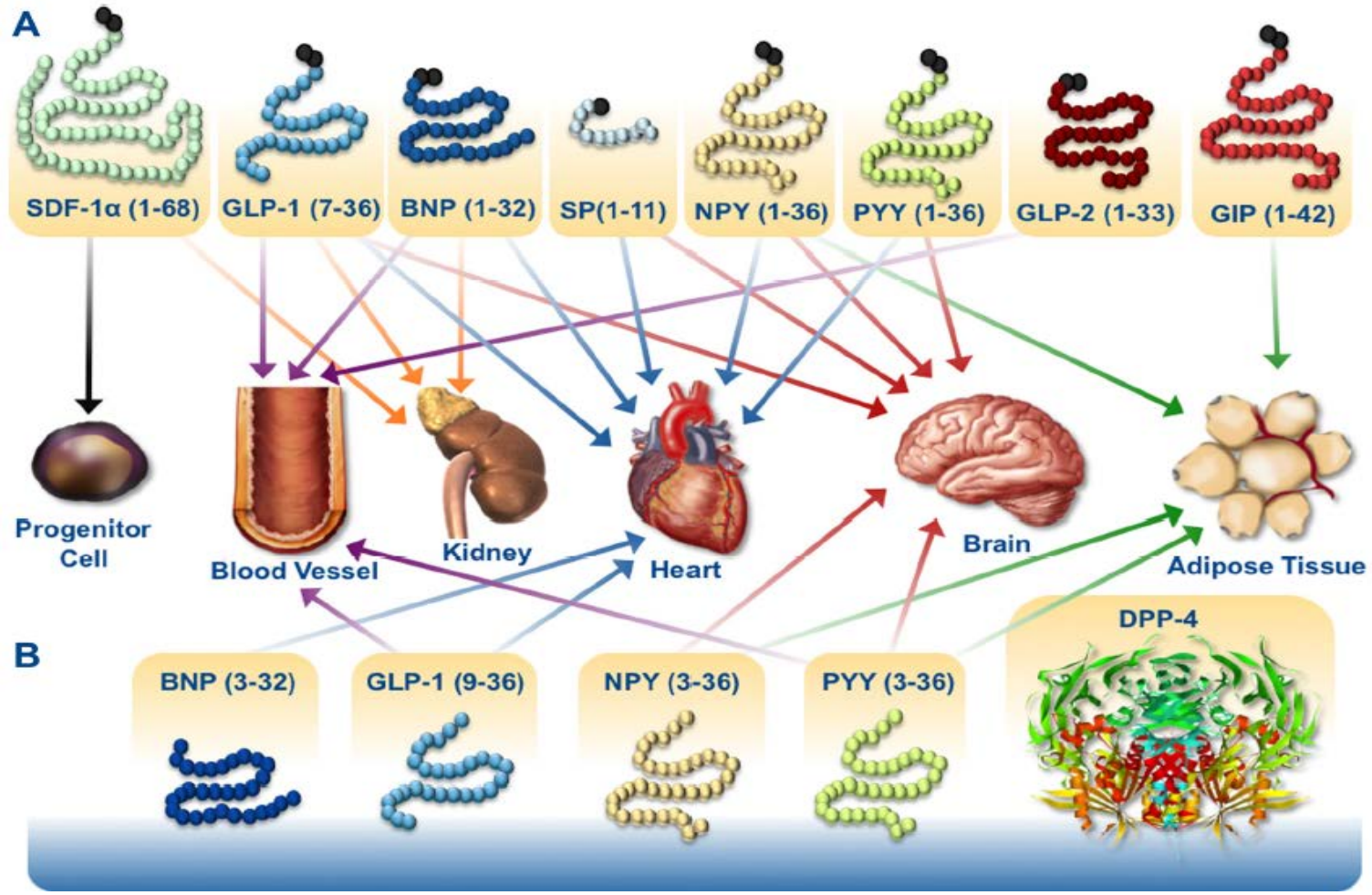
DPP4i: a quale paziente?

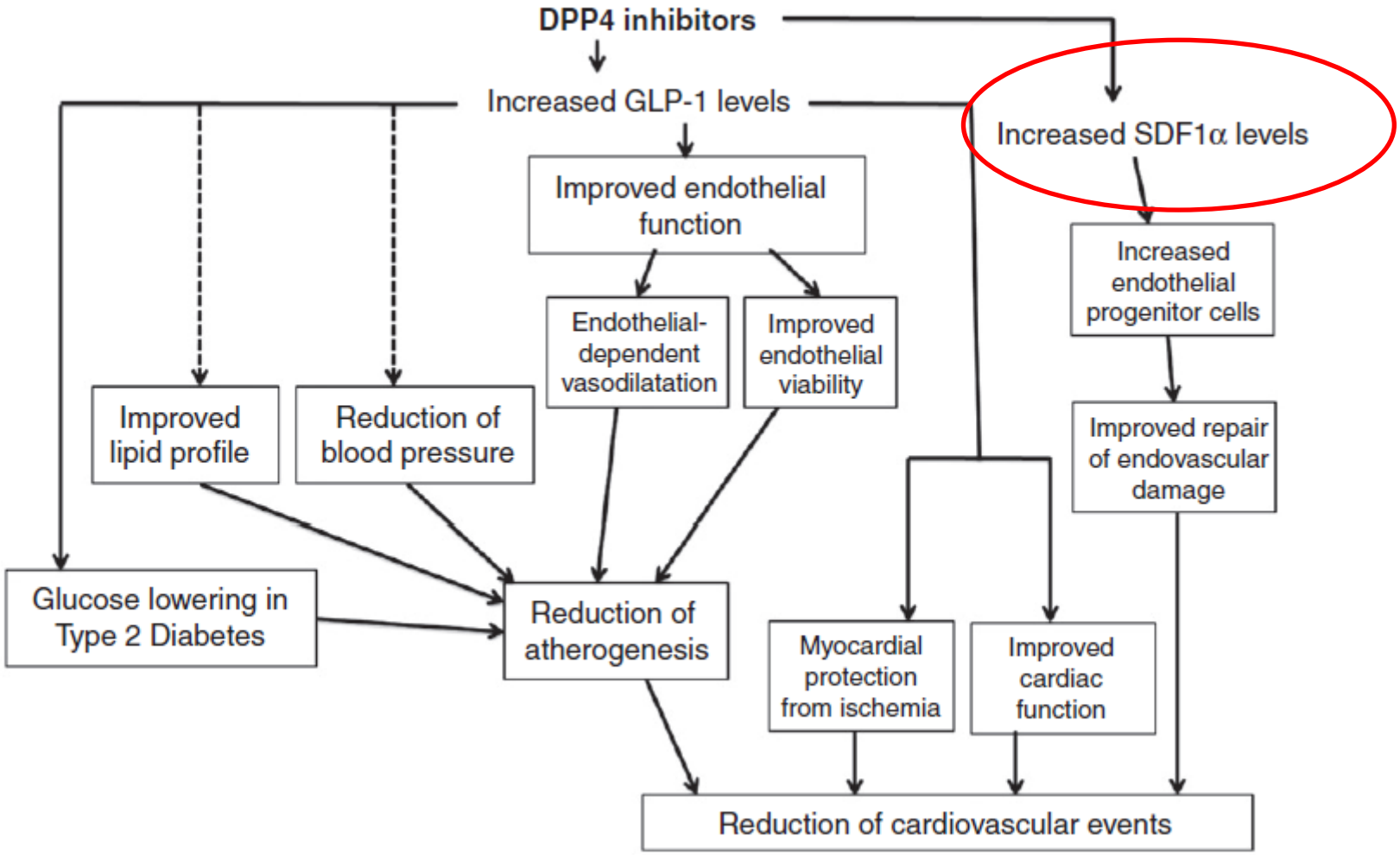
Ilaria Giordani
ACISMOM Togliatti
Roma

Substrati di DPP-4 che regolano direttamente o indirettamente la funzione cardiovascolare



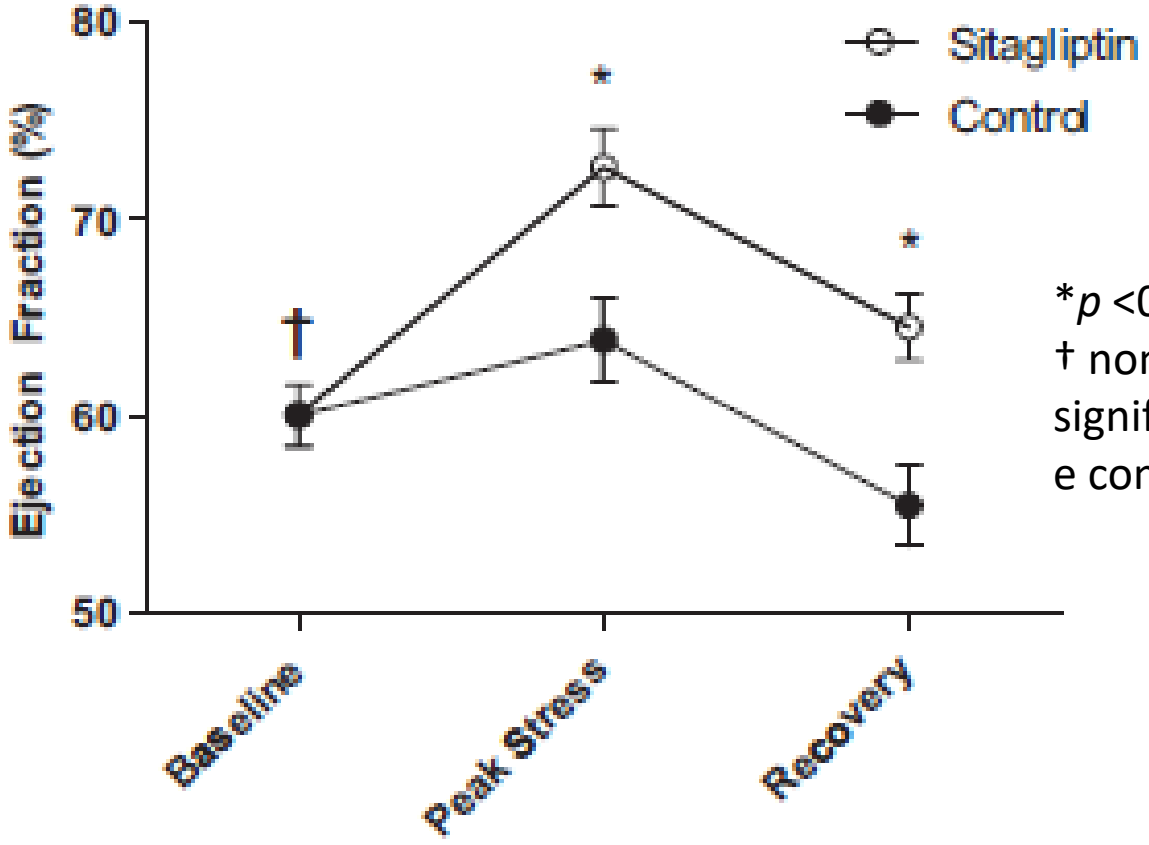
Ussher & Drucker, *Endocr Rev* 2012

Effetto dei DPP-4i sul sistema CV



Mannucci *Current Mediical Research & Opinion* 2012

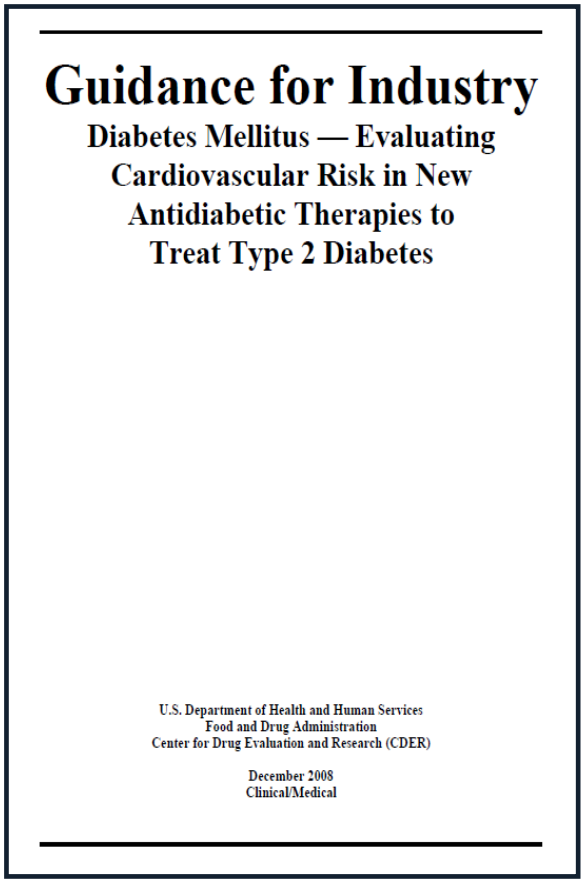
Funzione Vsin in paz con sindrome coronarica in attesa di rivascolarizzazione



**p* <0,001
† non differenza significativa tra sitagliptin e controlli

Read*C Circ Cardiovasc Imaging* 2010

FDA raccomanda studi di *outcome* CV per le nuove terapia per il diabete



Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2008
Clinical/Medical

Le linee guida 2008 FDA richiedono per l'approvazione di farmaci per il diabete non più la prova dell'efficacia ma una forte dimostrazione di sicurezza CV

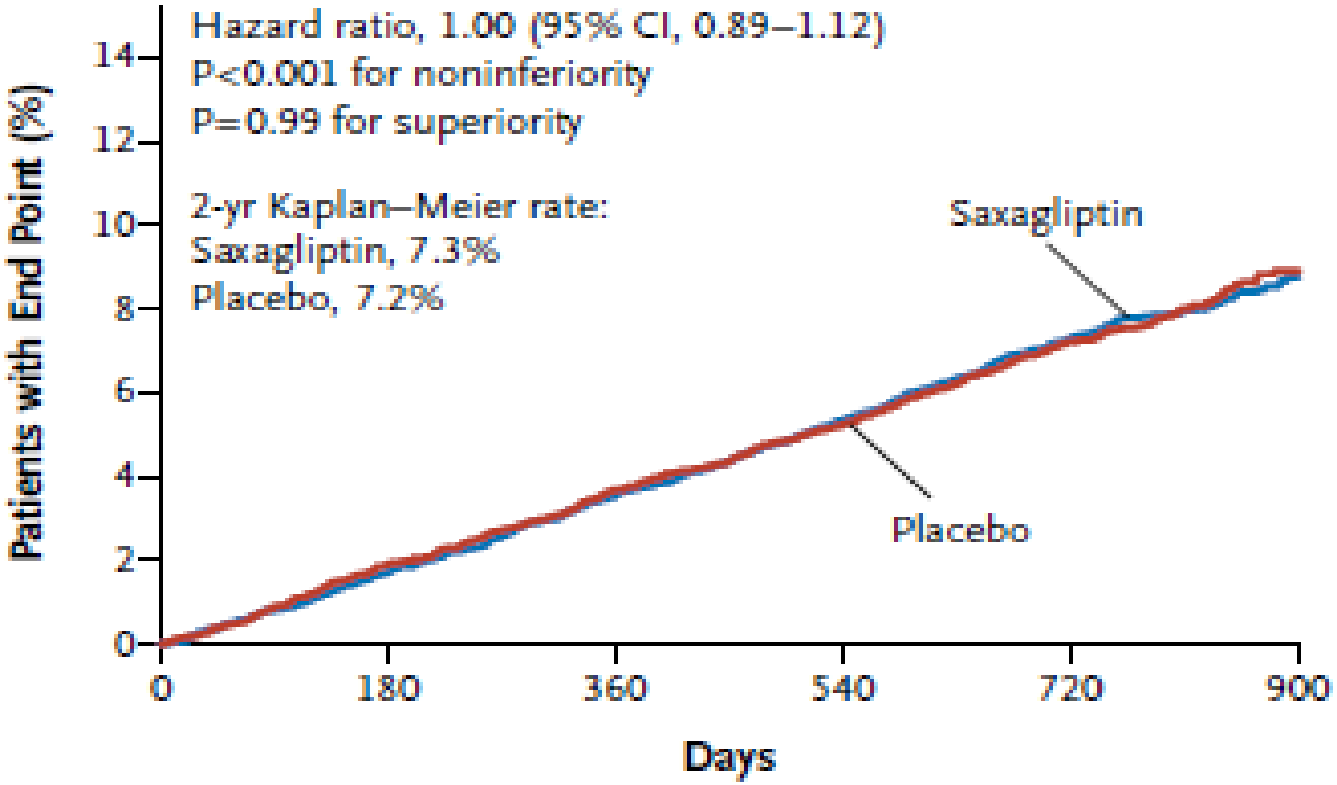
Valutazione del rischio CV negli studi di fase 2/3 per tutti gli antidiabetici commercializzati: limite superiore necessario del *two-sided 95% CI* per il *risk ratio* stimato

