

**INVECCHIAMENTO
E LONGEVITÀ:
PIÙ GENI O
PIÙ AMBIENTE**

Firenze
Palazzo dei Congressi
30 Novembre
4 Dicembre 2010

55°
CONGRESSO
NAZIONALE

SOCIETÀ ITALIANA
DI GERONTOLOGIA
E GERIATRIA

11° CORSO PER INFERMIERI
9° CORSO DI RIABILITAZIONE
6° CORSO PER PSICOLOGI
5° CORSO PER ASSISTENTI SOCIALI

PROGRAMMA

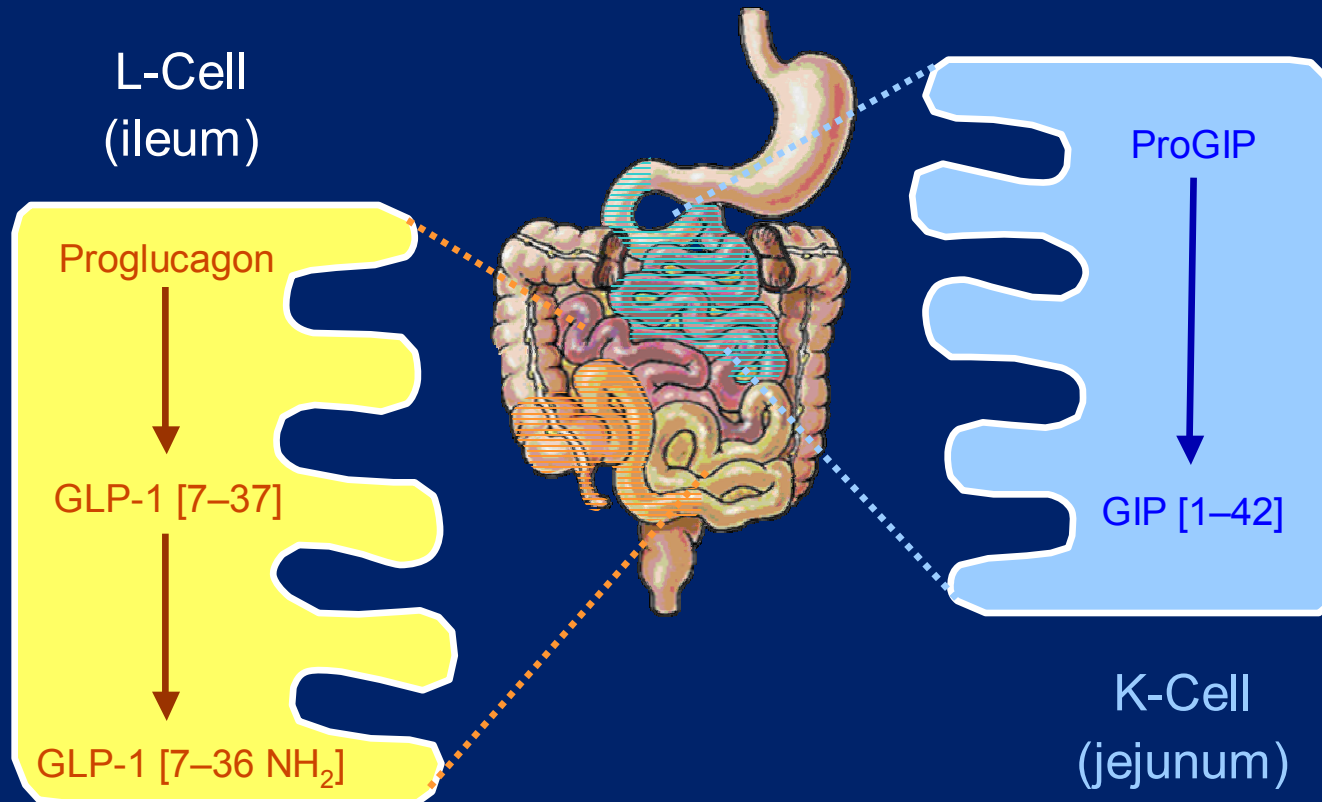
Innovazione terapeutica nel diabete tipo 2: l'inibizione della DPP-4

Edoardo Mannucci

*Agenzia Diabetologia
Azienda Ospedaliero-Universitaria Careggi
Firenze*

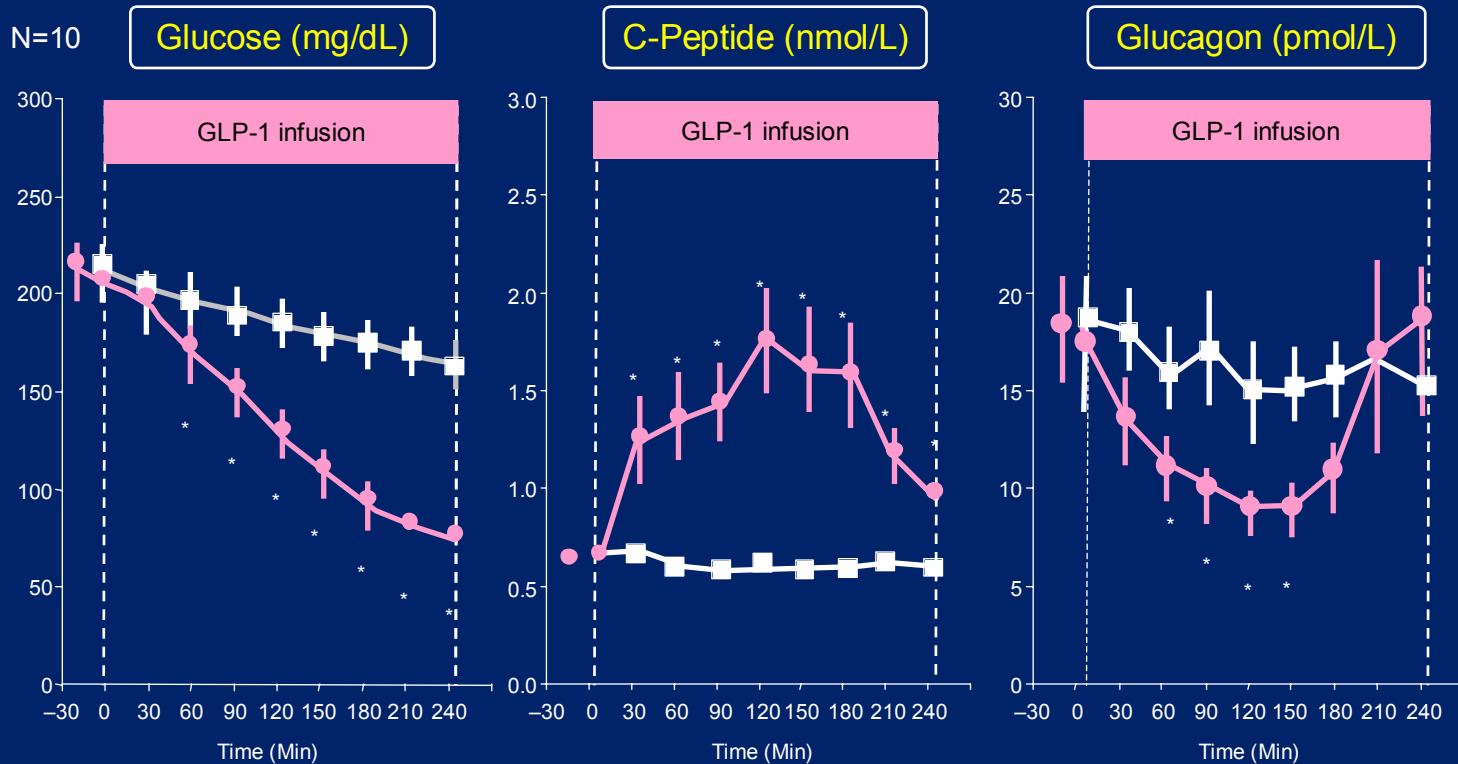


GLP-1 and GIP Are Synthesized and Secreted from the Gut in Response to Food Intake



GIP=glucose-dependent insulintropic peptide; GLP-1=glucagon-like peptide-1
Adapted from Drucker DJ. *Diabetes Care*. 2003; 26: 2929-2940.

