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NAZIONALE
2015 

Centro Congressi
Magazzini del Cotone
Genova 13|16
MAGGIO 2015

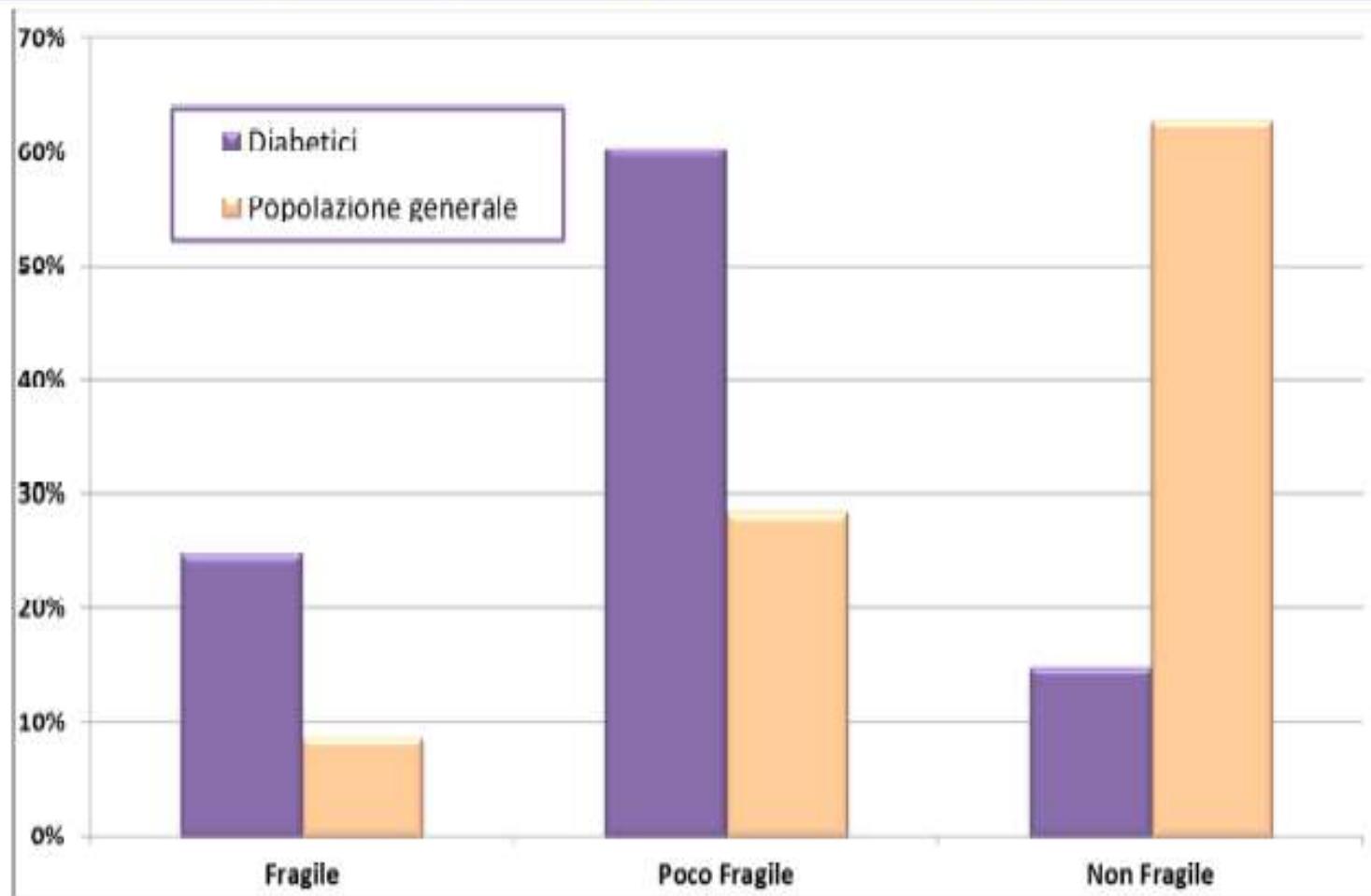
“BURNING POINTS” nella gestione del Paziente Diabetico

*Innovazione nella Protezione del
Paziente Diabetico*

Domanda Chiave

Quale fra i nostri
pazienti dobbiamo
proteggere e da che
cosa dobbiamo
prottegerlo?

Prevalence of frailty in the general population and in people with diabetes



La Fragilità: dai modelli teorici alla valutazione delle esperienze

Ravenna's Frailty and Diabetes Registry

Progr. Cooperazione Transfrontaliera Italia-Slovenia 2007 - 2013/ Progr. c \acute{e} seznejnega sodelovanja Slovenija-Italija 2007 - 2013: "E-health"
Pasquale Falasca, Ravenna, 12 ottobre 2012



Fragilità nella popolazione con Diabete AUSL Prov di Ravenna

Dossier Diabete 2012

Il profilo assistenziale della popolazione con diabete dell'Ausl di Ravenna tratto dal registro di patologia

curata dall'
Azienda USL Provincia di Ravenna in collaborazione con
il Centro Diabetologico e il Dipartimento di Cura Primaria
Azienda Oasi di Ravenna
12 dicembre 2012

Proporzione dei soggetti per classi di rischio di
fragilità, età e genere (al 2009)

	Fragile	Poco Fragile	Non Fragile
Maschi	35,8%	51,9%	62,6%
Femmine	56,8%	48,1%	37,4%
Età media Maschi	77,3	67,7	56,0
Età media Femmine	79,7	68,0	48,2
Punteggio medio di fragilità Maschi	36,9	8,1	3,9
Punteggio medio di fragilità Femmine	40,5	9,0	4,0

Morbidity of hypoglycaemia in diabetes



Brain

Seizures, coma
Cognitive dysfunction
Psychological effects



Cardiovascular

Myocardial ischaemia
(angina and infarction)
Cardiac arrhythmias



Musculoskeletal

Falls, accidents
Fractures, dislocations
Motor vehicle accidents

References:

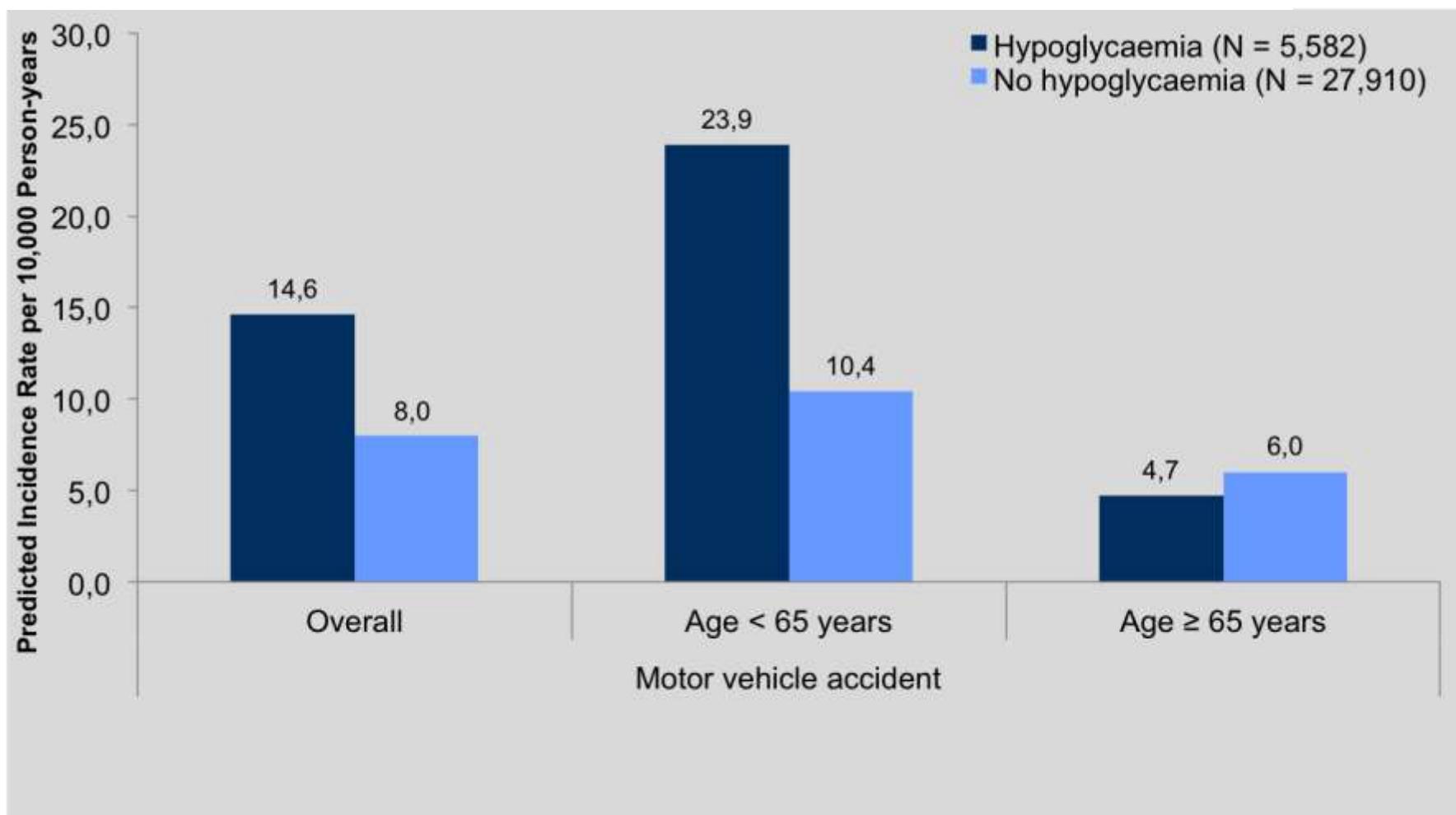
- Neil WP, Hemmen TM (2011) Neurologic Manifestations of Hypoglycemia In: Rigobelo E (Ed.) *Diabetes - Damages and Treatments*. Available at: <http://bit.ly/SNFct3> (accessed 05.11.2012)
- Frier BM (2011) *Br J Diabetes Vasc Dis* **11**: (Suppl. 1) S10–2
- Frier BM (2008) *Diabetes Obes Metab* **24**: 87–92
- Johnston SS et al (2012) *Diabetes, Obes Metab* **14**: 634–43

Hypoglycaemia and cognitive function



- Cognitive function deteriorates at blood glucose <3.0 mmol/l
- Complex tasks are consistently impaired
 - Memory and attention
 - Concentration/abstract thought
 - Rapid decision making
 - Hand-eye coordination
- Accuracy is preserved at expense of speed
- Cognitive function does not fully recover for at least 45 minutes after hypoglycaemia

Hypoglycaemia and accident risk in people with type 2 diabetes mellitus treated with non-insulin antidiabetes drugs



Association between hypoglycaemic events and fall-related

Population with type 2 diabetes and nature of accident	Number (%)		Hazard ratio (95% CI)	Predicted incidence rate per 10 000 person-years (95% CI)	
	Hypoglycaemia	No hypoglycaemia		Hypoglycaemia	No hypoglycaemia
Age <65 years	(n = 3347)	(n = 18 496)			
Any accident	175 (5.2)	507 (2.7)	1.35 (1.14, 1.61)*	138.5 (114.1, 162.9)	102.8 (90.3, 115.3)
Accidental fall	62 (1.9)	193 (1.0)	1.17 (0.88, 1.57)	42.7 (30.4, 55.1)	36.4 (29.5, 43.4)
Motor vehicle accident	28 (0.8)	49 (0.3)	2.31 (1.44, 3.70)*	23.9 (12.4, 35.5)	10.4 (6.3, 14.4)
Other accident	96 (2.9)	275 (1.5)	1.43 (1.13, 1.81)*	76.0 (57.2, 94.7)	53.1 (43.7, 62.5)
Age ≥65 years	(n = 2235)	(n = 9414)			
Any accident	133 (6.0)	270 (2.9)	1.46 (1.18, 1.80)*	135.5 (108.0, 162.9)	92.9 (78.9, 106.9)
Accidental fall	99 (4.4)	176 (1.9)	1.52 (1.18, 1.95)*	78.9 (58.3, 99.4)	52.0 (41.4, 62.6)
Motor vehicle accident	4 (0.2)	16 (0.2)	0.79 (0.26, 2.38)	4.7 (0.0, 9.7)	6.0 (2.6, 9.4)
Other accident	33 (1.5)	86 (0.9)	1.23 (0.82, 1.85)	38.0 (23.6, 52.3)	30.8 (23.1, 38.6)

