Simposio Aziendale a cura di Takeda

La gestione del diabete nei soggetti ad alto rischio cardiovascolare: oltre la metformina

I Trial di outcome cardiovascolare nel diabete: focus sul paziente con sindrome coronarica acuta

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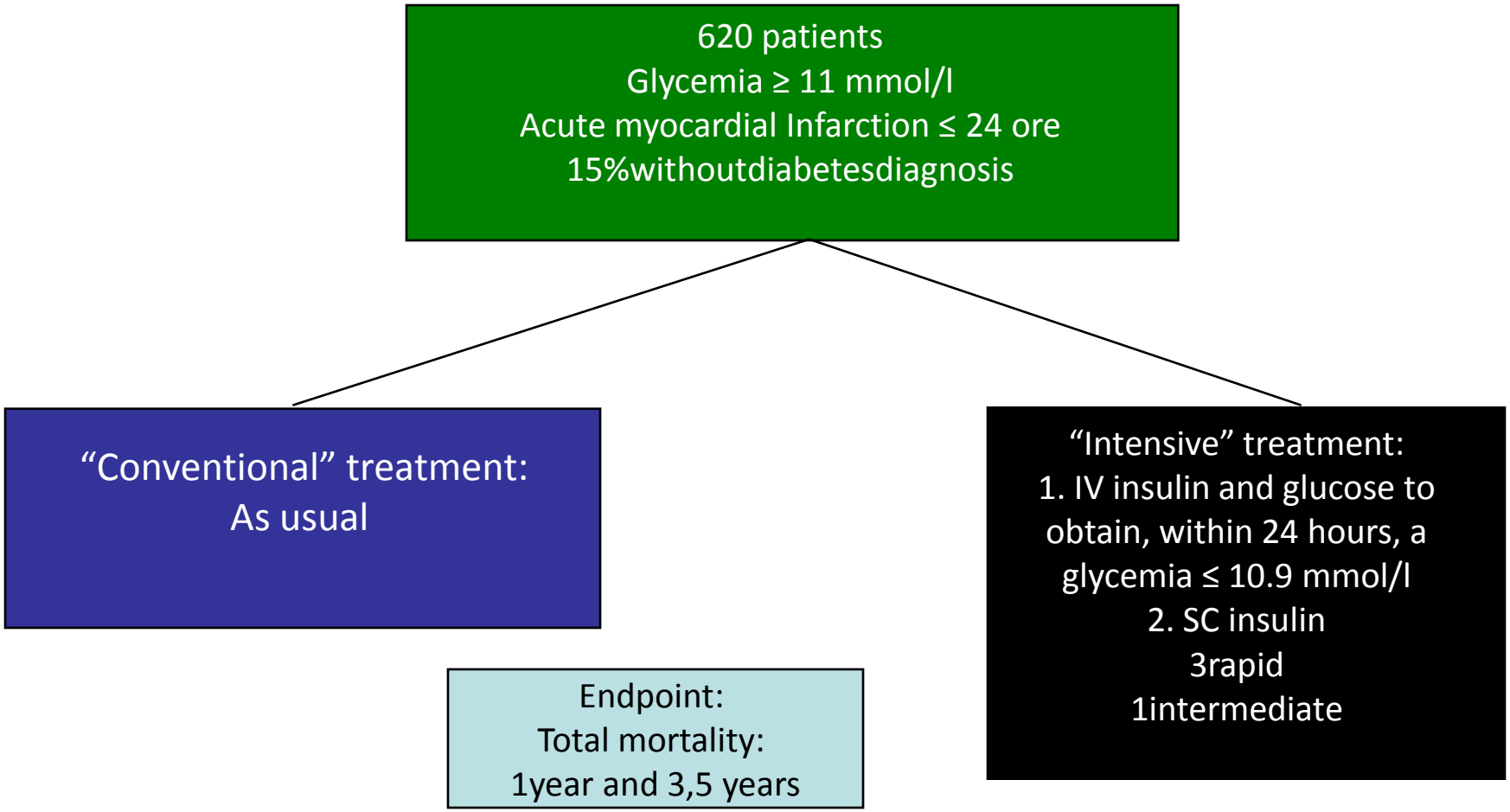
Disclosure Statement

- Stefano Genovese, in the last three years, has received speaking and/or consulting fees from:
  - Abbott Diabetes Care
  - AstraZeneca
  - BoehringerIngelheim
  - Bristol-Myers Squibb
  - Eli Lilly
  - Janssen
  - Lifescan
  - Merck Sharp &Dohme
  - Novartis
  - Novo Nordisk
  - Takeda
- and research grants from
  - Novartis

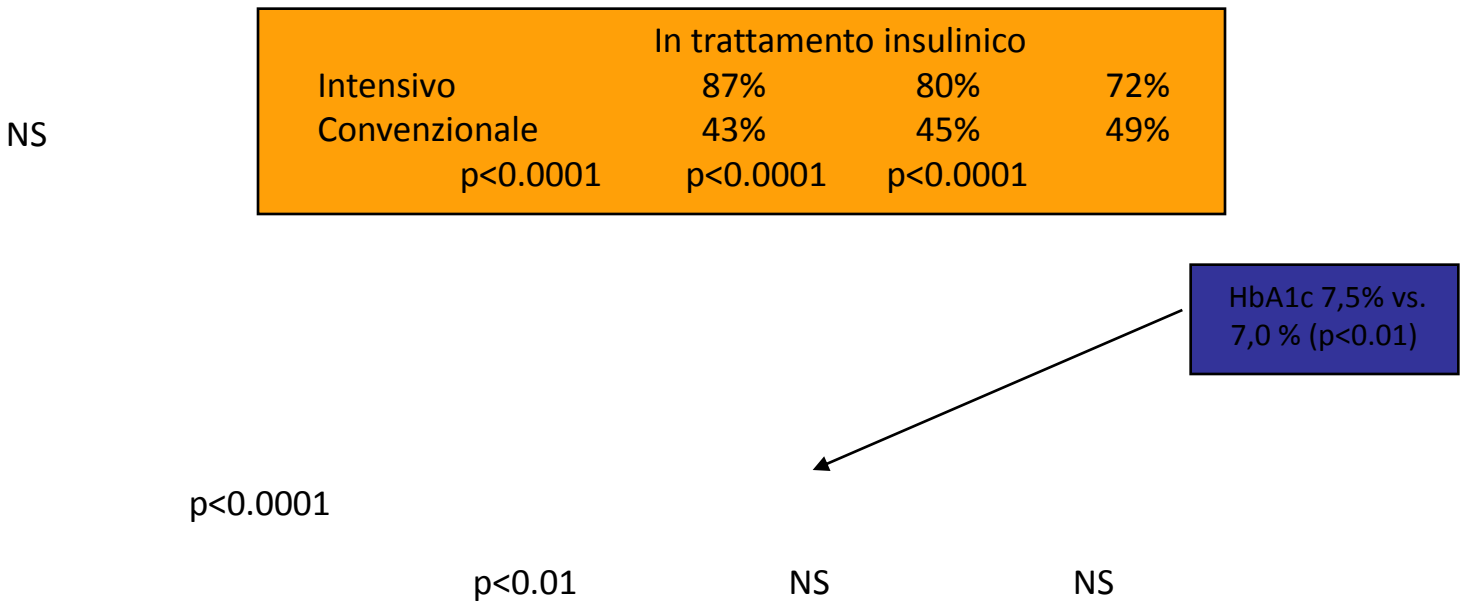
Insulin

Prospectiverandomisedstudyof intensive insulin treatment on long termsurvivalafter acute myocardialinfarction in patientswithdiabetesmellitus



Malbergk BMJ 1997: 24;314(7093):1512-5

Randomized trial of Insulin-Glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year



MalbergKet al JACC 1995

Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus.

- Mortalità totale nello studio DIGAMI ad 1 anno e dopo un follow up medio di 3 anni e mezzo
- La riduzione assoluta del rischio è del 7% dopo 1 anno e dell'11% dopo 3 anni e 1/2
- Il NumberNeededtoTreat è 9

p=0.01

p=0.03

Malbergk BMJ 1997: 24;314(7093):1512-5

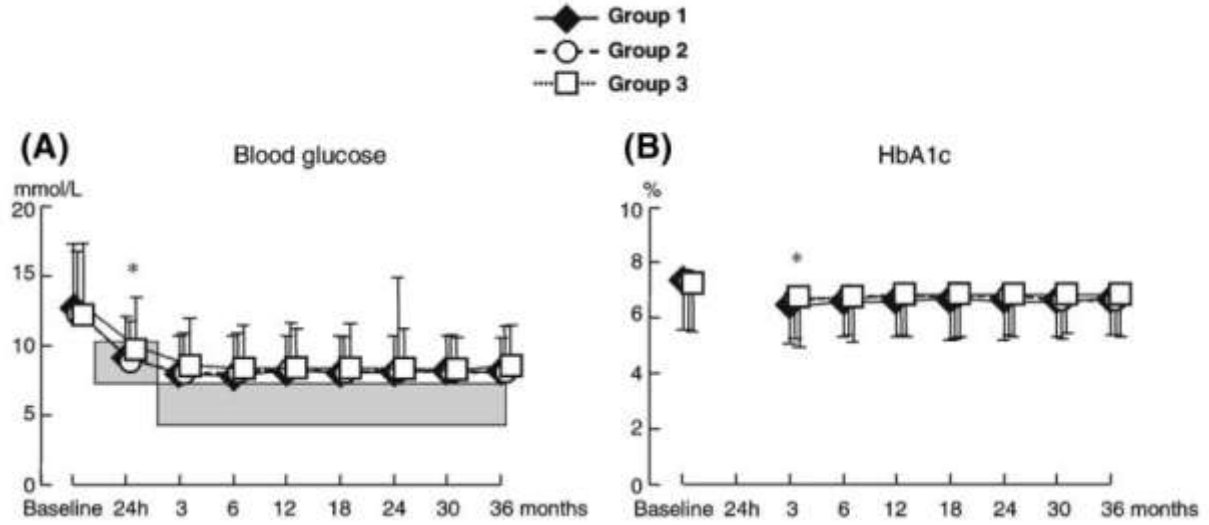
Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. Malberg K for the DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group