GLP-1 Restores Insulin and Glucagon Responses in a Glucose-Sensitive Manner in Patients with T2DM

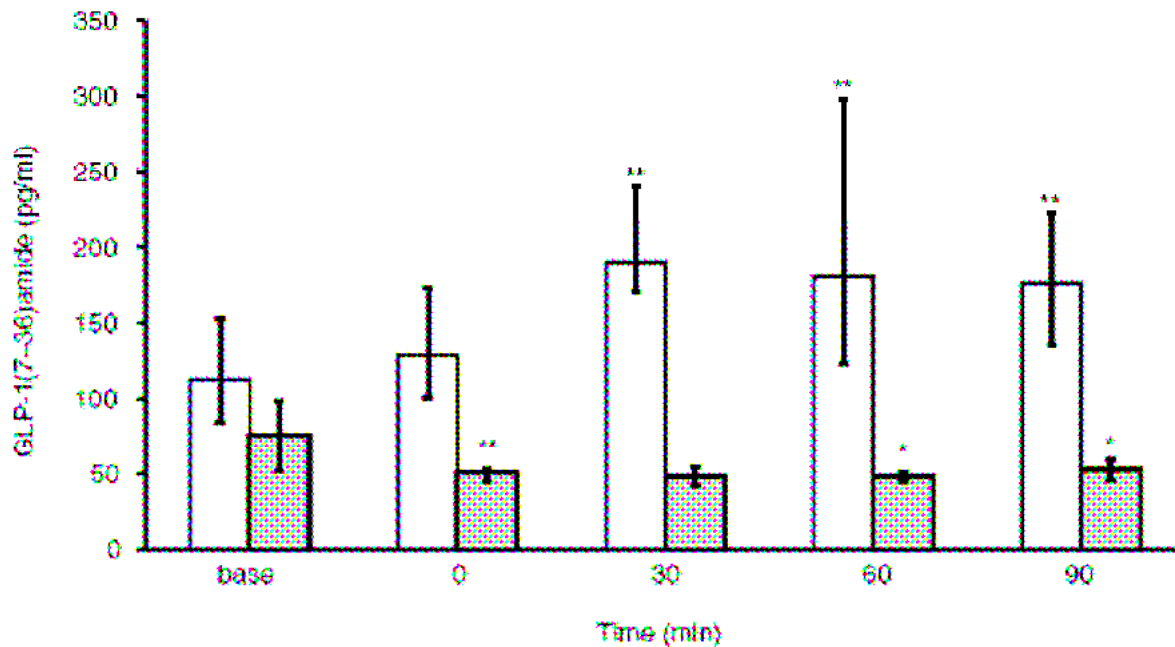


GLP-1=glucagon-like peptide-1; T2DM=type 2 diabetes mellitus
 *P < 0.05
 †GLP-1(7-36 amide) infused at 1.2 pmol/kg/min for 240 minutes.
 Adapted from Nauck MA, et al. *Diabetologia*. 1993; 36: 741-744.

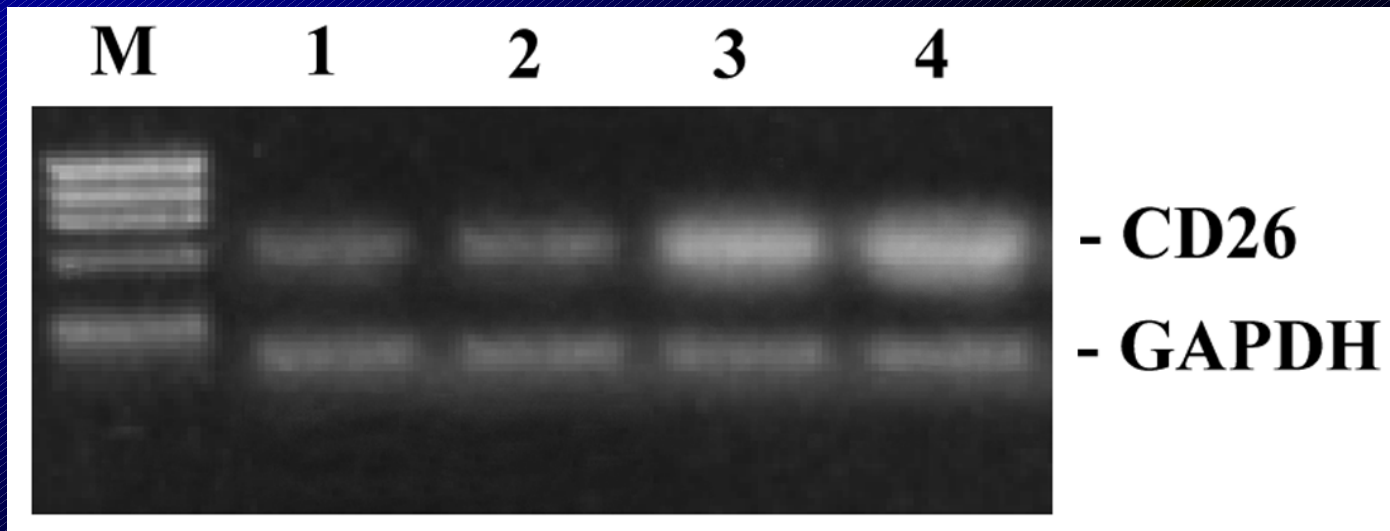
● GLP-1† ■ Placebo

Glucagon-like peptide (GLP)-1 and leptin concentrations in obese patients with Type 2 diabetes mellitus

E. Mannucci*, A. Ognibenet, F. Cremasco*, G. Bardini*, A. Mencucci*, E. Pierazzuoli*, S. Ciani*, A. Fanellit, G. Messerit and C. M. Rotella*



