VI Convegno Nazionale Centro Studi e Ricerche - Fondazione AMD

Napoli, 18-20 ottobre 2012

Luci e ombre dei nuovi farmaci: i tiazolidinedioni hanno un futuro?

Stefano Genovese

Diabetologia e Malattie Metaboliche

IRCCS MultiMedica
Dipartimento Cardiovascolare e Metabolico

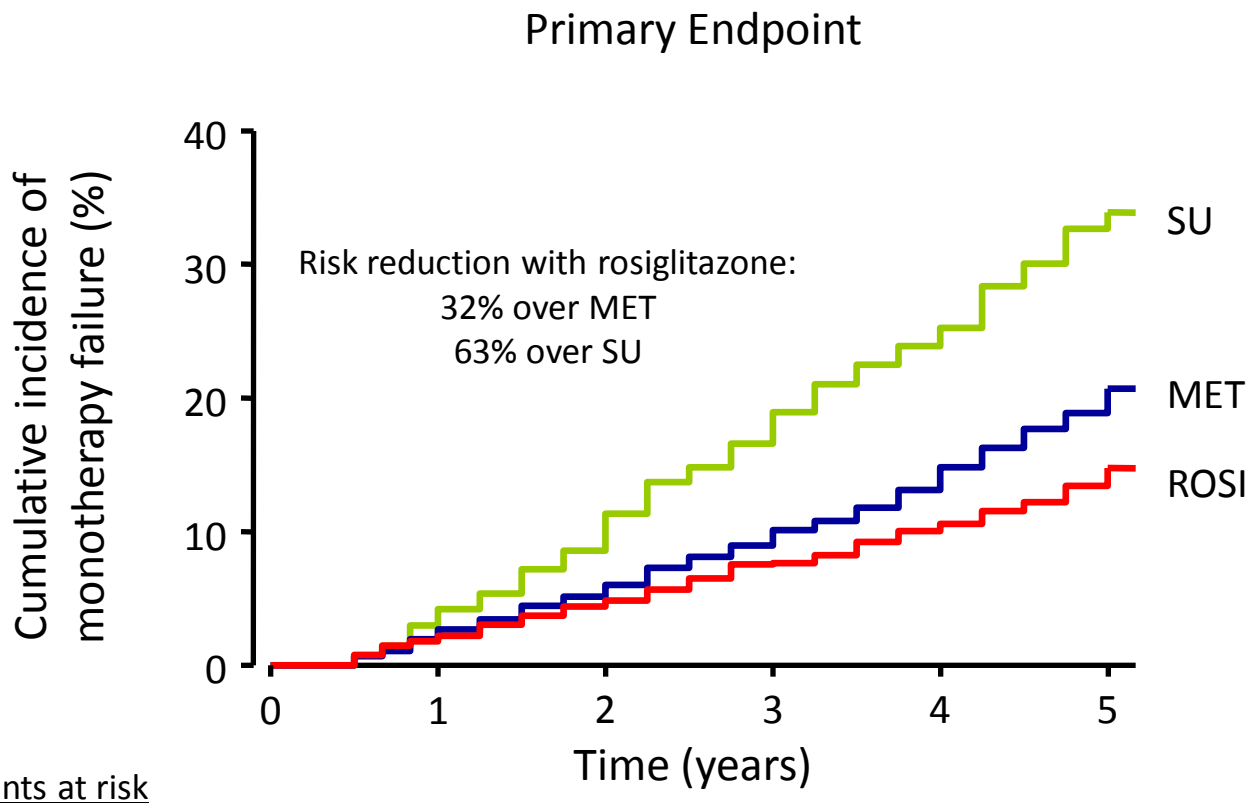
Studia il passato se vuoi prevedere il futuro

Confucio

Il passato

ADOPT: A Diabetes Outcome Progression Trial

Reduced Rate of Monotherapy Failure with rosiglitazone (FPG >180 mg/dL)

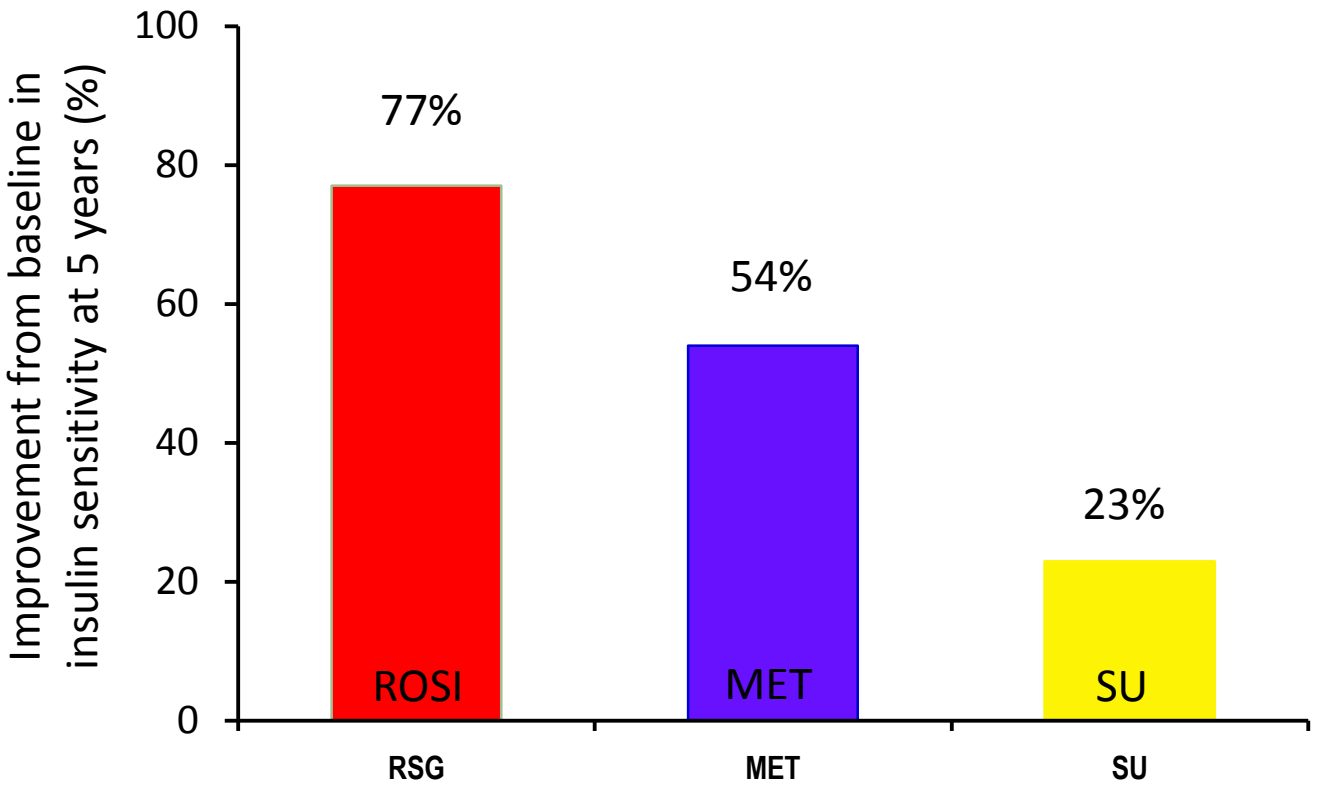


Patients at risk						
ROSIGLITAZONE	1393	1207	1078	957	844	324
MET	1397	1205	1076	950	818	311
SU	1337	1114	958	781	617	218

Kahn SE et al. *N Engl J Med.* 2006;355:2427–2443.

ADOPT: A Diabetes Outcome Progression Trial

Rosiglitazone Improved Insulin Sensitivity*†

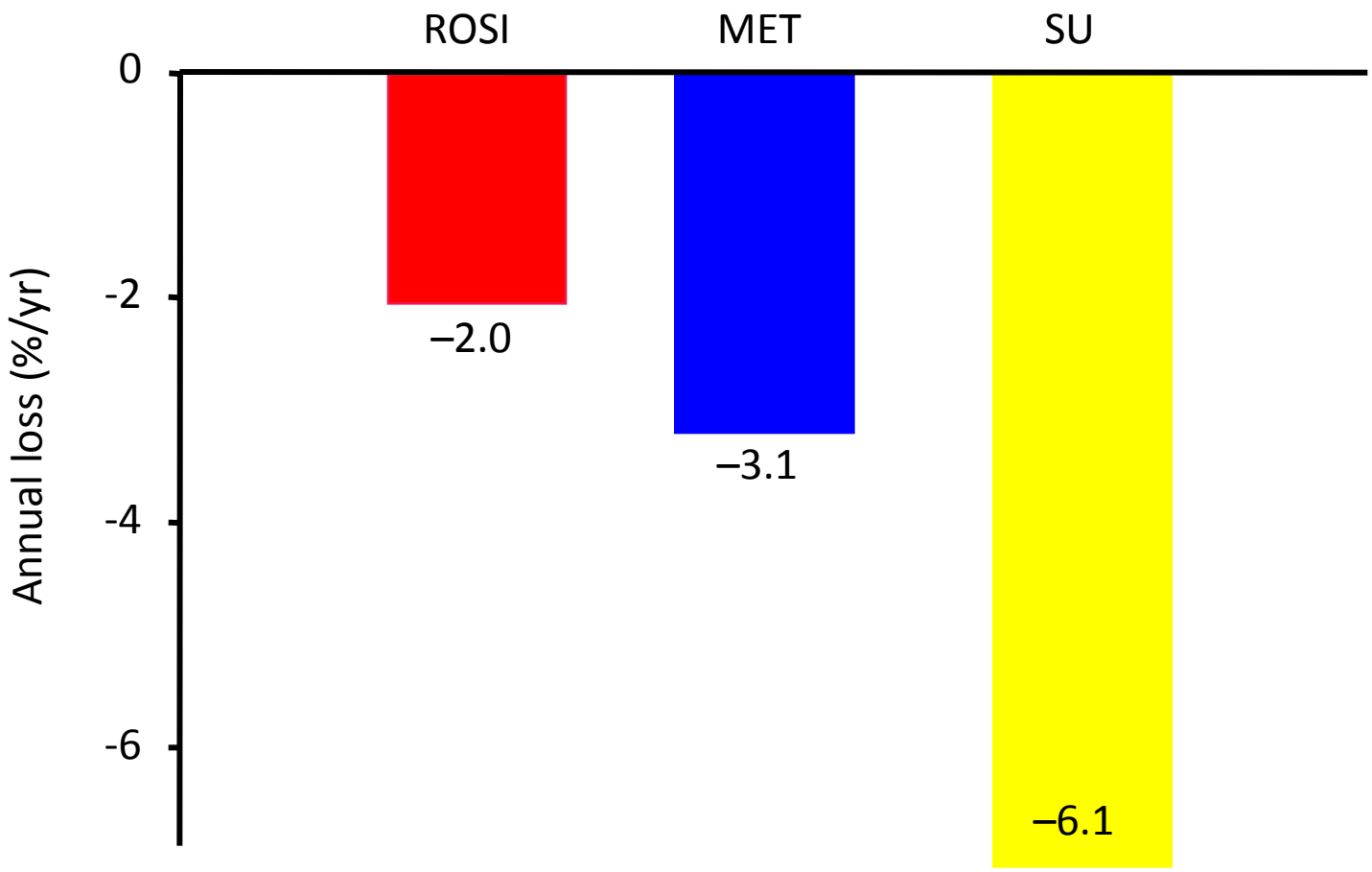


*As estimated by Homeostasis Model Assessment (HOMA-S).
†Based on mean values from a repeated measures model with log-transformed data beginning at 6 months.

Data on file, GlaxoSmithKline

ADOPT: A Diabetes Outcome Progression Trial

Rosiglitazone Slowed Loss of β-cell Function*†



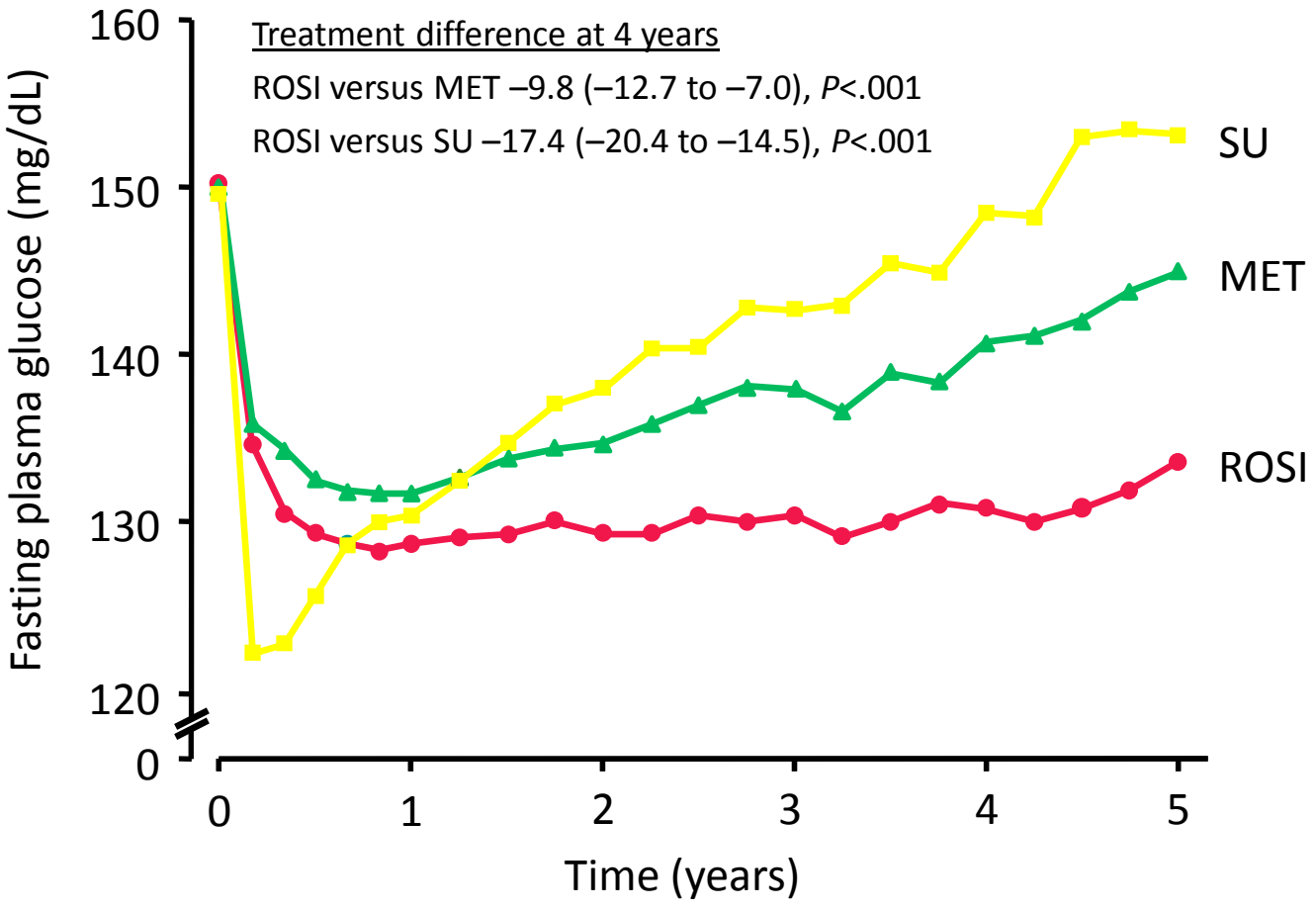
*As estimated by Homeostasis Model Assessment (HOMA-B).

