"Ridurre i rischi cardiovascolari nel paziente diabetico"

Come le terapie ipoglicemizzanti possono migliorare *(o peggiorare)* la prognosi del diabete

Matteo Monami

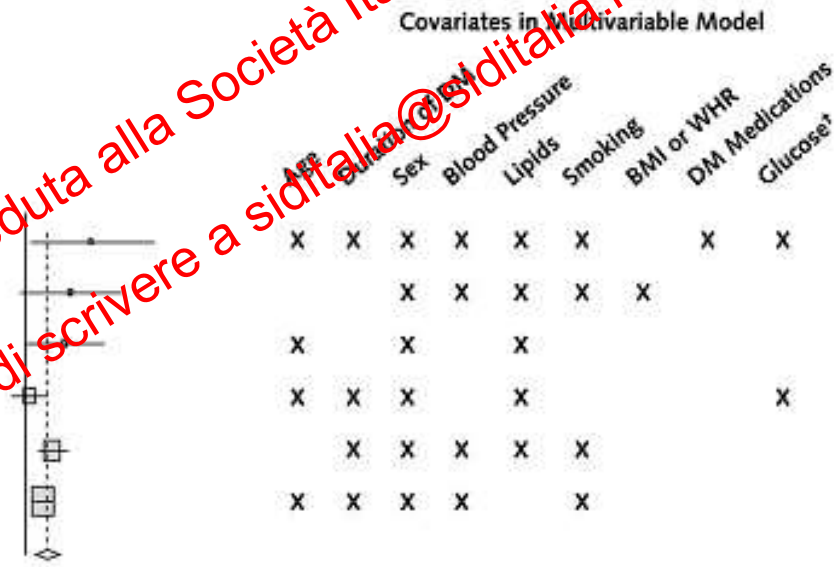
Servizio di Diabetologia, AOU Careggi, Firenze

Diabetes and CV risk

A meta-analysis

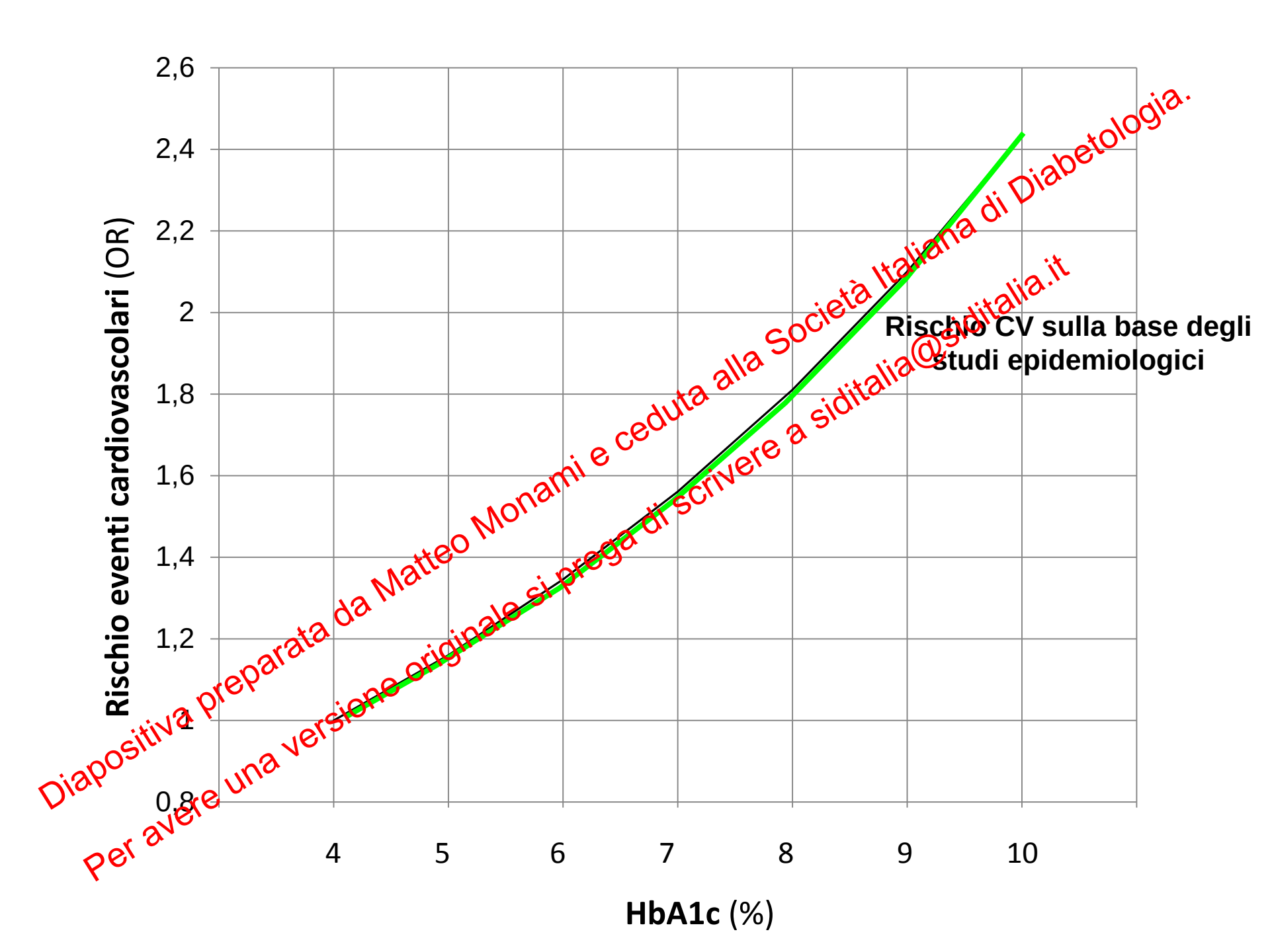
Type 2 diabetes

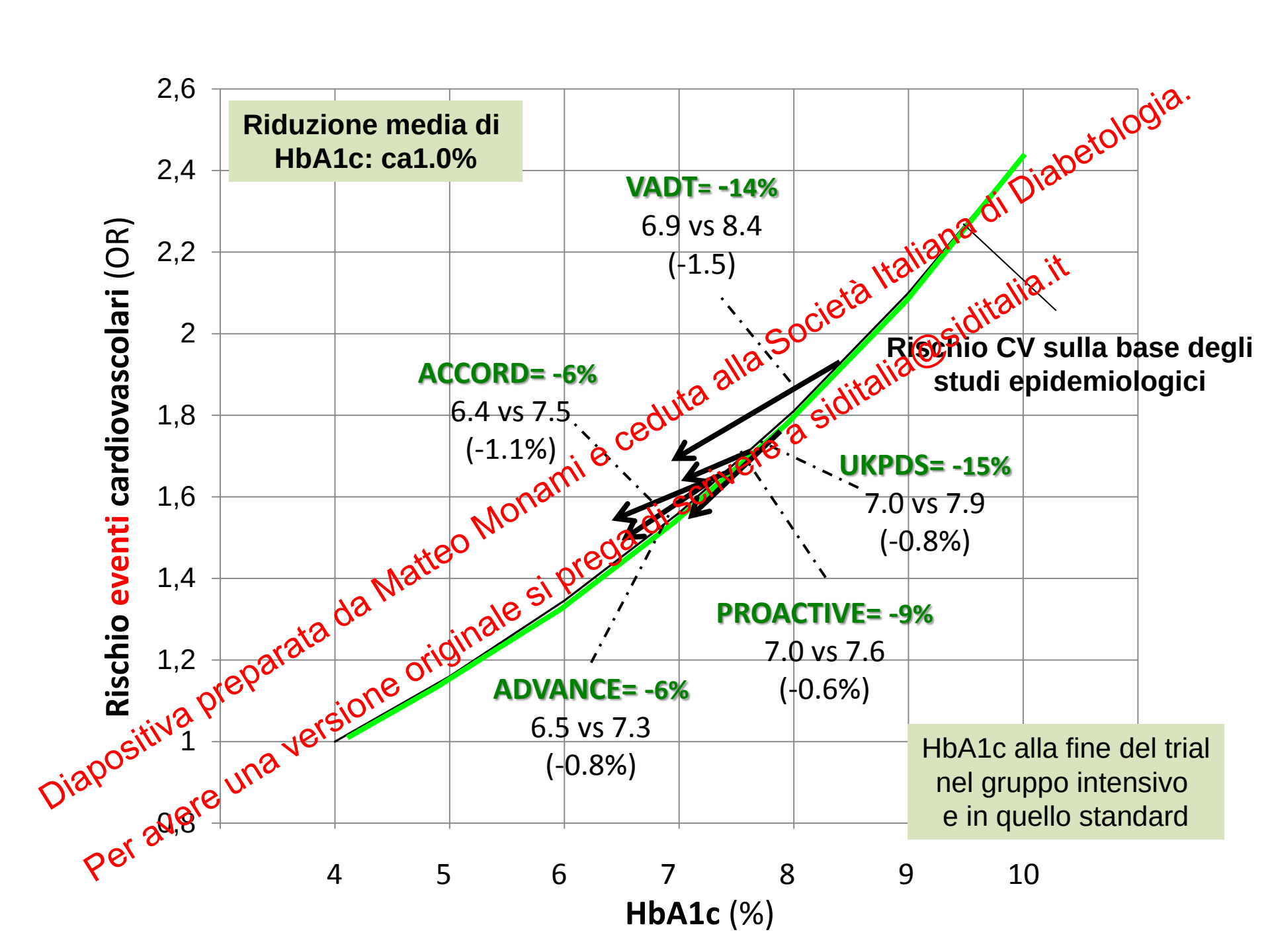
Study, Year (Reference)	Events/Persons, *n/n**	RR (95% CI)
Coronary heart disease (fatal and nonfatal)		
Florkowski et al., 1998 (24)	92/422	1.43 (1.02–2.00)
Kuusisto et al., 1994 (36)	33/229	1.29 (0.98–1.70)
Mattock et al., 1998 (53)	20/138	1.25 (1.01–1.55)
Lehto et al., 1997 (32)	256/1059	1.03 (0.96–1.15)
Stratton et al., 2000 (40)	606/3642	1.16 (1.09–1.27)
Moss et al., 1994 (44)	243/1194	1.10 (1.04–1.17)
Pooled	1248/6684	1.13 (1.06–1.20)



Rischio cardiopatia ischemica: 13%
(Ictus: 14%; IMA: 16%; Morte CV: 15%)

Selvin E, et al. *Ann Intern Med* 2004; 141:421-431


2,6
2,4
2,2
2
1,8
1,6
1,4
1,2
1
0,8
Rischio eventi cardiovascolari (OR)
4
5
6
7
8
9
10
HbA1c (%)
Rischio CV sulla base degli studi epidemiologici
Diapositiva preparata da Matteo Monami e ceduta alla Società Italiana di Diabetologia.
Per avere una versione originale si prega di scrivere a siditalia@siditalia.it


Riduzione media di HbA1c: ca1.0%
VADT= -14%
6.9 vs 8.4
(-1.5)
ACCORD= -6%
6.4 vs 7.5
(-1.1%)
UKPDS= -15%
7.0 vs 7.9
(-0.8%)
PROACTIVE= -9%
7.0 vs 7.6
(-0.6%)
ADVANCE= -6%
6.5 vs 7.3
(-0.8%)
Rischio CV sulla base degli studi epidemiologici
HbA1c alla fine del trial nel gruppo intensivo e in quello standard
Rischio eventi cardiovascolari (OR)
HbA1c (%)
2,6
2,4
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Diapositiva preparata da Matteo Monami e ceduta alla Società Italiana di Diabetologia.
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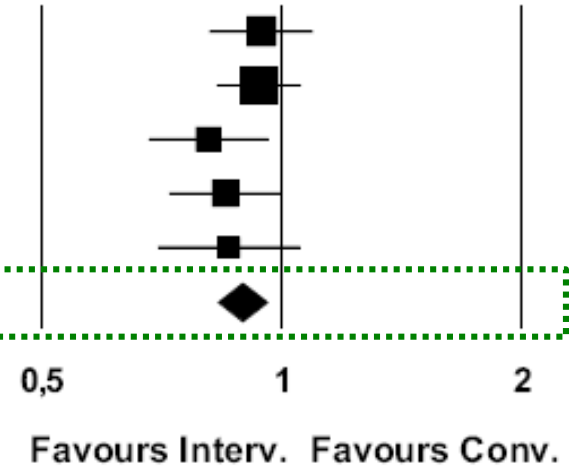
Prevention of cardiovascular disease through glycemic control in type 2 diabetes:

A meta-analysis of randomized clinical trials

Cardiovascular events

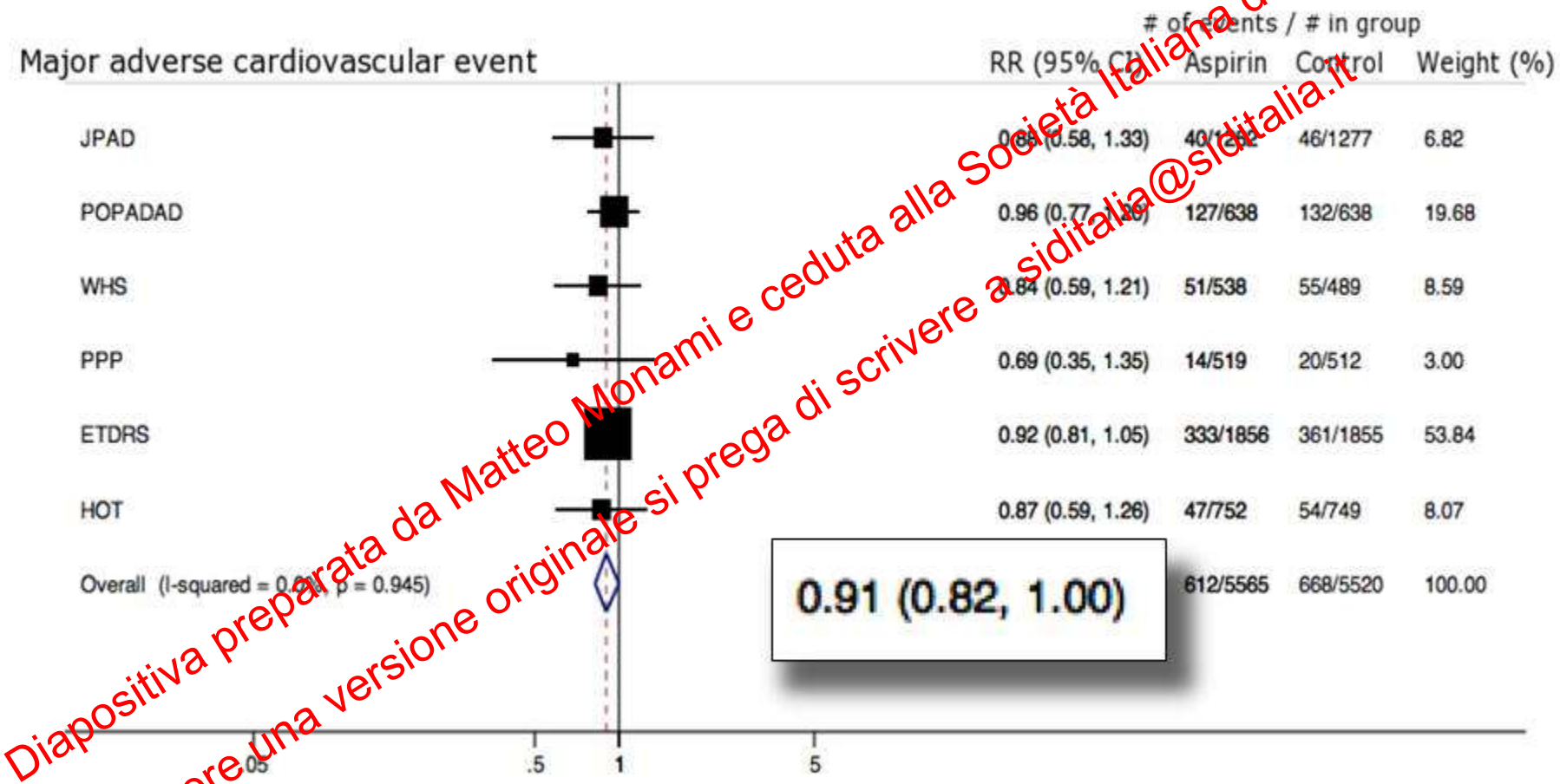
Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
ACCORD	0,944	0,811	1,098	-0,746	0,456
ADVANCE	0,937	0,830	1,059	-1,035	0,301
PROACTIVE	0,811	0,681	0,966	-2,346	0,019
UKPDS 33+34	0,852	0,723	1,003	-1,920	0,055
VADT	0,861	0,700	1,058	-1,425	0,154
OVERALL	0,893	0,838	0,957	-3,182	0,001



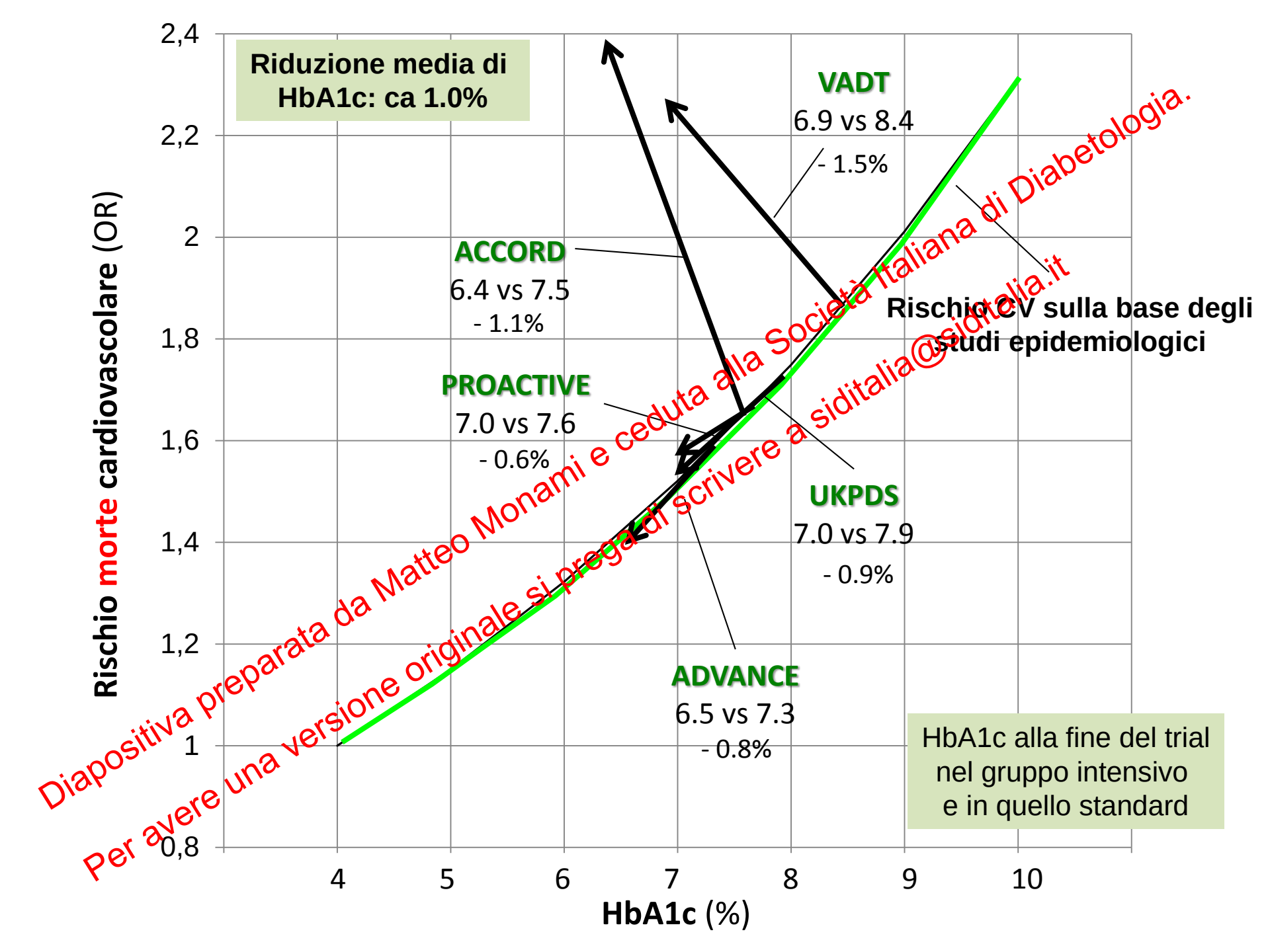
Mannucci E, Monami M, Lamanna C, Gori F, Marchionni N.
Nutr Metab Cardiov Dis 2009; 19:604-612

ASA and CVD in diabetes

Meta-analysis of RCTs



Butalia S et al., *Cardiovasc Diabetol* 2011; 10:25.