DPP-IV mRNA in GENC



1: Glucose 5.5. mM

3: Glucose 22 mM

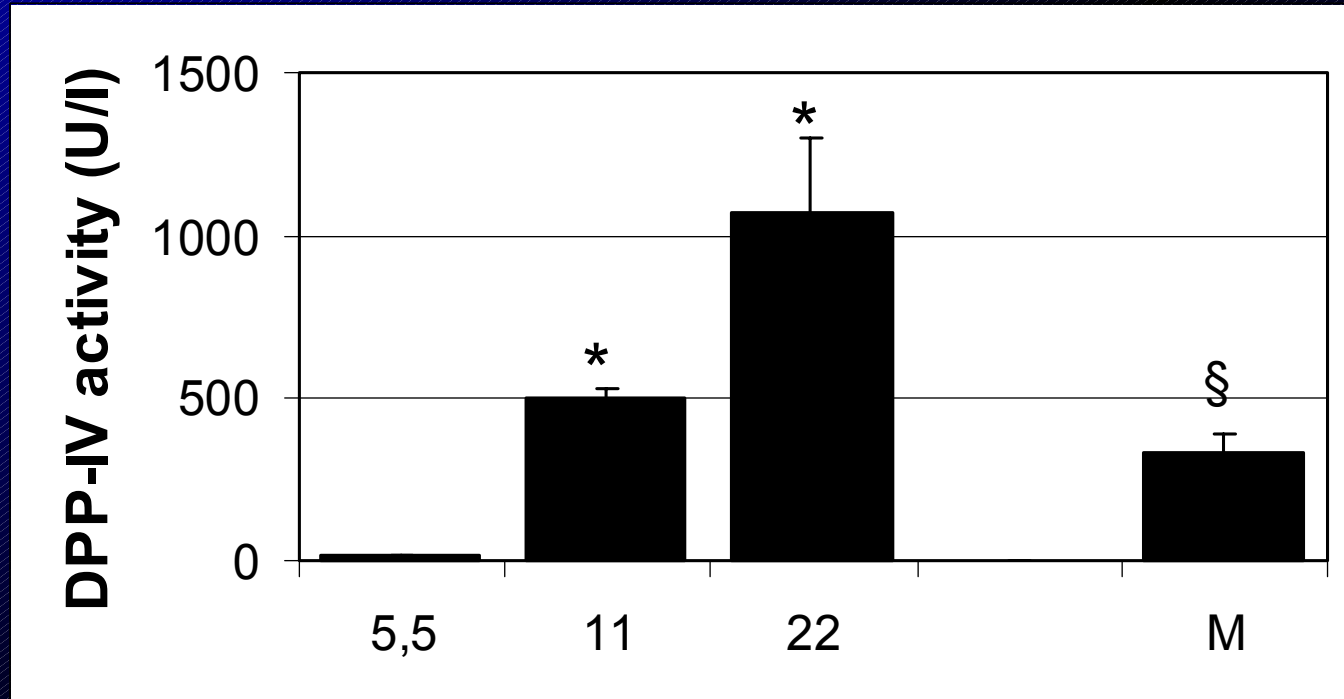
2: Glucose 11 mM

4: Glucose 5.5+ Mannitol 17.5

Pala et al., *Biochem Biophys Res Commun*, 2003



DPP-IV in GENC

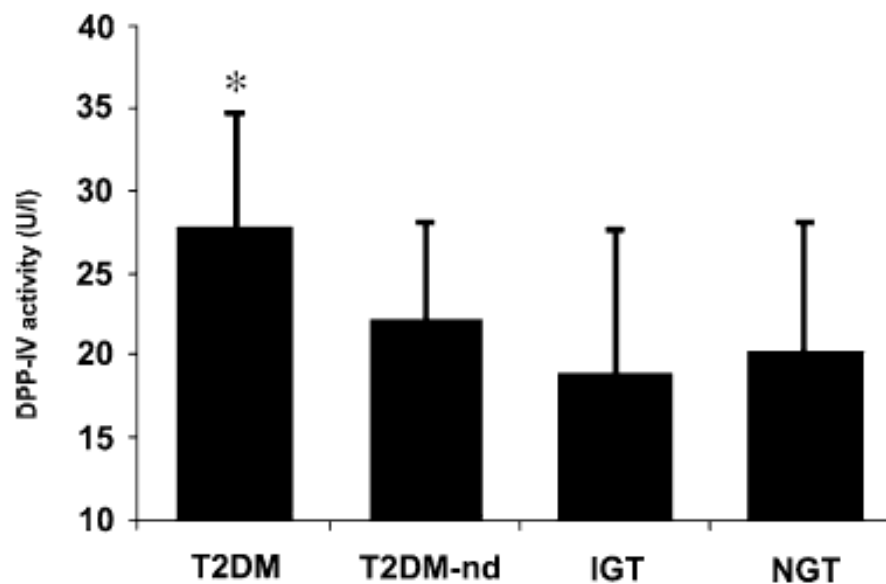


Pala et al., Biochem Biophys Res Commun, 2003



E. Mannucci · L. Pala · S. Ciani · G. Bardini ·
A. Pezzatini · I. Sposato · F. Cremasco · A. Ognibene ·
C. M. Rotella

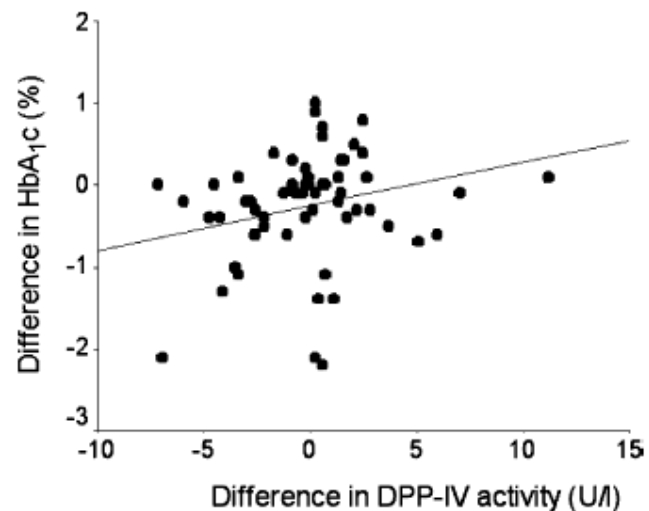
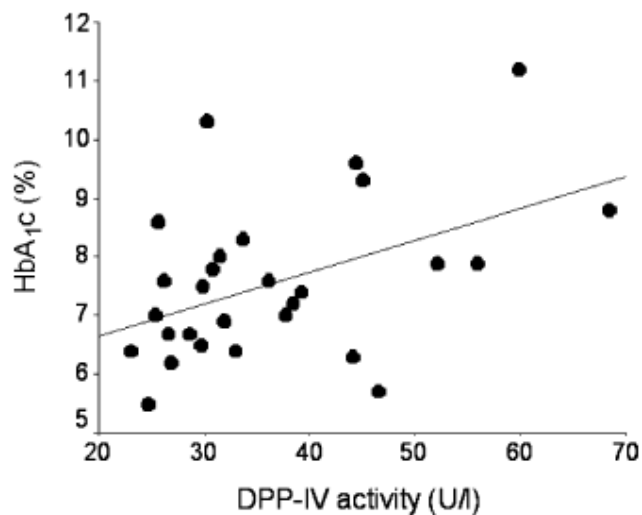
Hyperglycaemia increases dipeptidyl peptidase IV activity in diabetes mellitus



ARTICLE

E. Mannucci · L. Pala · S. Ciani · G. Bardini ·
A. Pezzatini · I. Sposato · F. Cremasco · A. Ognibene ·
C. M. Rotella

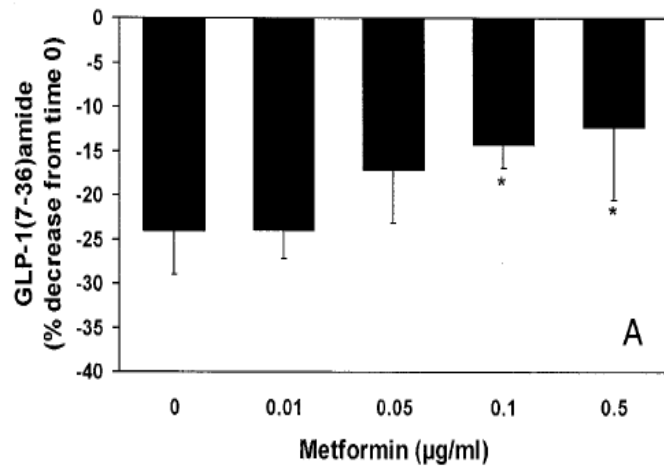
Hyperglycaemia increases dipeptidyl peptidase IV activity in diabetes mellitus



