Sitagliptin nella pratica quotidiana:

dalla neodiagnosi all'anziano fragile

Domenico Cucinotta

I farmaci inibitori di DPP-IV
(gliptine)

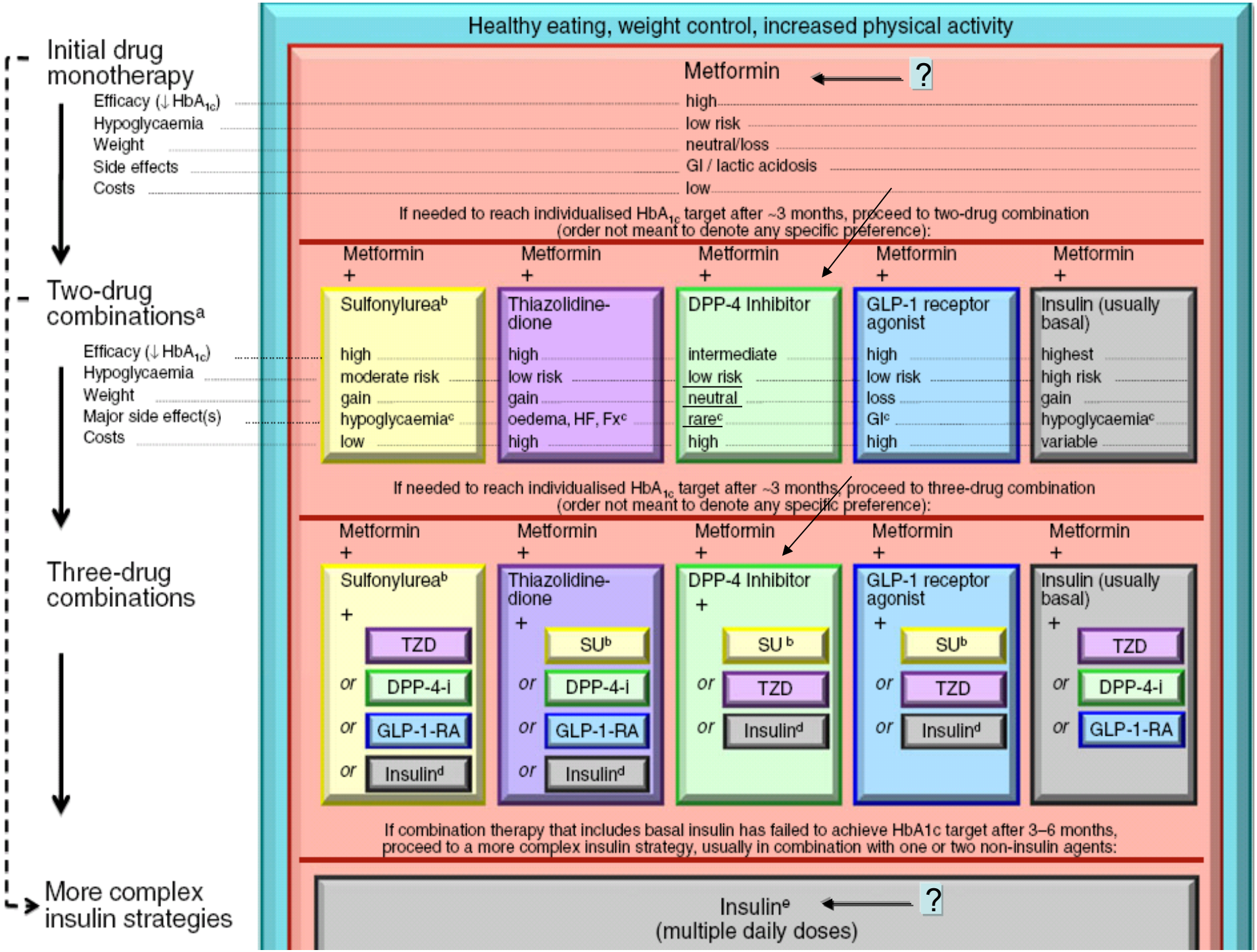
- *Quando ?*
- *Quando Sitagliptin ?*

Diabetologia
DOI 10.1007/s00125-012-2534-0

POSITION STATEMENT

Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

S. E. Inzucchi · R. M. Bergenstal · J. B. Buse · M. Diamant · E. Ferrannini · M. Nauck · A. L. Peters · A. Tsapas · R. Wender · D. R. Matthews


Healthy eating, weight control, increased physical activity
Initial drug monotherapy
Efficacy (↓ HbA1c)
Hypoglycaemia
Weight
Side effects
Costs
Metformin
?
high
low risk
neutral/loss
GI / lactic acidosis
low
If needed to reach individualised HbA1c target after ~3 months, proceed to two-drug combination
(order not meant to denote any specific preference):
Two-drug combinations[a]
Efficacy (↓ HbA1c)
Hypoglycaemia
Weight
Major side effect(s)
Costs
Metformin + Sulfonylurea[b]
high
moderate risk
gain
hypoglycaemia[c]
low
Metformin + Thiazolidine-dione
high
low risk
gain
oedema, HF, Fx[c]
high
Metformin + DPP-4 Inhibitor
intermediate
low risk
neutral
rare[c]
high
Metformin + GLP-1 receptor agonist
high
low risk
loss
GI[c]
high
Metformin + Insulin (usually basal)
highest
high risk
gain
hypoglycaemia[c]
variable
If needed to reach individualised HbA1c target after ~3 months, proceed to three-drug combination
(order not meant to denote any specific preference):
Three-drug combinations
Metformin + Sulfonylurea[b] + TZD or DPP-4-i or GLP-1-RA or Insulin[d]
Metformin + Thiazolidine-dione + SU[b] or DPP-4-i or GLP-1-RA or Insulin[d]
Metformin + DPP-4 Inhibitor + SU[b] or TZD or Insulin[d]
Metformin + GLP-1 receptor agonist + SU[b] or TZD or Insulin[d]
Metformin + Insulin (usually basal) + TZD or DPP-4-i or GLP-1-RA
If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3–6 months,
proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents:
More complex insulin strategies
Insulin[e] (multiple daily doses)
?

Effetto del miglioramento del controllo metabolico sulla mortalità cardiovascolare in funzione del rischio ipoglicemico, nei grandi trial sul diabete di tipo 2

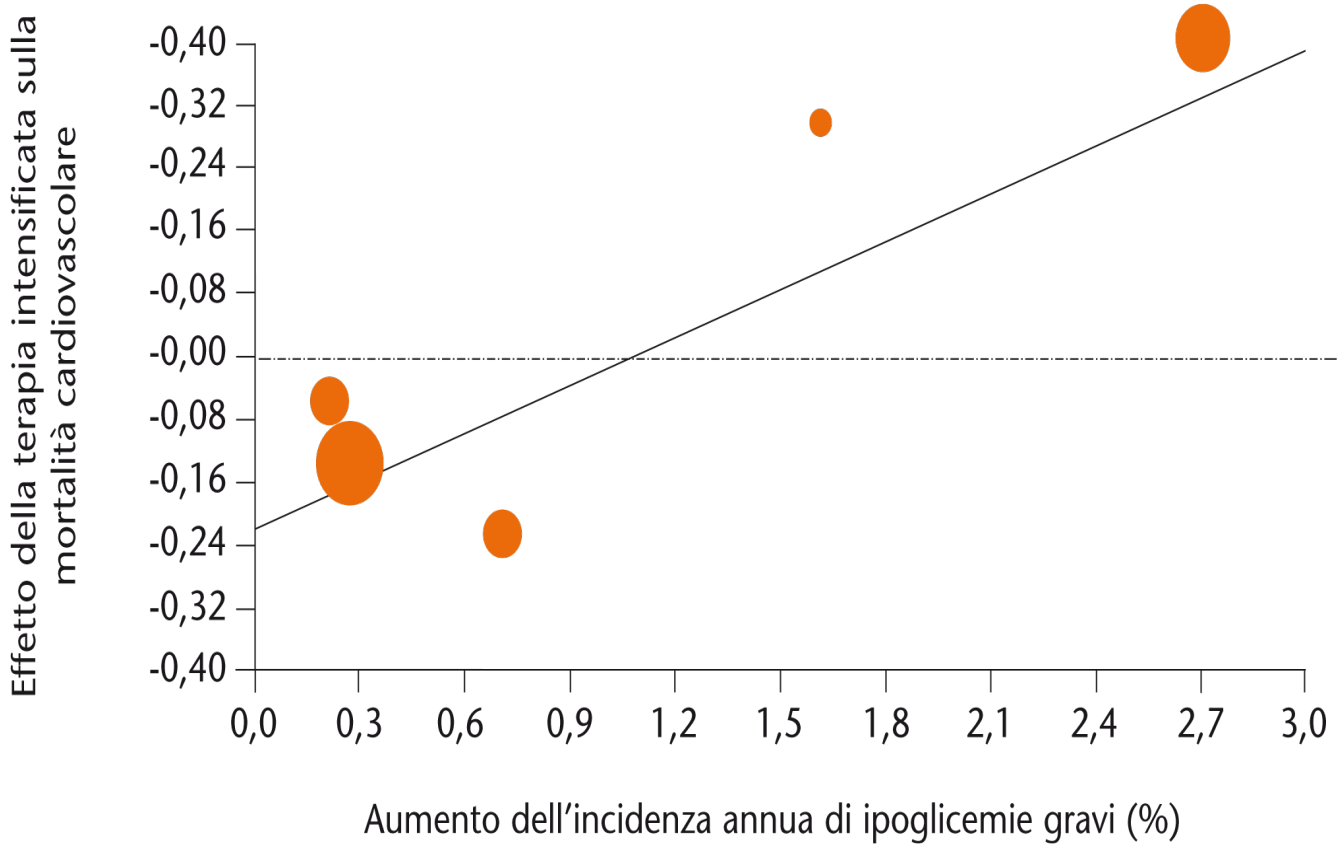


Figura 1.1

Modificata da Mannucci E, et al. Nutr Metab Cardiovasc Dis 2009; 19: 604-612.

