Inibitori DPPIV: meccanismo d'azione, efficacia e tollerabilità

MASSIMO FEDERICI

DISCLOSURE

- Il Prof. Massimo Federici dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Merck Sharpe Dohme
- SANOFI
- Boerhringer Ingelheim
- Lilly
- Janssen
- Ogilvy

- *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.).*

TABLE 1 Commonly used classes of non-insulin anti-hyperglycaemic agents

Diabetes Obes Metab. 2018;20(Suppl. 1):34–46.

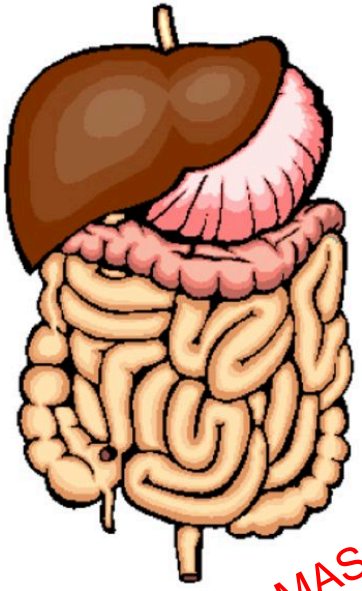
Drug class		Commonly used agents	Mechanism of action	Main anti-hyperglycaemic effects	Main side effects (less common/rare side effects)
Biguanides	Oral	Metformin	Activate hepatocyte and enterocyte AMPK; inhibit hepatocyte mitochondrial function, increase GLP-1 secretion, alter intestinal microbiome	Reduce hepatic glucose output, improve insulin sensitivity, increase gut glucose utilization	Abdominal discomfort; nausea; diarrhoea; flatulence (lactic acidosis)
Sulphonylureas	Oral	Glibenclamide/Glyburide, Gliclazide, Glimepiride, Glipizide	Close β-cell K_{ATP} channel	Cause insulin secretion (glucose independent)	Hypoglycaemia; weight gain
Meglitinides	Oral	Nateglinide, Repaglinide	Close β-cell K_{ATP} channel	Cause insulin secretion (glucose independent)	Hypoglycaemia; weight gain
Thiazolidinediones	Oral	Pioglitazone, (Rosiglitazone)	Activate a family of nuclear receptors (PPARs)	Reduce insulin resistance	Weight gain, oedema, (increased fracture risk; increased bladder cancer risk)
DPP-4 inhibitors	Oral	Alogliptin, Linagliptin, Saxagliptin, Sitagliptin, Vildagliptin	Reduce DPP-4-mediated degradation of endogenous incretin hormones	Enhance insulin synthesis/secretion (glucose dependent), suppress glucagon secretion (glucose dependent)	Generally well tolerated
GLP-1 receptor agonists	Injection	Albiglutide, Dulaglutide, Exenatide, Liraglutide, Lixisenatide, Semaglutide	Activate GLP-1 receptor	Enhance insulin synthesis/secretion (glucose dependent), suppress glucagon secretion (glucose dependent), reduce appetite	Nausea (vomiting; diarrhoea)
α-Glucosidase inhibitors	Oral	Acarbose, Miglitol, Voglibose	Slow digestion of complex carbohydrates	Reduce intestinal glucose absorption	Diarrhoea; flatulence; abdominal discomfort
SGLT-2 inhibitors	Oral	Canagliflozin, Dapagliflozin, Empagliflozin	Inhibit activity of glucose transporter in proximal tubule	Increase renal glucose excretion	Urinary tract/genital infections (ketoacidosis; dehydration)

Abbreviations: AMPK, AMP-activated protein kinase; K_{ATP} channel, ATP-sensitive potassium channel; PPAR, peroxisome proliferator-activated receptors.

Cosa cerchiamo da un farmaco per la cura del diabete?

	Vantaggi e Opportunità	*Rischi e pericoli*
Interno	**Qualità e Punti di Forza** Deve essere un farmaco che modifica la malattia	**Sicurezza e Rischi** Deve limitare ipoglicemie o eventi avversi come aumento di peso, tumori, aumento di CVD
Esterno	**Efficacia e Manegevolezza** Deve essere efficace in combinazione con diversi agenti terapeutici e personalizzabile sul paziente	**Sostenibilità** Deve ridurre i costi della terapia e i rischi di ospedalizzazione

Spectrum of gut hormones produced by enteroendocrine cells.

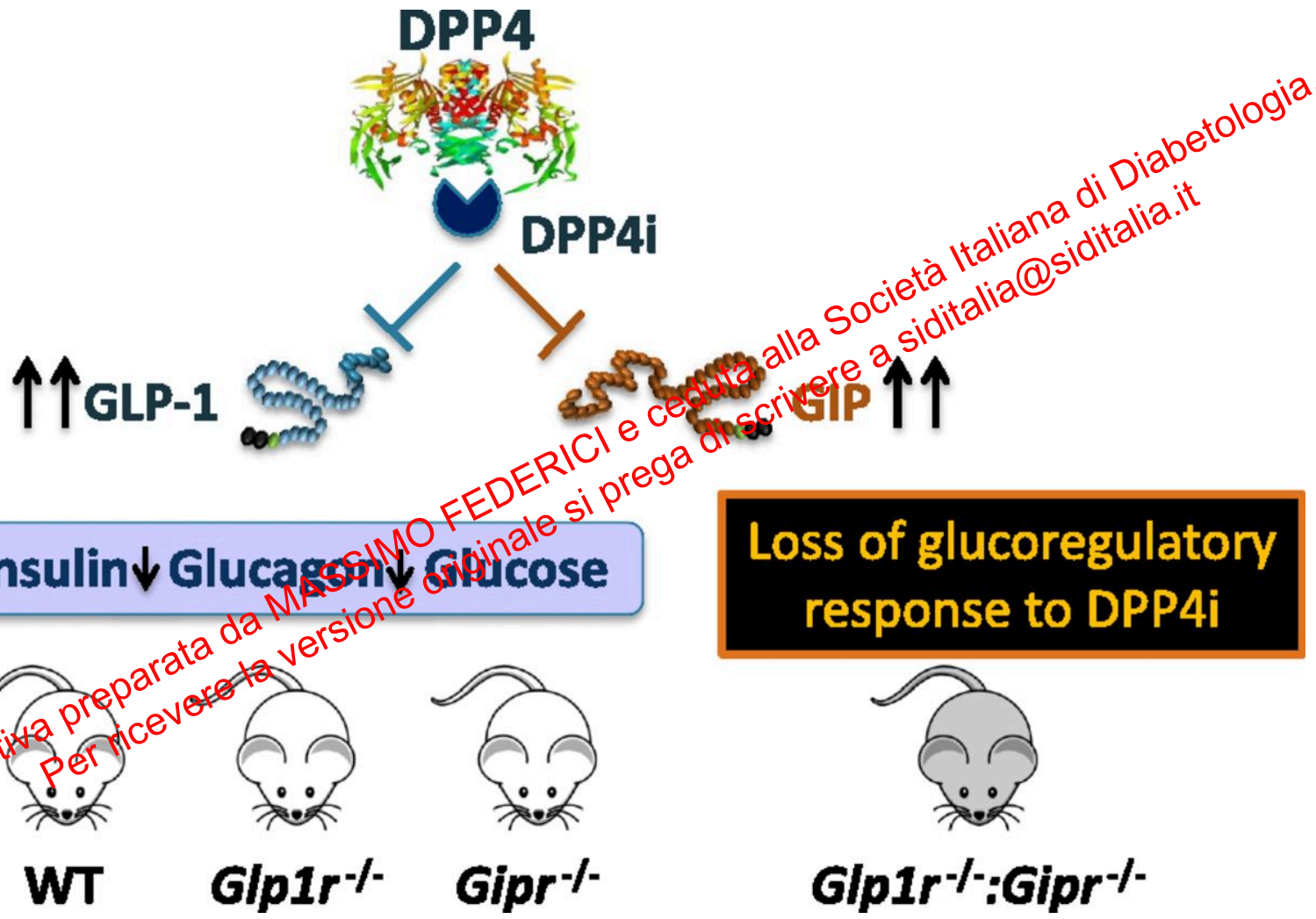


Apelin, Amylin
Bombesin
Calcitonin Gene-Related Peptide
Cholecystokinin
Galanin
Gastric Inhibitory Polypeptide
Gastrin
Gastrin-releasing Peptide
Ghrelin
Glucagon, Glicentin, GLP-1, GLP-2, Oxyntomodulin
Motilin
Neuropeptide Y
Neurotensin, Neuromedins, Neurokinins
Peptide YY
Pancreatic Polypeptide
Pituitary Adenylate Cyclase Activating Peptide
Secretin
Somatostatin
Tachykinins
Thyrotropin Releasing Hormone
Vasoactive Intestinal Peptide

Daniel J. Drucker Diabetes 2015;64:317-326

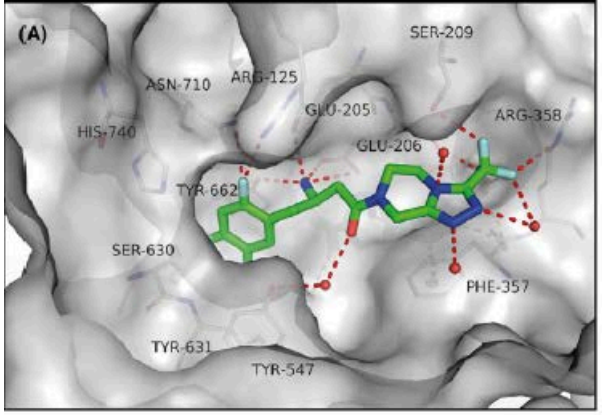
American Diabetes Association

Mechanisms through which DPP-4i lower blood glucose.

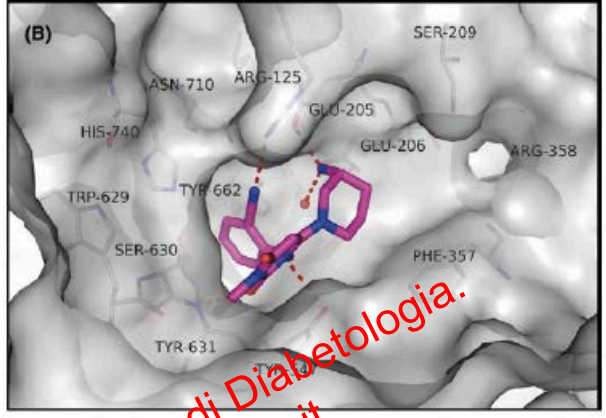


Daniel J. Drucker Diabetes 2015;64:317-326

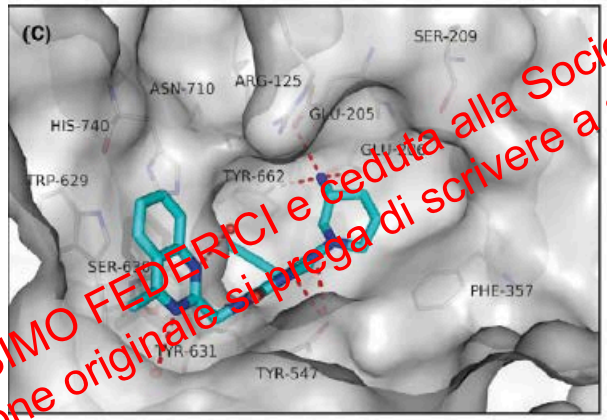
American Diabetes Association.



