La terapia ipoglicemizzante nell'anziano diabetico

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Caso Clinico

- D.C., di anni 80, sesso maschile, sposato con figli, ex impiegato statale. Peso kg. 90, altezza cm. 175. Ex fumatore
- Diabete mellito di tipo 2 diagnosticato all'età di 65 anni, in occasione di un infarto acuto del miocardio. Nello stessa circostanza anche diagnosi di ipertensione arteriosa.
- Da alcuni mesi modica dispnea dopo sforzo, modesti edemi perimalleolari serotini. Riferisce anche 2 episodi di ipoglicemia sintomatica nel tardo pomeriggio/prima di cena, risoltisi con l'assunzione di zucchero per os

Principali dati clinici

- Condizioni generali buone. PA 140/80. FC 64 bpm. Rinforzo II tono aortico. Modica epatomegalia. Succulenza perimalleolare.
- Terapia praticata:
  - glibenclamide + metformina 1 c. pranzo e ½ c. a cena
  - enalapril+idroclorotiazide 1 c/die
  - ASA 100 mg/die
  - simvastatina 40 mg/die
  - atenololo 50 mg/die

Principali dati di laboratorio

- HbA1c 7.2%
- Glicemia a digiuno 110-130 mg/dl, postprandiale 120-170
- Colesterolo totale 154, HDL 38, trigliceridi 186
- Creatininemia 1.4, creatinina clearance 76 ml/min, albuminuria 80 mg/24 h

Principali dati strumentali

- Ecocardiogramma: cardiopatia ischemico-ipertensiva, FEV 45%
- Fundus oculi: retinopatia non proliferante
- Ecocolordoppler vasi sopraortici: scleroateromasia diffusa con stenosi plurisegmentarie 30-40%

In questo paziente…

- Quali dovrebbero essere gli obiettivi glicemici ?
- Con quali farmaci andrebbero raggiunti ?

Standard Italiani per la Cura del Diabete Mellito

Obiettivi glicemici in diabetici adulti di tipo 1 e 2

$HbA_{1c} < 7,0\%$* (< 6,5% in singoli pazienti)
Glicemia a digiuno e pre-prandiale 70-130 mg/dl
Glicemia post-prandiale§ < 180 mg/dl§#

*Facendo riferimento ai valori di 4,0-6,0% della popolazione non diabetica, con il metodo utilizzato dal DCCT.

§La misurazione della glicemia post-prandiale deve essere effettuata 2 ore dopo l'inizio del pasto.

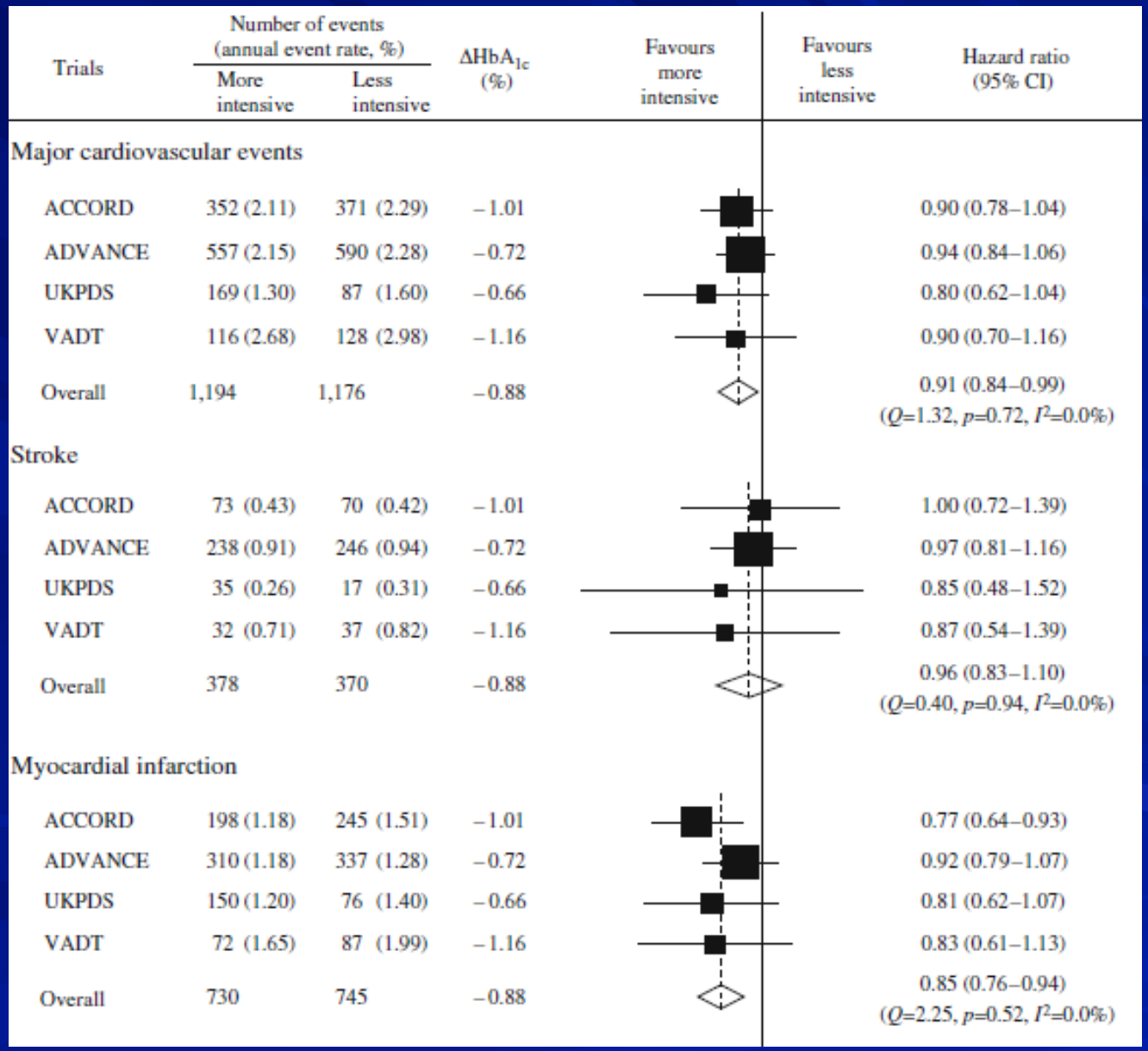
#Valori post-prandiali < 140 mg/dl sono perseguibili nel diabete tipo 2 (IDF 2007).

