DPP4 Inibitori

e Studi in Ambito Cardiovascolare

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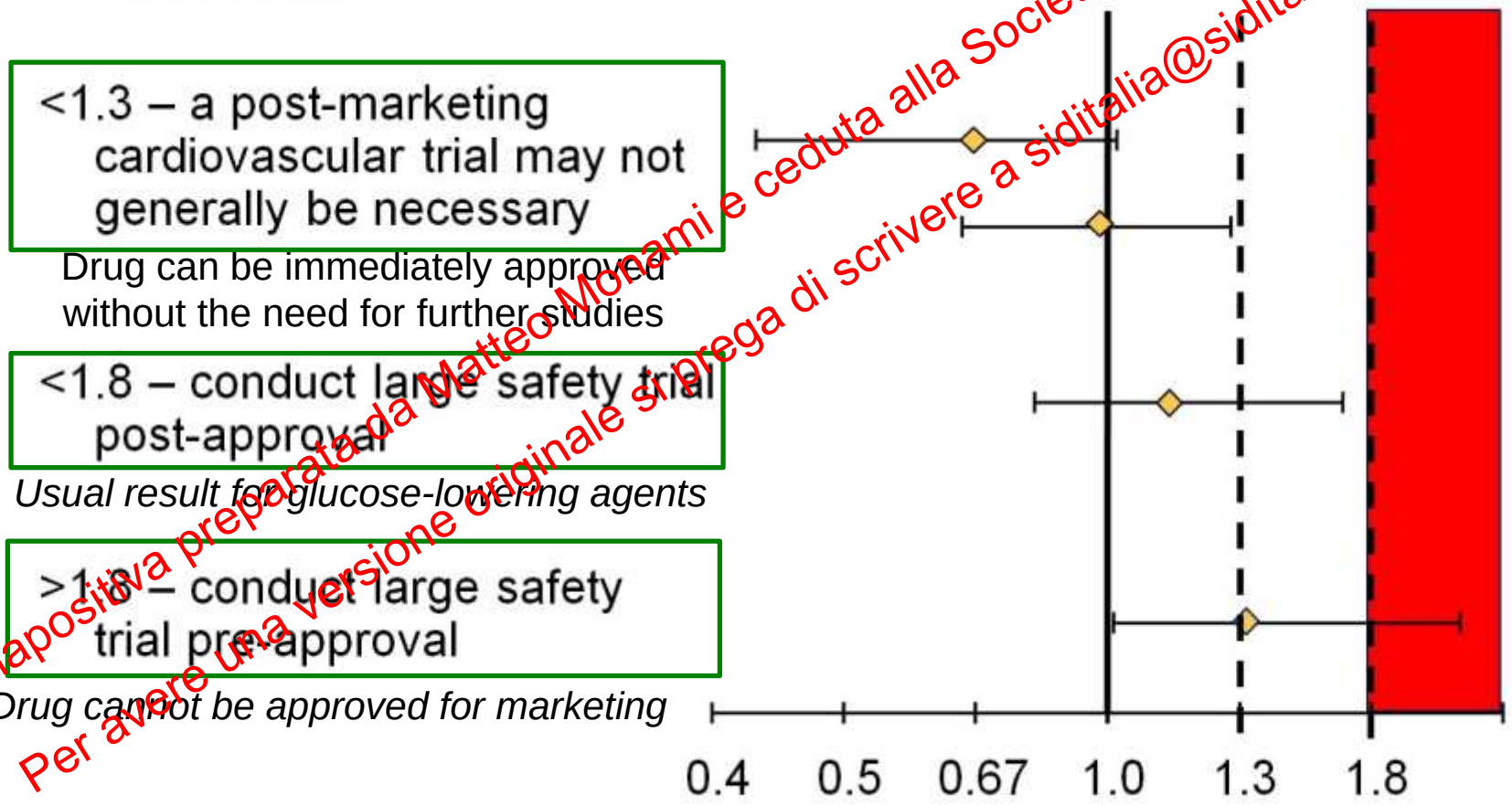
FDA Guidance on diabetes drugs

- From 2009 onwards, all new glucose-lowering agents are required to present data from meta-analysis or pooled analysis of individual phase 2 and 3 studies assessing the risk of MACE and their confidence intervals



<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

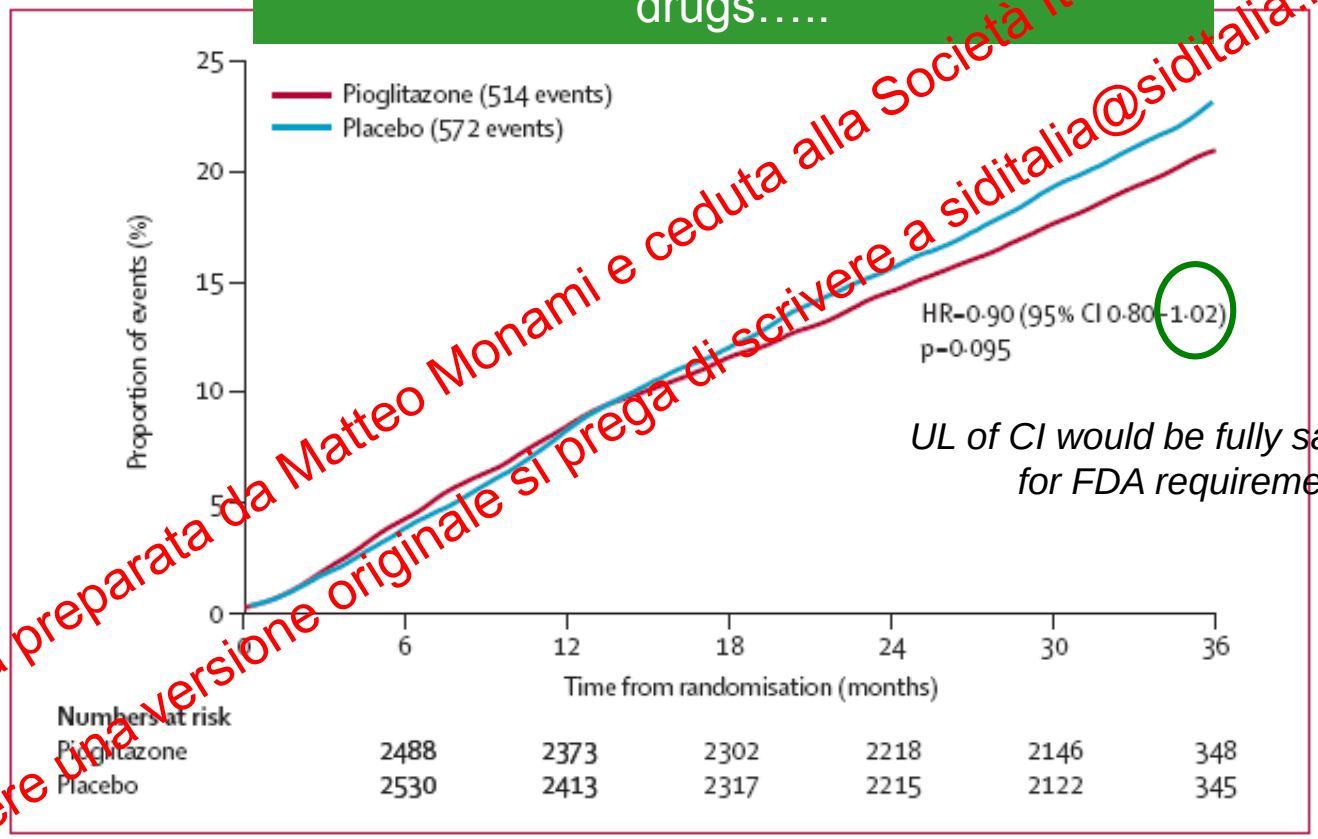
Food and Drug Administration, 2008. Available from: http://www.fda.gov/downloads/Drugs/guidanceComplianceRegulatoryInformation/guidances/ucm071627.pdf. Last accessed July 2013.

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

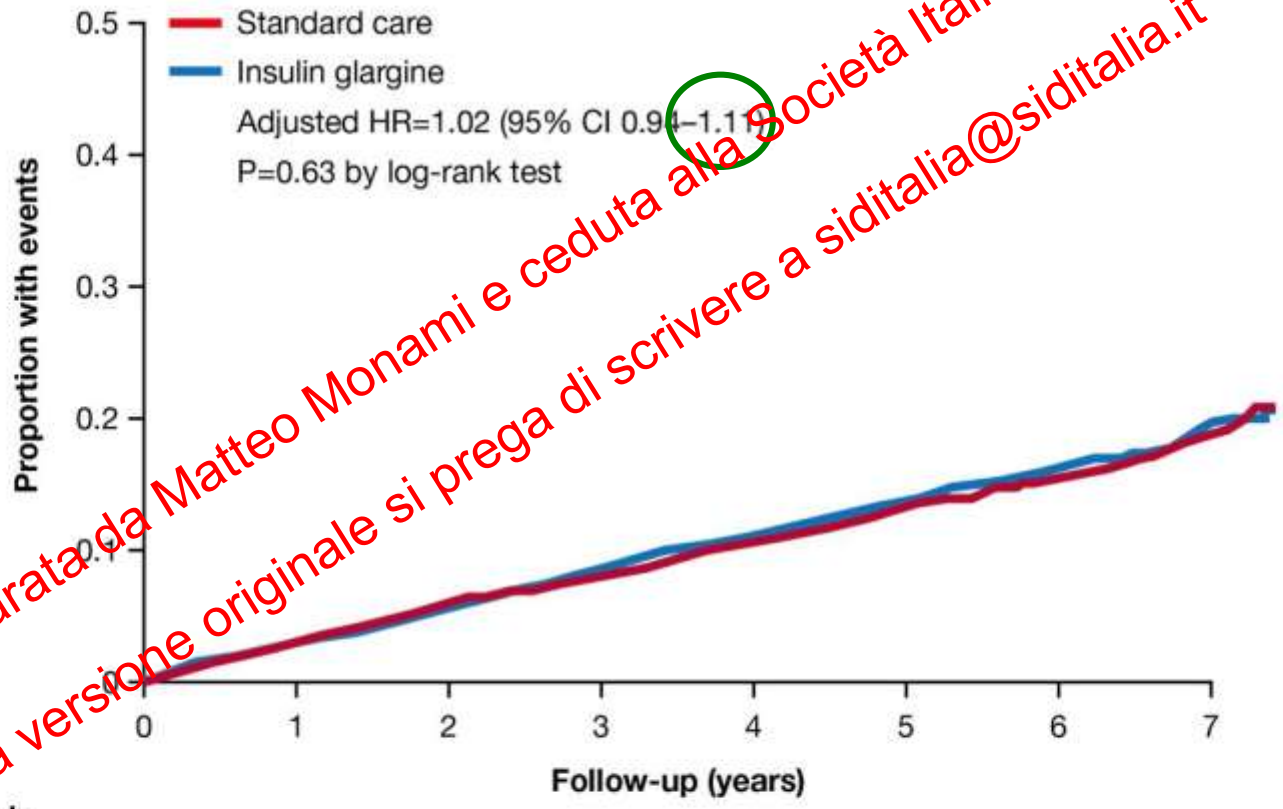
Figure 2: Kaplan-Meier curve of time to primary endpoint*

*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

UK Prospective Diabetes Group

	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

Lancet 1998;352;854–65.

Cardiovascular safety of sulfonylureas

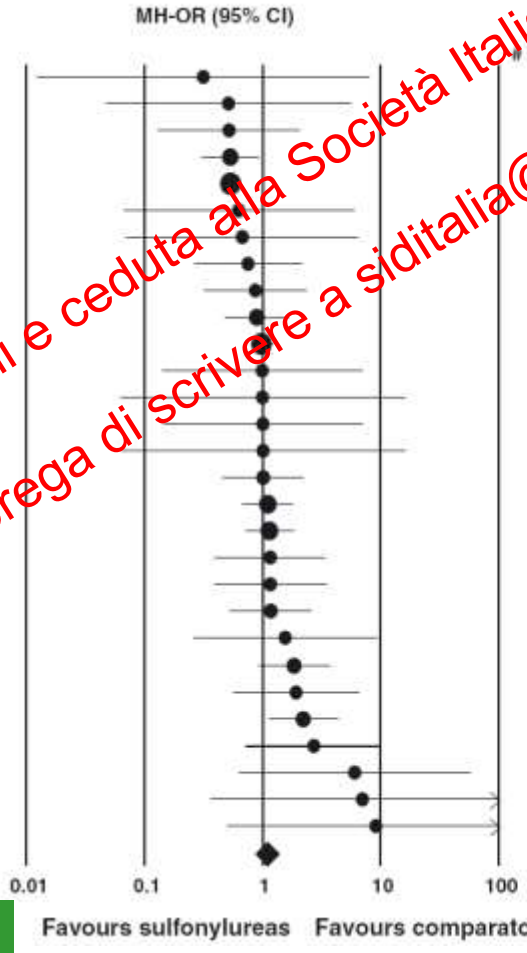
A meta-analysis of randomized clinical trials

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

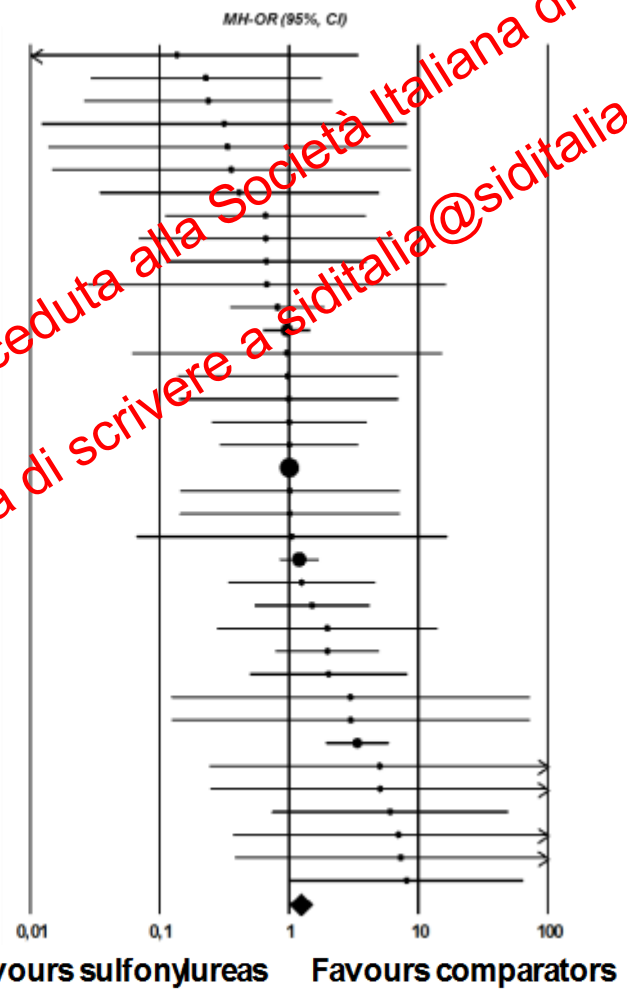
A meta-analysis of randomized clinical trials

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

Diabetes, Obesity and Metabolism 2013.

All-cause mortality

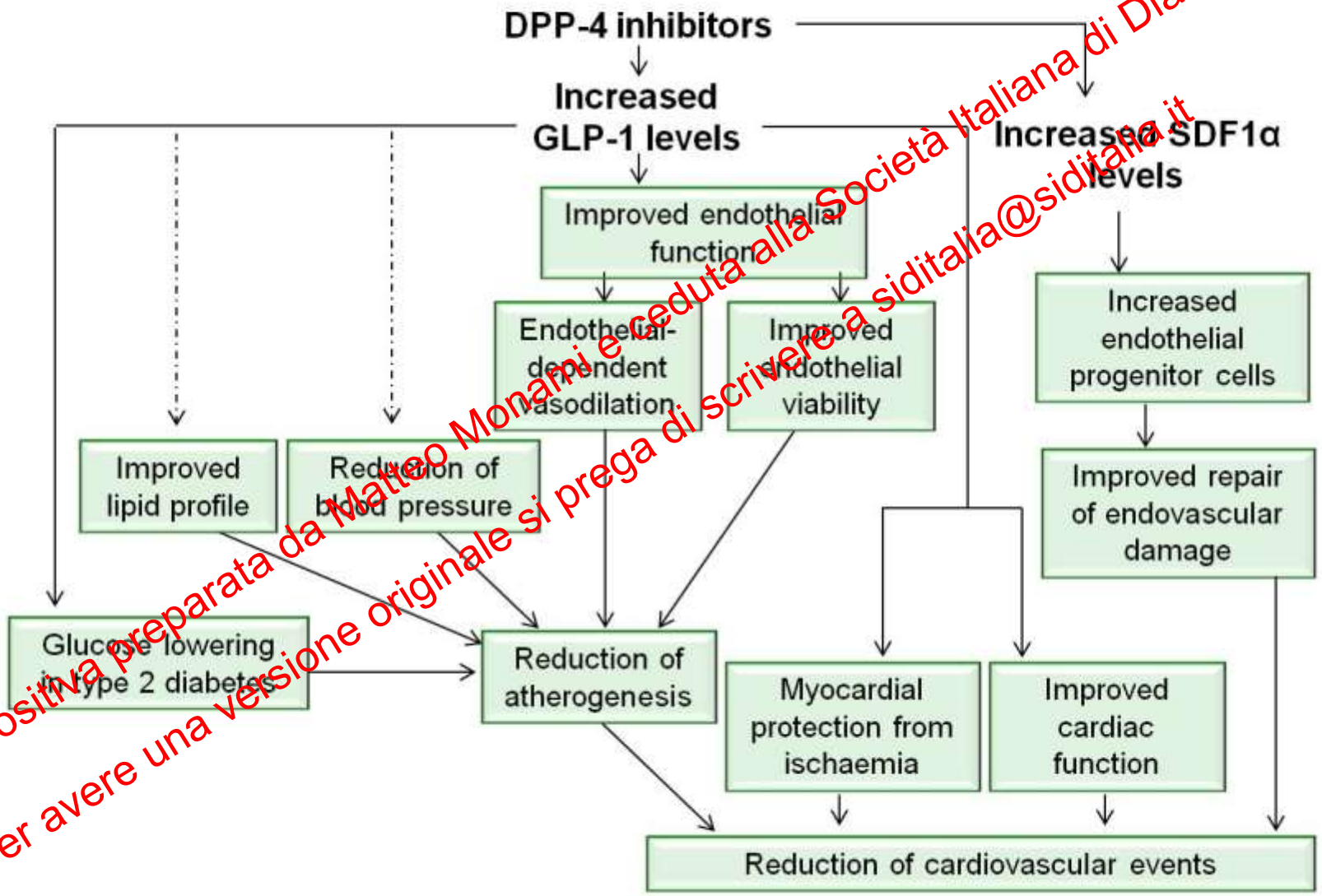
First autor (Year)	MH-OR	LL (95%. CI)	UL (95%. CI)	p
Yki-Jarvinen 1999	0,14	0,01	3,48	0,23
Rubin 2008	0,23	0,03	1,80	0,16
Tan 1977	0,24	0,03	2,19	0,20
Birkeland 1996	0,32	0,01	8,27	0,49
Mazzone 2006	0,33	0,01	8,26	0,50
Bakris 2006	0,36	0,01	8,83	0,53
Alvarsson 2010	0,41	0,03	5,03	0,49
Nissen 2008	0,66	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**