Riduzione media di HbA1c: ca 1.0%
VADT
6.9 vs 8.4
- 1.5%
ACCORD
6.4 vs 7.5
- 1.1%
PROACTIVE
7.0 vs 7.6
- 0.6%
UKPDS
7.0 vs 7.9
- 0.9%
ADVANCE
6.5 vs 7.3
- 0.8%
Rischio CV sulla base degli studi epidemiologici
HbA1c alla fine del trial nel gruppo intensivo e in quello standard
Rischio morte cardiovascolare (OR)
HbA1c (%)
2,4
2,2
2
1,8
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Diapositiva preparata da Matteo Monami e ceduta alla Società Italiana di Diabetologia.
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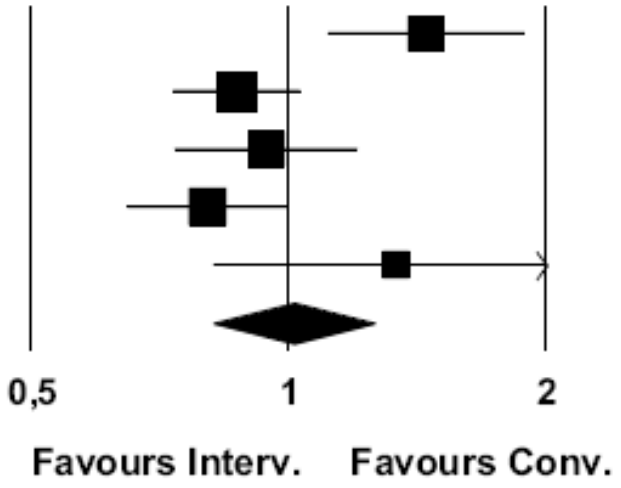
Prevention of cardiovascular disease through glycemic control in type 2 diabetes:

A meta-analysis of randomized clinical trials

Cardiovascular mortality

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
ACCORD	1,447	1,108	1,888	2,718	0,007
ADVANCE	0,869	0,731	1,033	-1,589	0,112
PROACTIVE	0,941	0,734	1,206	-0,480	0,631
UKPDS 33+34	0,805	0,647	1,001	-1,950	0,051
VADT	1,335	0,816	2,184	1,150	0,250
OVERALL	1,012	0,815	1,257	0,110	0,912



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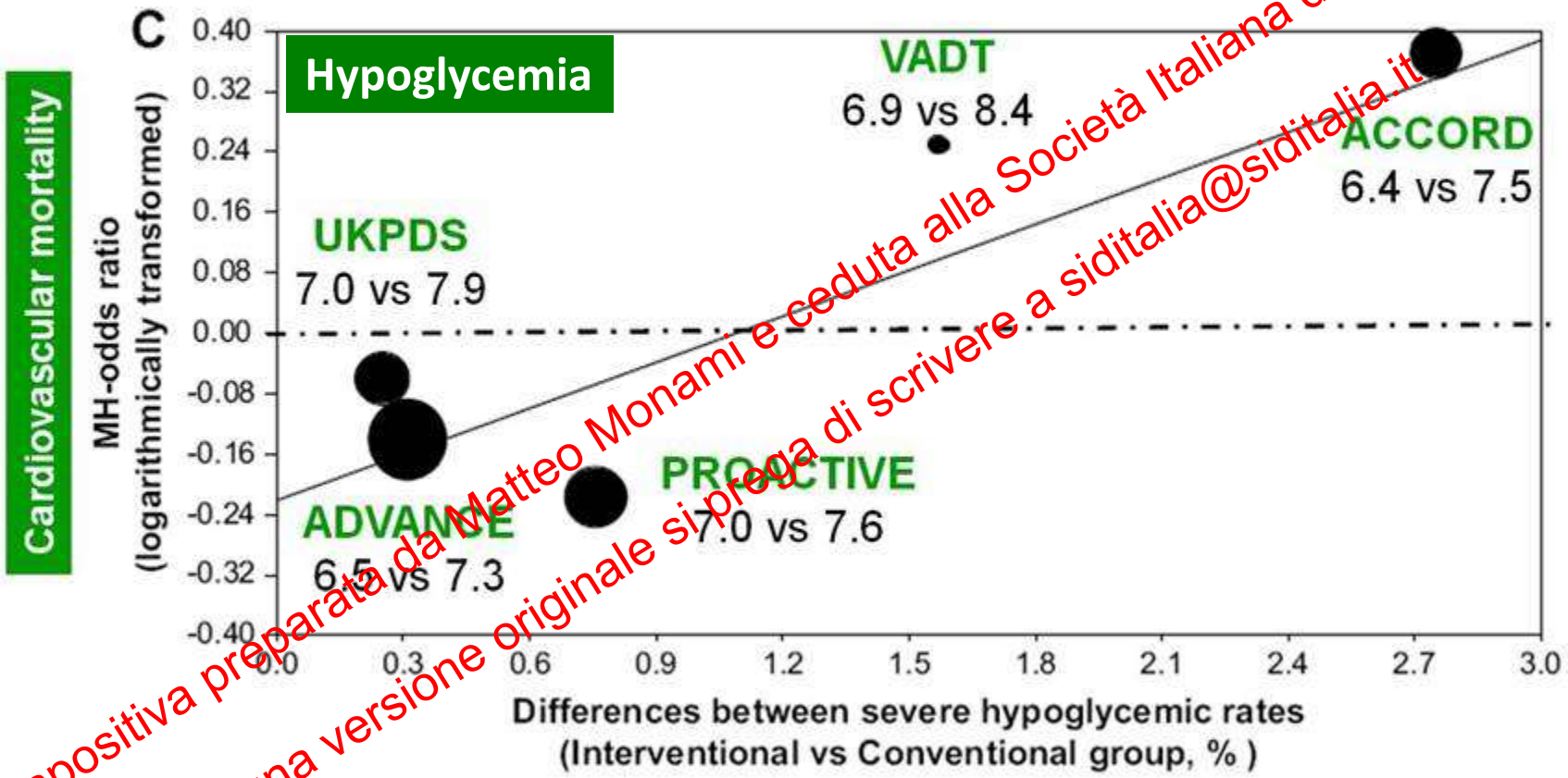
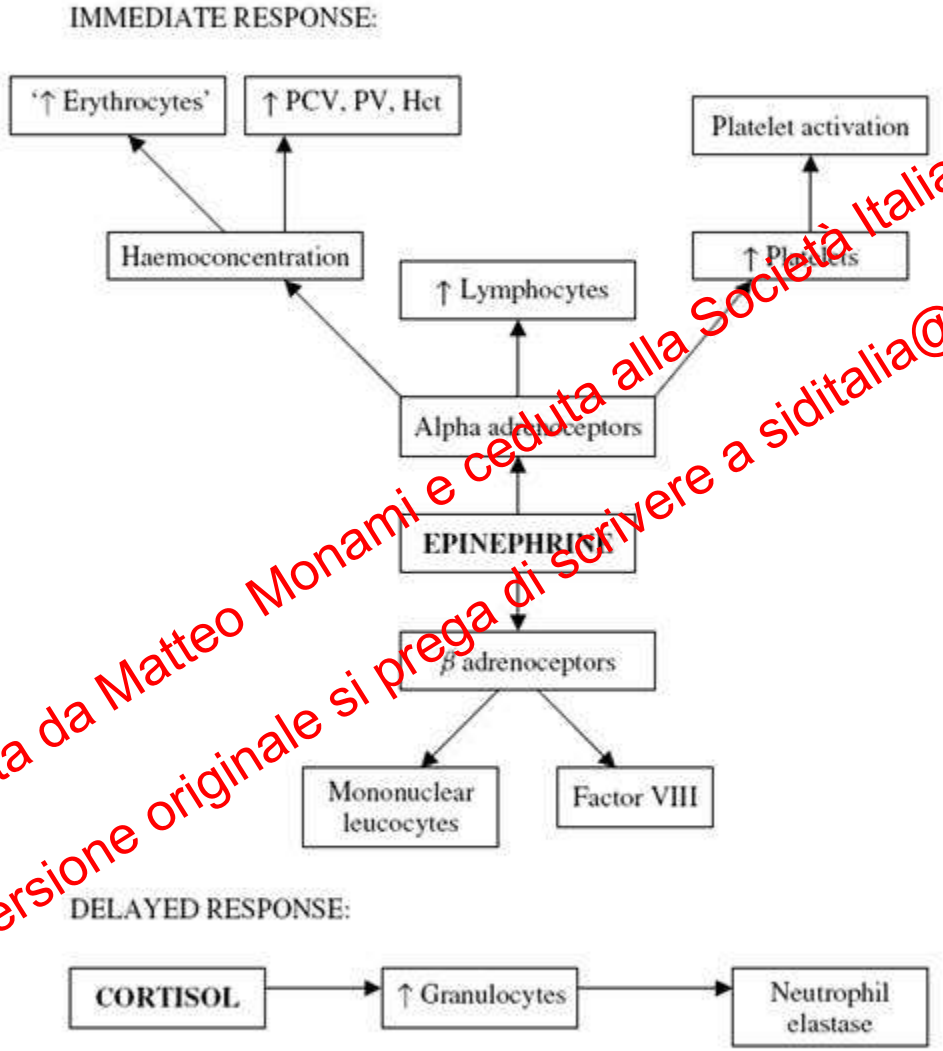
Prevention of cardiovascular disease through glycemic control in type 2 diabetes

A meta-analysis of randomized clinical trials



Mannucci E, Monami M, Lamanna C, Gori F, Marchionni N.
NMCD 2009; 19: 604-612

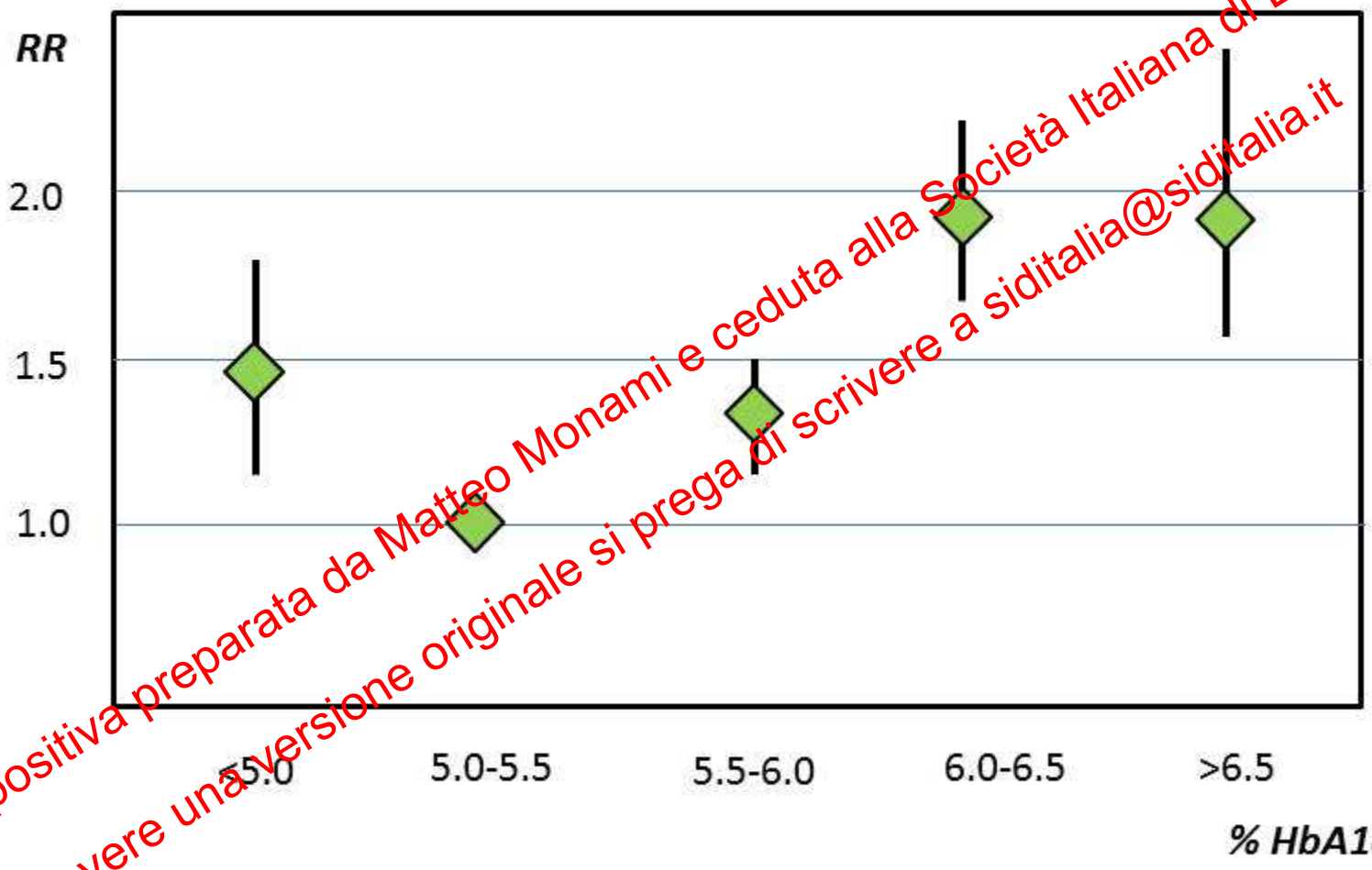
Hypoglycemia and CV death



Wright RJ, Frier BM. *Diabetes Metab Res Rev* 2008; 24: 353-365.

