



Studi sperimentali ed evidenze osservazionali nei DPP4i

*(Experimental and observational evidence with
DPP4-inhibitors)*

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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



Disclosures



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

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DPP-4 inhibitors and efficacy

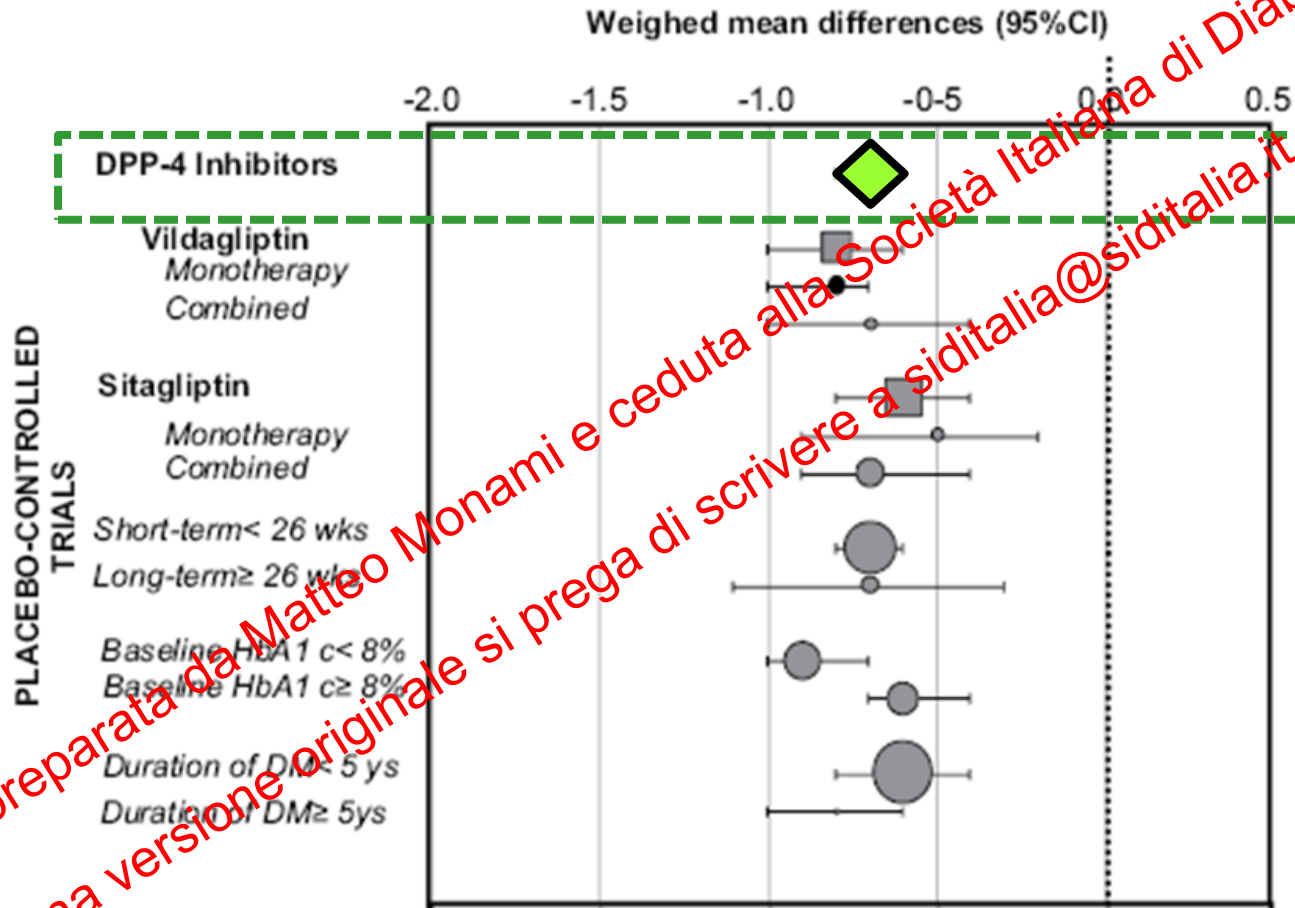


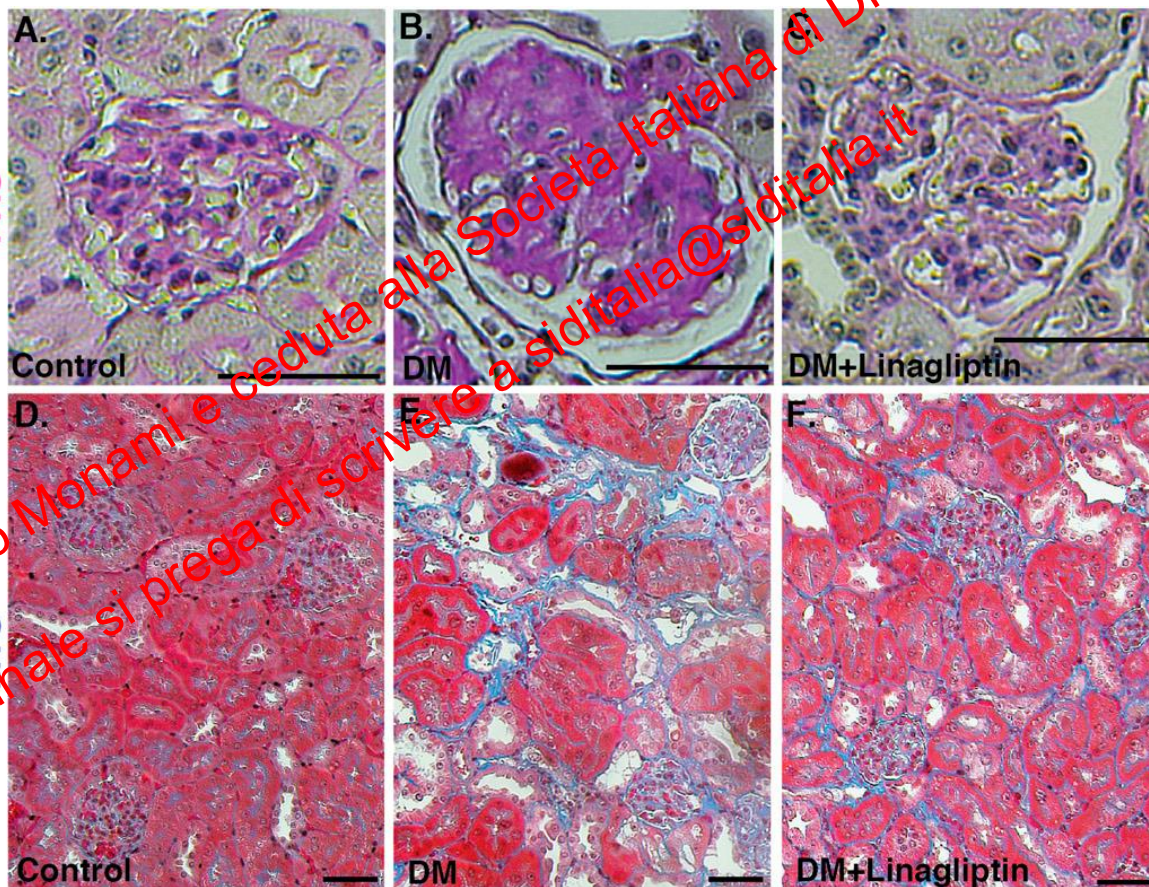
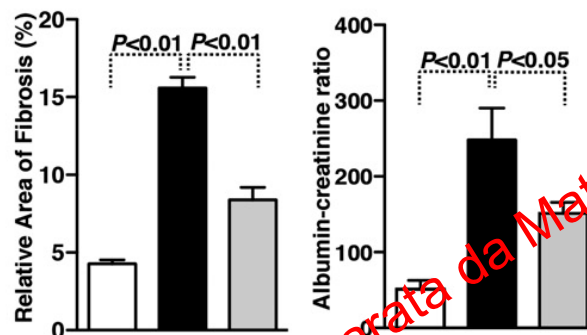
Figure 2 Standardized differences (with 95% CI) of mean HbA1c at endpoint.

