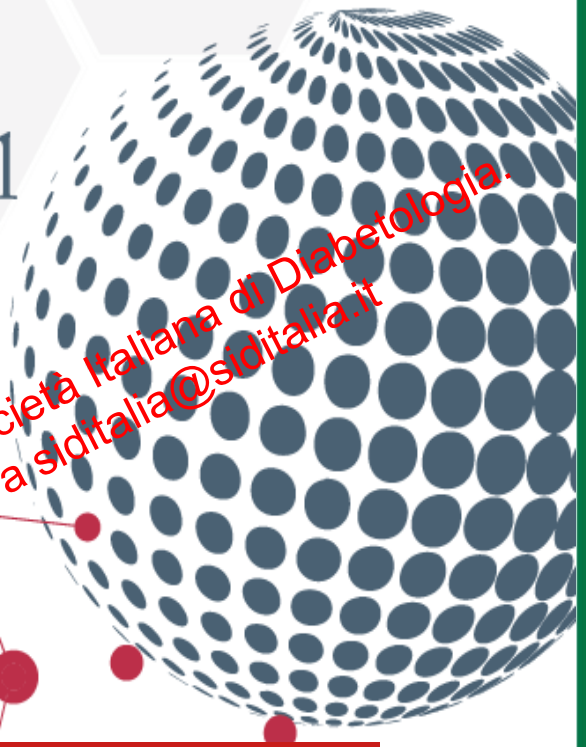
Gestione del rischio globale del

diabetico di tipo 2:

un ruolo per i DPP4?



Oltre il Cardio-Vascolare: potenziali effetti sistemici

Antonio C. Bossi - Treviglio (BG)

9 novembre 2019

Milano

Hilton Milan

Disclosures

Nell'arco degli ultimi tre anni dichiaro di aver ricevuto onorari per conferenze, collaborazioni scientifiche, lavori di ricerca clinica e documentale dalle seguenti Aziende:

- ***Lilly Italia Spa***
- ***Novo Nordisk Italia SpA***
- ***Johnson & Johnson SpA***
- ***Boehringer Ingelheim SpA***
- ***Pikdare SpA***
- ***Takeda SpA***
- ***Bayer SA***
- ***Sanofi SpA***
- ***Astra Zeneca SpA***
- ***MSD Italia SpA***

Se oggi sono qui in qualità di relatore è perché la SID ha contribuito alla mia formazione culturale, scientifica, clinica.

Oltre il Cardio-Vascolare:
potenziali effetti sistemici dei DPP4-inibitori

AGENDA

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CONCLUSIONI

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Centro Regionale Diabete
Centro Studi Aterosclerosi

Oltre il Cardio-Vascolare: potenziali effetti sistemici dei DPP4-inibitori

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- CONCLUSIONI

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Centro Studi Aterosclerosi

Gli inibitori DPP4 sono in grado di modulare la natriuresi in pazienti con diabete mellito tipo 2?

1) SI
2) NO
3) NON SO

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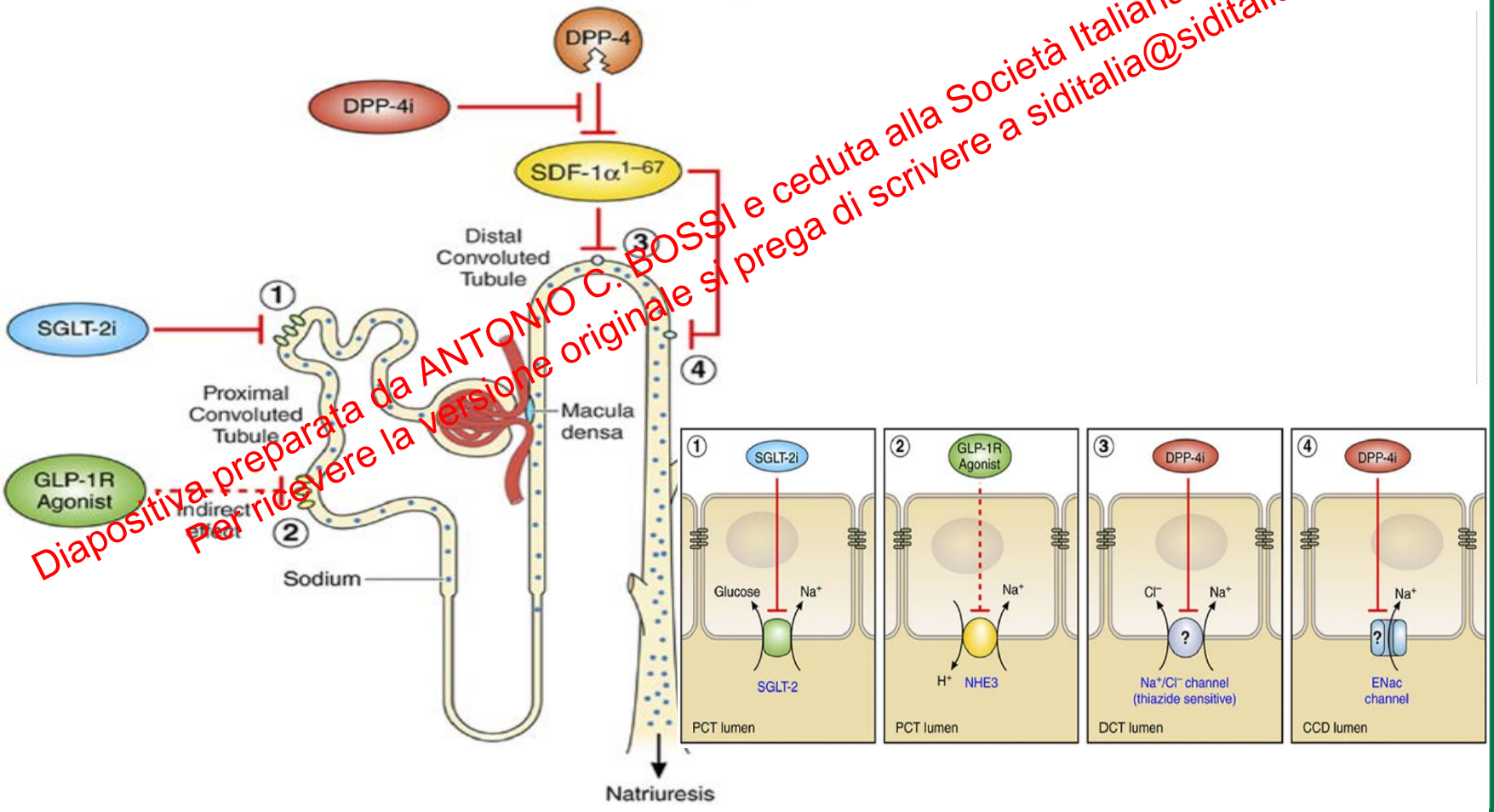
Dipeptidyl Peptidase-4 Inhibition Stimulates Distal Tubular Natriuresis and Increases in Circulating SDF-1α$^{1-67}$ in Patients With Type 2 Diabetes