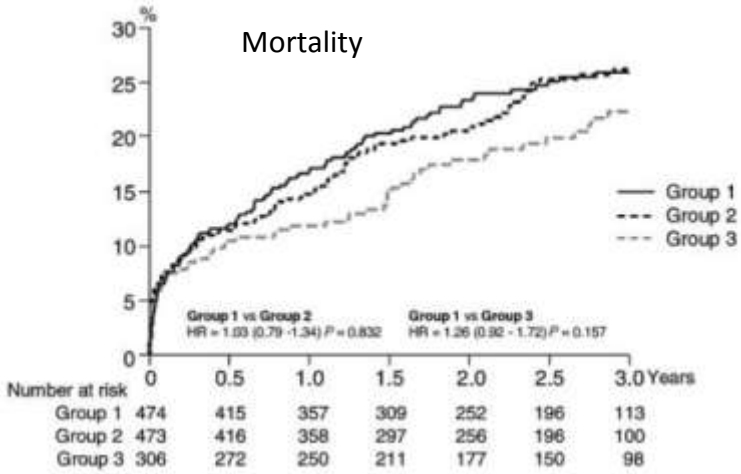
- Scomposizione del dato della mortalità in 4 gruppi:
  - **1. Non trattamento insulinico pregresso, basso rischio cardiovascolare (44% della popolazione)**
  - 2. Non trattamento insulinico pregresso, alto rischio cardiovascolare (21% della popolazione)
  - 3. Trattamento insulinico pregresso, basso rischio cardiovascolare (19% della popolazione)
  - 4. Trattamento insulinico pregresso, alto rischio cardiovascolare (16% della popolazione)

p=0.004

Malbergk BMJ 1997: 24;314(7093):1512-5

DIGAMI 2: Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction





Conclusion: … an epidemiological analysis confirms that the glucose level is a strong, independent predictor of long-term mortality in this patient category, underlining that glucose control seems to be an important part of their management.

MalbergKet al. Eur Heart J. 2005 Apr;26(7):650-61.

DIGAMI 2: post hoc analysis

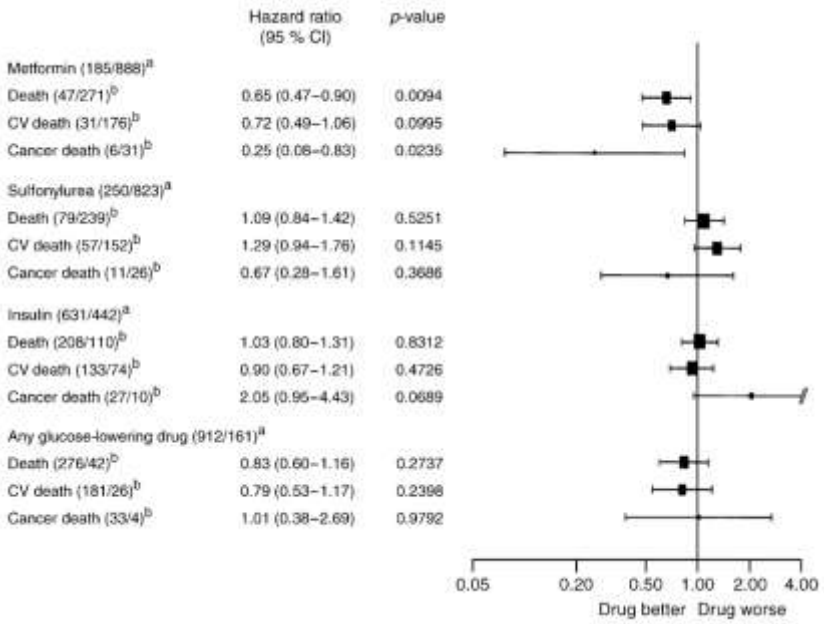


Table 4 The effect of insulin treatment from the time of hospital discharge for patients discharged alive (n=1073)

Patients on insulin	OR (95% CI)	p value
Mortality		
Insulin[a]	1.30 (0.9–1.81)	0.1292
New on insulin[b]	1.00 (0.65–1.55)	0.9921
CV death		
Insulin[a]	1.15 (0.79–1.67)	0.4616
New on insulin[b]	1.06 (0.65–1.74)	0.8043
Reinfarction		
Insulin[a]	1.94 (1.34–2.81)	0.0004
New on insulin[b]	2.04 (1.29–3.21)	0.0021
Reinfarction/stroke		
Insulin[a]	1.89 (1.35–2.63)	0.0002
New on insulin[b]	2.12 (1.40–3.21)	0.0004
Death/reinfarction/stroke		
Insulin[a]	1.78 (1.32–2.38)	0.0001
New on insulin[b]	1.65 (1.14–2.40)	0.0086

Conclusions/interpretation: Patients with type 2 diabetes and myocardial infarction have a poor prognosis. Glucose lowering drugs appear to be of prognostic importance. Insulin may be associated with an increased risk of nonfatal cardiac events, while metformin seems to be protective against risk of death.

Mellbin LG et al. Diabetologia (2011) 54:1308–1317

Pioglitazone

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

- 5238 patients with T2DM with high CV risk
- Pioglitazone 15-45 mg *vs* placebo with mean follow-up of 34,5 months
- Primary endpoint: composite of all-cause mortality, non fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle
- Main secondary endpoint: composite of all-cause mortality, non-fatal myocardial infarction, and stroke

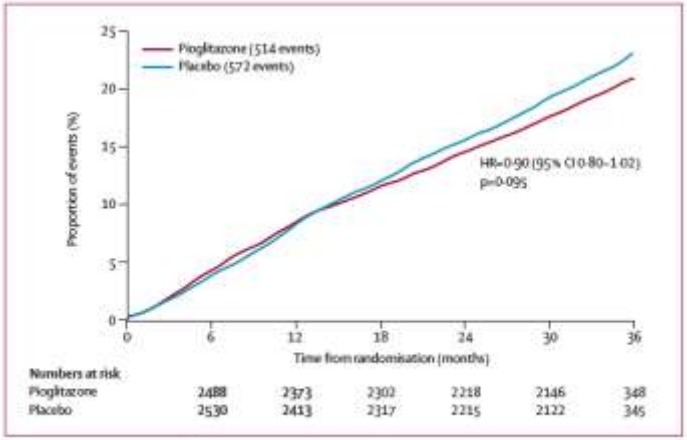


Figure 2: **Kaplan-Meier curve of time to primary endpoint***
*Death from any cause, non-fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, leg amputation, coronary revascularisation, or revascularisation of the leg.

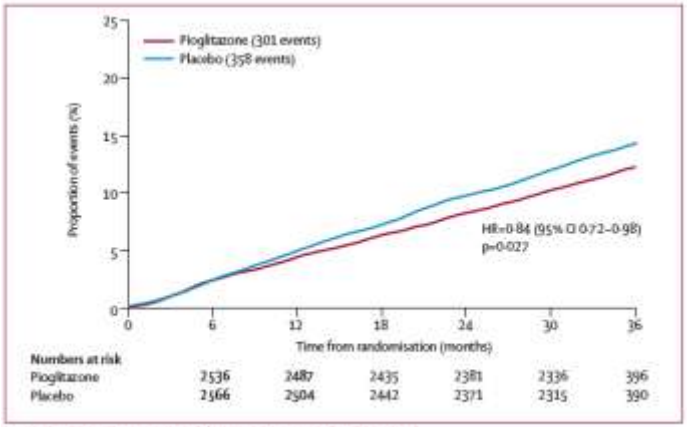
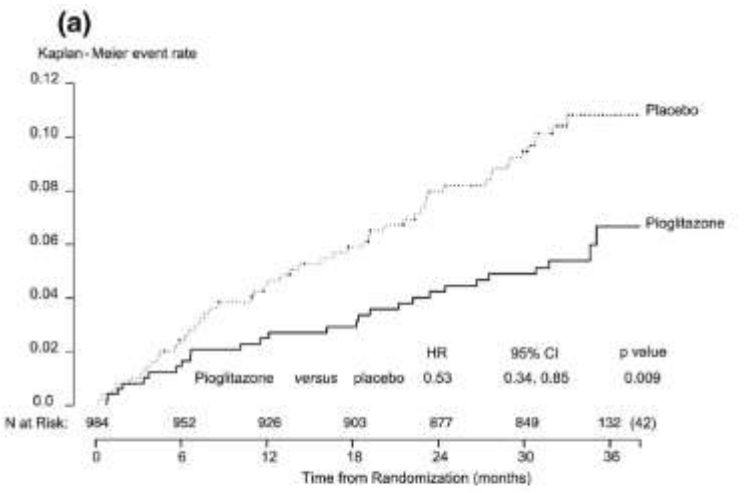


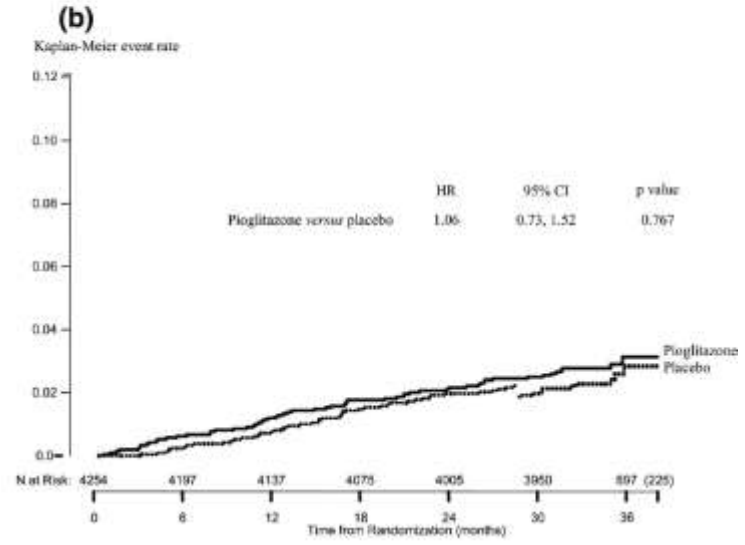
Figure 3: **Kaplan-Meier curve of time to main secondary endpoint***
* Death from any cause, non-fatal myocardial infarction (excluding silent myocardial infarction), or stroke.