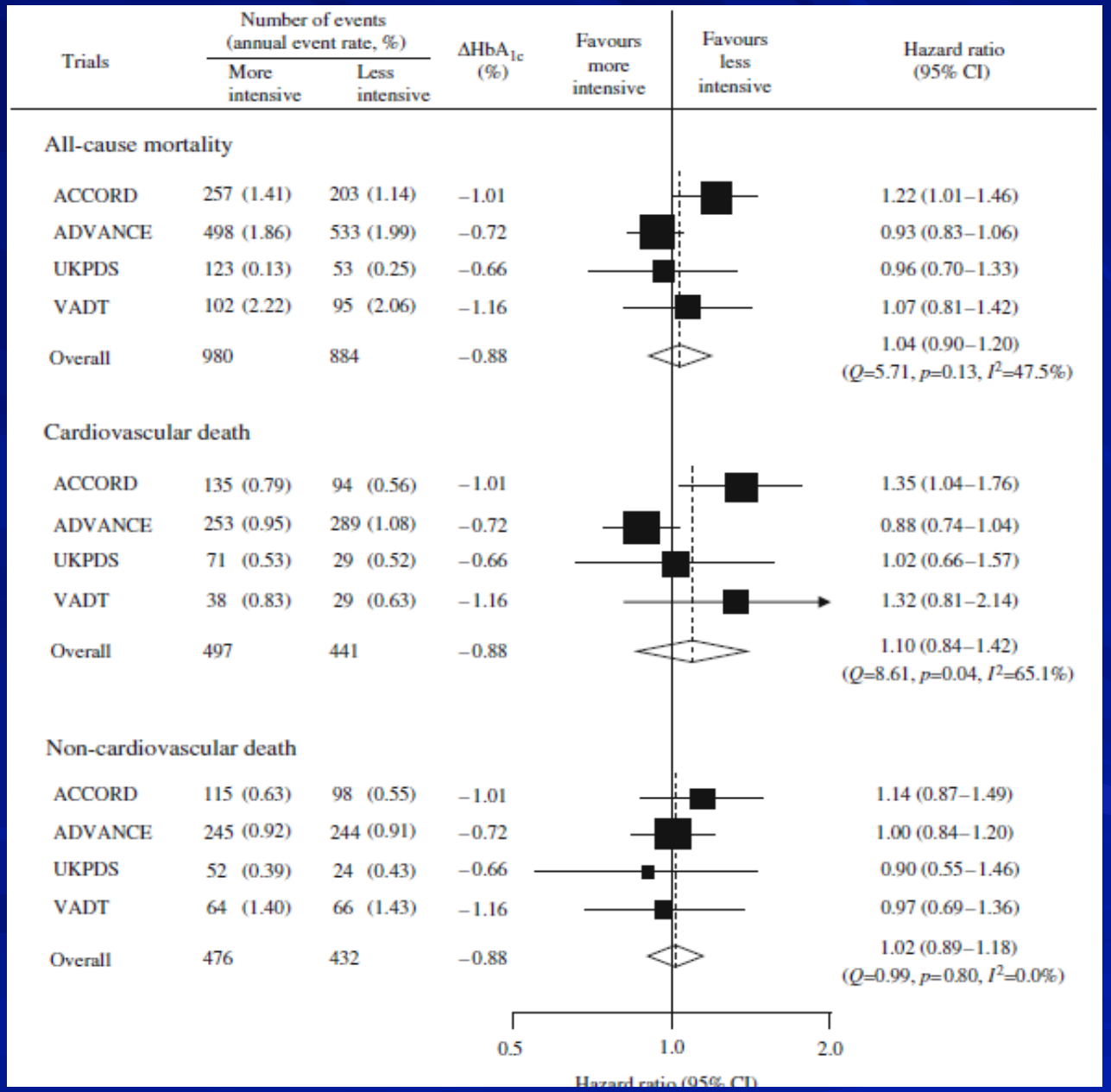
Diabetologia (2009) 52:2288–2298
DOI 10.1007/s00125-009-1470-0