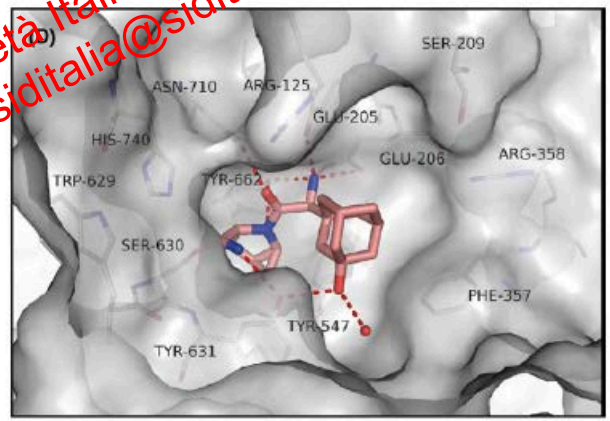
Sitagliptin (1X70)



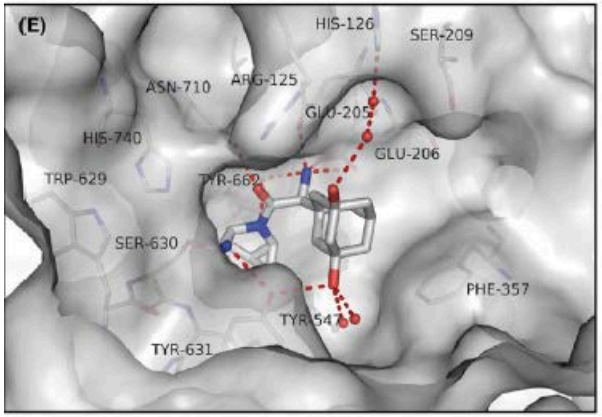
Alogliptin (3G0B)



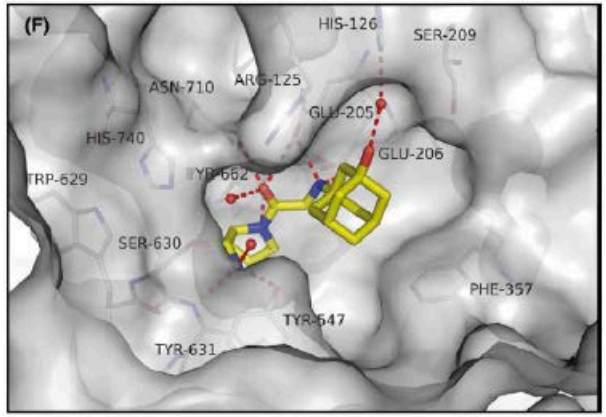
Linagliptin (2RGU)



Saxagliptin (3BJM)

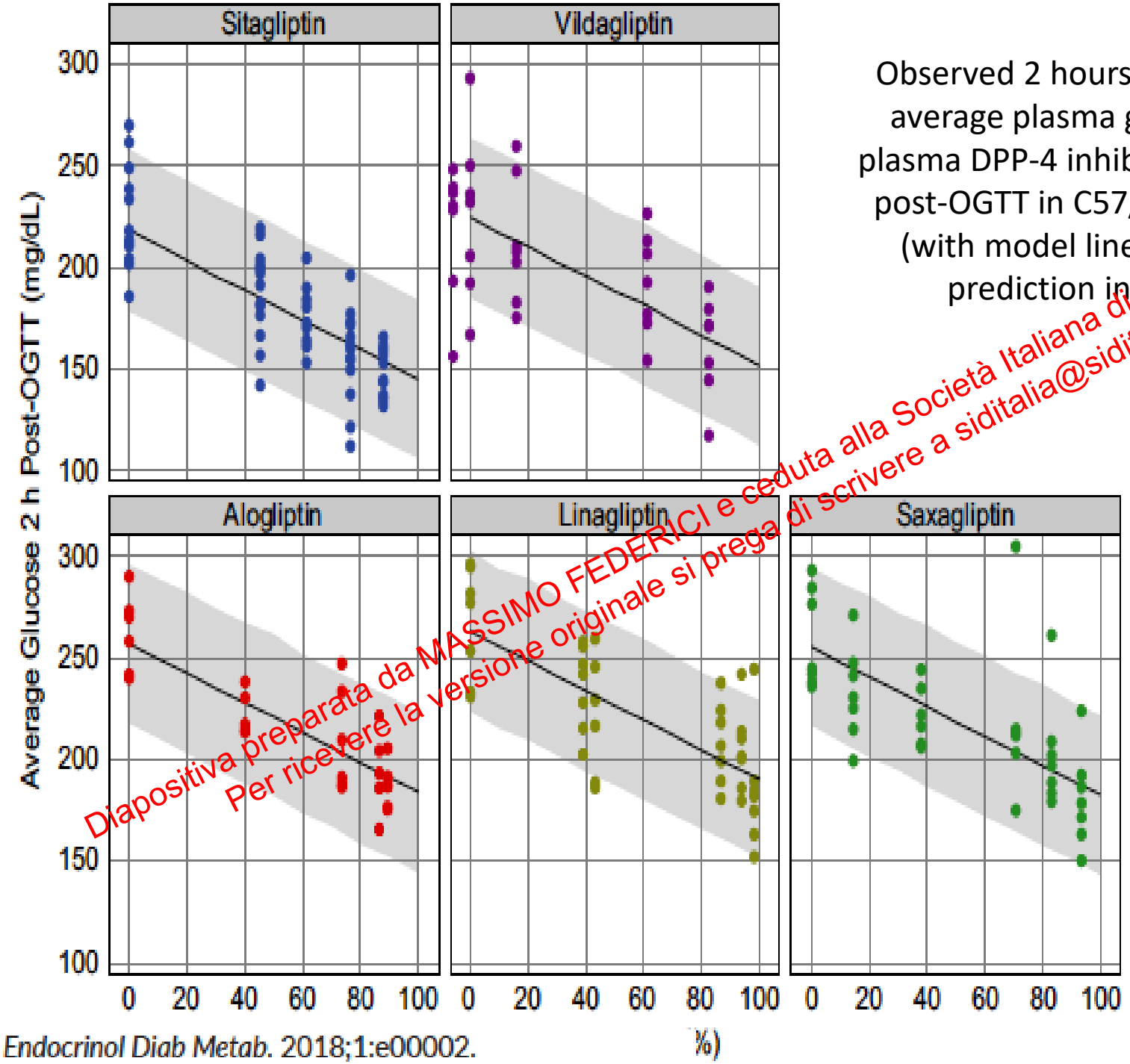


Saxagliptin M2 (6B1O)



Vildagliptin (6B1E)

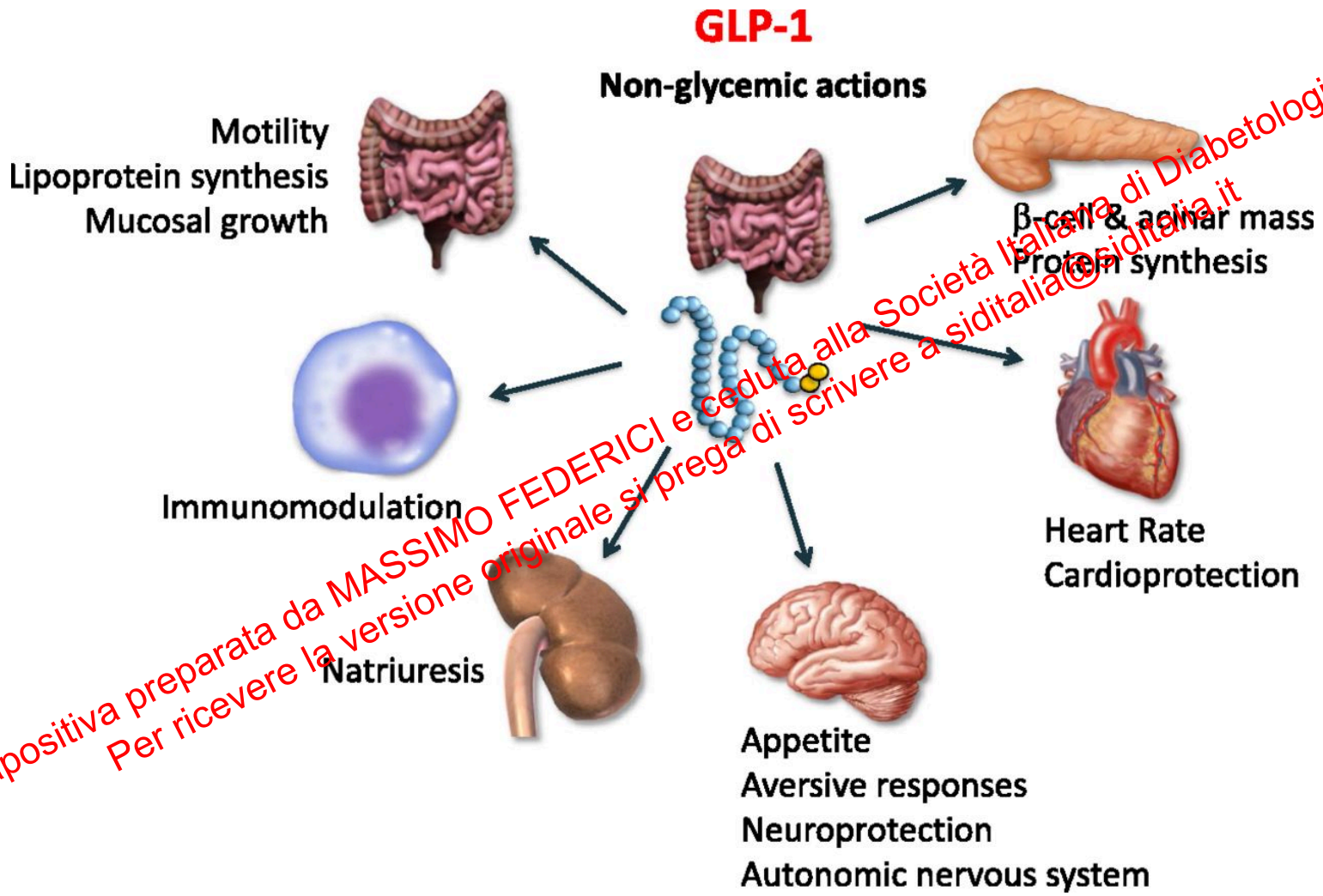
Endocrinol Diab Metab. 2018;1:e00002.



