Terapia del diabete tipo 2:
un algoritmo basato su efficacia e farmaco-economia

L' anziano

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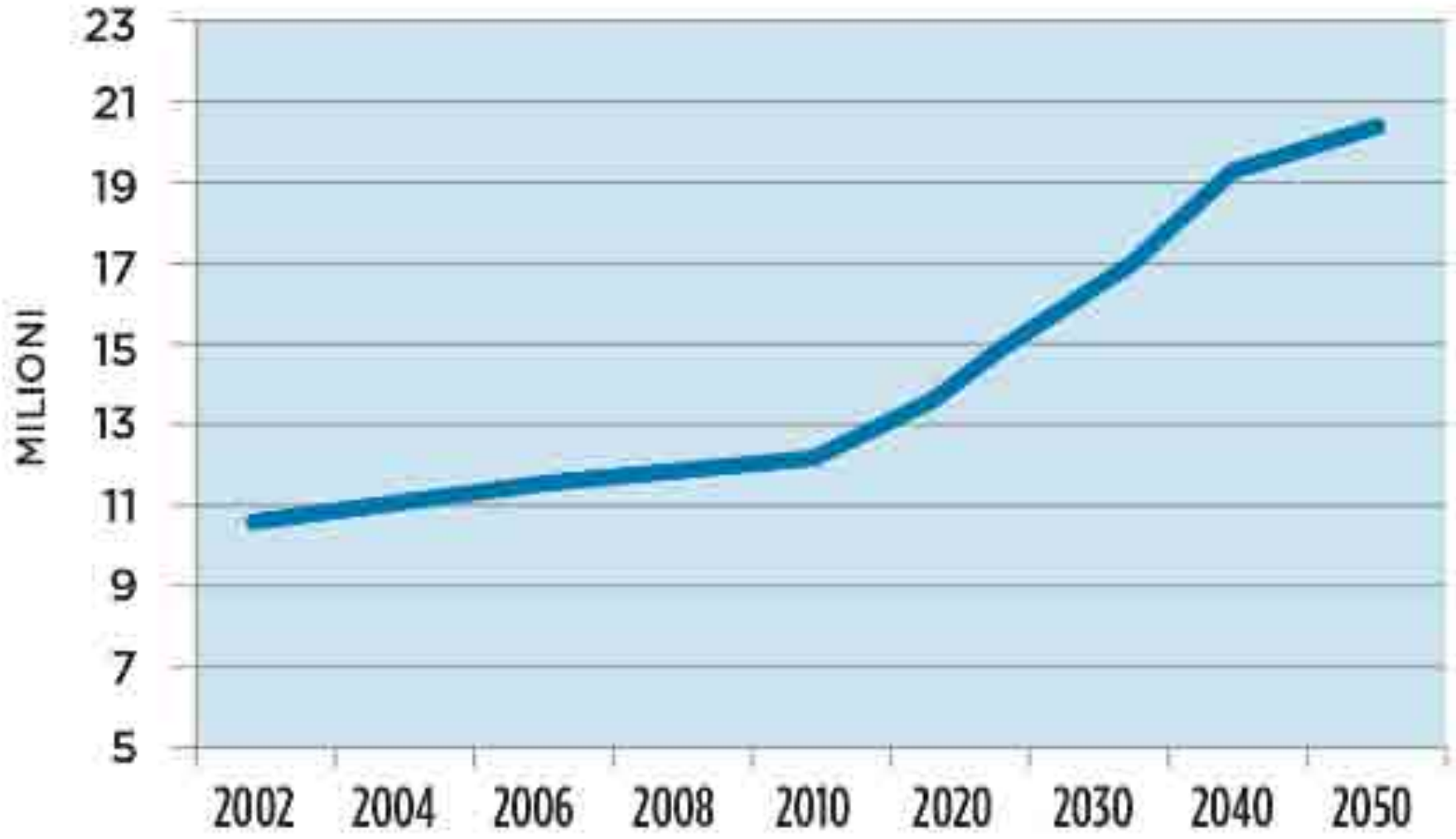


Figura 2. Stime di crescita della popolazione di età ≥65 anni in Italia (ISTAT)

I diabetici over 65 sono oltre 1.5 milioni,

entro dieci anni saranno 2.5 milioni.

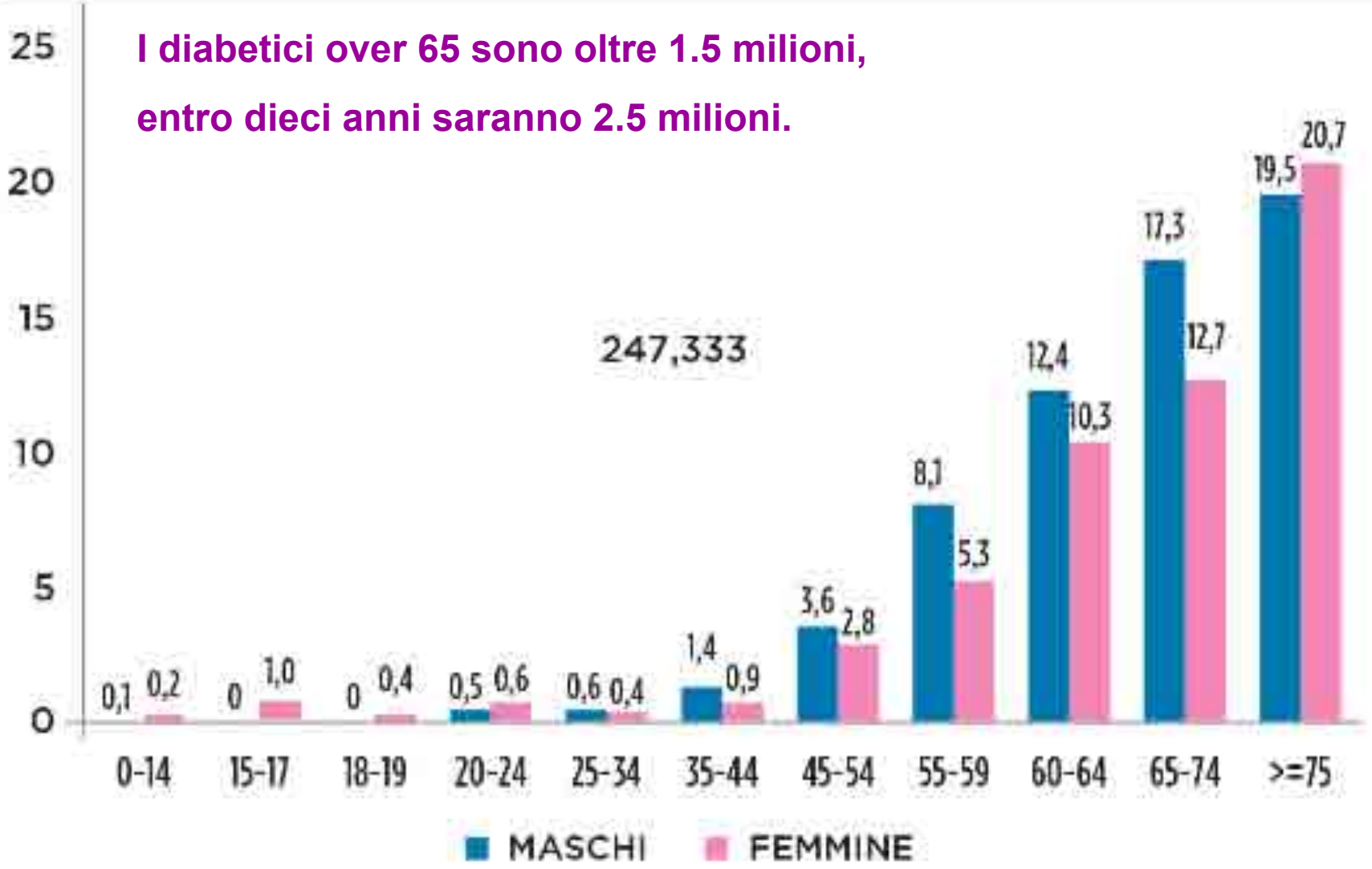


Figura 1. Prevalenza del diabete in Italia per fasce di età e sesso. Dati ISTAT 2012.