Valori di HbA_{1c} da usare indicativamente come target nel DM2

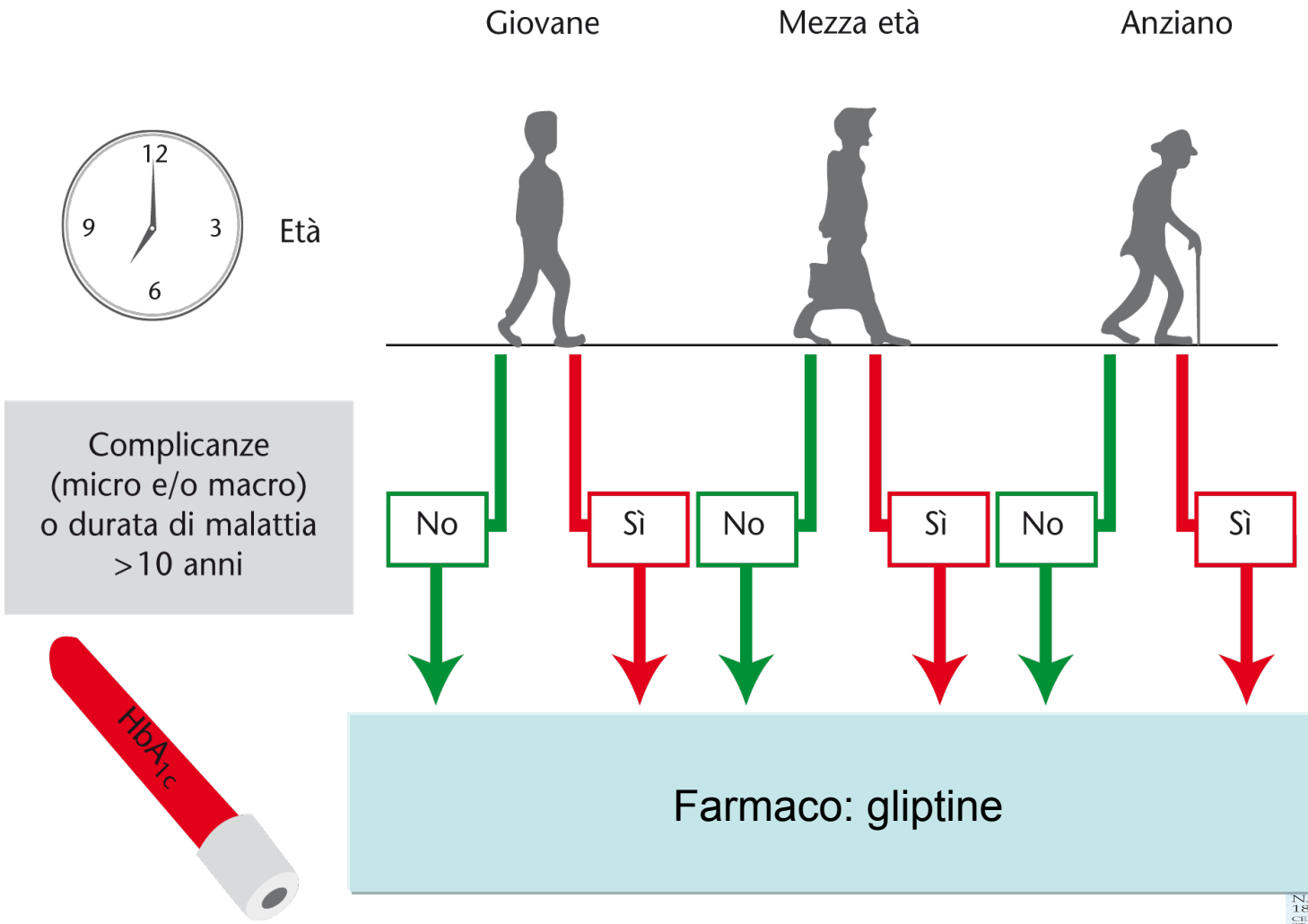


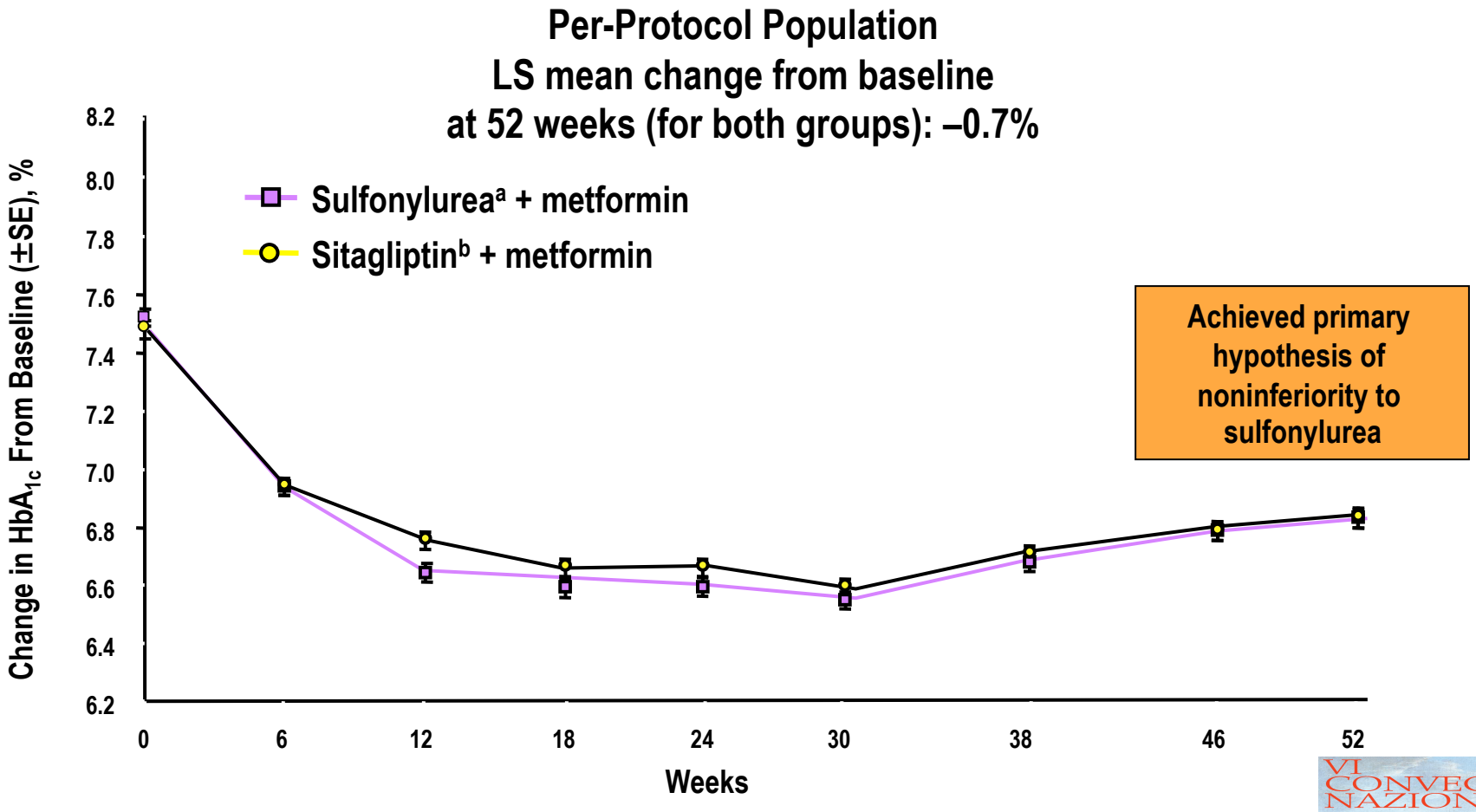
Figura 2.2

Modificata da Pozzilli P, et al. Diabetes Metab Res Rev 2010; 26: 239-244.

- *Sitagliptin: cosa sappiamo dopo 6 anni ?*

Efficacia di Sitagliptin nel ridurre la HbA1C negli studi di Add-on

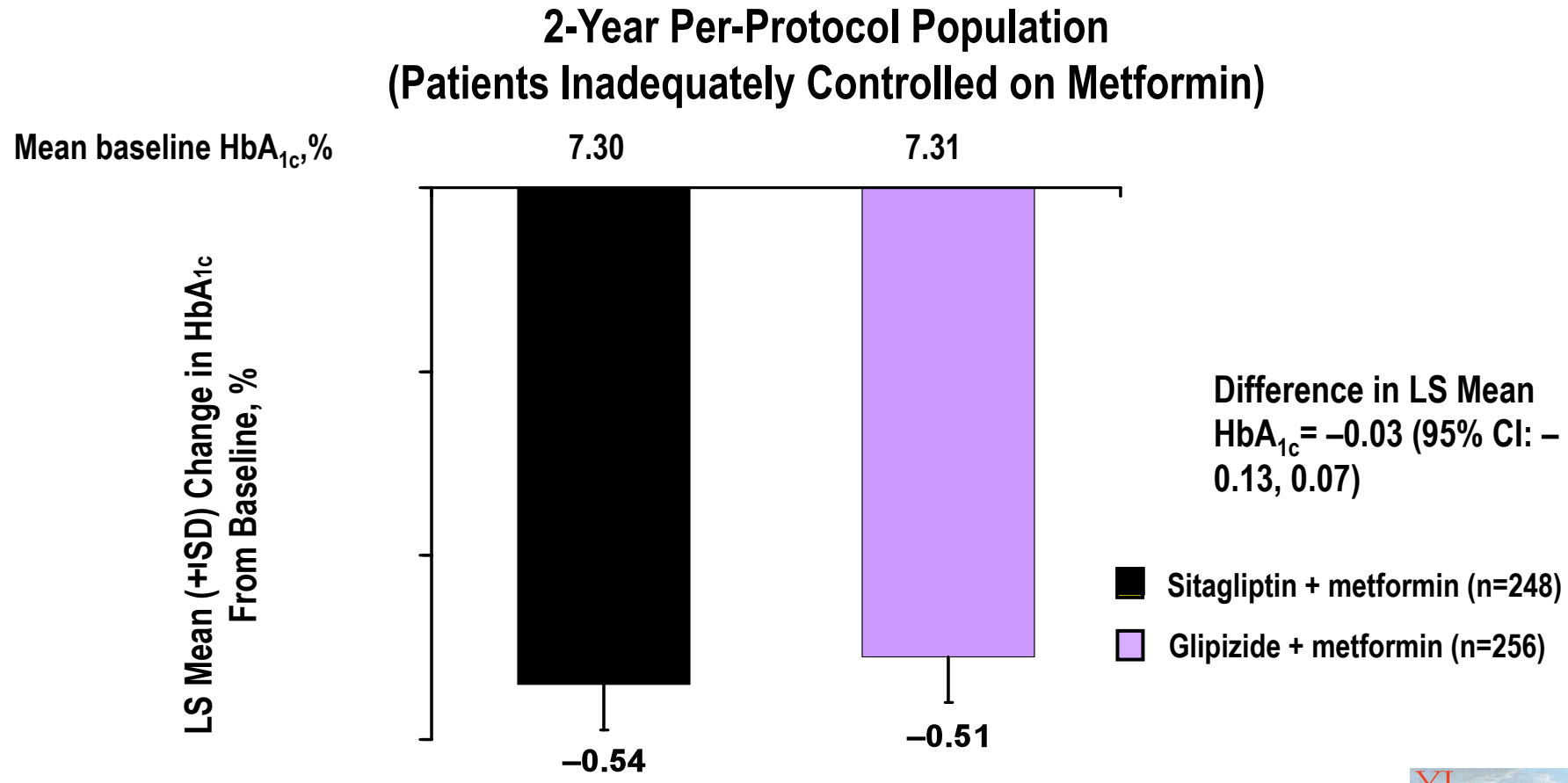
Risultati ad un anno (endpoint primario)



LS=least-squares; SE=standard error.
[a]Specifically glipizide ≤20 mg/day; [b]Sitagliptin 100 mg/day with metformin (≥1,500 mg/day).
Adapted from Nauck MA, Meininger G, Sheng D, et al, 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. *Diabetes Obes Metab.* 2007;9(2):194–205 with permission from Blackwell Publishing Ltd., Boston, MA.