Hypoglycaemia was associated with falls in people aged > 65 and fall-related fractures in insurance claim databases

Achievement of therapeutic targets in patients with diabetes and chronic kidney disease: insights from the Associazione Medici Diabetologi Annals initiative

Salvatore De Cosmo¹, Francesca Viazzi², Antonio Pacilli¹, Carlo Giorda³, Antonio Ceriello⁴, Sandro Gentile⁵, Giuseppina Russo⁶, Maria Chiara Rossi⁷, Antonio Nicolucci⁷, Pietro Guida⁸, Paolo Di Bartolo⁹, Roberto Pontremoli² and the AMD-Annals Study Group

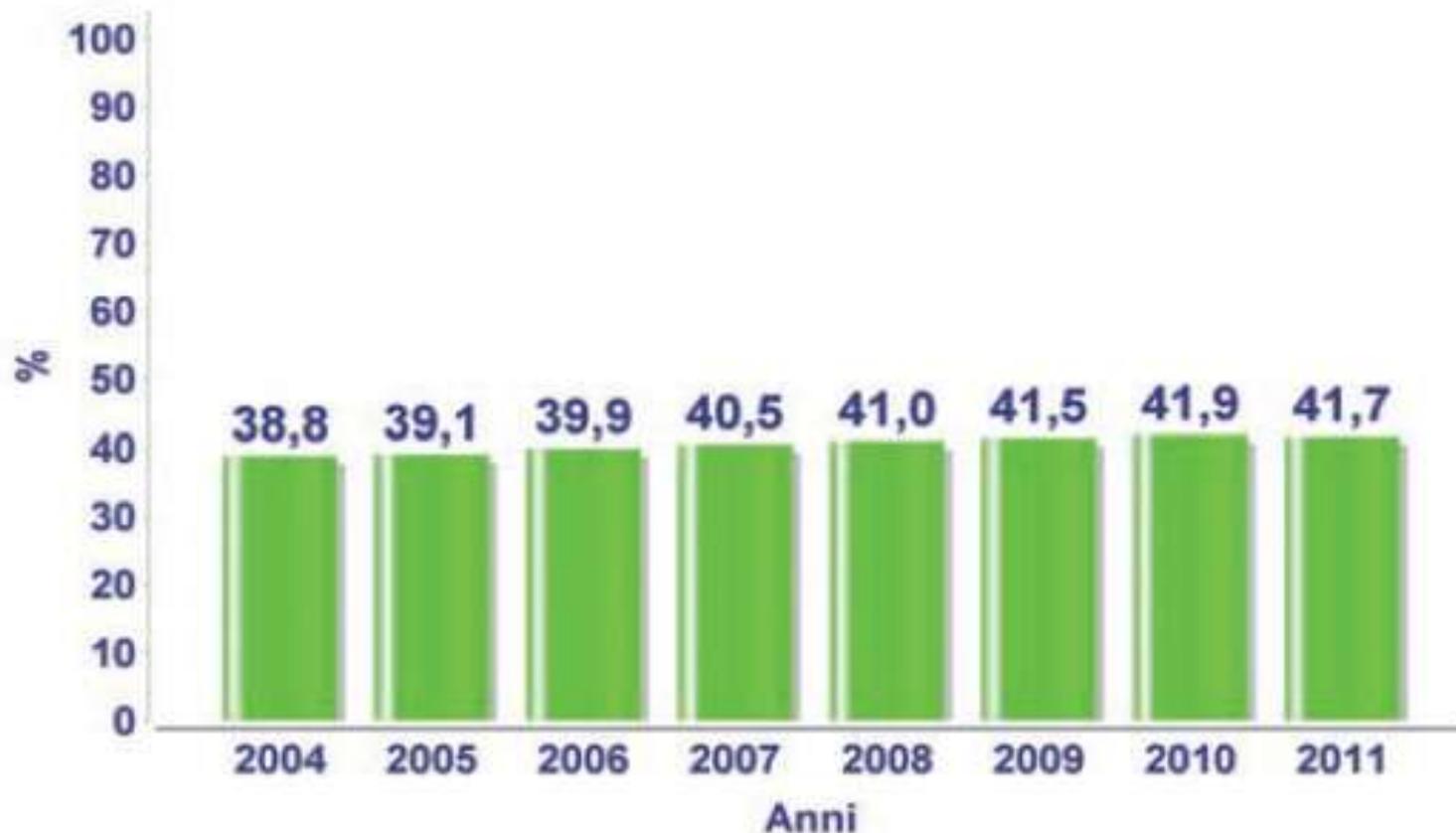
Table 1. Clinical features of 116 777 patients with T2DM

Male gender, n (%)	66 260 (56.7)
Age (years)	67 ± 11
BMI (kg/m ²)	30 ± 5
Serum creatinine (mg/dL)	0.97 ± 0.52
eGFR (mL/min/1.73 m ²)	77 ± 21
eGFR < 60 mL/min/1.73 m ² , n (%)	24 514 (21.0)
High albuminuria, n (%)	31 354 (26.9)

Annali AMD 2012

www.infodiabete.it

Soggetti con BMI $\geq 30 \text{ kg/m}^2$



Barriere irrazionali che ritardano l'inizio della terapia insulinica

Più della metà sono preoccupati di iniziare con l'insulina

Metà pensano che iniziare la terapia insulinica voglia dire aver fallito con la gestione del proprio diabete

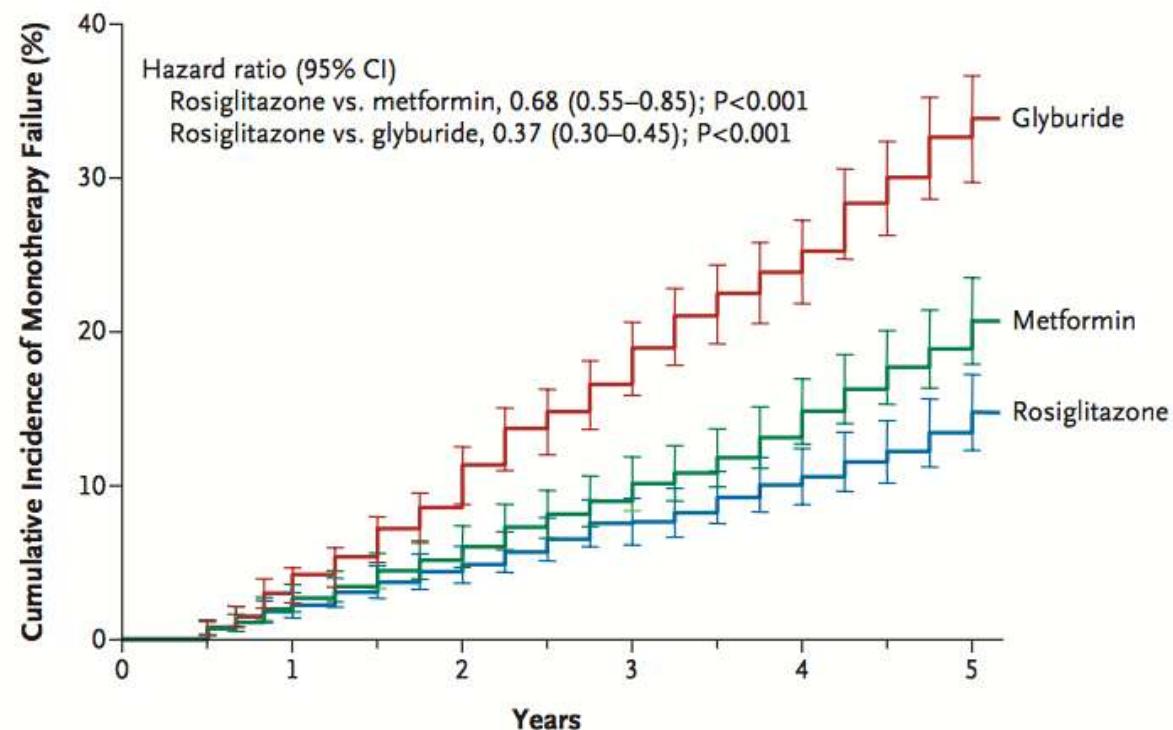
Solo una persona su cinquanta crede che l'insulina possa migliorare la gestione del proprio diabete

Più di un terzo del personale sanitario rinvia l'inizio dell'insulina a quando è "indispensabile"

Due terzi dei medici utilizza l'insulina come minaccia nei confronti dei propri pazienti



DURABILITY OF GLYCEMIC CONTROL IN TYPE 2 DIABETES



No. at Risk

Rosiglitazone	1393	1207	1078	957	844	324
Metformin	1397	1205	1076	950	818	311
Glyburide	1337	1114	958	781	617	218

Figure 2. Kaplan-Meier Estimates of the Cumulative Incidence of Monotherapy Failure at 5 Years.

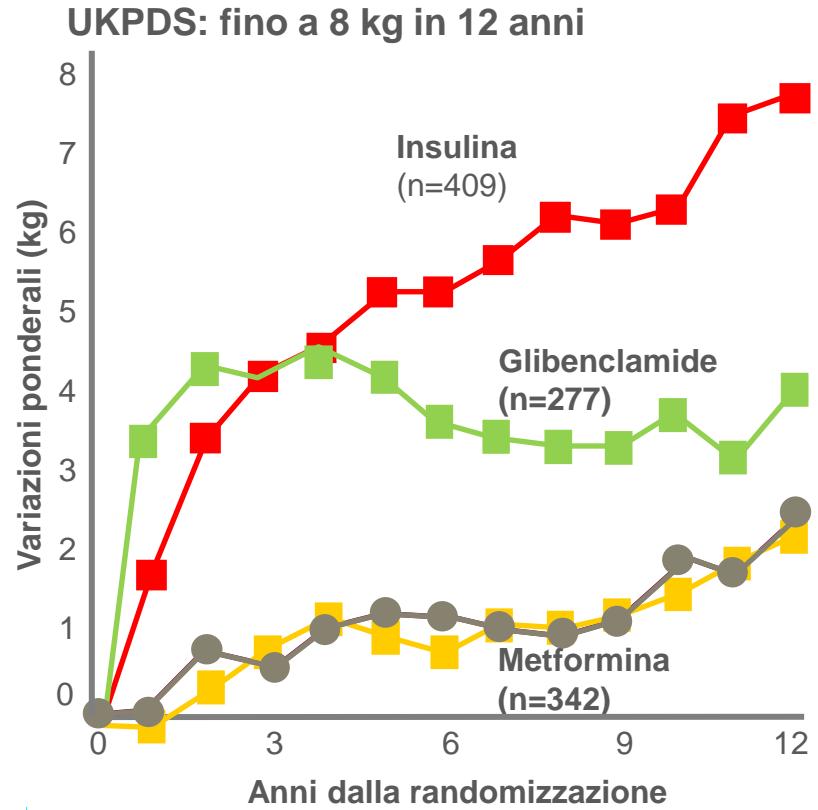
Paziente “Robusto”:

- Aumento ponderale
- Ipoglicemie
- Esaurimento Beta Cell.
- Terapia insulinica

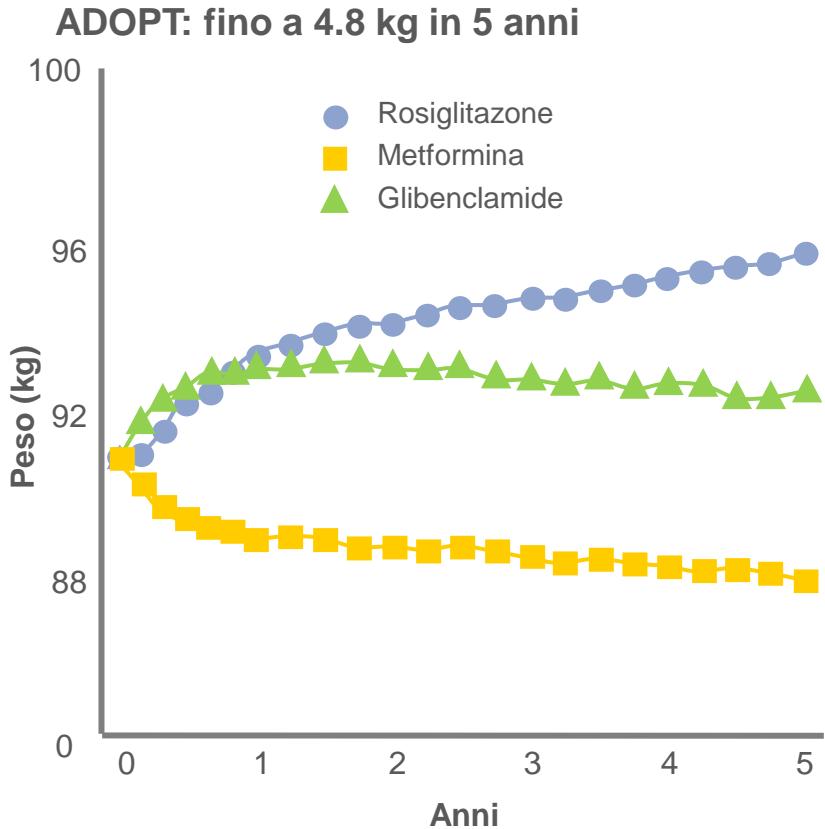
Paziente “Fragile”:

- Ipoglicemie
- Funzione renale
- Terapia insulinica

La maggior parte delle terapie comportano aumento di peso nel tempo



- Terapia convenzionale (n=411); inizialmente dieta poi se FPG >15 mmol/L sulfaniluree, insulina e/o metformina.