Observed 2 hours post-OGTT average plasma glucose vs. plasma DPP-4 inhibition 10 min post-OGTT in C57/Bl6N mice (with model line and 90% prediction interval)

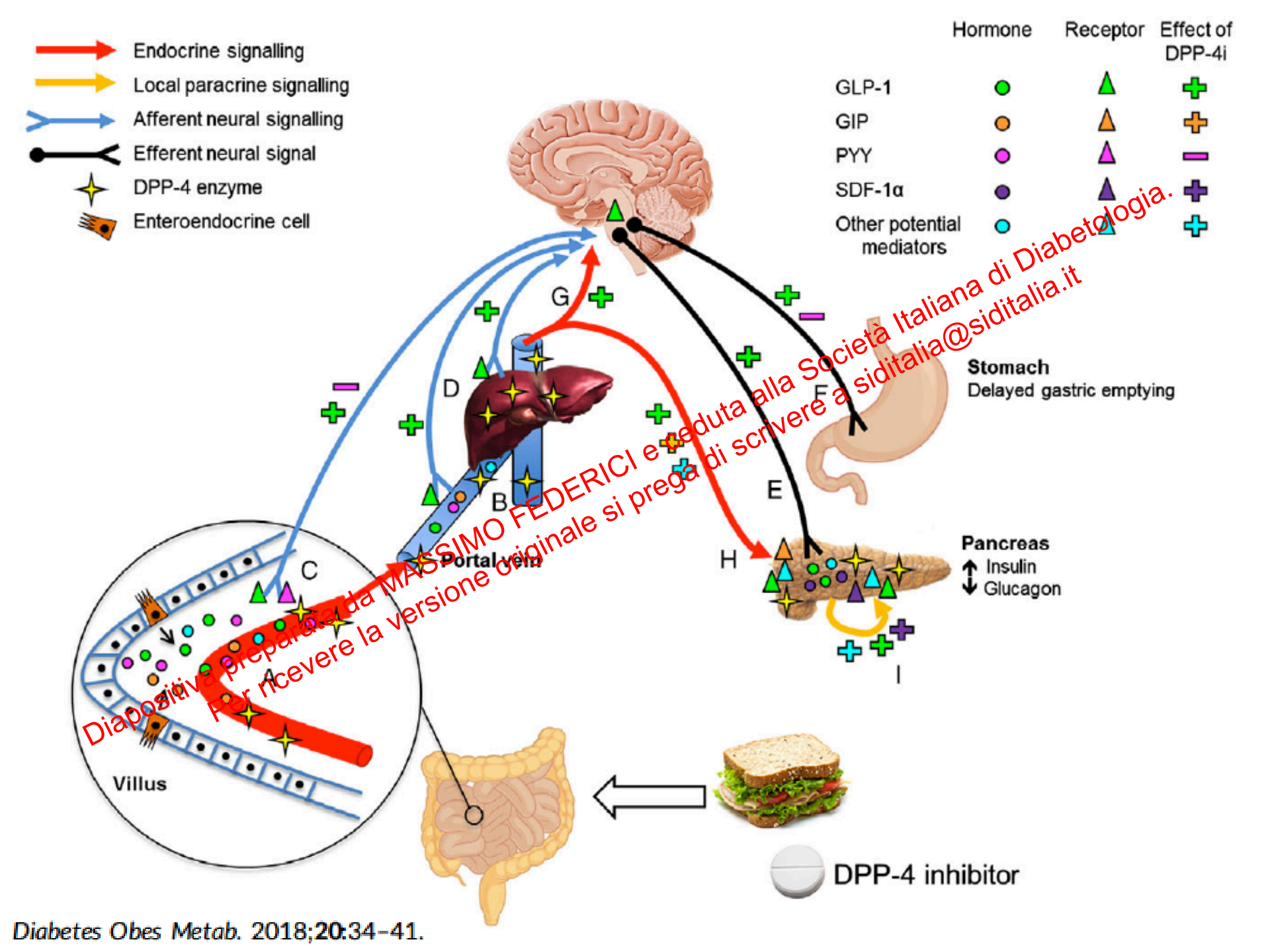
Endocrinol Diab Metab. 2018;1:e00002.

Nonglycemic actions of GLP-1 on organs that express a functional GLP-1R.

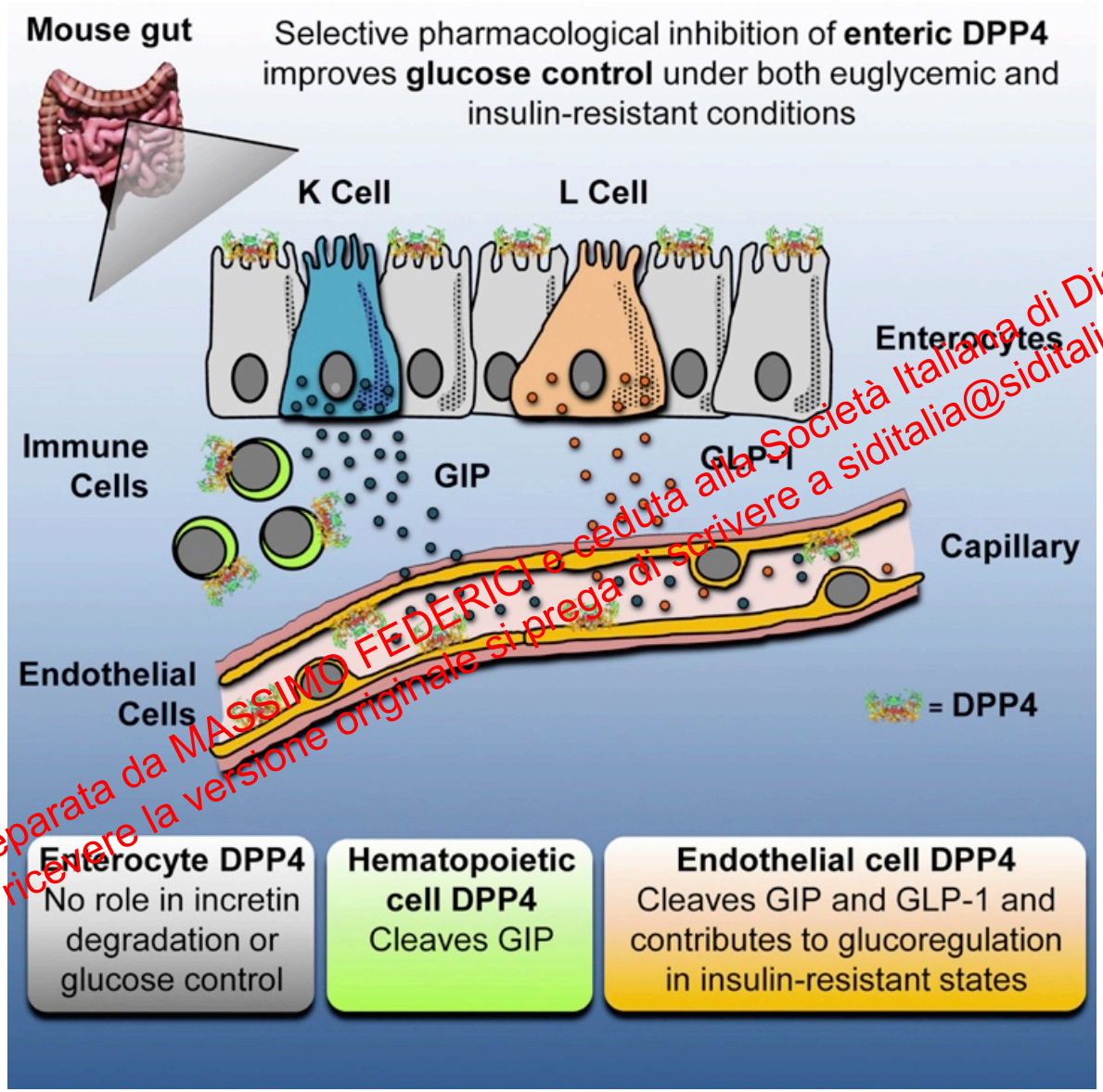


Daniel J. Drucker Diabetes 2015;64:317-326

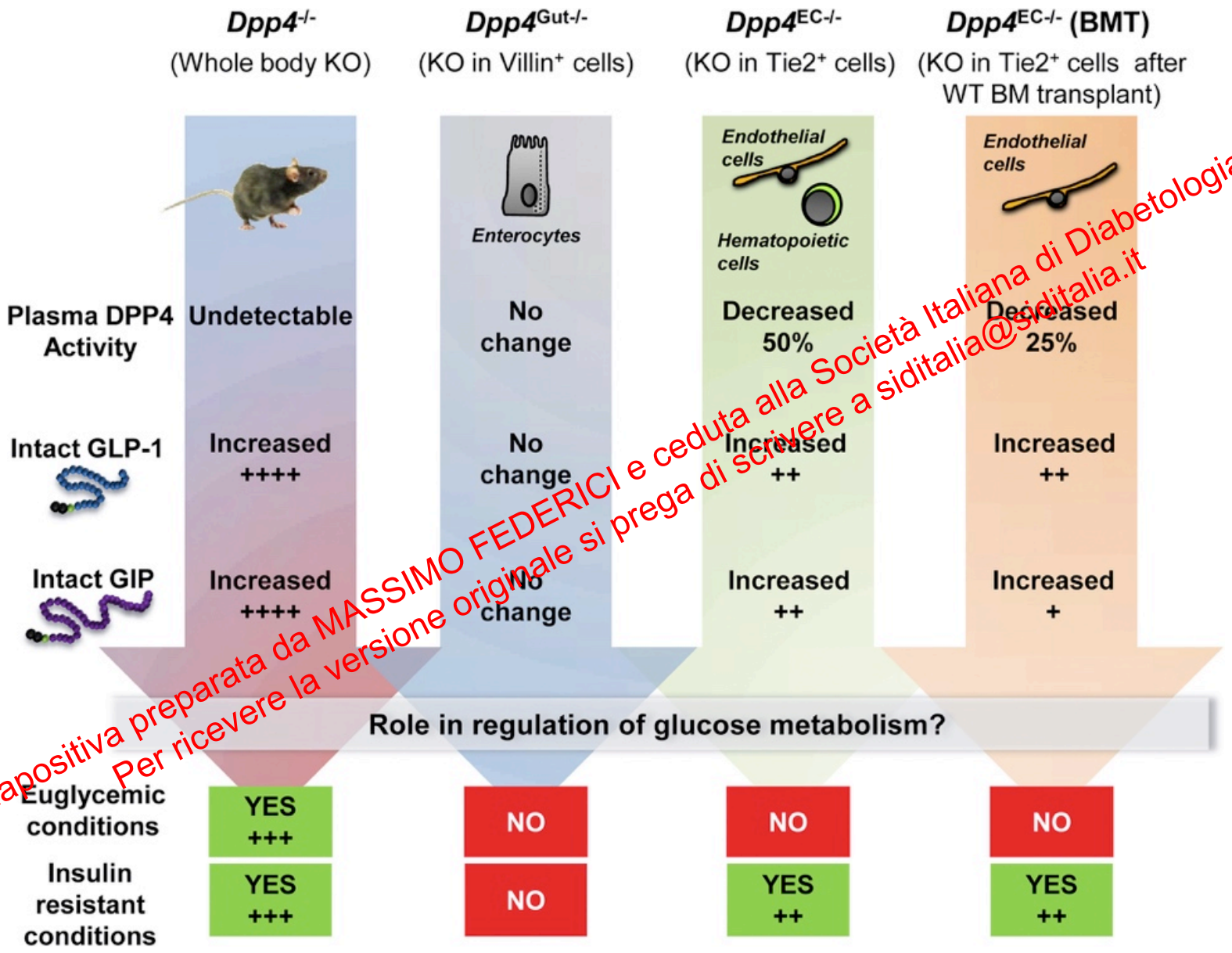
American Diabetes Association



Diabetes Obes Metab. 2018;20:34–41.