All-cause mortality in population

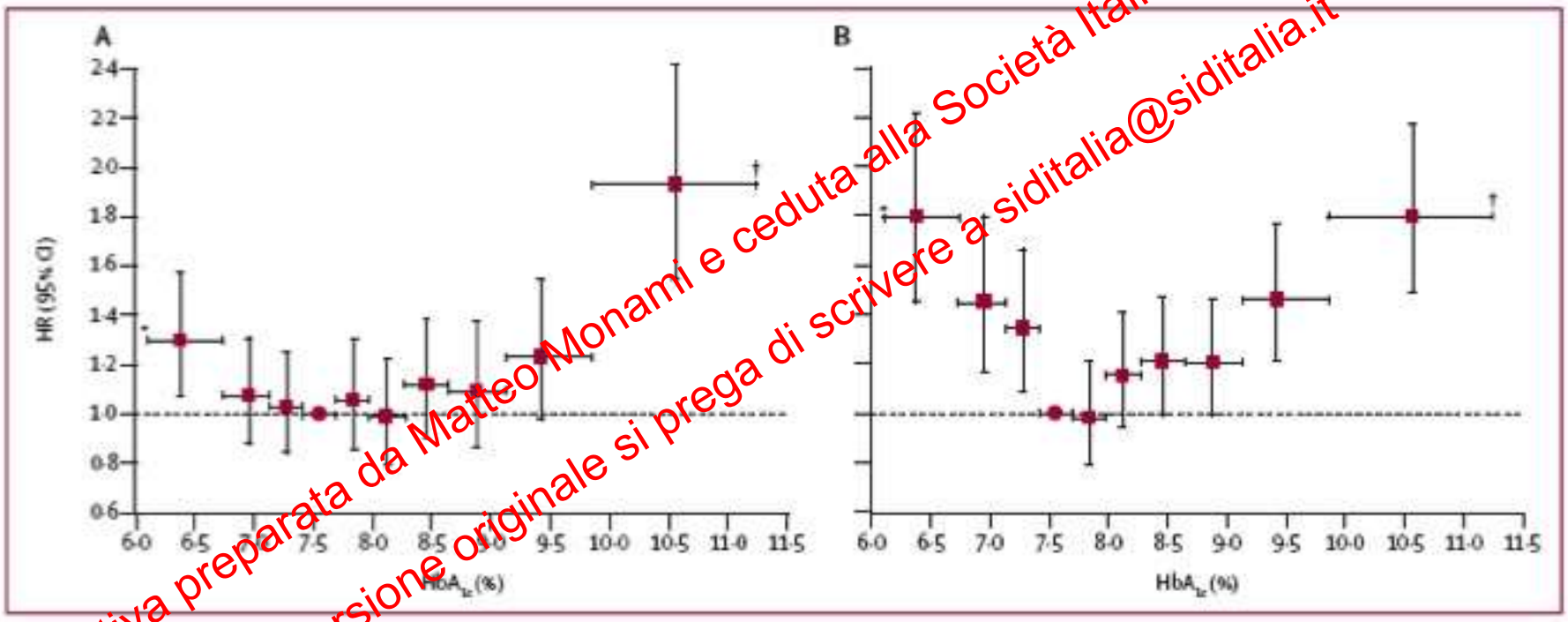
Relationship with HbA1c



Selvin E et al. *N Engl J Med* 362:800-11, 2012

All-cause mortality in T2DM

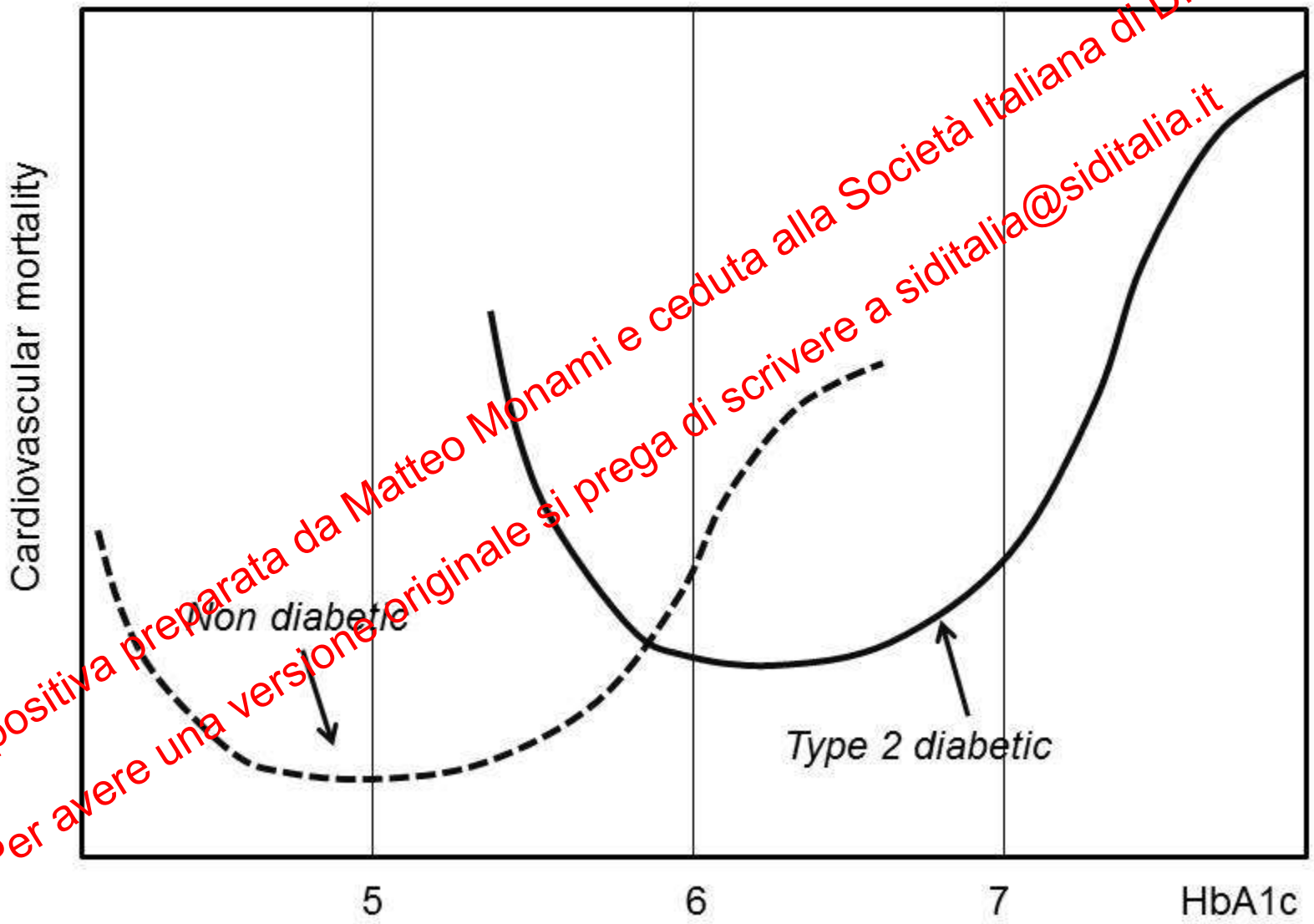
Relationship with HbA1c



Currie CJ et al. *Lancet* 315:481-9, 2010

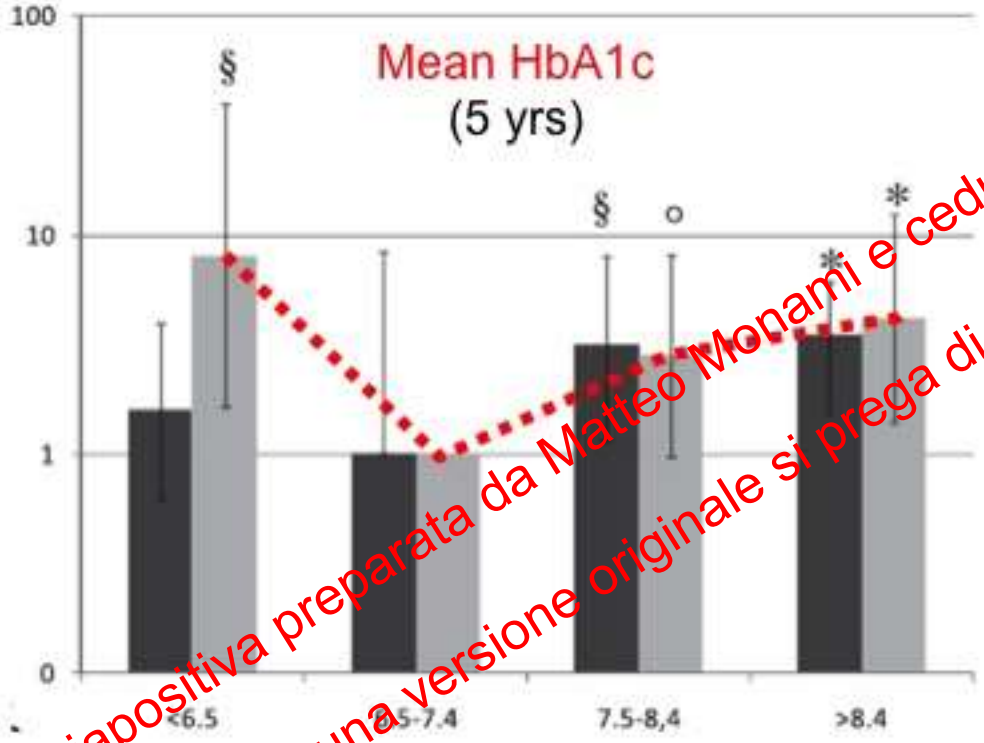
HbA1c and mortality

Type 2 DM vs non-diabetic



All-cause mortality in T2DM

Relationship with HbA1c



Non-insulin treated patients

Insulin treated patients

mean follow-up of 5.7 ± 3.5 years

Survivors	Dead
427 (44.0)	427 (47.8)

Monami M et al. *Nutr Metab Cardiovasc Dis*, 2012

Rosiglitazone and MI

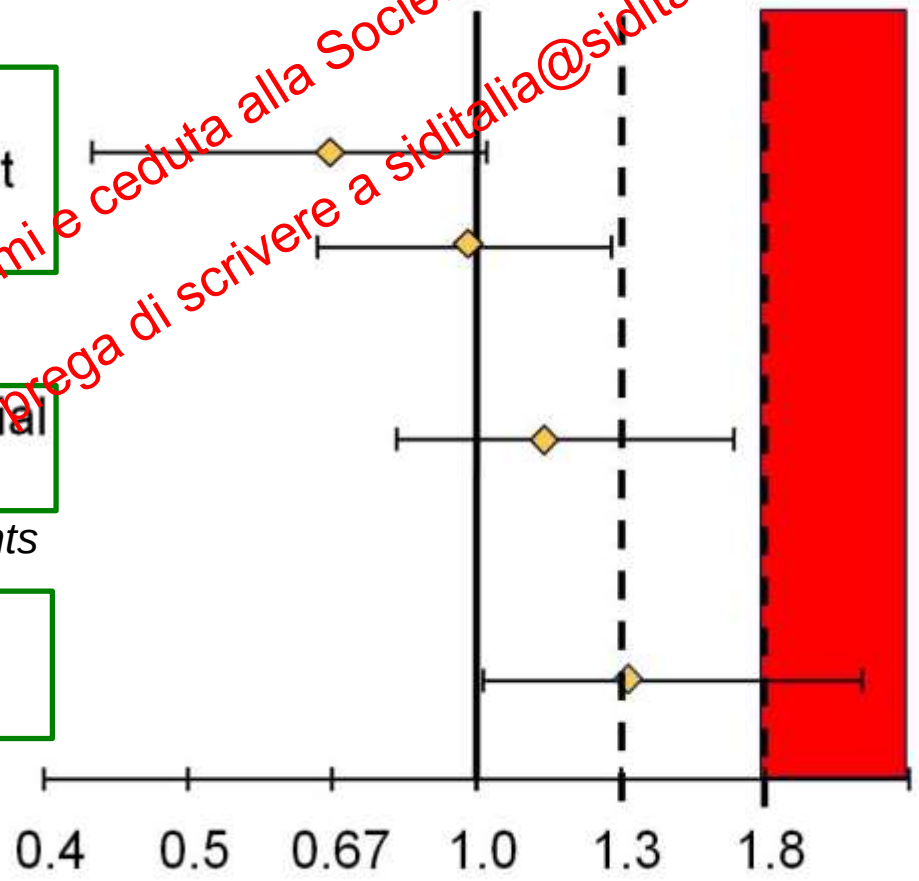
A meta-analysis of RCTs

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)	22/6,006 (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**

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

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

Drug can be immediately approved without the need for further studies

<1.8 – conduct large safety trial post-approval

Usual result for glucose-lowering agents

>1.8 – conduct large safety trial pre-approval

Drug cannot be approved for marketing

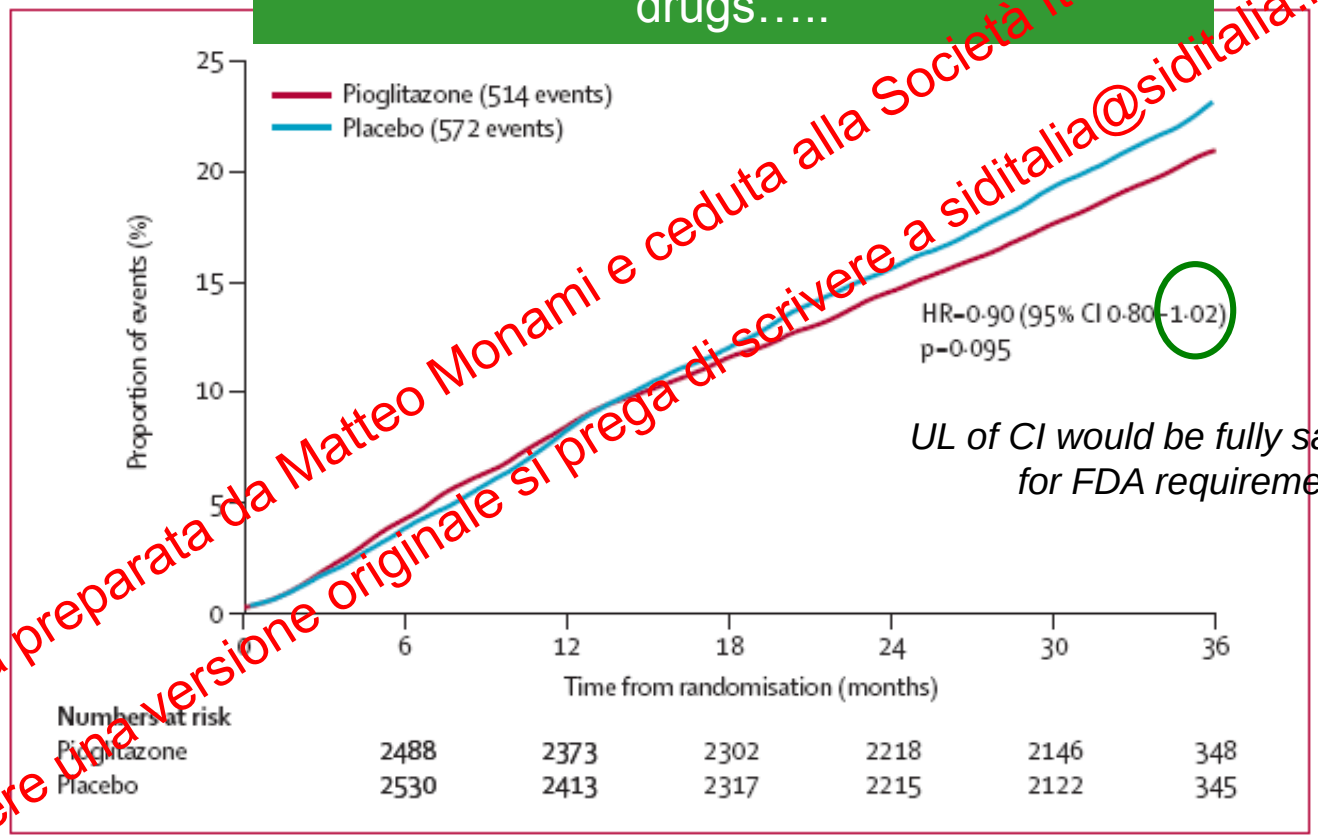
Food and Drug Administration, 2008. Available from: http://www.fda.gov/downloads/Drugs/guidanceComplianceRegulatoryInformation/guidances/ucm071627.pdf. Last accessed July 2013.

Secondary prevention of macrovascular events in patients with type 2 diabetes

The PROACTIVE Study

John A Dormandy, Bernard Charbonnel, David J A Eckland, Erland Erdmann, Massimo Massi-Benedetti, Ian K Moules, Allan M Skene, Meng H Tan

If this regulation had to be applied to older drugs…..



UL of CI would be fully satisfactory for FDA requirements

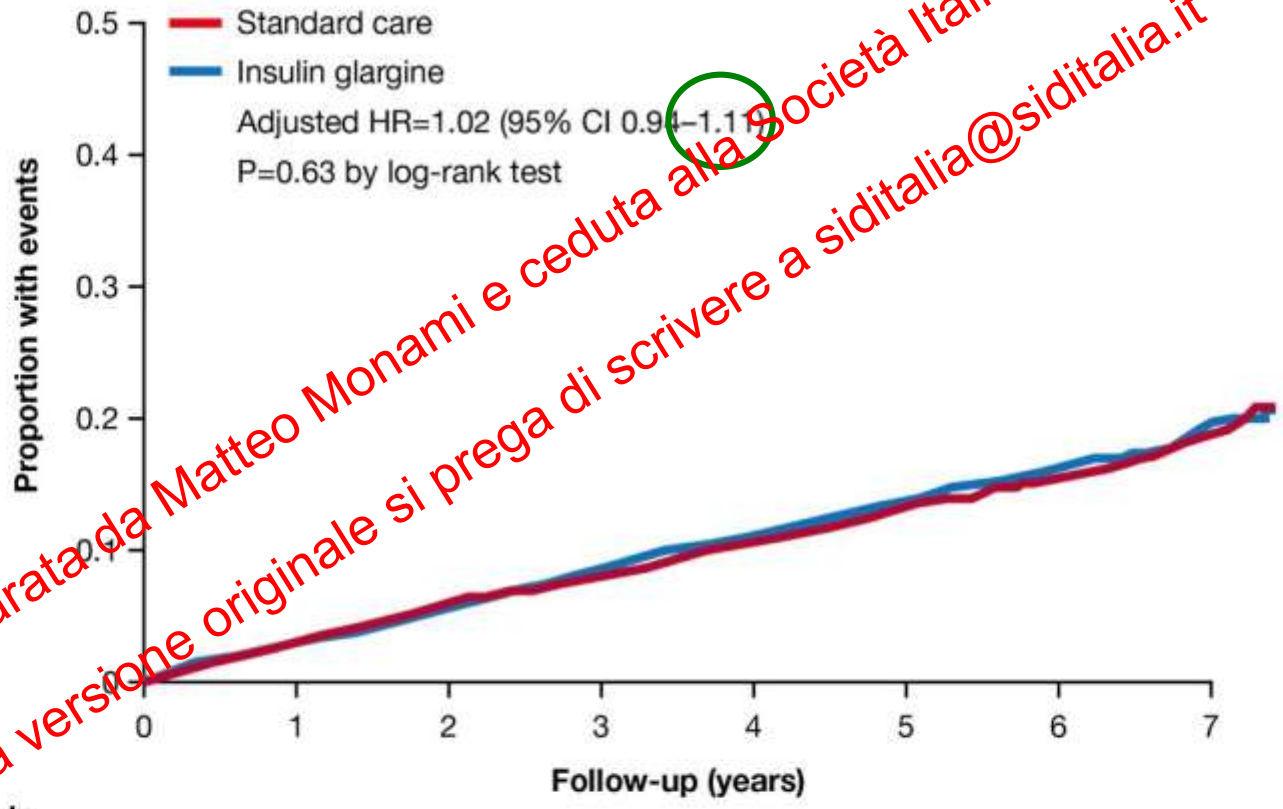
Figure 2: Kaplan-Meier curve of time to primary endpoint*

*Death from any cause, non-fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, leg amputation, coronary revascularisation, or revascularisation of the leg.

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.

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

The UKPDS 34 study

	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

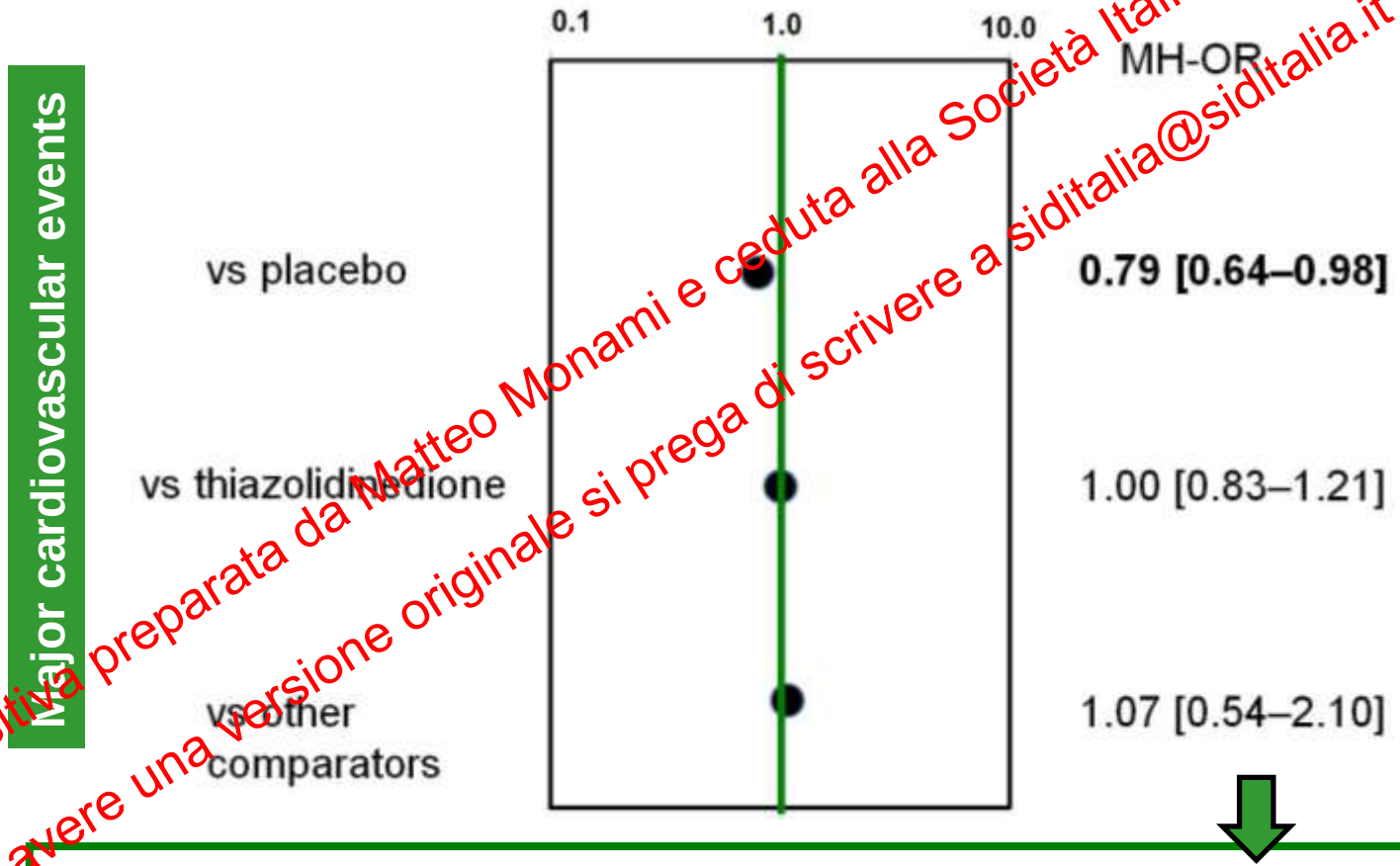
*P<0.05 vs conventional; †P<0.05 vs insulin/SU

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

Effect of metformin on cardiovascular events and mortality

A meta-analysis of randomized clinical trials

C. Lamanna[1], M. Monami[2], N. Marchionni[2] & E. Mannucci[1]



Metformin vs other therapies/PBO: **MH-OR 0.94 [0.82–1.07]**, p = 0.34

Diabetes, Obesity and Metabolism 13: 221–228, 2011

Cardiovascular safety of sulfonylureas

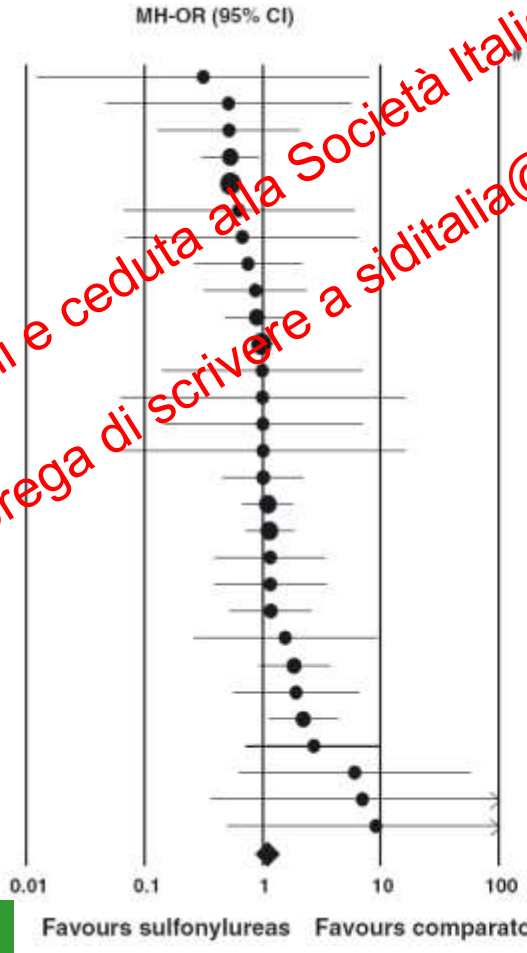
A meta-analysis of randomized clinical trials