Bologna, 3 febbraio 2014

Gruppo Multidisciplinare sui Farmaci per il Diabete

Indicatori di prescrizione regionale di farmaci ipoglicemizzanti orali

Dati preliminari 2013



Agenzia Sanitaria e Sociale – Servizio Politica del Farmaco
Direzione Generale Sanità e Politiche Sociali

Raccomandazione 1 – Sulfaniluree (inclusa repaglinide)

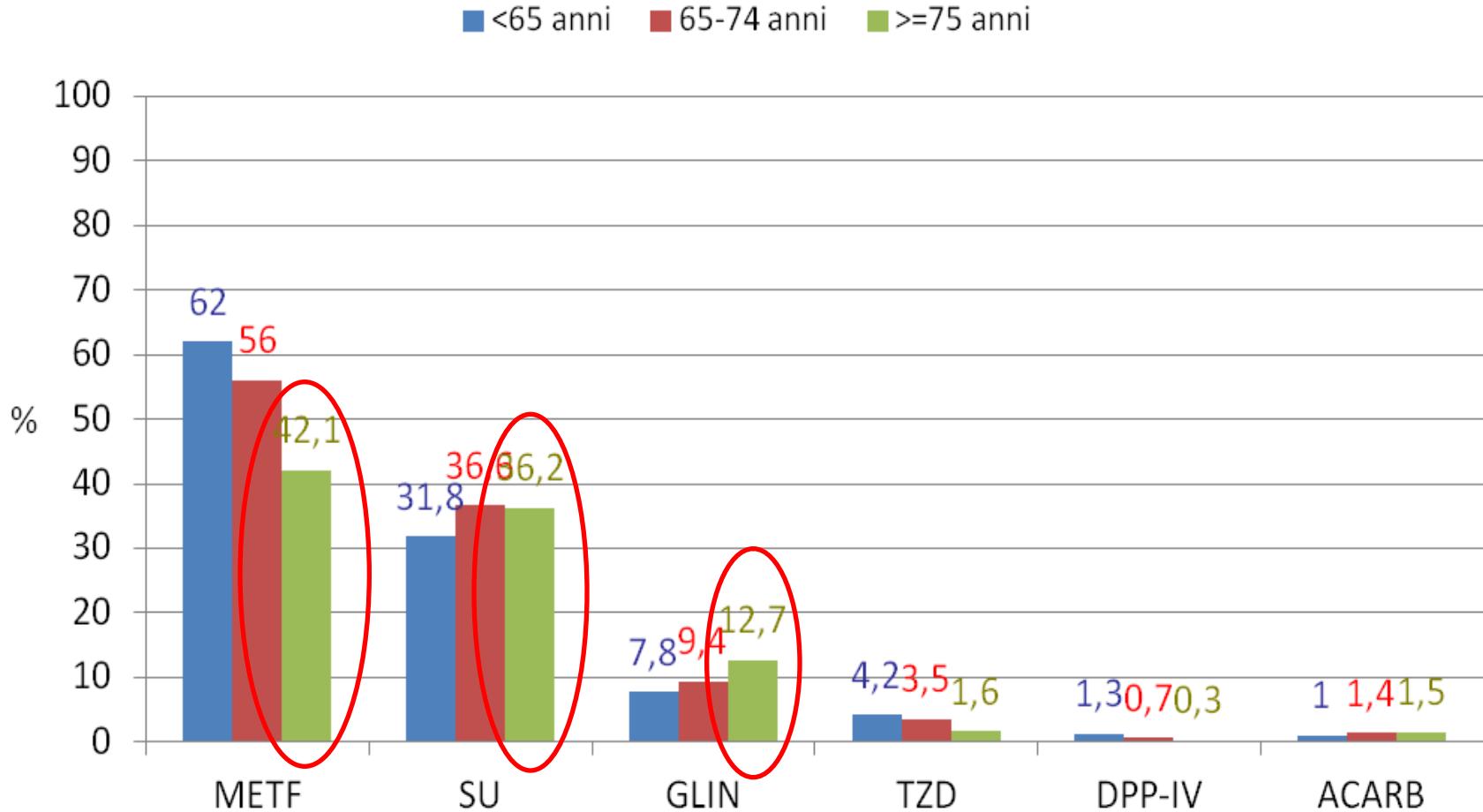
.....il secondo ipoglicemizzante è una SULF nella maggior parte dei casi.

Indicatore

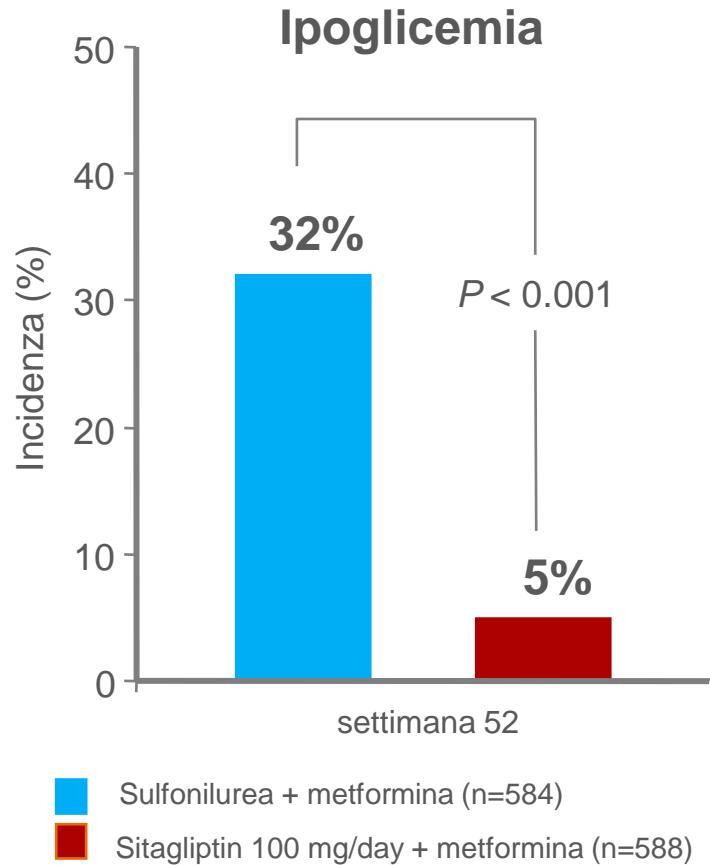
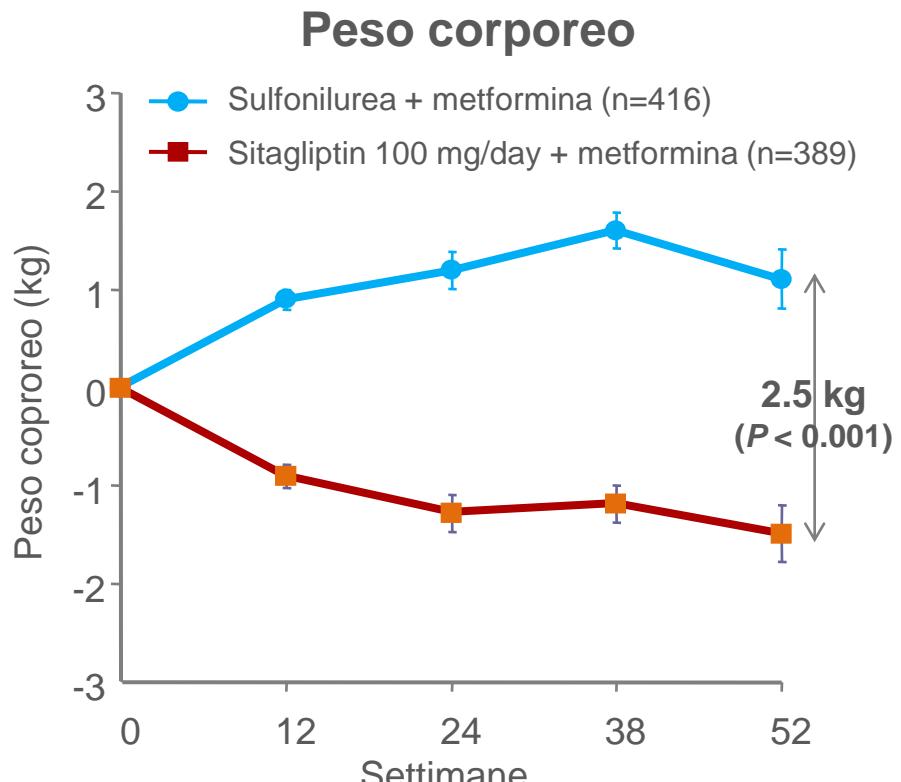
Tasso atteso di utilizzo di SULF: almeno il 60% delle persone con DM2 che a un trattamento in monoterapia con metformina aggiungono un secondo farmaco orale

$$\frac{\text{Incidenza MET+SULF}}{\text{anno in corso}} \geq 60\%$$
$$\frac{\text{Incidenza MET+2° farmaco}}$$

Utilizzo delle diverse classi di antidiabetici orali (da sole o in associazione) sulla popolazione divisa per classi di età