1. Nauck MA et al. *Diabetes Obes Metab.* 2007;9(2):194–205.

Risultato a due anni[1]



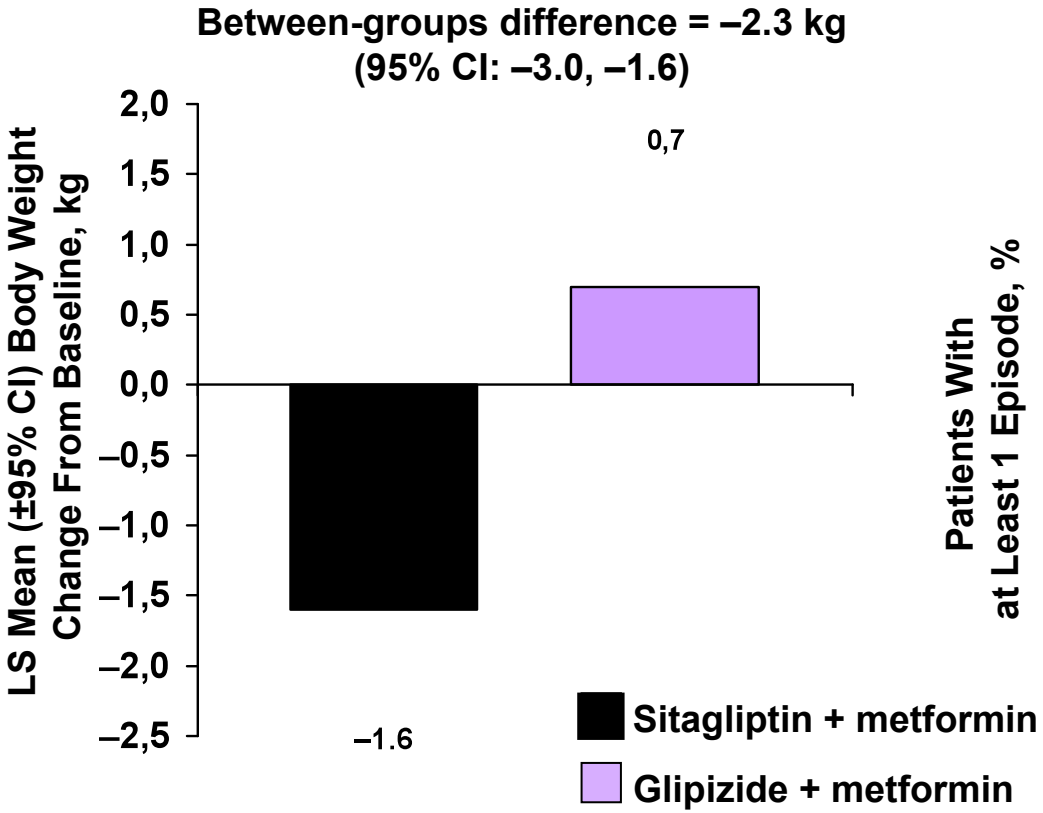
LS=least-squares; SD=standard deviation.

1. Seck T et al. *Int J Clin Pract*. 2010;64(5):562–576.

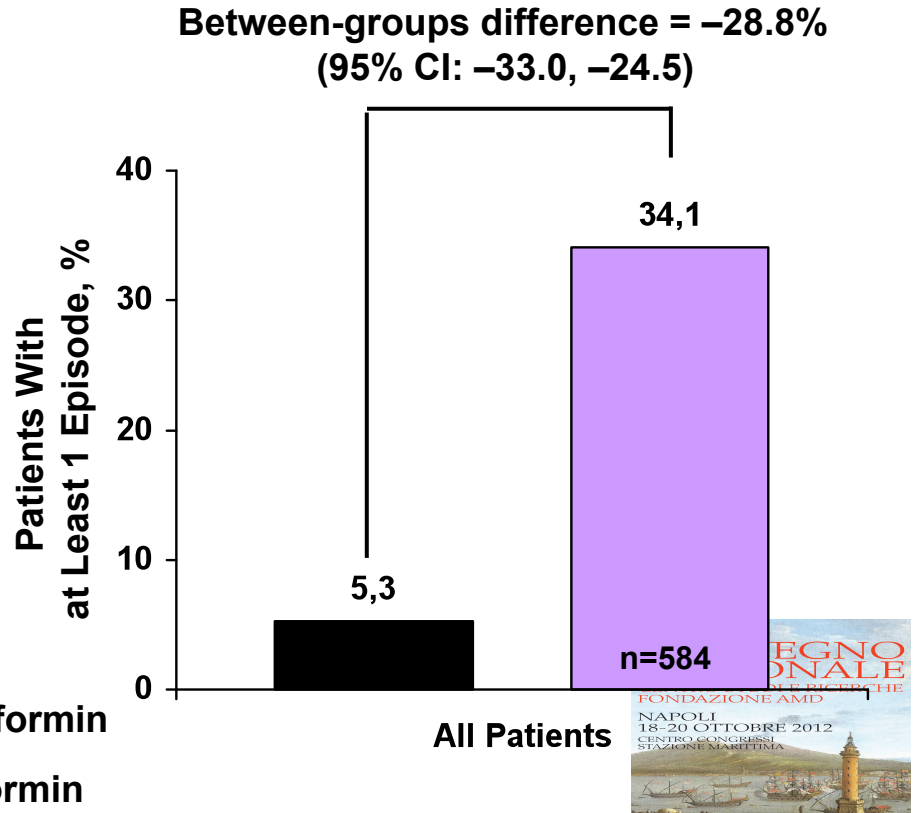
Sitagliptin vs Glipizide: variazione del peso corporeo e incidenza di ipoglicemia

APaT Population
(Patients Inadequately Controlled on Metformin)

Body weight at week 104



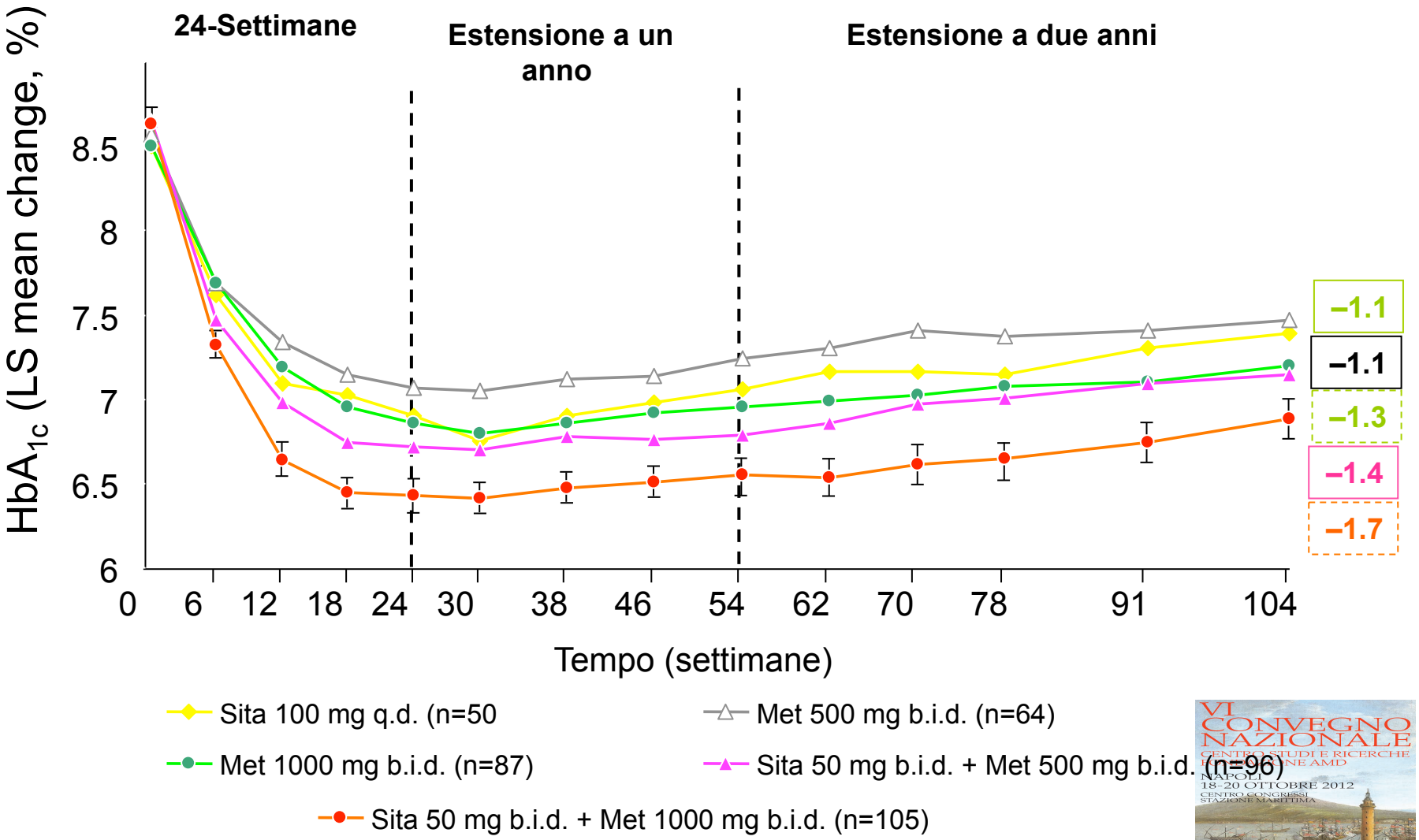
Hypoglycemia over 104 weeks



APaT=all-patients-as-treated.