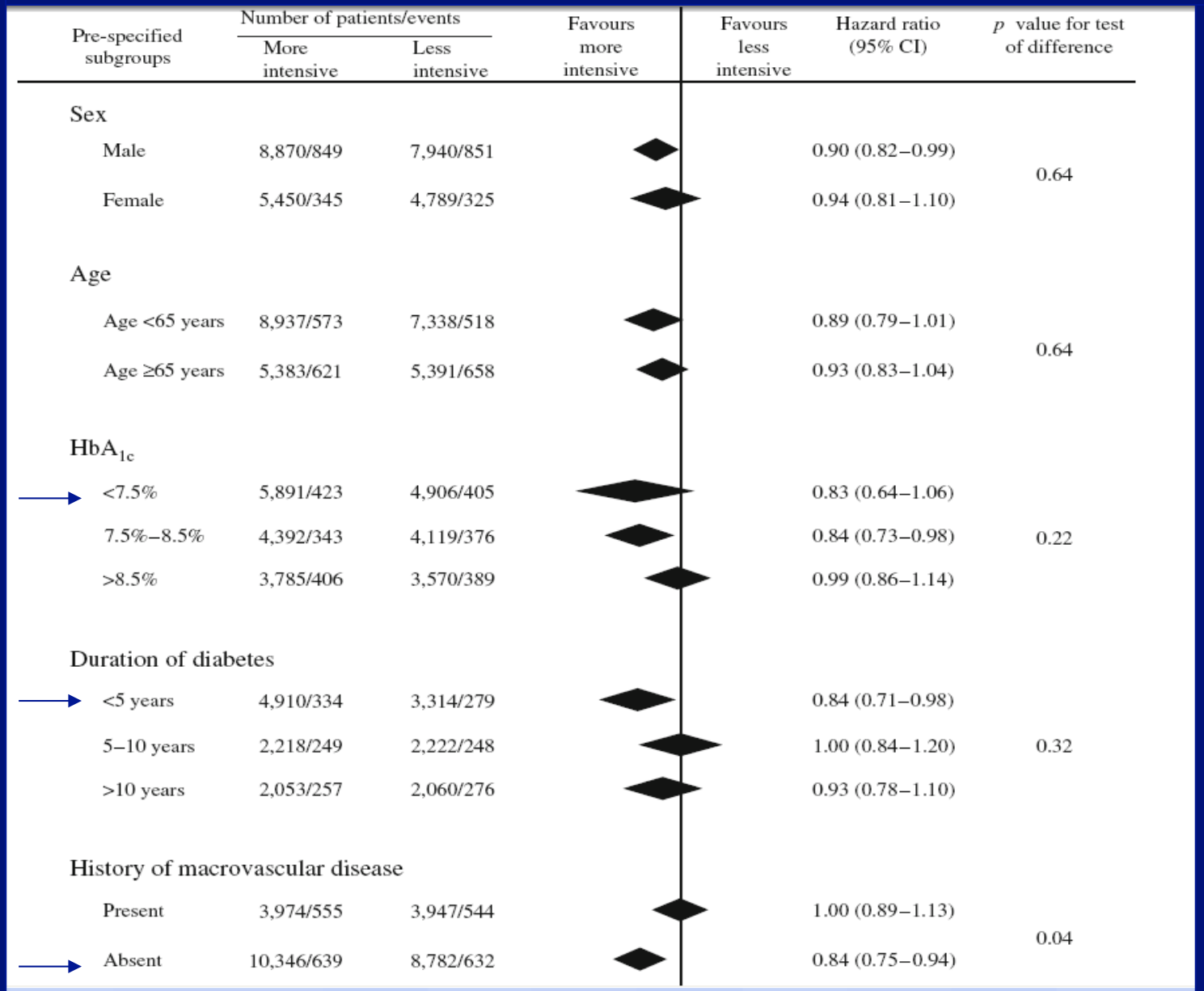
META-ANALYSIS

Intensive glucose control and macrovascular outcomes in type 2 diabetes

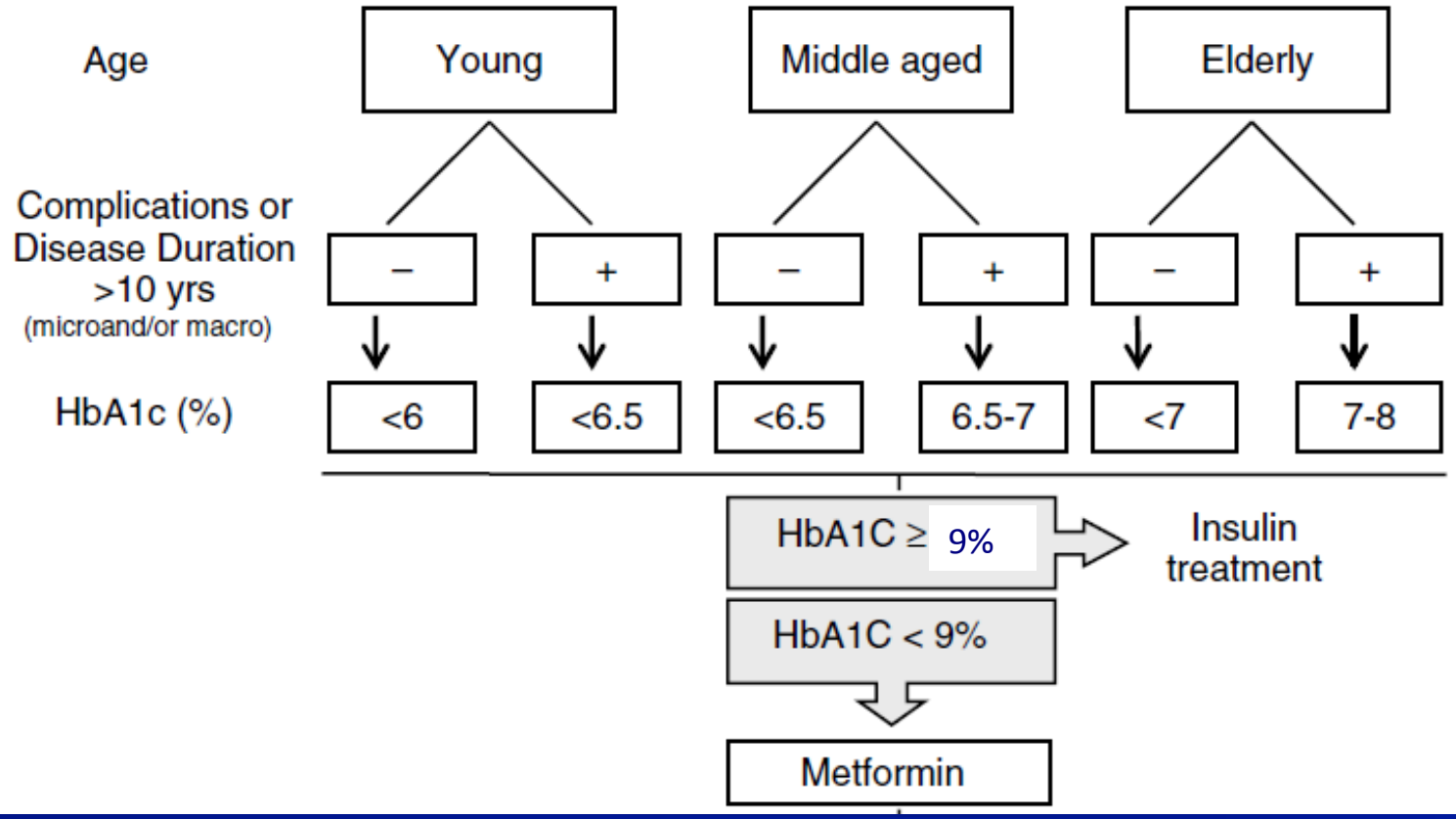
F. M. Turnbull · C. Abraira · R. J. Anderson · R. P. Byington · J. P. Chalmers · W. C. Duckworth · G. W. Evans · H. C. Gerstein · R. R. Holman · T. E. Moritz · B. C. Neal · T. Ninomiya · A. A. Patel · S. K. Paul · F. Travert · M. Woodward


