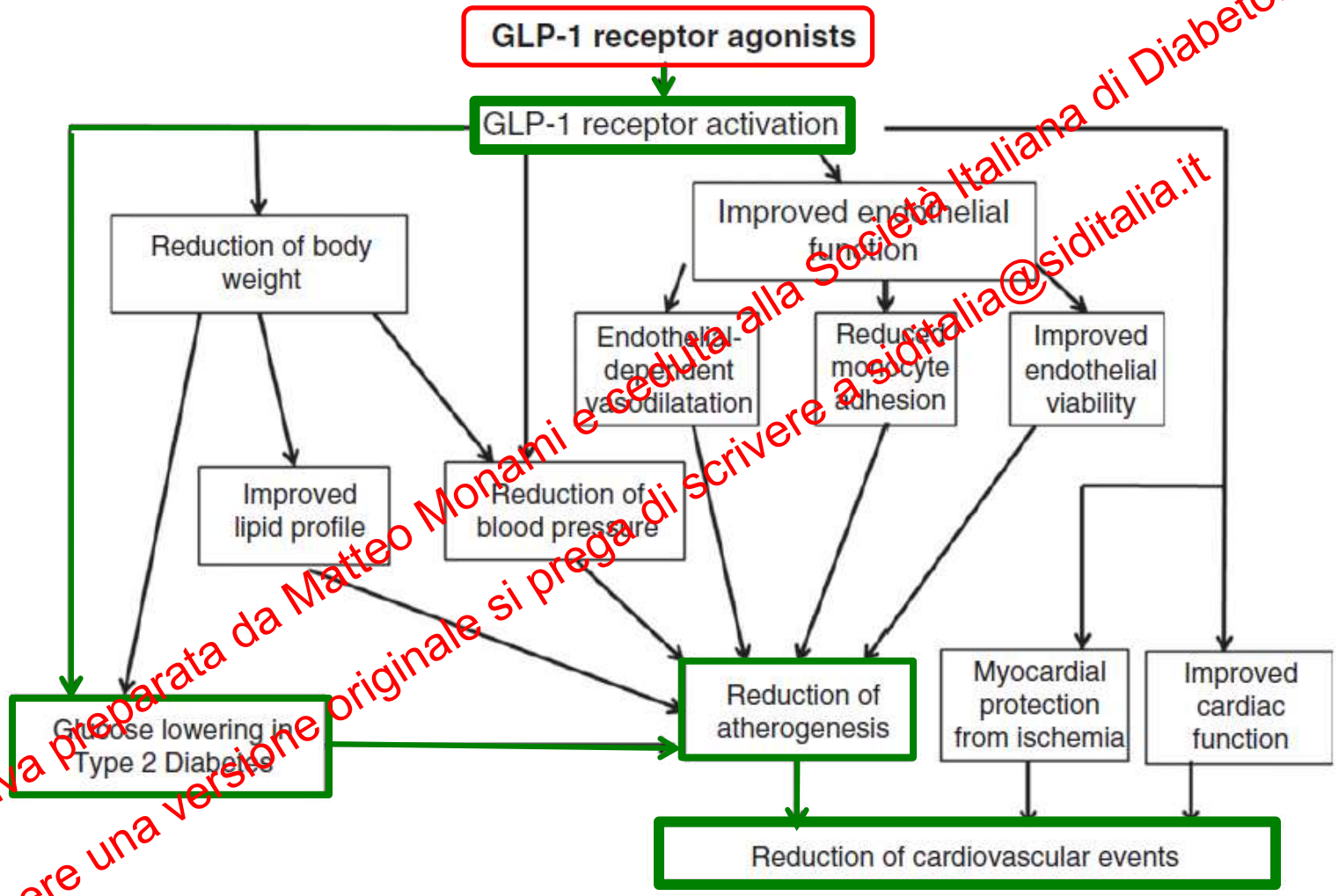
Monami M, Dicembrini I, Nardini C, Fiordelli I, Mannucci E.
Diabetes Obes Metab 2013

CV effects of GLP1-RA



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

CV effects of GLP1-RA



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Noninsulin antidiabetic drugs added to metformin therapy

A meta-analysis of randomized clinical trials

Table 2. Results of Traditional Meta-analysis Comparing Noninsulin Antidiabetic Drugs With Placebo on Change in HbA_{1c}, HbA_{1c} Goal Achieved, Change in Body Weight, and Overall Hypoglycemia

	% Change in HbA_{1c}		HbA_{1c} Goal Achieved		Change in Body Weight, kg		Overall Hypoglycemia	
Group vs Placebo	No. of Trials	WMD (95%CI)	No. of Trials	RR (95%CI)	No. of Trials	WMD (95%CI)	No. of Trials	RR (95%CI)
All drugs	20	−0.79 (−0.90 to −0.68)[a]	13	2.56 (1.99 to 3.28)[b]	12	0.14 (−1.37 to 1.65)[a]	19	1.43 (0.89 to 2.30)
Sulfonylureas	3	−0.79 (−1.15 to −0.43)[a]	1	3.38 (2.01 to 5.83)	2	1.99 (0.86 to 3.12)	3	2.63 (0.76 to 9.13)[a]
Glinides	2	−0.71 (−1.24 to −0.17)	1	3.0 (1.47 to 7.58)	2	0.91 (0.35 to 1.46)	2	7.92 (1.45 to 43.21)
Thiazolidinediones	3	−1.00 (−1.62 to −0.38)[b]	1	1.69 (1.24 to 2.33)	1	2.30 (1.70 to 2.90)	2	2.04 (0.50 to 8.23)
AGIs	2	−0.65 (−1.11 to −0.19)	0	NA	1	−1.80 (−2.83 to −0.77)	2	0.60 (0.08 to 4.55)
DPP-4 inhibitors	8	−0.79 (−0.94 to −0.63)[b]	6	2.44 (1.78 to 3.33)[b]	4	−0.09 (−0.47 to 0.30)[b]	8	0.67 (0.30 to 1.50)
GLP-1 analogs	2	−0.99 (−1.19 to −0.78)	1	3.96 (2.37 to 6.79)	2	−1.76 (−2.90 to −0.62)	2	0.94 (0.42 to 2.12)