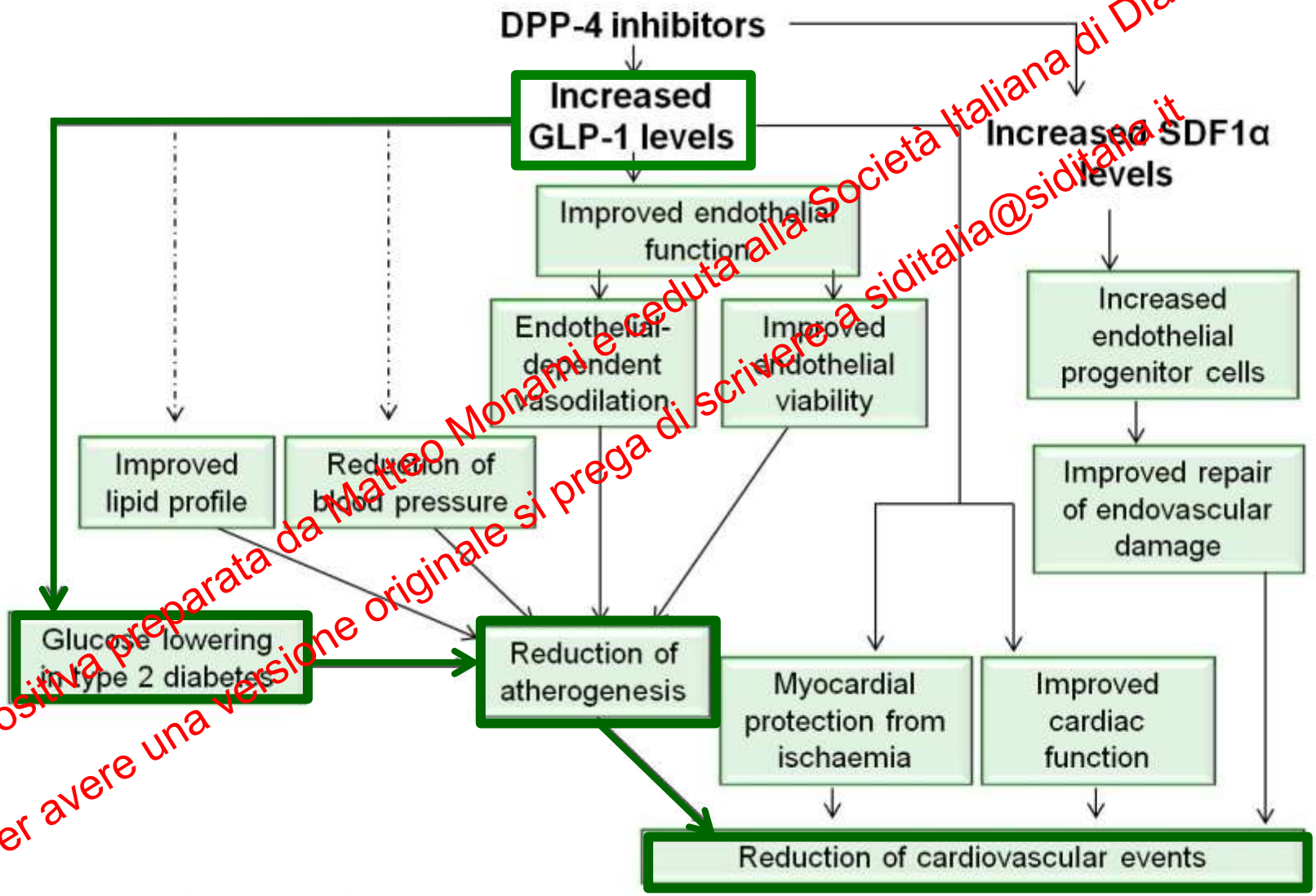
SUs would not be approved by any regulatory authority

CV effects of DPP-4 inhibitors



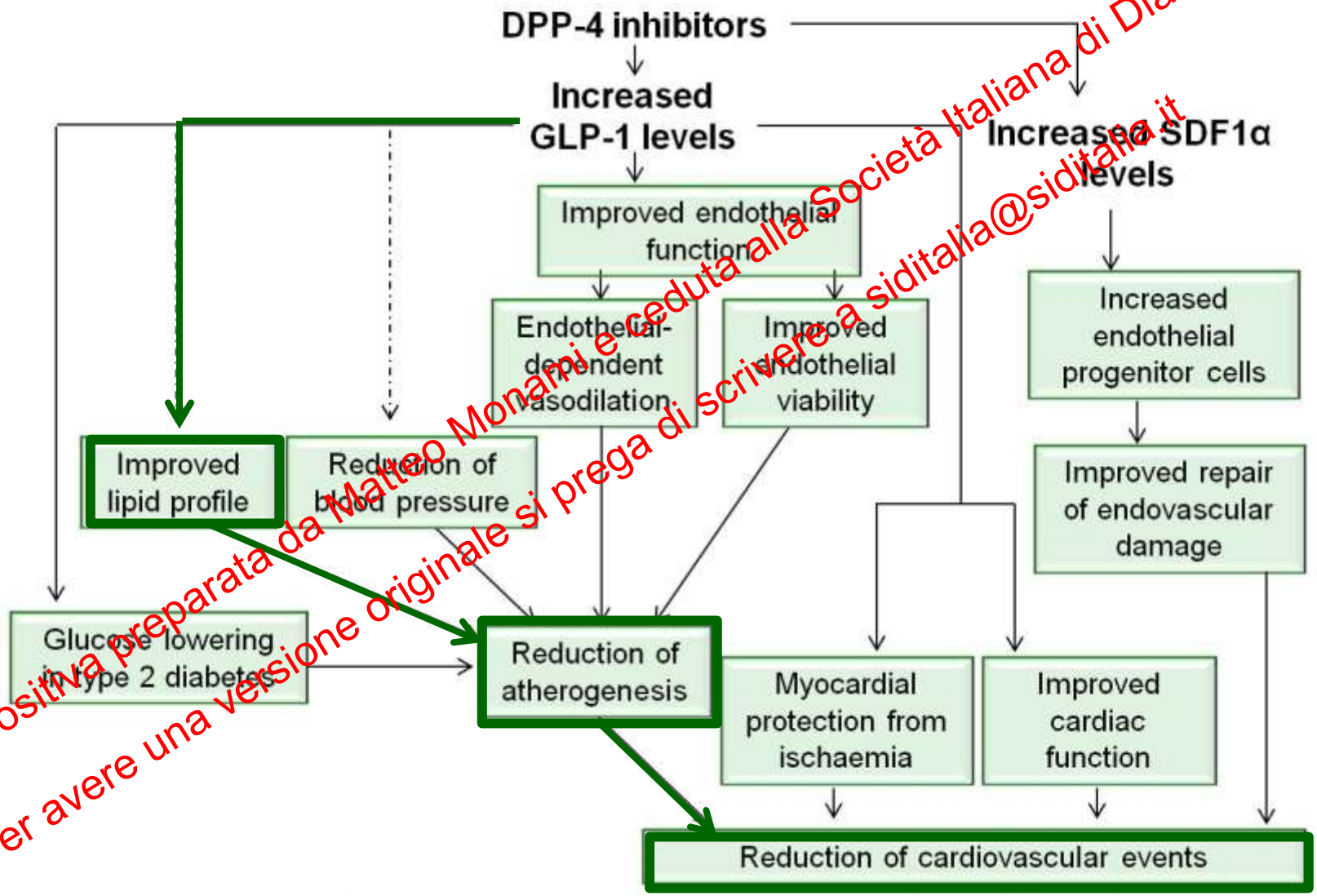
Mannucci E, Dicembrini I. *Curr Med Res Opin* 2012;28:715–21.

CV effects of DPP-4 inhibitors



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

CV effects of DPP-4 inhibitors



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

DPP-4 Inhibitors and Lipids:

Systematic Review and Meta-Analysis

Matteo Monami · Caterina Lamanna · Carla Maria Desideri · Edoardo Mannucci

Total cholesterol

Study name[Reference]	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-value	*P*-value
Rosenstock 2006[20]	0.000	0.008	0.000	−0.015	0.015	0.000	1.000
Williams-Herman 2010[24]	0.000	0.021	0.000	−0.041	0.041	0.000	1.000
Hollander 2010[19]	0.000	0.052	0.003	−0.101	0.101	0.000	1.000
Bolli 2009[26]	−0.355	0.004	0.000	−0.362	0.348	−94.639	0.000
Bergenstal 2010[22]	−0.100	0.007	0.000	−0.113	−0.087	−14.962	0.000
Bergenstal 2010[22a]	0.070	0.007	0.000	0.057	0.083	10.419	0.000
Charbonnel 2006[21]	−0.120	0.008	0.000	−0.136	−0.104	−15.050	0.000
DeFronzo 2008[17]	−0.393	0.009	0.000	−0.411	−0.375	−43.500	0.000
Pratley 2009[18]	−0.140	0.007	0.000	−0.153	−0.127	−20.667	0.000
Pratley 2011[23]	0.080	0.006	0.000	0.068	0.092	13.098	0.000
Rosenstock 2007[8]	−0.440	0.014	0.000	−0.467	−0.413	−31.677	0.000
Dejager 2007[25]	−0.172	0.008	0.000	−0.188	−0.156	−22.949	0.000
Rosenstock 2007[8a]	−0.726	0.014	0.000	−0.754	−0.698	−50.244	0.000
Overall	−0.177	0.007	0.003	−0.289	−0.065	−3.101	0.002

Statistics for each study

Difference in means and 95% CI

−0.50 −0.25 0.00 0.25 0.50

Favors DPP-4i Favors comparator

Triglycerides

Triglycerides

Study name[Reference]	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-value	*P*-value
DeFronzo 2008[17]	−0.821	0.028	0.001	−0.875	−0.767	−29.760	0.000
Hollander 2010[19]	0.000	0.059	0.003	−0.115	0.115	0.000	1.000
Rosenstock 2006[8]	−0.139	0.011	0.000	−0.160	−0.118	−12.861	0.000
Charbonnel 2006[21]	−0.426	0.010	0.000	−0.445	−0.407	−44.743	0.000
Pratley 2011[23]	0.010	0.017	0.000	0.042	−0.022	−0.606	0.545
Williams-Herman 2010[31]	0.000	0.013	0.000	−0.026	0.026	0.000	1.000
Rosenstock 2007[8]	0.032	0.007	0.000	−0.019	−0.045	4.728	0.000
Rosenstock 2007[8a]	0.163	0.008	0.000	0.147	0.179	19.923	0.000
Dejager 2007[25]	−0.159	0.011	0.000	−0.180	−0.138	−14.644	0.000
Bolli 2009[26]	−0.110	0.005	0.000	−0.119	−0.101	−24.437	0.000
Overall	−0.147	0.059	0.004	−0.263	−0.031	−2.486	0.013

Statistics for each study

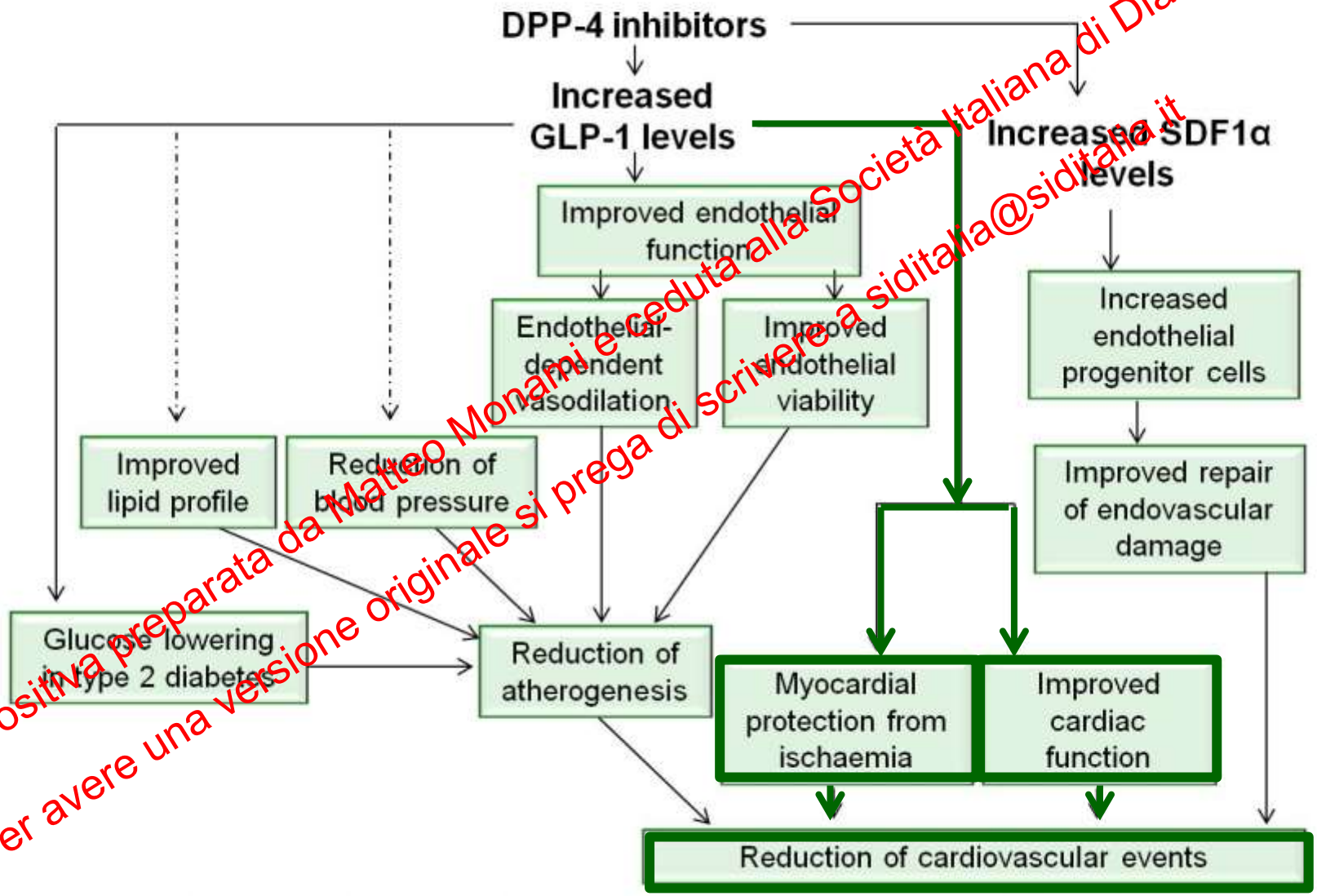
Difference in means and 95% CI

−1.00 −0.50 0.00 0.50 1.00

Favors DPP-4i Favors controls

Adv Ther (2012) 29(1):14-25.