Trials
Number of events (annual event rate, %)
More intensive
Less intensive
ΔHbA1c (%)
Favours more intensive
Favours less intensive
Hazard ratio (95% CI)
Major cardiovascular events
ACCORD 352 (2.11) 371 (2.29) −1.01 0.90 (0.78–1.04)
ADVANCE 557 (2.15) 590 (2.28) −0.72 0.94 (0.84–1.06)
UKPDS 169 (1.30) 87 (1.60) −0.66 0.80 (0.62–1.04)
VADT 116 (2.68) 128 (2.98) −1.16 0.90 (0.70–1.16)
Overall 1,194 1,176 −0.88 0.91 (0.84–0.99)
(Q=1.32, p=0.72, I²=0.0%)
Stroke
ACCORD 73 (0.43) 70 (0.42) −1.01 1.00 (0.72–1.39)
ADVANCE 238 (0.91) 246 (0.94) −0.72 0.97 (0.81–1.16)
UKPDS 35 (0.26) 17 (0.31) −0.66 0.85 (0.48–1.52)
VADT 32 (0.71) 37 (0.82) −1.16 0.87 (0.54–1.39)
Overall 378 370 −0.88 0.96 (0.83–1.10)
(Q=0.40, p=0.94, I²=0.0%)
Myocardial infarction
ACCORD 198 (1.18) 245 (1.51) −1.01 0.77 (0.64–0.93)
ADVANCE 310 (1.18) 337 (1.28) −0.72 0.92 (0.79–1.07)
UKPDS 150 (1.20) 76 (1.40) −0.66 0.81 (0.62–1.07)
VADT 72 (1.65) 87 (1.99) −1.16 0.83 (0.61–1.13)
Overall 730 745 −0.88 0.85 (0.76–0.94)
(Q=2.25, p=0.52, I²=0.0%)


Trials
Number of events (annual event rate, %)
More intensive
Less intensive
ΔHbA1c (%)
Favours more intensive
Favours less intensive
Hazard ratio (95% CI)
All-cause mortality
ACCORD 257 (1.41) 203 (1.14) −1.01 1.22 (1.01–1.46)
ADVANCE 498 (1.86) 533 (1.99) −0.72 0.93 (0.83–1.06)
UKPDS 123 (0.13) 53 (0.25) −0.66 0.96 (0.70–1.33)
VADT 102 (2.22) 95 (2.06) −1.16 1.07 (0.81–1.42)
Overall 980 884 −0.88 1.04 (0.90–1.20)
(Q=5.71, p=0.13, I²=47.5%)
Cardiovascular death
ACCORD 135 (0.79) 94 (0.56) −1.01 1.35 (1.04–1.76)
ADVANCE 253 (0.95) 289 (1.08) −0.72 0.88 (0.74–1.04)
UKPDS 71 (0.53) 29 (0.52) −0.66 1.02 (0.66–1.57)
VADT 38 (0.83) 29 (0.63) −1.16 1.32 (0.81–2.14)
Overall 497 441 −0.88 1.10 (0.84–1.42)
(Q=8.61, p=0.04, I²=65.1%)
Non-cardiovascular death
ACCORD 115 (0.63) 98 (0.55) −1.01 1.14 (0.87–1.49)
ADVANCE 245 (0.92) 244 (0.91) −0.72 1.00 (0.84–1.20)
UKPDS 52 (0.39) 24 (0.43) −0.66 0.90 (0.55–1.46)
VADT 64 (1.40) 66 (1.43) −1.16 0.97 (0.69–1.36)
Overall 476 432 −0.88 1.02 (0.89–1.18)
(Q=0.99, p=0.80, I²=0.0%)
0.5
1.0
2.0
Hazard ratio (95% CI)


Pre-specified subgroups
Number of patients/events
More intensive
Less intensive
Favours more intensive
Favours less intensive
Hazard ratio (95% CI)
p value for test of difference
Sex
Male 8,870/849 7,940/851 0.90 (0.82–0.99)
0.64
Female 5,450/345 4,789/325 0.94 (0.81–1.10)
Age
Age <65 years 8,937/573 7,338/518 0.89 (0.79–1.01)
0.64
Age ≥65 years 5,383/621 5,391/658 0.93 (0.83–1.04)
HbA1c
<7.5% 5,891/423 4,906/405 0.83 (0.64–1.06)
7.5%–8.5% 4,392/343 4,119/376 0.84 (0.73–0.98) 0.22
>8.5% 3,785/406 3,570/389 0.99 (0.86–1.14)
Duration of diabetes
<5 years 4,910/334 3,314/279 0.84 (0.71–0.98)
5–10 years 2,218/249 2,222/248 1.00 (0.84–1.20) 0.32
>10 years 2,053/257 2,060/276 0.93 (0.78–1.10)
History of macrovascular disease
Present 3,974/555 3,947/544 1.00 (0.89–1.13)
0.04
Absent 10,346/639 8,782/632 0.84 (0.75–0.94)