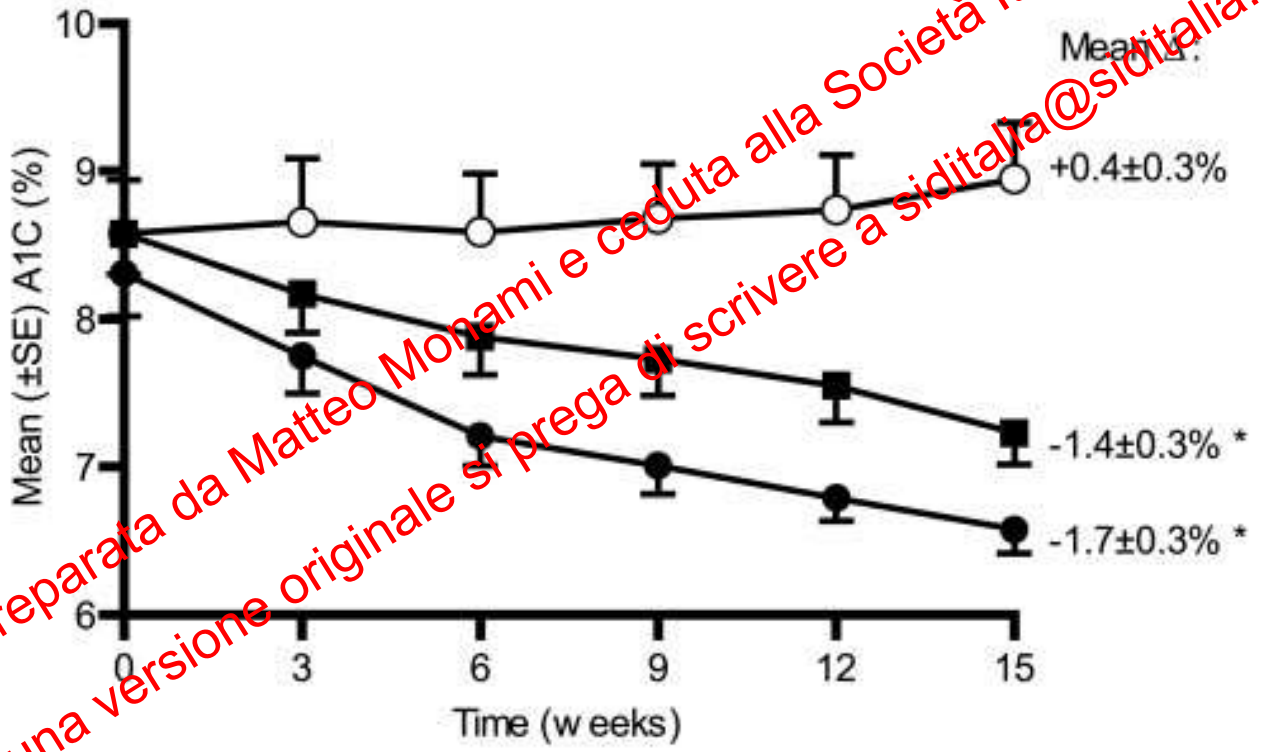
Abbreviations: AGIs, α-glucosidase inhibitors; CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HbA_{1c}, glycated hemoglobin A_{1c}; NA, not applicable; RR, relative risk; WMD, weighted mean difference.

[a] $I^2 \geq 75\%$.

[b] $I^2 = 50\%$–75%.

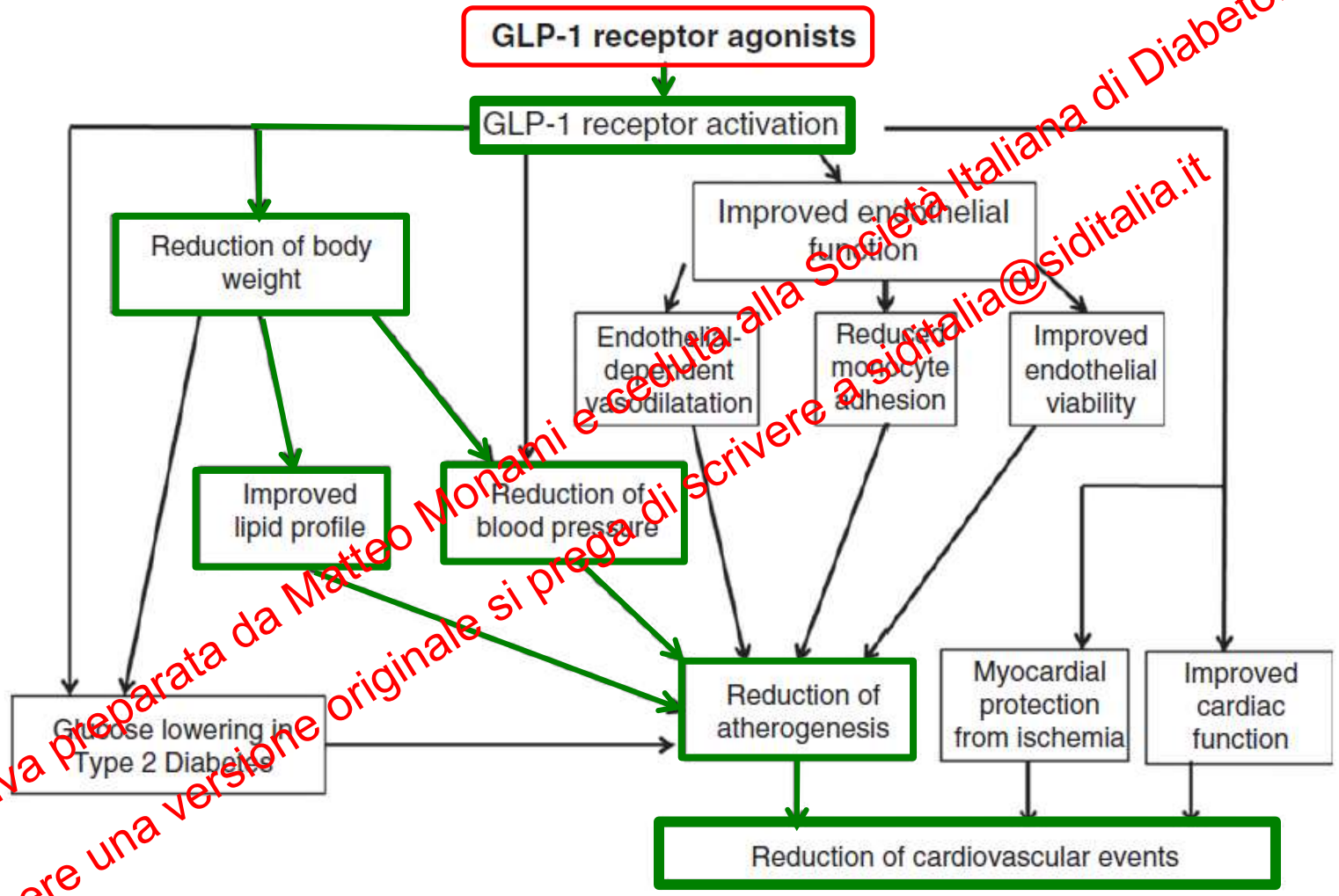
Phung OJ, JAMA 2010 – vol. 303, No 14

Effects of Once-Weekly Dosing of a Long-Acting Release Formulation of Exenatide on Glucose Control and Body Weight