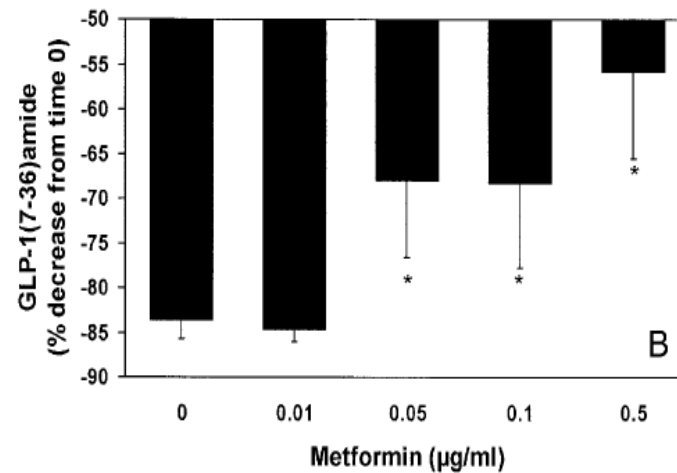
Effect of Metformin on Glucagon-Like Peptide 1 (GLP-1) and Leptin Levels in Obese Nondiabetic Subjects

EDOARDO MANNUCCI, MD¹
AGOSTINO OGNIBENE, MD²
FRANCESCO CREMASCO, MD¹
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ANTONELLA MENCUCI, MD¹

ENRICA PIERAZZUOLI, MD¹
SILVIA CIANI, BS¹
GIANNI MESSERI, MS²
CARLO M. ROTELLA, MD¹



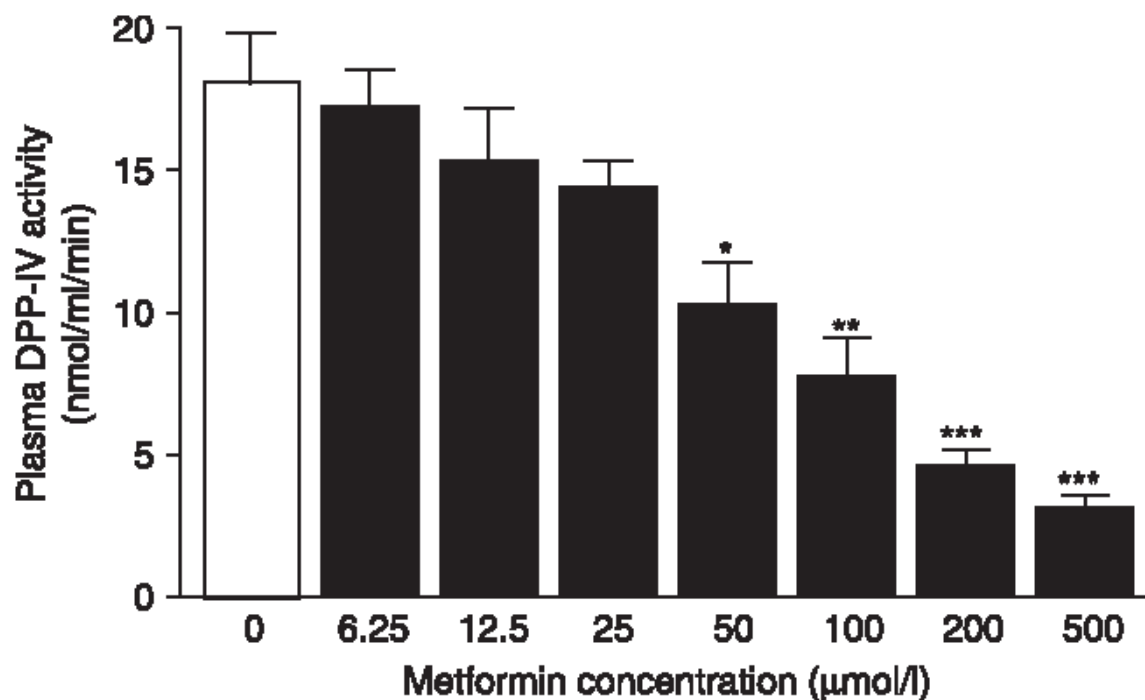
Human plasma



Purified DPP-IV in buffer solution

Inhibition of dipeptidyl peptidase IV activity by oral metformin in Type 2 diabetes

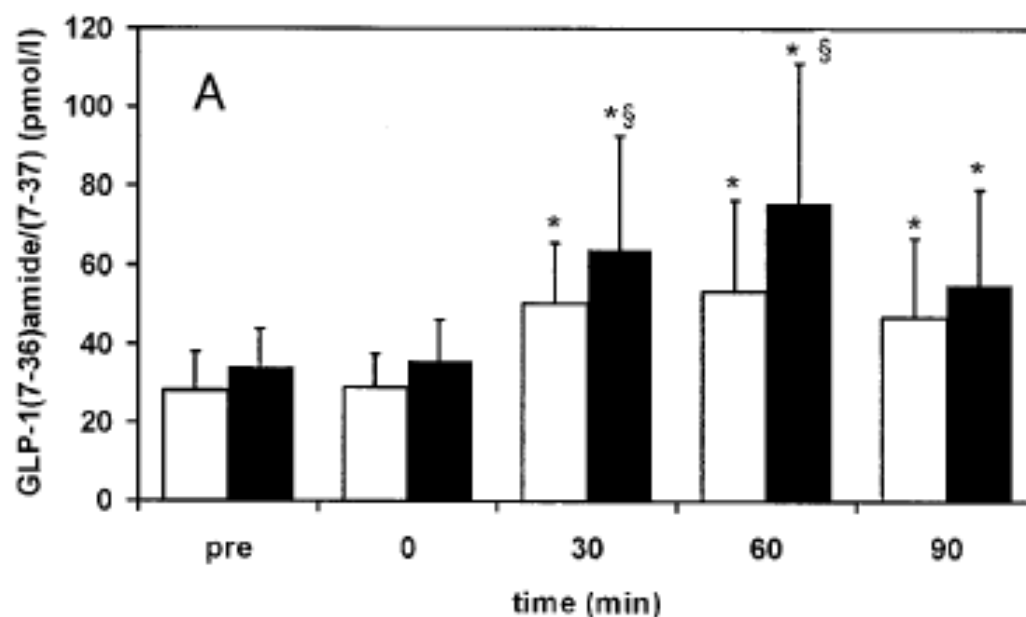
J. R. Lindsay*, N. A. Duffyt, A. M. McKillopt, J. Ardill‡, F. P. M. O'Hartet, P. R. Flattt and P. M. Bell*



Effect of Metformin on Glucagon-Like Peptide 1 (GLP-1) and Leptin Levels in Obese Nondiabetic Subjects