Proposta di differenti strategie e obiettivi terapeutici nel diabete di tipo 2



Diabetes Metab Res Rev, 2010

Standard Italiani per la Cura del Diabete Mellito 2010

RACCOMANDAZIONI

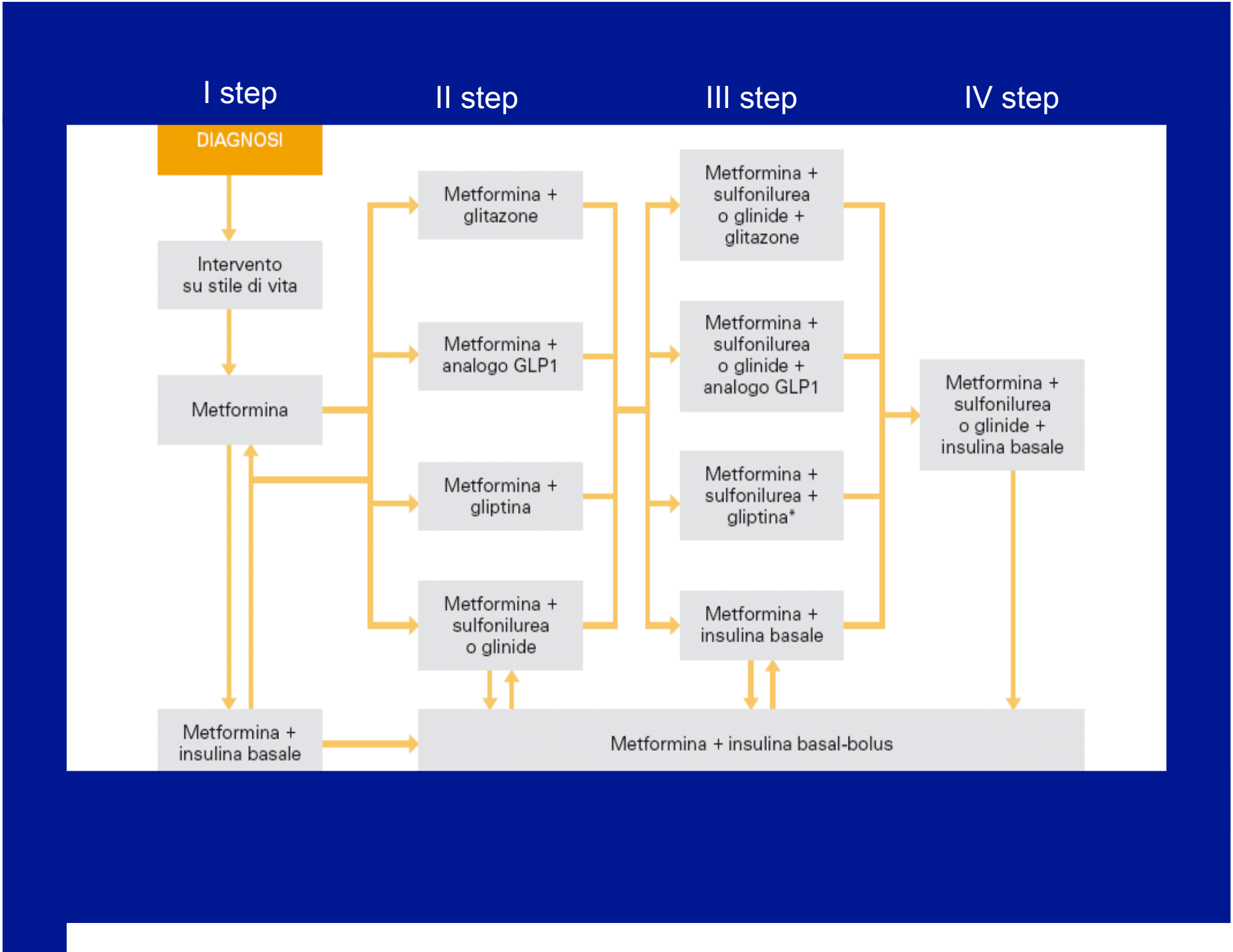
Il compenso glicemico e il trattamento ipoglicemizzante

- Nei diabetici anziani gli obiettivi glicemici dovrebbero essere individualizzati. Se le condizioni generali sono relativamente buone, il valore di HbA_{1c} potrà essere compreso tra 6,5 e 7,5%. (**Livello della prova VI, Forza della raccomandazione B**)

- Negli anziani fragili (con complicanze, affetti da demenza, con pluripatologie, nei quali il rischio di ipoglicemia è alto e nei quali i rischi di un controllo glicemico intensivo superino i benefici attesi) è appropriato un obiettivo meno restrittivo, con valori di HbA_{1c} compresi tra 7,5 e 8,5%. (**Livello della prova VI, Forza della raccomandazione B**)

In questo paziente…

- Quali dovrebbero essere gli obiettivi glicemici ?
- Con quali farmaci andrebbero raggiunti ?

