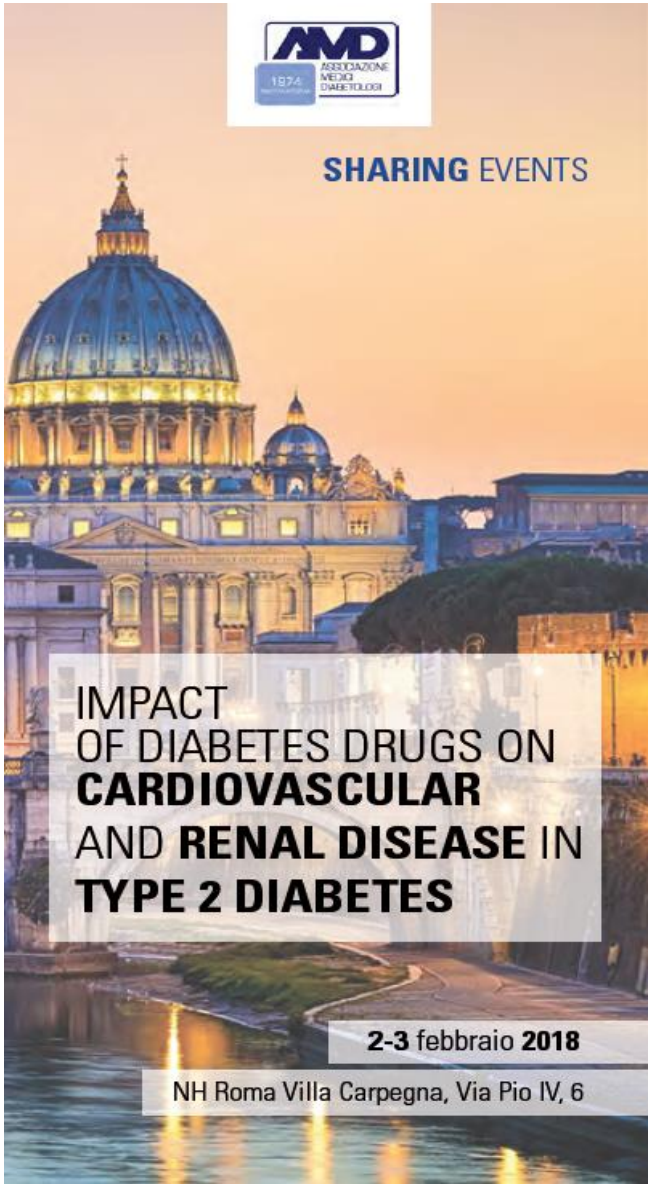


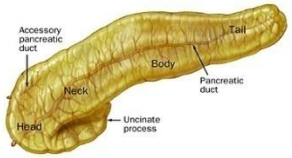
I DPP4-i: oltre la sicurezza CV

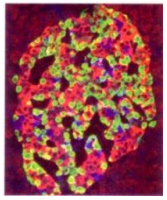
Graziano Di Cianni

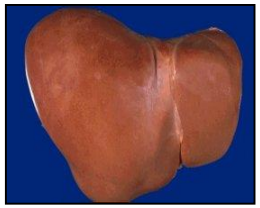
UOC Diabetologia e Mal Metabolismo

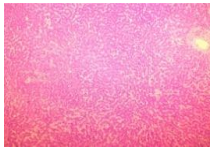
ASL Toscana Nordovest

Fisiopatologia del DM2
anni 80-90
"il triumvirato"



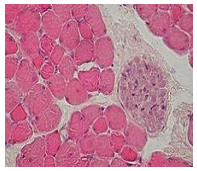


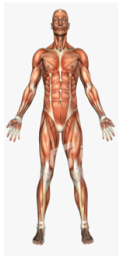




Fegato
Aumentata produzione di glucosio

Pancreas endocrino
Ridotta secrezione insulinica

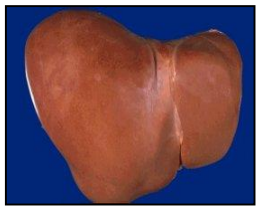


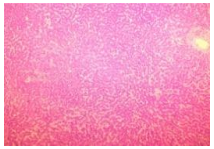


Muscolo scheletrico
Ridotta utilizzazione di glucosio (trasporto, deposito, ossidazione)

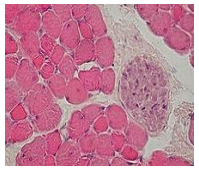
Diabete tipo 2: patogenesi sistemica

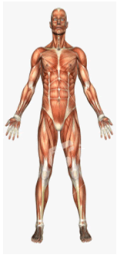
"ottetto minaccioso"



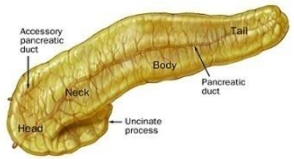


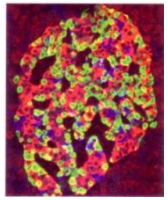
Fegato
Aumentata produzione di glucosio





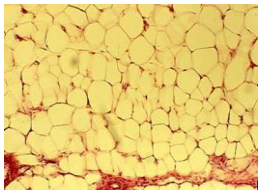
Muscolo scheletrico
Ridotta utilizzazione di glucosio (trasporto, deposito, ossidazione)





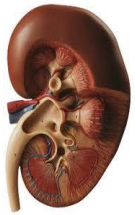
Pancreas endocrino
Ridotta secrezione insulinica
Aumentata secrezione di glucagone

Iperglicemia

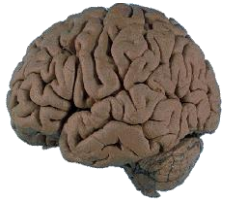


Tessuto adiposo
Rilascio di molecole diabetologene

Intestino
Ridotto effetto incretinico



Rene
Aumentato riassorbimento di glucosio



Cervello
Alterato controllo metabolico

Physiology of the Incretin System

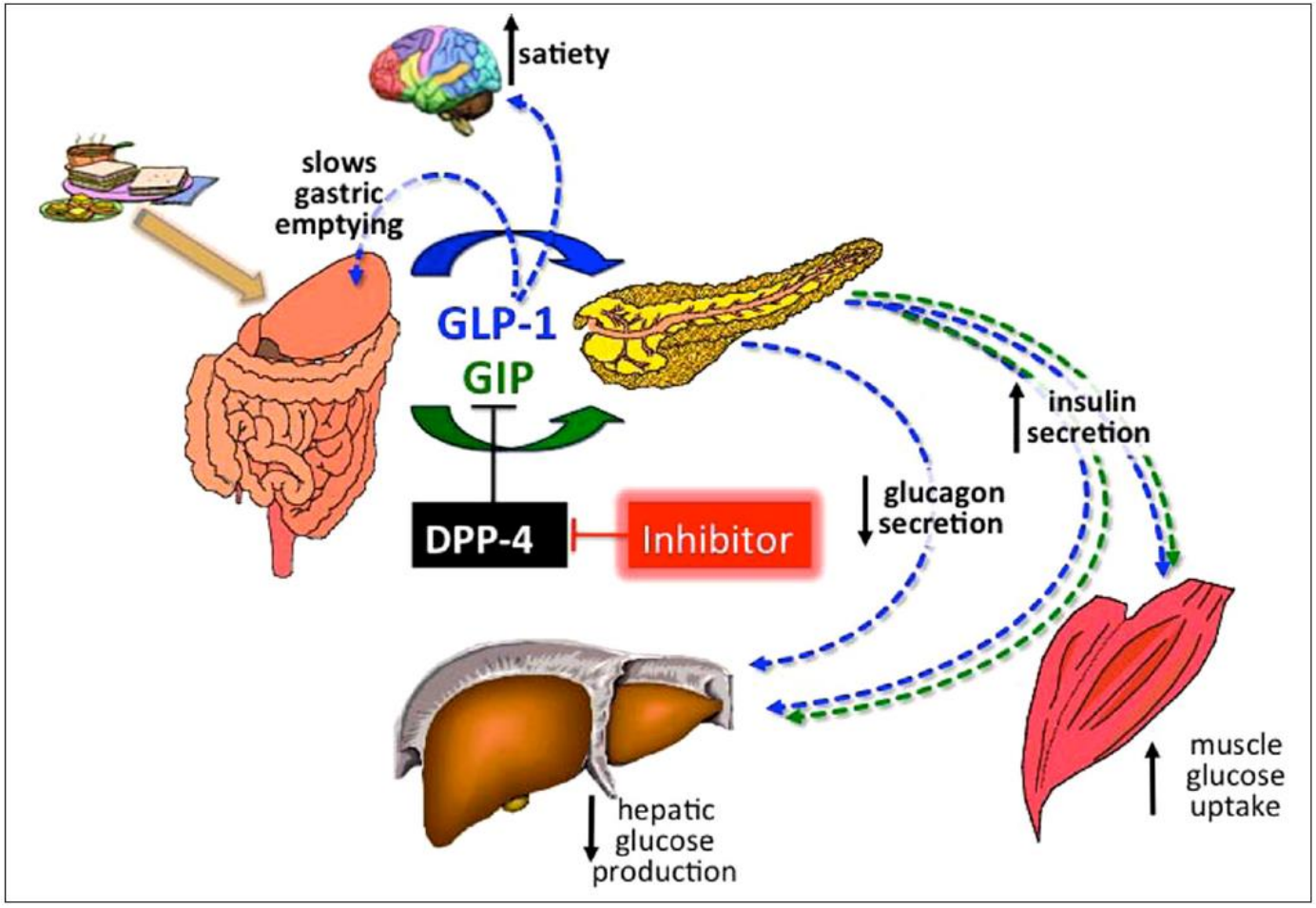
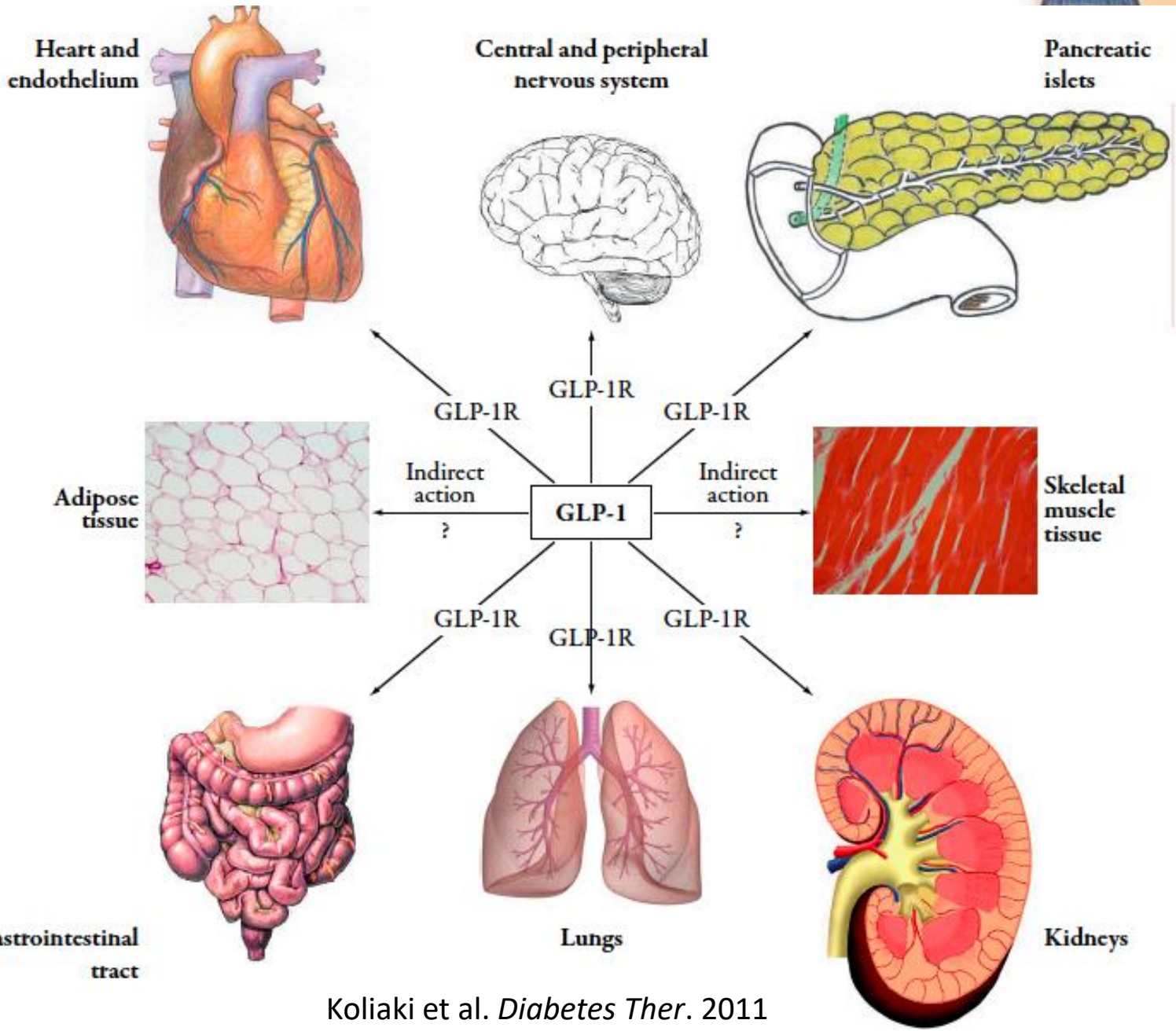