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)





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

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

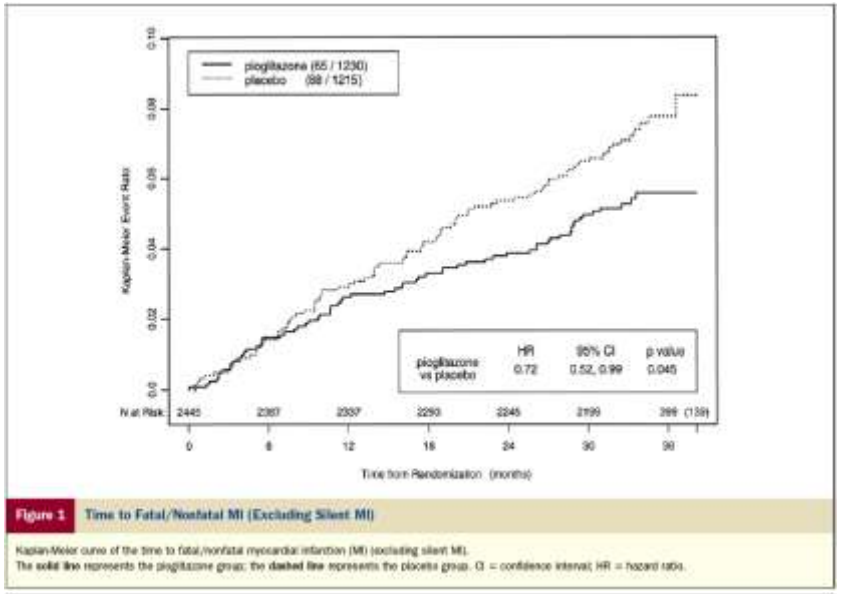


Figure 1 Time to Fatal/Nonfatal MI (Excluding Silent MI)

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.

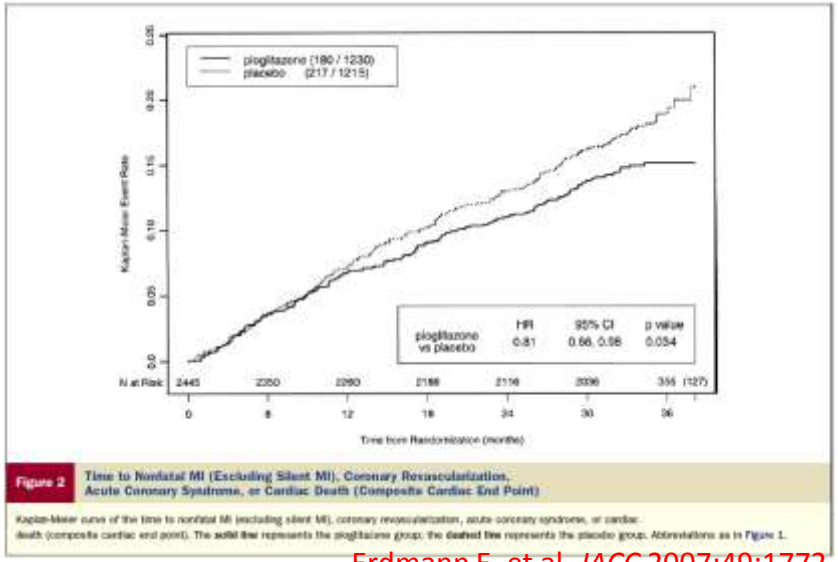
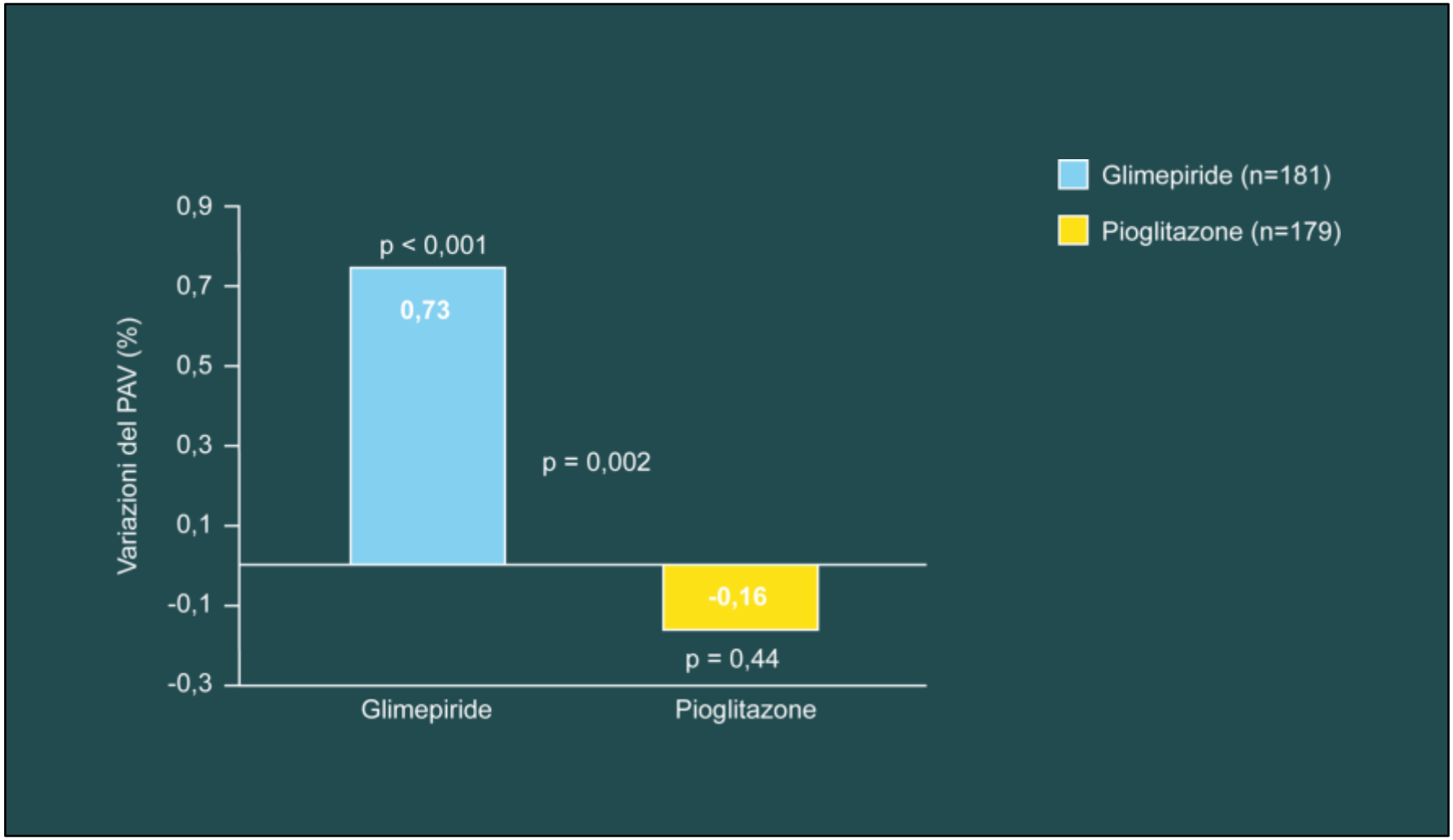


Figure 2 Time to Nonfatal MI (Excluding Silent MI), Coronary Revascularization, Acute Coronary Syndrome, or Cardiac Death (Composite Cardiac End Point)

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.