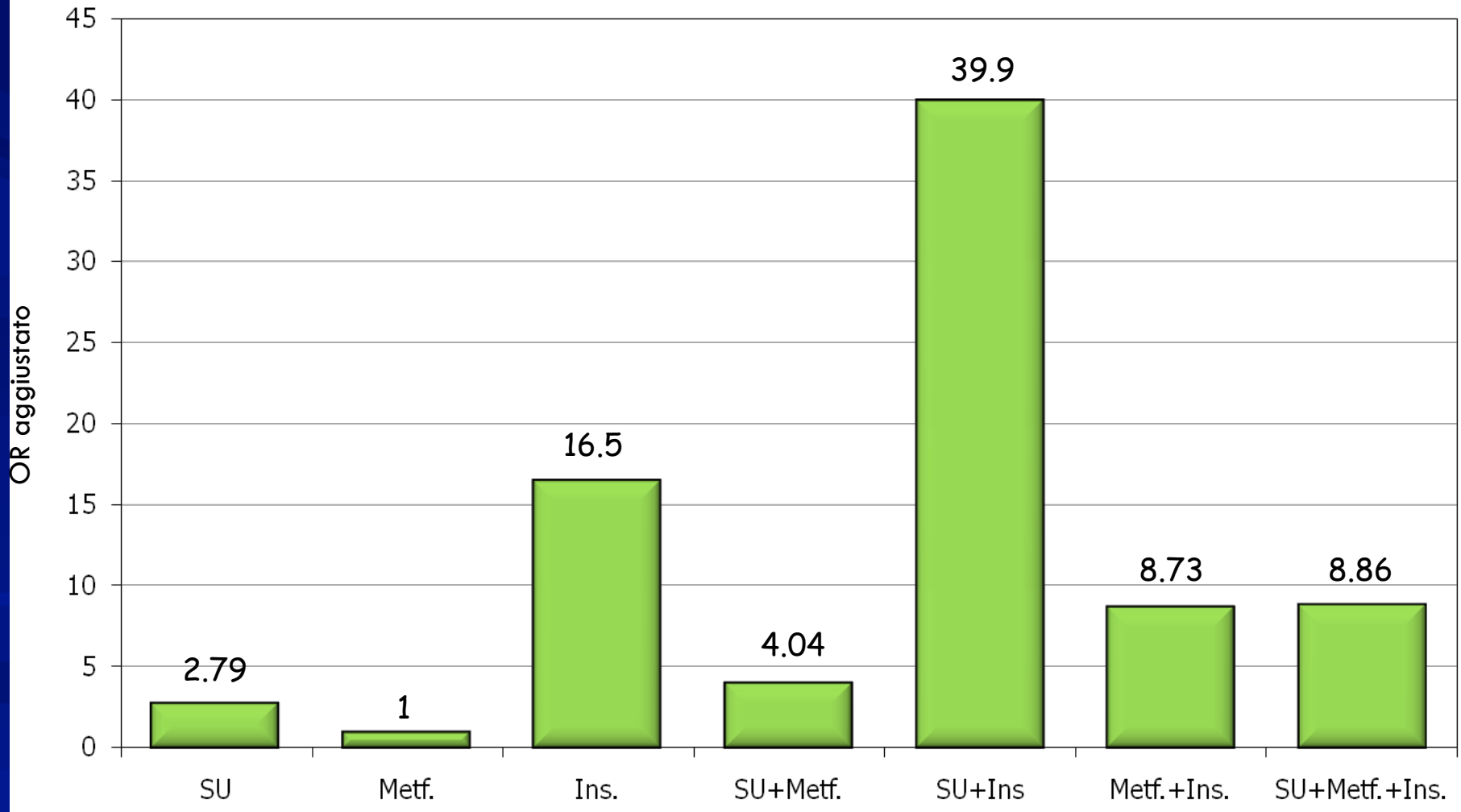

I step
II step
III step
IV step
DIAGNOSI
Intervento su stile di vita
Metformina
Metformina + insulina basale
Metformina + glitazone
Metformina + analogo GLP1
Metformina + gliptina
Metformina + sulfonilurea o glinide
Metformina + sulfonilurea o glinide + glitazone
Metformina + sulfonilurea o glinide + analogo GLP1
Metformina + sulfonilurea + gliptina*
Metformina + insulina basale
Metformina + sulfonilurea o glinide + insulina basale
Metformina + insulina basal-bolus

Farmaci ipoglicemizzanti orali
Principali effetti collaterali/eventi avversi

- Sulfoniluree *(repaglinide):*
  - Ipoglicemia
  - Aumento di peso
- Acarbose:
  - Intolleranza gastrointestinale
- Metformina:
  - Intolleranza gastrointestinale
  - Acidosi lattica (molto rara)
- Glitazoni:
  - Edemi/scompenso cardiaco
  - Aumento di peso
  - Rischio di fratture (nelle donne)
  - Rischio cardiovascolare (rosiglitazone)*?*
- Inibitori DPP-IV:
  - Non noti

Metformin, Sulfonylureas, or Other Antidiabetes Drugs and the Risk of Lactic Acidosis or Hypoglycemia

A nested case-control analysis



Modificato da: Bodmer M, Diabetes Care 2008, 31: 2086-2091

- Se in un soggetto anziano è indicata una terapia con antidiabetici orali, non è opportuno l'utilizzo di clorpropamide e glibenclamide. (**Livello della prova V, Forza della raccomandazione B**)

- In diabetici anziani la metformina è utilizzabile con cautela fino a un VFG stimato di 30 $ml \cdot min^{-1} \cdot 1{,}73m^{-2}$, purché siano attentamente considerati i fattori di rischio di peggioramento della funzione renale; al di sotto di tali valori non è opportuno l'uso di metformina, dato il maggior rischio di acidosi lattica. (**Livello della prova IV, Forza della raccomandazione B**)

- In diabetici anziani trattati con metformina il controllo del filtrato glomerulare stimato dovrebbe essere effettuato almeno una volta all'anno e in occasione di ogni incremento posologico. (**Livello della prova VI, Forza della raccomandazione C**)

NEPHROLOGY

Nephrology **15** (2010) 412–418

Review Article

Review: Metformin: Potential benefits and use in chronic kidney disease

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While the use of metformin should remain contraindicated in dialysis patients, it is possible that its use in patients with CKD and after renal transplantation would result in cardiovascular and survival benefits. Thus the recommendations of the Australian Diabetes Guidelines to liberalize the GFR guidelines for the use of metformin appear sensible. A clear GFR cut-off has not been established in the literature; however, the risk of lactic acidosis is extremely low while the potential benefits are substantial.

Risk of Acute Myocardial Infarction, Stroke, Heart Failure, and Death in Elderly Medicare Patients Treated With Rosiglitazone or Pioglitazone

David J. Graham, MD, MPH
Rita Ouellet-Hellstrom, PhD
Thomas E. MaCurdy, PhD
Farzana Ali, BA
Christopher Sholley, BS
Christopher Worrall, BS
Jeffrey A. Kelman, MD, MMSc

Context Studies have suggested that the use of rosiglitazone may be associated with an increased risk of serious cardiovascular events compared with other treatments for type 2 diabetes.

Objective To determine if the risk of serious cardiovascular harm is increased by rosiglitazone compared with pioglitazone, the other thiazolidinedione marketed in the United States.

Design, Setting, and Patients Nationwide, observational, retrospective, inception cohort of 227 571 Medicare beneficiaries aged 65 years or older (mean age, 74.4 years) who initiated treatment with rosiglitazone or pioglitazone through a Medicare Part D prescription drug plan from July 2006-June 2009 and who underwent follow-up for up to 3 years after thiazolidinedione initiation.

Main Outcome Measures Individual end points of acute myocardial infarction (AMI), stroke, heart failure, and all-cause mortality (death), and composite end point of AMI, stroke, heart failure, or death, assessed using incidence rates by thiazolidinedione, attributable risk, number needed to harm, Kaplan-Meier plots of time to event, and Cox proportional hazard ratios for time to event, adjusted for potential confounding factors, with pioglitazone as reference.

Results A total of 8667 end points were observed during the study period. The adjusted hazard ratio for rosiglitazone compared with pioglitazone was 1.06 (95% confidence interval [CI], 0.96-1.18) for AMI; 1.27 (95% CI, 1.12-1.45) for stroke; 1.25 (95% CI, 1.16-1.34) for heart failure; 1.14 (95% CI, 1.05-1.24) for death; and 1.18 (95% CI, 1.12-1.23) for the composite of AMI, stroke, heart failure, or death. The attributable risk for this composite end point was 1.68 (95% CI, 1.27-2.08) excess events per 100 person-years of treatment with rosiglitazone compared with pioglitazone. The corresponding number needed to harm was 60 (95% CI, 48-79) treated for 1 year.