PAZIENTI DIABETICI ANZIANI: UNA BOMBA SOCIO-SANITARIA

I diabetici over 65 sono oltre 1,5 milioni, entro dieci anni saranno 2,5 milioni – Lo dice lo studio Hysberg, il più importante su scala mondiale per dimensione del campione – Le ipoglicemie negli anziani: un fenomeno con gravi impatti sul piano sociale, sanitario ed economico – *Federanziani, Italian Barometer Diabetes Observatory e Consorzio Mario Negri Sud,* insieme per comprendere il fenomeno del diabete nell'anziano e stimolare scelte politiche e gestionali per il presente e per il futuro – Tra 10 e 11 miliardi all'anno la spesa sanitaria complessiva per questa patologia

5.6% della spesa sanitaria generale

Perché la cura del diabete mellito tipo 2 nell'anziano è una grande sfida?

Peculiarità cliniche del paziente diabetico anziano

Anziani

Giovani (65-75aa)

Veri (76-85aa)

Grandi (>85aa)

Soggetto diabetico da molti anni che invecchia

Soggetto anziano con diabete di nuova insorgenza

- ↓ massa magra ↑ massa grassa
- ↓ attività fisica/scarsa mobilità
- dieta povera di fibre e ricca di CHO semplici e grassi
- terapie concomitanti
- comorbidità

- ↓ soglia di filtrazione renale
- ↓ sensibilità centri ipotalamici alle variazioni osmotiche (rischio di disidratazione)
- osteoporosi
- deficit cognitivi ↔ iperglicemia

CRONICITÀ
FRAGILITÀ
DISABILITÀ

Clinical Frailty Scale

1 Very Fit – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 Well – People who have no active disease symptoms but are less fit than category 1. Often, they exercise or are very active occasionally, e.g. seasonally.

3 Managing Well – People whose medical problems are well controlled, but are not regularly active beyond routine walking.

4 Vulnerable – While not dependent on others for daily help, often symptoms limit activities. A common complaint is being "slowed up", and/or being tired during the day.

5 Mildly Frail – These people often have more evident slowing, and need help in high order IADLs (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 Moderately Frail – People need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing.

7 Severely Frail – Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 Very Severely Frail – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9 Terminally Ill – Approaching the end of life. This category applies to people with a life expectancy <6 months, who are not otherwise evidently frail.

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia,** recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia,** they cannot do personal care without help.

Moorhouse P, Rockwood K.
J R Coll Physicians Edinb 2012;42:333-340.

J Am Geriatr Soc 61:734–738, 2013.

Exclusion of Older Adults from Ongoing Clinical Trials About Type 2 Diabetes Mellitus

Alfonso J. Cruz-Jentoft, MD, PhD, Marina Carpena-Ruiz, MD, Beatriz Montero-Errasquín, MD, Carmen Sánchez-Castellano, MD, and Elisabet Sánchez-García, MD

OBJECTIVE: To assess the extent of exclusion of older individuals from ongoing clinical trials regarding type 2 diabetes mellitus.

DESIGN: Cohort study.

SETTING: World Health Organization Clinical Trials Registry Platform.

PARTICIPANTS: Using the Participation of the Elderly in Clinical Trials methodology, data from ongoing clinical trials on type 2 diabetes mellitus were extracted from the platform on July 31, 2011.

MEASUREMENTS: Proportion of trials excluding individuals using an arbitrary upper age limit or other exclusion criteria that might indirectly cause limited recruitment of older individuals. Exclusion criteria were classified as justified or poorly justified.

RESULTS: Of 440 trials investig
2 diabetes mellitus, 289 (65.7%
using an arbitrary upper age limit.
nificantly more common in trials
sizes of less than 100 subjec
$P = .002$). Exclusion for comorbi
trials (76.8%); this exclusion wa
trials (53.6%). Exclusion for p
trials), cognitive impairment (18.4
(8.9%), and other poorly justifie
could limit the inclusion of older i
ent. Only six trials (1.4%) were
study older adults.

CONCLUSION: Despite the recommendations of international regulatory agencies, exclusion of older individuals from ongoing trials regarding type 2 diabetes mellitus is frequent—higher than reported for other age-related diseases. This exclusion limits the value of the evidence that clinicians use when treating old, frail, complex patients with diabetes mellitus. **J Am Geriatr Soc 61:734–738, 2013.**

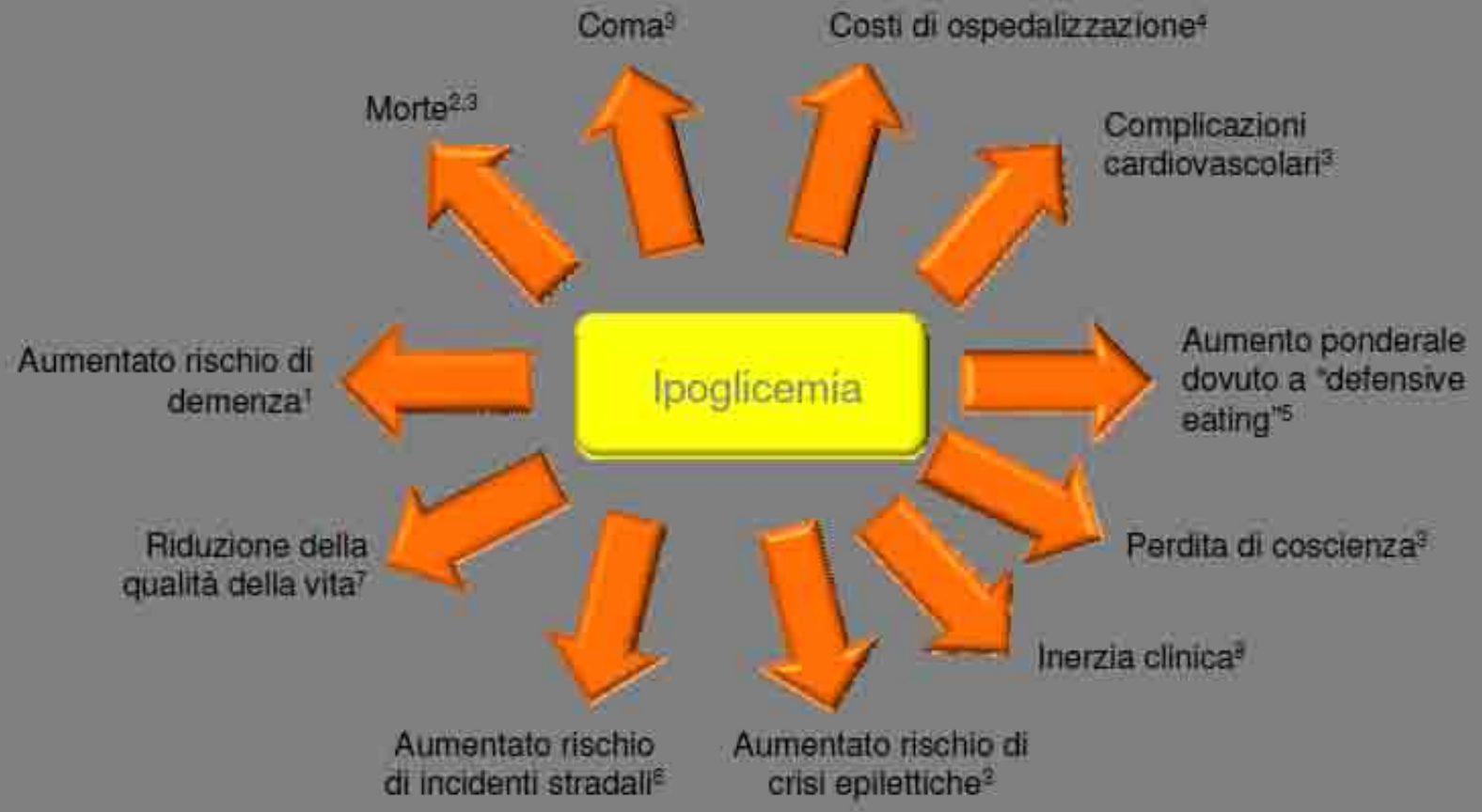
Key words: type 2 diabetes mellitus; ageism; clinical trial; registries; research subject selection