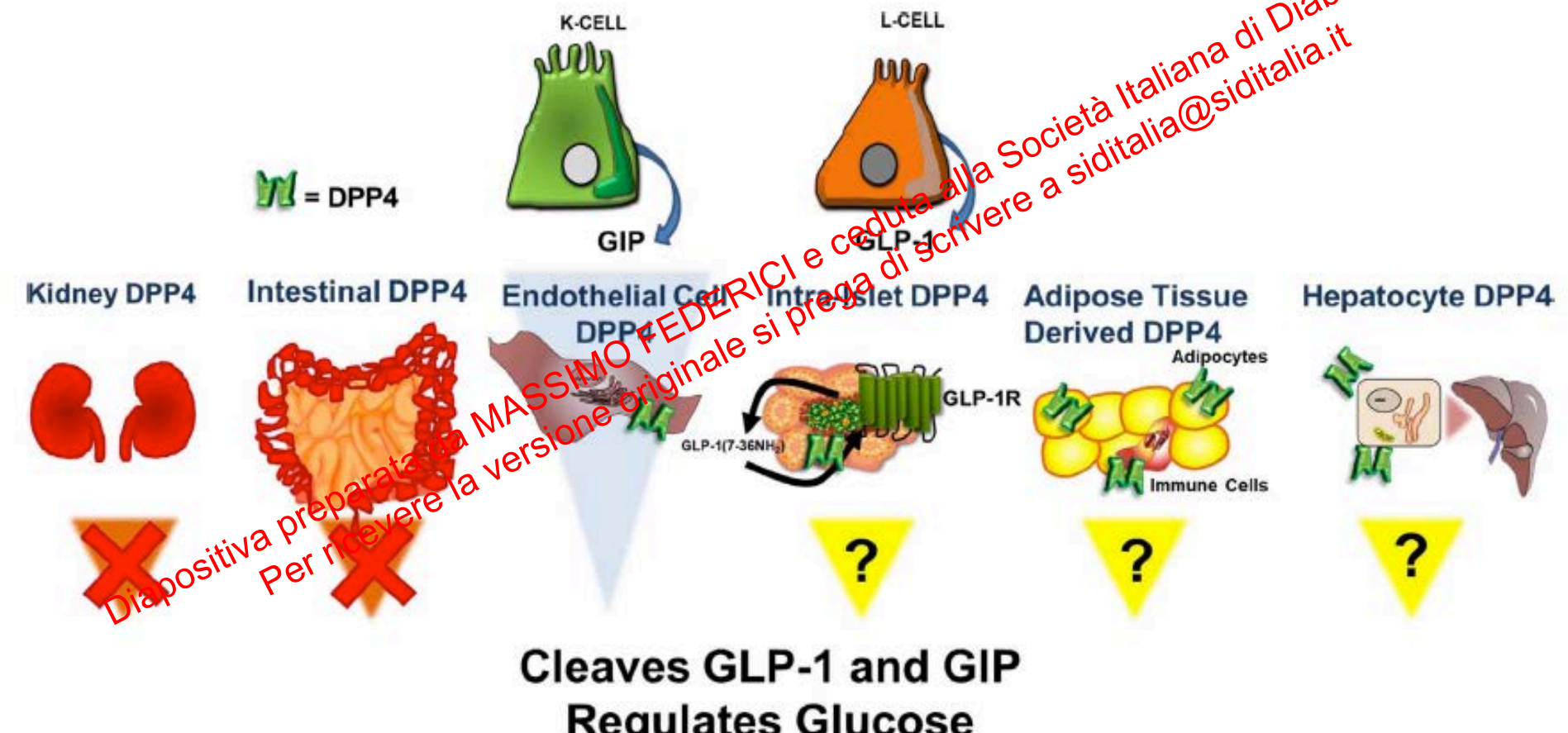
Cell Metabolism 25, 152–165, January 10, 2017



Cell Metabolism 25, 152–165, January 10, 2017

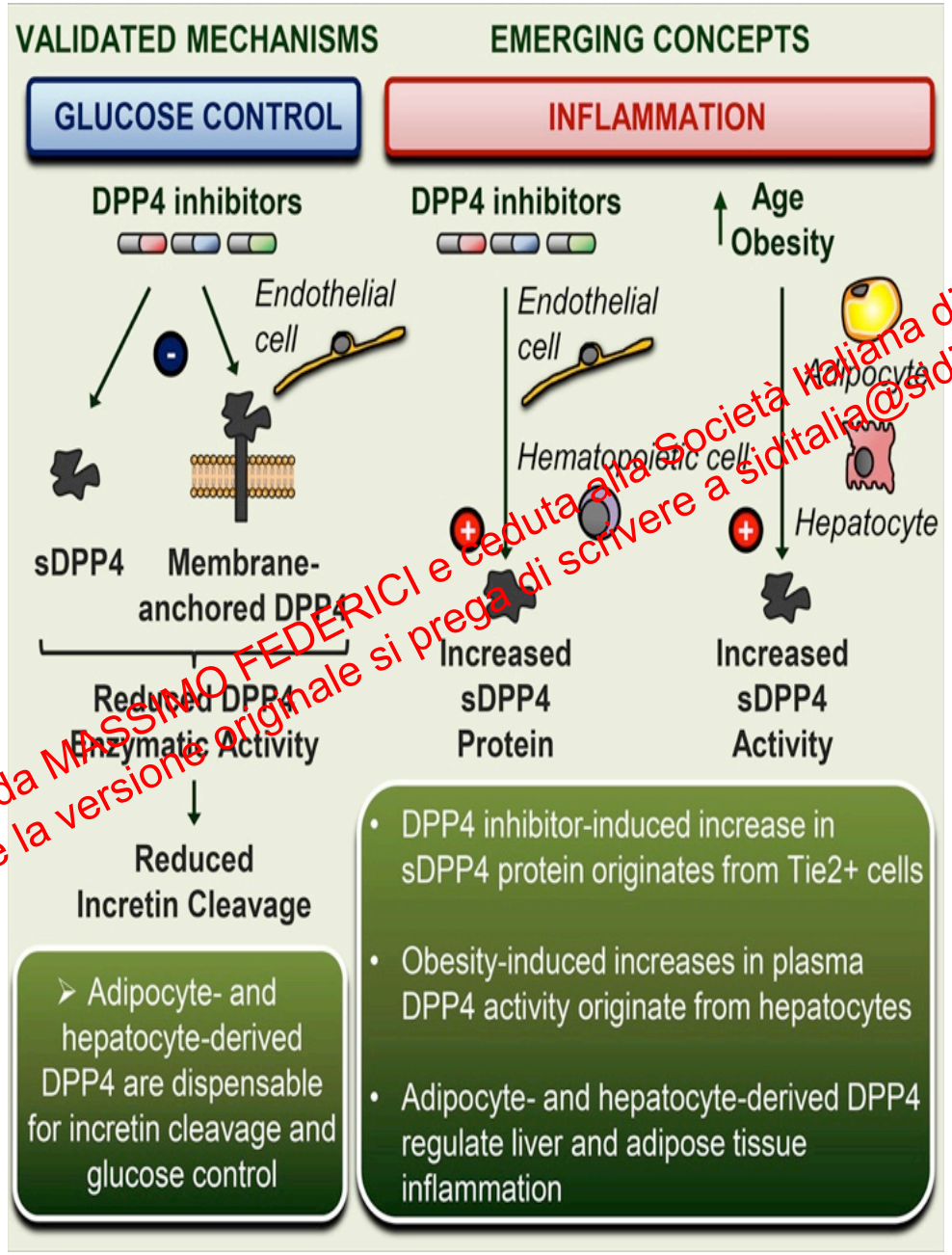
Peptides 100 (2018) 158–164

What Cellular Source of DPP4 is Important for GLP-1 Cleavage and Control of Glycemia?

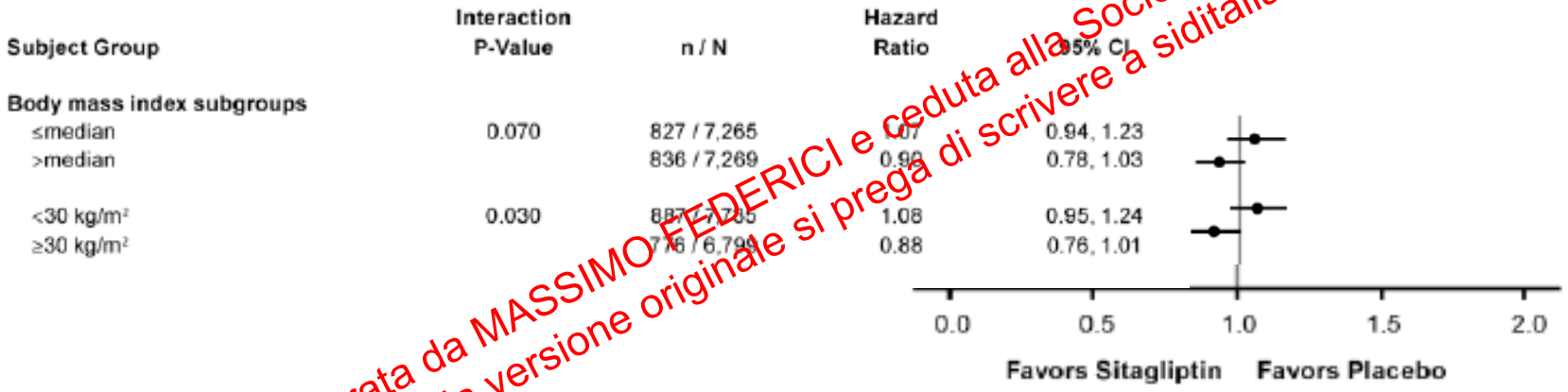


Cleaves GLP-1 and GIP
Regulates Glucose

Cell Metab. 2019 Feb 5;29(2):320-334.e5.