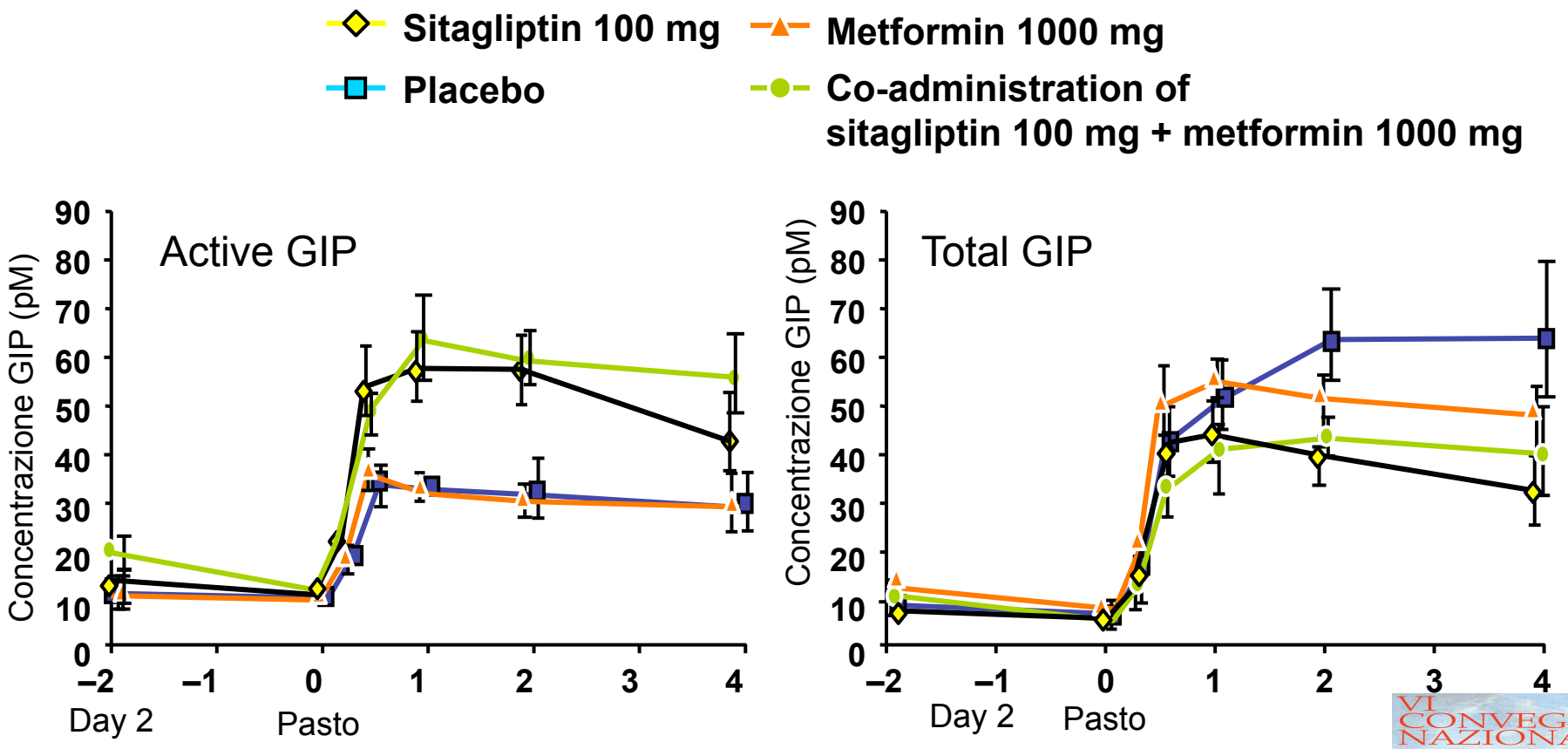
Seck T et al. *Int J Clin Pract*. 2010;64(5):562–576.

Sitagliptin e Metformina
Studio di combinazione iniziale



Williams Herman D. Diabetes Obes Metab. 2010; 12(5):442-51

Effetti di Sitagliptin e Metformina sulle incretine

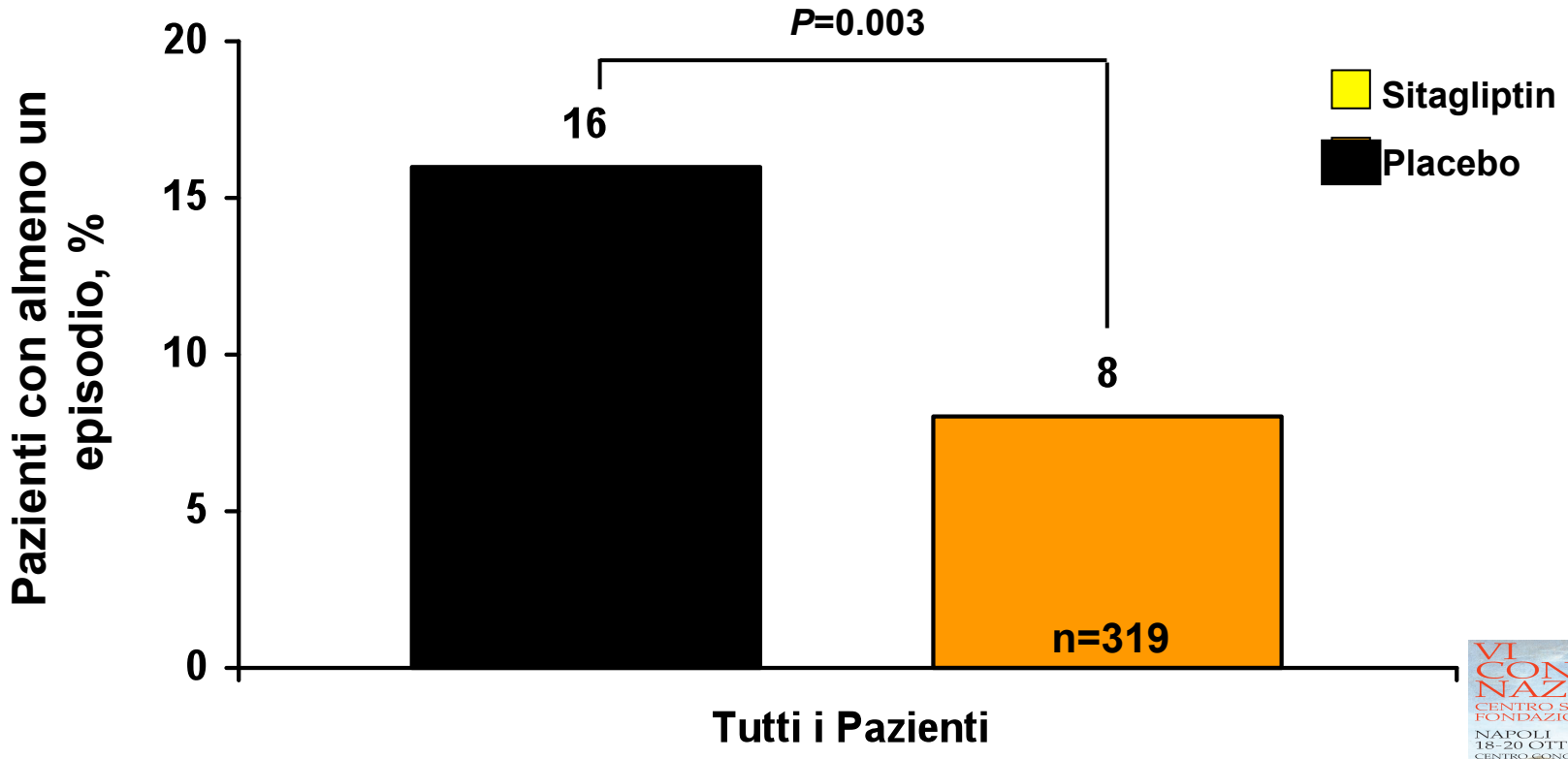


Values represent geometric mean ± SE

Migoya EM Clinical Pharm & Therapeutics 88; 6; 2010

Sitagliptin associato a terapia insulinica combinata o meno con metformina: incidenza di Ipoglicemia

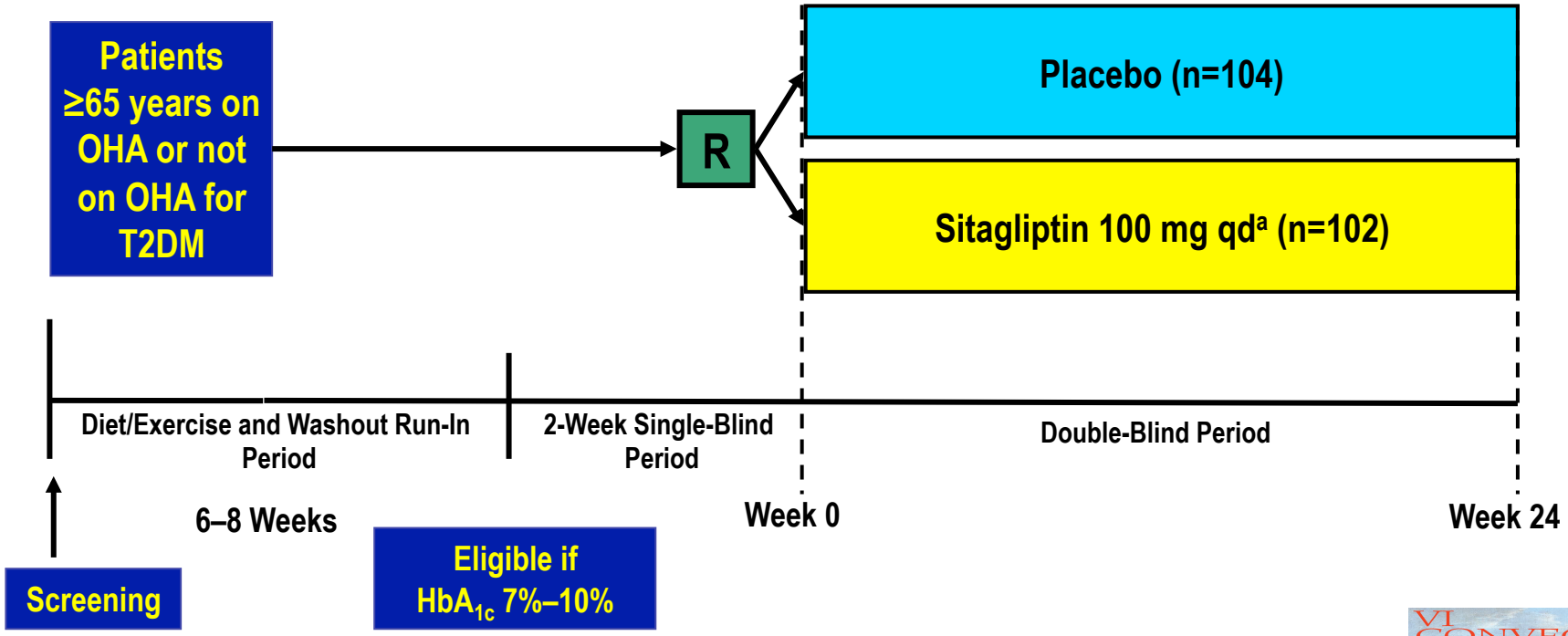
Popolazione APaT a settimana 24[a]



[a]Esclusi I dati dopo inizio della terapia rescue.
APaT=all patients as treated.
Vilsbøll T et al. *Diabetes Obes Metab*. 2010;12(2):167–177.