Diabetes mellitus is the most common long-term metabolic condition in older people. Although prevalence seems to depend on the criteria used to define diabetes mellitus, 21% of subjects aged 65 and older living in the community have diagnosed or undiagnosed diabetes mellitus.[1] The prevalence may reach one in three in older nursing home residents.[2] As life expectancy increases, the number of older individuals with diabetes mellitus is

CONCLUSION: Despite the recommendations of international regulatory agencies, exclusion of older individuals from ongoing trials regarding type 2 diabetes mellitus is frequent—higher than reported for other age-related diseases. This exclusion limits the value of the evidence that clinicians use when treating old, frail, complex patients with diabetes mellitus. J Am Geriatr Soc 61:734–738, 2013.

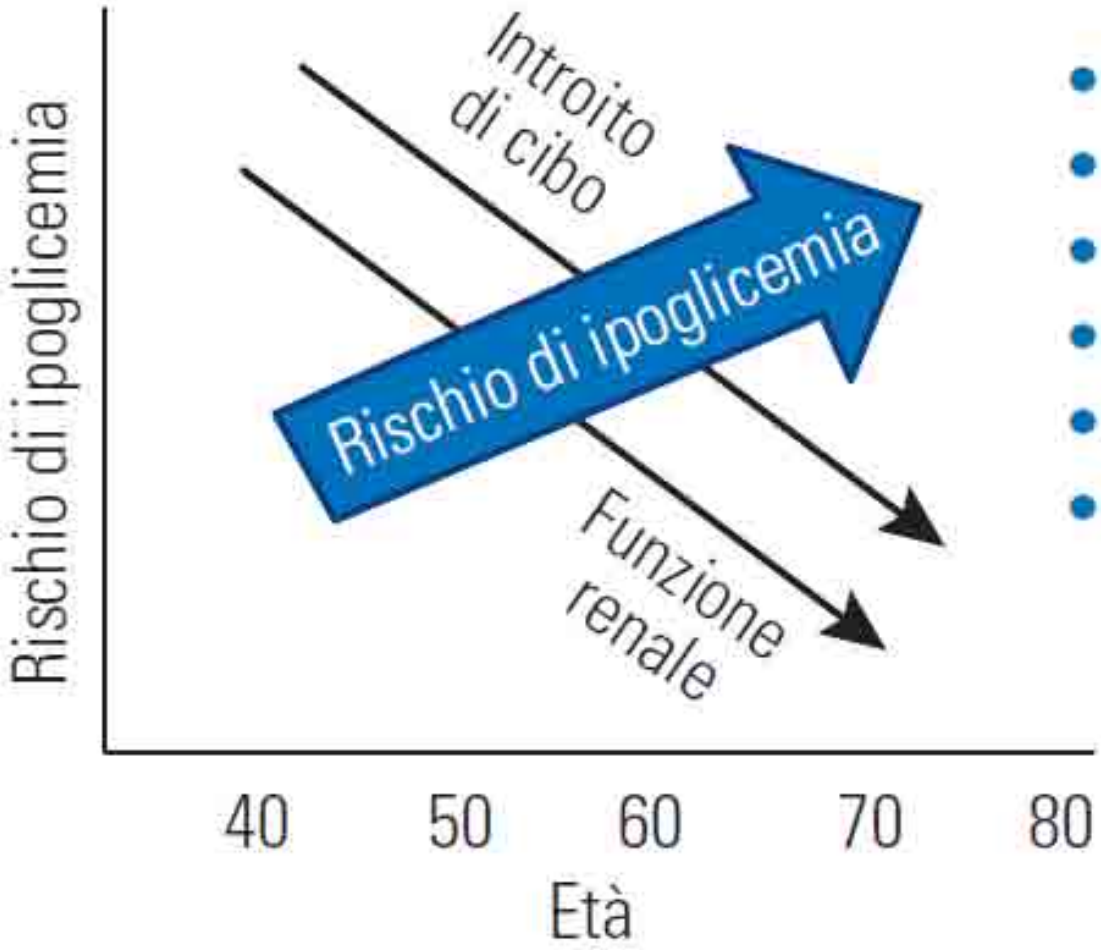
in drug trials is not unusual. A recent review of 109 clinical trials showed that 20.2% exclude individuals older than a specified age and that almost half (45.6%) of the remaining trials exclude individuals using criteria that could disproportionately affect older adults.[8] This is true for many age-related diseases, even in recently planned clinical trials, in which it would be expected that underrepresentation of older adults would be avoided.[9,10] Recently, when the authors of the current study were

Le conseguenze dell'ipoglicemia



1. Whitmer RA et al. JAMA. 2009; 301: 1565–1572. 2. Bonds DE et al. Br Med J. 2010; 340: b4909. 3. Barnett AH. Curr Med Res Opin. 2010; 26: 1333–1342. 4. Johnson L et al. Value Health. 2006; 9: 193–198. 5. Foley JE & Jordan J. Vasc Health Risk Manag. 2010; 6: 541–548. 6. Segal R et al. Can J Diabetes. 2003; 27: 159–162. 7. McEwan P et al. Diabetes Obes Metab. 2012; 12: 431–436. 8. Lacy AR, et al. Health Qual Life Outcomes. 2009; 6: 73

Rischio di ipoglicemia nel soggetto anziano diabetico



- Declino funzionale renale
- Comorbidità
- Polifarmacoterapia
- Scorretta alimentazione
- Deficit cognitivi
- Ridotta percezione delle ipoglicemie

www.beyondglycemia.com – anno 1, inserto 4, 2012

Fattori predisponenti e precipitanti l'ipoglicemia

Fattori predisponenti

1. Età
2. Peso corporeo
3. Durata della malattia
4. Storia di ipoglicemia severa
5. Uso di sulfaniluree
6. Terapia insulinica
7. Insufficienza renale
8. Epatopatia cronica
9. Ridotta risposta controregolatrice
10. Alterazioni cognitive

Fattori precipitanti

1. Agenti antidiabetici (sulfaniluree, nateglinidi, insulina)
2. Potenziatori delle sulfaniluree
3. Sovradosaggio
4. Saltare o ritardare o ridurre i pasti
5. Assunzione di alcol
6. Patologie acute (associate a scarso intake alimentare)
7. Morbo di Addison
8. Aumentata attività fisica
9. Gastroparesi

Evitare l'ipoglicemia

In uno studio, effettuato in 12 ASL della regione Puglia nel periodo 2002-2010, che individuava 385.527 soggetti con diabete, furono registrati 10.362 ricoveri per ipoglicemia relativi a 9021 pazienti.
La spesa calcolata per tali ricoveri fu di 31 milioni di euro (pari a 3000 euro circa per ricovero con degenza media di 7 giorni)

(*Laura Monti*)

Estrapolando questi dati per l'intera Italia è possibile stimare che le ipoglicemie severe provochino una media di 15.000 ricoveri l'anno per una spesa di 45 milioni di euro l'anno.