DENNIS K., Diabetes Care 30:1487–1493, 2007

CV effects of GLP1-RA

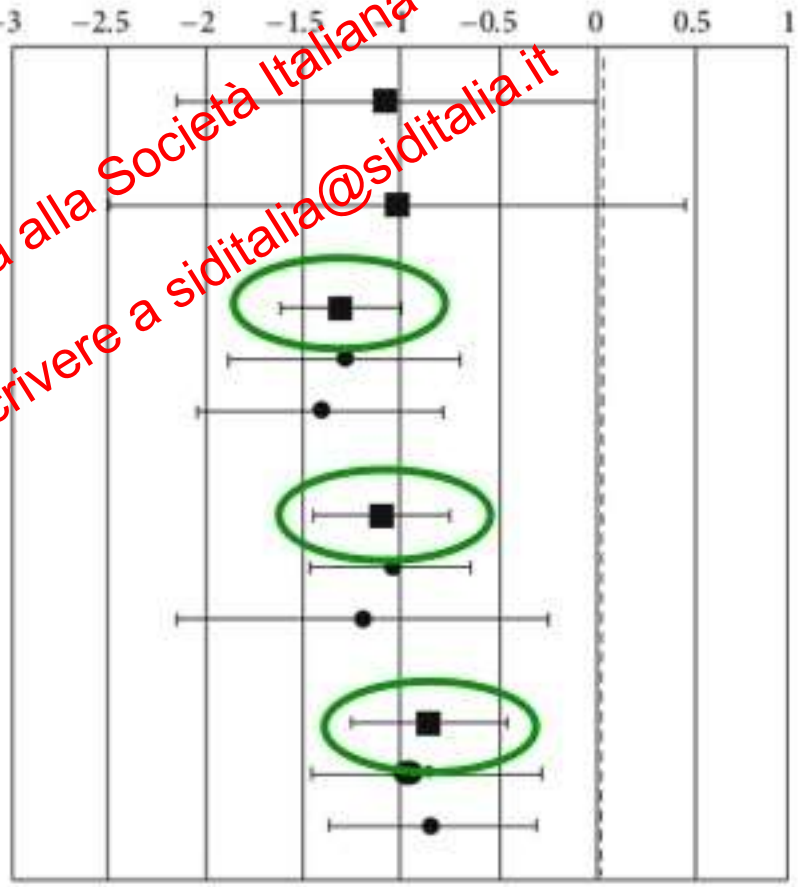


M. Monami, I. Dicembrini, C. Nardini, I. Fiordelli, E. Mannucci,
Diabetes Obes Metab. 2014; 16:38-47

GLP-1 RA and body weight

A meta-analysis of available RCTs

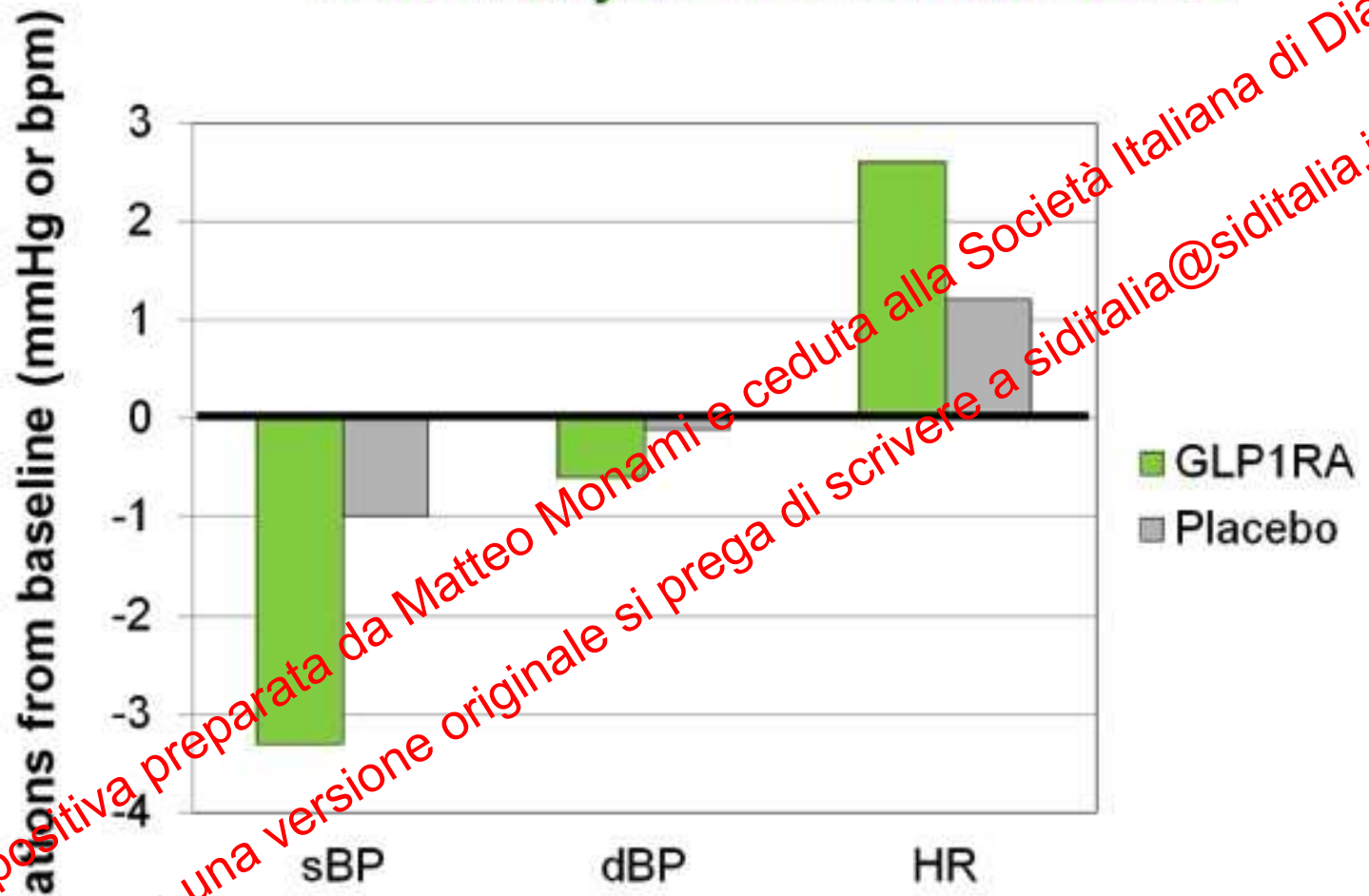
	MD	LL,95% CI	UL,95% CI	*P*	Number of trials
DPP-4 inhibitors	−1.08	−2.15	0.001	0.05	2
Thiazolidinediones	−1.02	−2.49	0.45	0.17	2
Sulfonylureas	−1.31	−1.62	−1	<0.001	4
Exenatide	−1.29	−1.88	−0.7	<0.001	2
Liraglutide	−1.41	−2.03	−0.79	<0.001	2
Insulin	−1.1	−1.45	−0.75	<0.001	6
Exenatide	−1.05	−1.45	−0.64	<0.001	4
Liragl./Exen. LAR	−1.2	−2.15	−0.3	0.021	2
Placebo	−0.967	−1.342	−0.591	<0.001	9
Exenatide	−1.058	−1.563	−0.554	<0.001	5
Liraglutide	−0.85	−1.375	−0.315	0.002	4



Monami M, Dicembrini I, Marchionni N, Rotella CM, Mannucci E.
Exp Diabetes Res ID 672658, 2012