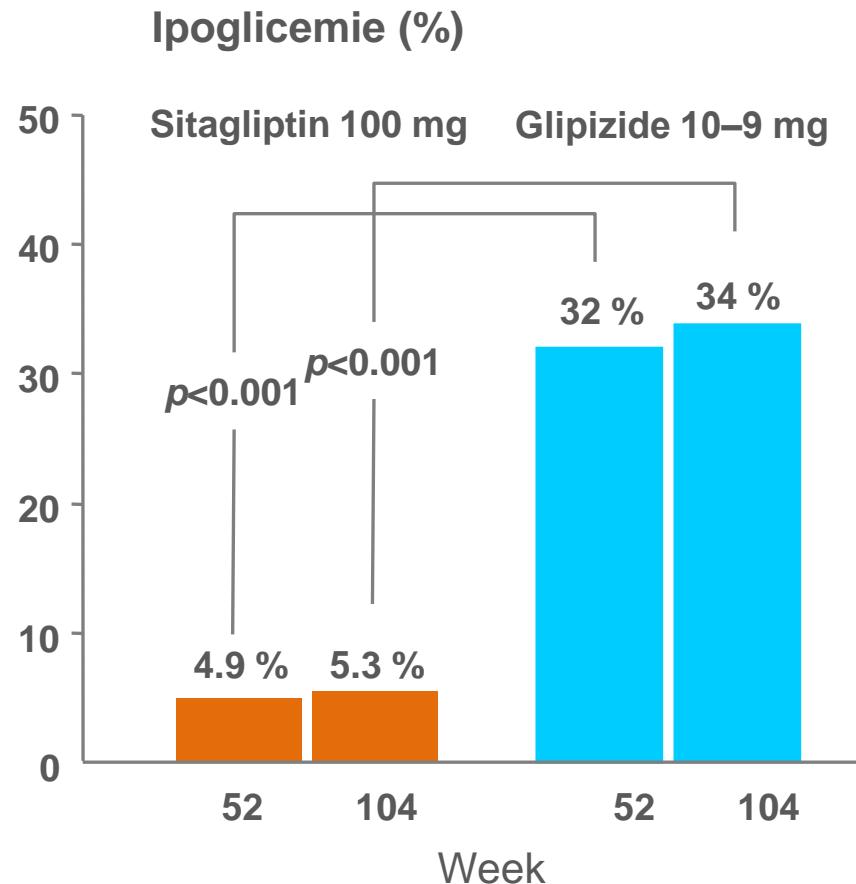


Sitagliptin confronto con Glipizide ad 1 anno: Peso Corporeo - Ipoglicemie



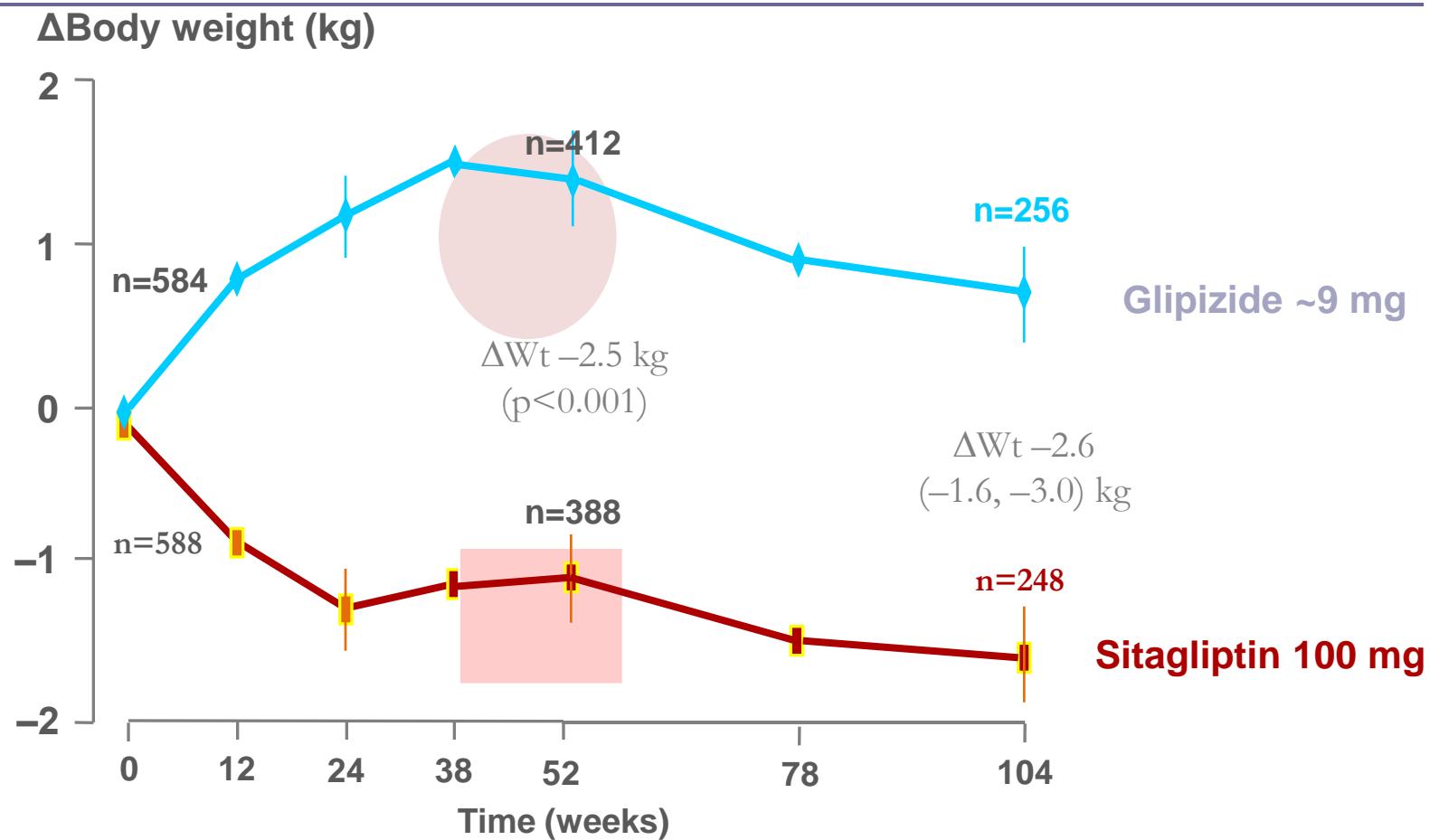
Confronto con glipizide a 2 anni: Ipoglicemie

	Studio ad 1 anno		Studio a 2 anni	
	basale	1 anno	basale	2 aa
glipizide	7.5	6.9	7.3	6.8
difference	-0.0 (-0.1, 0.1)		-0.0 (-0.1, 0.1)	
sitagliptin	7.5	6.8	7.3	6.8



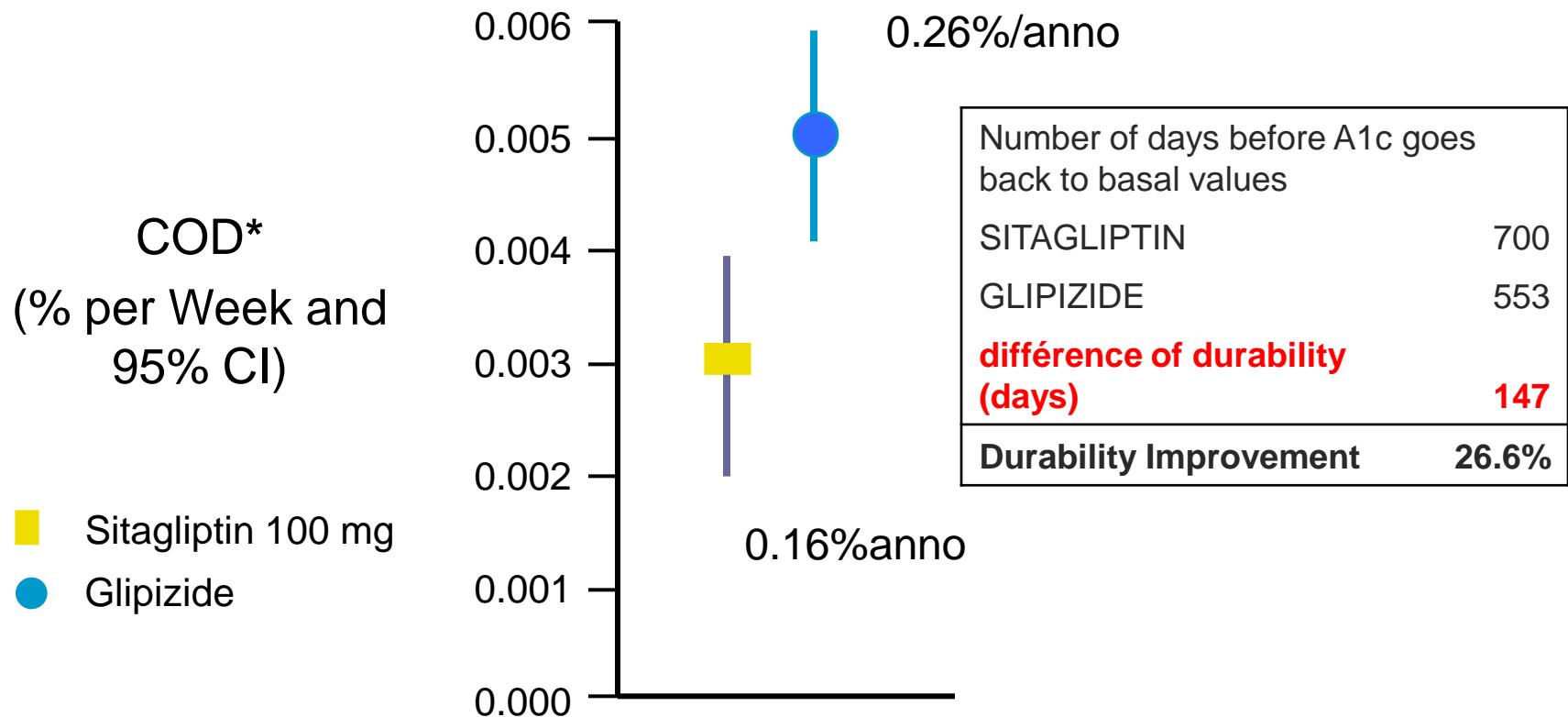
Nauck et al, Diabetes Obes Metab, 2007; Seck et al, Int J Clin Pract, 2010

Confronto con glipizide a 2 anni: Peso Corporeo



Coefficient of Durability Determined Using A1C LS Means Week 24 to Week 104

Per Protocol Population



* Slope of the time profile of mean change from baseline in A1C

Treatment maintenance duration of dual therapy with metformin and sitagliptin in type 2 diabetes: The ODYSSEE observational study

P. Valensi^a, G. de Pouvourville^b, N. Benard^c, C. Chanut-Vogel^c, C. Kempf^d, E. Eymard^{c,*},
C. Moisan^c, J. Dallongeville^e



Aim. – The study compared the duration of maintenance of treatment in patients with type 2 diabetes (T2D) using dual therapy with either metformin and sitagliptin (M-Sita) or metformin and a sulphonylurea (M-SU).

Materials and methods. – This observational study included adult patients with T2D who had responded inadequately to metformin monotherapy and therefore had started de-novo treatment with Met-Sita or Met-SU within the previous eight weeks. Patient follow-up and changes to treatment were performed according to their general practitioner's usual clinical practice. The primary outcome was time to change in treatment for whatever cause. HbA_{1c} and symptomatic hypoglycaemia were also documented.

ODYSSÉE: Study objectives

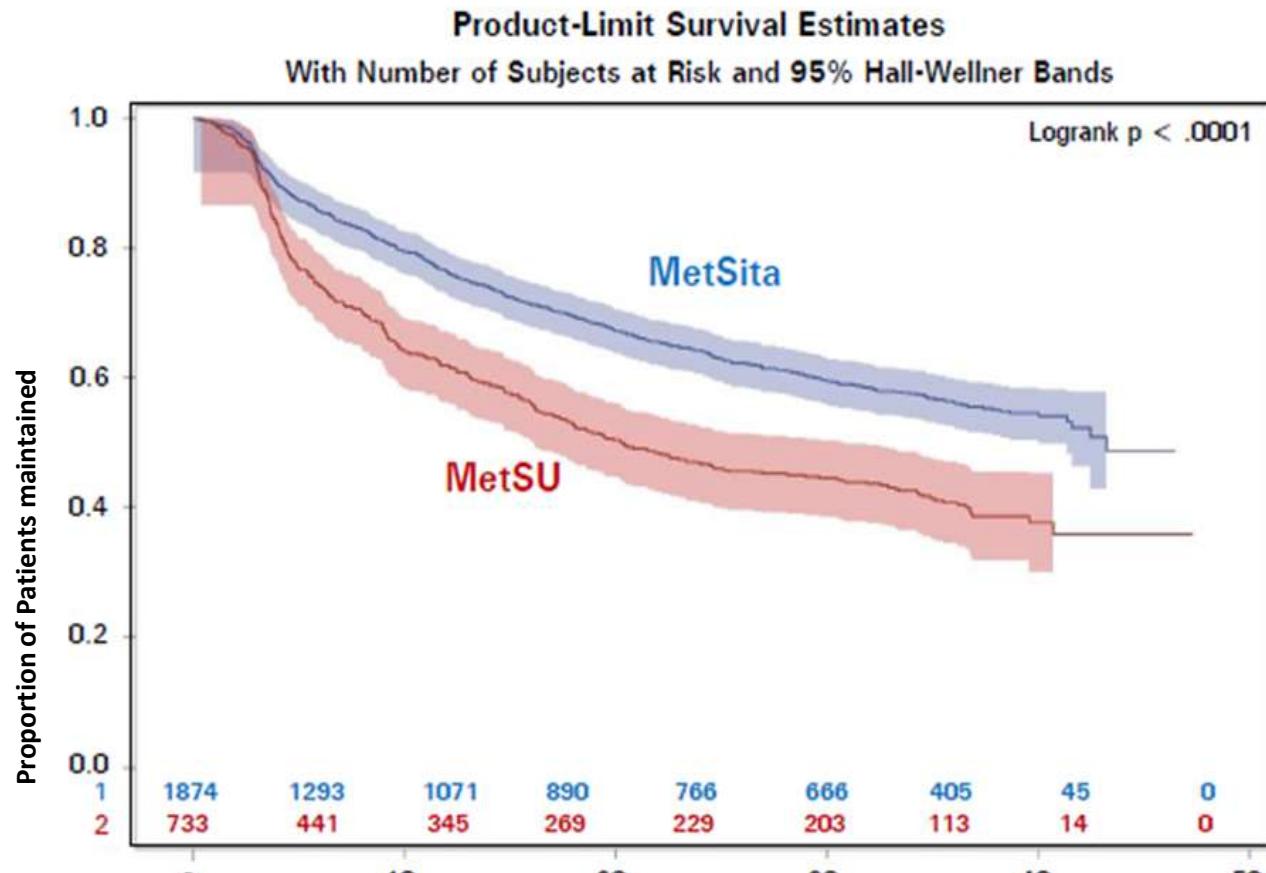
- **Primary objective**

Demonstrate superiority in number of days with no change in treatment* (maintenance duration) in patients with type 2 diabetes receiving oral dual therapy with metformin + sitagliptin *versus* metformin + sulfonylurea

