Inibitori DPP4: meccanismo d'azione, efficacia e tollerabilità

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Disclosures

- Advisory Boards: AstraZeneca, Eli Lilly, Merck Sharp & Dohme, Mundipharma, NovoNordisk, Roche Diabetes Care.
- Consultant: AstraZeneca, Eli Lilly, Roche Diabetes Care, Boehringer-Ingelheim, Lifescan, Sanofi.
- Research Support: Eli Lilly, Lifescan, Takeda.

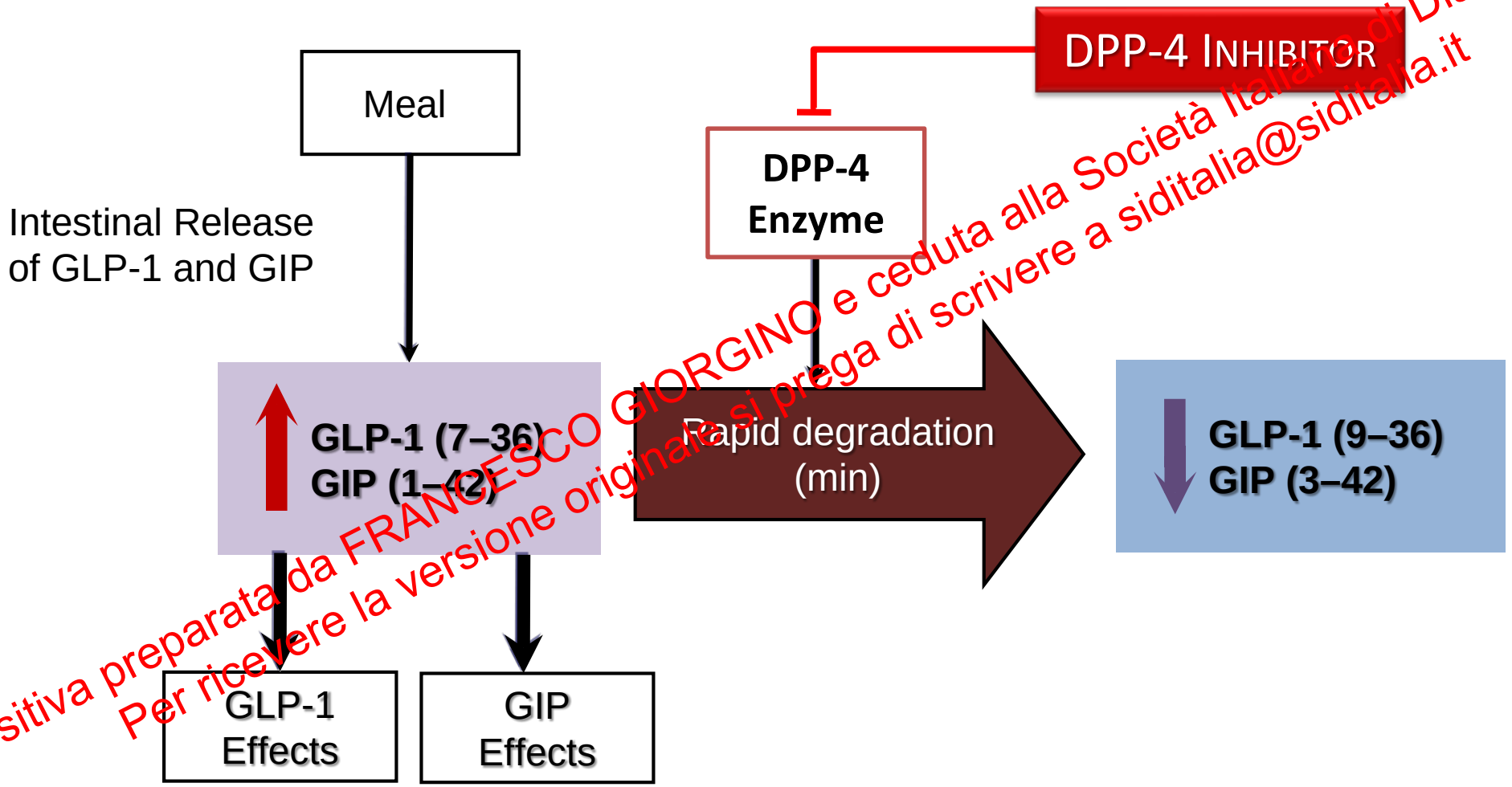
Con quale meccanismo i DPP4 inibitori riducono la iperglicemia?

A. Aumentando i livelli ematici di GLP-1
B. Aumentando i livelli di insulina
C. Riducendo i livelli di glucagone
D. Favorendo la sopravvivenza delle beta-cellule pancreatiche

Quale è l'effetto avverso più frequente dei DPP4 inibitori?

A. Ipoglicemia
B. Pancreatite acuta
C. Dolori articolari
D. Scompenso cardiaco

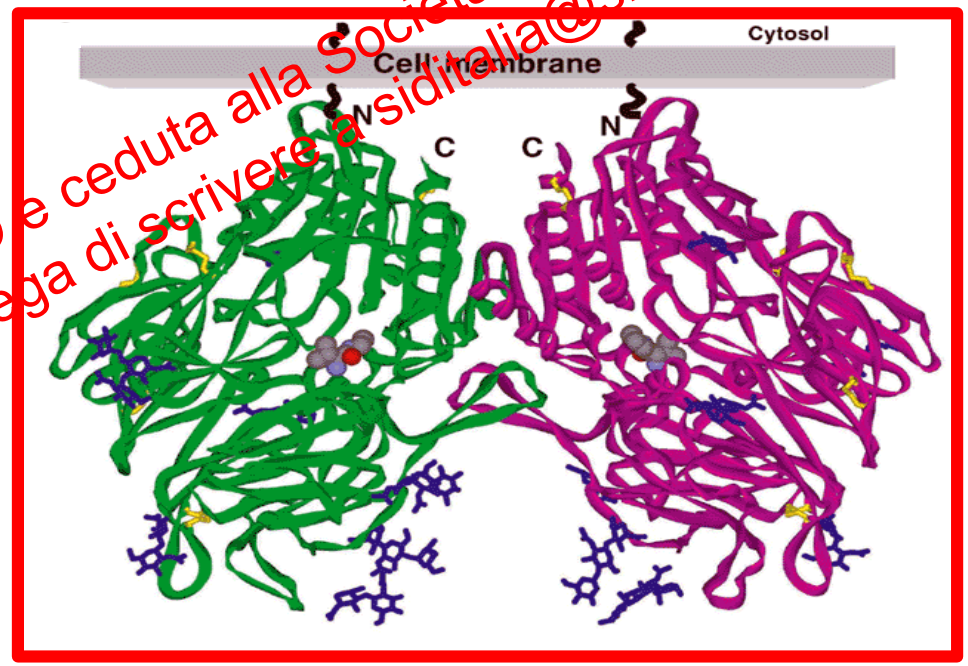
DPP-4 Inhibitors (Incretin Enhancers)



Adapted from Deacon CF, et al. *Diabetes* 1995;44:1126–31; Kieffer TJ, et al. *Endocrinology* 1995;136:3585–96; Ahrén B. *Curr Diab Rep* 2003;3:365–72; Deacon CF, et al. *J Clin Endocrinol Metab* 1995;80:952–7; Weber AE . *J Med Chem* 2004;47:4135–41.

Dipeptidyl Peptidase IV (DPP4)

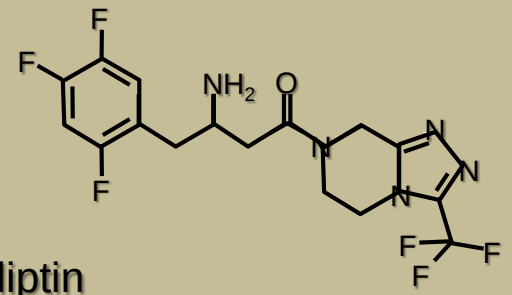
- Cell surface serine dipeptidase; member of the prolyl oligopeptidase family
- Cleaves the N-terminal dipeptide from peptides with proline or alanine in the penultimate position
- Widely expressed
- Shed into the circulation in a soluble form lacking the transmembrane region
- Identical to CD26, a marker for activated T cells.



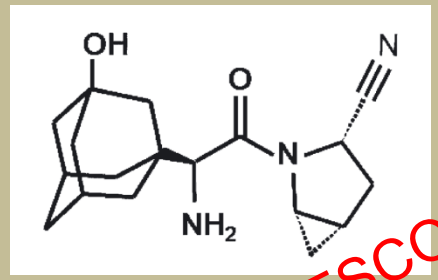
Rasmussen et al. Nature Structural Biology 2002;10:19–25