Effect of SITAGLIPTIN on obese subjects in TECOS trial



Green JB, Bethel MA, Armstrong PW, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015;373:232-42

Efficacy of DPP-4 inhibitors in the clinical phase III programmes with at least 52 weeks duration as add on therapy to metformin compared to sulfonylureas

TABLE 1 | Efficacy of DPP-4 inhibitors in the clinical phase III programmes with at least 52 weeks duration as add on therapy to metformin compared to sulfonylureas.

Substance/study [References]	Observation time [weeks]	Intervention	Change in HbA1c [%]	*n* [pat.]	HbA1c <7.0% [% pat.]	Change in body weight [kg]	Hypoglycaemic episodes [% pat.]
Alogliptin	104	Alogliptin 12.5 mg	−0.68	874	45.6*	−0.68 ←	1.4
Del Prato (23)		Alogliptin 25 mg	−0.72		48.5**	−0.89 ←	1.4
		Glipizide >5 mg	−0.59		42.8	+0.95	23.2 ←
Linagliptin	104	Linagliptin 5 mg	−0.16	1551	30.0*	−1.4 ←	7.0
Gallwitz (24)		Glimepiride >1 mg	−0.36		35.0	+1.3	36.0 ←
Saxagliptin	104	Saxagliptin 5 mg	−0.41	858	23.1	−1.5 ←	3.5
Göke (25)		Glipizide 5–20 mg	−0.35		22.7	+1.3	38.4 ←
Sitagliptin	104	Sitagliptin 100 mg	−0.54	1172	63.0	−1.6 ←	5.0
Seck (26)		Glipizide 5–20 mg	−0.51		59.0	+0.7	34.0 ←
Vildagliptin	52	Vildagliptin 2 × 50 mg	−0.81	1007	30.0*	+0.08	n.a.
Filozof (27)		Gliclazide <320 mg	−0.85		32.0	+1.36	
Vildagliptin	104	Vildagliptin 2 × 50 mg	−0.10	3118	37.0	−0.3	2.0
Matthews (28)		Glimepiride <6 mg	−0.10		38.0	+1.2	18.0

*Alogliptin (23) *p < 0.001 vs. sulfonylurea (SU) (non inferiority shown), **p < 0.010 vs. SU (superiority shown). Linagliptin (24) *p < 0.05 vs. SU (completers, two-sided). Vildagliptin (27) *p = 0.257 vs. SU (non inferiority shown).*

Gallwitz B (2019) Clinical Use of DPP-4 Inhibitors. Front. Endocrinol. 10:389.

Cardiovascular Actions and Clinical Outcomes With GLP-1RAs and DPP-4Is (10.1161/CIRCULATIONAHA.117.028136)

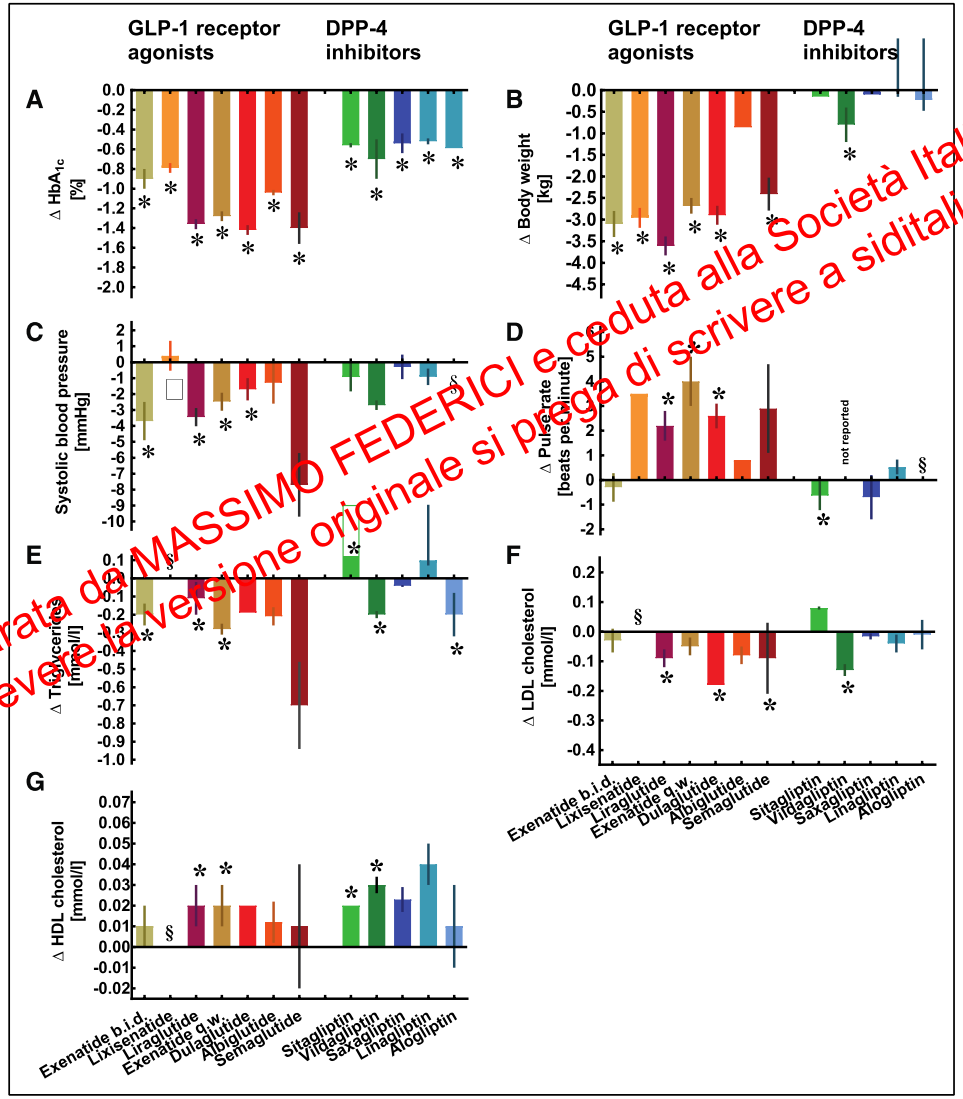
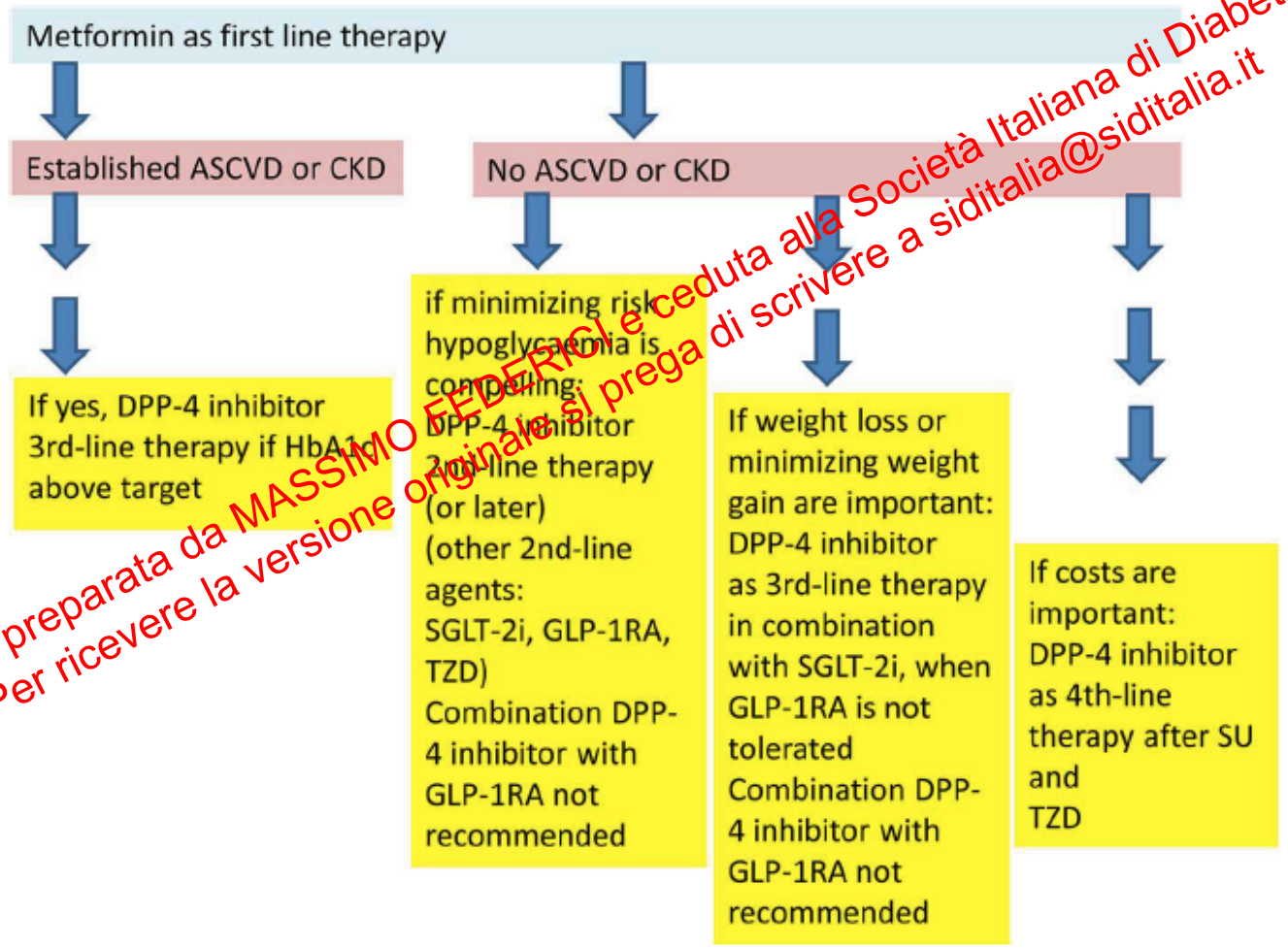


TABLE 2 Cardiovascular safety outcome trials with dipeptidyl peptidase-4 (DPP-4) inhibitors