CV effects of DPP-4 inhibitors



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

Myocardial effects of GLP1

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

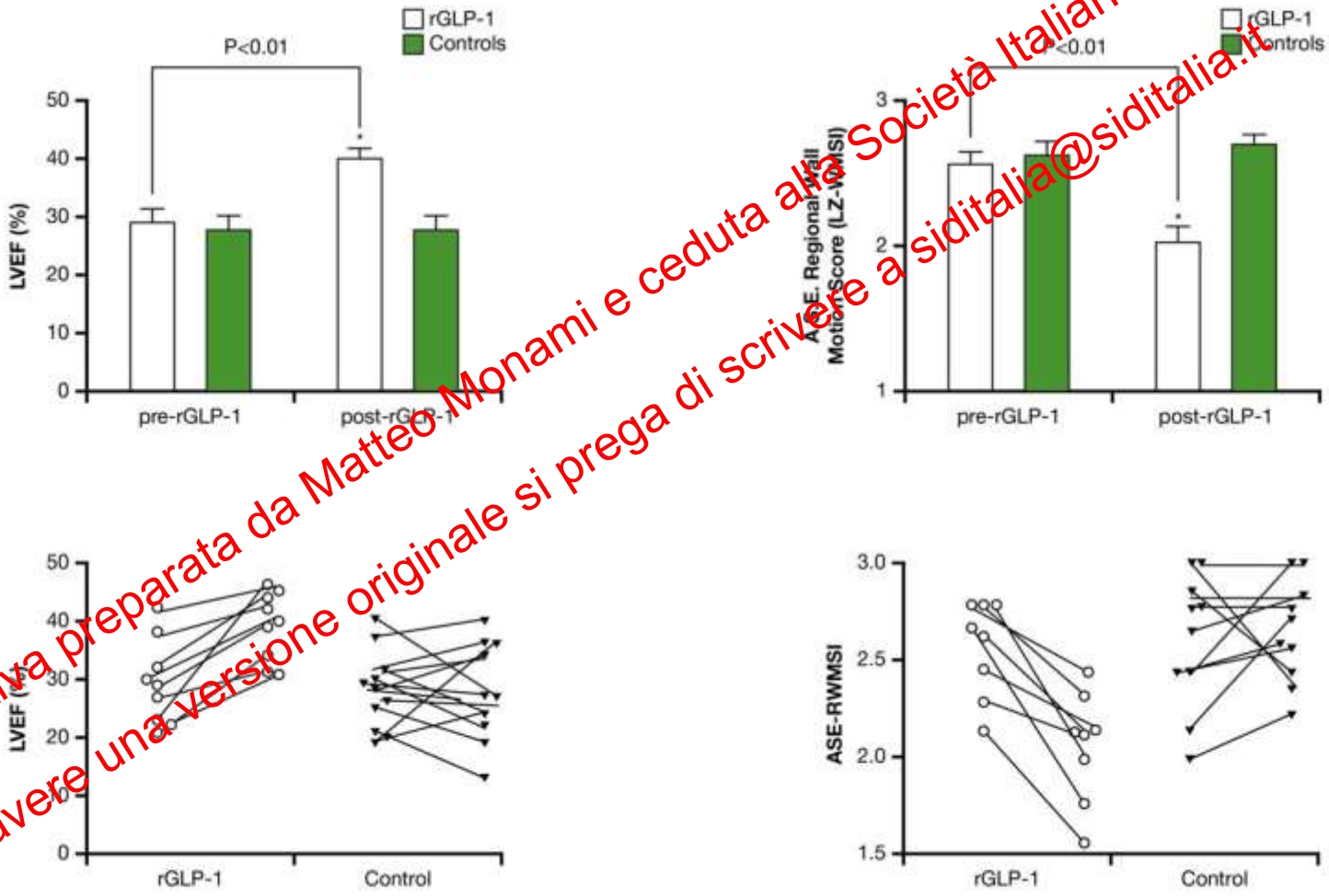
PBS

Exenatide

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

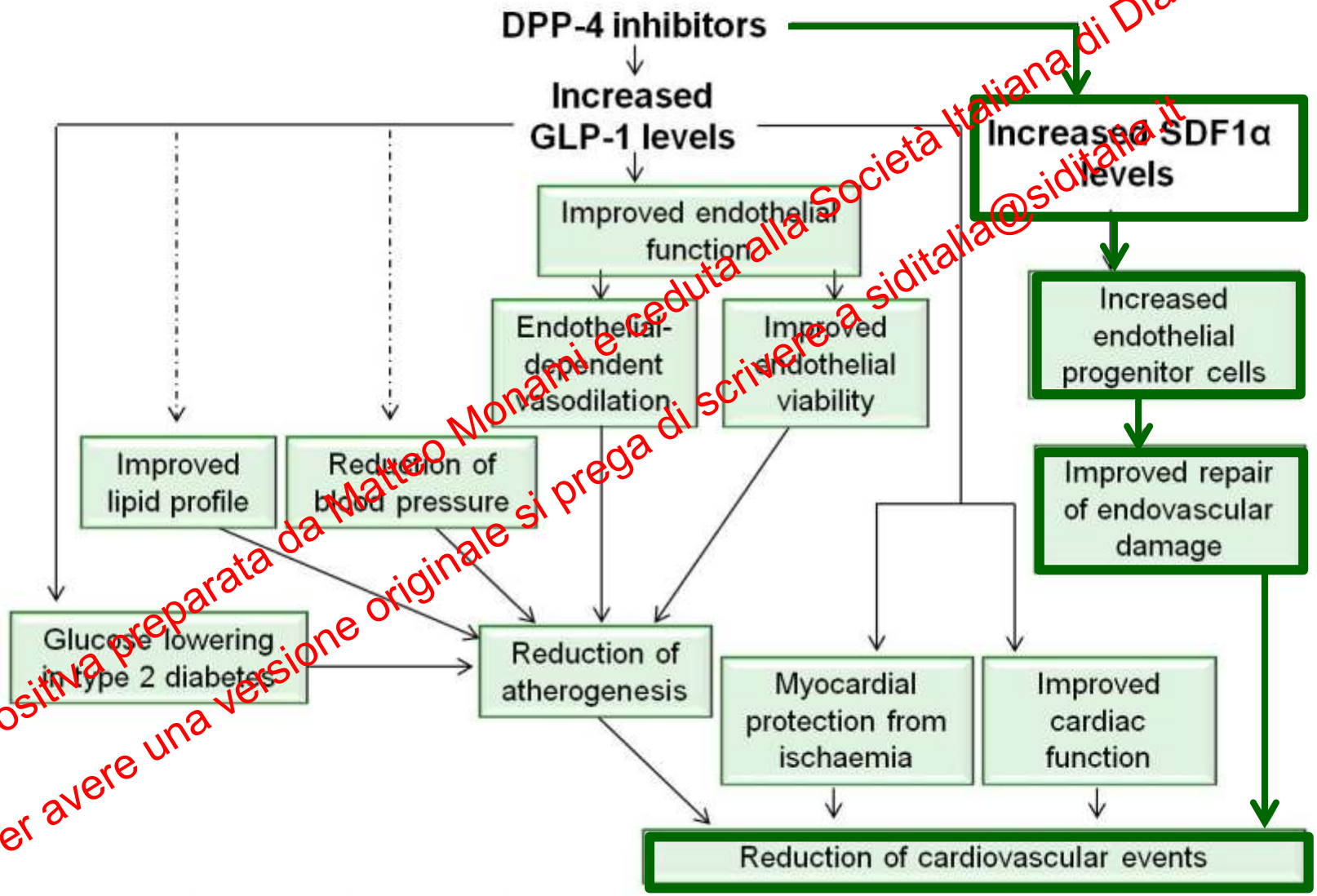
Myocardial effects of GLP-1

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



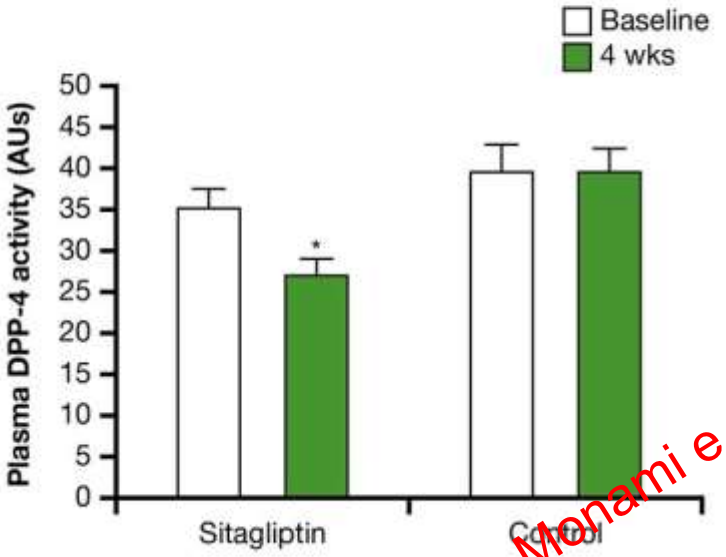
Nikolaidis LA, *et al. Circulation* 2004;109:962–5.

CV effects of DPP-4 inhibitors

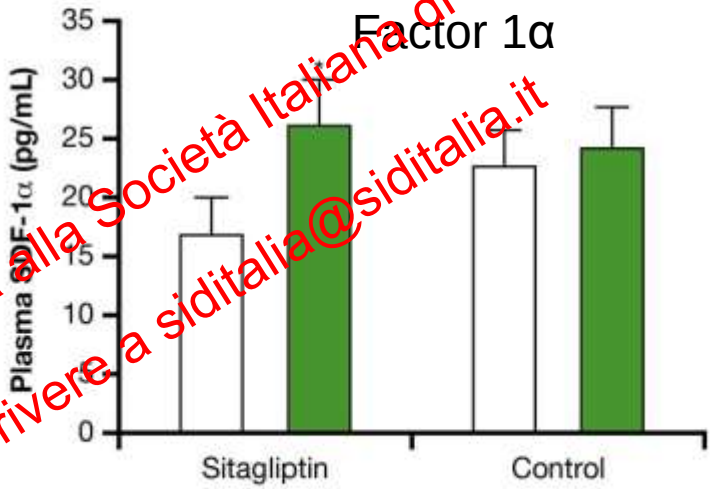


Mannucci E, Dicembrini I. *Curr Med Res Opin* 2012;28:715–21.

DPP-4 inhibitors and SDF-1α

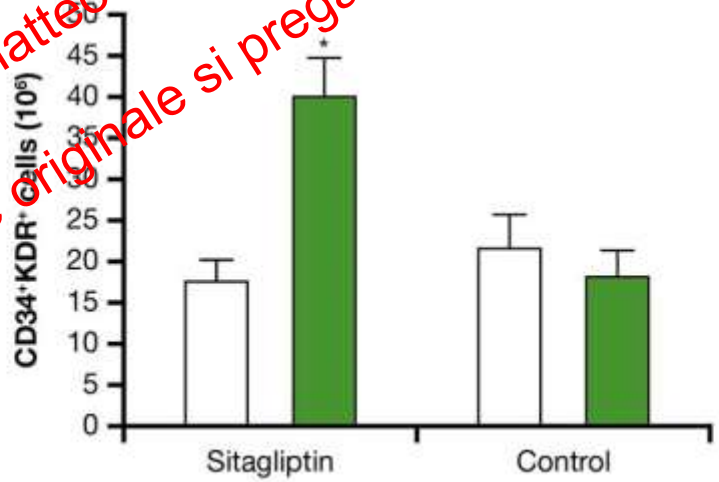


Stromal Cell-Derived Factor 1α



Vascular endothelial growth factors

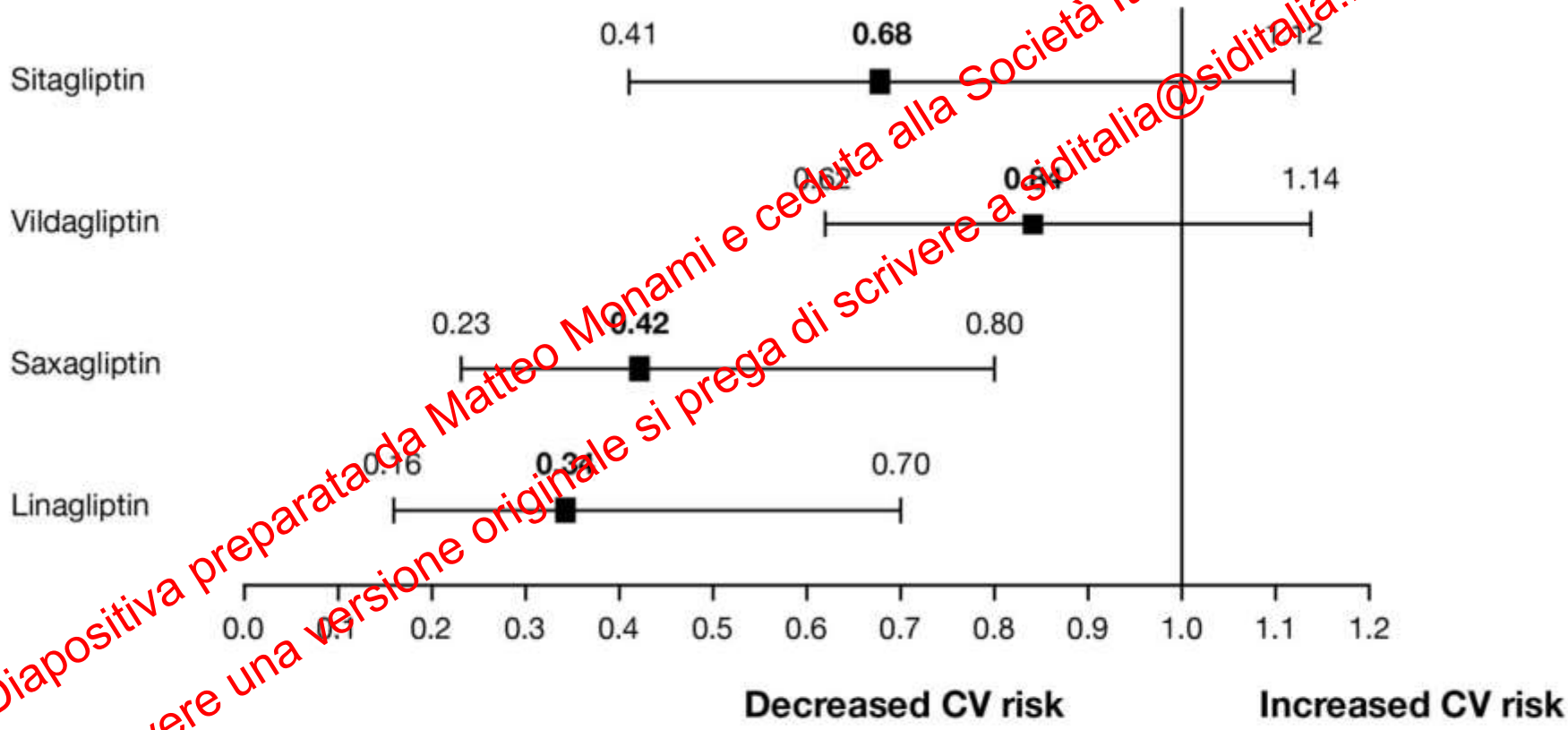
Precursors of endothelial cells



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

DPP-4 inhibitors and MACE

Pooled analyses of Phase II–III trials



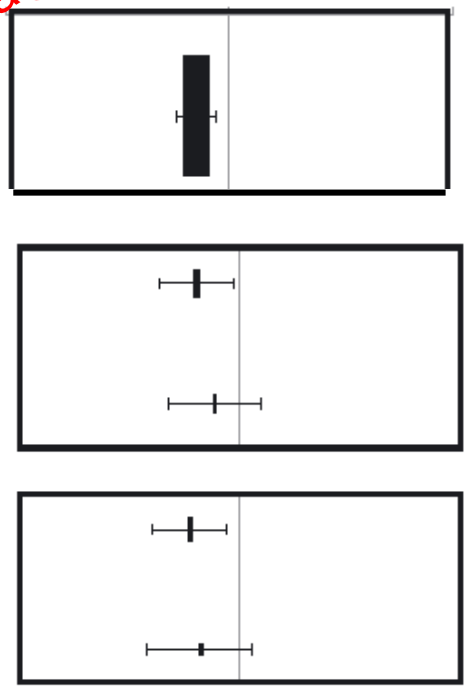
1. Williams-Herman D, *et al. BMC Endocr Disord* 2010;10:7; 2. Schweizer A, *et al. Diabetes Obes Metab* 2010;12:485–94; 3. Frederich R, *et al. Postgrad Med* 2010;122:16–27; 4. Johansen O, *et al. Cardiovasc Diabetol* 2012;11:3.

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.

EXAMINE study design

n=5,380 patients

Patients with type 2 diabetes mellitus receiving:

- Monotherapy or combination antidiabetic therapy (with the exception of a DPP-4 inhibitor or GLP-1 analogue) before screening
- Well-defined ACS event in 15–90 days prior to randomisation

Double-blind, noninferiority trial with a prespecified noninferiority margin of 1.3 for the primary end point

Alogliptin
6.25, 12.5 or 25 mg/day plus usual care

All other diabetes therapy per treating doctors

Placebo
plus usual care

Follow-up visits 1, 3, 6, 9 and 12 months post-randomisation during the first year of study and every 4 months after

Duration

- First unblinded analysis after 80 events†
- If necessary, subsequent analyses after 100, 125 and 150 events†
- If necessary, analyses after 600 and 650 events‡

Final visit

Primary endpoint

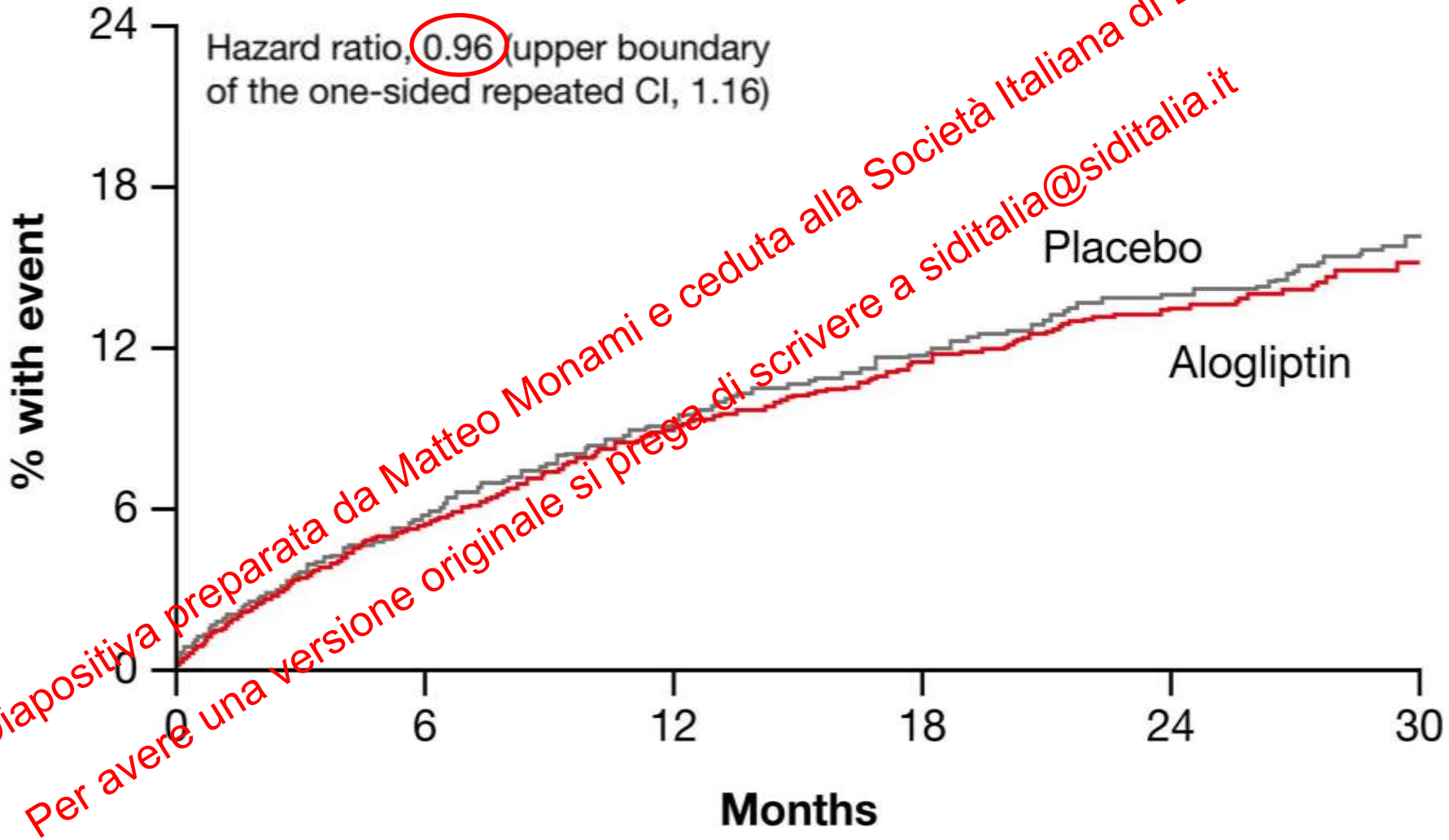
- CV death, non-fatal myocardial infarction, non-fatal stroke

*Target enrollment; †To rule out upper bound of CI >1.8; ‡To rule out upper bound of CI >1.3.

White WB, *et al. N Engl J Med* 2013;DOI: 10.1056/NEJMoa1305889; White W, *et al. Am Heart J* 2011;162:620–6.