(*Laura Monti*)

Diabetes in the frail elderly

Individualization of glycemic management

Tessa Laubscher MB ChB CCFP FCFP **Loren Regier** **Julia Bareham**

Older adults with diabetes who are otherwise healthy and who have considerable life expectancy (more than 10 years) should generally receive diabetes care with goals and targets similar to those for younger adults. However, it is important to individualize treatment goals for those frail elderly who have comorbidities, limited function, limited life expectancy, impaired cognition, or a high risk of adverse events from treatment.[1,2] In such individuals, treatment goals might need to be relaxed. When individualizing therapy, it is important to consider overall benefits and harms, and to avoid acute complications of hypoglycemia and hyperglycemia.

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Laubscher T, et al. Can Fam Physician. 2012 May;58(5):543-6.

Table 1. Trials of intensive versus less-intensive BG lowering: *No RCTs studying the effects of intensive glycemic control have included frail elderly patients.*

RCT TRIAL	MEAN AGE, Y	TRIAL DURATION, Y	HBA_{1c} ATTAINED, %	BENEFITS OR HARMS IN MORE-INTENSIVE GLUCOSE-LOWERING ARM (LOWER HBA_{1c}) VS LESS-INTENSIVE TREATMENT ARM
UKPDS-33[4]	54	10	7.0 vs 7.9	• No difference in major clinical outcomes* at 10 y[†] • Benefits on surrogate outcomes (less microvascular disease after ≥6 y) • Increase in serious hypoglycemia • A follow-up study after 20 y saw decreased MI and all-cause death[6]
ADVANCE[7]	66	5	6.5 vs 7.3	• No difference in major clinical outcomes* at 5 y • Decrease in microvascular end points (NNT = 67 at 5 y), mostly nephropathy surrogates • Increase in serious hypoglycemia (NNH = 83 at 5 y)
VADT[8] (most participants had a history of CV problems)	60	5.6	6.9 vs 8.4	• No difference in major clinical outcomes* at 5.6 y • Increased rate of serious adverse events (NNH = 15 at 5.6 y) • Increase in serious hypoglycemia (NNH = 83 at 5.6 y)
ACCORD[9] (35% of participants had a history of CV problems)	62	3.5	6.4 vs 7.5	• More death with intensive treatment (NNH = 95 at 3.5 y) (any macrovascular benefit outweighed by increase in death) • Increase in serious hypoglycemia (NNH = 9 at 3.5 y)

ACCORD—Action to Control Cardiovascular Risk in Diabetes, ADVANCE—Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation, BG—blood glucose, CV—cardiovascular, HbA_{1c}—glycated hemoglobin A_{1c}, MI—myocardial infarction, NNT—number needed to treat for 1 additional person to benefit, NNH—number needed to treat for 1 additional person to be harmed, RCT—randomized controlled trial, T2DM—type 2 diabetes mellitus, UKPDS—United Kingdom Prospective Diabetes Study, VADT—Veterans Affairs Diabetes Trial.

*Major clinical outcomes included CV death, MI, stroke, end-stage renal disease, and blindness.

†The UKPDS-34[5] found a decrease in death (NNT = 14 at 10.7 y) and decrease in stroke (NNT = 48 at 10 y) when metformin specifically was used compared with standard treatment in obese patients with T2DM (HbA_{1c} achieved was 7.4% vs 8.0%).

Laubscher T, et al. Can Fam Physician. 2012 May;58(5):543-6.

Evitare l'ipoglicemia

- Il paziente anziano necessita di un approccio diagnostico e terapeutico particolare, visti i cambiamenti fisiologici legati a età, comorbidità e polifarmacoterapia.
- Gli obiettivi glicemici devono tener conto della situazione clinica individuale multidimensionale e dell'aspettativa di vita.

Obiettivo primario della terapia ipoglicemizzante:

prevenire l'ipoglicemia!

Terapia dell'anziano diabetico

L'approccio terapeutico così come il target glicemico devono tener conto delle comorbodità, dello stato funzionale e dell'aspettativa di vita, pertanto le scelte terapeutiche non saranno sempre univoche ed uniformi.

Target glicemici e di HbA1c nel paziente diabetico anziano

Individualizzare i target glicemici e di HbA1c
ADA-EASD

HbA1c < 6.5% in soggetti selezionati (breve durata della malattia, lunga aspettativa di vita, no patologia CV)

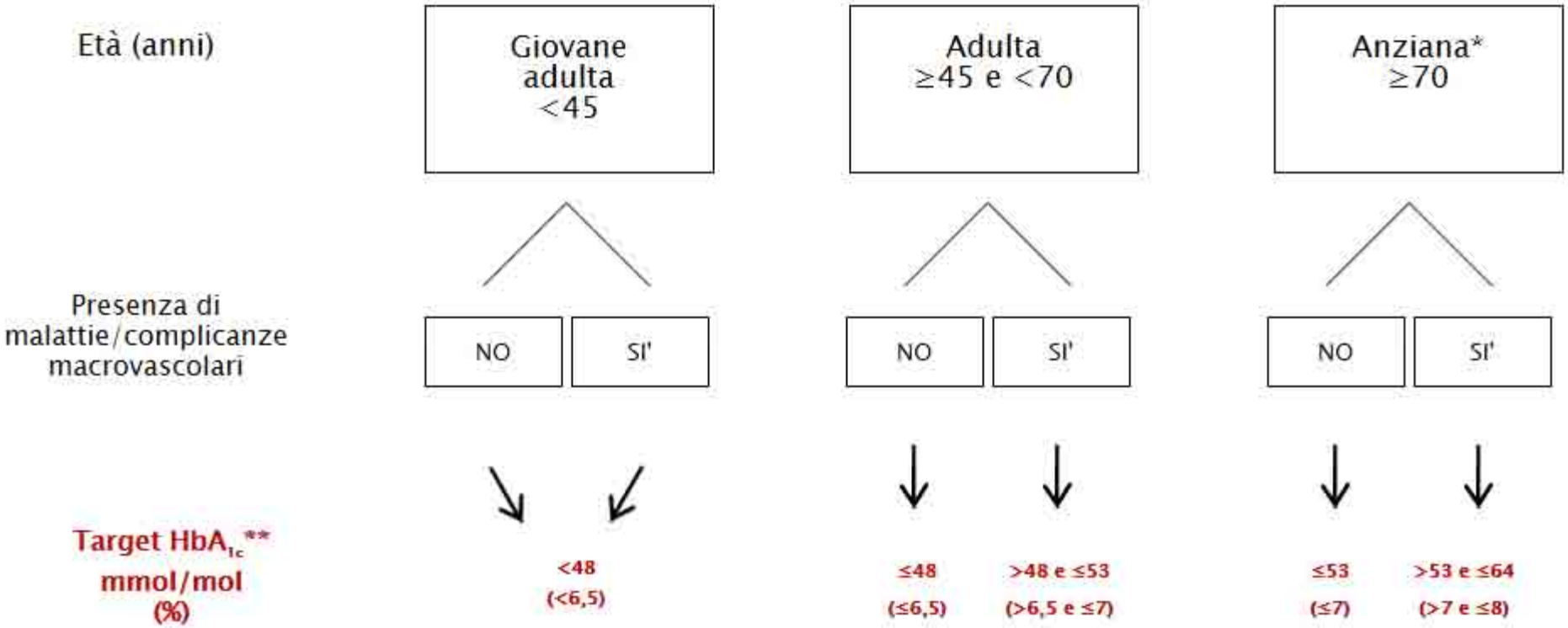
HbA1c < 7% in soggetti selezione (giovani adulti diabetici) media glicemica 150-160 mg7dl

Glicemia a digiuno e pre prandiale < 130 mg/dl
" e post-prandiale < 180 mg/dl

ANZIANI FRAGILI

HbA1c < 7,5-8 % o anche < 8,5% (pz con storia di iperglicemia severa, presenza di comorbidità, ridotta aspettativa di vita……..)