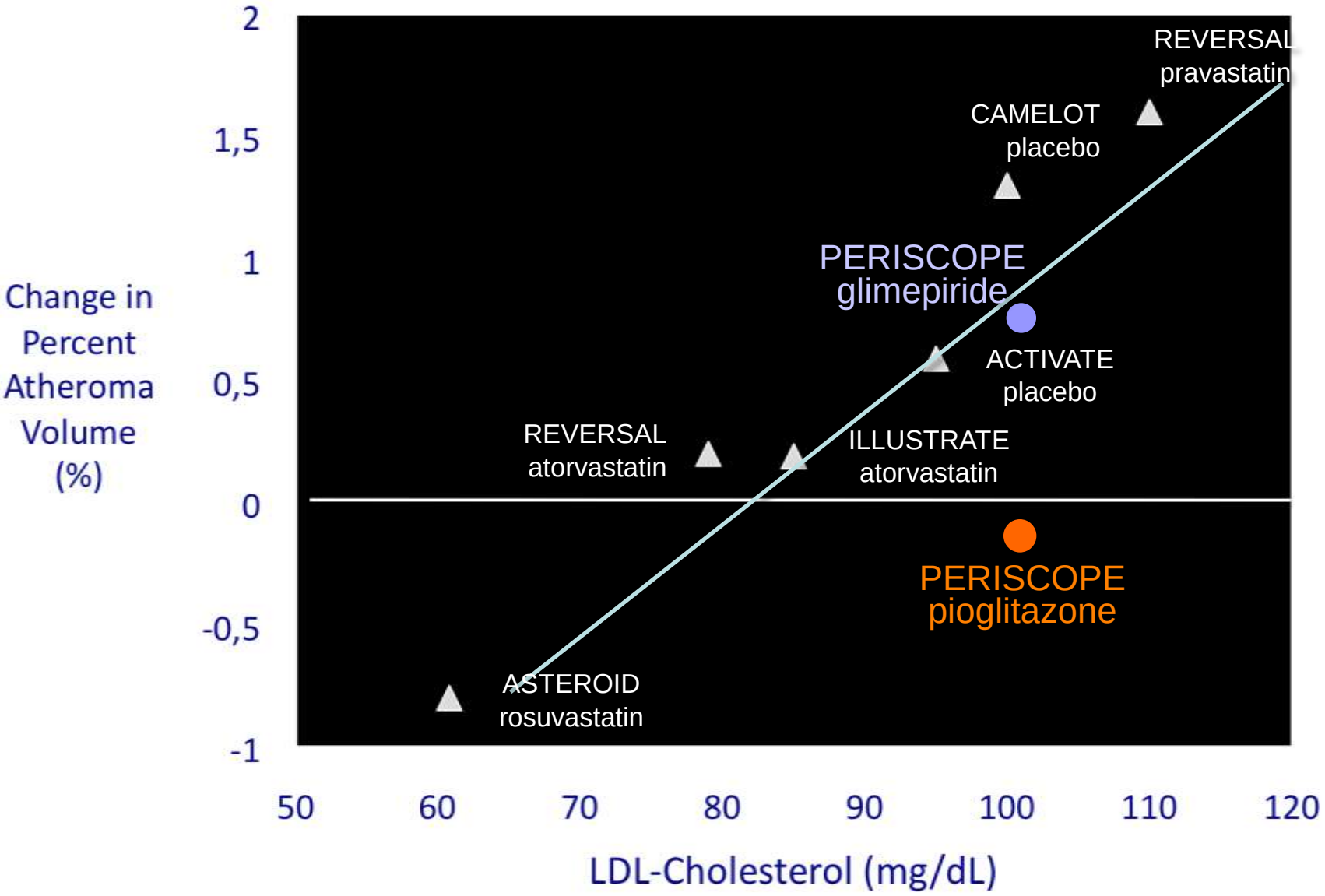
Erdmann E. et al. *JACC* 2007;49:1772-80

PERISCOPE Study: PrimaryEndpoint Variationsof ateroma volume (%)

