
*MISURARE I PROCESSI DI SALUTE E ASSISTENZIALI PER MIGLIORARE GLI OUTCOME DI SALUTE E DI CURA*
*LA VISON DI AMD*

# LE RICADUTE CLINICHE DELL'IMPIEGO PRECOCE DEGLI INIBITORI DEL DPP-4 PER MIGLIORARE GLI ESITI DI CURA

*Si ringraziano Roche Pharma, Eli Lilly, GSK, Astra Zeneca e Bristol MS per l'opportunià di crescita formativa offerta nell'ultimo biennio*

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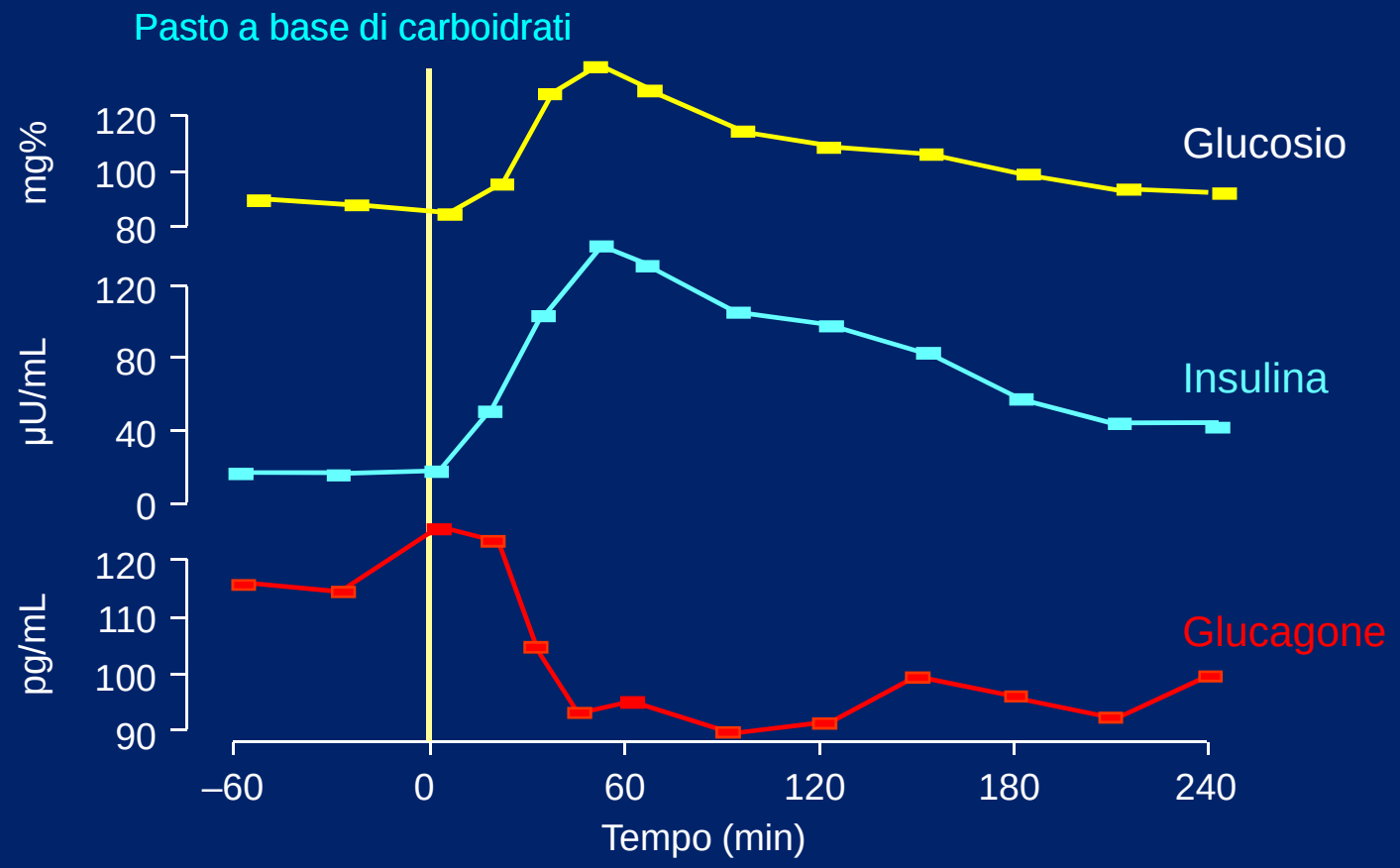
Seconda Università di Napoli

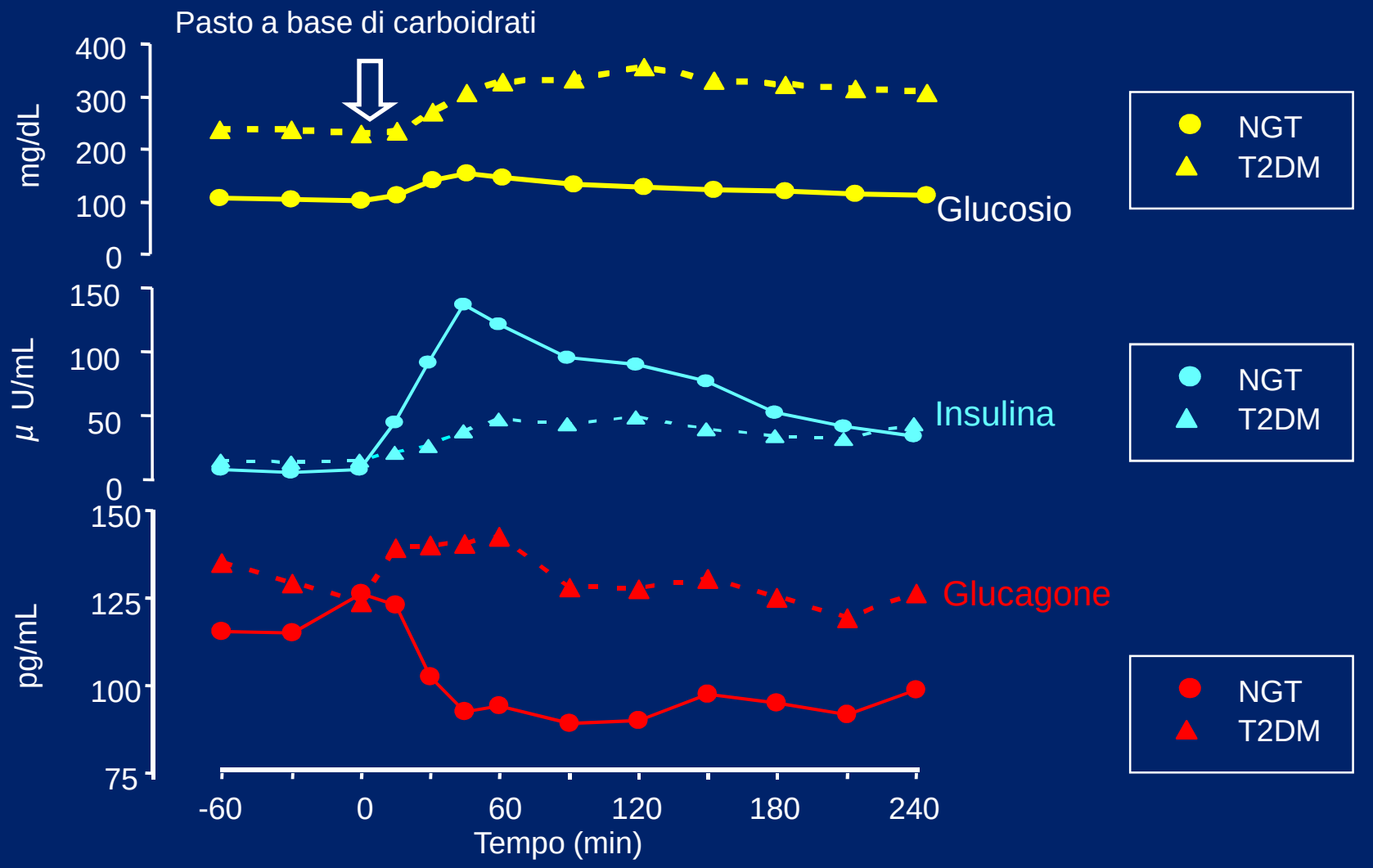
# Cinetica di insulina e glucagone in soggetti sani

Insulina post-prandiale e glucagone nei soggetti sani




Adattato da Unger RH, *et al*. *N Engl J Med.* 1971;285:443–449.

# Nel T2DM, l'alterata secrezione di insulina e glucagone determinano iperglicemia



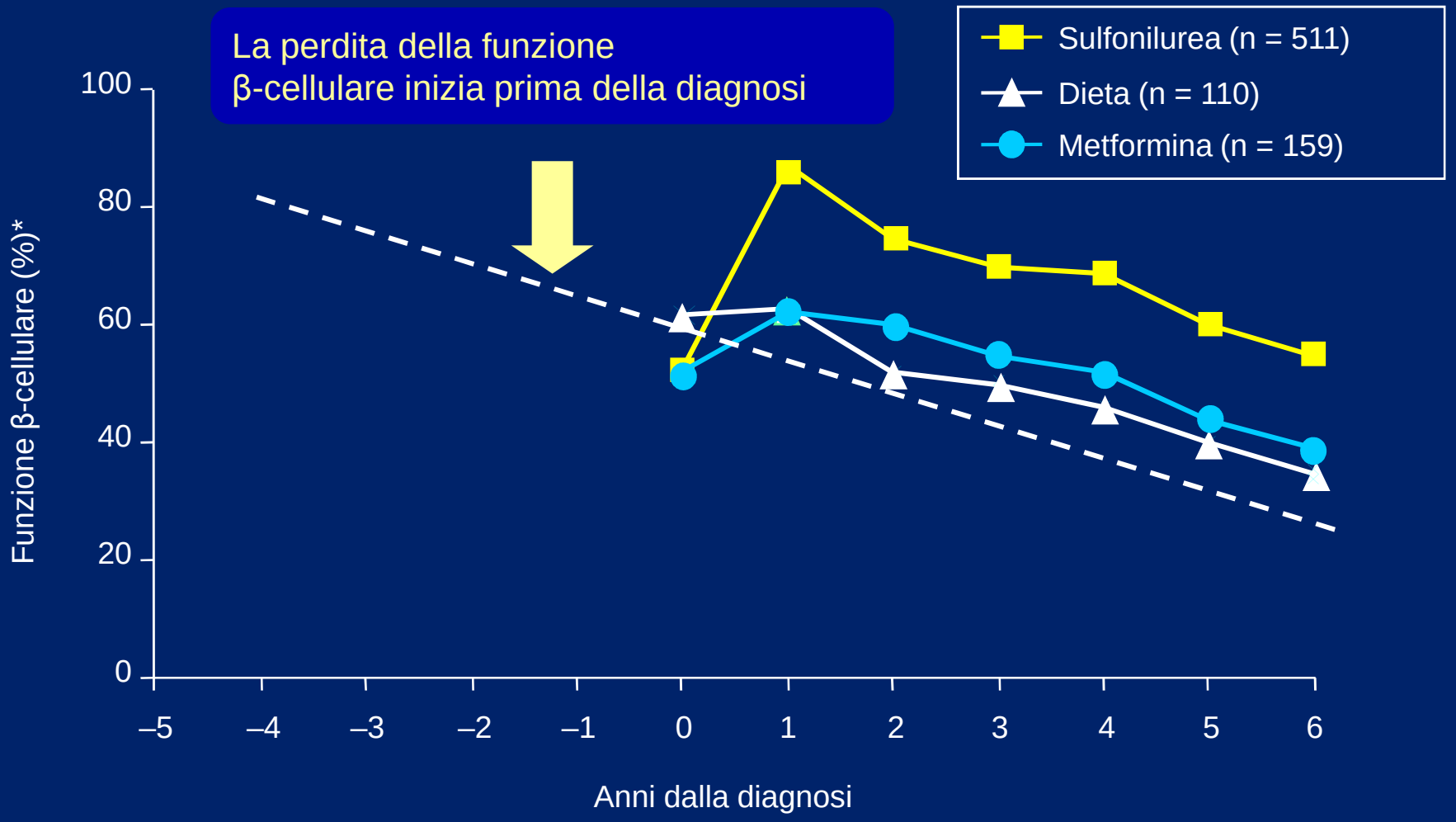

Adattato da Muller WA, *et al*. *N Engl J Med*. 1970;283:109–115.

# Glucagone

- Il glucagone contribuisce insieme all'insulina all'omeostasi glucidica
- Nel T2DM la ridotta sensibilità al glucosio delle α-cellule determina un' inappropriata secrezione di glucagone
- L' eccessiva secrezione di glucagone contribuisce all'iperglicemia caratteristica dell'IGT e del T2DM
- La riduzione delle concentrazioni di glucagone costituisce un valido obiettivo terapeutico nel trattamento del T2DM

IGT = intolleranza al glucosio

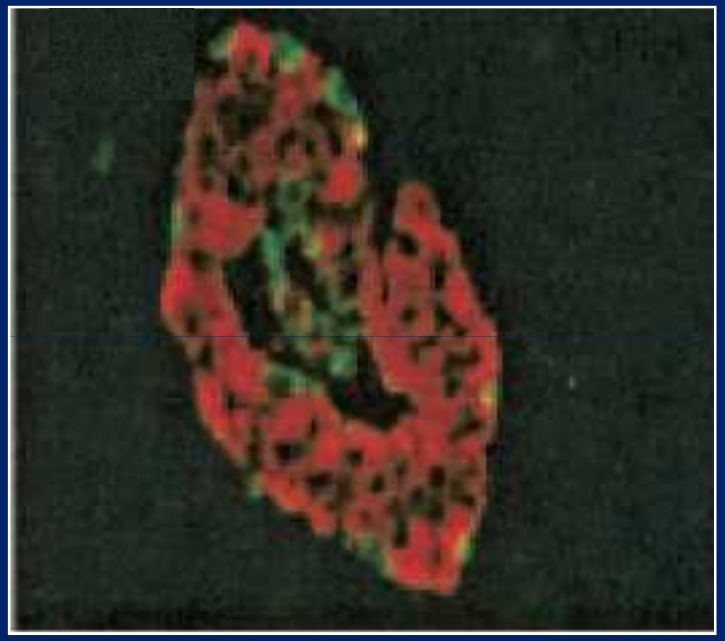
# Il deterioramento della funzione β-cellulare è indipendente dalla terapia (UKPDS)




*La funzione β-cellulare viene misurata dall' homeostasis model assessment (HOMA) che è un indice di resistenza insulinica (glicemia a digiuno x insulinemia a digiuno/22.5; valore normale intorno a 2)
Adattato da UKPDS Group. *Diabetes*. 1995;44:1249–1258.