M. Monami[1], S. Genovese[2] & E. Mannucci[3]

115 selected trials

Major cardiovascular events

First author (Year)	MH-OR	LL (95%. CI)	UL (95% CI)	p	Sulfonylureas # Events	Sulfonylureas # Patients	Comparator # Events	Comparator # Patients	Variance (%)
Birkeland 1996 [33]	0.315	0.012	8.269	0.489	0	18	1	18	0.07
Chou 2008 [41]	0.516	0.046	5.729	0.590	1	227	2	230	0.21
Perriello 2006 [99]	0.522	0.128	2.131	0.365	3	137	6	146	0.64
Gerstein 2010 [67]	0.534	0.301	0.945	0.031	18	339	35	333	3.42
UKPDS 33 1998 [130]	0.537	0.443	0.650	0.000	278	1234	432	1807	41.45
Hanefeld 2007 [76]	0.629	0.065	6.083	0.689	1	203	3	384	0.28
Seino 2010 [114]	0.674	0.069	6.545	0.734	1	132	3	268	0.28
Charbonnel 2005 [40]	0.755	0.259	2.201	0.607	6	313	8	317	1.00
Matthews 2005 [39]	0.871	0.314	2.416	0.790	7	626	8	624	1.07
Rubin 2008 [109]	0.896	0.475	1.693	0.736	14	591	32	1214	3.28
Home 2009 [80]	0.983	0.774	1.249	0.888	154	1105	158	1117	20.22
Arechavaleta 2011 [29]	0.994	0.140	7.085	0.995	2	519	2	516	0.28
van der Laar 2004 [132]	1.000	0.061	16.463	1.000	1	48	1	48	0.14
Mazzone 2006 [90]	1.009	0.141	7.224	0.993	2	228	2	230	0.28
Riddle 1998 [106]	1.014	0.062	16.529	0.992	1	72	1	73	0.14
Giles 2010 [70]	1.015	0.454	2.268	0.972	13	149	13	151	1.85
Tolman 2009 [126]	1.112	0.668	1.852	0.683	32	1046	29	1051	3.34
Kahn 2006 [85]	1.144	0.701	1.858	0.587	26	1441	46	2910	4.13
Goke 2010 [71]	1.164	0.388	3.492	0.787	7	430	6	428	0.93
Garber 2009 [65]	1.167	0.386	3.522	0.785	7	248	6	247	0.93
Nissen 2008 [5]	1.177	0.518	2.676	0.697	13	273	11	270	1.71
Ristic 2007 [118]	1.260	0.256	6.190	0.630	3	129	2	133	0.36
Ferrannini 2009 [56]	1.851	0.912	3.754	0.088	22	1393	12	1396	2.42
Bakris 2006 [30]	1.922	0.5[illegible]	6.679	0.304	7	180	4	194	0.78
Gallwitz 2012 [63]	2.210	1.07	4.412	0.025	26	775	12	776	2.21
Jain 2006 [83]	2.722	0.714	10.380	0.143	8	251	3	251	0.78
Johnston 1998 [84]	6.034	0.619	58.837	0.122	3	92	1	180	0.28
Nauck 2011 [96]	7.265	0.362	136.640	0.197	3	401	0	400	0.21
Mark 2010 [112]	9.124	0.490	169.948	0.138	4	584	0	588	0.28
Overall	**1.041**	**0.825**	**1.312**	**0.736**	**617**	**13.327**	**878**	**16.456**	**100**



MH-OR: 1.04[0.82–1.31]

not be sufficient for approval by the FDA today

Diabetes, Obesity and Metabolism 2013.

Cardiovascular safety of sulfonylureas

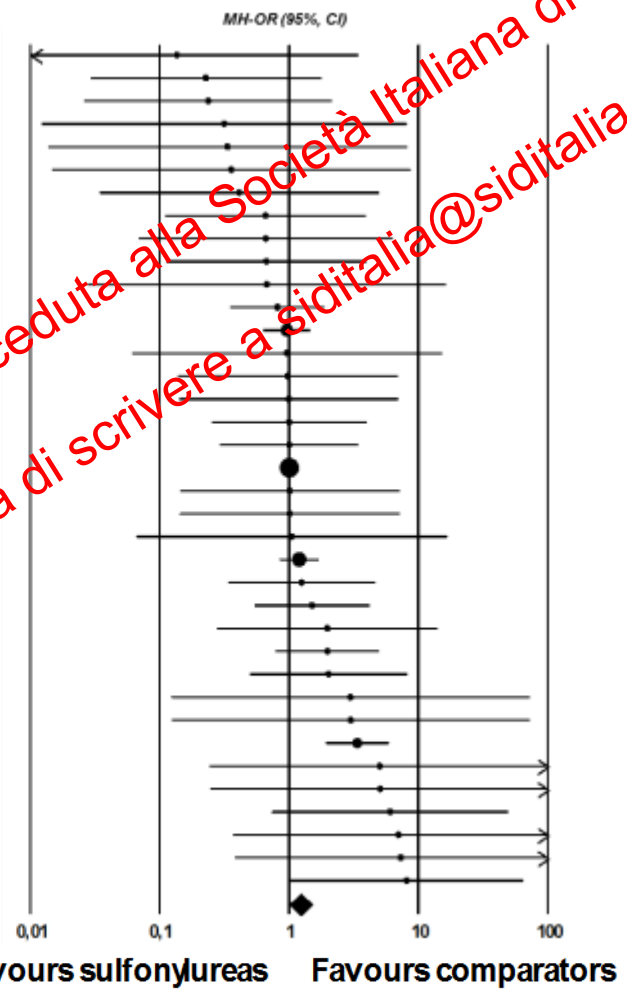
A meta-analysis of randomized clinical trials

M. Monami[1], S. Genovese[2] & E. Mannucci[3]

Diabetes, Obesity and Metabolism 2013.

All-cause mortality

First autor (Year)	MH-OR	LL (95%. CI)	UL (95%. CI)	p
Yki-Jarvinen 1999	0,14	0,01	3,48	0,23
Rubin 2008	0,23	0,03	1,80	0,16
Tan 1977	0,24	0,03	2,19	0,20
Birkeland 1996	0,32	0,01	8,27	0,49
Mazzone 2006	0,33	0,01	8,26	0,50
Bakris 2006	0,36	0,01	8,83	0,53
Alvarsson 2010	0,41	0,03	5,03	0,49
Nissen 2008	0,66	0,11	3,96	0,65
Marbury 1999	0,66	0,07	6,40	0,72
Ferrannini 2009	0,67	0,11	4,00	0,66
Seino 2010	0,67	0,03	16,63	0,81
Gerstein 2010	0,81	0,35	1,91	0,63
Kahn 2006	0,96	0,62	1,48	0,86
Filozof 2012	0,96	0,06	15,44	0,98
Hamann 2008	0,98	0,14	6,98	0,98
Goke 2010	1,00	0,14	7,10	1,00
Gallwitz 2012	1,00	0,25	4,02	1,00
Gallwitz 2012 (1)	1,01	0,29	3,56	0,99
UKPDS 33 1998	1,01	0,84	1,20	0,93
Charbonnel 2005	1,01	0,14	7,24	0,99
Giles 2010	1,01	0,14	7,29	0,99
Gerich 2005	1,05	0,07	16,87	0,97
Home 2009	1,13	0,83	1,53	0,32
Charbonnel 2004	1,30	0,33	4,27	0,74
Foley 2009	1,51	0,53	4,27	0,44
Johnston 1998	1,98	0,27	14,27	0,50
Hong 2012	1,99	0,16	5,07	0,15
Clarke 2007	2,02	0,49	8,29	0,33
Nathanavaleta 2011	2,99	0,12	73,53	0,50
Garber 2009	3,00	0,12	74,00	0,50
UGDP Group 1974	3,37	1,90	5,98	0,00
Jain 2006	5,04	0,24	105,51	0,30
Matthews 2005	5,10	0,24	106,58	0,29
Tolman 2009	6,06	0,73	50,40	0,10
Mark 2011	7,04	0,36	136,64	0,20
Barnett 2006	7,34	0,38	142,83	0,19
Seck 2010	8,15	1,02	65,39	0,05
Overall	**1.22**	**1.01**	**1.49**	**0.047**



Overall	**1.22**	**1.01**	**1.49**	**0.047**

SUs would not be approved by any regulatory authority

GLP1-RA and MACE

Meta-analysis of available RCTs

All trials

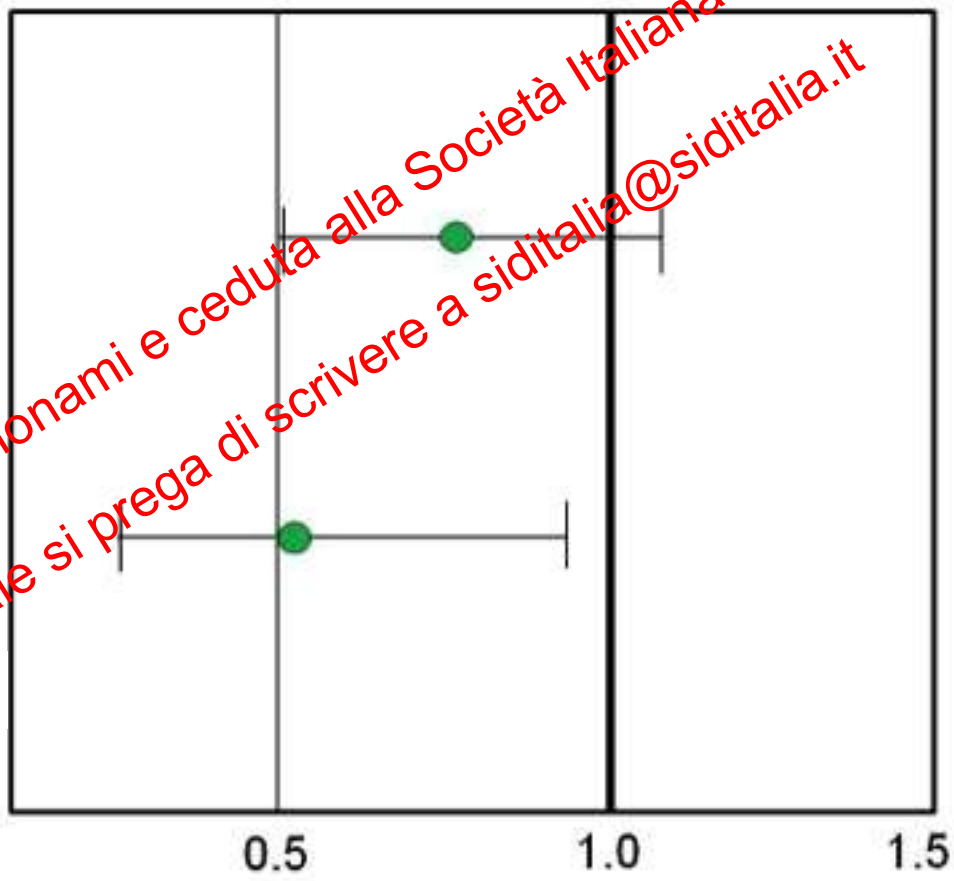
N= 25 RCTs

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

vs. placebo

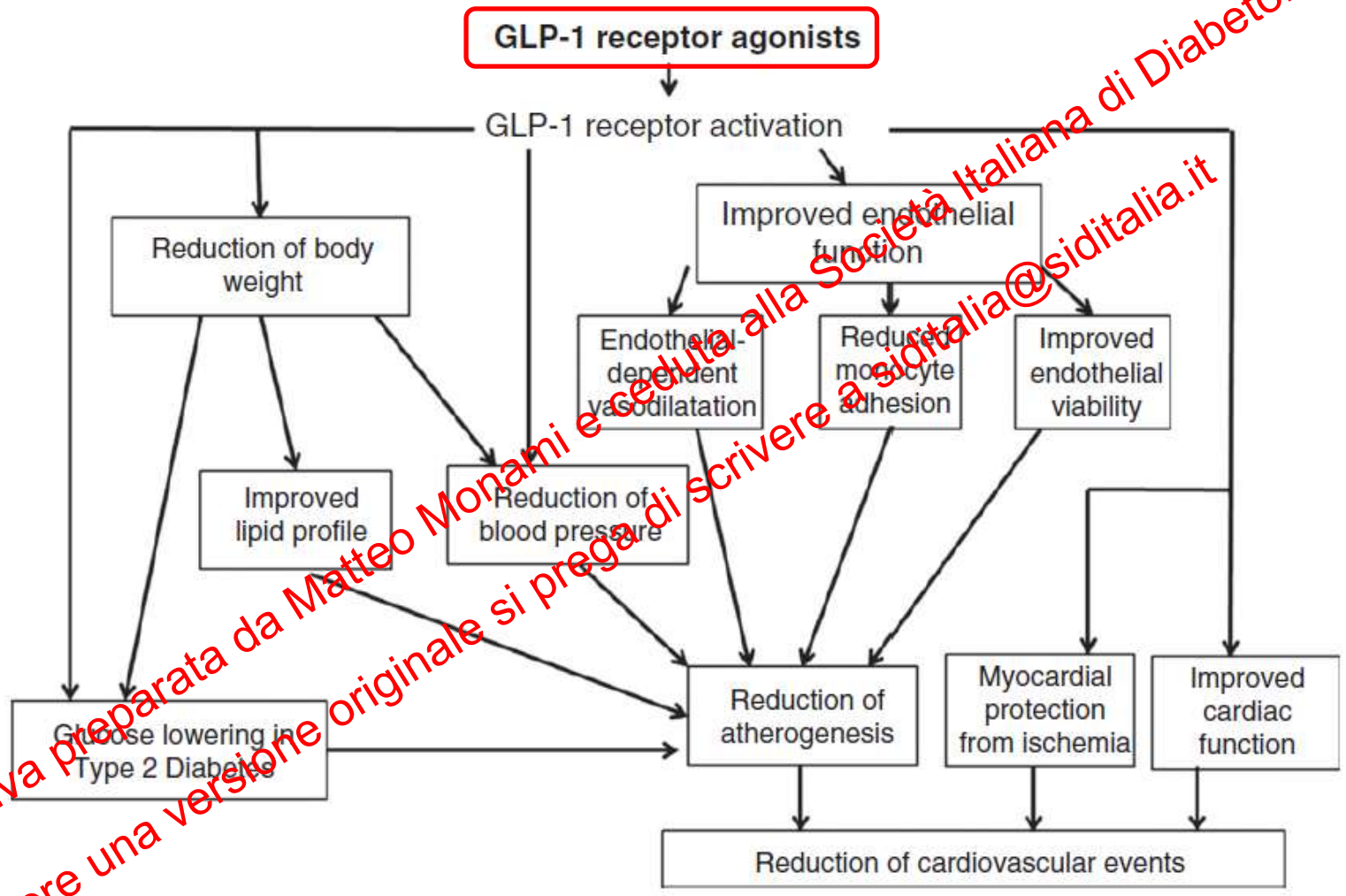
N= 12 RCTs

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



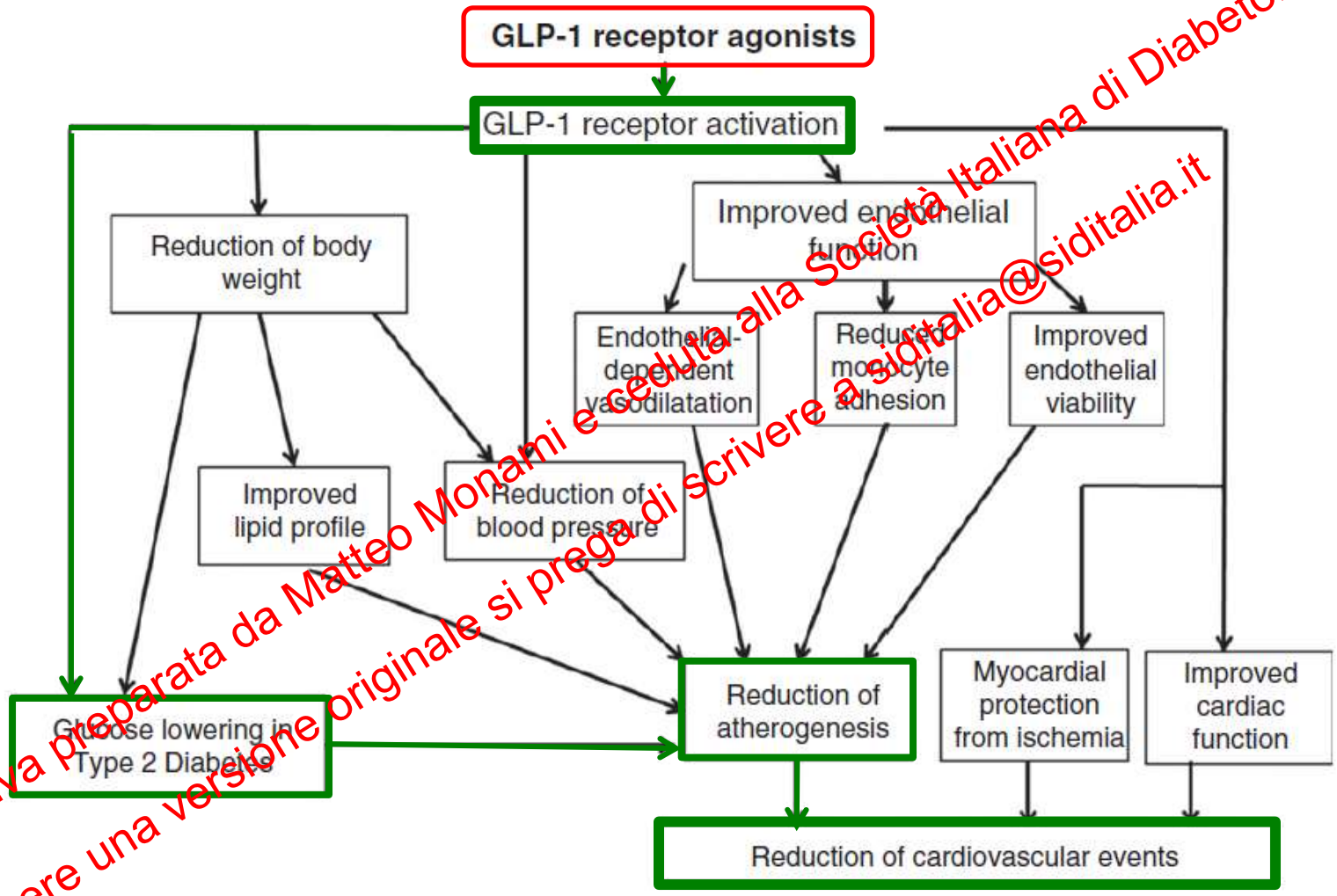
Monami M, Dicembrini I, Nardini C, Fiordelli I, Mannucci E.
Diabetes Obes Metab 2013

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



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

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)