†Based on mean values from a repeated measures model with log-transformed data beginning at 6 months. *P*<.05 versus MET and SU.

Kahn SE et al. *N Engl J Med.* 2006;355:2427–2443.

ADOPT: A Diabetes Outcome Progression Trial

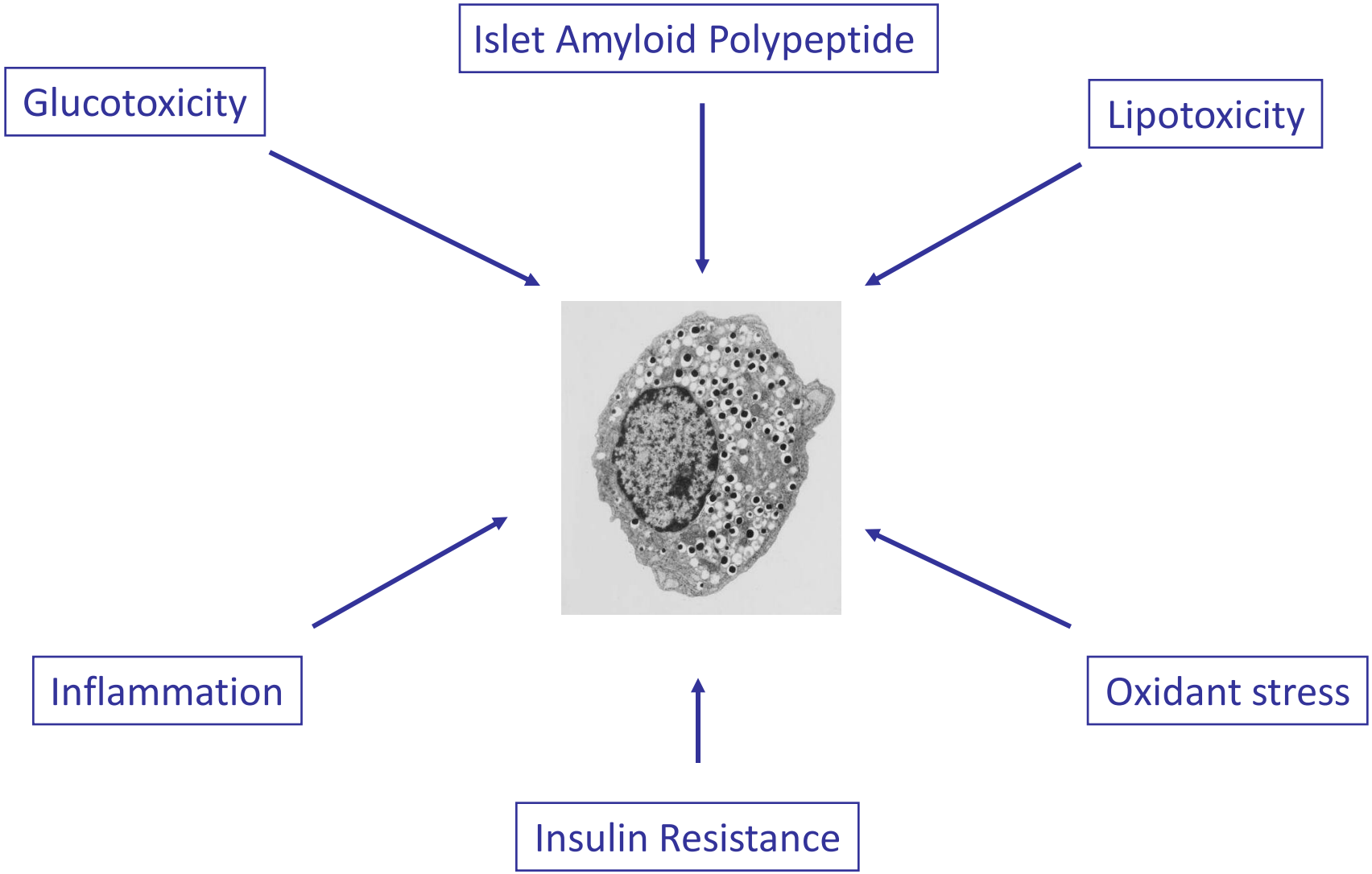
Rosiglitazone sustained fasting plasma glucose over time



Number of patients:	4118	3408	3054	2647	2242	840

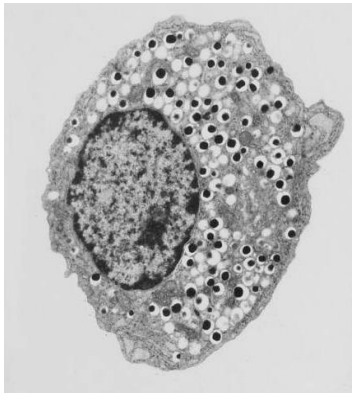
Kahn SE et al. *N Engl J Med.* 2006;355:2427–2443.

Insults to the Beta-Cell



Protecting the Beta-Cell from Insults

E. Bonora, NMCD 2008; 18: 74-83



Islet Amyloid Polypeptide

Glitazones

Glucotoxicity

Lifestyle
Acarbose
Metformin
SU & Glinides
Glitazones
Incretin system drugs
Insulin

Lipotoxicity

Lifestyle
Metformin
Orlistat
Glitazones

Inflammation

Lifestyle
Metformin
Glitazones
RAS inhibitors
Statins

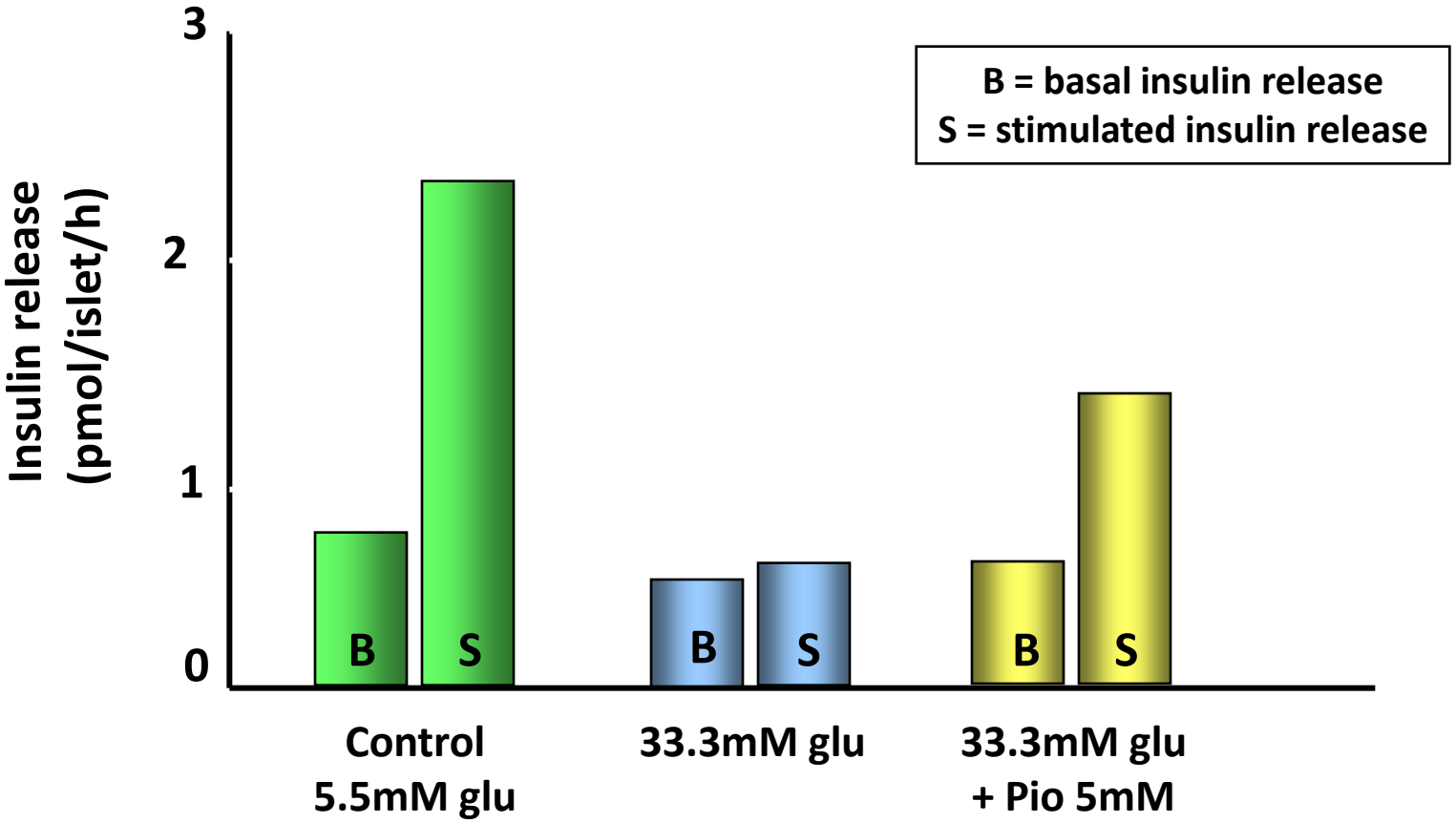
Insulin Resistance

Lifestyle
Metformin
Glitazones

Oxidant stress

Lifestyle
Metformin
Glitazones
RAS inhibitors
Statins

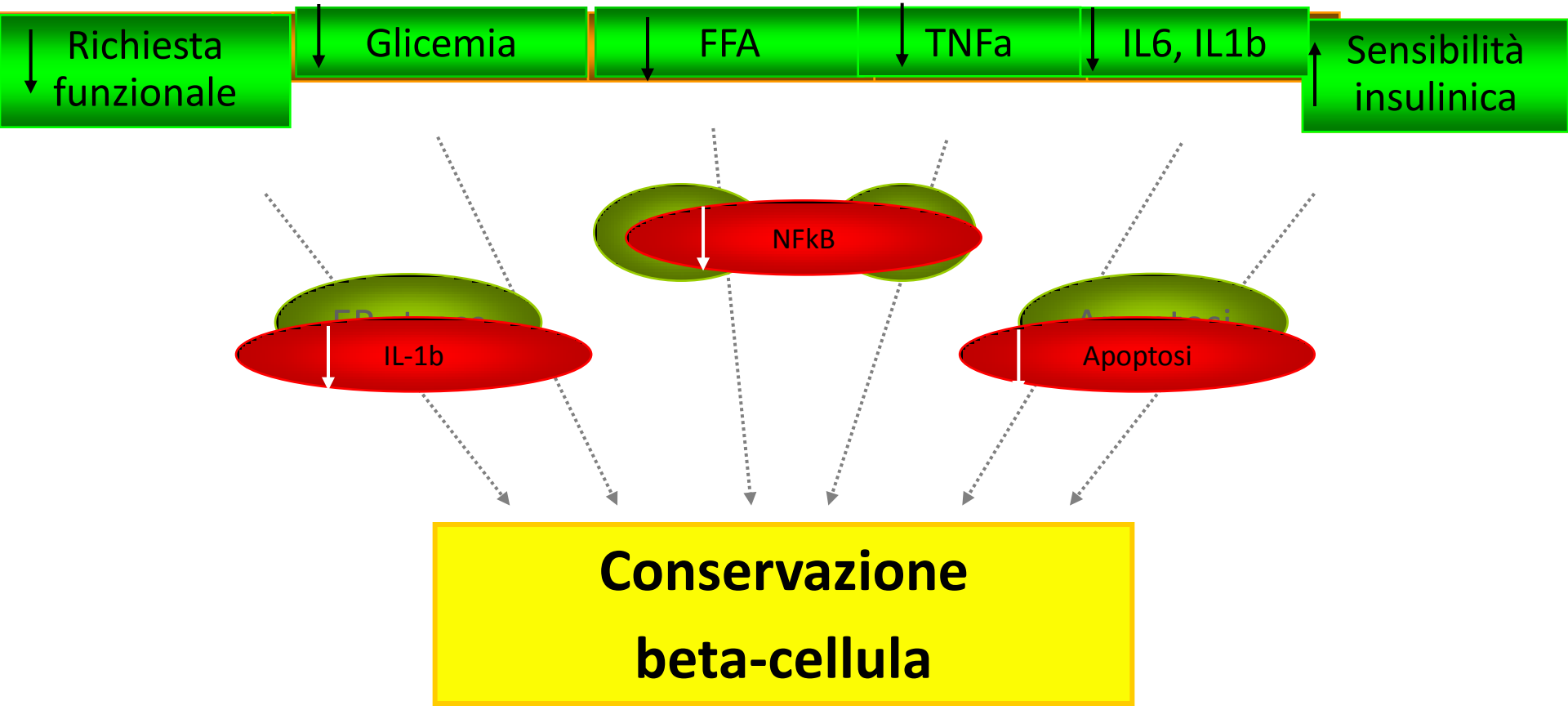
Pioglitazone Protects Human Islets against Hyperglycemia-Induced Impaired Function



Islets cultured for 4 days ± pio in 33.3mM glucose
insulin secretion determined over 1hr

