SID
Società Italiana di Diabetologia

AMD
ASSOCIAZIONE MEDICI DIABETOLOGI
1974

XX

Riunione Scientifica Annuale Regionale SID AMD

REGIONE SARDEGNA



DIABETE UNA PATOLOGIA COMPLESSA A VALENZA MULTIDISCIPLINARE

Terapia nell'anziano: farmaci tradizionali e farmaci innovativi

Gian Pio Sorice

Centro per le Malattie Endocrine e Metaboliche
Fondazione Policlinico Universitario Agostino Gemelli IRCCS
www.teamdiabete.it

TEAM DIABETE
Gemelli

Il Dott. Sorice Gian Pio dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

Lilly, Mundipharma, Astrazeneca, Merck

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

fonti

SID Società Italiana di Diabetologia

SOCIETÀ ITALIANA DI GERONTOLOGIA E GERIATRIA

POSITION STATEMENT

Personalizzazione del trattamento dell'iperglicemia nell'anziano con diabete tipo 2

Autori per la Società Italiana di Gerontologia e Geriatria:

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Autori per la Società Italiana di Diabetologia:

Enzo Bonora, Andrea Giaccari, Gianluca Perseghin, Francesco Purrello, Giorgio Sesti

AMD 1974 ANNO DI FONDAZIONE ASSOCIAZIONE MEDICI DIABETOLOGI

L'approccio clinico assistenziale
al paziente anziano
con diabete mellito tipo 2

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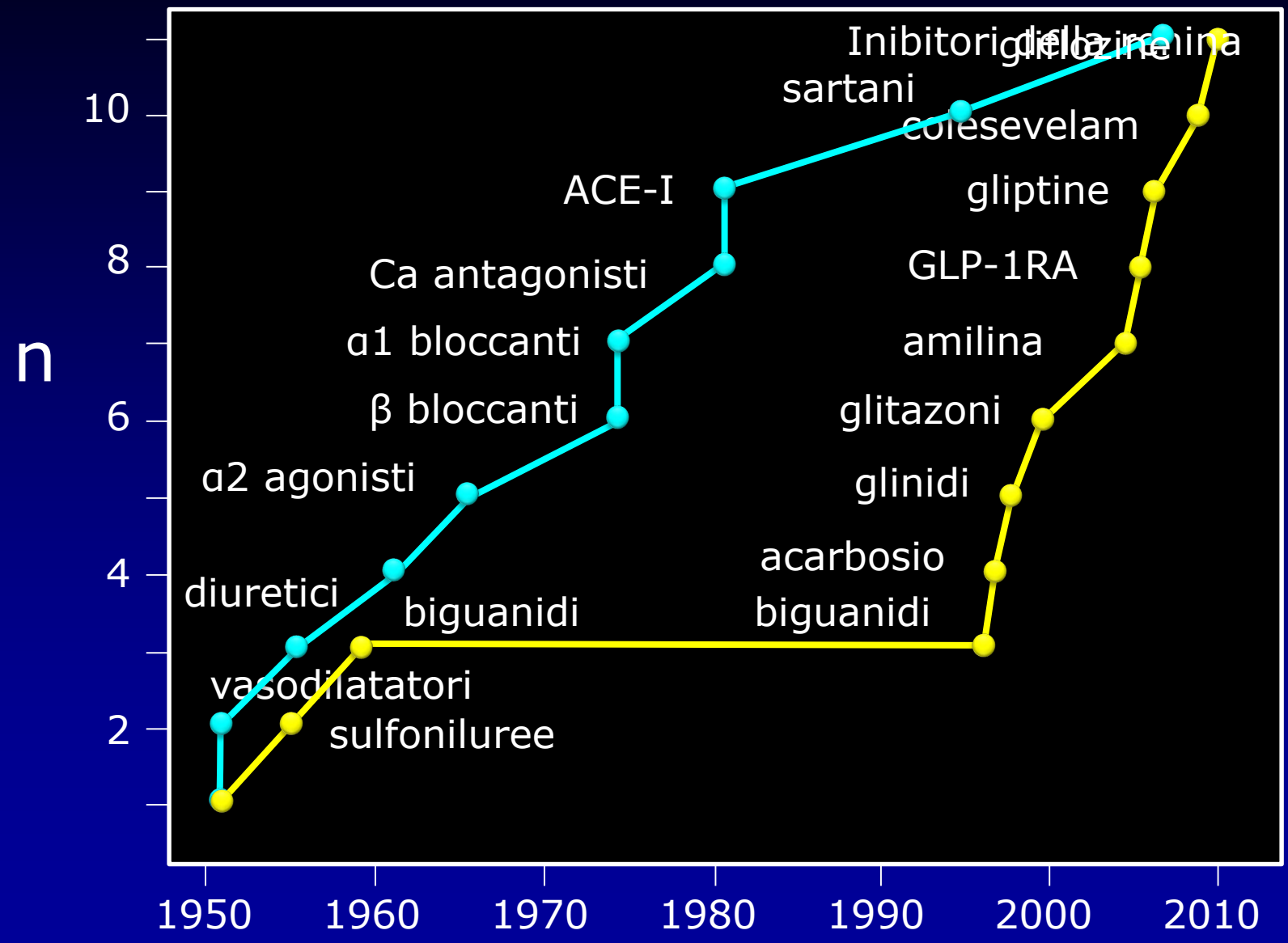
STANDARD ITALIANI PER LA CURA DEL DIABETE MELLITO

2018

SID Società Italiana di Diabetologia

Da pag 288 a 306

dai farmaci tradizionali a quelli innovativi



Terapia farmacologica nell'anziano:

Principali fattori da considerare:

- rischio di ipoglicemia
- insufficienza renale
- pregresso ictus/IMA
- storia di scompenso cardiaco
- profilo glicemico
- riserva funzionale beta cellula
- stato nutrizionale
- facilità di somministrazione

Classi di farmaci per diabete mellito tipo 2

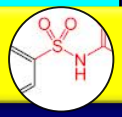
- Detemir
- Glargine
- Glargine U300
- Degludec
- NPH

INSULINA



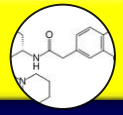
- Gliclazide
- Glibenclamide/glyburide
- Glimepiride
- Gliquidone
- Glipizide

SU



- Nateglinide
- Repaglinide

GLINIDI



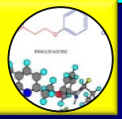
- Metformin

BIGUANIDI



- Pioglitazone

TZDs



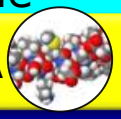
- Sitagliptin
- Saxagliptin
- Vildagliptin
- Linagliptin
- Alogliptin

GLIPTINE



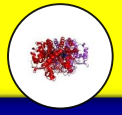
- Exenatide LAR
- Liraglutide
- Lixisenatide
- Dulaglutide

GLP-1 RA



- Acarbose
- Miglitol

INIBITORI ALPHA GLUCOSIDASI



- Dapagliflozin
- Canagliflozin
- Empagliflozin

INIBITORI SGLT2



Terapia farmacologica nell'anziano:

- rischio di ipoglicemia
- insufficienza renale
- pregresso ictus/IMA
- storia di scompenso cardiaco
- profilo glicemico
- riserva funzionale beta cellula
- stato nutrizionale
- facilità di somministrazione

Classi di farmaci per diabete mellito tipo 2

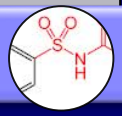
- Detemir
- Glargine
- Glargine U300
- Degludec
- NPH

INSULINA



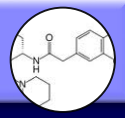
- Gliclazide
- Glibenclamide/glyburide
- Glimepiride
- Gliquidone
- Glipizide

SULFONILUREA



- Nateglinide
- Repaglinide

GLINIDI



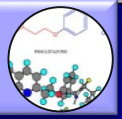
- Metformina

BIGUANIDI



- Pioglitazone

TZDs



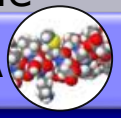
- Sitagliptin
- Saxagliptin
- Vildagliptin
- Linagliptin
- Alogliptin

GLIPTINE



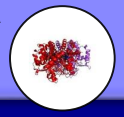
- Exenatide LAR
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GLP-1 RA



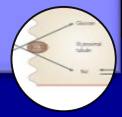
- Acarbose
- Miglitol

INIBITORI ALFA GLUCOSIDASI

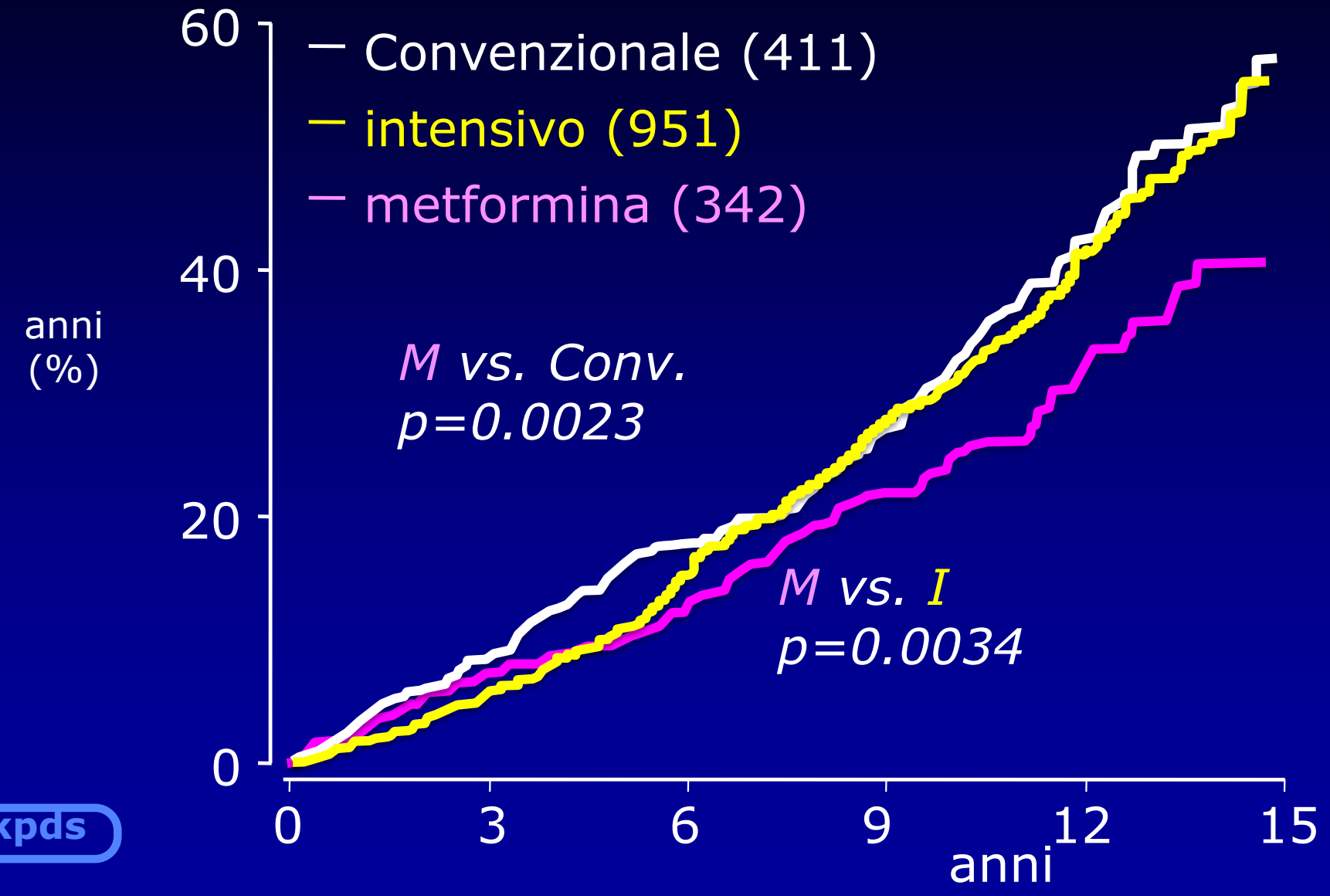


- Dapagliflozin
- Canagliflozin
- Empagliflozin

INIBITORI SGLT2

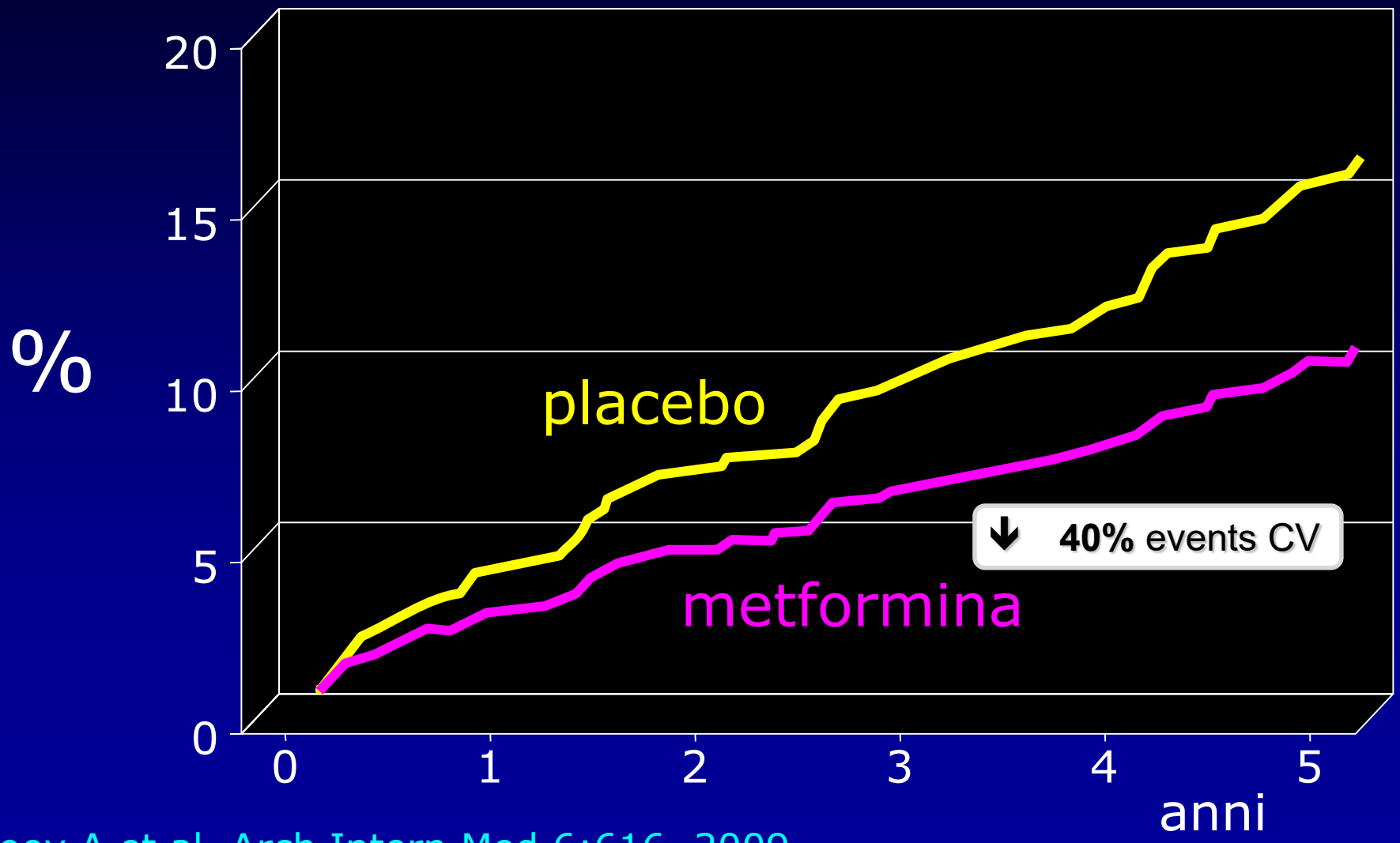


UKPDS: eventi correlati al diabete
(solo negli obesi)



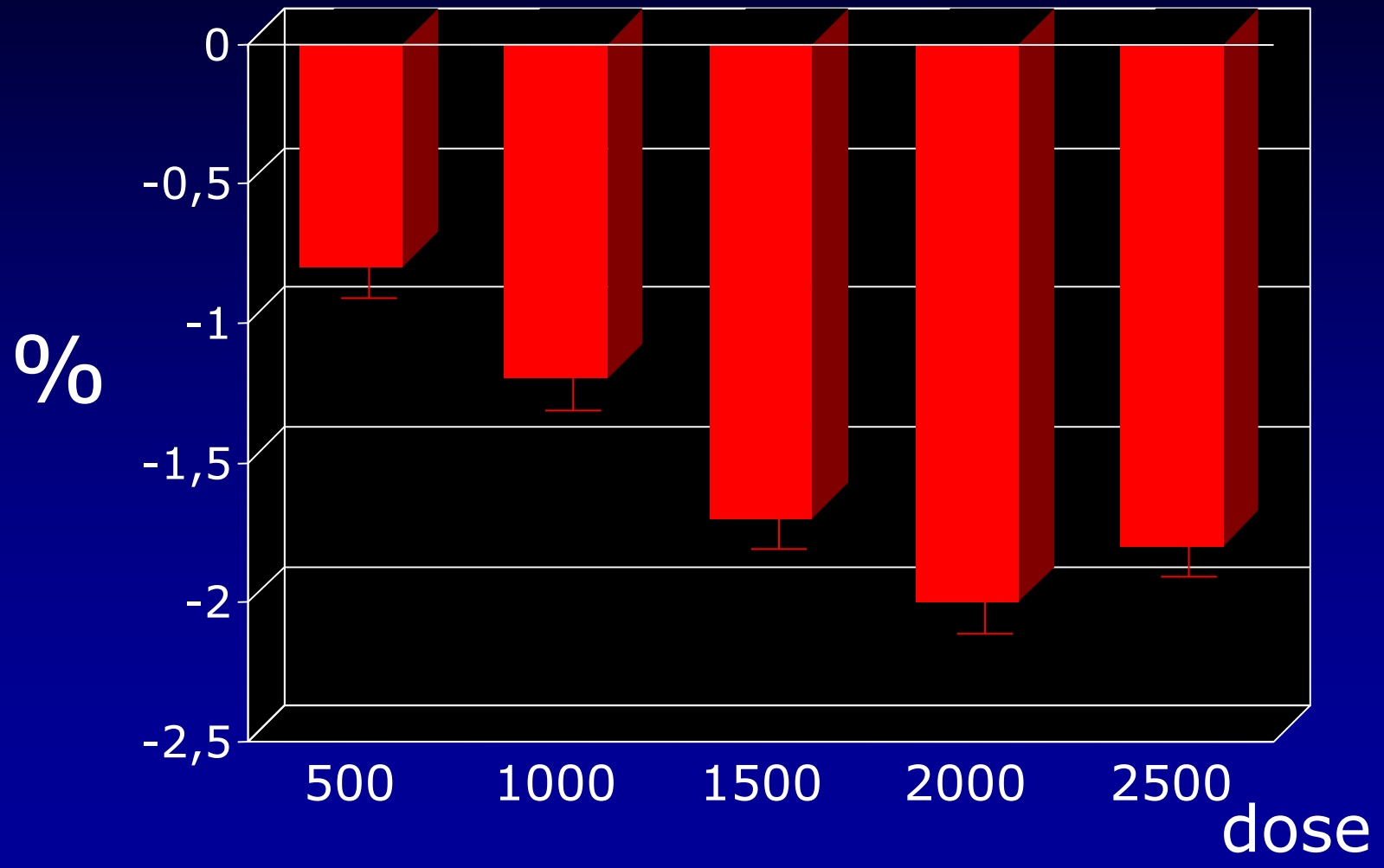
ukpds

metformina *add on* a insulina:CVD



Kooy A et al. Arch Intern Med 6:616, 2009

metformina: dose / risposta e riduzione di HbA1c



Garber AJ. Am J Med 1997; 103: 491-7

Metformin and metformin-containing medicines

Summary | Key facts | All documents

Use of metformin to treat diabetes now expanded to patients with moderately reduced kidney function

Recommendations for patients with kidney impairment updated in product information

The European Medicines Agency (EMA) has concluded that metformin-containing medicines can now be used in patients with moderately reduced kidney function (GFR [glomerular filtration rate]=30–59 ml/min) for the treatment of type 2 diabetes. The product information for these medicines will be updated to revise the current contraindication and give information about doses, monitoring and precautions in patients with reduced kidney function.

The recommendations are the result of a review by EMA of metformin-containing medicines following concerns that current scientific evidence does not justify a contraindication in patients with moderate reduction of kidney function. The current product information also varies between countries and products in the EU and is no longer consistent with clinical guidelines.

Metformin may increase the risk of a rare but serious complication called lactic acidosis, which occurs when naturally produced lactic acid builds up in the blood faster than it can

Current status: Opinion provided by Committee for Medicinal Products for Human Use

More information on Metformin and metformin-containing medicines

- Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 25-28 January 2016 (29/01/2016)
- Competact : EPAR
- Ebymect : EPAR
- Efficib : EPAR
- Eucreas : EPARs
- Glubrava : EPAR
- Icandra (previously Vildagliptin /

4 regole per la metformina

1. Almeno 2 gr al giorno, 1 gr se a XR
2. Run-in
3. Tutti i pazienti con T2D
4. Attenzione all' *e*GFR
    a. *Monitorare se eGFR < 60 mL/min*
    b. *Interrompere se eGFR < 30 mL/min*
    c. *Interrompere (temp.) in caso di procedure a rischio per IRA (es. mezzo di contrasto iodato)*

metformina: pro & contro

pro
sicuro
economico
no ipo
prevenzione primaria eventi CV

contro
non indicata con eGFR <30 ml/min
eventi avversi GI (meno per lento rilascio)

anziano
2 o 3 volte die
cp grandi

Terapia farmacologica nell'anziano

	rischio di IPO	uso in IRC	prev CVD	scomp card	fen glic	riserva β-cell	stato nutr.	facilità somm.
Metformina	NO	no<30	SI	NO	digiuno	=	−	XR
SU e glinidi								
pioglitazone								
Gliptine								
GLP-1 RA								
Gliflozine								
Insulina bas								

Classi di farmaci per diabete mellito tipo 2

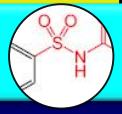
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- NPH

INSULINA



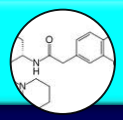
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SULFONILUREE



- Nateglinide
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GLINIDI



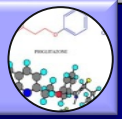
- Metformin

BIGUANIDI



- Pioglitazone

TZDs



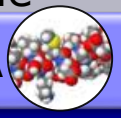
- Sitagliptin
- Saxagliptin
- Vildagliptin
- Linagliptin
- Alogliptin

GLIPTINE



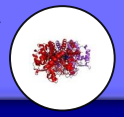
- Exenatide LAR
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- Dulaglutide

GLP-1 RA



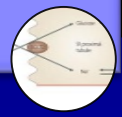
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- Miglitol

INIBITORI ALFA GLUCOSIDASI



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- Empagliflozin

INIBITORI SGLT2



SUlphonylurea Receptors (SUR)

classe	sede	stimolo	azione	effetto
SUR 1	pancreas	SUL FO NI LU REA	chiude	secrezione
SUR 2A	cuore		chiude	aumenta potenziale aumenta lavoro
SUR 2B	cellule muscolari lisce		chiude	contrae fibre vasocostringe

SU / GLINIDE

Effects on the incidence of cardiovascular events of the addition of pioglitazone versus sulfonylureas in patients with type 2 diabetes inadequately controlled with metformin (TOSCA.IT): a randomised, multicentre trial

OBIETTIVI DELLO STUDIO

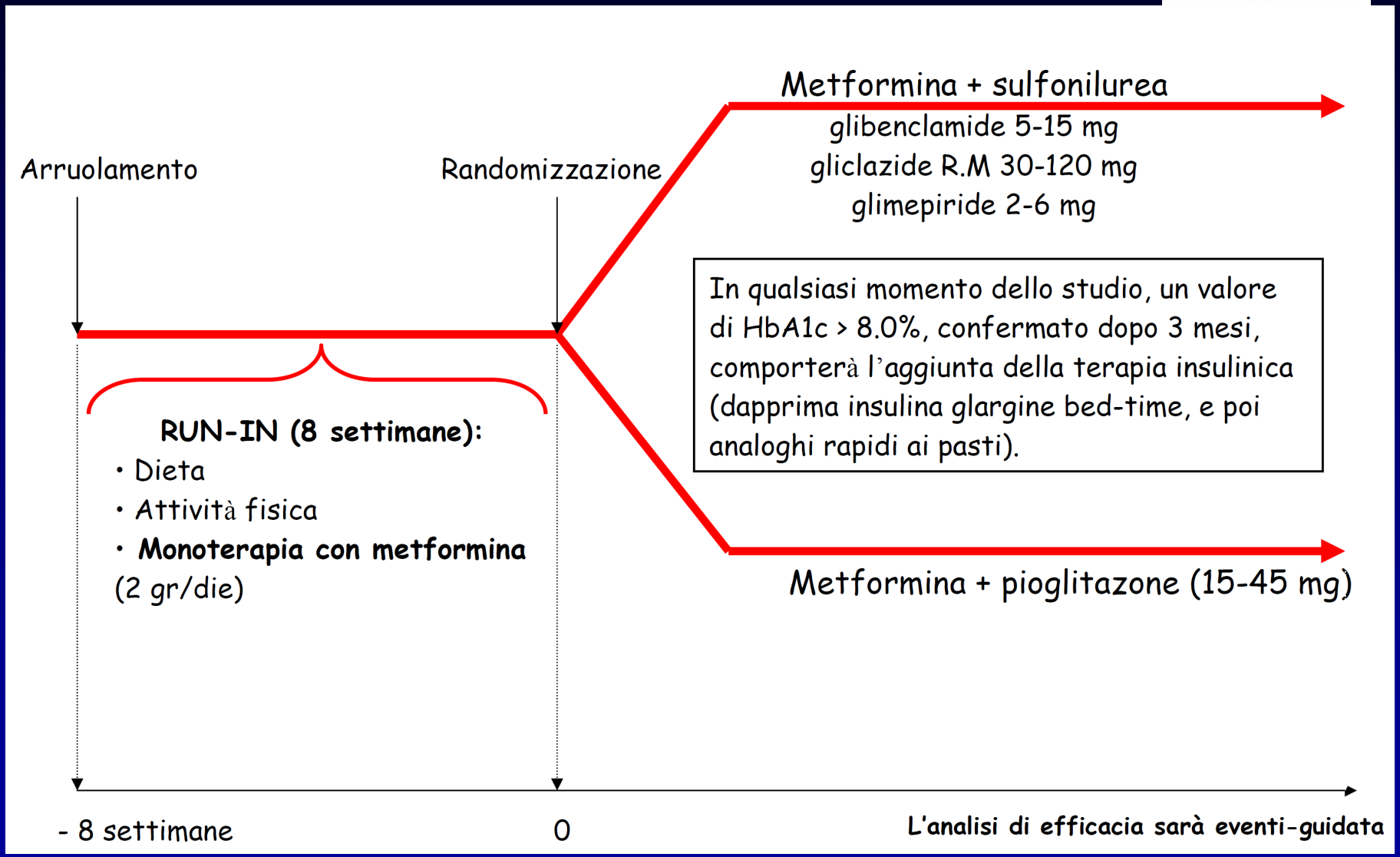
Valutare se in pazienti con diabete mellito tipo 2 non adeguatamente compensati con metformina, l'aggiunta di pioglitazone rispetto all'aggiunta di una sulfonilurea riduce l'incidenza di eventi cardiovascolari. I due trattamenti verranno anche confrontati in termini di efficacia sul compenso glicemico, sui maggiori fattori di rischio cardiovascolare, sicurezza, tollerabilità e costi.

Outcome primario:

L'outcome primario sarà un endpoint composito comprendente: morte per tutte le cause, infarto miocardico non fatale (incluso IMA silente), ictus non fatale, rivascolarizzazione coronarica non programmata.