Monami M, Iacomelli I, Marchionni N, Mannucci E.
Nutr Metab Cardiovasc Dis. 2010; 20:224-35

DPP-4 Inhibitors and fibrotic diabetic kidney disease model

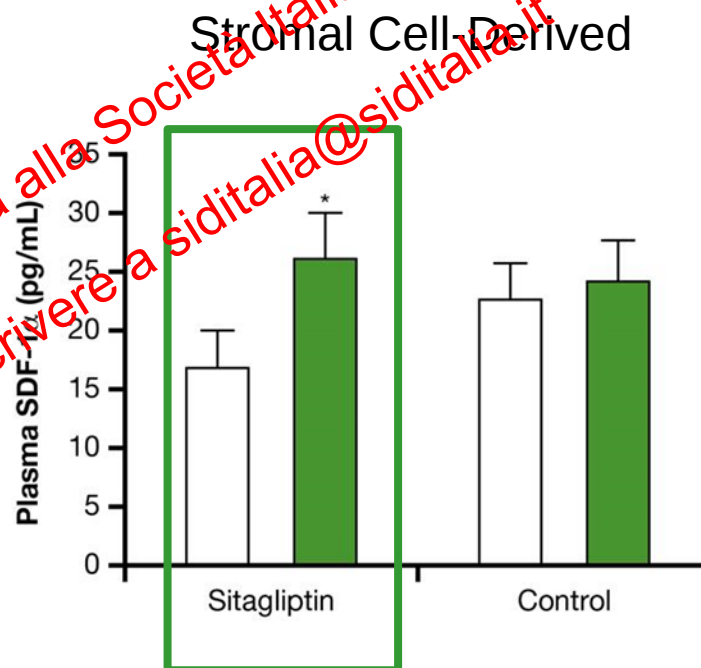
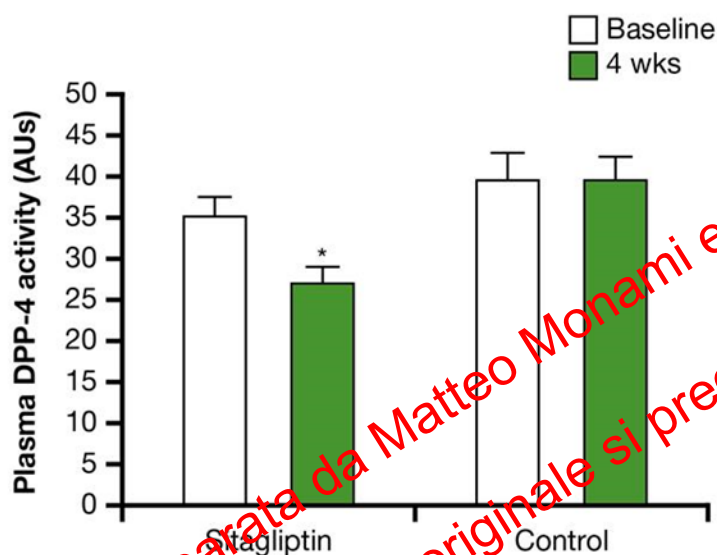
DPP-4i reduces:

- *TGF- β 2-induced endothelial-to-mesenchymal transition*



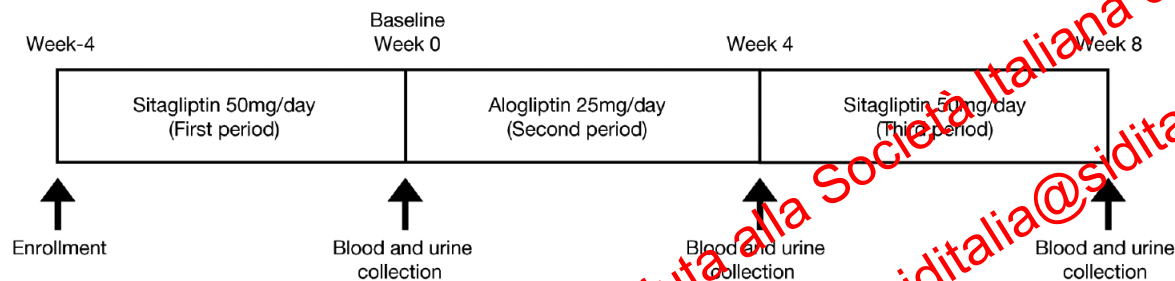
Eight-week-old male CD-1 mice injected intraperitoneally with streptozotocin