Sitagliptin in Older Patients With Type 2 Diabetes: Study Design[1]

Objective: To assess the efficacy and safety of sitagliptin monotherapy over 24 weeks in elderly patients (≥65 years of age) with type 2 diabetes who had inadequate glycemic control



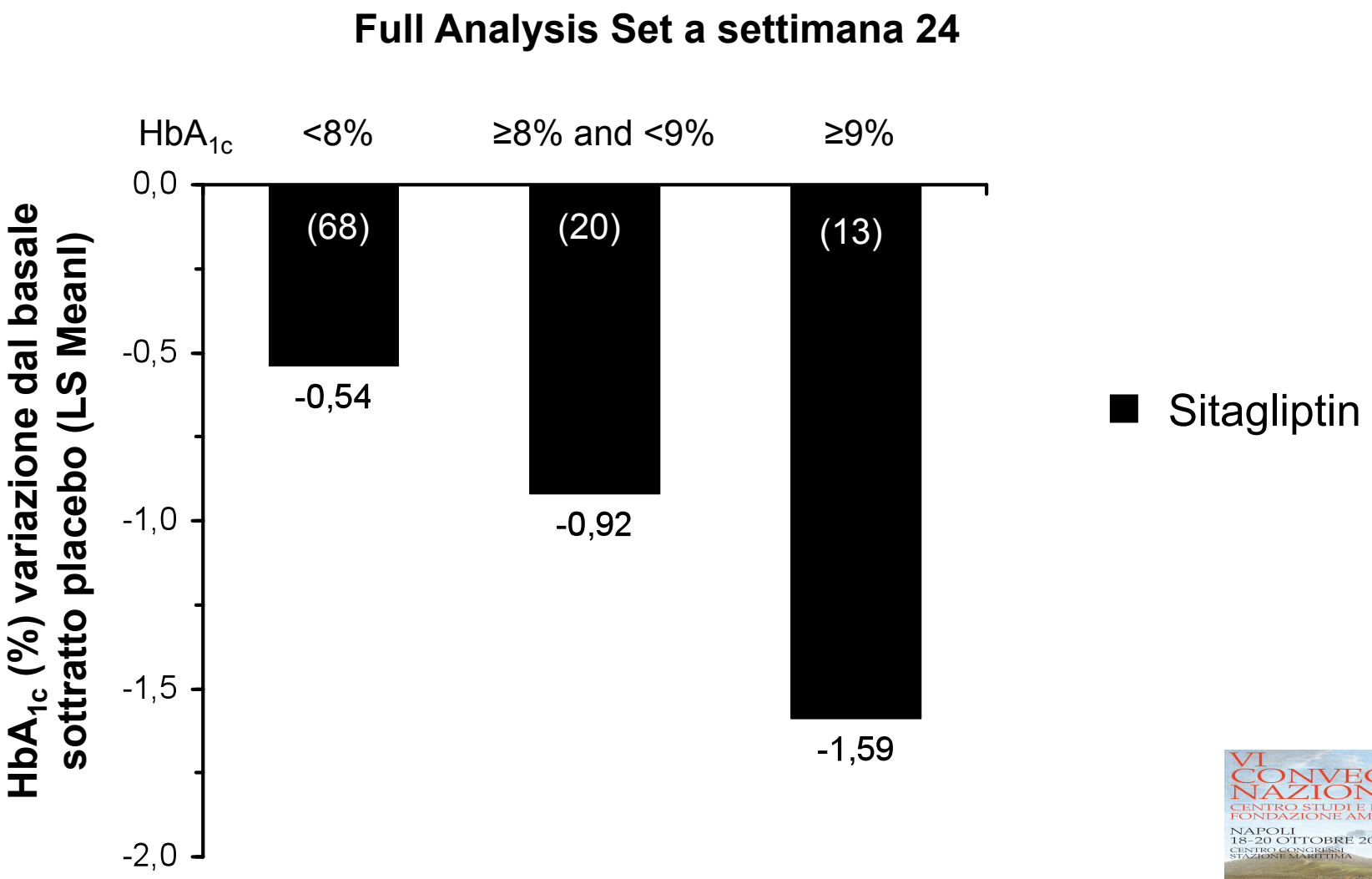
- Primary efficacy end point: change from baseline in HbA_{1c} at 24 weeks
- Selected secondary end point: change in 4-point fingerstick glucose average at day 3 and day 7

OHA=oral antihyperglycemic agent; qd=once daily; R=randomization; T2DM=type 2 diabetes mellitus.

[a]Sitagliptin was down-titrated to 50 mg (1 tablet instead of 2) in patients with CrCl <50 mL/min; patients with CrCl <30 mL/min were discontinued.

Barzilai N et al. *Curr Med Res Opin*. 2011;27:1049–1058.

Variazioni della HbA1c dal basale



Barzilai et al Curr Med Res Op 27, 2011; 1049-1058

Presentation #834
48th EASD Annual Meeting
October 1-5, 2012
Berlin, Germany

Sitagliptin Provides Similar Glycaemic Improvement With Less Hypoglycaemia in the Elderly With Type 2 Diabetes Mellitus Compared to Sulphonylurea

Ravi Shankar, Samuel S. Engel, Lei Xu, Gregory T. Golm, Michael J. Davies, Keith D. Kaufman, Barry J. Goldstein

Merck Sharp & Dohme Corp., Whitehouse Station, NJ USA

Abstract

Background and aims: The global burden of type 2 diabetes mellitus (T2DM) in the elderly (≥65 years), who present unique therapeutic challenges due to comorbidities, is estimated to increase by 134% in 2030 compared to 2000. Sulphonylurea use is associated with greater risk for hypoglycaemia in the elderly and its use increases with age. Hypoglycaemia and its consequences may be more pronounced in the elderly. Sitagliptin, a DPP-4 inhibitor, improves glycaemic control, with a low risk of hypoglycaemia when used alone or with metformin. The present *post hoc* analyses compared the efficacy and safety of sitagliptin versus sulphonylurea in elderly patients with T2DM.

Methods: The data of patients ≥65 years of age were pooled from 3 double-blind studies to compare the effects of sitagliptin (100 mg/day) or sulphonylurea (in titrated doses) on change from baseline in HbA_{1c}, fasting plasma glucose (FPG), and body weight and incidence of symptomatic hypoglycaemia. Patients on diet alone or metformin were randomized to sitagliptin or glipizide for 104 weeks (Studies 1-2) or glimepiride for 30 weeks (Study 3); hence, the analyses included 373 elderly patients who completed trials through 30 weeks.

Results: Both HbA_{1c} and FPG decreased with sitagliptin and sulphonylurea, with no statistical difference between treatments (Table). The proportion of patients with an HbA_{1c} <6.5% was similar between treatments. Significantly lower incidence of symptomatic hypoglycaemia was observed with sitagliptin relative to sulphonylurea. Body weight decreased significantly from baseline with sitagliptin. Significantly more patients on sitagliptin than sulphonylurea achieved the composite endpoint of >0.5% HbA_{1c} reduction with no hypoglycaemia or body weight gain at 30 weeks.

Conclusion: Sitagliptin provided similar glycaemic efficacy, with less hypoglycaemia and with body weight loss compared to sulphonylurea in elderly patients, suggesting that sitagliptin is an effective and well-tolerated treatment option for elderly patients with T2DM.

	Sitagliptin N = 178	Sulphonylurea N = 195
Baseline HbA_{1c}, %	7.5 ± 0.7	7.5 ± 0.8
Δ HbA_{1c}, %	-0.73 (-0.84, -0.61)	-0.78 (-0.89, -0.67)
HbA_{1c} <6.5%, n (%)	63 (35.4)	73 (37.4)
Baseline FPG, mmol/L	8.4 ± 1.8	8.7 ± 2.1
Δ FPG, mmol/L	-1.2 (-1.5, -0.9)	-1.3 (-1.6, -1.0)
Patients with HYPO AE, n (%)	11 (6.2)	55 (28.2)*
Baseline BW, kg	84.6 ± 14.6	83.6 ± 15.1
Δ BW, kg	-1.7 (-2.3, -1.2)	0.4 (-0.1, 1.0)*
Composite†, n (%)	78 (44.1)	31 (15.9)*

AE = adverse event.
Data are mean ± SD, LS mean change (SE) from baseline (95% CI), or counts (proportion of patients).
*p<0.001 for difference between sitagliptin and sulphonylurea.
†Composite = patient proportion of an HbA_{1c} decrease >0.5% with no symptomatic hypoglycaemia and no body weight gain.

Introduction

- The global burden of type 2 diabetes mellitus (T2DM) in the elderly (≥65 years) is estimated to increase by 134% in 2030 compared to 2000
- Presently, 45% of US patients with T2DM are elderly
- The elderly present unique therapeutic challenges for their diabetes due to comorbidities
- Sulphonylurea treatment is associated with greater risk for hypoglycaemia in the elderly
- Sulphonylurea use is increased in older patients with T2DM compared to younger patients
- Hypoglycaemia and its consequences may be more pronounced in the elderly
- Sitagliptin, a DPP-4 inhibitor, improves glycaemic control, with a low risk of hypoglycaemia when used alone or with metformin

Objective

To compare the efficacy and safety of sitagliptin versus sulphonylurea in elderly patients with T2DM

Results

Table 1. Baseline characteristics

	Sitagliptin n = 178	Sulphonylurea n = 195
Age, years	69.1 ± 3.3	69.3 ± 3.8
Age (min, max)	(65, 79)	(65, 80)
Gender, male, n (%)	105 (59)	126 (65)
Body weight, kg	84.6 ± 14.6	83.6 ± 15.1
Body mass index, kg/m²	30.3 ± 4.3	29.7 ± 4.3
Duration of T2DM, years*	6.0	6.0
HbA_{1c}, %	7.5 ± 0.7	7.5 ± 0.8
FPG, mg/dL	150.9 ± 32.8	157.4 ± 36.4

Data are mean ± SD or counts (proportion of patients) unless otherwise indicated. *median.

Table 2. Sulphonylurea dose (mg/day) at or near endpoint HbA_{1c} measurement

Study	Mean ± SD
Study 1 (glipizide)	10.0 ± 7.1
Study 2 (glipizide)	10.4 ± 7.5
Study 3 (glimepiride)	2.2 ± 1.5

Results

Figure 1. LS mean change (SE) from baseline in HbA_{1c}

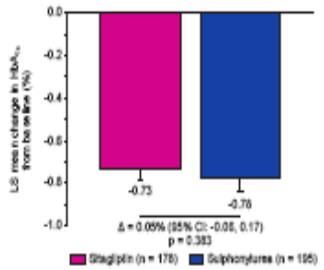


Figure 2. LS mean change (SE) from baseline in fasting plasma glucose (FPG)

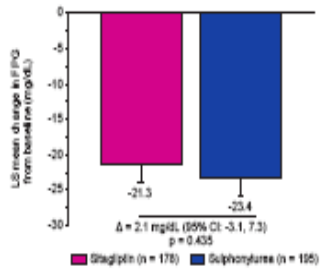


Figure 3. LS mean change (SE) from baseline in body weight (BW)

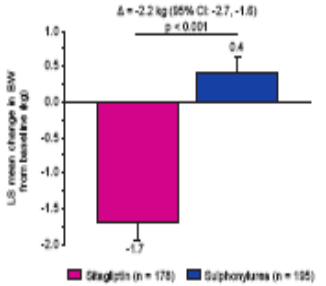


Figure 4. Proportion of patients with at least one episode of symptomatic hypoglycaemia

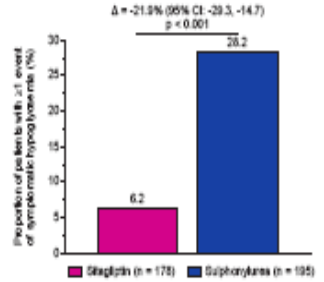


Table 3. Proportion of patients with an HbA_{1c} <6.5%

	Sitagliptin n = 178	Sulphonylurea n = 195
HbA_{1c} <6.5%, n (%)	63 (35.4)	73 (37.4)