Chemical Structure of DPP-4 Inhibitors

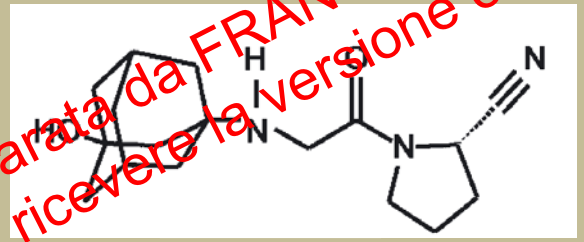
DPP-4 inhibitors mimicking dipeptides



Sitagliptin



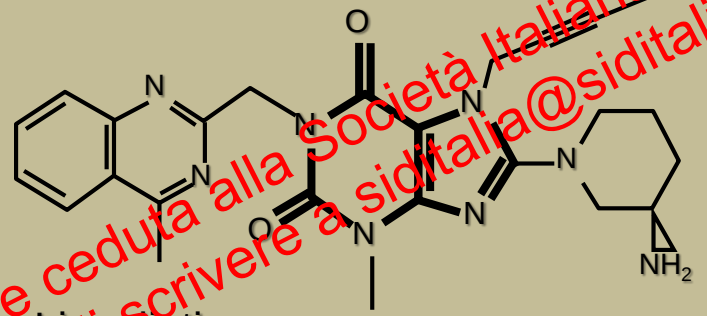
Saxagliptin



Vildagliptin

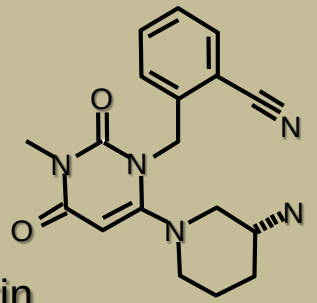
Peptidomimetic DPP-4 inhibitors

DPP-4 inhibitors directly binding to the active site of the enzyme



Linagliptin

Xanthine-based structure

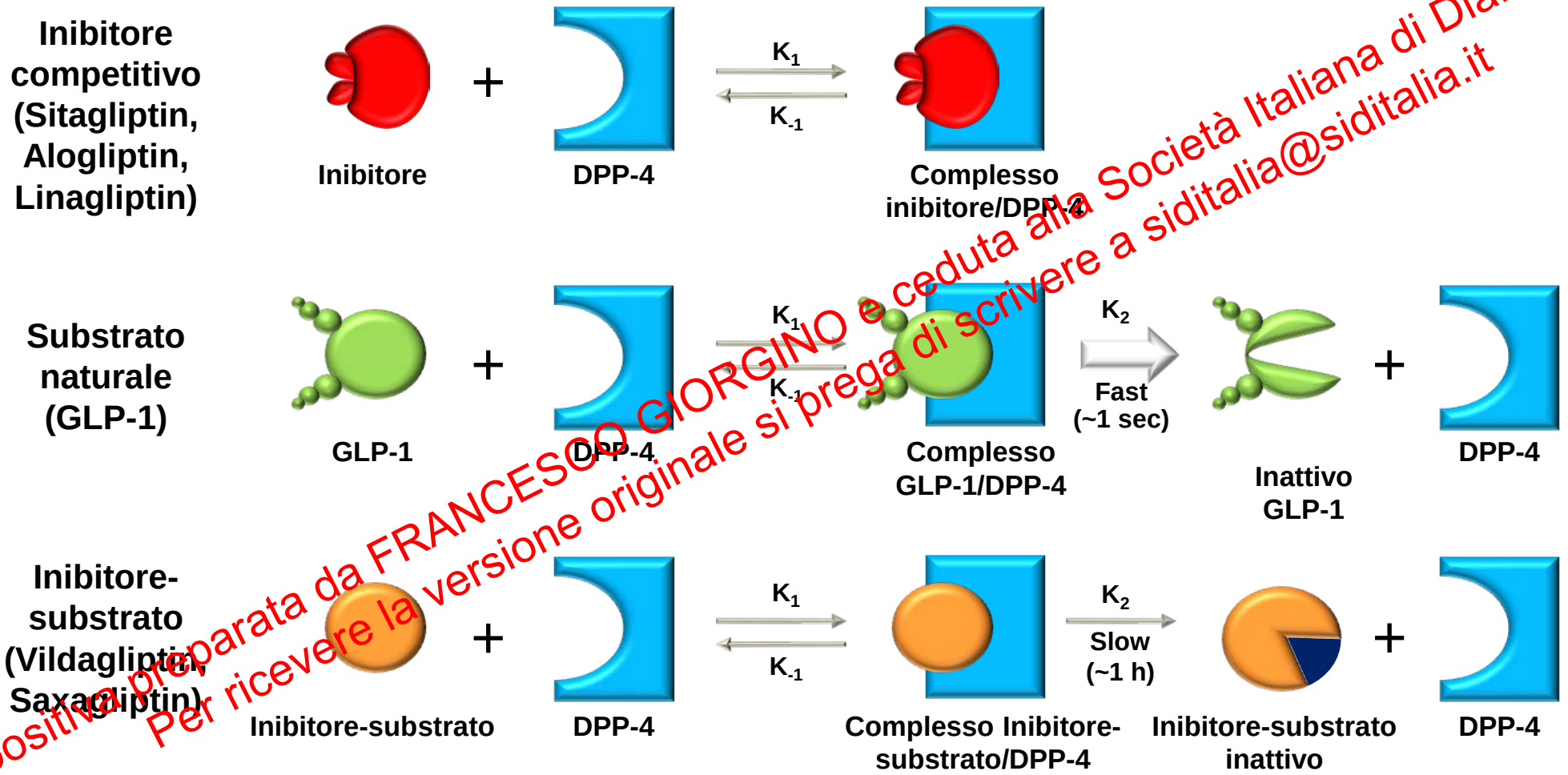


Alogliptin

Non-peptidomimetic DPP-4 inhibitors

Adapted from Deacon CF. *Diabetes Obes Metab*. 2011; 13: 7–18.

Cinetica di Legame con la DPP-4 e Meccanismo di Inibizione



DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1.

Burkey BF, et al. Poster 0788 presented at EASD 2006; Deacon CF, Holst JJ. *Adv Ther.* 2009; 26: 488–499;
Miller SA, St Onge EL. *Ann Pharmacother.* 2006; 40: 1336–1343; Neumiller JJ. *J Am Pharm Assoc.* 2009; 49: S16–S29;
White JR. *Clin Diabetes.* 2008; 26: 53–57.

DPP-4 Inhibitors: Selectivity for DPP-4 Compared to QPP*/DPP-2, DPP-8 and DPP-9

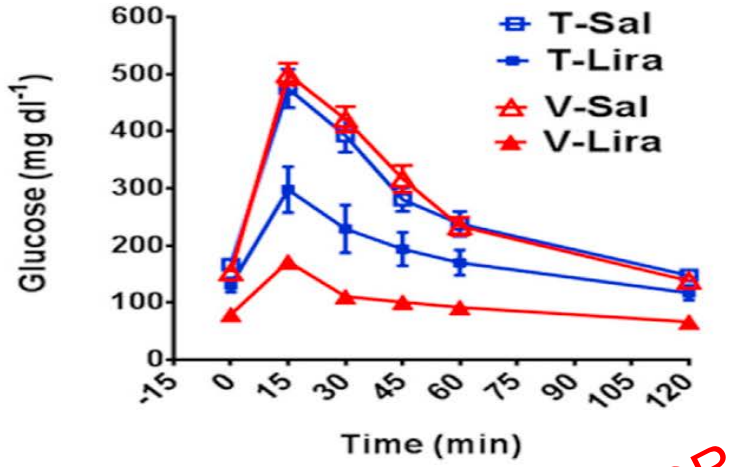
	QPP*/DPP-2	DPP-8	DPP-9
Linagliptin	> 100,000	40,000	> 10,000
Sitagliptin	> 5,500	> 2,660	> 5,500
Vildagliptin	> 100,000	270	32
Saxagliptin	> 50,000	390	77
Alogliptin	> 14,000	> 14,000	> 14,000

* Quiescent cell proline dipeptidase

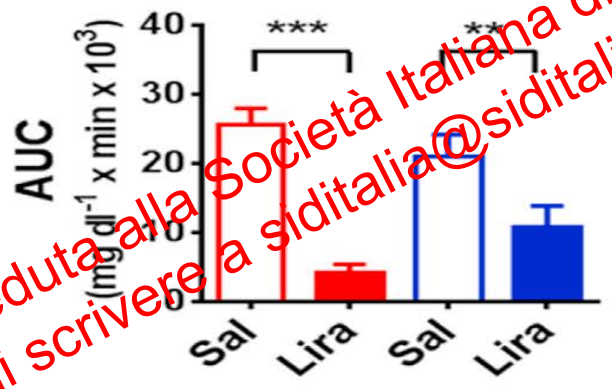
Modified from Deacon CF. *Diabetes, Obes Metab.* 2011;13(1):7–18.

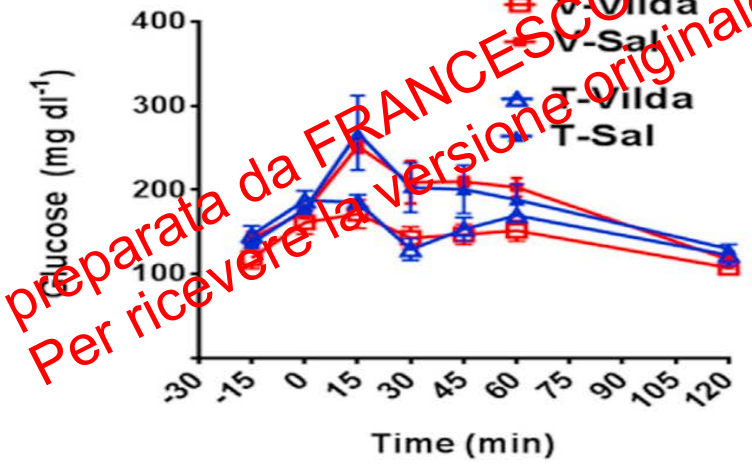
The Action of Long-Acting GLP-1 Agonists, but not DPP-4i, Are Impaired with Beta-Cell Knockdown of Glp1r