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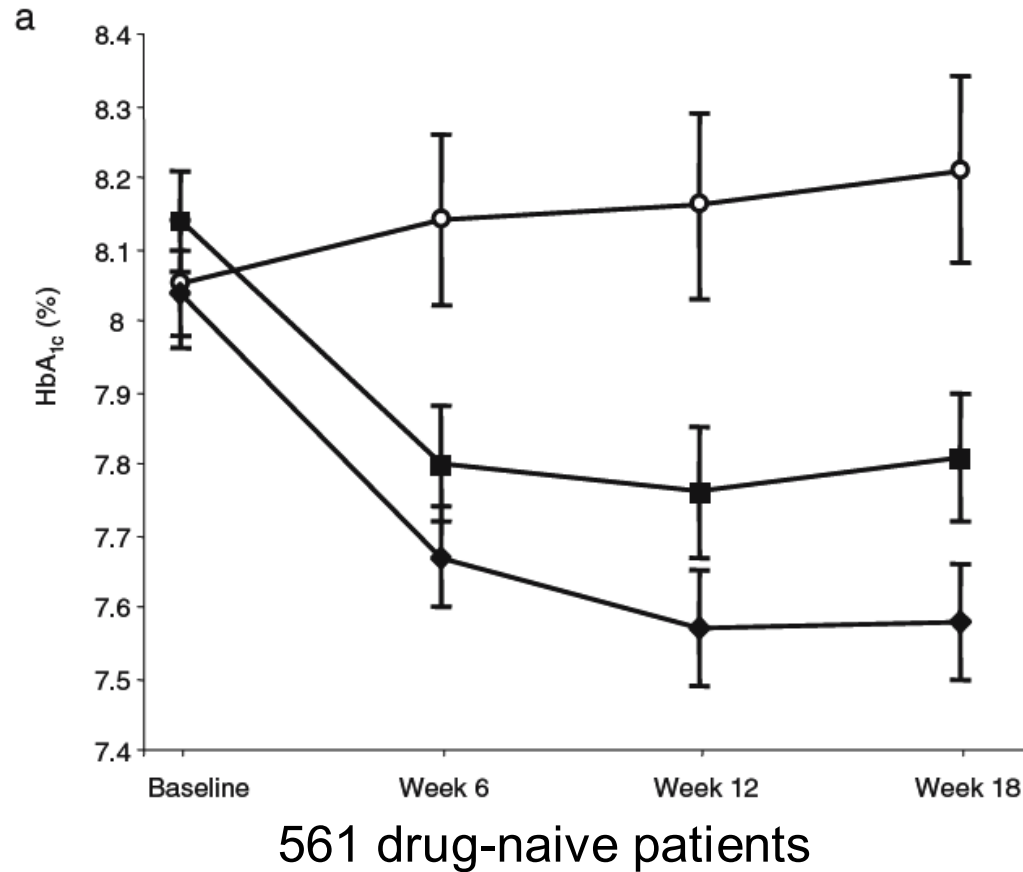
ENRICA PIERAZZUOLI, MD¹
SILVIA CIANI, BS¹
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Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy in patients with type 2 diabetes mellitus

I. Raz · M. Hanefeld · L. Xu · C. Caria
D. Williams-Herman · H. Khatami ·
Sitagliptin Study 023 Group

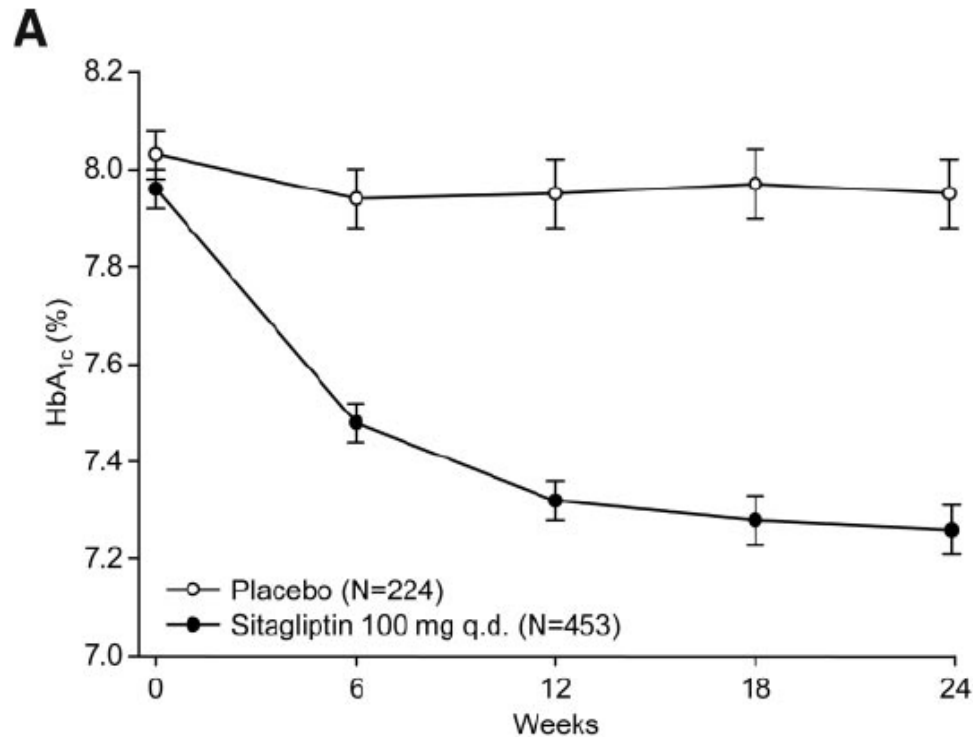
Diabetologia (2006) 49:2564–2571



Efficacy and Safety of the Dipeptidyl Peptidase-4 Inhibitor Sitagliptin Added to Ongoing Metformin Therapy in Patients With Type 2 Diabetes Inadequately Controlled With Metformin Alone

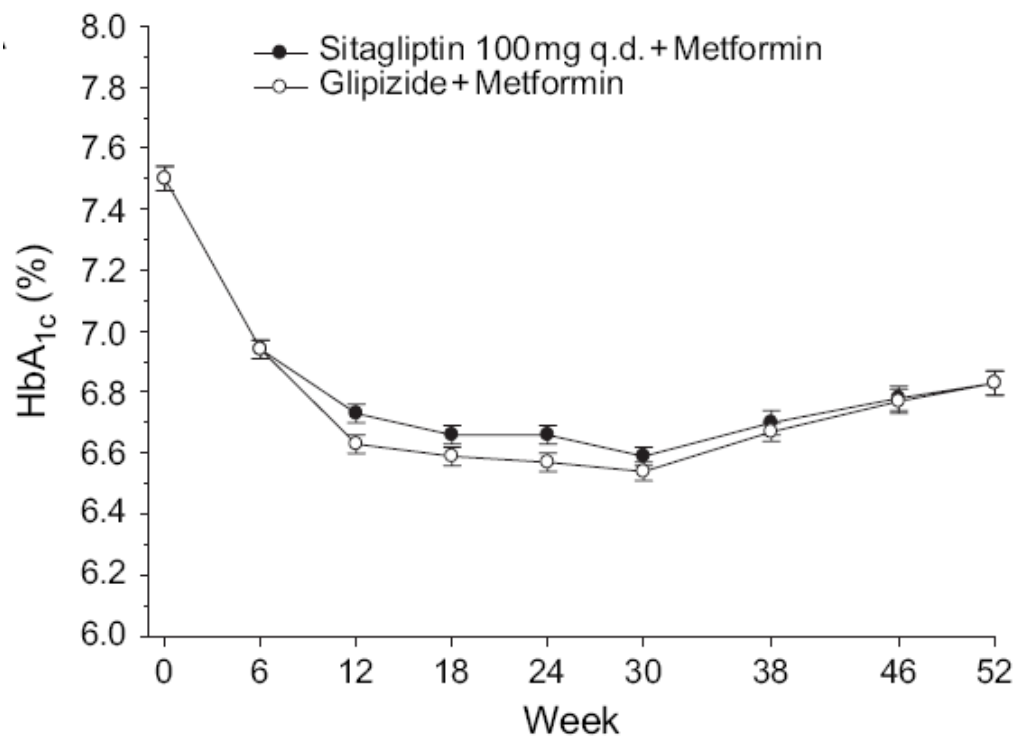
BERNARD CHARBONNEL, MD¹
AVRAHAM KARASIK, MD²
JI LIU, MA³
MEI WU, MS³
GARY MEININGER, MD³
FOR THE SITAGLIPTIN STUDY 020 GROUP*