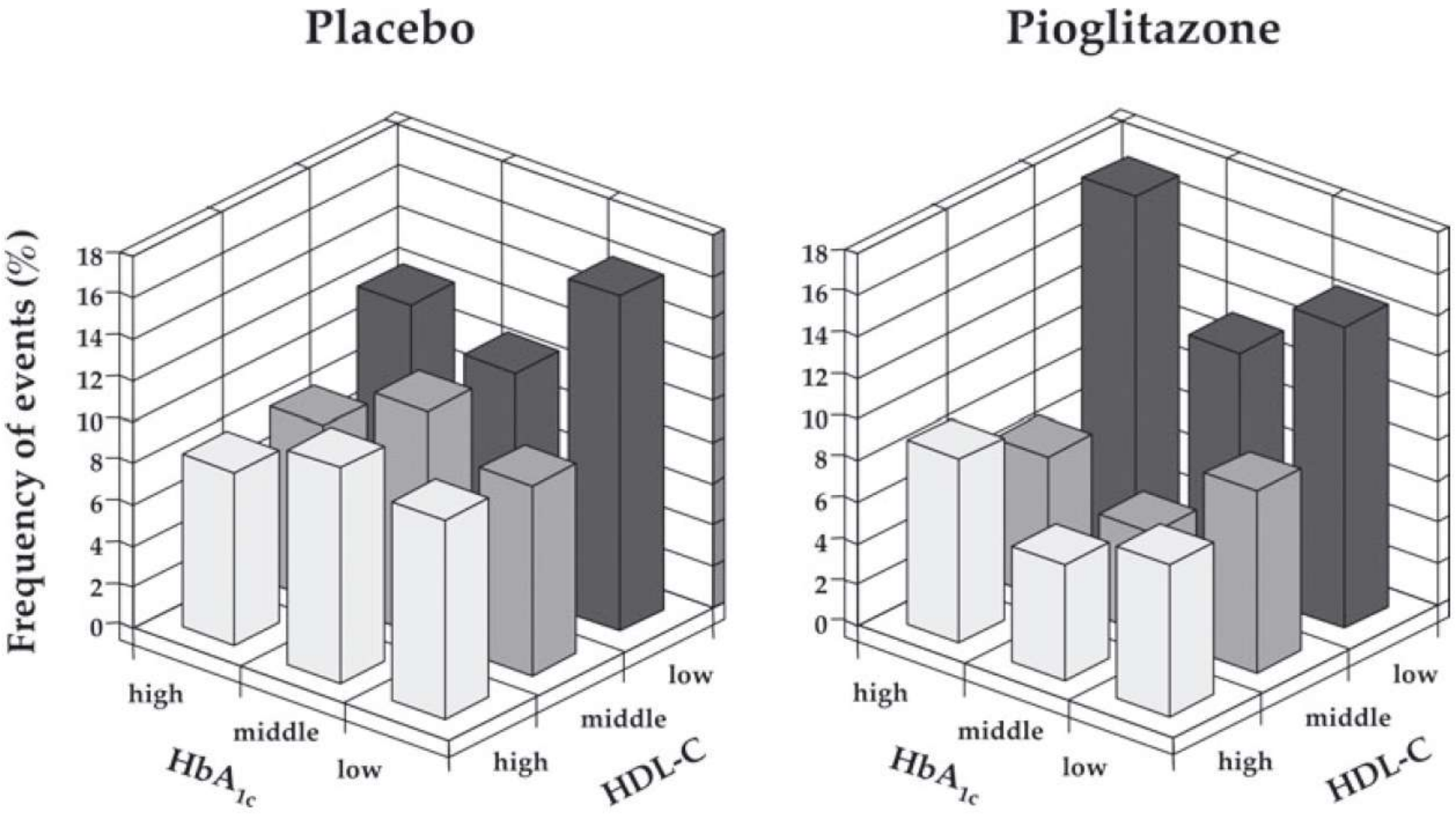


Nissen SE et al. JAMA 299(13):1561-1573, 2008

PERISCOPE: Comparison with other trials

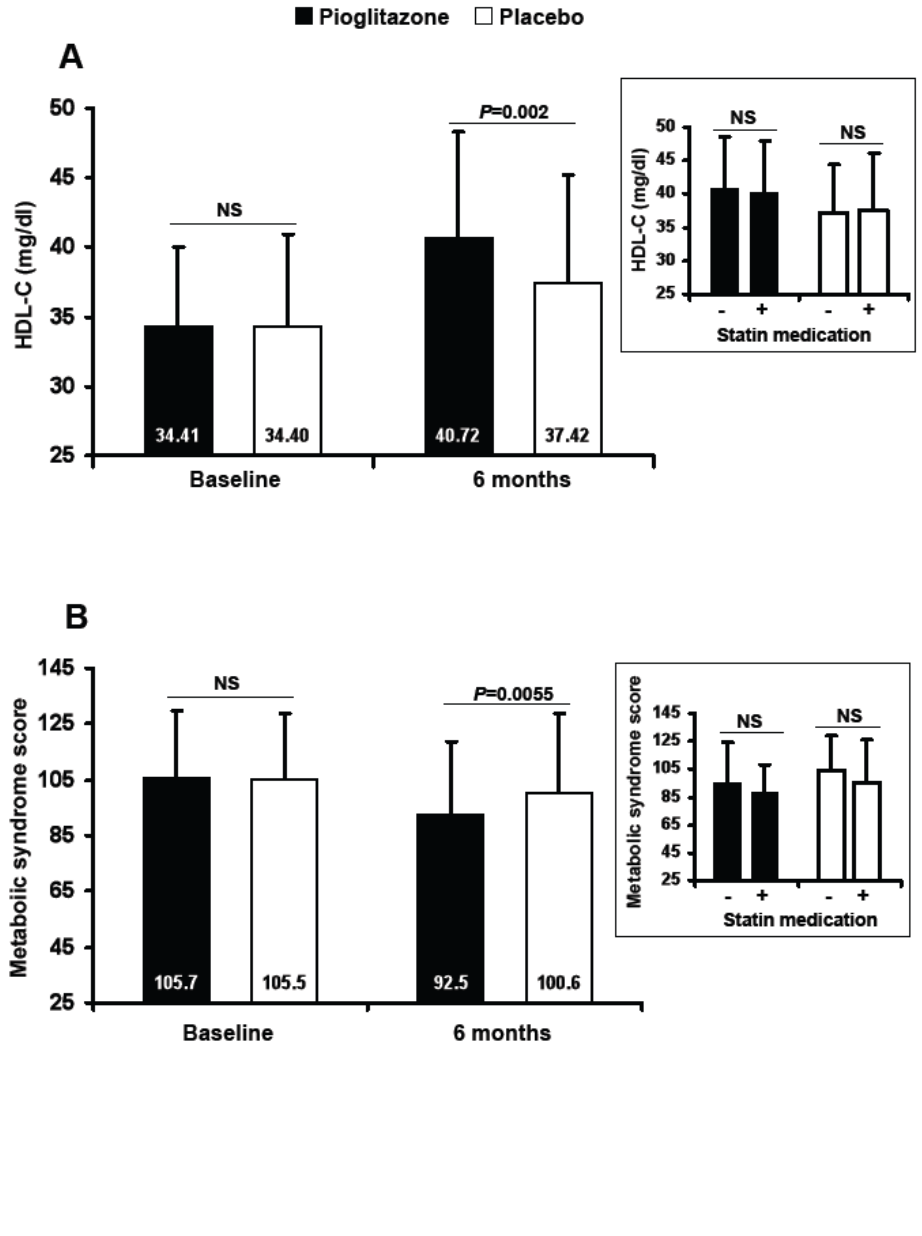


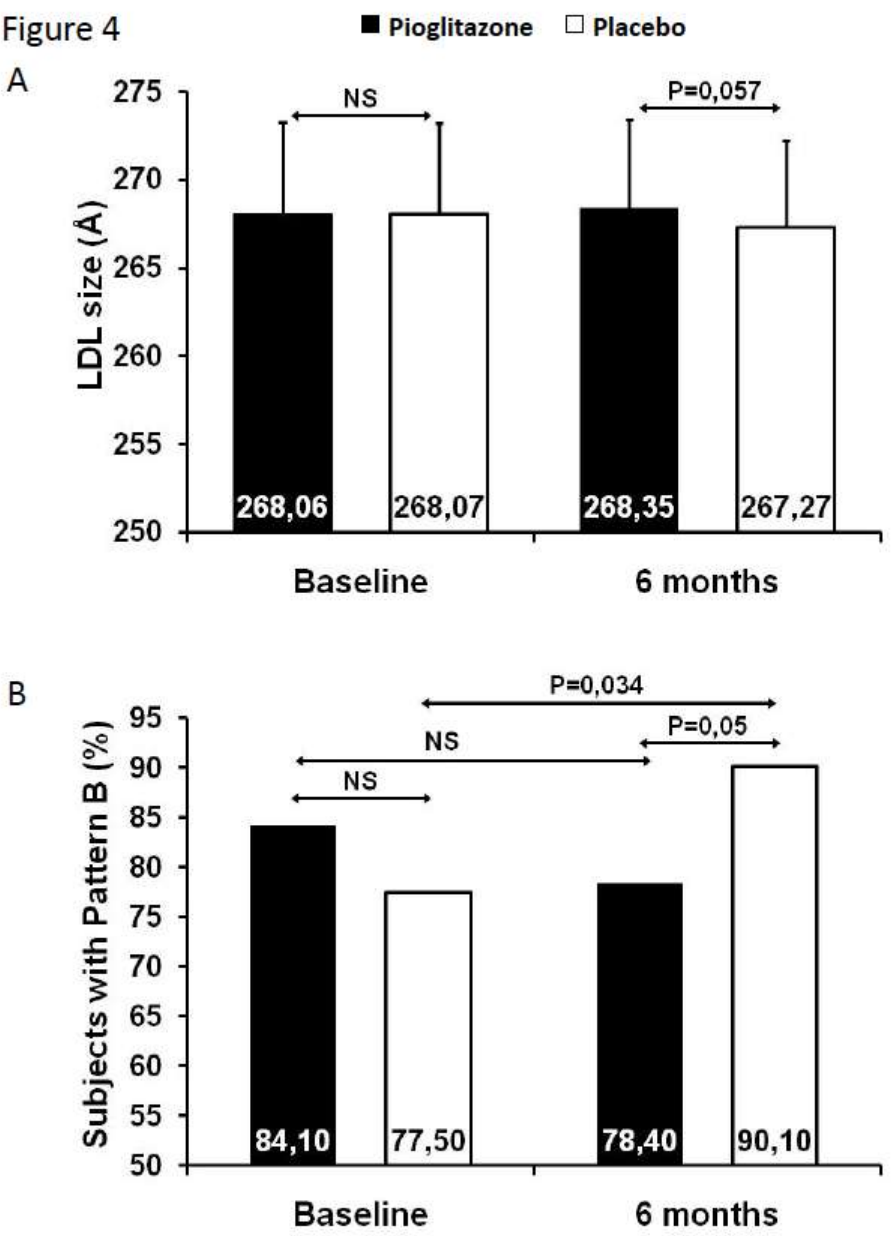
High-density lipoprotein-cholesterol and not HbA1c was directly related to cardiovascular outcome in PROactive



Ferrannini E et al. DiabetesObesMetab. 2011 Aug;13(8):759-64.

Figure 4





Genovese Set al,JEndocrinolInvest. 2013 Mar 19. [Epubaheadofprint]

Effect of Pioglitazone Versus Metformin on Cardiovascular Risk Markers in Type 2 Diabetes

Table 2 Laboratory efficacy and safety variables with pioglitazone versus metformin

Parameter	Pioglitazone Baseline	Pioglitazone Week 16	Metformin Baseline	Metformin Week 16	*P* value
Number of patients	24	24	26	26	–
Markers of inflammatory response					
CRP (mg/L)	1.8 (1.1–4.7)	1.4 (0.5–2.5)*	2.0 (1.1–2.9)	1.8 (0.8–3.7)	0.04
P-selectin (μg/mL)	56.9 (26.7–140)	52.2 (29.3–126.8)	41.3 (31.2–68.1)	47.5 (29.2–74.1)	0.73
E-selectin (μg/mL)	70.2 (52.6–81.5)	57.8 (53.7–83.8)**	65.1 (59.1–79.9)	68.5 (62.9–78.3)	0.01
ICAM-1 (μg/mL)	292 (233–322)	269 (241–312)	251 (230–296)	252 (215–309)	0.87
CD40L (pg/mL)	1.6 (0.5–2.9)	2.0 (0.4–3.6)	1.3 (0.8–2.5)	1.4 (0.8–2.4)	0.98
Markers of platelet activation and thrombogenesis					
TXB2 (pg/mg creatinine)	146 (82–221)	121 (87–198)	123 (85–304)	159 (106–191)	0.61
TF (pg/mL)	113 (102–131)	139 (113–172)	141 (100–189)	145 (111–223)	0.23
PAI-1 (ng/mL)	55.1 (21.0–82.4)	35.8 (23.8–66.1)	32.7 (24.3–81.7)	39.5 (31.7–46.2)	0.69
Markers of oxidative stress					
Nitrotyrosine (nM)	6.7±1.5	6.6±1.6	6.5±1.4	6.3±1.0	0.82

Genovese Setal. AdvTher 2013; 30 (2) 190-202

Glucose parameters					
FPG (mg/dL)	153±40	126±25***	144±47	135±48*	0.01
HbA_{1c} (%)	6.9±0.9	6.5±0.8**	6.7±0.7	6.5±0.7*	0.36
Insulin (mU/L)	8.3 (6.7–14.7)	6.3 (4.7–9.2)***	10.0 (5.3–12.8)	8.1 (5.6–10.6)	0.014
HOMA index	3.2 (2.1–5.4)	2.0 (1.3–2.9)***	3.2 (2.0–4.1)	2.3 (2.1–3.3)	0.015
Lipid parameters					
Total cholesterol (mg/dL)	212±24	222±35**	215±35	212±35	0.05
HDL-C (mg/dL)	41±10	45±11*	40±9	42±9***	0.19
LDL-C (mg/dL)	141±26	148±34	147±29	142±27	0.07
VLDL-C (mg/dL)	22.8 (18.2–33.5)	23.8 (16.0–32.2)	24.3 (17.4–36.4)	26.4 (17.8–37.2)	0.94
FFA (mmol/L)	0.4 (0.3–0.5)	0.4 (0.2–0.5)	0.4 (0.3–0.5)	0.4 (0.3–0.6)	0.07
Triglycerides (mg/dL)	114 (91–168)	119 (80–161)	122 (87–182)	132 (89–186)	0.94
Safety parameters					
Hemoglobin (g/dL)	14.4±1.1	14.1±1.0	14.6±1.0	14.4±1.1	0.58
WBCs (10^9/L)	6.2±1.5	5.9±1.4**	6.5±1.9	6.3±1.7	0.60
Neutrophils (%)	51.4±8.0	50.2±7.2	53.5±7.8	53.7±9.3	0.72
ALT (U/L)	26.5 (20.5–33.0)	19.0 (17.0–23.5)***	28.0 (23.0–48.0)	27.5 (23.0–46.0)	<0.0001
AST (U/L)	20.0 (18.0–23.0)	18.5 (15.0–22.0)*	20.0 (17.0–24.0)	21.0 (16.0–26.0)	0.003
γGT (U/L)	28.0 (21.0–36.5)	19.5 (14.0–26.5)***	35.5 (24.0–40.0)	32.0 (23.0–40.0)	<0.0001

Genovese Setal. AdvTher 2013; 30 (2) 190-202

DPPIV-Inhibitors

EXAMINE

Cardiovascular Outcomes With Alogliptin in Patients With Type 2 Diabetes Mellitus and Recent Acute Coronary Syndrome

William B. White, MD
for the EXAMINE Investigators
Cardiology Center, University of Connecticut
School of Medicine, Farmington, Connecticut
USA

September 2013 EUCAN/ALO/2013-10101

EXAMINE: studyobjecives and endpoints

Objective: To demonstrate that major CV event rates are not higher with alogliptin versus placebo in Type 2 diabetes patients with recent acute coronary syndrome (ACS) who are receiving standard of care for diabetes and secondary CV prevention