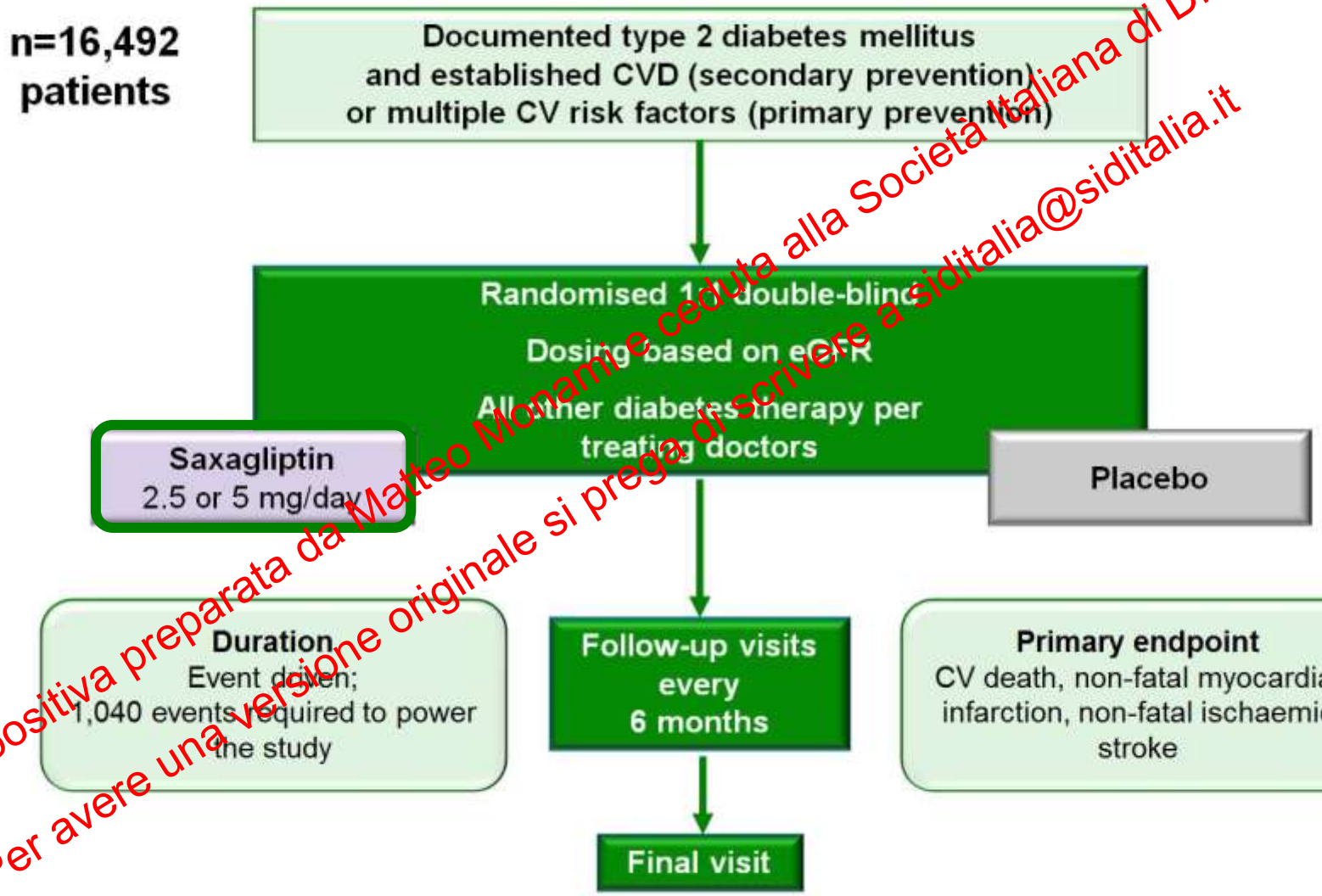
Alogliptin after Acute Coronary Syndrome in patients with type 2 diabetes

The EXAMINE trial



White WB et al., *N Engl J Med* 2013; 369:1327-1335

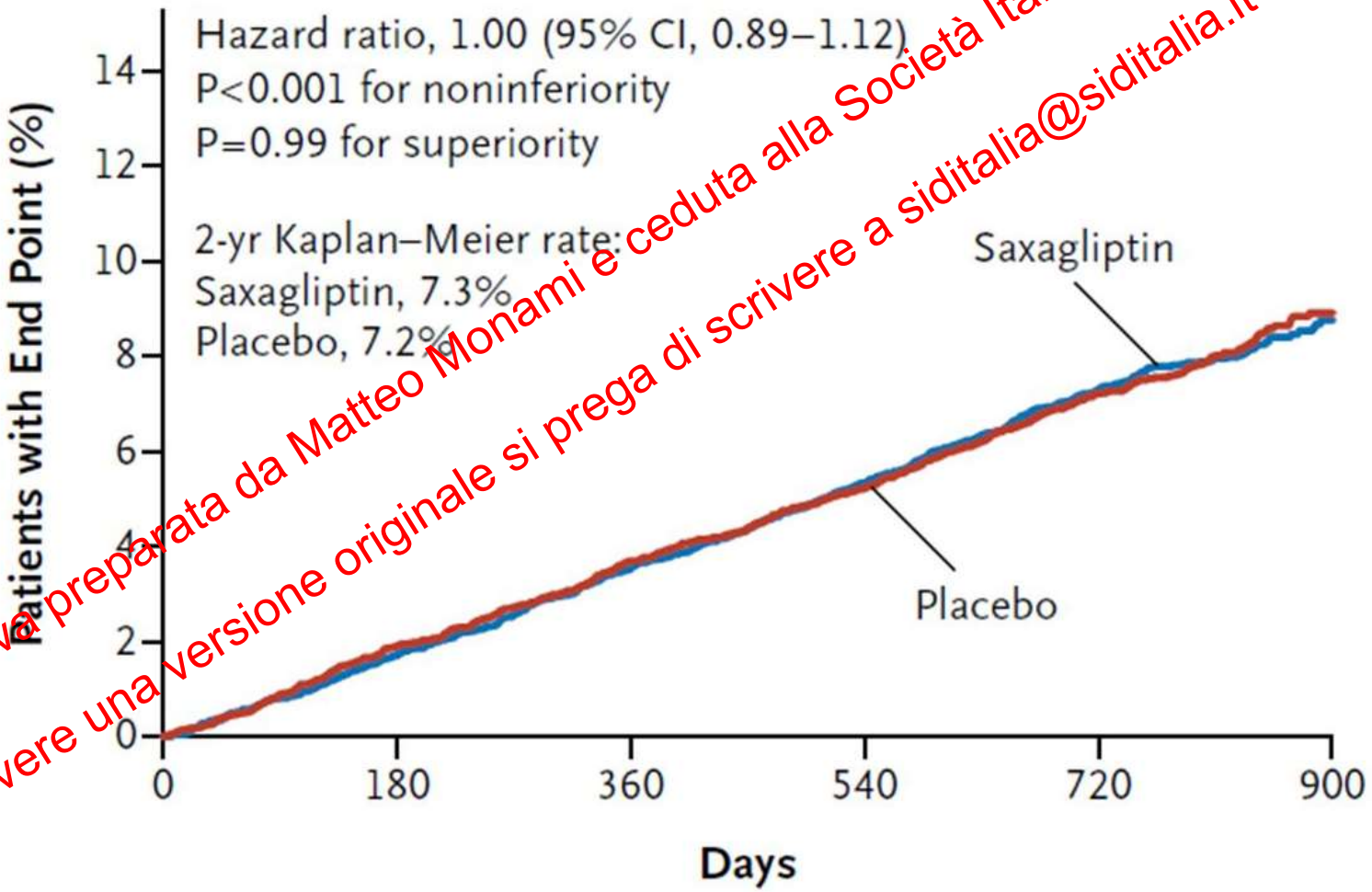
SAVOR-TIMI 53 study design



Scirica BM, *et al. N Engl J Med 2013.* 369:1317-1326.

Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus

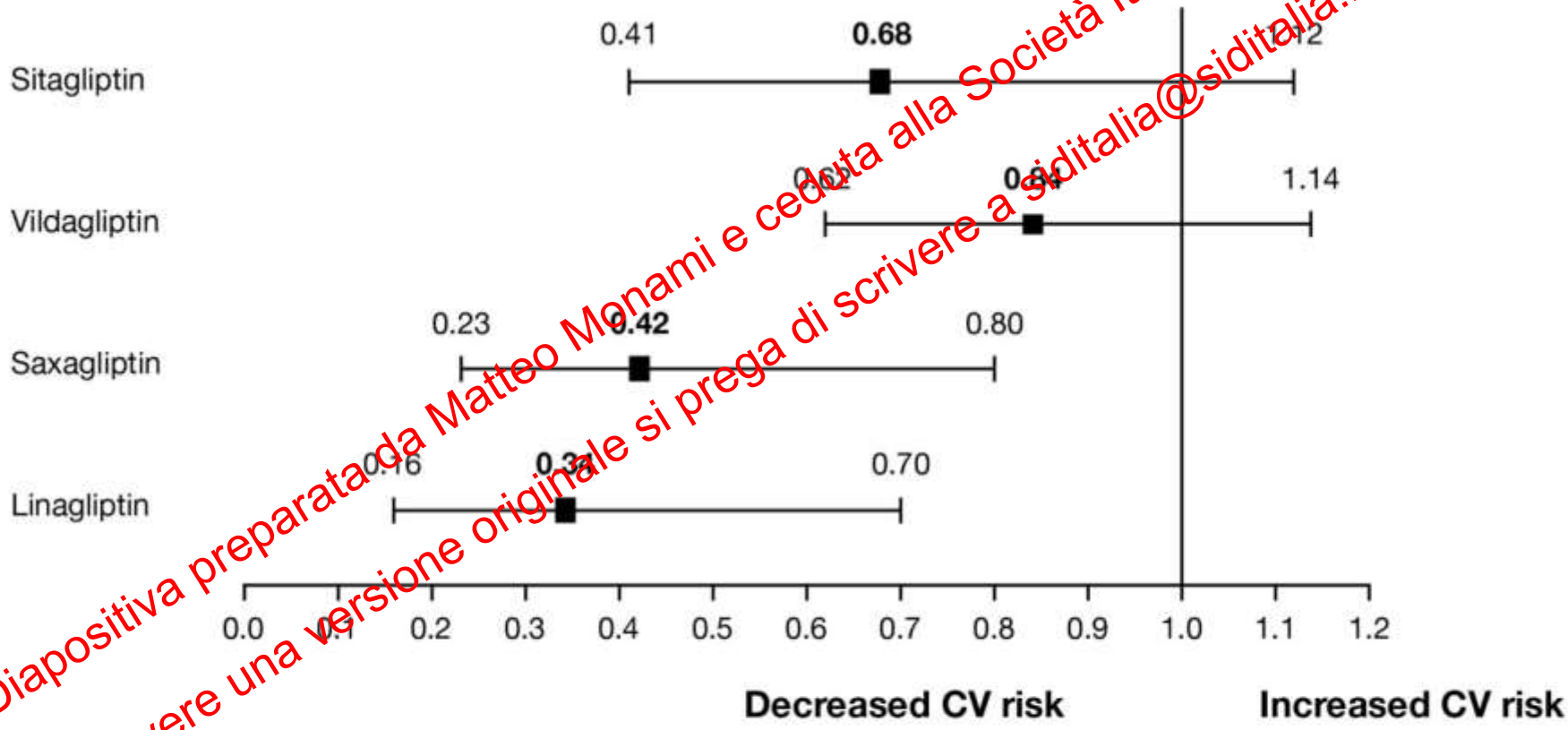
The SAVOR trial



Scirica BM et al., N Engl J Med 2013; 369:1317-1326

DPP-4 inhibitors and MACE

Pooled analyses of Phase II–III trials



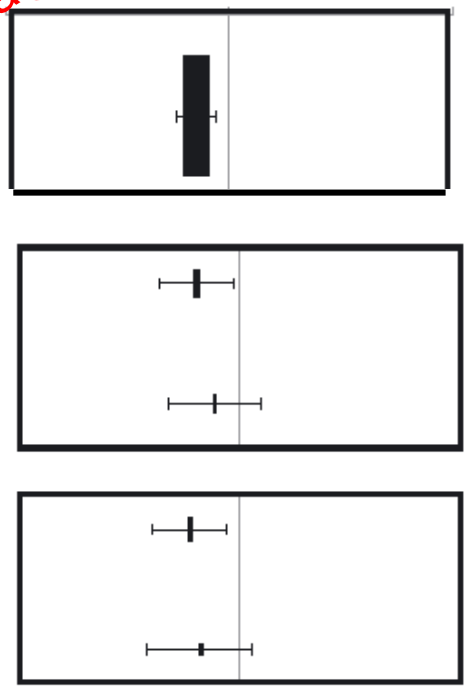
1. Williams-Herman D, *et al. BMC Endocr Disord* 2010;10:7; 2. Schweizer A, *et al. Diabetes Obes Metab* 2010;12:485–94; 3. Frederich R, *et al. Postgrad Med* 2010;122:16–27; 4. Johansen O, *et al. Cardiovasc Diabetol* 2012;11:3.

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 and MACE

Results of the EXAMINE trial

Patients at a very high CV risk…..

	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)

….really very hard to obtain any positive results

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

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

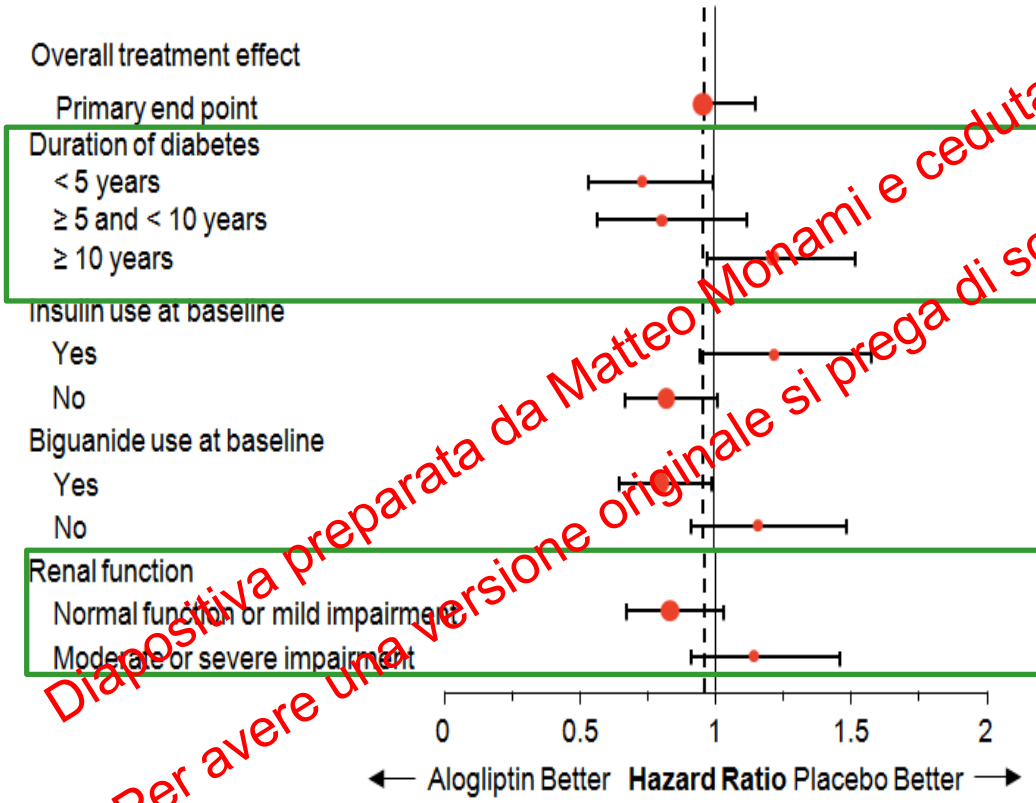
	SAVOR *	Meta-analysis**
Number of patients	16,492	41,959
Number of events	1,222	495
Duration of follow-up (years)	2.1 (median)	~1.0 (mean)
Incidence of MACE (/100 py)	3.5	1.1
Mean age (years)	65	55
Mean duration of diabetes (years)	12	5
Mean BMI (kg/m^2)	31.1	31.1
Mean HbA$_{1c}$ (%)	8.0	8.2
Insulin-treated (%)	43	<5
Previous CV (%)	75	~30
Nephropathy(%)	18	<5

* 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

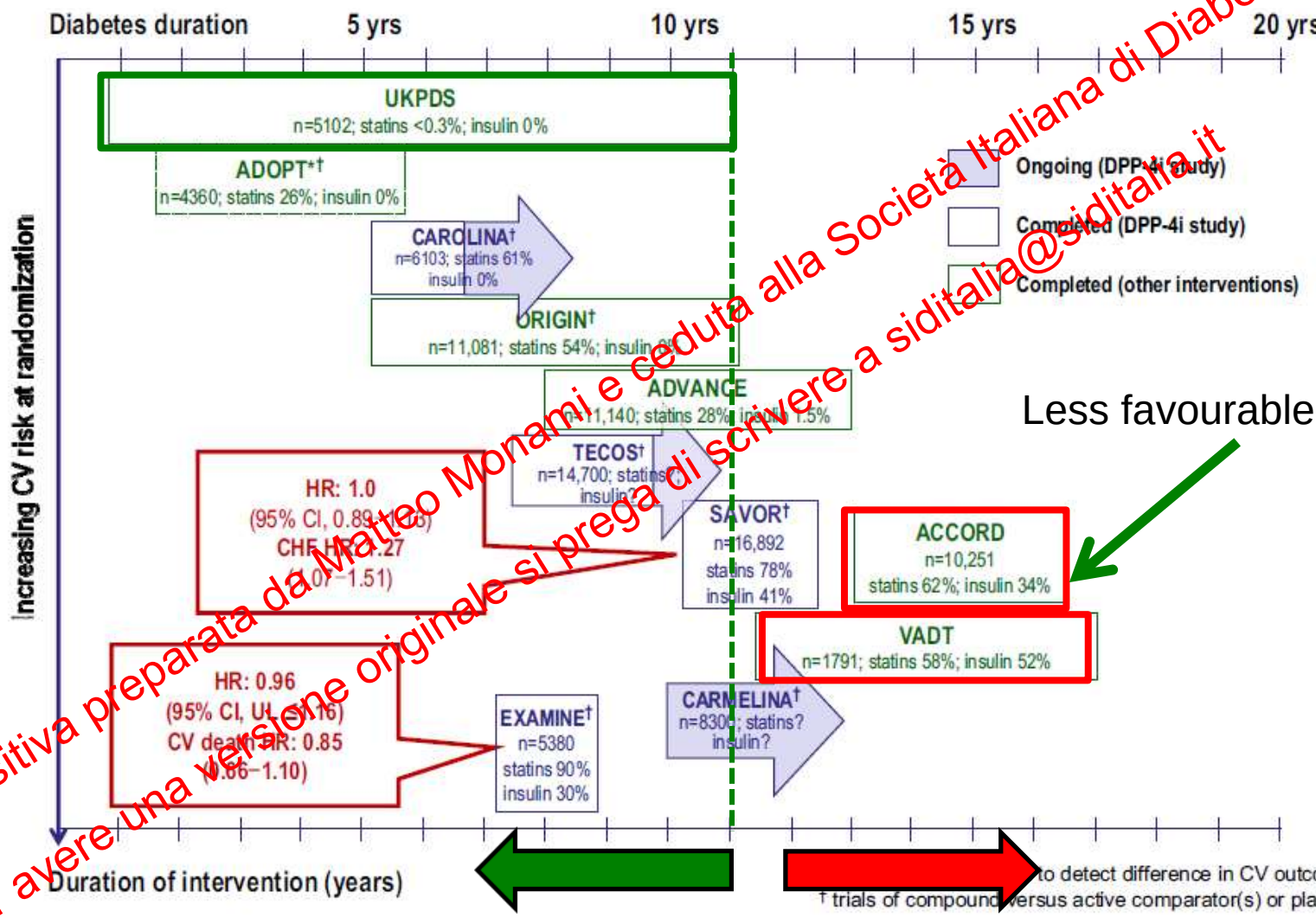
The EXAMINE trial: subgroup analyses



	Placebo		Alogliptin		Hazard Ratio	95% CI	Interaction With Treatment P value
	n	%	n	%			
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	665	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

White WB et al., *N Engl J Med* 2013; 369:1327-1335

Recent CVOTs in context of diabetes duration, CV risk and duration of intervention



Johansen et al, OP - 49th *EASD*, Barcelona 2013

Saxagliptin and MACE

Results of the SAVOR trial: secondary endpoint

End Point	Saxagliptin (N=8280)	Placebo (N=8212)	Hazard Ratio (95% CI)	P Value
	no. (%)			
Cardiovascular death, myocardial infarction, or stroke: primary efficacy end point	613 (7.3)	609 (7.2)	1.00 (0.89–1.12)	0.99
Cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, heart failure, or coronary revascularization: secondary efficacy end point	1069 (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	[illegible]	[illegible]	1.27 (1.07–1.51)	0.007
Hospitalization for coronary revascularization	423 (5.2)	459 (5.6)	0.91 (0.80–1.04)	0.18

Scirica BM, *et al. N Engl J Med* 2013 369:1317-1326.