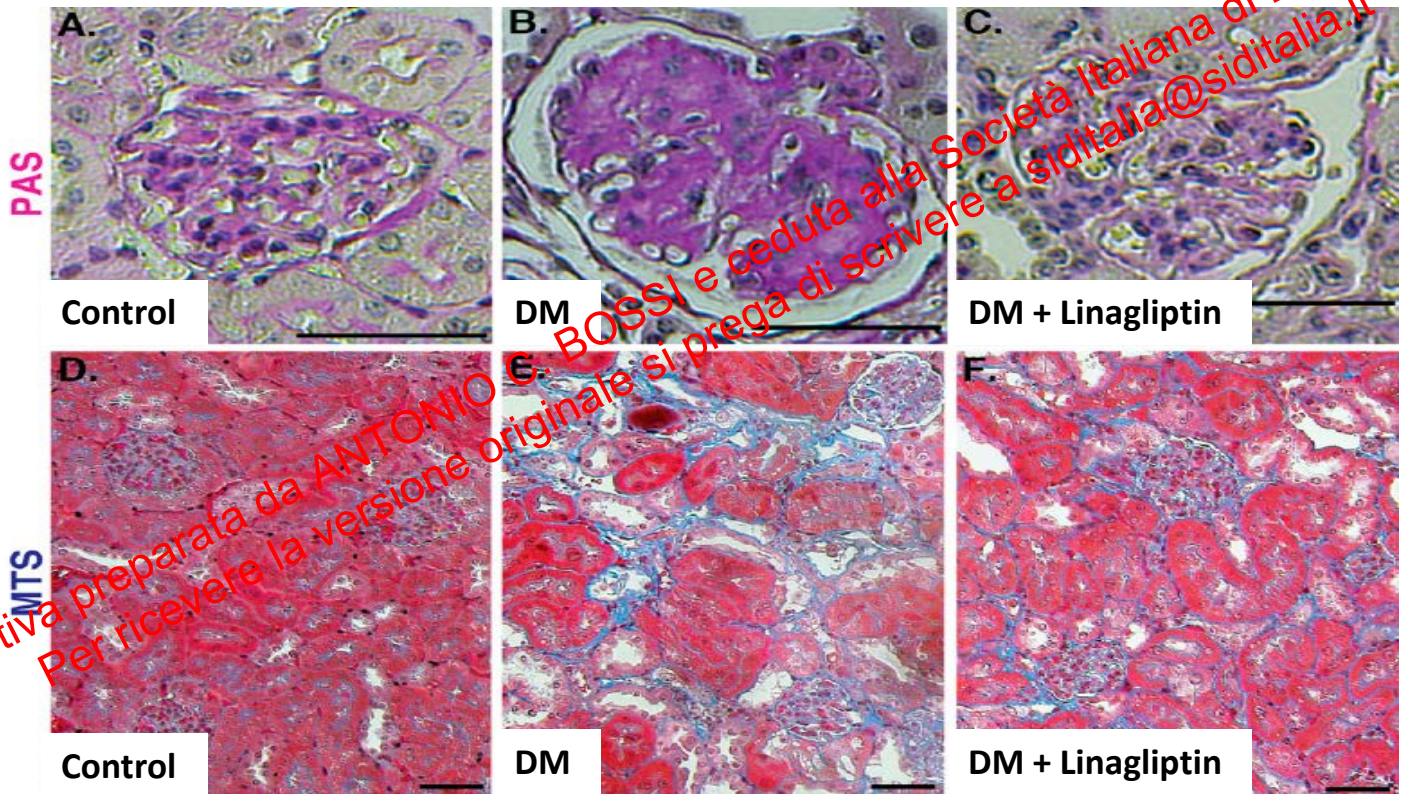
Julie A. Lovshin,[1,2] Harindra Rajasekeran,[1] Yulyia Lytvyn,[1] Leif E. Lovblom,[3] Shajiha Khan,[1] Robel Alemu,[1] Amy Locke,[1] Vesta Lai,[1] Huaibing He,[4] Lucinda Hittle,[4] Weixun Wang,[4] Daniel J. Drucker,[2,3] and David Z.I. Cherney[1,5,6]