MIPcreER;Glp1rf/f mice

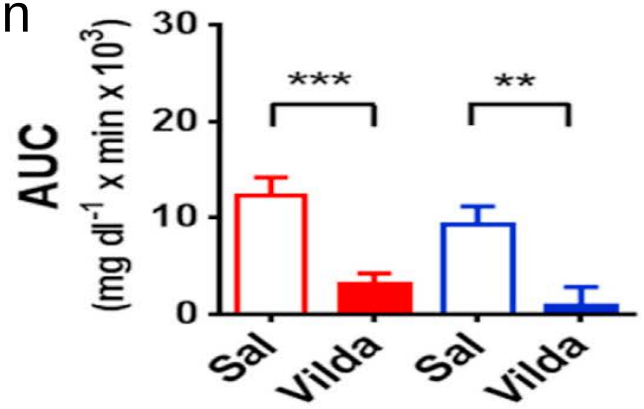


IPGTT
Liraglutide



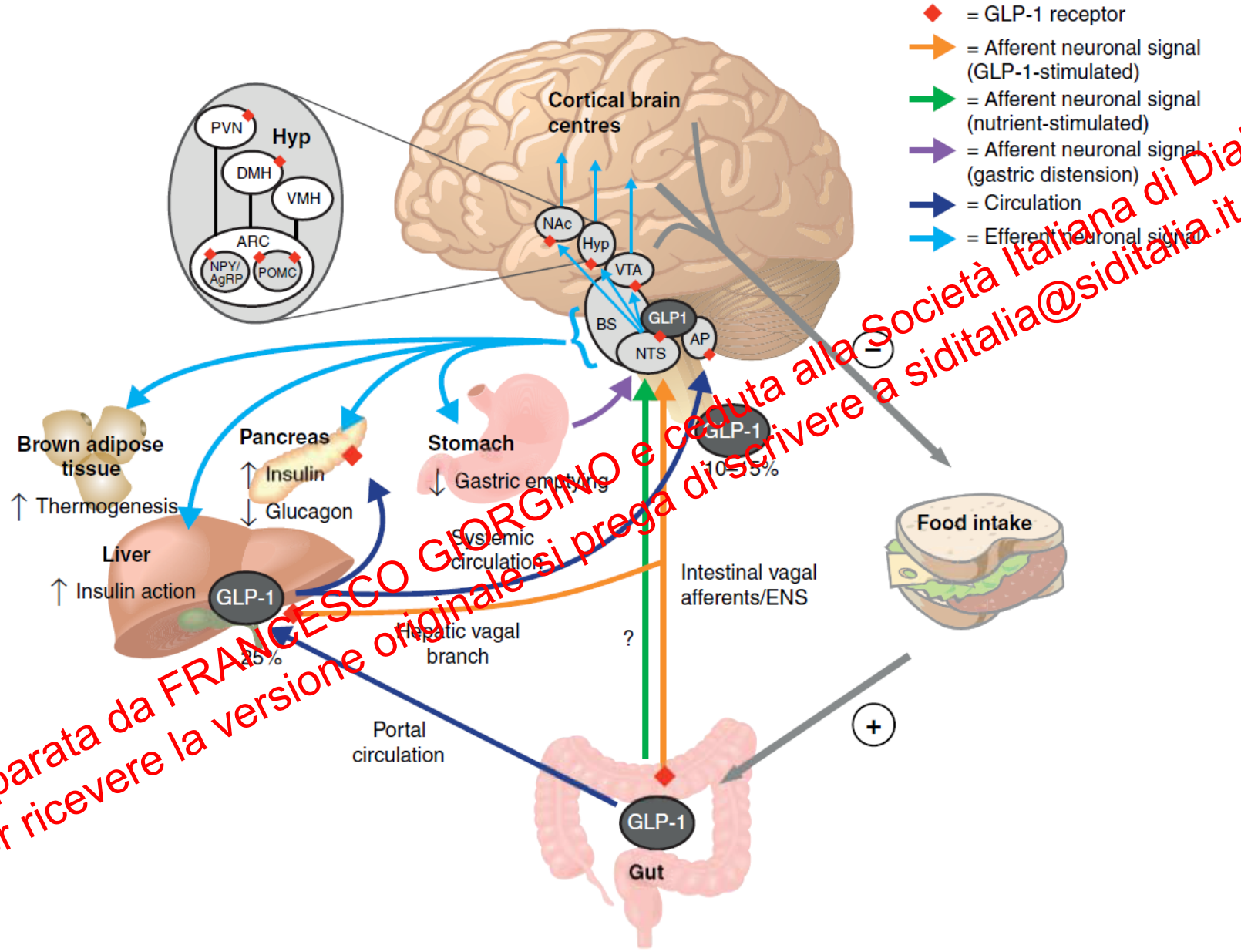


OGTT
Vildagliptin



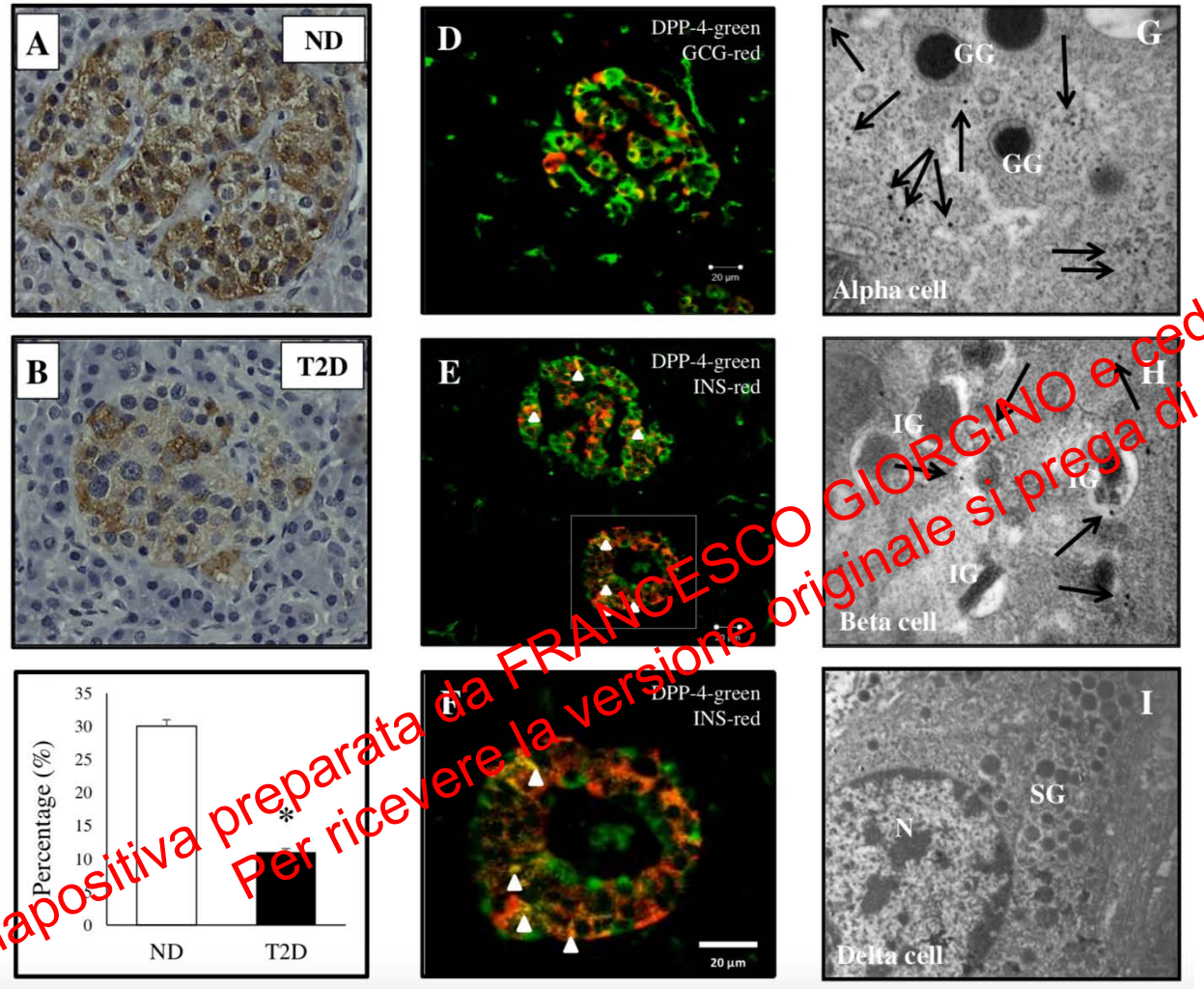
Beta-cell GLP-1 R knockdown: off on

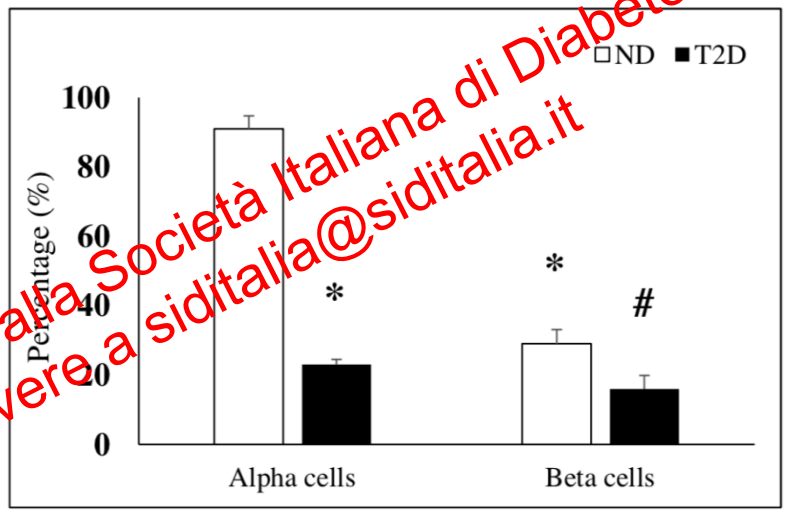
Smith EP et al, *Cell Metab* 2014

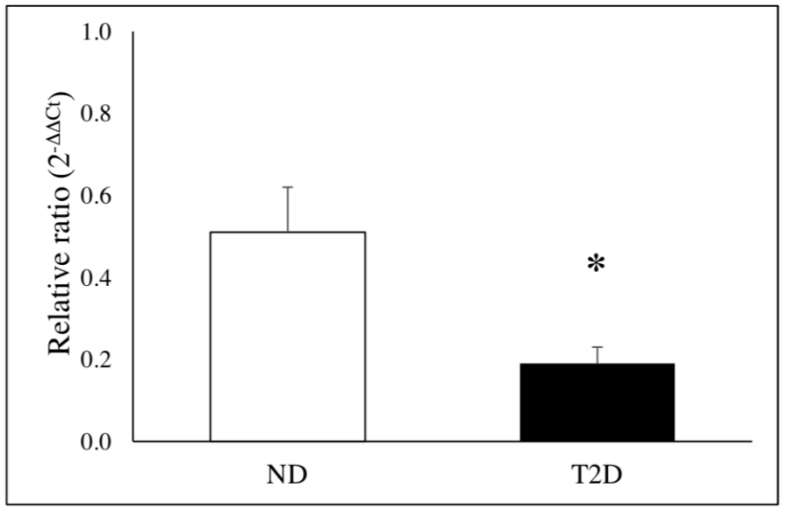


van Bloemendaal L et al, *J Endocrinol* 2014

DPP-4 is Expressed in Human Pancreatic Islets and Is Downregulated in Type 2 Diabetes