GLP1-RA and CV risk

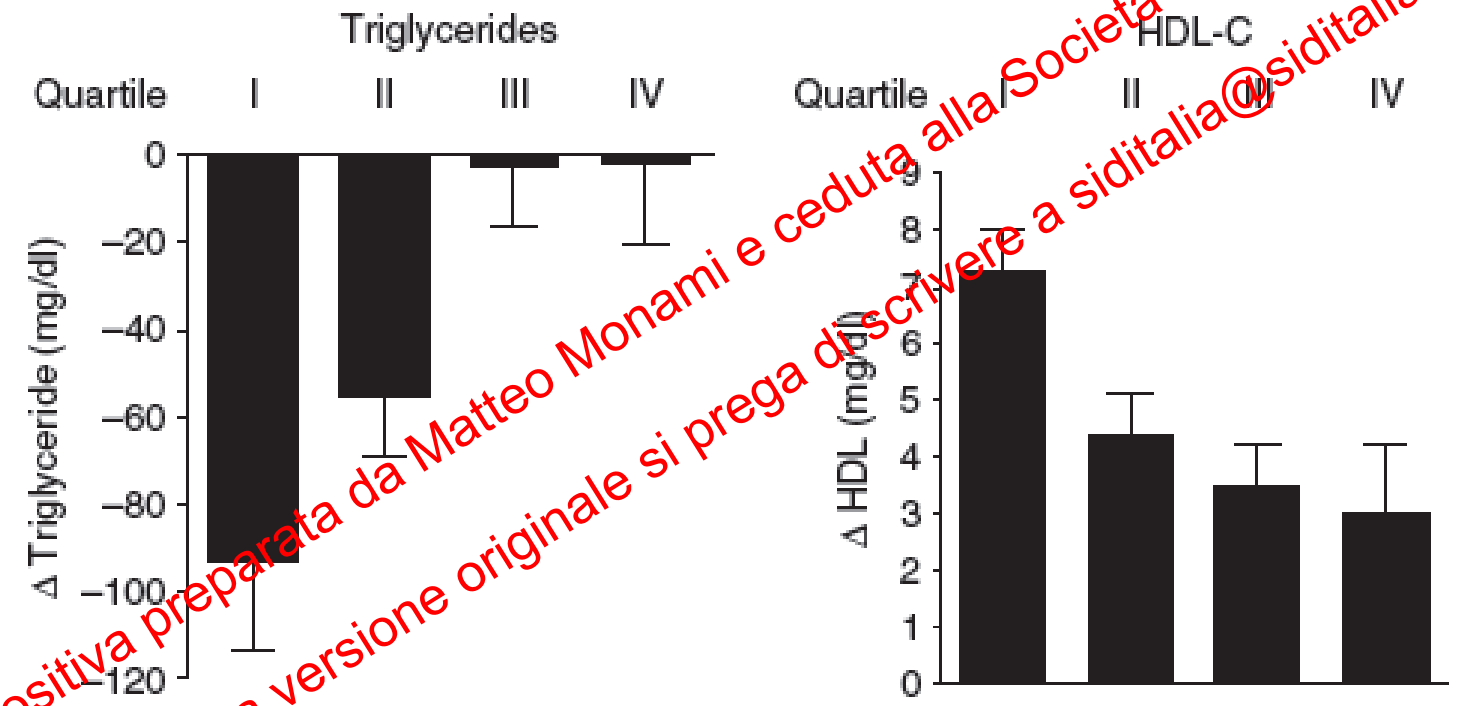
Meta-analysis of available RCTs



Monami M, Dicembrini I, Nardini C, Fiordelli I, Mannucci E.
Diabetes Obes Metab 2013

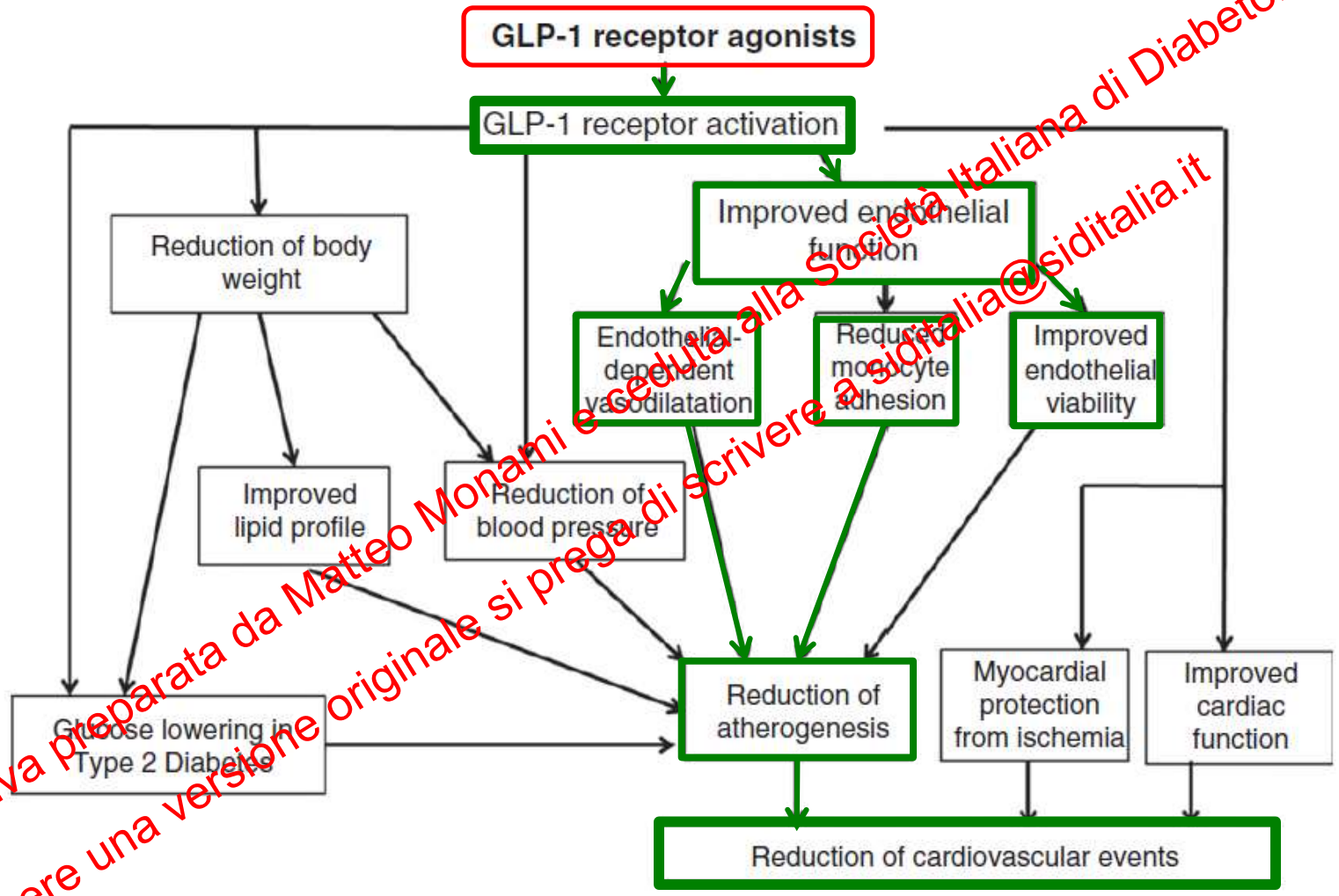
Effects of exenatide on cardiovascular risk factors over 82 weeks