DPP-4 inhibitors and SDF-1 α



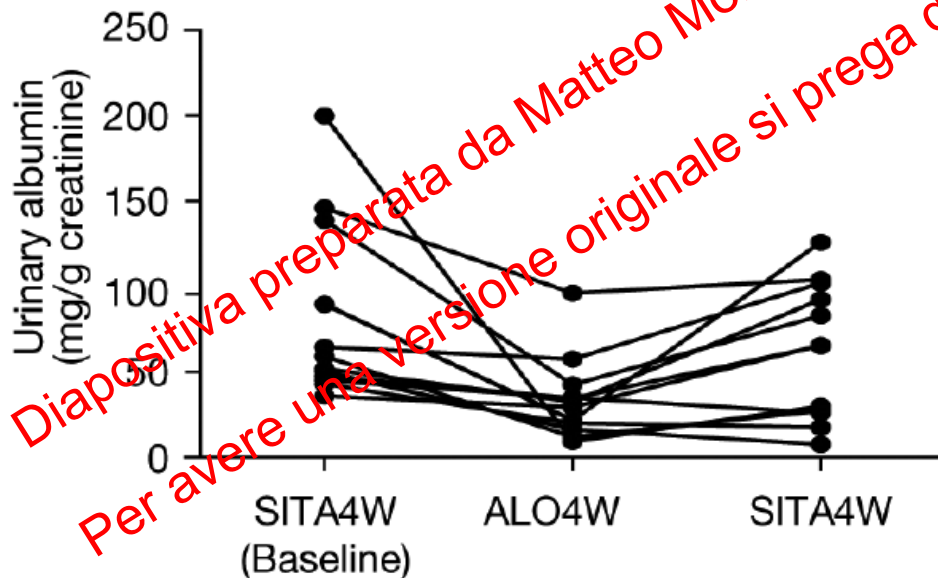
DPP-4 inhibitors and albuminuria

N= 12 T2DM



$p < 0.01$

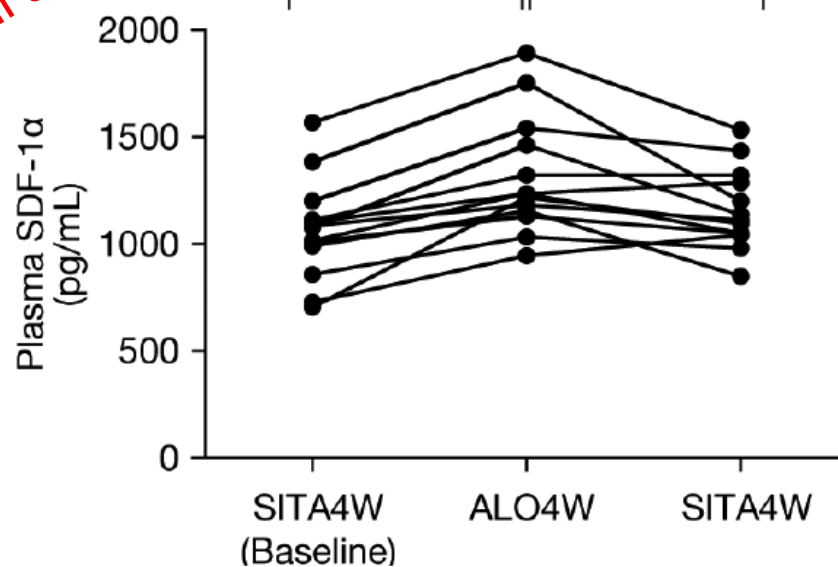
NS



up-regulation of SDF-1 α

$p < 0.001$

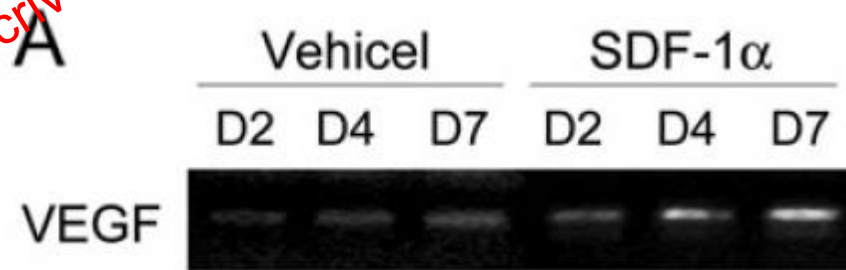
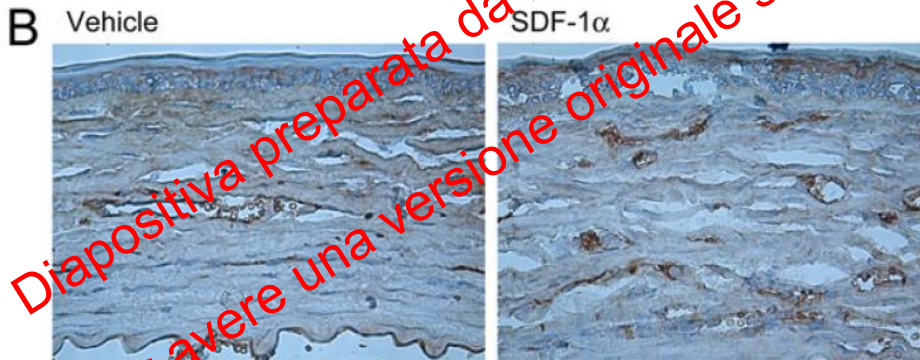
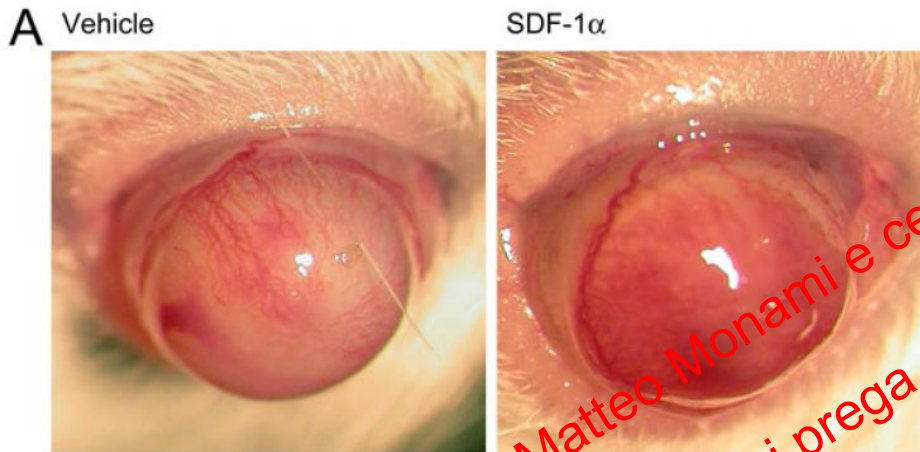
NS



SDF-1 α and VEGF: neovascularization

Experimental corneal neovascularization (CNV)

Enhancement in intraocular VEGF expression was greater in SDF-1 α -treated mice than in control mice after injury



Alkali-induced CNV in mice

DPP-4i and retinal capillary flow

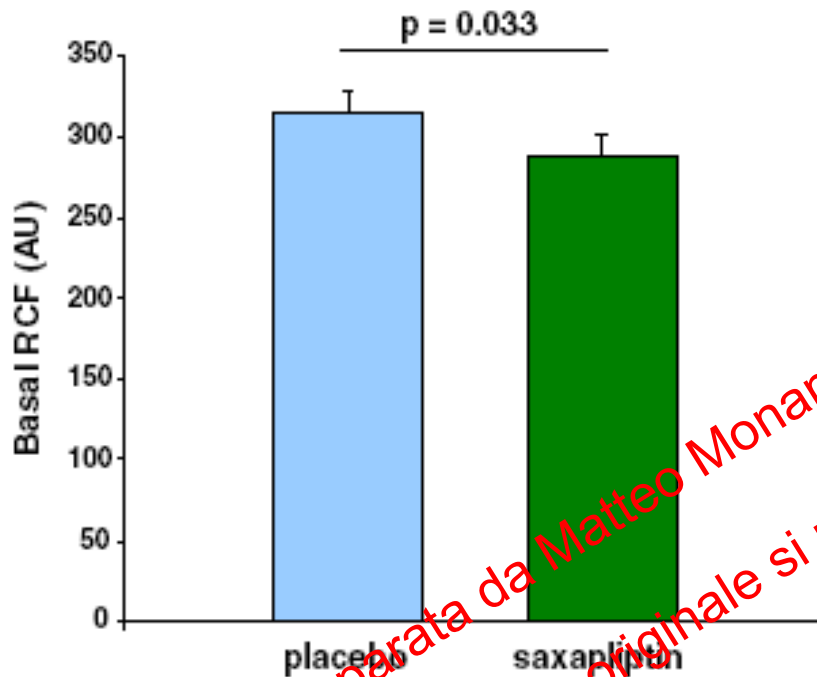


Table 1 Clinical Characteristics (n = 42)

	Placebo	saxagliptin	p-value
HbA1c (%)	7.10 ± 0.17	6.84 ± 0.15	< 0.001
Glucose postprandial (mmol/L)	10.1 ± 0.4	9.27 ± 0.4	0.001
Glucose fasting (mmol/L)	7.49 ± 0.3	7.21 ± 0.3	0.097

Double-blind, controlled, cross-over trial 50 patients (without signs of microvascular alterations) with T2DM were randomized to receive placebo or 5 mg saxagliptin for 6 weeks.

Figure 2 Retinal capillary flow (RCF) after 6 weeks of treatment with placebo and saxagliptin. Flicker light (vasodilatory capacity)

DPP-4i and retinal capillary flow

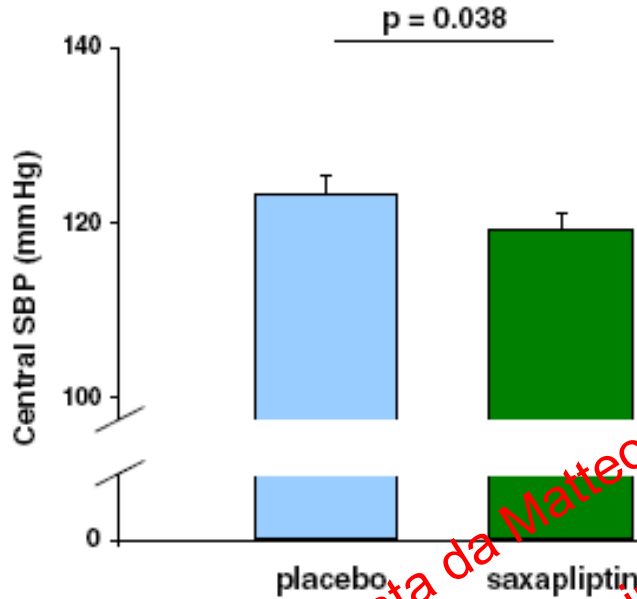


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Figure 3 Central hemodynamics after 6 weeks of treatment with placebo and saxagliptin. a: Central systolic BP.