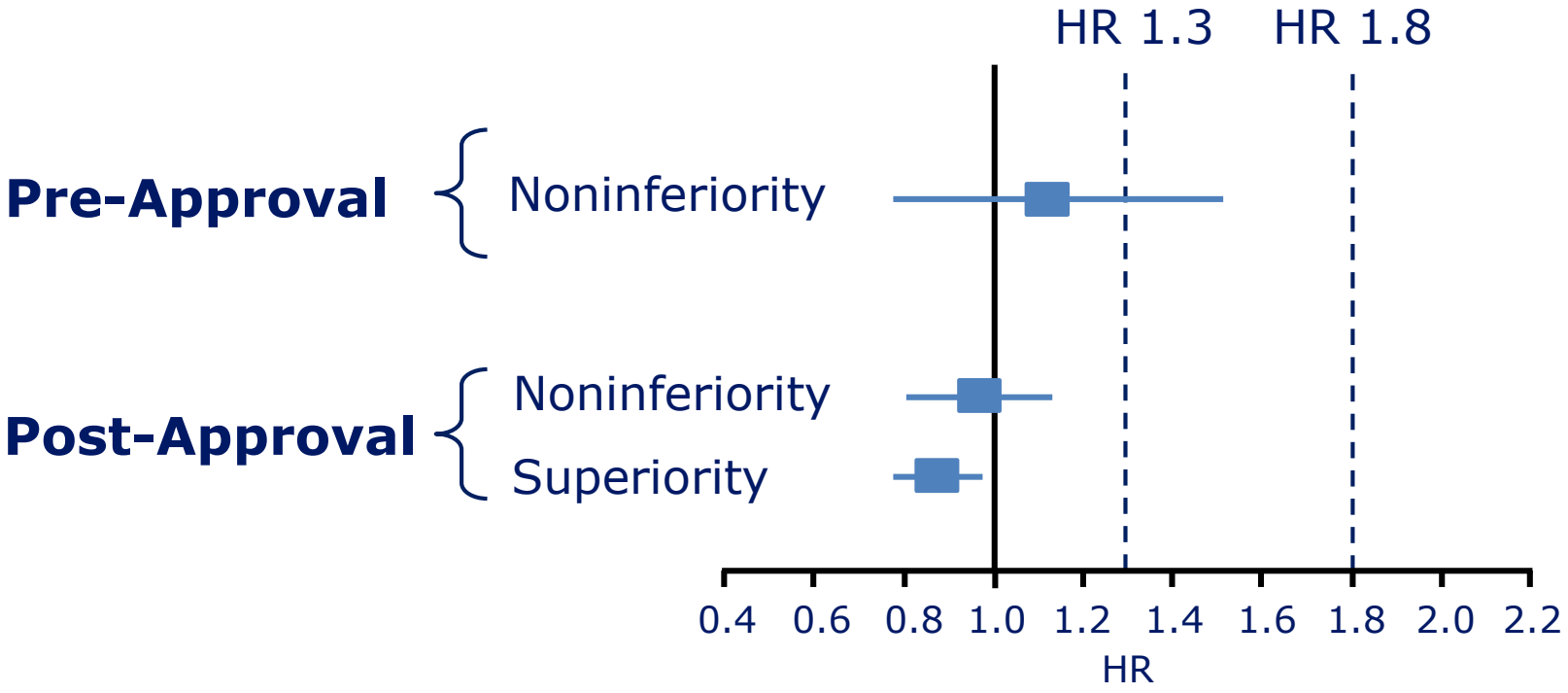
Figure 1. Physiology of the incretin system. After meal ingestion, as blood glucose levels rise, neuroendocrine cells of the intestine

Diabetes & Vascular Disease Research
9(2) 109–116



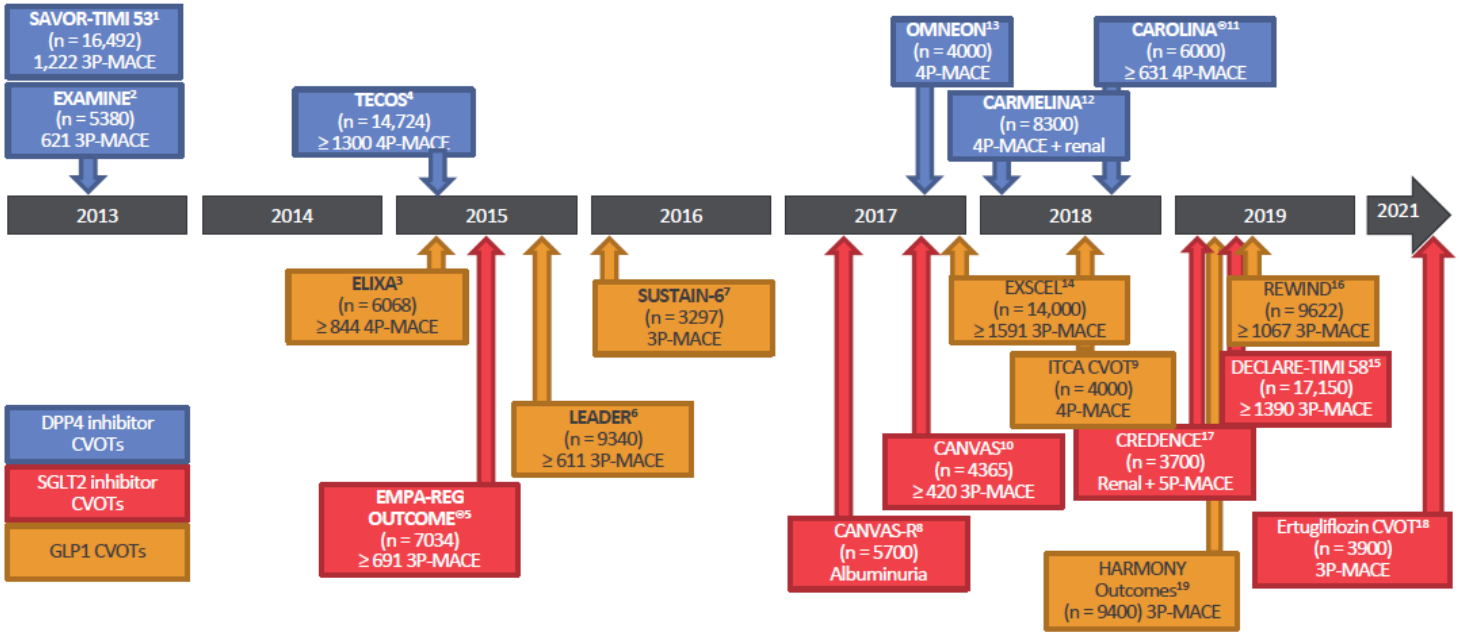
Koliaki et al. *Diabetes Ther*. 2011

FDA Criteria for Assessing CV Risk



Adequately powered for non inferiority

CV safety trials are being conducted for each compound within the newer classes

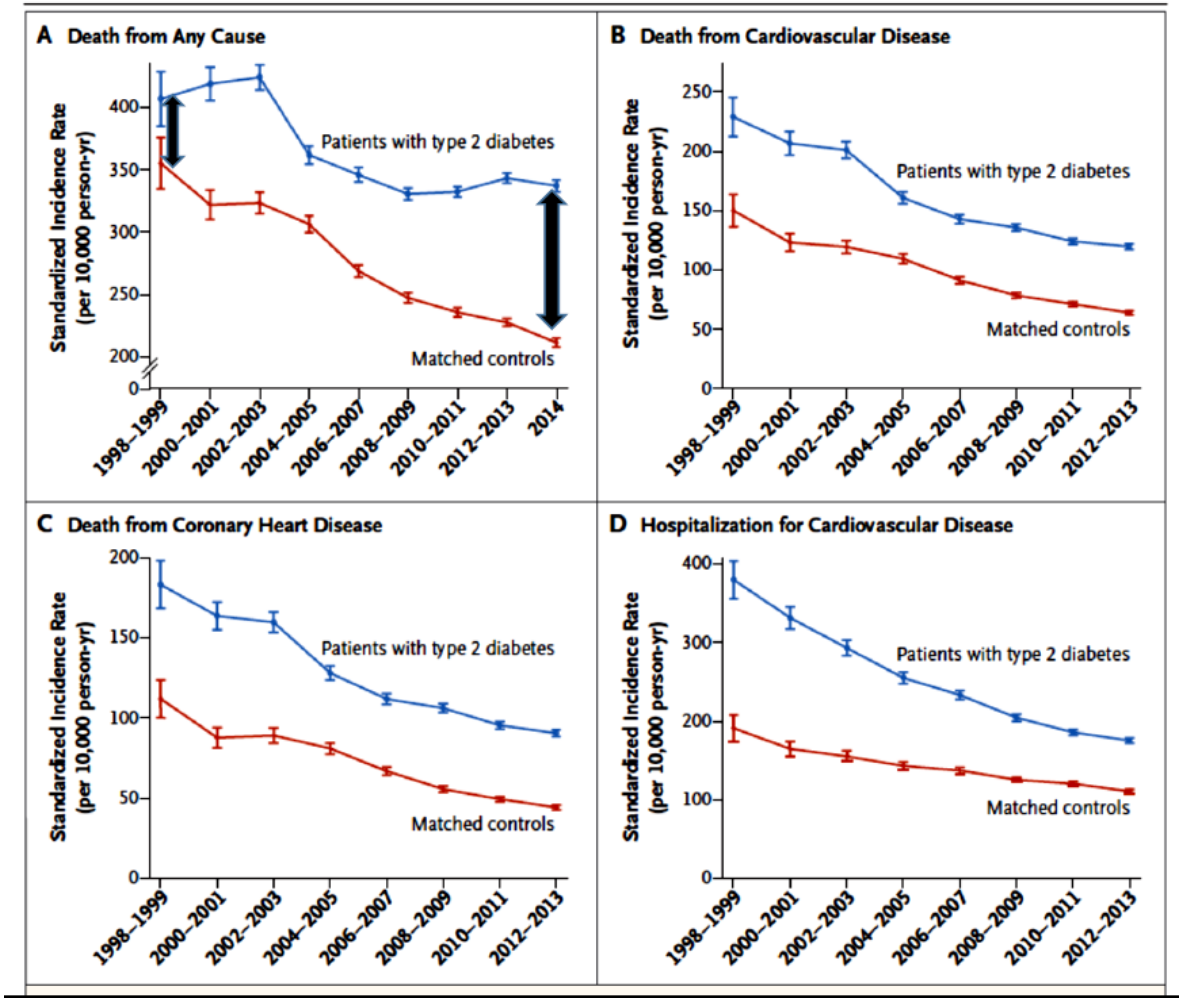


Timings represent estimated completion dates as per ClinicalTrials.gov.
Adapted from Johansen. World J Diabetes 2015;6:1092–96. (references 1–19 expanded in slide notes)