Lancet/diabetes-endocrinology, Sept 2017

SU / GLINIDE


Arruolamento
Randomizzazione
Metformina + sulfonilurea
glibenclamide 5-15 mg
gliclazide R.M 30-120 mg
glimepiride 2-6 mg
In qualsiasi momento dello studio, un valore di HbA1c > 8.0%, confermato dopo 3 mesi, comporterà l'aggiunta della terapia insulinica (dapprima insulina glargine bed-time, e poi analoghi rapidi ai pasti).
RUN-IN (8 settimane):
• Dieta
• Attività fisica
• Monoterapia con metformina (2 gr/die)
Metformina + pioglitazone (15-45 mg)
- 8 settimane
0
L'analisi di efficacia sarà eventi-guidata

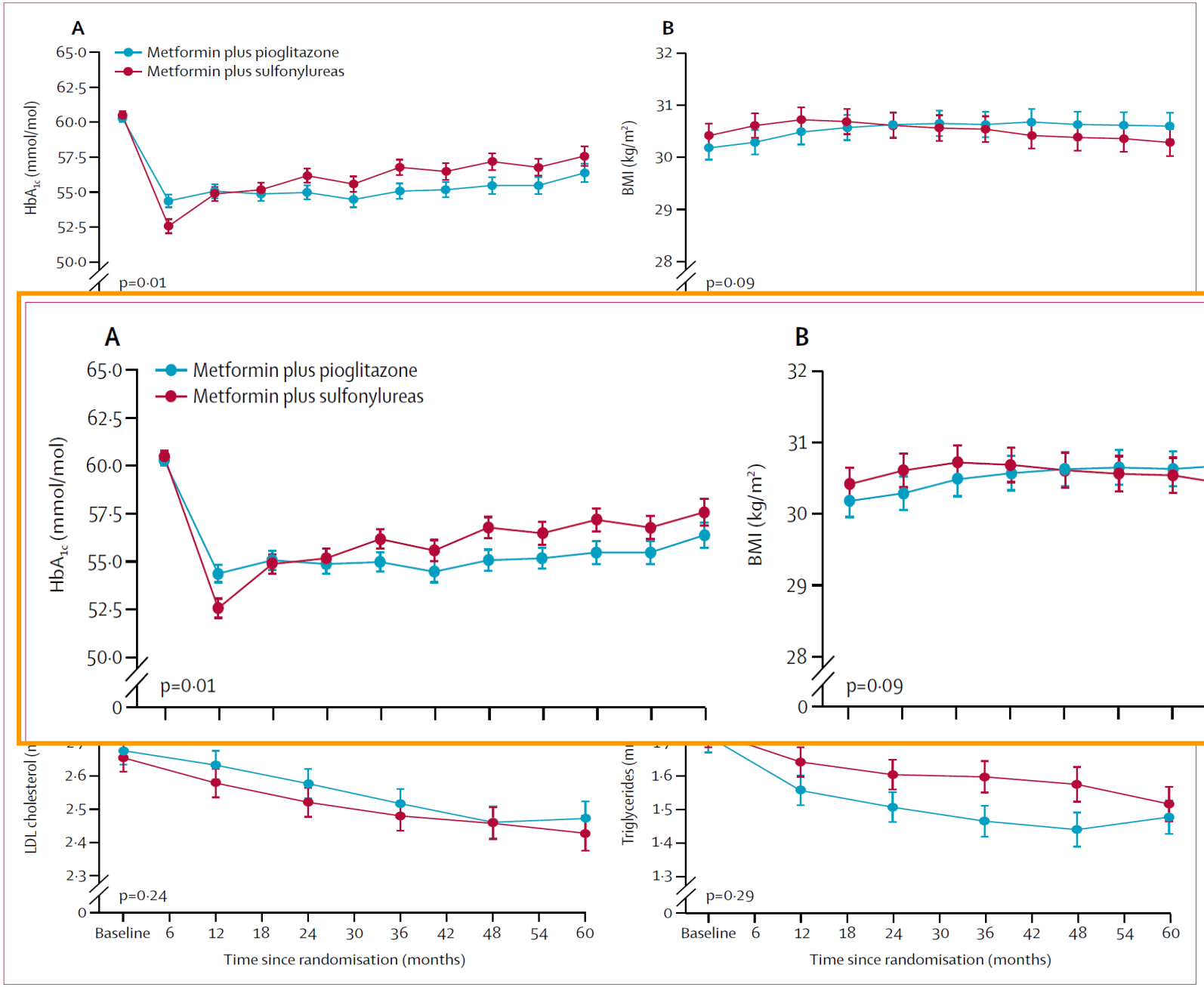
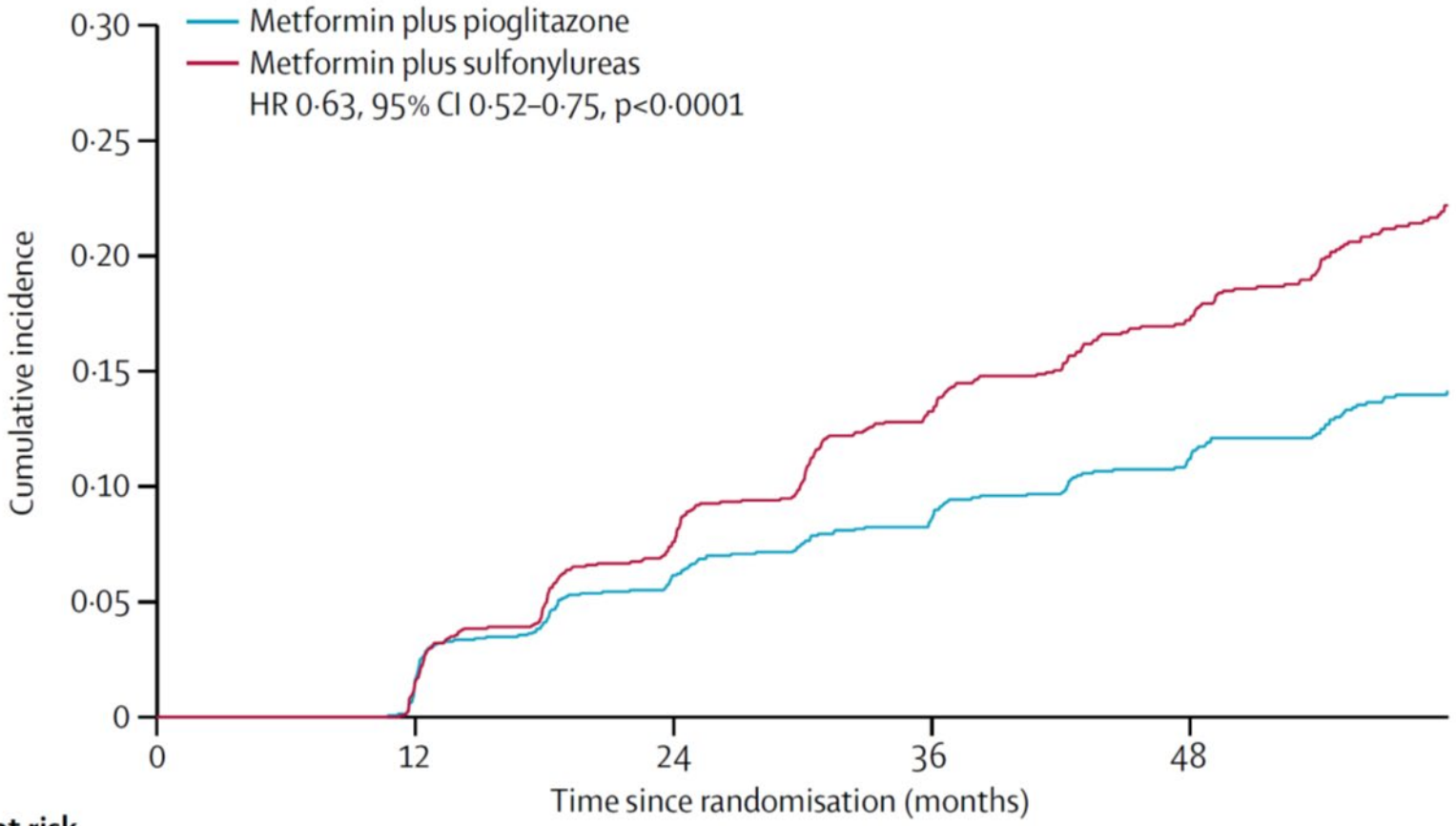


Figure 3: **Cardiovascular risk factors over time**
Data are mean values for HbA_{1c} (A), BMI (B), waist circumference (C), HDL cholesterol (D), LDL cholesterol (E), and triglycerides (F) during the trial period. Error bars show SEs. Data were estimated on the basis of measurements taken at scheduled visits. The analyses are based on a mixed model for repeated measurements, taking into account within-participant correlation. p values were calculated with a mixed model for repeated measurements.

SU / GLINIDE



Number at risk (events)					
Metformin plus pioglitazone	1535 (19)	1449(70)	1321 (33)	1223 (33)	990 (29)
Metformin plus sulfonylureas	1493 (18)	1418 (90)	1287 (77)	1145 (49)	928 (48)

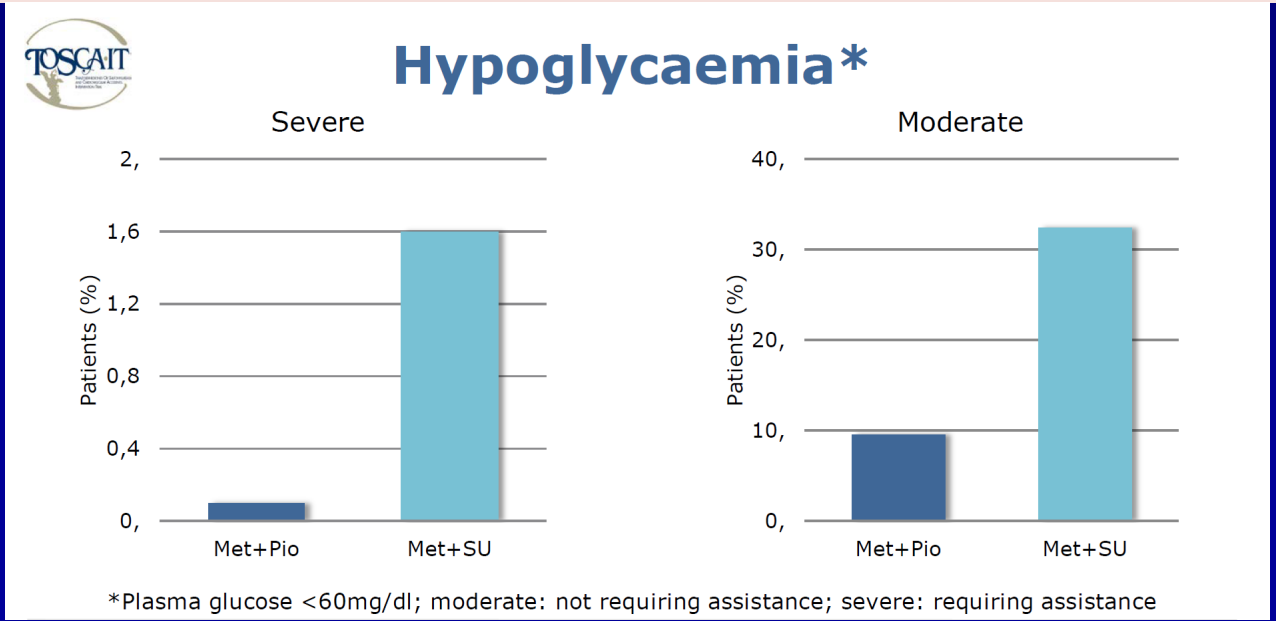
Figure 4: **Cumulative incidence of treatment failure**
Failure of hypoglycaemic treatment was defined as HbA_{1c} of 8% (64 mmol/mol) or above on two consecutive visits 3 months apart. HR=hazard ratio.

SU / GLINIDE

	Metformin plus pioglitazone (n=1535)		Metformin plus sulfonylurea (n=1493)		Incidence rate ratio (95% CI)	p value
	Patients	Events	Patients	Events		
Severe hypoglycaemic events	1 (<1%)	2	24 (2%)	33	0·06 (0·01–0·25)	<0·0001
Moderate hypoglycaemic events	147 (10%)	515	484 (32%)	1868	0·27 (0·24–0·30)	<0·0001

Data are n (%) or n, unless otherwise specified. Hypoglycaemic events were defined as a glucose value lower than 3·3 mmol/L and graded as moderate (not requiring help for treatment) or severe (requiring assistance for treatment). Data are shown for patients who received at least one dose of assigned study drugs.

***Table 4*: Hypoglycaemic events**



SU / GLINIDE

…determinano …to ponderale

…possono caus …ale

…sembrano co …diaco

…aumentano i

AMD ASSOCIAZIONE MEDICI DIABETOLOGI 1974

SID Società Italiana di Diabetologia

Roma, 3 aprile 2015

Oggetto: Glibenclamide e Gliclazide

Gentilissimo Prof. Pani,

scriviamo perché riteniamo opportuno che AIFA prenda una posizione ufficiale in merito a due farmaci della categoria delle sulfoniluree che sono usati per il trattamento del diabete. Questa categoria di farmaci, nella quale potrebbe essere inserita anche repaglinide, che possiede identico meccanismo di azione (1,2), è ancora largamente utilizzata in Italia (quasi il 50% dei diabetici tipo 2)(3,4). Le sulfoniluree, che determinano un significativo e non desiderabile incremento ponderale, stimolano la secrezione di insulina con meccanismo glucosio-indipendente e per questo motivo possono causare ipoglicemia, anche severa e prolungata e talora fatale (5-10). Le sulfoniluree, soprattutto glibenclamide, legandosi ai propri recettori cardiaci e vascolari, sembrano interferire con il fenomeno del precondizionamento ischemico (11-14). In accordo con questi dati, numerosi studi osservazionali e meta-analisi degli stessi suggeriscono che le sulfoniluree aumentino il rischio di eventi cardiovascolari maggiori e di mortalità cardiovascolare e/o per tutte le cause (15-27). Tali effetti avversi sono ben più evidenti per glibenclamide che per altre molecole della classe. La molecola con il più basso rischio di ipoglicemia, il minore impatto sul precondizionamento ischemico e la più bassa associazione con la malattia cardiovascolare e la mortalità è gliclazide (15,17,20,27-30). Il maggiore rischio legato all'uso di glibenclamide è citato nelle principali linee guida e anche nell'algoritmo AIFA per la terapia del diabete. Da notare che nel 2013 gliclazide ha sostituito glibenclamide nella lista dei farmaci essenziali periodicamente redatta dal WHO e che in tale documento glibenclamide viene ricordata solo per non essere adatta ai soggetti di età superiore ai 60 anni.

Con la presente lettera ci permettiamo di suggerire ad AIFA di pronunciarsi in maniera ufficiale raccomandando ai medici che curano le persone con diabete di non usare glibenclamide e di preferire gliclazide in caso di ricorso alle sulfoniluree per la terapia della malattia.

Grazie per l'attenzione e cordiali saluti.

Prof. Antonio Ceriello
Presidente
Associazione Medici Diabetologi

Prof. Enzo Bonora
Presidente
Società Italiana di Diabetologia

SU / GLINIDE: pro & contro

pro
rapido
poco costoso

contro
ipoglicemia!
rapido fallimento beta cellulare
aumento di peso
aumentato rischio CV
non indicato in IRC

anziano
aumentato rischio di infarto del miocardio

Terapia farmacologica nell'anziano

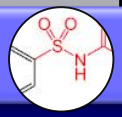
	rischio di IPO	uso in IRC	prev CVD	scomp card	fen glic	riserva β-cell	stato nutr.	facilità somm.
Metformina	NO	no<30	SI	NO	digiuno	=	−	XR
SU e glinidi	SI	gliclazide only	rischio	neutro	vario	SI	+	no
pioglitazone								
Gliptine								
GLP-1 RA								
Gliflozine								
Insulina bas								

Classi di farmaci per diabete mellito tipo 2

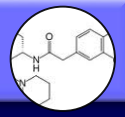
- Detemir
- Glargine
- Glargine U300
- Degludec
- NPH

INSULINA 

- Gliclazide
- Glibenclamide/glyburide
- Glimepiride
- Gliquidone
- Glipizide

SULFONILUREA 

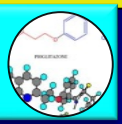
- Nateglinide
- Repaglinide

GLINIDI 

- Metformin

BIGUANIDI 

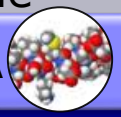
- Pioglitazone

TZDs 

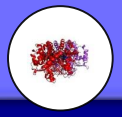
- Sitagliptin
- Saxagliptin
- Vildagliptin
- Linagliptin
- Alogliptin

GLIPTINE 

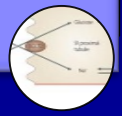
- Exenatide LAR
- Liraglutide
- Lixisenatide
- Dulaglutide

GLP-1 RA 

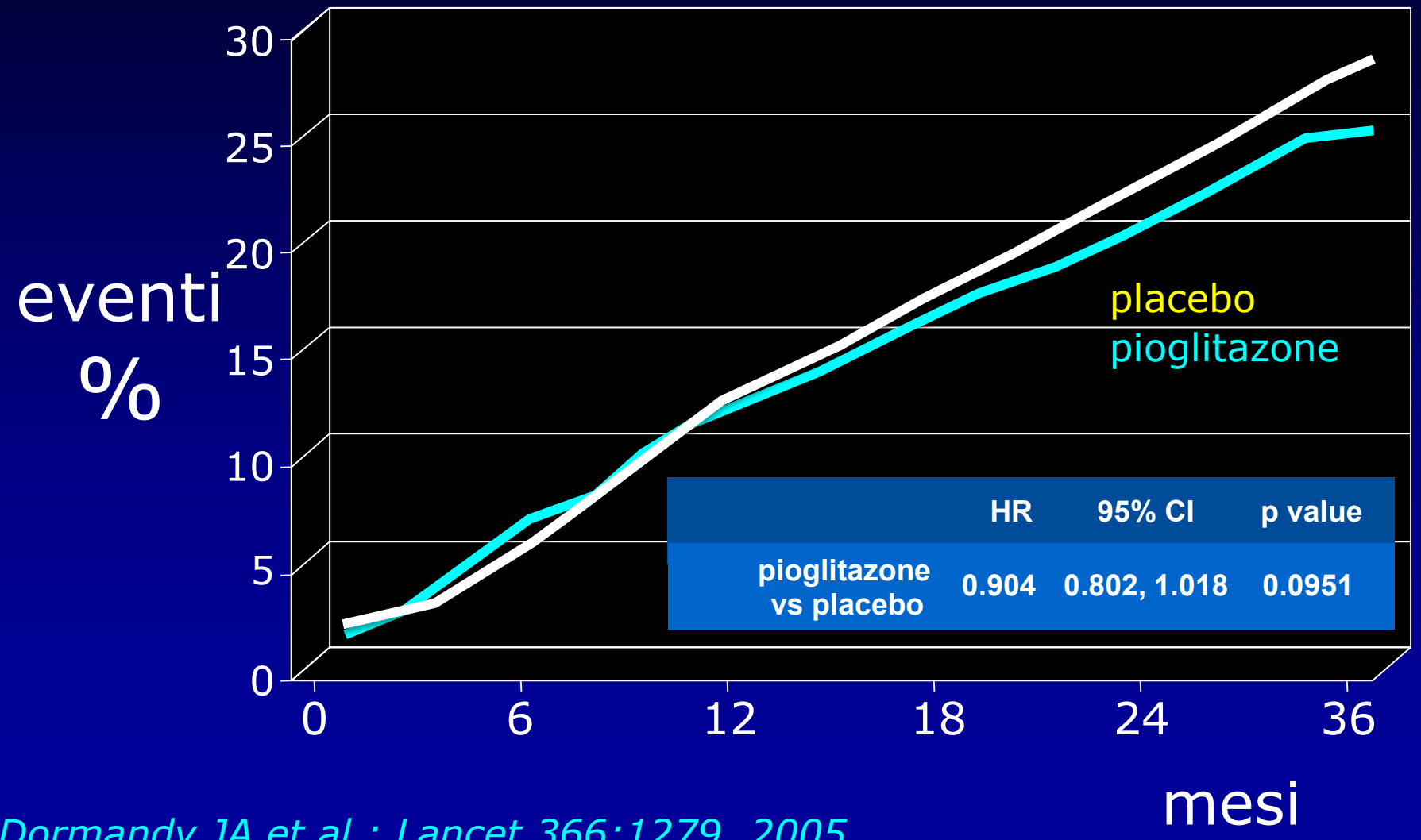
- Acarbose
- Miglitol

INIBITORI ALFA GLUCOSIDASI 

- Dapagliflozin
- Canagliflozin
- Empagliflozin

INIBITORI SGLT2 

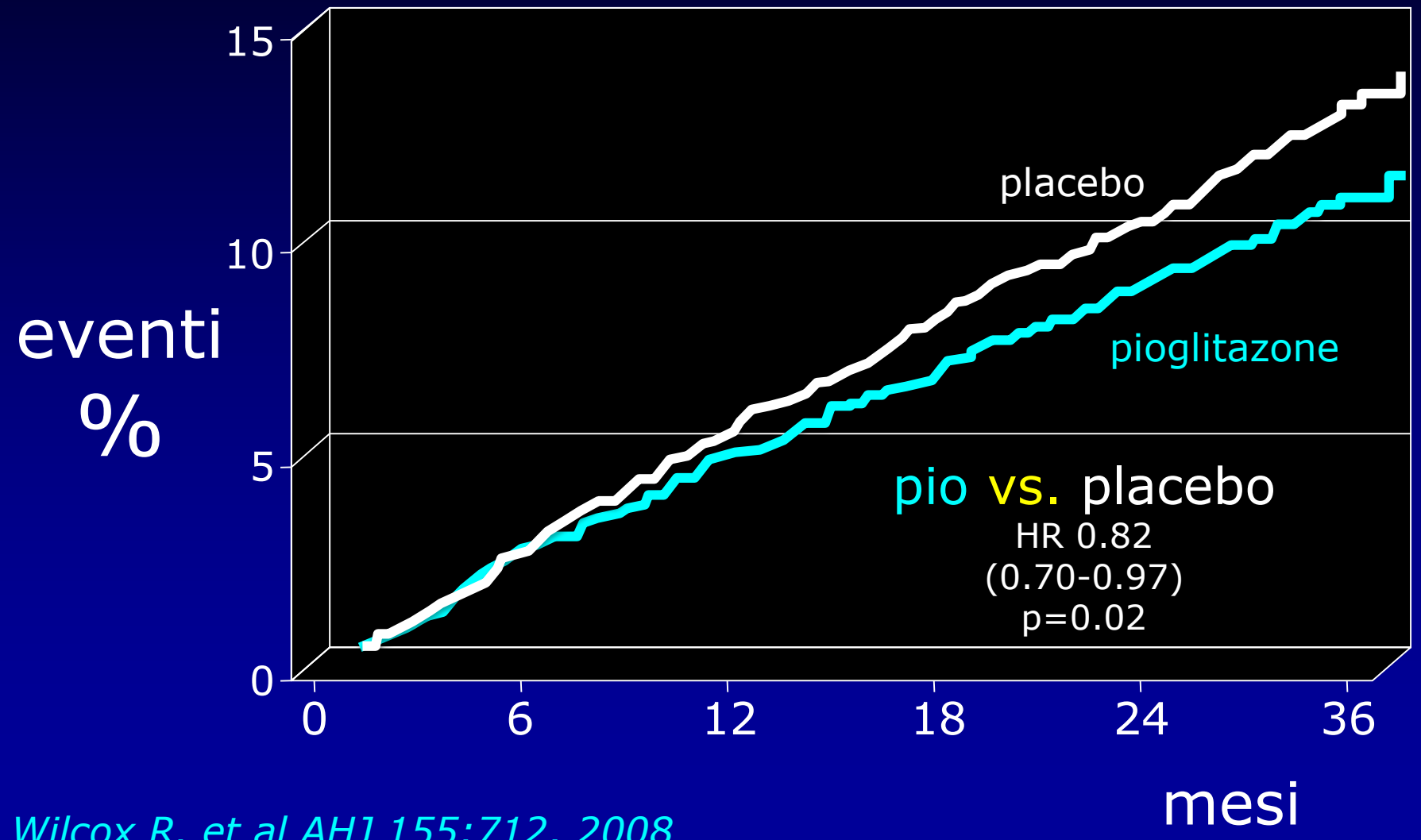
PROACTIVE: outcome primario



Dormandy JA et al.: Lancet 366:1279, 2005

PROACTIVE: MACE

IMA, stroke and mortalità CV

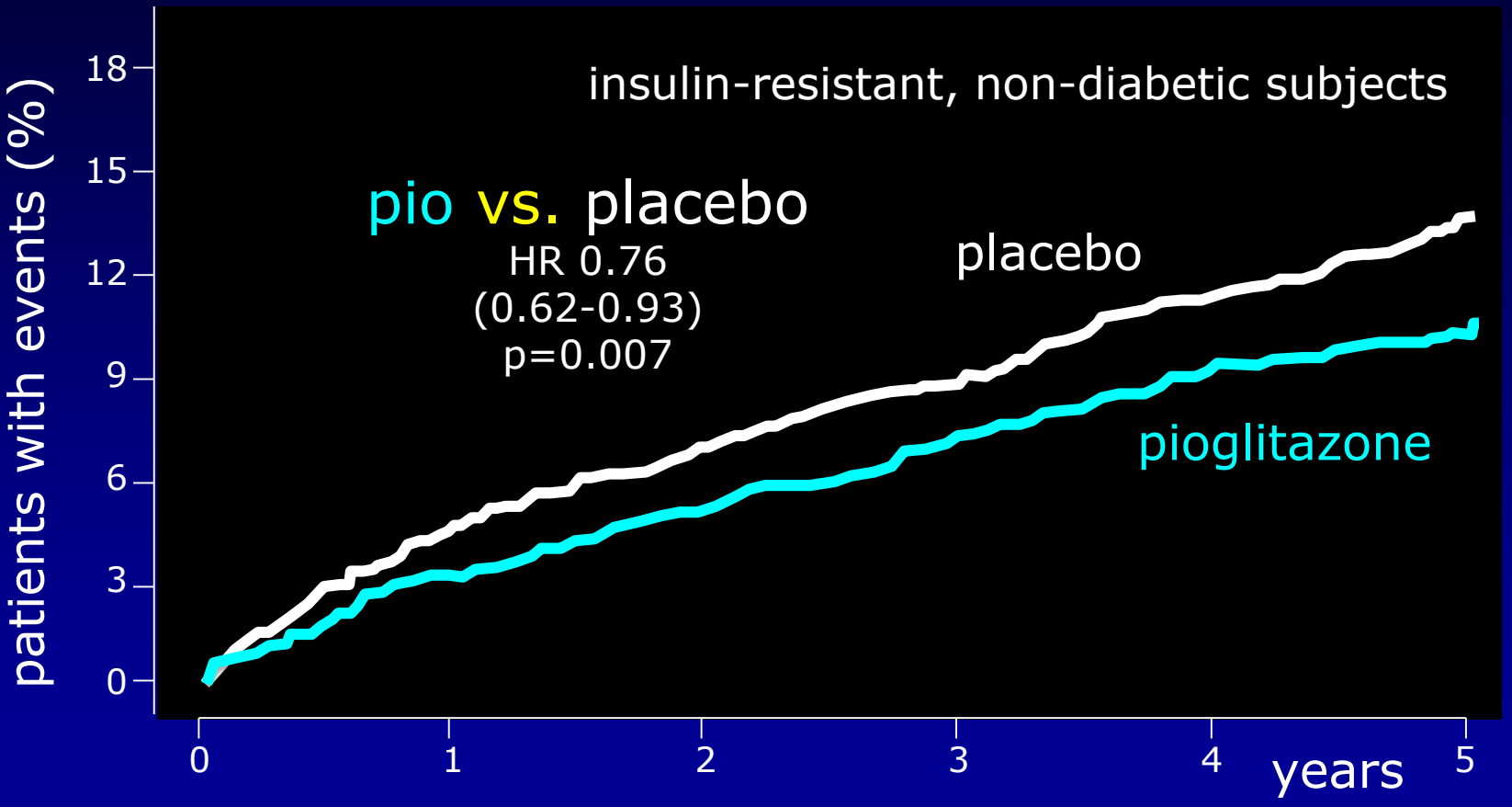


Wilcox R. et al AHJ 155:712, 2008

IRIS primary endpoint

(stroke or MI, fatal or non-fatal)

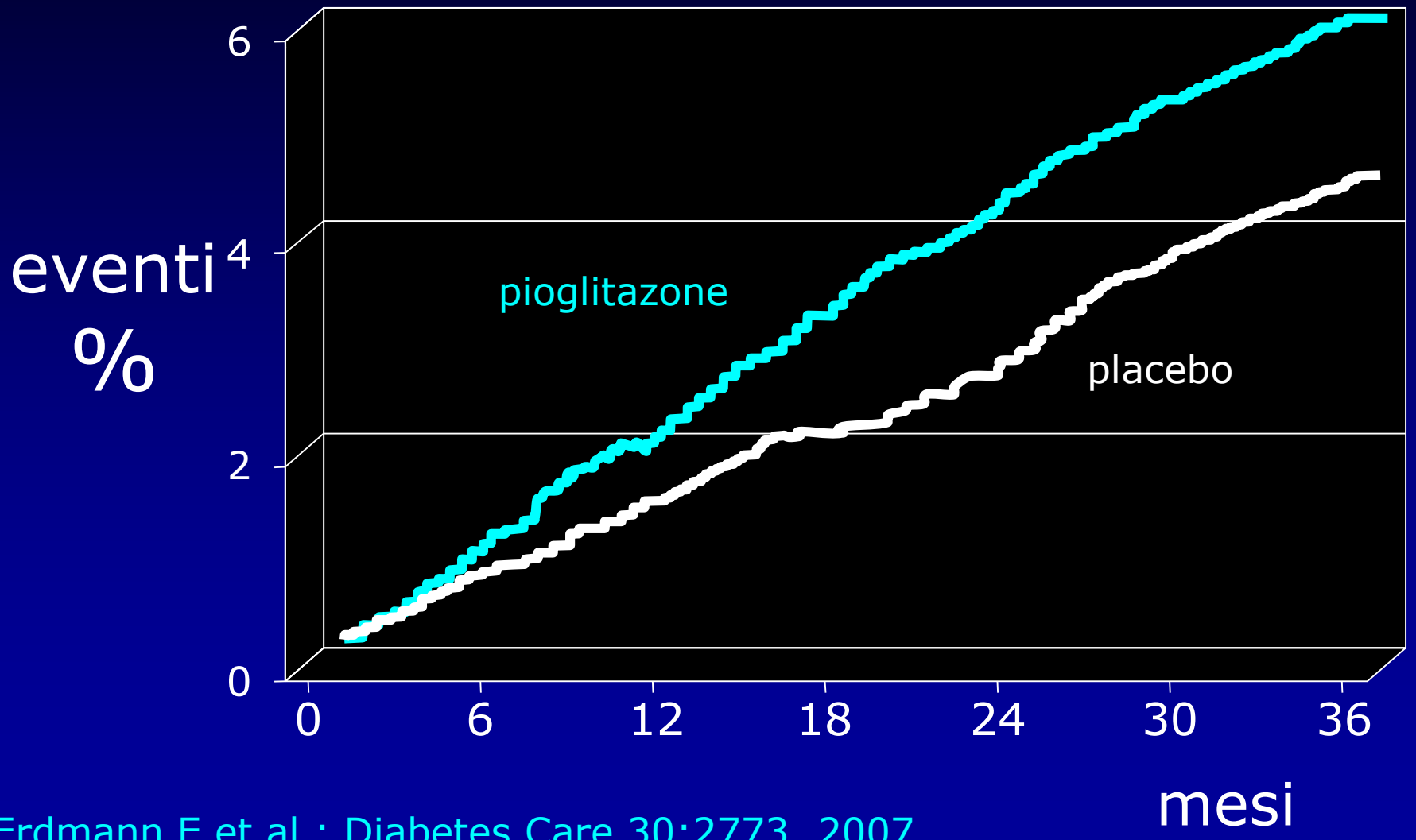
Insulin Resistance Intervention after Stroke