DPP-4i and diabetic retinopathy



Eye disorders

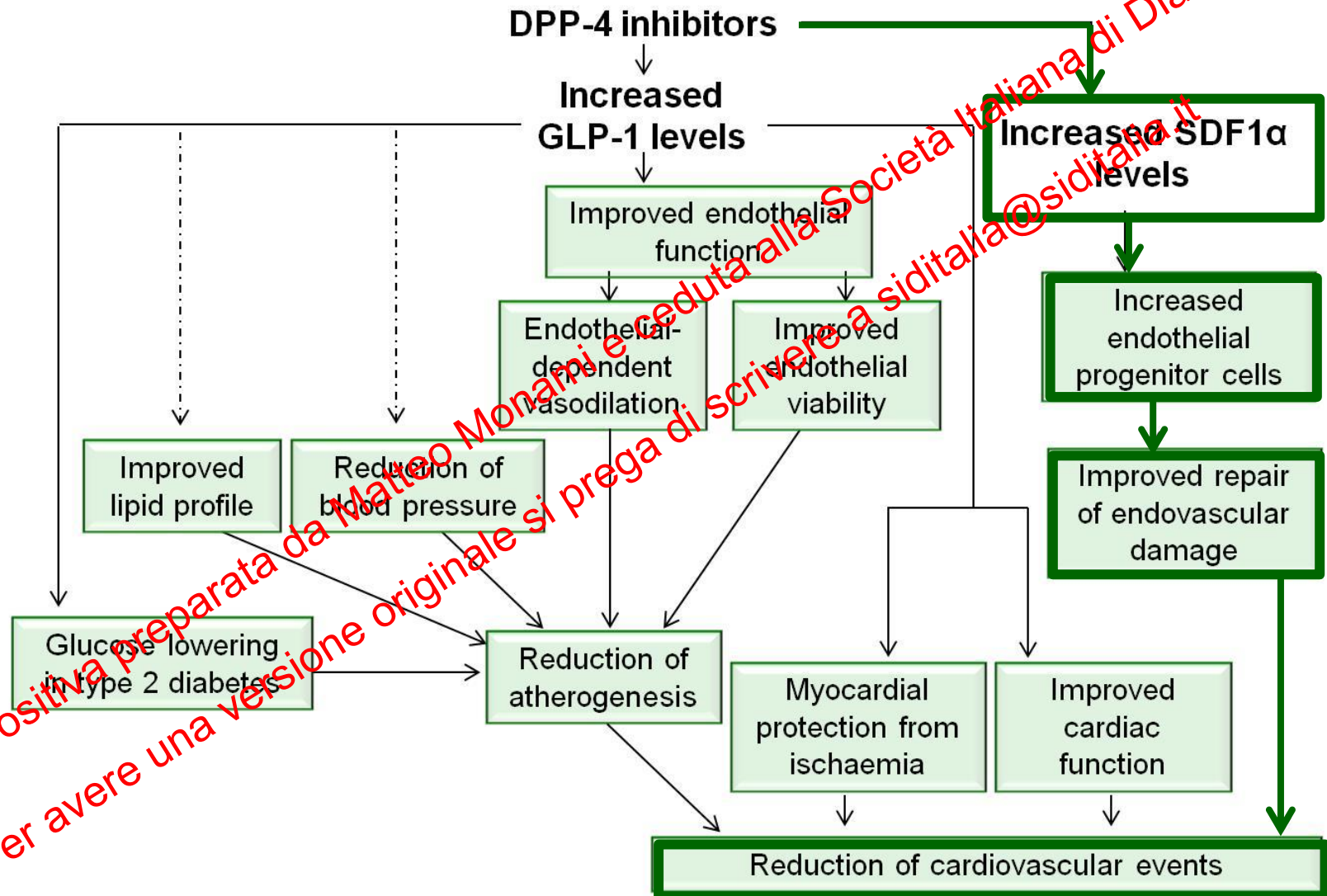
	Placebo	Alogliptin
Cataract		
# participants affected / at risk	6/2679 (0.22%)	5/2701 (0.19%)
Diabetic retinopathy † 1		
# participants affected / at risk	1/2679 (0.04%)	1/2701 (0.04%)
Vitreous haemorrhage † 1		
# participants affected / at risk	2/2679 (0.07%)	0/2701 (0.00%)
Amaurosis † 1		
# participants affected / at risk	1/2679 (0.04%)	0/2701 (0.00%)
Cataract subcapsular † 1		
# participants affected / at risk	0/2679 (0.00%)	1/2701 (0.04%)
Lacrystenosis acquired † 1		
# participants affected / at risk	0/2679 (0.00%)	1/2701 (0.04%)
Open angle glaucoma † 1		
# participants affected / at risk	0/2679 (0.00%)	1/2701 (0.04%)

EXAMINE TRIAL

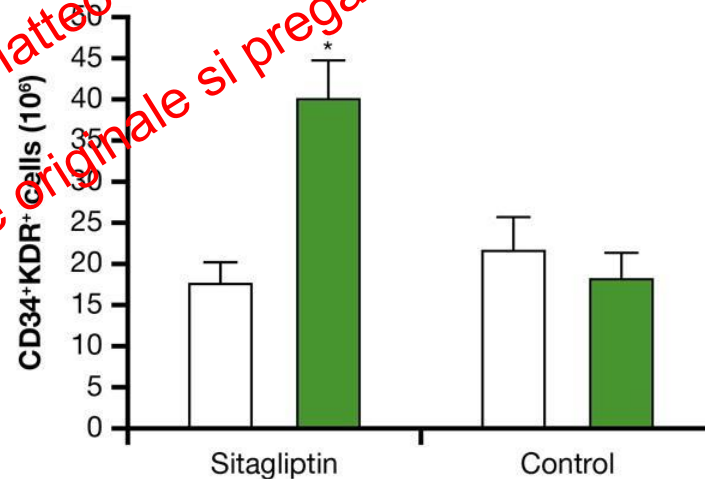
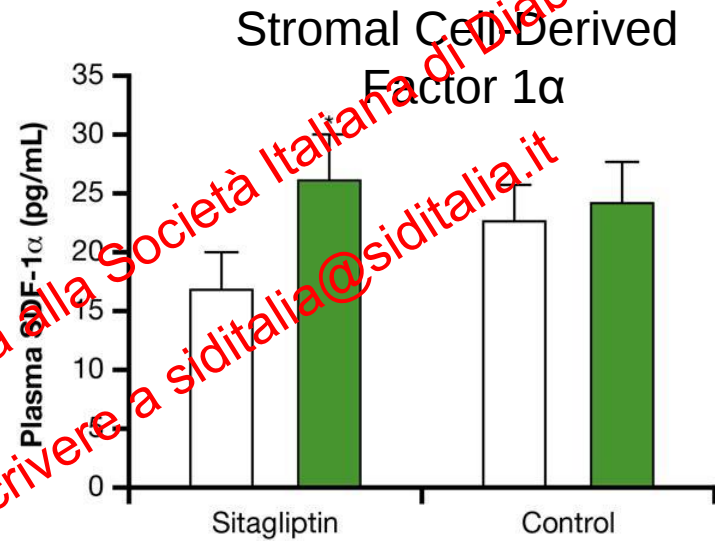
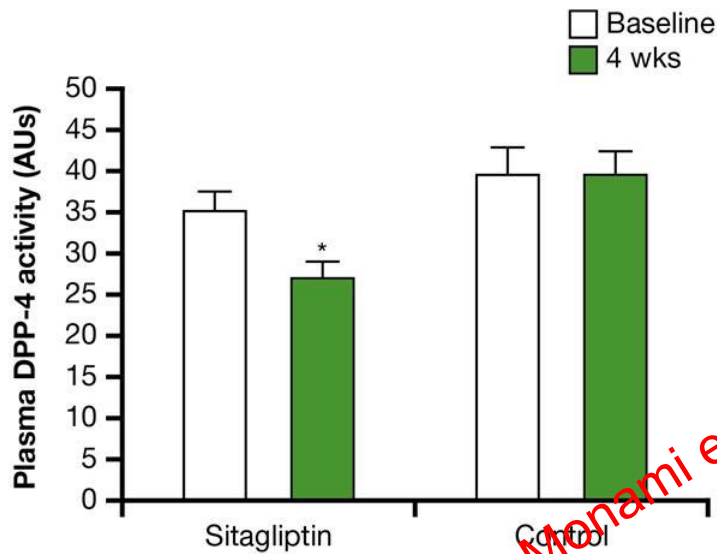
EXAMINE TRIAL