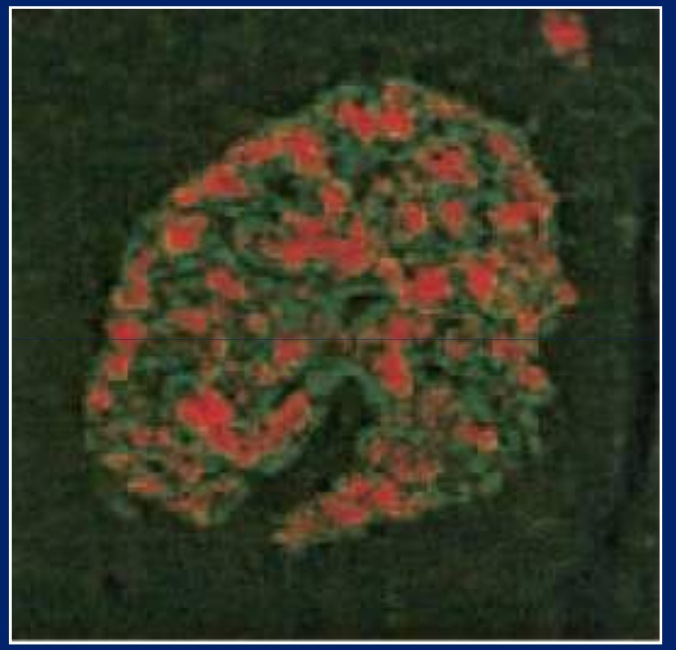
# Nel T2DM, la massa di β-cellule è ridotta significativamente

Controllo



$$\frac{35\%\ \alpha\text{-cellule}}{65\%\ \beta\text{-cellule}} = 0{,}54$$

T2DM



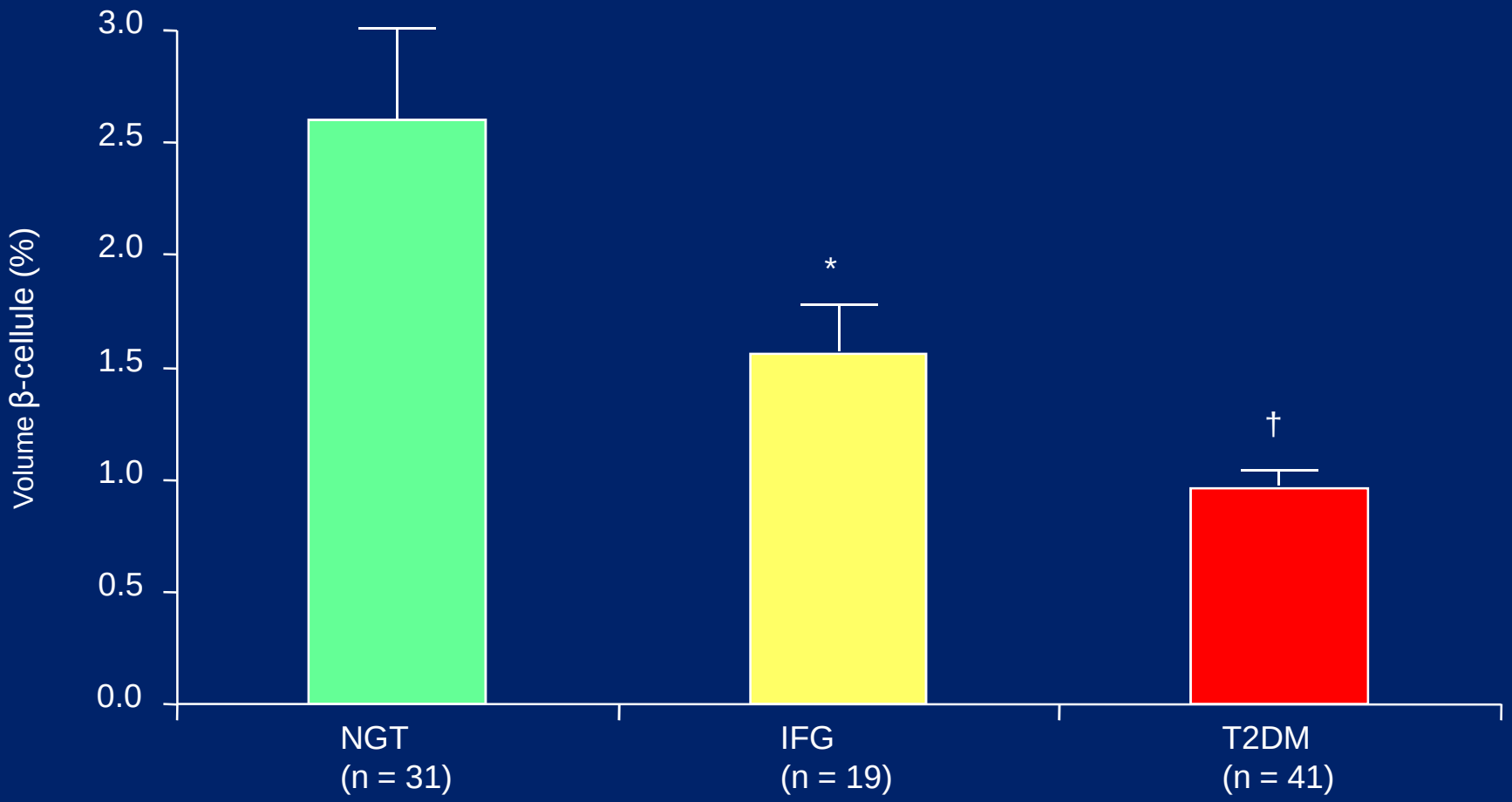
$$\frac{52\%\ \alpha\text{-cellule}}{48\%\ \beta\text{-cellule}} = 1{,}08$$

$P < .01$

T2DM = diabete mellito di tipo 2

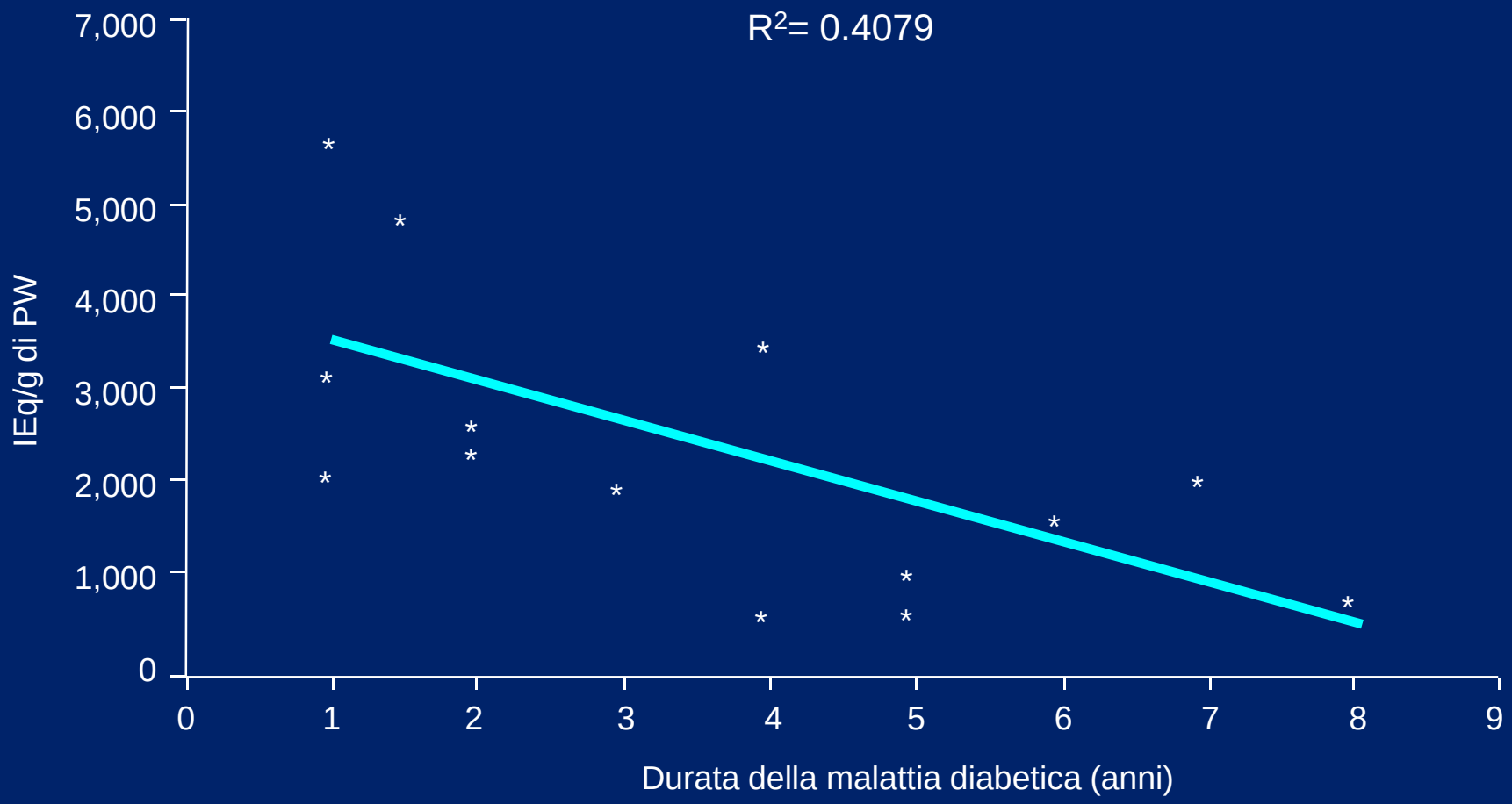
Adattato da Deng S, et al. *Diabetes* 2004; 53:624–632.

# Il volume delle β-cellule è significativamente ridotto nei pazienti obesi con IFG e con T2DM



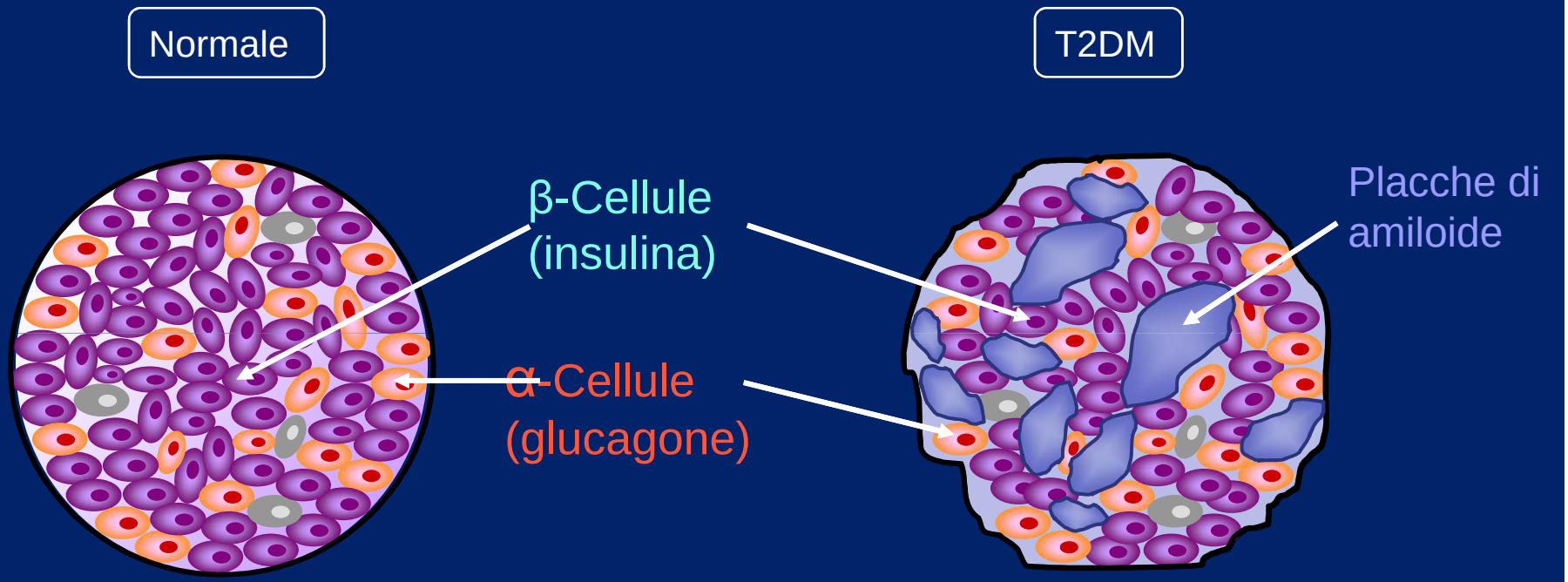

IFG = alterazione della glicemia a digiuno; NGT = normale tolleranza al glucosio; T2DM = diabete mellito di tipo 2
*$P$ <.05 vs NGT; †$P$ <.001 vs NGT
Adattato da Butler AE, et al. *Diabetes*. 2003;52:102–110.

# Le β-cellule diminuiscono con la progressione del T2DM




IEq= Isole Equivalenti; PW= Peso pancreatico
Adattato da Deng S, *et al*. *Diabetes* 2004; 53:624–632.

# Morfologia delle isole pancreatiche: evidenti difetti strutturali nel T2DM

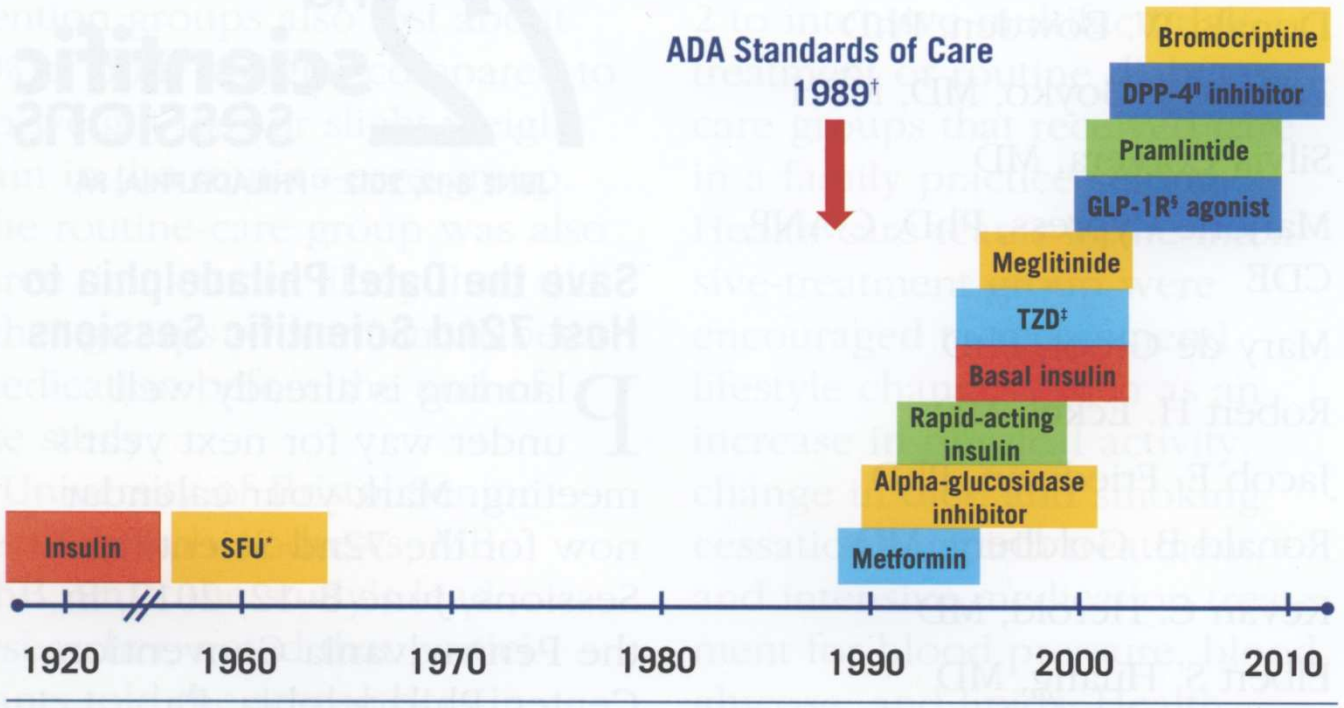



- riduzione della massa β-cellulare
- iperplasia delle cellule α
- Placche di amiloide (AIPP)*
- fibrosi
- ialinizzazione

* Polipeptide Amiloide Insulare

Adattato da Rhodes CJ. *Science.* 2005; 307:380–384.

# History of U.S. Diabetes Therapeutic Advances



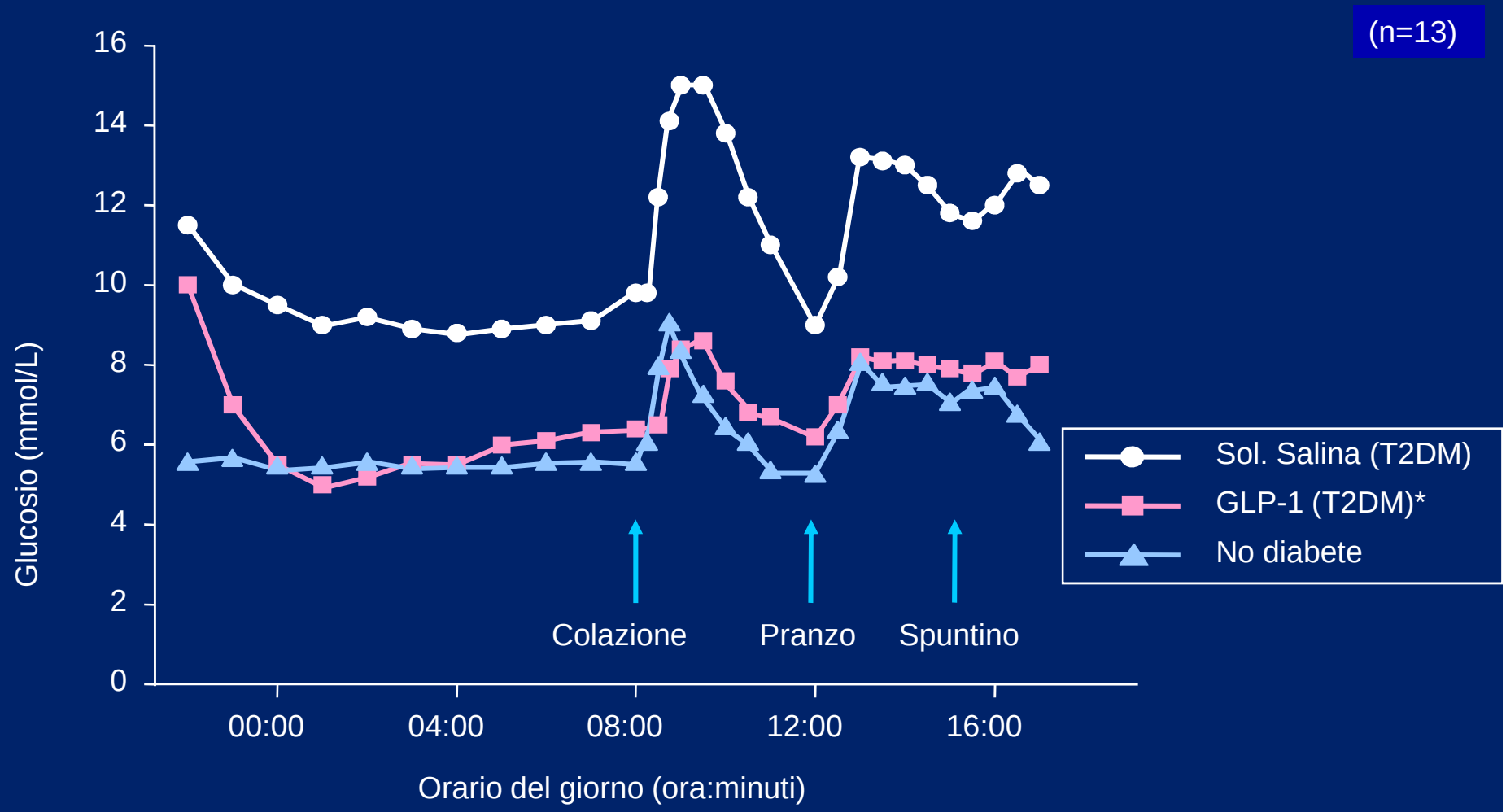

*Sulfonylureas
†The first year that the American Diabetes Association published standards of medical care for diabetes.
‡Thiazolidinedione
§Glucagon-like peptide 1 receptor
‖Dipeptidyl peptidase-4

American Diabetes Association.