Kernan WN et al. NEJM 374:1321, 2016

The NEW ENGLAND JOURNAL of MEDICINE

PROACTIVE: *Heart failure risk*



Erdmann E et al.: Diabetes Care 30:2773, 2007

pioglitazone: pro & contro

pro
prevenzione CV secondaria
no ipoglicemia
economico

contro
azione lenta
ritenzione di liquidi e scompenso cardiaco
aumento di peso
fratture

anziano
aumento di peso (per i sottopeso)

Terapia farmacologica nell'anziano

	rischio di IPO	uso in IRC	prev CVD	scomp card	fen glic	riserva β-cell	stato nutr.	facilità somm.
Metformina	NO	no<30	SI	NO	digiuno	=	−	XR
SU e glinidi	SI	gliclazide only	rischio	neutro	vario	SI	+	no
pioglitazone	NO	no<15	SI	SI	digiuno	=	+	si
Gliptine								
GLP-1 RA								
Gliflozine								
Insulina bas								

Classi di farmaci per diabete mellito tipo 2

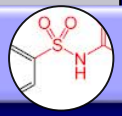
- Detemir
- Glargine
- Glargine U300
- Degludec
- NPH

INSULINA



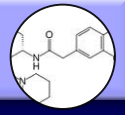
- Gliclazide
- Glibenclamide/glyburide
- Glimepiride
- Gliquidone
- Glipizide

SULFONILUREA



- Nateglinide
- Repaglinide

GLINIDI



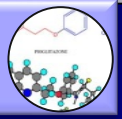
- Metformin

BIGUANIDI



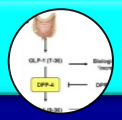
- Pioglitazone

TZDs



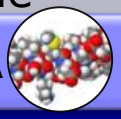
- Sitagliptin
- Saxagliptin
- Vildagliptin
- Linagliptin
- Alogliptin

GLIPTINE



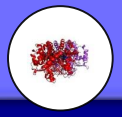
- Exenatide LAR
- Liraglutide
- Lixisenatide
- Dulaglutide

GLP-1 RA



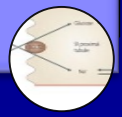
- Acarbose
- Miglitol

INIBITORI ALFA GLUCOSIDASI



- Dapagliflozin
- Canagliflozin
- Empagliflozin

INIBITORI SGLT2

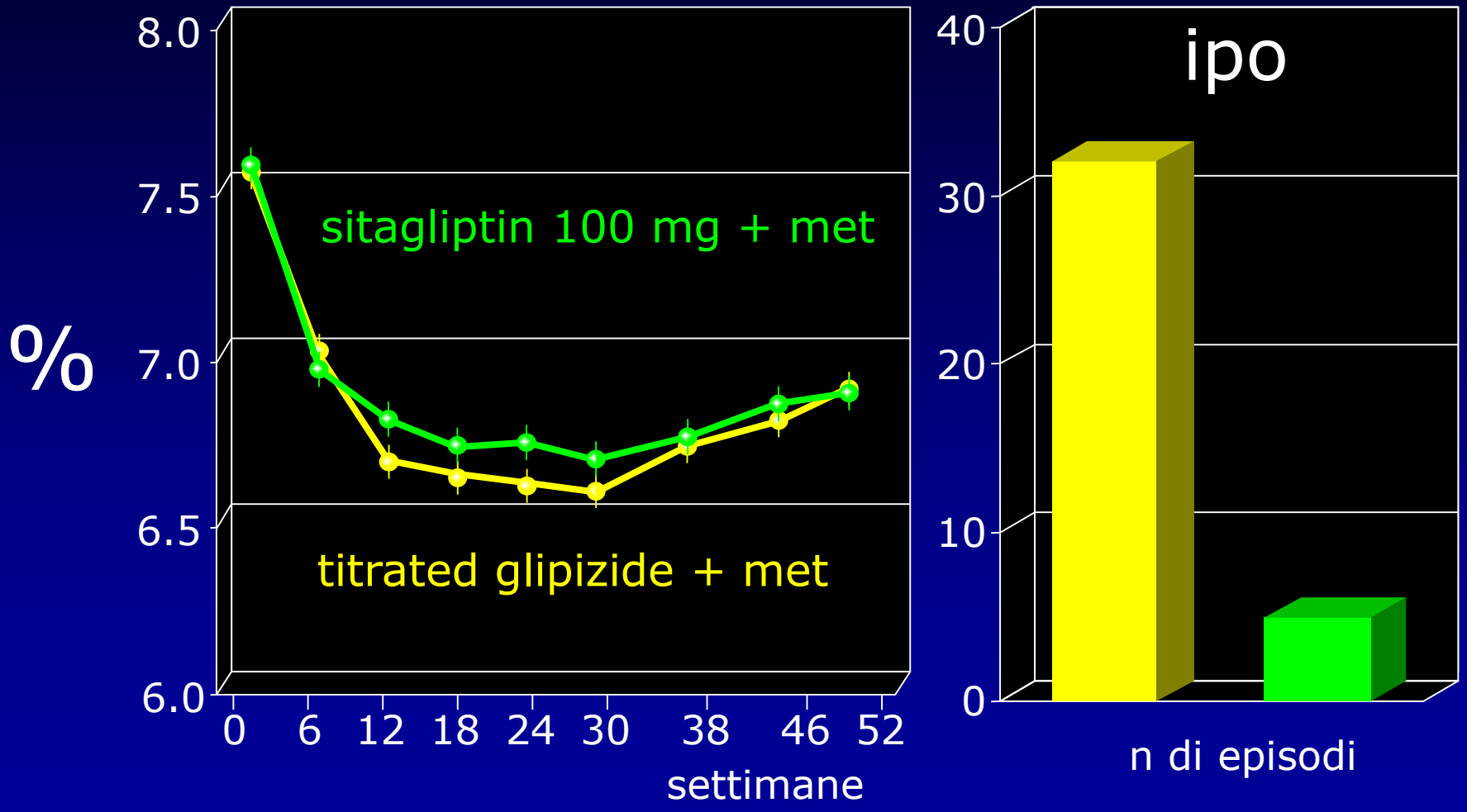


effetto incretinico

- stimola secrezione insulinica ‘glucosio-dipendente’
- inibisce glucagone
- rallenta svuotamento gastrico
- anoressizzante
- aumenta massa b-cellulare

gliptine vs. glipizide

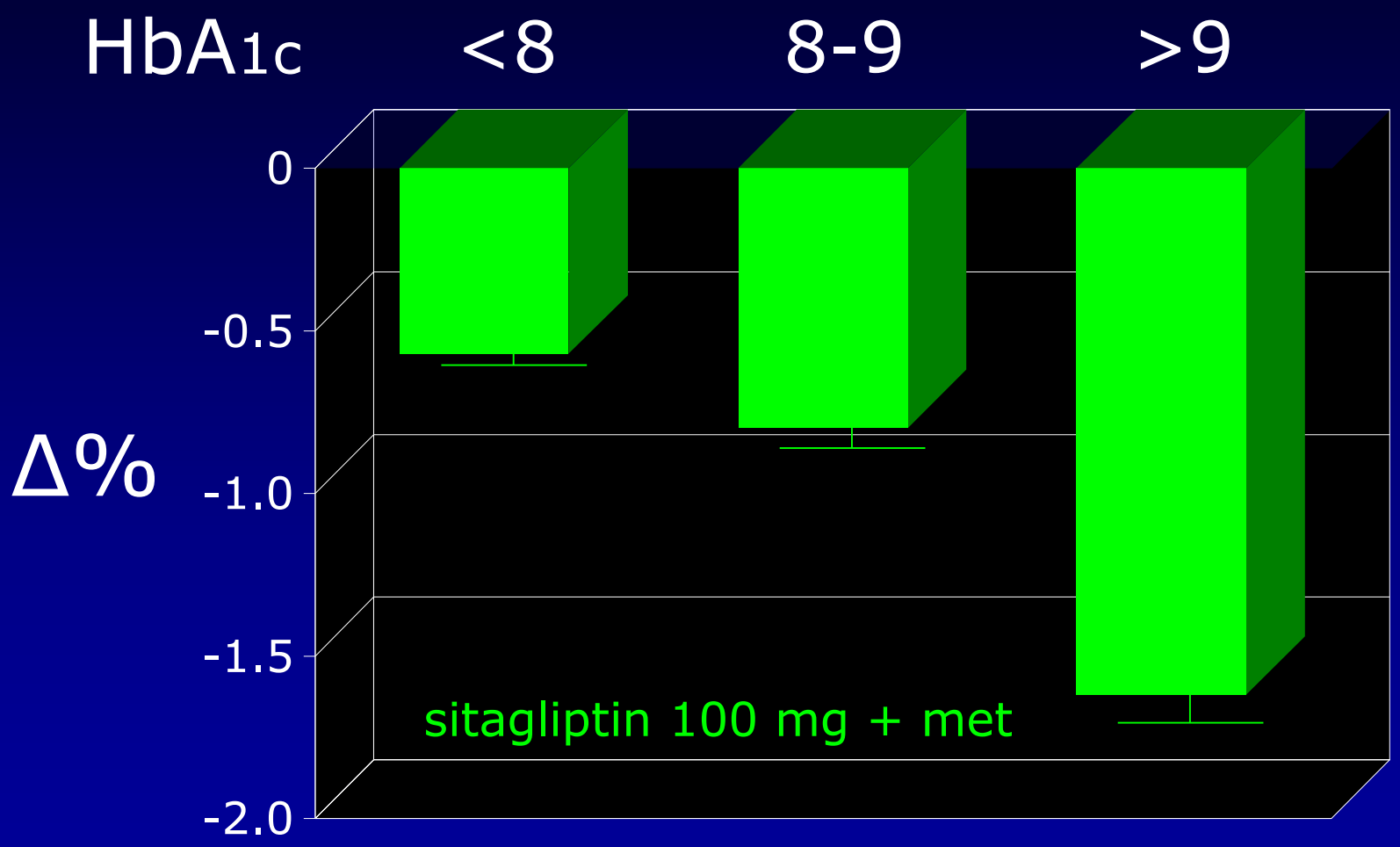
add-on a metformina



Nauck MA Diab Ob Metab 9:194, 2007

gliptine: efficacia 'graduata'

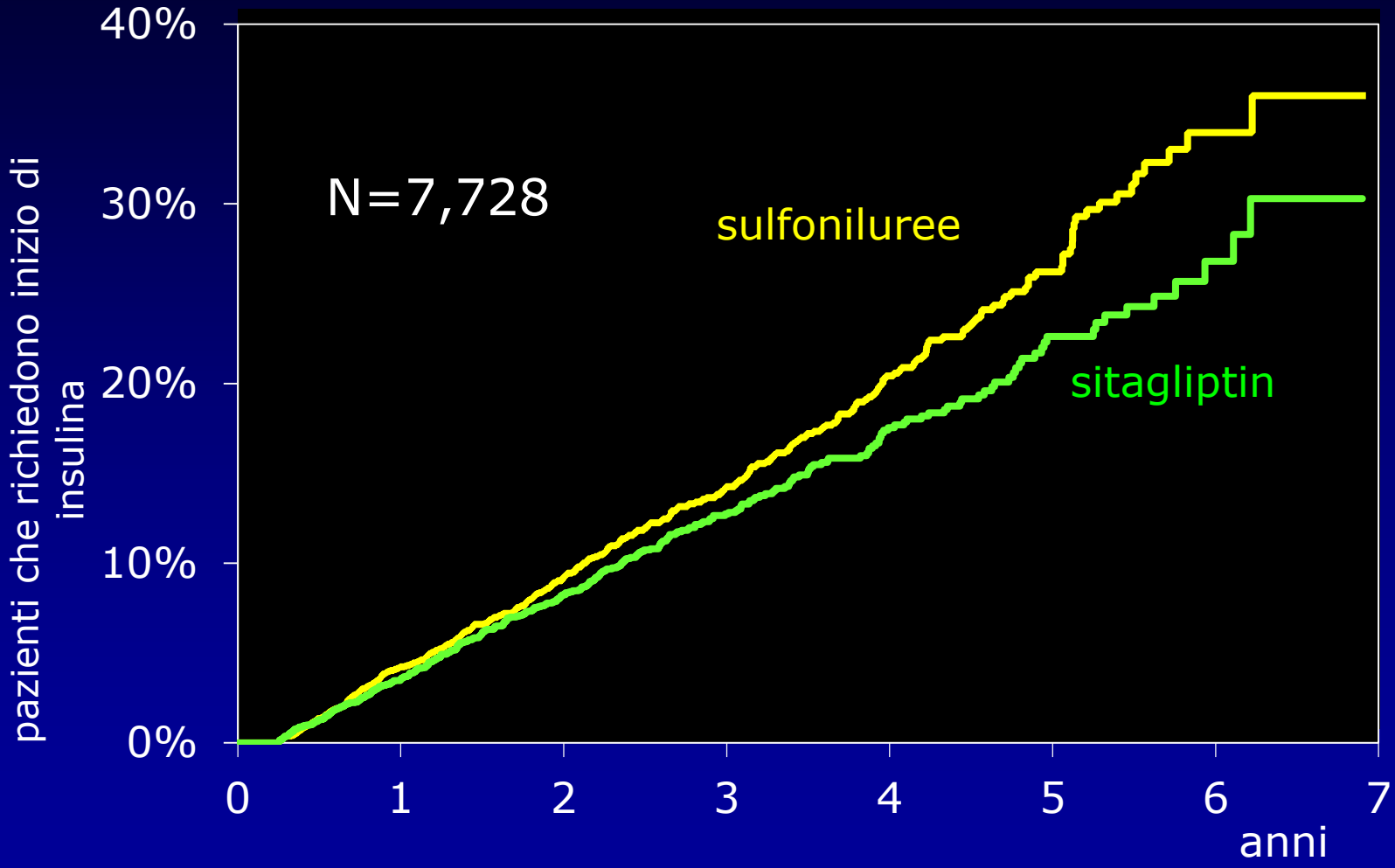
the higher is HbA1c, the higher is efficacy



Reductions are placebo-subtracted

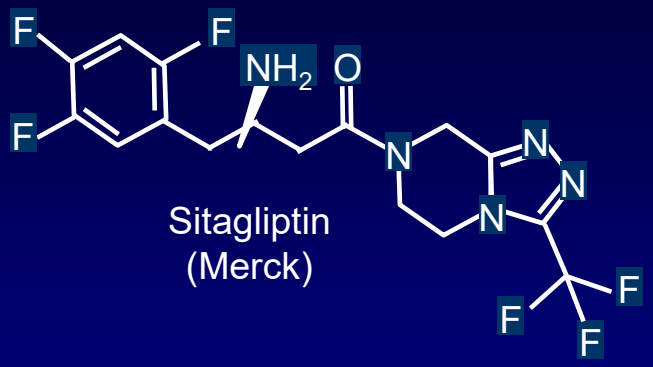
Nauck MA Diab Ob Metab 9:194, 2007

gliptine: tempo per inizio tp insulinica

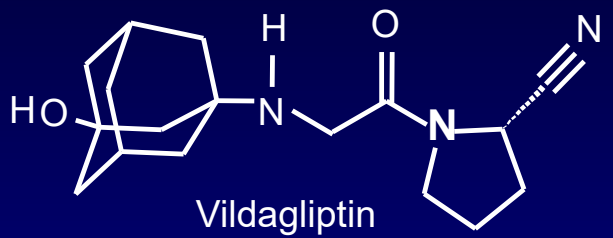


Valensi P et al. for The Odyssee Observational Study: Diabetes Metab 41:231, 2015

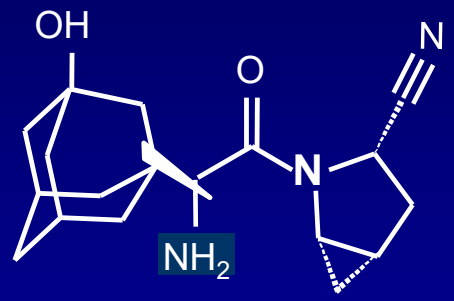
...ma...
DPP-4 inibitori sono differenti



Sitagliptin
(Merck)



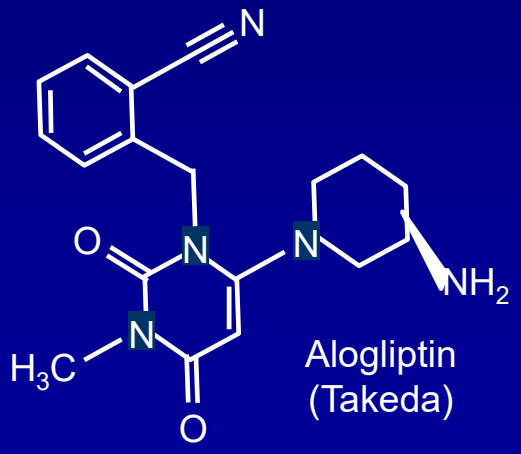
Vildagliptin
(Novartis)



Saxagliptin
(BMS/Astra Zeneca)



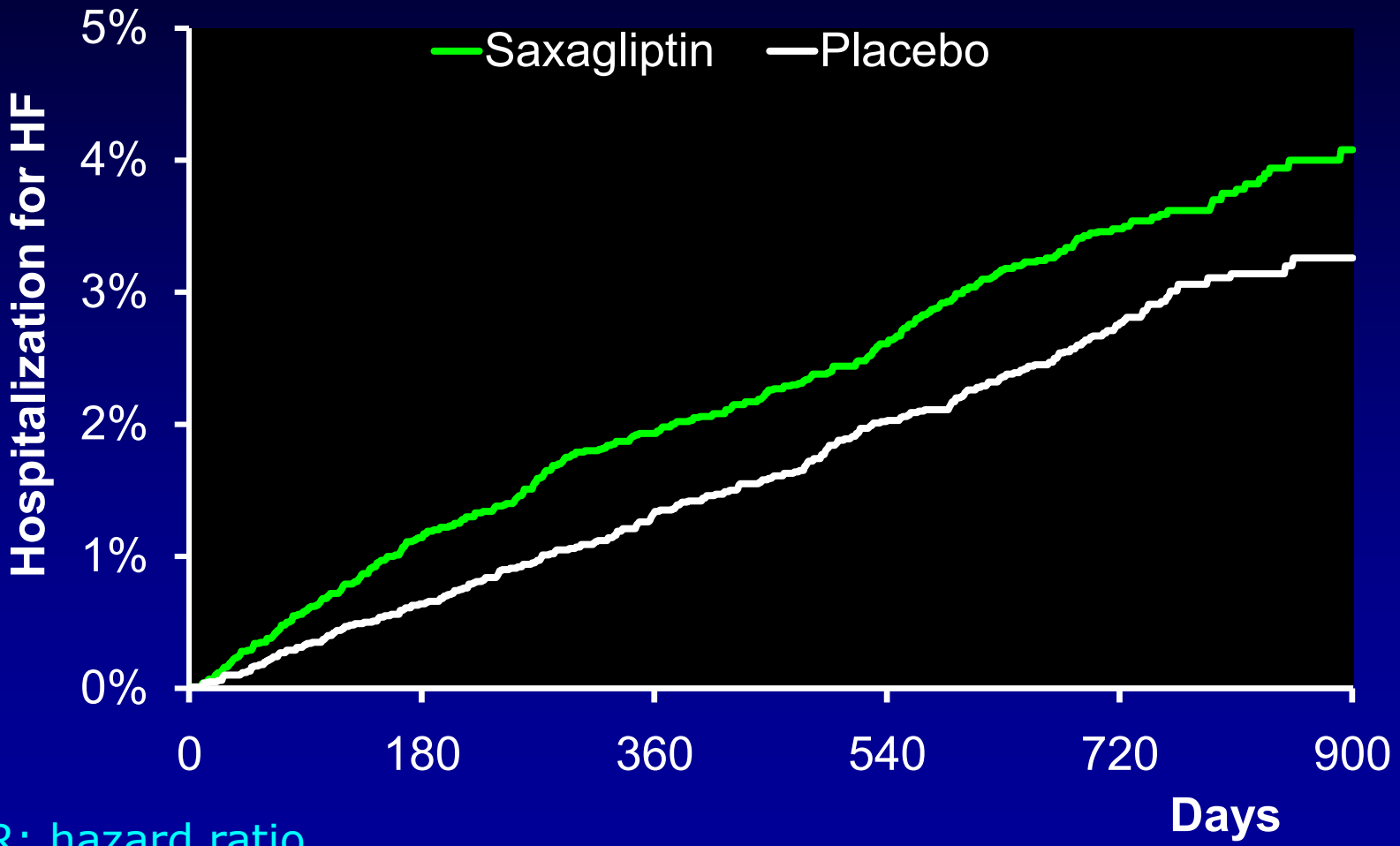
Linagliptin
(Boehringer Ingelheim)



Alogliptin
(Takeda)

Source: CF Deacon

SAVOR: Rates of Risk of Hospitalization for HF Over Time

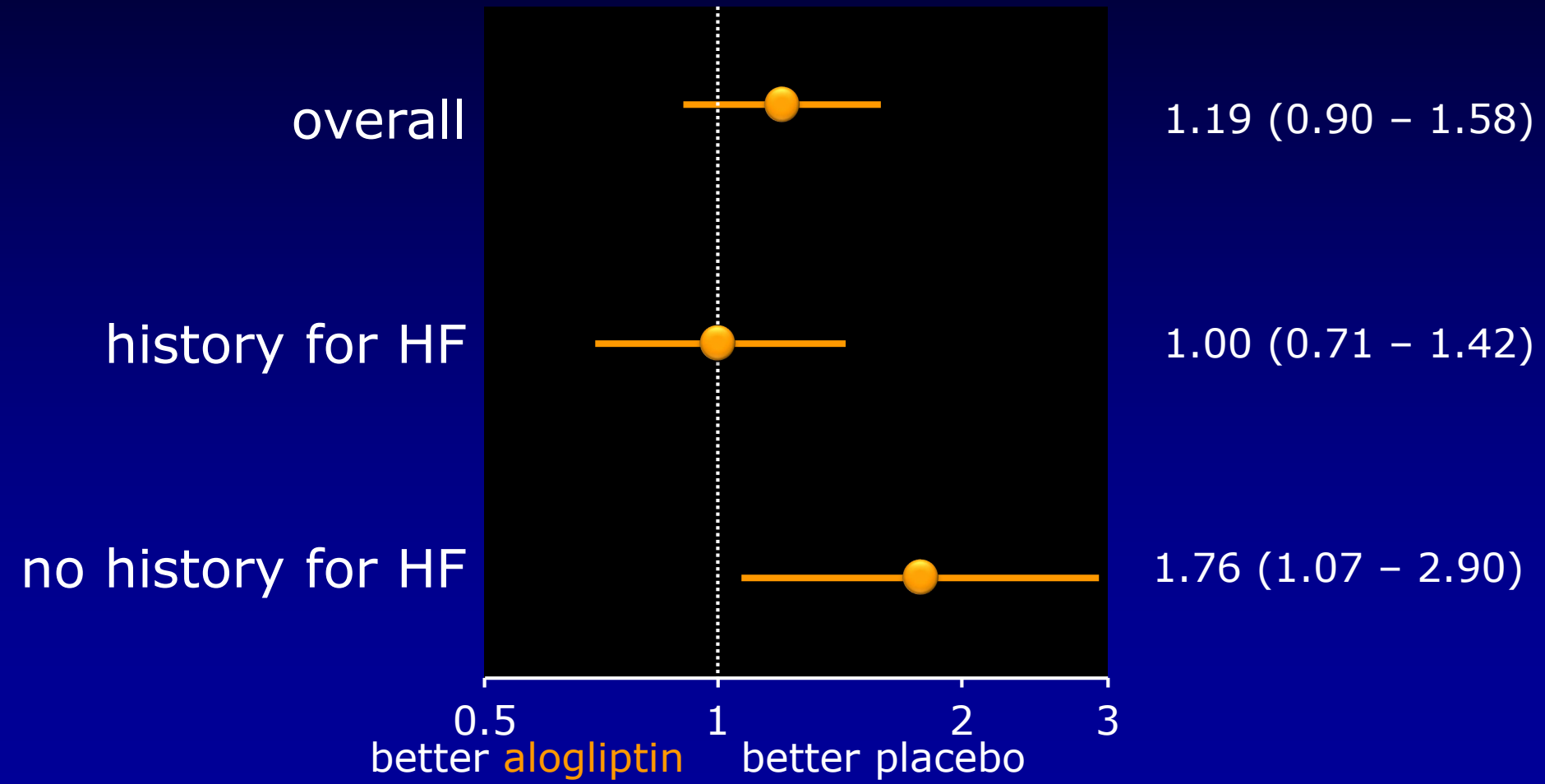


HR: hazard ratio

Scirica BM, et al. November 2013.

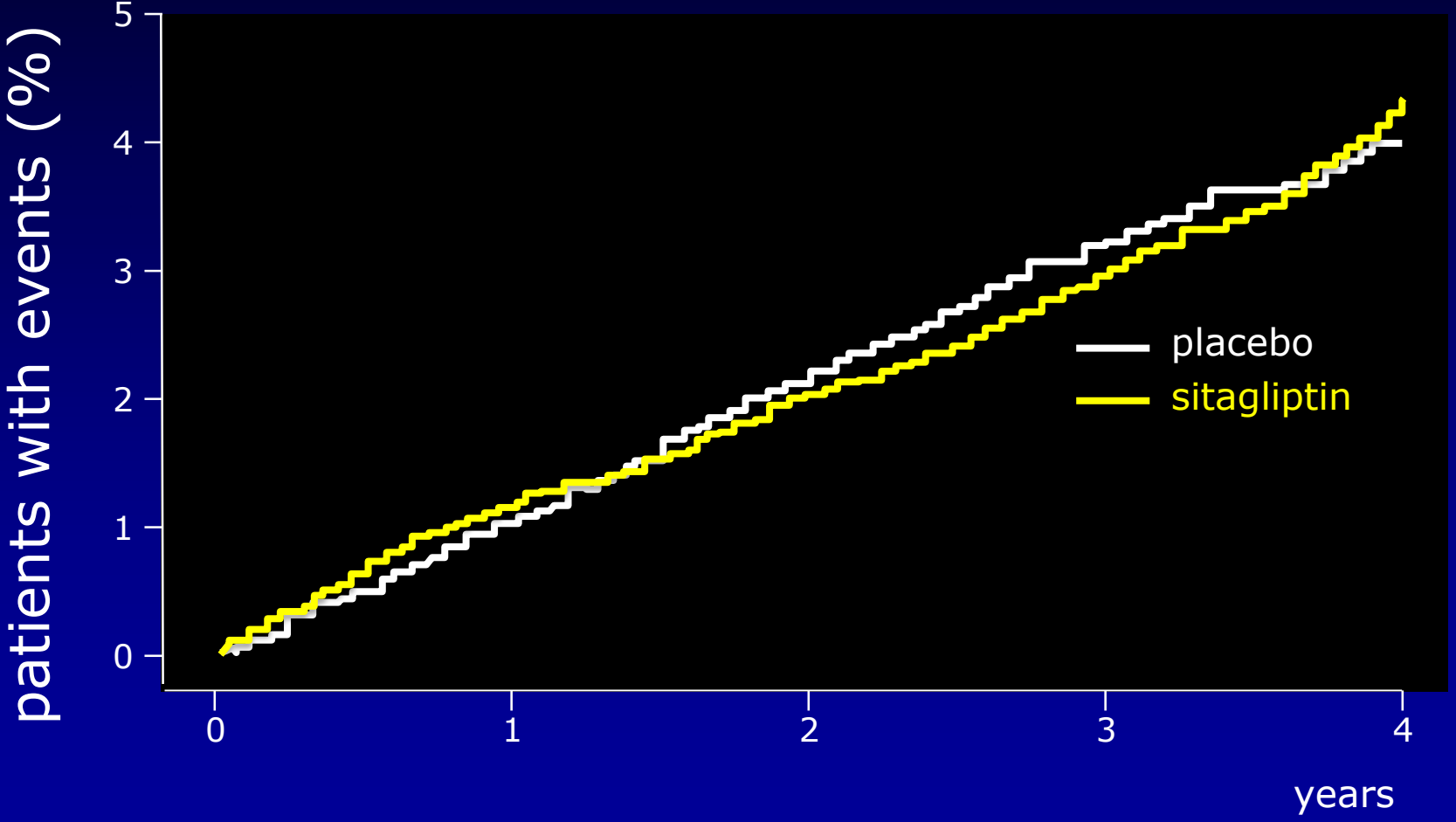
EXAMINE: HF Hospitalizations

(by history of Heart Failure)