	CV safety outcome trials						
Inhibitor	Saxagliptin	Alogliptin	Sitagliptin	Linagliptin	Linagliptin	Vildagliptin	Meta-analysis of non-CV DPP-4i trials
Trial name/study	SAVOR-TIMI[9]	EXAMINE[10]	TECOS[11]	CAROLINA[12]	CARMELINA[13]	No outcome trial planned	Monami et al.[14]
Comparator	Placebo	Placebo	Placebo	Glimepiride	Placebo		Placebo/active
History of CVD (%)	78	100 (ACS)	100	34	57		Low (CVD often an exclusion criterion)
eGFR <60 mL/min/1.73 m^2 (%)	16	29	9 (<50 mL/min/1.73 m^2)	18	62		Low (renal disease often an exclusion criterion)
Number	16 492	5380	14 671	6103	6980		41 959
Follow-up (y)	2.1	1.5	3.0	Target ~4	Target ~4		0.85
Age (y)	65	61	66	64	66		55
Diabetes duration (y)	10	7.2	9.4	6	15		5
BMI (kg/m^2)	31	28.7	30.2	30	31.3		31
HbA1c (%)	8.0	8.0	7.9	7.2	7.9		8.2
% on insulin	41	30	23	0	58		n/a
% on Statin	78	90	80	64	n/a		n/a
% on Aspirin	75	91	79	50	68		n/a
% on ACEI/ARB	82	82	82	75	81		n/a
CV events (*n*)	1222	621	1690	Target 631	Target 611		495
MACE hazard ratio (95% CI)	1.00 (0.89; 1.12)	0.96 (upper, 1.16)	0.98 (0.88, 1.09)	Results expected 2018	Results expected 2018		0.71

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; BMI, body mass index; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; MACE, major adverse cardiovascular events.

Placement of DPP-4 inhibitors into the treatment algorithm according to the recommendations of the American (ADA)- and European (EASD) Diabetes Associations



Gallwitz B (2019) Clinical Use of DPP-4 Inhibitors. Front. Endocrinol. 10:389.

TABLE 3 Commonly used classes of anti-hyperglycaemic agents recommended for controlling glycaemia in patients with T2DM and kidney disease (data taken from prescribing information, indications may vary by country)

Diabetes Obes Metab. 2018;**20(Suppl. 1)**:34–46.

Drug class	Renal impairment				Comments
	Mild (eGFR ≥60 mL/min/1.73 m^2)	Moderate (eGFR ≥30 to <60 mL/min/1.73 m^2)	Severe (eGFR <30 mL/min/1.73 m^2)	ESRD on dialysis	
Biguanides	Yes	Yes, with dose reduction Caution for eGFR <45 mL/min/1.73 m^2	No	No	Increased risk of lactic acidosis with declining GFR
Sulphonylureas	Yes	Yes	No (glibenclamide/glyburide; glimepiride) Yes with caution (gliclazide, glipizide)	No (glibenclamide/glyburide; glimepiride) Yes with caution (gliclazide, glipizide)	Increased exposure to parent or active metabolite (glibenclamide/glyburide; glimepiride); increased risk of hypoglycaemia
Meglitinides	Yes	Yes	Yes with caution Dose reduction may be required	Yes with caution Dose reduction may be required	Increased risk of hypoglycaemia
Thiazolidine-diones	Yes	Yes	Yes	No	Increased risk of fluid retention and chronic heart failure
DPP-4 inhibitors	Yes	Yes, with dose reduction of 50% Linagliptin: no adjustment	Yes, with dose reduction of 50% (saxagliptin, vildagliptin) or 75% (alogliptin, sitagliptin) Linagliptin: no adjustment	Yes, with dose reduction of 50% (saxagliptin, vildagliptin) or 75% (alogliptin, sitagliptin) Linagliptin: no adjustment	Dose reduction for renally eliminated DPP-4 inhibitors based on drug exposure, not safety or tolerability
GLP-1 receptor agonists	Yes	Yes Care with dose escalation for exenatide b.i.d.	No, except liraglutide	No	Increased frequency/severity of GI side effects; limited data in patients with eGFR <30 mL/min/1.73 m^2
α-Glucosidase inhibitors	Yes	Yes	No	No	Not studied/limited data in patients with GFR <30 mL/min
SGLT-2 inhibitors	Yes	No	No	No	Reduced glycaemic efficacy with declining GFR
Insulin	Yes	Yes	Yes	Yes	Decreased clearance of insulin; increased risk of hypoglycaemia

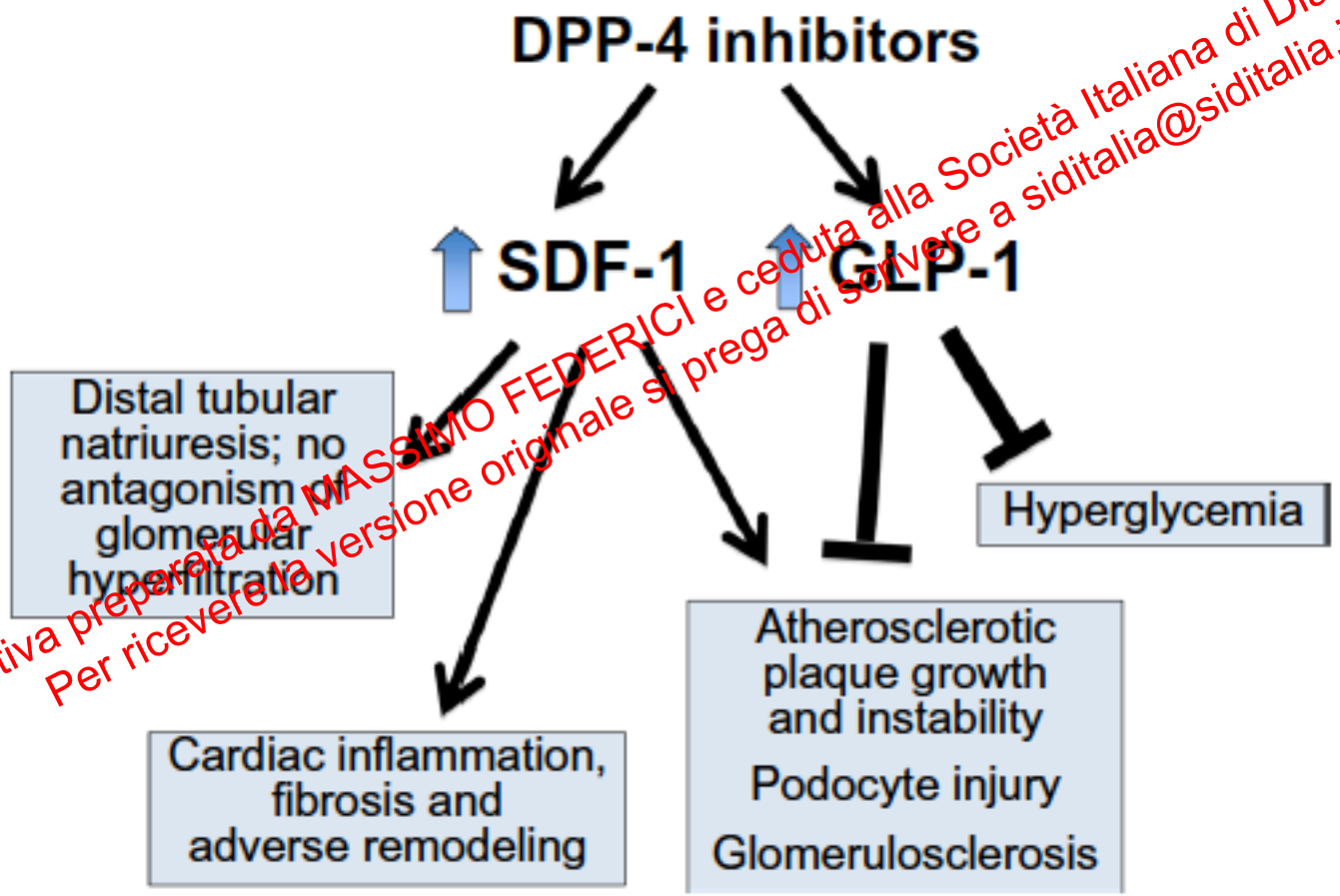
Abbreviations: DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; GLP-1, glucagon-like peptide-1.

TABLE 4 Tolerability and efficacy of DPP-4 inhibitors in patients with T2DM and kidney disease. Doses of the renally eliminated individual inhibitors (saxagliptin, sitagliptin, vildagliptin) are used at the recommended doses according to renal function

References	Drug	*n*	Study duration (wk)	Diabetes duration (y)	Renal status (eGFR)	% on insulin (mono- or combination therapy)	Baseline HbA1c (%)	ΔHbA1c (%)	Hypo-glycaemia (%)	Confirmed hypoglycaemia <2.8 mmol/L or severe requiring assistance (%)	ΔWeight (kg)	ΔeGFR (mL/min/1.73 m^2)
40	Sitagliptin	423	~54	~10	Moderate (in 70%) or severe (in 30%)	0	7.8	~0.8	6.2	1.4	−0.6	−3.9
	Glipizide							~0.6	17.0	2.8	+1.3	−3.3
41	Sitagliptin	148	24	19	Severe (20 mL/min/1.73 m^2)	50	7.5	~0.56	15	nr	nr	nr
	Vildagliptin							~0.54	16			
42	Vildagliptin	711	52	nr	Moderate (~40 mL/min/1.73 m^2)	71	7.9	~0.6	26	1.6	nr	−1.62
	Placebo							−0.2	17	3.4		−1.80
42	Vildagliptin	128	52	nr	Severe (~22 mL/min/1.73 m^2)	81	7.6	~0.8	18	11	nr	−1.98
	Placebo							−0.1	17	4.7		−2.44
43	Saxagliptin	160	52	>10 in 70%	Entire cohort: moderate (in 54%), severe (in 25%) or ESRD (in 21%)	~75	8.3	−1.08	38.2	9.4	0.7	No meaningful changes
	Placebo							−0.36	29.4	4.7	−01	
43	Saxagliptin	86	52		Sub-group: moderate		8.4	−0.94	29.2	10.4		
	Placebo							+0.19	38.1	7.1		
43	Saxagliptin	40	52		Sub-group: severe		7.9	−0.81	33.3	5.6		
	Placebo							−0.49	17.4	0		
43	Saxagliptin	34	52		Sub-group: ESRD		8.4	−1.13	21.1	10.5		
	Placebo							−0.99	25.0	5.0		
44	Linagliptin	133	52	>5 in 28%	Severe (~21 mL/min/1.73 m^2)	82	8.2	−0.71	63.2 (55.9% asymptomatic)	4.4	−1.83	−0.8
	Placebo							+0.01	49.2 (35.4% asymptomatic)	4.6	−0.29	−2.2
45	Sitagliptin	125	54	17	ESRD on haemo- (in 68%) or peritoneal (in 32%) dialysis	0	7.9	−0.7	6.3	0	−0.2	-
	Glipizide							−0.9	10.8	7.7	+0.8	-
46	Vildagliptin	60	24	nr	ESRD on haemodialysis	0	6.7	−0.6	0	0	0	-
	Control							0	0	0	0	-
47	Saxagliptin	82	24	nr	ESRD on haemodialysis	22	6.5	−0.6	0	0	0	-
	Control							−0.1	0	0	0	-