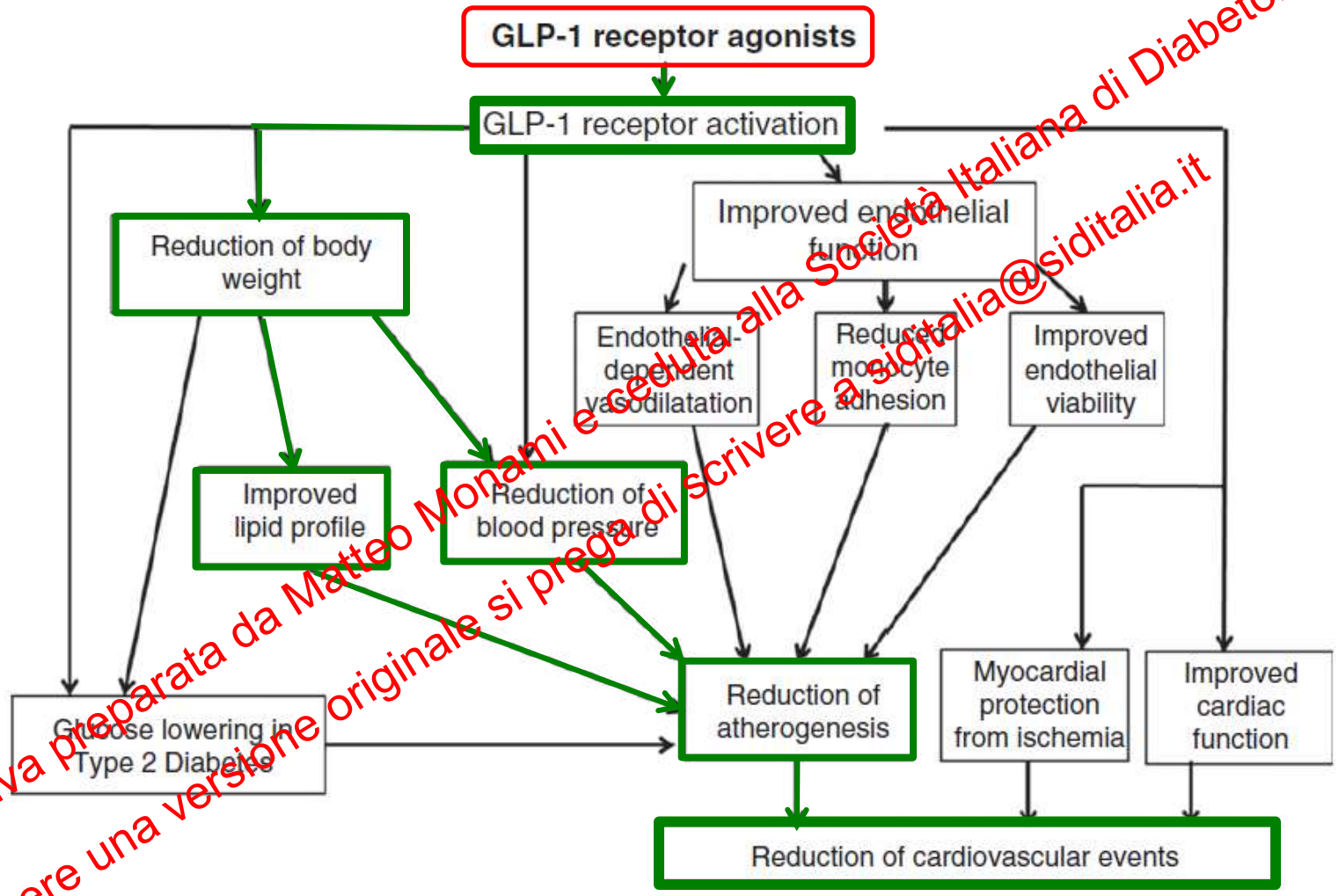
Abbreviations: AGIs, α-glucosidase inhibitors; CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HbA_{1c}, glycated hemoglobin A_{1c}; NA, not applicable; RR, relative risk; WMD, weighted mean difference.

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

[b] $I^2 = 50\%$–75%.

Phung OJ, JAMA 2010 – vol. 303, No 14

CV effects of GLP1-RA

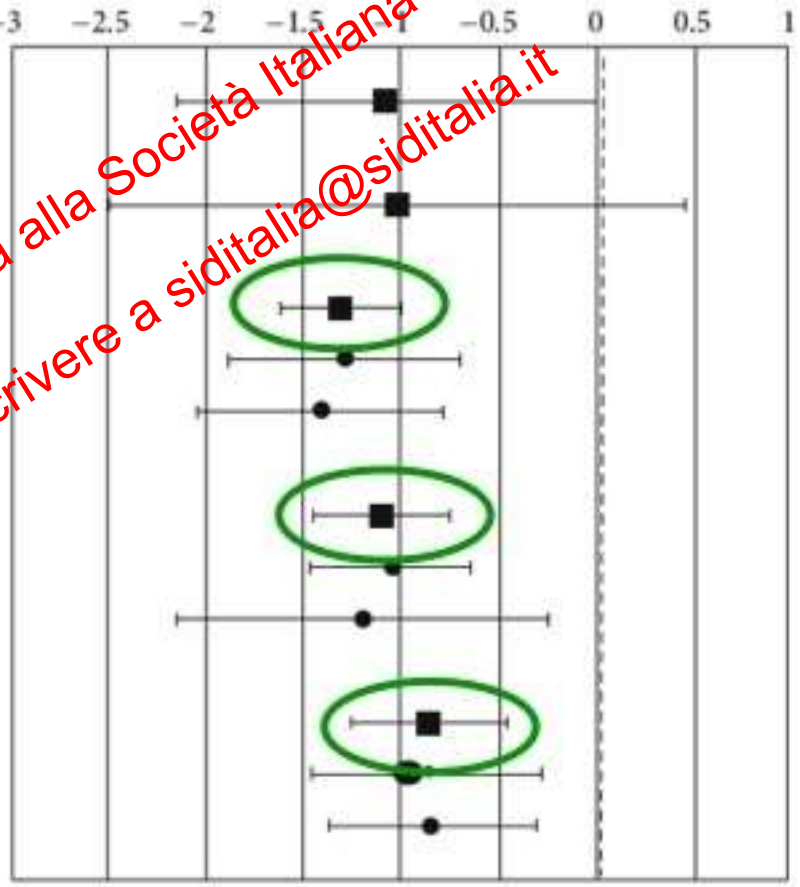


M. Monami, I. Dicembrini, C. Nardini, I. Fiordelli, E. Mannucci,
Diabetes Obes Metab. 2014; 16:38-47

GLP-1 RA and body weight

A meta-analysis of available RCTs

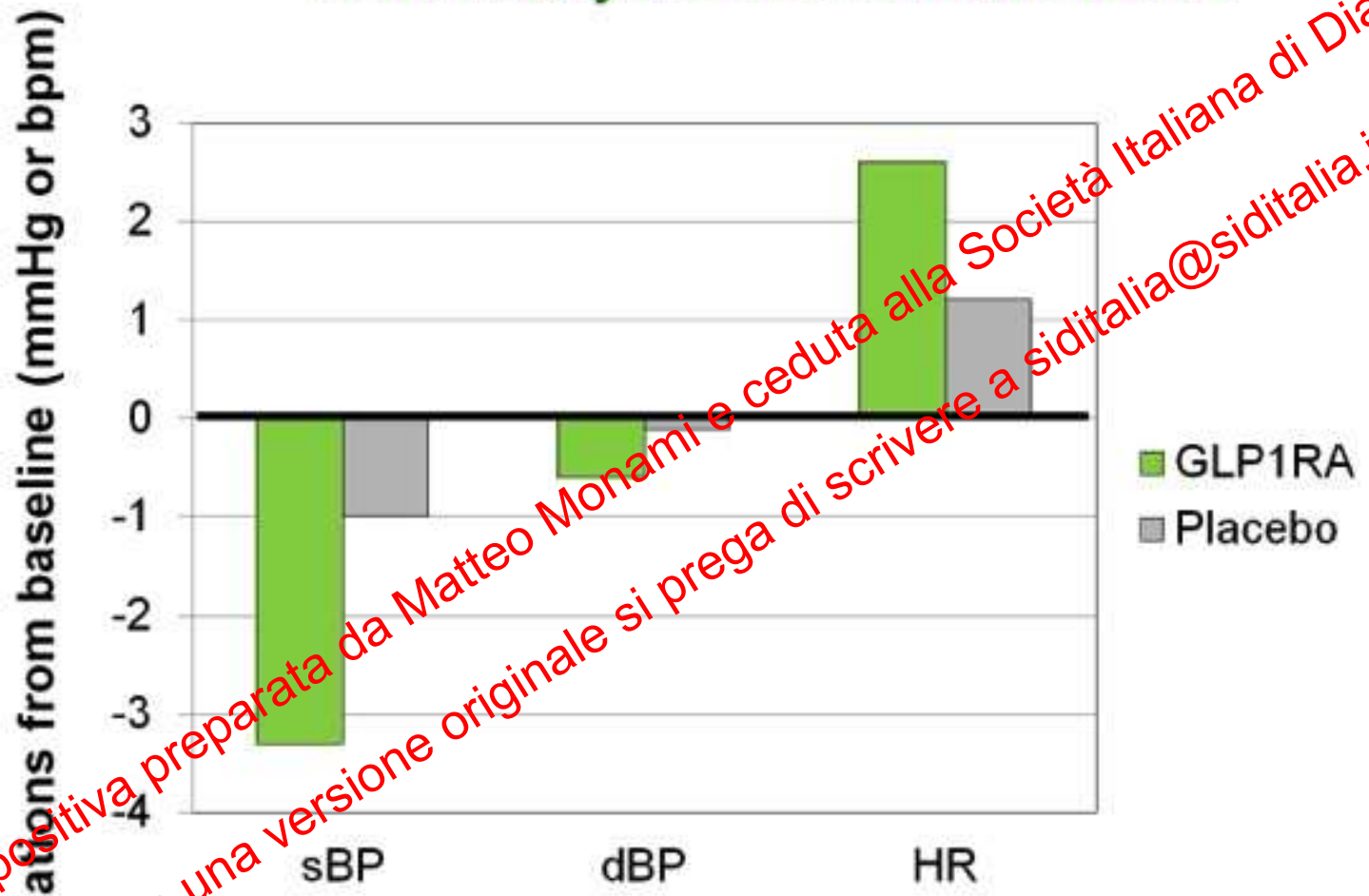
	MD	LL,95% CI	UL,95% CI	*P*	Number of trials
DPP-4 inhibitors	−1.08	−2.15	0.001	0.05	2
Thiazolidinediones	−1.02	−2.49	0.45	0.17	2
Sulfonylureas	−1.31	−1.62	−1	<0.001	4
Exenatide	−1.29	−1.88	−0.7	<0.001	2
Liraglutide	−1.41	−2.03	−0.79	<0.001	2
Insulin	−1.1	−1.45	−0.75	<0.001	6
Exenatide	−1.05	−1.45	−0.64	<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

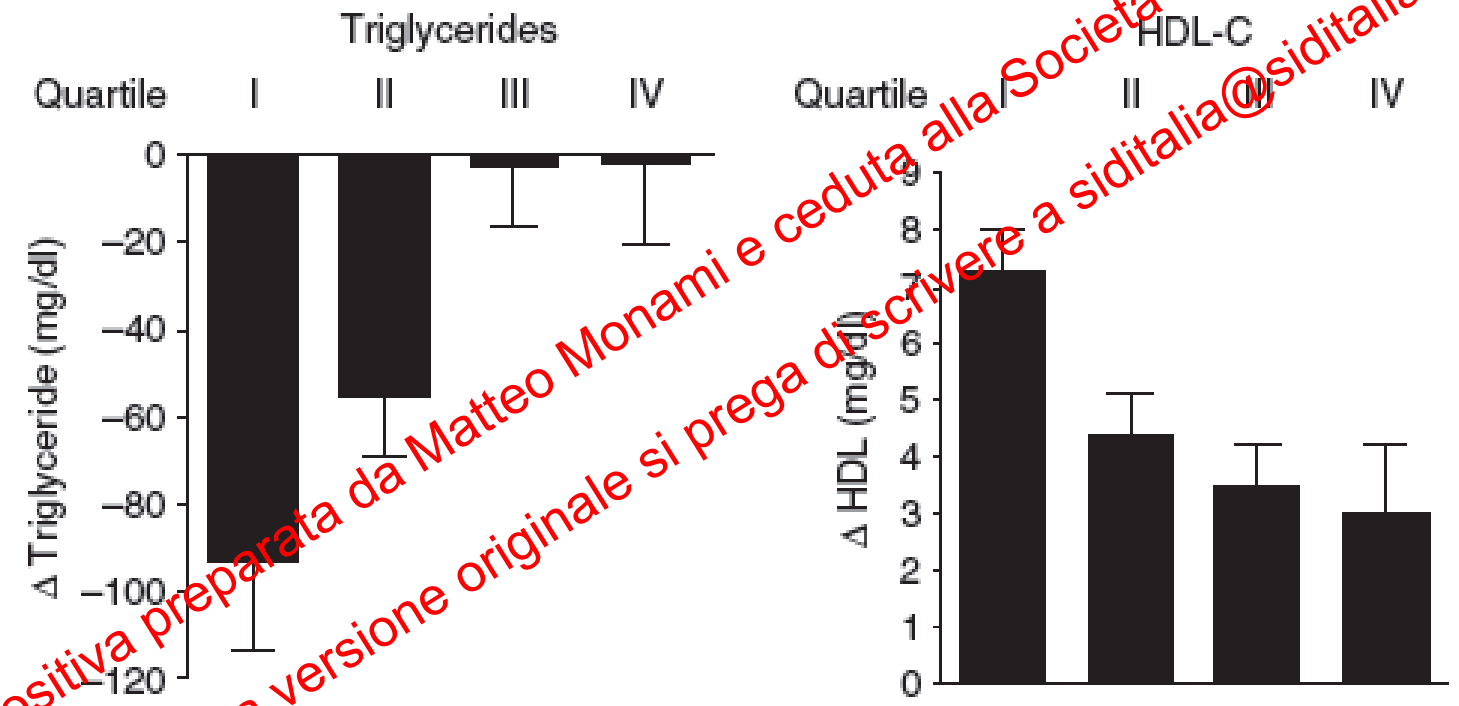
Meta-analysis of available RCTs



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

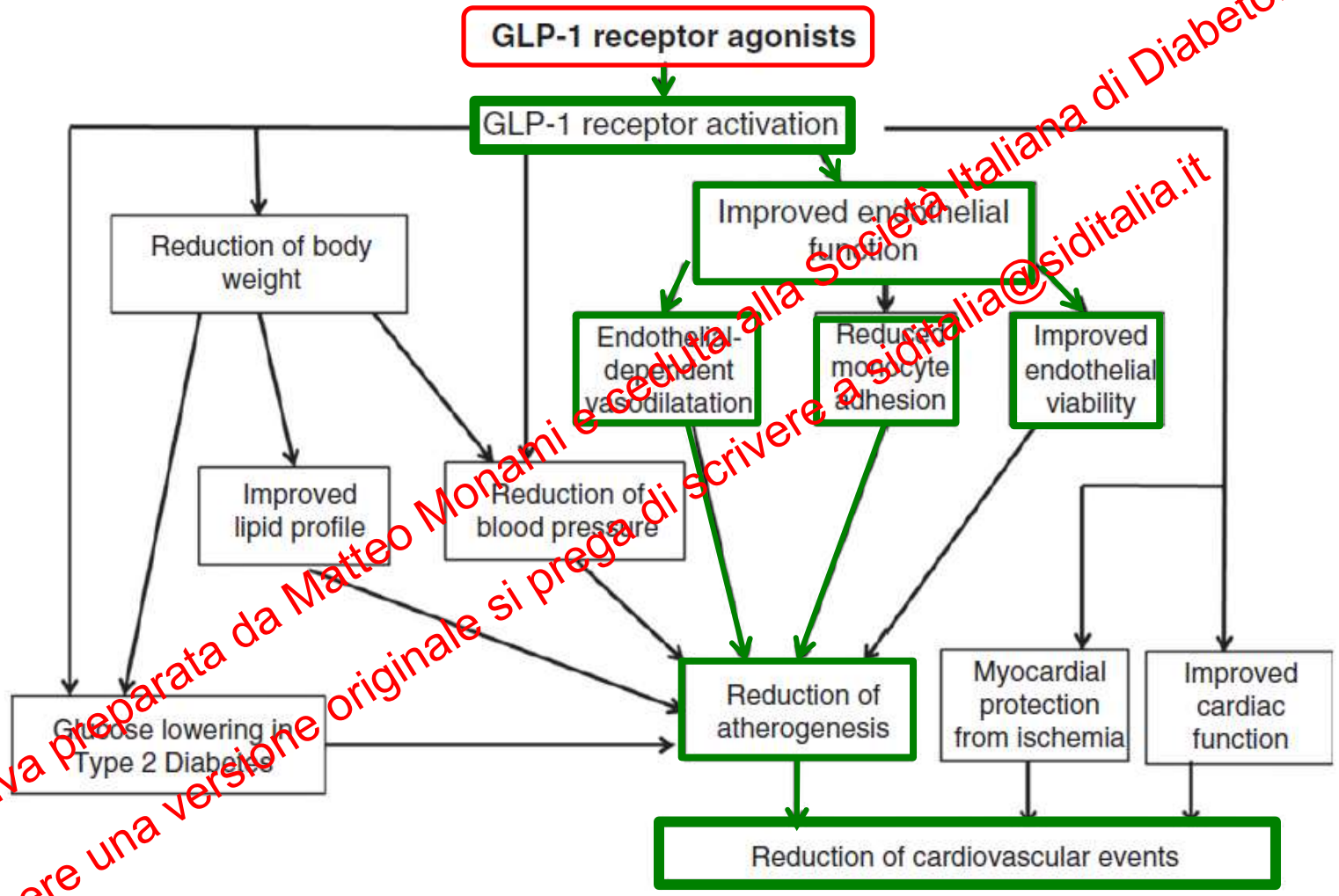
Effects of exenatide on cardiovascular risk factors over 82 weeks