Incretins and CV Outcomes in T2DM
Trials Recently Completed or Ongoing

Trial Name	Drug	Target Enrollment	Timing*
DPP-4 Inhibitors			
SAVOR	Saxagliptin	N=16,492	Began 2010; Complete
EXAMINE	Alogliptin	N=5384	Began 2009; Complete
TECOS	Sitagliptin	N=14,000	Began 2008; Complete
CAROLINA	Linagliptin	N=6000	Began 2010; Ending 2018
CARMELINA	Linagliptin	N=8300	Began 2013; Ending 2018
GLP-1 Agonists			
ELIXA	Lixisenatide	N=6000	Began 2010; Complet2014
EXSCEL	Exenatide	N=9500	Began 2010; Ending 2017
LEADER	Liraglutide	N=9340	Began 2010; Comple 2016
REWIND	Dulaglutide	N=9622	Began 2011; Ending 2019
SUSTAIN 6	Semaglutide	N=3260	Began 2013; Ending 2016

Major CV Outcomes in Patients with Type 2 Diabetes and Matched Controls



1998 - 2014

- HbA1c: 7.7% - 7.2%
- LDL: 3.1 mmol/L– 2.7 mmol/l
- Statins: 12% - 60%
- RRsyst: 148mmHg- 136mm Hg
- Antihypertensive: 50 - 75%

Rawshani et al. N Engl J Med 2017;376:1407-18.

Effects of Glucose Lowering Drugs on the Combined Endpoint CV Mortality, Nonfatal Myocardial Infarction and Stroke

Study	Antidiabetic drug	HR	P value
SAVOR*	Saxagliptin	1.00 (CI 0.89-1.12)	NS
EXAMINE	Alogliptin	O.96 (CI 0.80-1.15)	NS
ELIXA	Lixisenatide	1.02 (CI 0.89-1.17)	NS
TECOS	Sitagliptin	0.98 (CI 0.89-1.08)	NS
LEADER	Liraglutide	0.87 (CI 0.78-0.97)	0.01

*Hospitalization for HF p<0.007

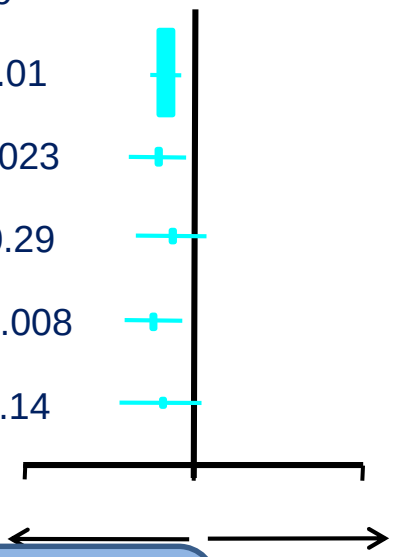
Schernthaner G and Sattar N. Journal of Diabetes and Its Complications 2014; 28: 430–433
Schernthaner G et al. Clin Ther. 2016; 38: 1288-1298

Incretin-Based Therapies Do Not Appear to Increase Cardiovascular Risk in T2DM

(Meta-Analyses of Individual Clinical Trials)

DPP-4 inhibitor vs comparators

	MH-OR	*p*
MACE	0.71 [0.59; 0.85]	<0.01
AMI	0.64 [0.44; 0.94]	0.023
Stroke	0.77 [0.48: 1.34]	0.29
Mortality	0.60 [0.41; 0.88]	0.008
CV Mortality	0.67 [0.39; 1.14]	0.14

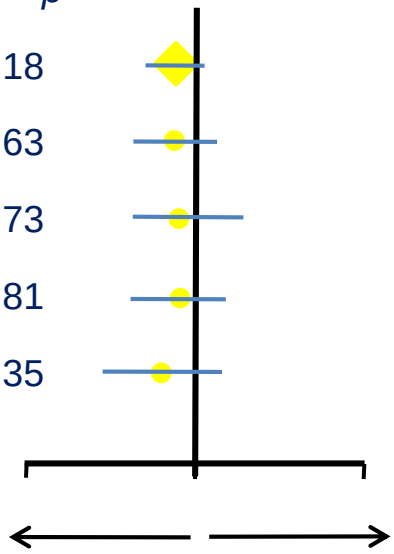


Caution required
Small numbers of events
Cannot compare effects of the 2 drug classes due to differences in trial designs

Monami et al; Diabetes Obes Metab 2013

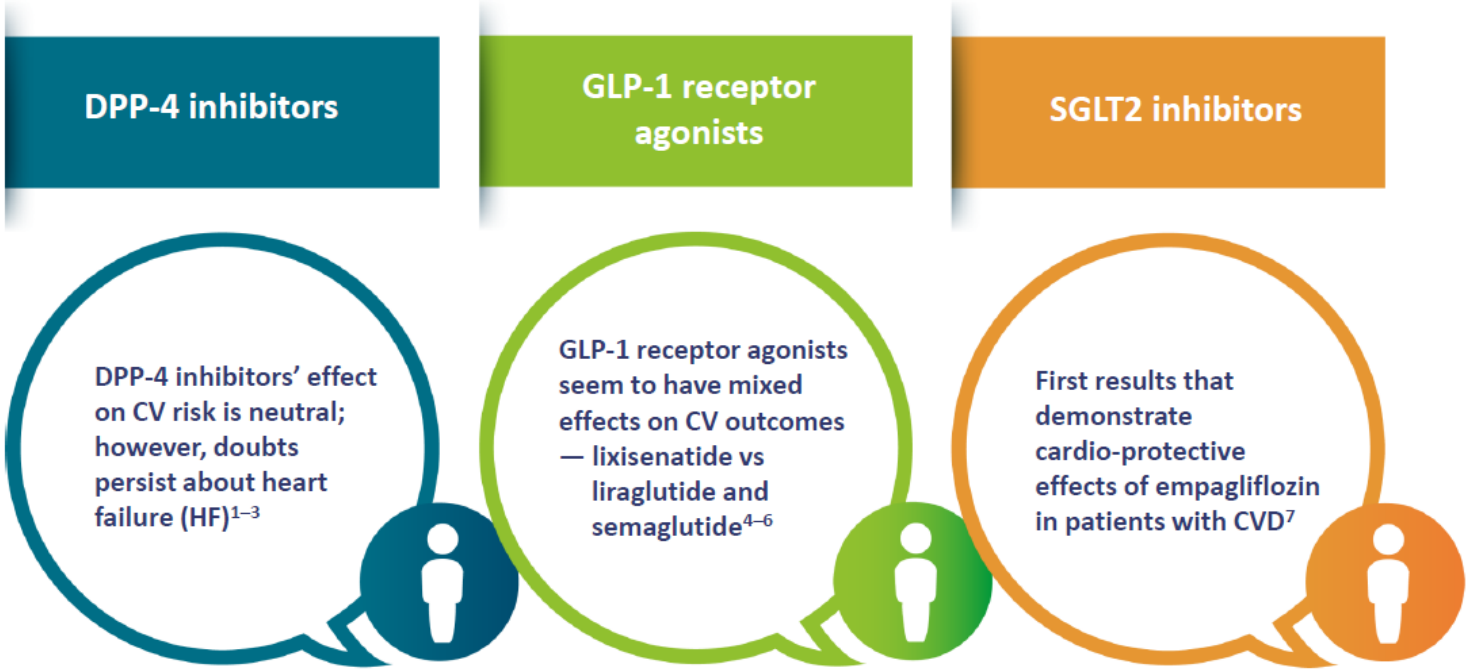
GLP-1 agonists vs comparators

MH-OR	*p*
0.78 [0.54; 1.13]	0.18
0.87 [0.48; 1.56]	0.63
0.87 [0.37: 2.03]	0.73
0.89 [0.46; 1.70]	0.81
0.63 [0.24; 1.66]	0.35



Monami et al; Diabetes Obes Metab 2013 [Epub]

CV TRIALS - RESULTS



'Class effects' cannot be assumed from the results of drug-specific trials

1. Scirica et al. N Engl J Med 2013;369:1317–1326. 2. White et al. N Engl J Med 2013;369:1327–1335. 3. Green et al. N Engl J Med 2015;373:232–242.
4. Pfeffer et al. N Engl J Med 2015;373:2247–2257. 5. Marso et al. N Engl J Med 2016; 375:311–322 6. Marso et al. N Engl J Med. 2016;375:1834–1844.
7. Zinman et al. N Engl J Med 2015;373:2117–2128.c

Potential cardiovascular protective properties of incretin-based therapies

INCRETIN-BASED THERAPY

METABOLIC EFFECTS

- ↑ Glycemic control
- ↓= Body weight
- ↓ Blood pressure
- ↓ CV risk factors
  - ↑ lipid profile
  - ↓ inflammation

CV EFFECTS

- ↑ *Endothelial function*
- ↑ *Anti-ischemic effect*
- ↑ *Angiogenesis*
- ↑ *Myocardial metabolism*
- ↑ *Cardiac function*

Nutrition, Metabolism & Cardiovascular Diseases (2014) xx, 1–8

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

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

Drug utilization, safety, and effectiveness of exenatide, sitagliptin, and vildagliptin for type 2 diabetes in the real world: Data from the Italian AIFA Anti-diabetics Monitoring Registry

S. Montilla [a,*], G. Marchesini [b], A. Sammarco [a], M.P. Trotta [a], P.D. Siviero [a], C. Tomino [a], D. Melchiorri [c], L. Pani [a] for the AIFA Anti-diabetics Monitoring C

Table 1A Baseline demographic/clinical data of the population with diabetes enrolled in the AIFA Anti-diabetics Monitoring Registry with glucose-lowering agents.