# Limiti degli attuali agenti stimolanti la β-cellula

- Stimolazione continua della secrezione insulinica
- Accumulo del farmaco
- Rischio di ipoglicemia
- Potenziali effetti CVS avversi (insufficiente sensibilità della β-cellula
- Aumento di peso (modesto)
- Insufficiente preservazione / perdita della massa β-cellulare

# L’infusione di GLP-1 normalizza il glucosio plasmatico nei pazienti con T2DM



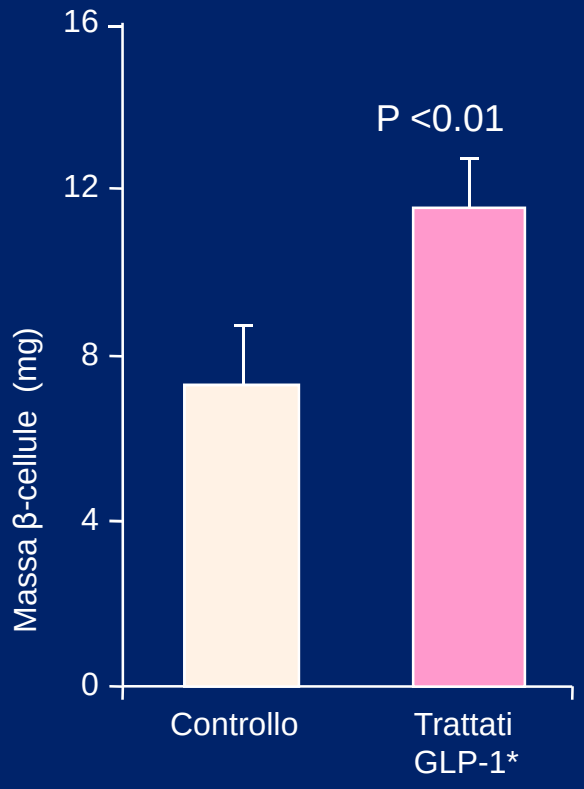

*GLP-1(7-36 amide)

Adattato da Rachman J, *et al*. *Diabetologia*. 1997;40:205-211.

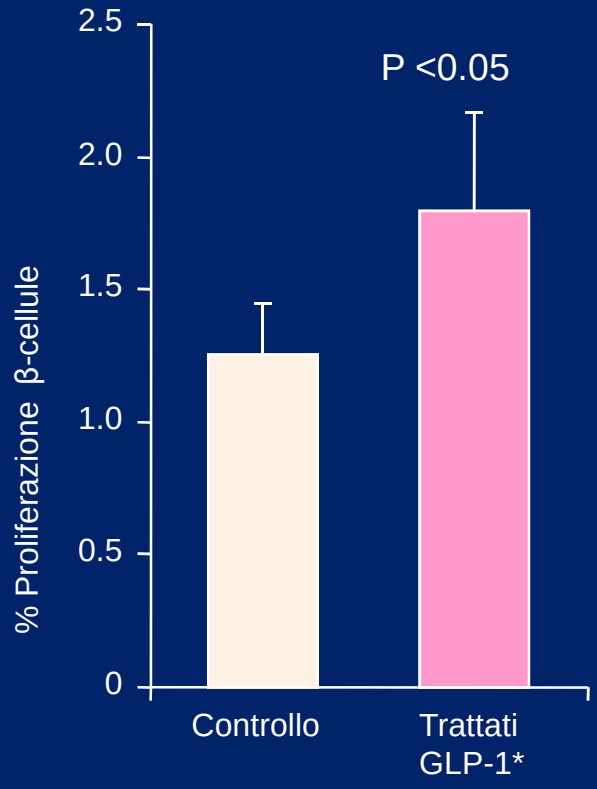
# GLP-1 aumenta la massa β-cellulare nei ratti diabetici obesi Zucker

(n=16)

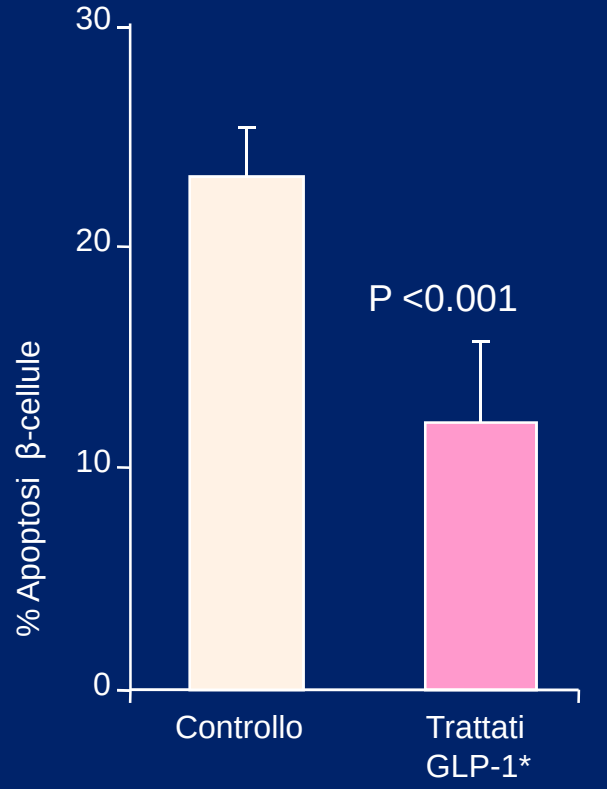
Massa β-cellule




Proliferazione β-cellule




Apoptosi β-cellule

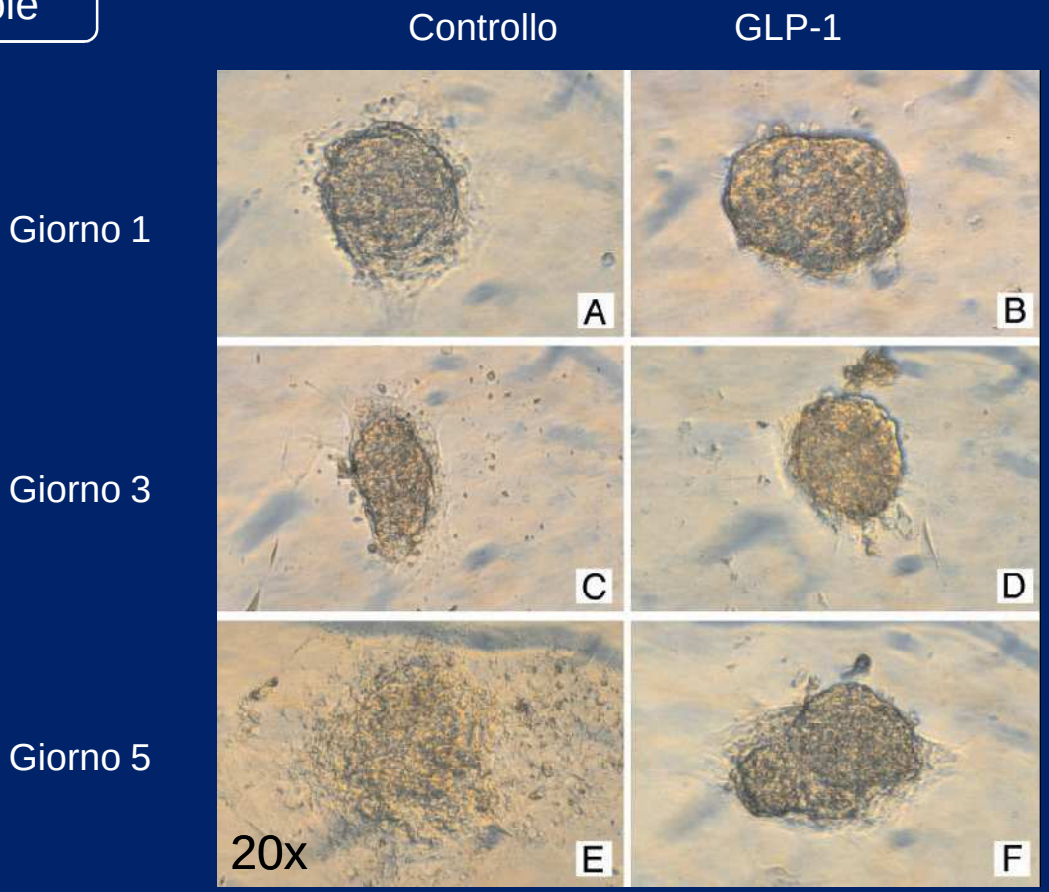



*GLP-1 infuso a 30 pmol/kg/min per 2 giorni

Adattato da Farilla L, *et al. Endocrinology.* 2002;143:4397–4408.

# GLP-1 aggiunto a isole pancreatiche umane*: evidenza istologica della preservazione morfologica e funzionale delle isole

Struttura 3-D Isole




*Isole pancreatiche umane di 3 donatori indipendenti poste in coltura per 1, 3, e 5 giorni in mezzo IM199 in presenza o assenza di GLP-1 (GLP-1 10nM, aggiunto ogni 12 ore)

†Sovrapposizione della colorazione dei nuclei DAPI (blu) e dell'insulina (rosso). Dati ottenuti dalla conta dei punti delle cellule doppio positivo divisa per il numero di cellule DAPI positive. Significatività statistica calcolata con *t* test di Student.

Adattato da Farilla L, *et al*. *Endocrinology*. 2003;144:5149-58.

# 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. Zhang[1]

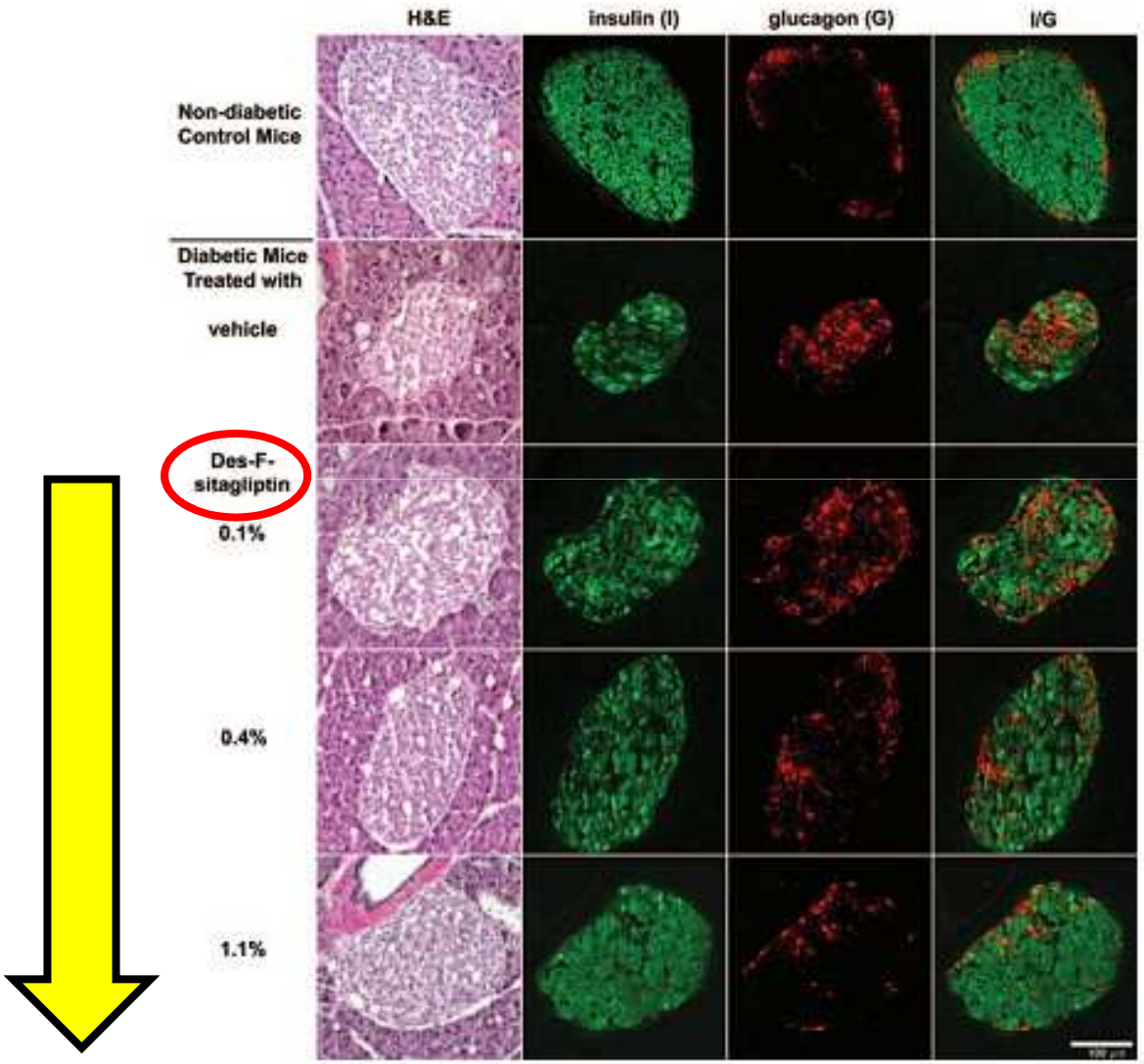



FIG. 3. Immunohistochemical analysis of pancreatic sections. HFD/STZ diabetic mice were treated with vehicle or des-fluoro-sitagliptin (des-F-sitagliptin) at indicated dosages for 11 weeks. Whole pancreas from each was cryopreserved, and consecutive sections were stained with hematoxylin and eosin (H&E), anti-insulin antibody (green), or anti-glucagon antibody (red). Shown are representative islets from each groups with each staining and the overlay of the insulin and glucagon staining (I/G).