An interim analysis in 314 overweight T2DM



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

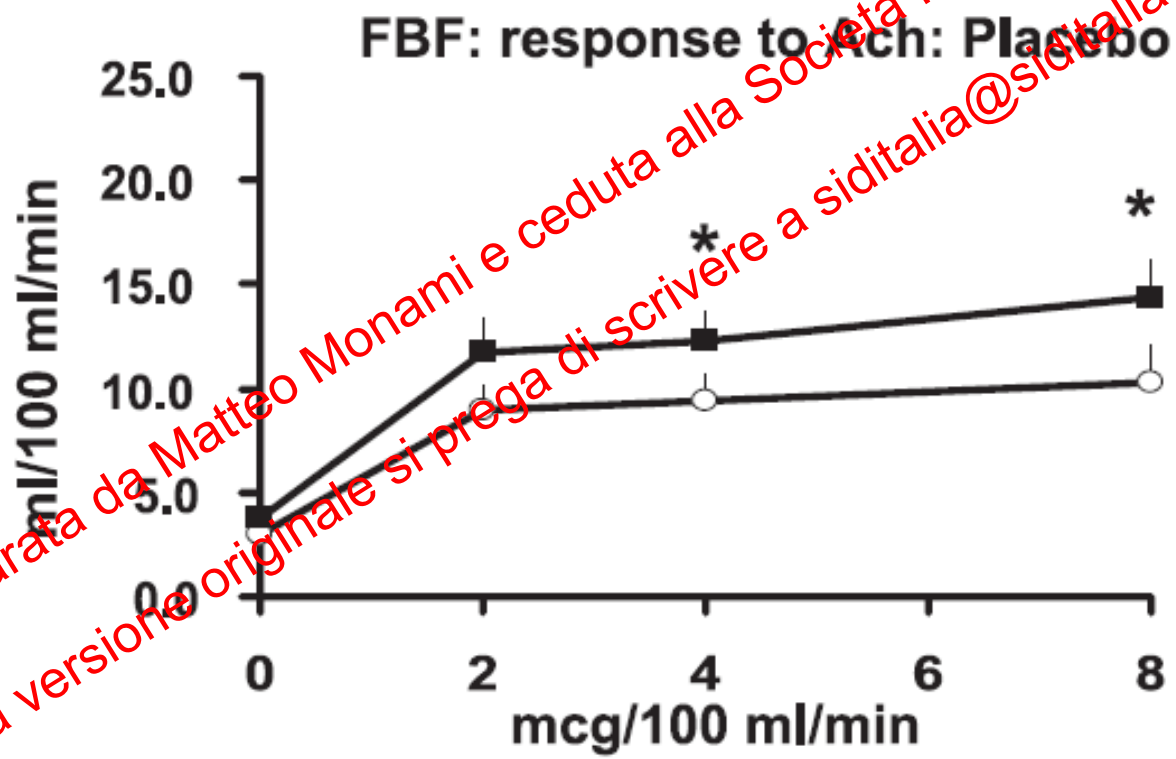
CV effects of GLP1-RA



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

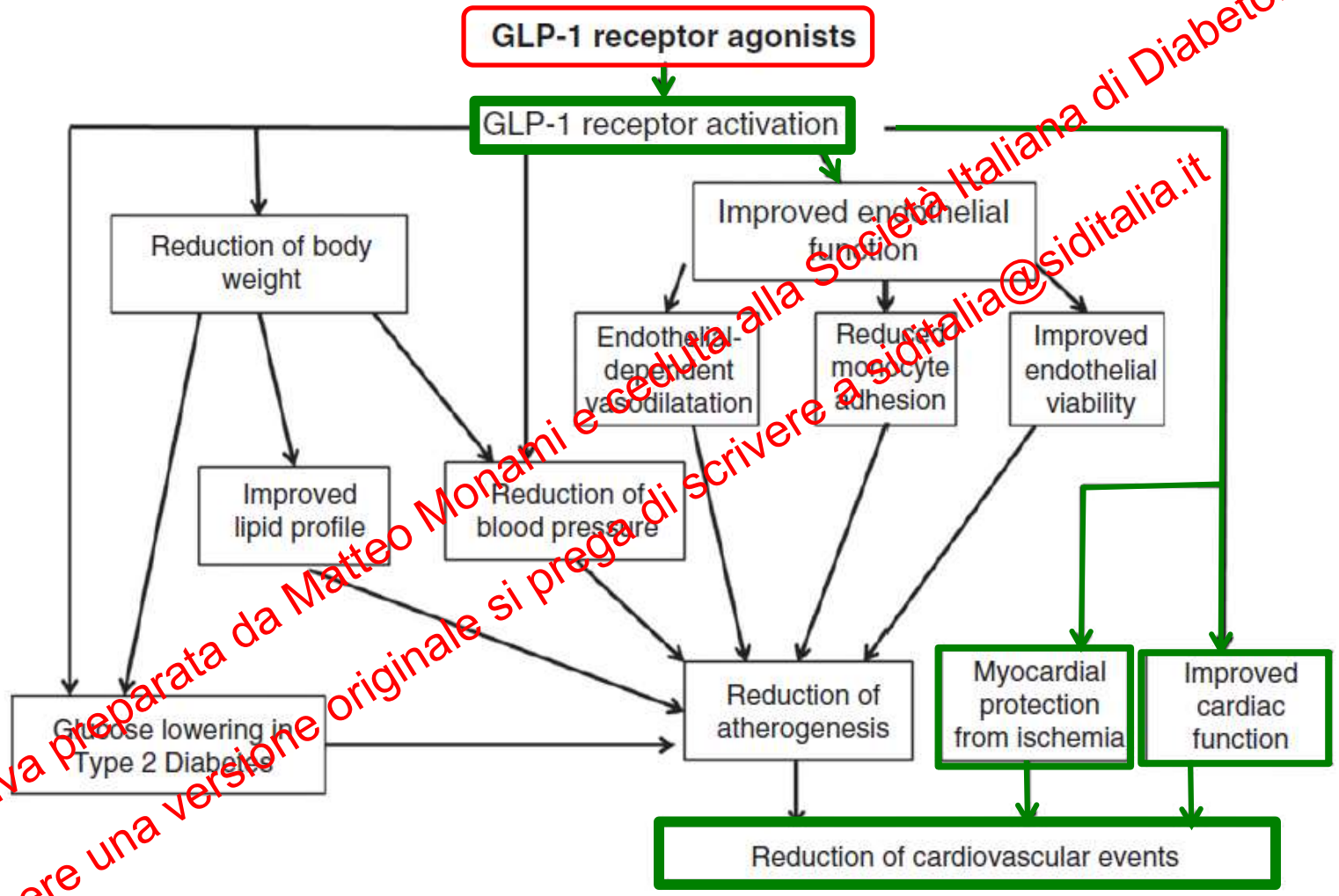
GLP-1 and Endothelial function

Controllare le due curve cosa sono



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

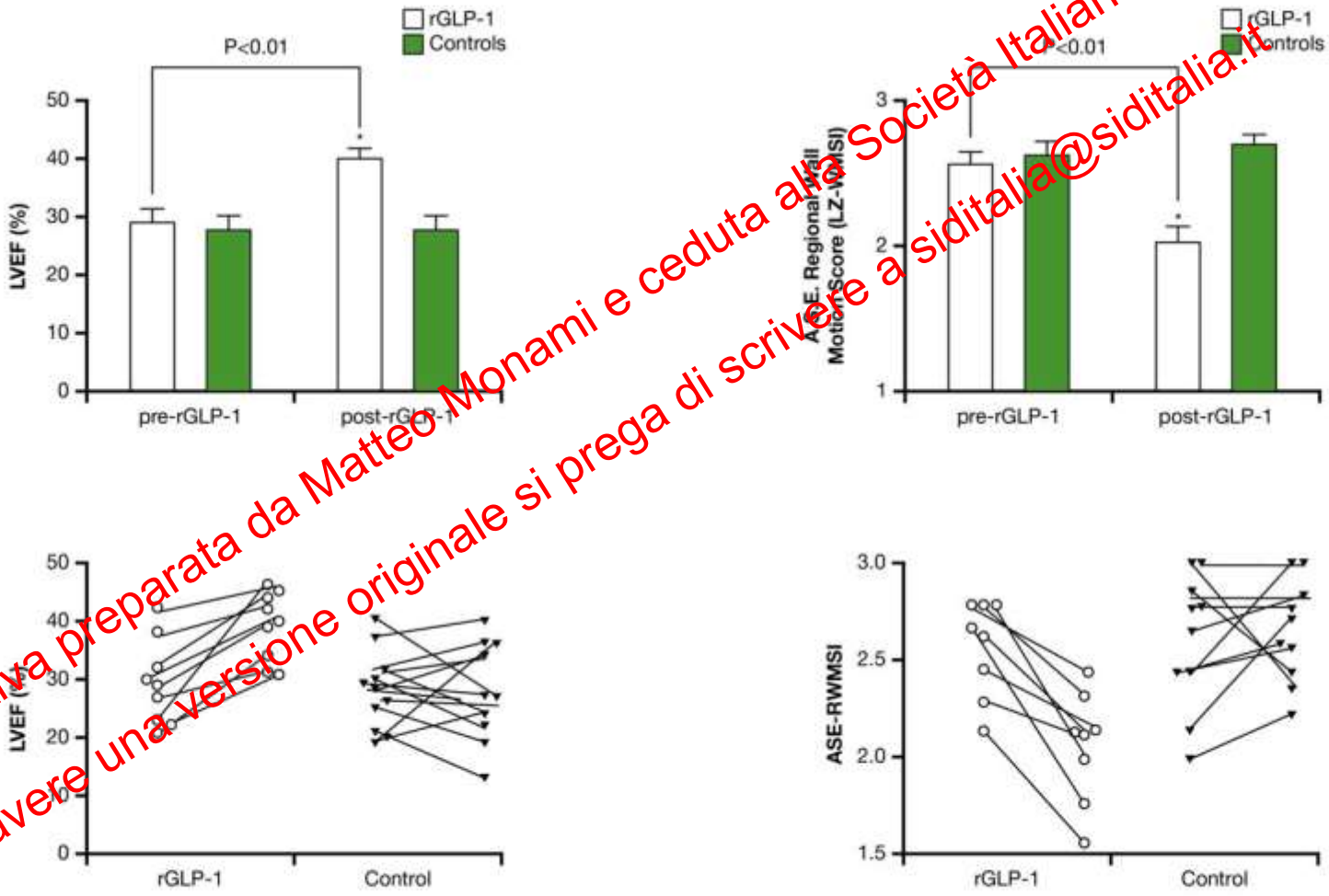
Exenatide

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.

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.

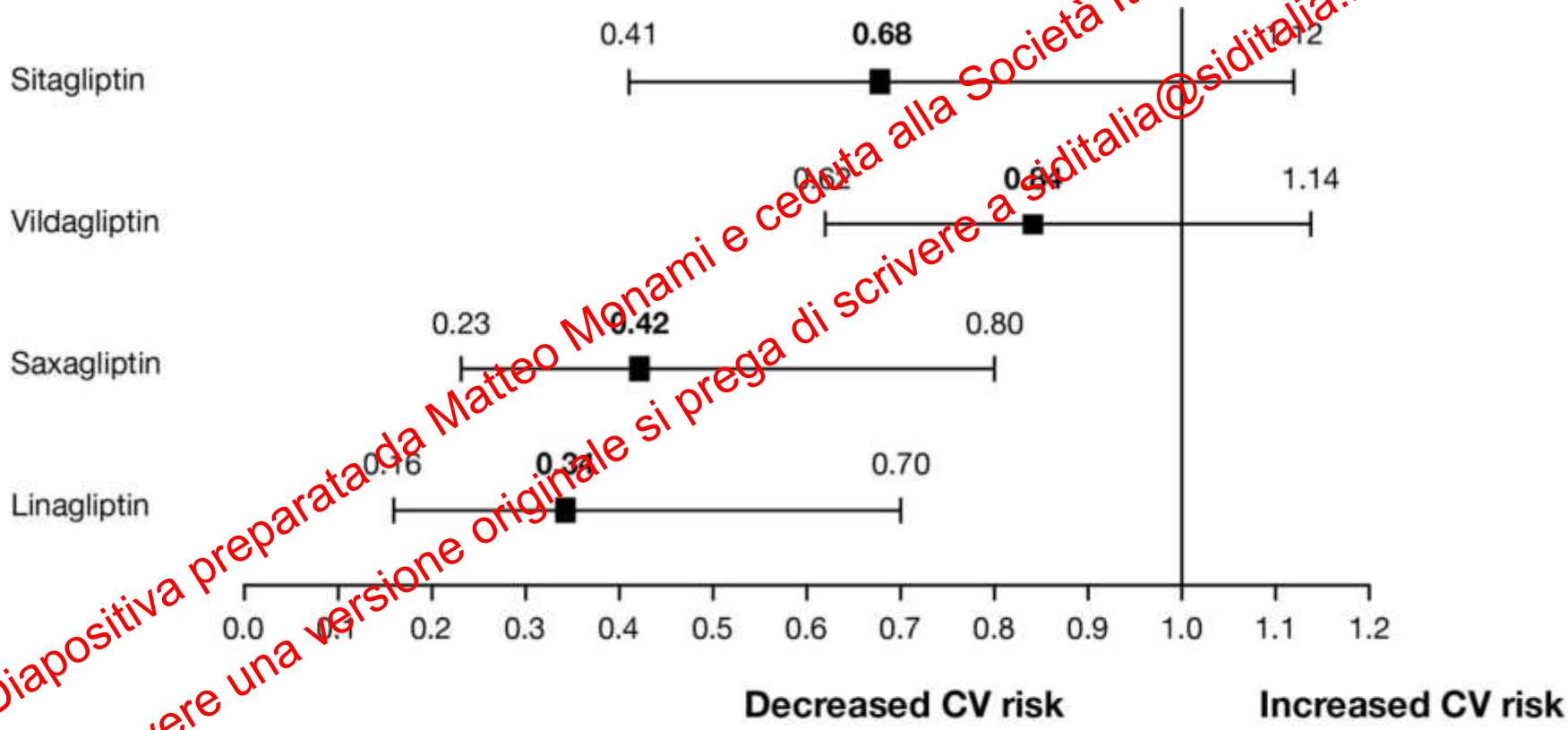
Sponsor:
Bristol-Myers Squibb
Collaborator:
AstraZeneca

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).]

DPP-4 inhibitors and MACE

Pooled analyses of Phase II–III trials



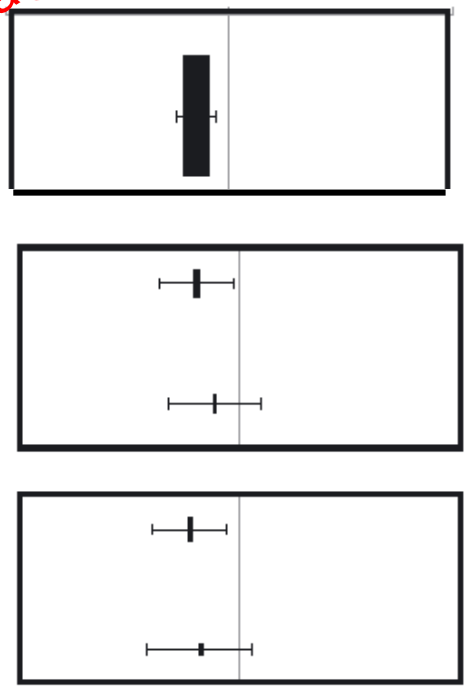
1. Williams-Herman D, *et al. BMC Endocr Disord* 2010;10:7; 2. Schweizer A, *et al. Diabetes Obes Metab* 2010;12:485–94; 3. Frederich R, *et al. Postgrad Med* 2010;122:16–27; 4. Johansen O, *et al. Cardiovasc Diabetol* 2012;11:3.

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]

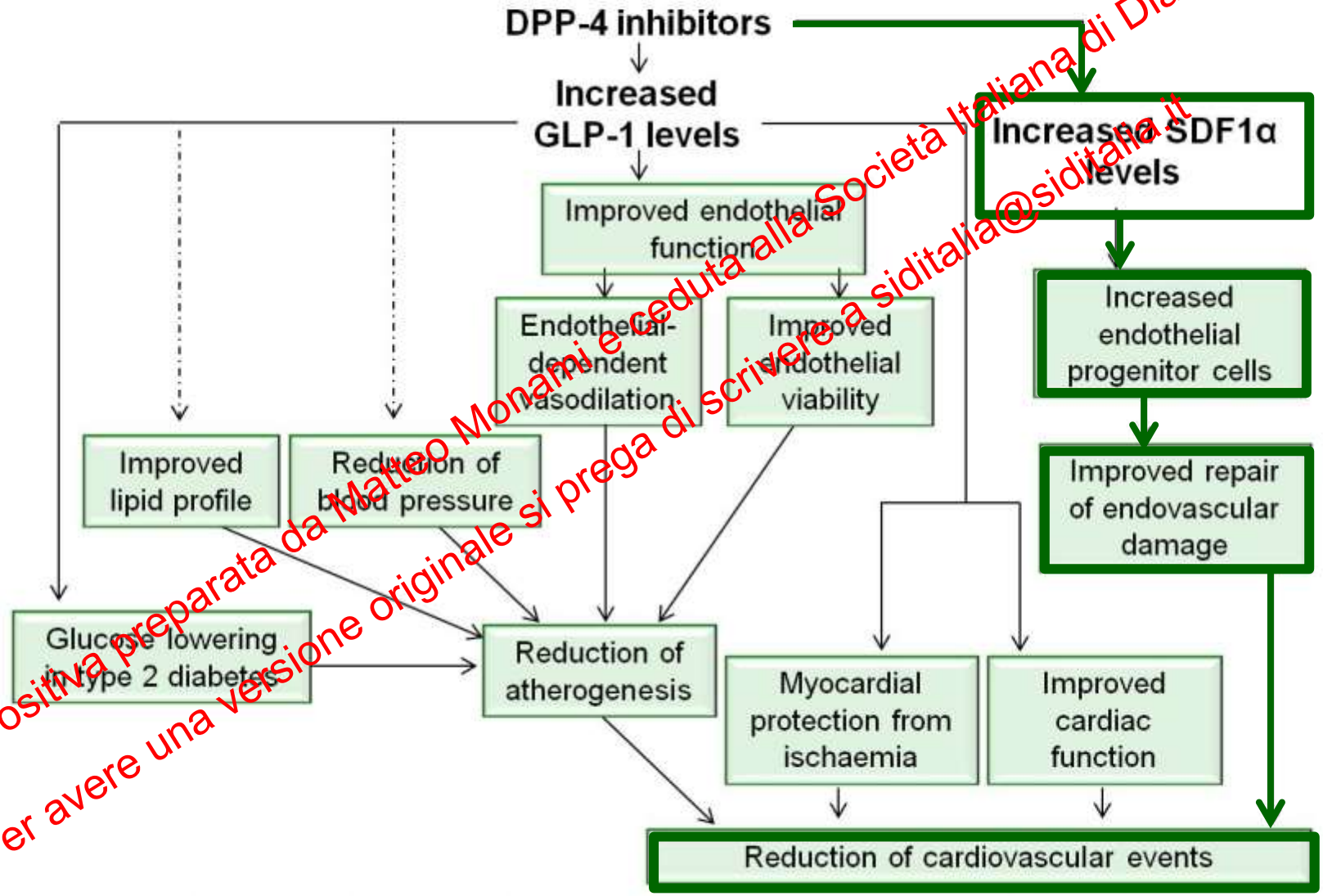
	# trials	# trials with events	# events (*DPP4i*)	# events (*Comparator*)	MH-OR [95%, CI]	p	Kendall's tau	p
MACE	70	63	263	232	0.71[0.59;0.86]	<0.001	0.04	0.64
AMI	62	41	61	59	0.64[0.44;0.94]	0.023	-0.13	0.27
Stroke	63	29	41	33	0.77[0.48;1.24]	0.290	-0.24	0.14
Mortality	53	30	30	51	0.60[0.41;0.88]	0.008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

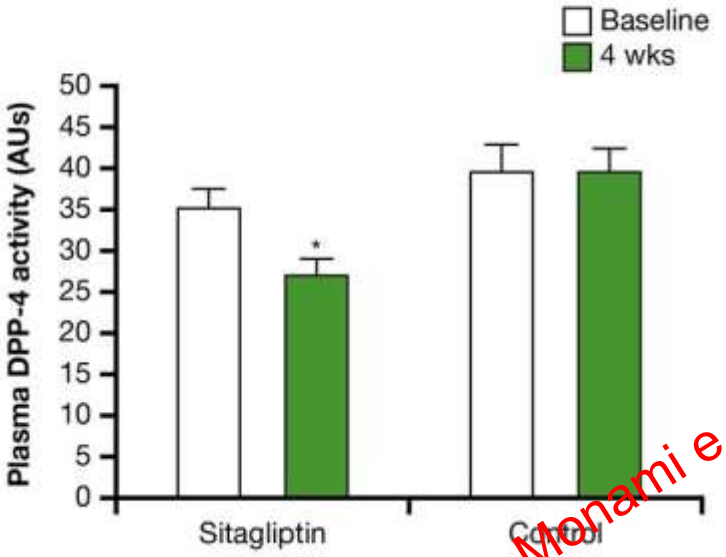
CV effects of DPP-4 inhibitors

Effects mediated by the increase of substrates of DPP-4i different from GLP-1/GIP

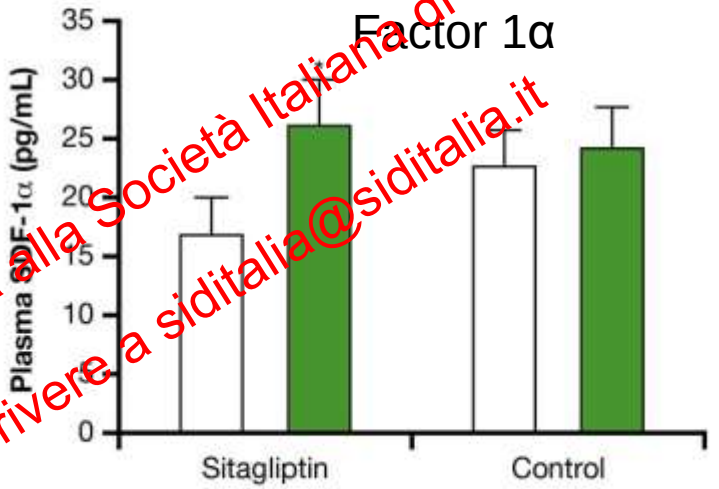


Mannucci E, Dicembrini I. *Curr Med Res Opin* 2012;28:715–21.