>1.8:	i dati non sono adeguati a supportare l'approvazione; deve essere condotto un ampio *trial* di sicurezzza
1.3–1.8:	esiste un potenziale pericolo CV ; è necessario un *trial* post-marketing adeguatamente disegnato per dimostrare un limite superiore <1.3
<1.3:	l'analisi rischio/beneficio supporta l'approvazione; un *trial* post-marketing non è necessario

FDA Guidance for Industry. Diabetes mellitus – evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. Available from: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf [Accessed Jan 2014]

SAVOR-TIMI 53

A Primary End Point



No. at Risk						
Placebo	8212	7983	7761	7267	4855	851
Saxagliptin	8280	8071	7836	7313	4920	847

Scirica, N Engl J Med 2013

SAVOR-TIMI 53

*Prespecified Clinical End Points**

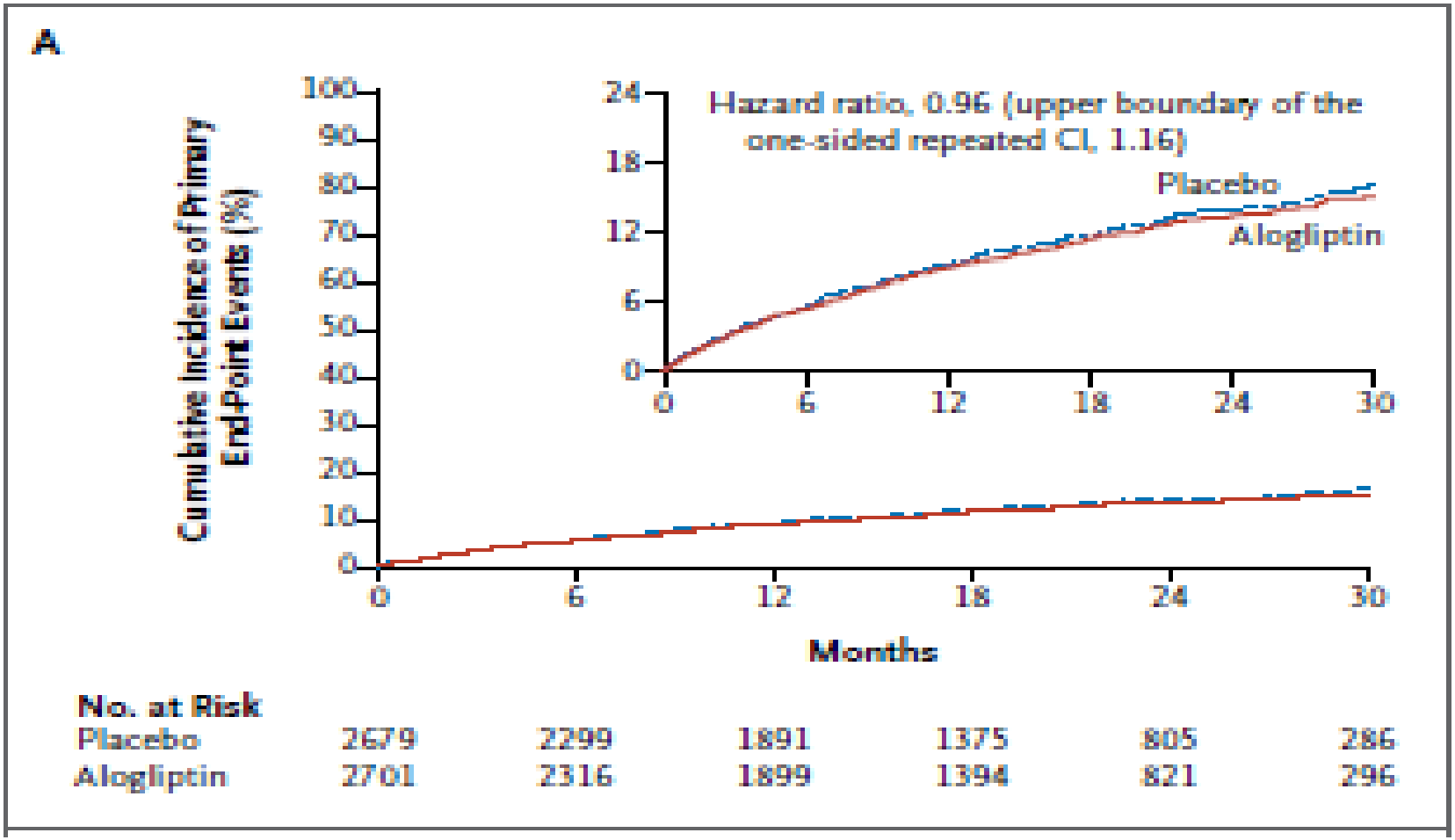
End Point	Saxagliptin (N=8280)	Placebo (N=8212)	Hazard Ratio (95% CI)	P Value
	no. (%)			
Cardiovascular death, myocardial infarction, or stroke: primary efficacy end point	613 (7.3)	609 (7.2)	1.00 (0.89–1.12)	0.99
Cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, heart failure, or coronary revascularization: secondary efficacy end point	1059 (12.8)	1034 (12.4)	1.02 (0.94–1.11)	0.66
Death from any cause	420 (4.9)	378 (4.2)	1.11 (0.96–1.27)	0.15
Death from cardiovascular causes	269 (3.2)	260 (2.9)	1.03 (0.87–1.22)	0.72
Myocardial infarction	265 (3.2)	278 (3.4)	0.95 (0.80–1.12)	0.52
Ischemic stroke	157 (1.9)	141 (1.7)	1.11 (0.88–1.39)	0.38
Hospitalization for unstable angina	97 (1.2)	81 (1.0)	1.19 (0.89–1.60)	0.24
Hospitalization for heart failure	289 (3.5)	228 (2.8)	1.27 (1.07–1.51)	0.007
Hospitalization for coronary revascularization	423 (5.2)	459 (5.6)	0.91 (0.80–1.04)	0.18
Doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine >6.0 mg/dl (530 μmol/liter)	194 (2.2)	178 (2.0)	1.08 (0.88–1.32)	0.46
Hospitalization for hypoglycemia	53 (0.6)	43 (0.5)	1.22 (0.82–1.83)	0.33

* Event rates and percentages are 2-year Kaplan–Meier estimates.

Scirica, N Engl J Med 2013

EXAMINE

Tempo alla prima occorrenza di ogni evento dei *primary*
MACE endpoint (morte CV, IM non fatale, stroke non fatale)



White, N Engl J Med 2013

EXAMINE: Pre-specified Exploratory Adjudicated MACE Composite

Prima occorrenza di mortalità per tutte le cause, IMA non fatale, stroke non fatale, rivascolarizzazione urgente per angina instabile, ospedalizzazione per HF

	Alogliptin N=2701 n (%)	Placebo N=2679 n (%)	HR (95% CI)	P-value
Exploratory endpoint: composite	433 (16.0)	441 (16.5)	0.98 (0.86, 1.12)	0.728
All-cause mortality	106 (3.9)	131 (4.9)	0.80 (0.62, 1.03)	0.081
Nonfatal MI	171(6.3)	155 (5.8)	1.10 (0.88, 1.37)	0.393
Nonfatal stroke	28 (1.0)	29 (1.1)	0.97 (0.58, 1.62)	0.898
Urgent revascularization due to unstable angina	43 (1.6)	47 (1.8)	0.90 (0.60, 1.37)	0.632
Hospitalization for HF	85 (3.1)	79 (2.9)	1.07 (0.79, 1.46)	0.657

Zannad F, et al. *Lancet.* 2015

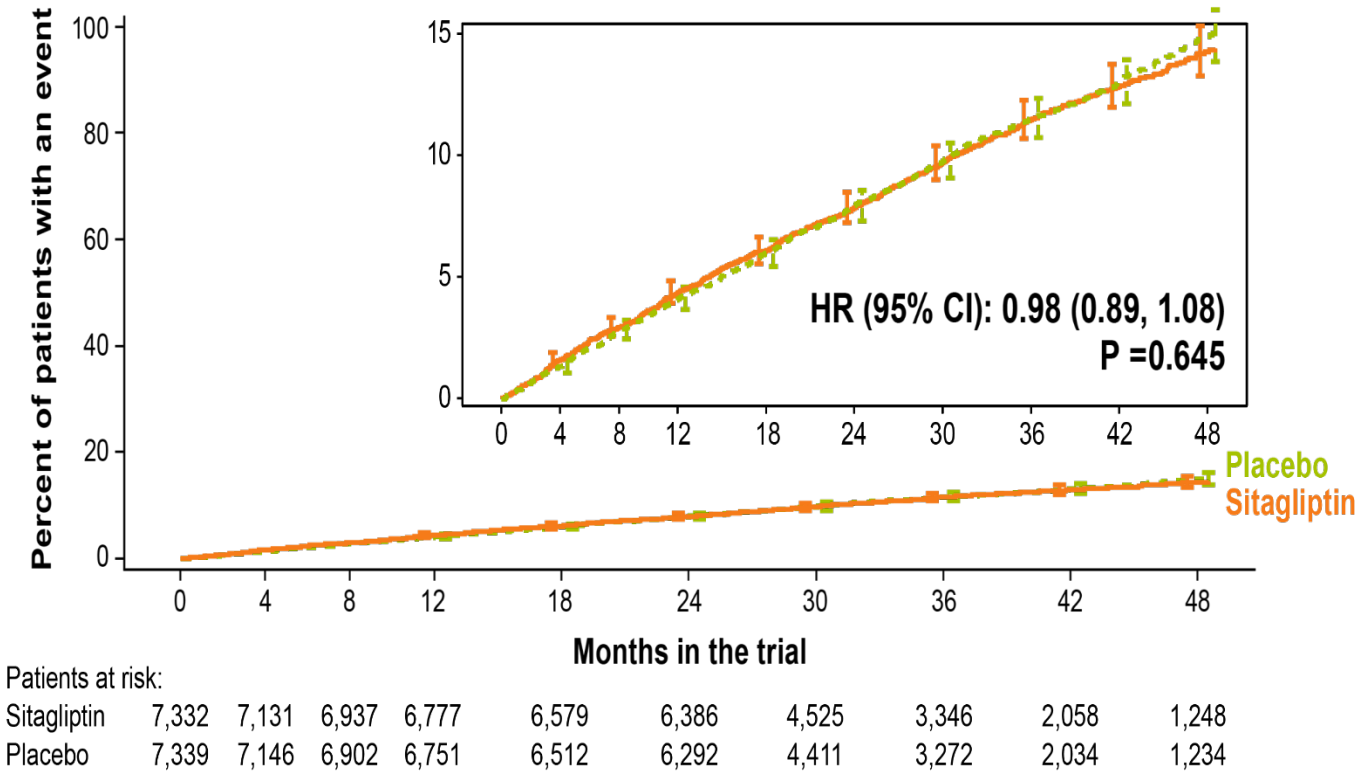
Ospedalizzazione per HF in base alla storia di HF

	Tutti I pazienti		Storia di HF prima della randomizzazione		Nessuna storia di HF prima della randomizzazione	
	Alogliptin N=2701	Placebo N=2679	Alogliptin N=771	Placebo N=762	Alogliptin N=1930	Placebo N=1917
HHF, n (%)	106 (3.9)	89 (3.3)	63 (8.2)	65 (8.5)	43 (2.2)	24 (1.3)
Hazard ratio (HHF)	1.19		1.00		1.76	
95% CI*	0.90, 1.58		0.71, 1.42		1.07, 2.90	
P-value	0.220		0.996		0.026	

*Treatment by any history of heart failure, interaction P-value: 0.068

Zannad F, et al. *Lancet.* 2015

TECOS: outcome primario composito CV*



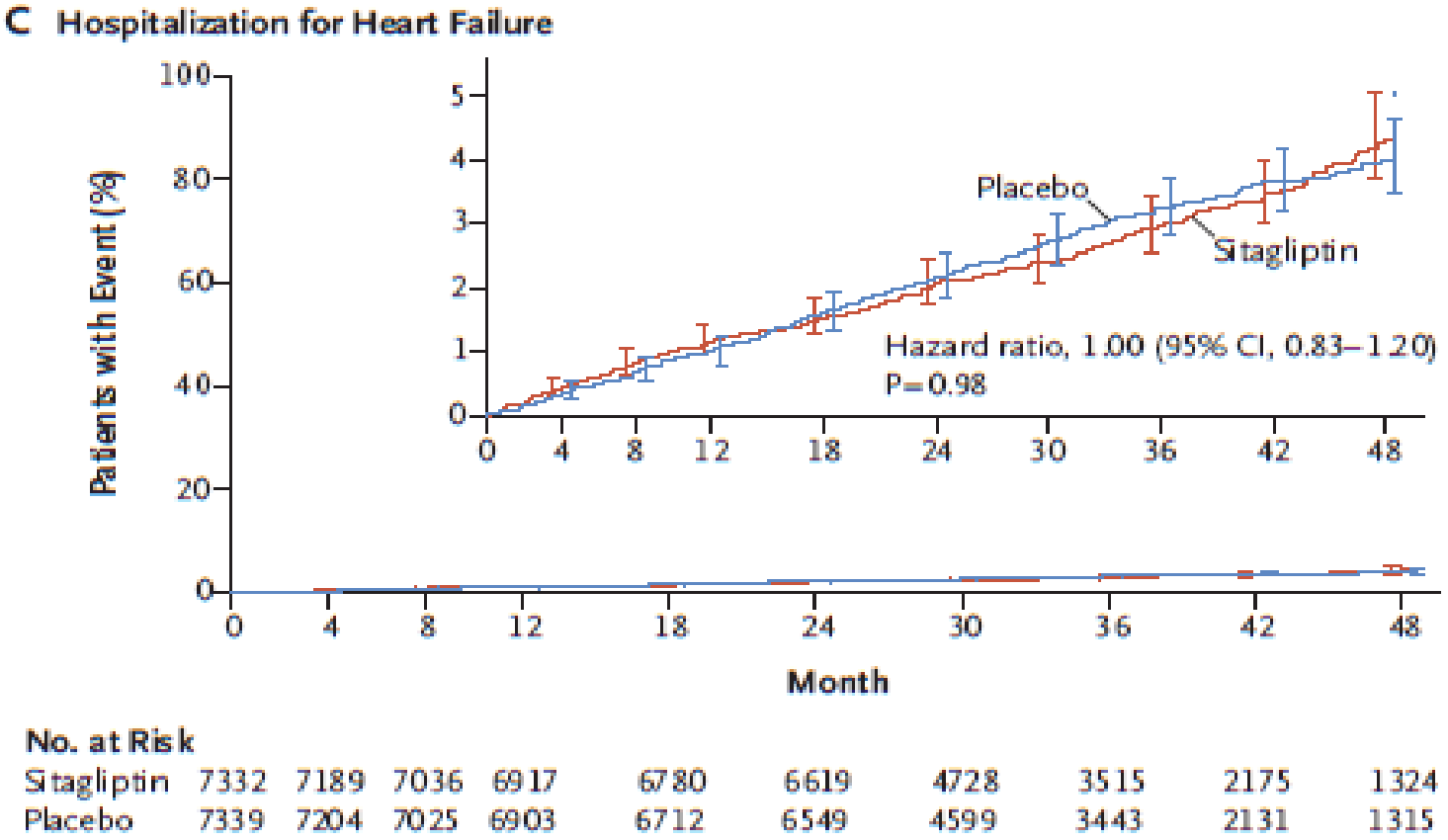
Patients at risk:

Sitagliptin	7,332	7,131	6,937	6,777	6,579	6,386	4,525	3,346	2,058	1,248
Placebo	7,339	7,146	6,902	6,751	6,512	6,292	4,411	3,272	2,034	1,234

** CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina*

Green JB et al. NEJM 2015

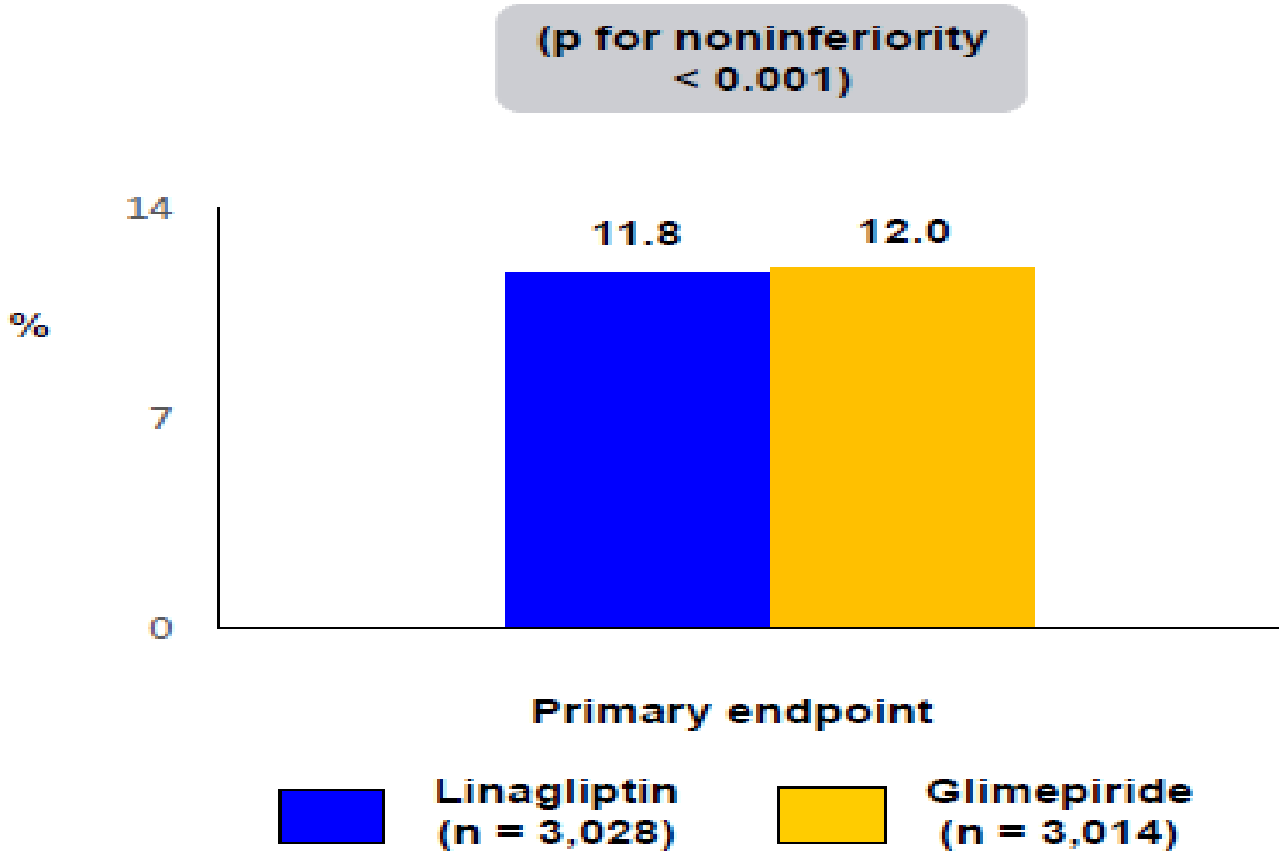
TECOS: ospedalizzazione per HF



Green JB et al. NEJM 2015

CAROLINA

Primary outcome: morte CV, IM o stroke



Rosenstock J, JAMA 2019

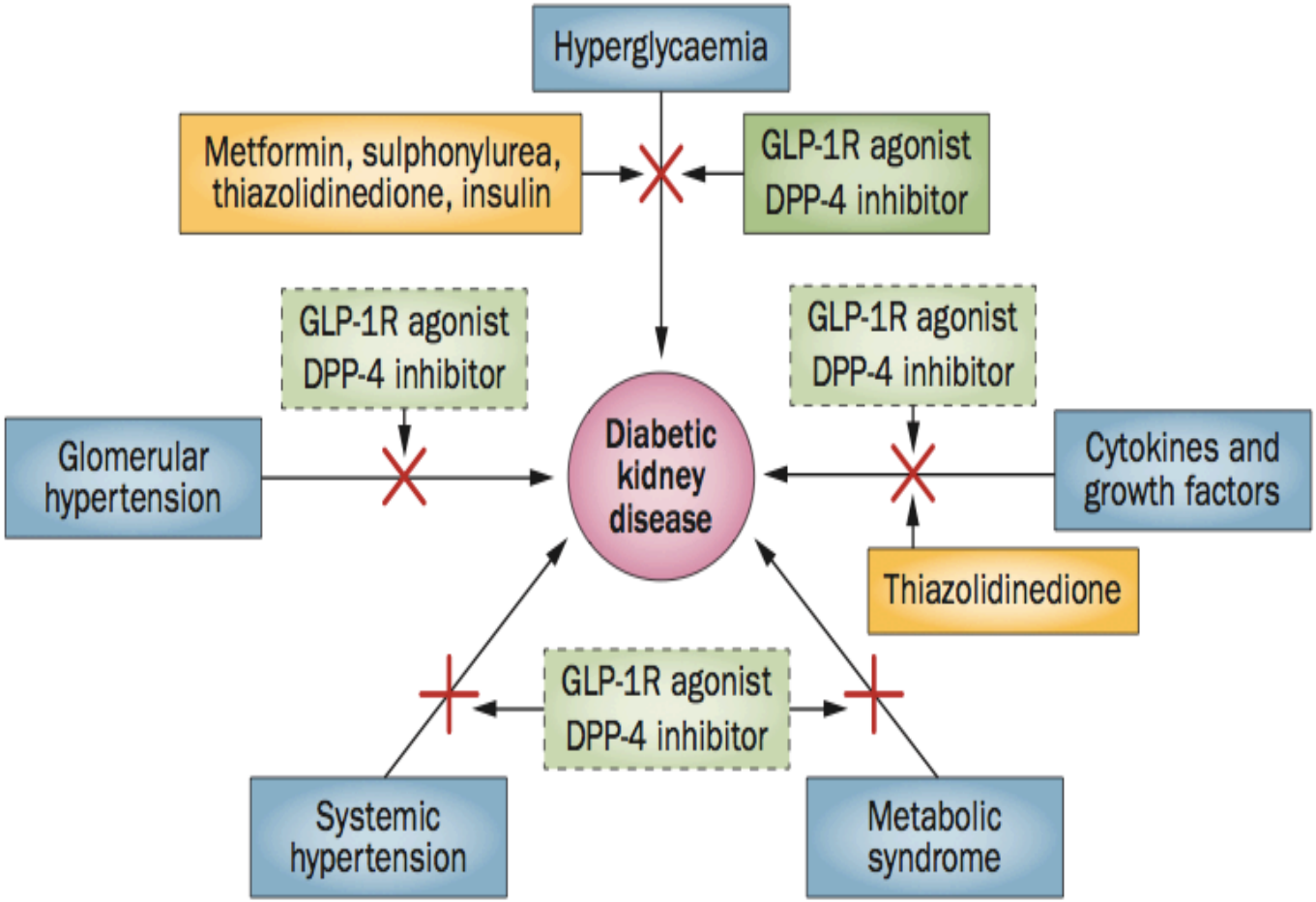
Perché le evidenze *in vitro* ed *in vivo* di effetti benefici a livello vascolare da parte di DPP-4i non sono confermate nei *trial* di fase IV?

Motivo	Commento
Durata dei *trial* di fase IV (2.3 anni)	Nel diabete, le strategie volte a ridurre il rischio CV possono richiedere fino a 10 anni per mostrare completamente il loro effetto
Fenotipo dei pazienti nei *trial* di fase IV (CVD)	In paz diabetici con CVD diagnosticata o avanzata, la possibilità di osservare riduzione importante del rischio CV è piccola
Effetti dei DPP4i sulla microangiopatia	Le azioni vascolari dirette dei DPP4i si traducono principalmente nella protezione microvascolare, ma non macrovascolare. Ciò nonostate ridurre la microangiopatia può ridurre il rischio CV nel lungo termine
La complessità clinica sovrasta i dati preclinici	La presunta attività vascolare dei DPP4i non esercita effetti significativi su pazienti con concomitanti fattori di rischio e complessi regimi di terapia
La pleiotropia dei DPP4i porta ad effetti indesiderati “oltre il bersaglio”	I possibili favorevoli effetti vascolari sono controbilanciati da altri, meno conosciuti, effetti negativi *off-target*, mediati da diversi substrati di DPP4 (per es sostanza P)

Fadini *Vascular Pharmacology* 2015

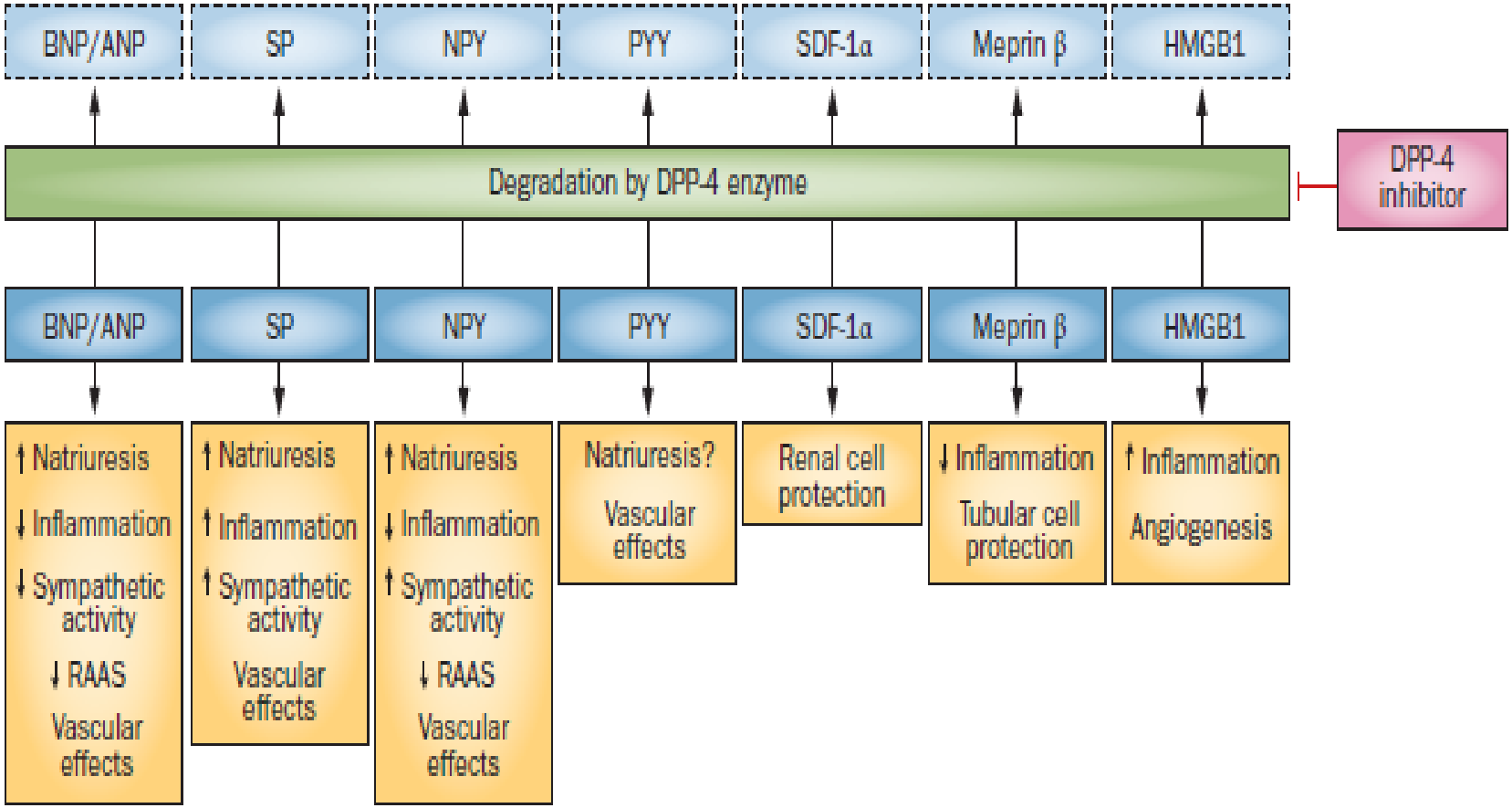
DPP4i: a quale paziente?