Saxagliptin and heart failure

Is this a casual finding (by chance)?

Is this a drug-specific phenomenon?

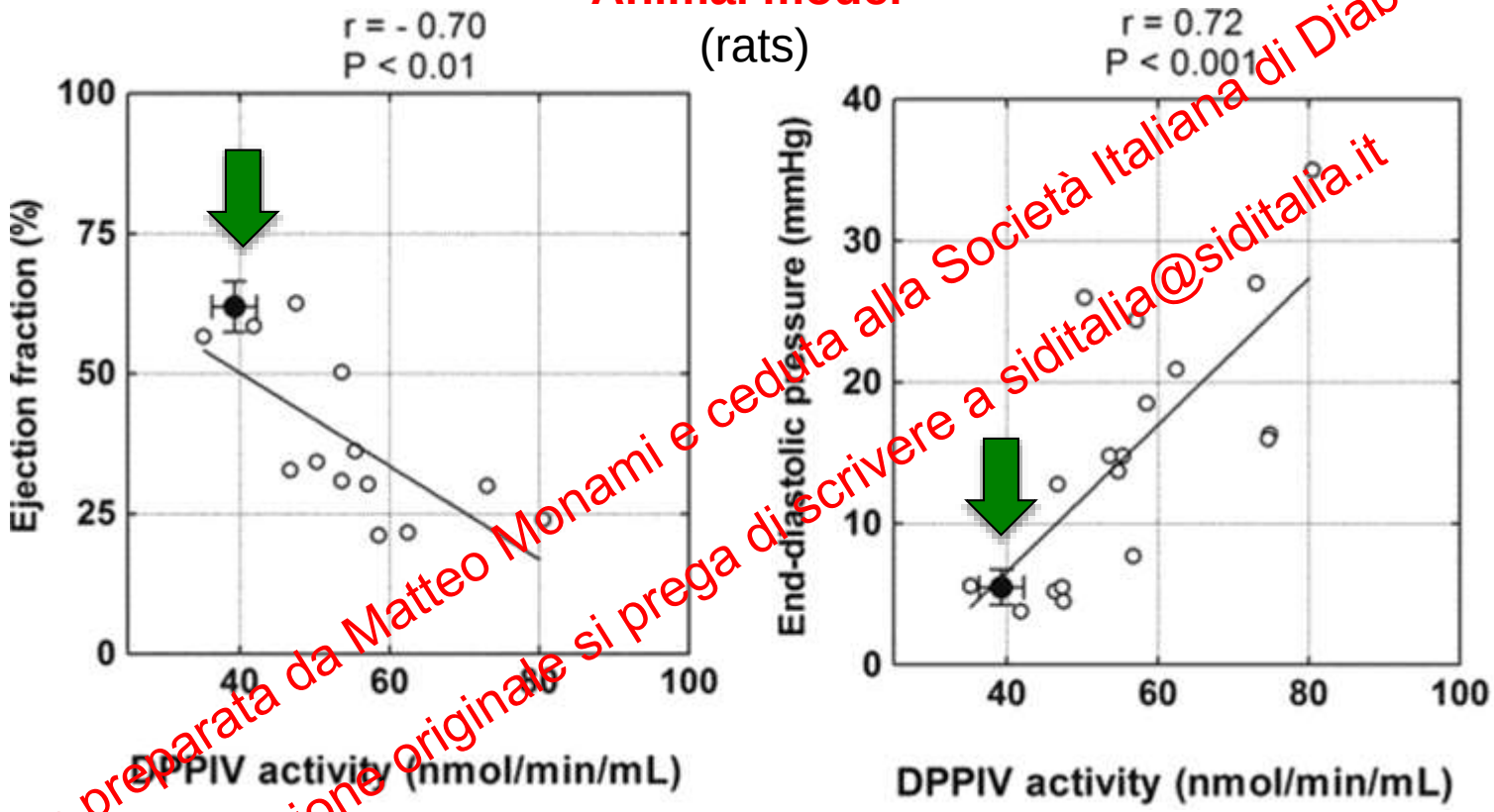
Is this a class effect common to all DPP4 inhibitors?

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

DPP-4 activity and heart failure

Animal model

(rats)



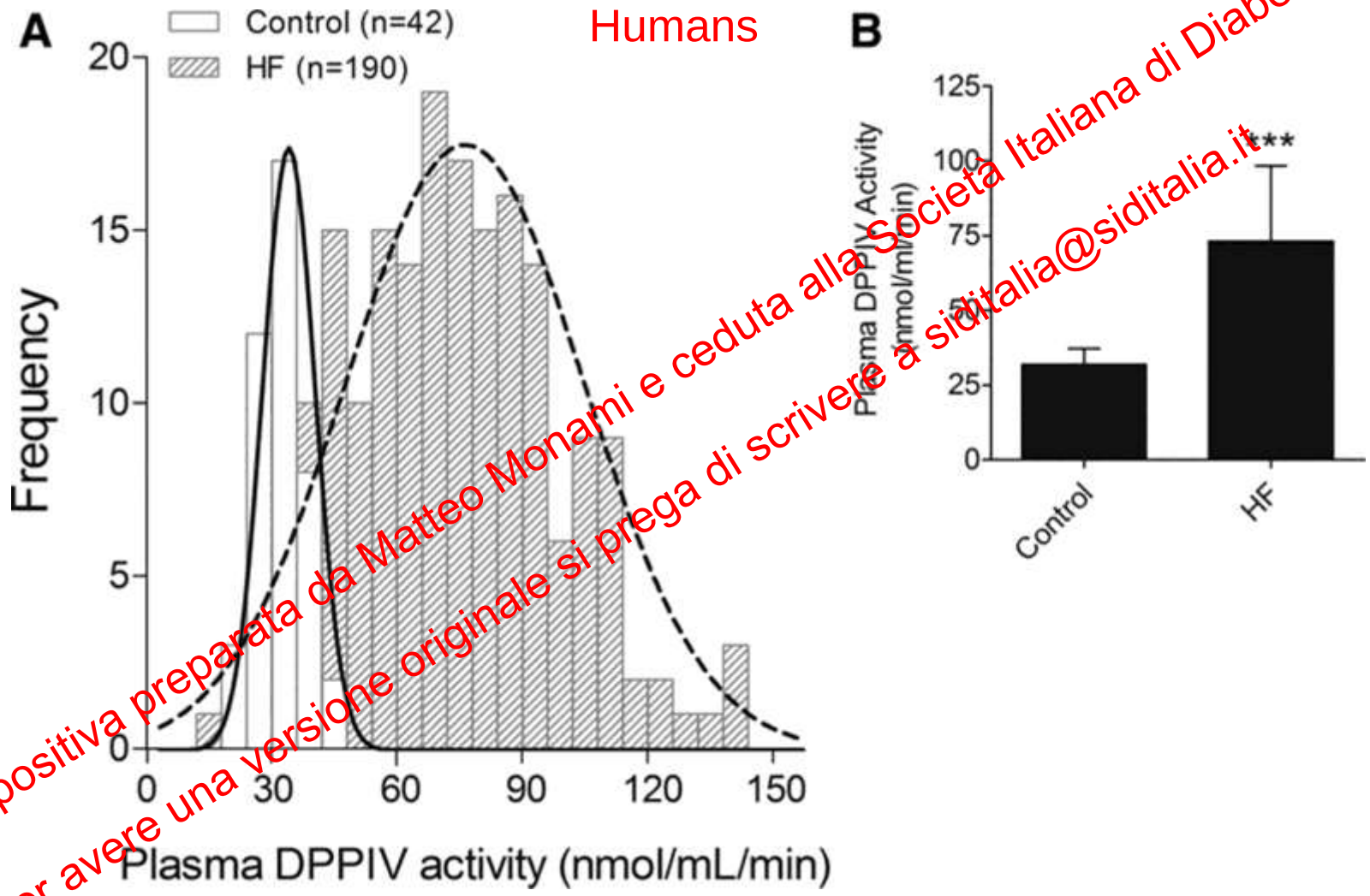
Inverse correlation between cDDP-4 activity and cardiac function

Control group

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

DPP-4 activity and heart failure

Humans



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

DPP-4 activity and heart failure

- DPP4 activity has something to do with heart failure
- The clinical impact of these findings is unknown
- It could be even possible that the increased DPP-4 activity in heart failure is a compensatory mechanism, impaired by the use of DPP-4 inhibitors.

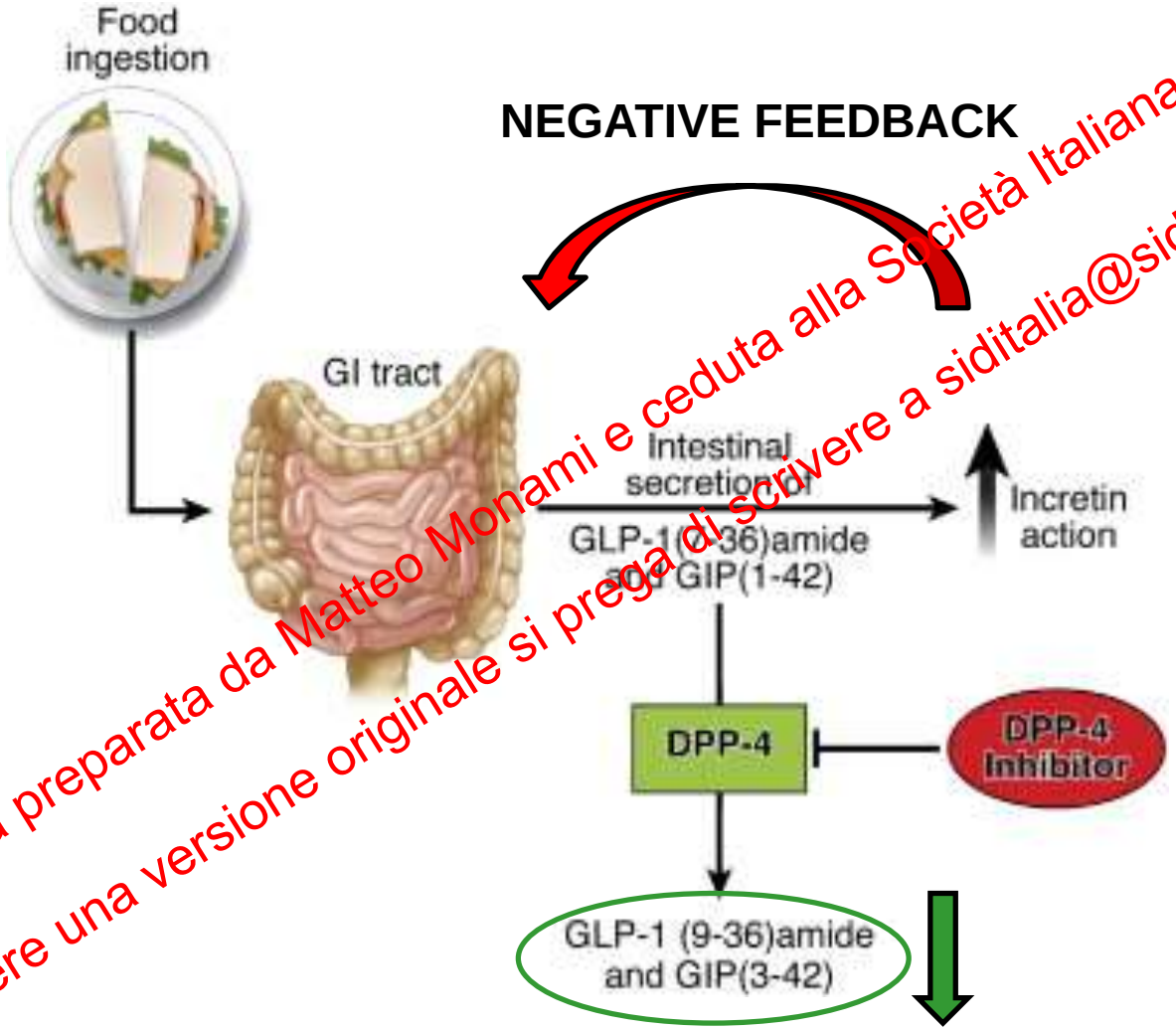
Saxagliptin and heart failure

Hypothetical mechanisms

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

From a mechanistic point of view, we could imagine several different mechanisms through which saxagliptin could induce an increased hospitalization for HF.

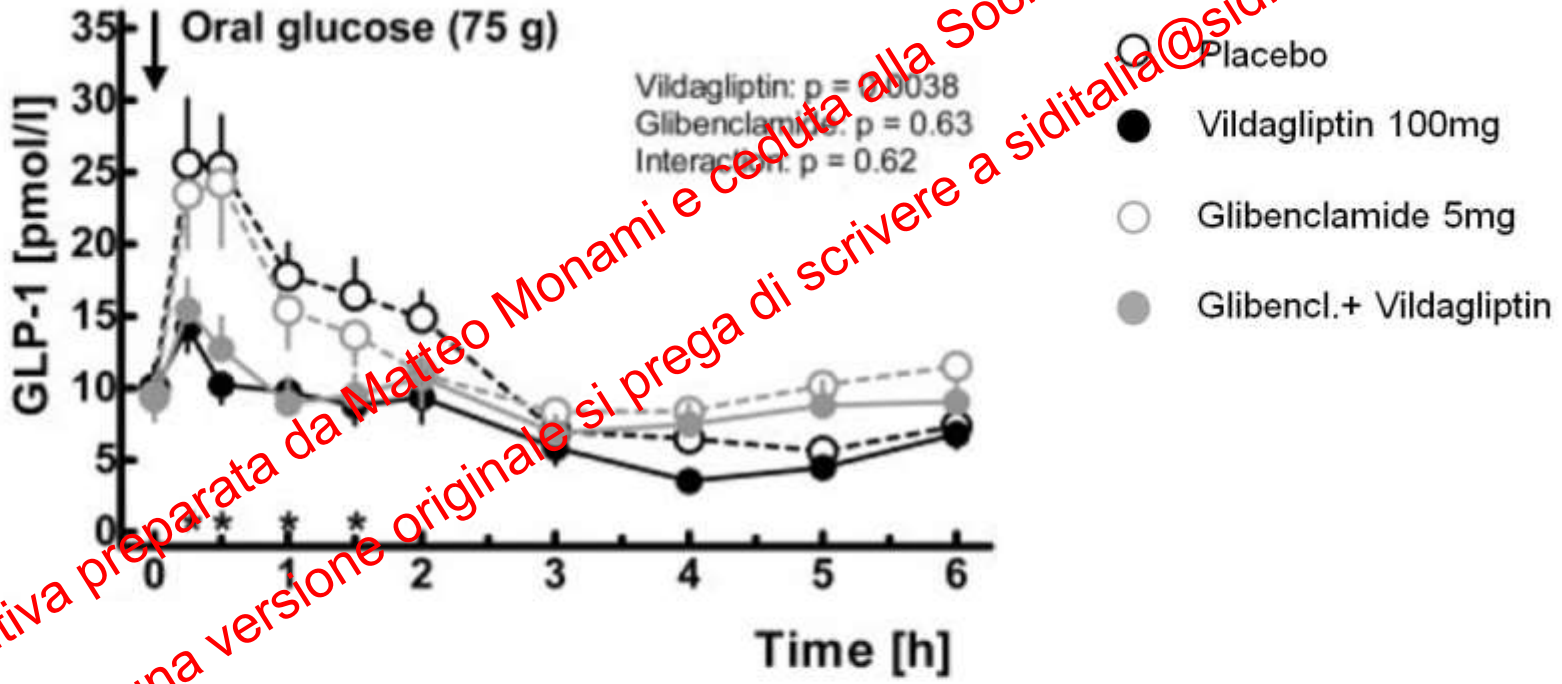
GLP-1 (7-36) and GLP-1 (9-36): effects of the inhibition of DPP-4



Adapted from: Baggio L et al., *Gastroenterology* 2007, 132:2131-2157

DPP4i and GLP-1 secretion

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

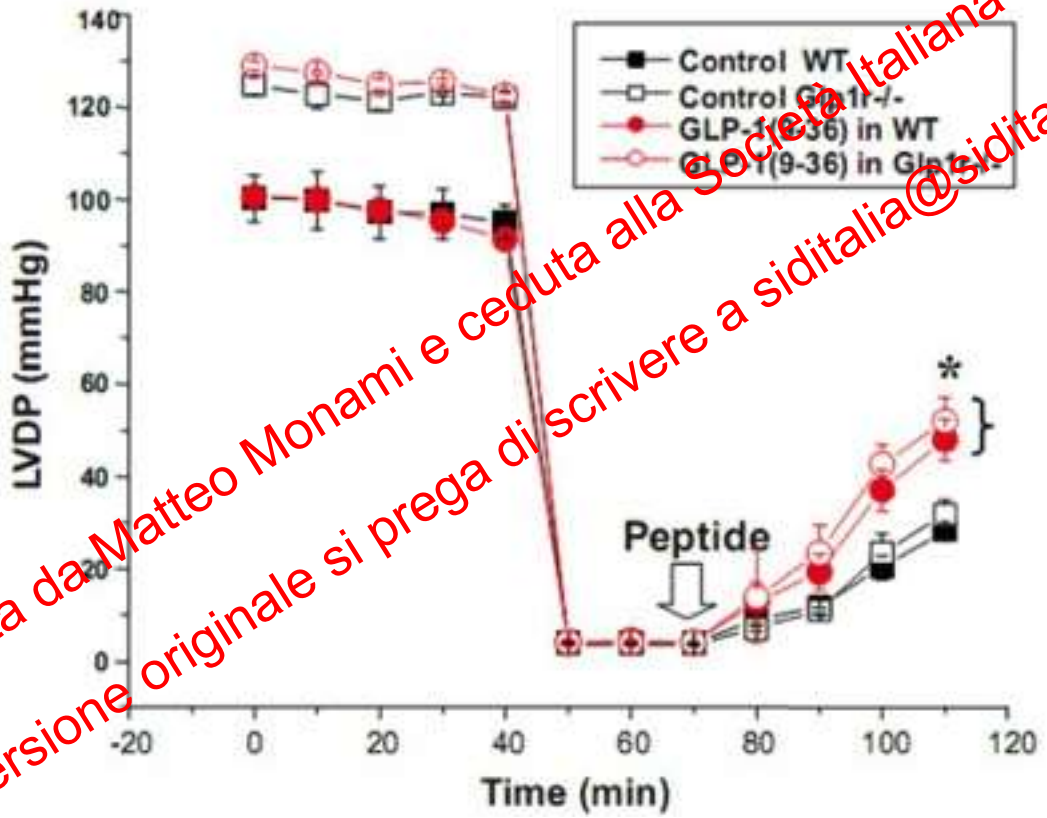


DPP-4i determines a 4-fold increase of GLP-1 (7-36), so the overall reduction of cGLP-1 levels is mainly attributable to a reduction of GLP-1 (9-36).