Parametri per l'inquadramento/caratterizzazione del paziente con diabete di tipo 2



* Valutare (alla presentazione e nel tempo) il filtrato glomerulare, il possibile rischio di ipoglicemie (particolare cautela nell'impiego di sulfoniluree e glinidi), l'assetto nutrizionale, la presenza di comorbilità e fragilità.

** I valori target di HbA_{1c} proposti, sono da intendersi come obiettivi da perseguire in sicurezza, limitando il rischio di ipoglicemia

Scegliere la caratteristica principale del paziente con diabete di tipo 2:

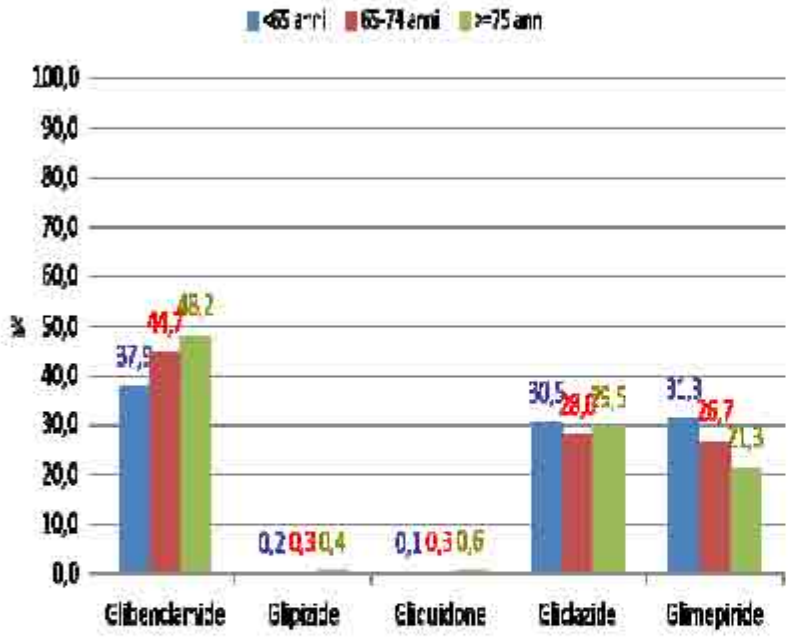
ALGORITMO A	ALGORITMO B	ALGORITMO C
HbA_{1c} ≥75 mmol/mol (≥9%)	BMI <30 e HbA_{1c} 48-75 mmol/mol (tra 6,5 e <9%)	BMI ≥30 e HbA_{1c} 48-75 mmol/mol (tra 6,5 e <9%)

ALGORITMO D	ALGORITMO E	ALGORITMO F
Rischio professionale per possibili ipoglicemie (HbA_{1c} 48-75 mmol/mol [tra 6,5 e <9%])	IRC e HbA_{1c} 48-75 mmol/mol (tra 6,5 e <9%)	Anziano fragile con iperglicemia lieve/moderata (HbA_{1c} <75 mmol/mol [<9%])

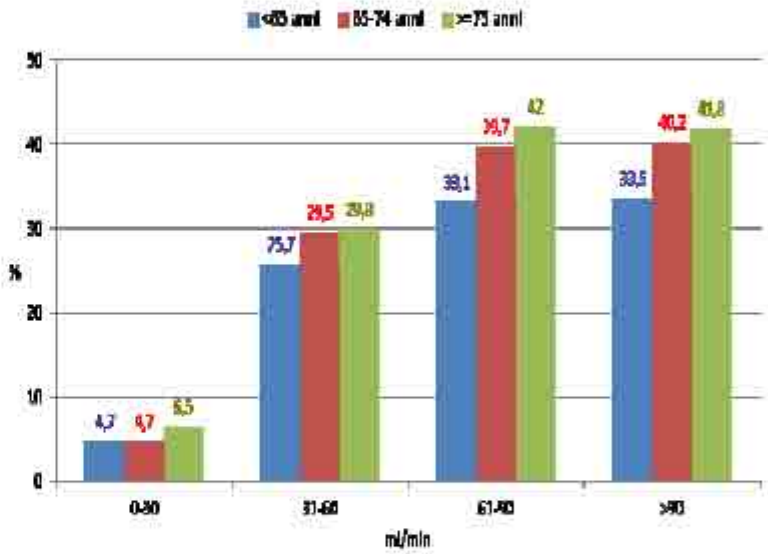
Sconsigliato il perseguimento di una glicemia a digiuno < a 6,0 mmol/L (**Not below 6** - 108 mg/dl) e di non iniziare un trattamento ipoglicemizzante se la glicemia a digiuno non è stabilmente > 7,0 mmol/L (**NOT before 7** - 126 mg/dl).

Andranno, perciò, privilegiati i farmaci che non provocano ipoglicemia.

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



Percentuale di pazienti trattati con sulfaniluree in relazione alla classe di età e ai livelli di filtrato glomerulare.



Sulfonylureas and CV Mortality

Observational trials comparing any sulfonylureas (monotherapy or combination) vs any non-sulfonylurea treatment, including insulin

	Sulfonylurea		Non-sulfonylurea		Odds Ratio
Author(s), y	Alive	Deaths	Alive	Deaths	(95% CI)
Evans et al, 2006	5308	373	2248	38	4.16 (2.971 5.83)
Johnson et al, 2005	2899	320	862	61	1.56 (1.17, 2.07)
Schramm et al, 2011	57,757	3942	42,513	827	3.51 (3.25, 3.79)
Schramm et al, 2011	5278	961	2737	169	2.95 (2.49, 3.49)
Sillars et al, 2010	396	137	503	81	2.15 (1.58, 2.91)
Random effects model					**2.72 (1.95, 3.79)**

Forst T, et al. *Diab Vasc Dis Res*. 2013;10:302-314.[7]

Terapia ipoglicemizzante nei soggetti diabetici anziani

Farmaci	Possibili interazioni	Ulteriori considerazioni
Metformina	Insufficienza renale GFR< 30	- Evitare in pz > 80 aa a meno di GFR nella norma - Basso rischio ipoglicemico - Cardioprotezione - Riduzione del peso
Acarbose – inibitore dell'alfa glucosidasi	Insufficienza renale	- Effetti collaterali: gastrointestinali - Ipoglicemia rara
Sulfoniluree Glinidi	Aumentato rischio ipoglic Aumento peso	- Evitare le sulfoniluree ad azione prolungata -Dimezzare la posologia - Evitare nei cardiopatici
Glitazoni	Cardiopatici Osteoporosi	- Rara l'ipoglicemia - Rischio di fratture - Controindicato nei cardiopatici
Insulina	Ridotta introduzione di cibo Disturbi del visus Può esser necessaria assistenza	- Efficacia - Detemir, Levemir, analogh rapidi - Monitoraggio glicemico - Educazione sanitaria - Uso di penne riduce gli errori posologici

JAGS 61:535–541, 2013

Contributions of Basal and Prandial Hyperglycemia to Total Hyperglycemia in Older and Younger Adults with Type 2 Diabetes Mellitus

Medha N. Munshi, MD, Naushira Pandya, MD,† Guillermo E. Umpierrez, MD,‡ Andres DiGenio, MD,§ Rong Zhou, PhD,‖ and Matthew C. Riddle, MD#*

OBJECTIVES: basal and pran older and young

DESIGN: Partic domized studie insulin glargine

SETTING: Pros trolled trials.

PARTICIPANTS: One thousand six hundred ninety-nine individuals: 509 (30%) aged 65 and older and 1,190 (70%) younger than 65.

MEASUREMENTS: Contributions of basal hyperglycemia

CONCLUSION: The relative contribution of BHG was lower, and that of PPHG was greater in older than in younger participants, suggesting that different therapeutic approaches may be required to treat hyperglycemia effectively in these different age groups. J Am Geriatr Soc 61:535–541, 2013.

efficient $(r) = 0.082$; ; $P = .03$) in younger proportion of older c, glucose-confirmed, g 24 weeks of treat-

ibution of BHG was ater in older than in younger participants, suggesting that different therapeutic approaches may be required to treat hyperglycemia effectively in these different age groups. J Am Geriatr Soc 61:535–541, 2013.