635 patients failing to metformin



Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial

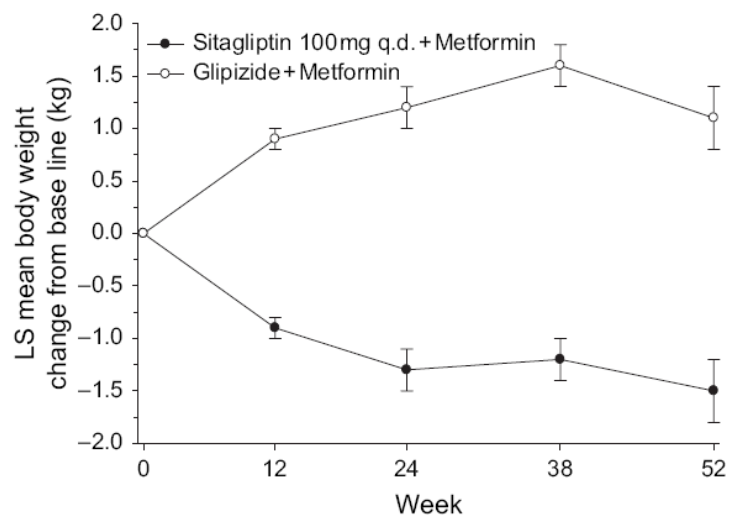
M. A. Nauck,¹ G. Meininger,² D. Sheng,² L. Terranella² and P. P. Stein² for the Sitagliptin Study 024 Group*



Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial

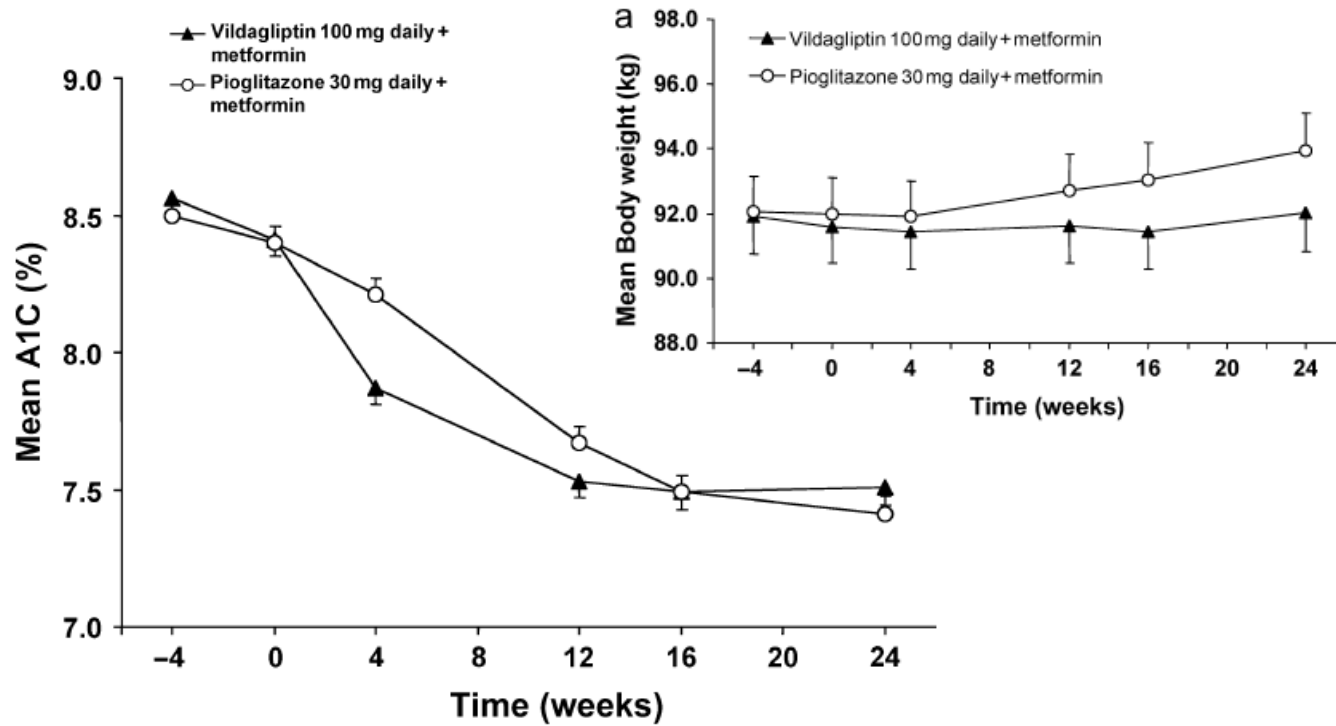
M. A. Nauck,¹ G. Meininger,² D. Sheng,² L. Terranella² and P. P. Stein² for the Sitagliptin Study 024 Group*

	Sitagliptin 100 mg q.d. + metformin (N = 588), n (%)	Glipizide + metformin (N = 584), n (%)
One or more AEs	419 (71.3)	444 (76.0)
Drug-related AEs*	85 (14.5)	177 (30.3)
SAEs	43 (7.3)	44 (7.5)
Drug-related SAEs*	0	2 (0.3)
Deaths	1 (0.2)	2 (0.3)
Discontinuations because of AEs	16 (2.7)	21 (3.6)
Discontinuations because of drug-related AEs	8 (1.4)	8 (1.4)
Discontinuations because of SAEs	6 (1.0)	7 (1.2)
Discontinuations because of drug-related SAEs	0	0
Clinical AEs of special interest Hypoglycaemia	29 (4.9)	187 (32.0)



Efficacy and tolerability of vildagliptin vs. pioglitazone when added to metformin: a 24-week, randomized, double-blind study*

G. Bolli,¹ F. Dotta,² E. Rochotte³ and S. E. Cohen⁴



André J. Scheen^{1*}
Guillaume Charpentier²
Carl Johan Östgren³
Åsa Hellqvist⁴
Ingrid Gause-Nilsson⁴

Efficacy and safety of saxagliptin in combination with metformin compared with sitagliptin in combination with metformin in adult patients with type 2 diabetes mellitus