Diabetes Care
Pubished Ahead of Print,
published online May 26, 2017

https://doi.org/10.2337/dc17-0061



Linagliptin-Mediated DPP-4 Inhibition Ameliorates Kidney Fibrosis in Streptozotocin-Induced Diabetic Mice by Inhibiting Endothelial-to-Mesenchymal Transition in a Therapeutic Regimen



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Mod. from: Kanasaki K et Al.
Diabetes 2014, 63, 2120-2131

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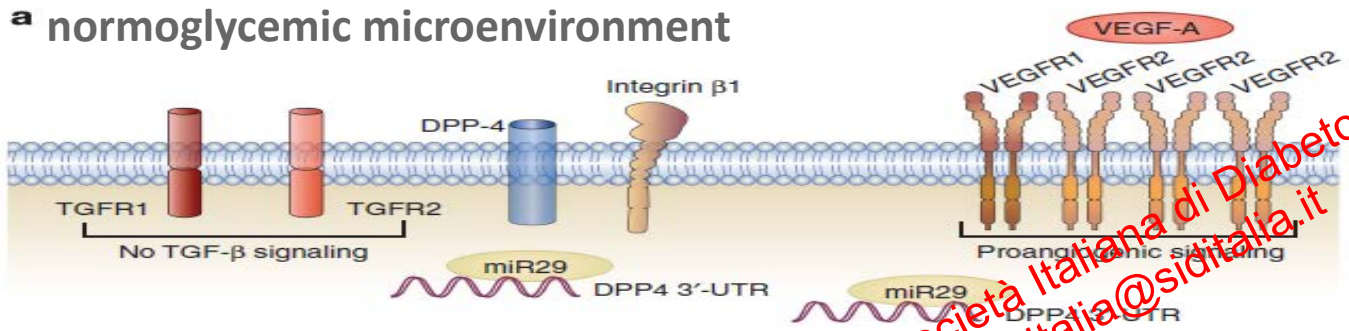
Evidence for antifibrotic incretin-independent effects of the DPP-4 inhibitor linagliptin



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Zeisberg M and Zeisberg EM.
Kidney International (2015) 88, 429.
doi:10.1038/ki.2015.175

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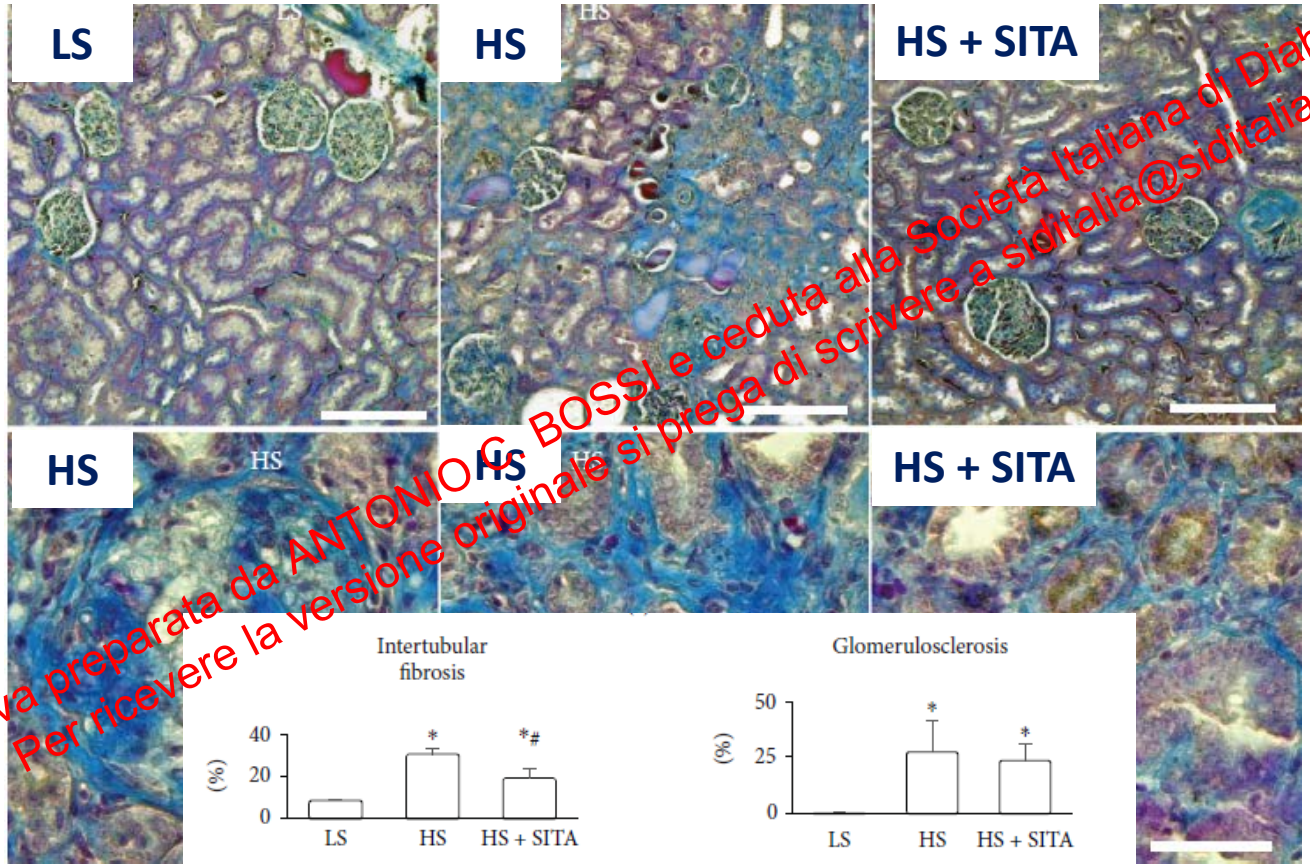
Research Article