ORIGINAL ARTICLE

doi: 10.1111/j.1463-1326.2006.00704.x

# 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

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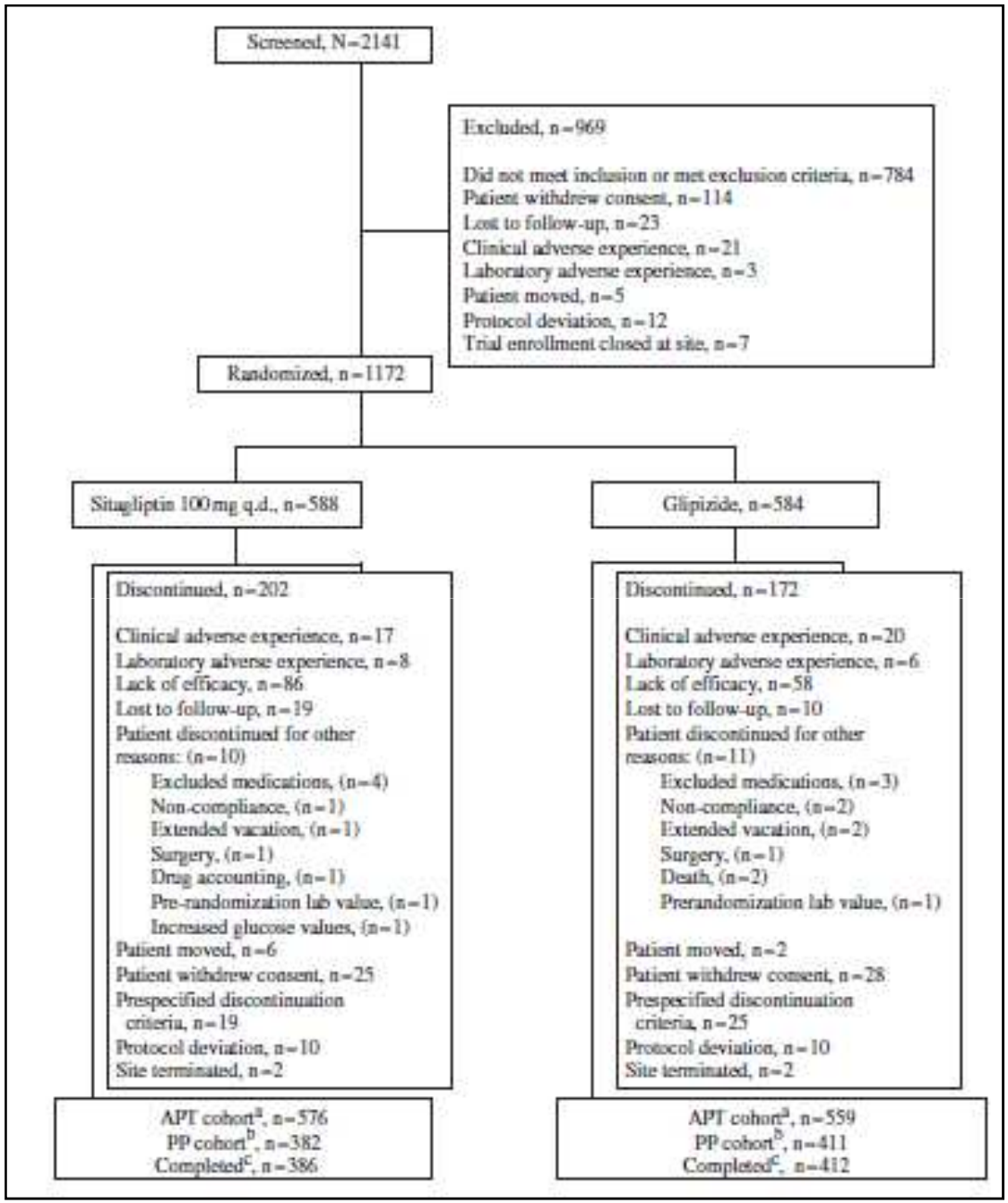
[1]Diabeteszentrum Bad Lauterberg im Harz, Bad Lauterberg, Germany
[2]Merck Research Laboratories, Rahway, NJ, USA

Diabetes, Obesity and Metabolism, **9**, 2007, 194–205

Efficacy and safety of sitagliptin vs glipizide in Type 2 diabetes



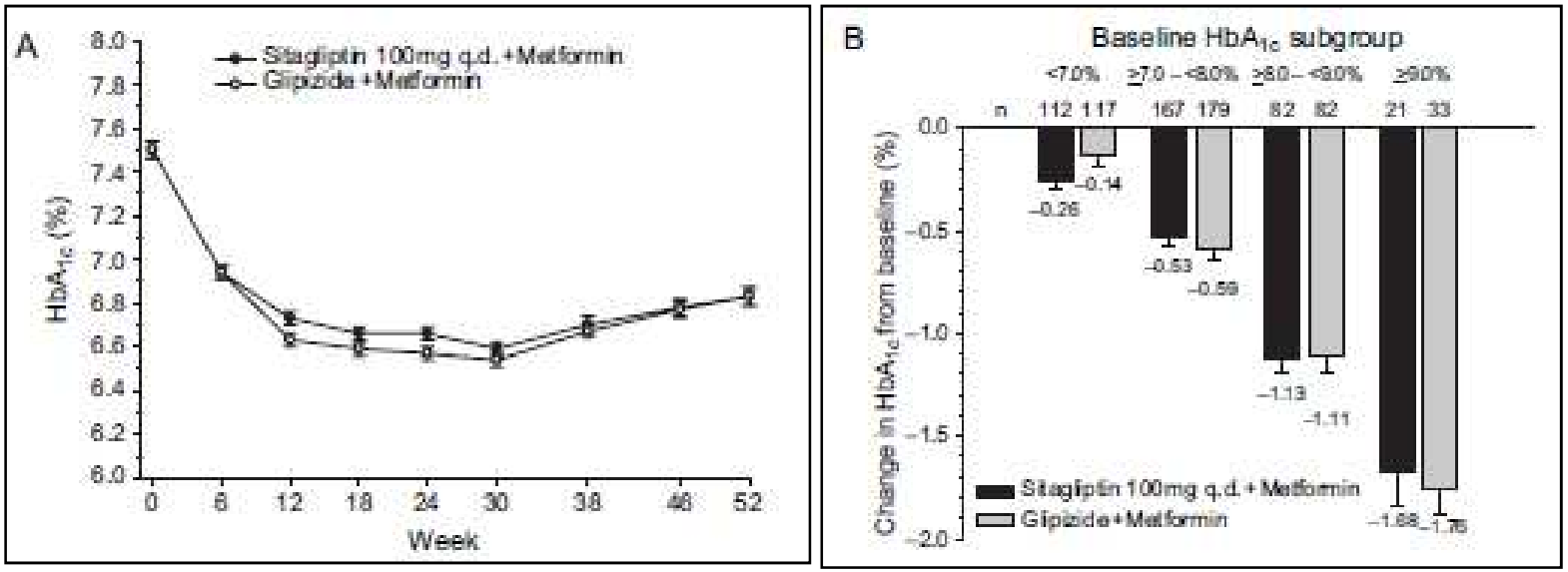



**Fig. 2** (A) For the per-protocol population, haemoglobin $A_{1c}$ ($HbA_{1c}$) change (±s.e.) over time in patients on ongoing metformin therapy treated with sitagliptin 100 mg q.d. or glipizide. (B) Mean $HbA_{1c}$ change (±s.e.) from baseline at Week 52 by baseline $HbA_{1c}$ subgroups.

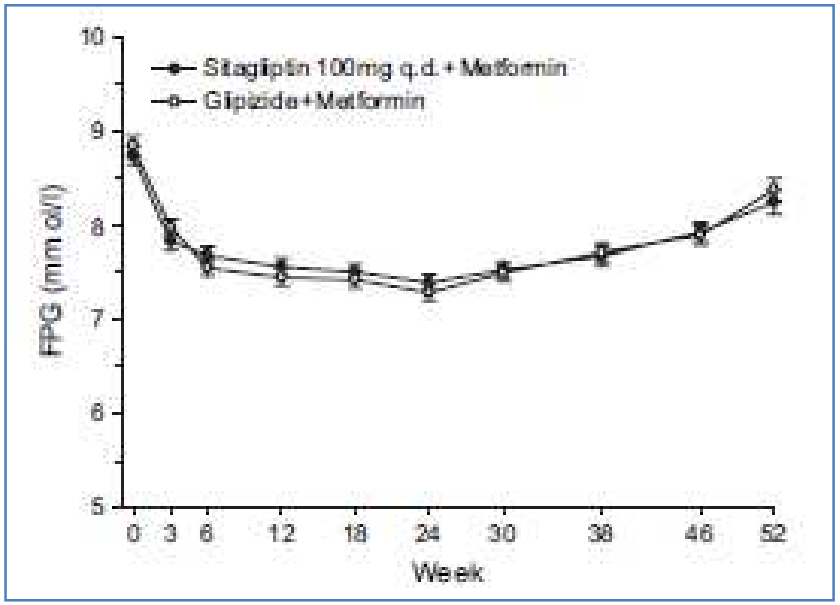



**Fig. 3** For the per-protocol population, fasting plasma glucose (FPG) change (±s.e.) over time in patients on ongoing metformin therapy treated with sitagliptin 100 mg q.d. or glipizide.

**Table 3** Safety results in the all-patients-as-treated population

| | 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* | 86 (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) |
| Prespecified selected gastrointestinal AEs | | |
| Abdominal pain | 16 (2.7) | 12 (2.1) |
| Nausea | 15 (2.6) | 16 (2.7) |
| Vomiting | 5 (0.9) | 9 (1.5) |
| Diarrhoea | 34 (5.8) | 32 (5.5) |

AE, adverse experience; $HbA_{1c}$, haemoglobin $A_{1c}$; SAE, serious AE.
*Considered by the investigator as possibly, probably, or definitely related to study drug.

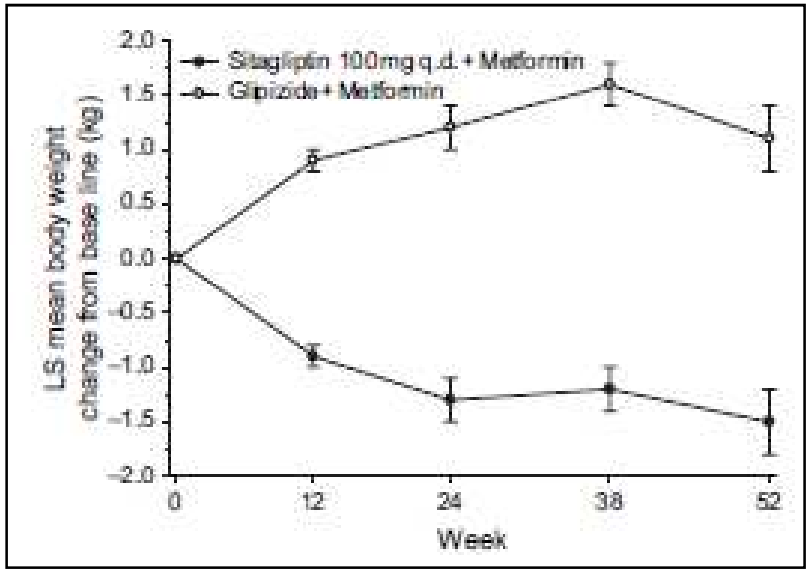
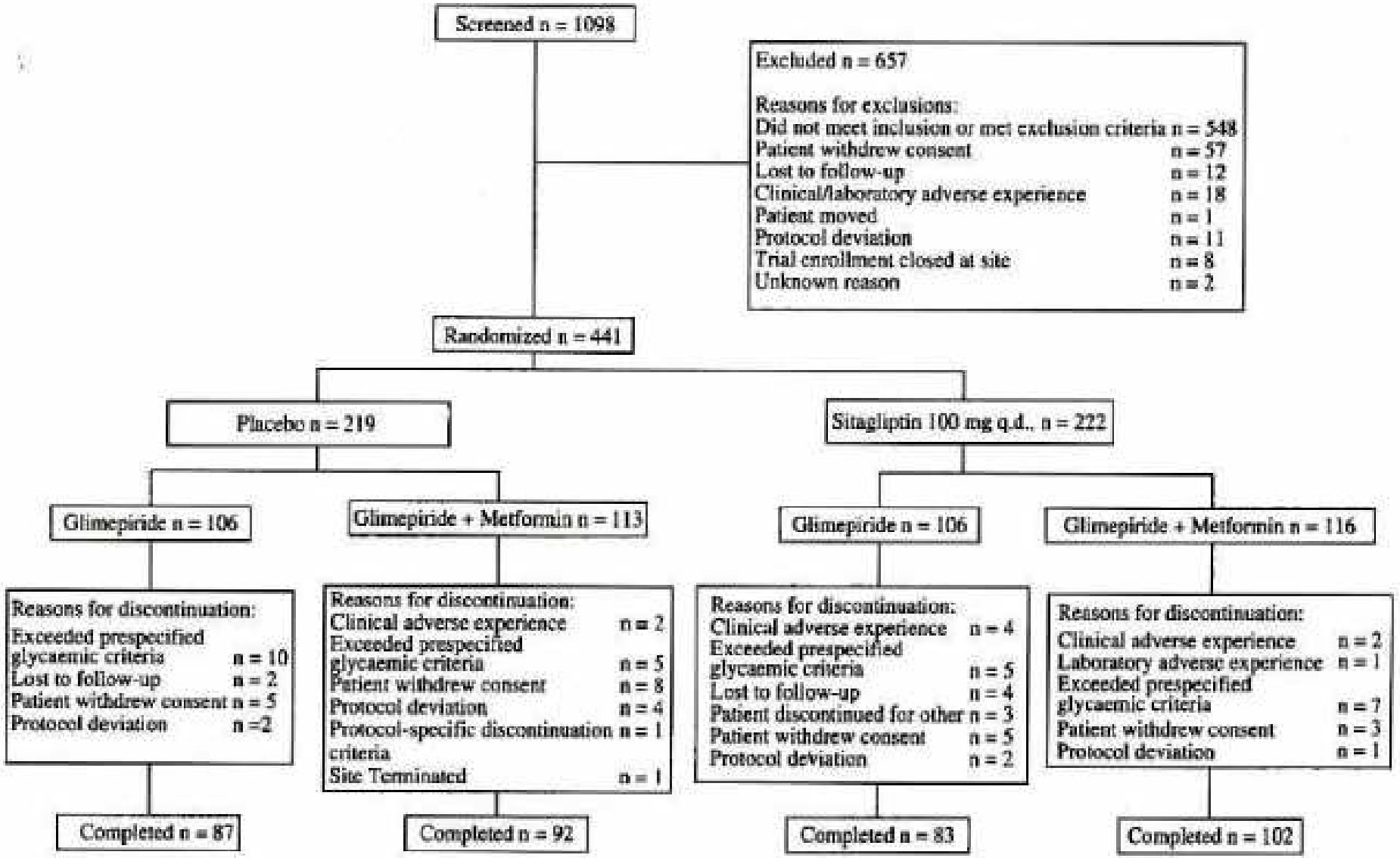


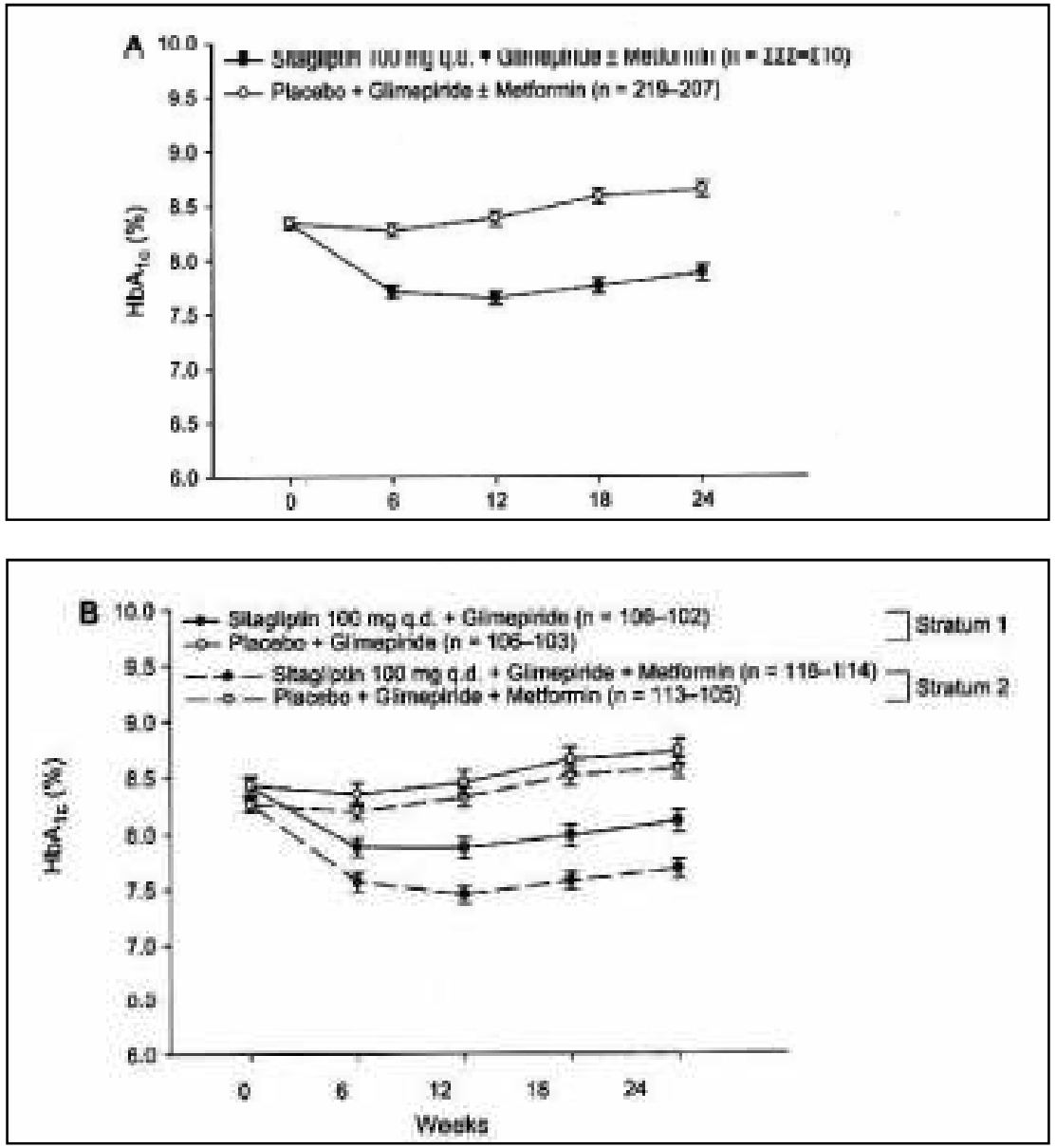

**Fig. 4** For the all-patients-as-treated population, least square mean body weight change (±s.e.) from baseline over time in patients on ongoing metformin therapy treated with sitagliptin 100 mg q.d. or glipizide.

# Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin

K. Hermansen,[1] M. Kipnes,[2] E. Luo,[3] D. Fanurik,[3] H. Khatami[3] and P. Stein,[3] for the Sitagliptin Study 035 Group*

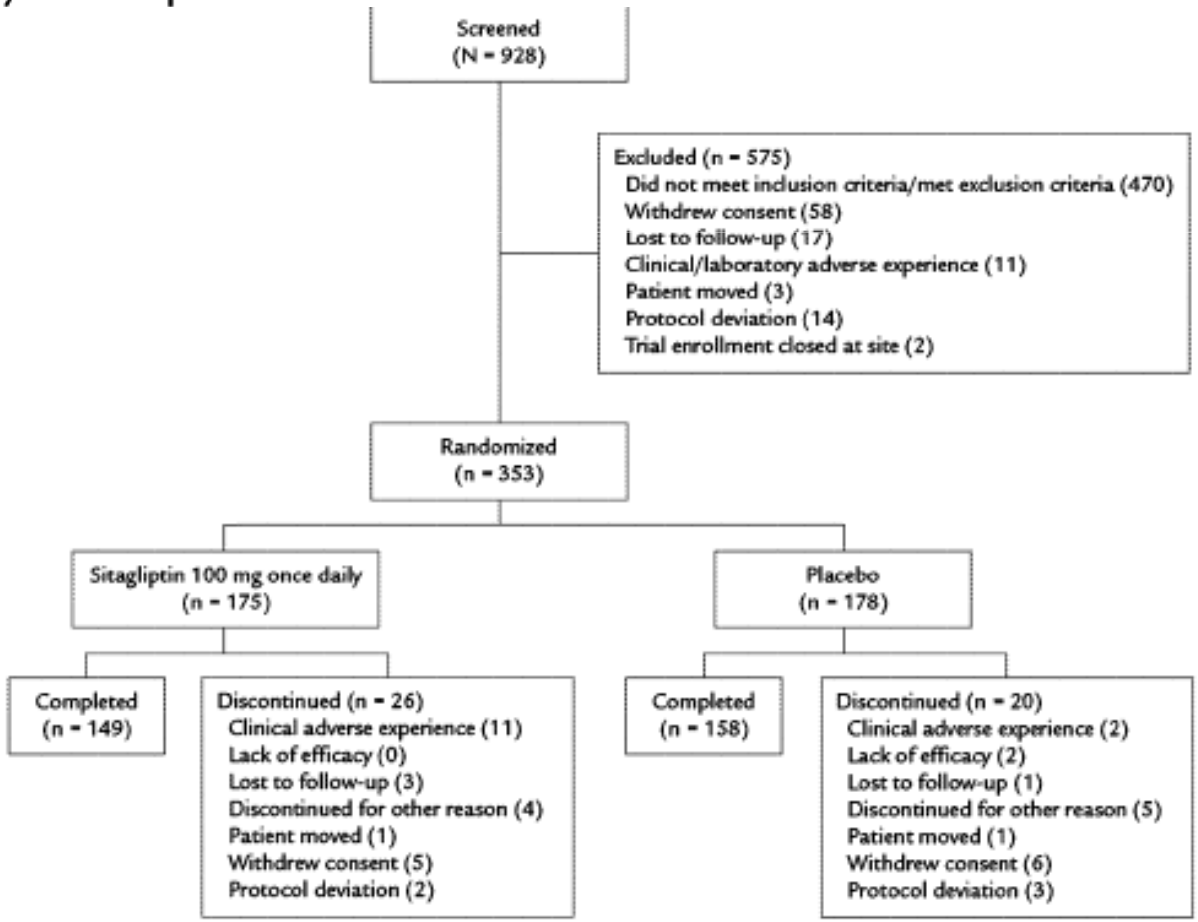
Diabetes, Obesity and Metabolism, 9, 2007, 733–745


Screened n = 1098
Excluded n = 657
Reasons for exclusions:
Did not meet inclusion or met exclusion criteria n = 548
Patient withdrew consent n = 57
Lost to follow-up n = 12
Clinical/laboratory adverse experience n = 18
Patient moved n = 1
Protocol deviation n = 11
Trial enrollment closed at site n = 8
Unknown reason n = 2
Randomized n = 441
Placebo n = 219
Sitagliptin 100 mg q.d., n = 222
Glimepiride n = 106
Glimepiride + Metformin n = 113
Glimepiride n = 106
Glimepiride + Metformin n = 116
Reasons for discontinuation:
Exceeded prespecified glycaemic criteria n = 10
Lost to follow-up n = 2
Patient withdrew consent n = 5
Protocol deviation n =2
Reasons for discontinuation:
Clinical adverse experience n = 2
Exceeded prespecified glycaemic criteria n = 5
Patient withdrew consent n = 8
Protocol deviation n = 4
Protocol-specific discontinuation criteria n = 1
Site Terminated n = 1
Reasons for discontinuation:
Clinical adverse experience n = 4
Exceeded prespecified glycaemic criteria n = 5
Lost to follow-up n = 4
Patient discontinued for other n = 3
Patient withdrew consent n = 5
Protocol deviation n = 2
Reasons for discontinuation:
Clinical adverse experience n = 2
Laboratory adverse experience n = 1
Exceeded prespecified glycaemic criteria n = 7
Patient withdrew consent n = 3
Protocol deviation n = 1
Completed n = 87
Completed n = 92
Completed n = 83
Completed n = 102

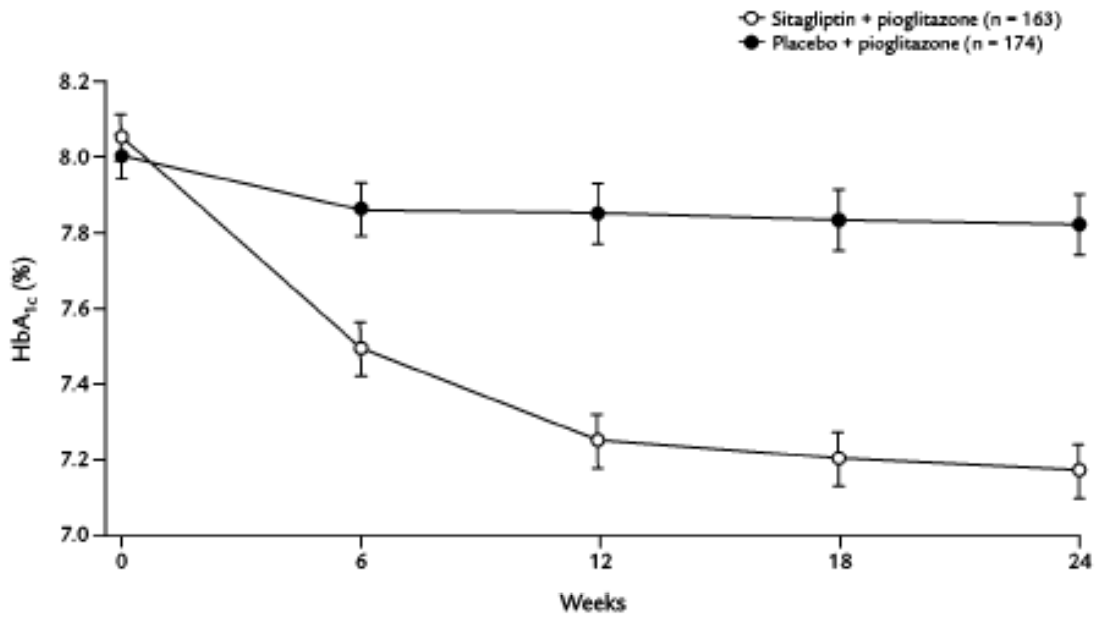

A
Sitagliptin 100 mg q.d. + Glimepiride ± Metformin (n = 222–210)
Placebo + Glimepiride ± Metformin (n = 219–207)
HbA1c (%)
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
0
6
12
18
24
B
Sitagliptin 100 mg q.d. + Glimepiride (n = 106–102)
Placebo + Glimepiride (n = 105–103)
Sitagliptin 100 mg q.d. + Glimepiride + Metformin (n = 115–114)
Placebo + Glimepiride + Metformin (n = 113–105)
Stratum 1
Stratum 2
HbA1c (%)
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
0
6
12
18
24
Weeks

# Efficacy and Safety of the Dipeptidyl Peptidase-4 Inhibitor Sitagliptin Added to Ongoing Pioglitazone Therapy in Patients with Type 2 Diabetes: A 24-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study

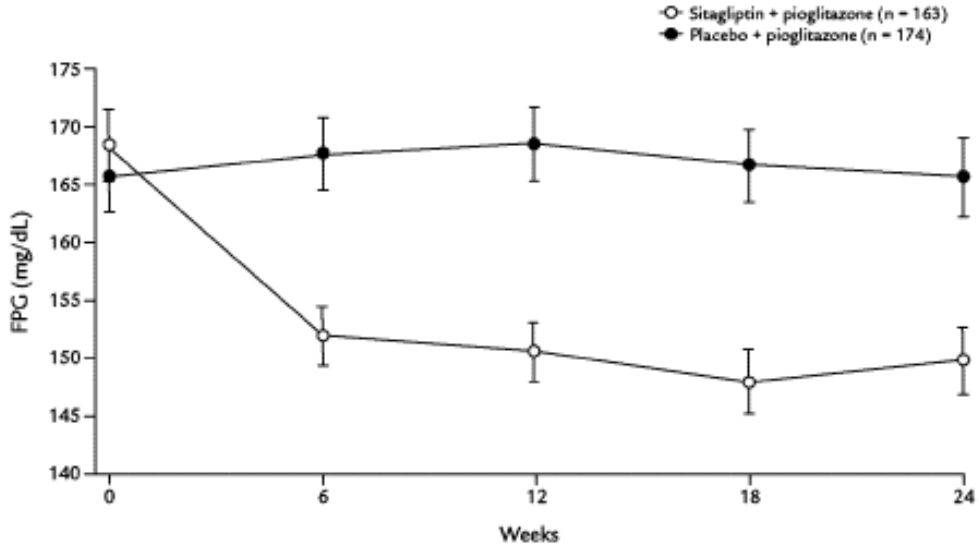
Julio Rosenstock, MD[1]; Ronald Brazg, MD[2]; Paula J. Andryuk, BS[3]; Kaifeng Lu, PhD[3]; and Peter Stein, MD[3]; for the Sitagliptin Study 019 Group*



Changes in mean (SE) glycosylated hemoglobin ($HbA_{1c}$) over time with sitagliptin 100 mg once daily or placebo added to ongoing pioglitazone therapy in patients with type 2 diabetes who had not achieved adequate glycemic control with pioglitazone alone.




Changes in mean (SE) fasting plasma glucose (FPG) over time with sitagliptin 100 mg once daily o placebo added to ongoing pioglitazone therapy in patients with type 2 diabetes who had not achieve adequate glycemic control with pioglitazone alone.



Least squares (LS) mean percent change in lipid end points from baseline (week 0) to week 24.*

| Variable | Week 0, Mean (SD) | Week 24, Mean (SD) | LS Mean % Change from Baseline (95% CI) | Difference in LS Mean % Change (95% CI) |
|---|---|---|---|---|
| TC, mg/dL | | | | |
| SITA + PIO (n = 151) | 198.0 (47.0) | 199.7 (43.1) | 1.6 (−1.3 to 4.4) | 0.0 (−3.3 to 3.3) |
| PBO + PIO (n = 162) | 194.3 (45.8) | 197.0 (43.2) | 1.6 (−1.1 to 4.2) | |
| LDL-C, mg/dL | | | | |
| SITA + PIO (n = 150) | 117.4 (41.3) | 118.6 (32.8) | 5.8 (1.2 to 10.4) | 3.3 (−2.0 to 8.6) |
| PBO + PIO (n = 162) | 112.9 (38.1) | 114.5 (36.5) | 2.5 (−1.7 to 6.8) | |
| TG, mg/dL | | | | |
| SITA + PIO (n = 151) | 156.8 (84.6) | 155.7 (104.4) | 1.1 (−8.2 to 10.4) | −11.2 (−22.0 to −0.4)† |
| PBO + PIO (n = 162) | 157.4 (81.7) | 169.5 (112.0) | 12.3 (3.7 to 21.0) | |
| HDL-C, mg/dL | | | | |
| SITA + PIO (n = 151) | 49.6 (12.9) | 49.7 (12.8) | 0.6 (−2.5 to 3.6) | 0.2 (−3.3 to 3.7) |
| PBO + PIO (n = 162) | 50.4 (13.5) | 49.8 (12.4) | 0.4 (−2.5 to 3.2) | |
| Non–HDL-C, mg/dL | | | | |
| SITA + PIO (n = 151) | 148.4 (48.0) | 150.0 (44.8) | 3.4 (−0.7 to 7.5) | 0.4 (−4.4 to 5.1) |
| PBO + PIO (n = 162) | 144.0 (44.4) | 147.2 (42.5) | 3.0 (−0.8 to 6.8) | |

TC = total cholesterol; SITA = sitagliptin 100 mg once daily; PIO = pioglitazone; PBO = placebo; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides; HDL-C = high-density lipoprotein cholesterol.

*Changes were calculated using an all-patients-treated approach with data carried forward.

†$P = 0.041$ for between-treatment difference.

## Summary of clinical adverse experiences (AEs) (no. [%] of patients).

| Variable | Sitagliptin 100 mg Once Daily + Pioglitazone (n = 175) | Placebo + Pioglitazone (n = 178) |
|---|---|---|
| ≥1 AE | 84 (48.0) | 93 (52.2) |
| Drug-related AEs* | 16 (9.1) | 16 (9.0) |
| Serious AEs | 5 (2.9) | 8 (4.5) |
| Drug-related serious AEs* | 1 (0.6) | 0 |
| Discontinuations due to: | | |
| AEs | 10 (5.7)† | 2 (1.1) |
| Drug-related AEs* | 1 (0.6) | 1 (0.6) |
| Serious AEs | 3 (1.7) | 1 (0.6) |
| Drug-related serious AEs* | 1 (0.6) | 0 |
| Clinical AEs of interest | | |
| Hypoglycemia | 2 (1.1) | 0 |
| Overall gastrointestinal AEs‡ | 24 (13.7) | 11 (6.2) |
| Selected gastrointestinal AEs‡ | | |
| Abdominal pain | 6 (3.4)† | 0 |
| Nausea | 2 (1.1) | 0 |
| Diarrhea | 3 (1.7) | 2 (1.1) |
| Vomiting | 1 (0.6) | 1 (0.6) |

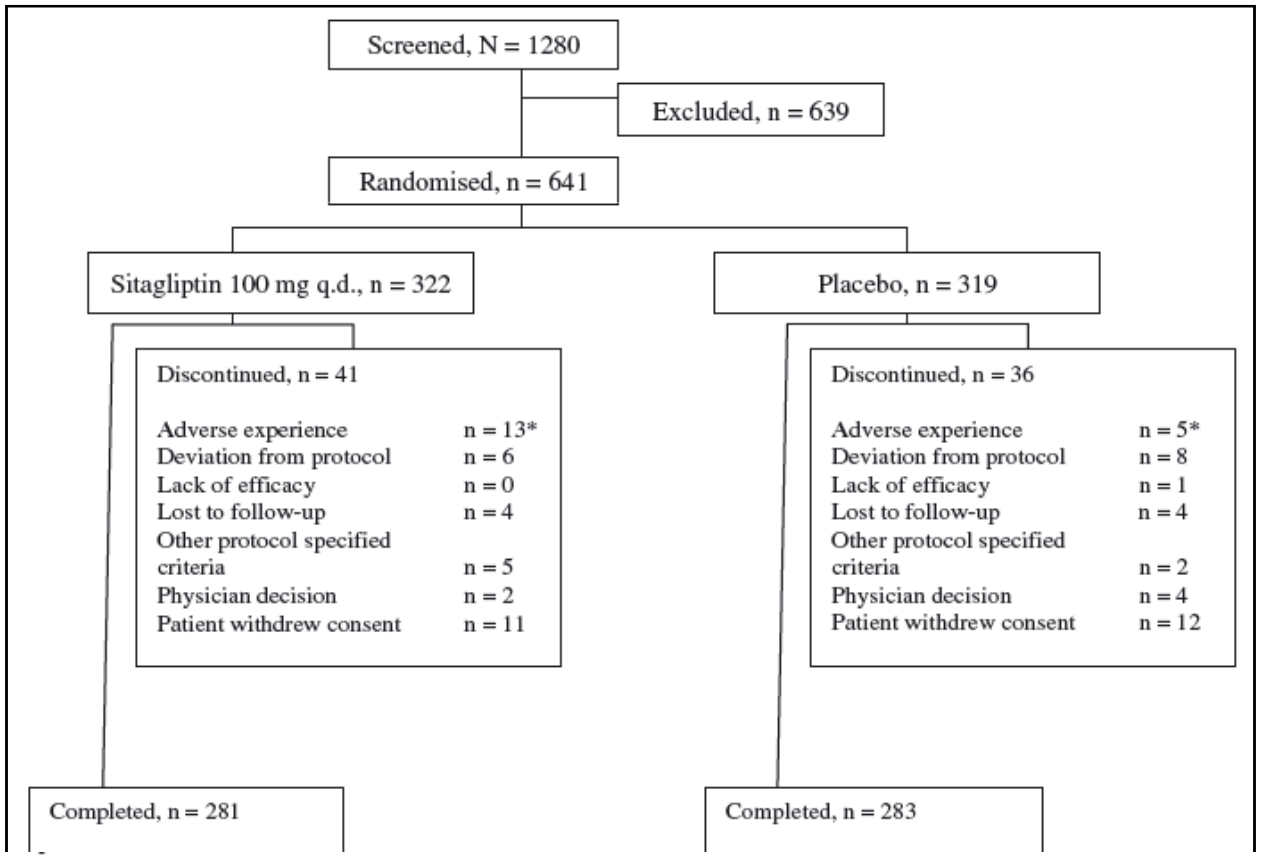
*Considered by the investigator as possibly, probably, or definitely related to study drug.
†$P < 0.05$ for between-treatment difference.
‡Excluding AEs occurring after the initiation of glycemic rescue therapy with metformin.

original article

*Diabetes, Obesity and Metabolism* 12: 167–177, 2010.