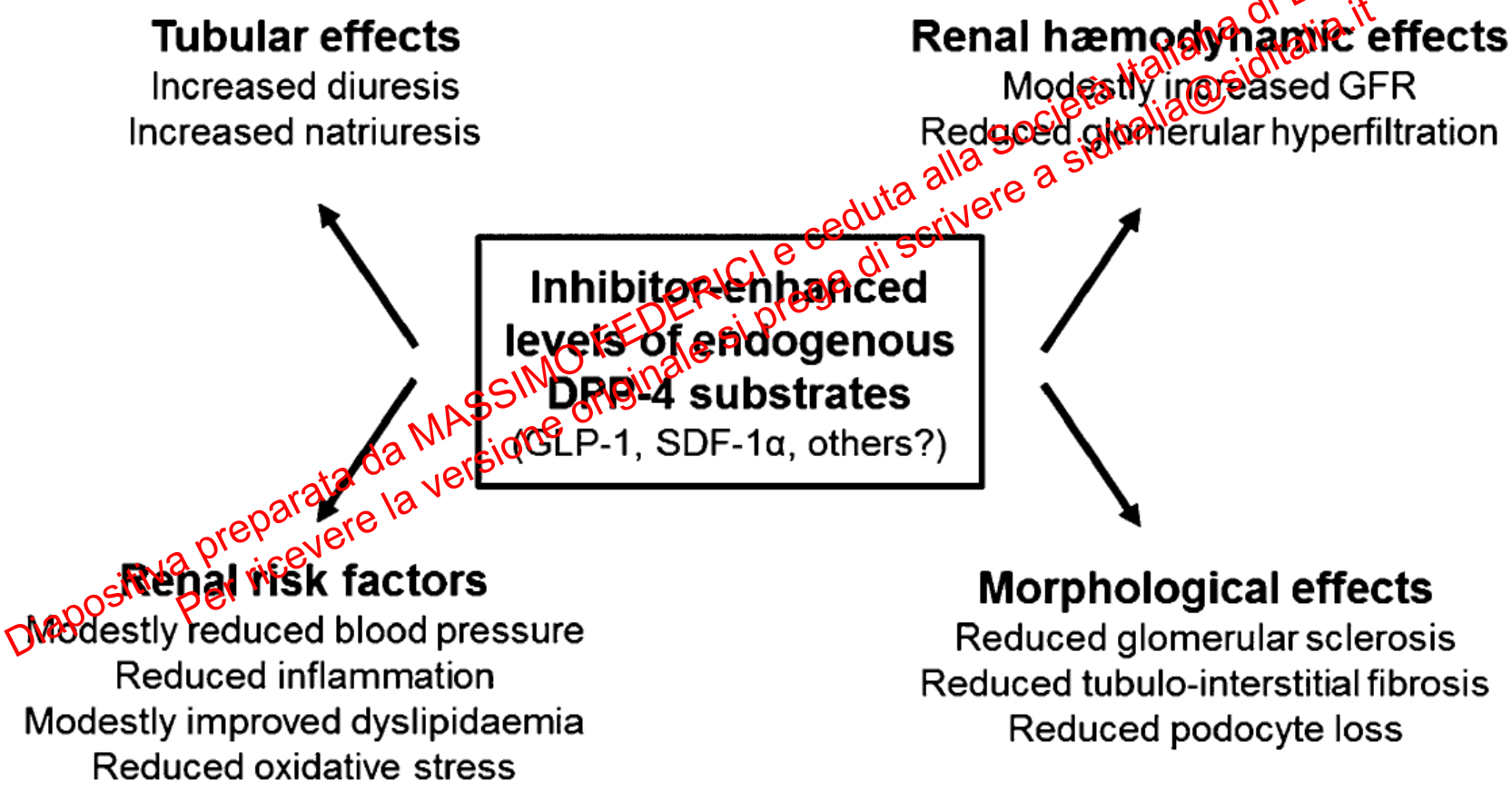
Abbreviations: DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; nr, not reported; T2DM, type 2 diabetes mellitus.

DUAL EFFECT OF DPP-4 INHIBITION?



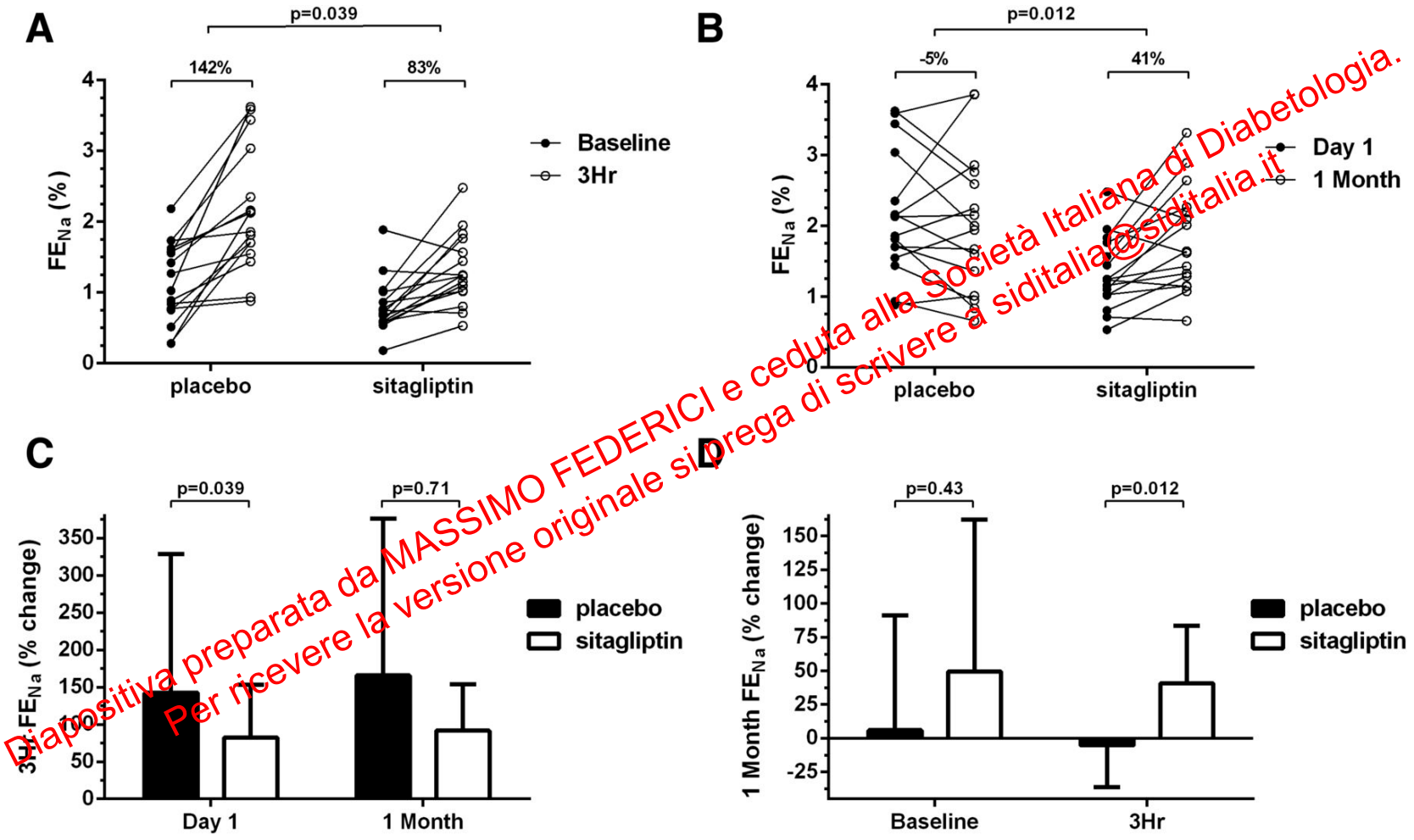
Packer *Cardiovasc Diabetol (2018) 17:9*

Potential mechanisms for DPP-4 inhibitor-mediated effects on the kidney.



Diabetes Obes Metab. 2018;**20(Suppl. 1)**:34–46.

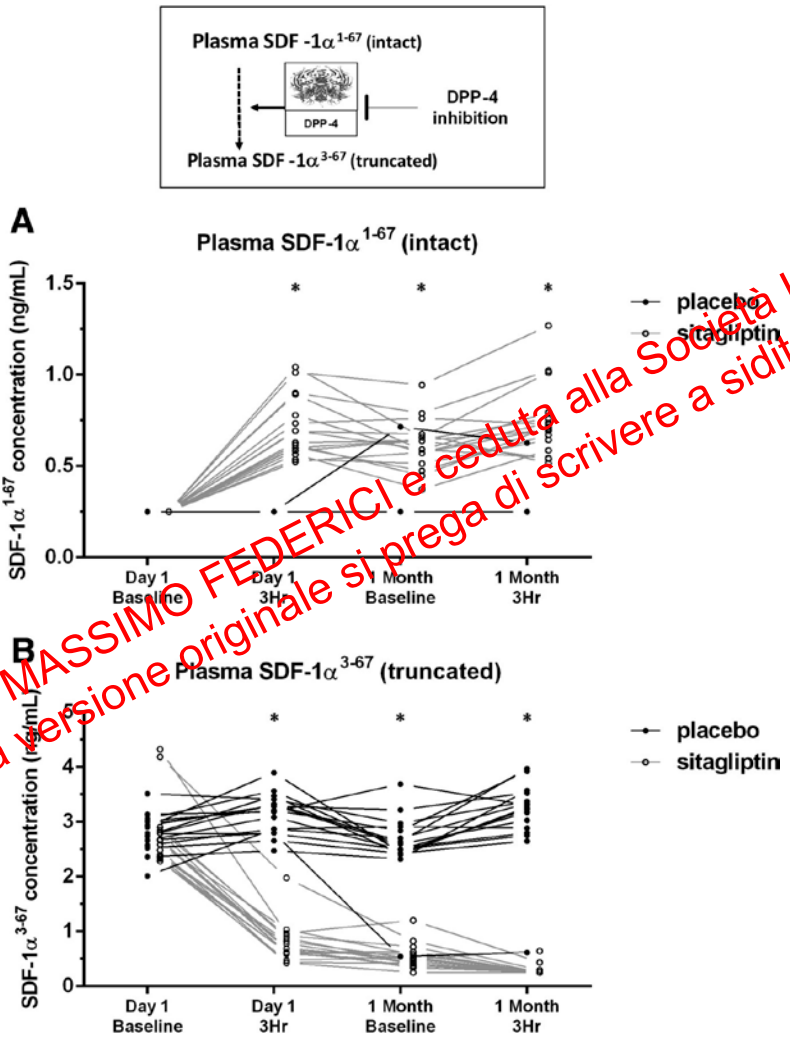
Acute and chronic changes in FENa in response to sitagliptin compared with placebo in patients with type 2 diabetes.