**Change in treatment : Discontinuation of a drug, switch between drugs, or addition of a new drug*

- **Main Secondary objectives**

- Changes in HbA1C
- Changes in weight
- Incidence of hypoglycemia



MetSita group : 43.2 months [95%CI: 41.4 – NE*]

MetSU group : 20.2 months [95%CI: 17.0 - 25.1]

*non-evaluable

ODYSSÉE Study

Reasons for treatment modification

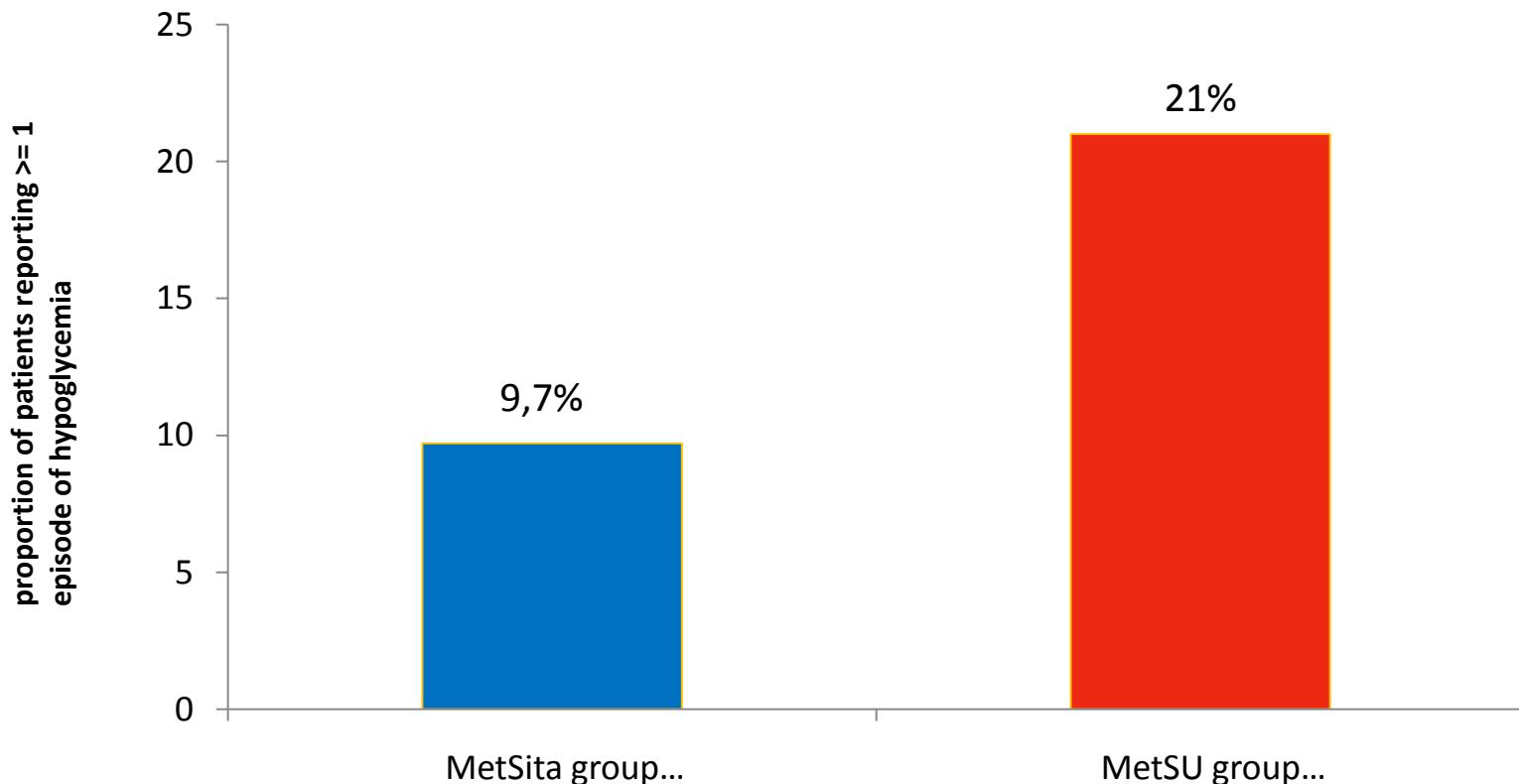
	Met+Sita patients (N=1874)	Met+SU patients (N=733)
Treatment modification	621 (33.1%)	341 (46.5%)
Reasons for treatment modification*	N = 433	N = 215
<i>Missing</i>	188	126
<i>Insufficient efficacy</i>	301 (69.5%)	138 (64.2%)
<i>Poor tolerability</i>	57 (13.2 %)	25 (11.6%)
<i>Hypoglycemia</i>	18 (4.2 %)	29 (13.5%)
<i>Other treatment event</i>	7 (1.6 %)	0 (2.8%)
<i>Patient decision</i>	19 (4.4 %)	10 (4.7%)
<i>Other</i>	54 (12.5 %)	38 (17.7%)

* % may exceed 100% because multiple reasons were possible

ODYSSÉE Study

Hypoglycemia

Incidence of hypoglycemia up to modification of initial treatment



*53.9% of the patients in the SU group were taking gliclazide, 24 % taking glibenclamide and 21.6% taking glimepiride

P.Valensi et al. Treatment Maintenance Duration of Dual Therapy with Metformin and Sitagliptin in Type 2 Diabetes: The Odyssee Observational Study. Diabetes 63(S1): LB-35 Abst 136-LB 2014 Jun 13-17 2014 - ADA 2014 74th American Diabetes Association Scientific Sessions, San Francisco, California Abst: 136-LB
Internal data

ODYSSÉE Study

Conclusions

The results of the ODYSSÉE study, carried out in everyday primary care practices and involving 3453 patients starting on sitagliptin or sulfonylurea (the most common being gliclazide)* in combination with metformin dual therapy between July 2009 and December 2010, showed that:

- Dual therapy with MetSita was maintained without treatment modification (defined as any add-on therapy, withdrawal or substitution) longer than dual therapy with MetSU*.
- The median duration of treatment maintenance was 43.2 months in the MetSita group versus 20.2 months in the MetSU* group.
- An HbA1c level decrease of 0.6% up to treatment modification occurred in both treatment groups.
- Symptomatic hypoglycemia occurred in 9.7% of patients in the MetSita group compared to 21% of patients in the MetSU* group.
- Despite some limitations, the data on effectiveness with respect to HbA1c level and occurrence of symptomatic hypoglycemia obtained in this naturalistic, real-life observational study are comparable to those described previously during the clinical development program for sitagliptin.

*53.9% of the patients in the SU group were taking gliclazide, 24 % taking glibenclamide and 21.6% taking glimepiride

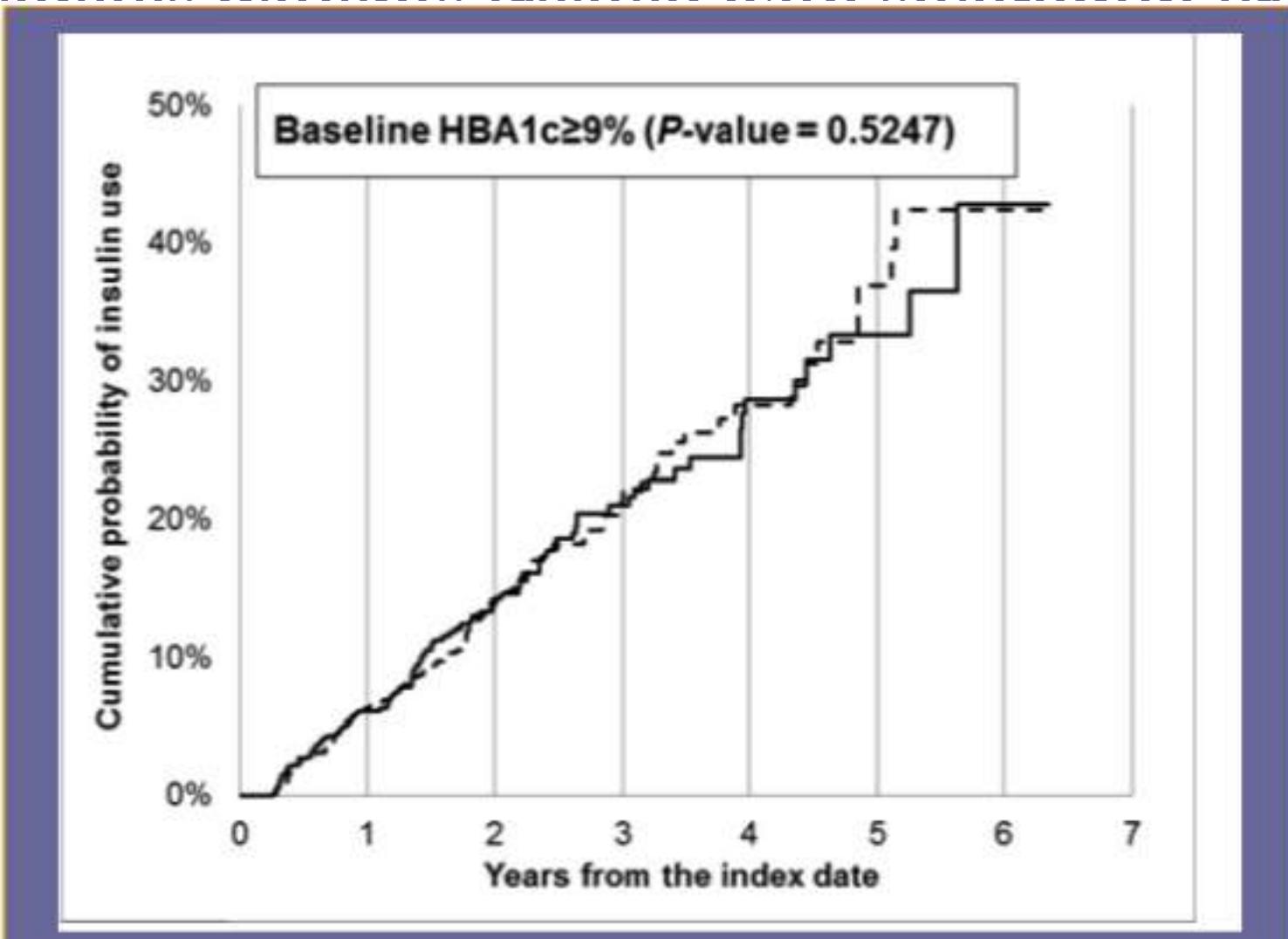
Assessing time to insulin therapy among type 2 diabetes patients treated with sitagliptin or sulfonylurea plus metformin dual therapy

Aims: Progressive decline in beta-cell function in patients with type 2 diabetes mellitus (T2DM) necessitates treatment intensification and often insulin initiation. However, time to insulin initiation may vary with different therapies. We assessed time to insulin initiation among patients treated with sitagliptin versus sulfonylurea as add-on to metformin.

Methods: This retrospective cohort study utilized GE Centricity electronic medical records and included patients aged ≥ 18 years with continuous medical records and an initial prescription of sitagliptin or sulfonylurea (index date) with metformin for ≥ 90 days during 2006-2013. Sitagliptin and sulfonylurea users were matched 1:1 using propensity score matching (PSM), and differences in insulin initiation were assessed using Kaplan-Meier (KM) curves and Cox regression. Conditional logistic regressions (CLR) examined the likelihood of insulin use 1 to 6 years post-index for each year.