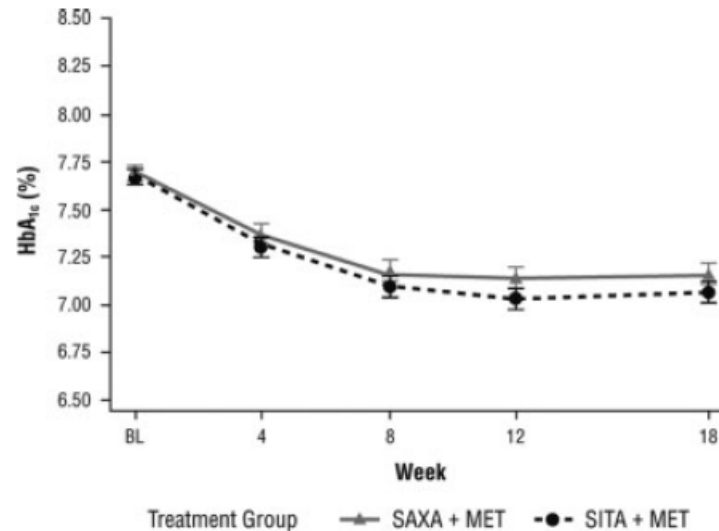


Figure 2. Mean (\pm SE) glycosylated haemoglobin (HbA_{1c}) values at each visit during the double-blind treatment period. MET, metformin; SAXA, saxagliptin; SITA, sitagliptin

Dipeptidyl peptidase-4 inhibitors in type 2 diabetes: A meta-analysis of randomized clinical trials

M. Monami*, I. Iacomelli, N. Marchionni, E. Mannucci

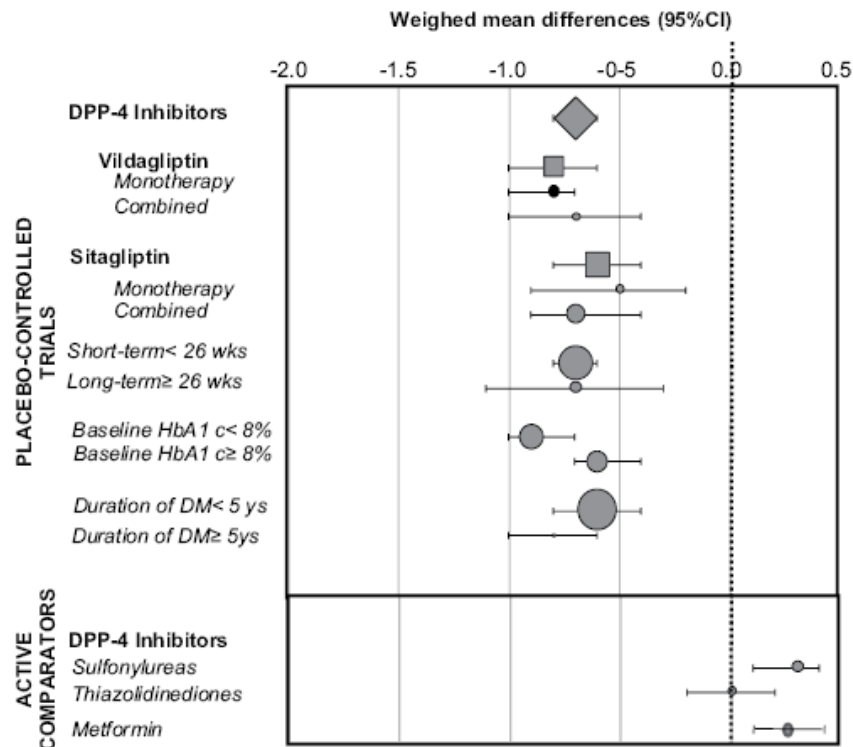


Figure 2 Standardized differences (with 95% CI) of mean HbA1c at endpoint.

Nutrition, Metabolism & Cardiovascular Diseases (2009)

Dipeptidyl peptidase-4 inhibitors in type 2 diabetes: A meta-analysis of randomized clinical trials

M. Monami*, I. Iacomelli, N. Marchionni, E. Mannucci

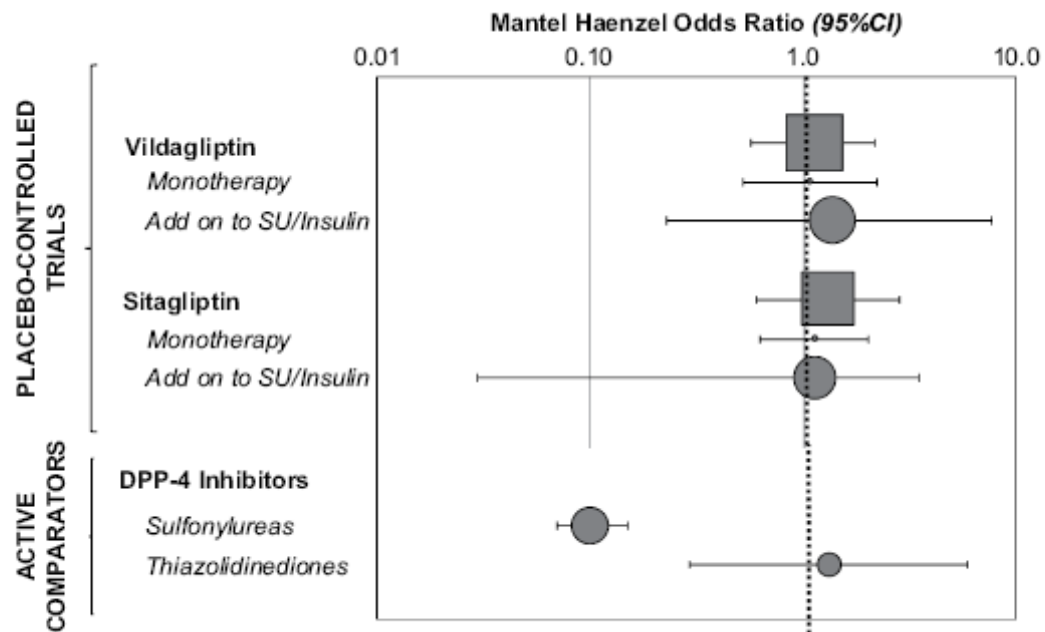


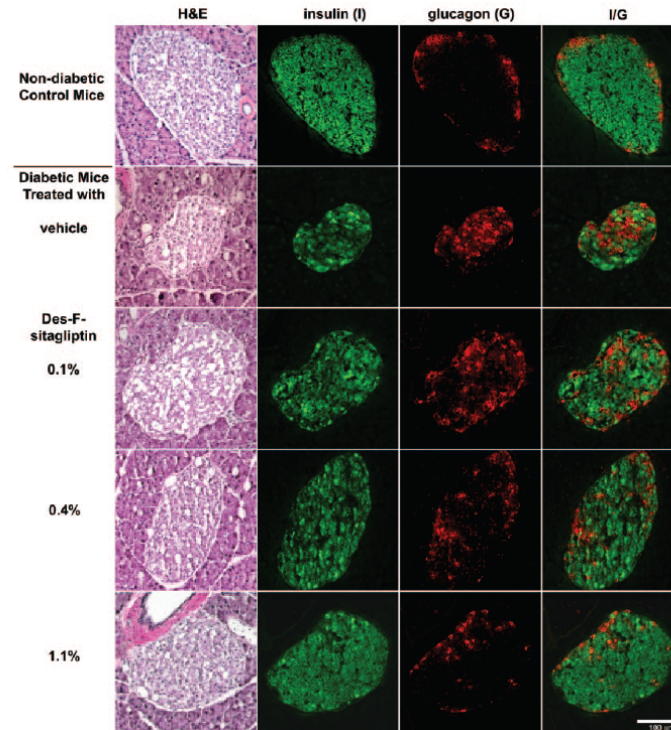
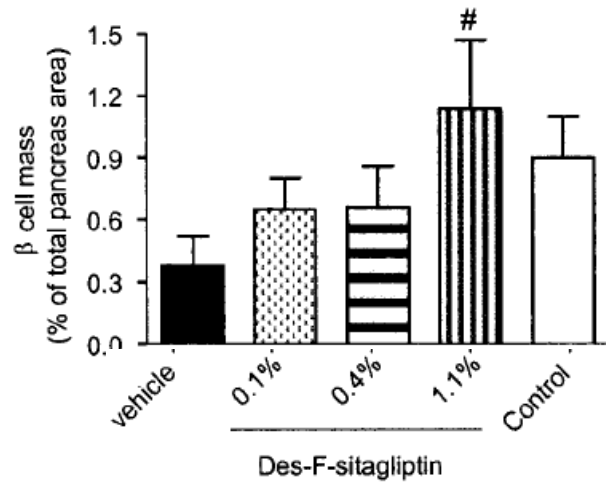
Figure 3 Mantel–Haenszel odds ratio (with 95% CI) for any hypoglycemia (logarithmic scale).