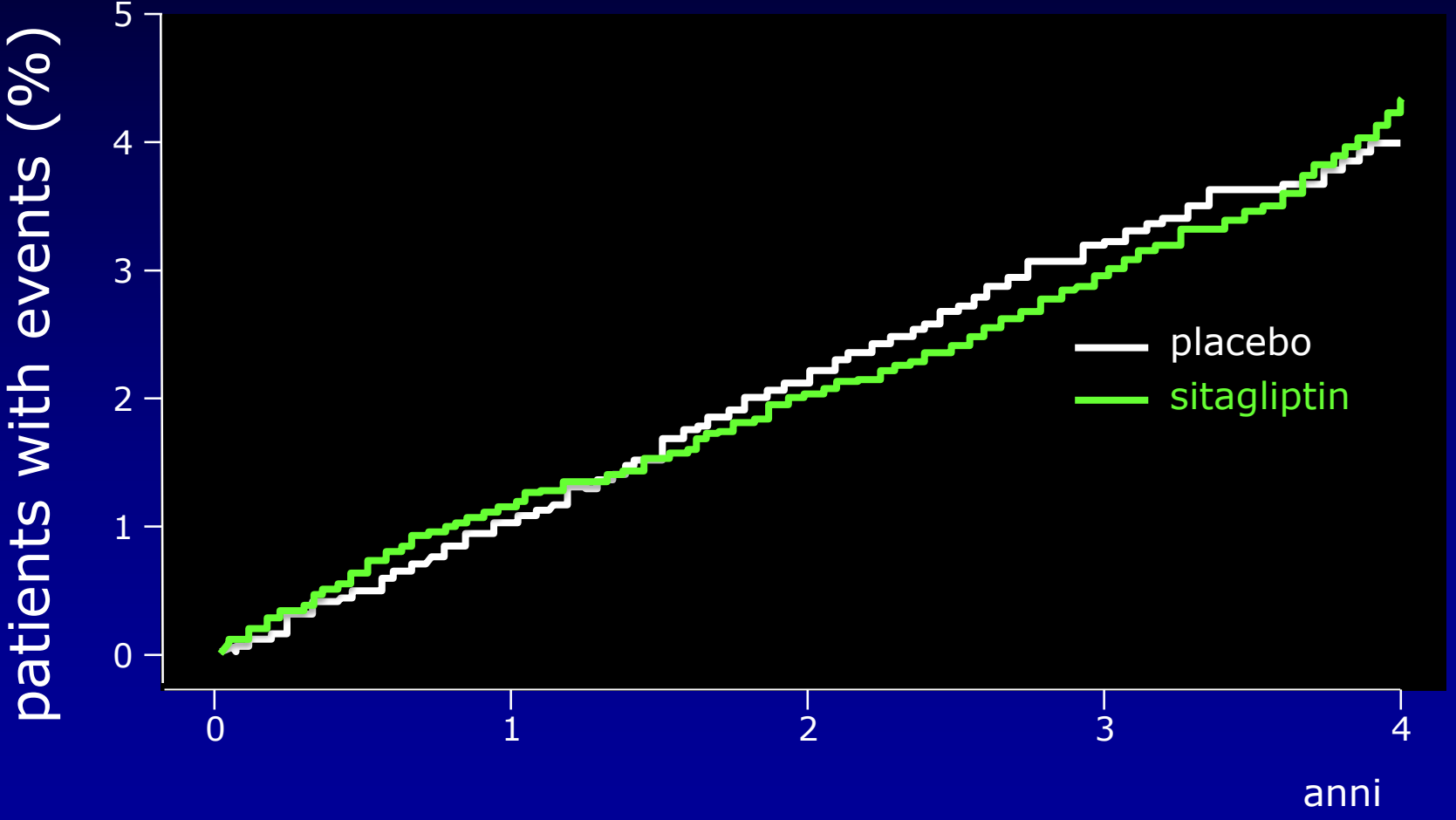
White WB et al. NEJM 369:1327; 2013

TECOS: First hospitalization for HF



TECOS, McGuire DK et al.: JAMA Cardiol 1:126, 2016

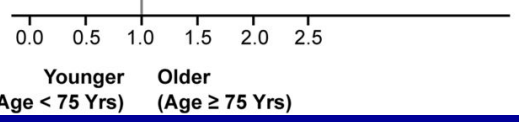
TECOS: primo ricovero per HF



TECOS, McGuire DK et al.: JAMA Cardiol 1:126, 2016

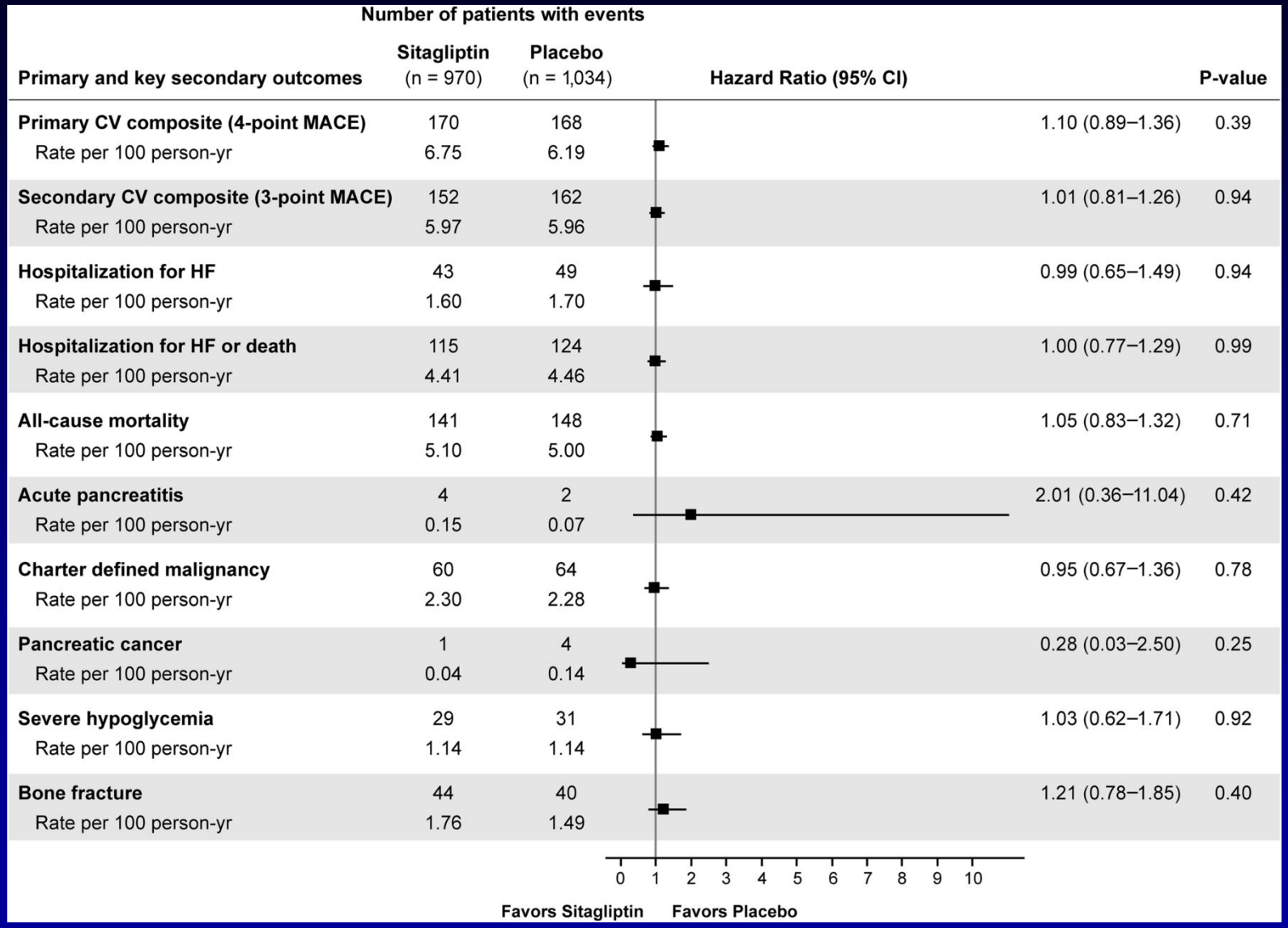
TECOS: anziani a maggior rischio

Primary and key secondary outcomes	Number of patients with events: Age ≥ 75 Yrs (n = 2,004)	Number of patients with events: Age < 75 Yrs (n = 12,347)	Hazard Ratio (95% CI)	P-value
Primary CV composite (4-point MACE)	338	1,281	1.72 (1.52–1.94)	<0.001
Rate per 100 person-yr	6.46	3.67		
Secondary CV composite (3-point MACE)	314	1,117	1.86 (1.63–2.11)	<0.001
Rate per 100 person-yr	5.96	3.17		
Hospitalization for HF	92	359	1.48 (1.18–1.87)	<0.001
Rate per 100 person-yr	1.70	1.00		
Hospitalization for HF or death	239	789	2.02 (1.75–2.34)	<0.001
Rate per 100 person-yr	4.44	2.20		
All-cause mortality	289	757	2.52 (2.20–2.89)	<0.001
Rate per 100 person-yr	5.04	2.03		
Acute pancreatitis	6	29	1.17 (0.48–2.83)	0.73
Rate per 100 person-yr	0.11	0.08		
Charter defined malignancy	124	427	1.76 (1.43–2.15)	<0.001
Rate per 100 person-yr	2.29	1.18		
Pancreatic cancer	5	18	1.52 (0.56–4.14)	0.41
Rate per 100 person-yr	0.09	0.05		
Severe hypoglycemia	60	238	1.53 (1.15–2.03)	0.004
Rate per 100 person-yr	1.14	0.68		
Bone fracture	84	287	1.84 (1.44–2.35)	<0.001
Rate per 100 person-yr	1.62	0.81		



Bethel MA et al. Dia Care 40:494, 2017

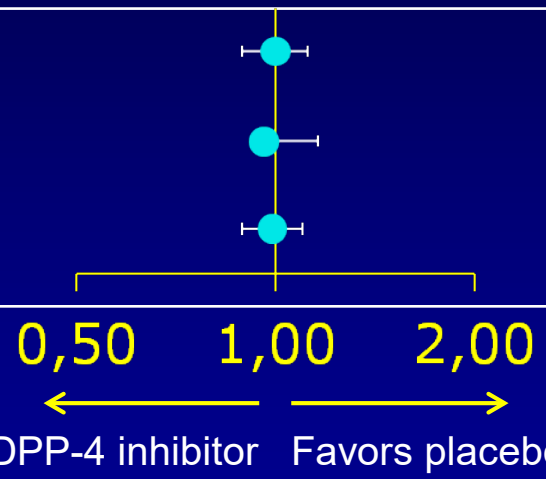
TECOS: sicurezza negli anziani



Bethel MA et al. Dia Care 40:494, 2017

inibitori DPP-4 – safety 3P-MACE

	HR (95% CI)	HR (95% CI)	*p*-value
SAVOR-TIMI 53[1]	1.00 (0.89, 1.12)		0.99
EXAMINE[2]	0.96 (n/a, 1.16)		0.32
TECOS[3]	0.99 (0.89, 1.10)		0.84

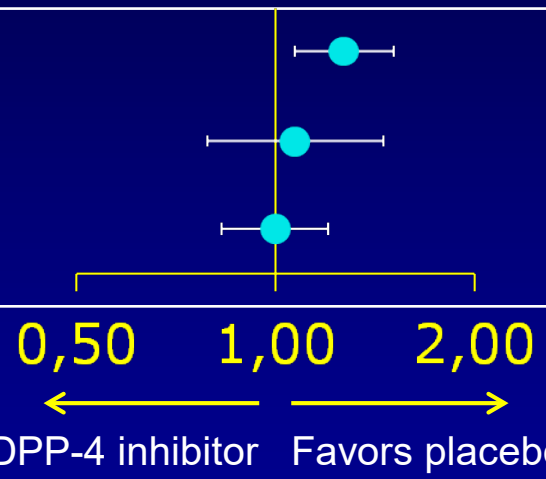


TECOS: Sitagliptin was noninferior to placebo for the primary composite cardiovascular outcome (hazard ratio, 0.98; 95% CI, 0.88 to 1.09; P<0.001)

1. Scirica BM et al. N Engl J Med 2013;369:1317;
2. White WB et al. N Engl J Med 2013;369:1327;
3. Green JB et al. N Engl J Med 2015;373:232

inibitori DPP-4 e HF

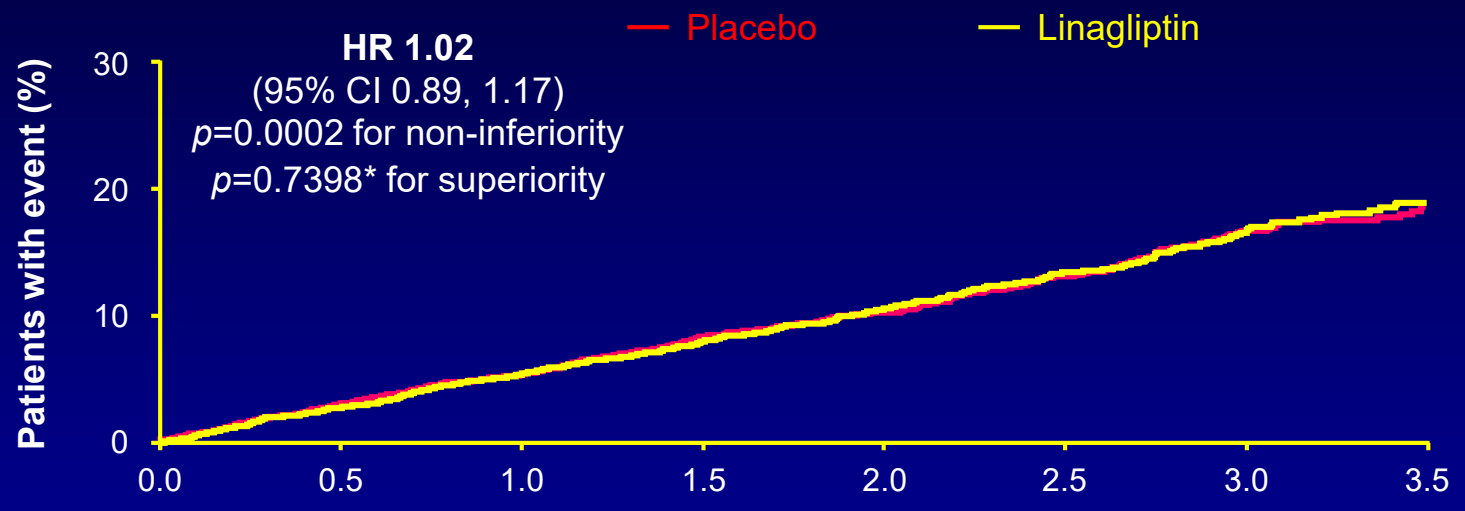
	HR (95% CI)	HR (95% CI)	*p*-value
SAVOR-TIMI 53[1]	1.27 (1.07, 1.51)		0.007
EXAMINE[2]	1.07 (0.79, 1.46)		0.657
TECOS[3]	1.00 (0.83, 1.20)		0.98



1. Scirica BM et al. N Engl J Med 2013;369:1317;
2. White WB et al. N Engl J Med 2013;369:1327;
3. Green JB et al. N Engl J Med 2015;373:232

linagliptin - long-term CV safety

Time to first occurrence of 3P-MACE



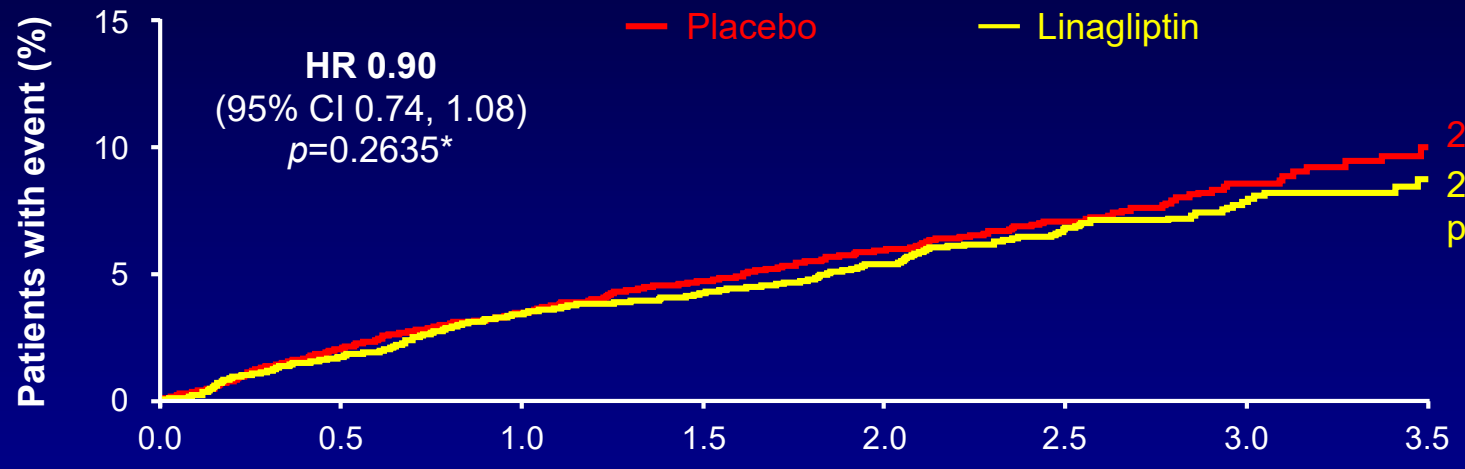
No. of patients								
Placebo (n)	3,485	3,353	3,243	2,625	1,931	1,285	758	251
Linagliptin (n)	3,494	3,373	3,254	2,634	1,972	1,306	778	269

3P-MACE, 3-point major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke)

Rosenstock J et al. JAMA 2018, 9 Nov

linagliptin – no rischio HF

Time to first occurrence of adjudication-confirmed HHF

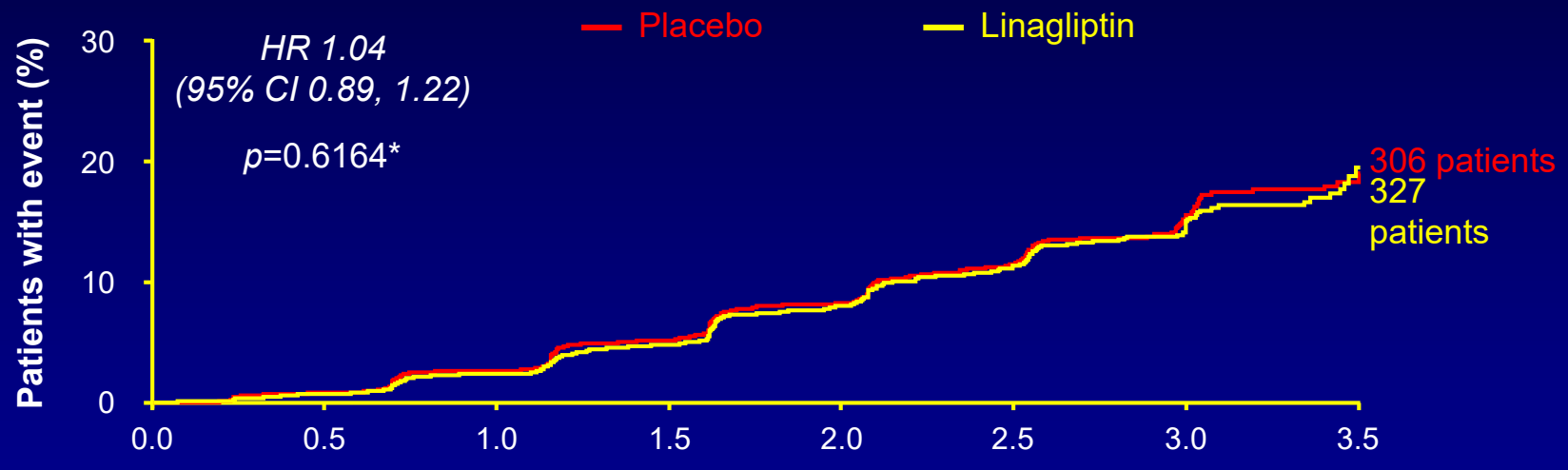


No. of patients							
Placebo (n)	3,485	3,336	3,222	2,621	1,923	1,285	767	258
Linagliptin (n)	3,494	3,361	3,243	2,647	1,979	1,317	787	280

Rosenstock J et al. JAMA 2018, 9 Nov

linagliptin - long-term kidney safety

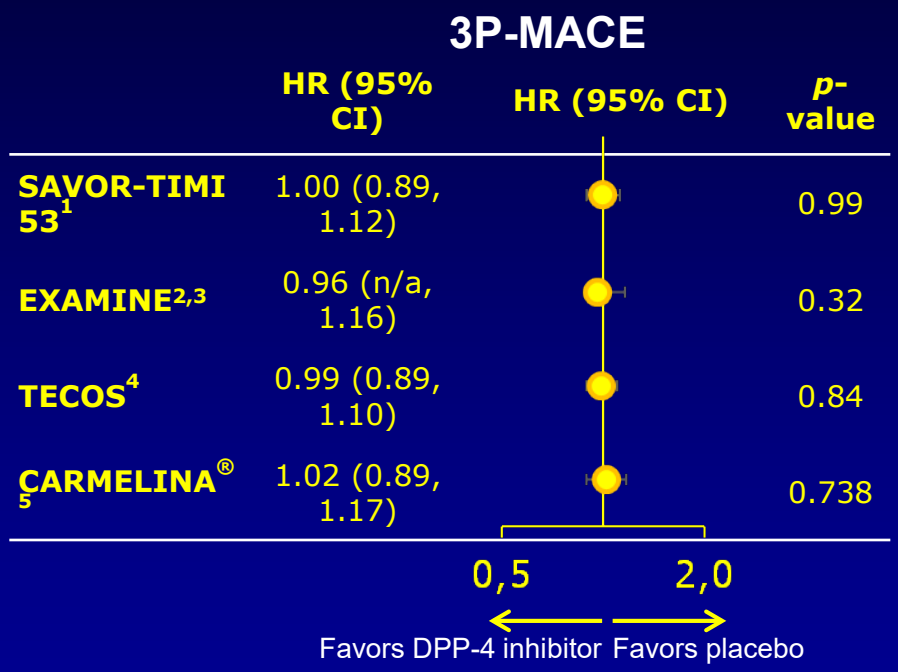
Time to death due to kidney disease, progression to ESKD or sustained eGFR decrease of ≥40%

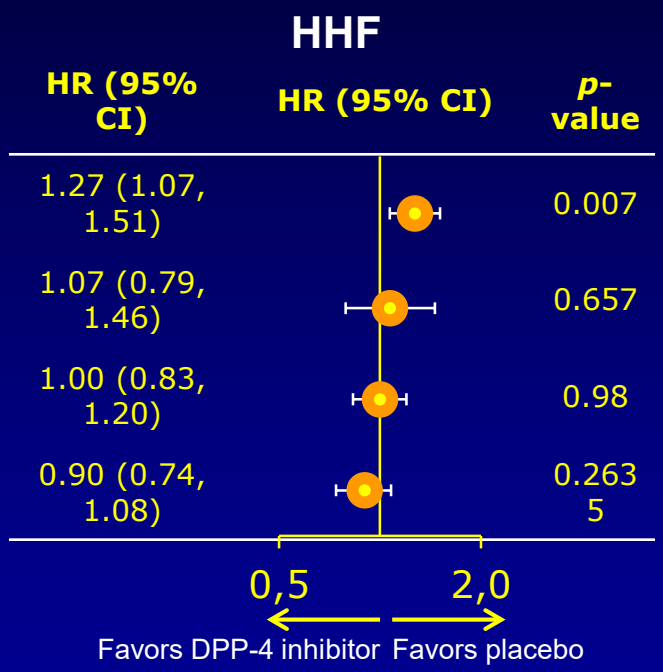


No. of patients								
Placebo (n)	3,485	3,213	2,995	2,298	1,608	1,005	496	103
Linagliptin (n)	3,494	3,227	3,018	2,345	1,675	1,040	518	109

Rosenstock J et al. JAMA 2018, 9 Nov

inibitori DPP-4 e CV / HF risk





gliptine: pro & contro

pro
assenza di ipoglicemia
stimola secr. insulina/inibisce secr glucagone
rari effetti collaterali
nessun effetto su fattori di rischio CV
nessun effetto collaterale gastrointestinale
nessuna titolazione (eccetto CKD)

contro
costi

anziano
scompenso cardiaco (solo alcuni)

Terapia farmacologica nell'anziano

	rischio di IPO	uso in IRC	prev CVD	scomp card	fen glic	riserva β-cell	stato nutr.	facilità somm.
Metformina	NO	no<30	SI	NO	digiuno	=	−	XR
SU e glinidi	SI	gliclazide only	rischio	neutro	vario	SI	+	no
pioglitazone	NO	no<15	SI	SI	digiuno	=	+	si
Gliptine	NO	SI	NO	farmaci diversi	dig/pra	SI	=	si
GLP-1 RA								
Gliflozine								
Insulina bas								

Classi di farmaci per diabete mellito tipo 2

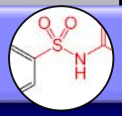
- Detemir
- Glargine
- Glargine U300
- Degludec
- NPH

INSULINA



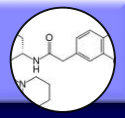
- Gliclazide
- Glibenclamide/glyburide
- Glimepiride
- Gliquidone
- Glipizide

SULFONILUREA



- Nateglinide
- Repaglinide

GLINIDI



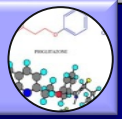
- Metformin

BIGUANIDI



- Pioglitazone

TZDs



- Sitagliptin
- Saxagliptin
- Vildagliptin
- Linagliptin
- Alogliptin

GLIPTINE



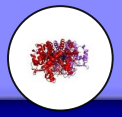
- Exenatide LAR
- Liraglutide
- Lixisenatide
- Dulaglutide

GLP-1 RA



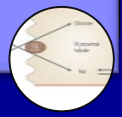
- Acarbose
- Miglitol

INIBITORI ALFA GLUCOSIDASI



- Dapagliflozin
- Canagliflozin
- Empagliflozin

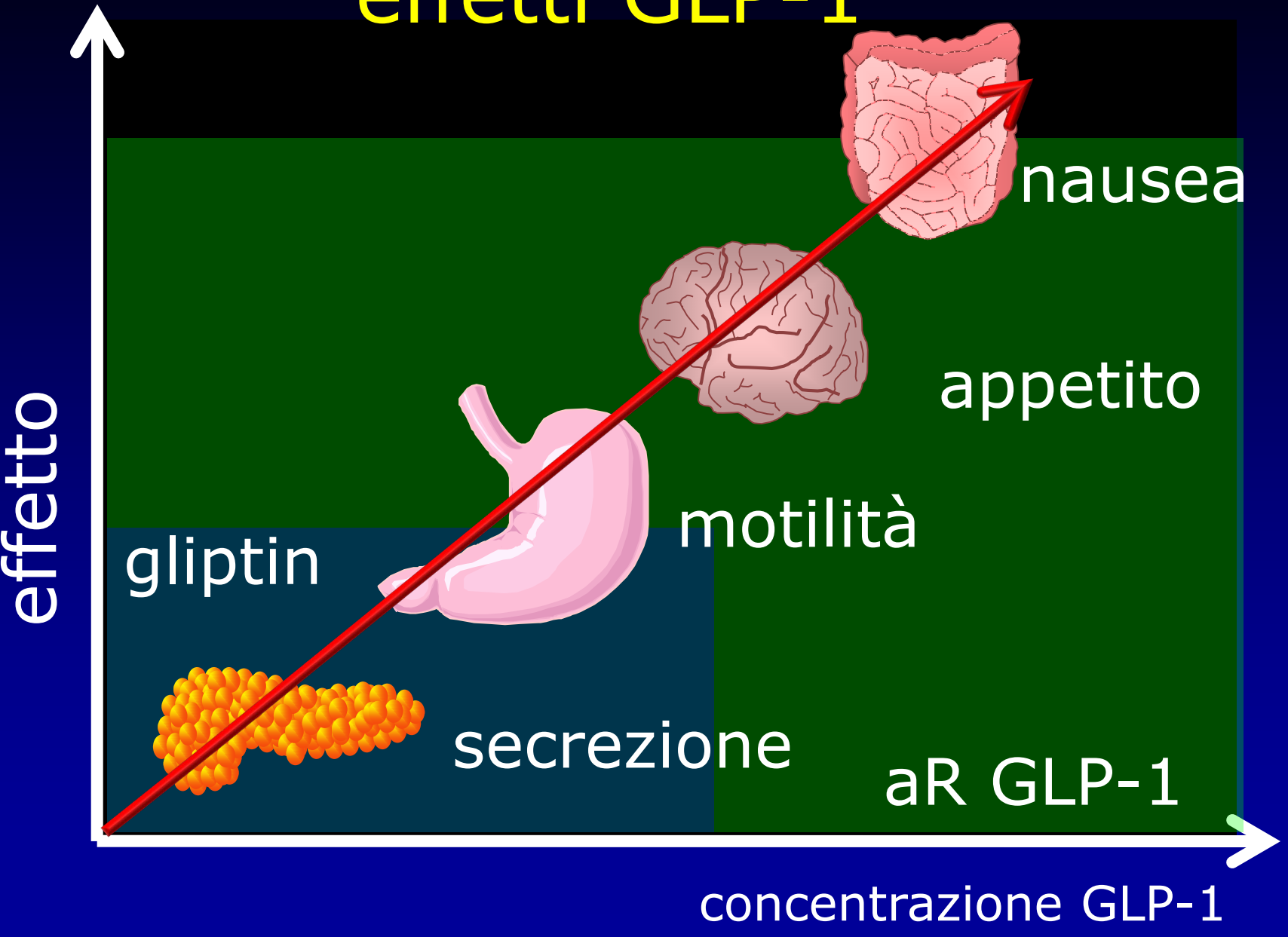
INIBITORI SGLT2



short and long-acting GLP-1R agonists

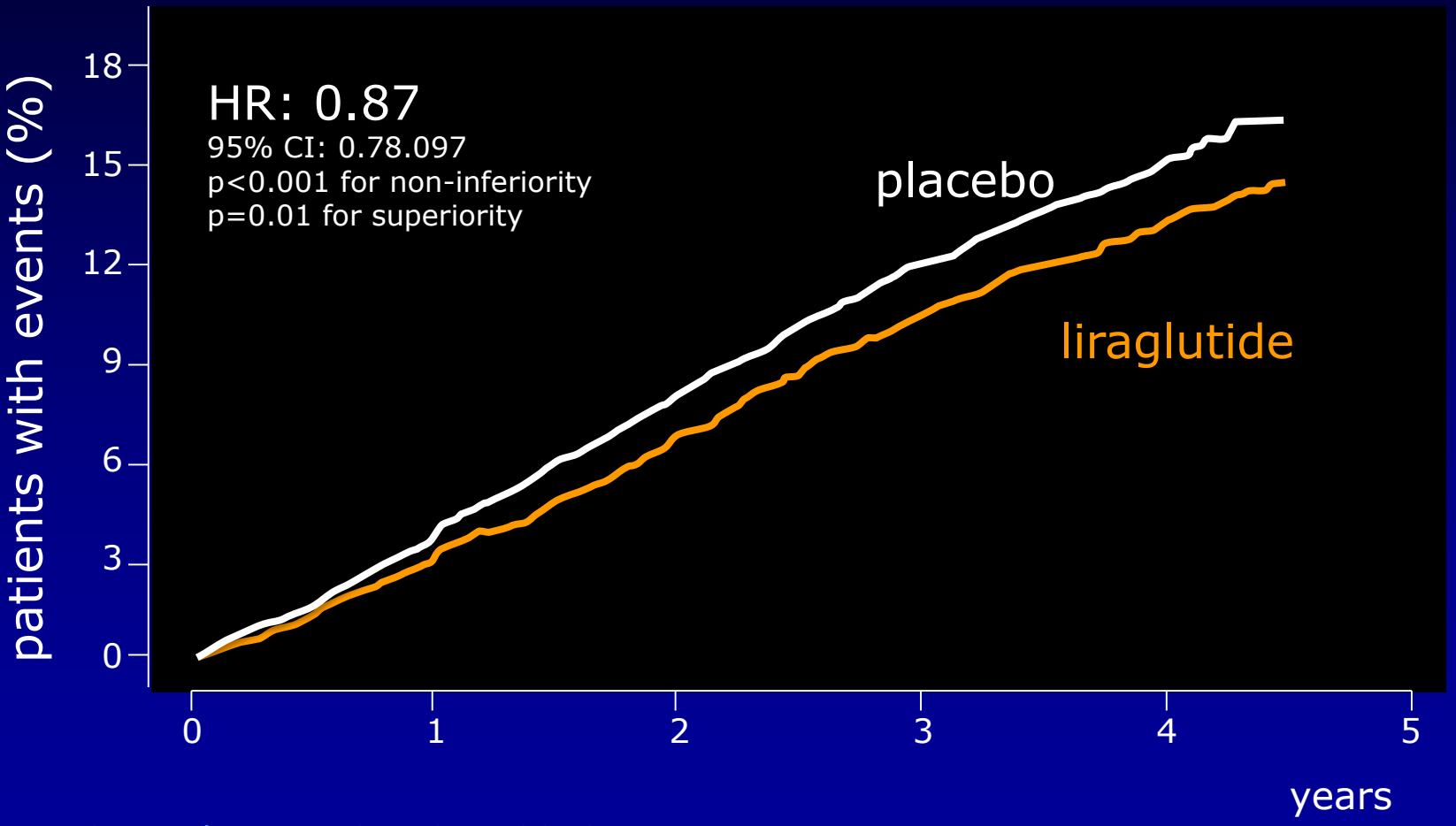
	Short-acting GLP-1 RA	Long-acting GLP-1 RA
riduzione FPG	+	+++
riduzione PPG	+++	++
riduzione HbA1c	++	+++
calo ponderale	++	++
rall svoutamento gastrico	+++	+
secrezione glucagone	+/Neutral	++
effetti GI	++	+
compliance	+	++