Effetti della terapia con incretine sui fattori di rischio renali nel DM2



Muskiet MHA, Nat Rev Nephrol 2014

Effetti GLP-1 indipendenti dei DPP-4i sugli *outcome* renali



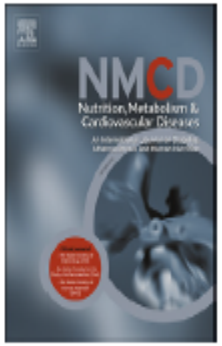
Muskiet *Nat Rev Neprhrol* 2013

Nutrition, Metabolism & Cardiovascular Diseases (2019) **29**, 1127–1150

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd



REVIEW

Diabetic kidney disease: New clinical and therapeutic issues. Joint position statement of the Italian Diabetes Society and the Italian Society of Nephrology on "The natural history of diabetic kidney disease and treatment of hyperglycemia in patients with type 2 diabetes and impaired renal function"

Giuseppe Pugliese [a,*], Giuseppe Penno [b], Andrea Natali [c], Federica Barutta [d], Salvatore Di Paolo [e], Gianpaolo Reboldi [f], Loreto Gesualdo [g], Luca De Nicola [h] on behalf of the Italian Diabetes Society and the Italian Society of Nephrology

Rischio di ipoglicemia nella terapia del paz con DM2 e IRC

Nutrition, Metabolism & Cardiovascular Diseases (2019) 29, 1127–1150

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

REVIEW

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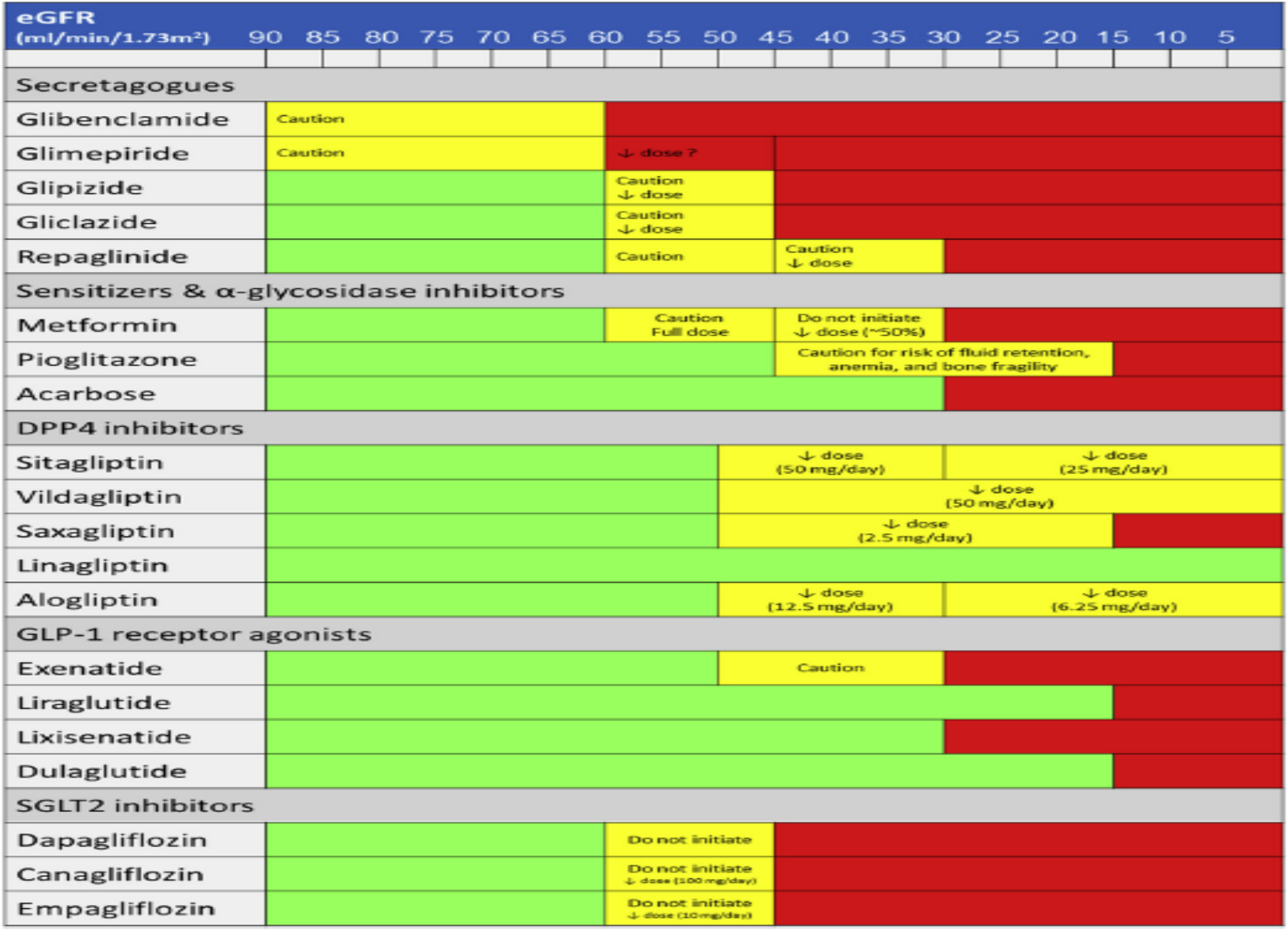
- Concentrazione di farmaci eliminati per via renale aumentata in paz con IRC
- IRC aumenta rischio di ipoglicemia poiché il rene contribuisce a ≈ 30% della produzione totale di glucosio[1]
- In paz con IRC l'ipoglicemia è favorita dalla malnutrizione e dall'atrofia muscolare che riduce i depositi epatici di glicogeno ed i substrati della gluconeogenesi[2]
- Paz con IRC hanno più frequentemente comorbidità per le quali assumono farmaci, con potenziali interazione con i farmaci per il diabete[3]

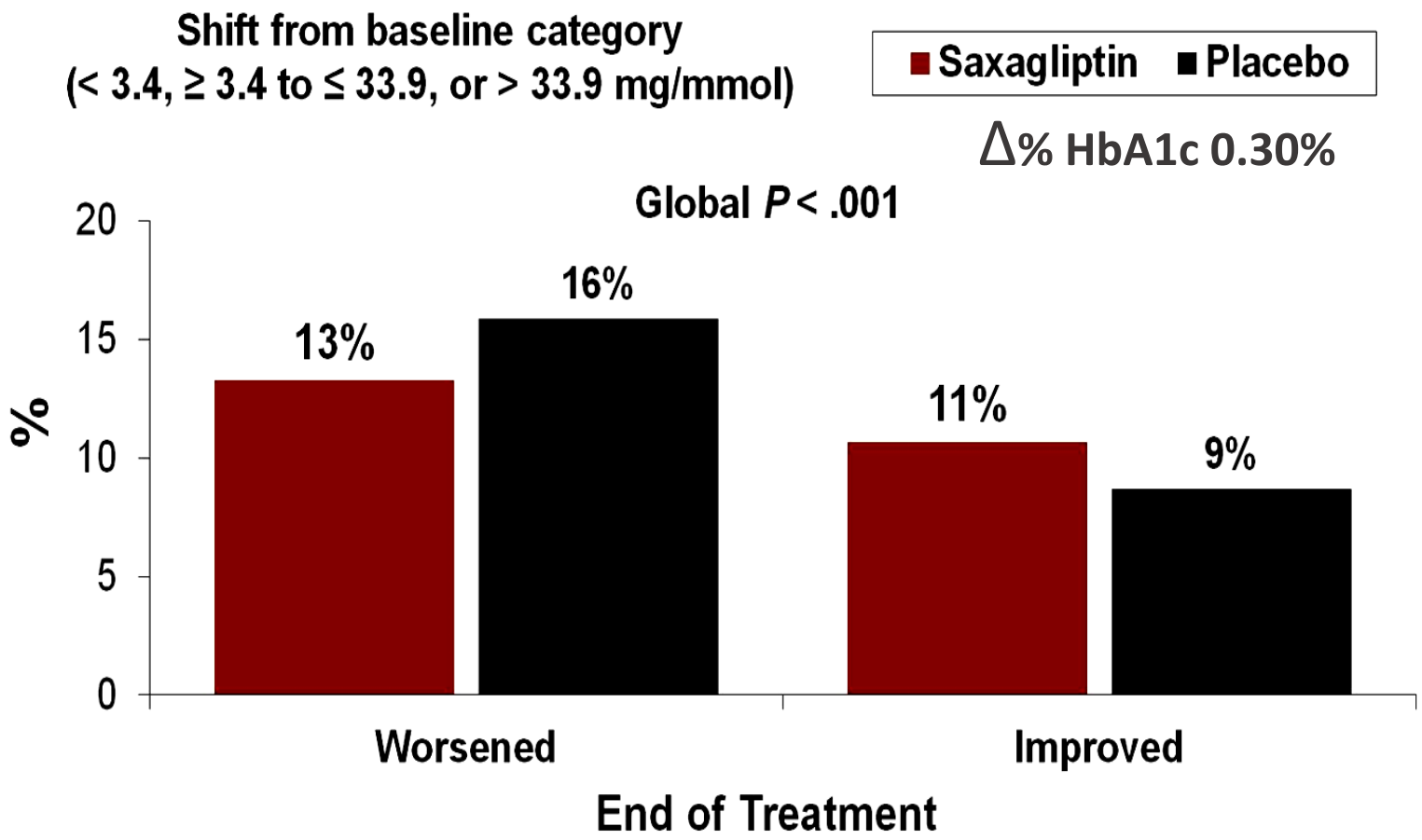
[1]Gerich JE, *DC* 2001; [2]Garber, *Diabetes* 1974; [3]Tonelli M, *Kidnery Int* 2015



Pugliese G, *NMCD* 2019

Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus

16,492 pazienti con una storia o a rischio di eventi CV



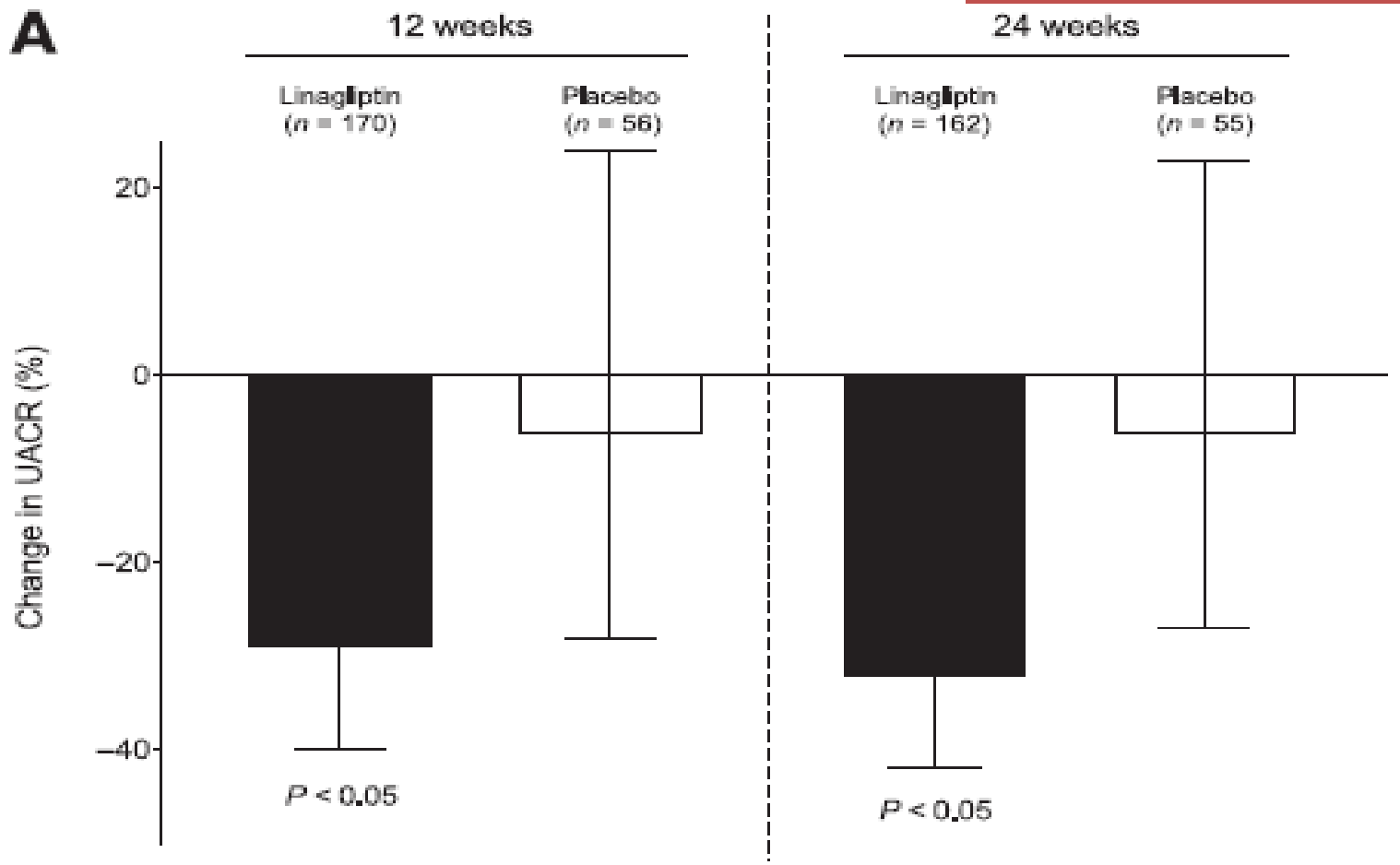
Differenza di trattamento nel numero e proporzione di pazienti con ACR che peggiorava, non si modificava o migliorava, definita come modifica dalla categoria *baseline* (<3.4, ≥3.4 to ≤33.9, or >33.9 mg/mmol).
†*P*<0.001 vs placebo; ‡*P* = 0.0058 vs placebo.

Scirica BM et al. N Engl J Med 369: 1317-1326, 2013

Linagliptin Lowers Albuminuria on Top of Recommended Standard Treatment in Patients With Type 2 Diabetes and Renal Dysfunction

Differenza tra gruppi -25%
CI95% -46 a +3%, *p* = 0.075

Differenza tra gruppi -28%
CI95% -47 a-2%, *p* = 0.0357

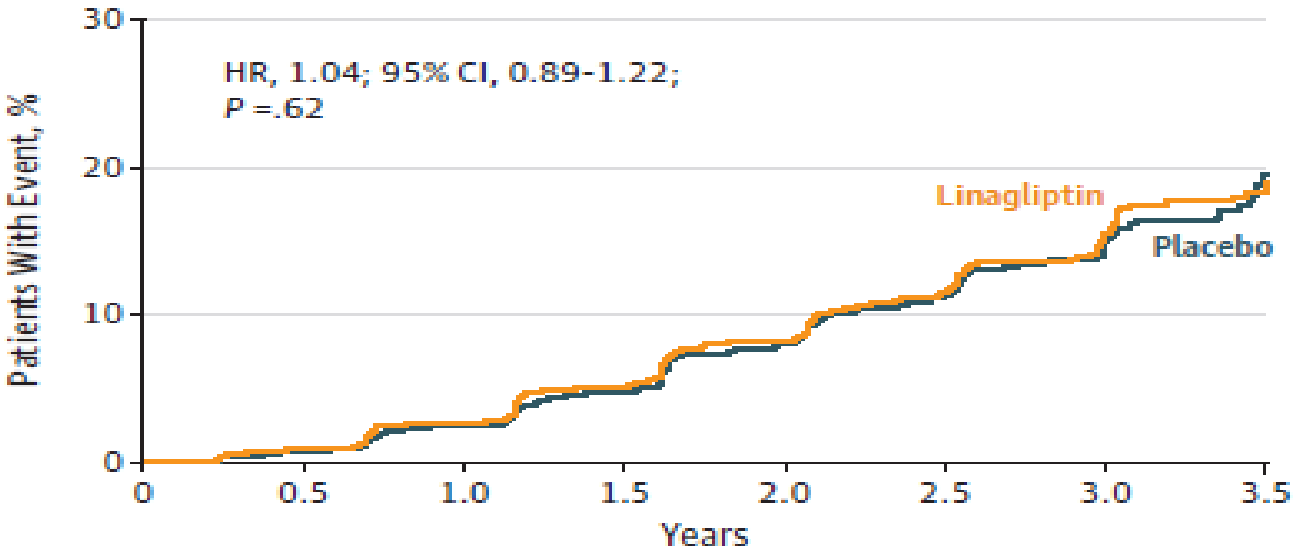


Groop P-E et al. Diabetes Care, 2013

Effetto di linagliptin sugli eventi CV maggiori in paz diabetici ad alto rischio CV e renale-