An interim analysis in 314 overweight T2DM



Blonde L. et al.,
Diabetes, Obesity and Metabolism, 8, 2006, 436–447

CV effects of GLP1-RA

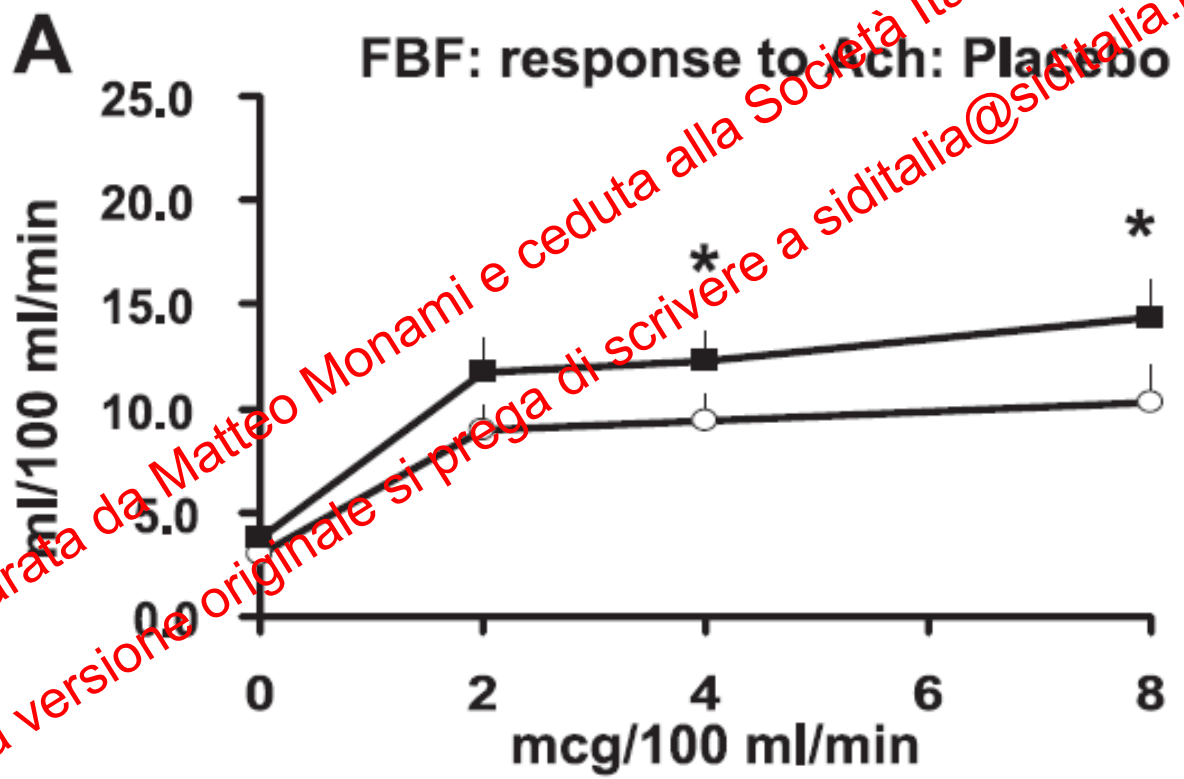


M. Monami, I. Dicembrini, C. Nardini, I. Fiordelli, E. Mannucci,
Diabetes Obes Metab. 2014; 16:38-47

Risposta endoteliale con GLP-1RA

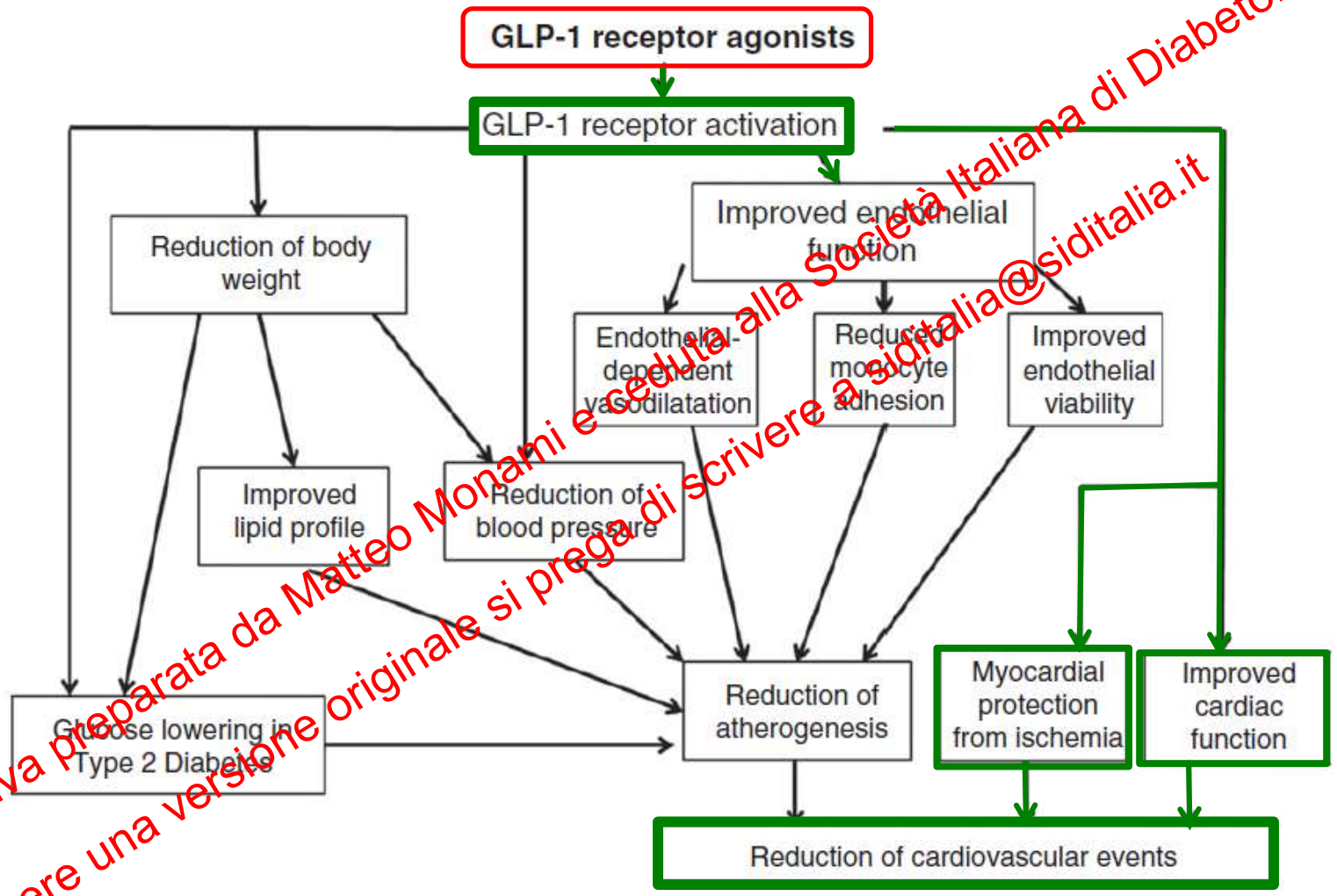
Ananda Basu,[1] Nisha Charkoudian,[2] William Schrage,[2] Robert A. Rizza,[1] Rita Basu,[1] and Michael J. Joyner[2]