Dipeptidyl Peptidase 4 Inhibition Ameliorates Chronic Kidney Disease in a Model of Salt-Dependent Hypertension



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Cappetta D et Al. 2019
Oxidative Medicine and Cellular Longevity
Article ID 8912768, 13 pages
https://doi.org/10.1155/2019/8912768

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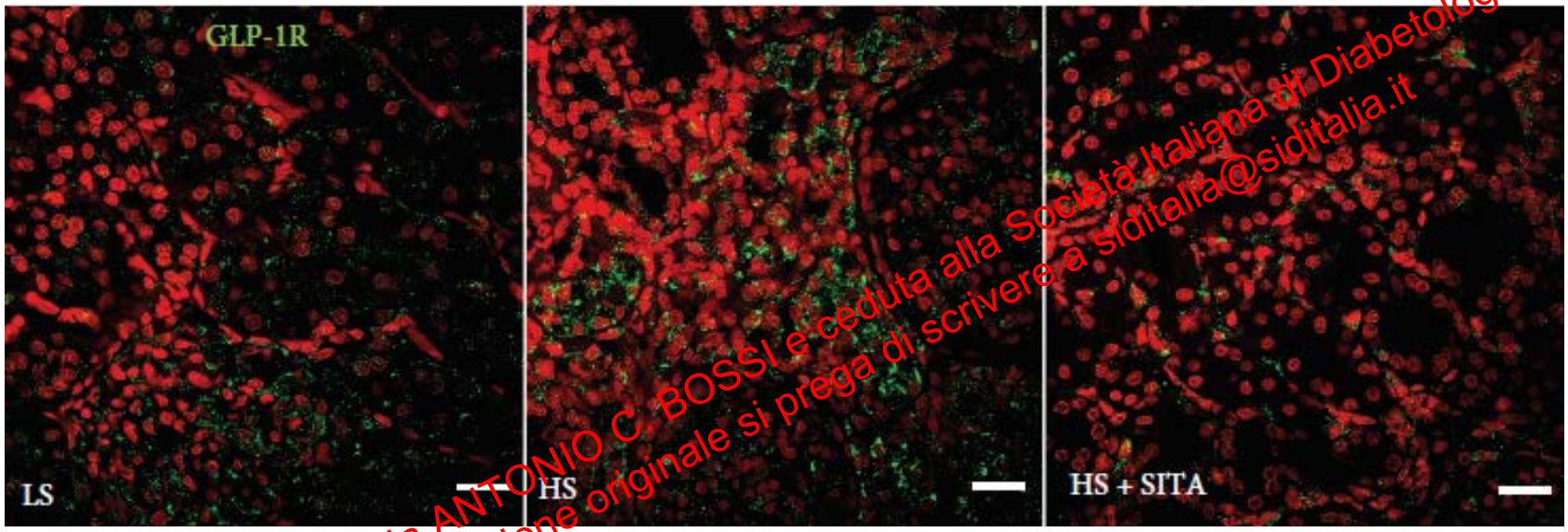