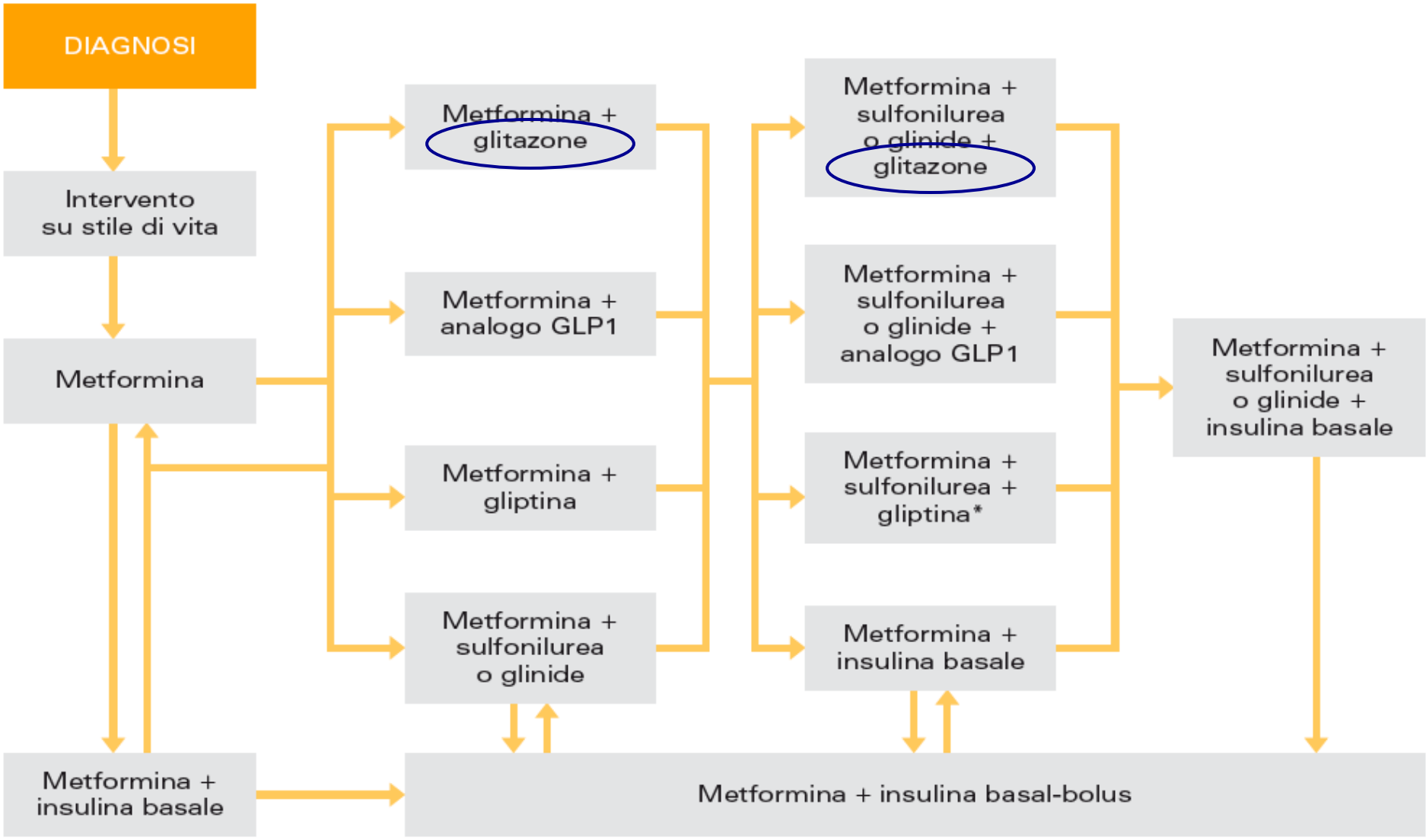
Zeender et al; J Clin Endocrinol Metab 89: 5059, 2004

Effetti Protettivi dei Glitazoni sulla beta-Cellula

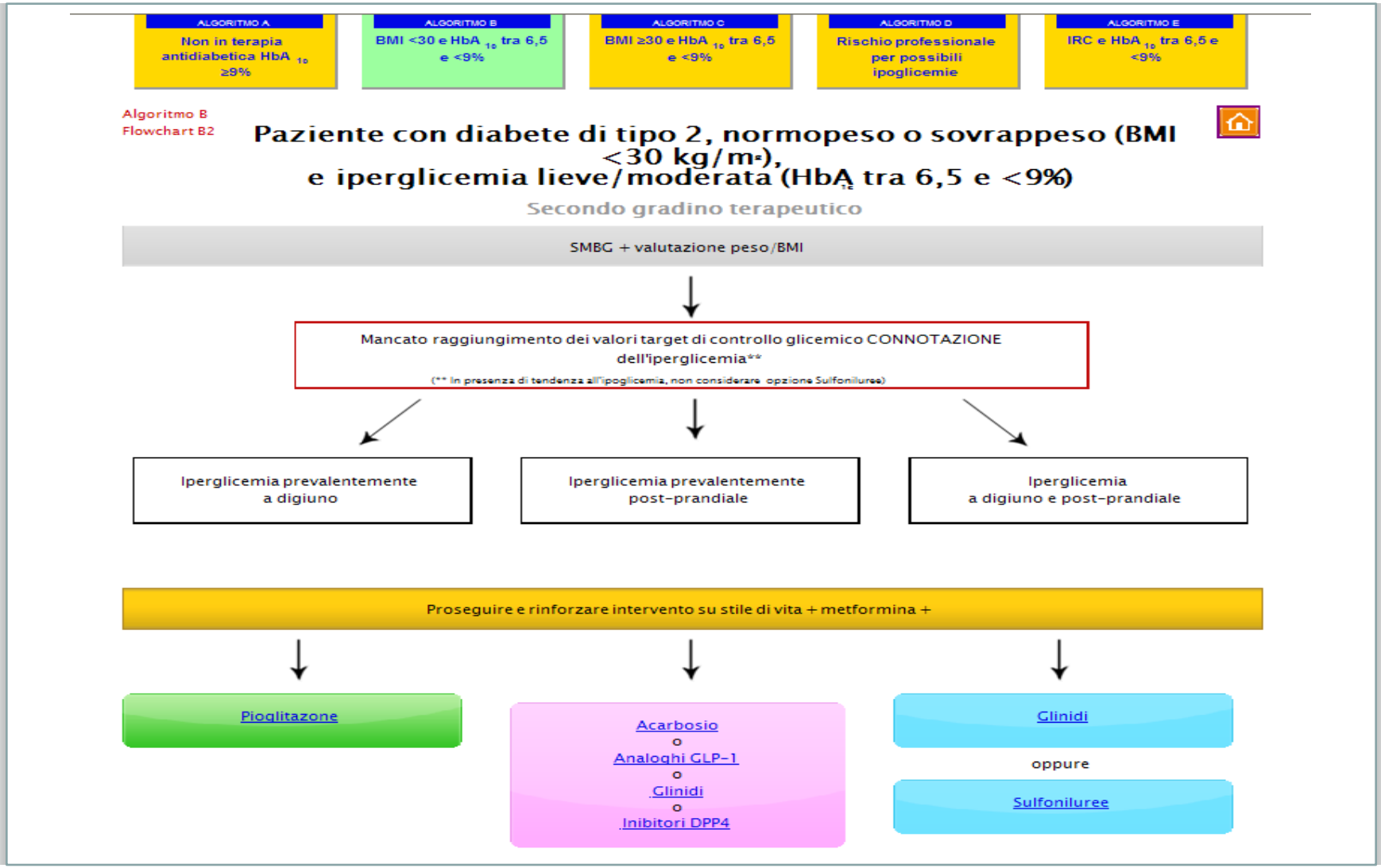


Il presente

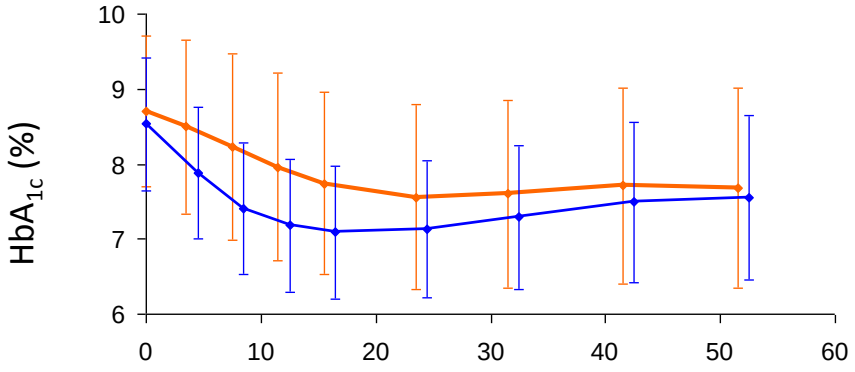
Flow-chart per la terapia del diabete mellito di tipo 2.

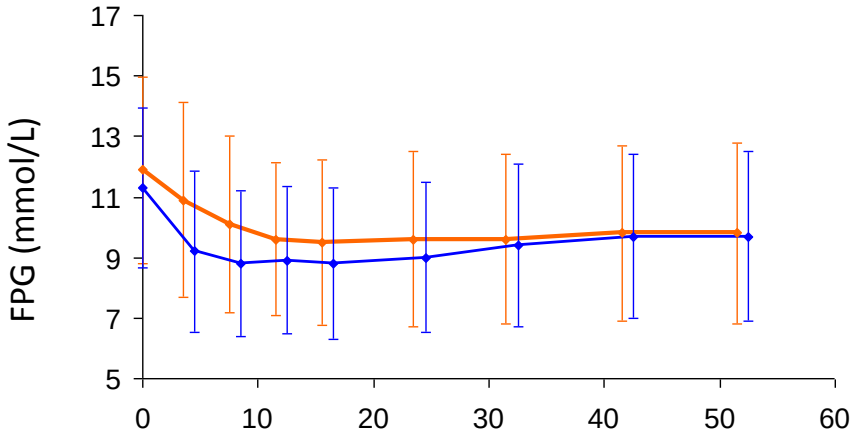


Algoritmo AMD



Pioglitazone + Met *vs* Gliclazide + Met (HbA1c e FPG)





Settimane di trattamento

ITT: 620 pazienti

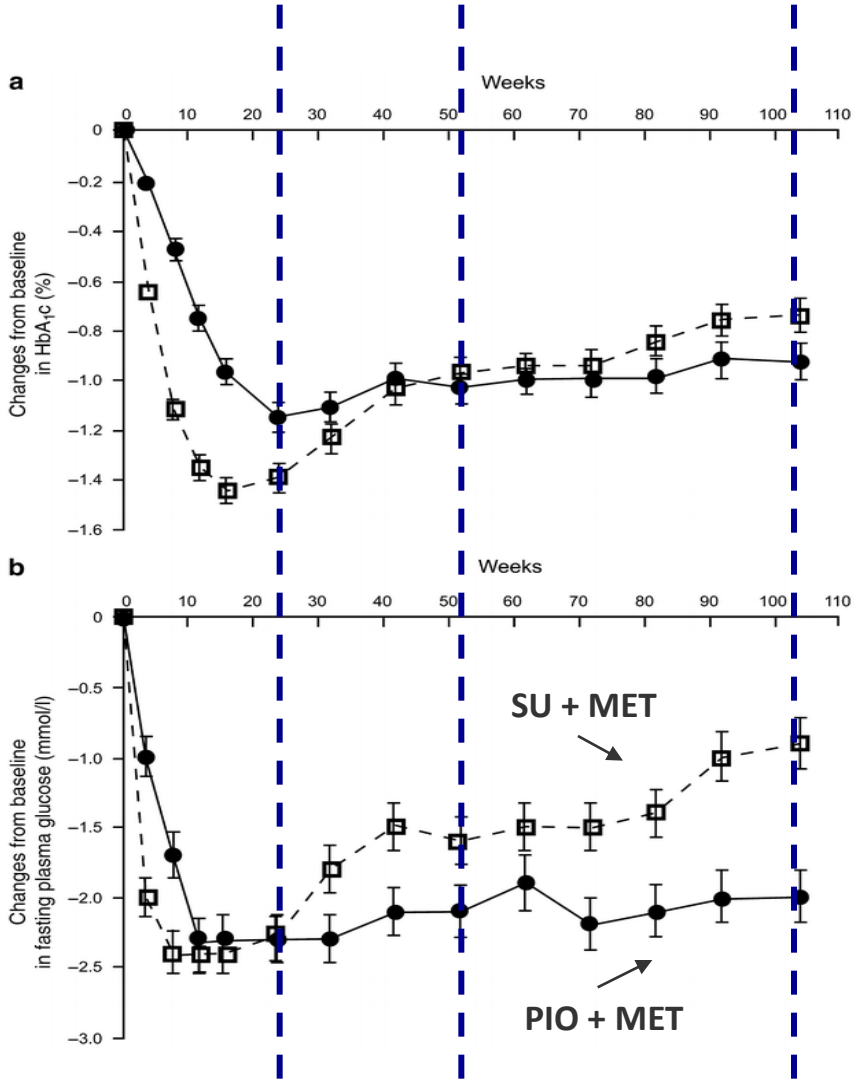
Pioglitazone + Met (15-30-45 mg/die)

clazide + Met (80-320 mg/die)

QUARTET

Matthews et al Diabetes Metabolism Res Rev 2005; 21: 167 - 174

Pioglitazone in associazione con met o con SU nel lungo periodo (104 settimane)



QUARTET

Charbonnel B, et al. Diabetologia 2005

…. non solo un ipoglicemizzante

Secondary prevention of macrovascolar events in patients with type 2 diabetes in the PROactive Study: a randomised controlled trial

- 5238 pazienti con DM2 con elevato rischio CV
- Pioglitazone 15-45 mg vs placebo con un follow-up medio di 34,5 mesi
- End point primario (Mortalità totale, IMA non fatale, ictus, sindromi coronariche acute, interventi di rivascolarizzazione coronarici o agli arti inferiori, amputazioni arto inferiore)
- End point secondario (Mortalità totale, IMA non fatale, ictus)

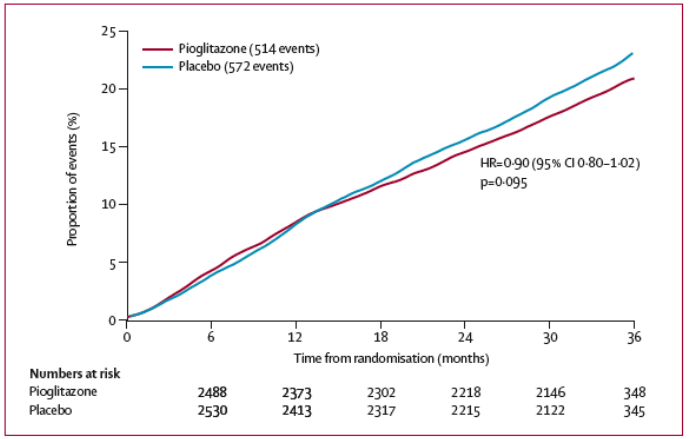


Figure 2: **Kaplan-Meier curve of time to primary endpoint***
*Death from any cause, non-fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, leg amputation, coronary revascularisation, or revascularisation of the leg.