Am J Physiol Endocrinol Metab 293: E1289–E1295, 2007



Basu A. et al., Am J Physiol Endocrinol Metab 293: E1289-95, 2007

CV effects of GLP1-RA



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

Myocardial effects of GLP1

- Porcine model of ischaemia-reperfusion injury: effect of exenatide

PBS

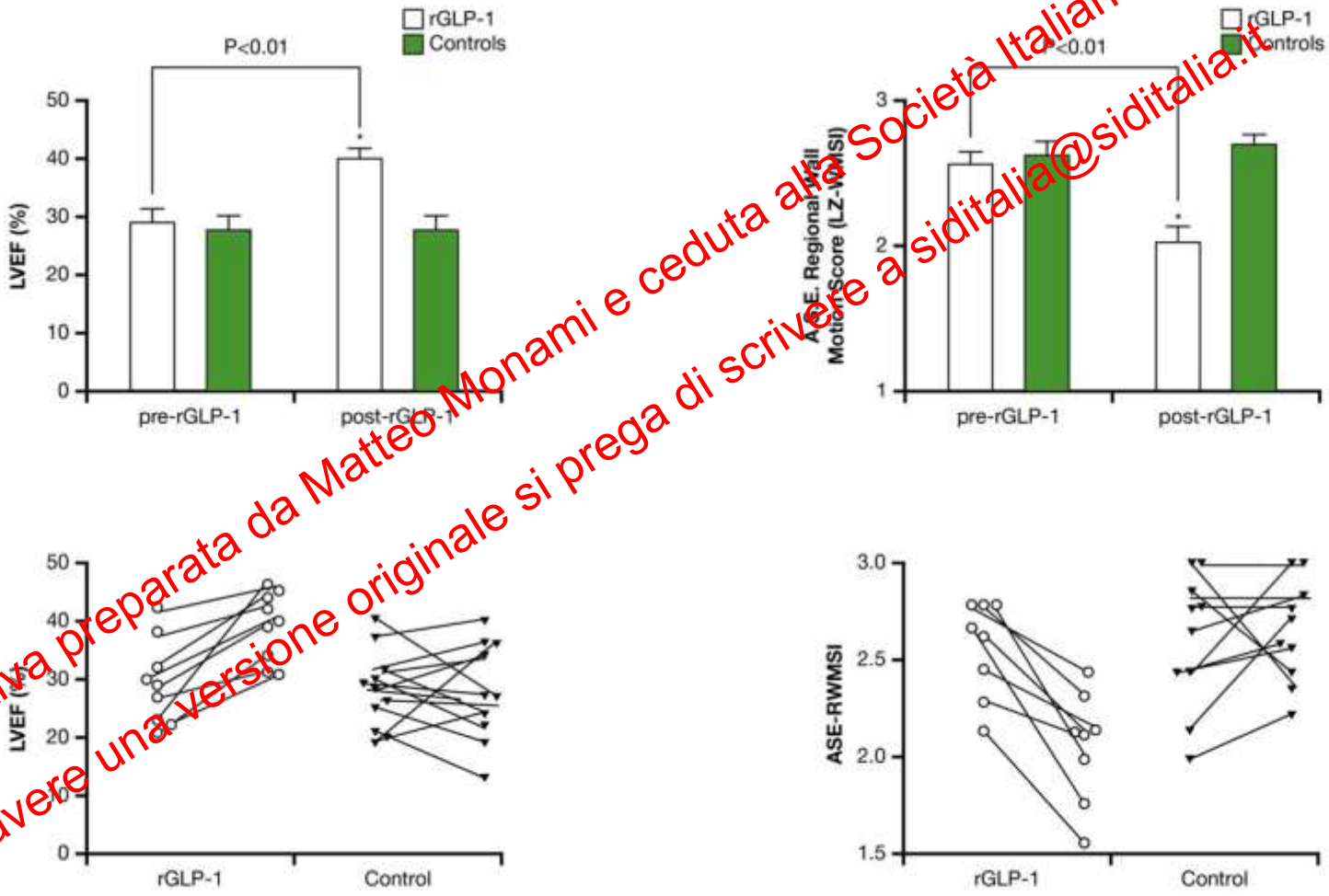
Exenatide

The infarction size is markedly reduced in animals pre-treated with exenatide in comparison with controls.

Timmers L, *et al. J Am Coll Cardiol* 2009;53;501–10.

Myocardial effects of GLP-1

- Patients with MI and PTCA; effect of 72h human GLP-1 infusion



Nikolaidis LA, *et al. Circulation* 2004;109:962–5.

GLP1-RA and MACE

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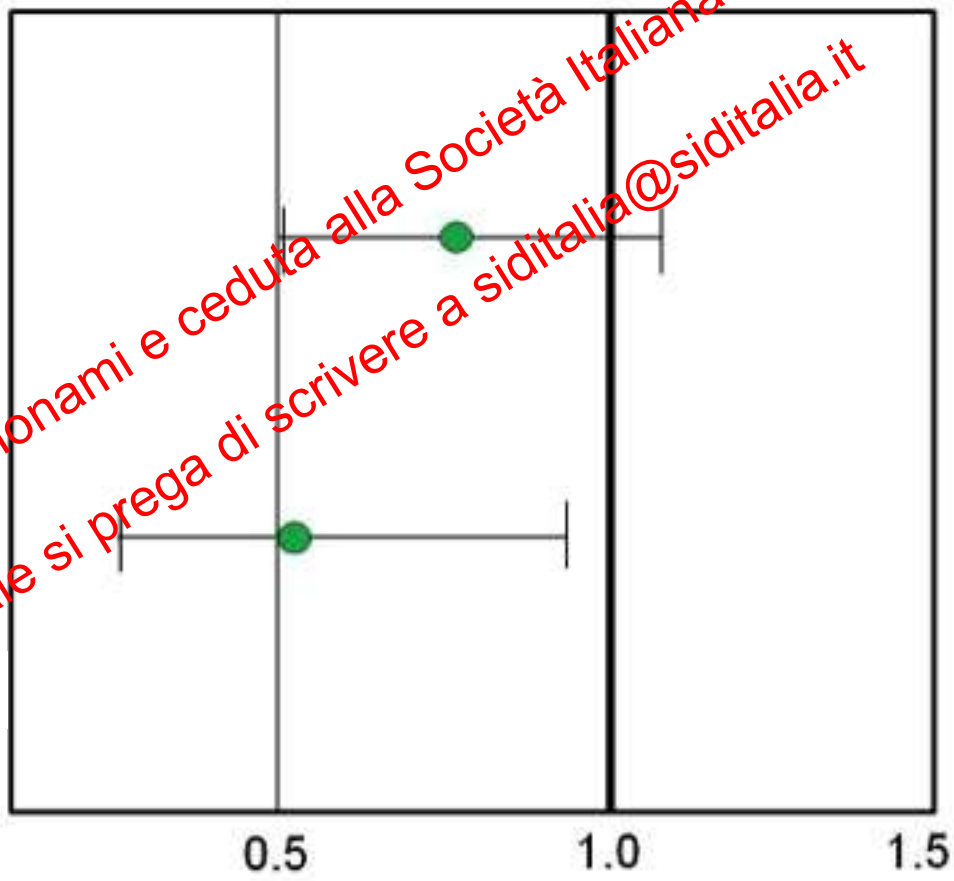
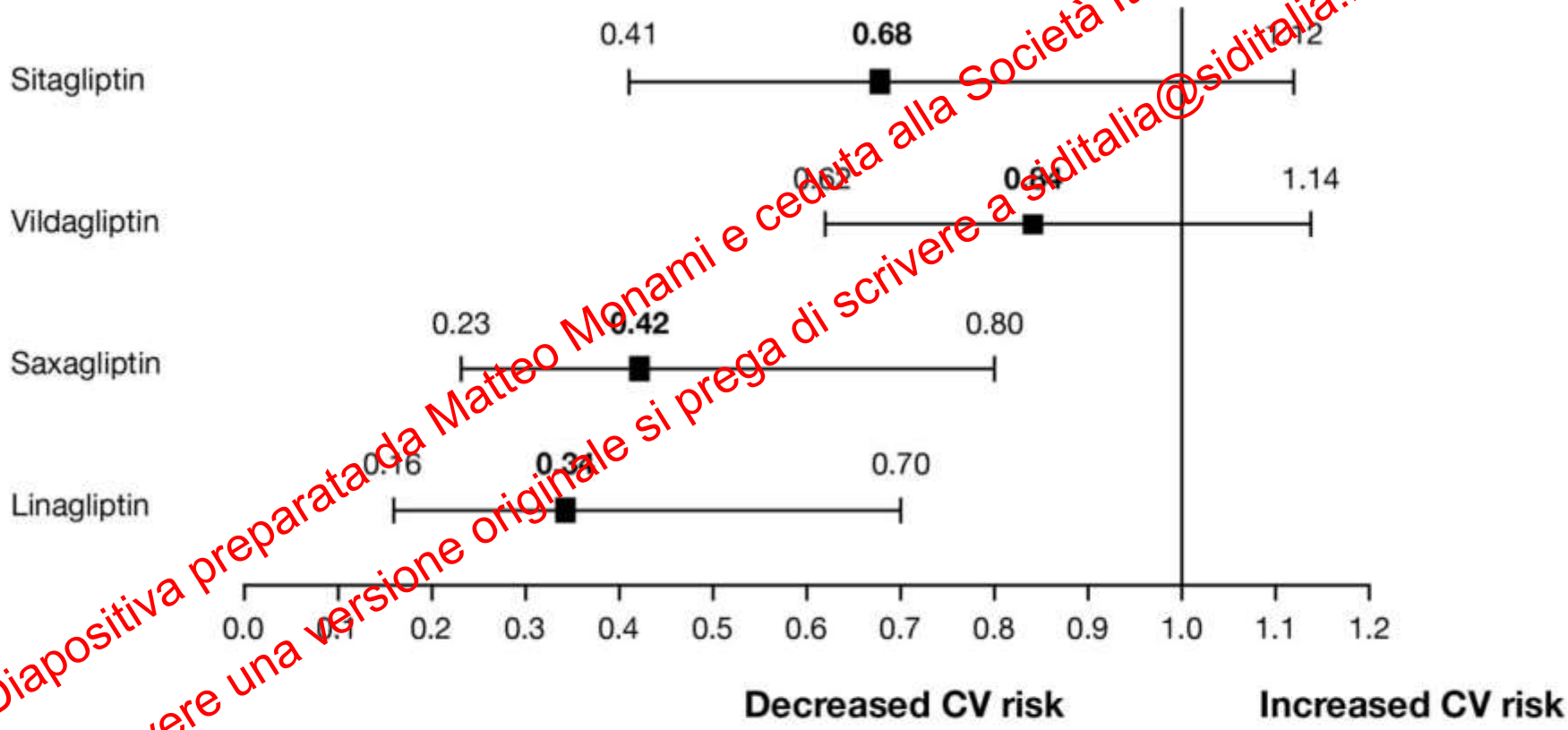