CARMELINA

B Time to secondary kidney outcome



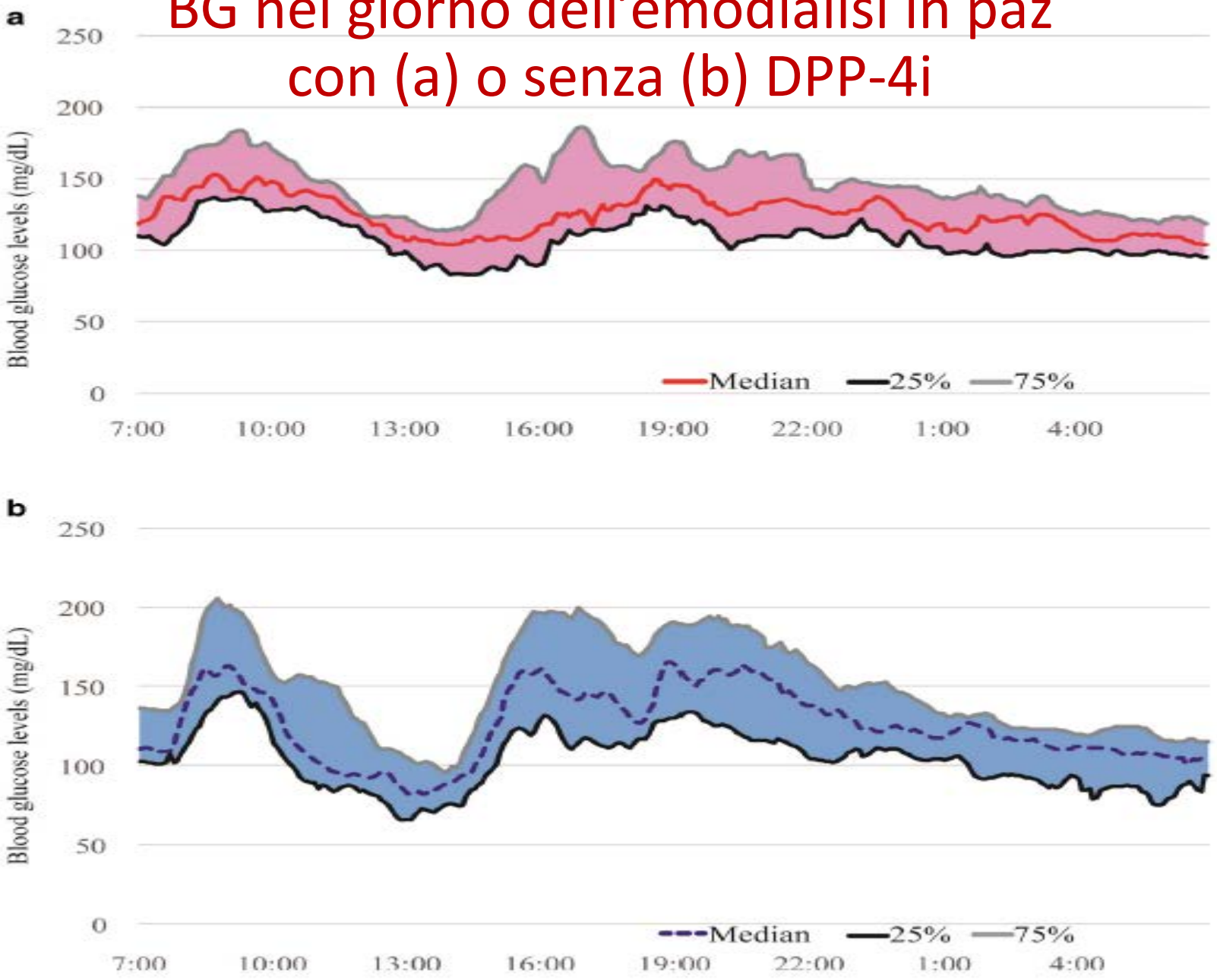
No. of patients

Placebo	3485	3213	2995	2298	1608	1005	496	103
Linagliptin	3494	3227	3018	2345	1675	1040	518	109

B, Time to secondary kidney outcome (first sustained end-stage renal disease, death due to renal failure, or sustained decrease of ≥40% in estimated glomerular filtration rate from baseline). Median observation time was 1.9 (IQR, 1.2-2.6) years for linagliptin and 1.7 (IQR, 1.2-2.5) years for placebo.

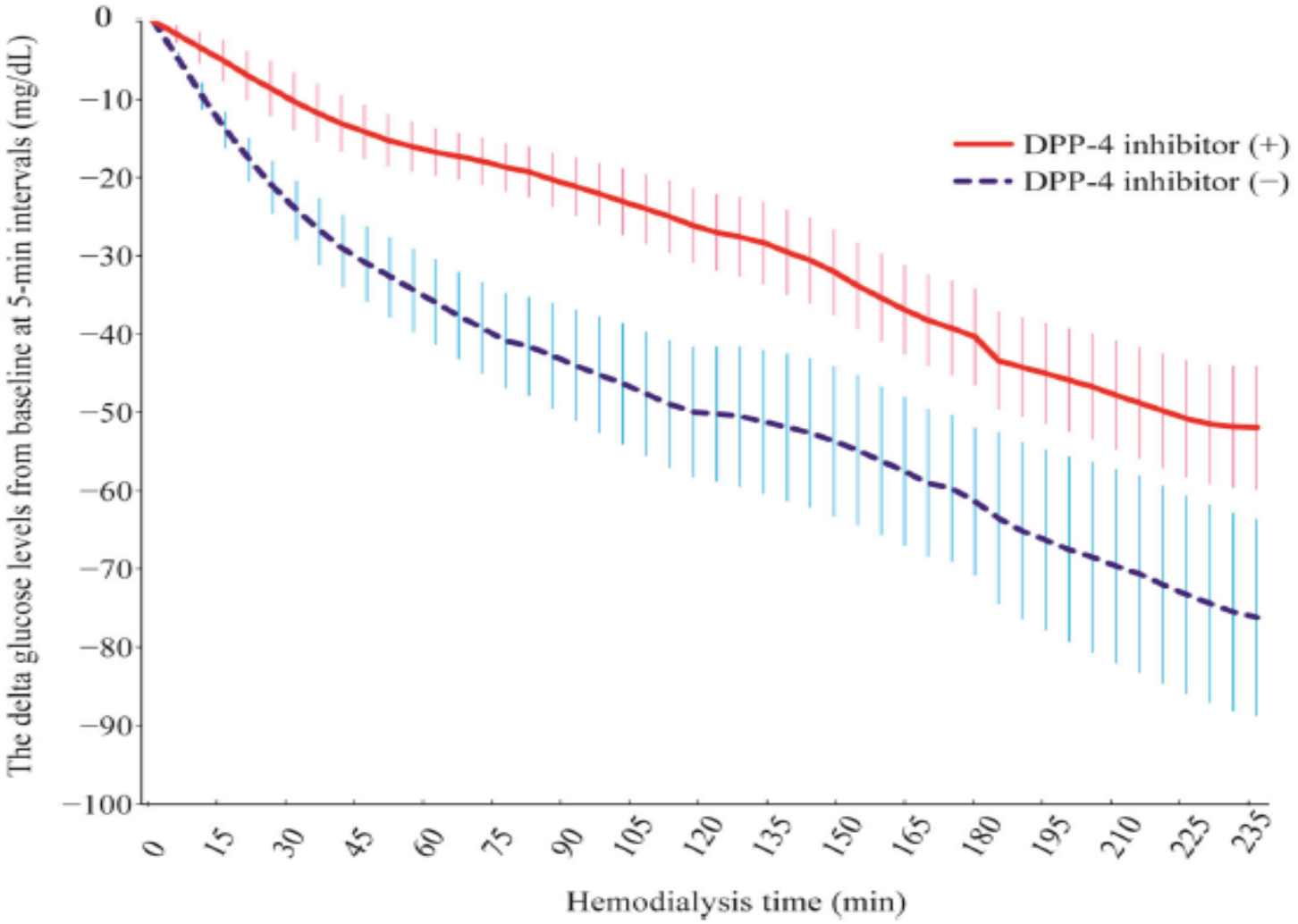
Rosenstock *JAMA*, 2018

BG nel giorno dell'emodialisi in paz con (a) o senza (b) DPP-4i



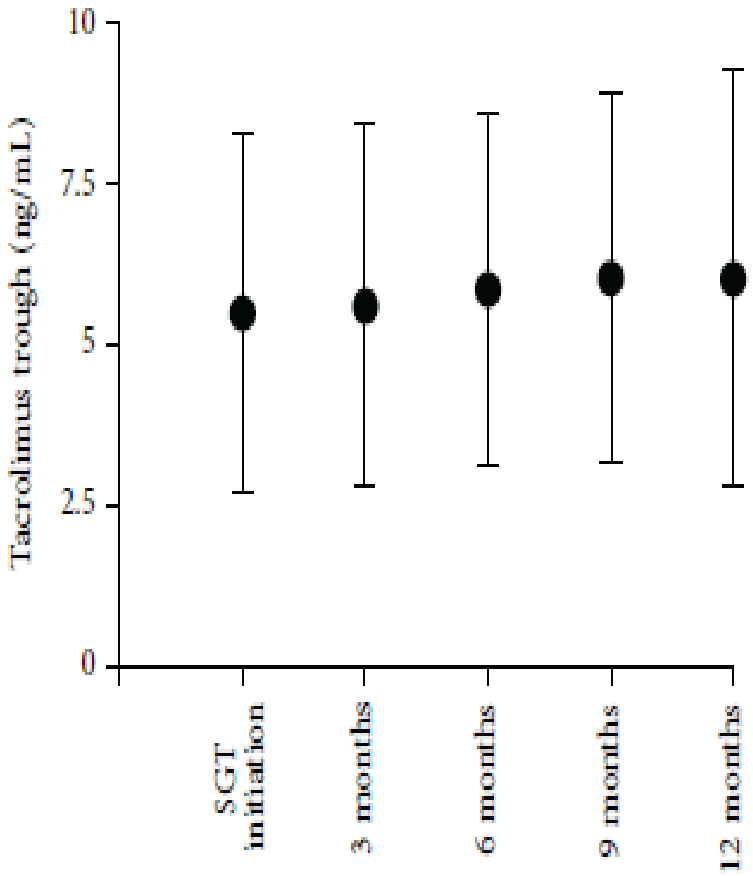
Ishikawa-Tanaka *Diabetes Ter* 2020

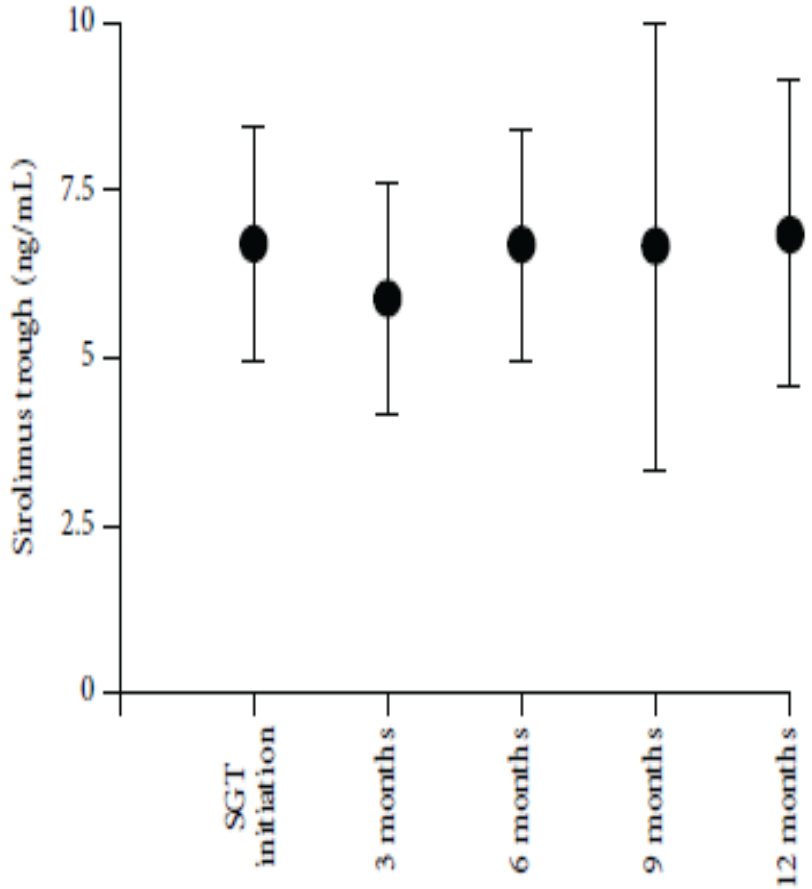
Differenze in BG dal baseline ad intervalli di 5 min durante ogni sessione di emodialisi in paz con (a) o senza (b) DPP-4i



Ishikawa-Tanaka *Diabetes Ter* 2020

Sitagliptin non altera i livelli di (a) tacrolimus e (b) sirolimus in NODAT (*New Onset Diabetes After Transplantation*)

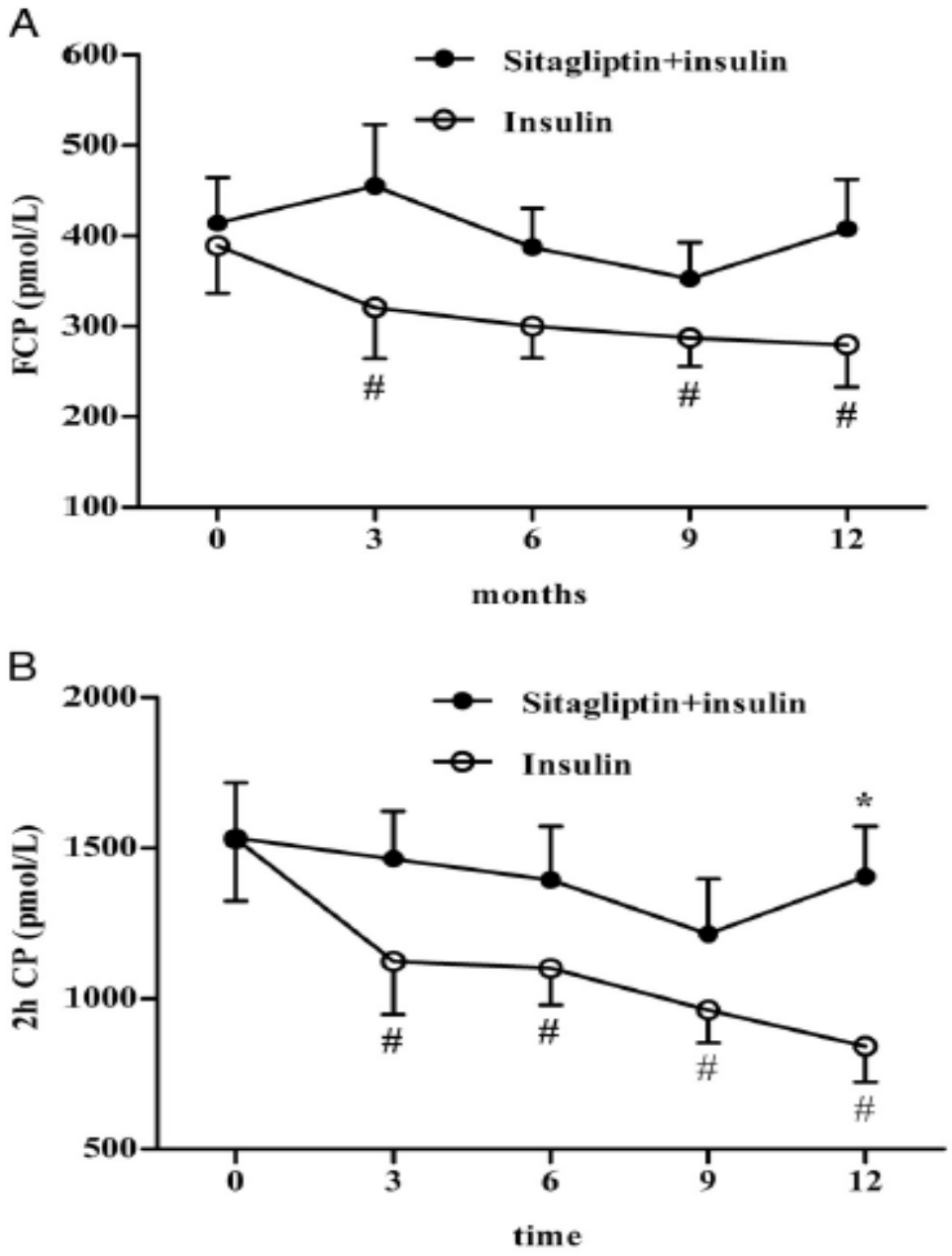




Boerner *Inter Journ Endocr* 2014

DPP4i…oltre il Diabete di Tipo 2?