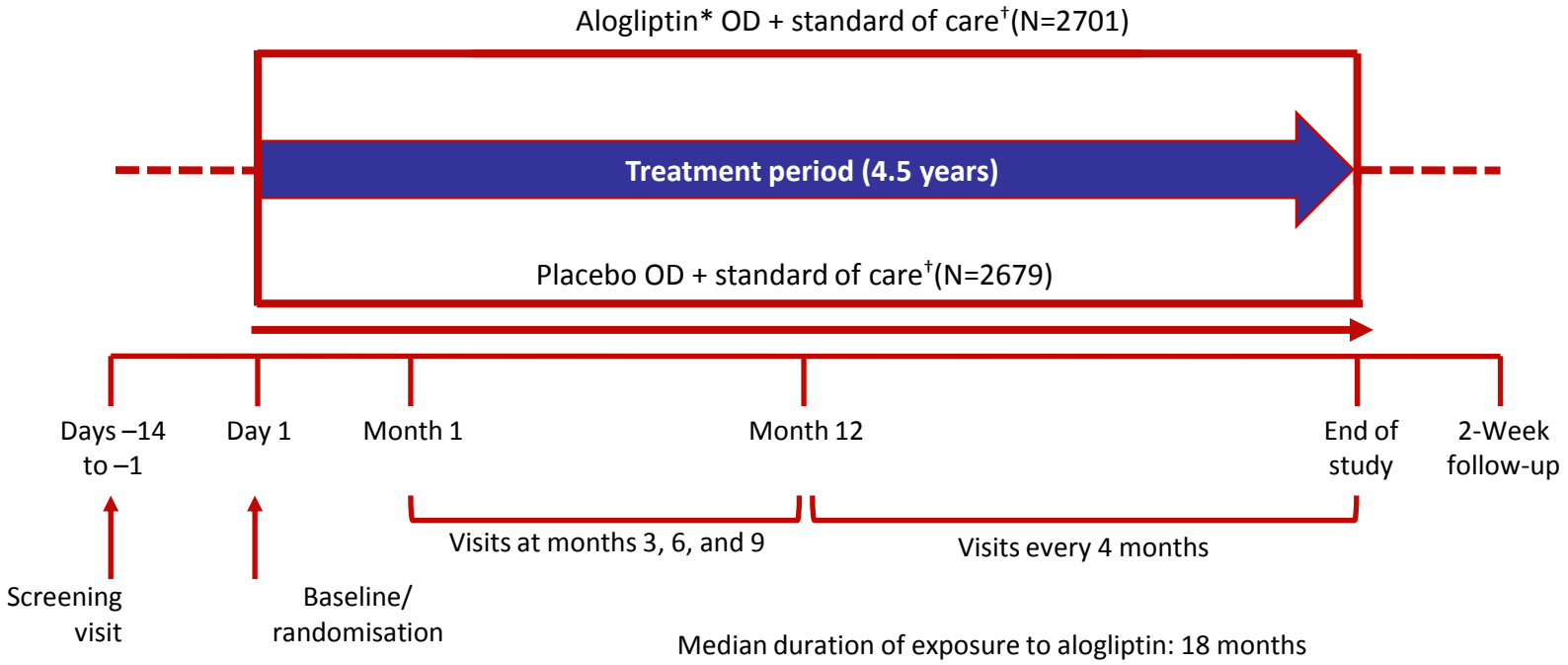
Primary endpoint	• Composite endpoint of major adverse cardiovascular events (MACE), defined as first occurrence of CV death, nonfatal myocardial infarction and nonfatal stroke
Secondary endpoint	• Time from randomisation to first occurrence of MACE plus urgent revascularisation due to unstable angina within 24 hours after hospital admission
Exploratory endpoints	• Death from CV causes • Death from any cause
Safety endpoints	• Incidence of angioedema, hypoglycaemia, pancreatitis, cancer, renal function*, ECGs • Standard safety endpoints and laboratory testing

*Changes in serum creatinine and eGFR, including the incidence of marked abnormalities and incidences of renal dialysis and kidney transplant

1. White WB, et al. *Am Heart J*. 2011;162(4):620–626
2. White WB, et al. *N Engl J Med*2013;369:1327-1335
3. EXAMINE Final Clinical Study Report SYR-332_402

Study design

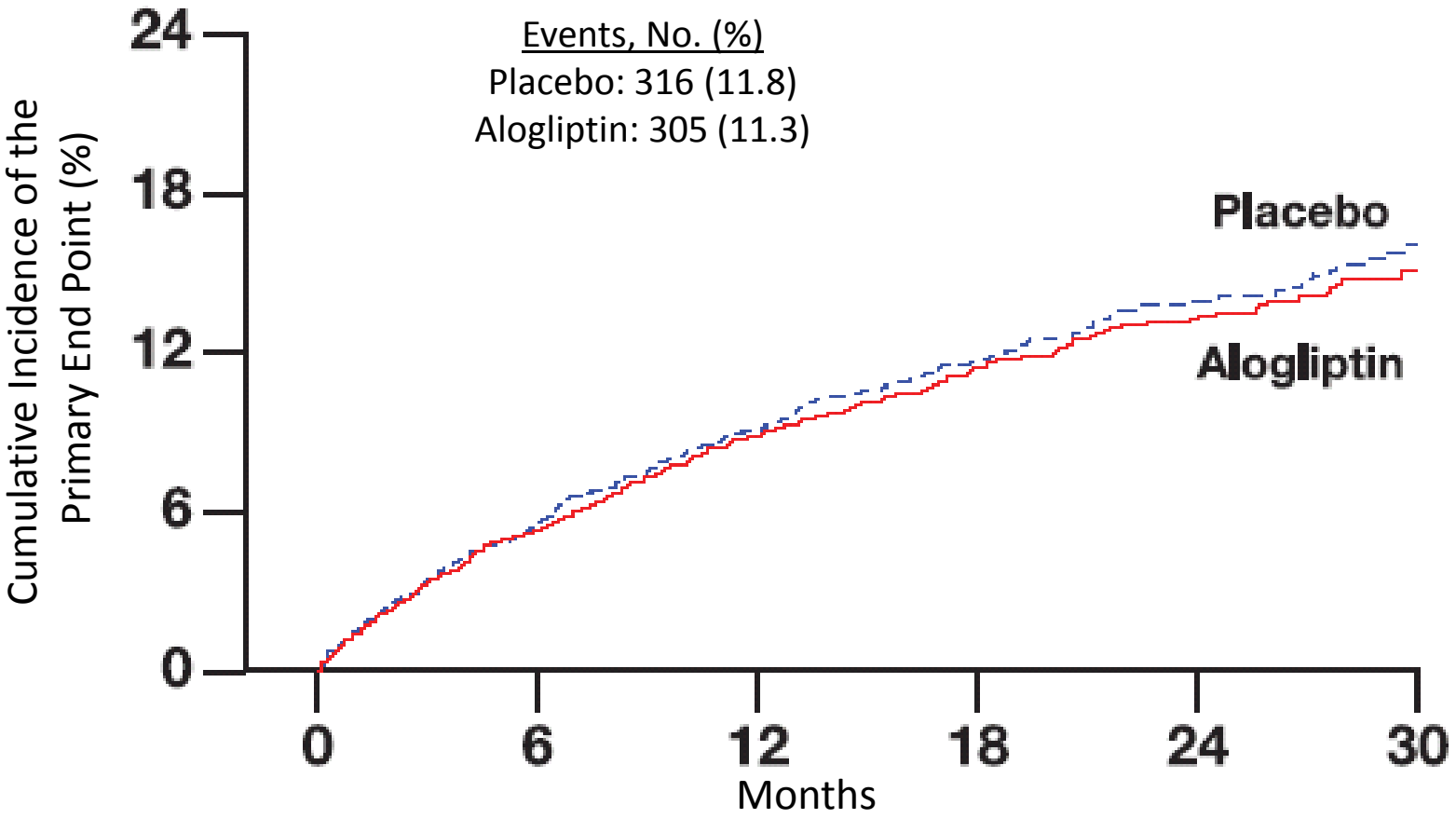
International, randomised, double-blind, placebo-controlled study of alogliptin with diabetes standard of care versus placebo with diabetes and cardiovascular standard of care



OD=once daily. *At randomisation, patients were assigned to receive 25, 12.5, or 6.25mg OD based on renal function. After randomisation, dose adjustments were allowed on the basis of changes in renal function. †Investigators were permitted to adjust any antidiabetictherapy in alogliptin and placebo arms if required (with the exception of the addition of a DPP-4 inhibitor or GLP-1 analogue)

White WB et al. *N Engl J Med.*2013;369:1327–1335

Time to Primary End Point (CV Death, Nonfatal MI, Nonfatal Stroke)



Hazard ratio, 0.96 (* one-sided repeated CI bound, 1.16)

White WB, et al. *N Engl J Med* 2013;369:1327–1335

Primary End Point by Components

	Alogliptin (N=2701)	Placebo (N=2679)	HR for Alogliptin Group (95% CI)
Primary end point: CV death, nonfatal MI, or nonfatal stroke, No. (%)	305 (11.3)	316 (11.8)	0.96 (≤1.16)*
CV death	89 (3.3)	111 (4.1)	0.79 (0.60 to 1.04)
Nonfatal MI	187 (6.9)	173 (6.5)	1.08 (0.88 to 1.33)
Nonfatal stroke	29 (1.1)	32 (1.2)	0.91 (0.55 to 1.50)

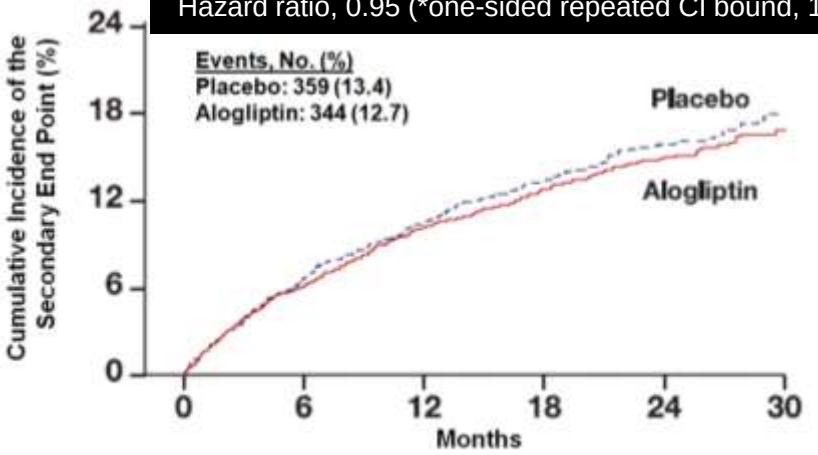
*99% one-sided confidence interval, P<0.001 for non-inferiority