Monami M, Dicembrini I, Nardini C, Fiordelli I, Mannucci E.
Diabetes Obes Metab 2013

DPP-4 inhibitors and MACE

Pooled analyses of Phase II–III trials



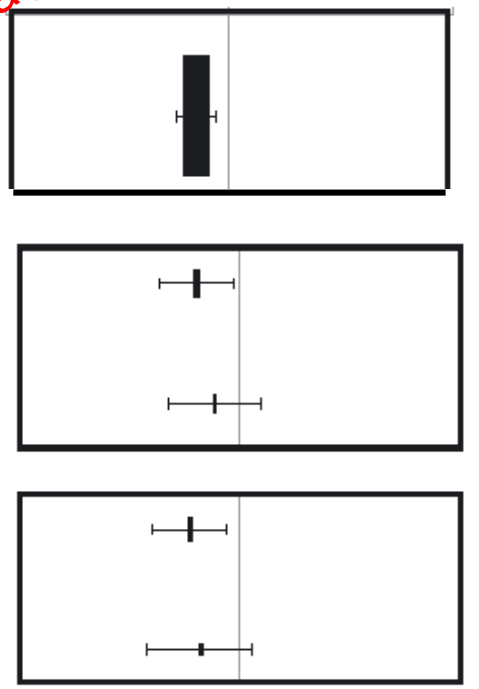
1. Williams-Herman D, *et al. BMC Endocr Disord* 2010;10:7; 2. Schweizer A, *et al. Diabetes Obes Metab* 2010;12:485–94; 3. Frederich R, *et al. Postgrad Med* 2010;122:16–27; 4. Johansen O, *et al. Cardiovasc Diabetol* 2012;11:3.

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]

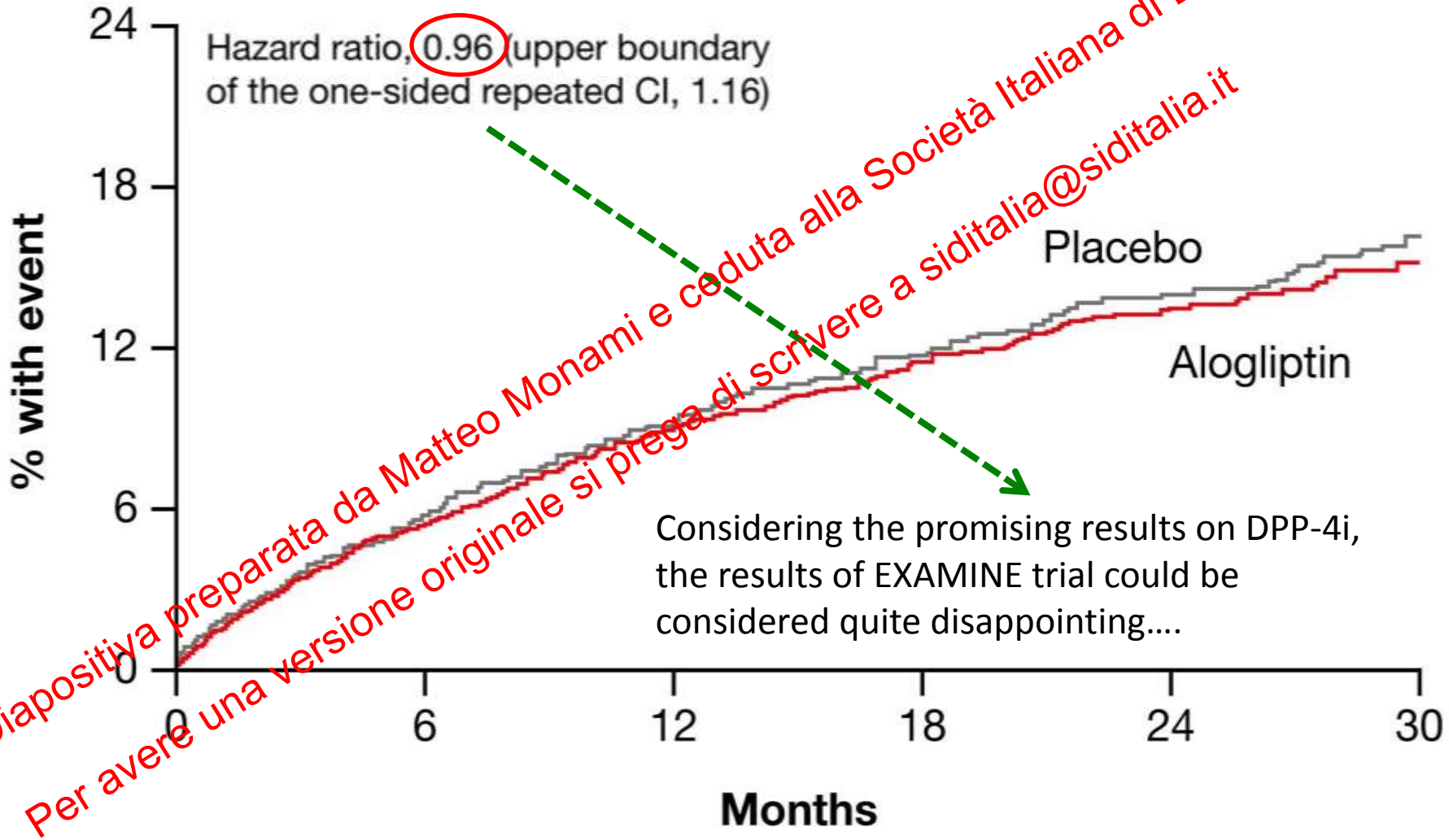
	# trials	# trials with events	# events (*DPP4i*)	# events (*Comparator*)	MH-OR [95%, CI]	p	Kendall's tau	p
MACE	70	63	263	232	0.71[0.59;0.86]	<0.001	0.04	0.64
AMI	62	41	61	59	0.64[0.44;0.94]	0.023	-0.13	0.27
Stroke	63	29	41	33	0.77[0.48;1.24]	0.290	-0.24	0.14
Mortality	53	30	30	51	0.60[0.41;0.88]	0.008	0.13	0.28
CV Mortality	48	20	26	26	0.67[0.39;1.14]	0.140	0.05	0.76