CV effects of DPP-4 inhibitors

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



DPP-4 inhibitors and SDF-1 α



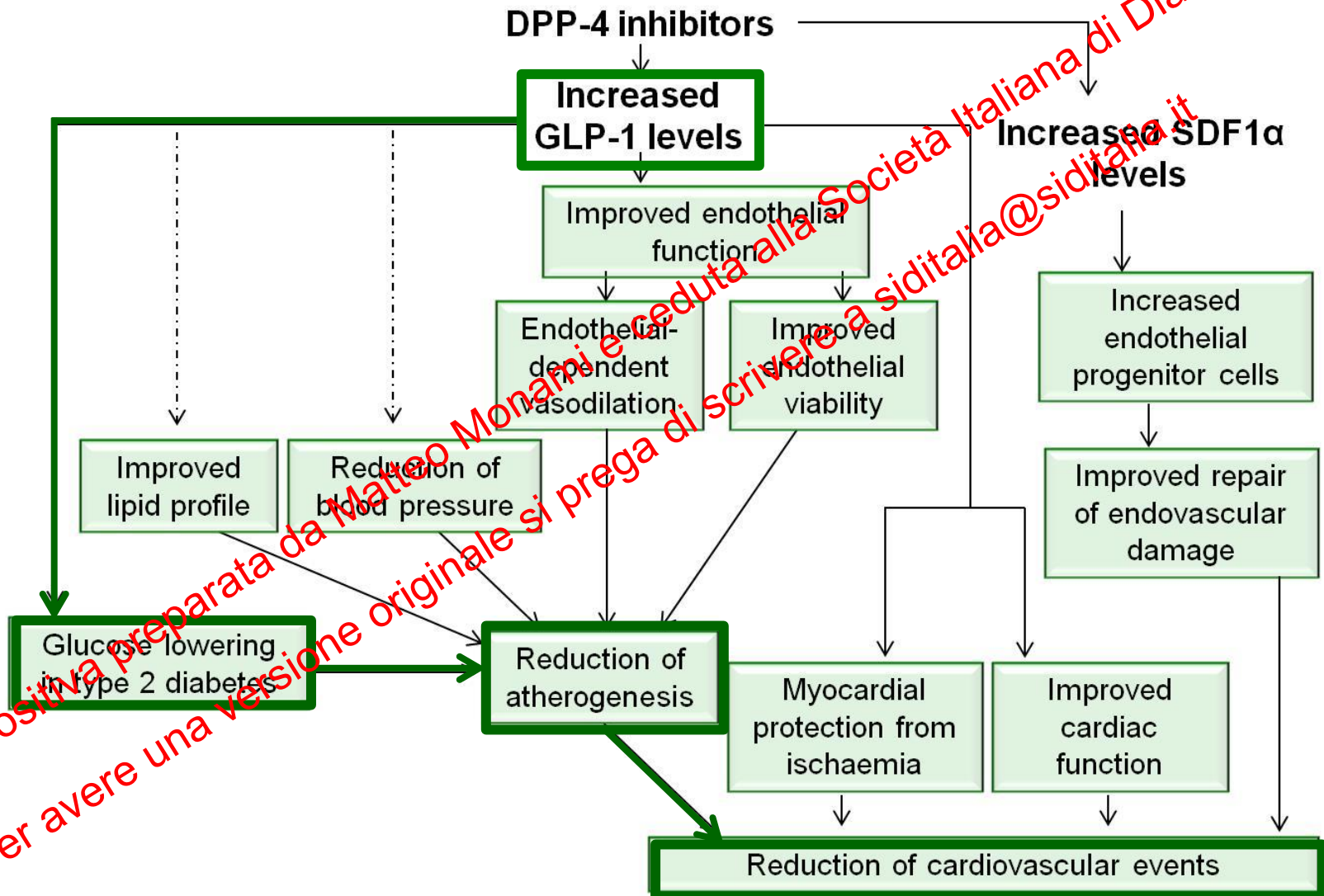
Precursors of
endothelial cells

Vascular endothelial
growth factors

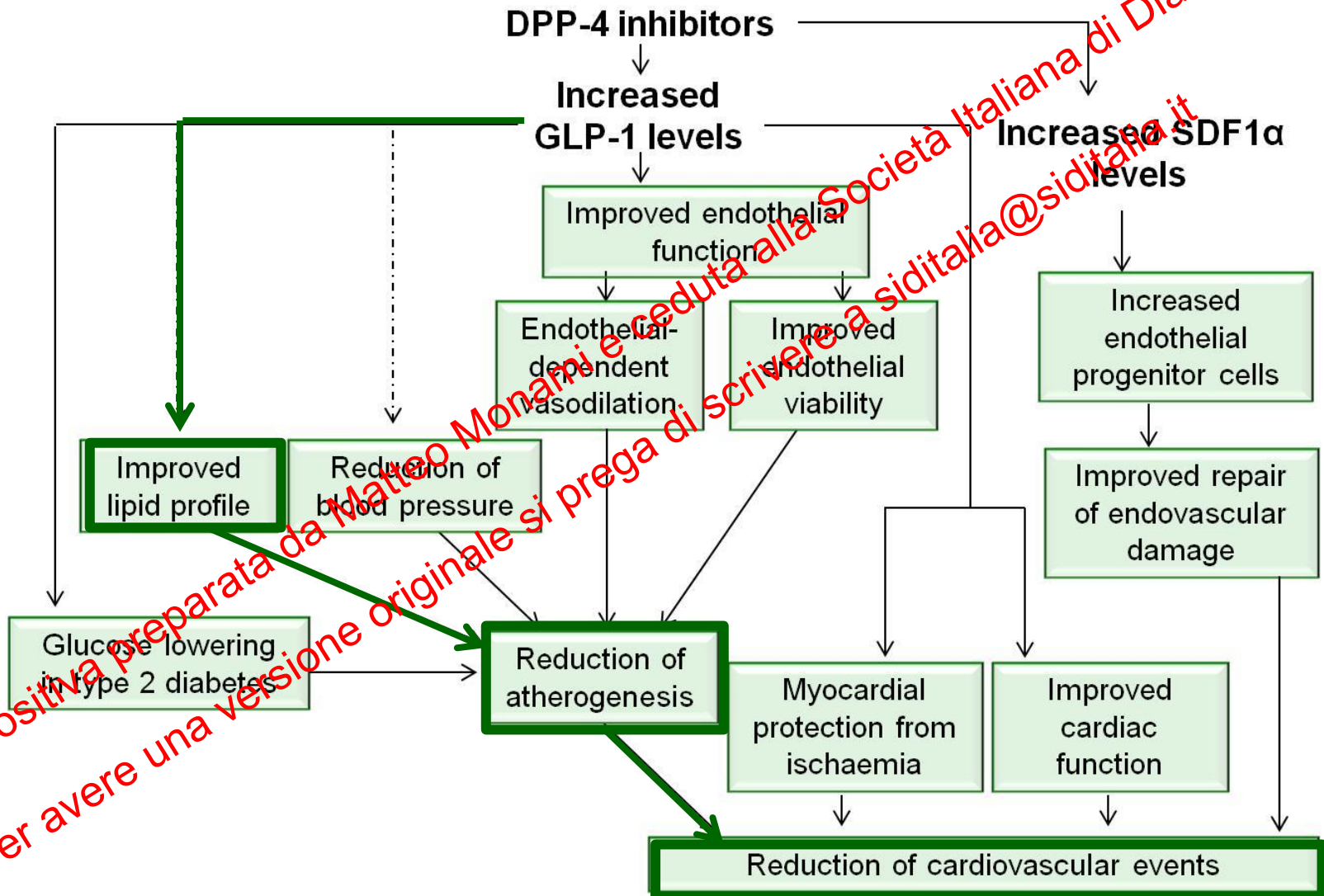


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CV effects of DPP-4 inhibitors