	Exenatide (n = 21,064)		Sitagliptin (n = 38,811)		Vildagliptin (n = 17,989)	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	58.9	9.9	61.7	10.4	61.9	10.4
Duration of diabetes (years)	10.0	15.4	9.1	7.1	8.2	6.5
Body mass index (kg/m^2)	36.1	6.8	30.8	5.7	30.5	5.5
Waist circumference (cm)	115.9	14.4	104.6	13.1	104.4	12.6
Fasting glucose (mg/dL)	187.8	49.8	170.8	41.6	171.9	41.1
HbA_{1c} (%) [mmol/mol]	8.8 [73]	1.3 [14]	8.3 [67]	1.1 [12]	8.2 [66]	1.1 [12]
Fasting C-peptide (ng/mL)	3.2	1.6	3.0	1.6	3.3	1.7
	N	%	*N*	%	*N*	%
Male gender	10,109	48.0	20,446	52.7	9741	54.1
Age > 75 years	723	3.4	3666	9.4	1736	9.7
BMI > 35	10,835	51.4	7870	20.3	3300	18.3
HbA_{1c} > 11% (>97 mmol/mol)	1496	7.1	1139	2.9	516	2.9

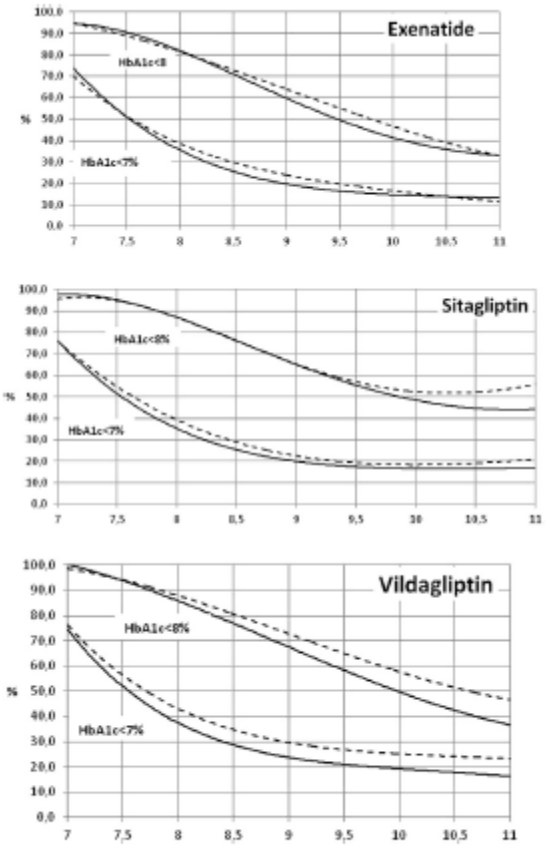


Figure 1 Probability of achieving the targets of metabolic control (HbA_{1c} <7%, lower lines; <8%, upper lines) at 3–4 months (continuous lines) or 8–9 months (broken lines) as function of entry HbA_{1c} values.

Registro AIFA: risultati dell'impiego di Analoghi del GLP-1 e Inibitori dell'enzima DPP-4 dopo 2 anni di trattamento

	Analoghi GLP-1	Inibitori DPP-IV
Peso Corporeo (kg)	**-4.5**	**-1.6**
HbA1c (%)	**-1.2**	**-1.0**
HbA1c (%) - *sottoanalisi su centri con almeno 80% follow-up completo per 1 molecola*	**-0.9 (HbA1c basale: 8.8%)**	**-0.9 (HbA1c basale: 8.2%)**
Episodi ipoglicemici (%)	**6.9**	**1.4**
Reazioni avverse (%)	**3.6**	**0.9**

BRIEF REPORT

Direct head-to-head comparison of glycaemic durability of dipeptidyl peptidase-4 inhibitors and sulphonylureas in patients with type 2 diabetes mellitus: A meta-analysis of long-term randomized controlled trials

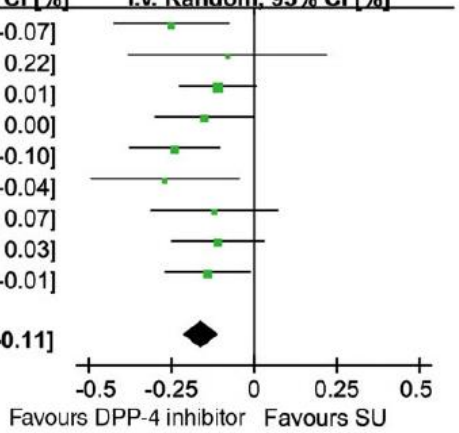
Diabetes Obes Metab. 2017;1–5.

(A)

Study or Subgroup	DPP-4 inhibitor Mean [%]	s.d. [%]	Total	SU Mean [%]	s.d. [%]	Total	Weight	Mean Difference i.v. Random, 95% CI [%]
Foley 2009	0.4	1.35	409	0.65	1.2	402	8.8%	-0.25 [-0.43, -0.07]
Ahren 2010	0.4	0.99	137	0.48	1.41	121	3.0%	-0.08 [-0.38, 0.22]
Matthews 2010	0.24	0.96	691	0.35	1.22	666	19.8%	-0.11 [-0.23, 0.01]
Seck 2010	0.21	0.89	248	0.36	0.84	256	11.9%	-0.15 [-0.30, 0.00]
Gallwitz 2012	-0.04	0.86	271	0.2	0.72	233	14.3%	-0.24 [-0.38, -0.10]
Goke 2013	0.18	0.88	165	0.45	1.12	147	5.4%	-0.27 [-0.50, -0.04]
Ahren 2014	0.38	1.14	300	0.5	1.28	302	7.3%	-0.12 [-0.31, 0.07]
Del 2014-12.5mg	0.09	1.32	880	0.2	1.18	437	13.7%	-0.11 [-0.25, 0.03]
Del 2014-25mg	0.06	1.07	885	0.2	1.18	437	15.8%	-0.14 [-0.27, -0.01]
Total (95% CI)			**3986**			**3001**	**100.0%**	**-0.16 [-0.21, -0.11]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.94$, df = 8 ($P = .76$); $I^2 = 0\%$

Test for overall effect: $Z = 5.97$ ($P < .00001$)

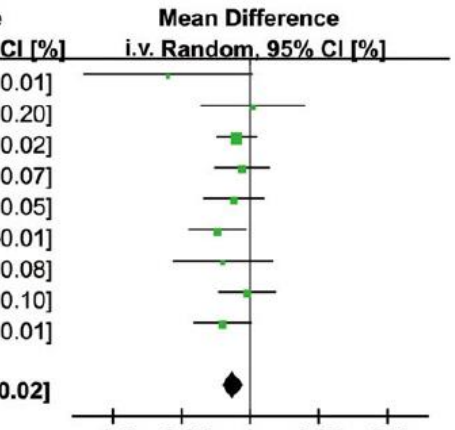


(B)

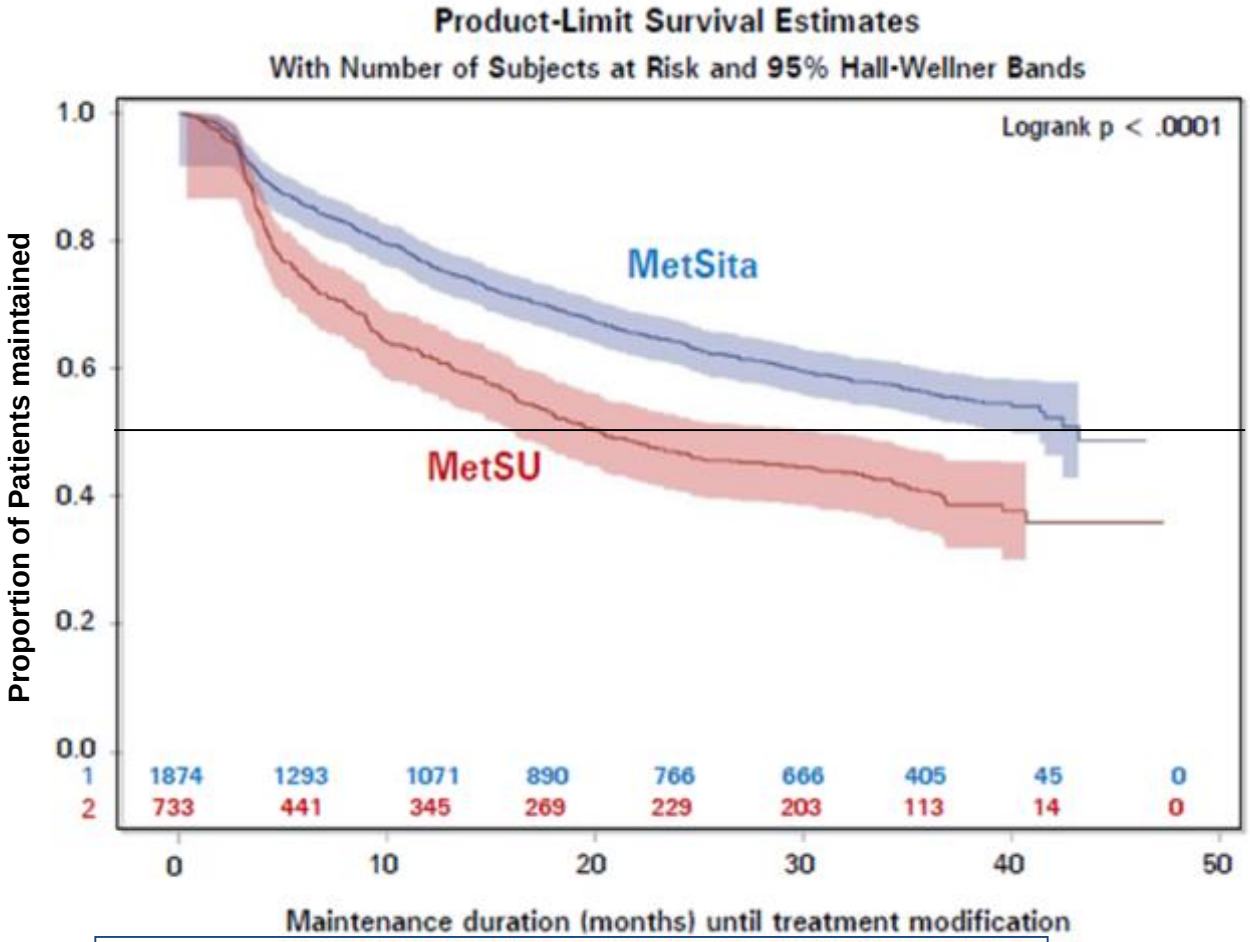
Study or Subgroup	DPP-4 inhibitor Mean [%]	s.d. [%]	Total	SU Mean [%]	s.d. [%]	Total	Weight	Mean Difference i.v. Random, 95% CI [%]
Foley 2009	0.3	2.2	409	0.6	2.3	402	1.5%	-0.30 [-0.61, 0.01]
Ahren 2010	0.34	0.81	137	0.33	0.74	121	4.0%	0.01 [-0.18, 0.20]
Matthews 2010	0.26	0.7	691	0.31	0.7	666	25.9%	-0.05 [-0.12, 0.02]
Seck 2010	0.28	0.57	248	0.31	0.6	256	13.8%	-0.03 [-0.13, 0.07]
Gallwitz 2012	0.08	0.66	271	0.14	0.61	233	11.7%	-0.06 [-0.17, 0.05]
Goke 2013	0.33	0.49	165	0.45	0.46	147	12.9%	-0.12 [-0.23, -0.01]
Ahren 2014	0.2	1.08	300	0.3	1.2	302	4.3%	-0.10 [-0.28, 0.08]
Del 2014-12.5mg	0.14	1.13	880	0.15	0.79	437	13.0%	-0.01 [-0.12, 0.10]
Del 2014-25mg	0.05	1.15	885	0.15	0.79	437	12.8%	-0.10 [-0.21, 0.01]
Total (95% CI)			**3986**			**3001**	**100.0%**	**-0.06 [-0.10, -0.02]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.06$, df = 8 ($P = .64$); $I^2 = 0\%$

Test for overall effect: $Z = 3.21$ ($P = .001$)



Maggiore Persistenza di Sitagliptin vs SU: Durability a 3,5 anni (4 anni / 3.543 pazienti)