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

Alogliptin after Acute Coronary Syndrome in patients with type 2 diabetes

The EXAMINE trial



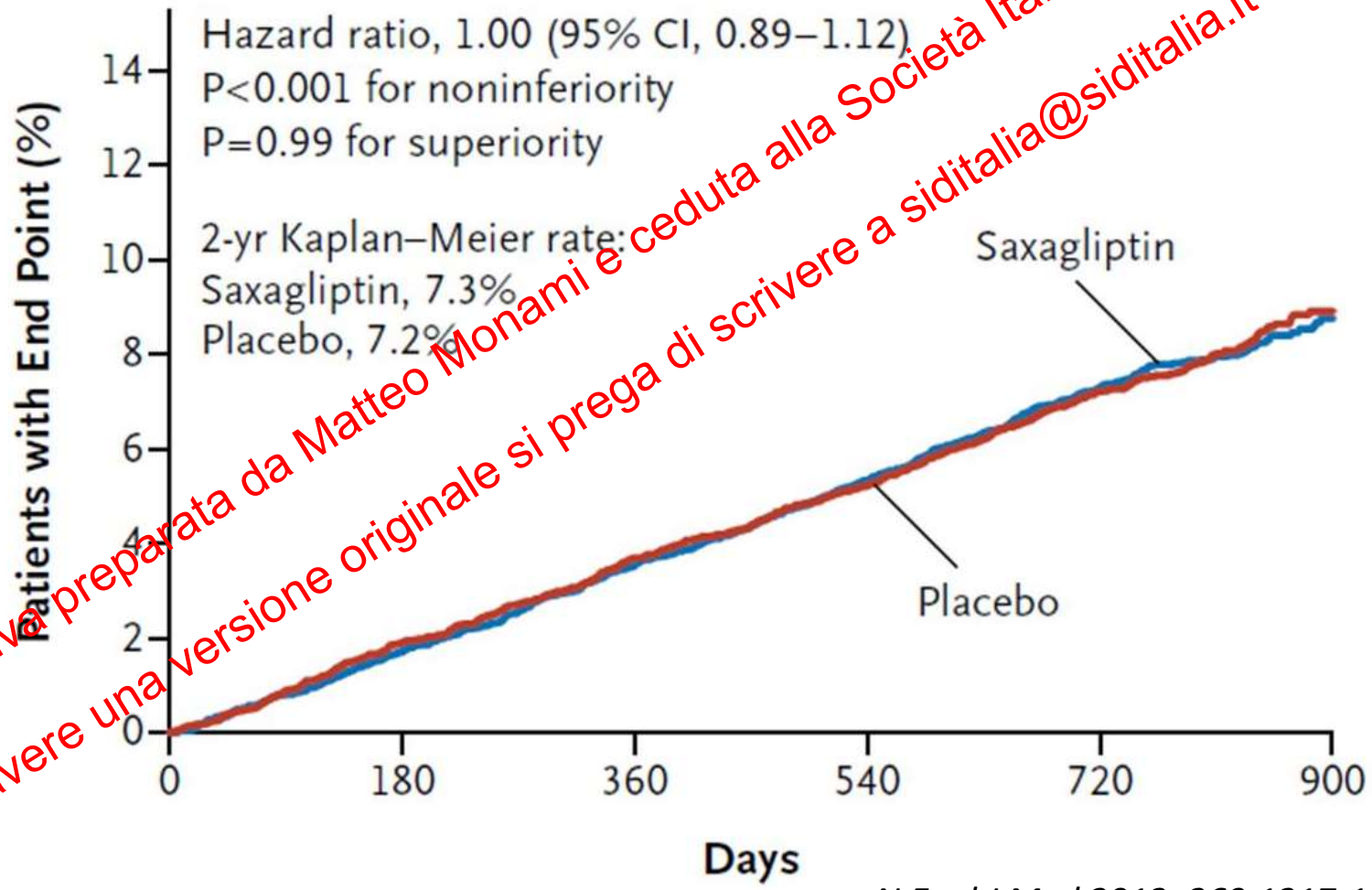
Considering the promising results on DPP-4i, the results of EXAMINE trial could be considered quite disappointing….

N Engl J Med 2013; 369:1327-1335

Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus

The SAVOR trial

Scirica BM et al.



N Engl J Med 2013; 369:1317-1326

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

Missclassification of events

These three limitations can be true for MACE, but not for all-cause mortality.

1. Diagnostic criteria are universally accepted….
2. No need for screening procedures
3. There is no possibility of misclassification….dead or alive.

…the reduction of all-cause mortality observed in meta-analyses of early metabolic trials with DPP-4i is simply true!

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.

Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results - A Long Term Evaluation (LEADER®)

This study is ongoing, but not recruiting participants.

Sponsor:

Novo Nordisk

ClinicalTrials.gov Identifier: NCT01179048

Enrollment: **9,340**

Study Start Date: August 2010

Estimated Study Completion Date: October 2015

Estimated Primary Completion Date: October 2015

Primary Outcome Measures:

Time from randomisation to first occurrence of **cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke** (a composite cardiovascular outcome)

[Time Frame: from randomisation up to 60 months]

***Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010* (Lixisenatide) (ELIXA)**

This study is ongoing, but not recruiting participants.

Sponsor:
Sanofi

ClinicalTrials.gov Identifier: NCT01147250
Enrollment: **6,000**
Study Start Date: August 2010
Estimated Study Completion Date: October 2015
Estimated Primary Completion Date: October 2015

Primary Outcome Measures: Time to the first occurrence of the primary cardiovascular (CV) event: **CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina**, positively adjudicated by the Cardiovascular Events Adjudication Committee (CAC) [Time Frame: week 0 to week 203]

Exenatide Study of Cardiovascular Event Lowering Trial (EXSCEL): A Trial To Evaluate Cardiovascular Outcomes After Treatment With Exenatide Once Weekly In Patients With Type 2 Diabetes Mellitus

This study is currently recruiting participants.

Sponsor:
Bristol-Myers Squibb
Collaborator:
AstraZeneca

ClinicalTrials.gov Identifier: NCT01144338
First received: June 10, 2010
Enrollment: **14,000**
Study Start Date: August 2010
Estimated Study Completion Date: April 2018
Estimated Primary Completion Date: December 2017

Primary Outcome Measures: The primary efficacy outcome variable is defined as the composite endpoint of cardiovascular death, nonfatal MI, or nonfatal stroke [Time Frame: Time to first event. Information collected during study period (anticipated to be up to 7.5 years).]