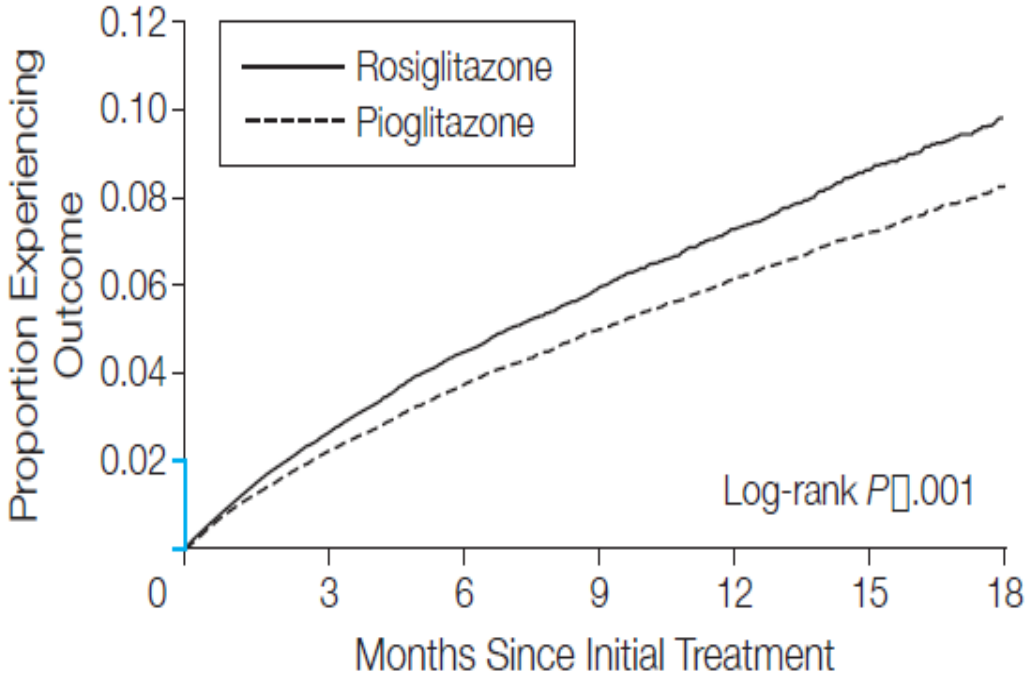
Conclusion Compared with prescription of pioglitazone, prescription of rosiglitazone was associated with an increased risk of stroke, heart failure, and all-cause mortality and an increased risk of the composite of AMI, stroke, heart failure, or all-cause mortality in patients 65 years or older.

JAMA. 2010;304(4):(doi:10.1001/jama.2010.920) www.jama.com

ROSIGLITAZONE AND PIOGLITAZONE are the only thiazolidinediones currently marketed in the United States. In mid-2007, a meta-analysis of 42 randomized controlled trials involving rosiglitazone reported a 1.4-fold increase in risk of acute myocardial infarction (AMI) compared with non-thiazolidinedione therapies.[1] Subsequently, a meta-analysis of 19 randomized controlled trials with pioglitazone found a statistically significant reduction in the composite outcome of nonfatal AMI, stroke, and all-cause mortality and a nearly statistically significant reduction in nonfatal AMI alone,[2] thereby suggesting a potential difference in cardiovascular risk between the 2 thiazolidinediones.

The cardiovascular risks of rosiglita-

Figure 2. Kaplan-Meier Cumulative Incidence of Time to Event for the Composite of Acute Myocardial Infarction, Stroke, Heart Failure, and All-Cause Mortality in Elderly Medicare Patients Treated With Rosiglitazone or Pioglitazone



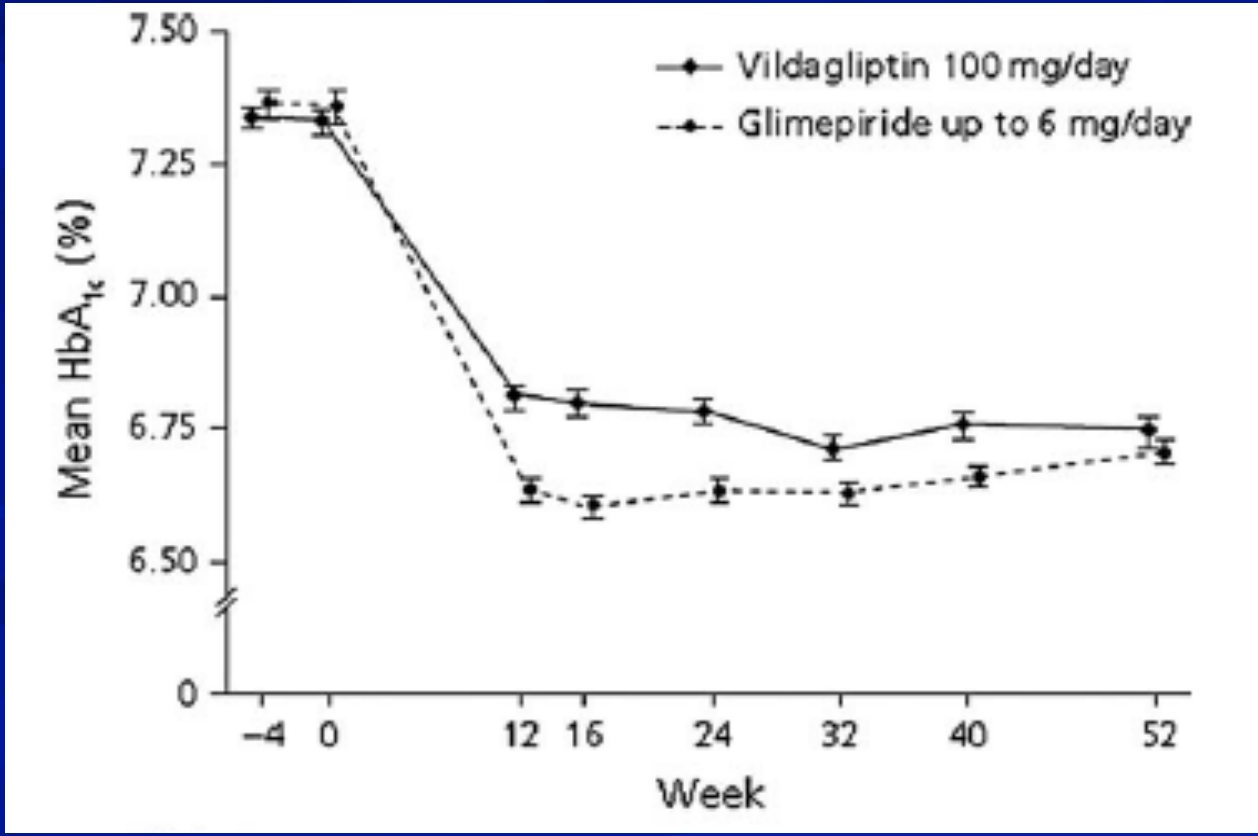
No. at risk							
Rosiglitazone	67 593	36 544	19 237	11 164	6606	4261	3063
Pioglitazone	159 978	86 281	47 929	31 096	21 083	14 486	10 132