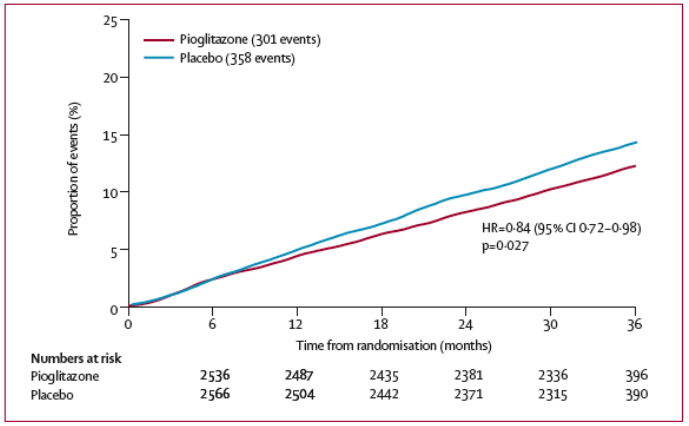
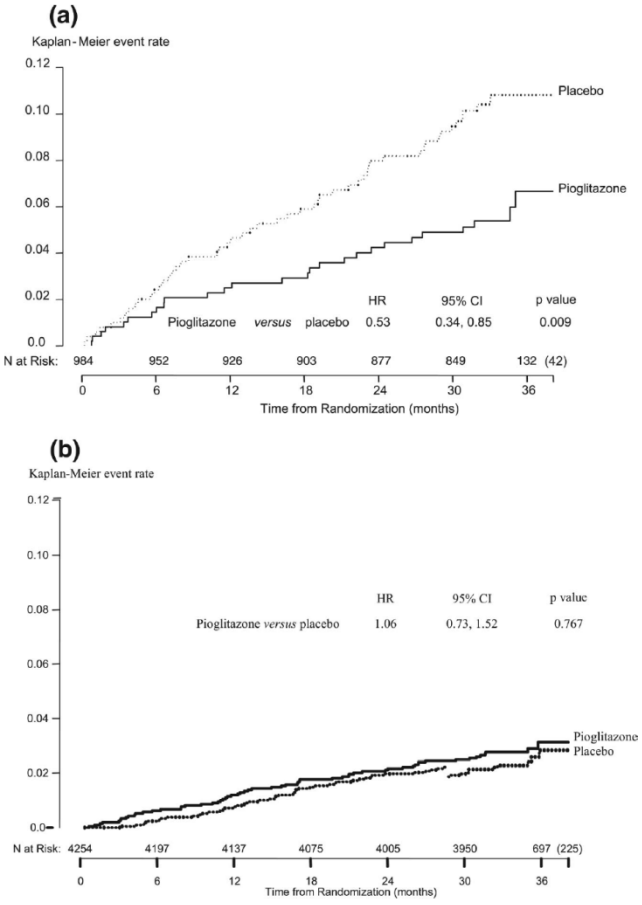


Figure 3: **Kaplan-Meier curve of time to main secondary endpoint***
* Death from any cause, non-fatal myocardial infarction (excluding silent myocardial infarction), or stroke.

Dormandy J.A. et al. Lancet 2005;366:1279-89

Effects of Pioglitazone in Patients With Type 2 Diabetes With or Without Previous Stroke

Results From PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04)



The Effect of Pioglitazone on Recurrent Myocardial Infarction in 2,445 Patients With Type 2 Diabetes and Previous Myocardial Infarction

Results From the PROactive (PROactive 05) Study

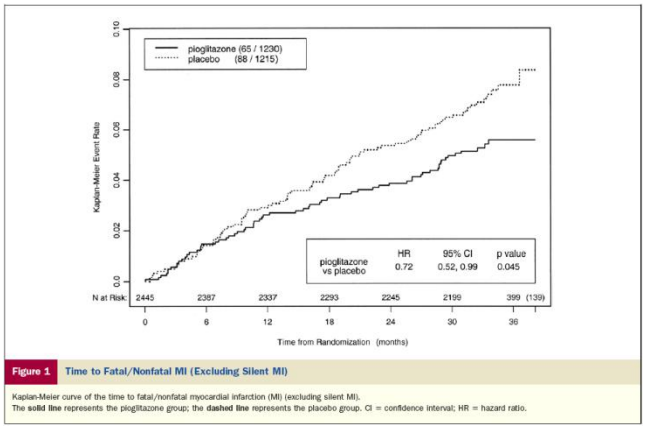


Figure 1 Time to Fatal/Nonfatal MI (Excluding Silent MI)

Kaplan-Meier curve of the time to fatal/nonfatal myocardial infarction (MI) (excluding silent MI). The **solid line** represents the pioglitazone group; the **dashed line** represents the placebo group. CI = confidence interval; HR = hazard ratio.

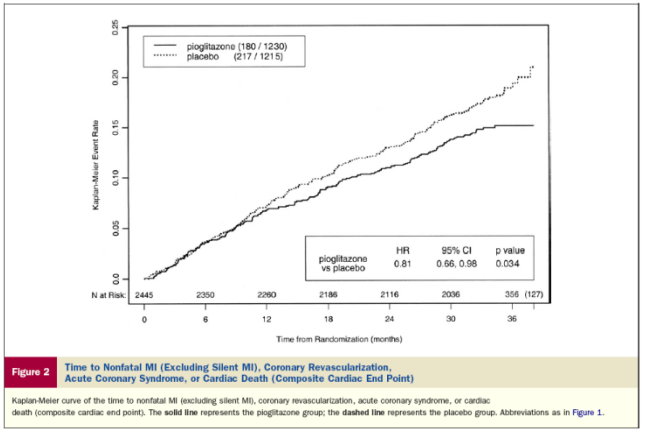


Figure 2 Time to Nonfatal MI (Excluding Silent MI), Coronary Revascularization, Acute Coronary Syndrome, or Cardiac Death (Composite Cardiac End Point)

Kaplan-Meier curve of the time to nonfatal MI (excluding silent MI), coronary revascularization, acute coronary syndrome, or cardiac death (composite cardiac end point). The **solid line** represents the pioglitazone group; the **dashed line** represents the placebo group. Abbreviations as in Figure 1.

Wilcox R. et al. *Stroke* 2007;38:865-73

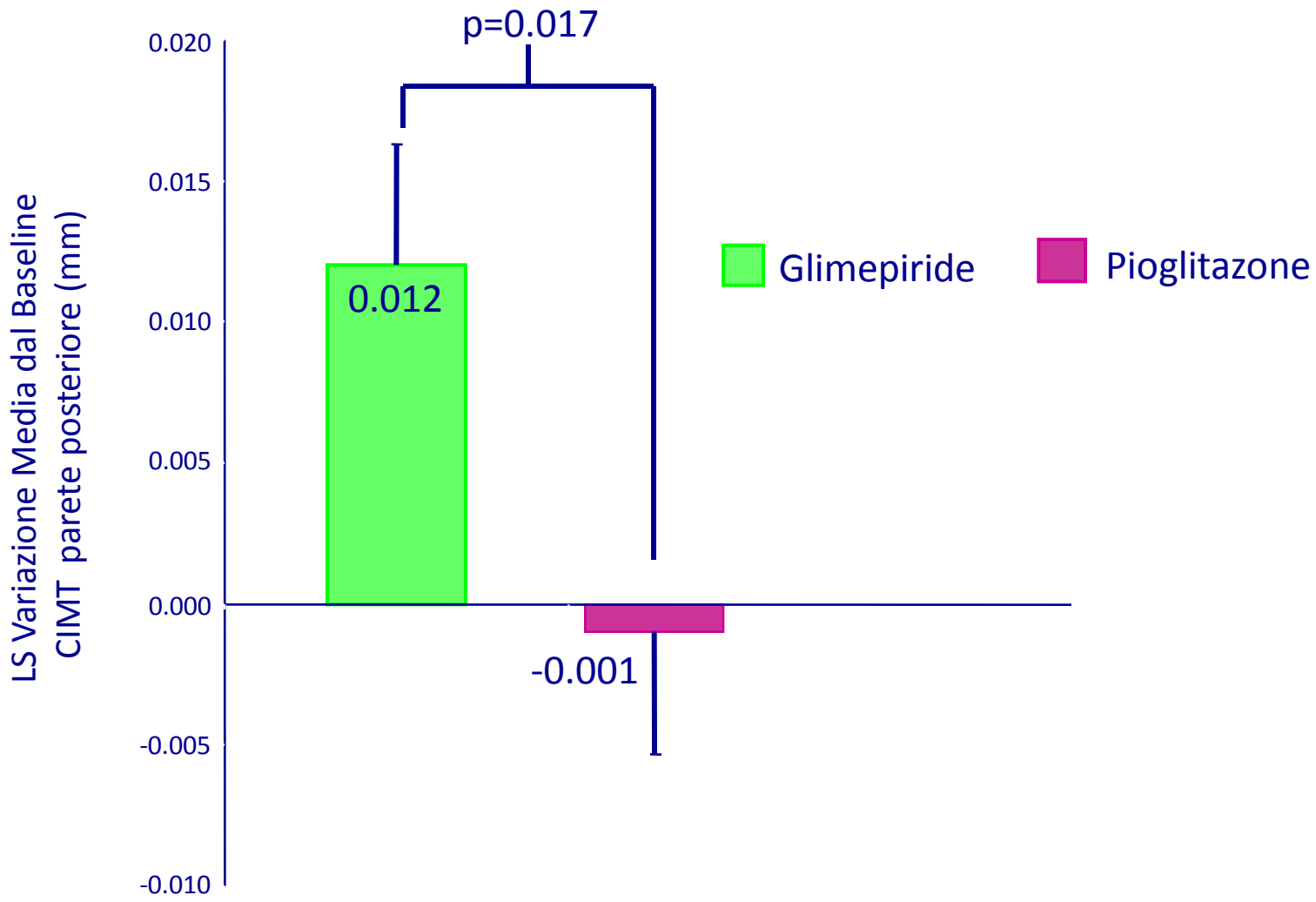
Erdmann E. et al. *JACC* 2007;49:1772-80

CHICAGO

A Study Evaluating Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone

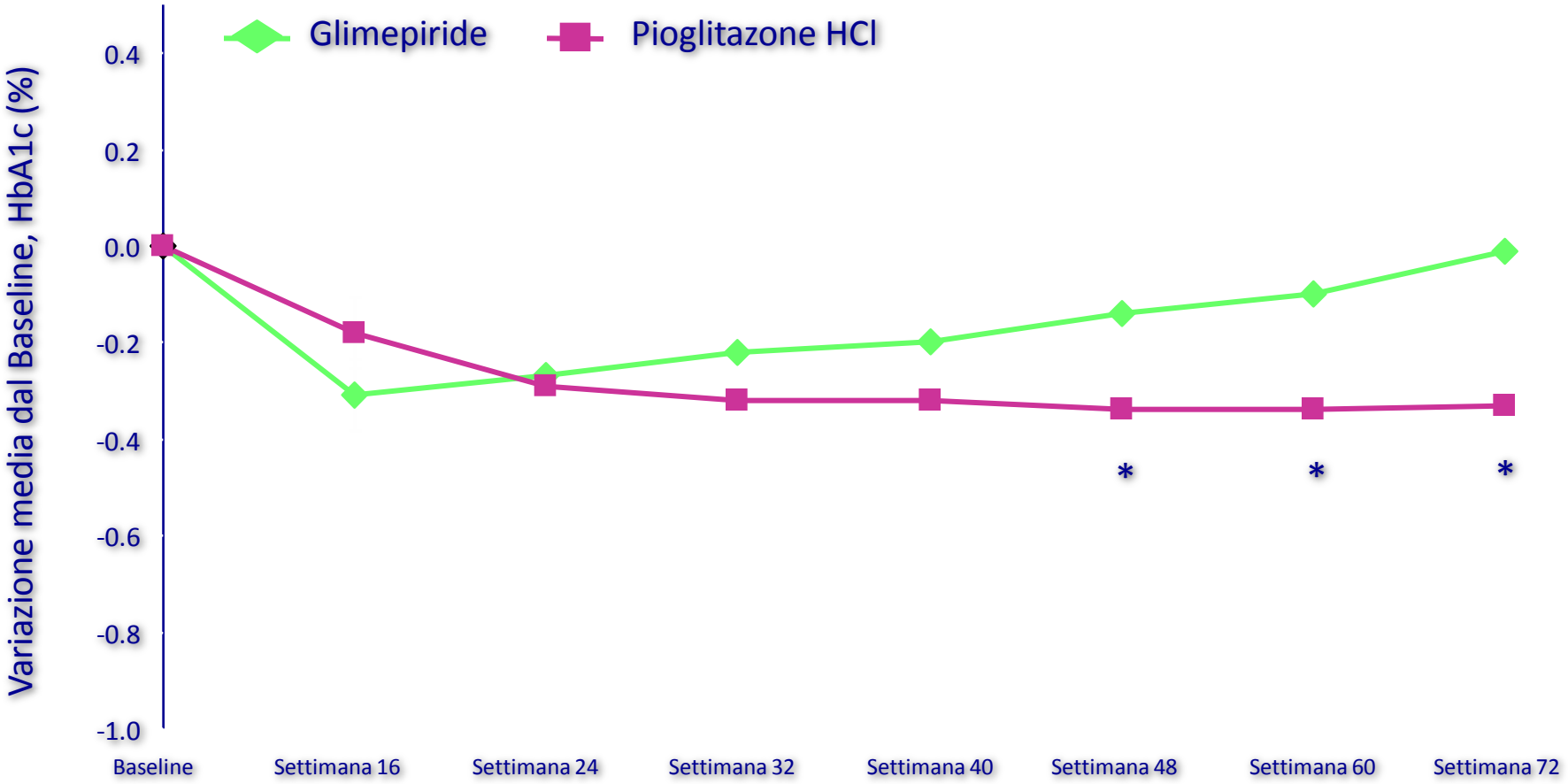
JAMA. 2006;296(21):2572-2581

Variazione Media del CIMT



Baseline CIMT	GLM (N=186)	PIO (N=175)	Differenza tra i gruppi, Final Visit
LS Mean (SE)	0.779 (0.0085) mm	0.771 (0.0085) mm	-0.013 (95% CI: -0.024,-0.002)