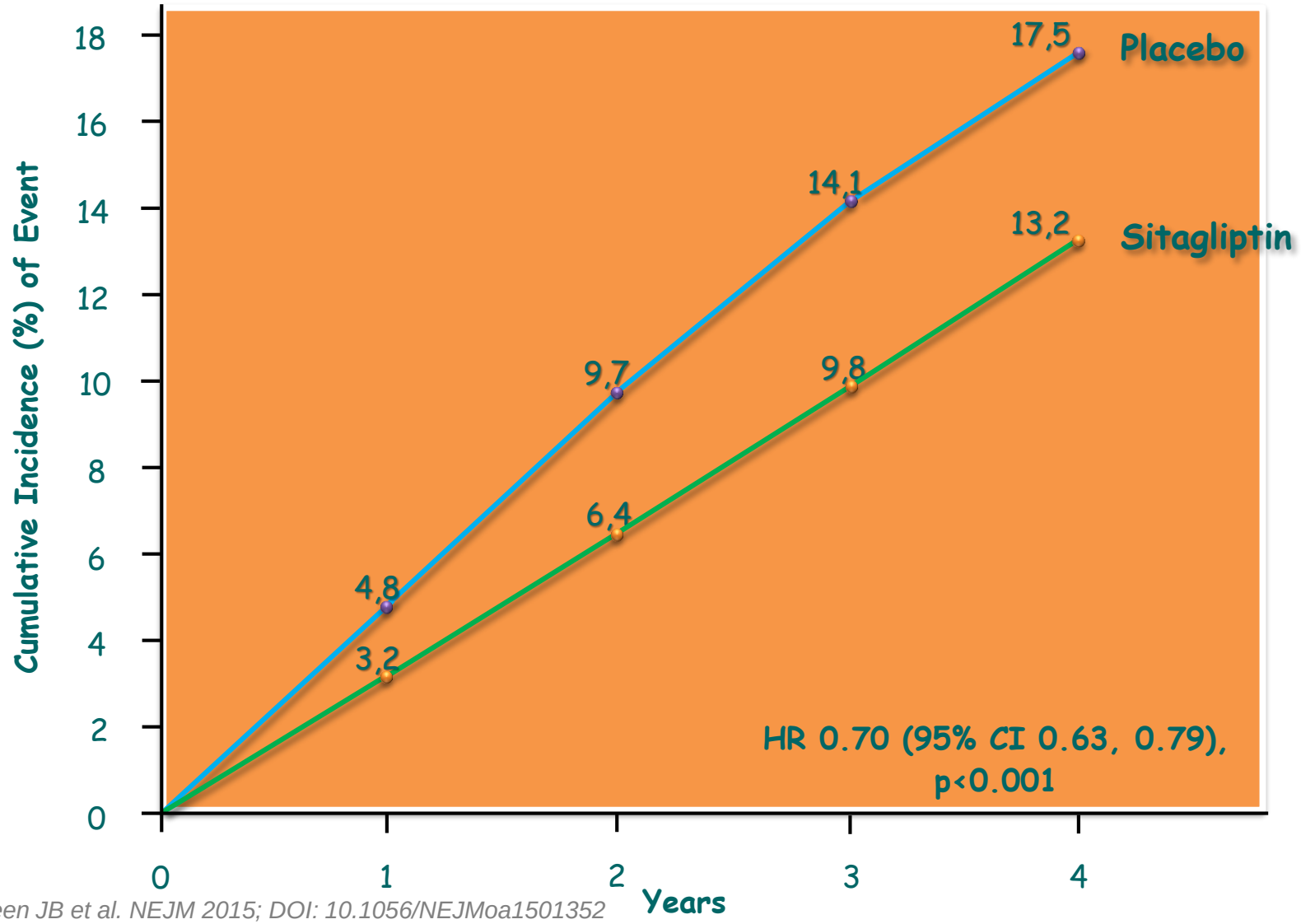
MetSita group : 43.2 months [95%CI: 41.4 – NE*]

MetSU group : 20.2 months [95%CI: 17.0 - 25.1]

*non-evaluable

Studio Odyssee_P.Valensi et al. Diabetes & Metabolism2015

Initiation of Chronic Insulin Therapy



Green JB et al. NEJM 2015; DOI: 10.1056/NEJMoa1501352

Adv Ther (2012) 29(1):14-25.
DOI 10.1007/s12325-011-0088-z

REVIEW

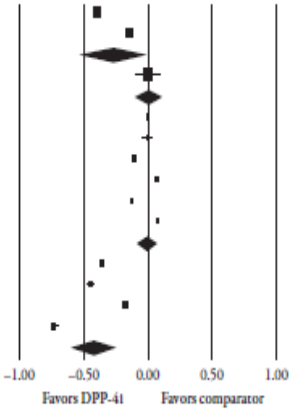
DPP-4 Inhibitors and Lipids: Systematic Review and Meta-Analysis

Matteo Monami · Caterina Lamanna · Carla Maria Desideri · Edoardo Mannucci

Figure 4. Effect of individual DPP-4 inhibitors on total cholesterol. DDP-4i=dipeptidyl peptidase-4 inhibitors.

Total cholesterol

Study name[Reference]	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value
DeFronzo 2008[57]	−0.393	0.009	0.000	−0.411	−0.375	−43.500	0.000
Pratley 2009[58]	−0.140	0.007	0.000	−0.153	−0.127	−20.667	0.000
Alogliptin	−0.266	0.126	0.016	−0.514	−0.018	−2.106	0.035
Hollander 2010[59]	0.000	0.052	0.003	−0.101	0.101	0.000	1.000
Saxagliptin	0.000	0.052	0.003	−0.101	0.101	0.000	1.000
Rosenstock 2007[6]	0.000	0.008	0.000	−0.015	0.015	0.000	1.000
Williams-Herman 2010[54]	0.000	0.021	0.000	−0.041	0.041	0.000	1.000
Bergenstal 2010[53]	−0.100	0.007	0.000	−0.113	−0.087	−14.962	0.000
Bergenstal 2010[52a]	0.070	0.007	0.000	0.057	0.083	10.419	0.000
Charbonnel 2006[51]	−0.120	0.008	0.000	−0.136	−0.104	−15.030	0.000
Pratley 2011[55]	0.080	0.006	0.000	0.068	−0.092	13.098	0.000
Sitagliptin	−0.012	0.038	0.001	−0.086	0.062	−0.310	0.757
Bolli 2009[56]	−0.355	0.004	0.000	−0.362	0.348	−94.639	0.000
Rosenstock 2007[6a]	−0.440	0.014	0.000	−0.467	−0.413	−31.620	0.000
Defager 2007[25]	−0.172	0.008	0.000	−0.188	−0.156	−21.549	0.000
Rosenstock 2006[20]	−0.726	0.014	0.000	−0.754	−0.698	−50.244	0.000
Vildagliptin	−0.423	0.086	0.007	−0.591	−0.255	−4.929	0.004



Conclusions: This meta-analysis suggests a possible beneficial effect of DPP-4 inhibitors on cholesterol, which, although small, could contribute to the reduction of cardiovascular risk.

A comparison of effects of DPP-4 inhibitor and SGLT2 inhibitor on lipid profile in patients with type 2 diabetes

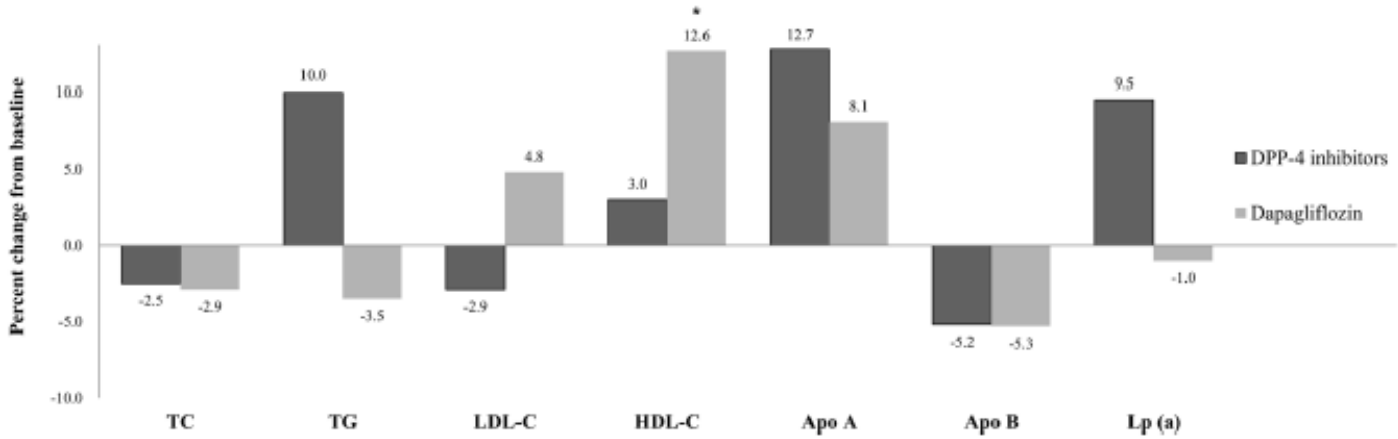


Fig. 1 Changes in plasma lipid profile (%) by treatment of DPP-4 inhibitor and SGLT2 inhibitor. TC Total cholesterol, TG Triglycerides, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, Apo A apolipoprotein A, Apo B apolipoprotein B, Lp (a) lipoprotein (a). * $p < 0.05$ (comparison between DPP-4 inhibitor group and SGLT2 inhibitor group)

Cha *et al. Lipids in Health and Disease* (2017) 16:58

Liu et al. Lipids in Health and Disease (2016) 15:204
DOI 10.1186/s12944-016-0372-7

Lipids in Health and Disease

RESEARCH Open Access

Impact of dipeptidyl peptidase-4 inhibitors on serum adiponectin: a meta-analysis

Xin Liu[1], Peng Men[2], Yuhui Wang[1], Suodi Zhai[2] and George Liu[1*]

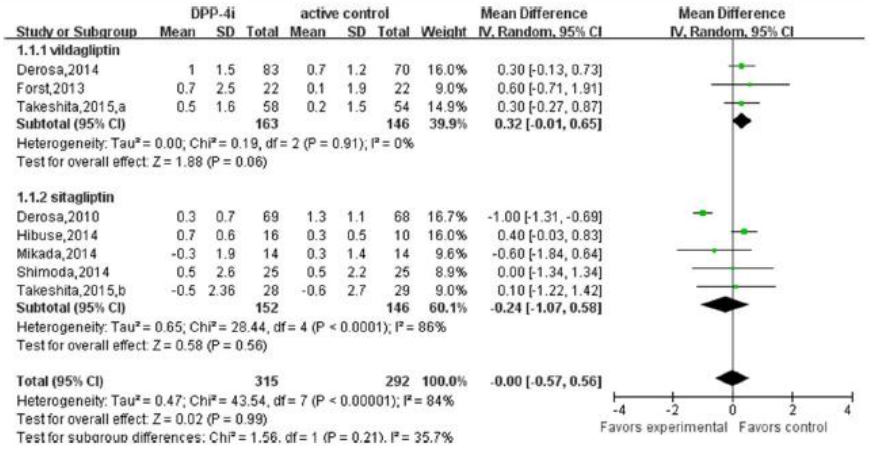


Fig. 4 Meta-analysis of the effect of DPP4i treatment versus active comparator on serum adiponectin levels