effetti GLP-1



LEADER: primary composite CV outcome

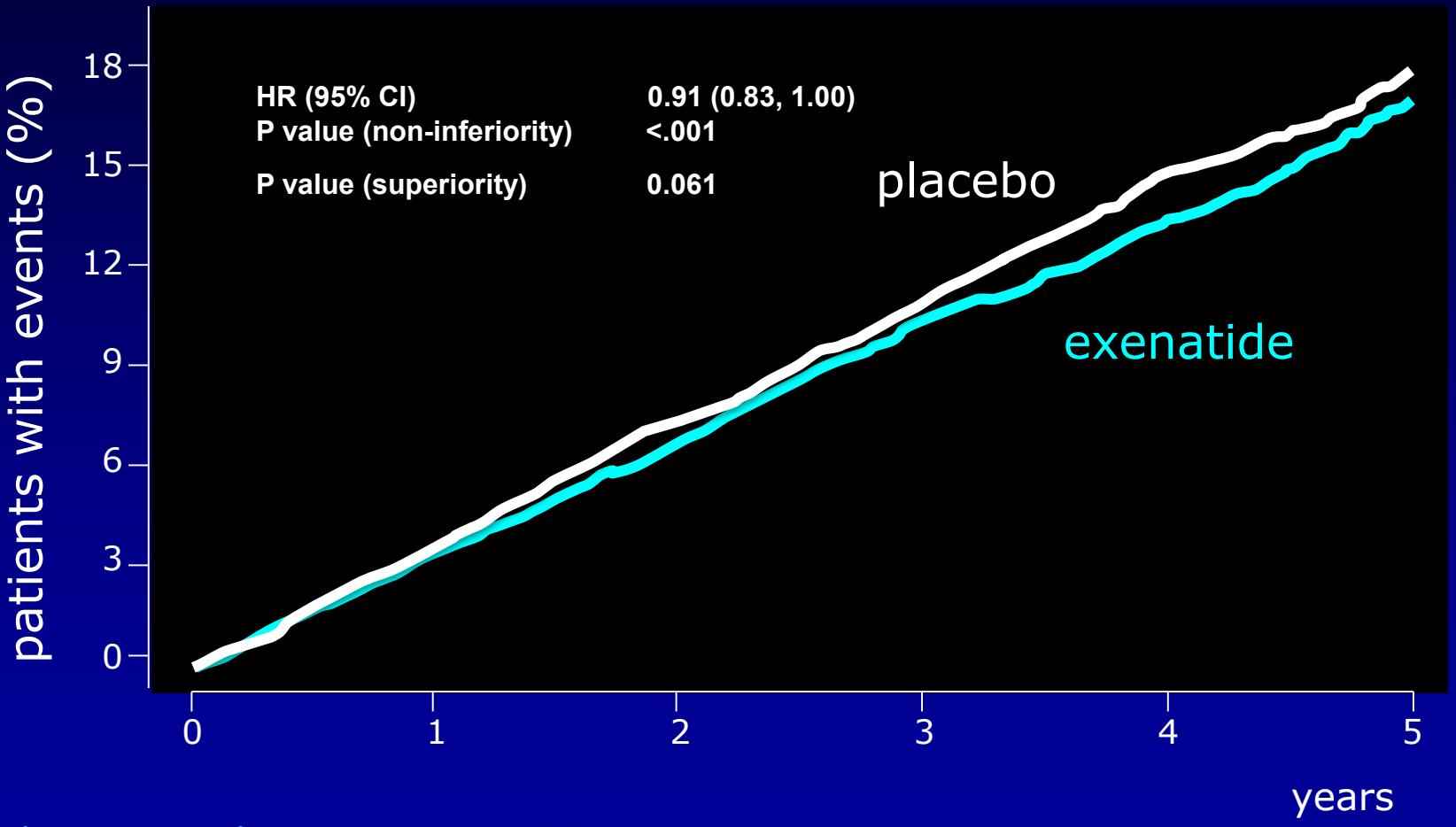
MACE 3: CV death, non-fatal MI or stroke



Marso SP et al.: NEJM 375:311, 2016

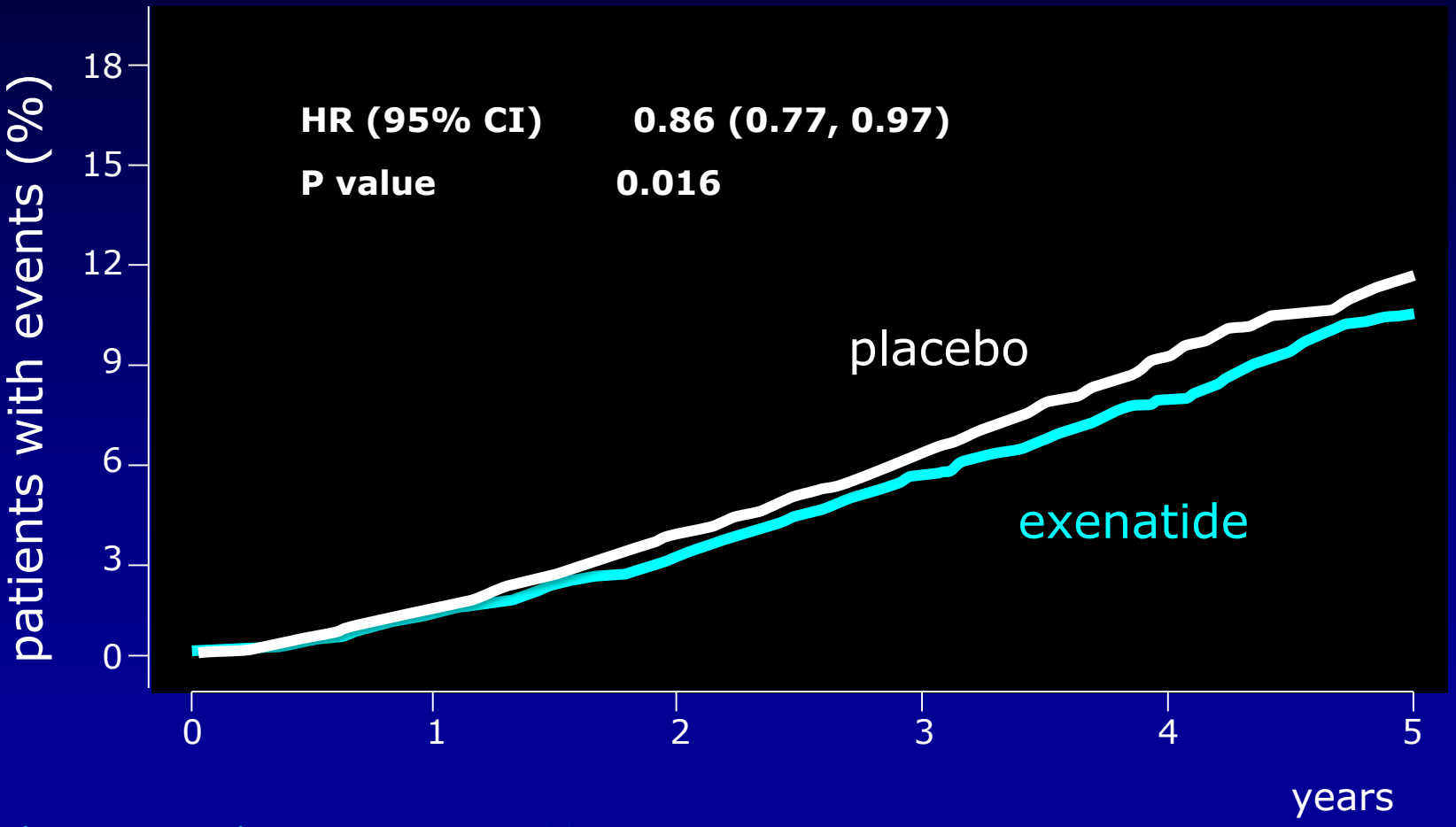
EXSCEL: primary composite CV outcome

MACE 3: CV death, non-fatal MI or stroke



Holman RR et al.: NEJM in press, 2017

EXSCEL: All cause mortality



Holman RR et al.: NEJM in press, 2017

REWIND: All cause mortality

(dulaglutide) demonstrates superiority in reduction of cardiovascular events for broad range of people with type 2 diabetes

November 5, 2018

Only 31 percent of REWIND trial participants had established CV disease

INDIANAPOLIS, Nov. 5, 2018 /PRNewswire/ -- (dulaglutide) significantly reduced major adverse cardiovascular events (MACE), a composite endpoint of cardiovascular (CV) death, non-fatal myocardial infarction (heart attack) or non-fatal stroke, meeting the primary efficacy objective in the precedent-setting REWIND trial. , once-weekly is the first type 2 diabetes medicine to demonstrate superiority in the reduction of MACE events in a clinical trial that included a majority of participants who did not have established CV disease.

Experience the interactive Multichannel News Release here: https://www.multivu.com/players/English/8442751-lilly-trulicity-rewind-trial-type-2-diabetes/

The study included a majority of patients without established CV disease at baseline, a first for the GLP-1 receptor agonist class. REWIND assessed the risk of MACE in adults with type 2 diabetes with a wide range of CV risk. The study compared the effect of once-weekly to placebo when added to standard of care.

GLP1-RA nei CVOT

	ELIXA[7]	LEADER[6]	SUSTAIN 6[5]	EXSCEL[2]	Harmony Outcomes[3]	REWIND[1,4]
Drug tested	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Albiglutide	Dulaglutide
Dose	20 µg/day	1.8 mg/day	0.5 or 1 mg/wk	2 mg/wk	30 mg/wk, up to 50mg/wk	1.5 mg/wk
N	6068	9340	3297	14,752	9463	9901
Mean age, years	60	64	65	62	64	66
Women, %	31	36	39	38	31	46
Prior CVD[a], %	100[d]	81[c]	83[b]	73[e]	100[f]	31[g]
Mean BMI, kg/m²	30	33	33	32	32	32
Mean HbA1c, %	7.7	8.7	8.7	8.0	8.7	7.3
Median follow up	2.1 years	3.8 years	2.1 years	3.2 years	1.6 years	5.4 years

[a]Prior CVD definitions differs by study
[b]SUSTAIN-6: established CVD, including CKD of stage 3 or higher
[c] LEADER: CVD, cerebrovascular disease, PVD, CRF, CHF.
[d] ELIXA: acute coronary event within 180 days before screening.
[e] EXSCEL: 73% at least one prior CV event (70% CAD, 24% PAD, 22% cerebrovascular disease).
[f] HARMONY: established CVD includes at least one of the following: CAD, cerebrovascular disease, or PAD
[g] REWIND: Prior MI or stroke; or coronary, carotid, or peripheral revascularization; or hospitalization for UA or history of MI by a stress test or cardiac imaging

- *1.Gerstein HC et al. Diabetes Obes Metab 2018;20(1):42-9*
- *2. Holman RR et al. N Engl J Med 2017;377(13):1228-39*
- *3. Hernandez AF, Green JB, Janmohamed S et al. Lancet. 2018; (published online Oct 2.)*
- *4. Eli Lilly and Company. 2018. Available at: https://investor.lilly.com/news-releases/news-release-details/trulicityr-dulaglutide-demonstrates-superiority-reduction. Accessed 5 Nov 2018.*
- *5. Marso SP, et al, New Eng J of Med. 2016;375(19):1834-1844.*
- *6. Marso SP et al, New Eng J of Med. 2016;375(4):311-322.*
- *7. Pfeffer MA et al, New Eng J of Med. 2015;373(23):2247-2257.*

agonisti GLP1: pro & contro

pro
no ipoglicemia
riduzione fattori di rischio CV
facile titolazione

contro
effetti collaterali gastrointestinali
iniettivi
costi

anziano
non indicato in CKD
perdita di peso

Terapia farmacologica nell'anziano

	rischio di IPO	uso in IRC	prev CVD	scomp card	fen glic	riserva β-cell	stato nutr.	facilità somm.
Metformina	NO	no<30	SI	NO	digiuno	=	−	XR
SU e glinidi	SI	gliclazide only	rischio	neutro	vario	SI	+	no
pioglitazone	NO	no<15	SI	SI	digiuno	=	+	si
Gliptine	NO	SI	NO	farmaci diversi	dig/pra	SI	=	si
GLP-1 RA	NO	NO	farmaci diversi	NO	vario	SI	−	farmaci diversi
Gliflozine								
Insulina bas								

Classi di farmaci per diabete mellito tipo 2

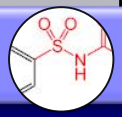
- Detemir
- Glargine
- Glargine U300
- Degludec
- NPH

INSULINA



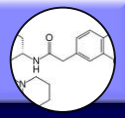
- Gliclazide
- Glibenclamide/glyburide
- Glimepiride
- Gliquidone
- Glipizide

SULFONILUREA



- Nateglinide
- Repaglinide

GLINIDI



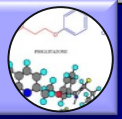
- Metformin

BIGUANIDI



- Pioglitazone

TZDs



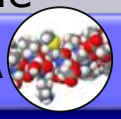
- Sitagliptin
- Saxagliptin
- Vildagliptin
- Linagliptin
- Alogliptin

GLIPTINE



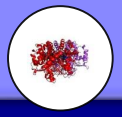
- Exenatide LAR
- Liraglutide
- Lixisenatide
- Dulaglutide

GLP-1 RA



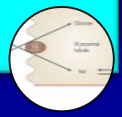
- Acarbose
- Miglitol

INIBITORI ALFA GLUCOSIDASI

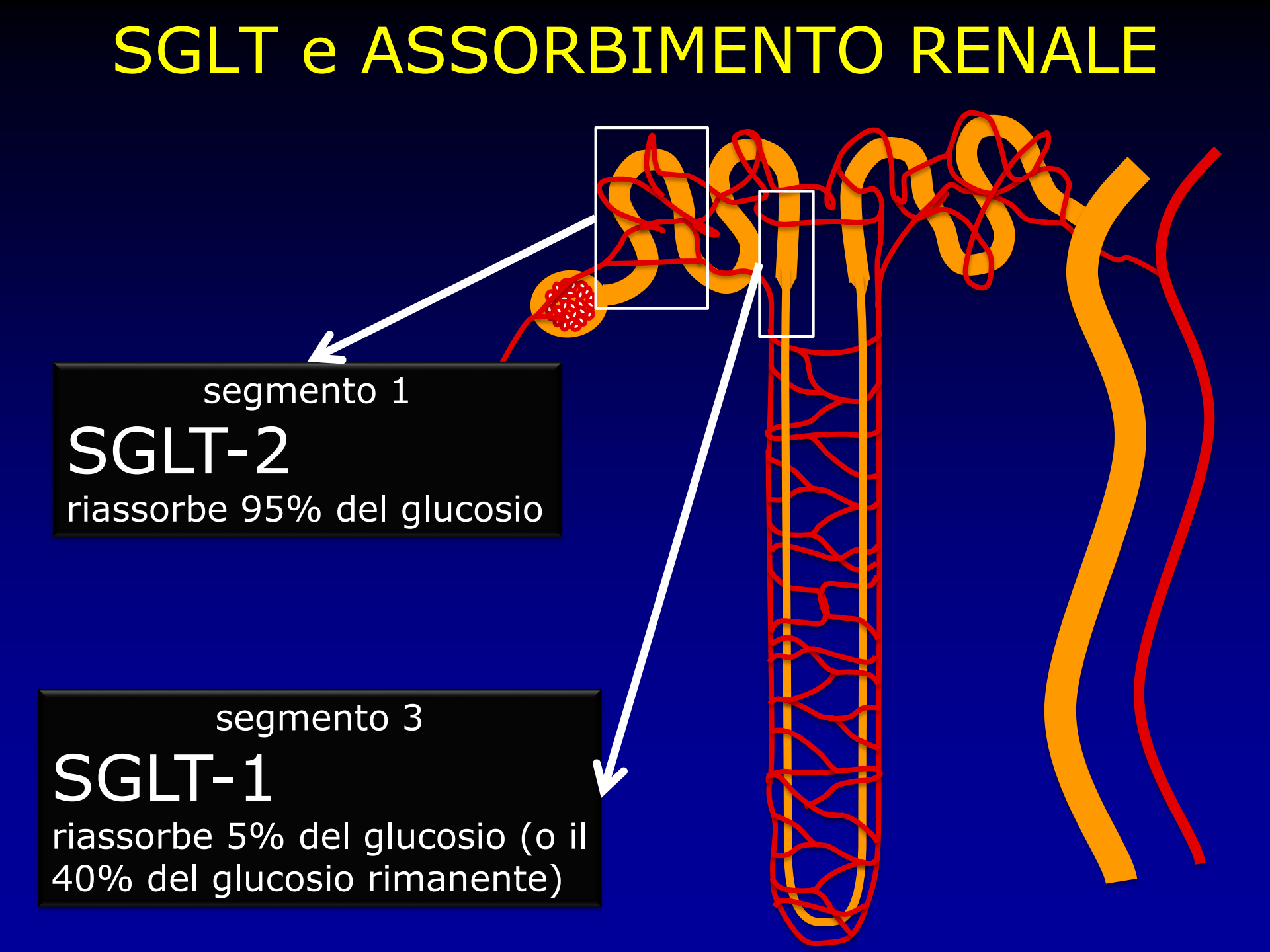


- Dapagliflozin
- Canagliflozin
- Empagliflozin

INIBITORI SGLT2



SGLT e ASSORBIMENTO RENALE



segmento 1

SGLT-2

riassorbe 95% del glucosio

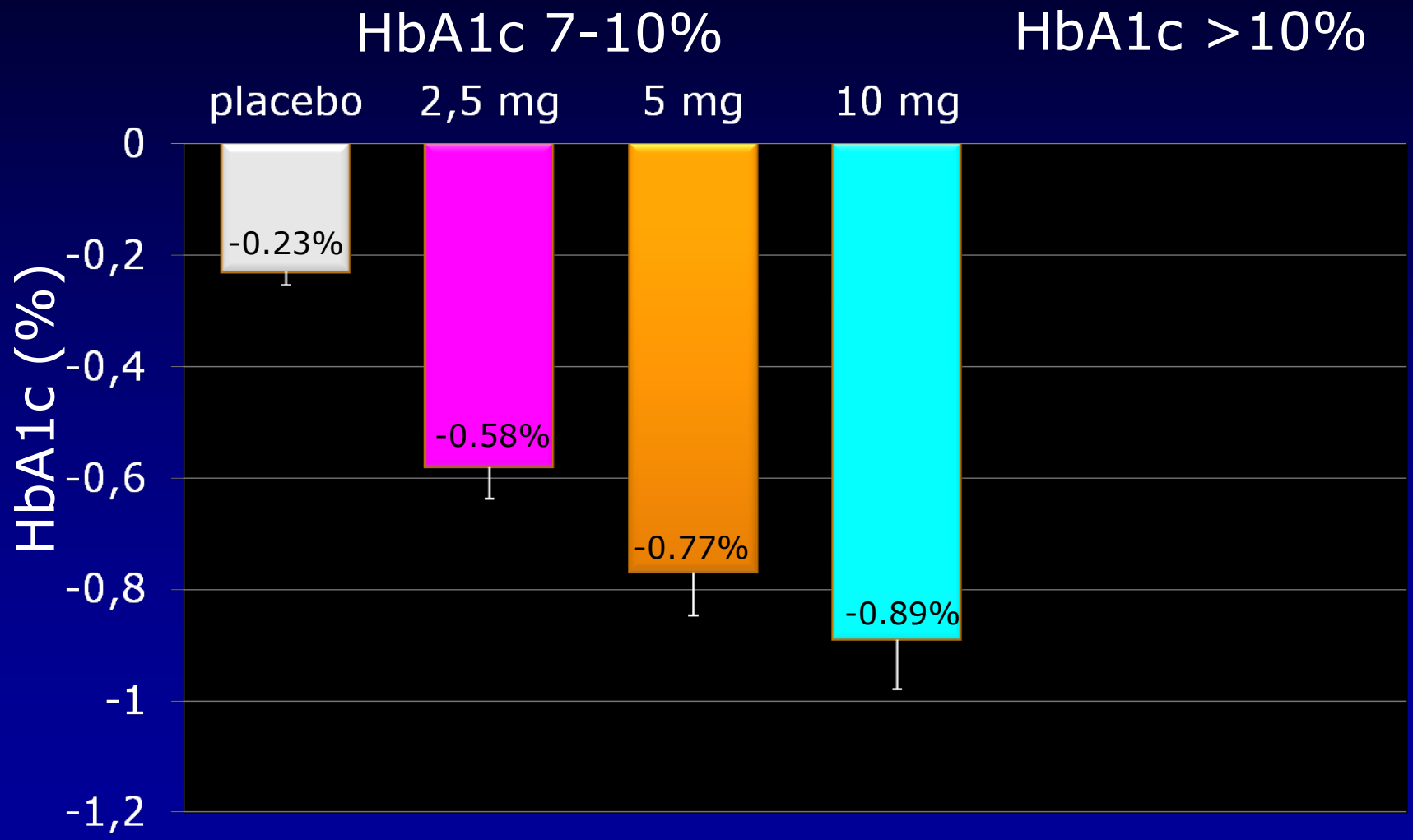
segmento 3

SGLT-1

riassorbe 5% del glucosio (o il 40% del glucosio rimanente)

gliflozina (monoterapia)

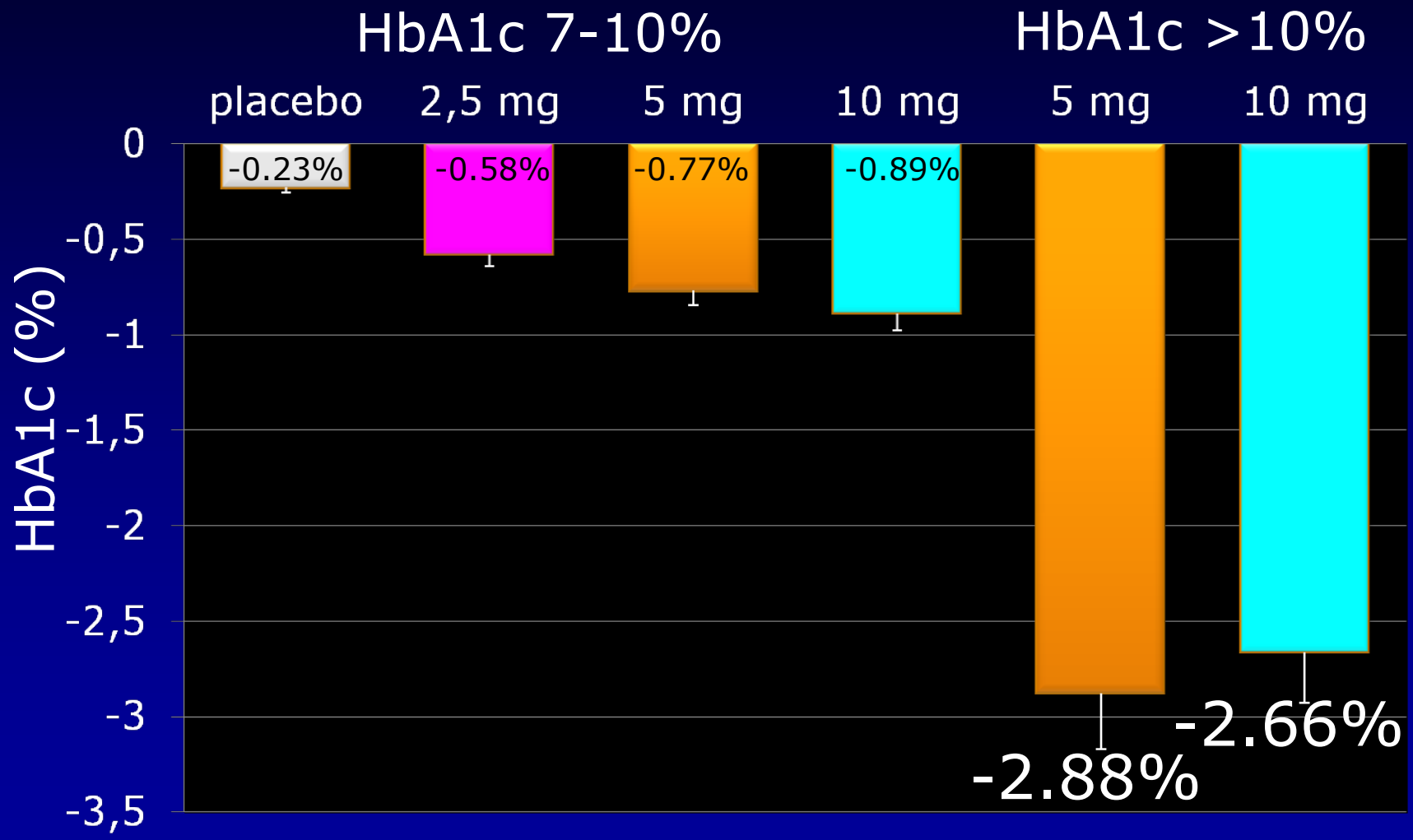
dapagliflozin – in pazienti drug naïve



Ferrannini E Diabetes Care 33:2217, 2010

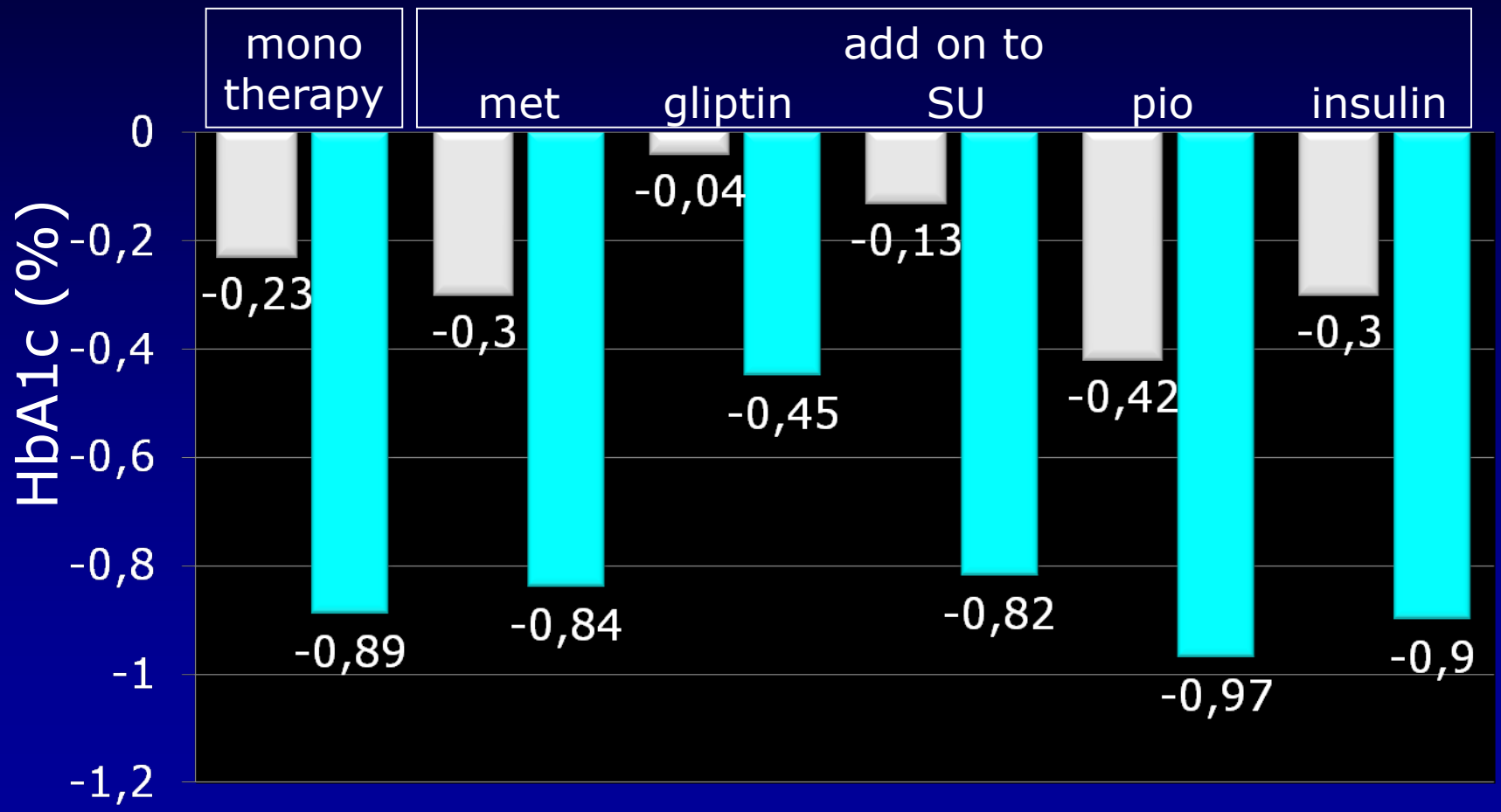
gliflozina (monoterapia)