CV effects of DPP-4 inhibitors

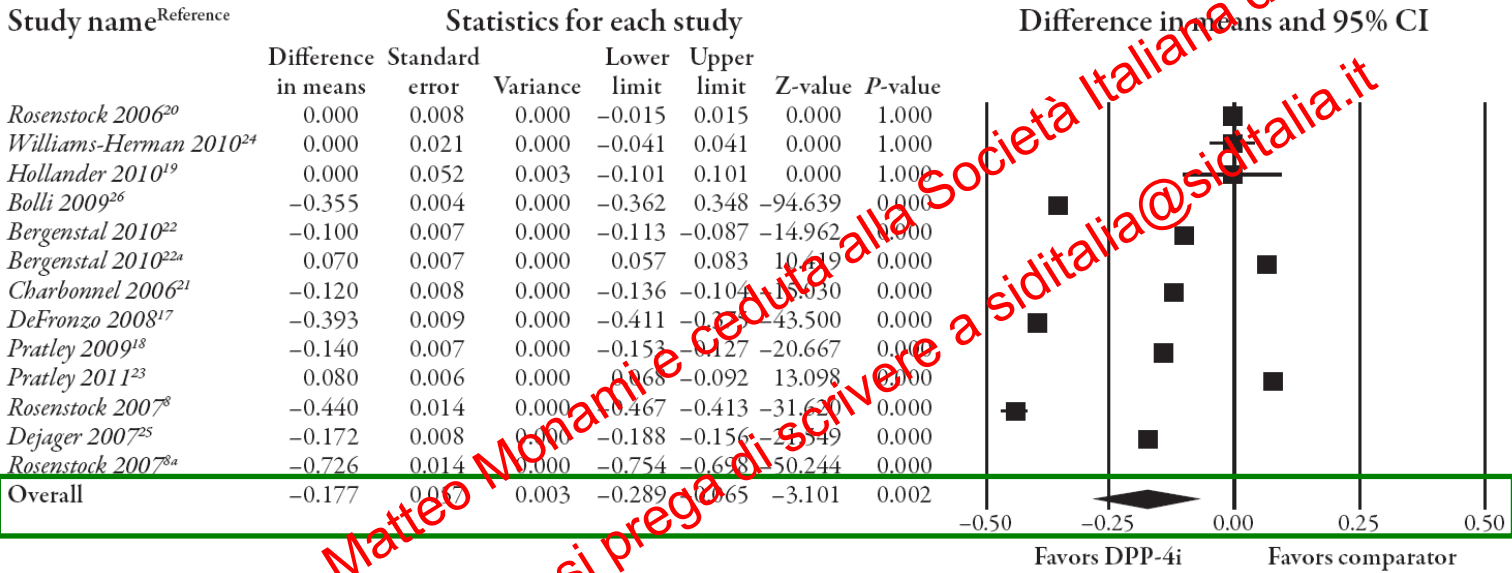


DPP-4 Inhibitors and Lipids:

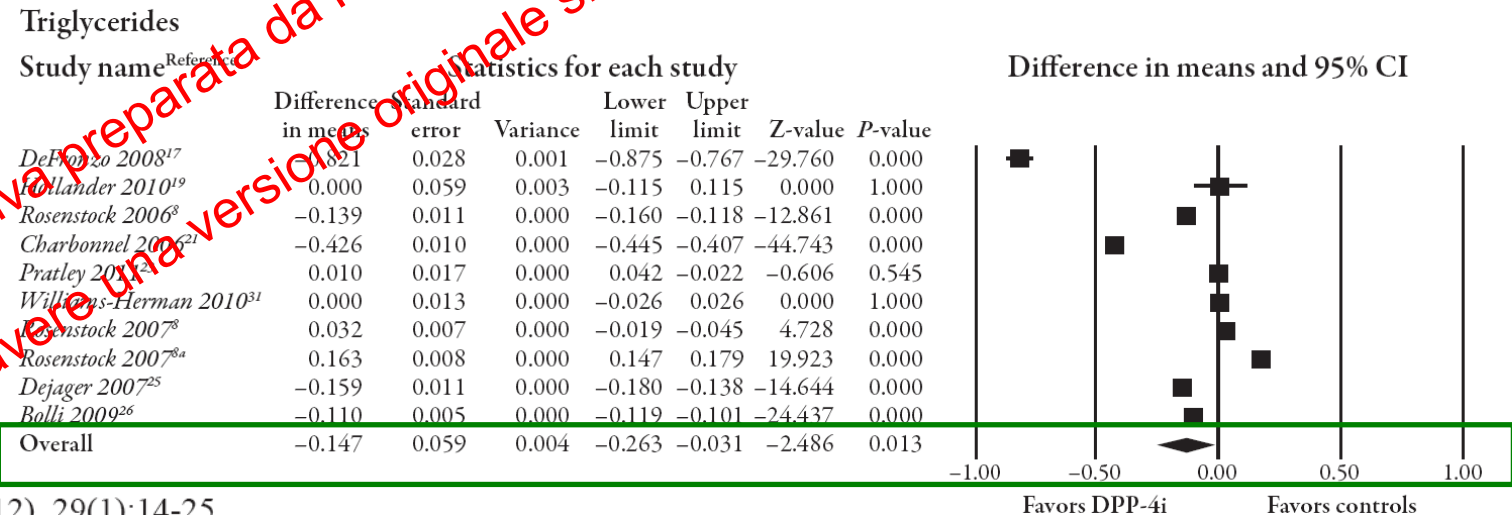
Systematic Review and Meta-Analysis

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

Total cholesterol



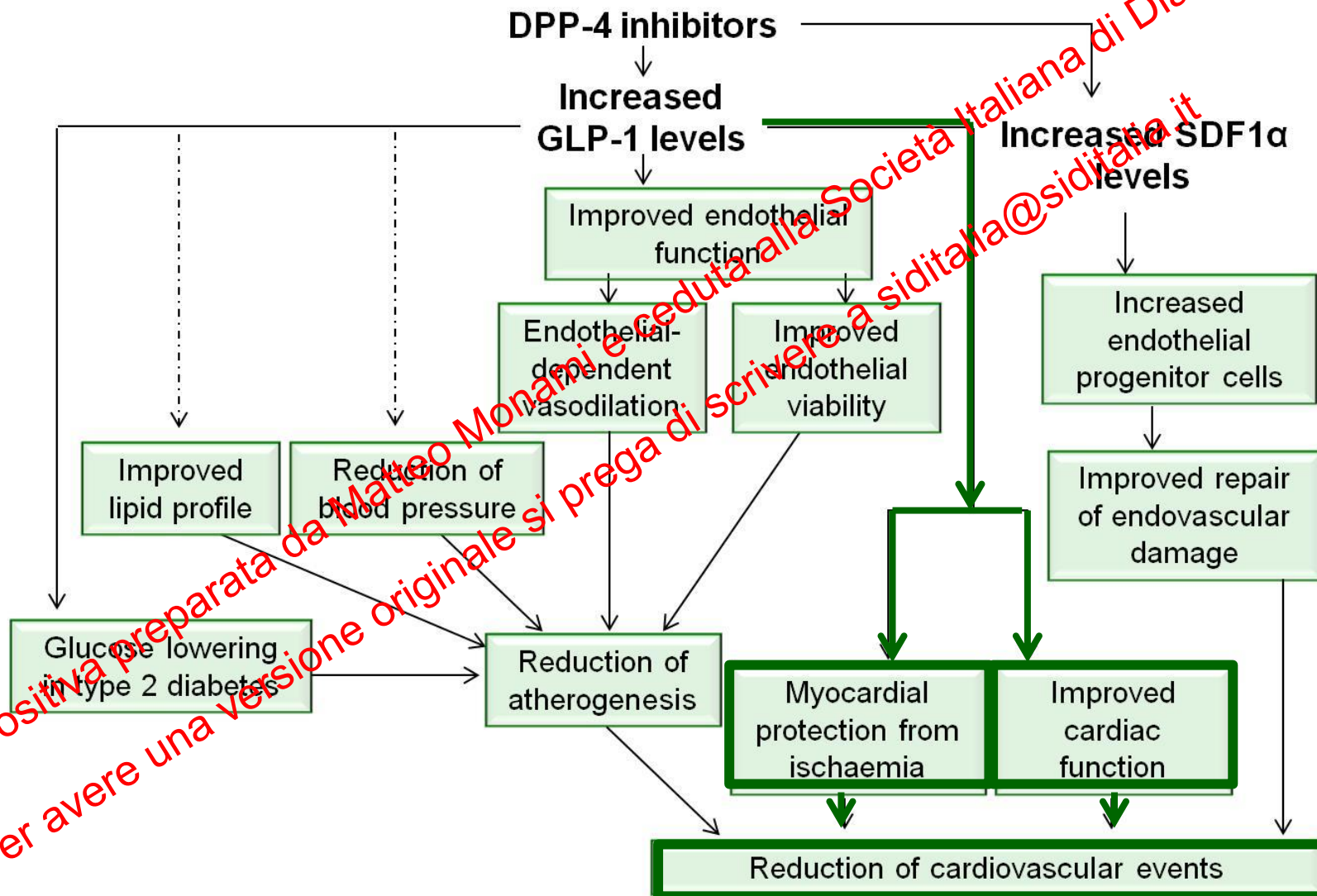
Triglycerides





CV effects of DPP-4 inhibitors

Positive effects independent from DPP-4i glucose-lowering effect



Myocardial effects of GLP1

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



PBS

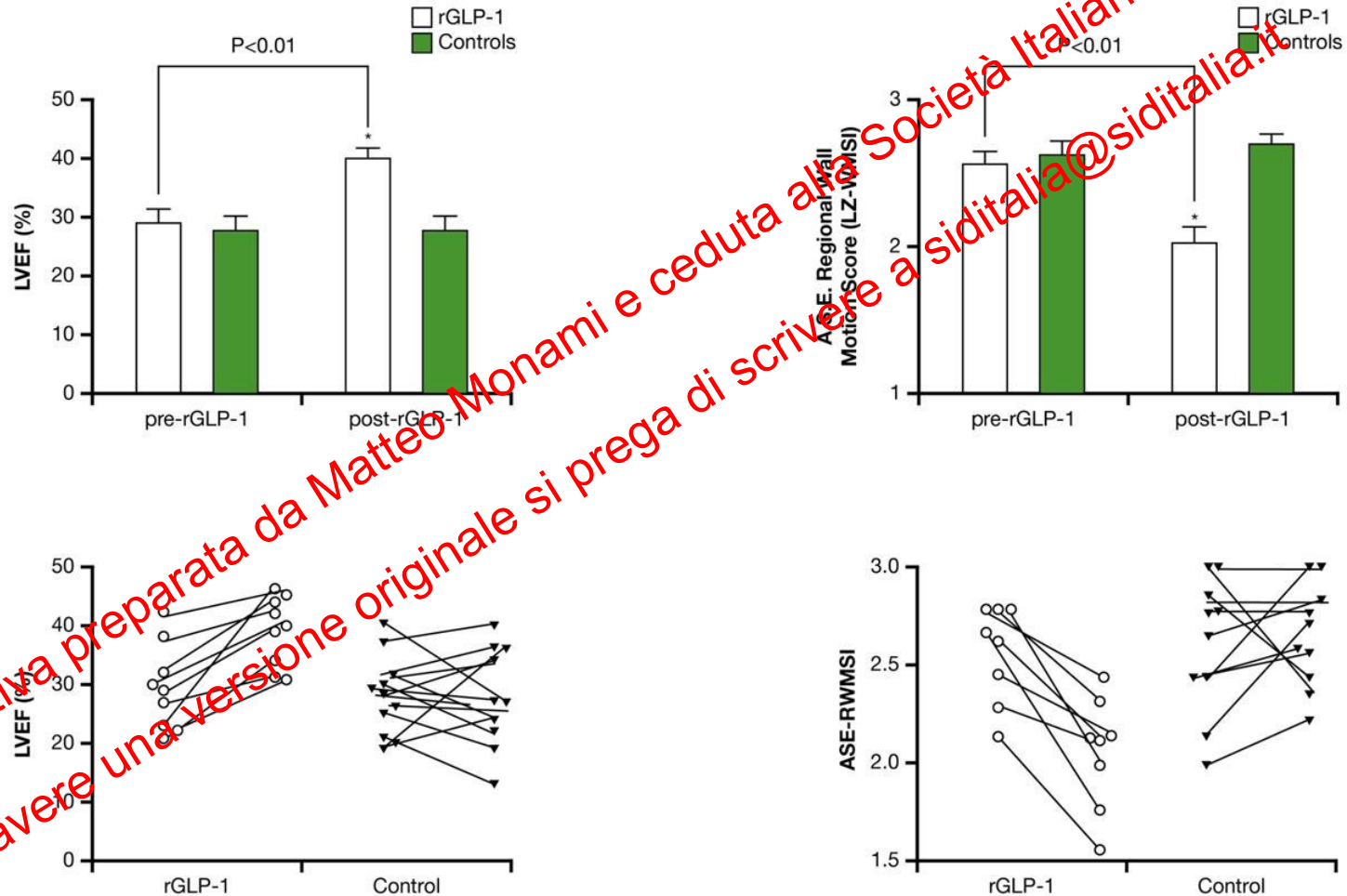


Exenatide

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

Myocardial effects of GLP-1

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

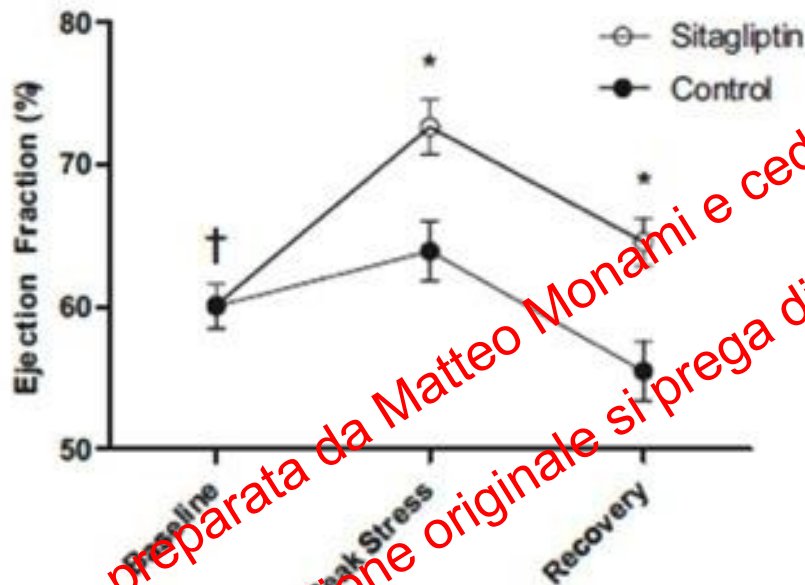




Sitagliptin and cardiac function



Results of a pilot study



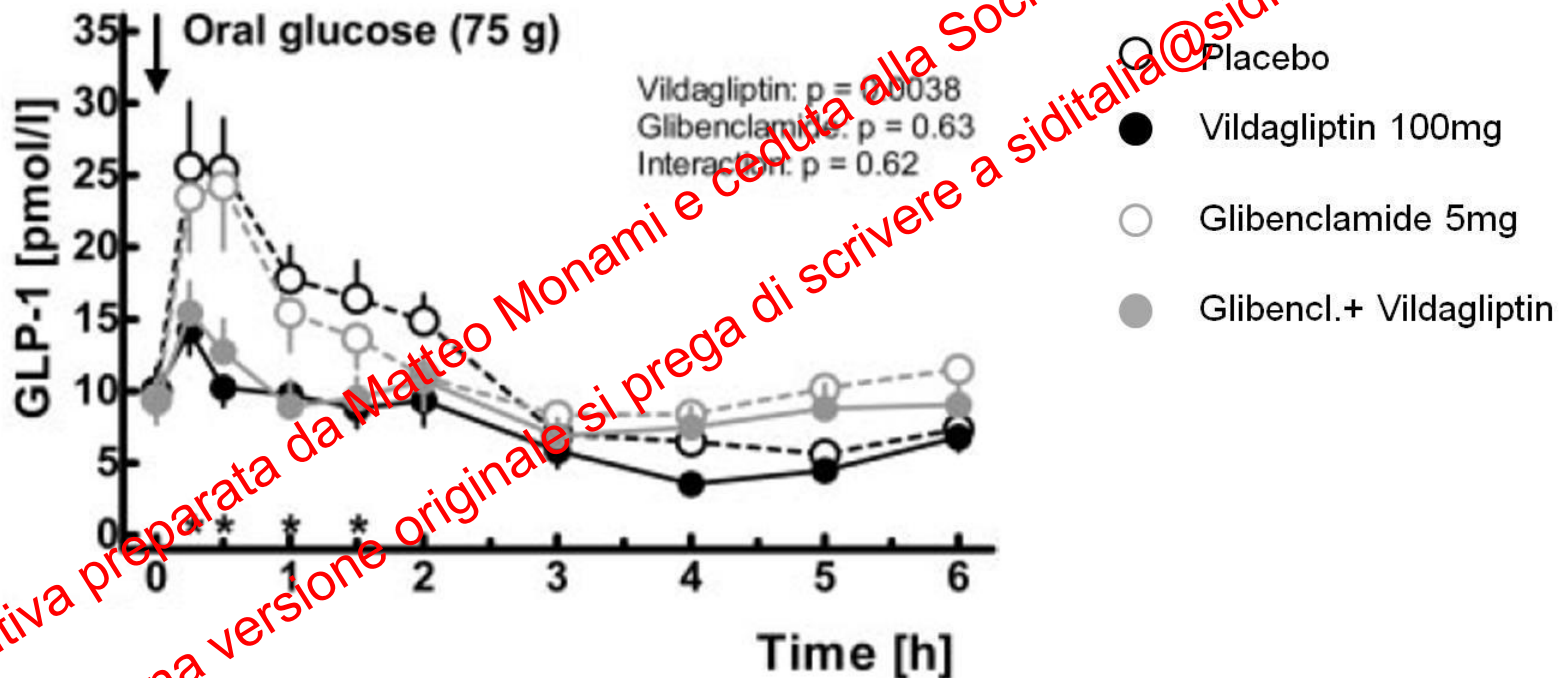
N=14 non-diabetic patients with CAD (single vessel in 71%) on waiting list for CABG/PTCA.

Stress echocardiography after a single dose of sitagliptin.

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

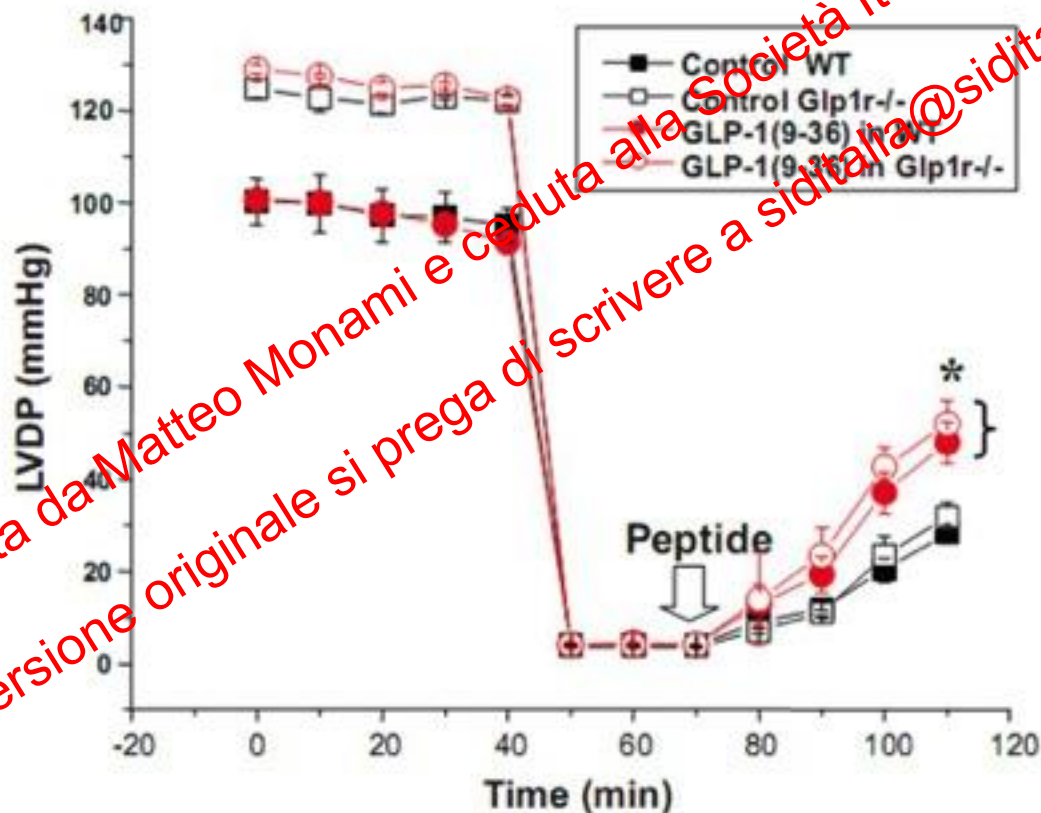
DPP4i and GLP-1 secretion

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



Myocardial effects of GLP-1(9-36)

Recovery after ischemia-reperfusion in rats