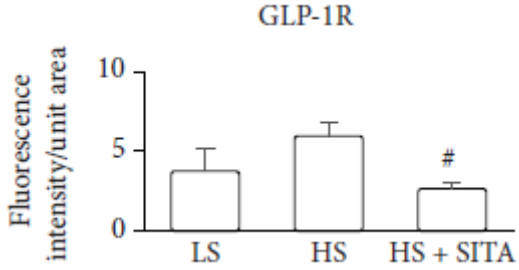

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Oxidative Medicine and Cellular Longevity
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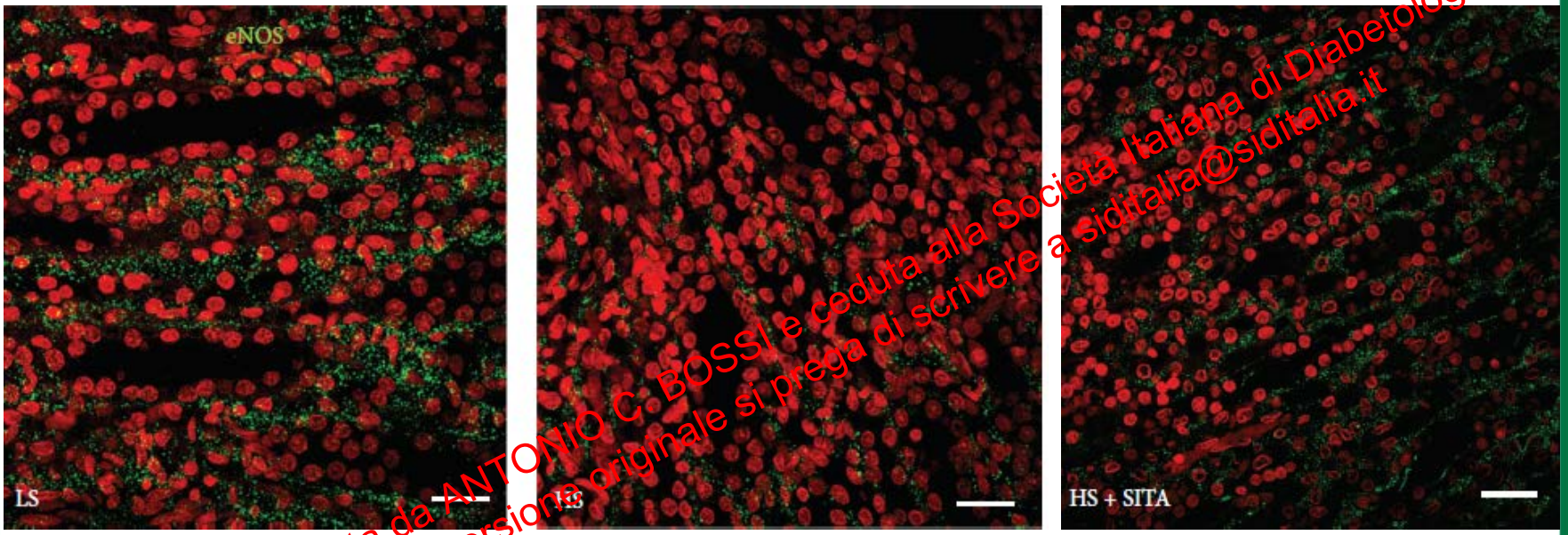

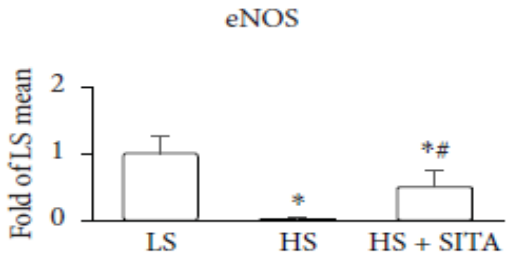

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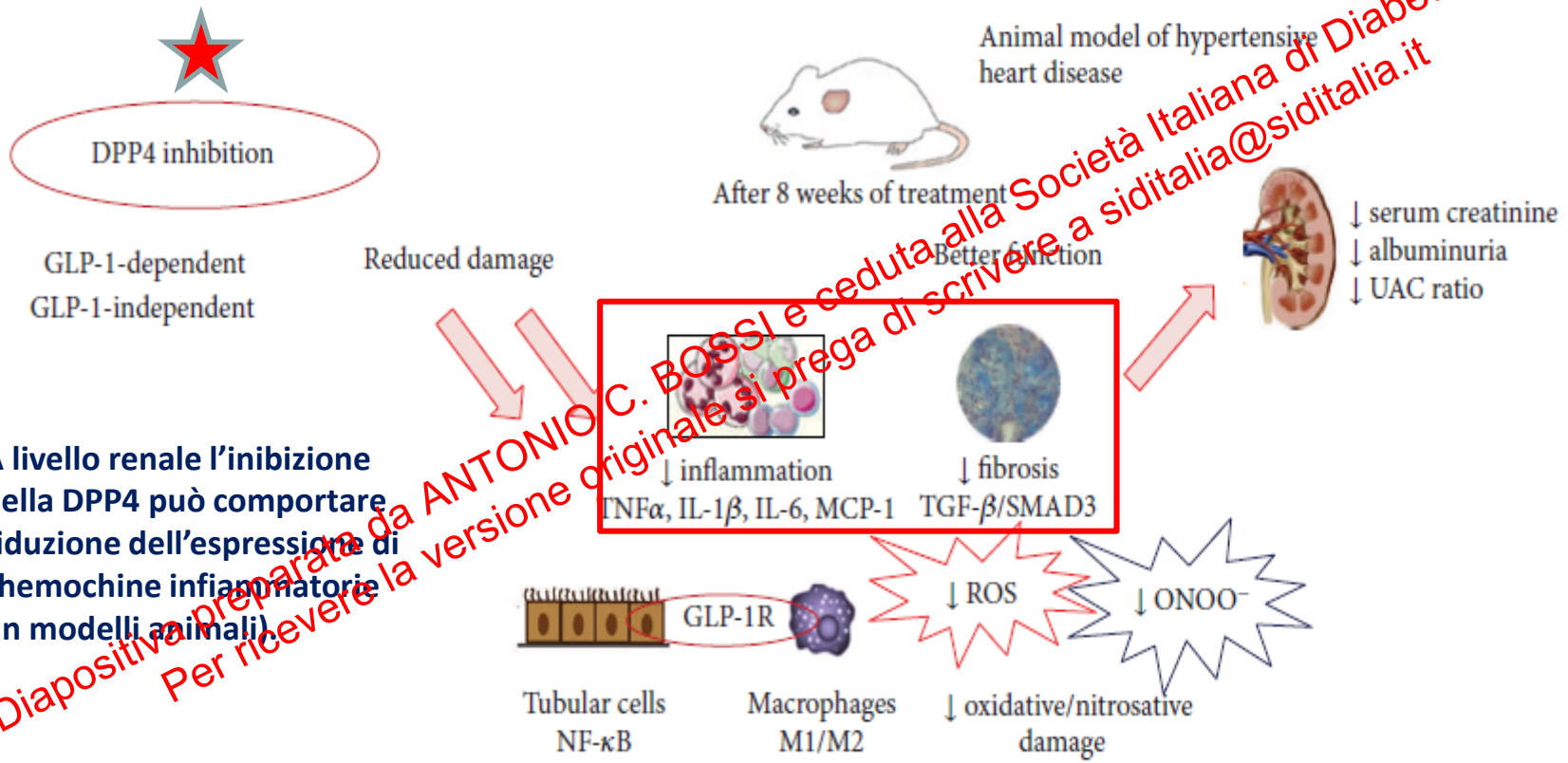

A livello renale l'inibizione della DPP4 può comportare riduzione dell'espressione di chemochine infiammatorie (in modelli animali).