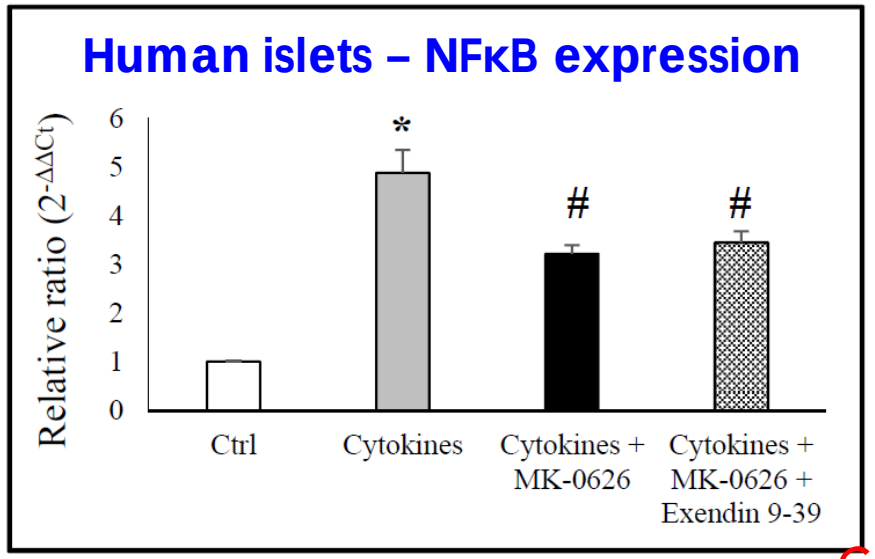


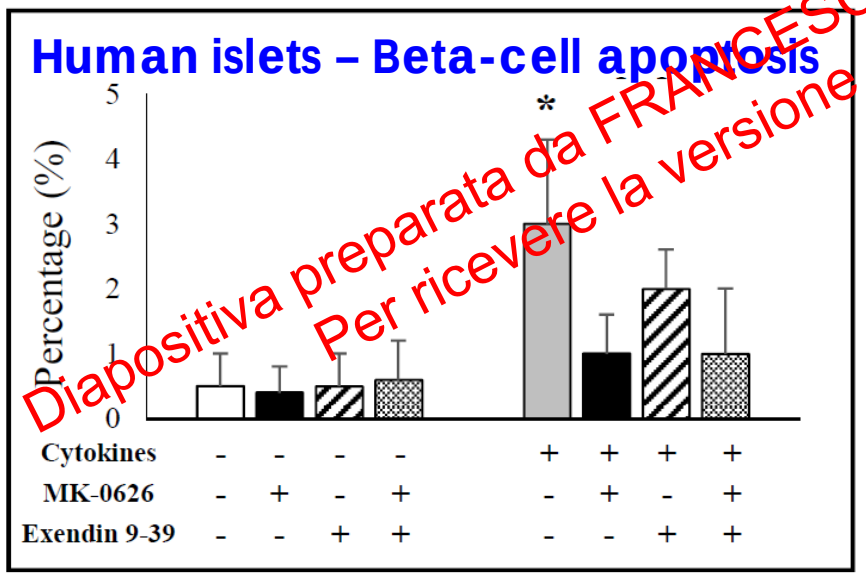


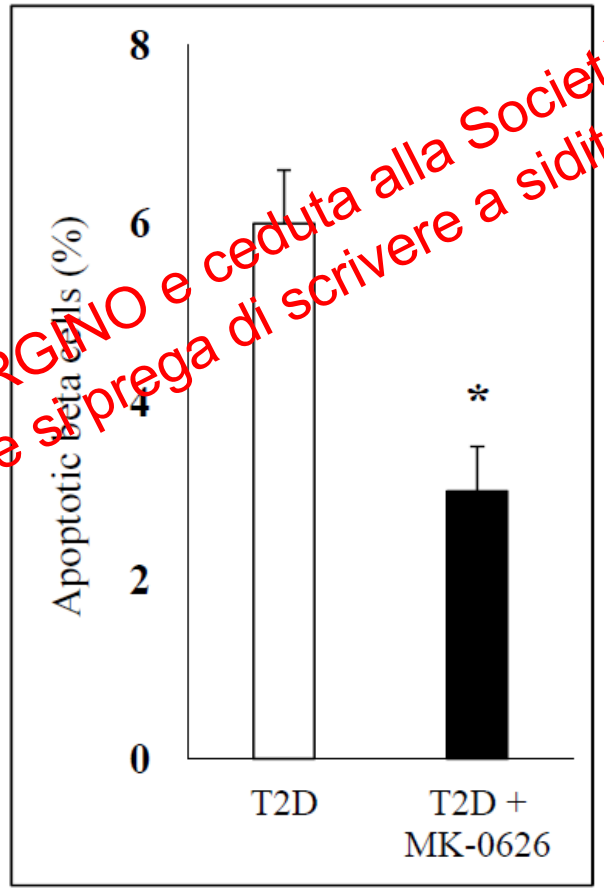


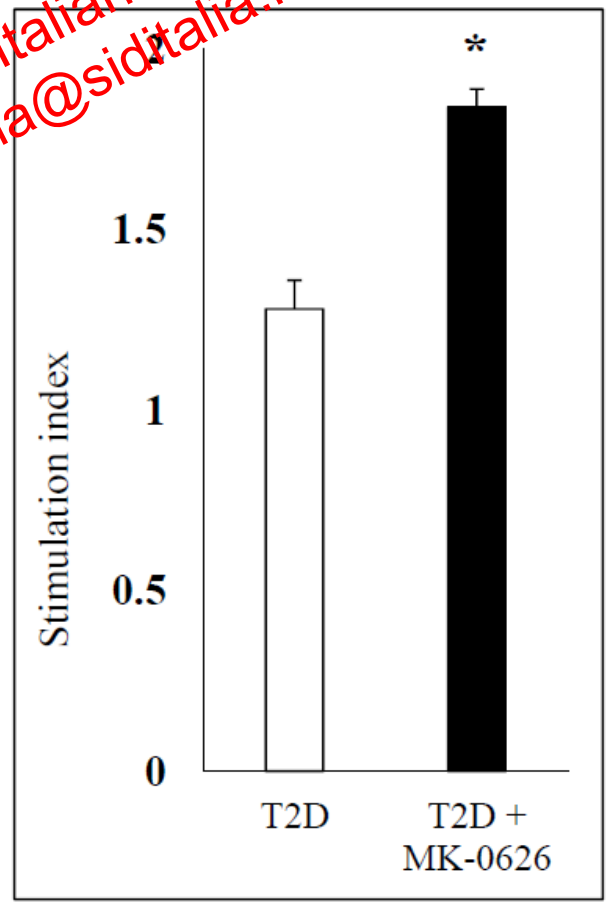
Bugliani M et al, *Mol Cell Endocrinol.* 2018

Direct Inhibition of DPP-4 in Human Pancreatic Islets Improves Beta-cell Function and Survival Independently of GLP-1



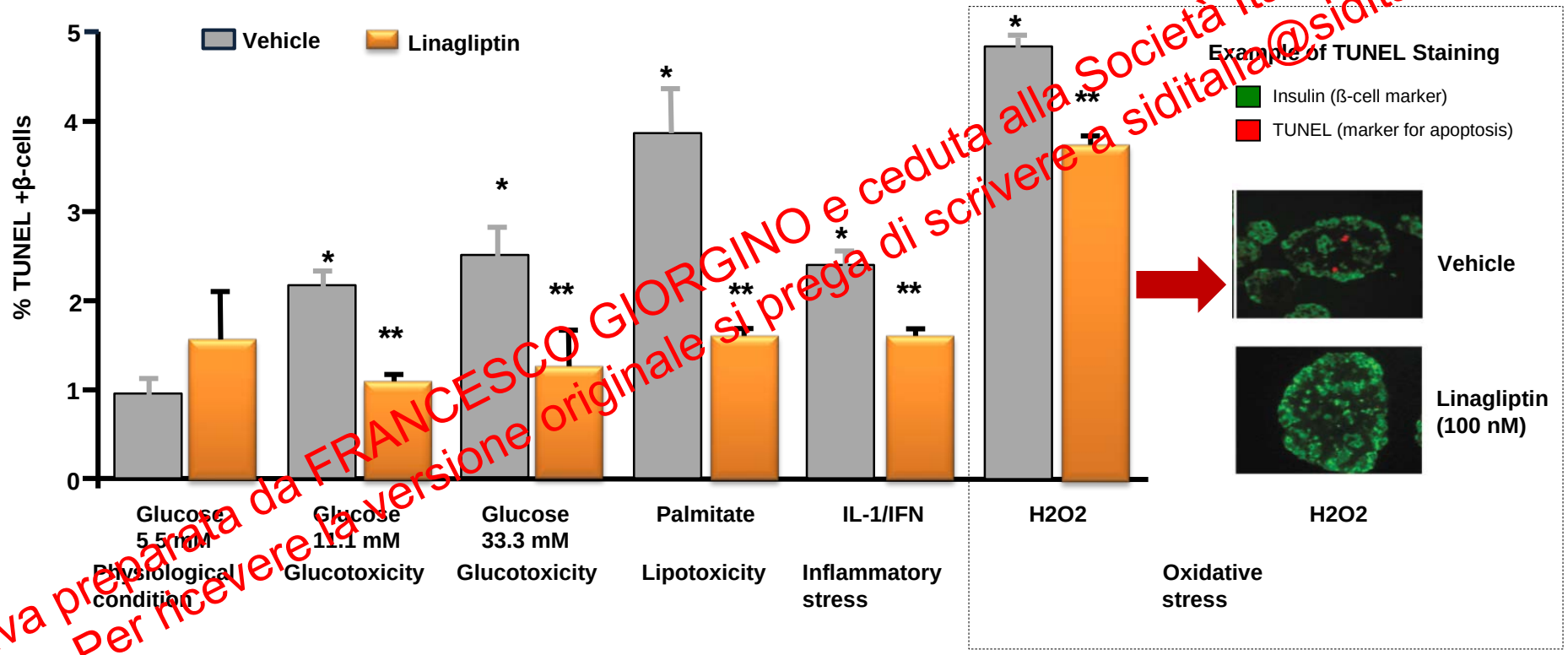






Bugliani M et al, *Mol Cell Endocrinol.* 2018

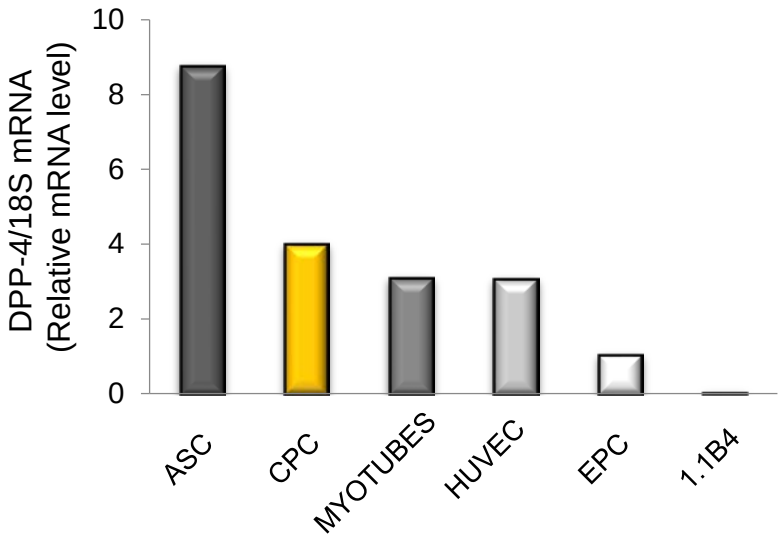
DPP-4 Inhibitors Restore ß-cell Survival in Isolated Human Islets

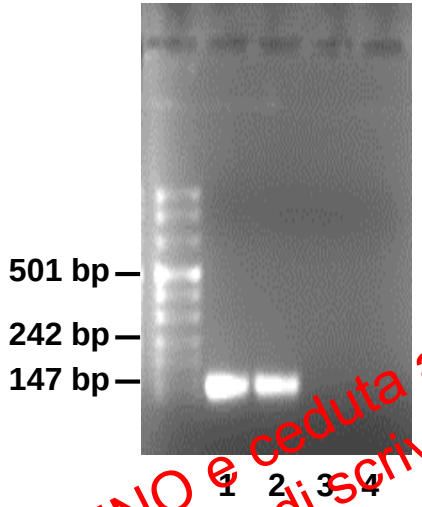


Note: Human isolated islets were exposed for 48 h. ß-cell apoptosis was analyzed by double labeling for the TUNEL assay and insulin. Results are means from 3 independent experiments from 3 donors *P<0.05 to 5.5 mM glucose alone, **P<0.05 to vehicle

Shah P et al., *JCEM* 2013

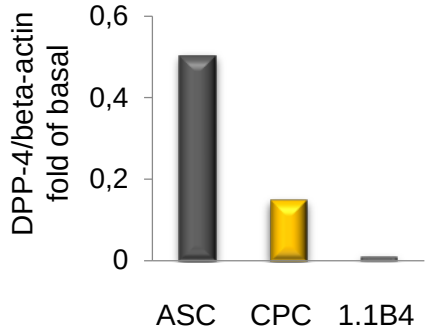
DPP-4 Expression in Human CPC

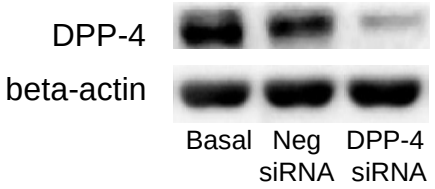


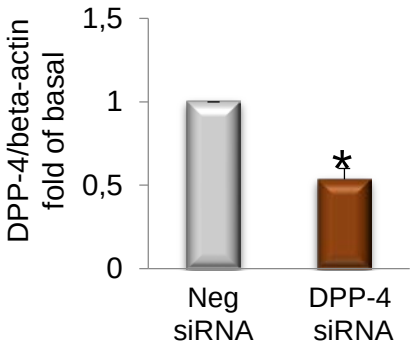


1. Human Adipose Stem Cells (ASC)
2. Human Cardiac Progenitor Cells (CPC)
3. Human Pancreatic Beta Cells (1.1B4)
4. BLANK

IF: DPP-4 CPC



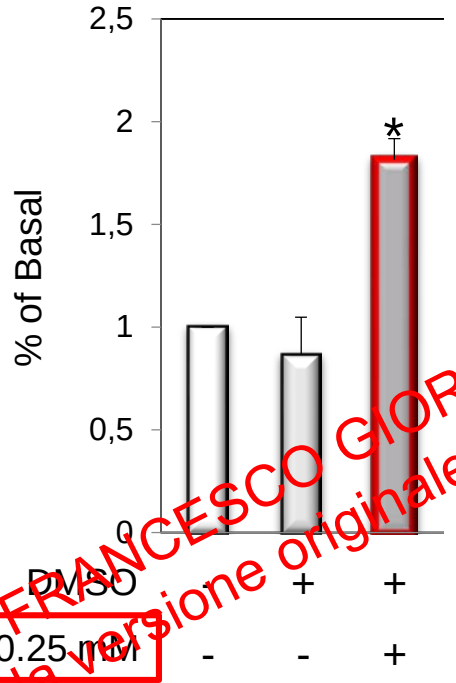




*p<0.01 DPP-4 siRNA vs Neg siRNA

Alogliptin, Alone or in Combination with Pioglitazone, Reduces Palmitate-Induced Apoptosis in Human CPC Isolated from Control Subjects