Effetto di sitagliptin sulla funzione β-cellulare in LADA neodiagnosticati

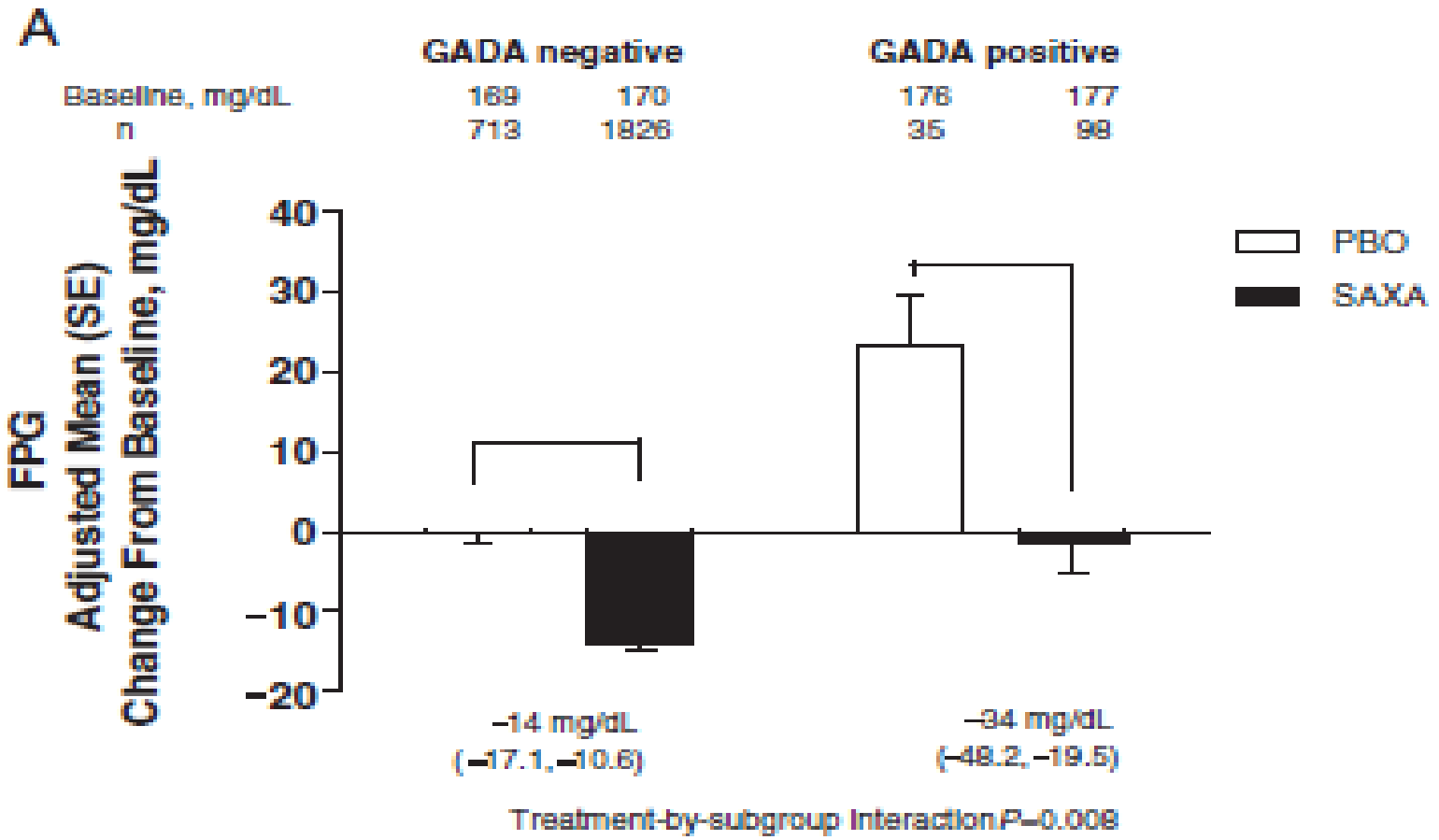


#*p* <0.05 *vs* baseline

**p*<0.05 vs gruppo controllo

Zhao JCEM 2014

Adjusted mean change from baseline in FPG (24 settimane)

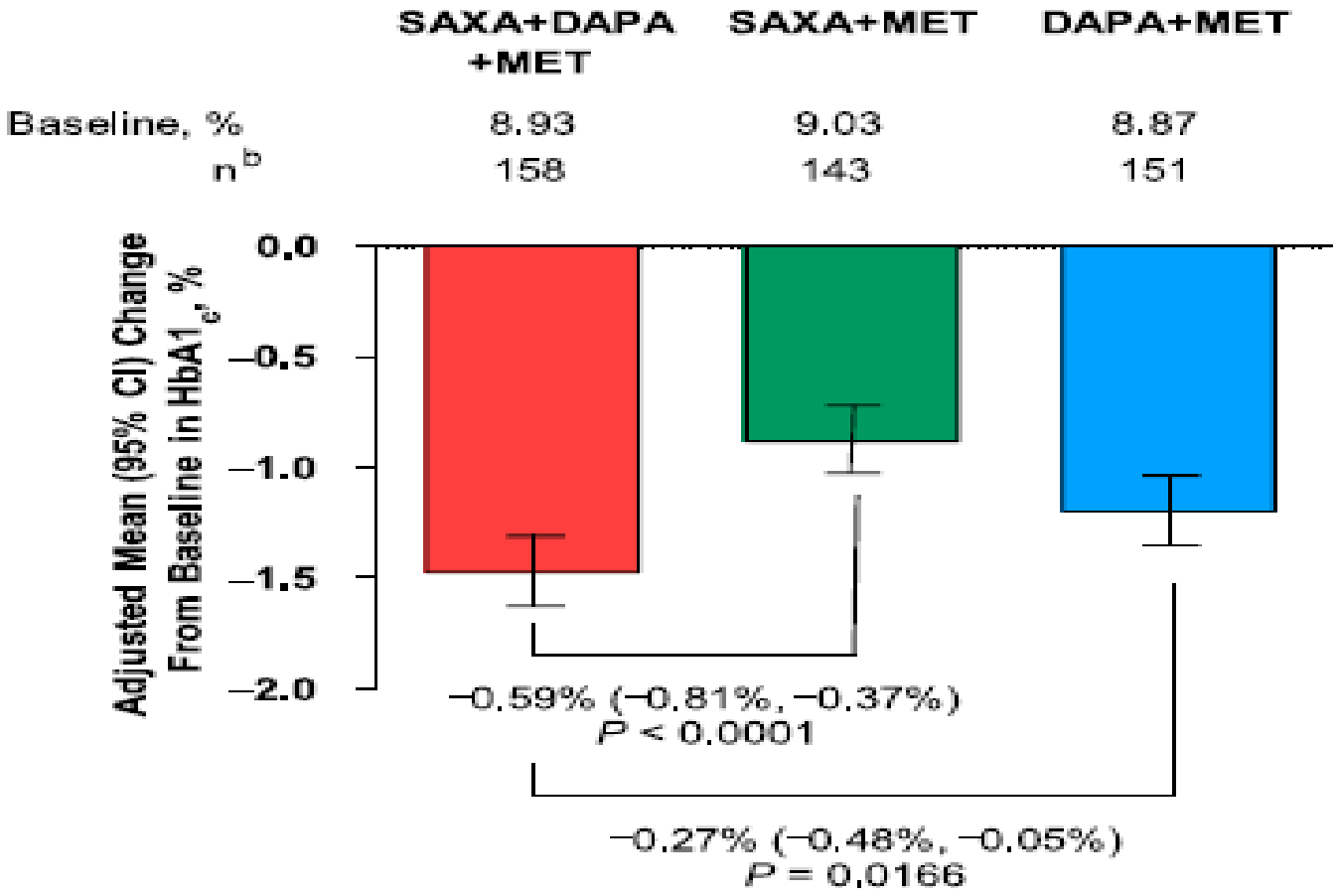


Buzzetti, Pozzilli *et al., Diabetes Metab Res Rev* C 2016

Saxagliptin/ Dapagliflozin	5/10 mg/die	• In associazione a metformina • In associazione a sulfanilurea (con o senza metformina)
Empagliflozin/ Linagliptin	10/5 mg/die 25/5 mg/die	• In associazione a metformina • In associazione a sulfanilurea (con o senza metformina)
Ertugliflozin	5 mg/die 15 mg/die	• Monoterapia • In associazione a metformina • In associazione a sitagliptin (con o senza metformina)
Ertugliflozin/ Metformina	2.5/1000 mg/die x 2 7.5/1000 mg/die x 2	• In associazione a sitagliptin

Terapia *dual add-on* in paz DM2 non controllati con metformina

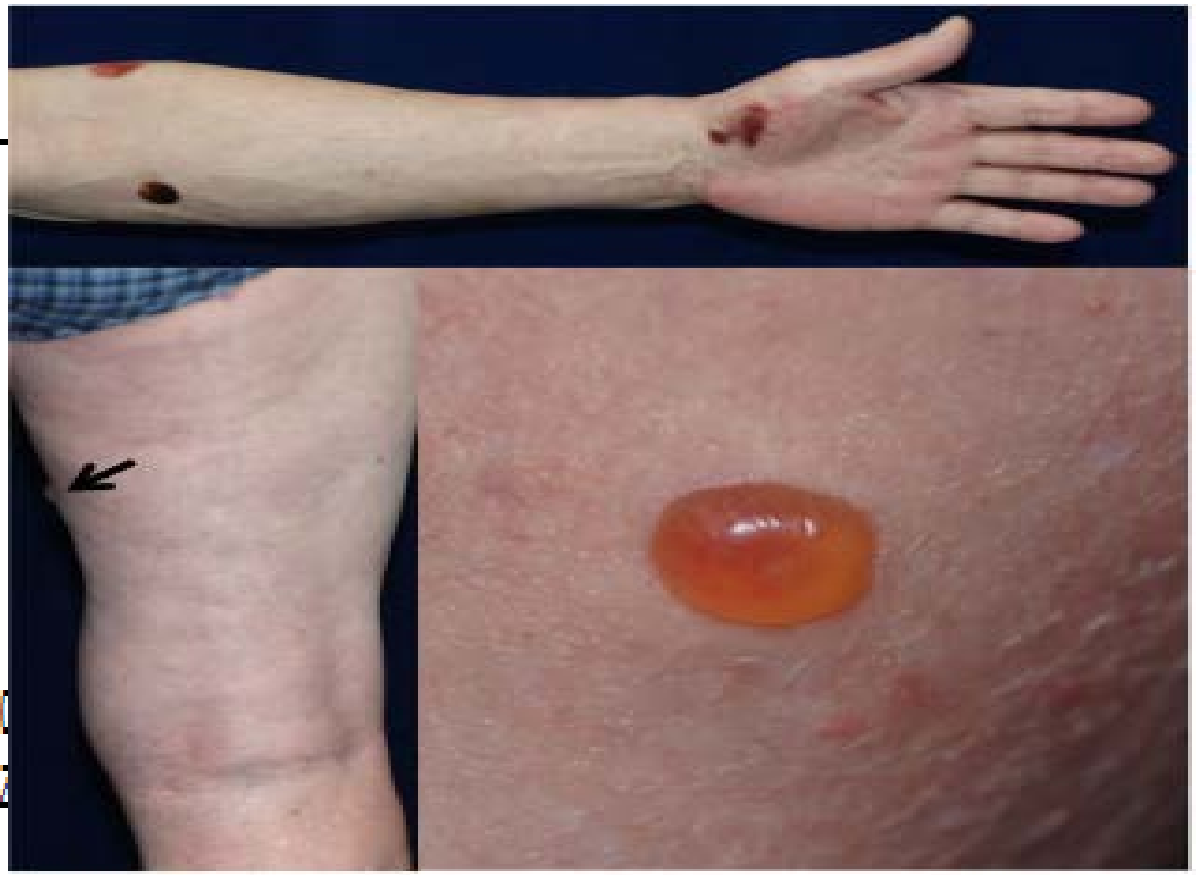
RCT *24 settimane*



Rosenstock, DC 2014

Associazione DPP4i – pemfigoide bolloso

Adjusted meta-analisi



Study or subgroup

DPPI vs. BP

Benzaquen 2018

Kridin 2018

Lee 2019

Schiffer 2017

Varpuluoma 2018

Subtotal (95% CI)

Heterogeneity: τ^2 = 0.0

Test for overall effect: Z

% CI

0.005 0.1 1 10 200

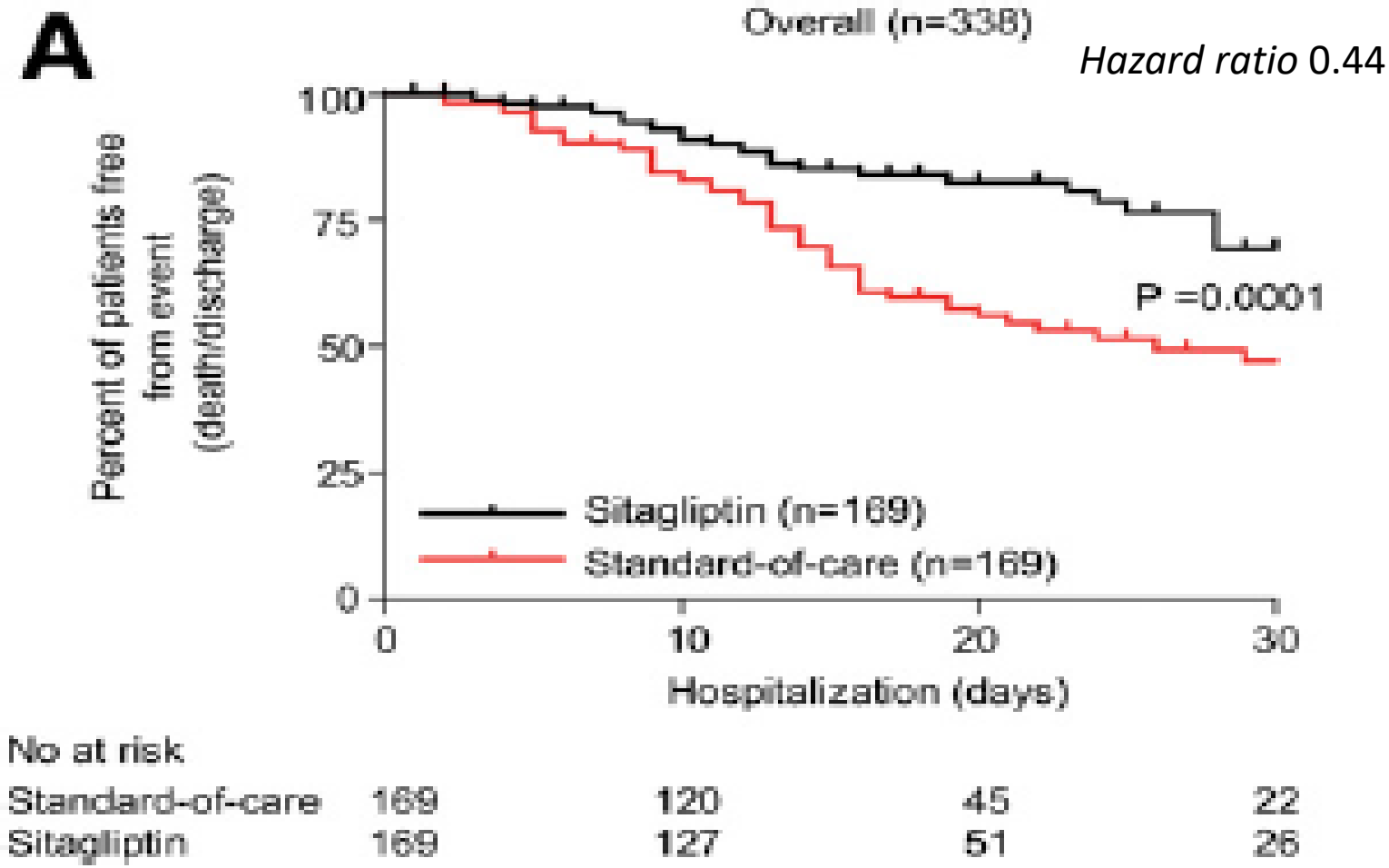
Favours no association Favours association