DPP-4 inhibitors and SDF-1α

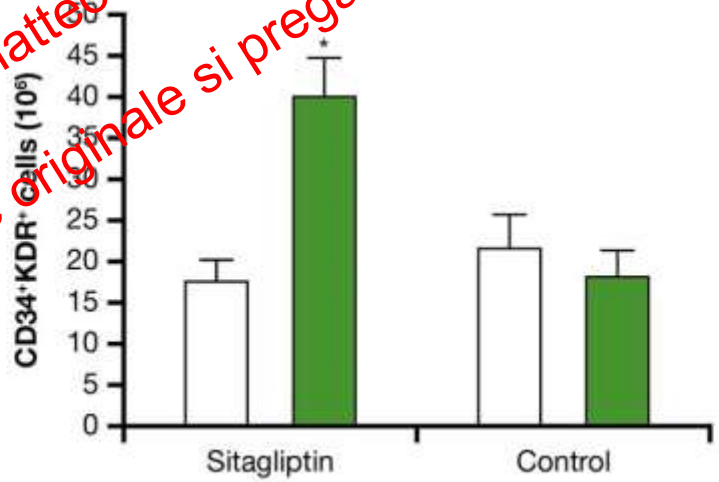


Stromal Cell-Derived Factor 1α



Vascular endothelial growth factors

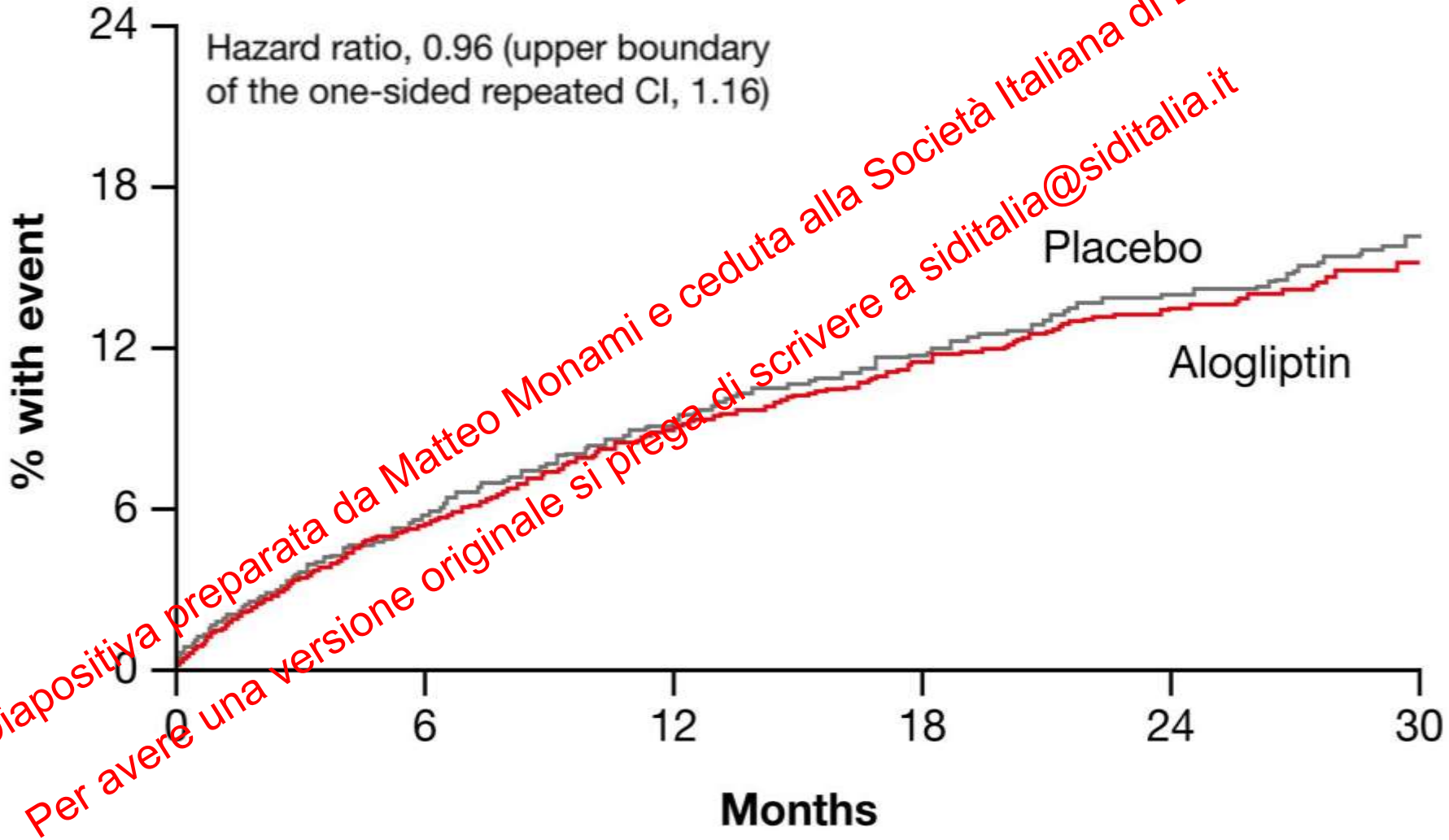
Precursors of endothelial cells



Fadini GP, *et al. Diabetes Care* 2010;33:1607–9.

Alogliptin after Acute Coronary Syndrome in patients with type 2 diabetes

The EXAMINE trial



N Engl J Med 2013; 369:1327-1335

Alogliptin after Acute Coronary Syndrome in patients with type 2 diabetes

The EXAMINE trial

White WB et al.

End Point	Placebo (N=2679)	Alogliptin (N=2701)	Hazard Ratio for Alogliptin Group (95% CI)
	no. (%)		
Primary end point†	316 (11.8)	305 (11.3)	0.96 (≤1.16)‡
Components of primary end point			
Death from cardiovascular causes	111 (4.1)	89 (3.3)	0.79 (0.60–1.04)
Nonfatal myocardial infarction	173 (6.5)	187 (6.9)	1.08 (0.88–1.33)
Nonfatal stroke§	32 (1.2)	29 (1.1)	0.91 (0.55–1.50)
Principal secondary end point‖	359 (13.4)	344 (12.7)	0.95 (≤1.14)‡
Other end points			
Death from any cause	173 (6.5)	153 (5.7)	0.88 (0.71–1.09)
Death from cardiovascular causes¶	130 (4.9)	112 (4.1)	0.85 (0.66–1.10)

N Engl J Med 2013; 369:1327-1335

Alogliptin and MACE

Results of the EXAMINE trial

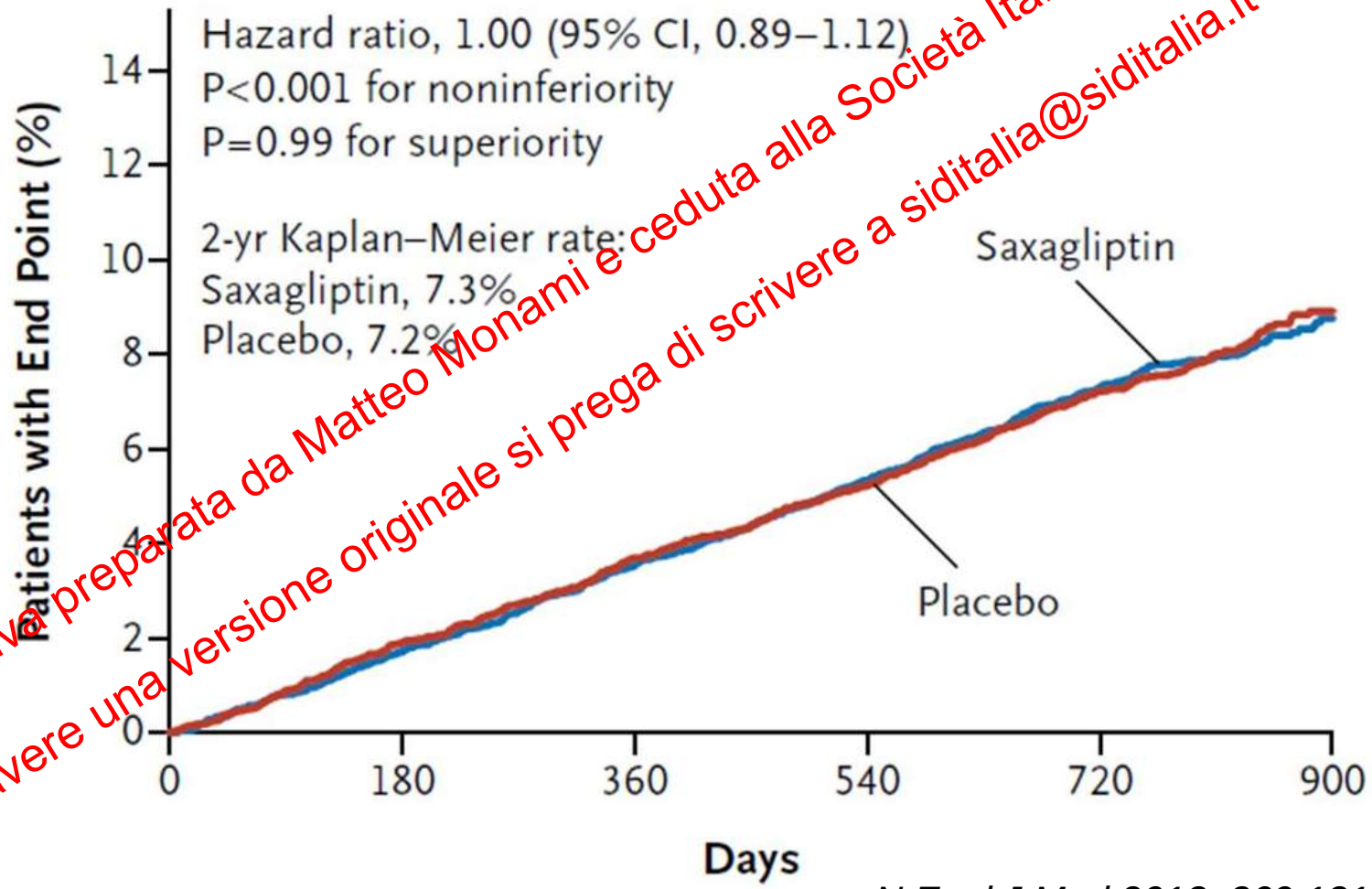
	Placebo (N=2679)	Alogliptin (N=2701)
Cardiovascular risk factors and history — no. (%)		
Current smoker	383 (14.3)	351 (13.0)
Hypertension	2240 (83.6)	2229 (82.5)
Myocardial infarction	2345 (87.5)	2389 (88.4)
Percutaneous coronary intervention	1683 (62.8)	1689 (62.5)
Coronary-artery bypass grafting	341 (12.7)	347 (12.8)
Congestive heart failure	744 (27.8)	757 (28.0)
Stroke	193 (7.2)	195 (7.2)
Peripheral arterial disease	252 (9.4)	262 (9.7)

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

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

Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus

The SAVOR trial

Scirica BM et al.

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 (7.4)	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	289 (3.5)	228 (2.8)	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

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

Short duration of studies

Small number of events (for rare adverse events)

Selection of relatively healthy populations

Missclassification of events

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)	3.0	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

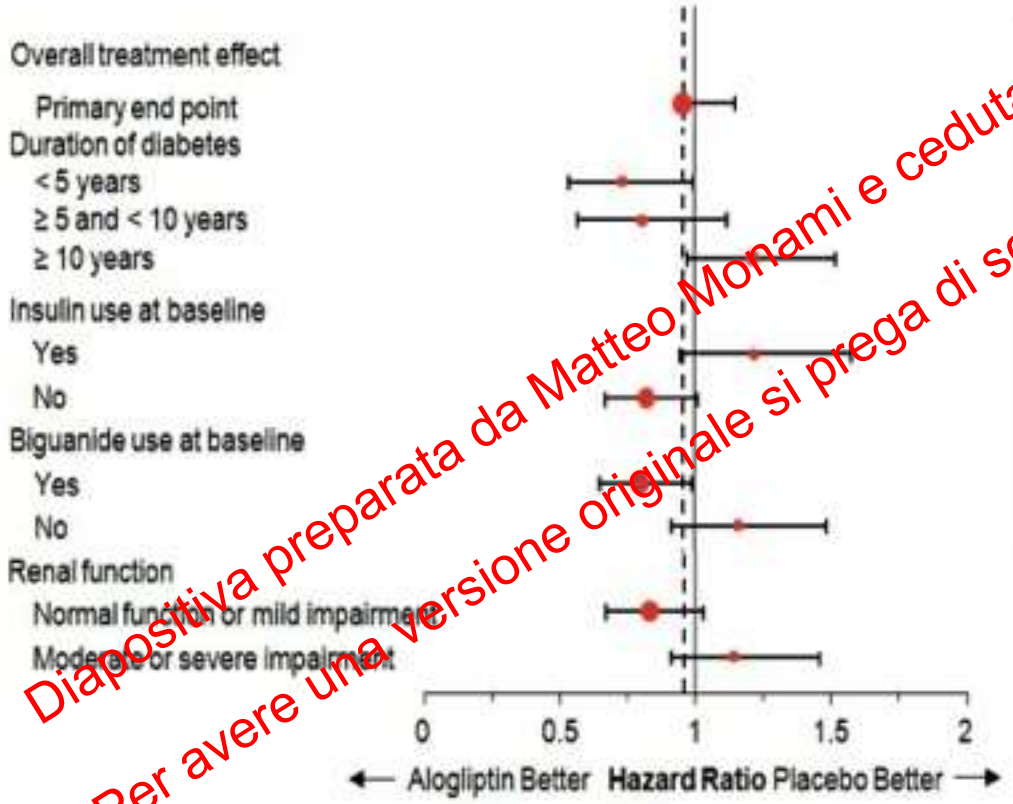
Why did the SAVOR trial have such different results from the meta-analysis of early trials?

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

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

Alogliptin after Acute Coronary Syndrome in patients with type 2 diabetes

The EXAMINE trial



	Placebo		Alogliptin		Hazard		Interaction With Treatment
	n	%	n	%	Ratio	95% CI	P value
Overall treatment effect							
Primary end point	2679	11.8	2701	11.3	0.96	(≤1.16)*	
Duration of diabetes							
< 5 years	973	9.7	1009	7.0	0.74	(0.54, 1.01)	
≥ 5 and < 10 years	965	11.9	645	9.6	0.81	(0.58, 1.13)	
≥ 10 years	1032	13.8	1035	16.5	1.22	(0.98, 1.53)	0.014
Insulin use at baseline							
Yes	812	13.3	793	16.1	1.23	(0.95, 1.59)	
No	1867	11.1	1908	9.3	0.83	(0.68, 1.02)	0.018
Biguanide use at baseline							
Yes	1808	10.9	1760	8.8	0.81	(0.66, 1.00)	
No	871	13.7	941	16.0	1.17	(0.92, 1.50)	0.029
Renal function							
Normal function or mild impairment	1886	9.8	1929	8.3	0.84	(0.68, 1.04)	
Moderate or severe impairment	793	16.6	772	18.8	1.15	(0.91, 1.46)	0.046

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.

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 (7.4)	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	289 (3.5)	228 (2.8)	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

N Engl J Med 2013; 369:1317-1326

Saxagliptin and heart failure

Is this a casual finding (by chance)?

Is this a drug-specific phenomenon?

Is this a class effect common to all DPP4 inhibitors?

Is this a common effect of all incretin-based therapies?

Post hoc Composite Endpoint Inclusive of Hospitalized Heart Failure

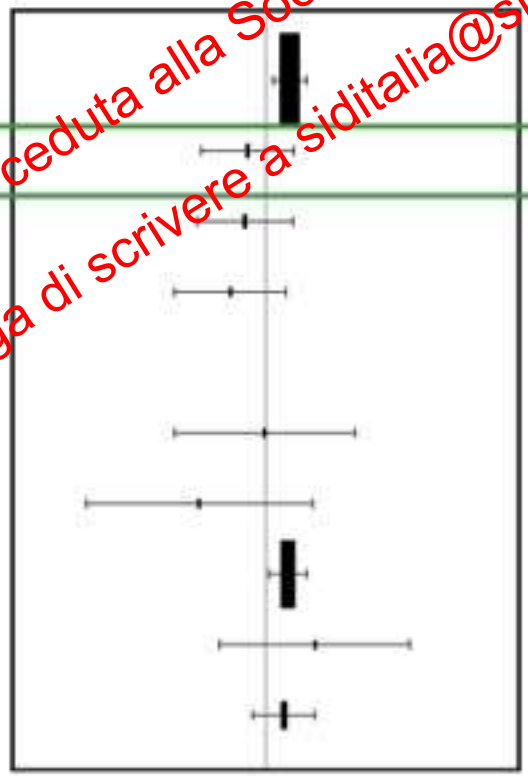
Number (%) of Subjects

	Alogliptin N=2701	Placebo N=2679	Hazard Ratio for Alogliptin Group (95% CI)	P-value
Composite endpoint of cardiovascular mortality and hospitalized heart failure	**201 (7.4)**	**201 (7.5)**	**0.98 (0.82, 1.21)**	**0.976**
Cardiovascular mortality	95 (3.5)	112 (4.2)	**0.84 (0.64, 1.10)**	**0.207**
Hospitalization for Heart Failure	106 (3.9)	89 (3.3)	**1.19 (0.90, 1.58)**	**0.220**

DPP4i and CHF

Meta-analysis of early RCTs

Heart failure
(n events)

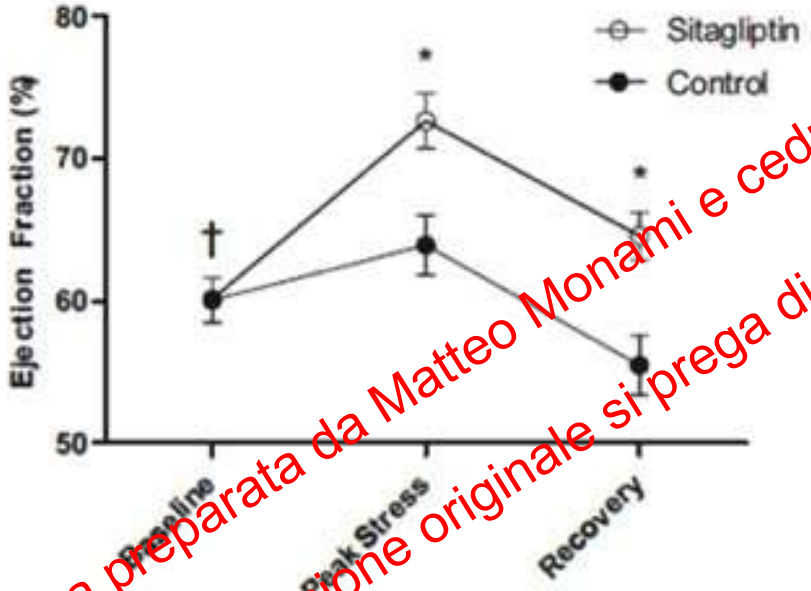


	N trials	DPP4i	Comparator	MH-OR	LL	UL	p
SAVOR+EXAMINE	2	395	317	1.24	1.07	1.45	0.004
Trials with non-CV end.	35	53	44	0.85	0.56	1.29	0.45
Excluding trials vs TZDs	33	52	41	0.83	0.54	1.28	0.41
Excluding trials vs TZDs/SUs	26	36	18	0.73	0.44	1.20	0.22
vs other comparators							
Sitagliptin	1	14	15	0.99	0.44	2.24	0.980
Vildagliptin	6	11	10	0.55	0.20	1.53	0.25
Saxagliptin	10	300	237	1.22	1.03	1.45	0.024
Linagliptin	5	16	8	1.56	0.66	3.65	0.310
Alogliptin	5	112	91	1.18	0.89	1.56	0.250

Manuscript submitted

Sitagliptin and cardiac function

Results of a pilot study



N=19 non-diabetic patients with CAD (single vessel in 71%) on waiting list for CABG/PTCA.