ELISA assay for cytoplasmic oligonucleosomes

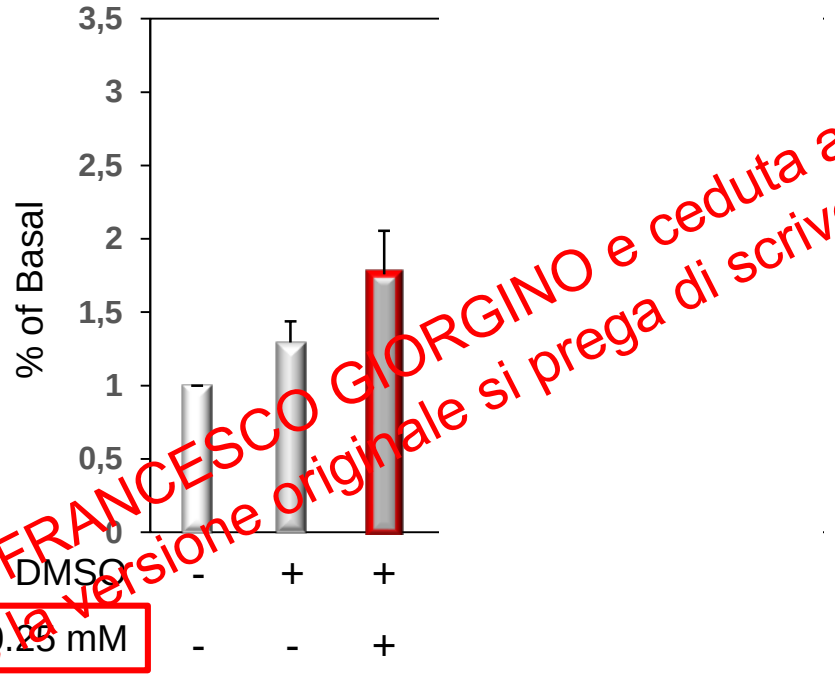


* p < 0.05 vs basal

#, p<0.05 vs palmitate

Alogliptin and Pioglitazone, Alone or in Combination, do not Reduce Palmitate-Induced Apoptosis in Human CPC Isolated from Type 2 Diabetic Patients

ELISA assay for cytoplasmic oligonucleosomes



n=2

Pharmacology of Current DPP-4 Inhibitors

Inhibitor	Chemistry	Metabolism	Elimination route	Compound $t_{1/2}$ (h)	Dosing
Sitagliptin	β-amino acid-based	Not appreciably metabolised	Renal (~80% unchanged as parent)	8–24	100mg qd
Vildagliptin	Cyanopyrrolidine	Hydrolysed to inactive metabolite (P450 enzyme independent)	Renal (22% as parent, 55% as primary metabolite)	11/2–41/2	50mg bid
Saxagliptin	Cyanopyrrolidine	Hepatically metabolised to active metabolite (via P450 3A4/5)	Renal (12–29% as parent, 21–52% as metabolite)	2–4 (parent) 3–7 (metabolite)	5mg qd
Linagliptin	Xanthine-based	Not appreciably metabolised	Biliary (>70% unchanged as parent); <6% via kidney	10–40	5mg qd
Alogliptin	Modified pyrimidinedion	Not appreciably metabolised	Renal (>70% unchanged as parent)	12–21	25mg qd

Deacon CF. *Diabetes Obes Metab* 2011;13:7–18

Pharmacological Characteristics of DPP-4 Inhibitors

		Linagliptin 5 mg QD	Sitagliptin 100 mg QD	Vildagliptin 50 mg bid	Saxagliptin 5 mg QD	Alogliptin 25 mg QD
Metabolism	Relevant organ for metabolism[1]	None	None	Liver	Liver	None
	Active metabolites	No	No	No	Yes	No
Excretion	Primary route of excretion	Bile & gut	Kidney	Kidney	Kidney	Kidney
	Share of renal excretion[2]	5%	87%	85%	75%	60 - 71%
Dosing and monitoring	Dose adjustment or limitations in RI[3]	No	Yes	Yes	Yes	Yes
	Drug-related monitoring	No	Kidney function	Kidney and liver function	Kidney function	Kidney function

1- If metabolized to a relevant degree
2- Including metabolites and unchanged drug; excretion after single dose administration of C14 labeled drug
3- As recommended in countries, where respective DPP-4 inhibitor is available

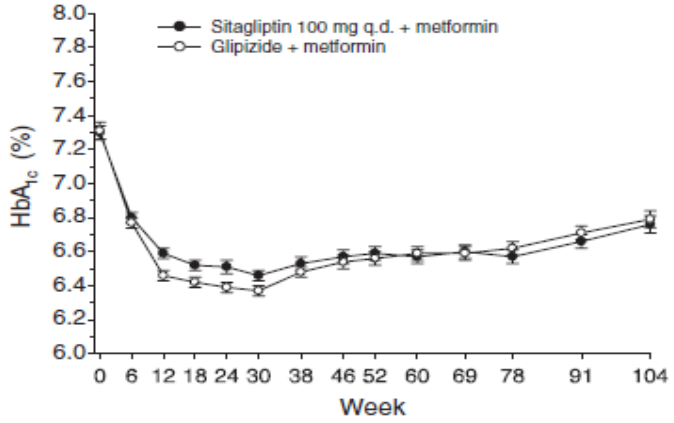
Linagliptin US PI; Saxagliptin US PI; Scheen AJ. *Diabetes Obes Metab*. 2010;12: 648–658; Deacon CF. *Diabetes Obes Metab*. 2011; 13: 7–18; Vincent et al. 2007, *Drug Metab Dispos* 35:533–538; He et al. 2009, *Drug Metab Dispos* 37:536–544; Christopher R et al. 2008 *Clin Ther* 30:513–527.

Comparison of DPP-4 Inhibitor Long-term Studies vs SU (Add-on to Metformin)

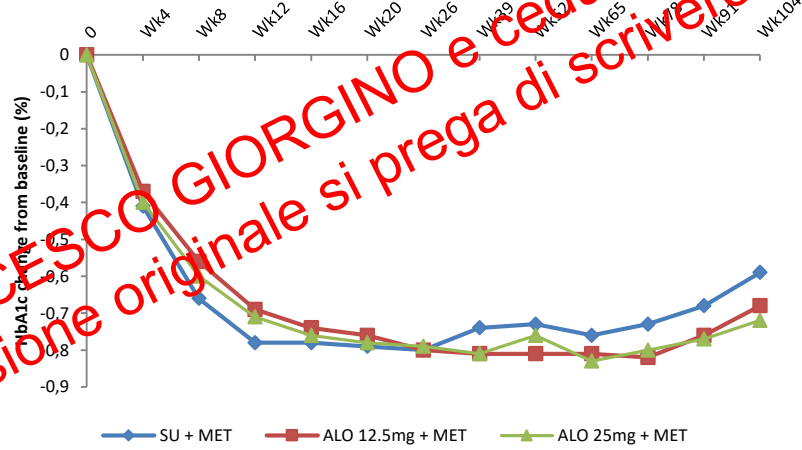
	Alogliptin* 25mg	Sitagliptin[1]* 100mg	Saxagliptin[2]** 5mg	Linagliptin[3]* 5mg	Vildagliptin[4]* 50mg bid
Study duration	104-week	104-week	104-week	104-week	104-week
Add-on to	Metformin	Metformin	Metformin	Metformin	Metformin
Comparator	Glipizide	Glipizide	Glipizide	Glimepiride	Glimepiride
Average SU dose	5.2mg	9.2mg	15mg	3.0mg	4.6mg
Baseline HbA1c (%)	7.59-7.61	7.30-7.31	7.7	7.69	7.3
HbA1c reduction (%)					
DPP-4 inhibitor	-0.72*	-0.54*	-0.41**	-0.35*	-0.1*
SU	-0.59*	-0.51*	-0.35**	-0.53*	-0.1*
	Superior	Non-inferior	Non-inferior	Non-inferior	Non-inferior
% achieving HbA1c <7%					
DPP-4 inhibitor	48.5**	63*	23.1 †	30**	36.9*
SU	42.7**	59*	22.7 †	35 **	38.3*

1. Seck T et al. *Int J Clin Pract.* 2010;**64**:562–576; 2. Göke B et al. *Int J Clin Pract*. 2013;**67**:307–316; 3. Gallwitz B et al. *Lancet* 2012;**380**:475–483; 4. Matthews D et al. *Diabetes Obesity Metabol.* 2013;**12**:780–789.

HbA1c over Time vs SU as Add-on to Metformin

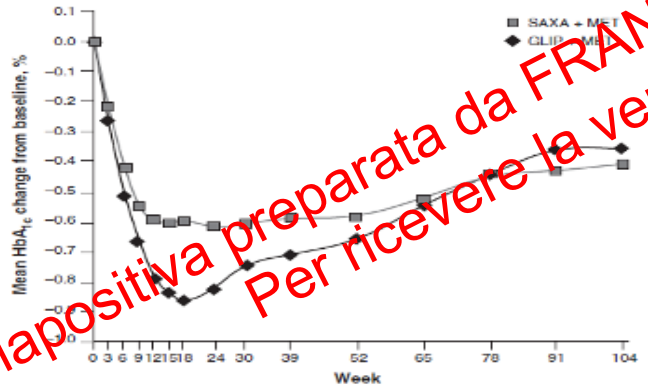


Sitagliptin vs glipizide[2]

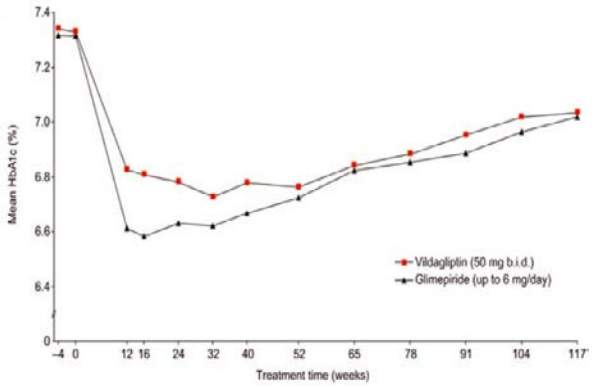


Alogliptin vs glipizide[1]

Linagliptin vs glimepiride[4]



Saxagliptin vs glipizide[3]



Vildagliptin vs glimepiride[5]

1. Del Prato S, et al. ADA 2013 Poster 66-LB. 2. Seck T et al. *Int J Clin Pract.* 2010;**64**:562–576; 3. Göke B et al. *Int J Clin Pract*. 2013;**67**:307–316. 4. Gallwitz B et al. *Lancet*. 2012;**380**:475–483. 5. Matthews D et al. *Diabetes Obesity Metabol*. 2013;**12**:780–789.