Gliptine: razionale per una maggiore efficacia ipoglicemizzante nel paziente anziano

	Massa a-cellulare*	Grado di iperglucagonemia*	Deficit di secrezione insulinica**	Deficit asse delle incretine***	Grado di PPG**
Pazienti < 75 anni	++	++	++	+++	++
Pazienti ≥ 75 anni	++++	++++	++++	++++	++++

*Basu R et al. Diabetes 2003; 52:1738-48; **Monami M et al. Diabetes Metabol Res Rev 2011; 27 (4): 362-372; ***Korosi J et al. J Gerontol A Biol Sci Med Sci 2001; 56 (9):M575-M579

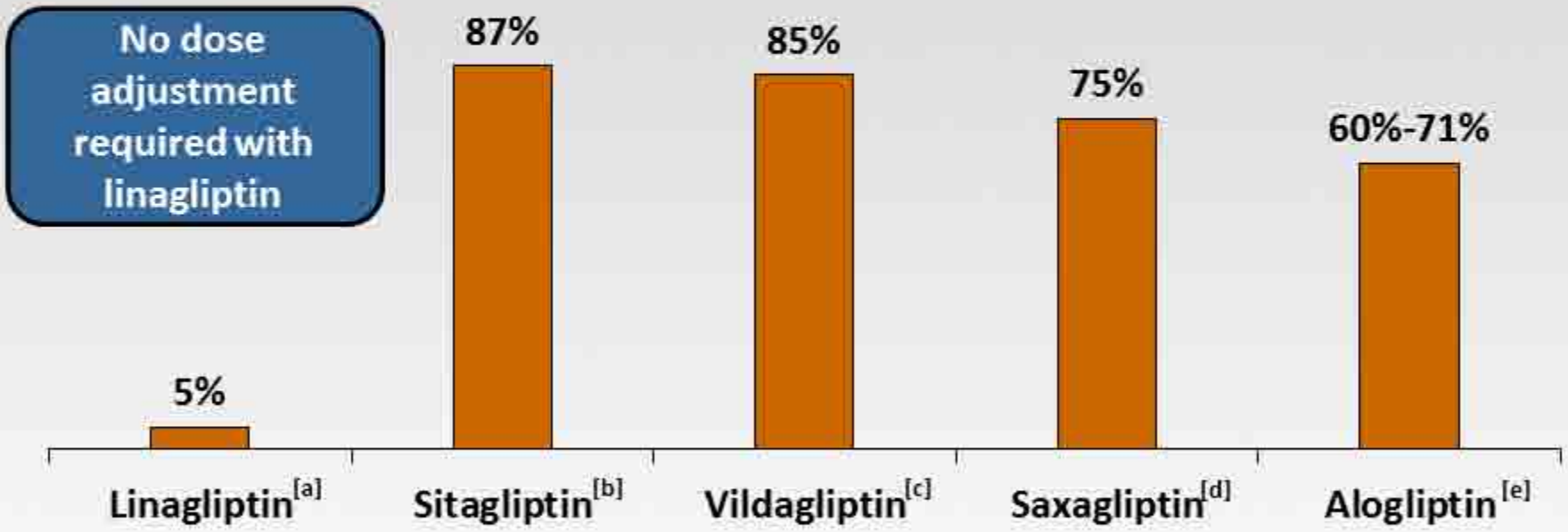
CLASSE	GLIPTINE	Meccanismo d'azione	Azioni principali
Inibitori DPP-4	Sitagliptin Vildagliptin Saxagliptin Linagliptin Alogliptin	Inibizione di DPP-4 Aumento delle concentrazioni di GLP-1 e GIP	Diminuzione della secrezione di glucagone ed aumento della secrezione di insulina, entrambi glucosio indotte
Analoghi GLP1	Exenatide Liraglitide Lixisenatide	Attivazione dei recettori di GLP1	Diminuzione della secrezione di glucagone, ed aumento della secrezione di insulina, entrambi glucosio indotte. Svuotamento gastrico rallentato. Aumentato senso di sazietà.

DIFFERENZE TRA AGONISTI RECETTORIALI DEL GLP-1 E INIBITORI DELLA DPP-4

	Agonisti recettoriali GLP-1	Inibitori DPP-4
Meccanismo d'azione	Stimolazione del R del GLP-1	Aumento dei livelli di GLP-1, GIP e altri peptidi
Concentrazioni circolanti	10-12 volte i livelli di GLP-1 endogeno	Aumentano di 2-4 volte i livelli di GLP-1 endogeno
Via di somministraz.	Sottocutanea	Orale
Azione prevalente	A digiuno postprandiale, in base alla cinetica	Post-prandiale
Efficacia sulla HbA1c	Elevata	Moderata
Eff. sul peso corporeo	Ridotto	Non modificato
Eff. collaterai GI	Presenti	Assenti
Eff. sulla PA	Riduzione	Nessuno
Eff. sulla FC	Aumento	Nessuno

DPP-4 Inhibitors: Share of Renal Excretion

Other DPP-4 inhibitors require dose-adjustments or are not recommended in patients with declining renal function.