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

Myocardial effects of GLP-1(9-36)

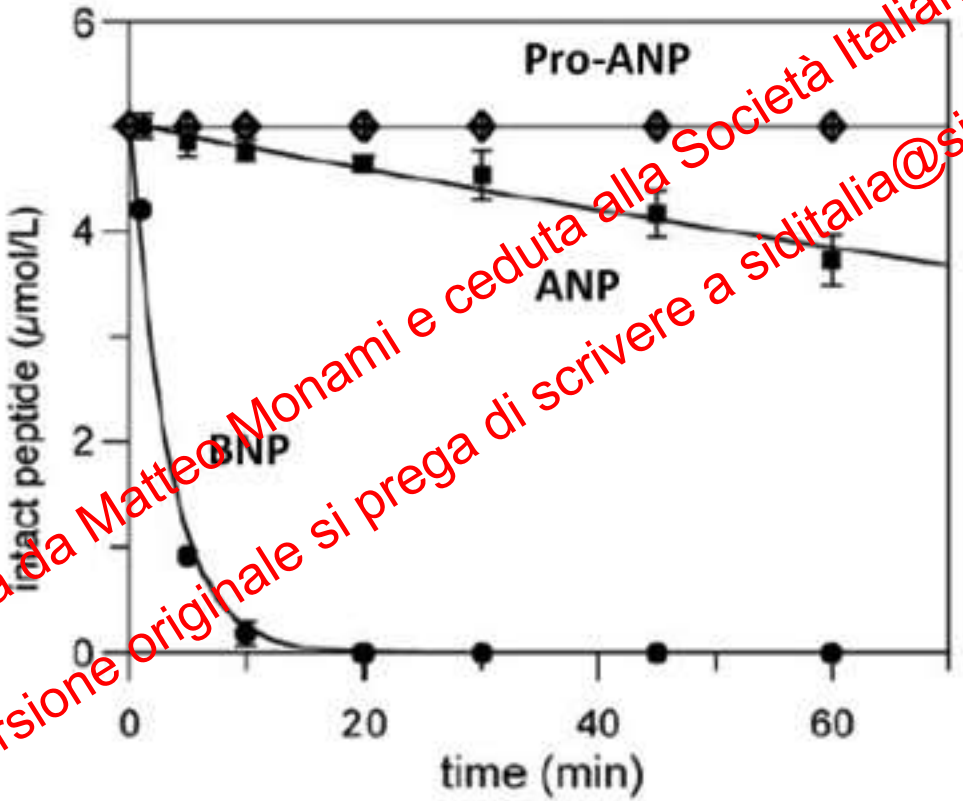
Recovery after ischemia-reperfusion in rats



These favorable effects seem to be mediated by GLP1 9-36 probably through other pathways different from the traditional GLP1R

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

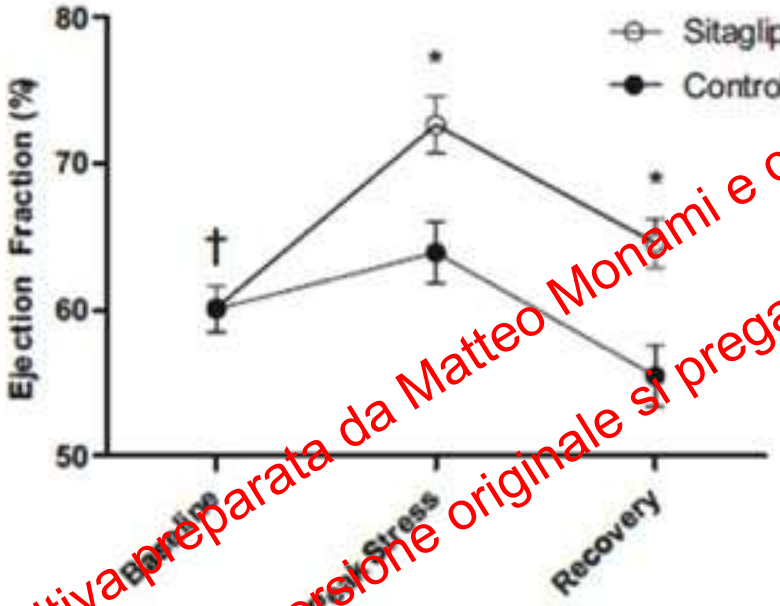
BNP as a substrate of DPP4



Brandt I et al. *Clin Chem* 2006, 52:82-87.

Sitagliptin and cardiac function

Results of a pilot study



N=14 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.

Sitagliptin Use in Patients With Diabetes and Heart Failure

7,620 patients with diabetes and incident HF

12% exposed to sitagliptin, 50% to metformin, 38% to SUs after incident HF

Primary endp.: all-cause hospital admission or death using a nested case-control analysis

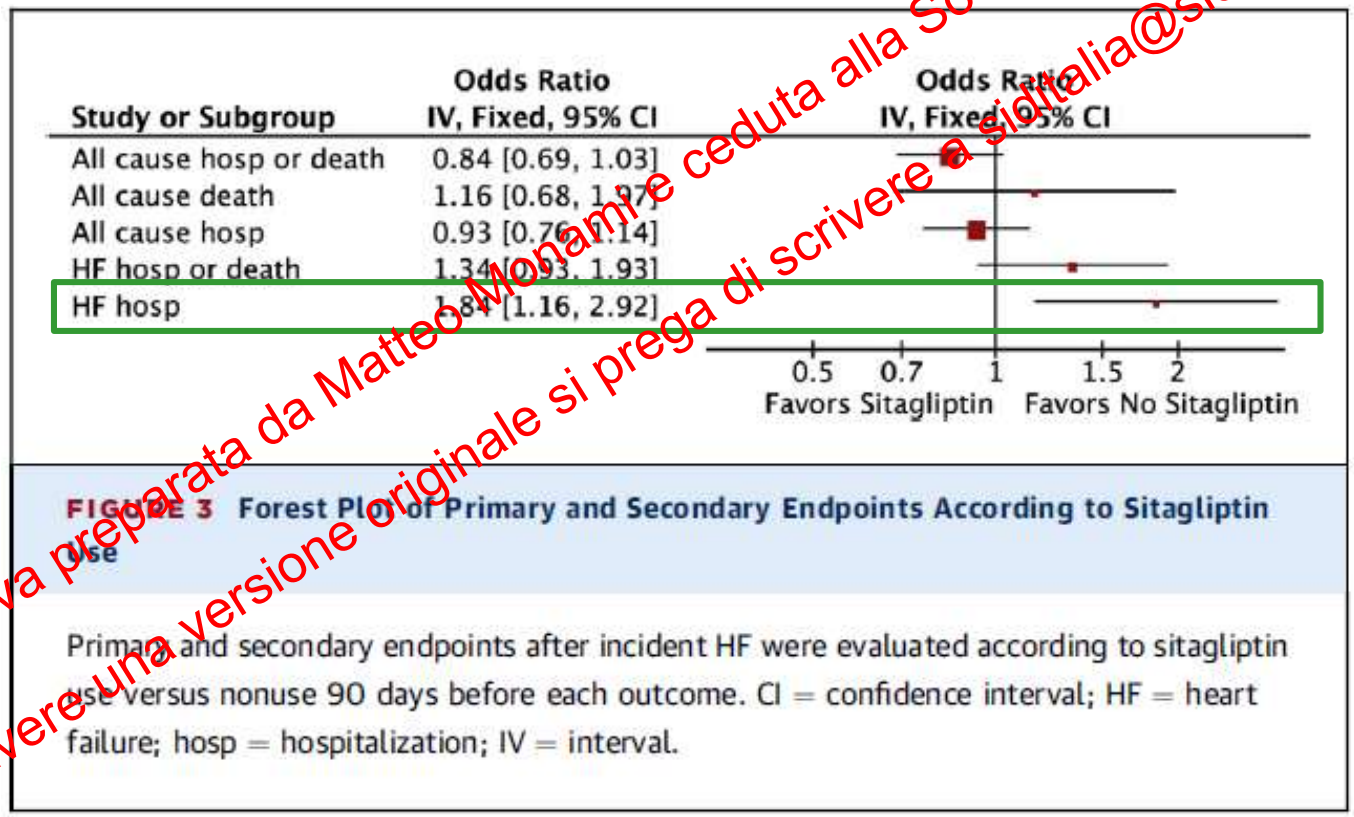


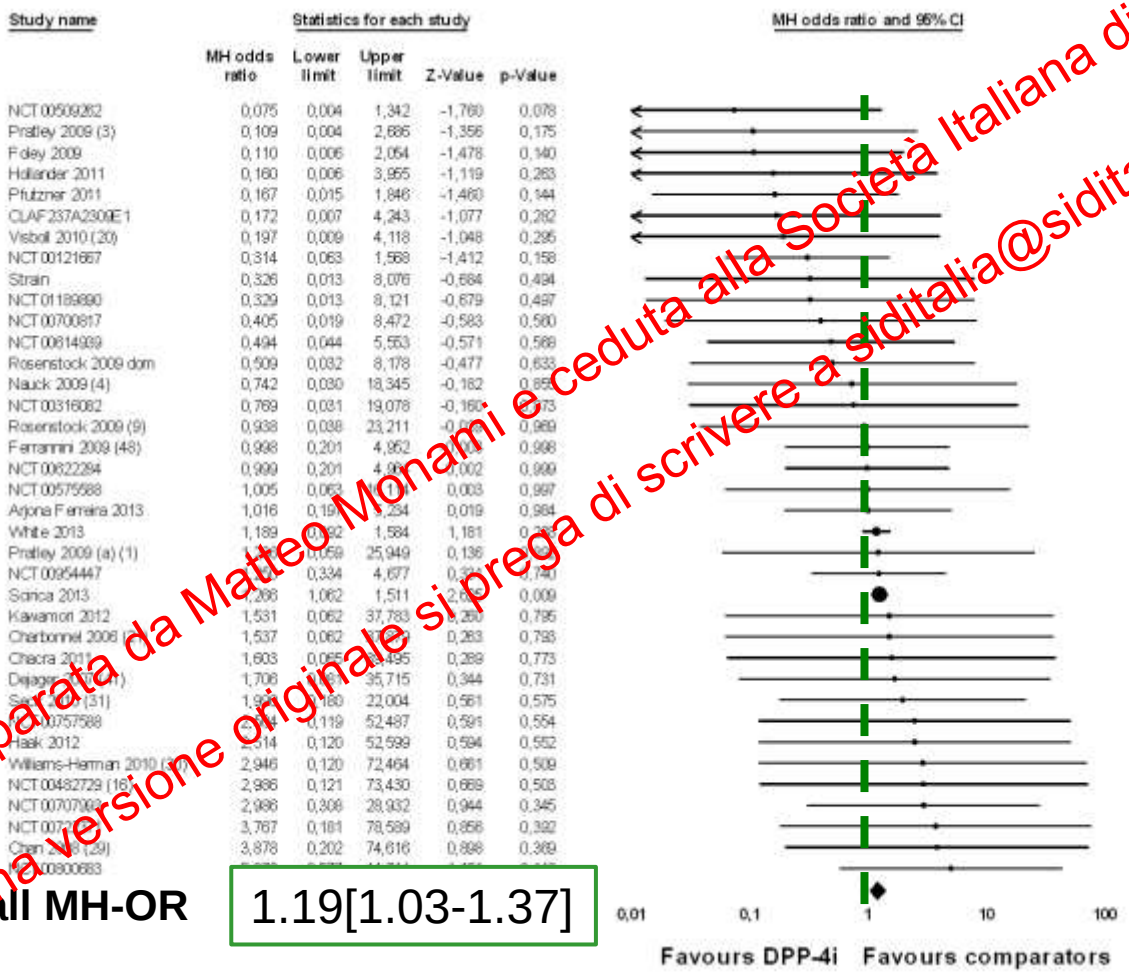
FIGURE 3 Forest Plot of Primary and Secondary Endpoints According to Sitagliptin Use

Primary and secondary endpoints after incident HF were evaluated according to sitagliptin use versus nonuse 90 days before each outcome. CI = confidence interval; HF = heart failure; hosp = hospitalization; IV = interval.

Weir D et al., *JACC Heart Failure*, 2014 Epub ahead of print

DPP4i and CHF

Meta-analysis of early RCTs



Overall MH-OR 1.19[1.03-1.37]

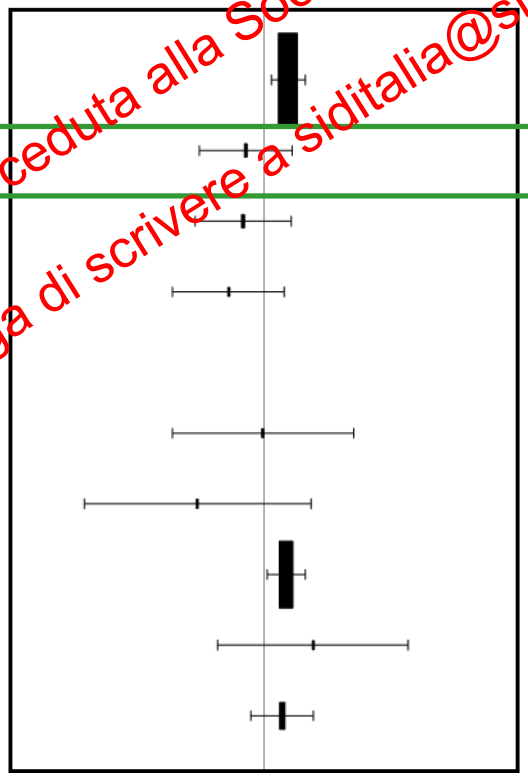
Monami M, Dicembrini I, Mannucci E. *Nutr Metab Cardiovasc Dis* 2014; 24:689-97

DPP4i and CHF

Meta-analysis of early RCTs

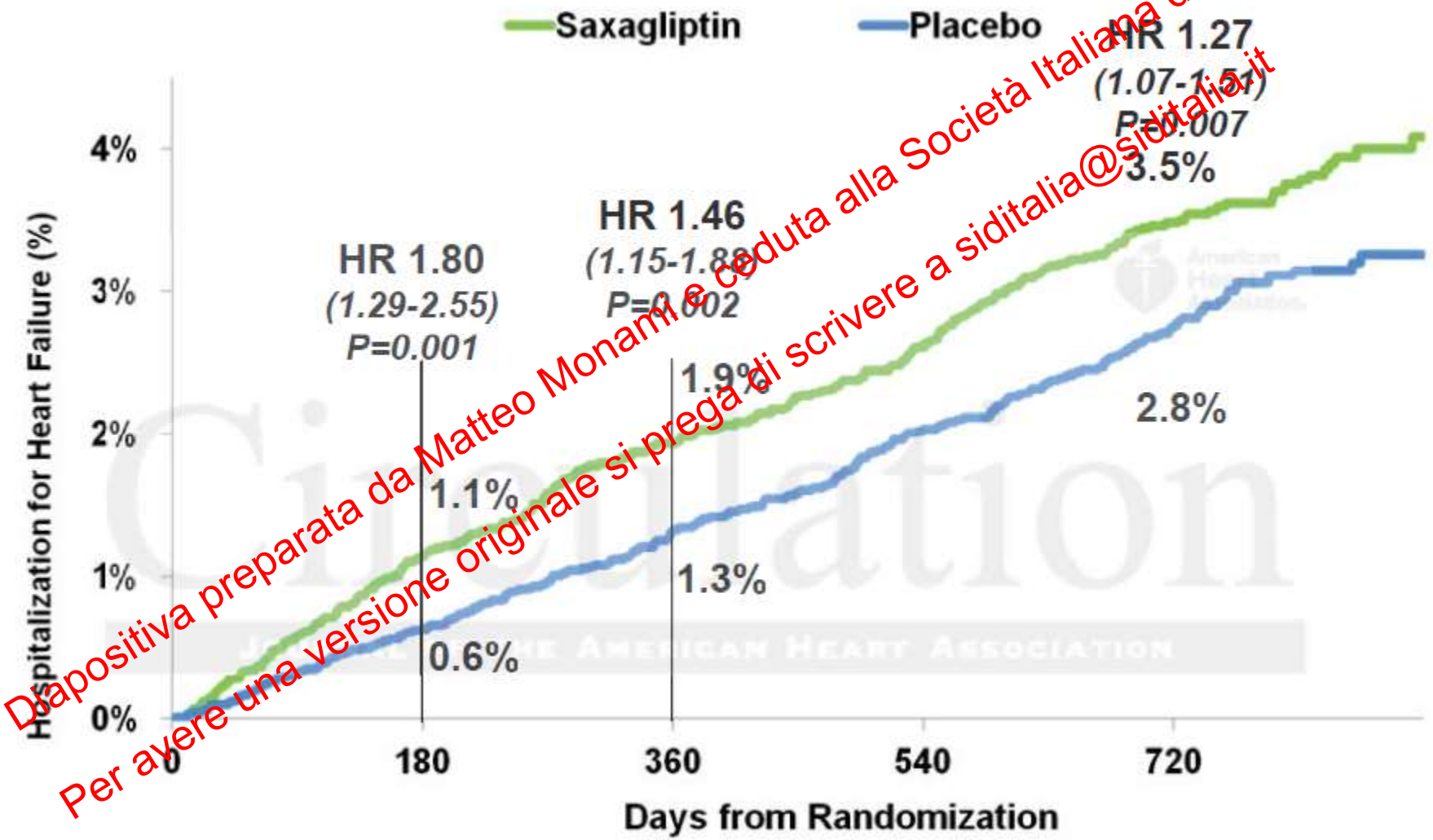
Heart failure
(n events)

	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	11	14	15	0.99	0.44	2.24	0.980
Vildagliptin	6	6	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