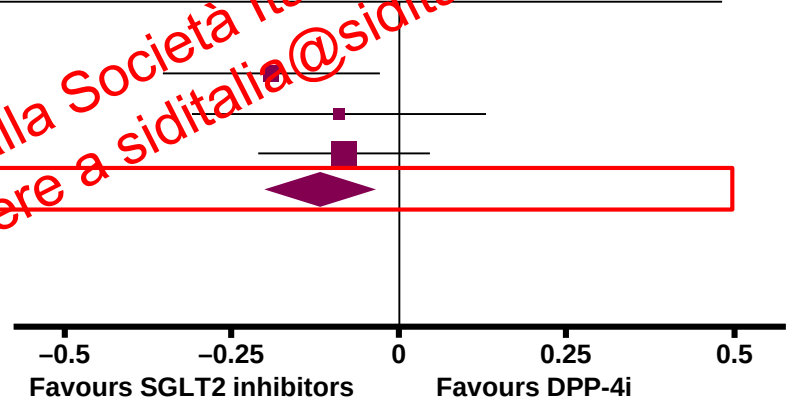
SGLT2 inhibitors provide larger reductions in HbA_{1c} and body weight at 52 weeks vs. DPP-4 inhibitors in patients with T2DM

HbA1c

Study or subgroup	SGLT2 inhibitors Mean	SD	Total	DPP-4i Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Change in HbA_{1c} at ≥52 weeks								
DeFronzo R	–0.67	0.7	277	–0.48	0.8	128	29.8%	–0.19 [–0.35, –0.03]
Ferrannini E	–0.49	0.85	332	–0.4	0.76	56	16.2%	–0.09 [–0.31, 0.13]
Lavalle-Gonzalez FJ	–0.81	0.95	725	–0.73	0.94	354	54.0%	–0.08 [–0.20, 0.04]
Subtotal (95% CI)			1334			538	100.0%	–0.11 [–0.20, –0.03]

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.21$, df = 2 (P=0.55); $I^2 = 0\%$

Test for overall effect: Z = 2.55 (P=0.01)

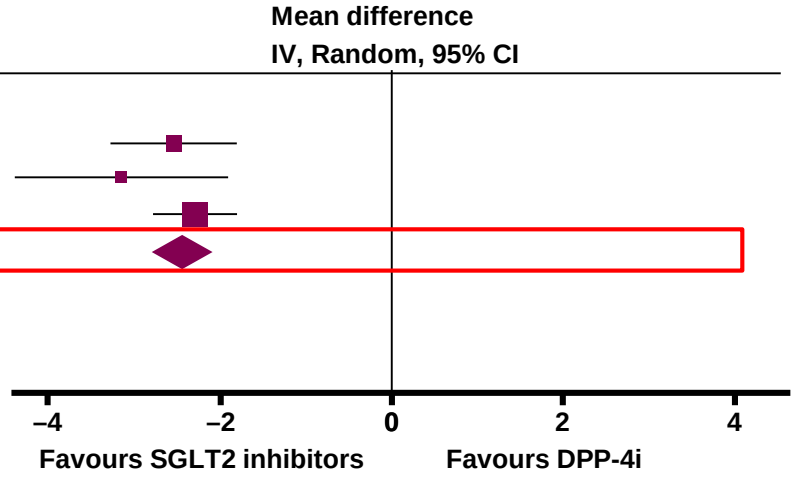


Body weight

Study or subgroup	SGLT2 inhibitors Mean	SD	Total	DPP-4i Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Change in body weight at ≥52 weeks								
Defronzo R	–2.85	3.84	277	–0.3	3.4	128	26.6%	–2.55 [–3.29, –1.81]
Ferrannini E	–3.55	4.92	332	–0.4	4.2	56	9.8%	–3.15 [–4.37, –1.93]
Lavalle-Gonzalez FJ	–3.5	3.8	725	–1.2	3.77	355	63.6%	–2.30 [–2.78, –1.82]
Subtotal (95% CI)			1334			539	100.0%	–2.45 [–2.83, –2.07]

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.71$, df = 2 (P=0.43); $I^2 = 0\%$

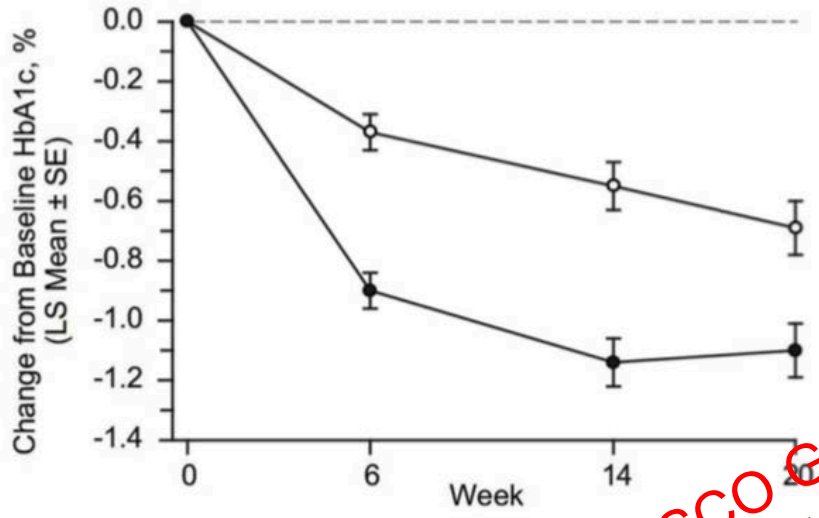
Test for overall effect: Z = 12.55 (P<0.00001)

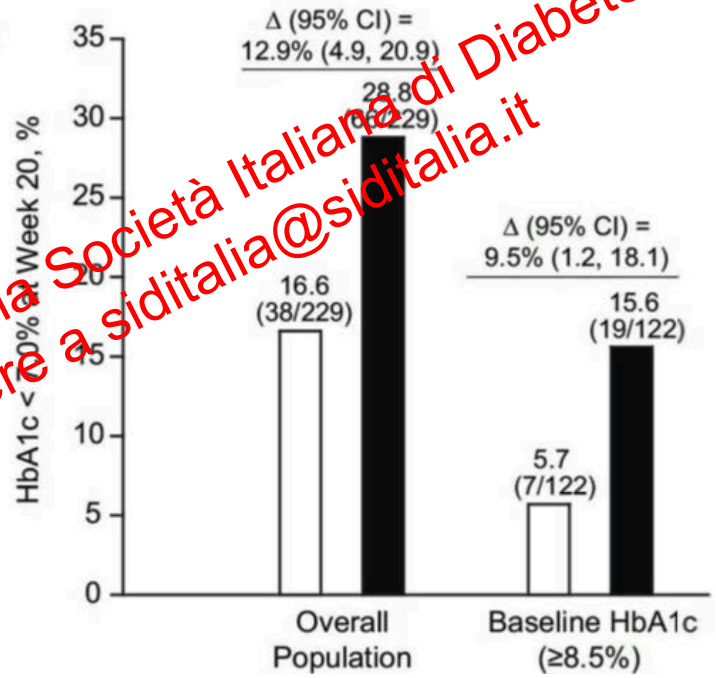


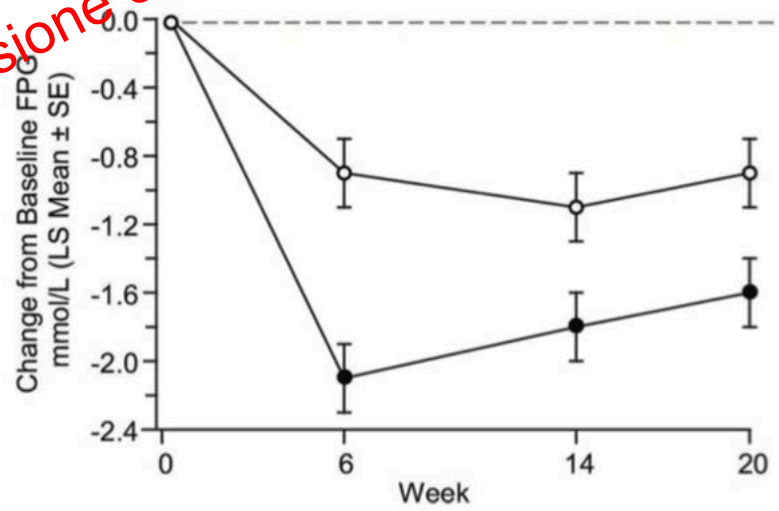
CI, confidence interval; DPP-4, dipeptidyl peptidase-4; HbA_{1c}, glycated haemoglobin; SD, standard deviation; SGLT2, sodium–glucose co-transporter 2; T2DM, Type 2 diabetes mellitus

Mishriky BM, et al. Diabetes Metab. 2018 Mar;44(2):112-120

CompoSITE-M: Efficacy and Safety of Early Initiation of Sitagliptin during Metformin Uptitration in T2D Patients

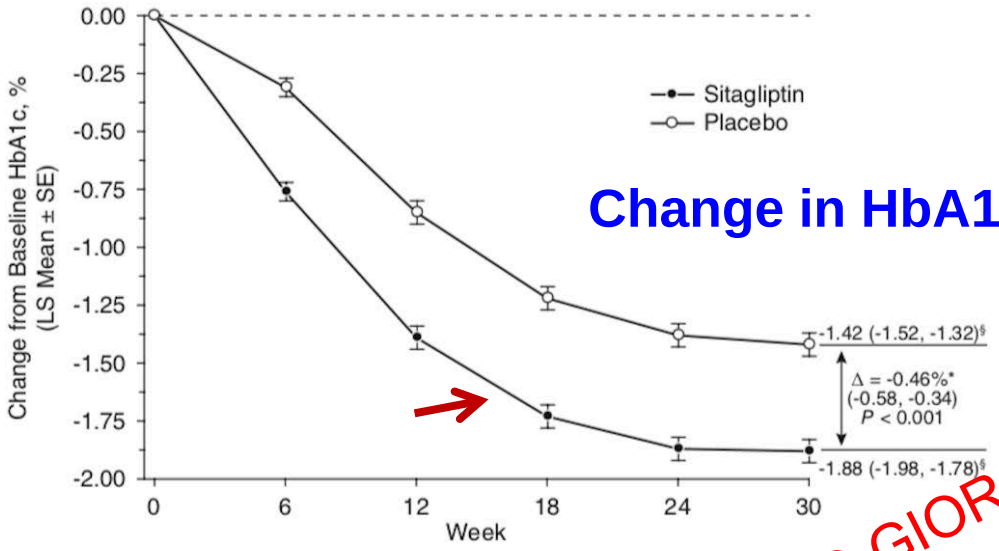




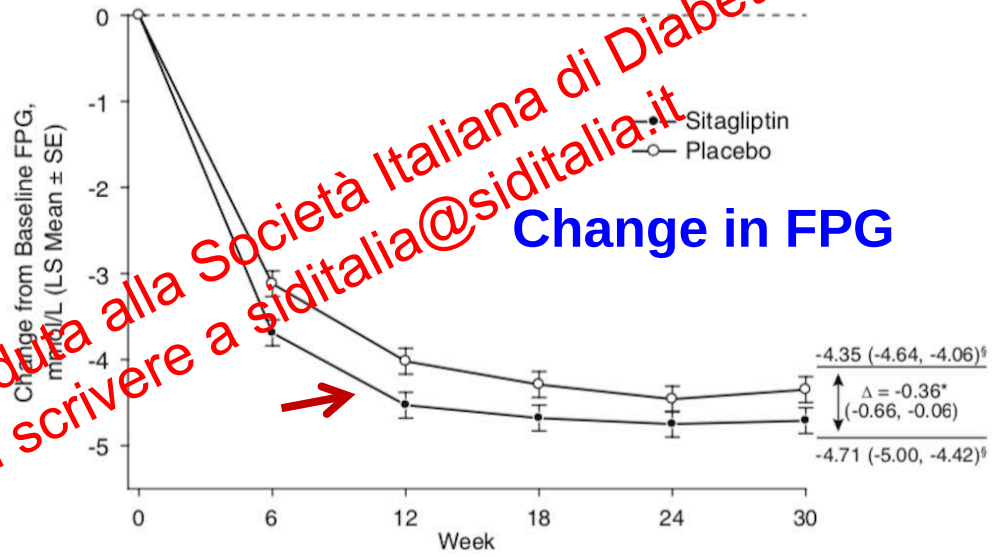


Frias JP et al, *Diabetes Obes Metab* 2019

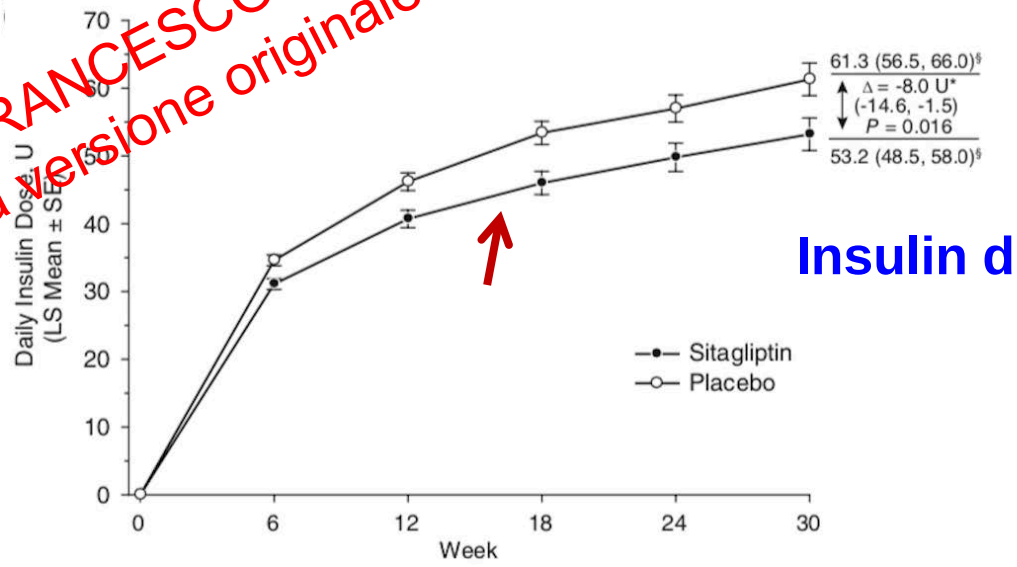
CompoSITE-I: Efficacy and Safety of Continuing or Discontinuing Sitagliptin When Initiating Insulin Glargine Therapy in Patients with T2D