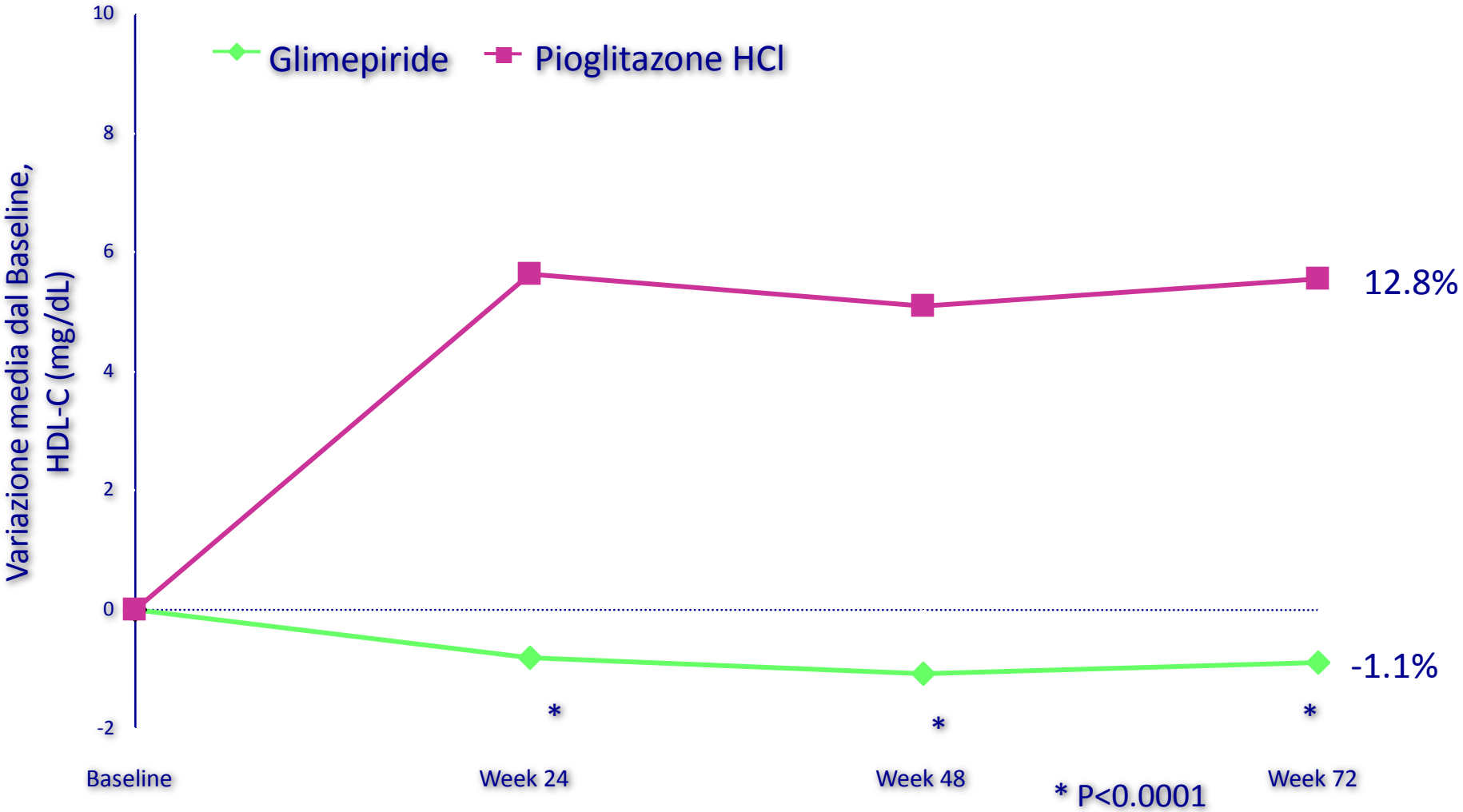
Effetti Glicemici



* P< 0.05

Baseline HbA1c (%)	GLM (N=206)	PIO (N=203)	Differenza tra I gruppi, Visita Finale
LS mean (SE)	7.36 (0.075)	7.42 (0.074)	-0.32 (95% CI: -0.522, -0.124)

Variazioni del Colesterolo-HDL



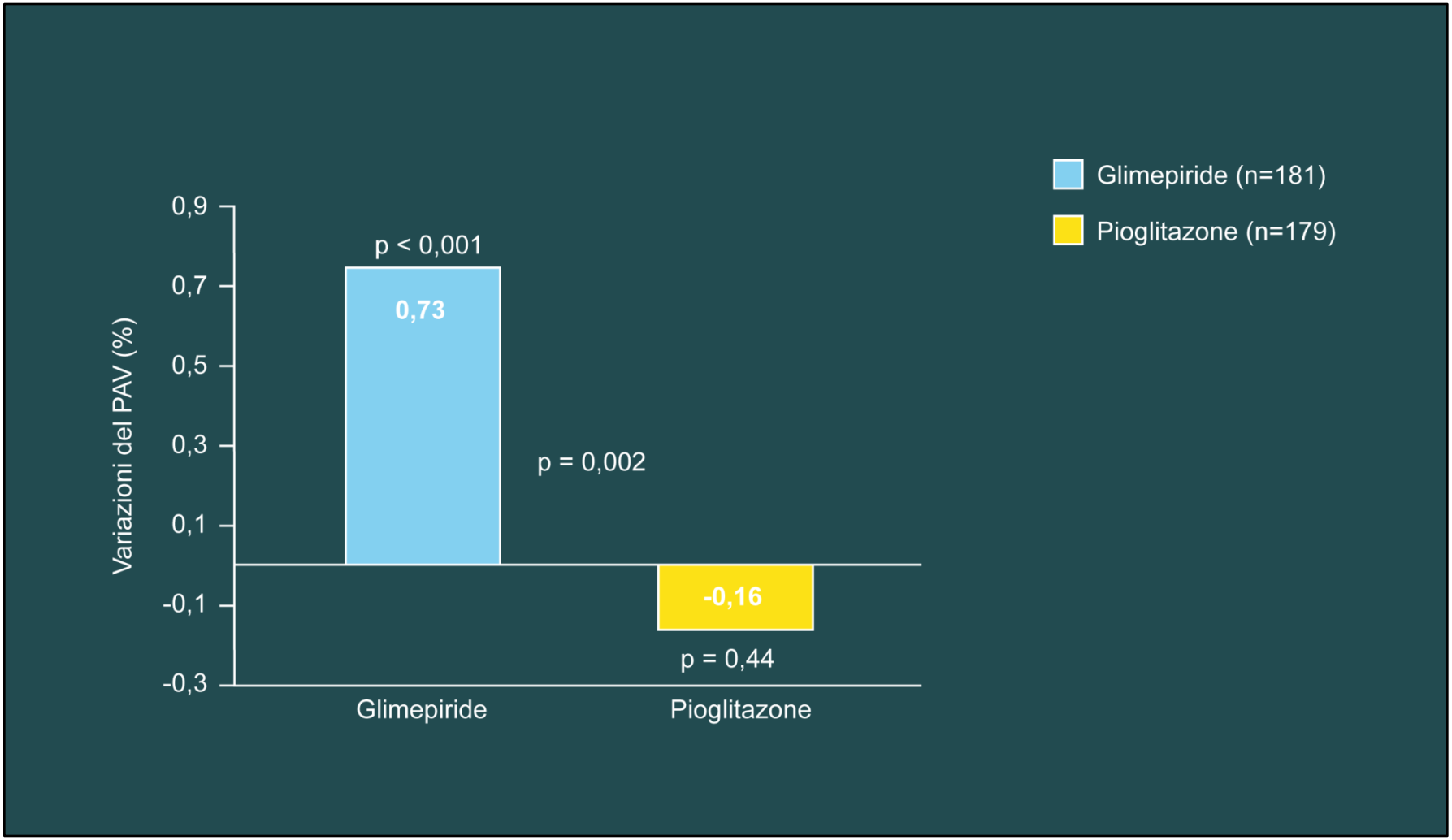
Baseline HDL-C (mg/dL)	GLM (N=206)	PIO (N=201)	Treatment group difference, Final Visit
LS mean (SE)	47.6 (0.91)	47.1 (0.90)	6.45 (95% CI: 4.97, 7.93)

PERISCOPE

Pioglitazone **E**ffect on **R**egression of
Intravascular **S**onographic **C**oronary
Obstruction **P**rospective **E**valuation

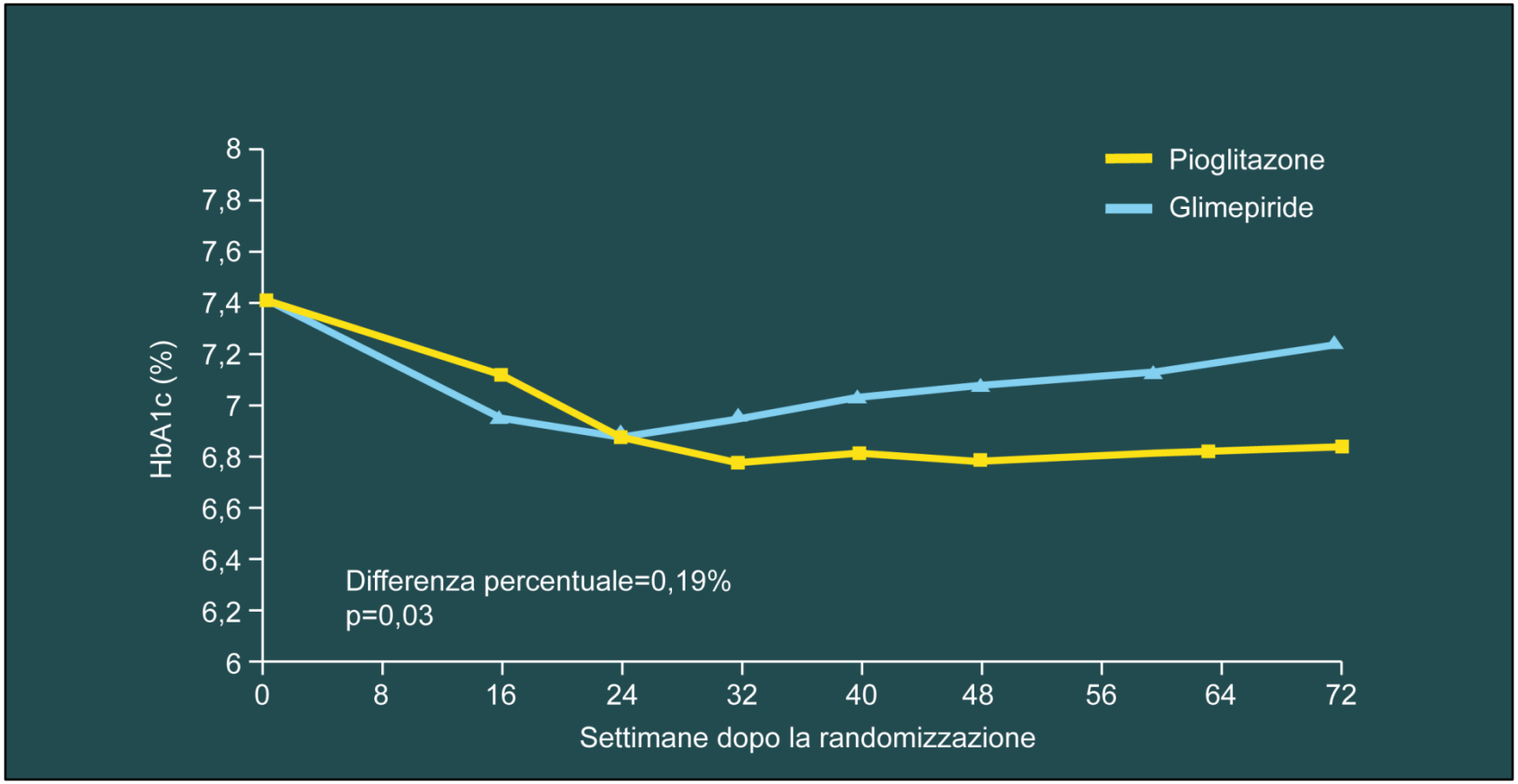
Nissen SE et al. JAMA 299(13):1561-1573, 2008

Parametro principale di efficacia
Variazioni percentuali del volume dell'ateroma (%)



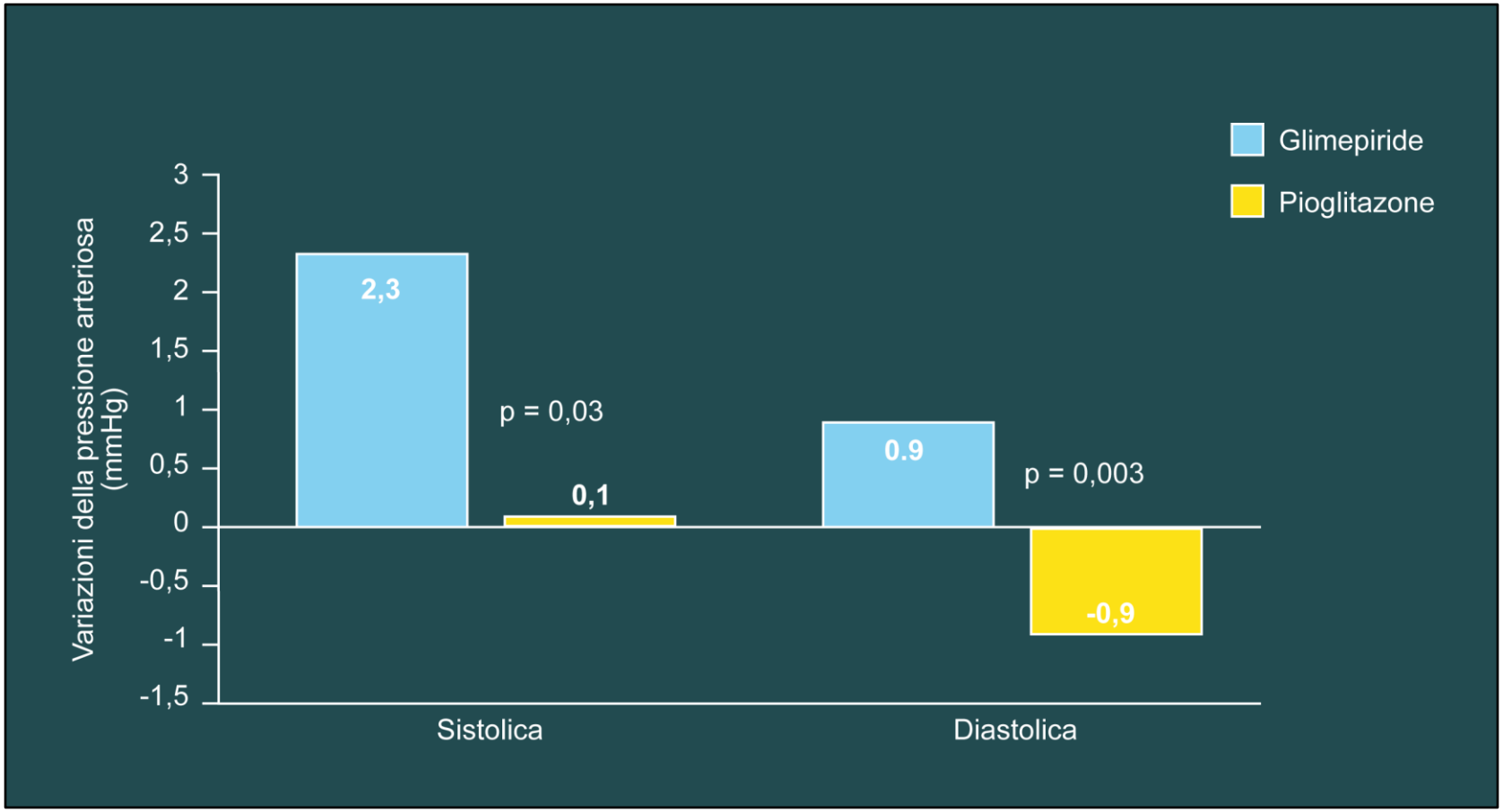
Nissen SE et al. JAMA 299(13):1561-1573, 2008