# Efficacy and safety of sitagliptin when added to insulin therapy in patients with type 2 diabetes

T. Vilsbøll[1], J. Rosenstock[2], H. Yki-Järvinen[3], W. T. Cefalu[4], Y. Chen[5], E. Luo[5], B. Musser[5], P. J. Andryuk[5], Y. Ling[5], K. D. Kaufman[5], J. M. Amatruda[5], S. S. Engel[5] & L. Katz[5]




*Includes three patients (two in the sitagliptin group and one on the placebo group) who discontinued due to adverse experiences with onset prior to initiation of study medication.

| Characteristic | Sitagliptin 100 mg q.d. + insulin (±MET) (n = 322) | Placebo + insulin (±MET) (n = 319) |
|---|---|---|
| Age, years | 58.3 ± 9.1 | 57.2 ± 9.3 |
| Sex, n (%), male | 157 (49) | 169 (53) |
| Race, n (%) | | |
| White | 228 (71) | 219 (69) |
| Black | 21 (6) | 23 (7) |
| Asian | 55 (17) | 61 (19) |
| Other | 18 (6) | 16 (5) |
| Ethnicity | | |
| Hispanic or Latino | 50 (16) | 39 (12) |
| Body weight, kg | 86.5 ± 18.6 | 87.3 ± 17.9 |
| Body mass index, kg/m$^2$ | 31 ± 5 | 31 ± 5 |
| $HbA_{1c}$, % | 8.7 ± 0.9 | 8.6 ± 0.9 |
| (Range)[a] | (6.6–12.1) | (6.6–11.7) |
| $HbA_{1c}$ distribution at baseline, n (%) | | |
| $HbA_{1c}$ <8% | 68 (21) | 83 (26) |
| $HbA_{1c}$ ≥8 to <9% | 137 (43) | 132 (41) |
| $HbA_{1c}$ ≥9% | 117 (36) | 104 (33) |
| Fasting plasma glucose, mg/dl | 175.6 ± 51.8 | 178.7 ± 59.6 |
| Duration of type 2 diabetes, years | 13 ± 7 | 12 ± 6 |
| Type of insulin, n (%) | | |
| Premixed | 87 (27) | 82 (26) |
| Total daily dose, IU/day | 67.4 ± 35.4 | 74.5 ± 36.9 |
| Long-acting or intermediate-acting | 235 (73) | 237 (74) |
| Total daily dose, IU/day | 44.2 ± 29.9 | 44.5 ± 25.7 |
| On metformin, n (%) | 229 (71) | 233 (73) |

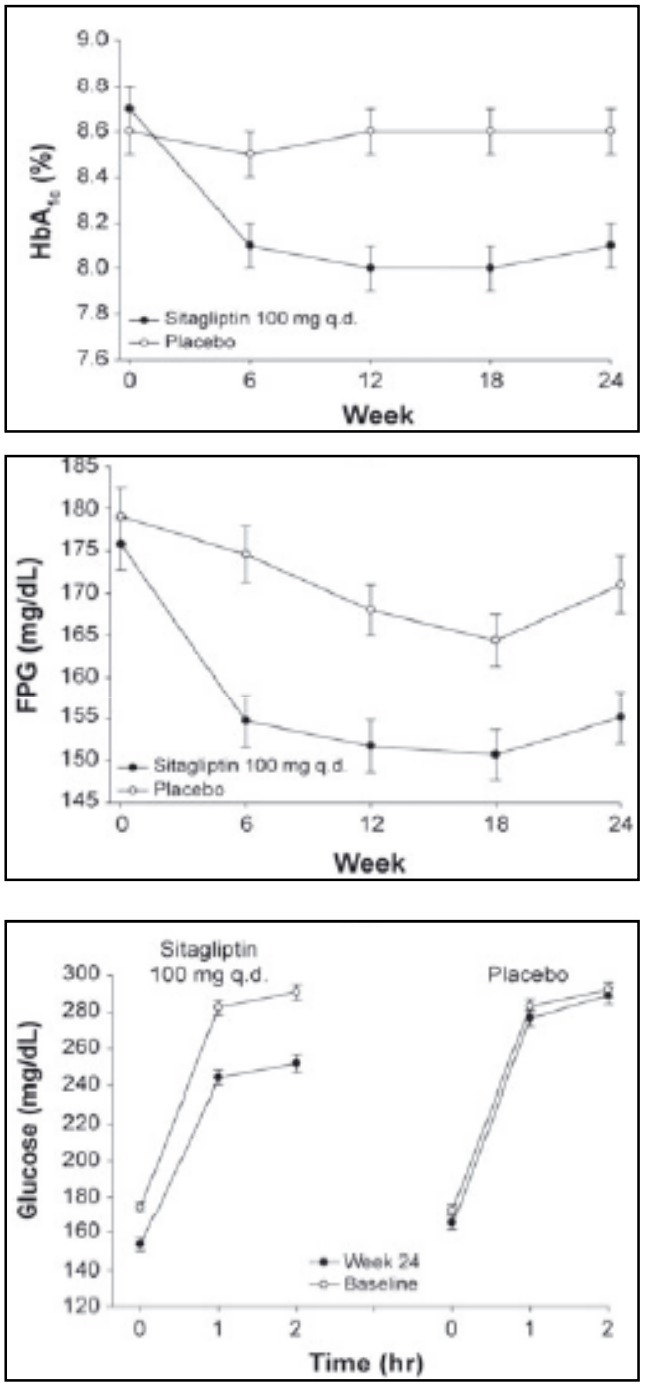



**Figure 2.** (A) HbA1c over time; (B) FPG over time; (C) 2-h glucose curves following a meal tolerance test at baseline and at week 24. Data are expressed as mean ± s.e.

# Le linee guida richiedono sia i valori dell'HbA1c che della glicemia postprandiale

| | AACE[1] | ADA[2] SID-AMD[3] | IDF[4] |
|---|---|---|---|
| **A1C (%)** *Normal: 4-6%* | ≤6.5 | <7.0 | <6.5 |
| **Fasting/Before-Meal (mg/dL)** plasma equivalent **(mmol/L)** | <110 <6.1 | 70 - 130 3.9 - 7.2 | <110 < 6.1 |
| **After-Meals (mg/dL)** **(mmol/L)** | <140 (1-2 hrs) <7.8 | <180 (Peak 1-2 s) <10 | <140 (2 hrs) <7.8 |

*1: The American Association of Clinical Endocrinologists. EndocrPract. 2007.*
*2: The American Diabetes Association. Diabetes Care 2009.*
*3: Standard italiani per la cura del diabete mellito 2009-2010*
*4. International Diabetes Association, 2005, 2007.*

Le linee guida nazionali e internazionali raccomandano valori specifici per la glicemia postprandiale.

# Le linee guida che raccomandano il controllo della glicemia postprandiale

**IDF (*International Diabetes Federation*, Federazione internazionale per il diabete)**
Linee guida del 2007 per la gestione della glicemia postprandiale.

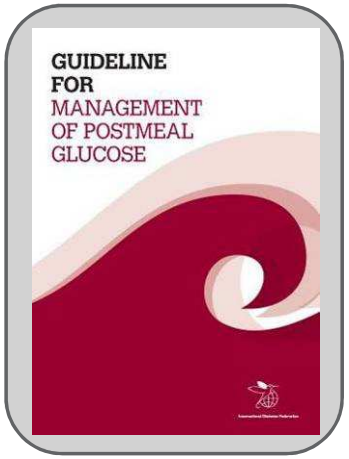
**ADA (*American Diabetes Association*, Associazione americana per il diabete)**
Dichiarazione del 2009.

| Guideline | mg/dL * | mmol/L * |
|---|---|---|
| ADA 2009 | < 180 | < 10.0 |
| IDF 2008 | < 140 | < 7.8 |

* 2-hour post-prandial plasma glucose

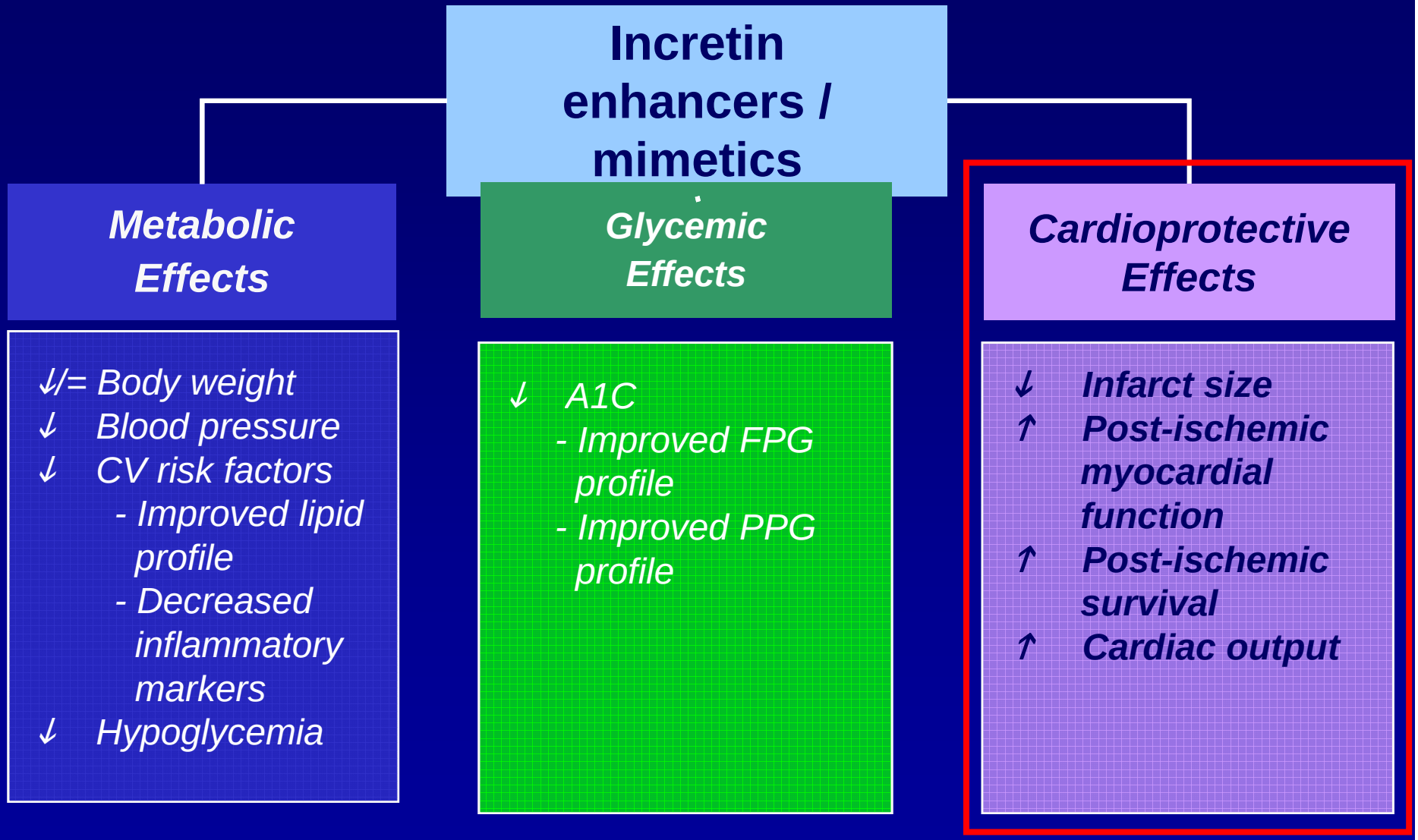
## RACCOMANDAZIONI

- La glicemia plasmatica postprandiale a 2 ore non deve superare i 7,8 mmol/l (140 mg/dl) purché si eviti l'ipoglicemia.
- Deve essere preso in considerazione l'automonitoraggio glicemico perché attualmente costituisce il metodo più pratico di monitoraggio della glicemia postprandiale.




**L'automonitoraggio glicemico è il metodo più pratico per conseguire questo livello di controllo.**

# Incretin-based Therapies : Benefits beyond Glycemic Control




Greeve et al. Br J Pharmacol 2009; 157: 1340-51. Mudaliar & Henry. Am J Med 2009; 122: S25-36

# Incretin-based therapy

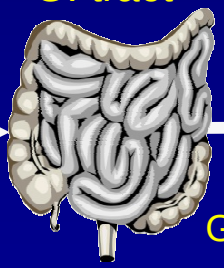
Ingestion of food

**GLP-1 R mimetics/ analogues Resistant to DPP-4 Exenatide, liraglutide**

Glucose dependent
↑ Insulin
from beta cells
(GLP-1 and GIP)

Insulin increases peripheral glucose uptake

GI tract



Release of incretin gut hormones

Active GLP-1 and GIP

Pancreas
Beta cells

Alpha cells

Blood glucose control

Sitagliptin

Vildagliptin

Saxagliptin

Linagliptin

DPP-4 enzyme rapidly degrades incretins

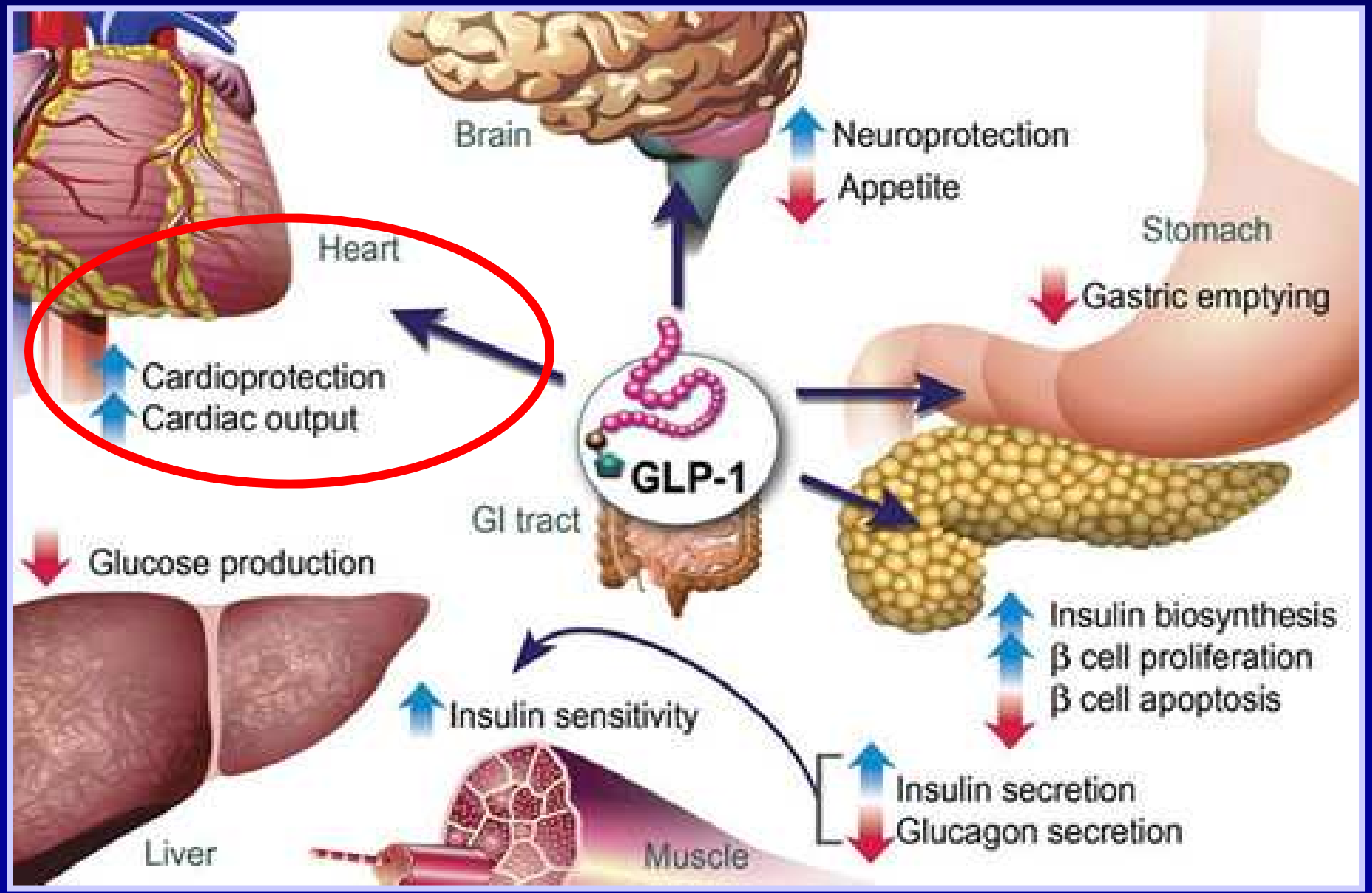
↓ Glucagon
from alpha cells
(GLP-1)
Glucose dependent