White WB, et al. *N Engl J Med* 2013;369:1327–1335

Other End Points

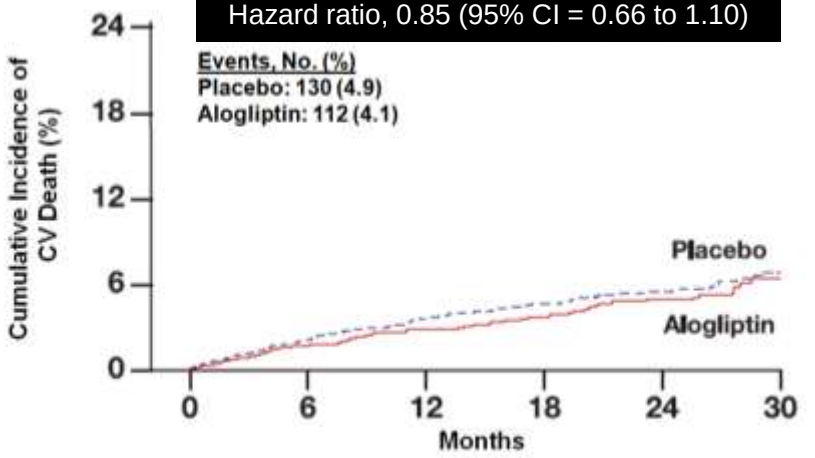
Secondary End Point

Hazard ratio, 0.95 (*one-sided repeated CI bound, 1.14)



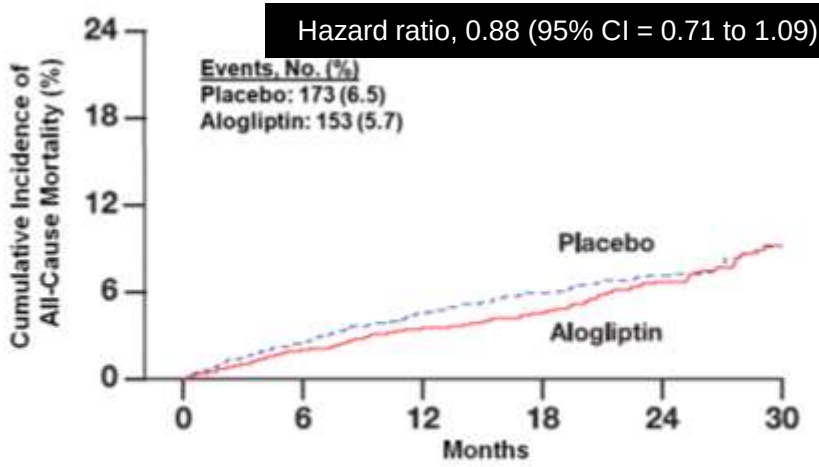
Placebo (n):	2679	2275	1861	1345	784	278
Alogliptin (n):	2701	2297	1873	1373	806	287

Hazard ratio, 0.85 (95% CI = 0.66 to 1.10)



Placebo (n):	2679	2384	1996	1477	889	324
Alogliptin (n):	2701	2402	2023	1504	894	320

Hazard ratio, 0.88 (95% CI = 0.71 to 1.09)



Placebo (n):	2679	2384	1996	1477	889	324
Alogliptin (n):	2701	2401	2023	1504	894	320

White WB, et al. *N Engl J Med*. 2013. [Epub ahead of print]

GLP1-RA

Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 (Lixisenatide) (ELIXA)

- Primary Objective:
  - To demonstrate that lixisenatide can reduce cardiovascular morbidity and mortality [composite endpoint of cardiovascular (CV) death, non-fatal myocardial infarction (MI), non-fatal stroke, hospitalization for unstable angina] compared to placebo in type 2 diabetic patients who recently experienced an acute coronary syndrome (ACS) event.
- Secondary Objectives:
  - To demonstrate that when compared to placebo, lixisenatide can reduce:
    - composite endpoint of cardiovascular death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, or hospitalization for heart failure
    - composite endpoint of cardiovascular death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, hospitalization for heart failure, or coronary revascularization procedure
    - urinary albumin excretion (based on the urinary albumin/creatinine ratio).
  - To assess the safety and tolerability of lixisenatide.

https://clinicaltrials.gov/ct2/show/NCT01147250?term=elixa&rank=1

Sulfonylureas

SU and Heart

- Tutte le SU (glimepiride compresa) riducono il flusso coronarico a riposo (LegtenbergR 1999 e 2001)
- Possibile riduzione del sopraslivellamentodel tratto ST nei pazienti in trattamento con SU (Huizar 2003)
- Dati contrastanti su un possibile effetto proaritmico della glibenclamide (NajeedS 2002, DheinS 2000)
- Effetti negativi della glibenclamide sulla contrattilità ventricolare nel coniglio in confronto alla metformina (RenJ 1999) e nell'uomo con DM2 in confronto all'insulina (Scognamiglio R 2002)

Sulfonylureasattenuate electrocardiographicST-Segmentelevationduringan acute myocardialinfarction in diabetics

I pazienti diabetici in trattamento con sulfonilurea corrono un rischio maggiore di non soddisfare i criteri per un trattamento trombolitico immediato

Huizar JF et al J Am CollCardiol 2003

SU e precondizionamento ischemico

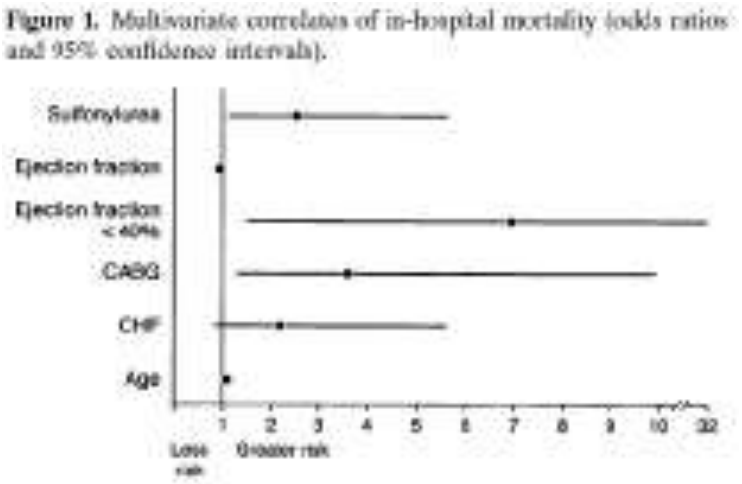
- Le SU inibiscono i canali del potassio ATP sensibili con depolarizzazione cellulare ed innalzamento del calcio intracellulare (Terzic A 1995, Ashcroft S 1992)
- In questo modo bloccano il precondizionamento (EnglerR 1996, Cleveland J 1997, Tomai F 1994)
- Cuori isolati di animali: le SU, tranne la glimepiride, annullano il precondizionamento, particolarmente la glibenclamide (HorimotoH 2002, GribbleF 1998, LegtenbergR 2001, MocanuM 2001, Nieszner E 2002)
- Occlusione sperimentale acuta di una coronaria nell'uomo, confronto doppio cieco fra placebo, glibenclamide e glimepiride: la glibenclamide sopprime il precondizionamento ischemico (KlepzigH 1999)

Sulfonylureasand ischaemicpreconditioning. A double-blind, placebo-controlledevaluationofglimepiride and glibenclamide