Change in HbA1c



Change in FPG



Insulin dose

Roussel R et al, *Diabetes Obes Metab* 2018

DPP-4 Inhibitors: Safety and Tolerability Issues

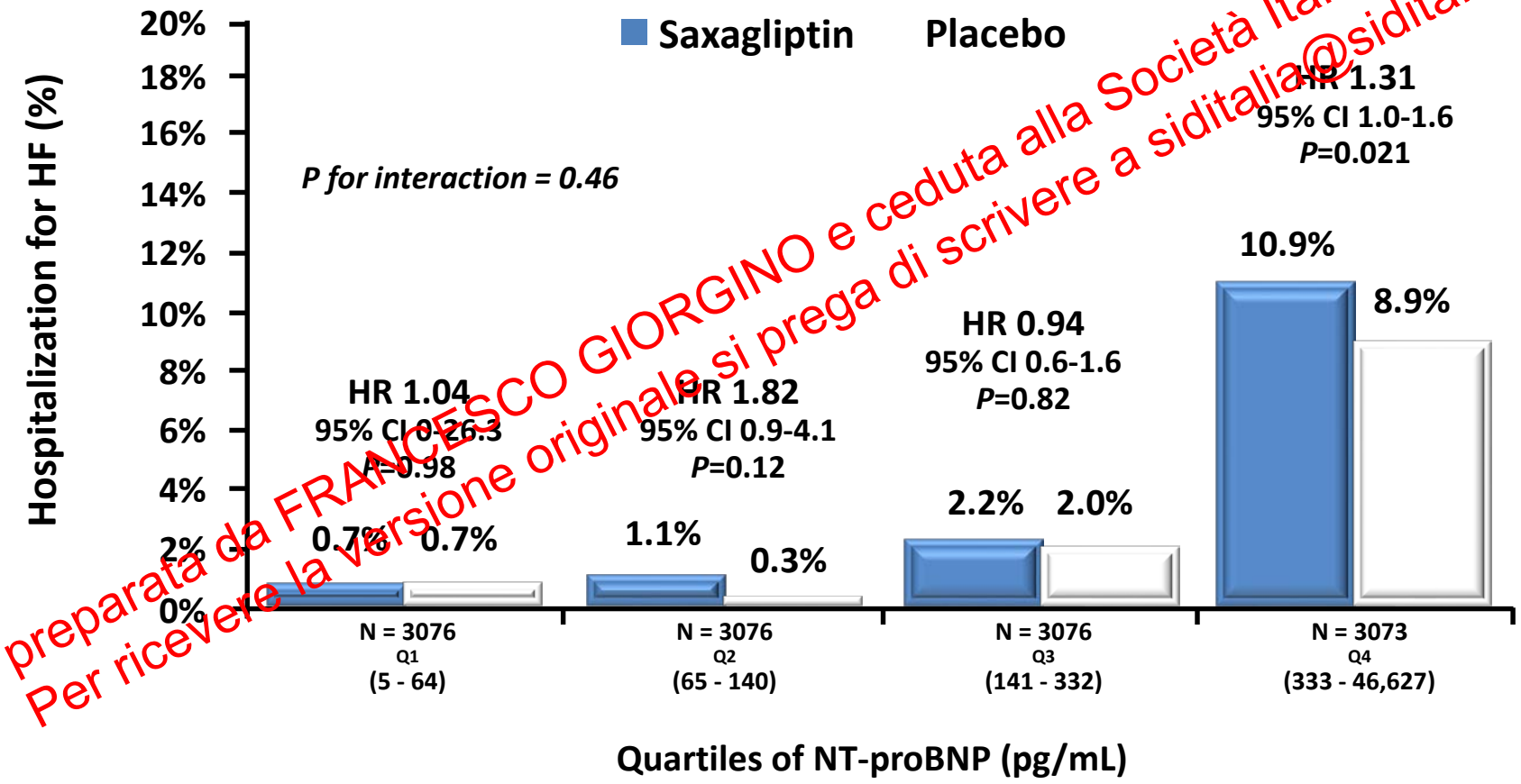
- Low risk of hypoglycemia
- Weight neutral
- Potential risk of heart failure (saxagliptin, alogliptin?)
- Dose adjustment in CKD (sitagliptin, saxagliptin, vildaglitpin, alogliptin)
- Potential risk of acute pancreatitis
- Joint pain

SAVOR-TIMI: CV Outcomes

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

Scirica BM et al., NEJM, 2013

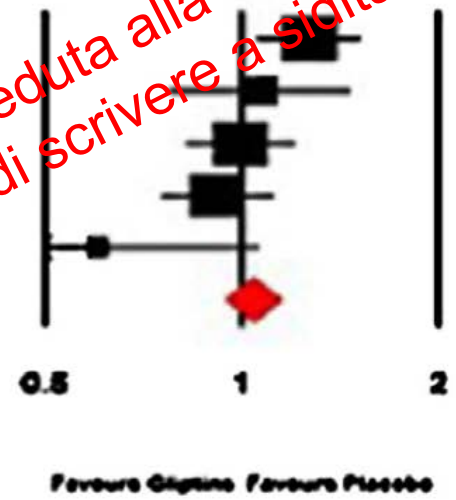
Risk of Hospitalization for HF According to Baseline NT-proBNP



Scirica BM, et al. American Heart Association Scientific Sessions. November 2013.

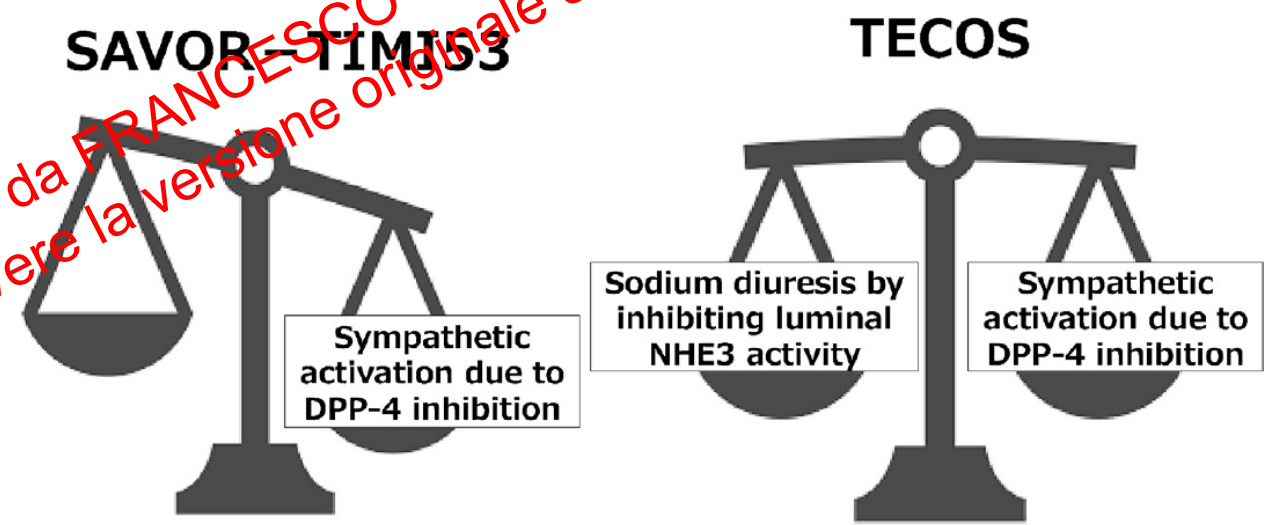
Risk of Hospitalization for HF
In DPP-4i CVOT

Study name	MH odds ratio	Lower limit	Upper limit	p-Value
SAVOR-TIMI 53	1.266	1.062	1.511	0.009
EXAMINE	1.069	0.783	1.460	0.673
TECOS	0.996	0.827	1.201	0.970
CARMELINA	0.917	0.755	1.114	0.385
OMARIGLIPTIN	0.605	0.348	1.057	0.078
	1.043	0.945	1.152	0.405



Sinha B, *Diabetes Res Clin Pract* 2019

DPP-4 inhibitor	Urinary excretion rate of the unchanged drug (%)	Hazard ratio or odds ratio for hospitalization or adverse events due to heart failure
Sitagliptin	80	TECOS (n=14,671) — **1.00** (0.83-1.20)
Alogliptin	70	EXAMINE (n=5,380) — **1.07** (0.79-1.46)
Saxagliptin	12-29	SAVOR (n=16,492) — **1.27** (1.06-1.51)
Vildagliptin	22	VIVIDD (n=252) — **1.31** (0.55-3.12)
Linagliptin	6	Pooled (n=8,778) — **1.88** (0.85-4.17)



All DPP-4 inhibitors tend to exacerbate heart failure through sympathetic activation. Sitagliptin and alogliptin do not increase the risk of heart failure because these drugs are mainly excreted in the urine and suppress renal NHE3 activity to promote sodium diuresis, while saxagliptin shows low urinary excretion and may increase the risk of heart failure.