Assessing time to insulin therapy among type 2 diabetes patients treated with metformin as first-line treatment

SU



489

Cox model on time-to-insulin after matching

	HR	95% CI	P-Value
Sitagliptin	1.195	(1.004, 1.422)	0.0446
Male			
Caucasian			
Commercial			
Residential			
Midwest			
North			
South			
Diabetes complications			
Diabetes duration			
Other kidney disease			
Liver disease			
Hypoglycemia			
Obesity			
Hyperlipidemia			
Malignancy			
Lab assays			
HbA1c			
Total cholesterol			
Diastolic blood pressure			
Systolic blood pressure			
Serum creatinine			
Alanine transaminase (ALT), U/L			
Aspartate transaminase (AST), U/L	1.195	(1.004, 1.422)	0.0446

p-values were assessed using Wald's statistics.

The durability of sitagliptin in elderly patients with type 2 diabetes

Aim: To evaluate the durability of sitagliptin and to assess changes in clinical chronic complications following sitagliptin monotherapy for 48 months in elderly patients with type 2 diabetes mellitus (T2DM).

Subjects and methods: We enrolled 76 drug-naïve patients (40 women and 36 men; mean age: 71.3 ± 11.7 years) with T2DM who received 25–100 mg of sitagliptin therapy from an outpatient clinic.

- ✓ The observational period for each patient was .48 months, beginning at the time sitagliptin therapy was initiated.
- ✓ The following were measured or performed at the beginning of each year: body mass index; serum total cholesterol, low-density lipoprotein, high-density lipoprotein; triglyceride levels; creatinine (Cr) levels; urine albumin and urine Cr; nonmydriatic fundusgraphy; and semiquantified neuropathy.
- ✓ The fasting plasma glucose and glycated hemoglobin (HbA1c) was measured every 3–6 months.

Table I The clinical and biochemical characteristics of patients before and after 48 months of sitagliptin

	Before sitagliptin use	After sitagliptin use (48 months)
Age (years)	71.3±11.7	
Sex (male/female)	36/40	36/40
Dose (mg)	69.4±24.4	67.3±23.6
FPG (mg/dL)	123±20.1	112±24.4
Creatinine (mg/dL)	1.36±0.73	1.32±0.67
eGFR (mL/minute/1.73 m ²)	53.4±24.3	57.6±23.0
HbA _{1c} (%)	7.1±0.8	6.4±0.4
BMI (kg/m ²)	26.5±4.5	26.1±4.2
TG (mg/dL)	159.2±94.2	161.1±111.4
TC (mg/dL)	176.5±40.5	178.8±38.7
HDL (mg/dL)	47.1±12.6	46.8±12.2
LDL (mg/dL)	99.1±35.1	100.1±31.6
Comorbidities (number)		
Hypertension	22	29
ARB or ACEI	22	23
Dyslipidemia	30	33
Statin	29	30
Retinopathy	1	1
Neuropathy	24	25
Nephropathy	19	20

Abbreviations: FPG, fasting plasma glucose; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; BMI, body mass index; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitor.

The durability of sitagliptin in elderly patients with type 2 diabetes

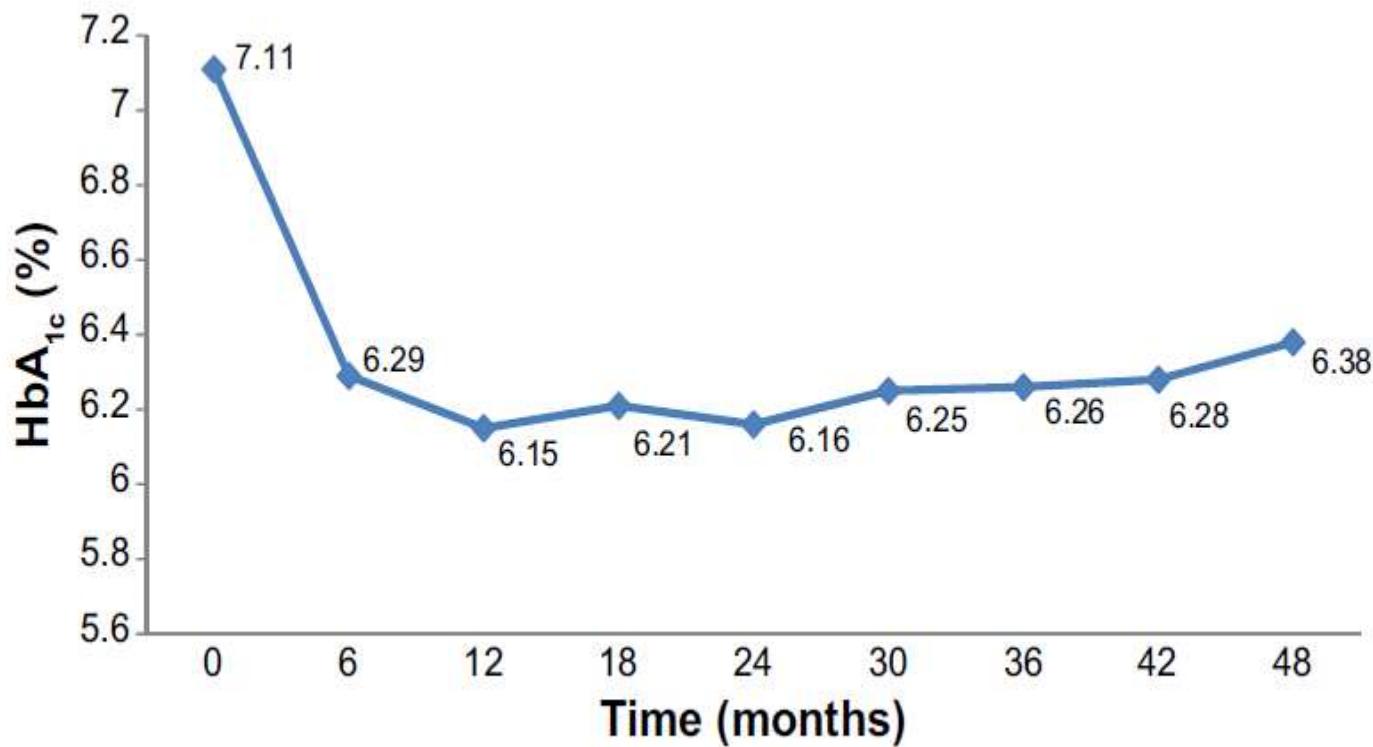


Figure 1 Change in the HbA_{1c} levels from baseline at 6-month intervals.

Abbreviation: HbA_{1c}, glycated hemoglobin.

The durability of sitagliptin in elderly patients with type 2 diabetes

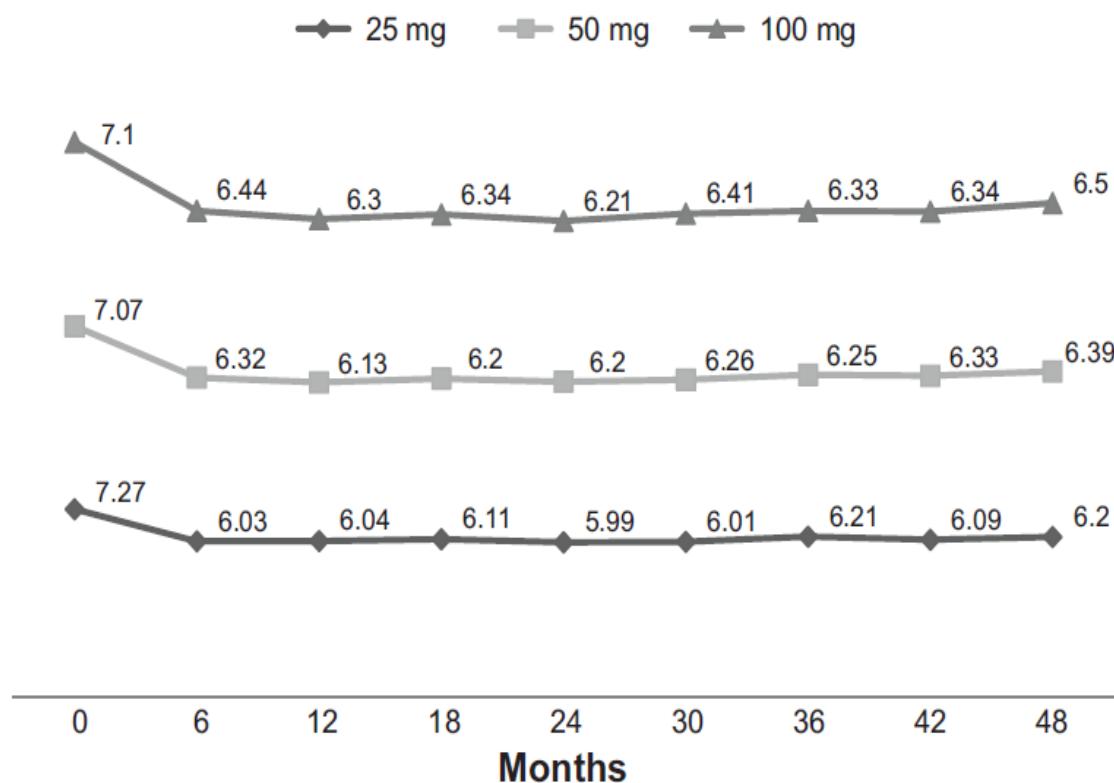


Figure 2 Change in HbA_{1c} levels as a function of sitagliptin dose.

Notes: The patients who received different doses of sitagliptin had apparent reductions in HbA_{1c} from baseline during the first 6 months of treatment. The HbA_{1c} levels remained stable in patients receiving different doses of sitagliptin between month 6 and month 48.

Abbreviation: HbA_{1c}, glycated hemoglobin.

Efficacy and tolerability of sitagliptin monotherapy in elderly patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial.

OBJECTIVE: Type 2 diabetes in the elderly is an important and insufficiently studied public health problem. This study evaluated sitagliptin monotherapy in patients with type 2 diabetes aged \geq 65 years.

RESEARCH DESIGN AND METHODS: This was a randomized, double-blind, placebo-controlled, parallel-group study conducted at 52 sites in the United States. Patients were treated with once-daily sitagliptin (100 or 50 mg, depending on renal function) or placebo for 24 weeks. Key endpoints included change from baseline in glycated hemoglobin (HbA_{1c}), 2-hour post-meal glucose (2-h PMG) and fasting plasma glucose (FPG) at week 24, and average blood glucose on treatment days 3 and 7.

CLINICAL TRIAL REGISTRATION: NCT00305604.

RESULTS: Among randomized patients (N = 206), mean age was 72 years and mean baseline HbA_{1c} was 7.8%. At week 24, HbA_{1c} decreased by 0.7%, 2-h PMG by 61 mg/dL, and FPG by 27 mg/dL in sitagliptin-treated patients compared with placebo (all p < 0.001). On day 3 of treatment, mean average blood glucose was decreased from baseline by 20.4 mg/dL in sitagliptin-treated patients compared with placebo (p < 0.001). In subgroups defined by baseline HbA_{1c} <8.0% (n = 132), \geq 8.0% to <9.0% (n = 42), and \geq 9.0% (n = 18), the placebo-adjusted reductions in HbA_{1c} with sitagliptin treatment were 0.5%, 0.9%, and 1.6%, respectively. Patients in the sitagliptin and placebo groups had similar rates of adverse events overall (46.1% and 52.9%, respectively); serious adverse events were reported in 6.9% and 13.5%, respectively. No adverse events of hypoglycemia were reported. Potential study limitations include a relatively small number of patients with more severe hyperglycemia (HbA_{1c} \geq 9.0%) and the exclusion of patients with severe renal insufficiency.