Figure 5. Total number of symptomatic hypoglycaemic events

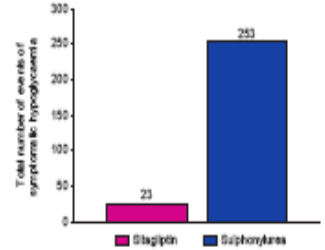
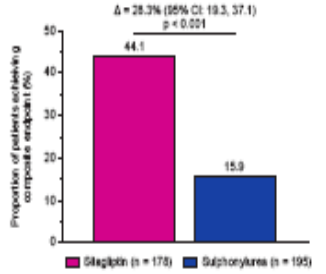


Figure 6. Proportion of patients meeting the composite endpoint of an HbA_{1c} decrease >0.5% with no symptomatic hypoglycaemia and no body weight gain



Conclusion

- Treatment with sitagliptin is associated with significantly less hypoglycaemia and with weight loss, while providing similar glycaemic efficacy compared to sulphonylurea in elderly patients with T2DM
- Sitagliptin appears to be an effective and well-tolerated treatment option for T2DM in patients ≥65 years

Methods

Data Source

In this *post hoc* analysis, data from 373 patients ≥65 years of age were pooled from 3 randomized, double-blind studies:

Study	HbA_{1c} entry criteria	Treatments (1:1 randomization ratio)	Duration	N*
Study 1	HbA_{1c} 6.5 to <10% on diet alone	Sitagliptin (100 mg qd) or Glipizide (in titrated doses)	104 weeks	16
Study 2	HbA_{1c} 6.5 to 10% on metformin	Sitagliptin (100 mg qd) or Glipizide (in titrated doses)	104 weeks	181
Study 3	HbA_{1c} 6.5 to 9% on metformin	Sitagliptin (100 mg qd) or Glimepiride (in titrated doses)	30 weeks	174

*Number of patients ≥65 years included in the present analyses.

Endpoints

- Change from baseline in HbA_{1c}, fasting plasma glucose (FPG), and body weight
- Proportion of patients with HbA_{1c} <6.5%
- Proportion of patients with at least one adverse event of symptomatic hypoglycaemia
- Proportion of patients meeting the composite endpoint of an HbA_{1c} decrease >0.5% with no symptomatic hypoglycaemia and no body weight gain

Statistics

Since Study 3 was 30 weeks in duration, measurements at or near this time point in Studies 1 and 2 were used for the analyses

- The analysis population included 373 elderly patients (n = 178 on sitagliptin and n = 195 on sulphonylurea) who completed their study through time points described below:
  - Study 1: Week 25 completers population for the HbA_{1c} analysis
  - Study 2: Week 30 per-protocol population for the HbA_{1c} analysis
  - Study 3: Week 30 per-protocol population for the HbA_{1c} analysis
- ANCOVA was used to compare the treatment groups for the endpoints below, focusing on change from baseline at time points described below. The model controlled for treatment, study, and baseline value:
  - Study 1: based on Week 25 data (HbA_{1c}, FPG, and body weight)
  - Study 2: based on Week 30 data (HbA_{1c} and FPG) or Week 24 (body weight)
  - Study 3: based on Week 30 data (HbA_{1c}, FPG, and body weight)
- The difference between treatment groups for efficacy endpoints was assessed by testing the difference in the least squares (LS) mean change from baseline
- The incidence of hypoglycaemia was assessed through Week 25 or 30 depending on the study
- Differences in proportions were assessed based on Miettinen & Nurminen method stratified by study

References

Study 1: Stein et al. Int J Clin Pract 2007
Study 2: Nauck et al. Diabetes Obes Metab 2007; Seck et al. Int J Clin Pract 2010
Study 3: Aschenbrenner et al. Diabetes Obes Metab 2011

Efficacy and Safety of Sitagliptin versus Glipizide in Patients with Type 2 Diabetes and Moderate to Severe Chronic Renal Insufficiency

Juan Camilo Arjona Ferreira[1], Michel Marre[2], Ton Rabelink[3], Nir Barzilai[4], George Bakris[5], Hua Guo[1], Christine McCrary Sisk[1], Keith D. Kaufman[1], Barry Goldstein[1]

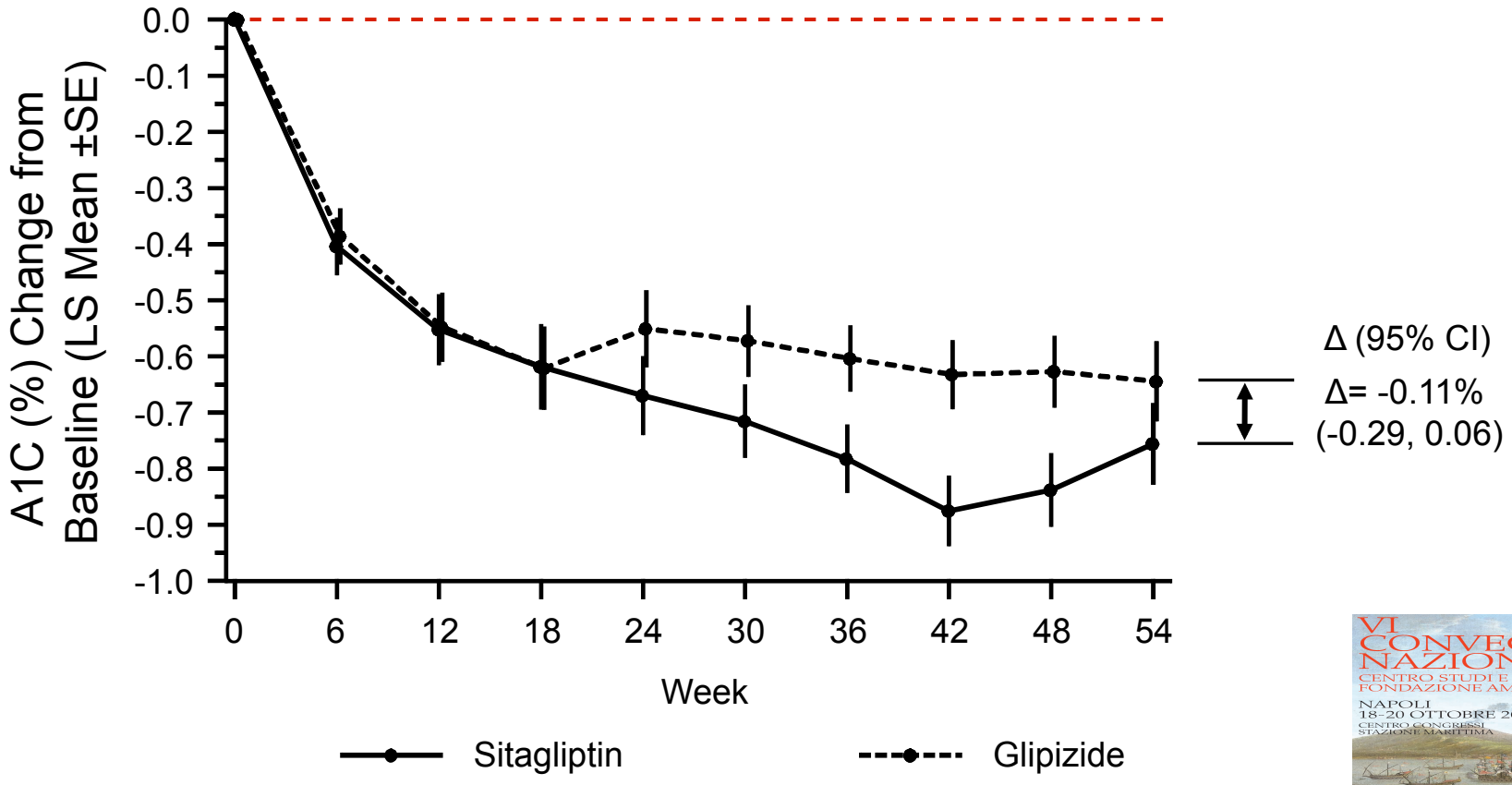
1. Merck Sharp & Dohme, New Jersey, USA
2. Bichat Hospital, Paris, France
3. Leiden University Medical Center, Leiden, The Netherlands
4. Albert Einstein College of Medicine, New York, USA
5. University of Chicago, Illinois, USA