ORIGINAL ARTICLE

doi: 10.1111/j.1463-1326.2008.00994.x

Fifty-two-week efficacy and safety of vildagliptin vs. glimepiride in patients with type 2 diabetes mellitus inadequately controlled on metformin monotherapy

E. Ferrannini,[1] V. Fonseca,[2] B. Zinman,[3] D. Matthews,[4] B. Ahrén,[5] S. Byiers,[6] Q. Shao[7] and S. Dejager[8]



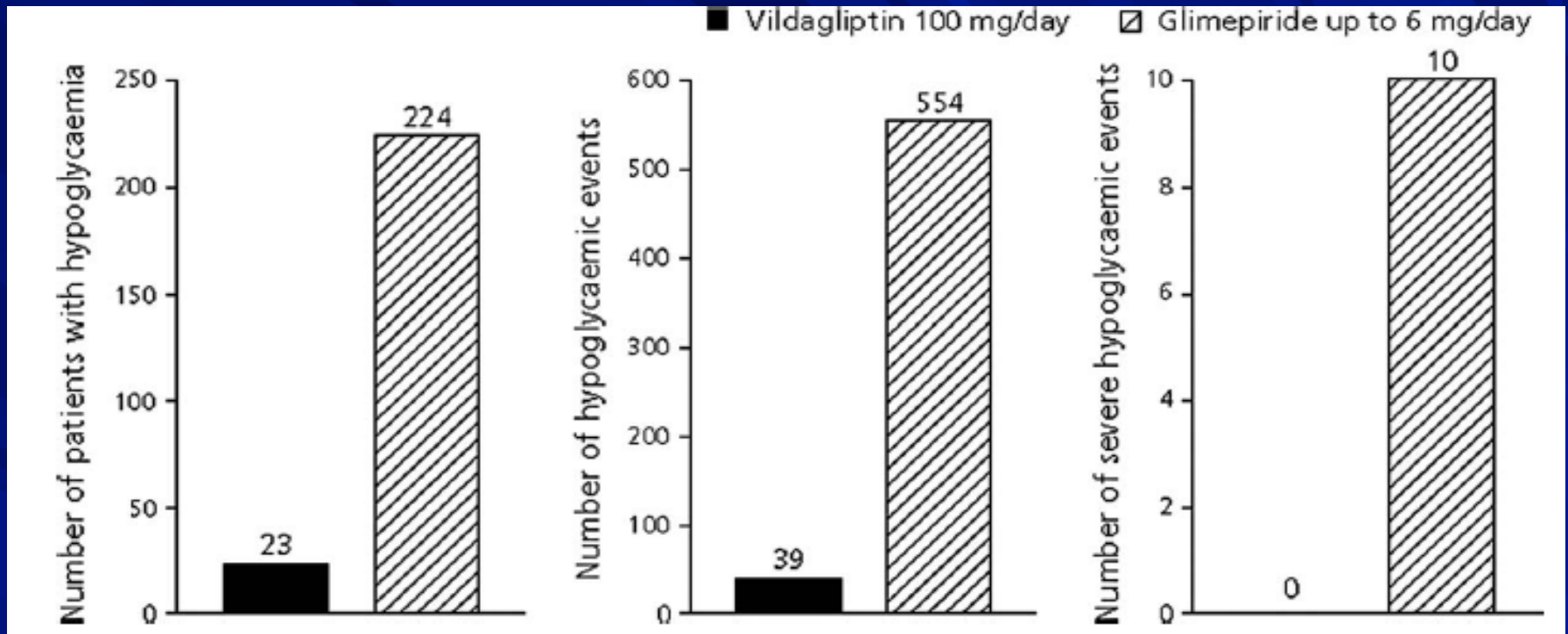


Fig. 4 Incidence and severity of hypoglycaemic events with vildagliptin and glimepiride during the 52-week treatment period (safety population).

analyses by age group also revealed a benefit with vildagliptin in the elderly (>65 years, n = 712, mean age of 68.4 years), with 10-fold fewer elderly patients experiencing a hypoglycaemic event in the vildagliptin group than in the glimepiride group (1.7 vs. 16.4% of patients respectively).

Treatment of Elderly Patients With Type 2 Diabetes Mellitus: A Systematic Review of the Benefits and Risks of Dipeptidyl Peptidase-4 Inhibitors

Sherwyn L. Schwartz, MD

Cetero Research, San Antonio, Texas; Founder and Director, Diabetes & Glandular Disease Clinic, PA, San Antonio, Texas

Conclusions: For elderly patients with type 2 DM, reductions in HbA_{1c} after treatment with a DPP-4 inhibitor were not significantly different from those in younger patients. Use of DPP-4 inhibitors in these studies was associated with a low risk of hypoglycemia, and these agents were weight neutral. (*Am J Geriatr Pharmacother.* 2010; 8:405–418)

Safety and efficacy of insulin aspart and soluble human insulin in elderly type 2 diabetics: results from UpGrade observational study

D. Cucinotta, A. Nicolucci, E. Orsi, G. Riccardi, E. Rossi, P. Sbraccia

…..Overall, in elderly type 2 diabetics >70 years, IAsp was associated with a significantly lower risk of both major and minor hypos vs. SHI. As in the overall population, IAsp also allowed a higher reduction of HbA1c over 26 weeks.

71st American Diabetes Association. scientificsessions
JUNE 24-28, 2011 • SAN DIEGO, CA

In questo paziente…

- L’obiettivo glicemico dovrebbe prevedere una HbA1c tra 7 e 8%
- Il farmaco da utilizzare, in aggiunta alla metformina, va scelto tra quelli che riducono il rischio di ipoglicemia e, se possibile, anche quello cardiovascolare

"Per diventare giovani, veramente giovani, ci vuole tempo"

(Pablo Picasso, 1970)