Ban K et al. *Circulation* 2008; 117:2340-2350.



Dipeptidyl peptidase-4 inhibitors and cardiovascular risk



A meta-analysis of randomized clinical trials

	# trials	# trials with events	# events (DPP4i)	# events (Comparator)	MH-OR [95%, CI]	p	Kendall's tau	p	Forest plot
MACE	70	63	263	232	0.71[0.59;0.86]	<0.001	0.04	0.64	
AMI	62	41	61	59	0.64[0.41;0.94]	0.023	-0.13	0.27	
Stroke	63	29	41	39	0.77[0.48;1.24]	0.290	-0.24	0.14	
Mortality	53	30	50	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	



Dipeptidyl peptidase-4 inhibitors and cardiovascular risk



A cohort and nested case-control study

UK Clinical Practice Research Datalink (CPRD)

Cohort study

(OR, 95% CI)

0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5

MACE

Crude 2.14[1.63;2.82] <0.001

Adj. 1.71[1.28;2.28] <0.001

MORTALITY

Crude 2.33[1.86;2.90] <0.001

Adj. 1.36[1.08;1.71] 0.01



SU vs DPP-4i (N= 29,863 vs 7,091)

Nested case-control (OR, 95% CI) *Propensity score-matched*

MACE

Crude 1.70[1.31;2.44] <0.001

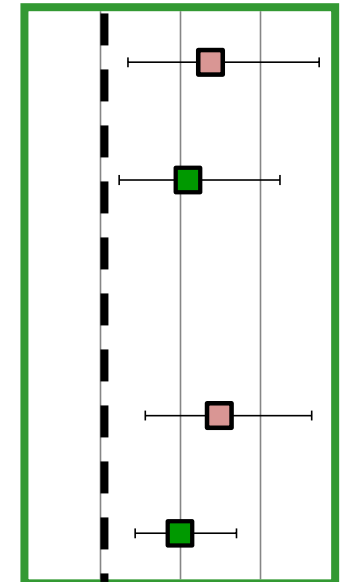
Adj. 1.55[1.08;2.22] <0.001

MORTALITY

Crude 1.80[1.21; 2.50] <0.001

Adj. 1.50[1.09; 2.05] 0.010

0.5 1.0 1.5 2.0 2.5



SU vs DPP-4i (N= 6,175 vs 6,229)