18-11-2012

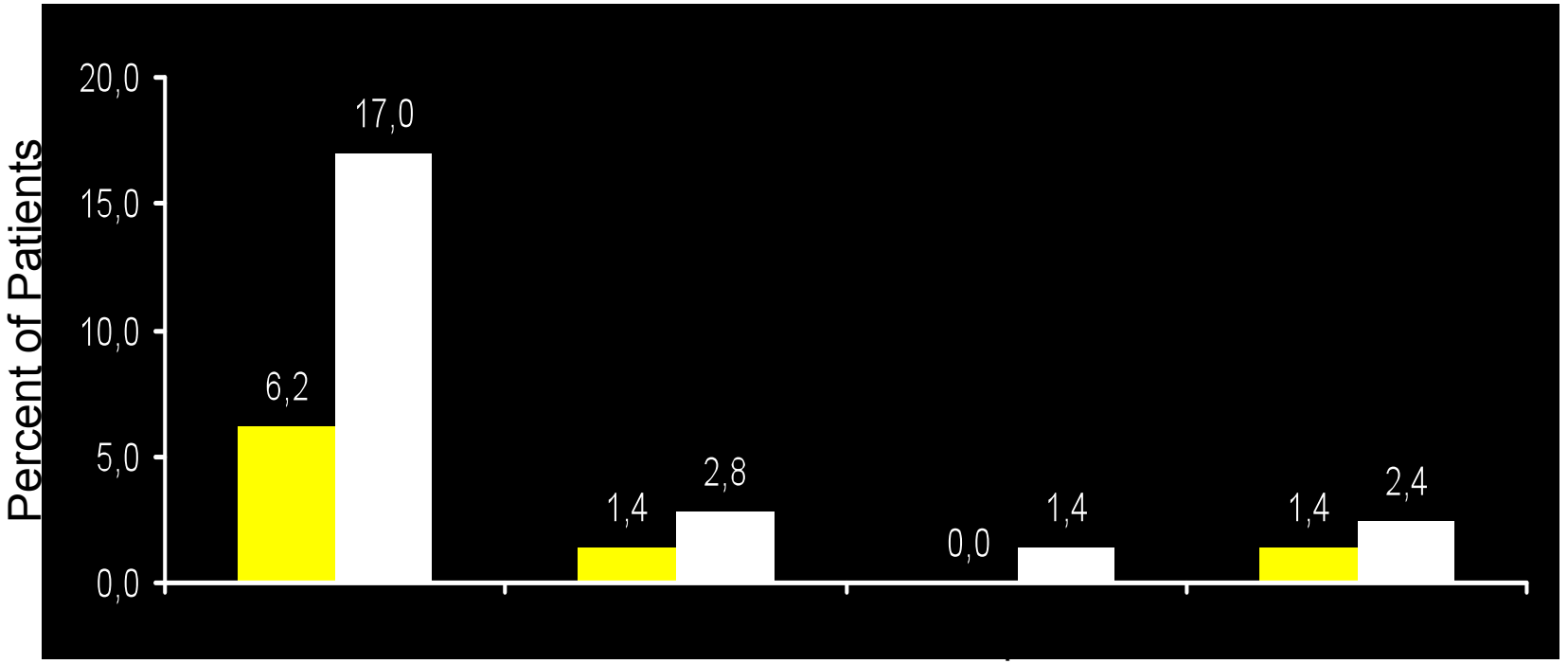
MK-0431-EN073

A1C Change from Baseline Over Time

Per-Protocol Population



Symptomatic Hypoglycaemia AEs



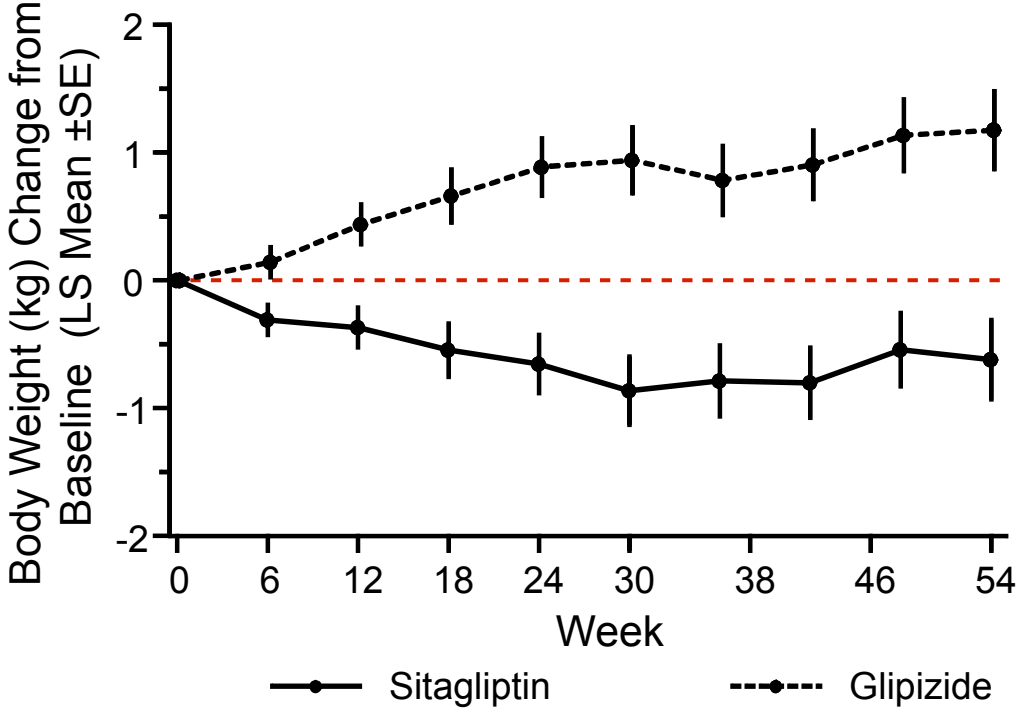
Δ (95% CI)

Sitagliptin (N=210)

Glipizide (N=212)

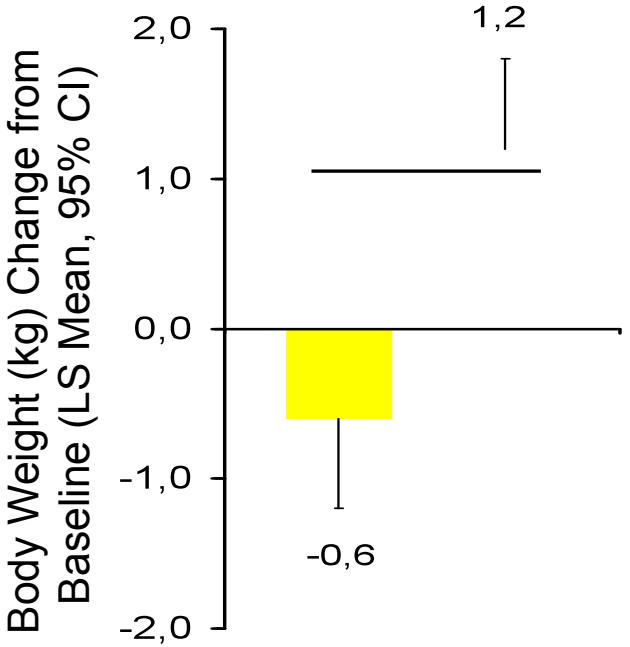
(APaT, excluding data after initiation of glycaemic rescue therapy)

Change from Baseline in Body Weight



Week 54

Δ = -1.8 kg; p<0.001

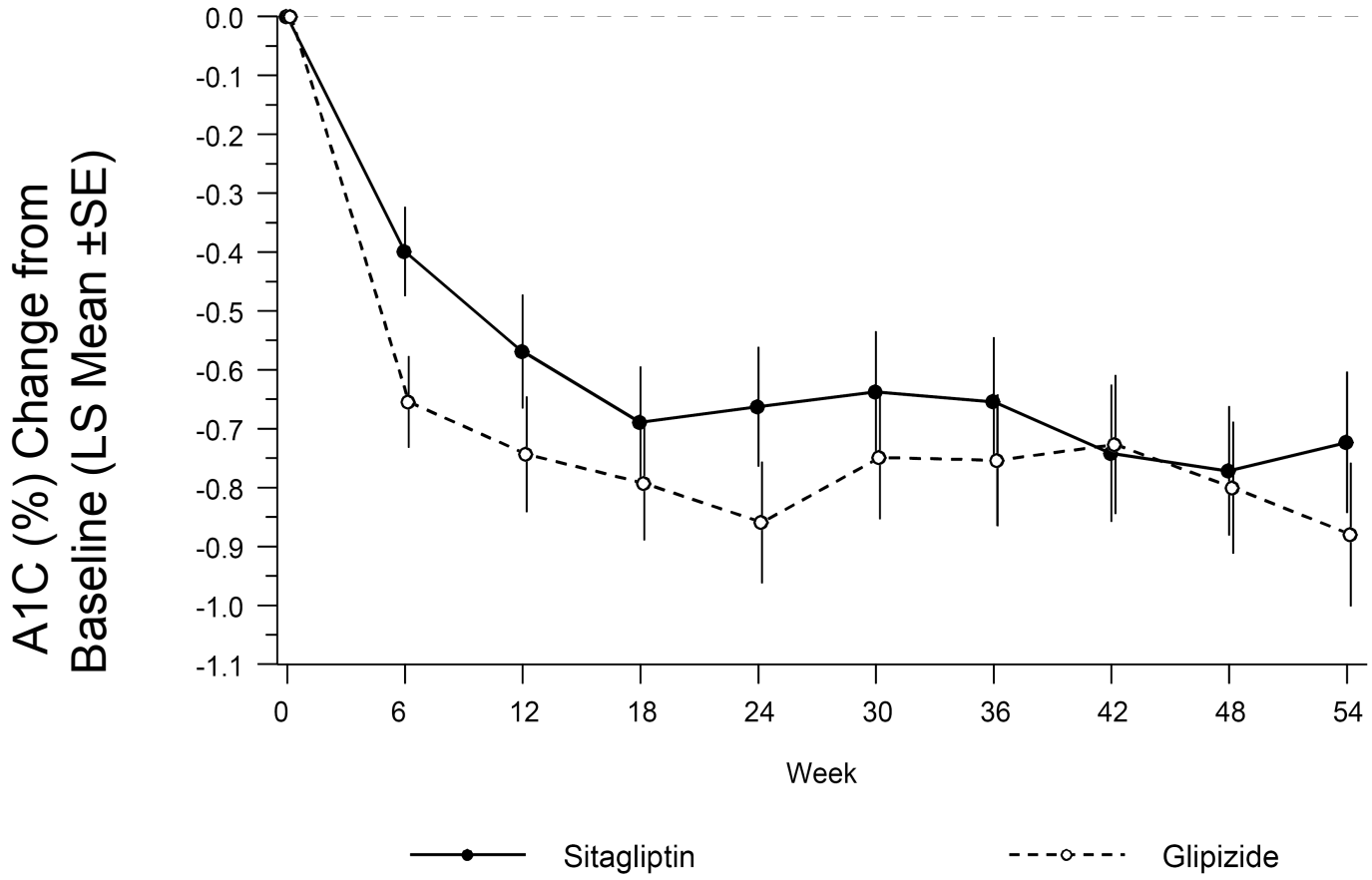


(APaT, excluding data after initiation of glycaemic rescue therapy)

Efficacy and Safety of Sitagliptin Versus Glipizide in Patients With Type 2 Diabetes Mellitus and End-Stage Renal Disease on Dialysis