Efficacy and Safety of Sitagliptin Versus Glipizide in Patients With Type 2 Diabetes and Moderate-to-Severe Chronic Renal Insufficiency

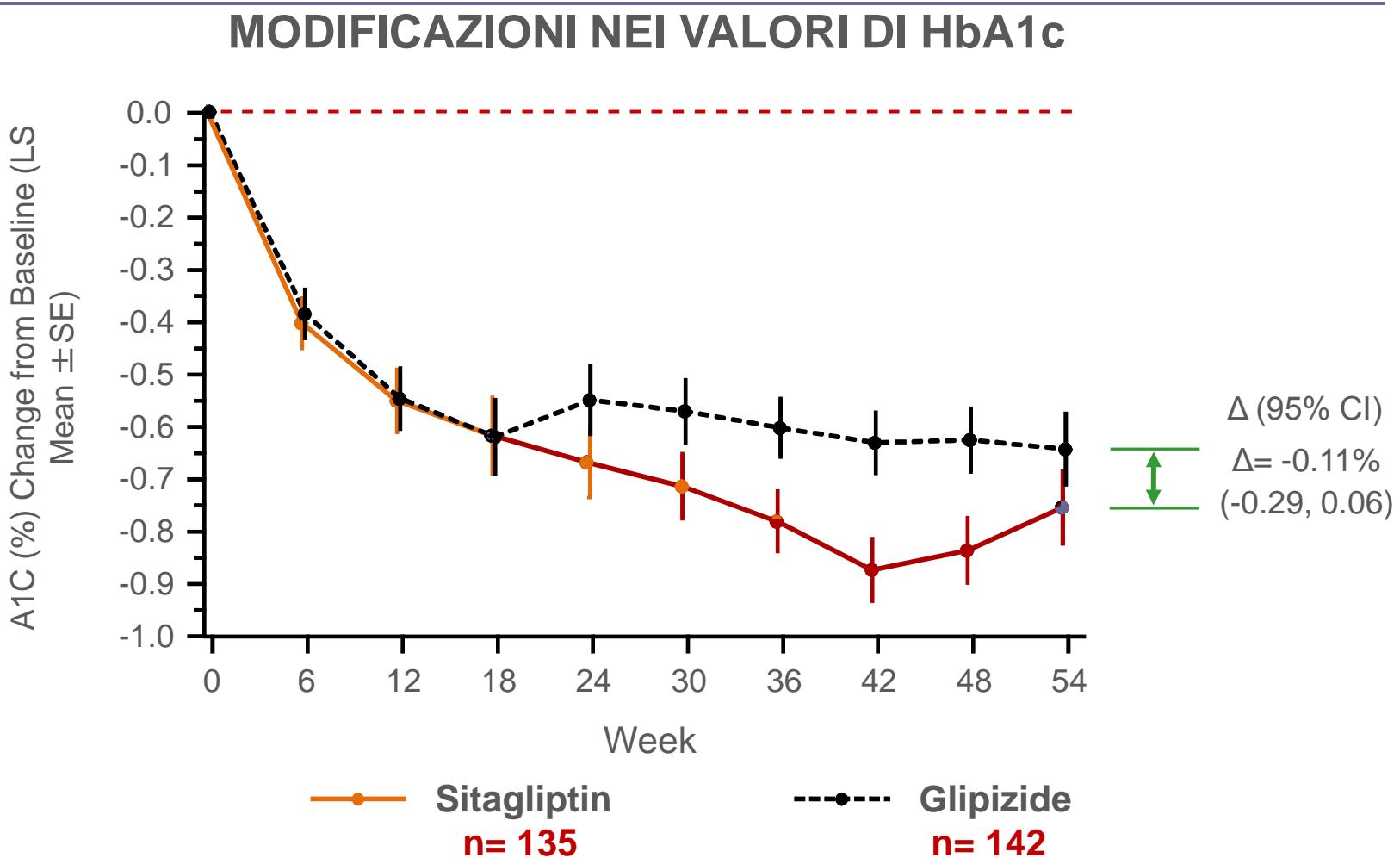
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HUA GUO, PhD¹

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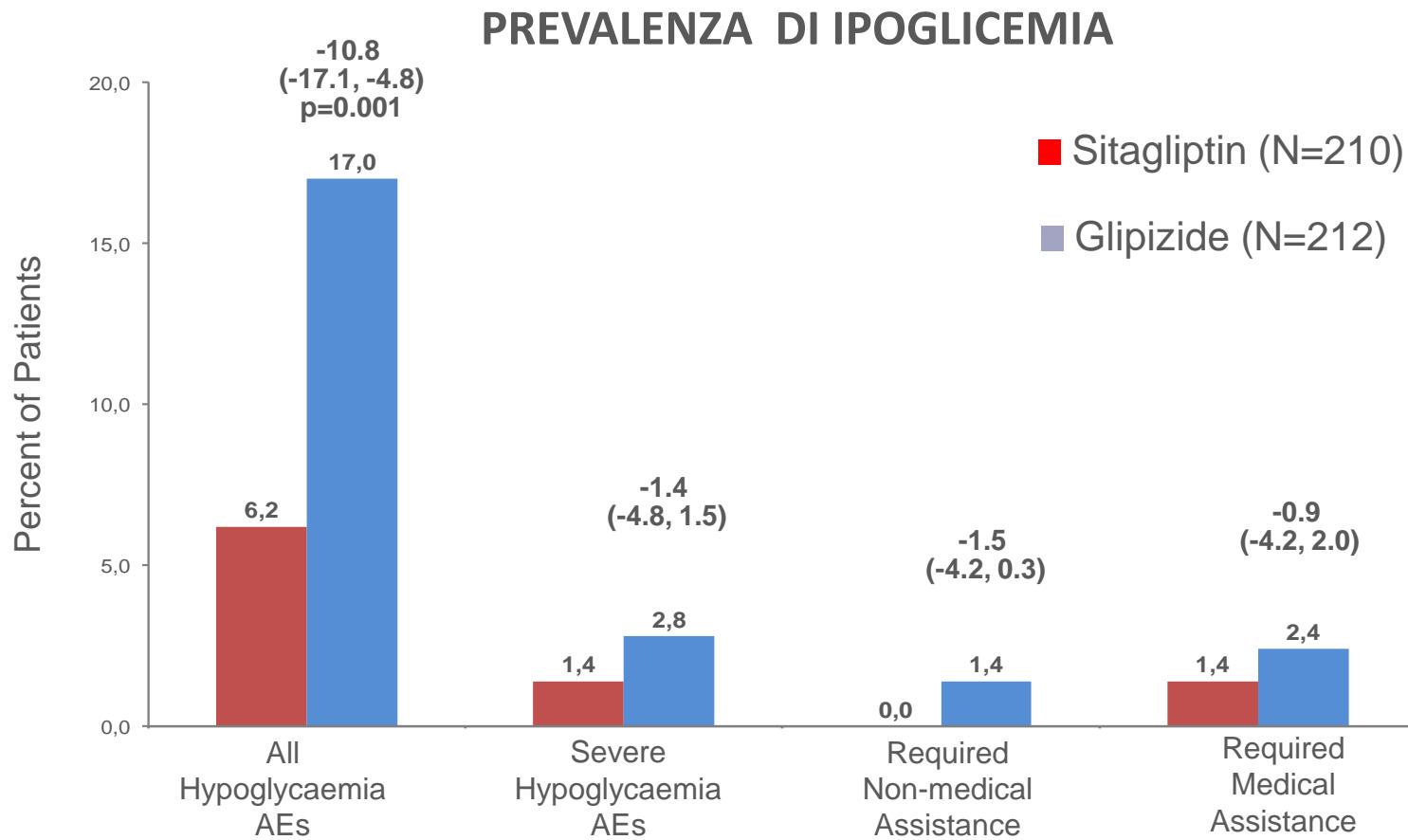
OBJECTIVE—Patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease have an increased risk of micro- and macrovascular disease, but limited options for antihyperglycemic therapy. We compared the efficacy and safety of sitagliptin with glipizide in patients with T2DM and moderate-to-severe chronic renal insufficiency and inadequate glycemic control.

RESEARCH DESIGN AND METHODS—Patients ($n = 426$) were randomized 1:1 to sitagliptin (50 mg every day [q.d.] for moderate renal insufficiency and 25 mg q.d. for severe renal insufficiency) or glipizide (2.5 mg q.d., adjusted based on glycemic control to a 10-mg twice a day maximum dose). Randomization was stratified by: 1) renal status (moderate or severe renal insufficiency); 2) history of cardiovascular disease; and 3) history of heart failure.

Efficacia di Sitagliptin e Glipizide in soggetti con DM2 ed Insufficienza Renale moderata o severa

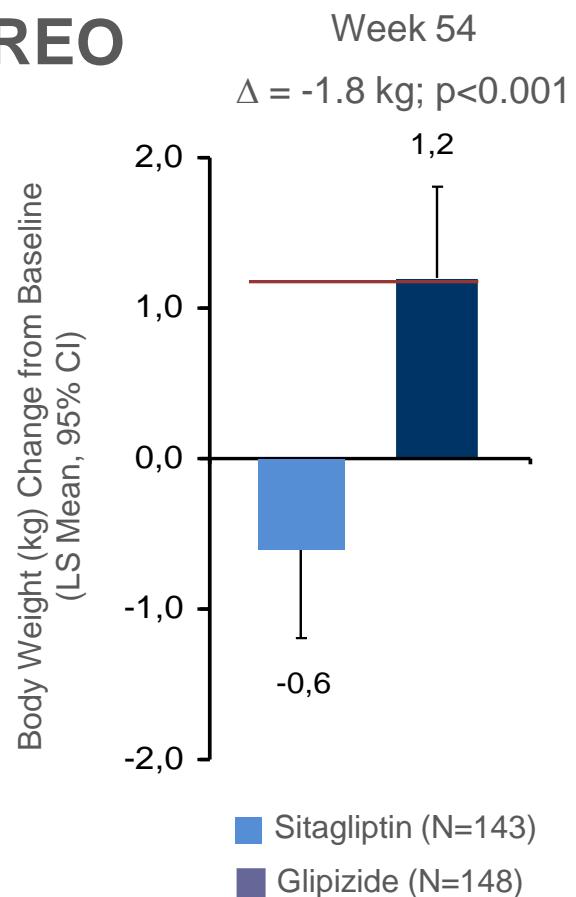
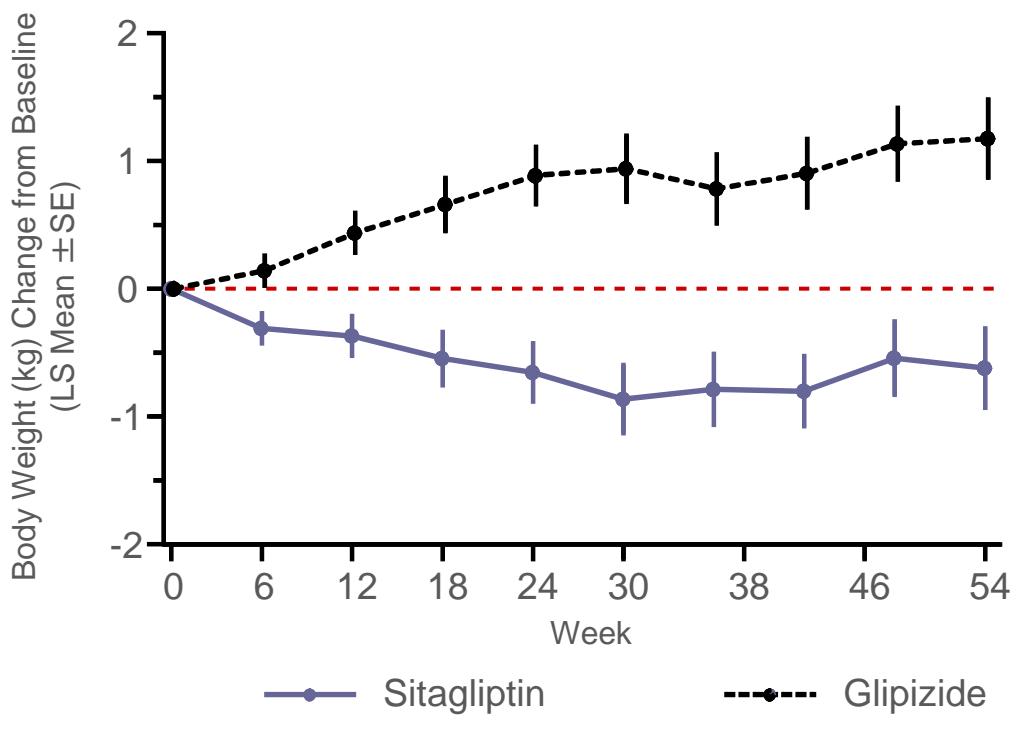


Sicurezza di Sitagliptin e Glipizide in soggetti con DM2 ed Insufficienza Renale moderata o severa



Sicurezza di Sitagliptin e Glipizide in soggetti con DM2 ed Insufficienza Renale moderata o severa

EFFETTI SUL PESO CORPOREO



Efficacy and Safety of Sitagliptin in Patients With Type 2 Diabetes and ESRD Receiving Dialysis: A 54-Week Randomized Trial

Study Design

54-week, randomized, double-blind, parallel-arm study.