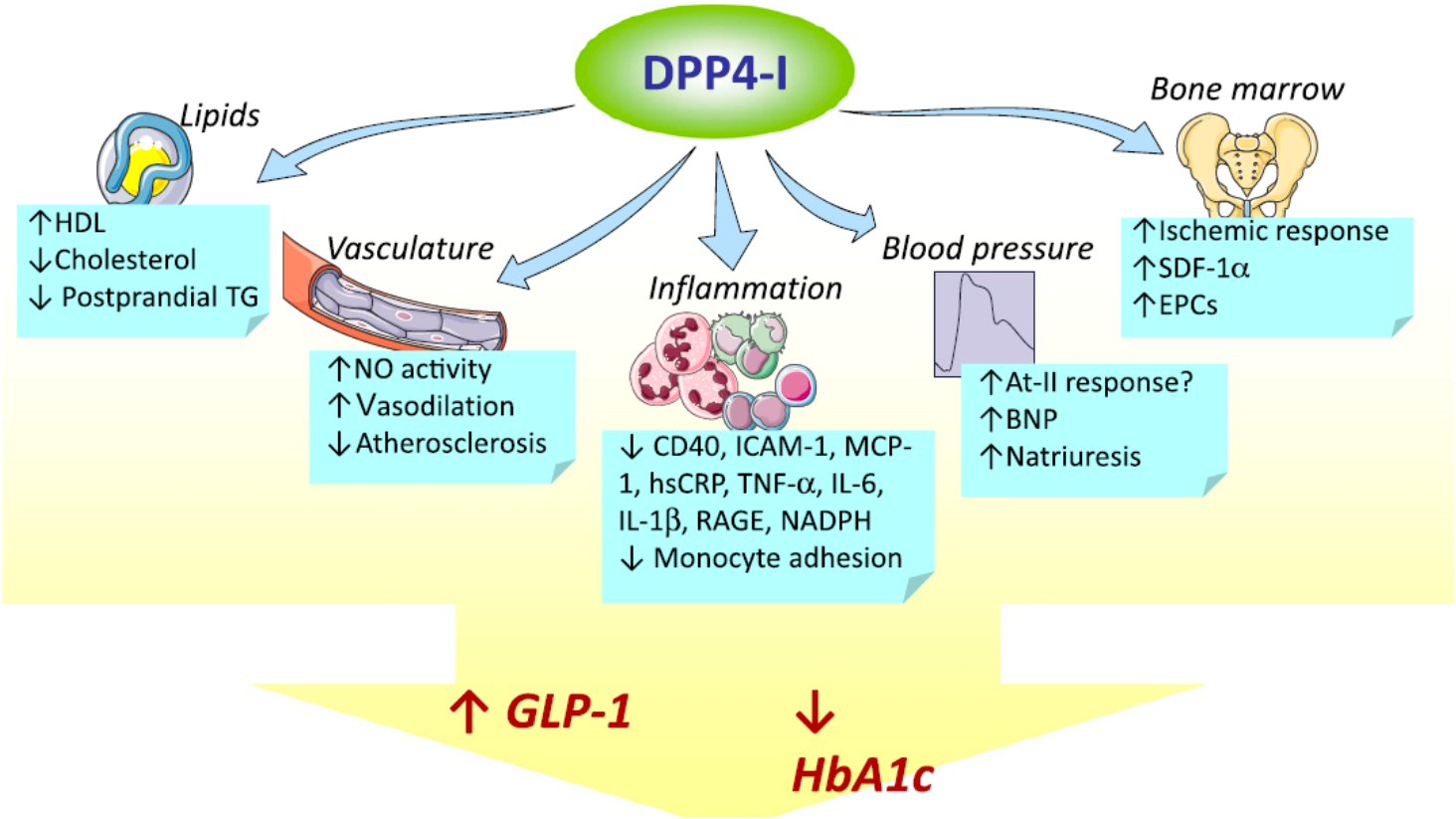
Conclusions

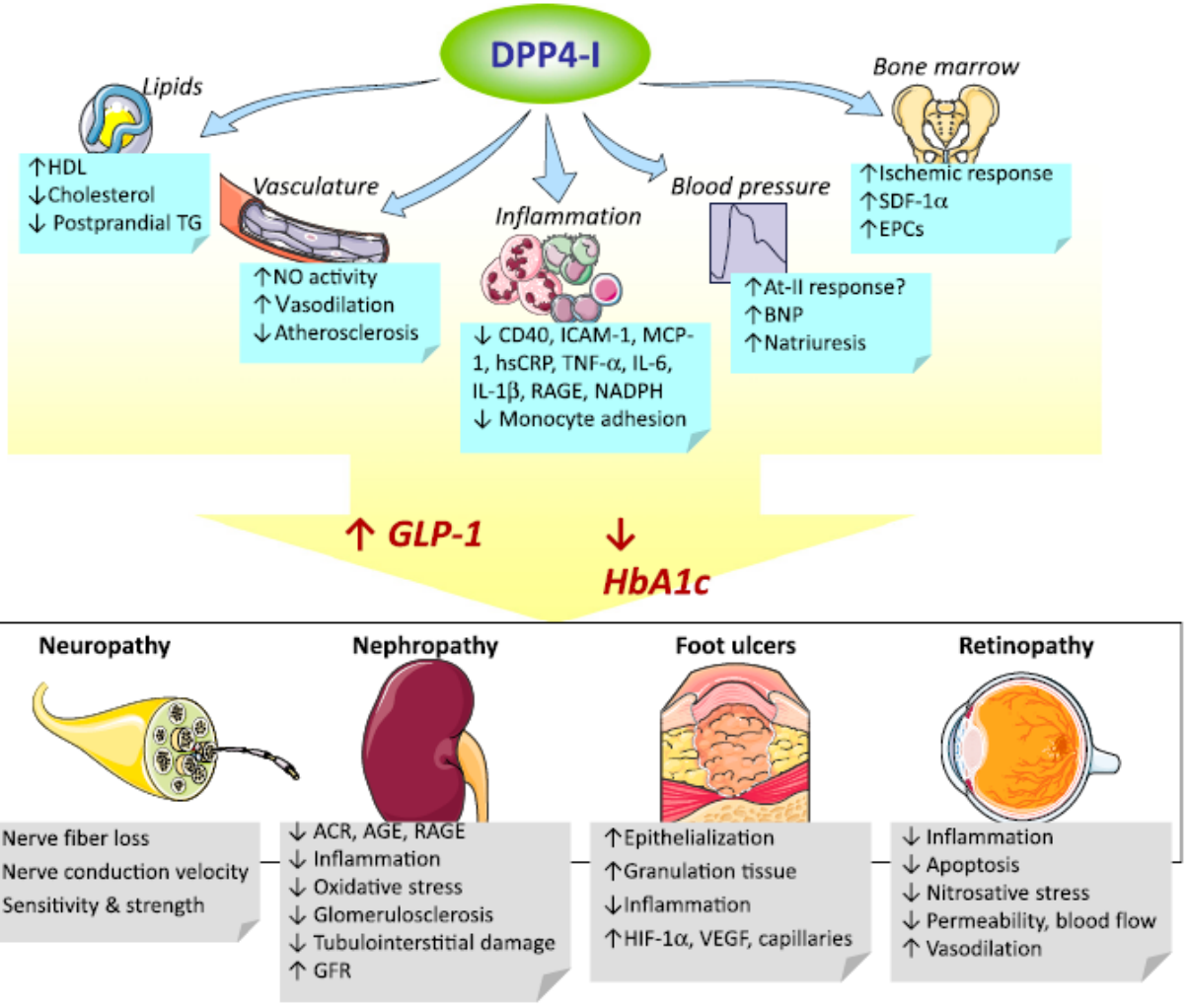
DPP4 inhibitors promote the secretion of serum adiponectin in T2DM patients, thereby indicating that these have a cardioprotective effect. Further trials with larger sample size are needed to confirm the results and investigate the association between serum adiponectin levels and treatment of other DPP4 inhibitors. Long-term effi-

The Effects of Dipeptidyl Peptidase-4 Inhibition on Microvascular Diabetes Complications

Angelo Avogaro and Gian Paolo Fadini

Diabetes Care 2014;37:2884–2894 | DOI: 10.2337/dc14-0865




DPP4-I
Lipids
↑HDL
↓Cholesterol
↓ Postprandial TG
Vasculature
↑NO activity
↑Vasodilation
↓Atherosclerosis
Inflammation
↓ CD40, ICAM-1, MCP-1, hsCRP, TNF-α, IL-6, IL-1β, RAGE, NADPH
↓ Monocyte adhesion
Blood pressure
↑At-II response?
↑BNP
↑Natriuresis
Bone marrow
↑Ischemic response
↑SDF-1α
↑EPCs
↑ GLP-1
↓ HbA1c
Neuropathy
↓ Nerve fiber loss
↑ Nerve conduction velocity
↑ Sensitivity & strength
Nephropathy
↓ ACR, AGE, RAGE
↓ Inflammation
↓ Oxidative stress
↓ Glomerulosclerosis
↓ Tubulointerstitial damage
↑ GFR
Foot ulcers
↑Epithelialization
↑Granulation tissue
↓Inflammation
↑HIF-1α, VEGF, capillaries
Retinopathy
↓ Inflammation
↓ Apoptosis
↓ Nitrosative stress
↓ Permeability, blood flow
↑ Vasodilation

Dipeptidyl peptidase-4 inhibition in chronic kidney disease and potential for protection against diabetes-related renal injury

G. Penno*, M. Garofolo, S. Del Prato

Nutrition, Metabolism & Cardiovascular Diseases (2016) 26, 361–373

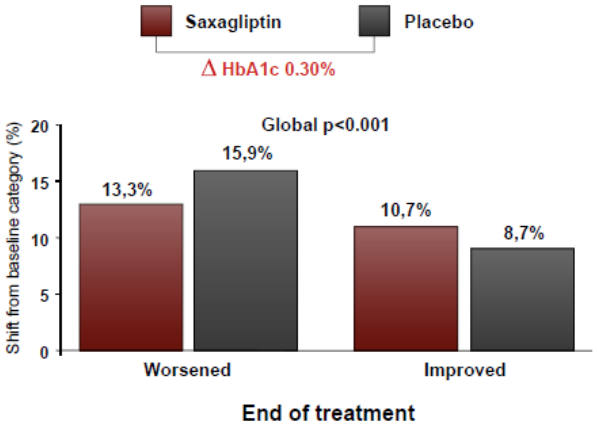
Table 1 Percentage change in adjusted geometric mean urinary ACR from baseline to 24 weeks observed in a pooled analysis of data from four similarly designed, 24-week, randomized, double-blind, placebo-controlled, phase III trials with linagliptin. The analysis includes 217 subjects with T2DM and prevalent albuminuria (urinary ACR 30–3000 mg/g creatinine) while on stable dosages of RAAS inhibitors.

	N. of subjects	Change in urinary ACR (%)	Change in urinary ACR (95% CIs)	*p*
All subjects	217	−32	−42 to −21	<0.05
All subjects at 12 weeks	226	−29	−40 to −17	<0.05
Mean baseline HbA1c < 8.25%	97	−29	−44 to −10	Treatment × baseline HbA1c
Mean baseline HbA1c ≥ 8.25%	65	−32	−48 to −10	interaction, $p = 0.81$
Mean baseline systolic BP < 137.4 mmHg	88	−31	−46 to −11	Treatment × baseline SBP
Mean baseline systolic BP ≥ 137.4 mmHg	74	−30	−46 to −9	interaction, $p = 0.65$
Subjects not previously treated with RAAS inhibitors[a]	183	−30	−40 to −19	<0.05

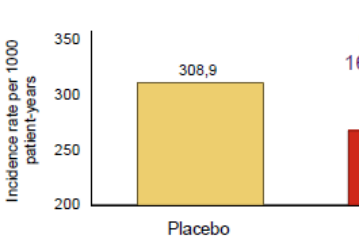
[a] Sensitivity analysis.