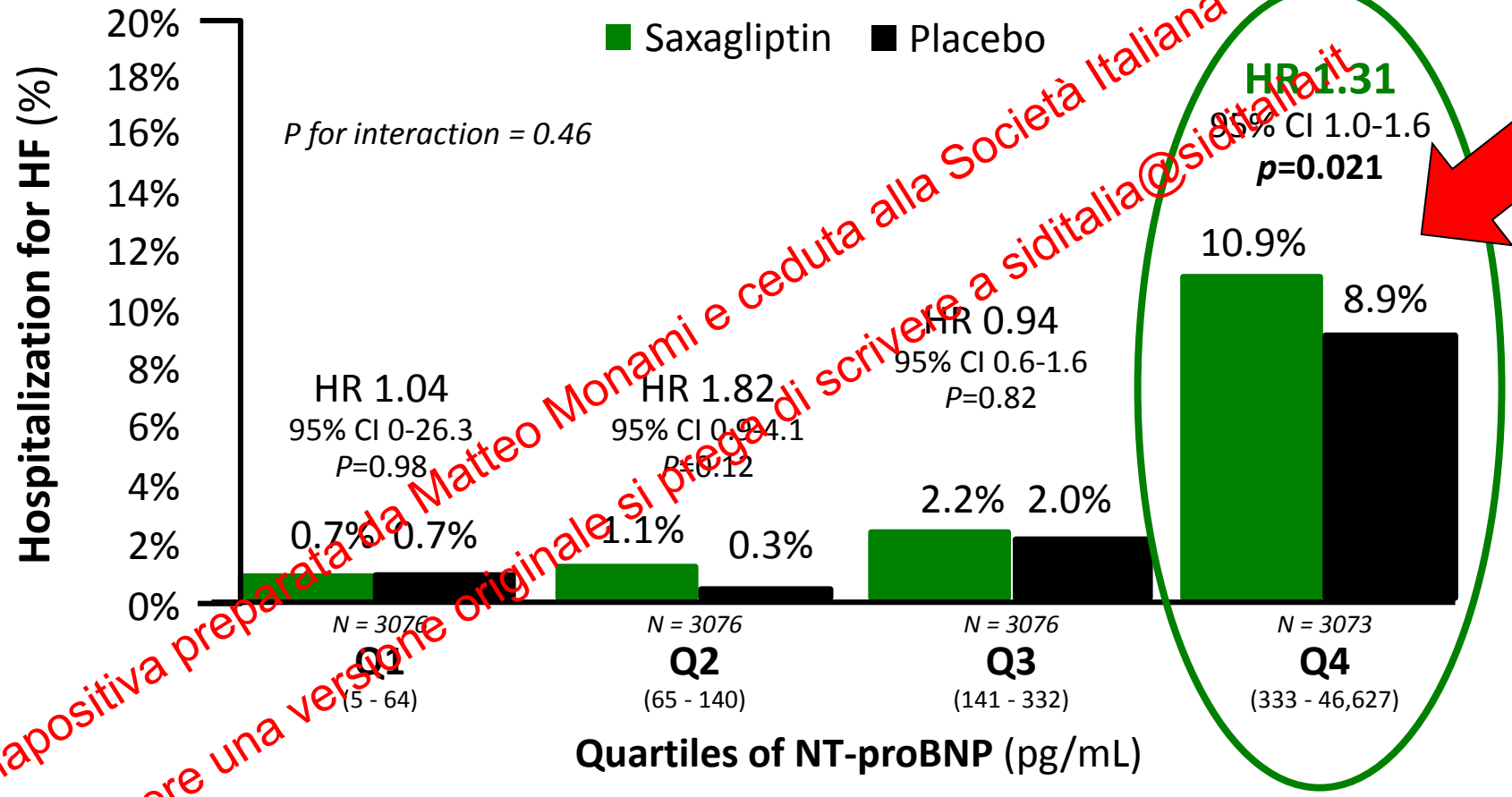
Monami M, Dicembrini I, Mannucci E. *Nutr Metab Cardiovasc Dis* 2014; 24:689-97

Heart failure and saxagliptin: the SAVOR trial



Scirica B et al., *Circulation* 2014, Epub-ahead of print

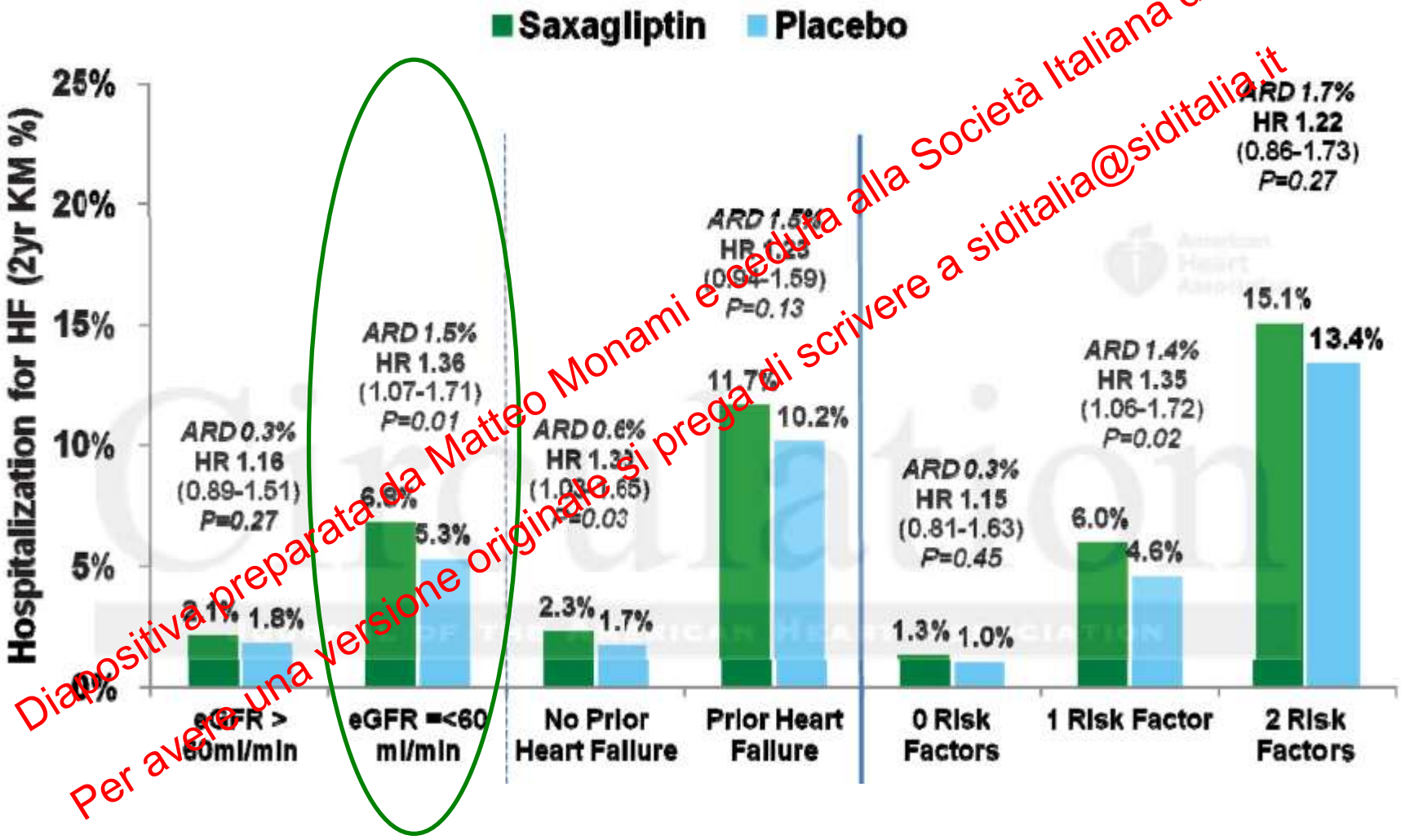
Heart failure and saxagliptin: the SAVOR trial



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

Scirica B et al., *Circulation* 2014, Epub-ahead of print

Heart failure and saxagliptin: the SAVOR trial



Scirica B et al., *Circulation* 2014, Epub-ahead of print

Microalbuminuria and saxagliptin: the SAVOR trial

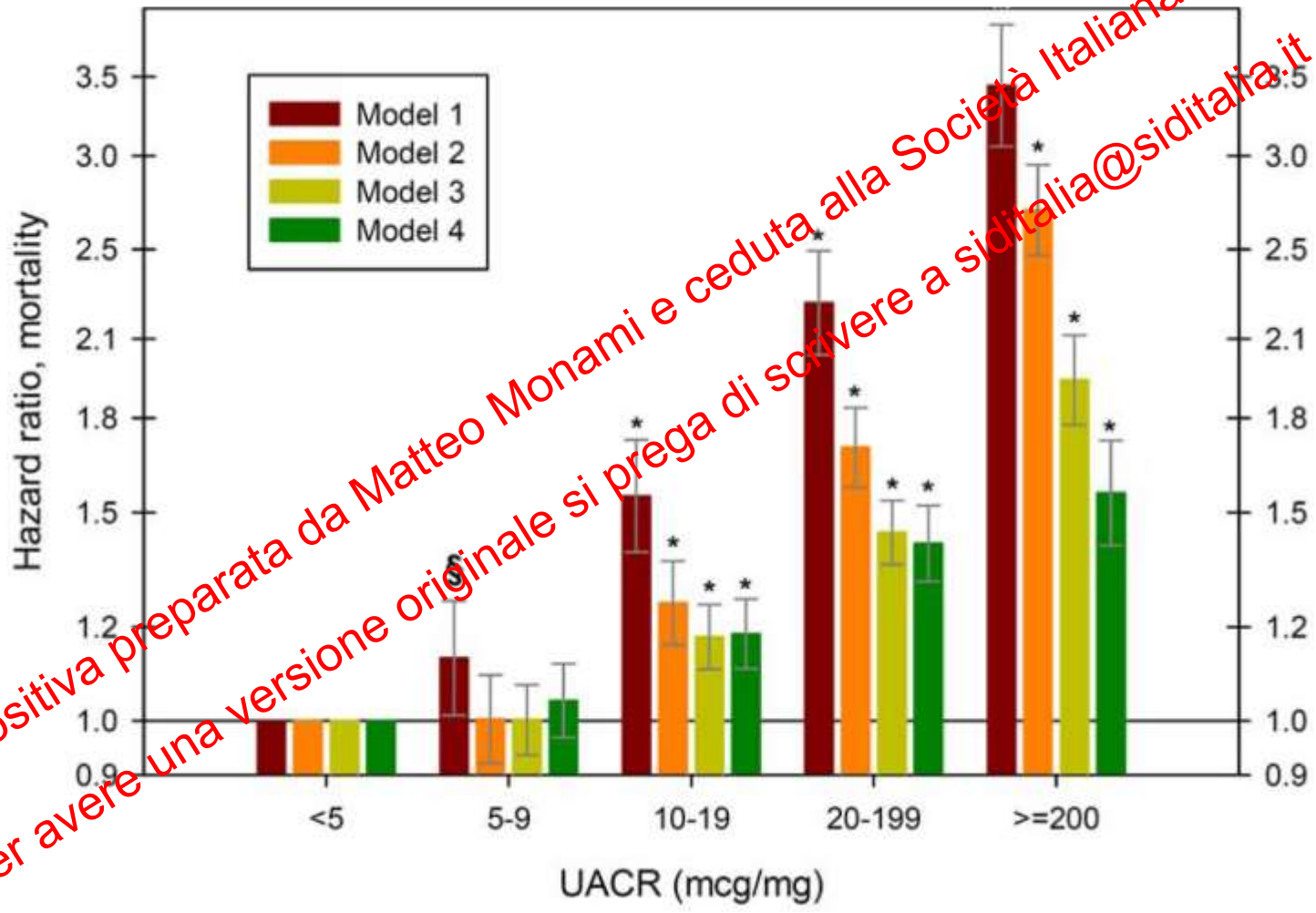
Treatment difference in the number and proportions of patients with worsening, no change, or improvement in albumin/creatinine ratio, pre-specified as a shift from baseline category (<3.4, >=3.4 - <=33.9, or >33.9 mg/mmol) at 1 year, 2 year, and end of treatment.

	Worsened N (%)	No change N (%)	Improved N (%)	P-value
1 year (n=13,184)				
Saxagliptin	628 (9.4%)	5244 (78.8)	782 (11.8)	<0.001
Placebo	747 (11.4)	5155 (78.9)	628 (9.6)	
2 year (n=6553)				
Saxagliptin	414 (12.4)	2550 (76.4)	372 (11.1)	0.0058
Placebo	457 (14.2)	2465 (76.6)	295 (9.2)	
End of Treatment (n=12,360)				
Saxagliptin	833 (13.3)	4762(76.0)	670 (10.7)	<0.001
Placebo	969 (15.9)	4594 (75.4)	532 (8.7)	

Scirica BM et al., *N Engl J Med* 2013; 369:1317-1326

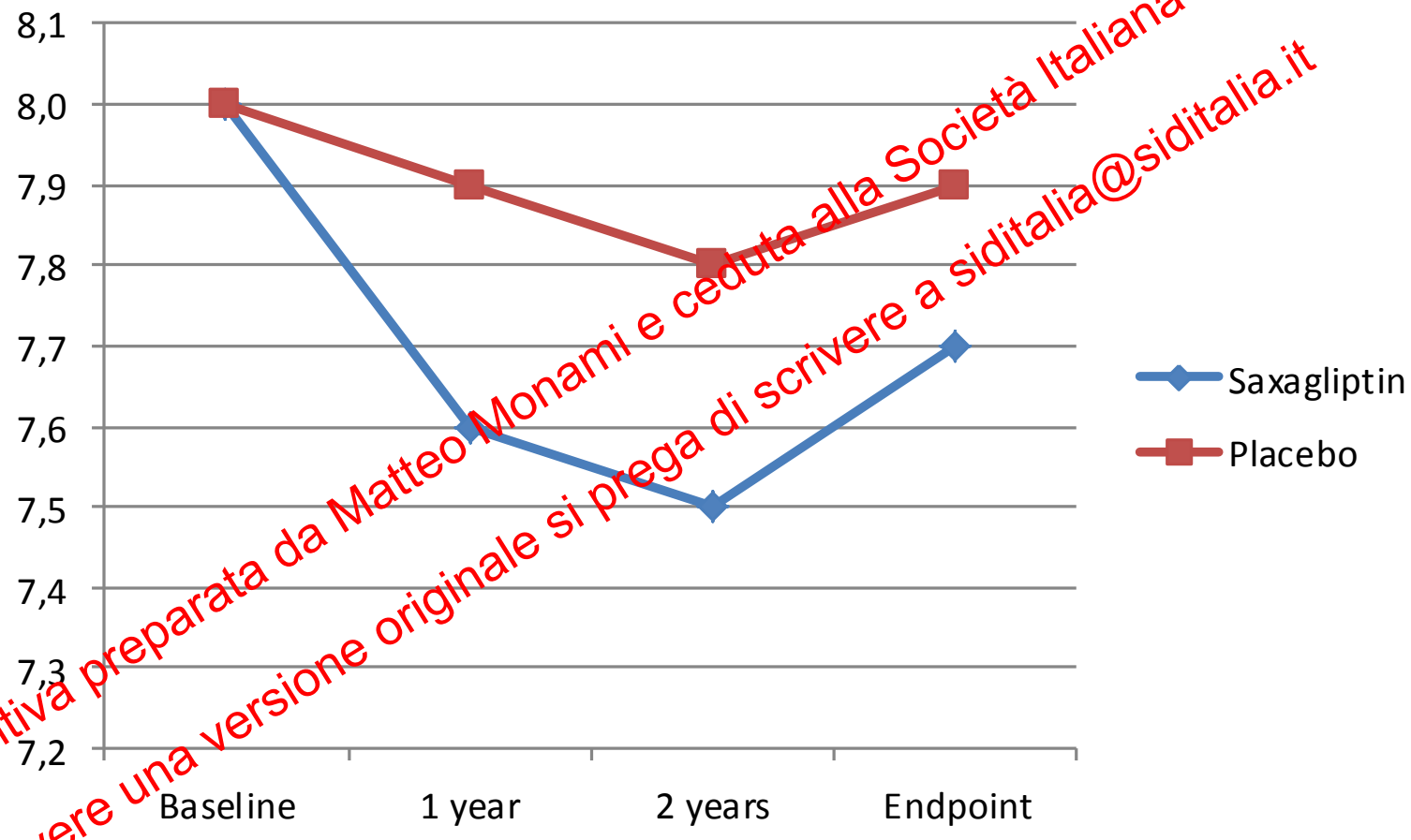
Urine microalbumin-creatinine ratio (UACR) and cardiovascular mortality in the general population