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Centro Regionale Diabete
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Cappetta D et Al. 2019
Oxidative Medicine and Cellular Longevity
Article ID 8912768, 13 pages
https://doi.org/10.1155/2019/8912768

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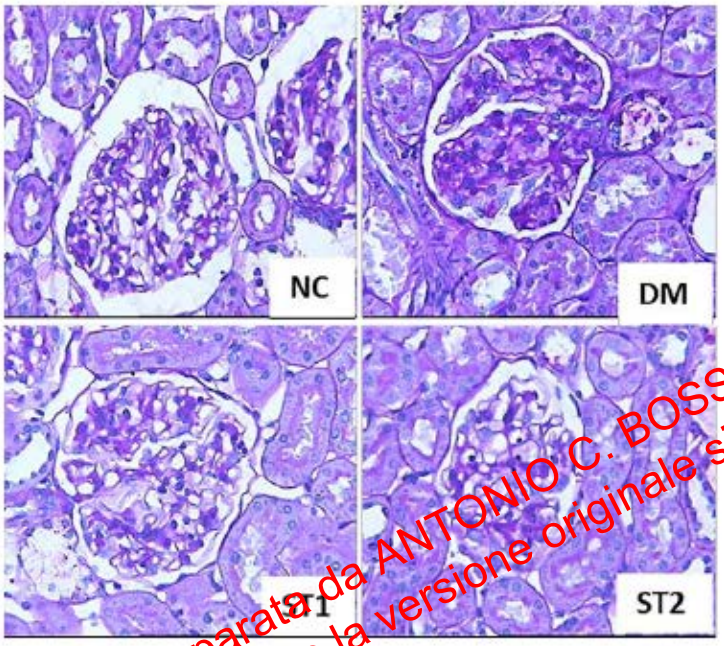
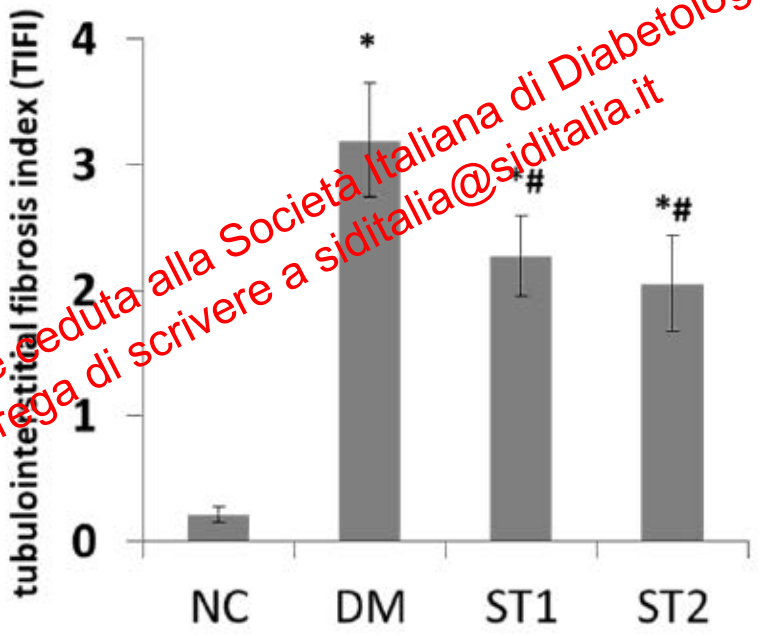
Effect of sitagliptin on tubulointerstitial Wnt/β-catenin signalling in diabetic nephropathy





Renal histopathological examination and tubulointerstitial fibrosis index (TIFI).
NC, normal control group; DM, diabetic model group;
ST1, low dose sitagliptin and ST2, high-dose sitagliptin intervention group.

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Mod. from: Ren X et Al.
Nephrology, 2019
doi: 10.1111/nep.13641

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Oltre il Cardio-Vascolare:
potenziali effetti sistemici dei DPP4-inibitori