Nutrition, Metabolism & Cardiovascular Diseases (2009)

Original Article

Chronic Inhibition of Dipeptidyl Peptidase-4 With a Sitagliptin Analog Preserves Pancreatic β -Cell Mass and Function in a Rodent Model of Type 2 Diabetes

James Mu,¹ John Woods,² Yun-Ping Zhou,¹ Ranabir Sinha Roy,¹ Zhihua Li,¹ Emanuel Zycband,² Yue Feng,¹ Lan Zhu,¹ Cai Li,¹ Andrew D. Howard,¹ David E. Moller,¹ Nancy A. Thornberry,¹ and Bei B. Zhang¹



Diabetes

55:1695–1704, 2006

Future perspectives on glucagon-like peptide-1, diabetes and cardiovascular risk

E. Mannucci ^{a,*}, C.M. Rotella ^b

Nutrition,
Metabolism &
Cardiovascular Diseases

Table 1 Actions of GLP-1 relevant for cardiovascular risk

	In vitro/ex vivo	Animals, in vivo	Humans, in vivo
<i>Metabolic actions</i>			
Fasting blood glucose	—	Reduced	Reduced
Post-prandial glucose	—	Reduced	Reduced
HDL cholesterol	—	Increased	?
Triglyceride	—	Reduced	?
Insulin sensitivity	Enhanced	Enhanced	Enhanced/unmodified
<i>Cardiovascular actions</i>			
Heart rate	—	Increased	Unmodified
Cardiac function	Enhanced	Enhanced	Enhanced
Protection from ischemia	—	Enhanced	Enhanced
Vascular function	Vasoconstriction/Vasodilation	Vasoconstriction/Vasodilation	Vasodilation
Blood pressure	—	Increased	Reduced
<i>Other effects</i>			
Body weight	—	Reduced	Reduced
PAI-1 expression	Reduced	?	?

Hormone effects demonstrated in vitro/ex vivo and in vitro, in animal models or humans. PAI-1: plasminogen activator inhibitor-1.



Safety and tolerability of sitagliptin in clinical studies: a pooled analysis of data from 10,246 patients with type 2 diabetes

Debora Williams-Herman*, Samuel S Engel, Elizabeth Round, Jeremy Johnson, Gregory T Golm, Hua Guo, Bret J Musser, Michael J Davies, Keith D Kaufman and Barry J Goldstein

Table 8: Serious adverse events irrespective of relationship to study drug that occurred at an incidence rate of ≥ 0.2 incident events per 100 patient-years in one or both groups

Adverse Event	Incidence Rate per 100 Patient-years†		Difference between Sitagliptin and Non-exposed (95% CI)*
	Sitagliptin 100 mg	Non-exposed	
Cardiac disorders SOC			
Acute myocardial infarction	0.1	0.2	-0.1 (-0.3, 0.0)
Angina pectoris	0.2	0.1	0.1 (-0.1, 0.3)
Coronary artery disease	0.2	0.4	-0.2 (-0.5, 0.0)
Myocardial infarction	0.2	0.2	0.0 (-0.2, 0.2)
Myocardial ischemia	0.0	0.2	-0.2 (-0.4, -0.1)

In the prespecified analysis, the risk ratio for sitagliptin-exposed relative to non-exposed patients was 0.68 (95% CI: 0.41, 1.12). In a sensitivity analysis using the Mantel-Haenszel approach, the results were consistent (risk ratio [95% CI] = 0.67 [0.39, 1.13]).

Assessing the cardio-cerebrovascular safety of vildagliptin: meta-analysis of adjudicated events from a large Phase III type 2 diabetes population

A. Schweizer¹, S. Dejager², J. E. Foley³, A. Couturier³, M. Ligueros-Saylan³ & W. Kothny³

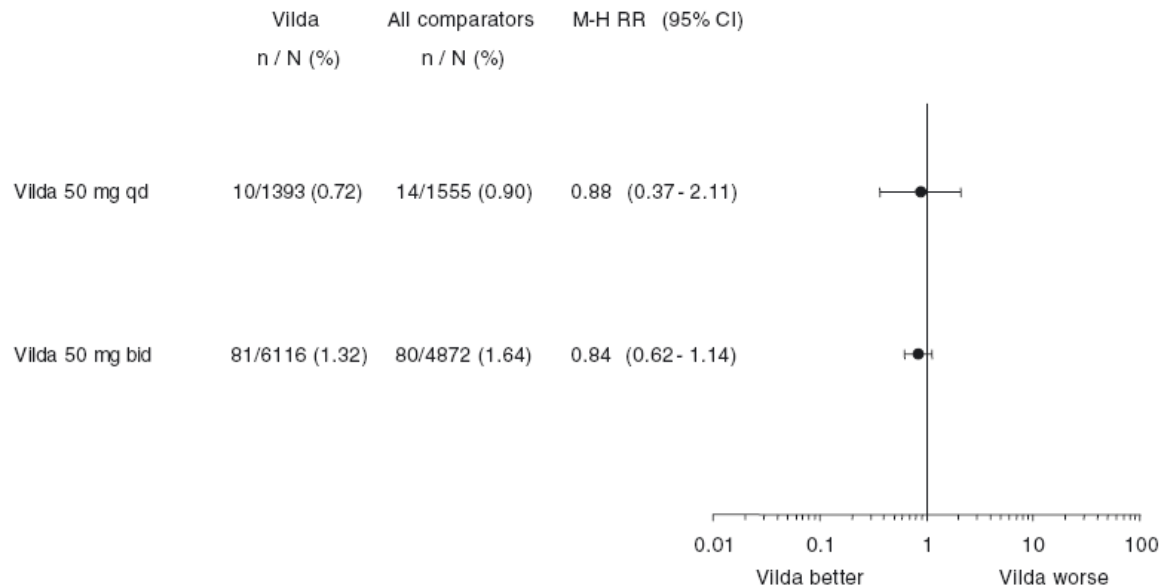


Figure 1. Incidences and risk ratios for adjudicated cardiovascular and cerebrovascular events [composite endpoint consisting of ACS, TIA (with imaging evidence of infarction), stroke and CCV death] with vildagliptin (50 mg qd or 50 mg bid) vs. all comparators (placebo and active comparators). Vilda, vildagliptin; M-H RR, Mantel-Haenszel risk ratio. Test for heterogeneity: $Q = 1.55$, $p = 0.956$ and $I^2 = 0.00$ (vildagliptin 50 mg qd); $Q = 4.08$, $p = 0.982$ and $I^2 = 0.00$ (vildagliptin 50 mg bid).