Livelli di emoglobina glicata durante lo studio



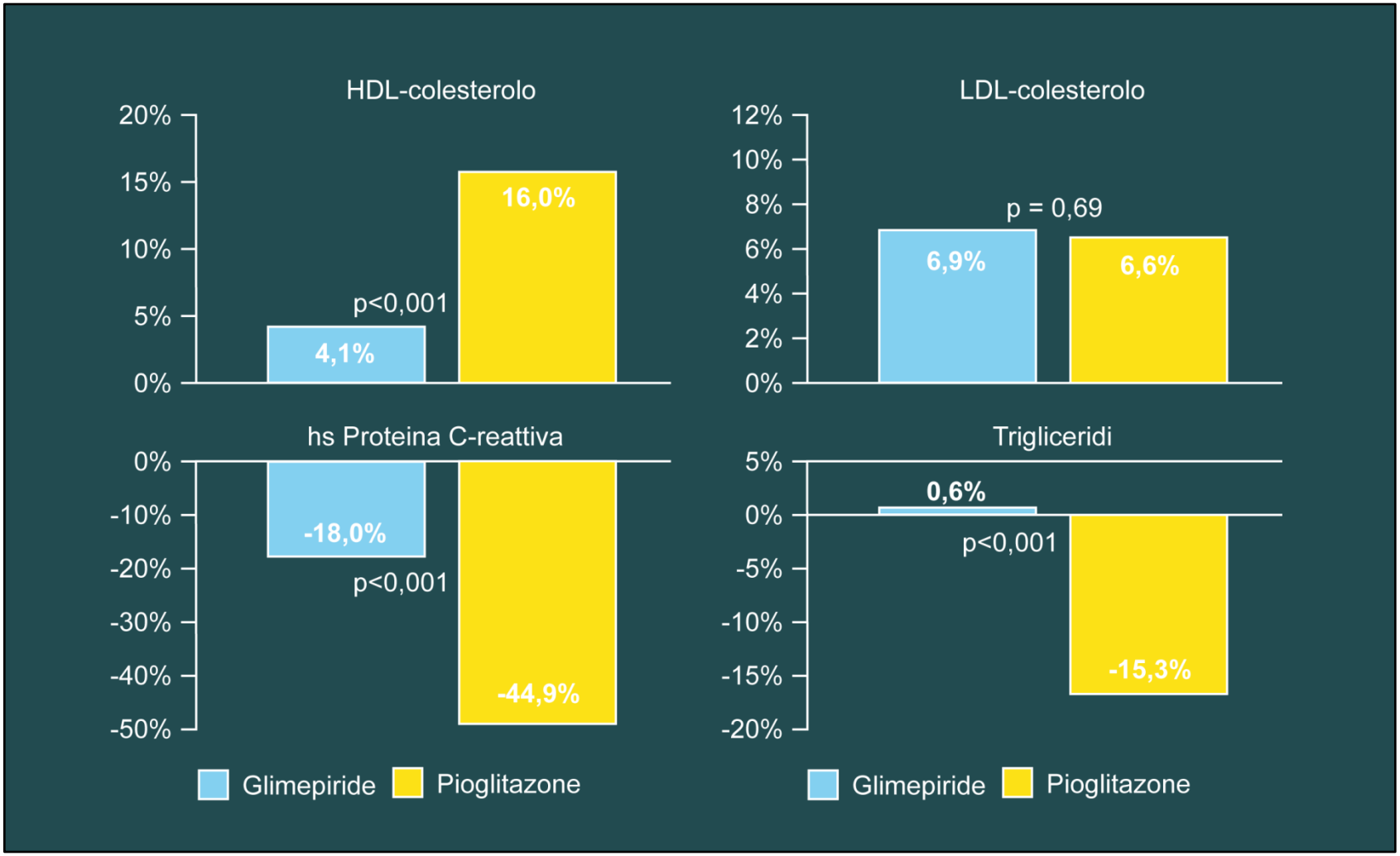
Nissen SE et al. JAMA 299(13):1561-1573, 2008

Variazioni medie della pressione arteriosa



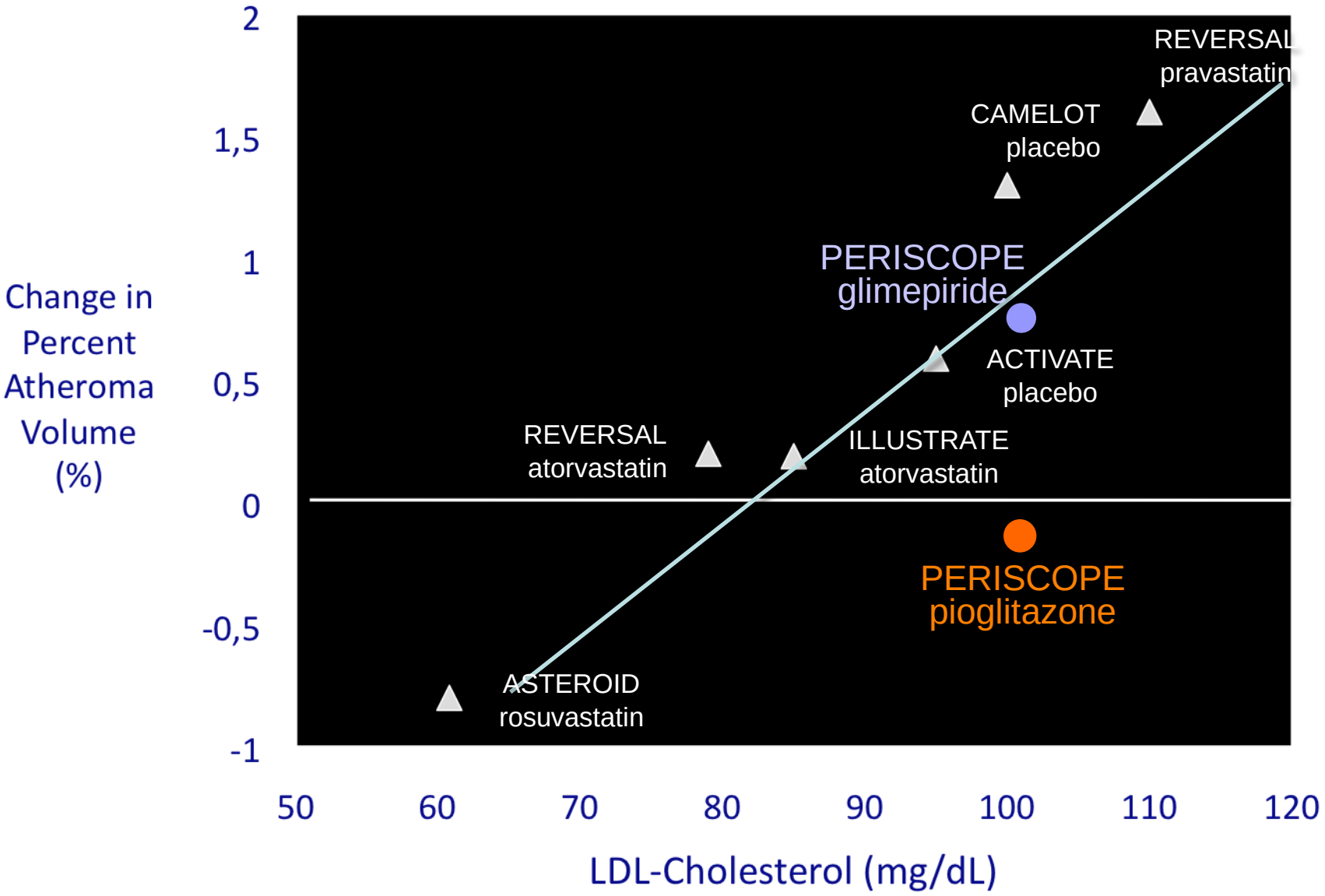
Nissen SE et al. JAMA 299(13):1561-1573, 2008