Renal Outcomes

Saxagliptin



Linagliptin



Renal events	306	448
Time at risk, years	991	1679
Patients, n	1961	3505

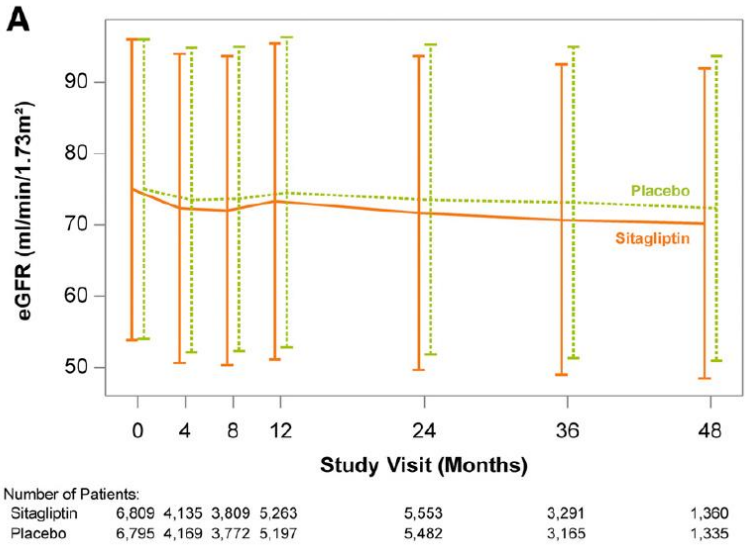
Microalbuminuria, macroalbuminuria, CKD (sCR >2.8 mg/dl), worsening of CKD (loss eGFR >50% of baseline, acute renal failure, death from any cause

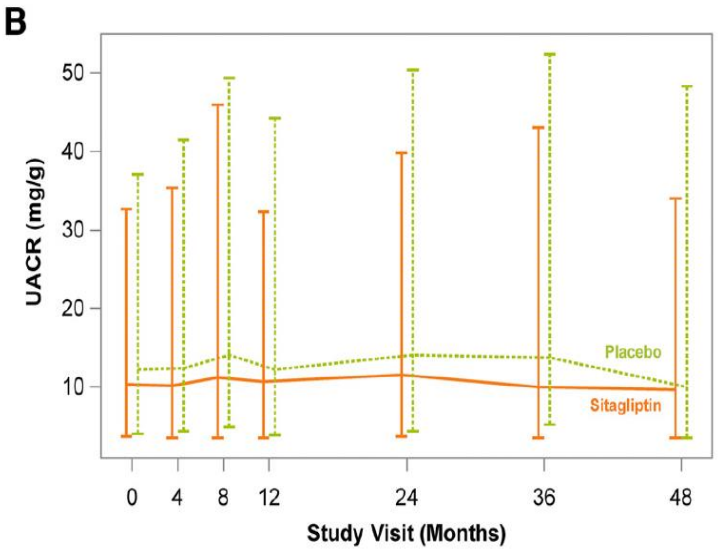
Figure 1 Renal outcomes with linagliptin: a meta-analysis of indi·

…Nephroprotective effect idependent of glucose lowering

Effect of Sitagliptin on Kidney Function and Respective Cardiovascular Outcomes in Type 2 Diabetes: Outcomes From TECOS

Diabetes Care 2016;39:2304–2310 | DOI: 10.2337/





Terapia non insulinca nel DM2 con IRC

Tabella 14. Terapia non insulinica nel diabete tipo 2 con insufficienza renale cronica

Stadio IRC	LIEVE	MODERATA	GRAVE	DIALISI
eGFR	eGFR >60	60 >eGFR >30	30 >eGFR >15	eGFR <15
Metformina	almeno 2 g	non indicato (utilizzabile)	NO	NO
Acarbosio	da titolare	da titolare	NO	NO
Sitagliptin	100 mg x 1	50 mg x1	25 mg x 1	25 mg x 1
Vildagliptin	50 mg x 2	50 mg x 1	50 mg x 1	50 mg x 1
Saxagliptin	5 mg x 1	2,5 mg x 1	2,5 mg x 1	NO
Linagliptin	5 mg x 1	5 mg x 1	5 mg x 1	5 mg x 1
Exenatide	da titolare	cautela	NO	NO
Liraglutide	da titolare	NO	NO	NO
Lixisenatide	da titolare	cautela	NO	NO
Sulfoniluree	da titolare	NO (1)	NO	NO
Repaglinide	da titolare	non indicato (utilizzato)	NO	NO
Pioglitazone	da titolare	da titolare	da titolare	NO

(1) Alcune sulfoniluree (gliquidone, glinizide e gliclazide) hanno metabolismo prevalentemente epatico, ma non

Standard Italiani per la Cura del Diabete - 2016

Tabella 16. Terapia non insulinica nel diabete di tipo 2 con insufficienza renale cronica

Stadio IRC	Lieve	moderata	grave	dialisi
eGFR	>60 ml/min	30-60 ml/min	15-30 ml/min	<15 ml/min
Metformina	≥2 g/die	Non indicato (utilizzabile)	NO	NO
Acarbosio	Da titolare	Da titolare	NO	NO
Gliptine				
Sitagliptin	100 mg/die	50 mg/die	25 mg/die	25 mg/die
Vildagliptin	100 mg/die	50 mg/die	50 mg/die	50 mg/die
Saxagliptin	5 mg/die	2.5 mg/die	2.5 mg/die	NO
Linagliptin	5 mg/die	5 mg/die	5 mg/die	5 mg/die
Alogliptin	25 mg/die	12.5 mg/die[a]	6.25 mg/die	6.25 mg/die
GLP1 agonisti				
Exenatide	Dosi usuali	Cautela[b]	NO	NO
Exenatide LAR	Dosi usuali	NO[c]	NO	NO
Liraglutide	Dosi usuali	Dosi usuali	NO	NO
Lixisenatide	Dosi usuali	Cautela[b]	NO	NO
Dulaglutide	Dosi usuali	Dosi usuali	NO	NO
Sulfoniluree	Da titolare	Da titolare[d]	NO	NO
Repaglinide	Da titolare	Non indicato (utilizzato)	NO	NO
Pioglitazone	Dosi usuali	Dosi usuali	Dosi usuali	NO[e]
Gliflozine				
Dapagliglozin	Dosi usuali	NO	NO	NO
Empagliflozin	Dosi usuali	NO	NO	NO
Canagliflozin	Dosi usuali	NO	NO	NO

NAPOLI, 17-20 MAGGIO 2017: XXI° CONGRESSO NAZIONALE ASSOCIAZIONE MEDICI DIABETOLOGI

EFFICACIA DI SITAGLIPTIN 50 MG IN MONOTERAPIA IN PAZIENTI CON DIABETE MELLITO TIPO 2 E INSUFFICIENZA RENALE CRONICA

Orsini P[1], Turco A[1], Occhipinti M[1], Lacaria E[1], Lencioni C[1], Pancani F[1], Pani G[1], Di Cianni G[1].

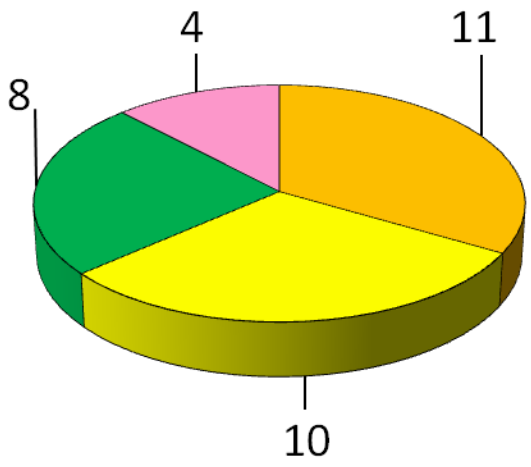
U.O. Diabetologia e Malattie del Metabolismo, Ospedale di Livorno, ASL Toscana Nordovest[2].

SCOPO DELLO STUDIO

- Valutare l'efficacia e la sicurezza di Sitagliptin in monoterapia in diabetici anziani fragili con DM2 e IRC.

SOGGETTI E METODI

- Dal database computerizzato (MyStar Connected®) abbiamo individuato 311 pazienti trattati con sitagliptin e da questi abbiamo estrapolato 33 pazienti in trattamento con sitagliptin 50 mg in monoterapia e IRC (GFR < 60 ml/min).
- In tutti i casi la precedente terapia era stata sospesa per l'alto rischio di ipoglicemie o peggioramento della funzione renale *(Tab.1)*.
- Abbiamo registrato i dati relativi alla visita basale e dopo 6, 12, 18 e 24 mesi valutando i parametri clinici e antropometrici.



- metformin (500-1500 mg/daily)
- repaglinide (1-4 mg/daily)
- metformin plus glibenclamide or repaglinide
- insulin injections (8-18 IU/daily)

STOP pharmacological diabetes therapy

33 Diabetic patients
(23 M, 10 F)
To START
Sitagliptin 50 mg
as monotherapy

Caratteristiche cliniche popolazione studiata	
Numero	33
Età (anni)	78±8
Femmine (N)	17
Maschi (N)	18
Durata diabete (anni)	10,5±8,2
Glicemia a digiuno (mg/dl)	125,3±36,8
HbA1c (%)	6,6 ±0,6
Creatininemia (mg/dl)	1,7±0,5
eGFR (mL/min)	40,6±13
Microalbuminuria (mg/l)	207±75
Colesterolo tot (mg/dl)	165±34,2
Colesterolo LDL (mg/dl)	94,8±29,8
Colesterolo HDL (mg/dl)	42,8±11,6
Trigliceridi (mg/dl)	144,2±60
Pressione arteriosa sistolica (mmHg)	147±20
Pressione arteriosa diastolica (mmHg)	77±5

Risultati

	Baseline	Dopo 24 mesi	p
HbA1c (%)	6,6 ±0,6	6,4±0,5	n.s.
Creatininemia (mg/dl)	1,7±0,5	1,7±0,4	n.s.
eGFR (mL/min)	40,6±13	43,5±9,6	n.s.
Microalbuminuria (mg/l)	207±75	225±71	n.s.
Colesterolo tot (mg/dl)	165±34,2	170±32,4	n.s.
Colesterolo LDL (mg/dl)	94,8±29,8	96,2±30,1	n.s.
Colesterolo HDL (mg/dl)	42,8±11,6	43,0±12,0	n.s.
Trigliceridi (mg/dl)	144,2±60	140,8±58	n.s.
Pressione arteriosa sistolica (mmHg)	147±20	145±21	n.s.
Pressione arteriosa diastolica (mmHg)	77±5	79±4	n.s.

Lo studio, sebbene condotto su una casistica numericamente poco rilevante, dimostra che la monoterapia con Sitagliptin può sostituire con efficacia terapie potenzialmente più pericolose, senza aggravare l'equilibrio metabolico e mettendo in sicurezza il paziente.

Contents available at ScienceDirect

Diabetes Research and Clinical Practice

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

ELSEVIER

International Diabetes Federation

The effects of sitagliptin, a DPP-4 inhibitor, on cognitive functions in elderly diabetic patients with or without Alzheimer's disease

Ahmet Turan Isik [a,*], *Pinar Soysal* [a], *Adnan Yay* [b], *Cansu Usarel* [a]

[a] *Center for Aging Brain and Dementia, Department of Geriatric Medicine, Dokuz Eylul University, Faculty of Medicine, Izmir, Turkey*
[b] *Department of Internal Medicine, Izmir Military Hospital, Izmir, Turkey*

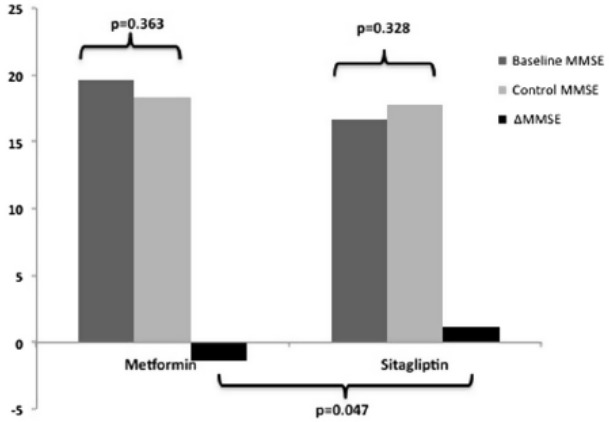


Fig. 2 – Comparison of MMSE scores and mean changes from baseline in MMSE scores in the patients with AD treated with metformin or sitagliptin monotherapy.