↑ insulin

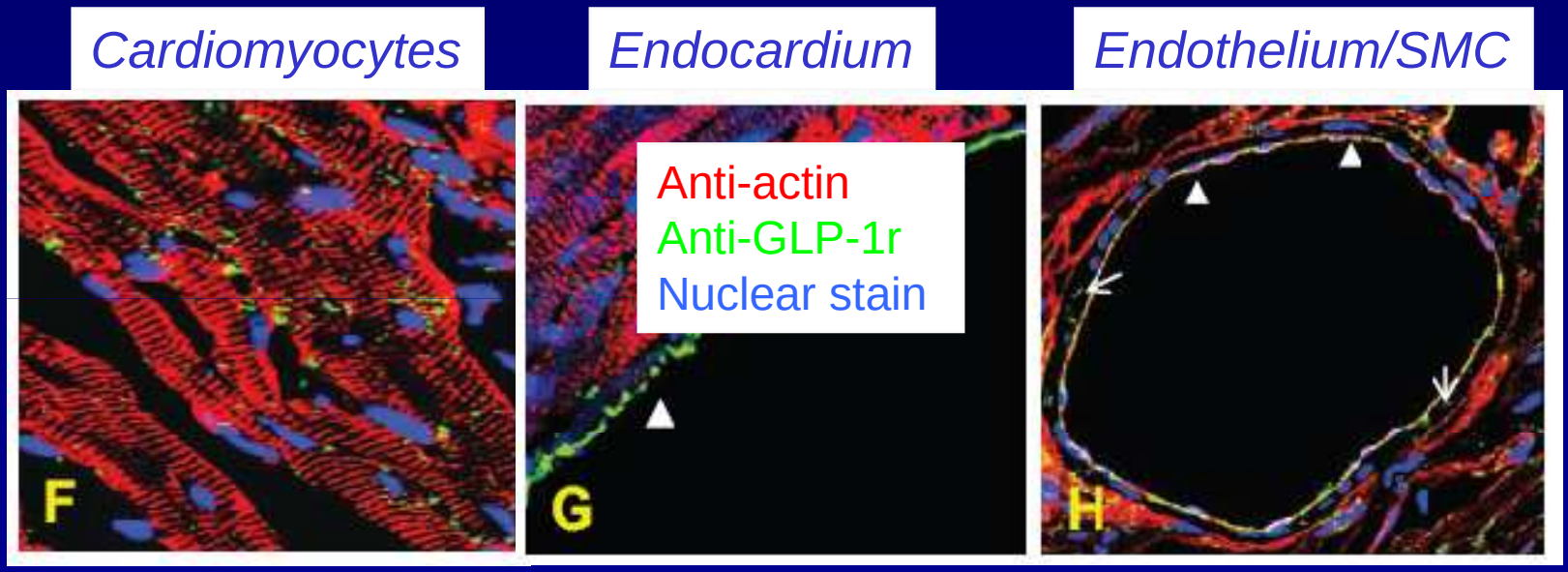
↓glucagon

↓ hepatic glucose output

# Pleiotropic effects of GLP-1



# EXPRESSION OF THE GLP-1R IN CV TISSUES

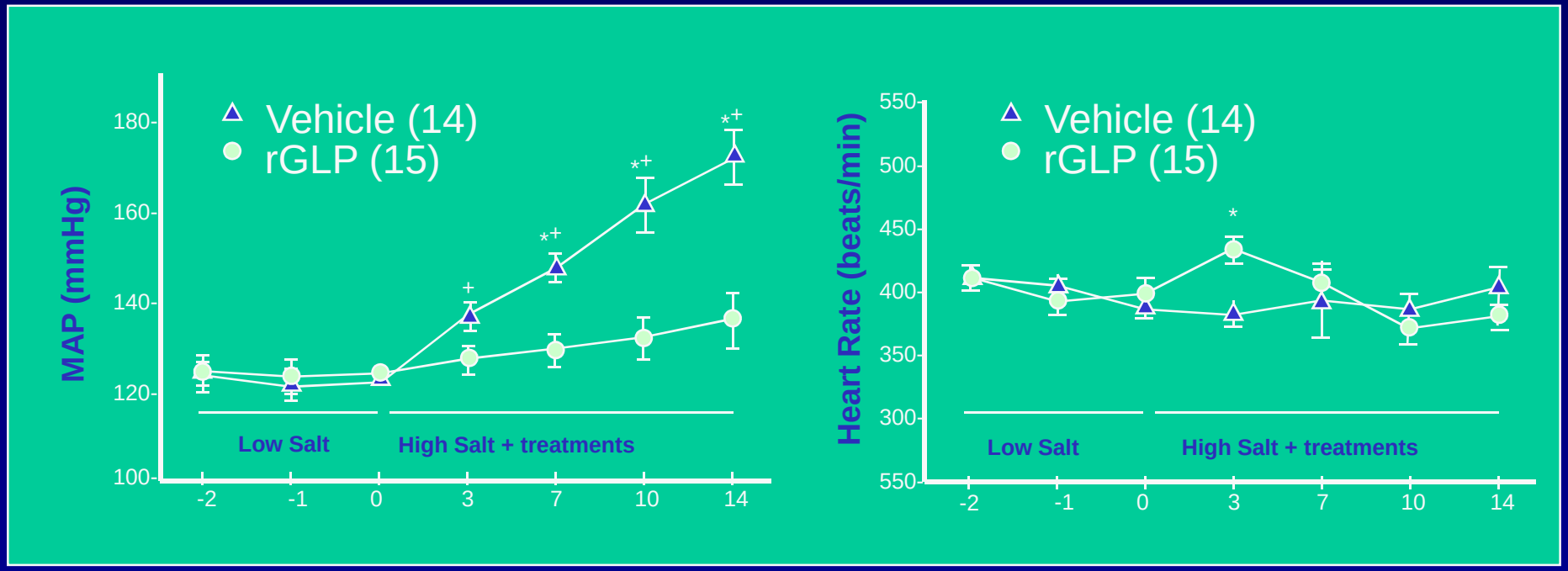



*K Ban et al, Circulation 2008; 117: 2340-50*

# The GLP-1 receptor and the Heart

1. The GLP-1r is expressed in cardiomyocytes and in vascular endothelial cell
2. Activation of the GLP-1r in cardiomyocytes *in vitro* increases cAMP levels and *glucose uptake*
3. GLP-1r knock-out mice have increased *ventricular thickness* and increased end-diastolic pressure
4. In rodents GLP-1 increases *HR* through a CNS pathway

# Effects of rGLP-1 on Mean Arterial Pressure and Heart Rate in Dahl Salt-Sensitive Rats

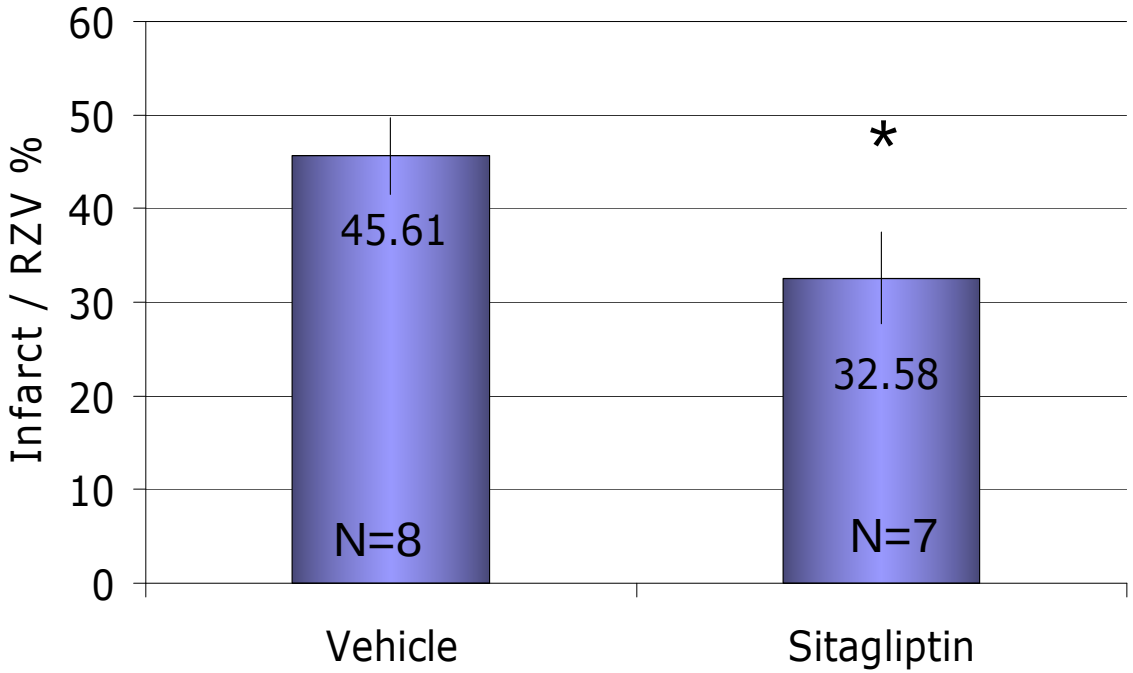



- Rats maintained on a low salt diet during a 3-day control period and then switched to a high salt diet for 14 days
- Rats received either
  - continuous i.v. infusion of recombinant glucagon-like peptide-1 (rGLP-1) (1 tg/kg per min)
  - or vehicle

*Antihypertensive effects of GLP-1 in Dahl salt-sensitive rats.* Yu M et al. *J Hypertens 21: 1125-35, 2003.*

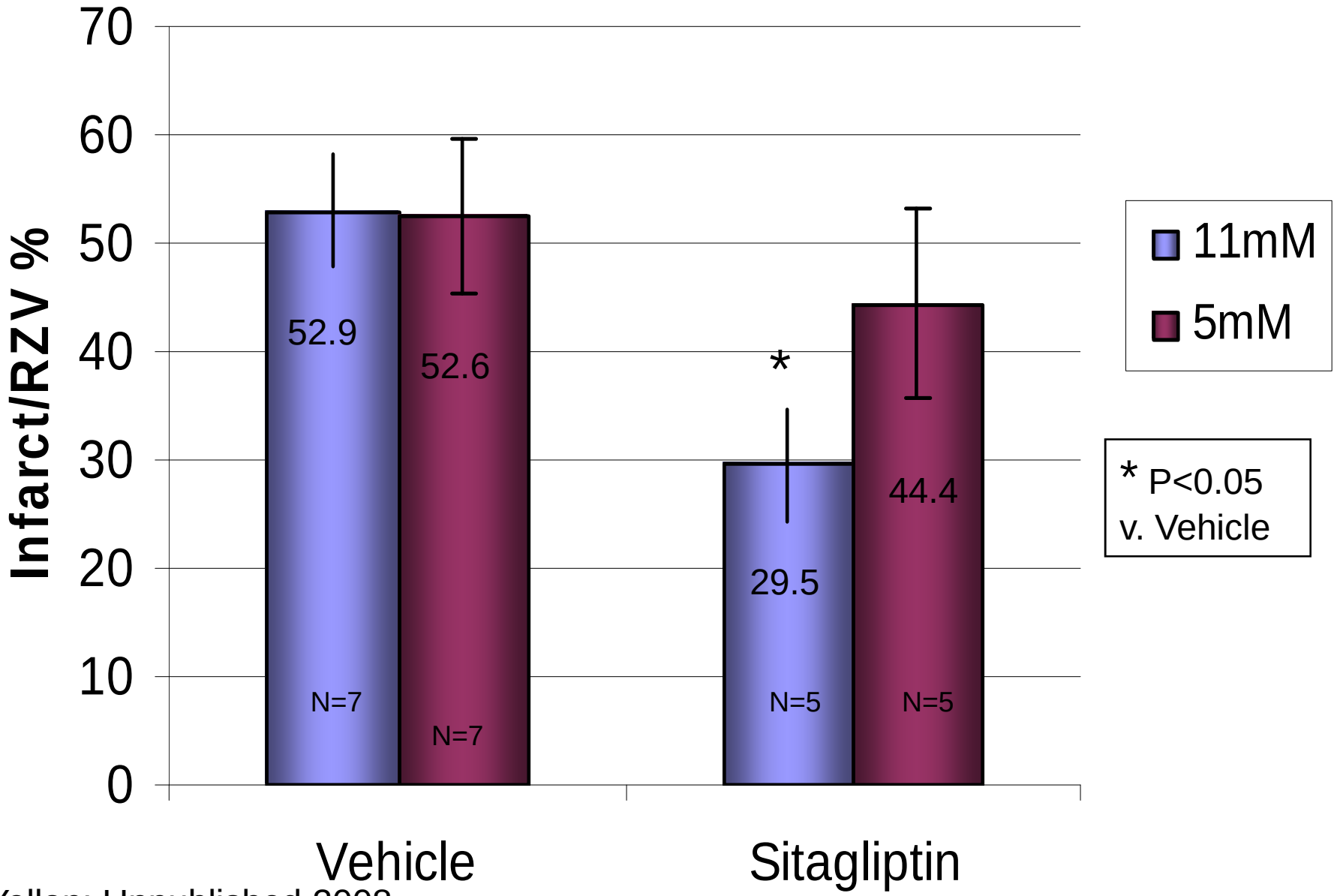
# Isolated Langendorff perfused SDR heart after SITAGLIPTIN (100mg/kg for 2 weeks) or $H_2O$ vehicle treatment

* P<0.05 v. Vehicle



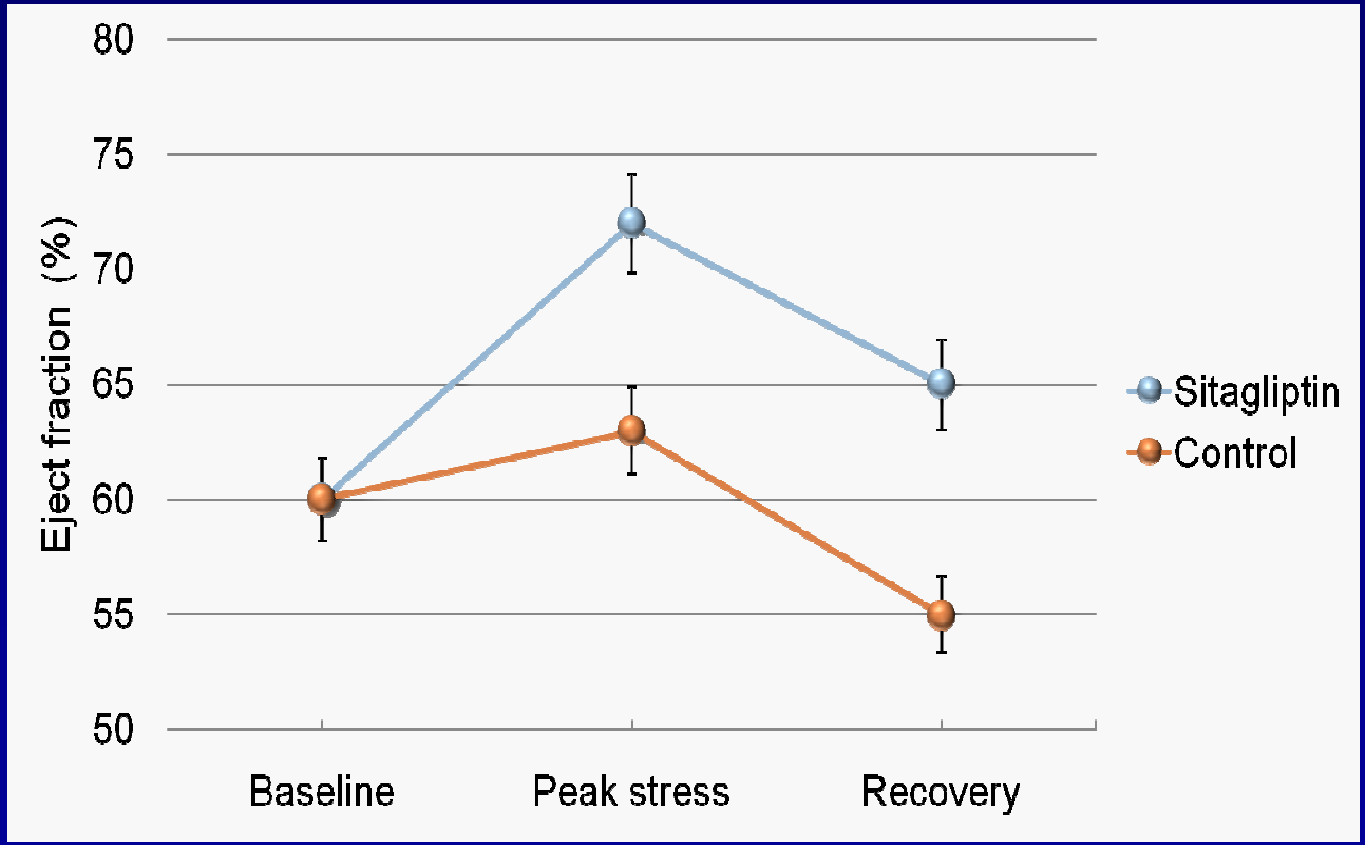

Yellon: Unpublished 2008

# Isolated perfused heart with 11mM / 5mM glucose SITAGLIPTIN (100mg/kg for 2 weeks) or $H_2O$ vehicle treatment




Yellon: Unpublished 2008

# DPP-4 Inhibition by SITAGLIPTIN Improves the *Myocardial Response to Dobutamine Stress* in Patients with Coronary Artery Disease