Test for subgroup differences: χ^2 = 6.71, df = 3 (*P* = 0.08), I^2 = 55.3%

Phgan, *Australian Journal of Dermatology* 2020

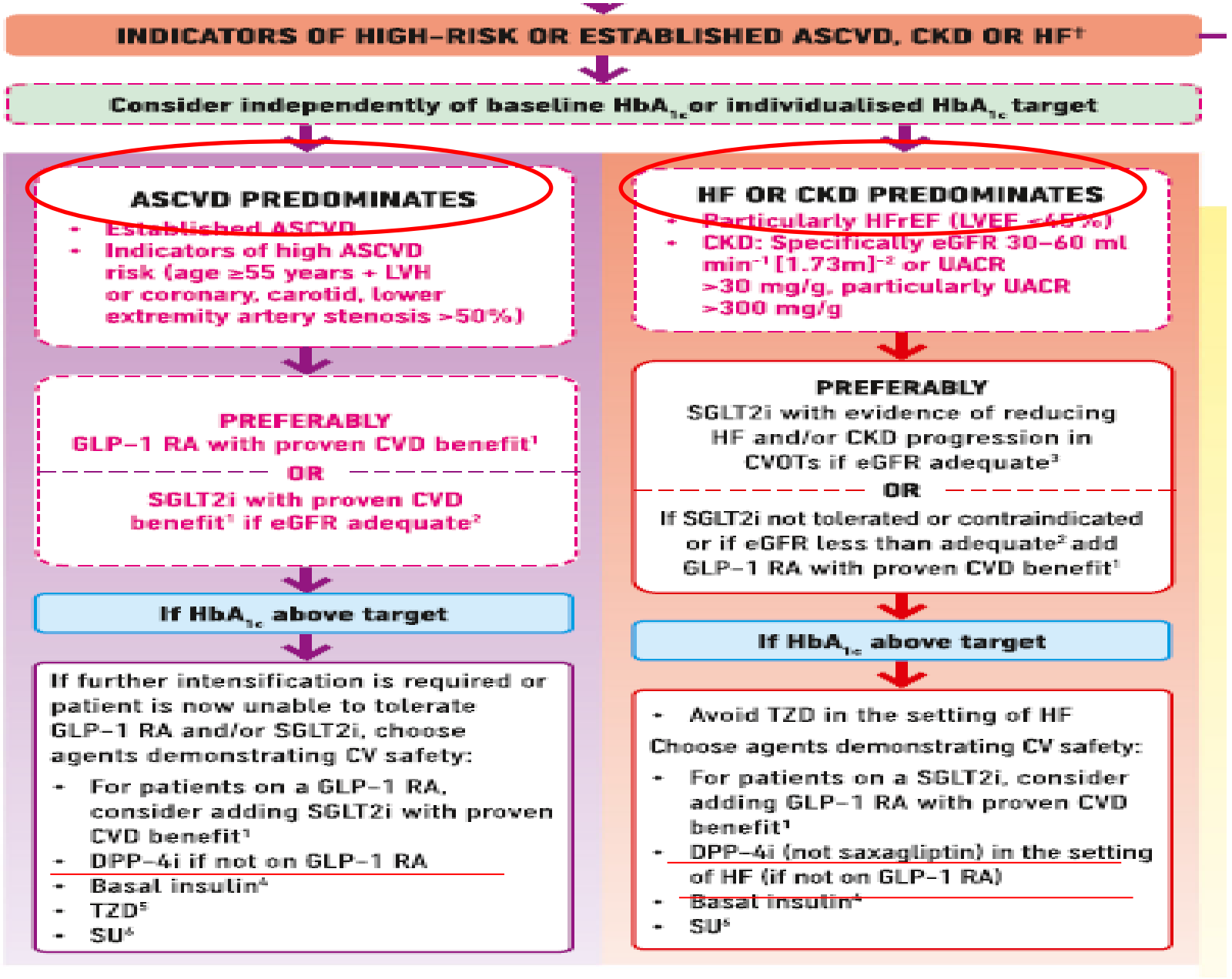
DPP4i: sviluppi futuri?

Trattamento con sitagliptin al momento dell'ospedalizzazione associato a ridotta mortalità in paz con DM2 e COVID-19

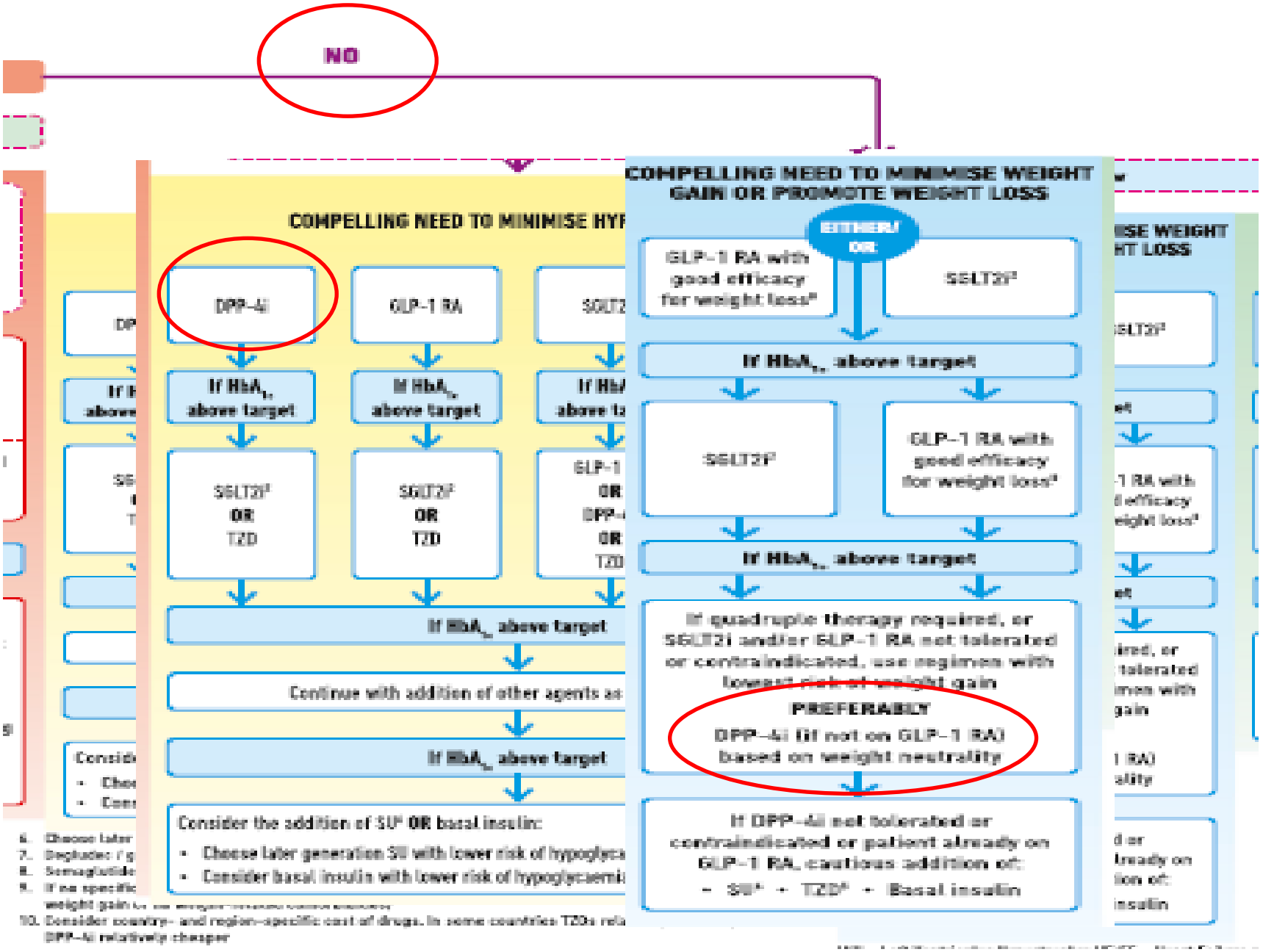


Solerte, DC 2020

DPP4i: a quale paziente?



Buse, *Diabetologia* 2020



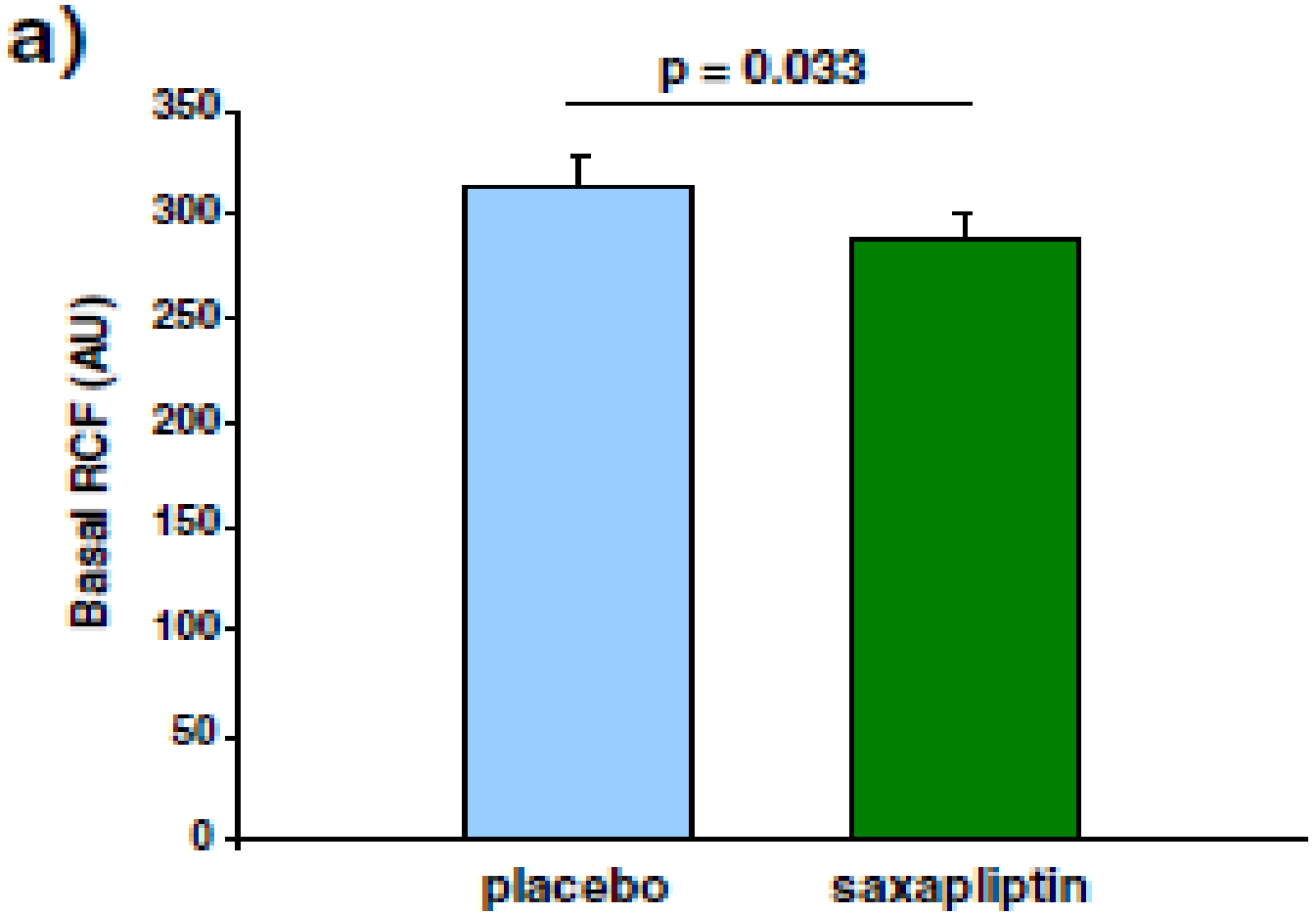
Buse, *Diabetologia* 2020
ADA-EASD 2018

Vantaggi……

- Sicurezza
- Dialisi
- Post trapianto renale in terapia immunosoppressiva
- LADA
- COVID-19??

GRAZIE

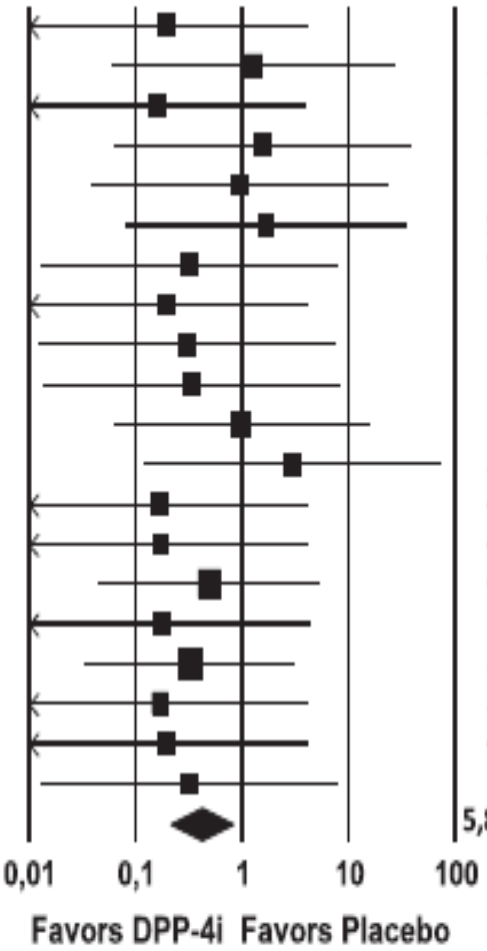
Retinal Capillary Blood Flow (RCF) dopo 6 settimane di tp con placebo o saxagliptin