Variazioni percentuali: parametri biochimici

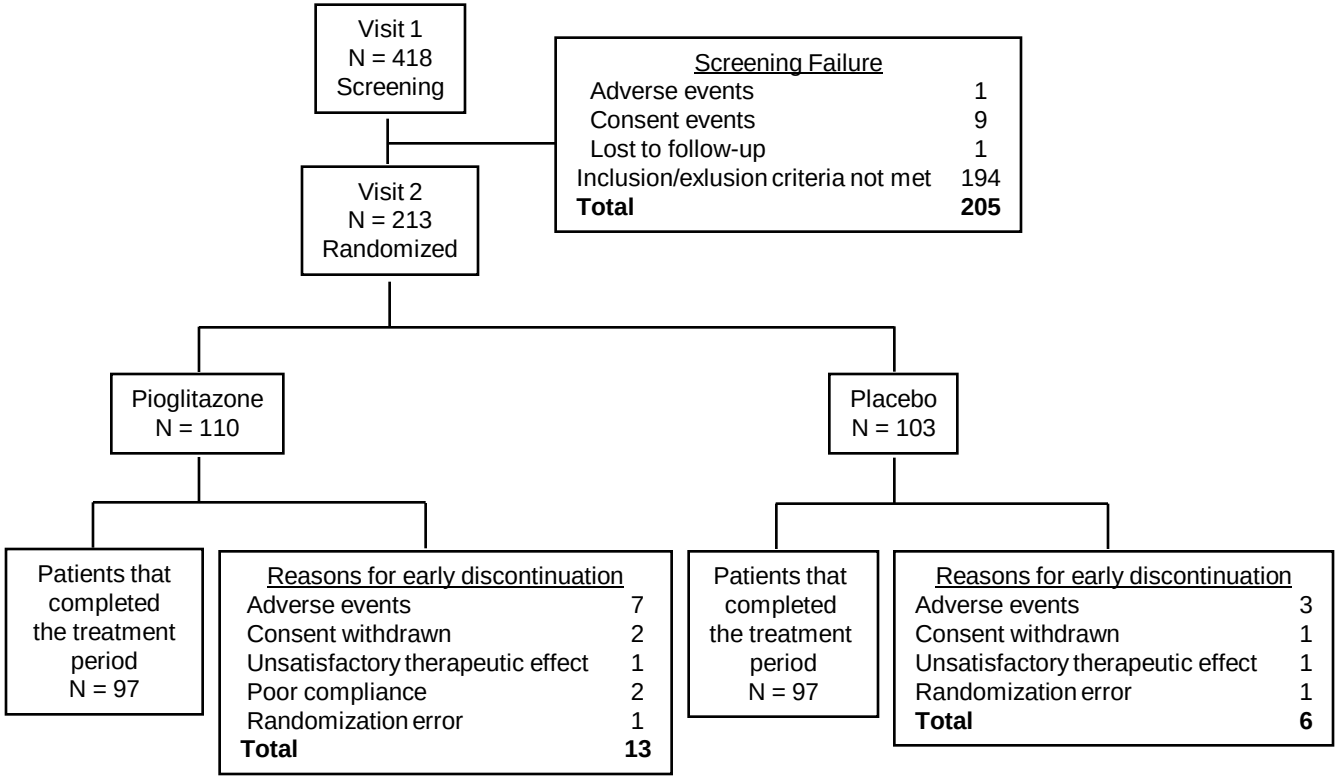


Nissen SE et al. JAMA 299(13):1561-1573, 2008

PERISCOPE: Comparison with other trials

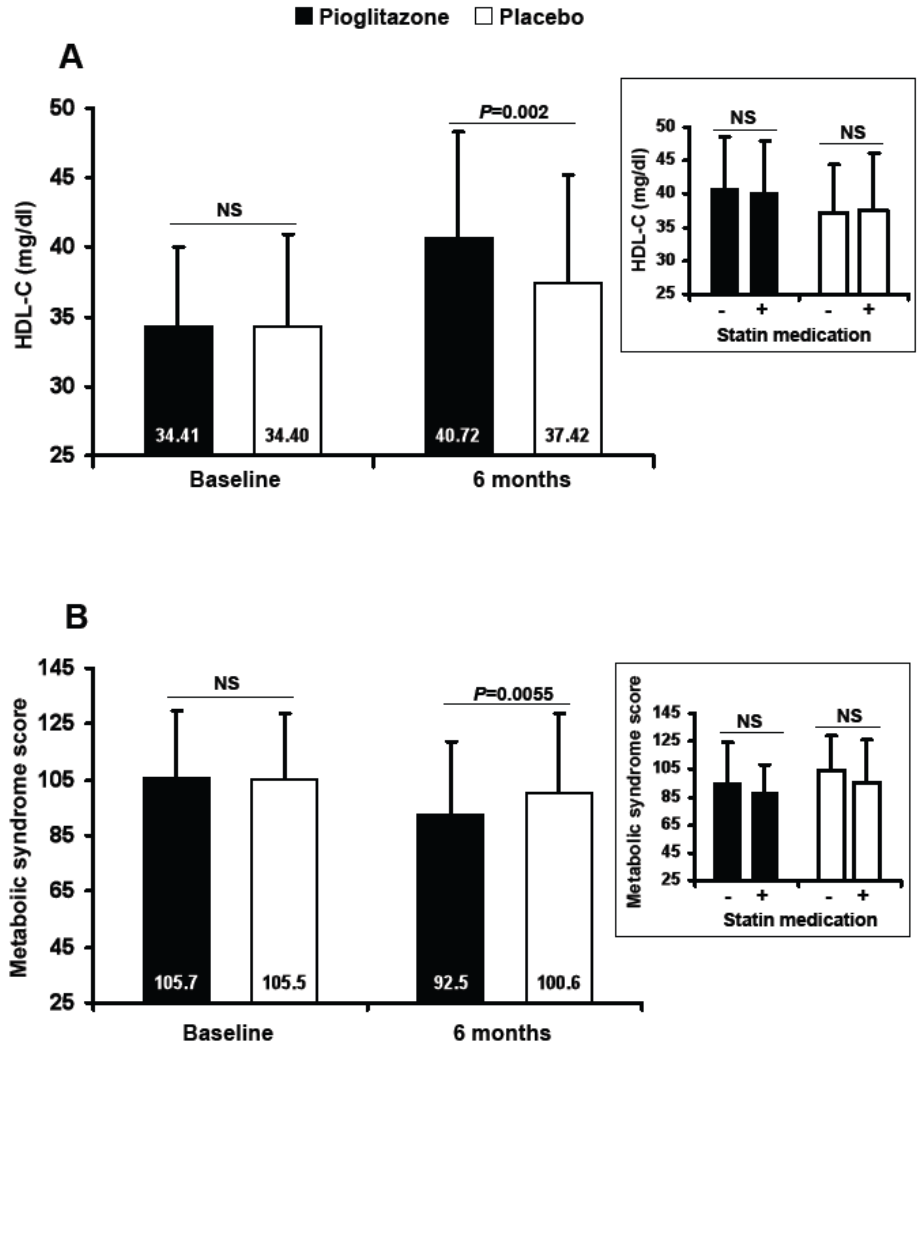


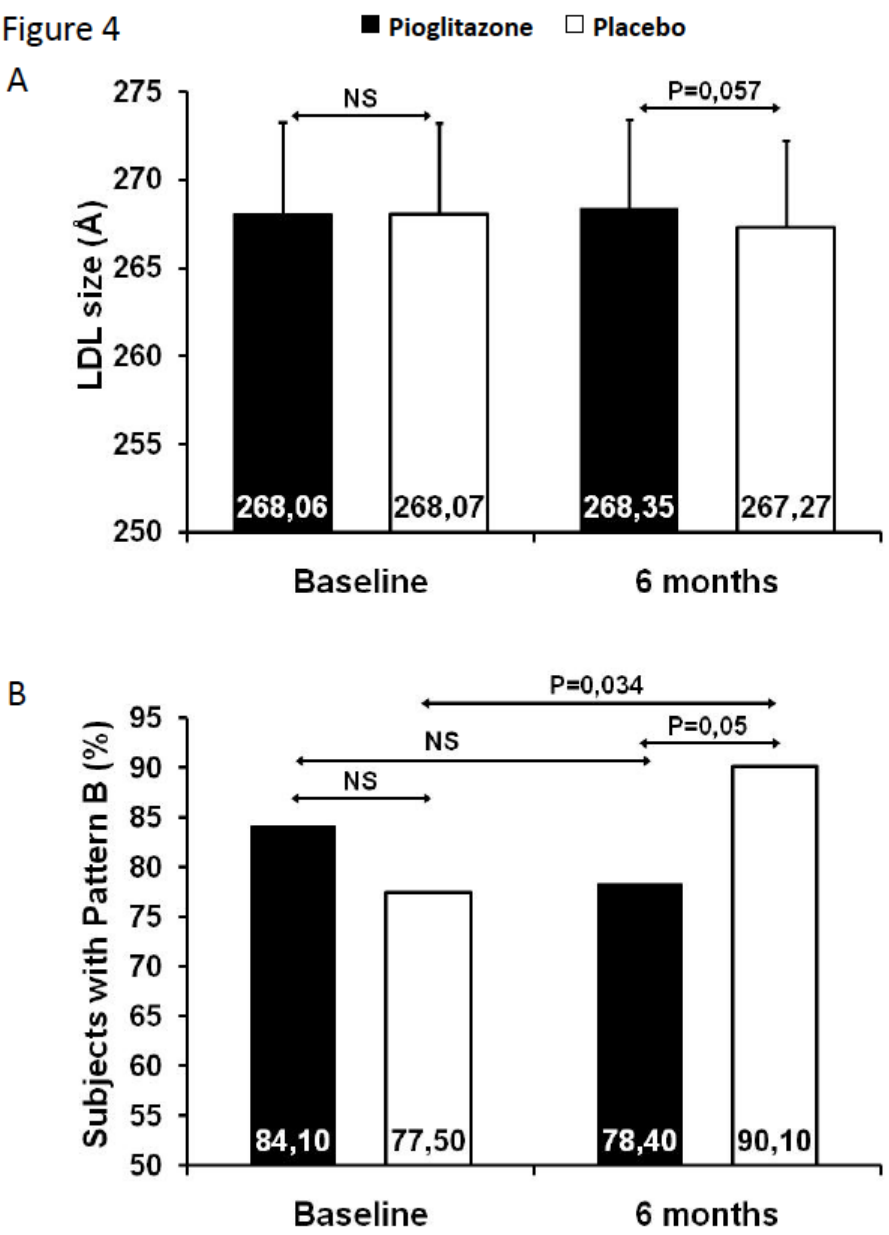
Pioglitazone Randomised Italian Study on Metabolic Syndrome (PRISMA): effect of pioglitazone with metformin on HDL-C levels in type 2 diabetic patient



Genovese S et al, submission

Figure 4





Genovese S et al, submission

Luci e ombre

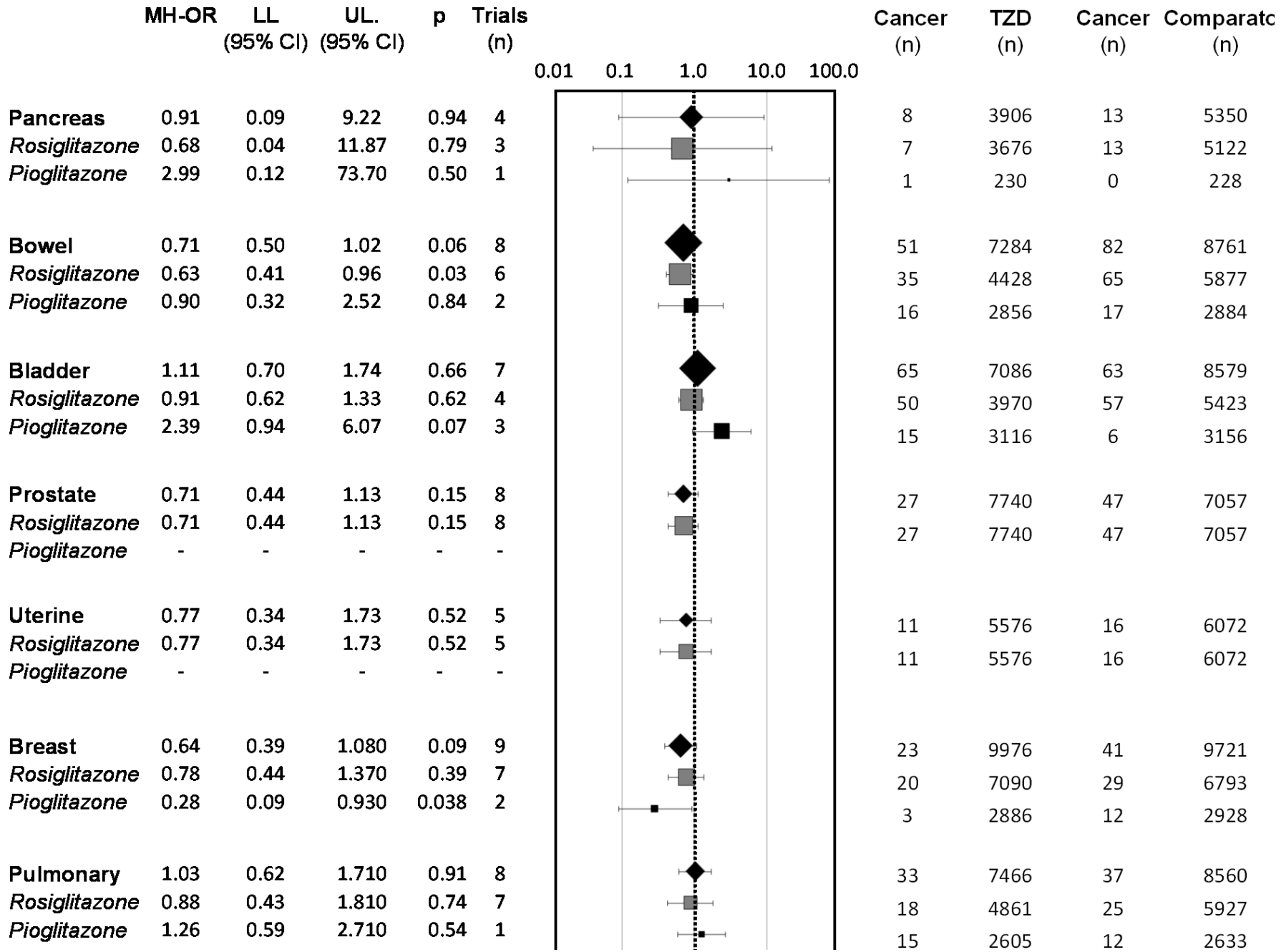
Decisione CHMP (EMA) 21 luglio 2011

- Le evidenze disponibili indicano un lieve aumento del rischio di carcinoma della vescica con pioglitazone
- Modifiche di RCP e FI con inserimento nelle controindicazioni di:
  - ✓ carcinoma della vescica attivo o anamnestico
  - ✓ ematuria macroscopica di natura non accertata
- Invio ai medici prescrittori di una “Dear Doctor Letter” e di materiale informativo
- Tali misure sono sufficienti per il controllo del rischio di K vescicale, già lieve, associato all’uso di pioglitazone
- Il rapporto rischio beneficio della terapia con pioglitazone rimane positivo

La posizione EMA

- CHMP ha rivisto tutti i dati disponibili sul rischio di K della vescica indotto da pioglitazone: dai preclinici al PROactive a quelli di popolazione
- CHMP ha anche considerato il parere di un gruppo di esperti in diabetologia e delle associazioni di pazienti
- CHMP ha osservato che ci sono pazienti che non possono essere adeguatamente trattati con altri farmaci e che traggono beneficio da pioglitazone

Considerati i rischi associati con pioglitazone e i suoi benefici, CHMP conclude che i benefici compensano i rischi nei pazienti che rispondono bene al farmaco


MH-OR
LL (95% CI)
UL. (95% CI)
p
Trials (n)
0.01
0.1
1.0
10.0
100.0
Cancer (n)
TZD (n)
Cancer (n)
Comparato (n)
Pancreas 0.91 0.09 9.22 0.94 4 8 3906 13 5350
Rosiglitazone 0.68 0.04 11.87 0.79 3 7 3676 13 5122
Pioglitazone 2.99 0.12 73.70 0.50 1 1 230 0 228
Bowel 0.71 0.50 1.02 0.06 8 51 7284 82 8761
Rosiglitazone 0.63 0.41 0.96 0.03 6 35 4428 65 5877
Pioglitazone 0.90 0.32 2.52 0.84 2 16 2856 17 2884
Bladder 1.11 0.70 1.74 0.66 7 65 7086 63 8579
Rosiglitazone 0.91 0.62 1.33 0.62 4 50 3970 57 5423
Pioglitazone 2.39 0.94 6.07 0.07 3 15 3116 6 3156
Prostate 0.71 0.44 1.13 0.15 8 27 7740 47 7057
Rosiglitazone 0.71 0.44 1.13 0.15 8 27 7740 47 7057
Pioglitazone - - - - -
Uterine 0.77 0.34 1.73 0.52 5 11 5576 16 6072
Rosiglitazone 0.77 0.34 1.73 0.52 5 11 5576 16 6072
Pioglitazone - - - - -
Breast 0.64 0.39 1.080 0.09 9 23 9976 41 9721
Rosiglitazone 0.78 0.44 1.370 0.39 7 20 7090 29 6793
Pioglitazone 0.28 0.09 0.930 0.038 2 3 2886 12 2928
Pulmonary 1.03 0.62 1.710 0.91 8 33 7466 37 8560
Rosiglitazone 0.88 0.43 1.810 0.74 7 18 4861 25 5927
Pioglitazone 1.26 0.59 2.710 0.54 1 15 2605 12 2633

Incidenza di tumori e patologie cardiovascolari nei pazienti con diabete

	Incidenza per 100.000 pazienti diabetici-anno
Eventi cardiovascolari maggiori[1]	5.000
Decessi cardiovascolari[1]	1.330
Neoplasie maligne [2]	1.308
Tumori colo-rettali[2]	198
Tumori polmonari[2]	159
Tumori della vescica[3]	69

[1] Becker et al Eur Heart Journal 2003;24:1406-1413
[2] Dormandy, et al. Lancet. 2005: 366(9493); 1279-1289
[3] KPNC 3rd interim analysis

NNH e NNT per pioglitazone

- NNH studio CNAMTS 10.620 K vescica
- NNH studio KPNC 7.874 K vescica
- NNT studio PROactive 144 MACE

Tra passato e futuro

Diabetologia
DOI 10.1007/s00125-011-2446-4

SYSTEMATIC REVIEW

Impact of current treatments on liver disease, glucose metabolism and cardiovascular risk in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of randomised trials

G. Musso · M. Cassader · F. Rosina · R. Gambino

Conclusions/interpretation Weight loss is safe, and improves liver histology and cardio-metabolic profile. For patients not responding to lifestyle intervention, pioglitazone improves histological disease activity, slows fibrosis progression and extensively ameliorates cardio-metabolic endpoints. Further randomised controlled trials (RCTs) of adequate size and duration will assess long-term safety and efficacy of proposed treatments on clinical outcomes.

Diabetologia: Published on line 27 January 2012

Il futuro

European Journal of
Cardiovascular
Prevention &
Rehabilitation

EUROPEAN
SOCIETY OF
CARDIOLOGY®

Original scientific paper

European Journal of Cardiovascular
Prevention & Rehabilitation
18(3) 415–423

Predictors of early-stage left ventricular dysfunction in type 2 diabetes: results of

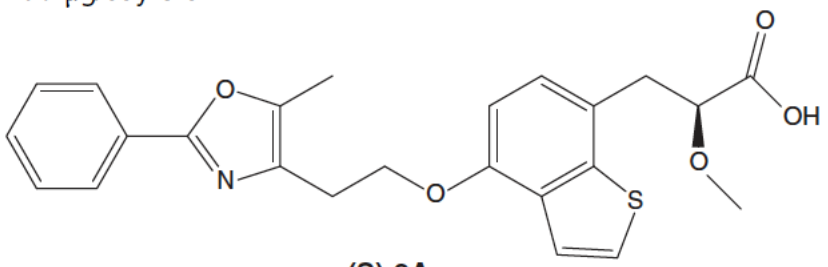
Conclusion: In asymptomatic and fairly controlled diabetic patients, age, worse HbA1c, traits of insulin resistance, such as visceral adiposity and triglycerides or treatment with metformin, and use of doxazosin indicate greater risk of LVD. Glitazones, at this stage, seem to be associated with better diastolic performance.