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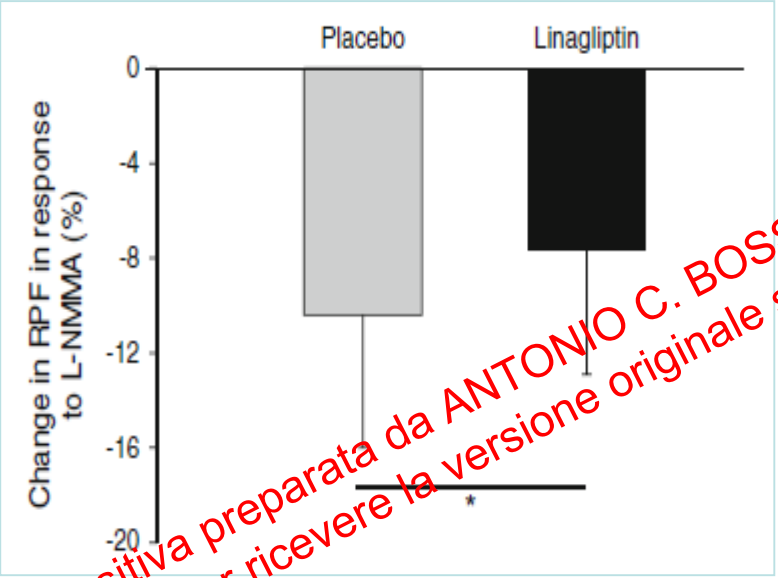
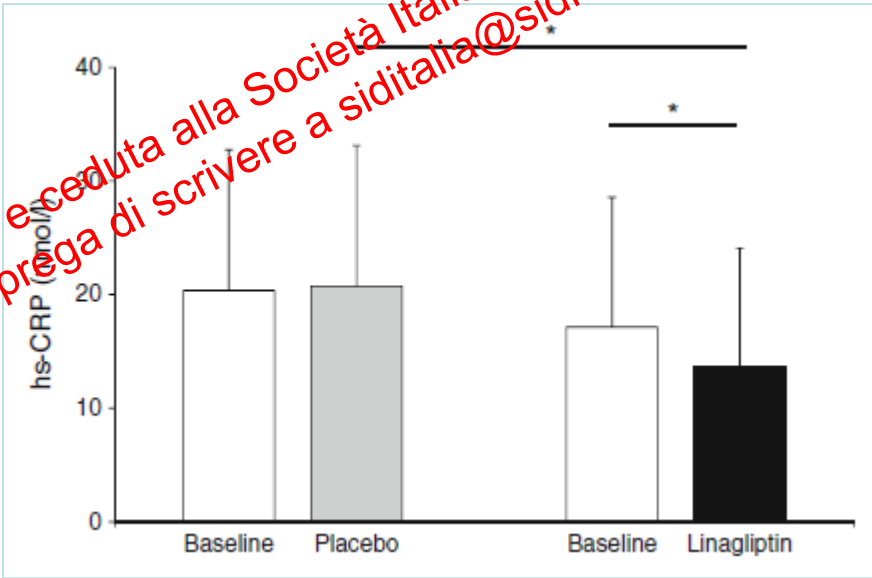
Diabetologia
DOI 10.1007/s00125-016-4083-4

Christian Ott[1] · Iris Kistner[1] · Mirjam Keller[1] · Stefanie Friedrich[1] · Carsten Willam[1] · Peter Bramlage[2] · Roland E. Schmieder[1]

ARTICLE

Effects of linagliptin on renal endothelial function in patients with type 2 diabetes: a randomised clinical trial





RPF: renal plasma flow
L-NMMA: NG-monomethyl-L-arginine (a NOS blocker)

hs-CRP: High-sensitivity C-reactive protein

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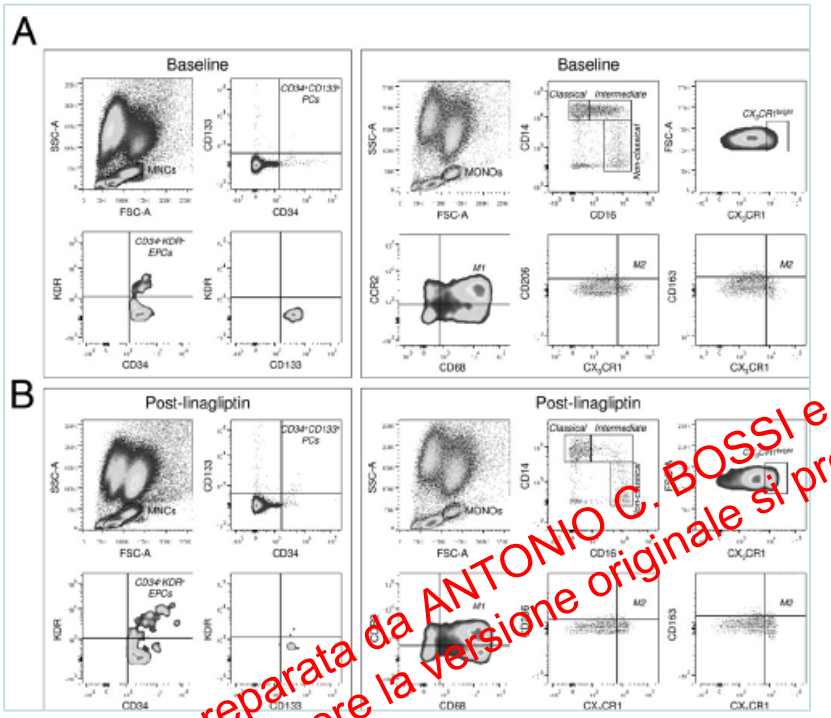
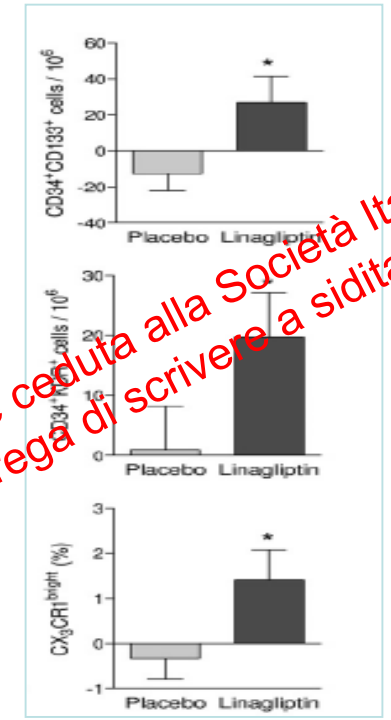
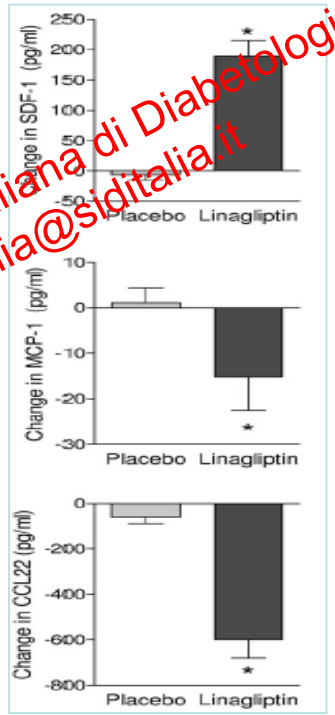
Acute Effects of Linagliptin on Progenitor Cells, Monocyte Phenotypes, and Soluble Mediators in Type 2 Diabetes