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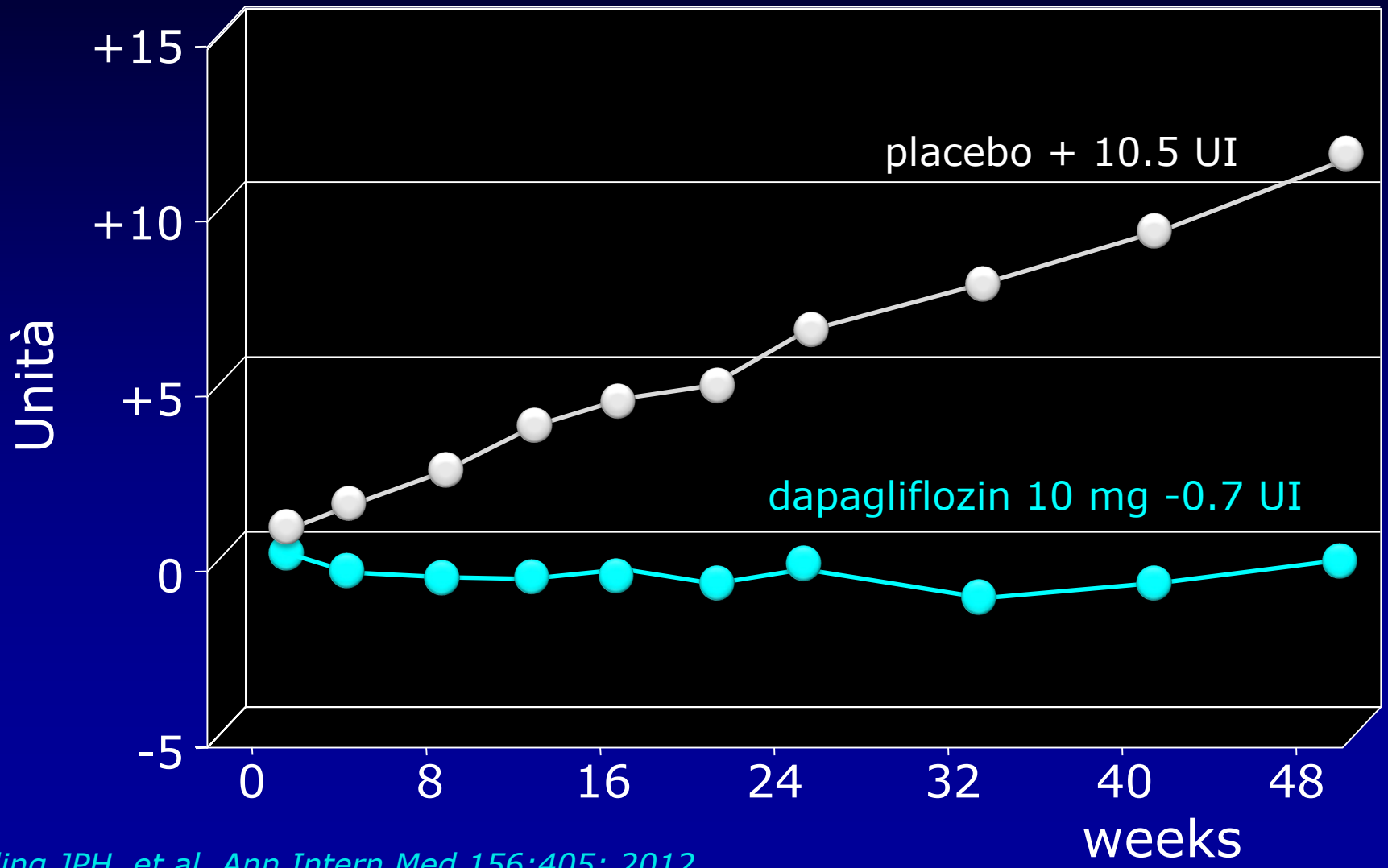
Ferrannini E Diabetes Care 33:2217, 2010

efficacia 'ubiquitaria' delle gliflozine
cfr a 24 sett vs. placebo



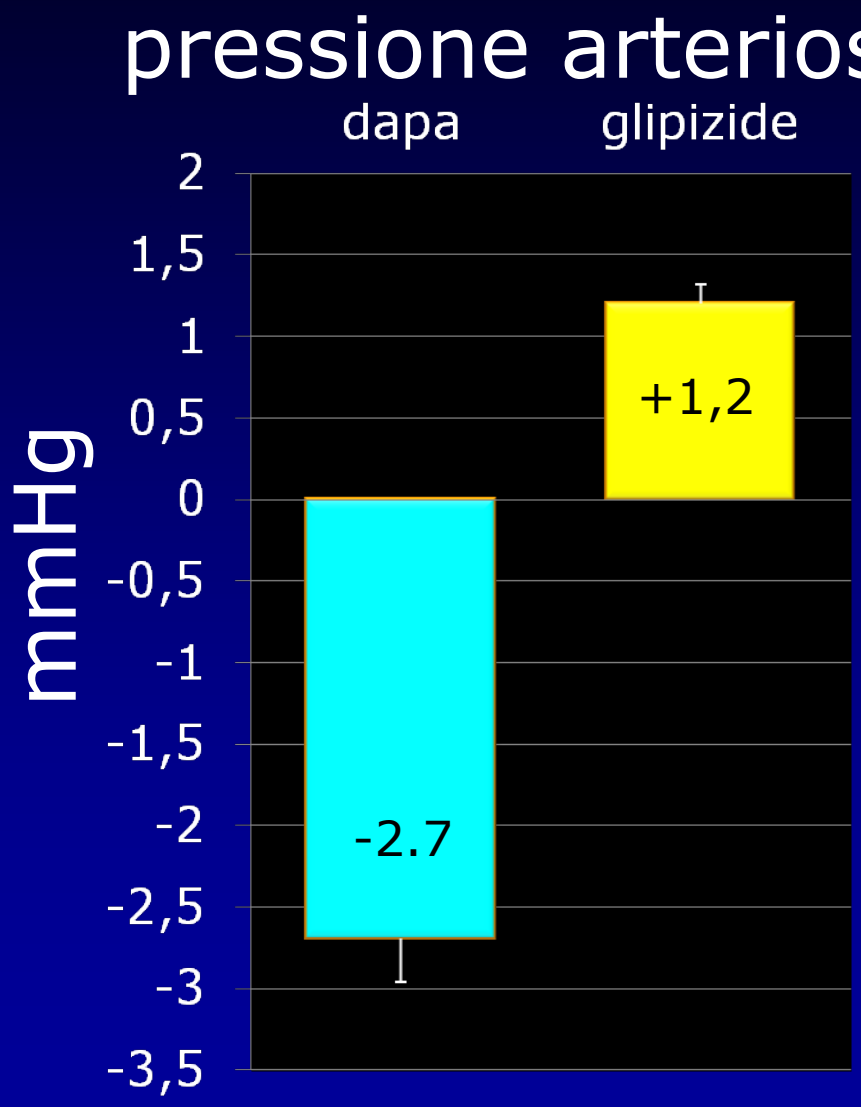
1Ferrannini E, et al. Diabetes Care 2010;33:2217-24. 2Bailey CJ, et al. Lancet 2010;375:2223-33. 3Jabbour et al., Diabetes Care, pub online 15Jan2014 ; 4Strojek K, et al. Diabetes Obes Metab 2011;13:928-38. 5Rosenstock J, et al. 71st ADA Scientific Sessions, San Diego, 24-28 June, 2011 Abstract 0986-P. 6Wilding J, et al. Diabetes. 2010;59 (Suppl 1):A21-A22. Abstract 0078-OR.

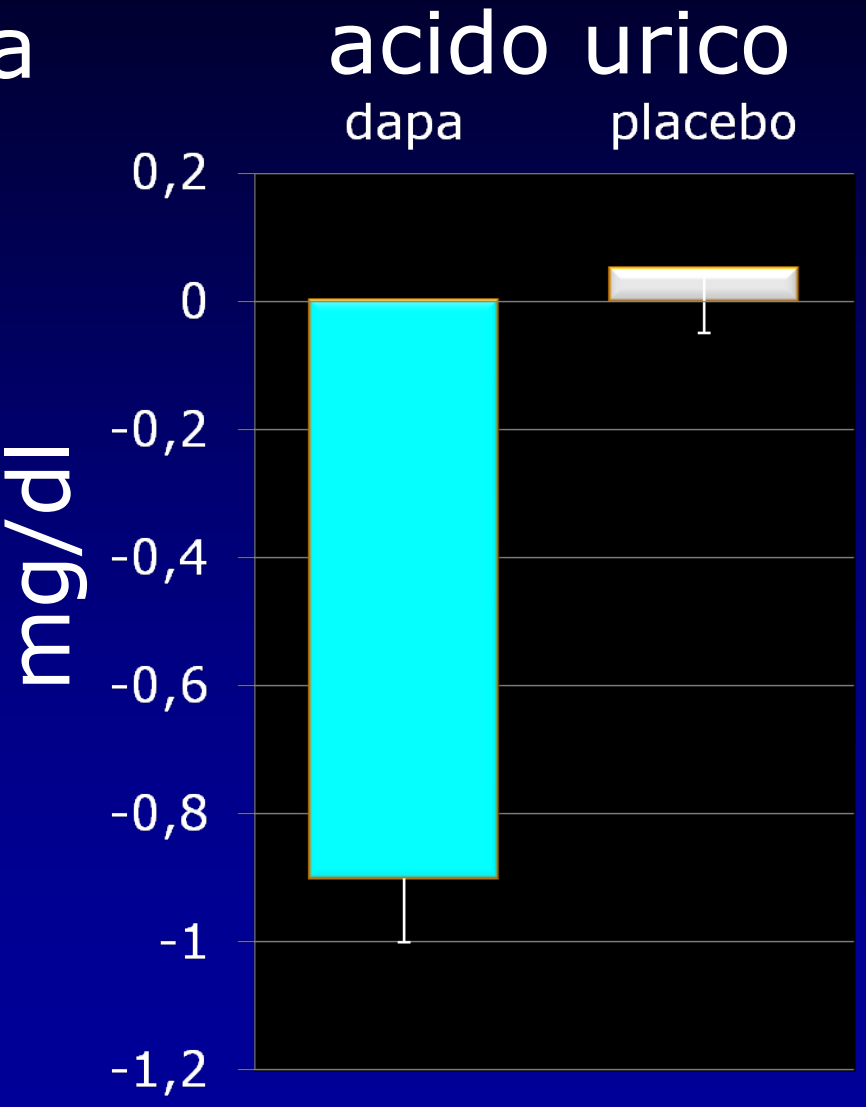
gliflozine riducono dose di insulina



Wilding JPH, et al. Ann Intern Med 156:405; 2012

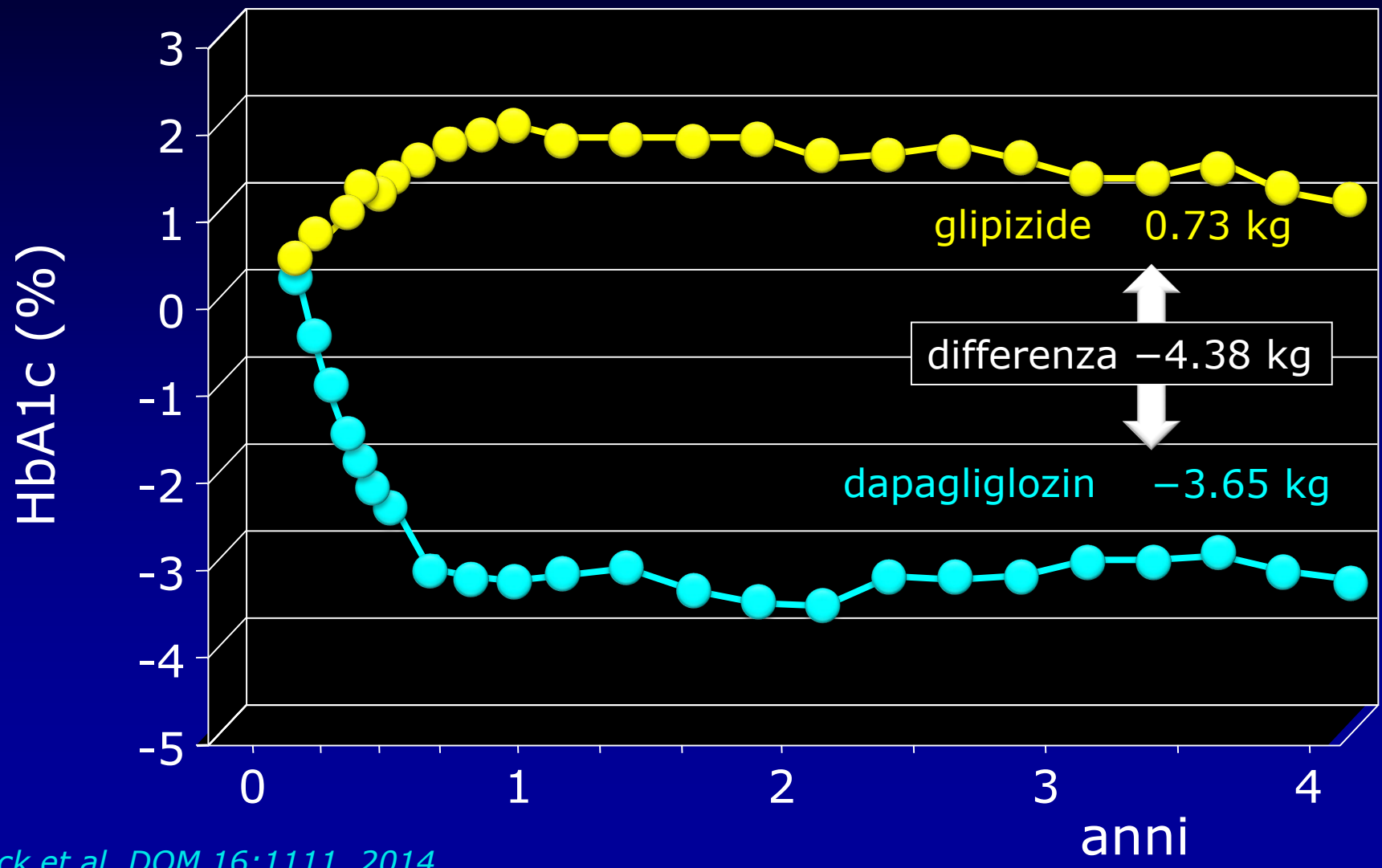
gliflozine: effetto su PA e Acido Urico





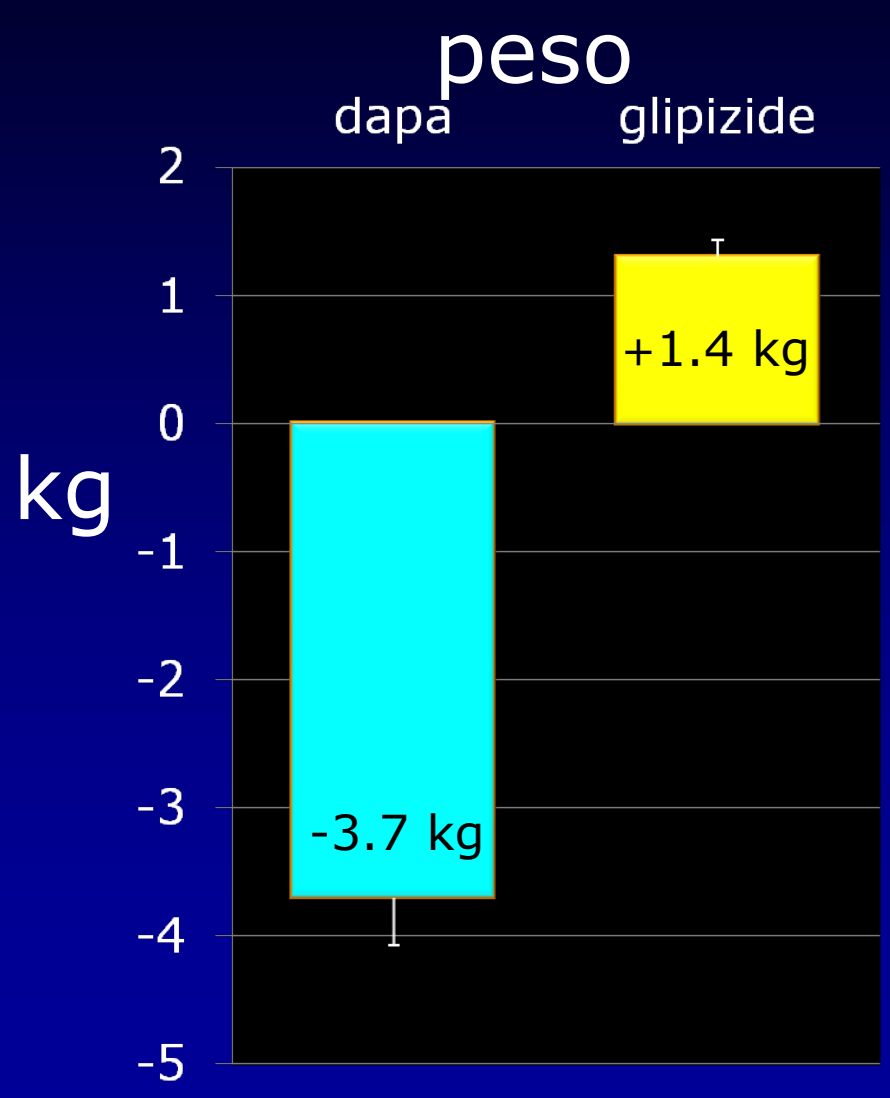
Nauck et al. DOM 16:1111, 2014

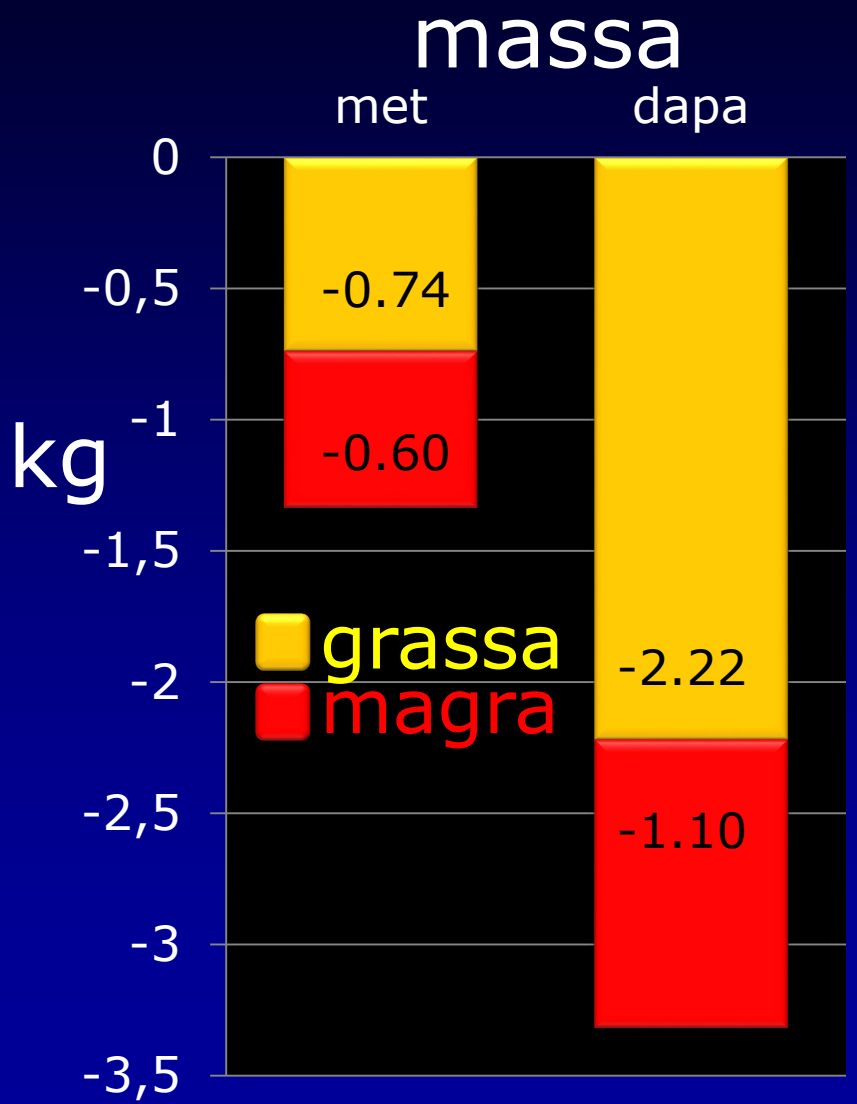
gliflozine inducono calo ponderale



Nauck et al. DOM 16:1111, 2014

gliflozine riducono la massa grassa

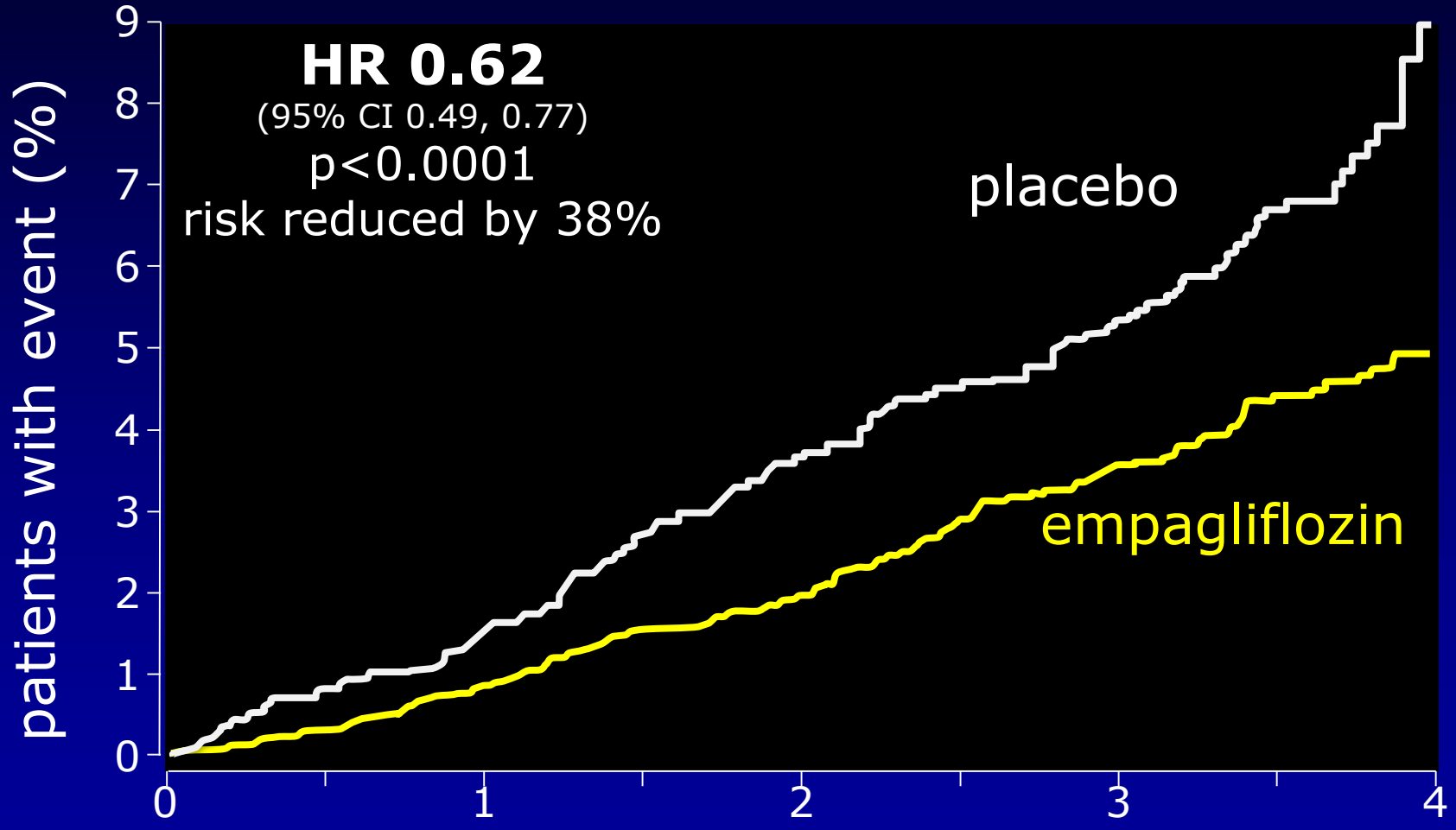




Nauck et al. DOM 16:1111, 2014

Bolinder et al JCEM 97:1020, 2012

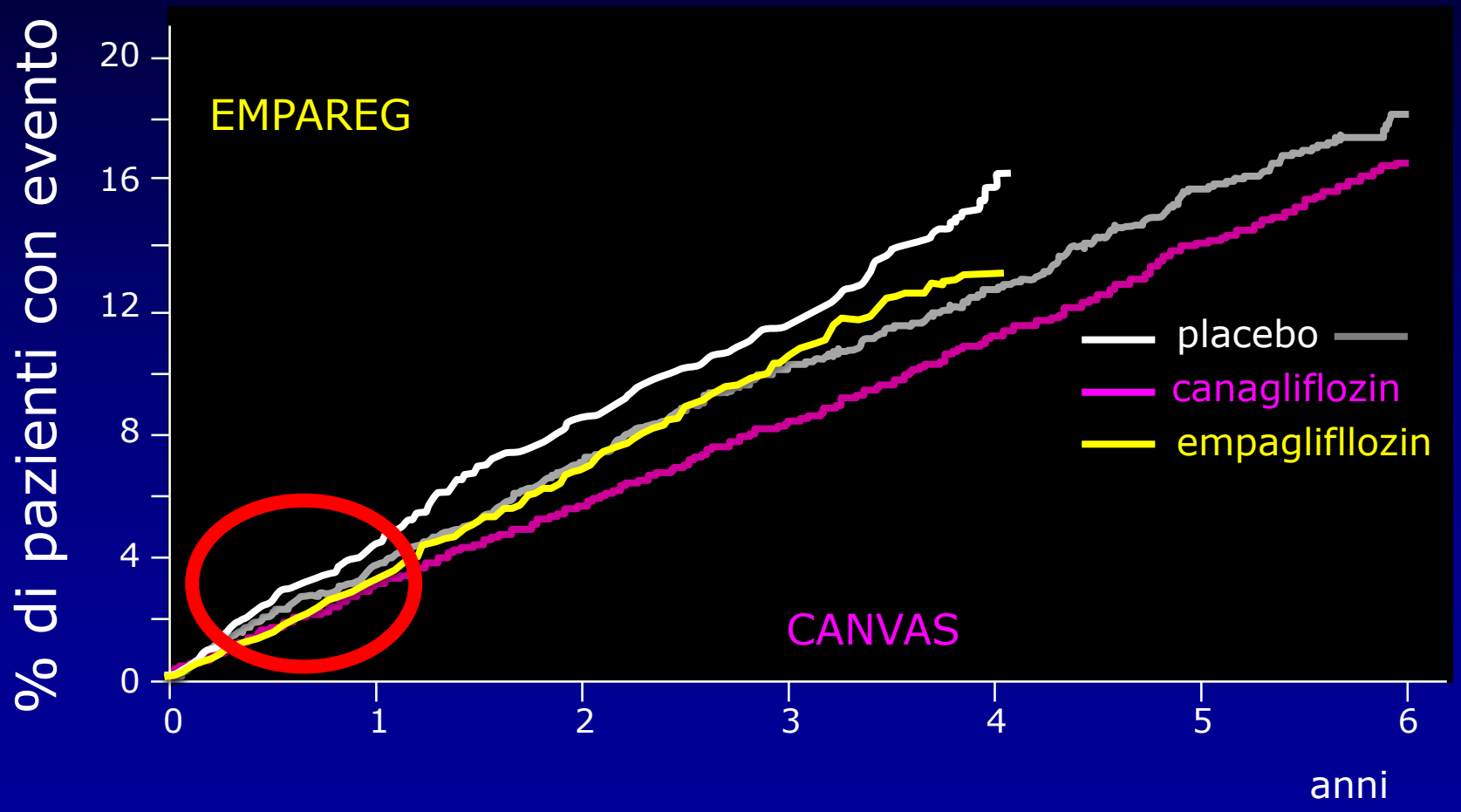
EMPAREG: mortalità CV



Zinman B et al.: NEJM 373:2117, 2015

CANVAS & EMPAREG

MACE-3: morte CV, IMA non fatale o stroke

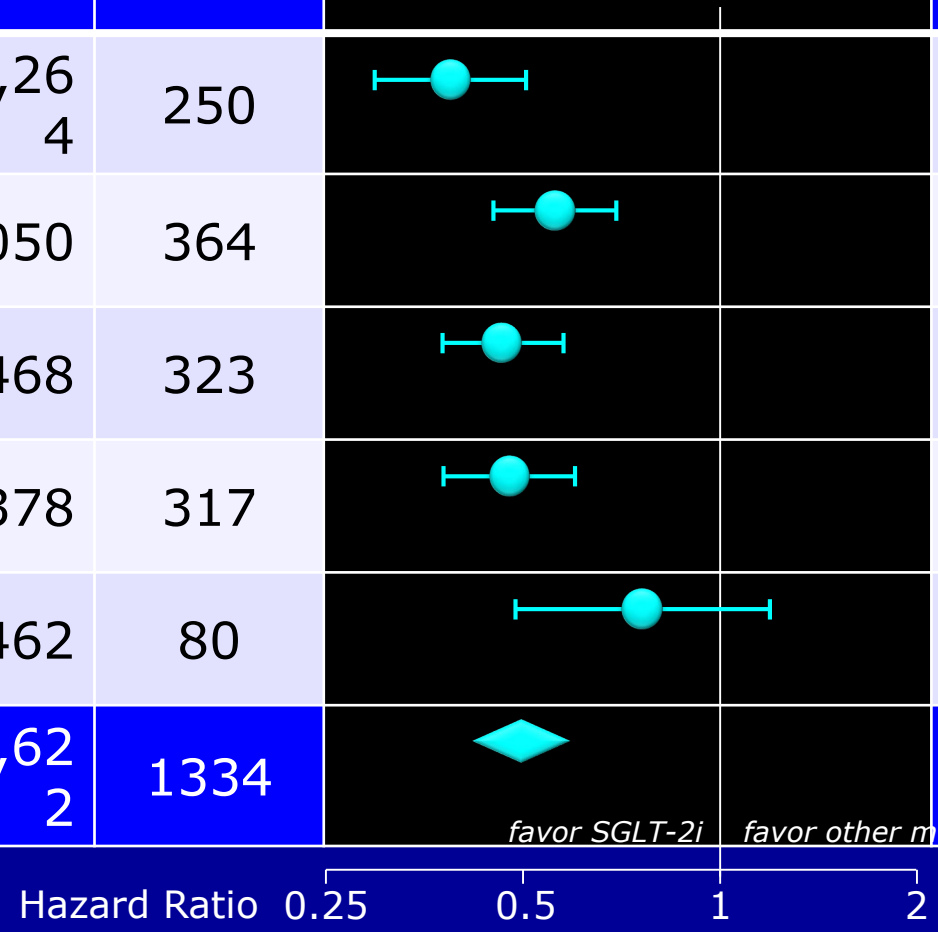


EMPAREG, Zinman B et al.: NEJM 373:2117, 2015
CANVAS, Neal B et al.: NEJM Jun 12, 2017