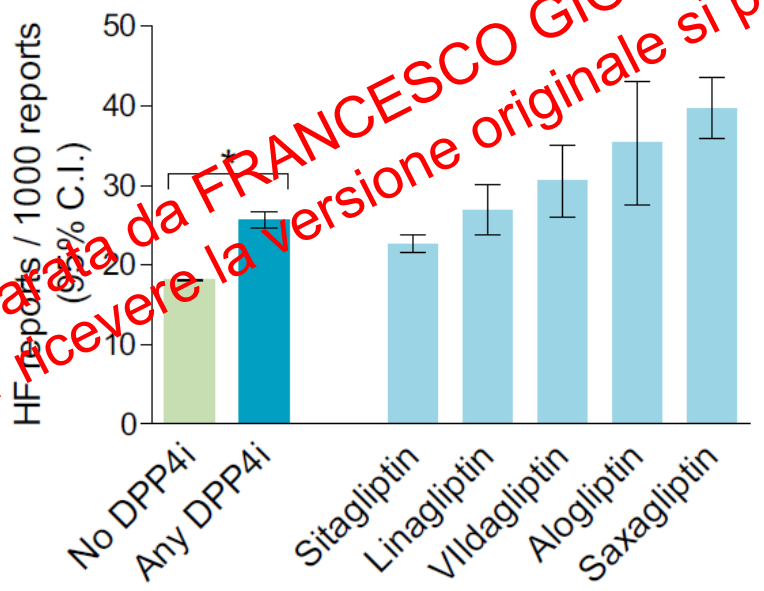
Sano M, *J Cardiol* 2018

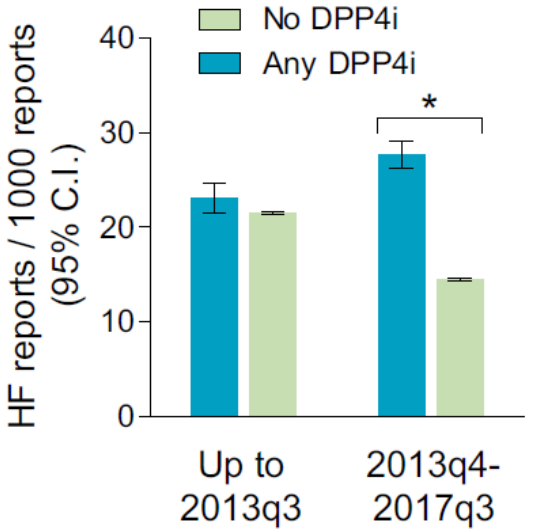
Diabetes Ther (2018) 9:851–861
https://doi.org/10.1007/s13300-018-0408-2

ORIGINAL RESEARCH

Pharmacovigilance Evaluation of the Association Between DPP-4 Inhibitors and Heart Failure: Stimulated Reporting and Moderation by Drug Interactions

Gian Paolo Fadini · Mayur Sarangdhar · Angelo Avogaro





DPP4i and Risk of Hospitalization for HF

Table 4. Effects of DPP-4is on the risk of heart failure or hospitalization for heart failure.

References	Type, country	Comparator	Criterion	Patients (n)	Events (N)	OR or HR	95% CI	*P*-value
Meta-analyses of RCTs								
Abbas et al 2016 [27]	2 CVOTs	Placebo	hHF	36,543	3334	1.12	1.00–1.25	0.05
McGuire et al 2016 [95]	(EXAMINE, SAVOR-TIMI 53, TECOS)							
Li et al 2016 [103]	36 RCTs	Placebo/active	HF	28,292	75	0.97	0.61–1.56	NS
Li et al 2016 [103]	5 RCTs (including 3 CVOTs)	Placebo	hHF	37,028	1144	1.13	1.00–1.26	0.05
Rehman et al 2017 [28]	36 RCTs	Placebo	HF	54,664	NA	1.13	1.01–1.26	NA
Elgendy et al 2017 [76]	90 RCTs (including 3 CVOTs)	Placebo	HF	66,736	1163	1.11	0.99–1.25	0.07
Kongwatcharapong et al 2016 [104]	54 RCTs	Placebo/active	HF	34,737	1361	1.106	0.995–1.228	0.062
Kongwatcharapong et al 2016 [104]	9 RCTs with saxagliptin	Placebo/active	HF	21,708	NA	1.215	1.028–1.437	0.022
Verma et al 2017 [105]	29 RCTs + 3 CVOTs	Placebo/active	HF	54,640	1244	1.13	1.01–1.26	0.03
Observational studies DPP-4i versus active comparator								
Wang et al 2014 [106]	Cohort with sitagliptin (Taiwan)	Active antidiabetic agents	hHF	16,576	614	1.21	1.04–1.42	0.017
Eurich et al 2016 [107]	Case-control with sitagliptin (US)	Active antidiabetic agents	HF	5027	457	0.75	0.38–1.46	0.40
Chang et al 2016 [108]	Cohort, sitagliptin (Taiwan)	Acarbose	hHF	290,130	7885	1.03	0.98–1.08	NS
Ou et al 2015 [32]	Cohort, DPP-4is, Taiwan	Sulphonylurea	hHF	20,178	200	0.78	0.57–1.06	NS
Seong et al 2015 [83]	Cohort, DPP-4is (Korea)	Sulphonylurea	HF	328,283	199	0.93	0.62–1.41	NS
Fadini et al 2015 [109]	Cohort, DPP-4is (Italy)	Sulphonylurea	hHF	110.757	1596	0.78	0.62–0.97	0.026
Kim et al 2017 [110]	Cohort, DPP-4is (Korea)	Sulphonylurea	hHF	511,382	1251	0.78	0.67–0.86	< 0.001
Ekstrom et al 2016 [82]	Cohort, DPP-4is (Sweden)	Sulphonylurea	HF	10,923	444	0.54	0.38–0.76	< 0.05
Kannan et al 2016 [111]	Cohort, DPP-4is, US	Sulphonylurea	HF	10,906	NA	1.104	1.04–1.17	0.001
Fu et al 2016 [112]	Cohort, DPP-4is with CVD (US)	Sulphonylurea	hHF	54,518	402	0.95	0.78–1.15	0.580
Fu et al 2016 [112]	Cohort, DPP-4is without CVD (US)	Sulphonylurea	hHF	164,038	93	0.59	0.38–0.89	0.013
Gokhale et al 2017 [86]	Cohort, DPP-4is (US)	Sulphonylurea	hHF	98,512	NA	0.87	0.77–0.97	NA
Toh et al 2016 [113]	Cohort, sitagliptin, (US)	Sulphonylurea	hHF	642,529	NA	0.86	0.77–0.95	NA
Toh et al 2016 [113]	Cohort, saxagliptin, (US)	Sulphonylurea	hHF	510,904	NA	0.69	0.54–0.87	NA
Observational studies saxagliptin versus sitagliptin								
Toh et al 2016 [113]	Cohort, saxagliptin (US)	Sitagliptin	hHF	288,731	NA	0.83	0.70–0.99	NA
Fu et al 2016 [112]	Cohort, saxagliptin, patients with CVD (US)	Sitagliptin	hHF	26,084	169	0.95	0.70–1.28	0.712
Fu et al 2016 [112]	Cohort, saxagliptin, patients without CVD (US)	Sitagliptin	hHF	86,804	47	0.99	0.56–1.75	0.972
Chang et al 2016 [108]	Cohort, saxagliptin (Taiwan)	Sitagliptin	hHF	197,891	NA	0.98	0.91–1.06	NS
Fadini et al 2017 [114]	Cohort, saxagliptin (Italy)	Sitagliptin	hHF	12,856	106	1.04	0.55–1.95	NS

CVD: cardiovascular disease. HF: heart failure. hHF: hospitalization for heart failure. RCTs: randomized controlled trials. OR: odds ratio. HR: hazard ratio. CI: confidence interval. CVOTs: cardiovascular outcome trials. NS: nonsignificant. NA: not available.

Scheen AJ, *Expert Opinion on Drug Safety* 2018

SCIENTIFIC REPORTS

OPEN

Dipeptidyl peptidase-4 inhibitors, pancreatic cancer and acute pancreatitis: A meta-analysis with trial sequential analysis

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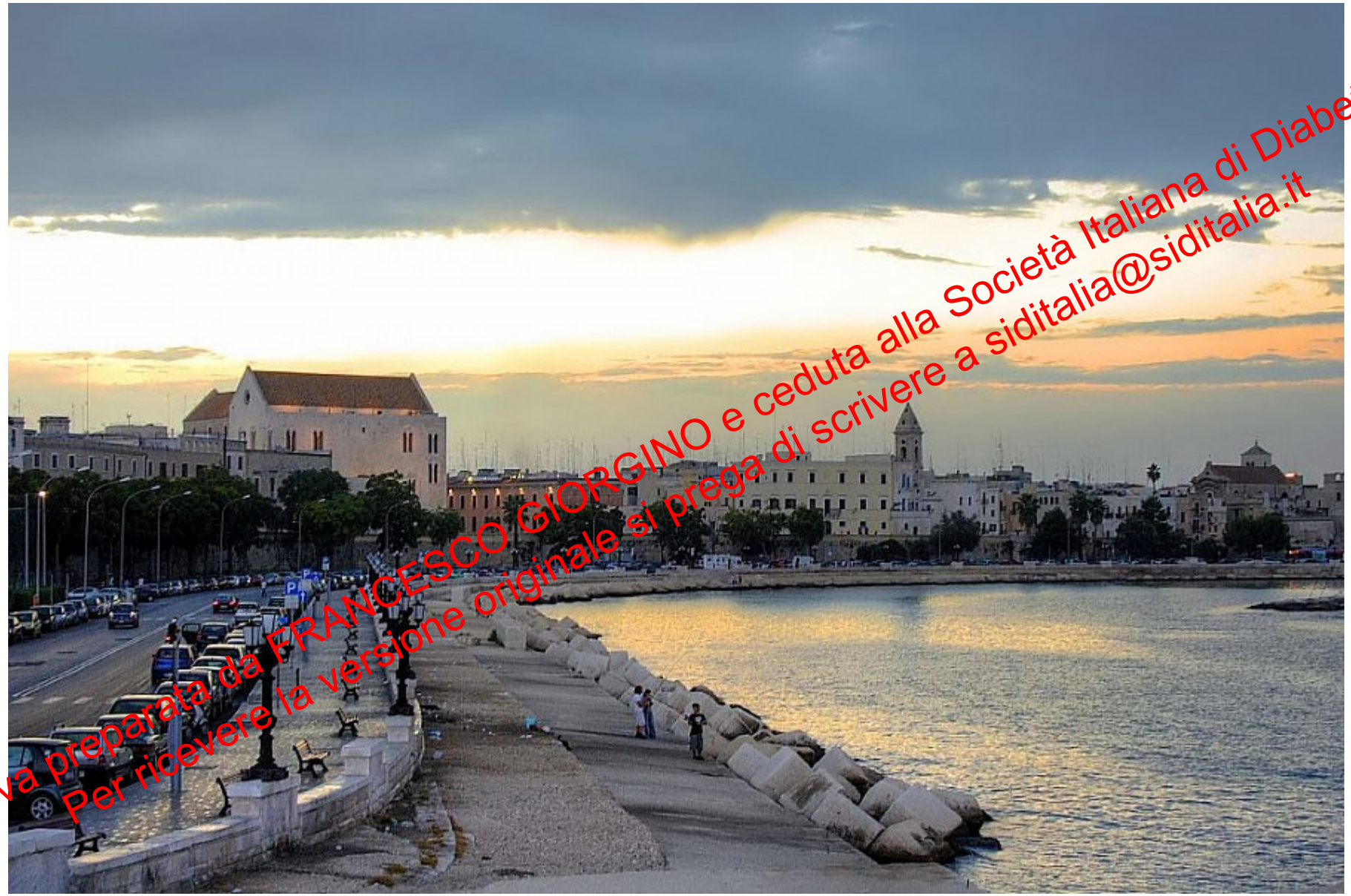
Lana C. Pinto, Dimitris V. Rados, Sabrina G. Barkan, Cristiane B. Leitão & Jorge L. Gross

There was no relationship between the use of DPP-4 inhibitors and pancreatic cancer (Peto odds ratio 0.65; 95% CI 0.35–1.21), and the optimal sample size was reached to determine a number needed to harm (NNH) of 1000 patients.

DPP-4 inhibitors were associated with increased risk for acute pancreatitis (Peto odds ratio 1.72; 95% CI 1.18–2.53), with an NNH of 1066 patients, but the optimal sample size for this outcome was not reached. In conclusion, there is no association between DPP-4 inhibitors and pancreatic cancer, and a small risk for acute pancreatitis was observed with DPP-4 inhibitor use, although the latter finding is not definitive.



Bari – Seafront and Old Town