I dati mostrano la differenza % fra la 2° e la 3° dilatazione del palloncino

KlepzigHet al Eur HeartJ 1999

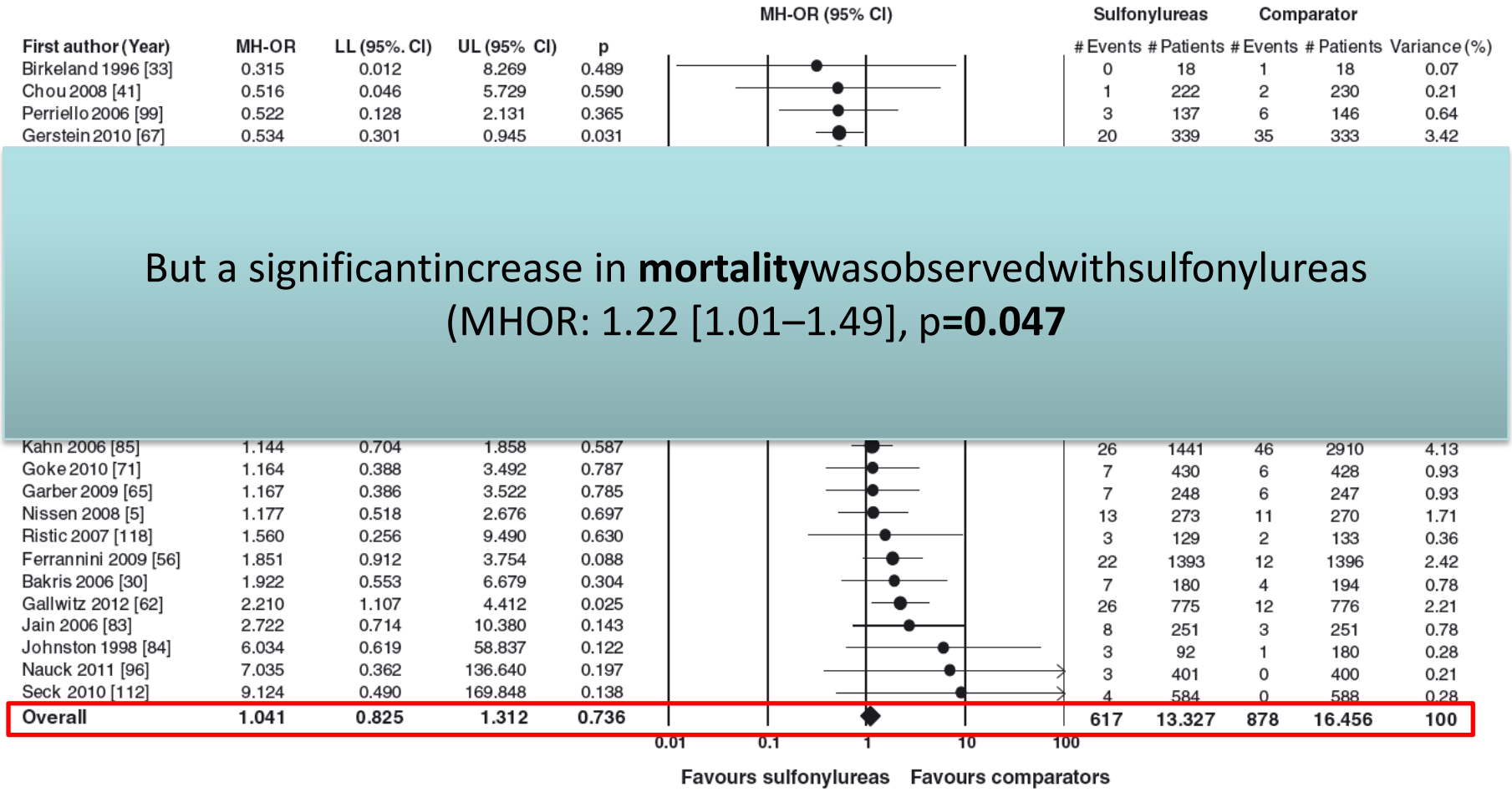
SU and PTCA



- O'Keefe (1998): La differenza di sopravvivenza fra PTCA e CABG si verifica solo nei pazienti diabetici trattati con SU

- Garratt (1999): I fattori di rischio per aumentata mortalità intra ospedaliera dopo angioplastica per IMA sono: LVEF < 40%, pregressa CABG, età e trattamento con SU

Cardiovascularsafetyofsulfonylureas: a meta-analysisofrandomizedclinicaltrials



But a significantincrease in **mortality**wasobservedwithsulfonylureas (MHOR: 1.22 [1.01–1.49], p=**0.047**

MonamiM, Genovese S, Mannucci E Diabetes Obes Metab. 2013 Oct;15(10):938-53.

Combination therapy with metformin plus sulphonylureas versus metformin plus DPP-4 inhibitors: association with major adverse cardiovascular events and all-cause mortality

Table 2. Sulphonylurea (SU) and dipeptidyl peptidase-4 inhibitor (DPP-4i) types at cohort entry and exit.

SU	SU generation	First prescription, n (%)		Last prescription, n (%)		DPP-4i	First prescription, n (%)		Last prescription, n (%)	
Gliclazide	2	30 301	(89.2)	30 297	(89.2)	Sitagliptin	5864	(74.6)	5857	(74.5)
Glimepiride	2	2337	(6.9)	2397	(7.1)	Saxagliptin	996	(12.7)	1012	(12.9)
Glipizide	2	896	(2.6)	883	(2.6)	Vildagliptin	730	(9.3)	678	(8.6)
Glibenclamide	2	330	(1.0)	279	(0.8)	Linagliptin	274	(3.5)	317	(4.0)
Tolbutamide	1	119	(0.4)	127	(0.4)					
		33 983	(100.0)	33 983	(100.0)		7864	(100.0)	7864	(100.0)

Table 3. Events, crude rates, risk ratios and adjusted hazard ratios (aHRs) for all-cause mortality in patients treated with metformin plus sulphonylurea (SU) versus metformin plus dipeptidyl peptidase-4 inhibitor (DPP-4i) dual therapy.

Study design	Cohort (in combination with metformin)	n	Events	Crude rates (per 1000 person-years)	Crude risk ratio (95% CI)	aHR (95% CI)	p
All subjects	SU	33 983	1133	16.9	2.327 (1.864–2.904)	1.357 (1.076–1.710)	0.010
	DPP-4i	7864	84	7.3			
Directly matched	SU	5447	96	10.2	2.108 (1.466–3.076)	1.850 (1.245–2.749)	<0.001
	DPP-4i	5447	40	4.9			
Propensity-matched	SU	6901	121	10.7	1.743 (1.289–2.379)	1.497 (1.092–2.052)	0.012
	DPP-4i	6901	63	6.2			

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Combination therapy with metformin plus sulphonylureas versus metformin plus DPP-4 inhibitors: association with major adverse cardiovascular events and all-cause mortality

Table 4. Events, crude rates, risk ratios and adjusted hazard ratios (aHRs) for first major adverse cardiovascular events (MACE) in patients treated with metformin plus sulphonylurea (SU) versus metformin plus dipeptidyl peptidase-4 inhibitor (DPP-4i) dual therapy.

Study design	Cohort (in combination with metformin)	n*	Events	Crude rates (per 1000 person-years)	Crude risk ratio (95% CI)	aHR (95% CI)	p
All subjects	SU	29 865	661	11.3	2.145 (1.629–2.824)	1.710 (1.280–2.285)	<0.001
	DPP-4i	7091	55	5.3			
Directly matched	SU	4423	58	7.7	1.469 (0.965–2.234)	1.323 (0.832–2.105)	0.237
	DPP-4i	4423	35	5.2			
Propensity-matched	SU	6175	88	8.8	1.688 (1.191–2.414)	1.547 (1.076–2.225)	0.019
	DPP-4i	6229	48	5.2			

*With no prior MACE.

Directly Matched Cohorts: Exposed (metformin plus DPP-4i) patients were matched to non-exposed (metformin plus SU) patients by age (±2 years), gender, year of index exposure, diabetes duration (±1 year), BMI (±3 kg/m2), serum creatinine (±10 μmol/L) and HbA1c [±1% (±11 mmol/mol)].

Propensity-matched Cohorts: Exposed patients were matched to non-exposed patients by propensity score, incorporating age, gender, year of index exposure, diabetes duration, BMI, serum creatinine, total cholesterol, SBP, GP contacts in the 12 months to index date, HbA1c, Charlson index, smoking status and line of therapy.

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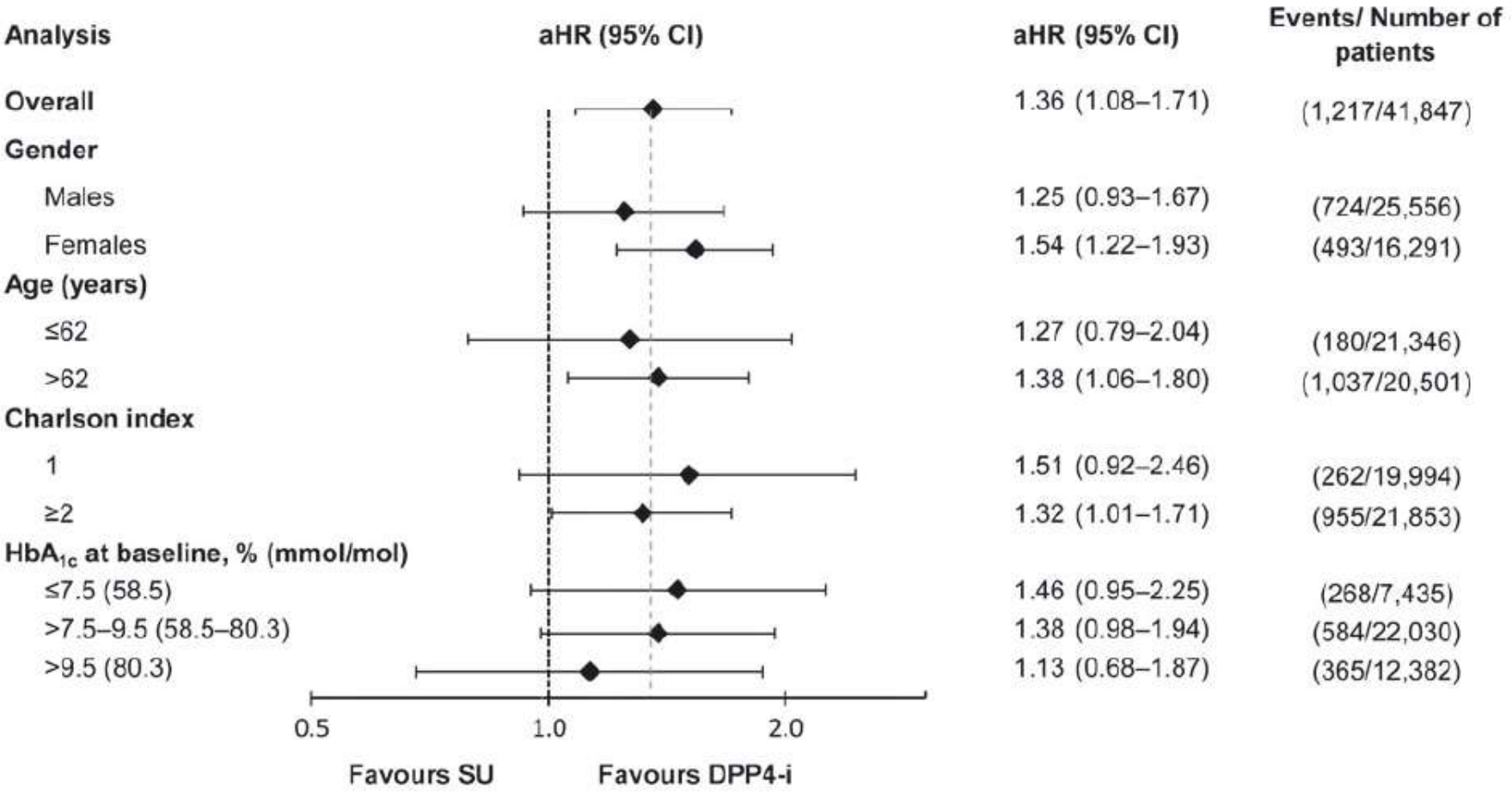

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Ceterumcenseosulfonilurea esse delendam

Adattata da:

Marco Porcio Catone “il Vecchio” 234 AC – 149 AC