Read PA et al. ***Circ Cardiovasc Imaging*** published online Jan 14, 2010

# The oral dipeptidyl peptidase-4 inhibitor sitagliptin increases circulating endothelial progenitor cells in patients with type 2 diabetes mellitus. Possible role of stromal derived factor-1α

Gian Paolo Fadini, MD; Elisa Boscaro, BSc; Mattia Albiero, PhD; Lisa Menegazzo, BSc; Vera Frison, MD; Saula de Kreutzenberg, MD PhD; Carlo Agostini, MD; Antonio Tiengo, MD; Angelo Avogaro, MD PhD

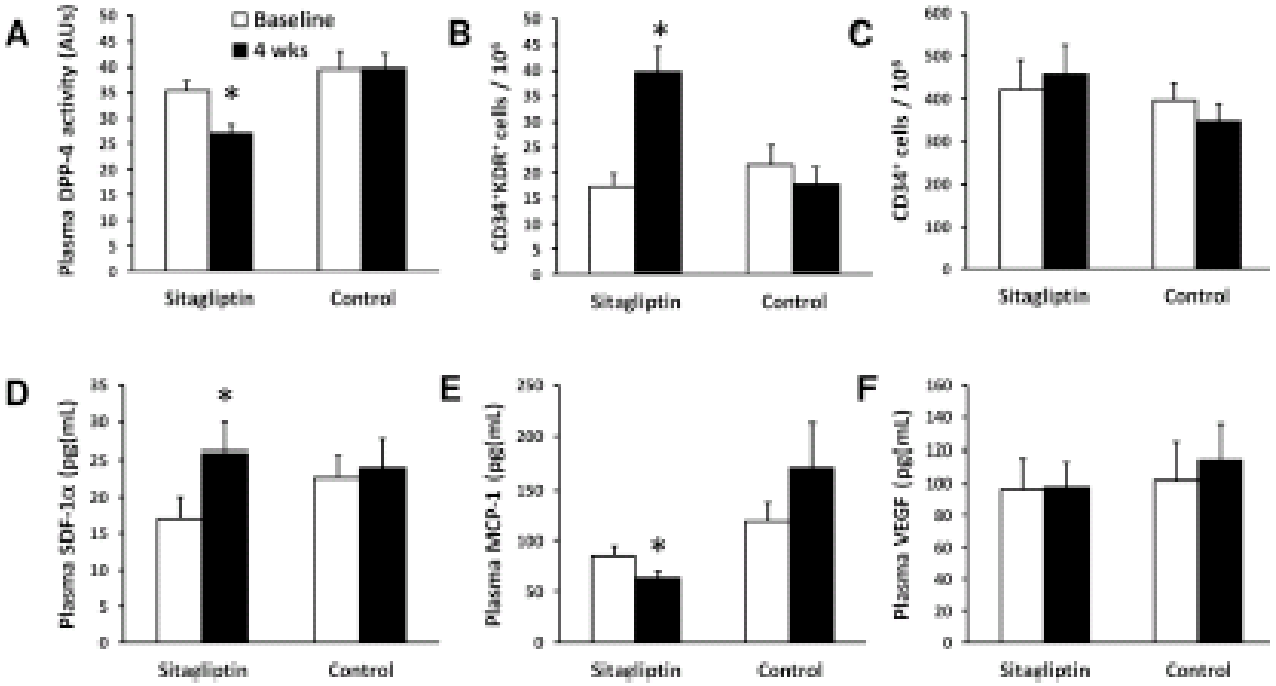



**Figure 1. Effects of sitagliptin on DPP-4 activity, progenitor cells, and soluble factors.** Plasma free DPP-4 activity (A), $CD34^+KDR^+$ EPCs levels (B), $CD34^+$ cell levels (C), and concentrations of SDF-1α (D), MCP-1 (E) and VEGF (F) were determined at baseline and at 4 weeks in the sitagliptin intervention group and in the control group. *p<0.05.

Diabetes Care Publish Ahead of Print, published online March 31, 2010

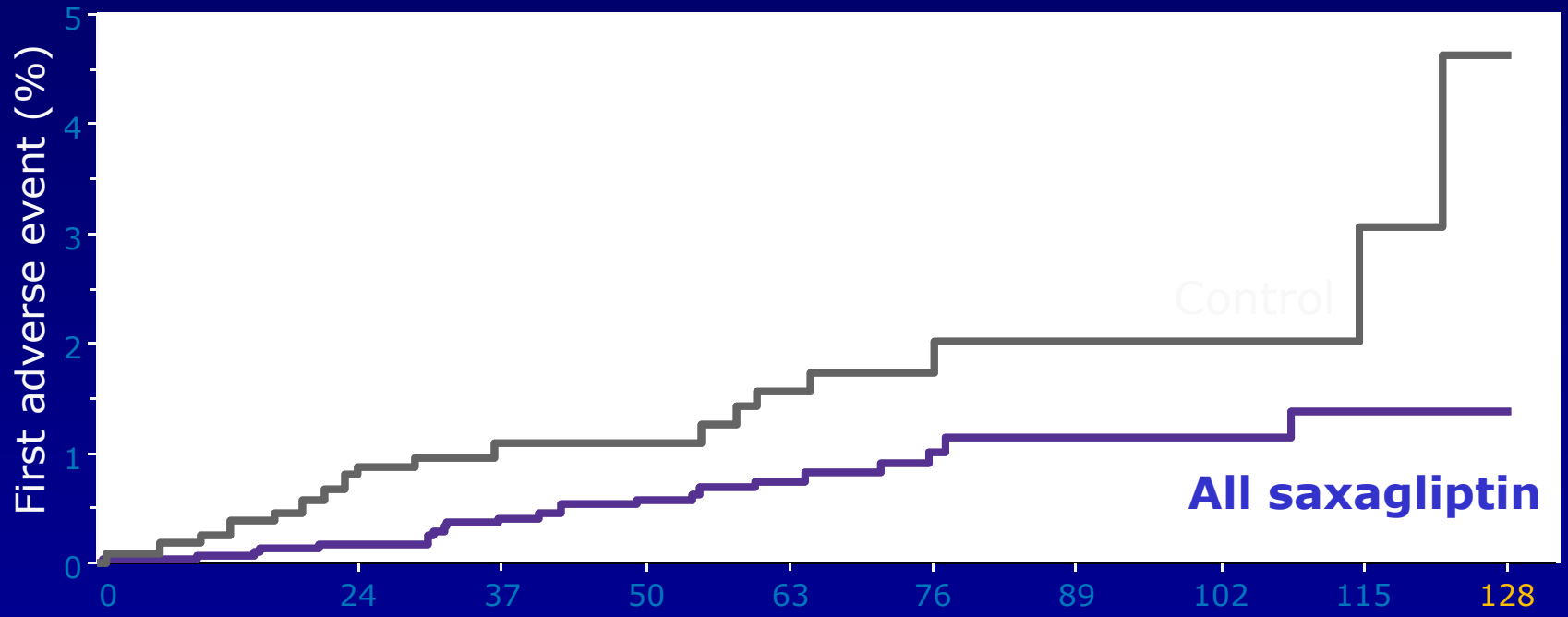
# Cardiovascular Effects of the Incretin Modulators

**Ongoing and planned cardiovascular trials in type 2 diabetes**

| Trial | Drug | Patients | Stage |
|---|---|---|---|
| **CV Safety Studies (Pre-registration)** | | | |
| T-emerge 8 | Taspoglutide | 2,000 | Started 01/2010 (Stop) |
| EXAMINE | Alogliptin | 5,400 | Started 09/2009<br>Est. completion 12/2014 |
| **CV Outcomes Trials** | | | |
| TECOS | **Sitagliptin** | **14,000** | Started 12/2008<br>Est. completion 12/2014 |
| LEADER | Liraglutide | 9,000 | Planned |
| EXSCEL | Exenatide LAR | 12,000 | Planned |
| SAVOR TIMI-53 | Saxagliptin | 12,000 | Start Spring 2010 |
| CAROLINA | Linagliptin | > 10,000 | Ongoing |

# Cardiovascular events:
## Saxagliptin controlled Phase 2b/3 pooled population

### Time to onset of first primary Major Adverse Cardiovascular Event (MACE)




| Patients at risk | | | | | | | | | | Weeks |
|---|---|---|---|---|---|---|---|---|---|---|
| **Control** | 1,251 | 935 | 860 | 774 | 545 | 288 | 144 | 123 | 102 | 57 |
| **All saxagliptin** | 3,356 | 2,615 | 2,419 | 2,209 | 1,638 | 994 | 498 | 436 | 373 | 197 |

Saxagliptin, FDA's Endocrinologic and Metabolic Drugs Advisory Committee Briefing Document for April 2009 Meeting: NDA 22-350. Available at http://www.fda.gov/OHRMS/DOCKETS/ac/09/briefing/2009-4422b1-02-Bristol.pdf. Accessed: 7 May, 09.

# *Sitagliptin*: Approvals & Launches

- Approved in **89** countries*
- Launched in **82** countries and territories*
- More than **16.7 million** total prescriptions have been dispensed worldwide**

## US 1

| Approved | Launched |
|---|---|
| US | √ |

## Japan 1

| Approved | Launched |
|---|---|
| Japan | √ |

## Latin America 25

| Latin America | |
|---|---|
| **Approved** | **Launched** |
| Antigua | √ |
| Argentina | √ |
| Aruba | √ |
| Bahamas | √ |
| Barbados | √ |
| Bermuda | √ |
| Bolivia | |
| Brazil | √ |
| Caymen Islands | √ |
| Chile | √ |
| Colombia | √ |
| Costa Rica | √ |
| Curacao | √ |
| Dominican Republic | √ |
| Ecuador | √ |
| El Salvador | √ |
| French Territories | √ |
| Guatemala | √ |
| Honduras | √ |
| Jamaica | √ |
| Mexico | √ |
| Nicaragua | √ |
| Peru | √ |
| Puerto Rico | √ |
| Trinidad | √ |
| Uruguay | |
| Venezuela | √ |

## EUCAN I / II 42

| Approved | Launched |
|---|---|
| Austria | √ |
| Bahrain | √ |
| Belgium | √ |
| Bulgaria | √ |
| Canada | √ |
| Croatia | |
| Cyprus | √ |
| Czech Republic | √ |
| Denmark | √ |
| Egypt | √ |
| Estonia | √ |
| Finland | √ |
| France | √ |
| Germany | √ |
| Greece | √ |
| Hungary | √ |
| Iceland | √ |
| Ireland | √ |
| Israel | √ |
| Italy | √ |
| Jordan | √ |
| Kuwait | √ |
| Latvia | |
| Lebanon | √ |
| Lithuania | |
| Luxembourg | √ |
| Malta | √ |
| Morocco | √ |
| Netherlands | √ |
| Norway | √ |
| Poland | |
| Portugal | √ |
| Qatar | √ |
| Reunion | √ |
| Romania | √ |
| Russia | √ |
| Saudi Arabia | √ |
| Serbia and Montenegro | √ |
| Slovakia | √ |
| Slovenia | √ |
| Spain | √ |
| Sweden | √ |
| Switzerland | √ |
| Turkey | √ |
| UAE | √ |
| UK | √ |
| Ukraine | |

## Asia-Pacific 13

| Approved | Launched |
|---|---|
| Australia | √ |
| China | √ |
| Hong Kong | √ |
| India | √ |
| Indonesia | √ |
| Korea | √ |
| Macau | √ |
| Malaysia | √ |
| New Zealand | √ |
| Philippines | √ |
| Singapore | √ |
| Taiwan | √ |
| Thailand | √ |

* As of March 28, 2010

**IMS Health, NPA™ Weekly, TRxs, week-ending October 20, 2006 through week-ending March 19, 2010

# ***Sitagliptin+Metformin***: Approvals & Launches

- ❖ Approved in **66** countries*
- ❖ Launched in **53** countries and territories*
- ❖ More than **4.8 million** total prescriptions have been dispensed worldwide**

## US 1

| Approved | Launched |
|---|---|
| US | √ |

## Latin America 16

| Approved | Launched |
|---|---|
| Argentina | √ |
| Bahamas | √ |
| Barbados | √ |
| Bermuda | √ |
| Bolivia | |
| Brazil | √ |
| Caymen Islands | √ |
| Chile | √ |
| Colombia | √ |
| Costa Rica | √ |
| Ecuador | |
| El Salvador | √ |
| Guatemala | √ |
| Mexico | √ |
| Nicaragua | √ |
| Peru | √ |
| Puerto Rico | √ |
| Venezuela | √ |

## EUCAN I / II 26

| Approved | Launched |
|---|---|
| Austria | √ |
| Bahrain | √ |
| Canada | √ |
| Croatia | |
| Cyprus | √ |
| Czech Republic | |
| Denmark | √ |
| Egypt | |
| Estonia | |
| Finland | √ |
| France | √ |
| Germany | √ |
| Greece | √ |
| Hungary | √ |
| Iceland | √ |
| Ireland | √ |
| Israel | √ |
| Italy | √ |
| Kuwait | √ |
| Latvia | |
| Lebanon | √ |
| Lithuania | |
| Luxembourg | √ |
| Malta | √ |
| Morocco | √ |
| Netherlands | √ |
| Norway | |
| Portugal | √ |
| Romania | |
| Slovakia | √ |
| Slovenia | √ |
| Spain | √ |
| Sweden | √ |
| Switzerland | √ |
| UAE | √ |

## Asia-Pacific 9

| Approved | Launched |
|---|---|
| Australia | √ |
| Hong Kong | √ |
| India | √ |
| Indonesia | |
| Korea | √ |
| Macau | √ |
| Malaysia | √ |
| New Zealand | |
| Philippines | √ |
| Singapore | √ |
| Taiwan | |
| Thailand | √ |

* As of March 28, 2009
**IMS Health, NPA™ Weekly, TRxs, week-ending October 20, 2006 through week-ending March 19, 2010

# Gliptine ed indicazioni approvate

| | sitagliptin | vildagliptin | saxagliptin |
|---|---|---|---|
| monoterapia | ✓ | | |
| metformina | ✓ | ✓ | ✓ |
| sulfonilurea | ✓ | ✓ | ✓ |
| pioglitazone | ✓ | ✓ | ✓ |
| met + sulfo | ✓ | | |
| met + pio | ✓ | | |
| insulina | ✓ | | |
| Insulina + met | ✓ | | |

# Messaggi da portare a casa

**Gli Inibitori del DPPIV hanno dimostrato di essere efficaci quanto le terapie tradizionali nel:**

- **Ridurre HbA1c**
- **Ridurre le fluttuazioni glicemiche giornaliere**
- **Ridurre il rischio di *IPOGLICEMIA***
- **Non determinare alcun aumento del peso corporeo**
- **Presentare effetti favorevoli su fattori di rischio CV quali dislipidemia e ipertensione arteriosa**

Avellino sabato 12 novembre 2011

Salerno giovedì 10 novembre 2011


# Grazie per l'attenzione

Napoli domenica 13 novembre 2011