Nationally representative cohort of 298,875 US veterans



Kovesdy CB et al., *JACC* 2014, Epub-ahead of print

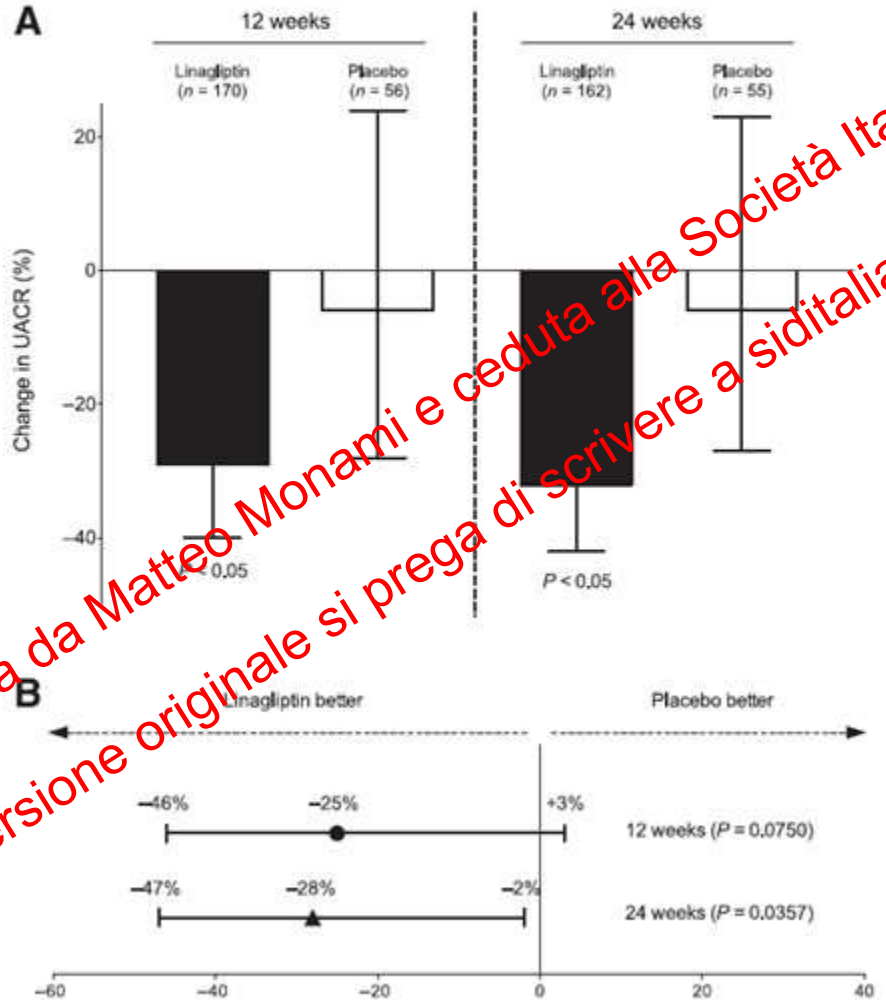
HbA1c and saxagliptin: the SAVOR trial



Adapted from: Scirica BM et al., *N Engl J Med* 2013; 369:1317-1326

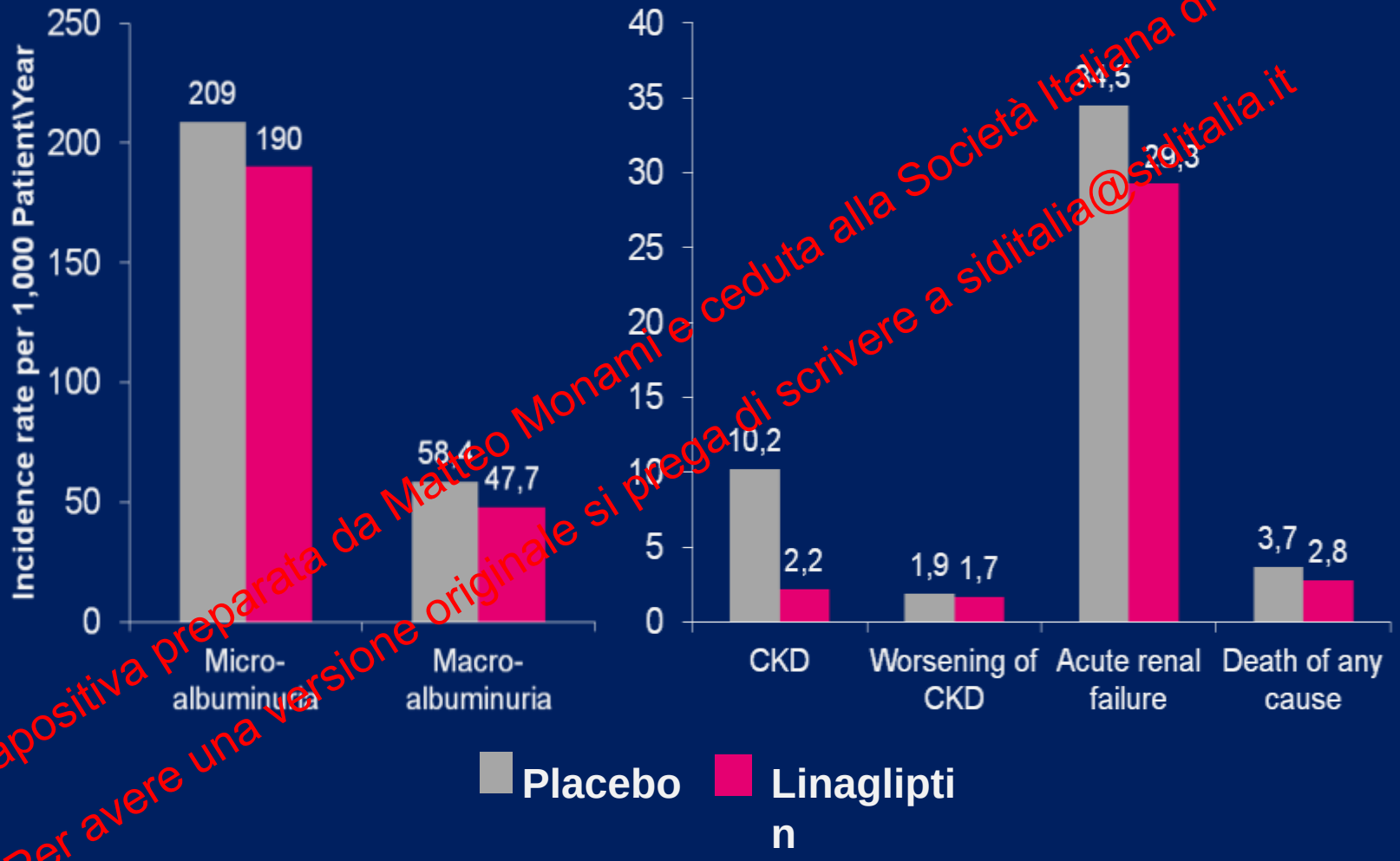
Linagliptin and albuminuria

Pooled analysis of RCTs vs placebo



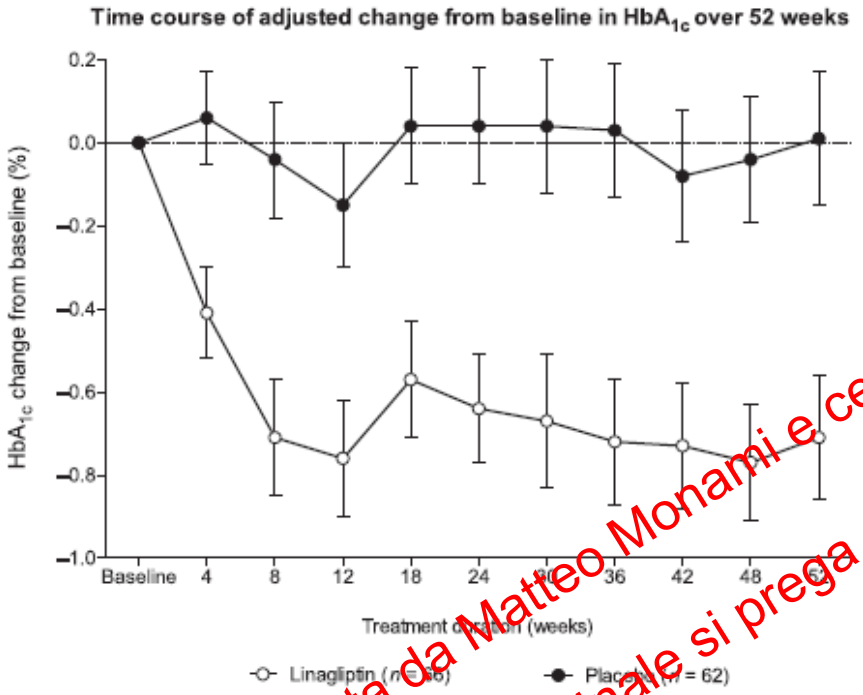
Groop PH et al. *Diabetes Care* 2013; 36:3460-8.

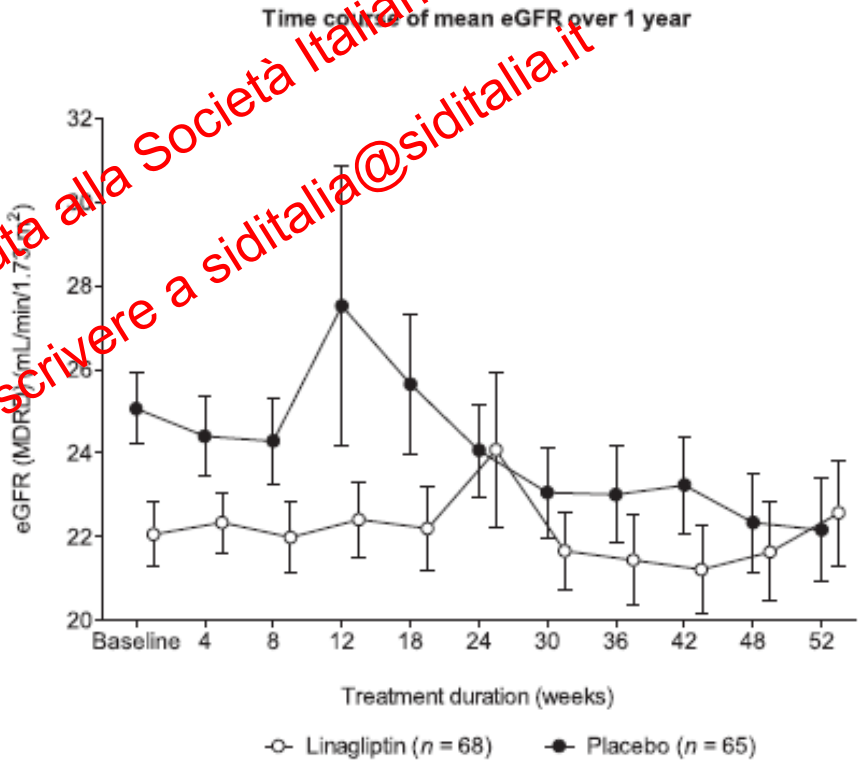
Meta-analysis suggests linagliptin is associated with fewer renal events than placebo



von Eynatten M, et. ASN 2012, Poster TH-PO530.

Renal insufficiency and linagliptin: Efficacy and safety





CONCLUSIONS —In patients with type 2 diabetes and severe RI, linagliptin provided clinically meaningful improvements in glycemic control with very low risk of severe hypoglycemia, stable body weight, and no cases of drug-related renal failure. The potential for linagliptin to spare insulin and provide long-term renal safety warrants further investigations.

McGill JB et al., *Diabetes Care* 2013; 36:237-244

CARMELINA

A CV and renal outcome study with linagliptin

will evaluate CV and renal safety of linagliptin in patients with T2DM at high CV and renal risk

Inclusion criteria:

1. T2DM with HbA_{1c} ≥ 6.5% and ≤ 10.0%
2. Drug naïve patients or pre-treated with stable background antidiabetic medication, excluding GLP-1, DPP4is, SGLT-2is
3. High risk of CV events

Linagliptin 5 mg versus Placebo

N = 8,300; approx. 4-year follow-up

Primary CV endpoint: Time to first occurrence of primary composite endpoint:

1. CV death (including fatal stroke and fatal MI)
2. Nonfatal MI
3. Nonfatal stroke
4. Hospitalization for unstable angina pectoris

Renal endpoint: Time to first occurrence of the composite endpoint:

1. Renal death
2. Sustained ESRD
3. Sustained decrease of ≥ 50% eGFR

Source: http://clinicaltrials.gov/ct2/show/NCT01897532.

MARLINA
A glycemic and renal effect study with linagliptin

will evaluate change from baseline in HbA_{1c} (primary) and in albuminuria with linagliptin in patients with T2DM with renal disease

Inclusion if all of the following are fulfilled:

1. Current therapy with ACEi or ARB at stable dose for ≥ 8 weeks
2. UACR 30–3,000 mg/g documented in the previous 12 months
3. eGFR > 30 mL/min

Linagliptin 5 mg versus Placebo

N = 404; treatment period 24 weeks

Outcome measures

1. Change from baseline in HbA_{1c} at Week 24
2. Time weighted average of percentage change from baseline in UACR at Week 24

ClinicalTrials.gov
NCT01792518.

Rationale and Design of the CAROLINA Trial: An Active Comparator CARdiOvascular Outcome Study of the DPP-4 Inhibitor LINAgliptin in Patients With Type 2 Diabetes at High Cardiovascular Risk

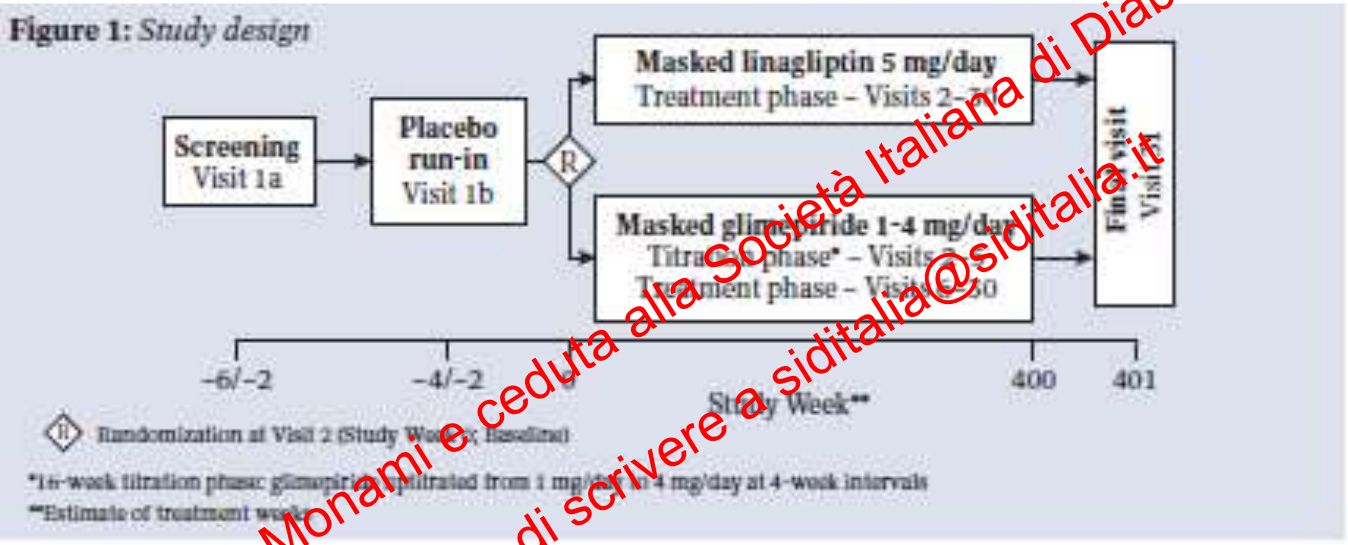
Julio Rosenstock[1], Nikolaus Marx[2], Steven E. Kahn[3], Bernard Zinman[4], John J. Kastelein[5], John Lachin[6], Erich Bluhmki[7], Arno Schlosser[8], Dietmar Neubacher[7], Sanjay Patel[9], Odd Erik Johansen[10], Hans-Juergen Woerle[11]

[1]Dallas Diabetes and Endocrine Center at Medical City, Dallas, TX, USA; [2]Department of Internal Medicine, University Hospital Aachen, Aachen, Germany; [3]Department of Medicine, University of Washington, Seattle, WA, USA; [4]Mount Sinai Hospital, University of Toronto, Toronto, Canada; [5]Department of Vascular Medicine, University of Amsterdam, Amsterdam, The Netherlands; [6]Biostatistics Center, George Washington University, Rockville, MD, USA; [7]Boehringer Ingelheim, Biberach, Germany; [8]Boehringer Ingelheim, Alkmaar, The Netherlands; [9]Boehringer Ingelheim, Bracknell, UK; [10]Boehringer Ingelheim, Asker, Norway; [11]Boehringer Ingelheim, Ingelheim, Germany

CAROLINA

NCT01243424

Figure 1: *Study design*



STUDY OBJECTIVES

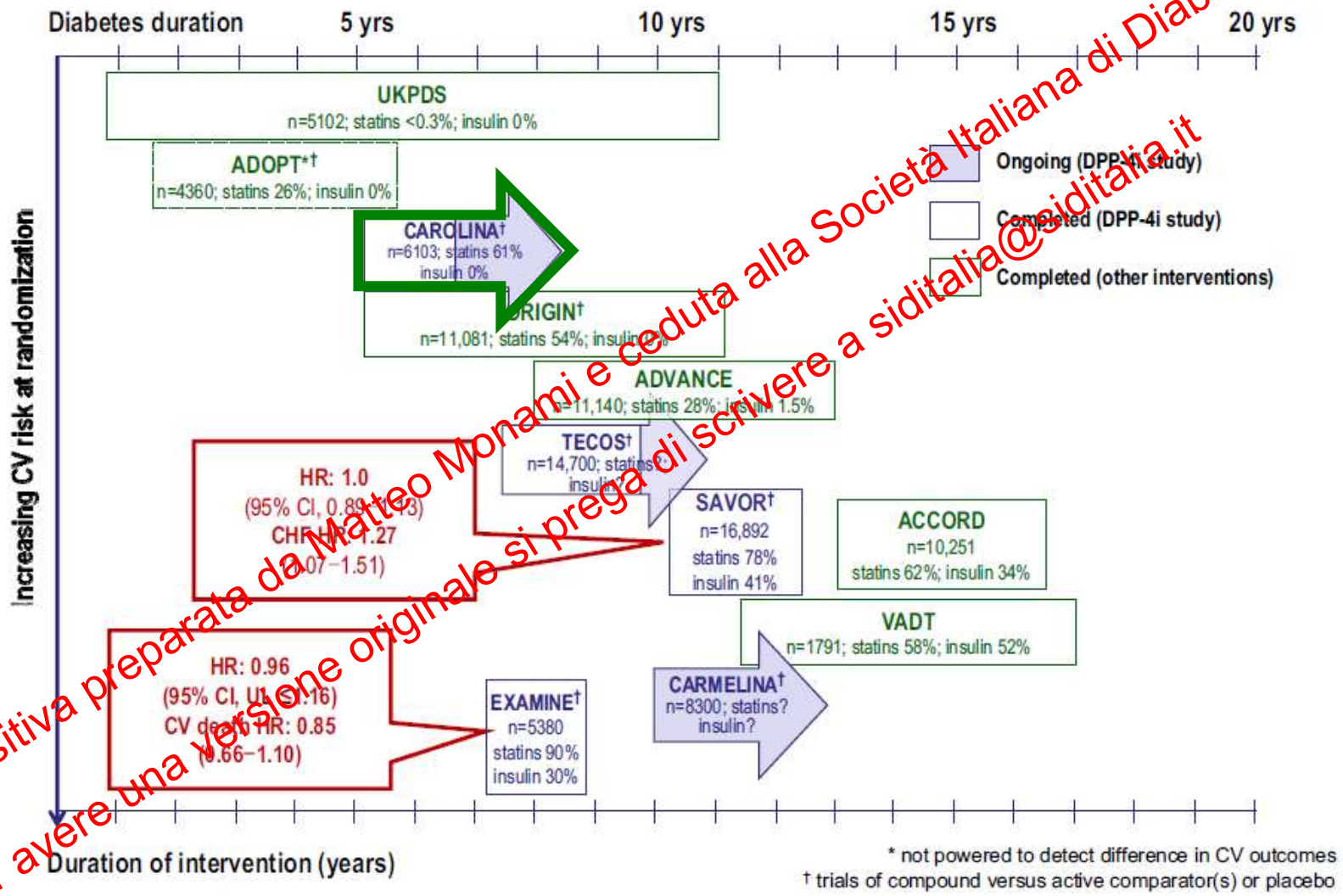
Primary Outcomes

- The time to the first occurrence of any of the following components of the MACE composite outcome:
  - CV death
  - Non-fatal myocardial infarction (MI)
  - Non-fatal stroke
  - Hospitalization for unstable angina pectoris

Patient Recruitment and Eligibility

- Approximately 700 trial centers in 45 countries will participate to ensure that at least 6000 patients are randomized
- Patients with T2DM without optimal glycemic control and at high risk of CV events will be enrolled

Recent CVOTs in context of diabetes duration, CV risk and duration of intervention



Johansen et al, OP - 49th *EASD*, Barcelona 2013