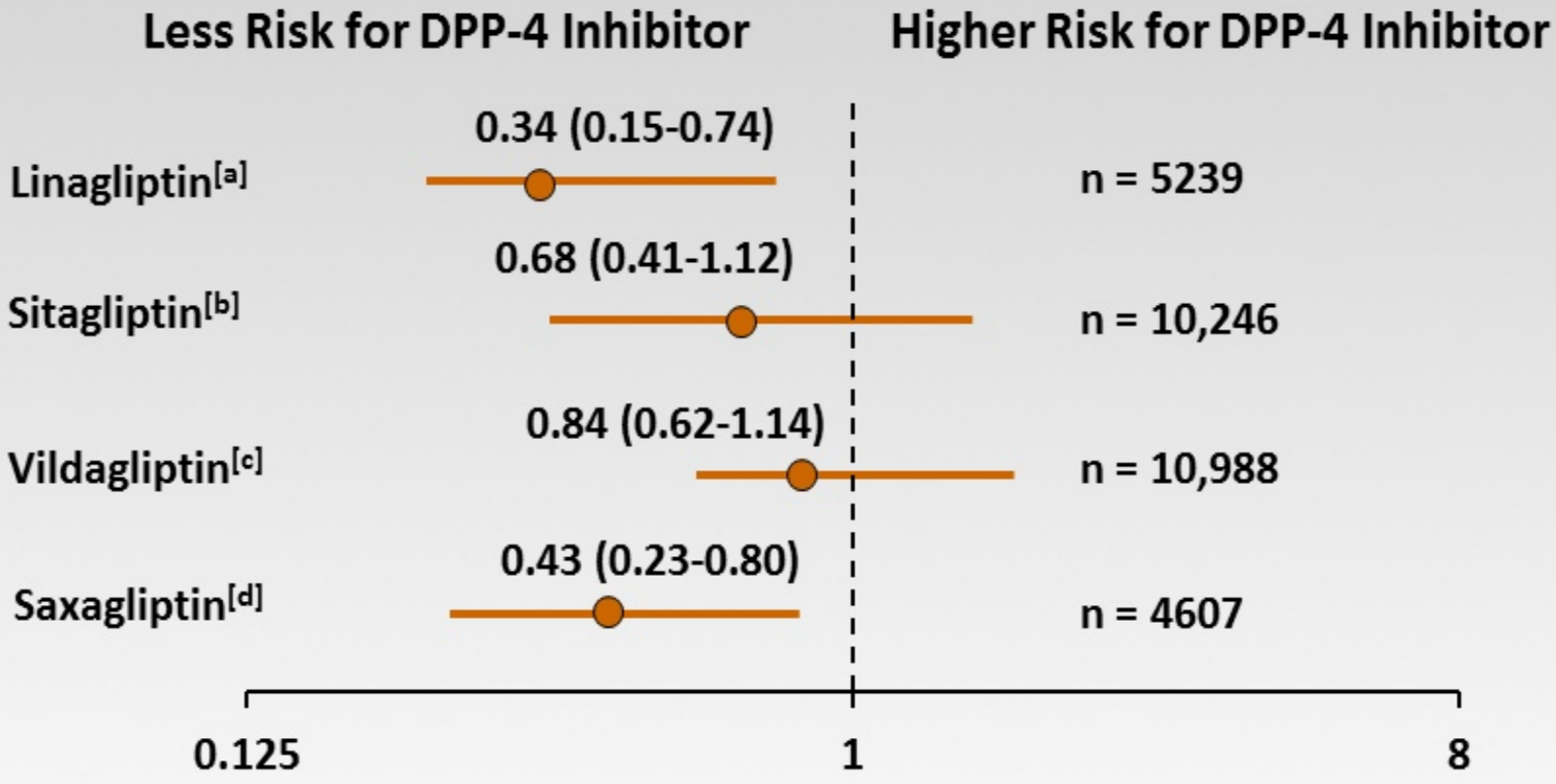


a. Blech S, et al. *Drug Metab Dispos*. 2010;38(4):667-678.
b. Vincent SH, et al. *Drug Metab Dispos*. 2007;35(4):533-538.
c. He H, et al. *Drug Metab Dispos*. 2009;37(3):545-554.
d. Bristol-Myers Squibb/AstraZeneca EEIG. http://onglyza.eu/sites/default/files/files/pdf/SmPC08.pdf. Accessed June 24, 2013.
e. Christopher R, et al. *ClinTher*. 2008;30(3):513-527.

Gli inibitori della Dpp-4 migliorano i fattori di rischio CV nei pz diabetici tipo 2

- Migliorano il controllo glicemico
- Hanno effetto neutro sul peso
- Possono ridurre PA
- Migliorano la lipemia post-prandiale (e persino a digiuno)
- Riducono i markers infiammatori
- Diminuiscono lo stress ossidativo
- Migliorano la funzione endoteliale
- Riducono l'aggregazione piastrinica
- Sono stati descritti effetti positivi sul miocardio in pazienti diabetici con malattia ischemica cardiaca.

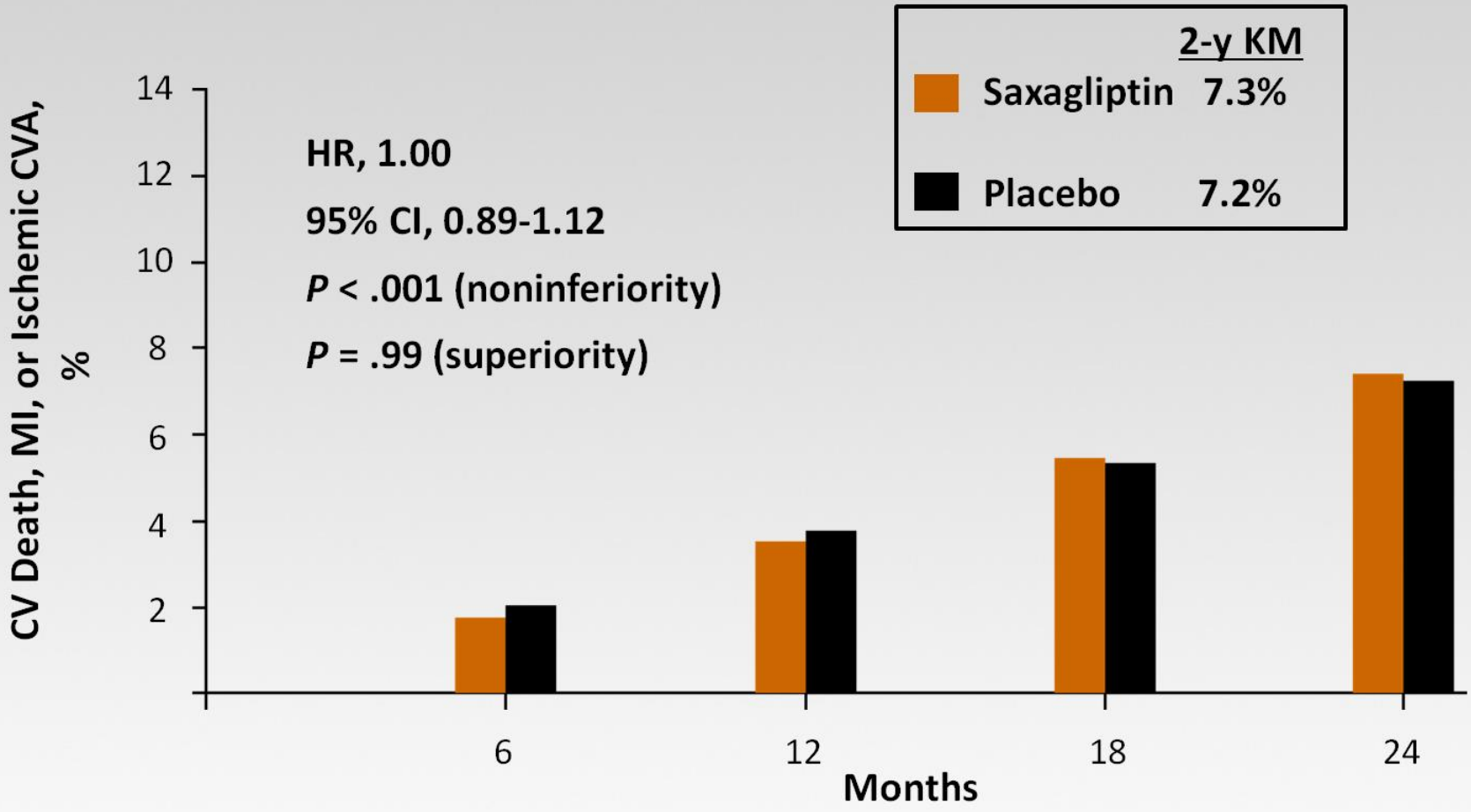
DPP-4 Inhibitors: Risk Rates* for CV Endpoints



*No direct comparison between the individual DPP-4 inhibitors

a. Johansen OE, et al. ADA 2011. Poster 30-LB.
b. Williams-Herman D, et al. *BMC Endocr Disord*. 2010;10:7.
c. Schweizer A, et al. *Diabetes Obes Metab*. 2010;12(6):485-494.
d. Frederich R, et al. *Postgrad Med*. 2010;122(3):16-27.