CVD-REAL: all cause death

primary analysis (N=215,622)

database	N	events	HR (95%CI)
US	143,264	250	0.38 (0.29, 0.50)
Norway	25,050	364	0.55 (0.44, 0.68)
Denmark	18,468	323	0.46 (0.37, 0.57)
Sweden	18,378	317	0.47 (0.37, 0.60)
UK	10,462	80	0.73 (0.47, 1,15)
Total	215,622	1334	0.49 (0.41, 0.57)



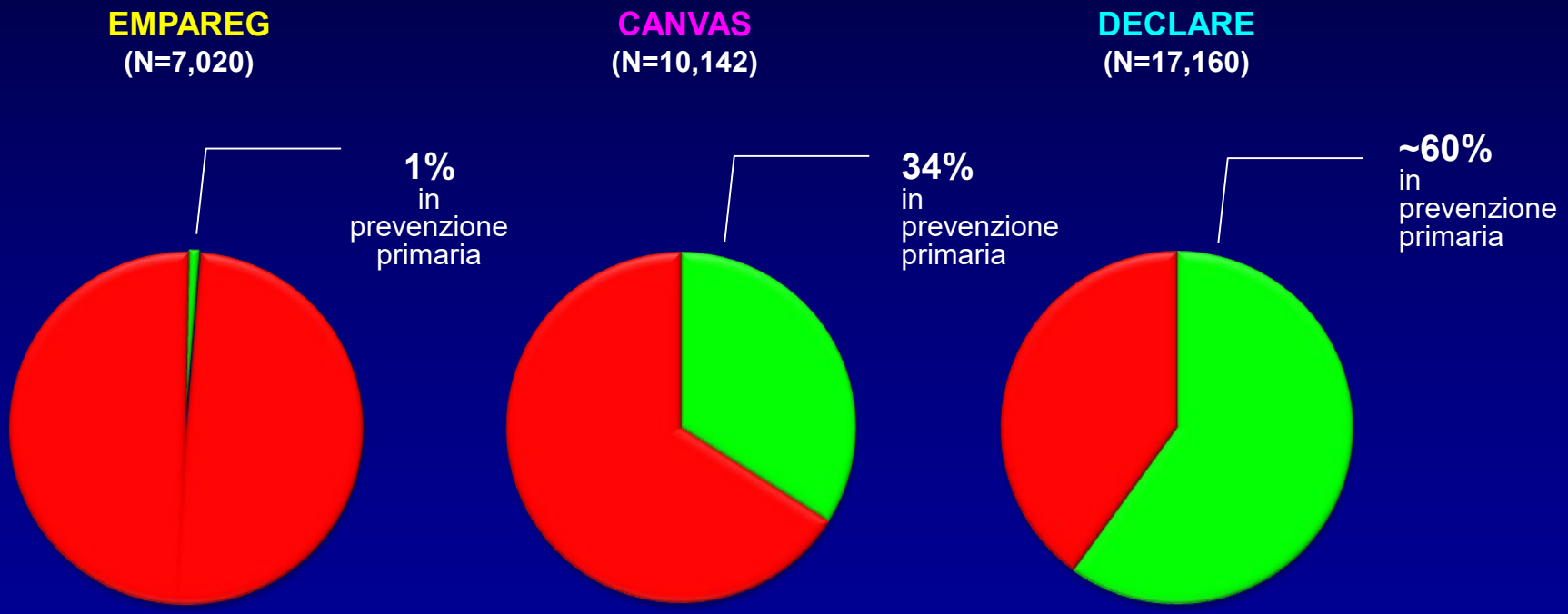
CVDREAL

Kosiborod M. et al.: Circulation 18:249, 2017

DECLARE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

La proporzione dei pazienti con e senza malattia CV accertata nei 3 CVOT con SGLT2i



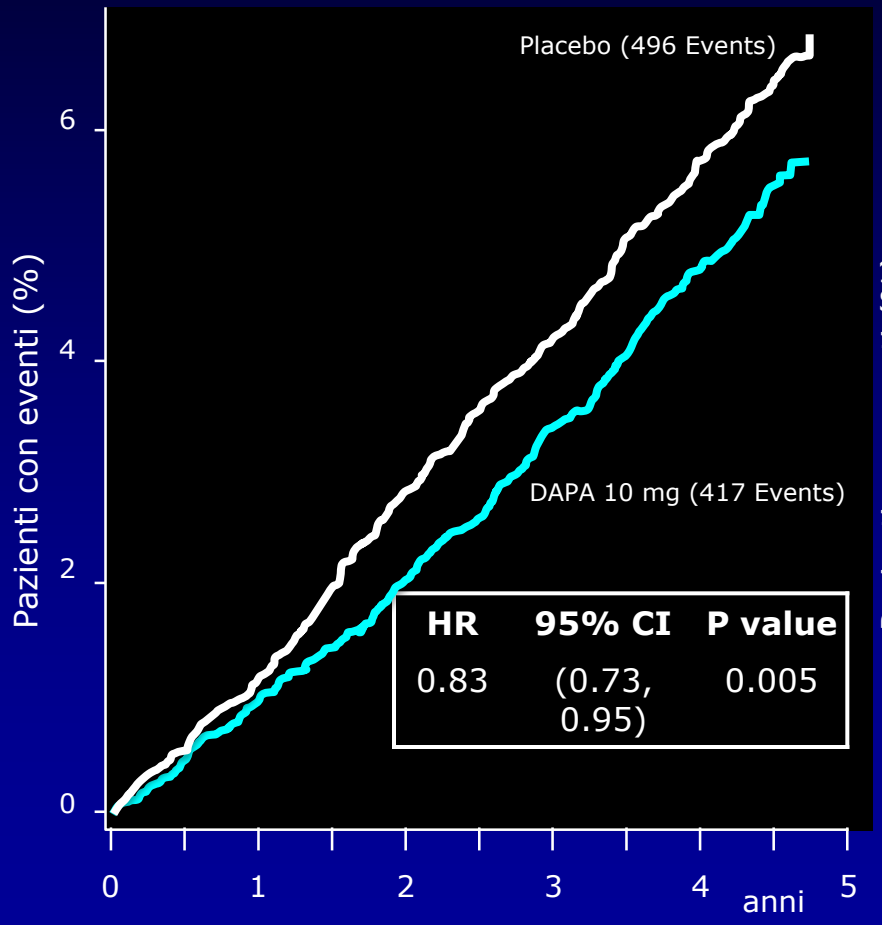
Wiviott SD et al. Online ahead of print. *N Engl J Med*. 2018, November 10

CV, cardiovascular; SGLT2, sodium glucose co-transporter 2; T2D, type 2 diabetes; eCVD, established CV disease.

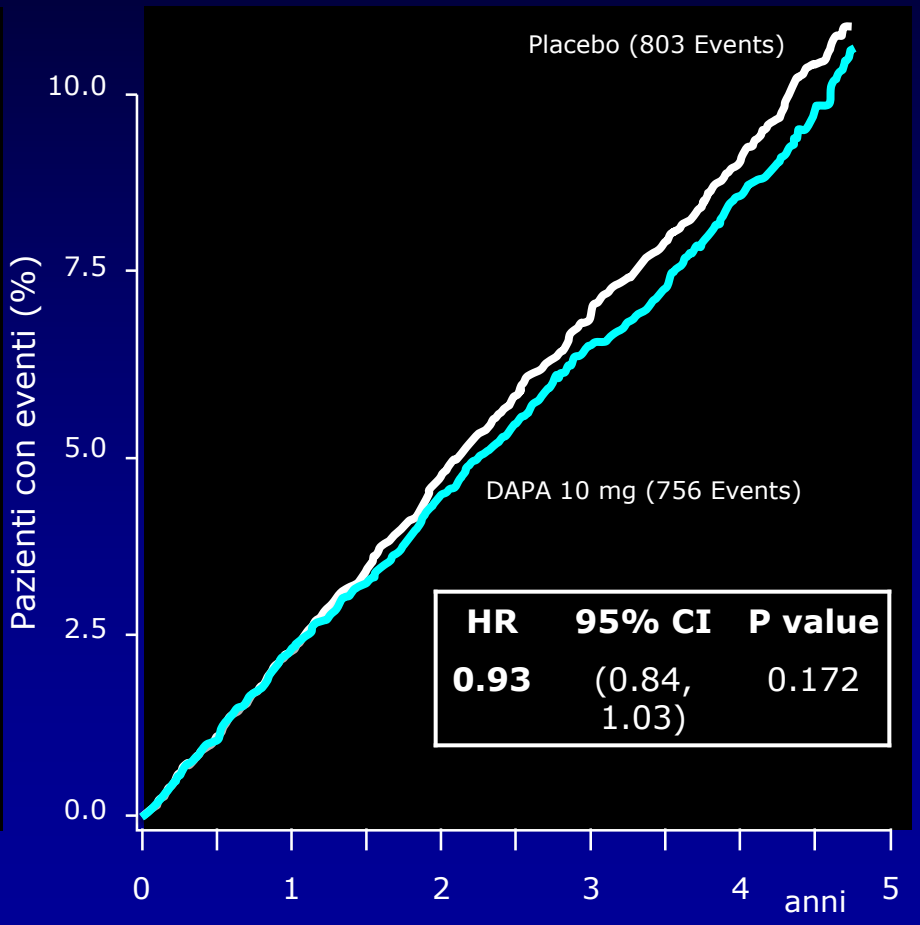
1. Zinman B, et al. *N Engl J Med* 2015;373:2117–2128;; 2. Neal B, et al. *N Engl J Med* 2017; DOI: 10.1056/NEJMoa1611925;3. Sattar Diabetologia (2013) 56:686–695 4. Raz I, et al. *Diabetes Obes Metab* 2018. http://dx.doi.org/10.1111/dom.13217

dapagliflozin e morte HF/CV e MACE

hHF/CVD



MACE

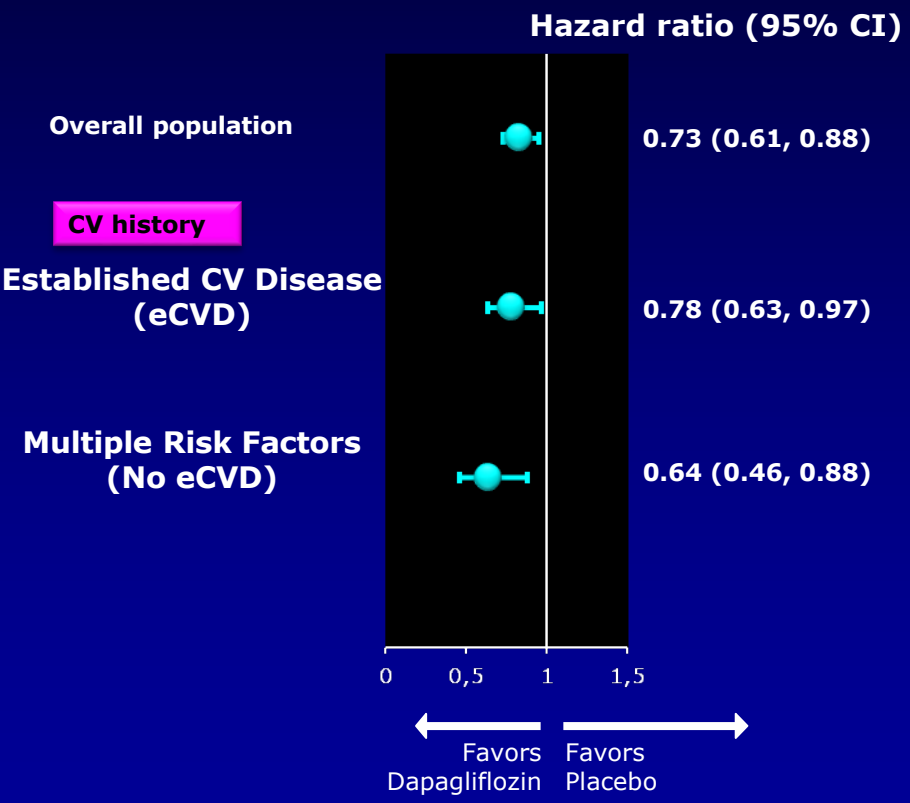


N at risk is the number of subjects at risk at the beginning of the period. 2-sided p-value is displayed; HR, CI, and p-value are from cox proportional hazard model.
CV, cardiovascular; Dapa, dapagliflozin; hHF, hospitalization for heart failure; MACE, major adverse cardiac event

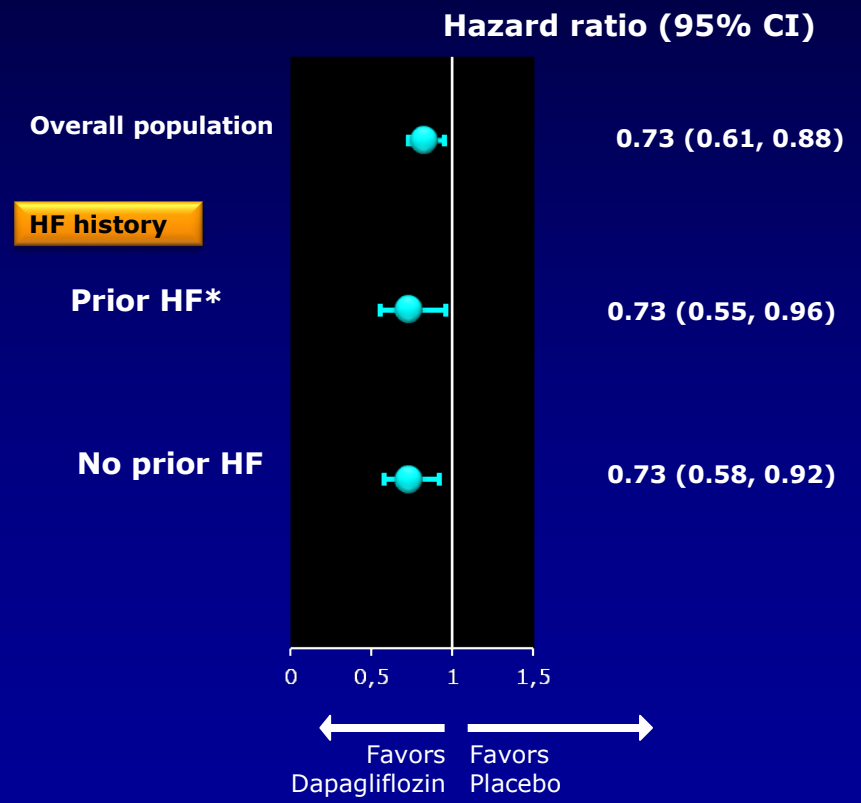
Wiviott SD et al. Online ahead of print. *N Engl J Med*. 2018, November 10

dapagliflozin e ricoveri per HF

hHF per **CV** history



hHF per **HF** history



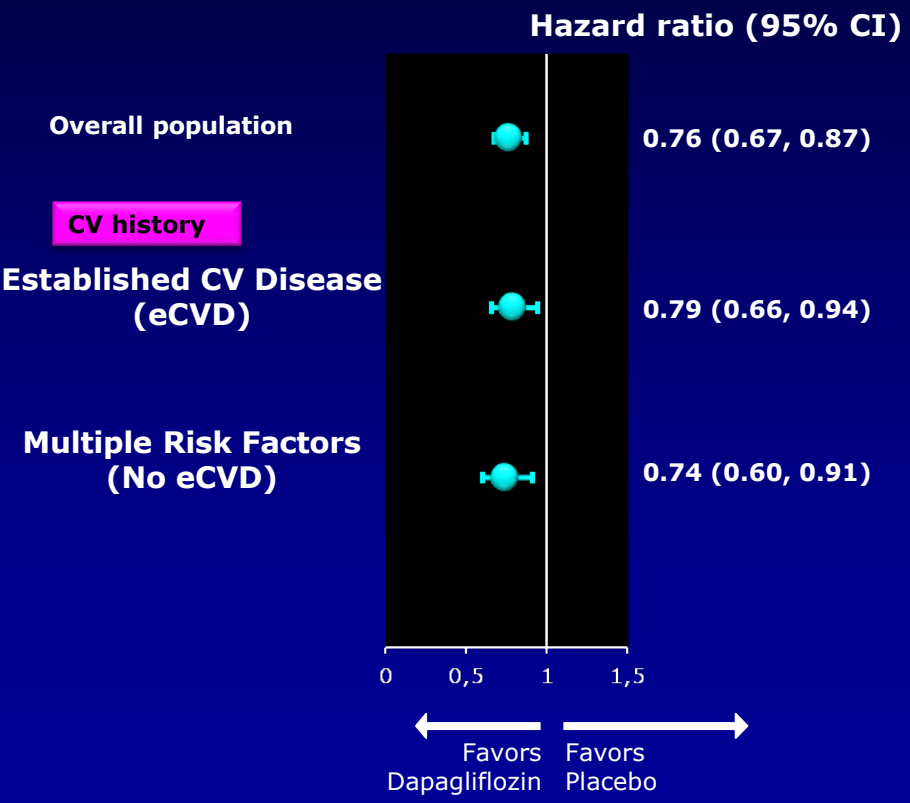
***10% of patients in DECLARE had prior HF**

CV, cardiovascular; eCVD, established CV disease; HF, heart failure; hHF, hospitalized heart failure; SGLT-2i, SGLT co-transporter 2 inhibitor; T2D, type 2 diabetes

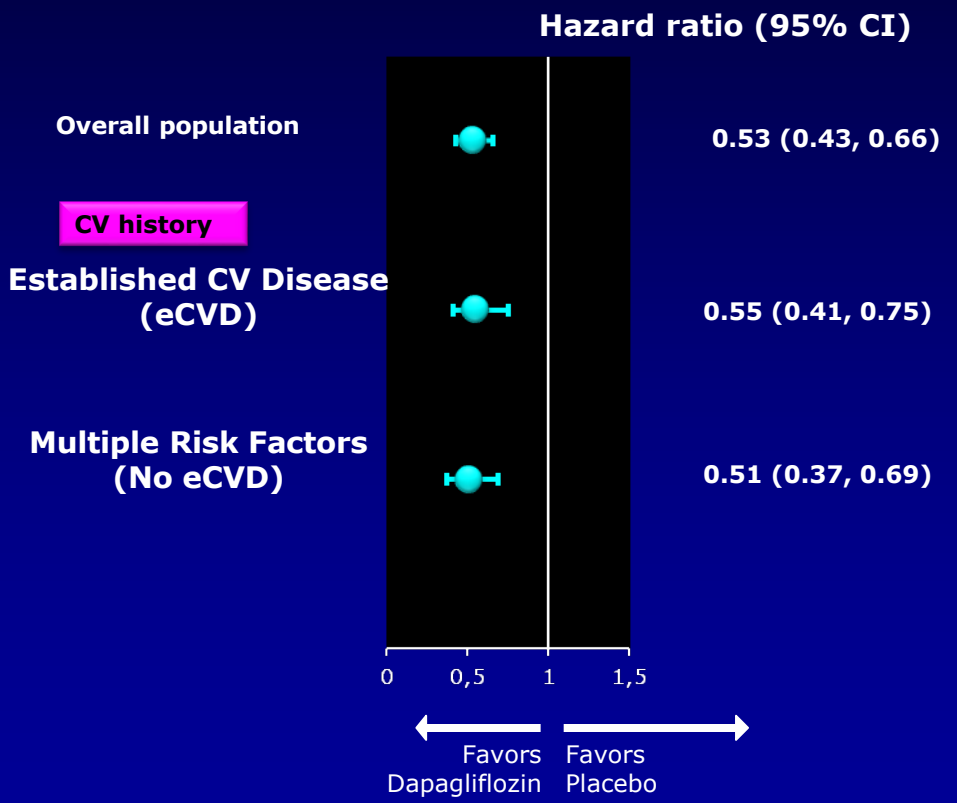
Wiviott SD et al. Online ahead of print. *N Engl J Med*. 2018, November 10

dapagliflozina e protezione renale

composite Renal & CV death



composite Renal



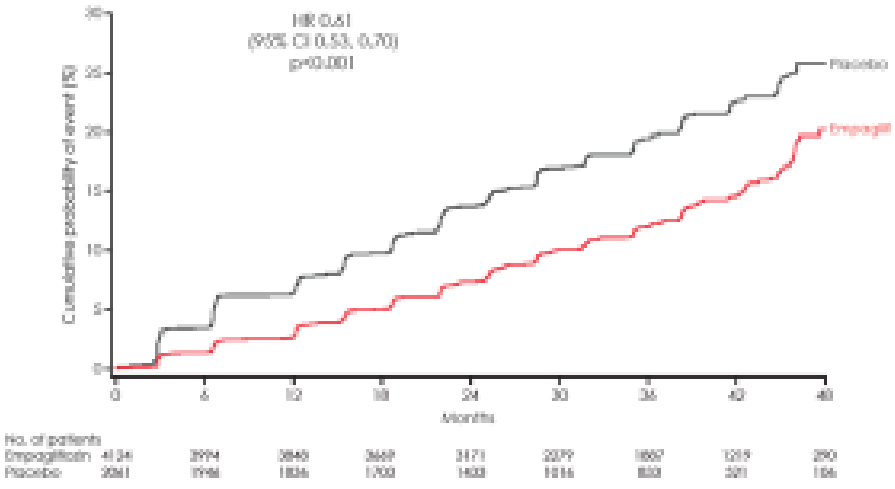
Renal-composite: riduzione ≥40% di eGFRa fino <60 mL/min/1.73 m2, ESRD, o morte renale

CV, cardiovascular; eCVD, established CV disease; HF, heart failure; hHF, hospitalized heart failure; SGLT-2i, SGLT co-transporter 2 inhibitor; T2D, type 2 diabetes

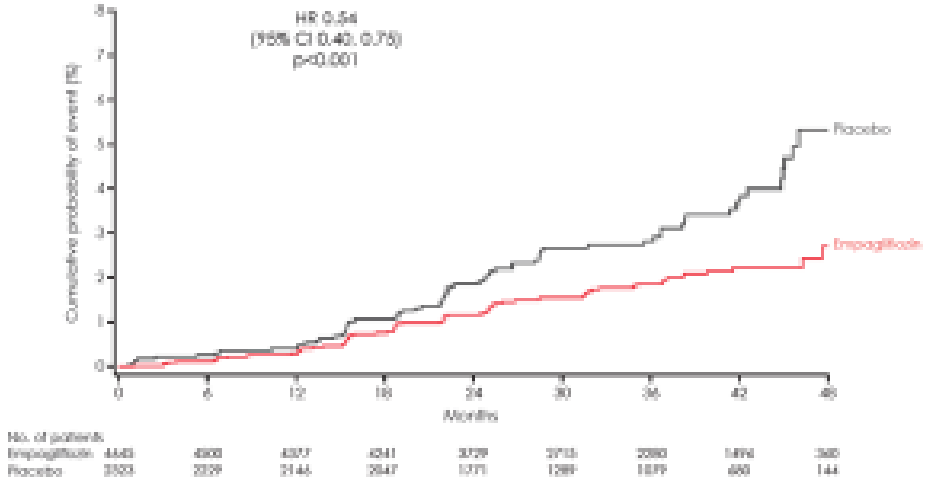
Wiviott SD et al. Online ahead of print. *N Engl J Med*. 2018, November 10

SGLT2-i e FUNZIONE RENALE

EMPA-REG OUTCOME-RENAL



Incident or worsening nephropathy

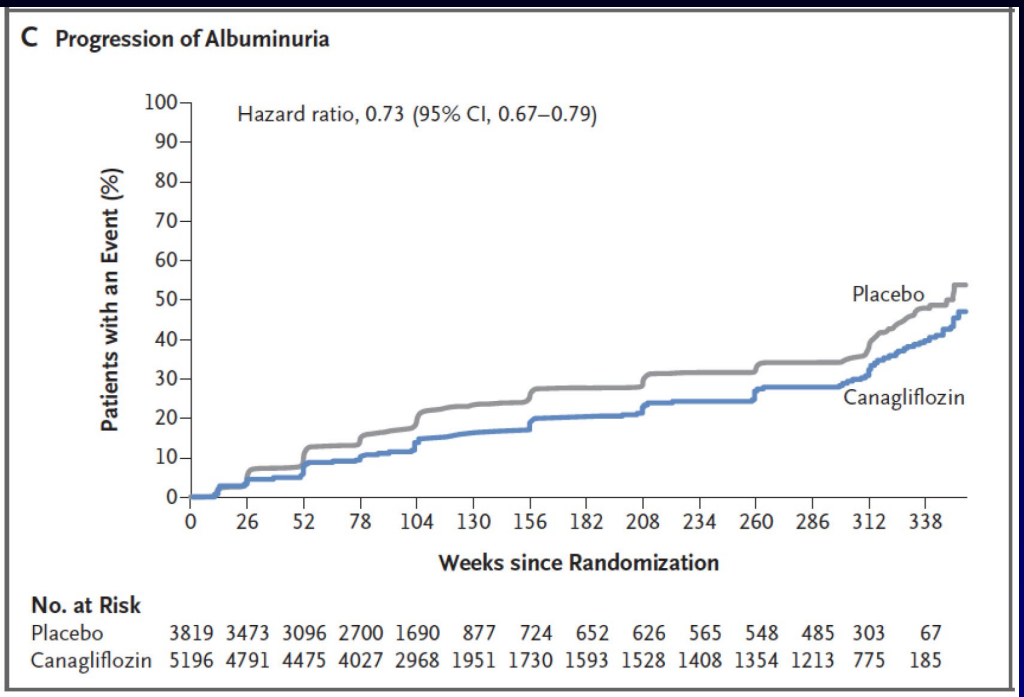


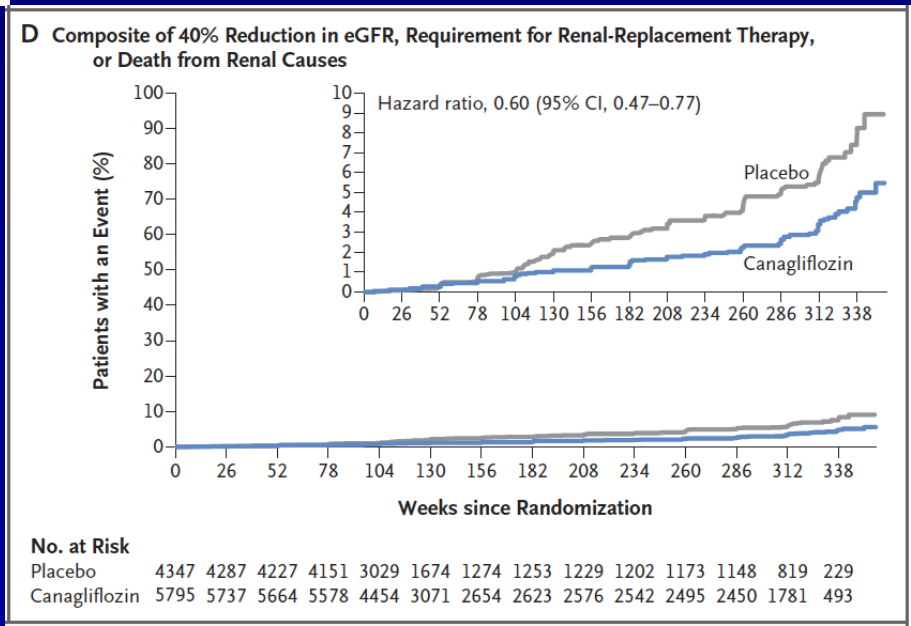
Doubling of serum creatinine*, initiation of renal replacement therapy, or death due to renal disease

Christoph Wanner et al. June 14, 2016, at NEJM.org

EMPA-REG OUTCOME®

SGLT2-i e FUNZIONE RENALE

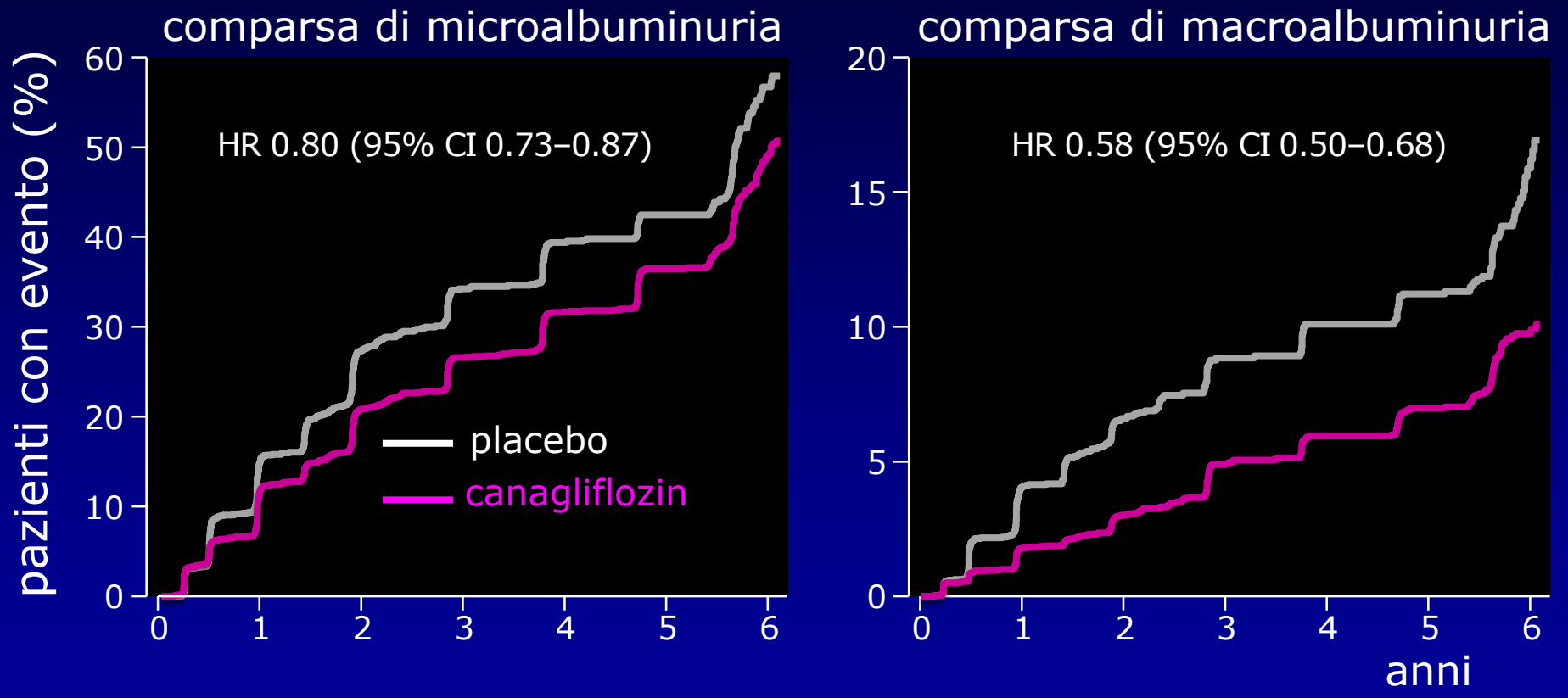




N Eng J Med 2017; 377: 644-657

SGLT2-i e FUNZIONE RENALE

new onset of micro and macro albuminuria



Perkovic V, et al. Lancet DE 6:691, 2018

SGLT2-i e FUNZIONE RENALE

Phase 3 CREDENCE Renal Outcomes Trial of [redacted] (canagliflozin) is Being Stopped Early for Positive Efficacy Findings

Jul 16, 2018
United States

[redacted] has the potential to be the first new therapy in more than 15 years for slowing the progression of chronic kidney disease in patients with type 2 diabetes

- Worldwide, 160 million patients with type 2 diabetes are at risk for developing chronic kidney disease[i]

- CREDENCE assessed I[redacted] for renal protection by evaluating the risk reduction of the composite endpoint of time to dialysis or kidney transplantation, doubling of serum creatinine, and renal or cardiovascular death, when used in addition to standard of care

RARITAN, N.J., July 16, 2018 -- The Janssen Pharmaceutical Companies of Johnson & Johnson today announced that the Phase 3 CREDENCE (**C**anagliflozin and **R**enal **E**vents in **D**iabetes with **E**stablished **N**ephropathy **C**linical **E**valuation) clinical trial, evaluating the efficacy and safety of INVOKANA® (canagliflozin) versus placebo when used in addition to standard of care for patients with chronic kidney disease (CKD) and type 2 diabetes (T2D), is being stopped early based on the achievement of pre-specified efficacy criteria.