A1C Change from Baseline Over Time

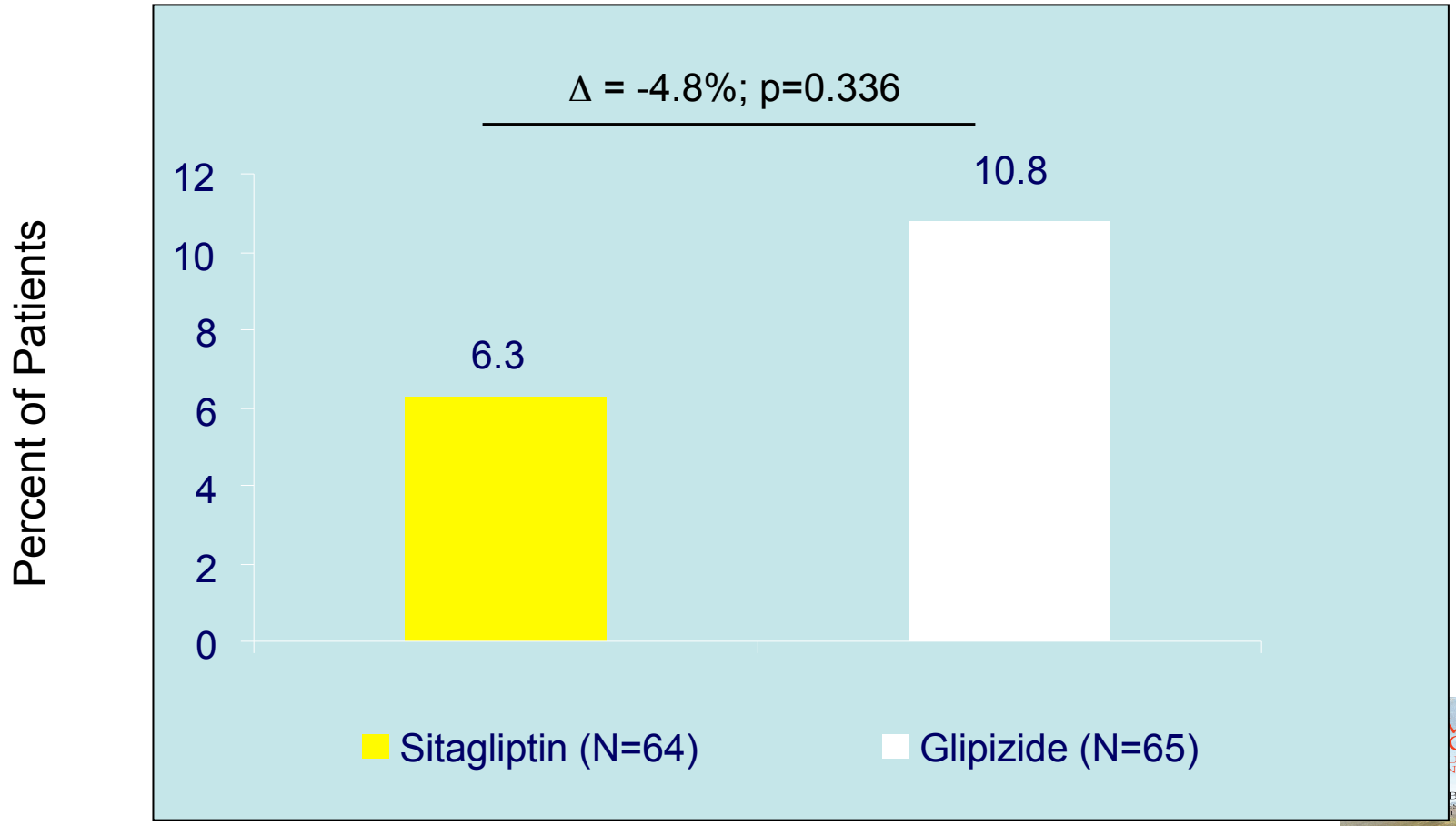
FAS/LOCF Population Week 54



ERM PN073-00 4/22/11

Symptomatic Hypoglycemia AEs

(APaT, Excluding Data After Initiation of Glycemic Rescue Therapy)

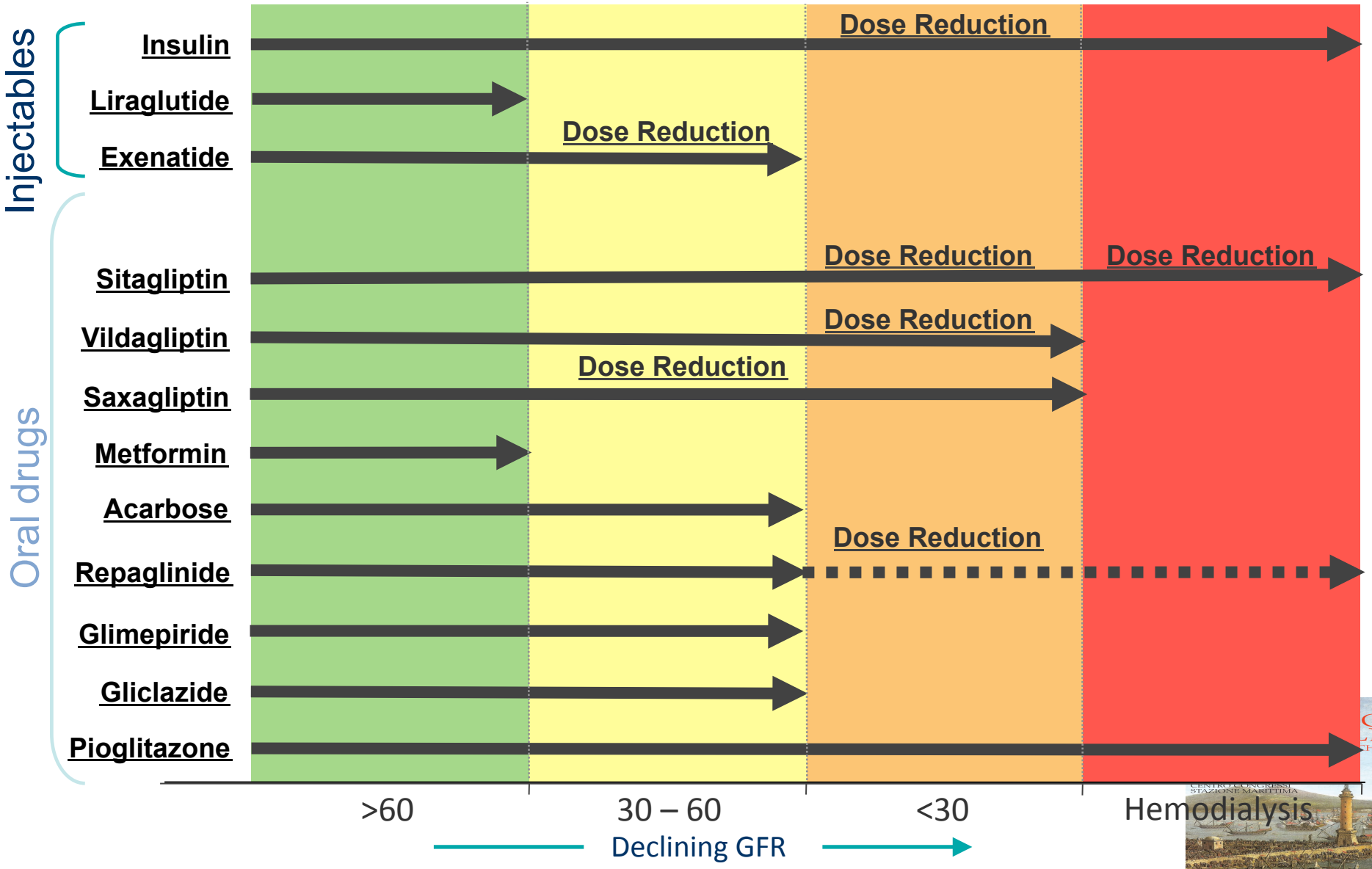


Hypoglycemia Adverse Events

(APaT, Excluding Data After Initiation of Glycemic Rescue Therapy)

	Sitagliptin N=64 n (%)	Glipizide N=65 n (%)	Difference in % vs. Glipizide Estimate (95% CI)
With one or more:			
AEs of symptomatic hypoglycemia	4 (6.3)	7 (10.8)	-4.8 (-15.7, 5.6)
Severe	0 (0.0)	5 (7.7)	-7.8 (-17.1, -1.9)
Requiring non-medical assistance	0 (0.0)	1 (1.5)	-1.7 (-8.6, 4.0)
Requiring medical assistance	0 (0.0)	4 (6.2)	-6.1 (-14.9, -0.1)

Current treatments for type 2 diabetes have limitations when renal function declines



Adapted from: Schernthaner G, et al. *Nephrol Dial Transplant*. 2011;26(2):454–7 and respective EMEA SmPCs

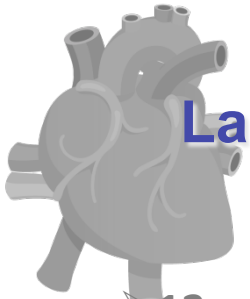
Sitagliptin - Analisi di Sicurezza raggruppata: Sommario degli eventi avversi

	Incidence Rate per 100 Patient-Years		
Adverse Experience	**Sitagliptin n=5,429**	**Non-exposed n=4,817**	**Between-Groups Difference, (95% CI)[a]**
Pancreatitis	0.08	0.10	–0.02 (–0.20, 0.14)
Chronic pancreatitis	0.04	0.03	0.02 (–0.11, 0.13)
Any malignancy	46/4,690 (1.0)	40/3,930 (1.0)	–0.0 (–0.5, 0.4)

- Preclinical and clinical trial data with sitagliptin to date do not indicate an increased risk of pancreatitis in patients with type 2 diabetes treated with sitagliptin.

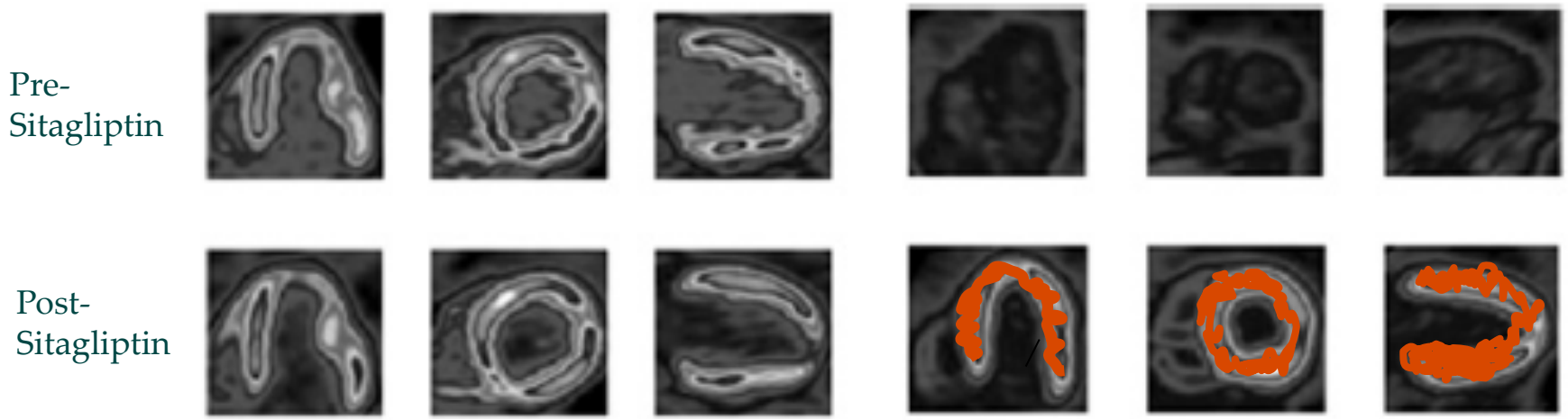
CI=confidence interval.

1. Engel SS et al. *Int J Clin Pract*. 2010;6497):984–990.



La terapia con Sitagliptin migliora l'uptake miocardico di glucosio in pazienti con cardiomiopatia

- 12 pazienti NON diabetici, affetti da cardiomiopatia dilatativa in terapia stabile
- Trattati per 4 settimane con l'obiettivo di valutare l'effetto di Sitagliptin sull'uptake miocardico di glucosio
- Prima e dopo il trattamento l'uptake di glucosio è stato valutato attraverso la PET con Fluorodesossiglucosio come radiotracciante



Non Responder

Aumento lieve dell'uptake di glucosio (<5%)

Responder

Aumento significativo dell'uptake di glucosio (>20%)

Witteles RM et al, Journal of Cardiac Failure Vol 18 No. 8S August 2012

TECOS: A Randomized, Placebo Controlled Clinical Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin in Patients with Type 2 Diabetes Mellitus and Inadequate Glycemic Control

- TECOS Study is Worldwide Clinical Trial
- 40 Countries *(12 Centri in Italia)*
- 14.000 Patients
- Assess the long-term (i.e, ~ 3 years duration) impact on CV events of Sitagliptin

Se son rose, fioriranno…..!