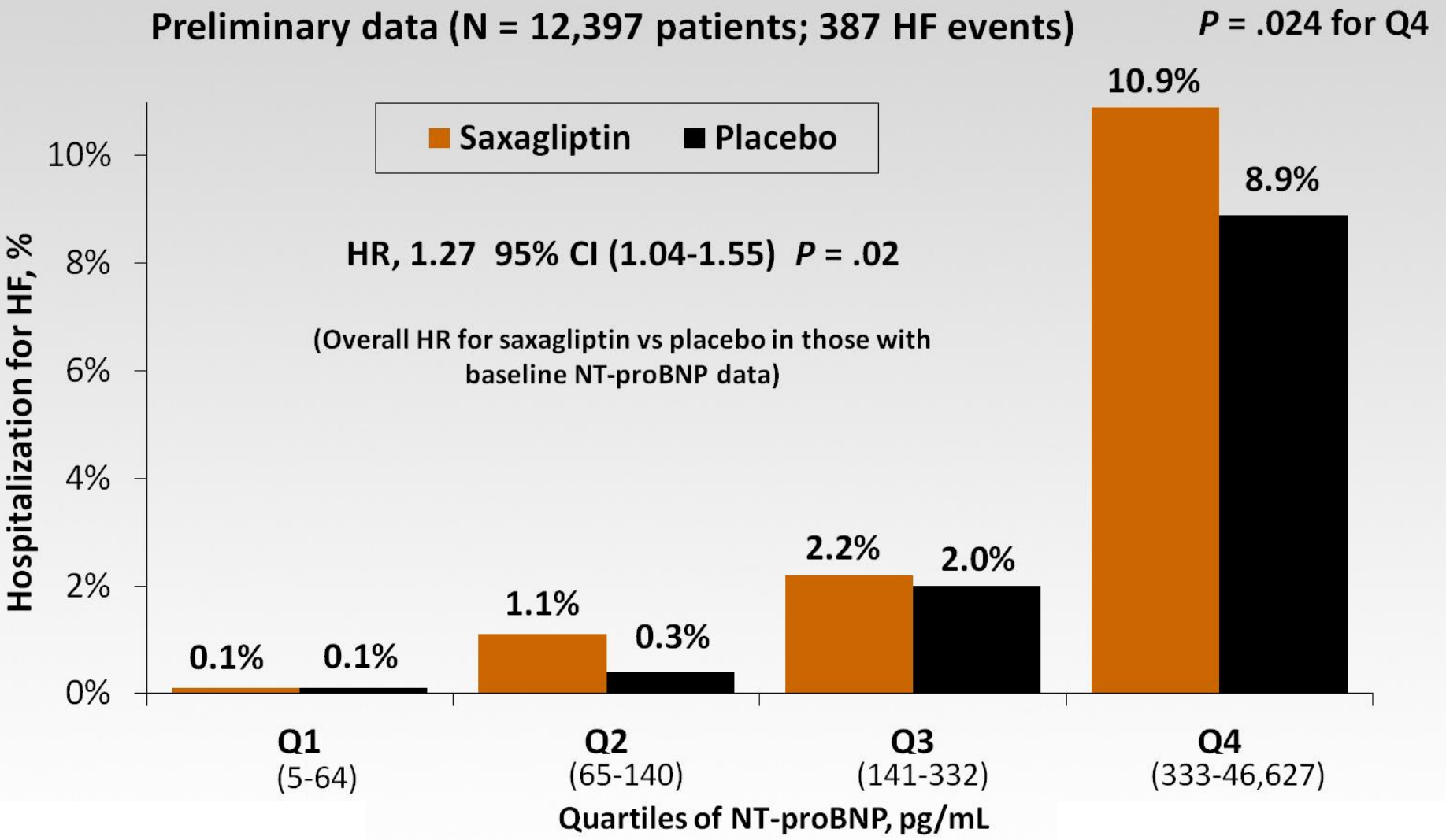
SAVOR-TIMI 53: Primary End Point



Placebo	8212	7983	7761	7267	4855
Saxagliptin	8280	8071	7836	7313	4920

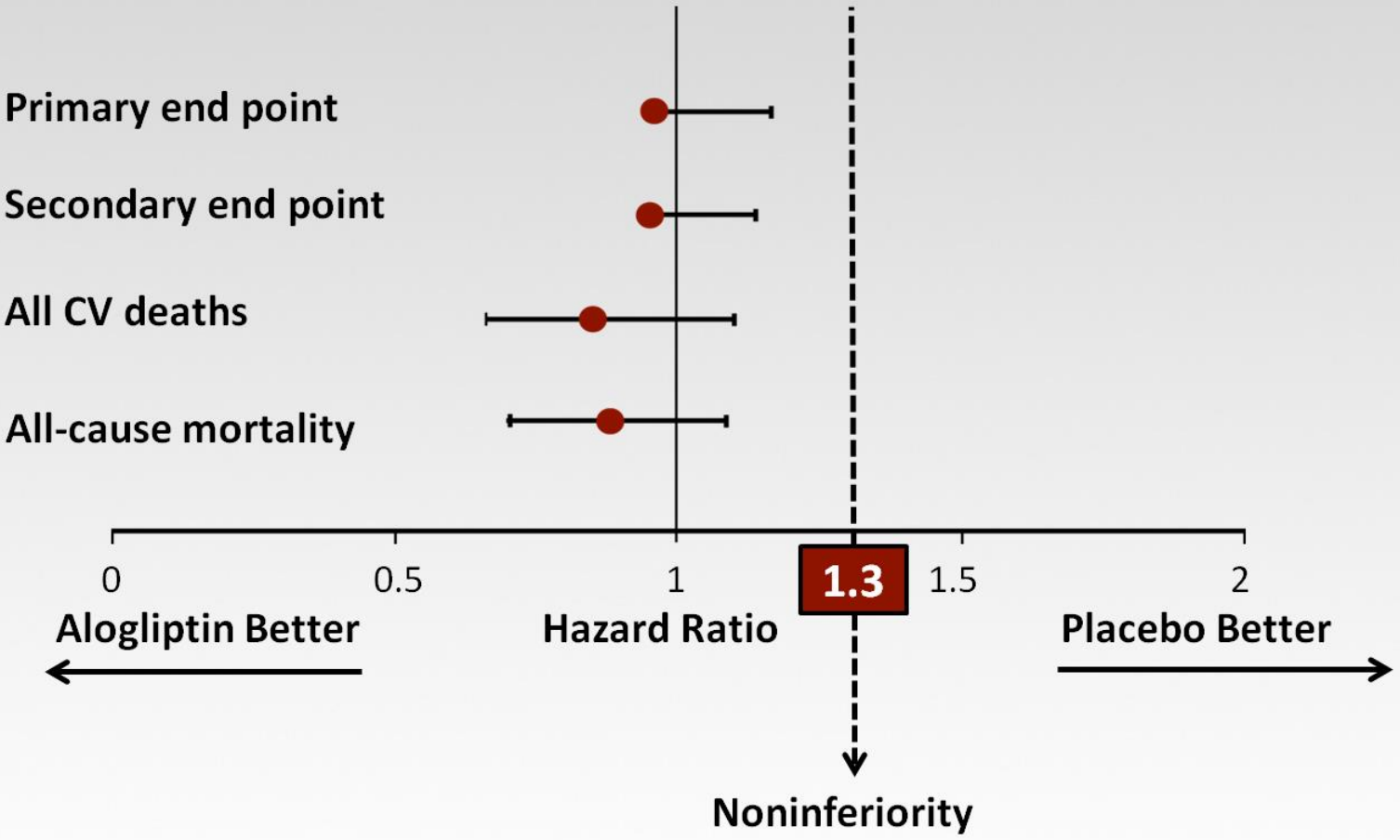
Scirica BM, et al. *N Engl J Med.* 2013;369:1317-1326.[7]

SAVOR-TIMI 53: Baseline NT-proBNP and Hospitalization for Heart Failure



Scirica BM, et al. *N Engl J Med.* 2013;369:1317-1326.[7]

EXAMINE: Noninferiority Met



White WB, et al. *N Engl J Med.* 2013;369:1327-1335.[11]

SAVOR-TIMI 53 and EXAMINE: Conclusions

	Saxagliptin	Alogliptin
CV events	No increase/decrease	No increase/decrease
Glycemic control	Improved	Improved
Hypoglycemia	Increased (when combined with sulfonylurea)	No increase
Need for insulin	Decreased	Decreased
Pancreatitis/ pancreatic cancer	No increase	No increase

Scirica BM, et al. *N Engl J Med.* 2013;369:1317-1326.[7]
White WB, et al. *N Engl J Med.* 2013;369:1327-1335.[11]

Terapia dell'anziano diabetico

CONCLUSIONI

- Prevenire l'ipoglicemia
- Controllare l'iperglicemia ed attenuare i suoi sintomi
- Prevenire un calo di peso indesiderato
- Salvaguardare la qualità di vita e mantenere o migliorare le condizioni generali del paziente

grazie