Stress echocardiography after a single dose of sitagliptin.

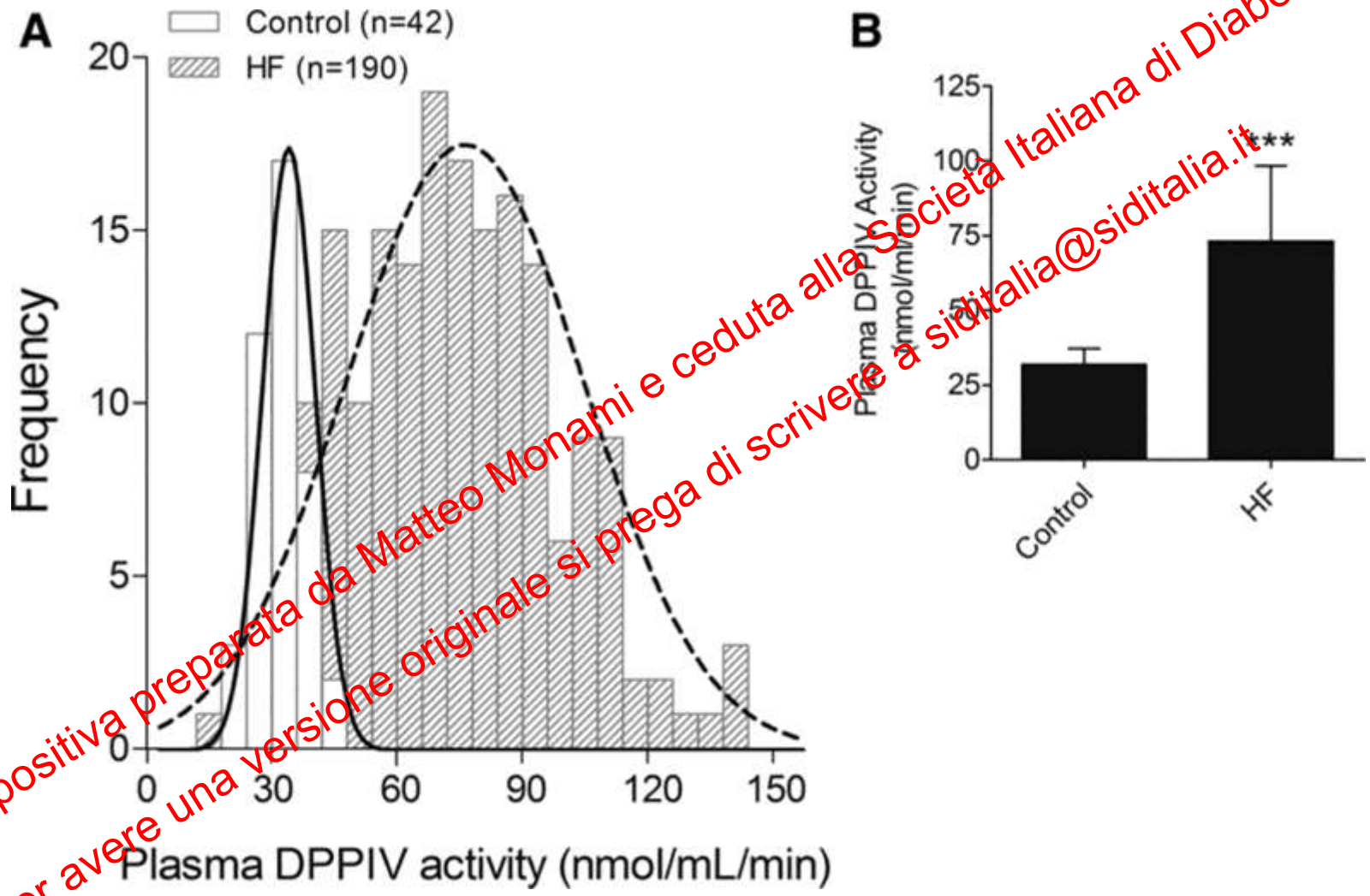
Read PA, et al. Circ Cardiovasc Imaging 2010;3:195-201.

Saxagliptin and heart failure

Hypothetical mechanisms

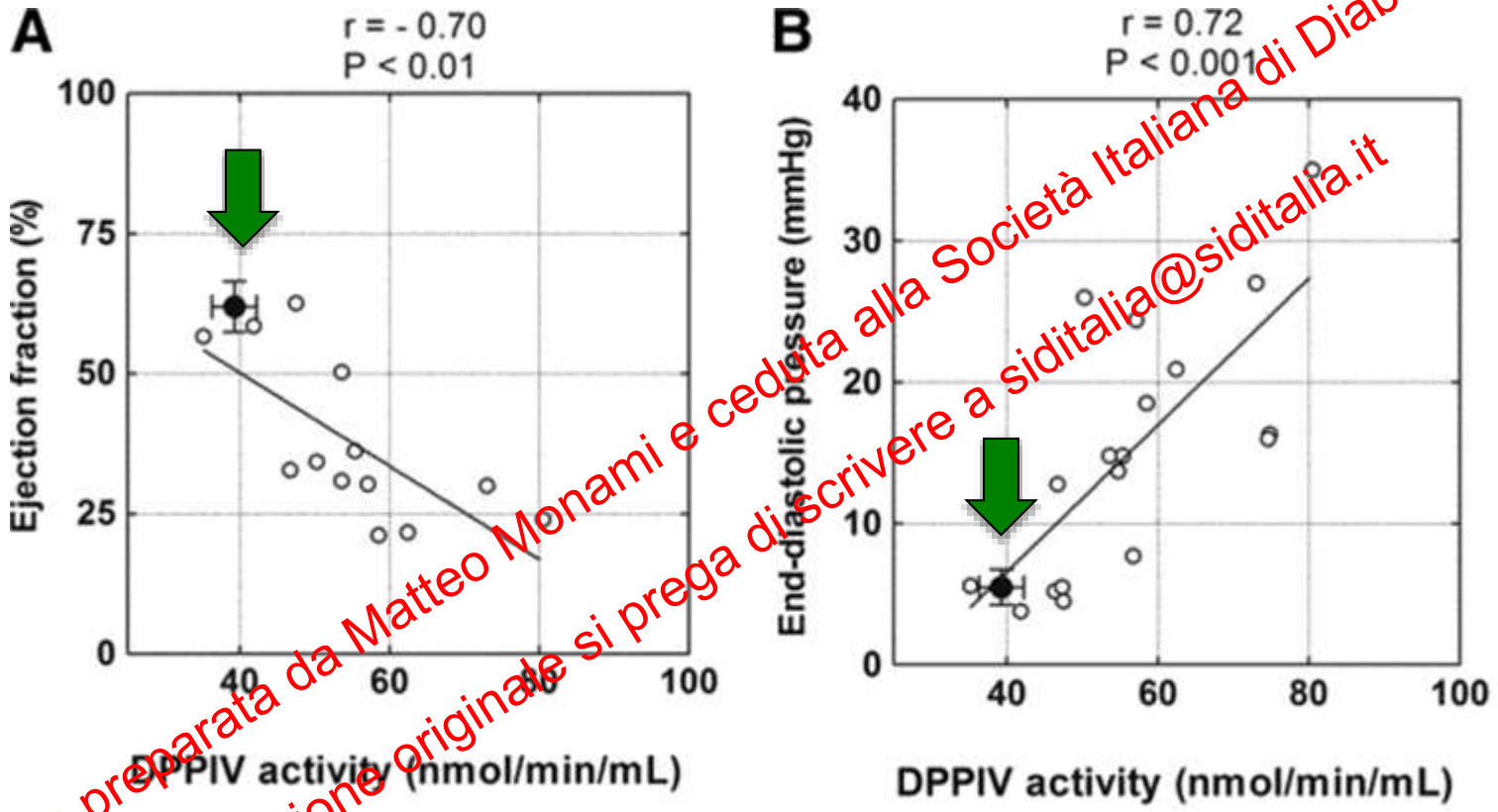
- Drug interaction (kinetics)
- Reduced GLP-1 (9-36)
- Effect of other substrates of DPP4 (BNP?)
- Possiblity of pharmacodynamic interactions

DPP-4 activity and heart failure



dos Santos L et al. *Circ Heart Fail* 2013;6:1029-1038

DPP-4 activity and heart failure



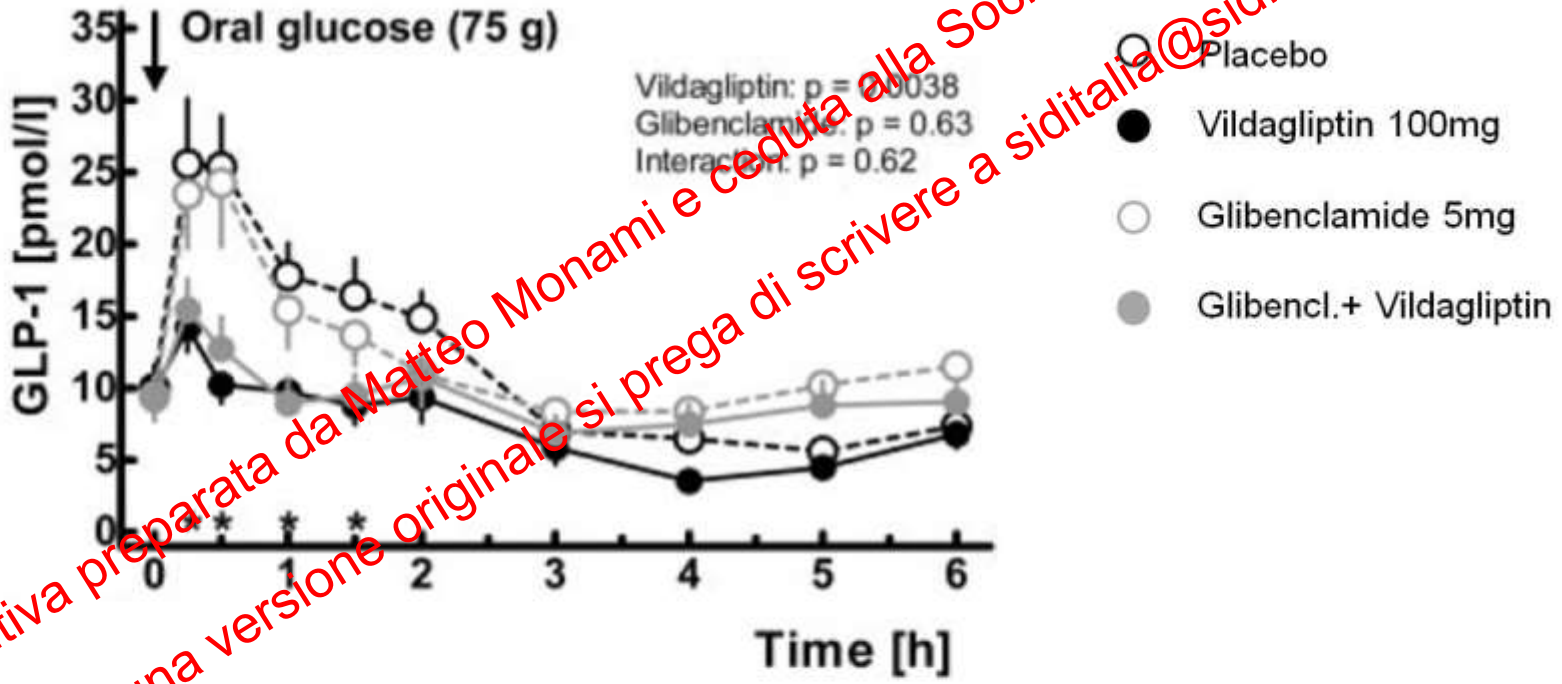
Modello sperimentale di ratti con HF

Topi di controllo

dos Santos L et al. *Circ Heart Fail* 2013;6:1029-1038

DPP4i and GLP-1 secretion

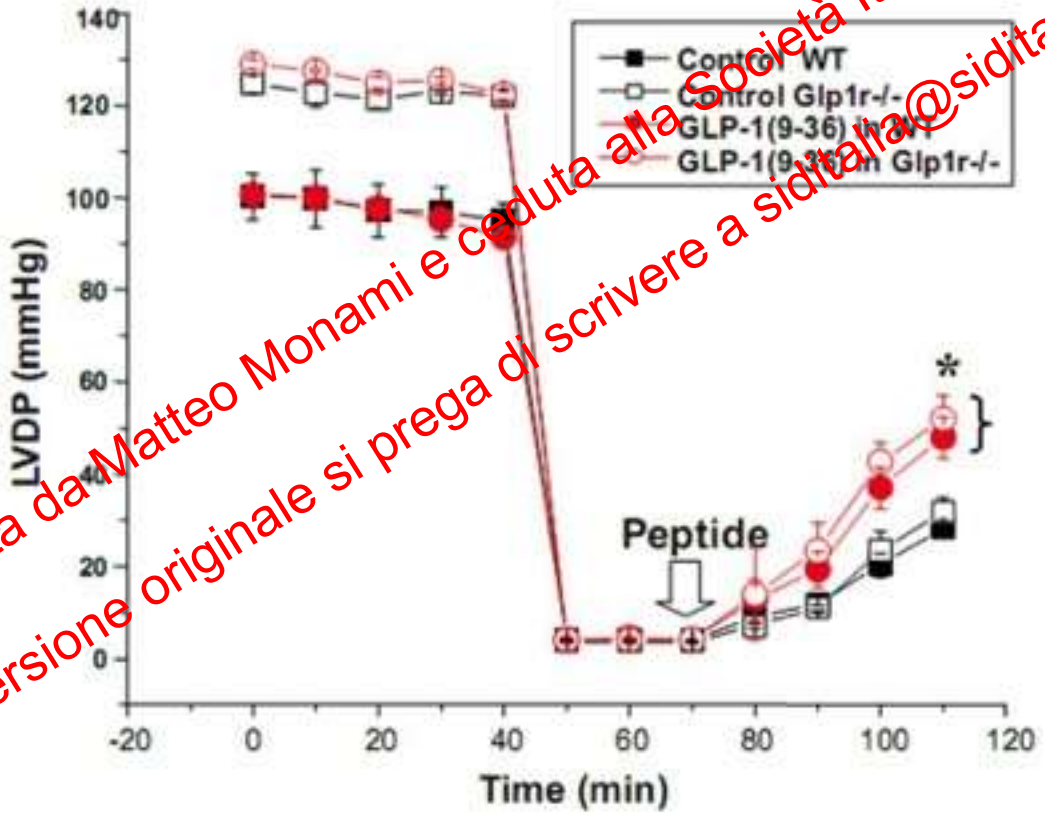
Effects of vildagliptin and glibenclamide on total GLP-1
16 healthy subjects, single-dose study



El-Ouaghlidi A et al. *J Clin Endocrinol Metab* 2007; 92:4165-71.

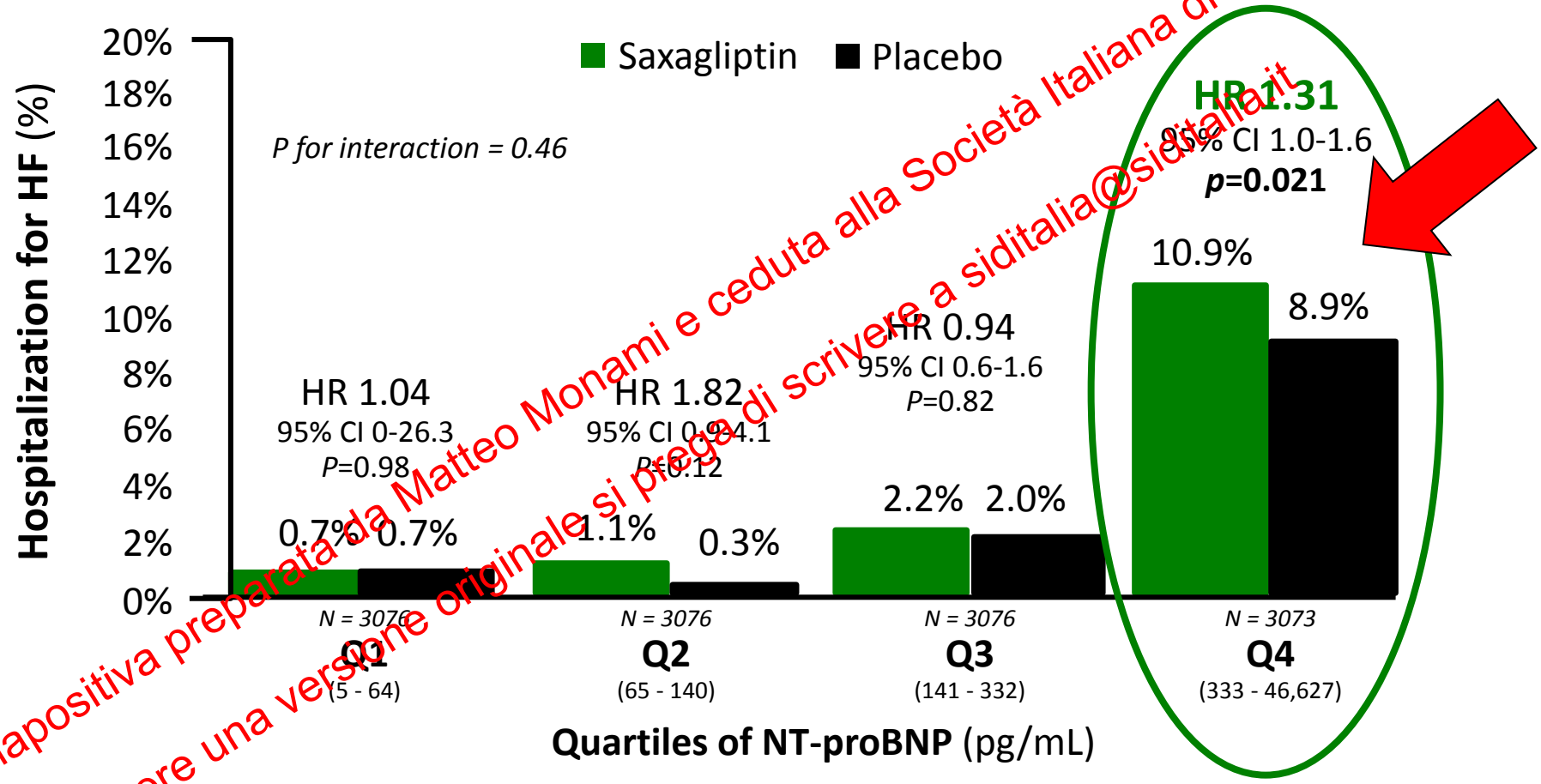
Myocardial effects of GLP-1(9-36)

Recovery after ischemia-reperfusion in rats



Ban K et al. *Circulation* 2008; 17:2340-2350.

Hospitalization for HF and BNP



NT-proBNP: N-terminal pro-brain natriuretic peptide; HHF: hospitalization for heart failure

Scirica BM, et al. *American Heart Association Scientific Sessions.* November 2013.