Julie A. Lovshin et al. Dia Care 2017;40:1073-1081

American Diabetes Association.

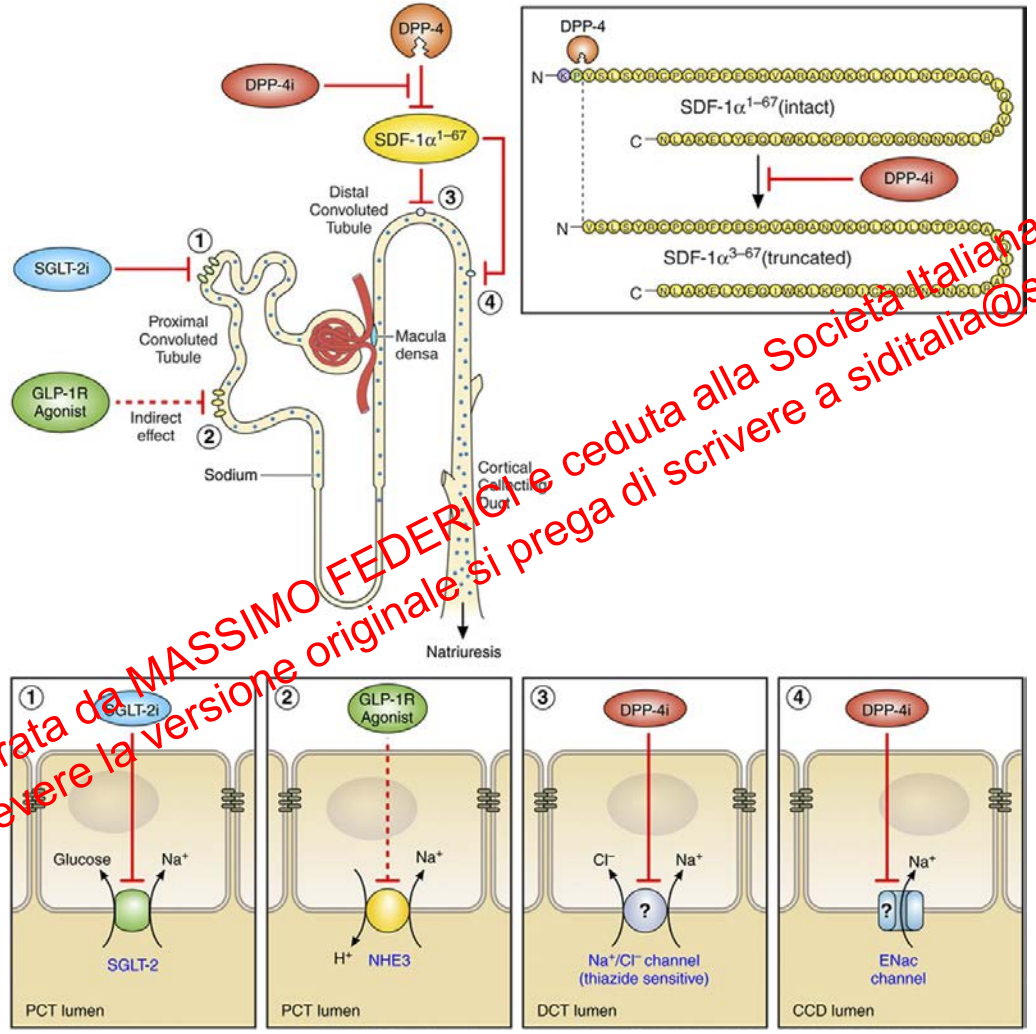
Immunoquantification of plasma SDF-1α in response to 1 month of sitagliptin administration compared with placebo in patients with type 2 diabetes.



Julie A. Lovshin et al. Dia Care 2017;40:1073-1081

American Diabetes Association.

Putative natriuretic mechanisms for DPP-4 inhibitors (DPP-4i).

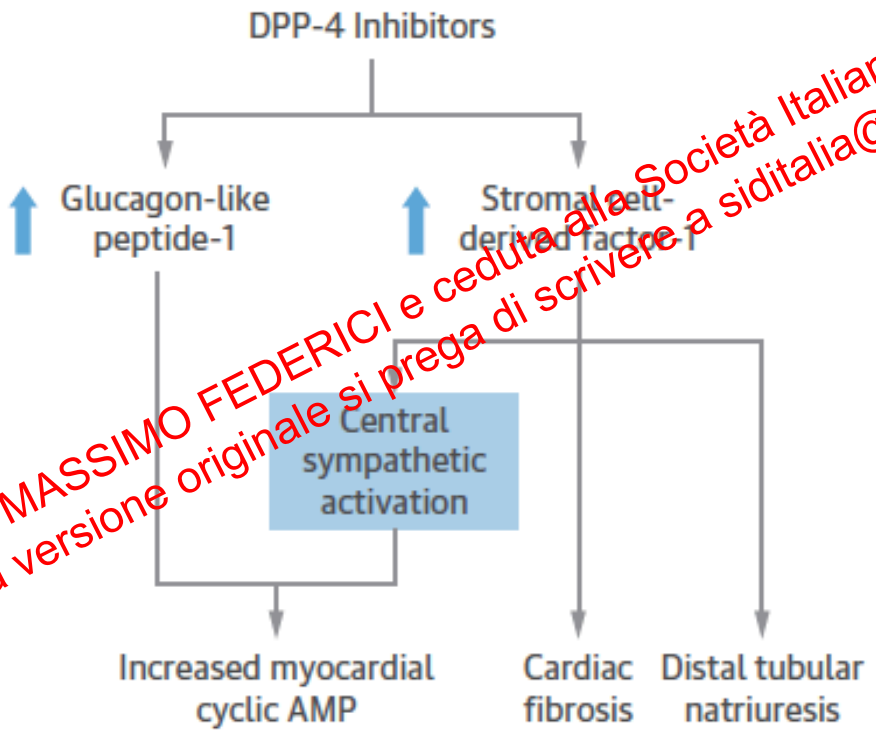


Julie A. Lovshin et al. Dia Care 2017;40:1073-1081

American Diabetes Association.

JACC: HEART FAILURE VOL. 6, NO. 6, 2018
JUNE 2018:445–51

CENTRAL ILLUSTRATION Actions of Dipeptidyl Peptidase-4 Inhibitors That Are Relevant to Their Effects in Patients With Chronic Heart Failure

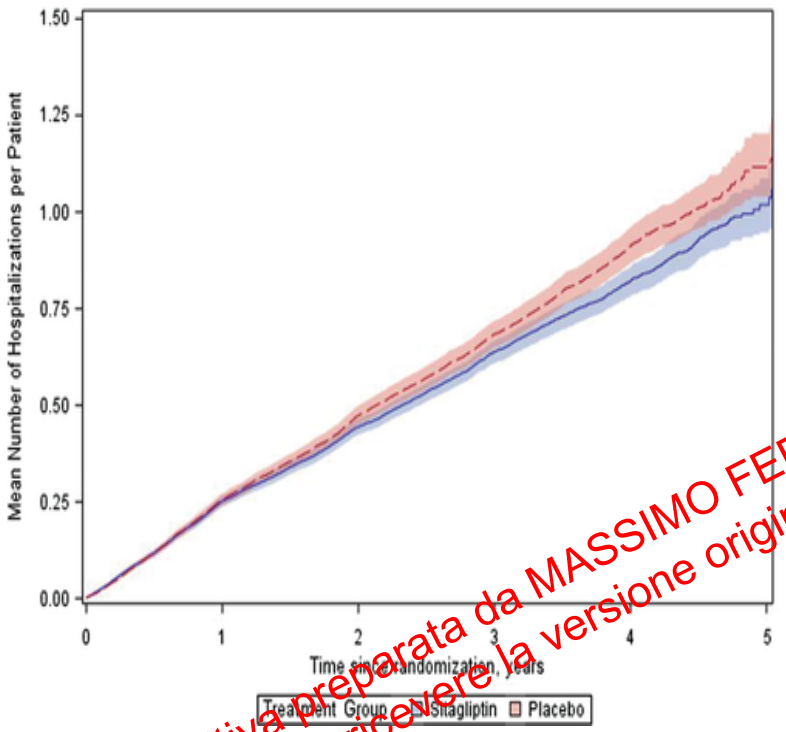


Packer, M. J Am Coll Cardiol HF. 2018;6(6):445–51.

AMP = adenosine monophosphate; DPP = dipeptidyl peptidase.

Longitudinal medical resources and costs among type 2 diabetes patients participating in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS).

Mean cumulative number of hospitalizations per patient by treatment group



Hospitalization rates and relative impact of sitagliptin on all-cause hospitalizations

Duration of follow-up (y)	N	Unadjusted[a]			Adjusted[b]	
		Sitagliptin	Placebo	Relative rate	Relative rate	*P* value[b]
≥ 2	13 700	0.203	0.223	0.91	0.94 (0.88-1.01)	.07
≥ 2.5	9674	0.200	0.227	0.88	0.90 (0.83-0.97)	.01
≥ 3	7189	0.199	0.225	0.88	0.90 (0.83-0.98)	.02
≥ 3.5	4440	0.183	0.213	0.86	0.89 (0.79-0.99)	.03
≥ 4	2641	0.186	0.215	0.86	0.89 (0.77-1.02)	.10

Lower hospitalization rates across time with sitagliptin slightly offset sitagliptin treatment costs over 3 years in type 2 diabetes patients at high risk for cardiovascular events

Reed SD et al., Diabetes Obes Metab. 2018;20:1732–1739.

CONCLUSIONI

Nuove ipotesi sul meccanismo d'azione dei DPP-4i

- L'inibizione della DPP-4 endoteliale spiega gli effetti metabolici dei DPP-4i, mediati da GLP-1
- L'aumento della DPP-4 correlato all'obesità origina dal tessuto epatico
- La DPP-4 epatica e adipocitaria è coinvolta nella regolazione dell'infiammazione d'organo
- Altri bersagli della DPP-4 come SDF-1 potrebbero contribuire agli effetti dei DPP-4i

…the DPP4 inhibitors remain the best tolerated of any glucose-lowering medications and, therefore, they should retain their position in the stepped approached to diabetes therapy…

(Philip Home DIABETOLOGIA 2019)