Ott *Cardiovascula Diabetology* 2014

Rischio di fratture ossee nei *trial* controllati con placebo

Study name	MH odds ratio	Lower limit	Upper limit	Z-Value	p-Value	#patients (DPP-4i/C)	Bone fractures (DPP-4i/C)
NCT00698932 (9A)	0,199	0,009	4,155	-1,042	0,297	280/280	0/2
NCT00316082 (9A)	1,287	0,061	27,088	0,162	0,871	291/74	2/0
Hollander 2010 (11A)	0,160	0,006	3,955	-1,119	0,263	381/184	0/1
Chacra 2009 (12A)	1,545	0,063	38,049	0,266	0,790	520/267	1/0
DeFronzo 2009 (13A)	0,956	0,039	23,562	-0,028	0,978	564/179	1/0
Jadzinsky 2009 (14A)	1,682	0,081	35,126	0,335	0,737	978/328	3/0
Raz 2008 (16A)	0,323	0,013	8,029	-0,689	0,491	96/94	0/1
Barzilai 2011 (17A)	0,200	0,009	4,218	-1,035	0,301	102/104	0/2
NCT01028391 (9A)	0,309	0,012	7,643	-0,717	0,473	164/153	0/1
Rosenstock 2006 (18A)	0,337	0,014	8,332	-0,664	0,506	175/178	0/1
Yoon 2011 (20A)	0,992	0,062	15,950	-0,005	0,996	261/259	1/1
Vilsboll 2010 (21A)	2,981	0,121	73,459	0,668	0,504	322/319	1/0
Charbonnel 2006 (22A)	0,170	0,007	4,182	-1,085	0,278	464/237	0/1
Aschner 2006 (23A)	0,172	0,007	4,245	-1,076	0,282	488/253	0/1
Reasner 2011 (24A)	0,496	0,045	5,484	-0,572	0,567	625/621	1/2
NCT00350779 (9A)	0,179	0,007	4,436	-1,051	0,293	170/92	0/1
Williams-Herman 2010 (27A)	0,325	0,034	3,139	-0,971	0,332	551/540	1/3
Garber 2008 (36A)	0,172	0,007	4,243	-1,077	0,282	305/158	0/1
NCT00396357 (9A)	0,200	0,010	4,177	-1,038	0,299	456/458	0/2
Scherbaum 2008 (41A)	0,318	0,013	7,878	-0,699	0,485	156/150	0/1
	0,415	0,212	0,815	-2,556	0,011	5,877/4,928	11/21

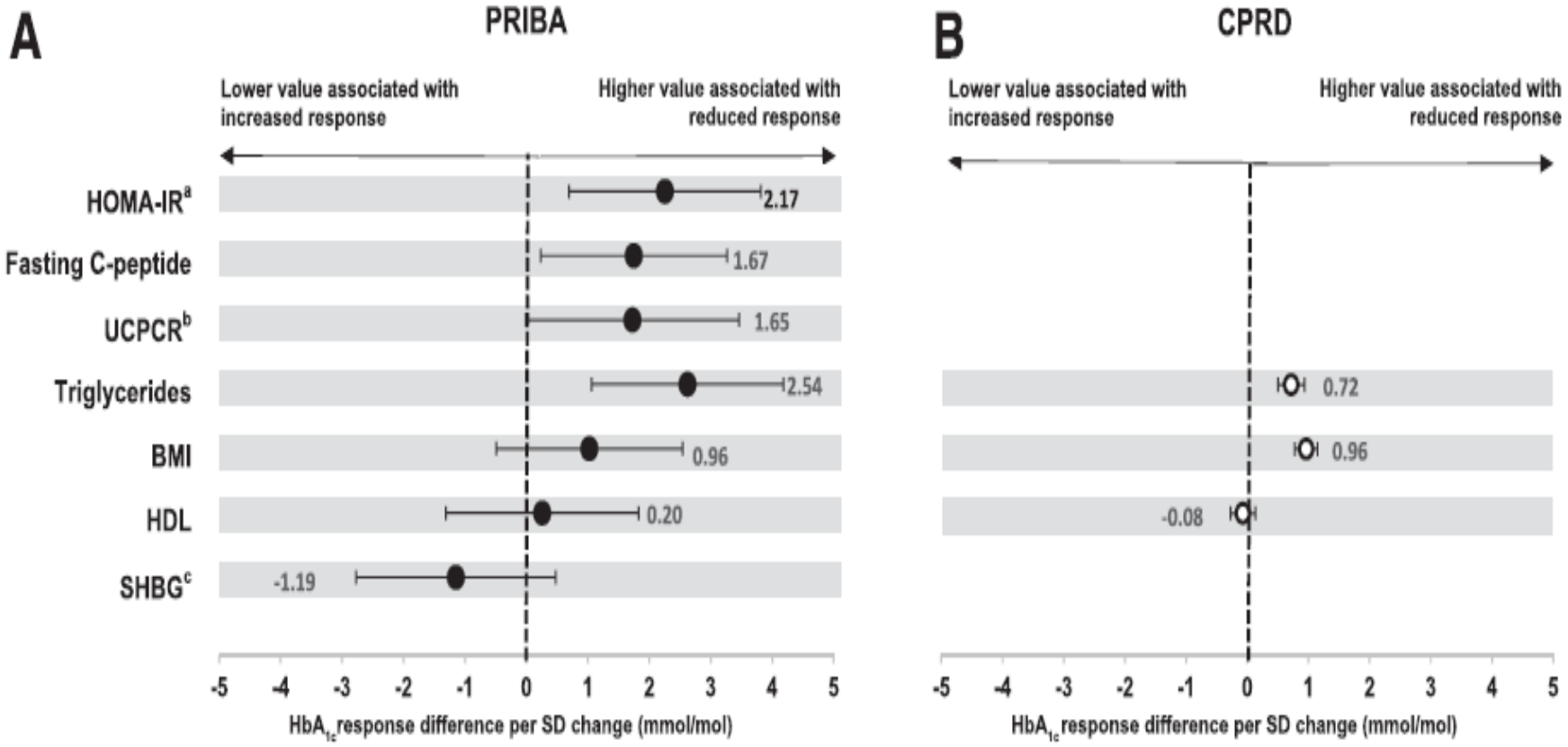


Monami *Diabetes Care* 2011

Associazione tra marcatori di insulino resistenza e risposta dell'HbA1c a 6 mesi

PRIBA *(Predictive Response to Incretine Base Agents)*

CPRD (*Clinical Practice Research Datalink)*



[a] HOMA2 measured insulin resistance [b] UCPCR = post meal urine C-peptide Creatinine ratio [c] SHBG = sex-hormone binding globulin

Dennis, DC 2018

Trattamento della NAFLD??
(non-alcoholic fatty liver disease)

- Sitagliptin come trattamento della NAFLD in pazienti con DM2: riduzione significativa di AST, ALT e γ-GT dopo 4 mesi di tp con sitagliptin
- Sitagliptin in pazienti diabetici con *nonalcoholic steatohepatitis*[2]: sitagliptin migliora i livelli di transaminasi, rigonfiamento degli epatociti in pazienti con NASH e DM2 dopo un anno di terapia

Iwasaki T et al., Hepatogastroenterology 58: 2103-5, 2011

[2]Yilmaz Y et al., Acta Gastroenterol Belg 75: 240-4, 2012

original article

Diabetes, Obesity and Metabolism 16: 1239–1246, 2014.

Durability of the efficacy and safety of alogliptin compared with glipizide in type 2 diabetes mellitus: a 2-year study†

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ORIGINAL ARTICLE

Aims: To evaluate the long-term durability of the efficacy of alogliptin compared with glipizide in combination with metformin in people with type 2 diabetes inadequately controlled on stable-dose metformin.

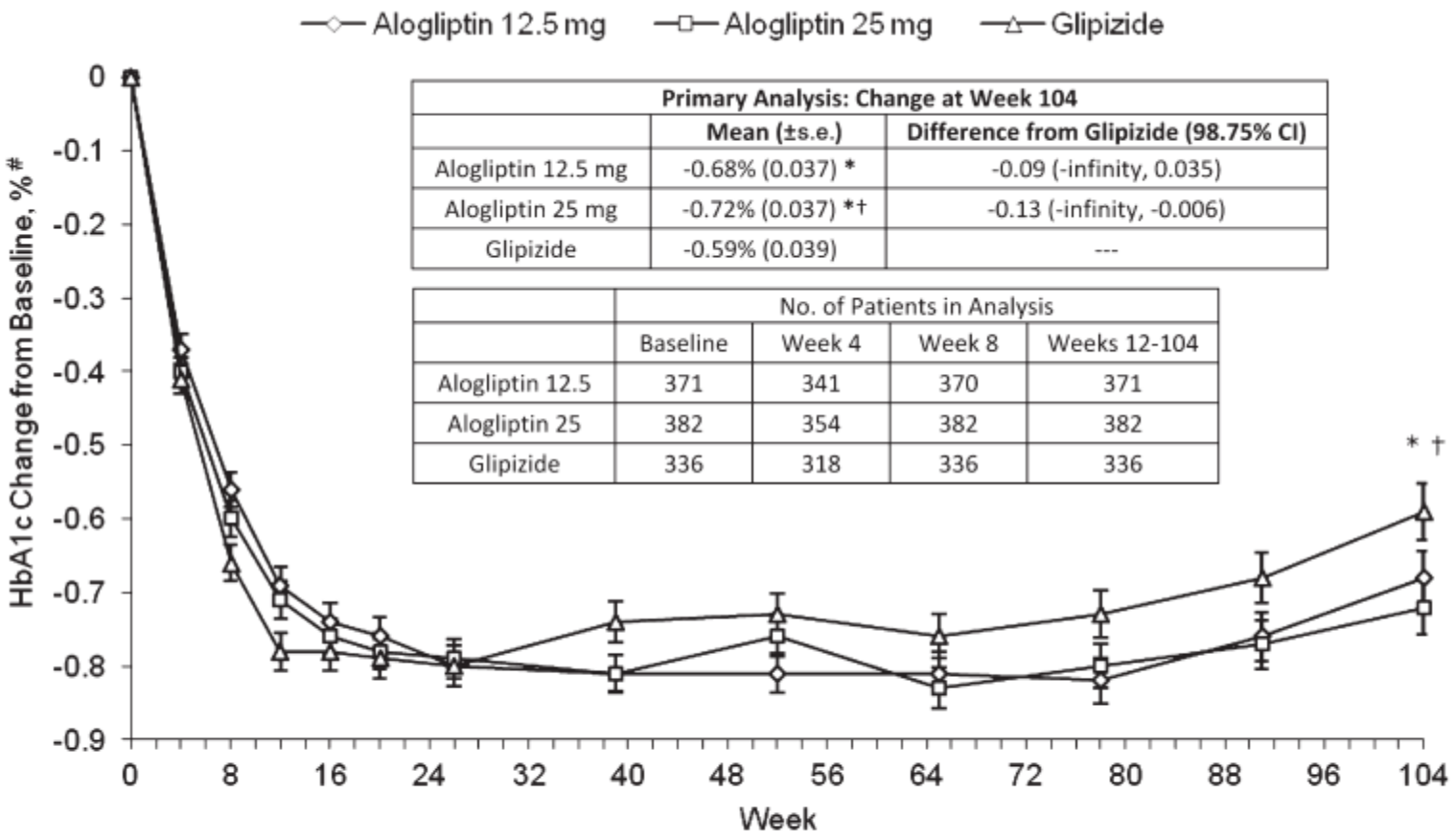
Methods: This multicentre, double-blind, active-controlled study randomized 2639 patients aged 18–80 years to 104 weeks of treatment with metformin in addition to alogliptin 12.5 mg once daily (n = 880), alogliptin 25 mg once daily (n = 885) or glipizide 5 mg once daily, titrated to a maximum of 20 mg (n = 874). The primary endpoint was least square mean change from baseline in HbA1c level at 104 weeks.

Results: The mean patient age was 55.4 years, the mean diabetes duration was 5.5 years and the mean baseline HbA1c was 7.6%. HbA1c reductions at week 104 were −0.68%, −0.72% and −0.59% for alogliptin 12.5 and 25 mg and glipizide, respectively [both doses met the criteria for non-inferiority to glipizide ($p<0.001$); alogliptin 25 mg met superiority criteria ($p=0.010$)]. Fasting plasma glucose concentration decreased by 0.05 and 0.18 mmol/l for alogliptin 12.5 and 25 mg, respectively, and increased by 0.30 mmol/l for glipizide ($p < 0.001$ for both comparisons with glipizide). Mean weight changes were −0.68, −0.89 and 0.95 kg for alogliptin 12.5 and 25 mg and glipizide, respectively ($p < 0.001$ for both comparisons with glipizide). Hypoglycaemia occurred in 23.2% of patients in the glipizide group vs. 2.5 and 1.4% of patients in the alogliptin 12.5 and 25 mg groups, respectively. Pancreatitis occurred in one patient in the alogliptin 25 mg group and three in the glipizide group.

Conclusions: Alogliptin efficacy was sustained over 2 years in patients with inadequate glycaemic control on metformin alone.

Keywords: antidiabetic drug, randomised trial, diabetes mellitus, DPP-IV inhibitor, glycaemic control, incretin therapy

Date submitted 2 May 2014; date of first decision 19 June 2014; date of final acceptance 4 August 2014



Primary Analysis: Change at Week 104		
	Mean (±s.e.)	**Difference from Glipizide (98.75% CI)**
Alogliptin 12.5 mg	-0.68% (0.037) *	-0.09 (-infinity, 0.035)
Alogliptin 25 mg	-0.72% (0.037) *†	-0.13 (-infinity, -0.006)
Glipizide	-0.59% (0.039)	---

	No. of Patients in Analysis			
	Baseline	Week 4	Week 8	Weeks 12-104
Alogliptin 12.5	371	341	370	371
Alogliptin 25	382	354	382	382
Glipizide	336	318	336	336

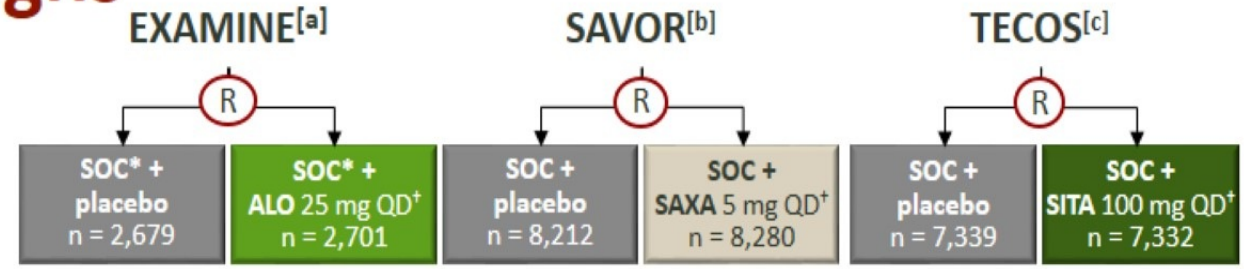
Baseline values were 7.6% in all three treatment groups.

* Alogliptin 12.5 and 25 mg noninferior to glipizide ($p<0.001$).

† Alogliptin 25 mg superior to glipizide ($p=0.010$).

Del Prato, DOM 2014

DPP-4 Inhibitor CV Outcomes Trials: Study Designs



	EXAMINE[a]	SAVOR[b]	TECOS[c]
Size, N	5,380	16,492	14,671
Key inclusion criteria	• T2DM receiving treatment* • HBA1C 6.5% to 11.0% (7.0%-10.0% if on insulin) • **ACS‡ within 15 to 90 days**	• T2DM • HBA1C 6.5% to 12.0% • **CVD or multiple risk factors for vascular disease**	• T2DM • HBA1C 6.5% to 8.0% on 1 to 2 oral antihyperglycemic agents or on insulin • **Established CVD**
Study duration	• Up to 40 months • Median 18 months	• Up to 2.9 years • Median 2.1 years	• Up to 5.7 years • Median 3.0 years
Primary endpoint: time to first occurrence of MACE	• CV death • Nonfatal MI • Nonfatal stroke	• CV death • Nonfatal MI • Nonfatal ischemic stroke	• CV death • Nonfatal MI • Nonfatal stroke • Hospitalization for UA

*Except DPP-4 inhibitors or GLP-1 receptor agonists; †Dosage adjustment based on renal function: ALO 12.5 mg QD for eGFR 30-60 mL/min, ALO 6.25 mg QD for eGFR < 30 mL/min, SAXA 2.5 mg QD for eGFR ≤ 50 mL/min, SITA 50 mg for eGFR 30-50 mL/min); ‡MI or UA requiring hospitalization.

a. White WB, et al. *N Engl J Med*. 2013;369:1327-1335.
b. Scirica BM, et al. *N Engl J Med*. 2013;369:1317-1326.
c. Green JB, et al. *N Engl J Med*. 2015;373:232-242.