SAGE

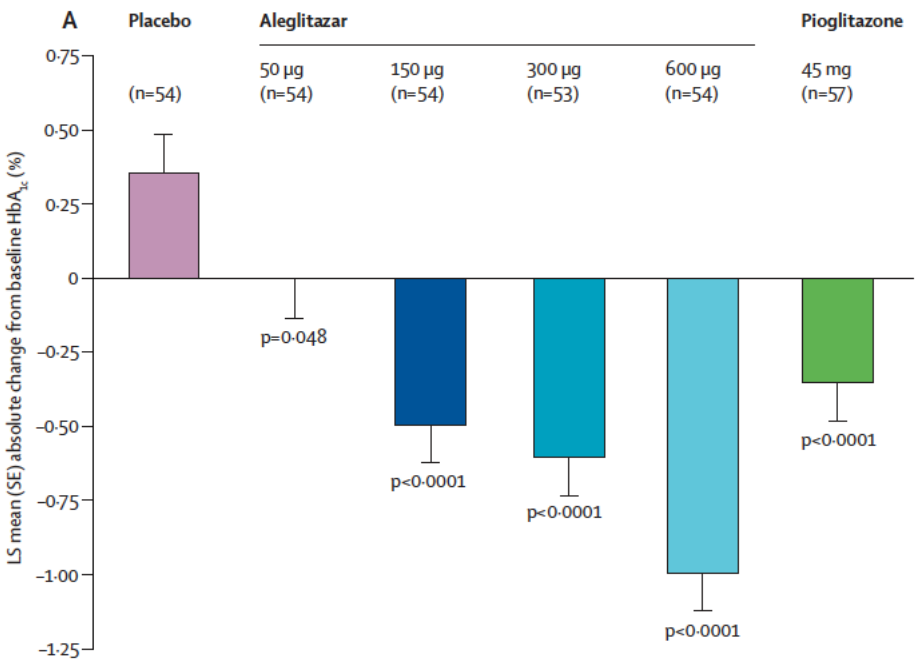
Carlo B Giorda[1], Giovanni Cioffi[2], Giovanni de Simone[3], Andrea Di Lenarda[4], Pompilio Faggiano[5], Roberto Latini[6], Donata Lucci[7], Aldo P Maggioni[7], Luigi Tarantini[8], Mario Velussi[9], Paolo Verdecchia[10] and Marco Comaschi[11] (on behalf of the DYDA Investigators*)

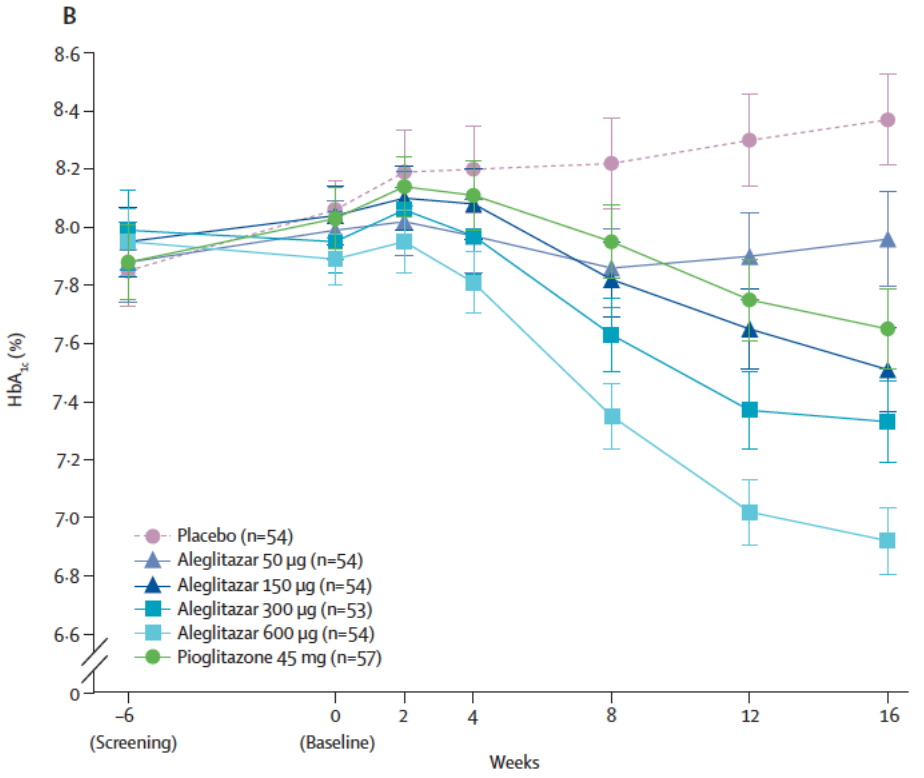
Aleglitazar

Box 1. Drug summary.

Drug name	Aleglitazar
Current phase	Phase III (ALECARDIO study)
Indication	Cardiovascular risk reduction in high risk type 2 diabetes mellitus
Pharmacology	Dual peroxisome proliferator-activated inhibitor α–γ agonist
Route	150 μg/day oral
Chemical structure	 **(S)-2Aa**
Pivotal trials	SYNCHRONY, ALECARDIO (ongoing)

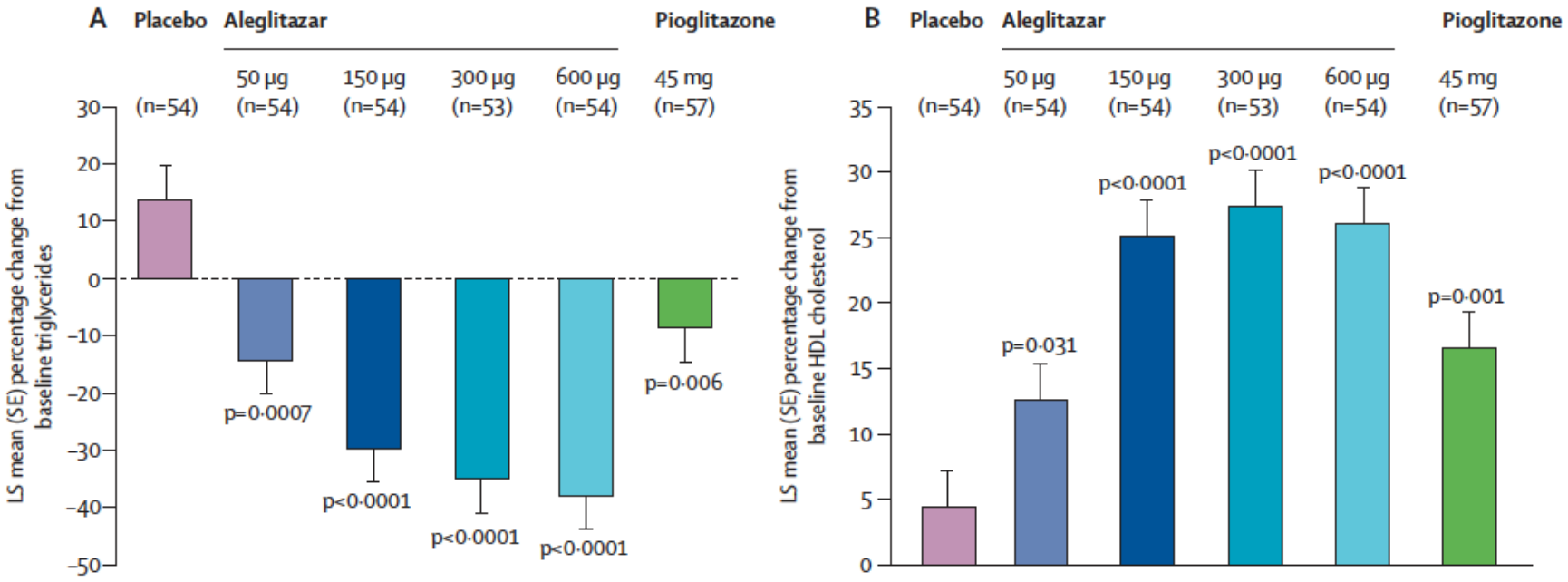
SYNCHRONY: Effect on HbA1c concentration





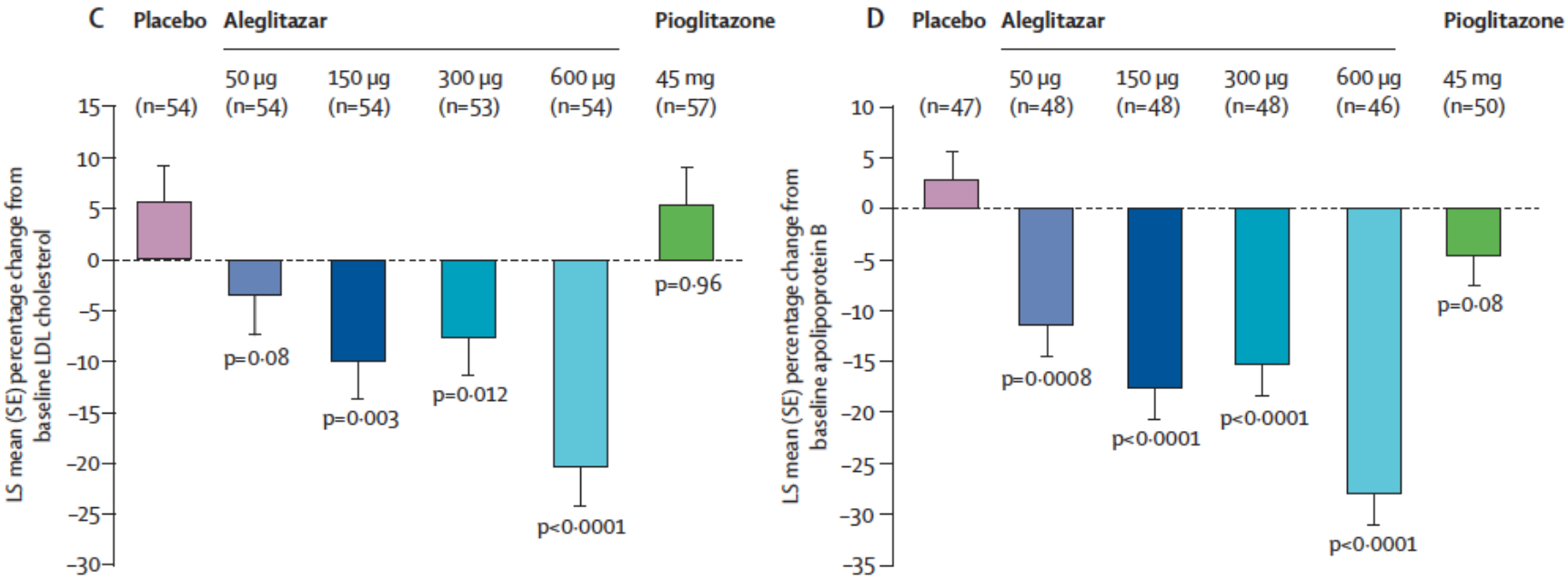
Lancet 2009; 374: 126–35

SYNCHRONY: Effect on lipid parameters



Lancet 2009; 374: 126–35

SYNCHRONY: Effect on lipid parameters



Lancet 2009; 374: 126–35

Safety of aleglitazar in SYNCHRONY

Event	Treatment group					
	placebo (n=55)	aleglitazar 50 mg (n=55)	aleglitazar 150 mg (n=55)	aleglitazar 300 mg (n=55)	aleglitazar 600 mg (n=55)	pioglitazone 45 mg (n=57)
Death (all-cause) [% pts]	0	0	0	0	0	0
Congestive heart failure (% pts)	0	0	0	2	2	0
Edema (% pts)	5	2	4	13	11	7
Change in weight compared with baseline (kg) [±SD]	−0.85±0.40	−0.24±0.40	0.52±0.39*	1.18±0.40**	2.72±0.39***	1.06±0.40**

pts = patients; * $p<0.05$, ** $p<0.005$, *** $p<0.0001$ vs placebo.

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Most frequently reported adverse events

	Placebo (n=55)	Aleglitazar				Pioglitazone 45 mg (n=57)
		50 µg (n=55)	150 µg (n=55)	300 µg (n=55)	600 µg (n=55)	
Peripheral oedema	3 (5%)	1 (2%)	2 (4%)	6 (11%)	5 (9%)	4 (7%)
Nasopharyngitis	4 (7%)	1 (2%)	3 (5%)	1 (2%)	3 (5%)	3 (5%)
Increased blood creatine phosphokinase	3 (5%)	0	1 (2%)	3 (5%)	5 (9%)	2 (4%)
Upper respiratory tract infection	3 (5%)	2 (4%)	1 (2%)	4 (7%)	2 (4%)	0
Arthralgia	2 (4%)	0	3 (5%)	0	1 (2%)	1 (2%)
Influenza	0	0	0	1 (2%)	2 (4%)	3 (5%)
Decreased haemoglobin	1 (2%)	0	0	0	4 (7%)	0
Decreased white blood cell count	0	0	0	0	3 (5%)	0

Data are number (%) of patients with adverse event. Adverse events presented are those reported by three or more patients in any one treatment group.

Lancet 2009; 374: 126–35

	Placebo	Aleglitazar				Pioglitazone 45 mg
		50 µg	150 µg	300 µg	600 µg	
Bodyweight (kg)						
Number of patients	54	54	54	53	54	57
LS mean baseline (SE)	86·7 (2·8)	81·3 (2·8)	82·1 (2·8)	88·0 (2·9)	83·3 (2·8)	82·5 (2·8)
LS mean absolute change from baseline (SE)	−0·85 (0·40)	−0·24 (0·40)	0·52 (0·39)	1·18 (0·40)	2·72 (0·39)	1·06 (0·40)
Haemoglobin (g/L)						
Number of patients	40	41	44	46	42	50
LS mean baseline (SE)	144·8 (1·7)	140·8 (1·7)	140·9 (1·7)	146·2 (1·7)	142·8 (1·7)	145·2 (1·7)
LS mean absolute difference from baseline (SE)	0·18 (1·38)	−2·20 (1·37)	−4·80 (1·32)	−8·83 (1·29)	−13·93 (1·35)	−6·12 (1·24)
Serum creatinine (µmol/L)						
Number of patients	41	42	45	47	45	50
LS mean baseline (SE)	73·6 (2·3)	72·7 (2·3)	69·1 (2·3)	71·7 (2·3)	74·2 (2·3)	70·6 (2·3)
LS mean percentage change from baseline (SE)	−0·32% (2·14)	4·84% (2·11)	7·16% (2·04)	13·24% (2·00)	15·70% (2·04)	3·18% (1·94)
Estimated GFR (mL/min/1·73 m²)						
Number of patients	41	42	45	47	45	50
LS mean baseline (SE)	86·4 (3·0)	87·6 (3·0)	93·7 (3·0)	92·6 (3·0)	82·5 (3·0)	89·1 (2·9)
LS mean percentage change from baseline (SE)	2·67% (2·10)	−3·91% (2·07)	−6·35% (2·00)	−11·5% (1·96)	−14·06% (2·00)	−1·35% (1·90)

Esiste una correlazione tra riduzione di prezzo/genericazione e sicurezza?