This prospective observational study demonstrated that 6-month sitagliptin therapy was associated with increased cognitive functions in the elderly diabetic patients with and without AD. Furthermore, it was also demonstrated that the need for insulin was lower in those treated with sitagliptin.

Contents lists available at ScienceDirect

Experimental Gerontology

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

Long-term inhibition of dipeptidyl peptidase-4 in Alzheimer's prone mice

Michele D'Amico [a,*,1], Clara Di Filippo [a,1], Raffaele Marfella [b], Angela Maria Abbatecola [b], Franca Ferraraccio [c], Francesco Rossi [a], Giuseppe Paolisso [b]

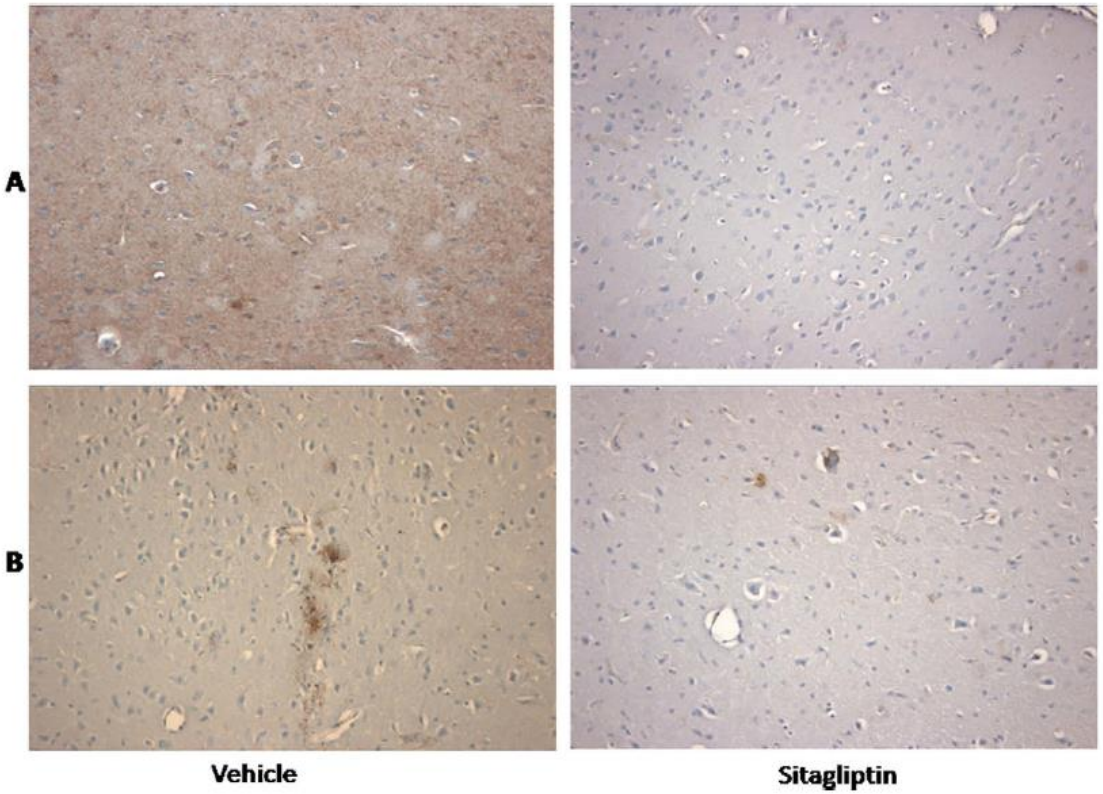


Fig. 5. Representative hippocampal immunostaining (200×) for (A) nitrotyrosine and (B) IL1-β within the brain of B6.Cg-Tg(APPswe,PSEN1dE9)85Dbo/J mice treated with vehicle or sitagliptin (20 mg/kg).

RESEARCH ARTICLE

The effects of dipeptidyl peptidase-4 inhibitors on bone fracture among patients with type 2 diabetes mellitus: A network meta-analysis of randomized controlled trials

Jun Yang[1☯‡], Chao Huang[1☯‡], Shanshan Wu[2☯‡], Yang Xu[1], Ting Cai[1], Sanbao Chai[3], Zhirong Yang[4], Feng Sun[1]*, Siyan Zhan[1]*

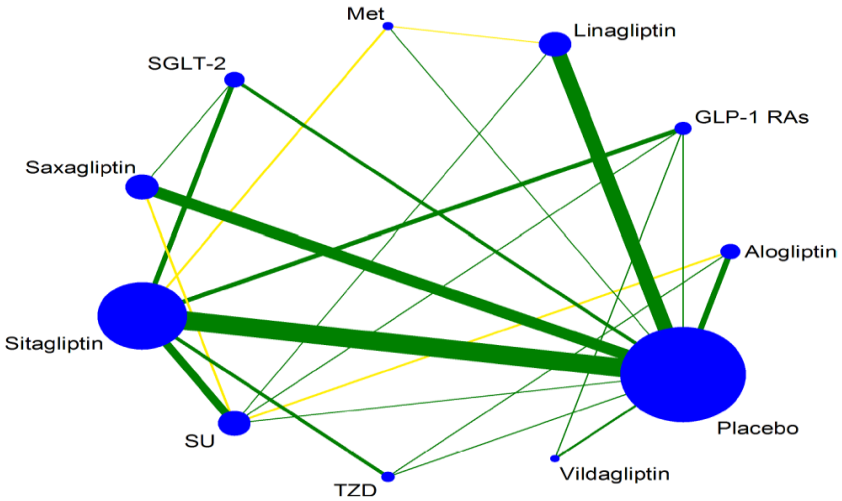


Fig 2. Evidence structure of eligible comparisons for NMA. Note: Lines connect the interventions that have been studied in head-to-head (direct) comparisons in the eligible RCTs. The width of the lines represents the cumulative number of RCTs for each pairwise comparison and the size of every node is proportional to the number of randomized participants (sample size). The yellow lines represent trials reporting unclear about allocation concealment, while the blue lines represent trials with low risk of allocation concealment. GLP-1RAs: Glucagon-like peptide-1 receptor agonists; SGLT-2: Sodium-Glucose co-Transporter2; Met: metformin; SU: sulphanylureas; TZD: thiazolidinediones.

Conclusion

Alogliptin may be associated with a lower risk of bone fracture compared with placebo, linagliptin, or saxagliptin, while other anti-diabetes did not seem to have an association with the risk of bone fracture.

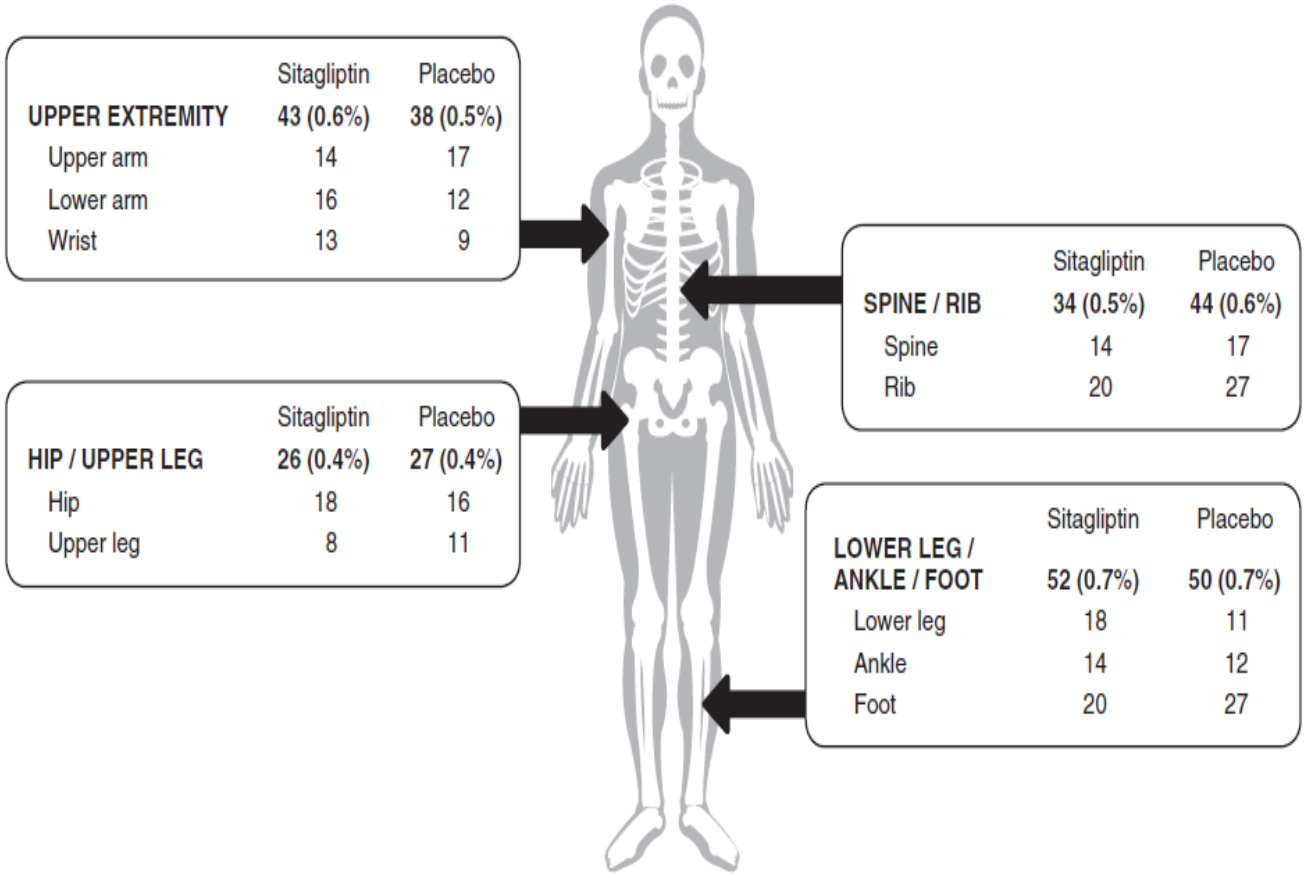


FIGURE 2 Frequency and location of incident fractures according to treatment assignment (sitagliptin vs placebo). Face, hand and other fractures excluded.

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ORIGINAL RESEARCH

Cost-consequence analysis of sitagliptin versus sulfonylureas as add-on therapy for the treatment of diabetic patients in Italy

Table 4 Cost-consequence analysis SITA versus SU over 3-year time horizon (INHS perspective)

Cost component	SITA+Met	SU+Met	Delta
Drug	€96,600,960	€13,212,990	€83,387,970
Distribution PHT	€16,807,081	€0	€16,807,081
Self-monitoring	€16,518,556	€80,368,536	–€63,849,980
Visits	€8,941,648	€7,221,703	€1,719,945
Hypos	€1,296,239	€6,255,716	–€4,959,477
MACE	€0	€23,501,390	–€23,501,390
Switch to insulin	€123,417,886	€184,868,478	–€61,450,592
Indirect costs	€0	€0	€0
Total costs	€263,582,370	€315,428,813	–€51,846,442

Abbreviations: hypos, hypoglycemic events; INHS, Italian National Health Service; MACE, major cardiovascular events; Met, metformin; SITA, sitagliptin; SU, sulfonylurea; PHT, drugs included in the National Hospital-Territory Formulary.

Conclusioni

- I DPP4-i sono farmaci efficaci nel ridurre la glicemia e sicuri per il rischio CV
- Effetti positivi si riscontrano anche sul profilo lipidico, sui markers infiammazione, sulla funzione endoteliale.
- Prevenzione delle complicanze macro e microangiopatice
- Efficacia clinica – riduzione dei costi