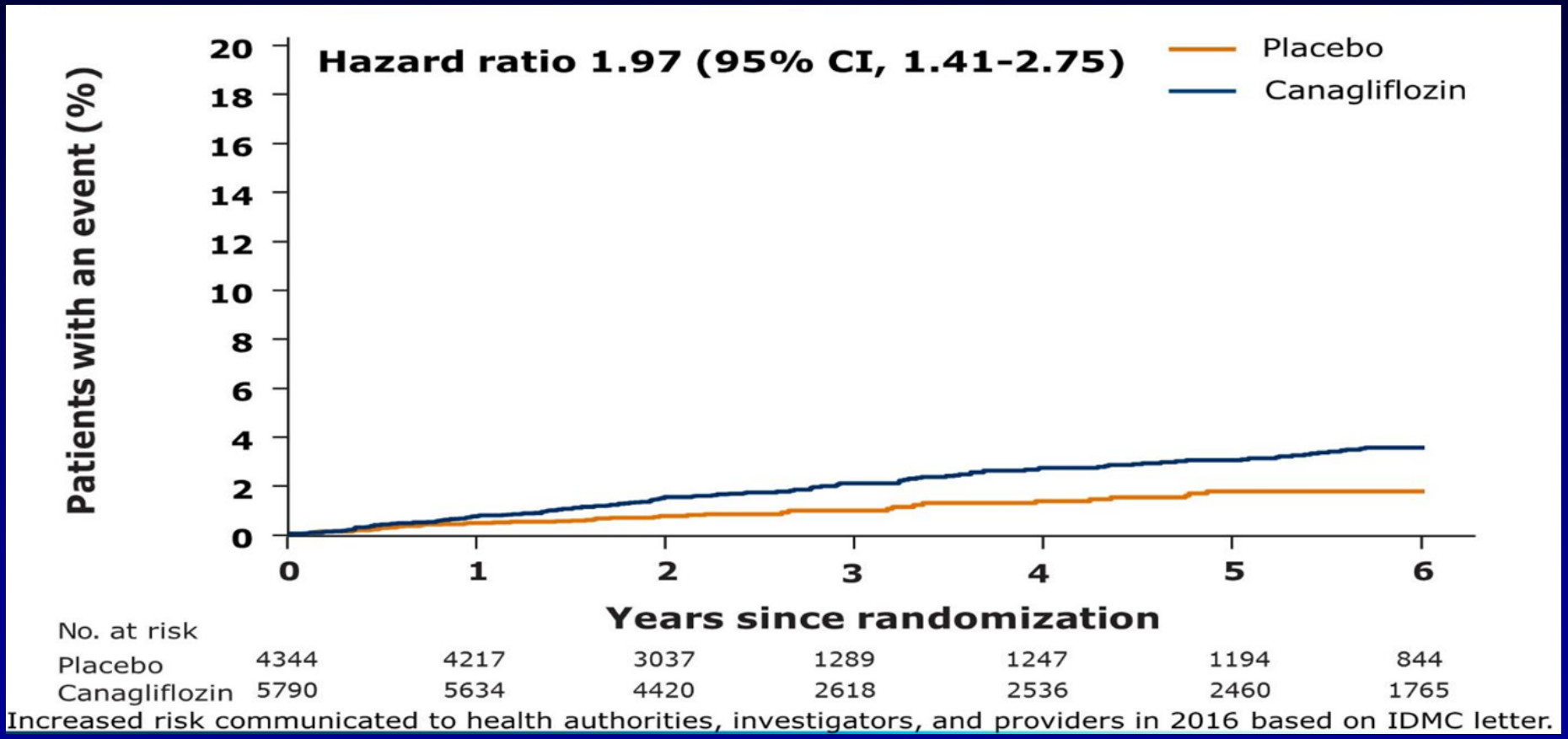
The decision is based on a recommendation from the study's Independent Data Monitoring Committee (IDMC) that met to review the data during a planned interim analysis. This recommendation was based on demonstration of efficacy, as the trial had achieved pre-specified criteria for the primary composite endpoint of end-stage kidney disease (time to dialysis or kidney transplantation), doubling of serum creatinine, and renal or cardiovascular (CV) death, when used in addition to standard of care.

"Nearly half of all people with type 2 diabetes will develop chronic kidney disease, causing a high risk of kidney failure and cardiovascular disease, and impacting their quality and length of life, even with the current best available care. This huge unmet need is why it was so important for us to initiate the landmark CREDENCE renal outcomes trial over four years ago," said Vlado Perkovic, M.B.B.S, Ph.D., F.A.S.N., F.R.A.C.P., CREDENCE Steering Committee co-chair, Professor of Medicine, University of New South Wales Sydney, and Executive Director, The George Institute for Global Health Australia. "We have accepted the advice of the Independent Data Monitoring Committee to stop the CREDENCE trial early due to demonstration of efficacy, and look forward to sharing the findings as soon as possible."

"Chronic kidney disease is a progressive condition that impacts a person's overall health and well-being, and with millions of people worldwide suffering from the disease, we know that there is a clear need for new treatment options," said James List, M.D., Ph.D., Global Therapeutic Area Head, Cardiovascular & Metabolism, Janssen Research & Development, LLC. "We are excited about the possibility of bringing forth INVOKANA® (canagliflozin) as the first therapy to treat patients with chronic kidney disease and type 2 diabetes in more than 15 years. We look forward to presenting the full data from the

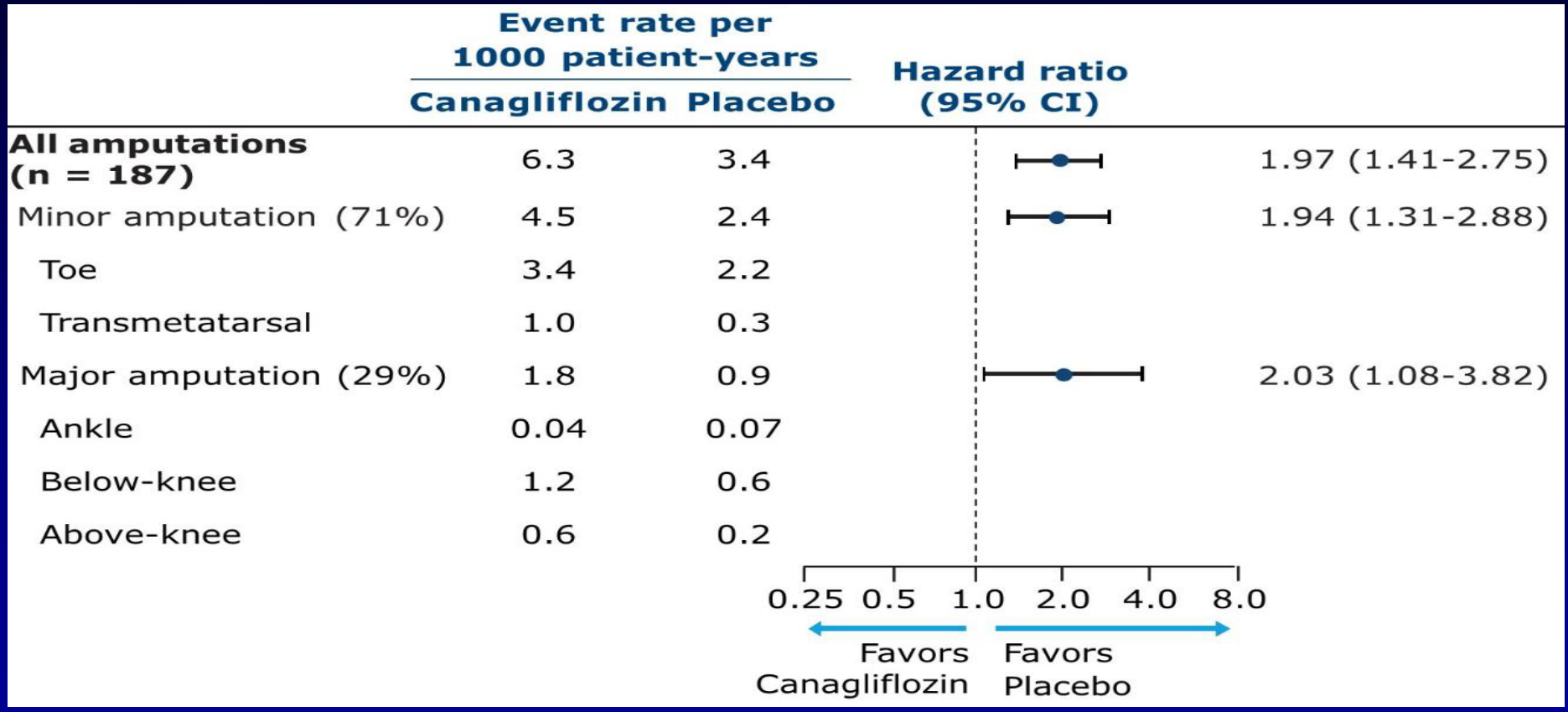
Am J Nephrol 2017; 46; 462-72

dark side delle gliflozine

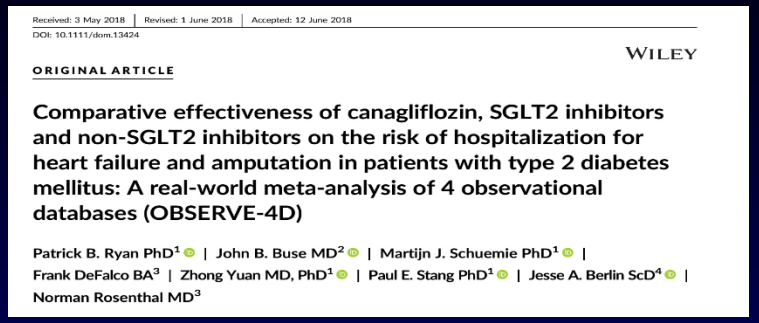


Increased risk communicated to health authorities, investigators, and providers in 2016 based on IDMC letter.

dark side delle gliflozine



gliflozine e amputazioni


Received: 3 May 2018 | Revised: 1 June 2018 | Accepted: 12 June 2018
DOI: 10.1111/dom.13424

WILEY

ORIGINAL ARTICLE

Comparative effectiveness of canagliflozin, SGLT2 inhibitors and non-SGLT2 inhibitors on the risk of hospitalization for heart failure and amputation in patients with type 2 diabetes mellitus: A real-world meta-analysis of 4 observational databases (OBSERVE-4D)

Patrick B. Ryan PhD[1] | John B. Buse MD[2] | Martijn J. Schuemie PhD[1] | Frank DeFalco BA[3] | Zhong Yuan MD, PhD[1] | Paul E. Stang PhD[1] | Jesse A. Berlin ScD[4] | Norman Rosenthal MD[3]

SCOPO DELLO STUDIO

Valutare in pazienti affetti da DMT2 e nuovi utilizzatori di canagliflozin, il rischio di:

- Ospedalizzazioni per Scompenso Cardiaco (HHF)
- Amputazioni al di sotto del ginocchio (BKLA)

Sono stati considerati due tempi primari per la valutazione del rischio:

- **ON TREATMENT:** per valutare il rischio DURANTE l'uso del farmaco
- **INTENT TO TREAT:** per valutare «overall» il rischio una volta che il trattamento è stato iniziato ed eventualmente anche sospeso

Eseguite sotto-analisi in pazienti con o senza anamnesi di malattia CV nota

Confronto: canagliflozin con altri iSGLT2 e altri anti-diabetici non iSGLT2

Ryan et al., Diabetes Obes Metab. 2018;1–13

SGLT2-i e AMPUTAZIONI

TABLE 4 Risk of BKLE amputation in the overall population for selected comparisons during on-treatment and intent-to-treat time-at-risk periods[a]

Comparison	Source	Exposure (n/PY) Target	Comparator	On-treatment Outcomes Target	Comparator	HR (95% CI)	P	Calibrated P	Intent-to-treat Outcomes Target	Comparator	HR (95% CI)	P	Calibrated P
Canagliflozin vs all non-SGLT2i	CCAE	60 073/29 965	217 583/125 189	24	190	0.56 (0.32-0.92)	.03	.06	144	467	1.01 (0.80-1.28)	.92	.85
	MDCD	5998/1775	38 172/16 482	10	61	1.35 (0.46-3.41)	.56	.46	30	236	1.05 (0.62-1.73)	.84	.71
	MDCR	9206/4707	42 744/30 668	9	57	1.16 (0.48-2.66)	.73	.62	26	138	0.88 (0.51-1.47)	.65	.77
	Optum	36 055/16 676	146 868/84 306	17	173	0.67 (0.35-1.18)	.19	.31	95	467	1.03 (0.78-1.36)	.82	.71
	Meta-analysis	111 332/53 125	445 367/256 646	60	481	0.75 (0.40-1.41) $I^2 = 0.18$	.25	.30	295	1308	1.01 (0.93-1.10) $I^2 = 0.00$	.71	.51
Canagliflozin vs select non-SGLT2i	CCAE	64 795/32 238	158 992/76 081	34	86	1.08 (0.65-1.75)	.76	.68	171	382	0.96 (0.77-1.21)	.75	.78
	MDCD	6727/1993	21 355/7401	10	15	3.11 (0.87-11.70)	.09	.08	34	109	1.21 (0.73-1.97)	.45	.43
	MDCR	10 217/5222	35 398/20 471	11	37	0.60 (0.19-1.64)	.36	.42	34	142	0.78 (0.48-1.24)	.31	.33
	Optum	39 142/18 081	104 231/45 912	23	71	1.30 (0.64-2.55)	.46	.42	110	363	1.10 (0.84-1.44)	.49	.46
	Meta-analysis	120 881/57 536	319 976/149 866	78	209	1.17 (0.55-2.47) $I^2 = 0.21$	.56	.43	349	996	1.01 (0.81-1.25) $I^2 = 0.00$	.93	.86
Canagliflozin vs other SGLT2i	CCAE	43 411/20 312	70 519/31 520	19	34	0.88 (0.38-2.01)	.77	.73	102	135	1.13 (0.81-1.57)	.46	.50
	MDCD	1424/403	1425/419	3	1	2.00 (0.19-43.01)	.62	.52	8	7	1.25 (0.33-5.05)	.75	.70
	MDCR	4395/2000	5041/2123	6	5	1.73 (0.28-13.34)	.58	.55	15	15	1.38 (0.58-3.39)	.47	.56
	Optum	20 324/8652	21 184/7603	12	13	1.40 (0.49-4.28)	.54	.54	46	52	1.06 (0.67-1.68)	.82	.85
	Meta-analysis	69 554/31 369	98 169/41 666	40	53	1.14 (0.67-1.93) $I^2 = 0.00$	.48	.53	171	209	1.13 (0.99-1.29) $I^2 = 0.00$	.06	.06
Other SGLT2i vs all non-SGLT2i	CCAE	54 324/24 642	175 500/96 683	23	143	0.59 (0.32-1.04)	.08	.14	87	327	0.78 (0.57-1.04)	.09	.15
	MDCD	1378/405	25 995/10 106	0	28	0.36 (NA-5.96)	—	—	5	111	0.99 (0.33-2.39)	.98	.96
	MDCR	4336/1837	31 228/21 522	4	37	1.65 (0.37-5.26)	.46	.39	13	85	1.56 (0.72-3.12)	.23	.17
	Optum	19 588/7076	118 027/64 041	12	115	1.02 (0.49-1.98)	.95	.77	45	306	1.31 (0.88-1.89)	.17	.13
	Meta-analysis	78 248/33 556	324 755/182 247	39	295	0.84 (0.27-2.55) $I^2 = 0.23$	.57	.68	150	829	$I^2 = 0.51$		

Abbreviations: BKLE, below-knee lower extremity; CI, confidence interval; HR, hazard ratio; CCAE, Truven MarketScan Commercial Claims and Encounters; MDCD, Truven MarketScan Multi-state Medicaid; MDCR, Truven MarketScan Medicare Supplemental Beneficiaries; NA, not available; PY, patient-years; SGLT2i, sodium glucose co-transporter 2 inhibitors.

Ryan et al., Diabetes Obes Metab. 2018;1–13

gliflozine: pro & contro

pro
efficace in tutti i pazienti
no ipoglicemia
rimuove gluco tossicità
riduzione pressione arteriosa

contro
non efficace con basso eGFR
infezioni GU

anziano
perdita di peso
Ipotensione

gliflozine: pro & contro

pro
efficace in tutti i pazienti
no ipoglicemia
rimuove gluco tossicità
riduzione pressione arteriosa

contro
non efficace con basso eGFR
infezioni GU

anziano
perdita di peso, *ma forse positiva*
Ipotensione, *o possibilità di ridurre tp antiIPT*

Terapia farmacologica nell'anziano

	rischio di IPO	uso in IRC	prev CVD	scomp card	fen glic	riserva β-cell	stato nutr.	facilità somm.
Metformina	NO	no<30	SI	NO	digiuno	=	−	XR
SU e glinidi	SI	gliclazide only	rischio	neutro	vario	SI	+	no
pioglitazone	NO	no<15	SI	SI	digiuno	=	+	si
Gliptine	NO	SI	NO	farmaci diversi	dig/pra	SI	=	si
GLP-1 RA	NO	NO	farmaci diversi	NO	vario	SI	−	farmaci diversi
Gliflozine	NO	NO	SI	prevent	dig/pra	=	−	si
Insulina bas								

ASSOCIAZIONE MEDICI DIABETOLOGI
1974
ANNO DI FONDAZIONE

L'approccio clinico assistenziale al paziente anziano con diabete mellito tipo 2

1) utilizzare insuline che possano **uniformarsi il più possibile al profilo fisiologico dell'insulino-secrezione**;
2) utilizzare **insuline con alta riproducibilità d'azione**;
3) utilizzare insuline con **assente o basso rischio** di indurre manifestazioni **ipoglicemiche**;
4) utilizzare **insuline prandiali ad azione ultrarapida** in associazione a basal-bolus.

BOX 6. Nell'eventualità sia necessaria la terapia insulinica, il trattamento con un'insulina basale è la prima scelta raccomandata in considerazione della sua efficacia, della sua semplicità di gestione, della monosomministrazione giornaliera e del minor rischio di indurre ipoglicemie.

Terapia farmacologica nell'anziano

	rischio di IPO	uso in IRC	prev CVD	scomp card	fen glic	riserva β-cell	stato nutr.	facilità somm.
Metformina	NO	no<30	SI	NO	digiuno	=	−	XR
SU e glinidi	SI	gliclazide only	rischio	neutro	vario	SI	+	no
pioglitazone	NO	no<15	SI	SI	digiuno	=	+	si
Gliptine	NO	SI	NO	farmaci diversi	dig/pra	SI	=	si
GLP-1 RA	NO	NO	farmaci diversi	NO	vario	SI	−	farmaci diversi
Gliflozine	NO	NO	SI	prevent	dig/pra	=	−	si
Insulina bas	SI	SI	NO	NO	dig	prand	+	no

Management of Diabetes in Older Adults
Sesti G., … and Ferrara N.
NMCD, Mar 2018

Tabella 8
Soggetti trattati con farmaci antidiabetici per classi di età

ATC	Descrizione	% trattati per classi di età					
		0-19 (N=3.117)	20-34 (N=7.745)	35-49 (N=30.227)	50-64 (N=108.470)	65-79 (N=208.574)	>=80 (N=100.400)
A10BA02	Metformina	18,5	37,5	62,0	70,8	63,9	46,2
A10AE04	Insulina glargine	61,5	36,8	20,3	13,4	13,1	14,1
A10BB09	Gliclazide	0,6	2,1	6,6	9,7	11,7	13,4

Terapia farmacologica nell'anziano:

- rischio di ipoglicemia ✓
- insufficienza renale ✓
- pregresso ictus/IMA ✓
- storia di scompenso cardiaco ✓
- profilo glicemico ✓
- riserva funzionale beta cellula ✓
- stato nutrizionale ✓
- facilità di somministrazione ✓


Declino funzionale
Declino cognitivo
Hypo unawereness
Rischio ipoglicemie
Performance secretiva e sensibilità insulinica
Istituzionalizzazione
Politerapia
Comorbidità (scompenso cardiaco - IRC)
56° ALGHERO 2017
SCALA PICCADA

Il compenso glicemico e il trattamento ipoglicemizzante

In assenza di studi clinici randomizzati di lunga durata, un paziente anziano posto in terapia con farmaci che non determinano un elevato rischio di ipoglicemia (metformina, DPP4 inibitori, pioglitazone, SGLT-2 inibitori, agonisti del recettore del GLP-1 ed acarbosio o loro combinazioni) è consigliabile un obiettivo terapeutico di HbA1c <7% e per ottenere questo target dovrebbe mantenere le glicemie a digiuno e pre-prandiali nell'ambito dei valori di norma senza indurre ipoglicemie. *VI B*

Qualora risulti indispensabile l'uso di farmaci a rischio di ipoglicemia (sulfoniluree, repaglinide, insulina) dovrà essere perseguito un obiettivo meno a rischio di ipoglicemie (HbA1c 7.0-7.5%) che potrà anche essere più elevato (7.5-8.0%) in presenza di fragilità, co-morbidità, decadimento cognitivo e trattamenti farmacologici complessi. *VI B*

In caso di pregresso evento cardiovascolare, nella terapia dell'iperglicemia deve essere presente un farmaco con documentati benefici cardiovascolari quali empagliflozin, canagliflozin, liraglutide o pioglitazone, salvo sua controindicazione o non indicazione oppure mancata tollerabilità. *II A*

Gli obiettivi metabolici vanno perseguiti in sicurezza, evitando o cercando di ridurre al minimo il rischio di ipoglicemia. Non è raccomandato il perseguimento di una glicemia a digiuno <108 mg/dl e si sconsiglia di iniziare un trattamento ipoglicemizzante se la glicemia a digiuno non è stabilmente >126 mg/dl. Gli obiettivi glicemici dovrebbero essere individualizzati tenendo conto dello stato funzionale, delle comorbilità, di pregressi eventi CV, storia e rischio di ipoglicemia, e presenza di complicanze microvascolari. *II A*

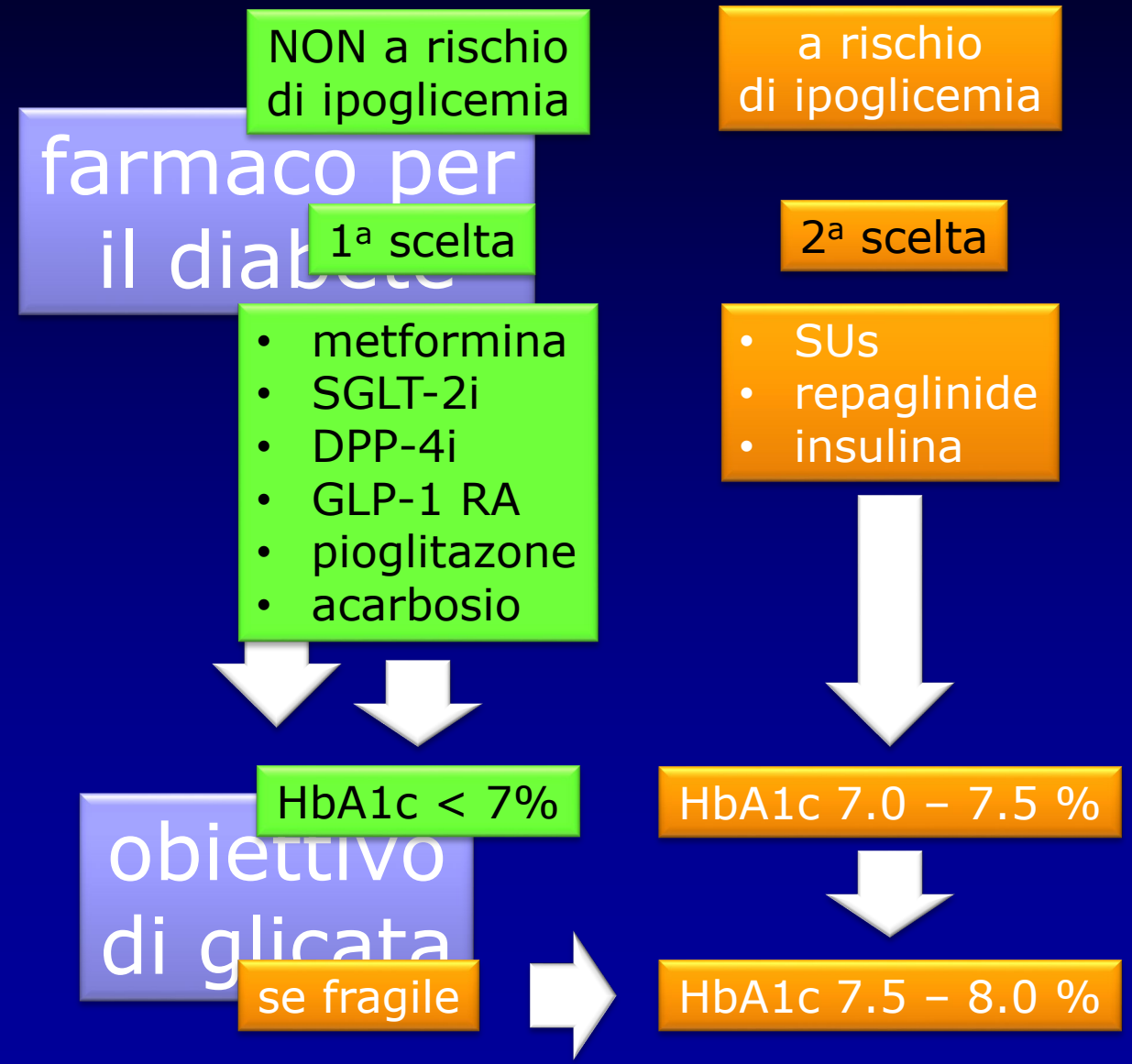
obiettivi e terapia del diabete

obiettivo
di glicata



farmaco per
il diabete

obiettivi e terapia del diabete




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DIABETE UNA PATOLOGIA COMPLESSA A VALENZA MULTIDISCIPLINARE

Terapia nell'anziano: farmaci tradizionali e farmaci innovativi

Gian Pio Sorice

Centro per le Malattie Endocrine e Metaboliche
Fondazione Policlinico Universitario Agostino Gemelli IRCCS
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