Setting & Participants

From 31 clinical sites in 12 countries, 129 patients 30 years or older with type 2 diabetes and ESRD who were on dialysis therapy and had a hemoglobin A_{1c} (HbA_{1c}) level of 7%-9% were randomly assigned 1:1 to treatment.

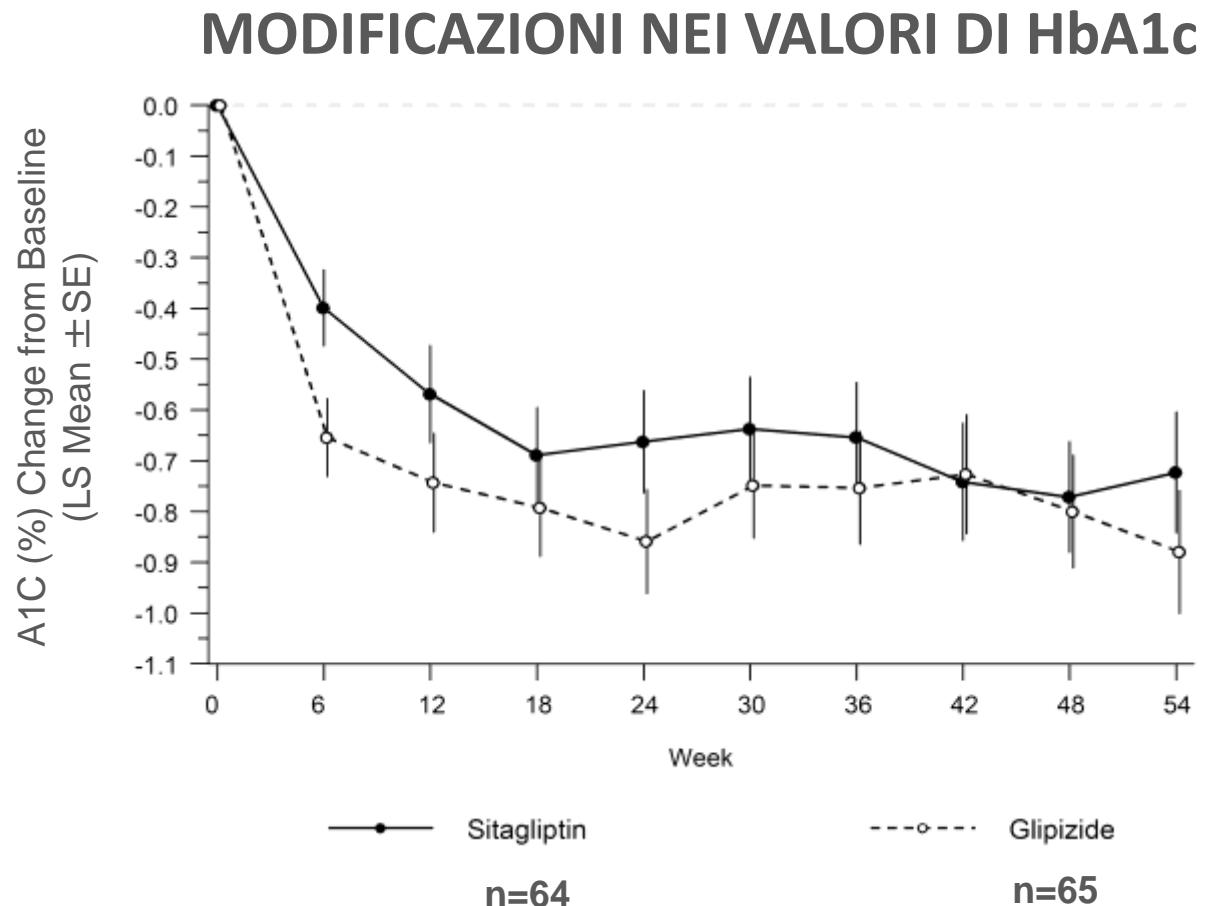
Intervention

Monotherapy with sitagliptin, 25 mg daily or glipizide (initiated with 2.5 mg daily and titrated up to a potential maximum dose of 10 mg twice daily or down to avoid hypoglycemia).

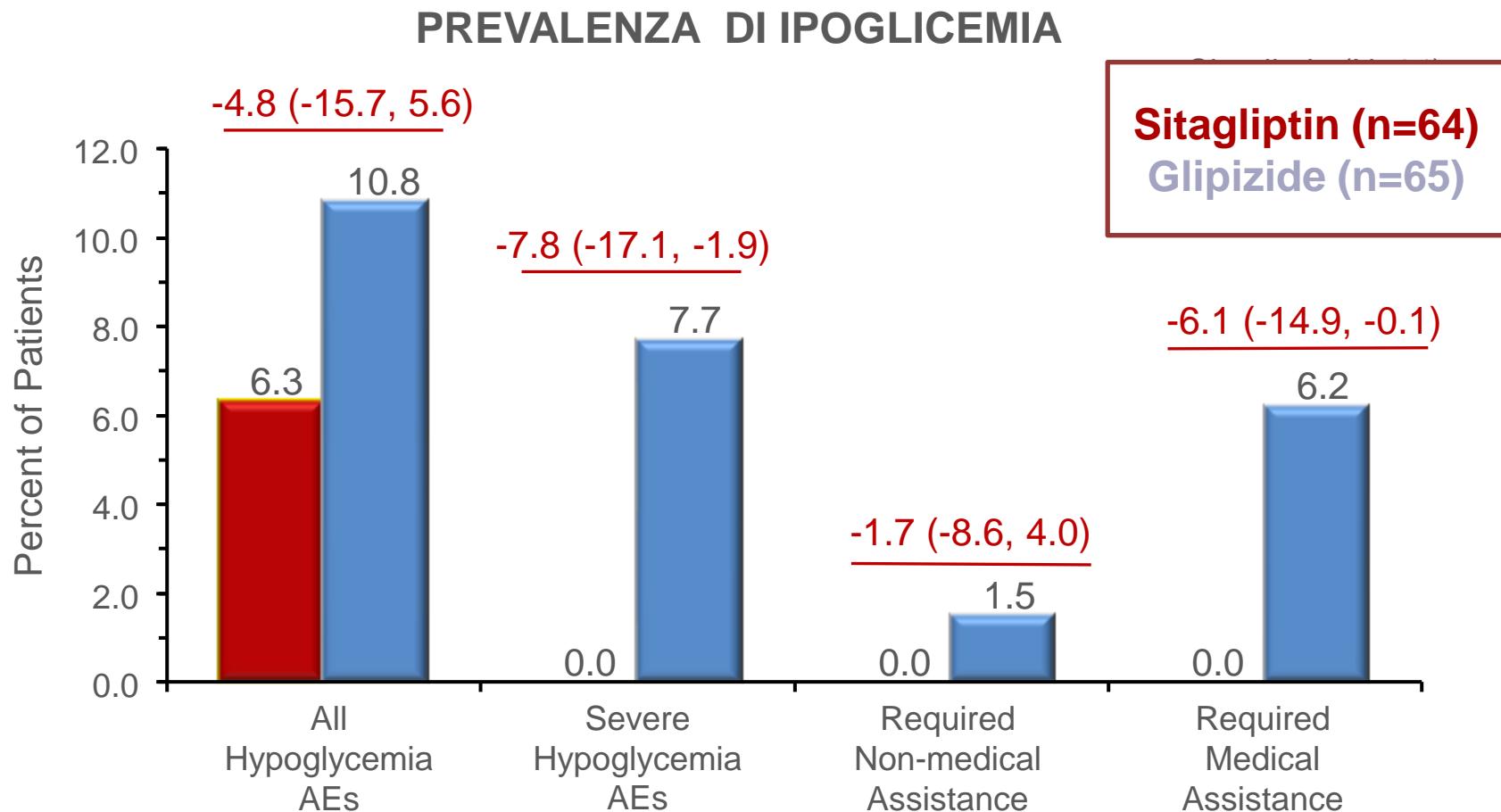
Outcomes

Primary end points were 54-week change in HbA_{1c} level from baseline and tolerability with sitagliptin. A secondary end point was the comparison of sitagliptin versus glipizide on the incidence of symptomatic hypoglycemia.

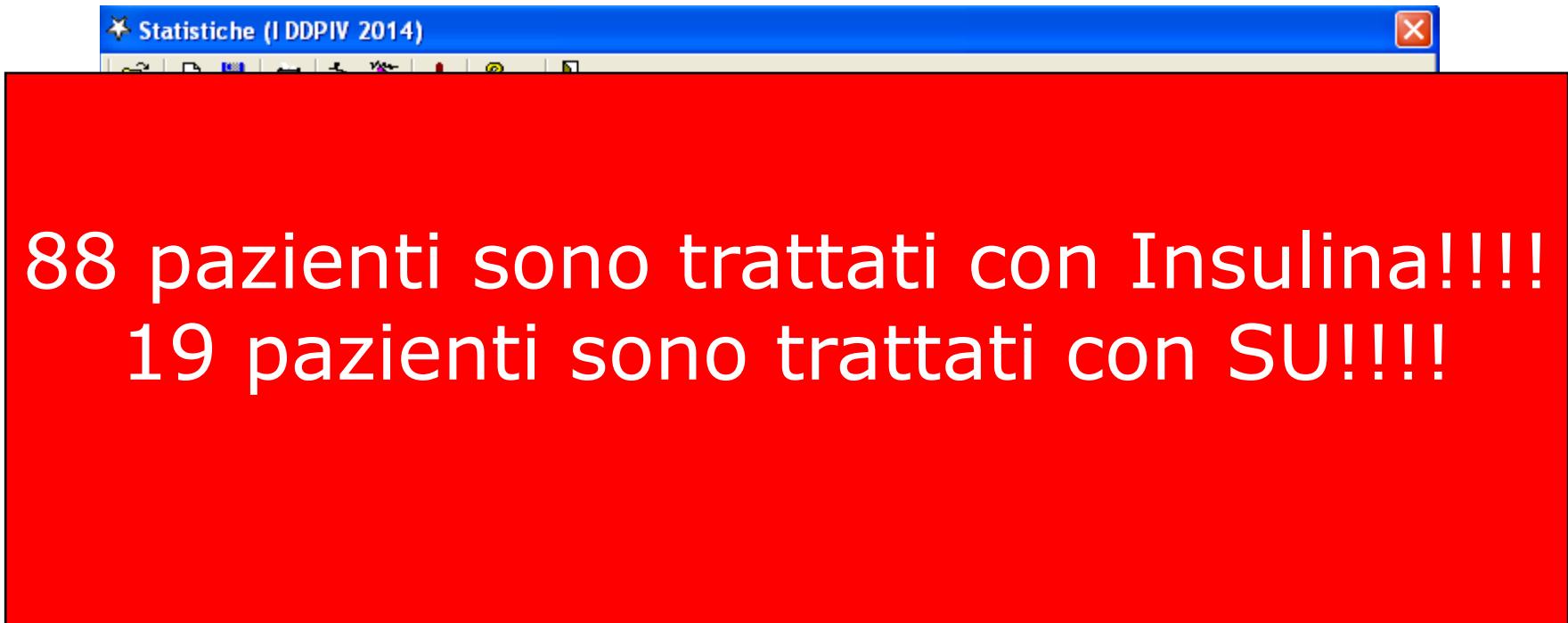
Efficacia di Sitagliptin e Glipizide in soggetti con DM2 ed Insufficienza Renale in trattamento Dialitico



Sicurezza di Sitagliptin e Glipizide in soggetti con DM2 ed Insufficienza Renale in trattamento Dialitico



Pazienti con T2DM Assistiti nel Primo Semestre 2014 con Clearance Creat \leq 30 ml/min



134 pazienti eleggibili +
27 già in Trattamento

Conclusioni

- Probabilmente non esiste un paziente con DMT2 che NON necessiti di “protezione”.
- Pur essendo gli elementi dai quali proteggere i nostri pazienti diversi, nei diversi pazienti, Sitagliptin si è dimostrato in grado, in ogni specifico scenario clinico, di garantire efficacia sia nel raggiungimento del target terapeutico, sia nella protezione del paziente