DPP-4 inhibition with linagliptin acutely increases putative vasculoregenerative and antiinflammatory cells.

Direct effects of DPP-4 inhibition may be important to lower vascular risk in diabetes, especially in the presence of CKD.

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Fadini GP et Al.
J Clin Endocrinol Metab 101: 748–756, 2016

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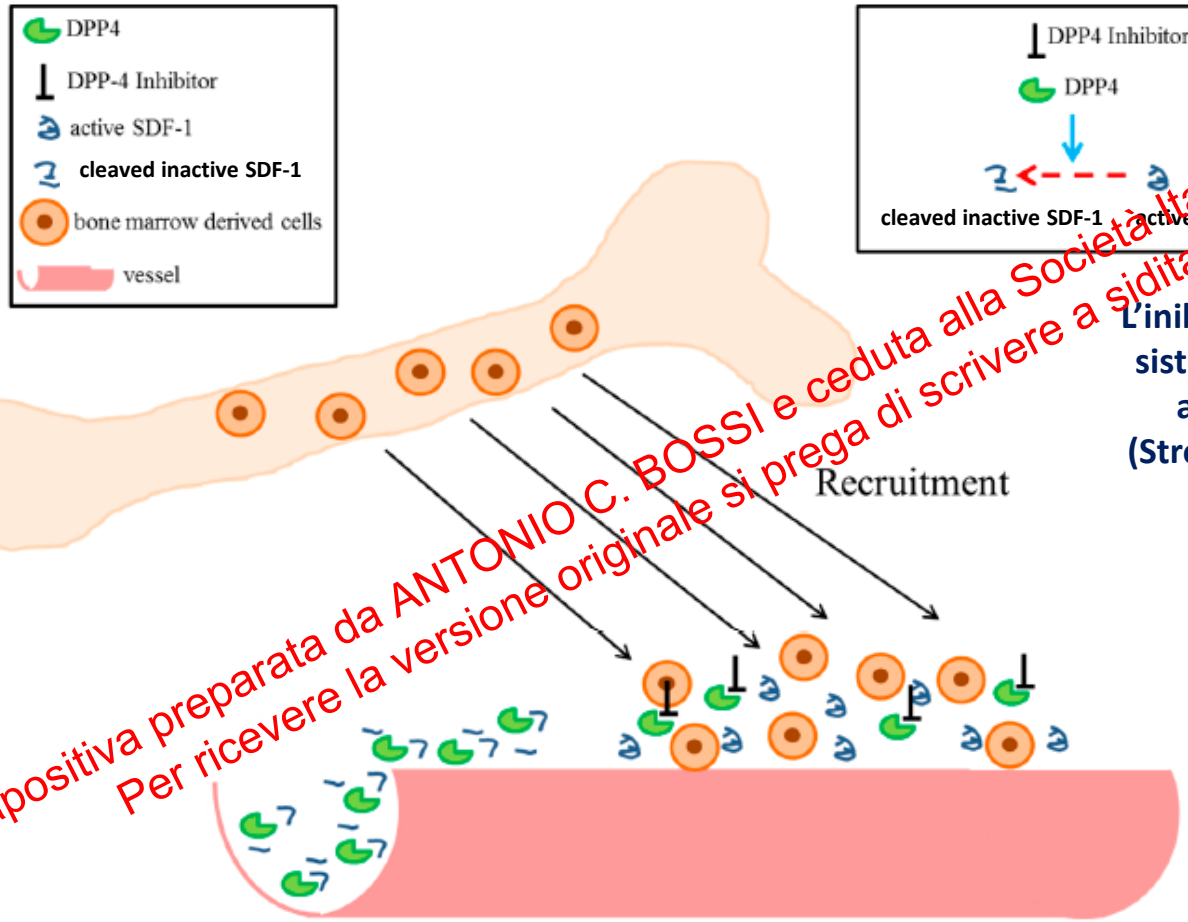
cells

Review

Is there a Chance to Promote Arteriogenesis by DPP4 Inhibitors Even in Type 2 Diabetes? A Critical Review



L'inibizione delle DPP4 a livello sistemico può determinare un aumento dei livelli di SDF-1 (Stromal cell Derived Factor-1) in grado di promuovere l'arteriogenesi

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Vedantham S, Kluever AK and Deindl E.
Cells 2018, 7, 181
doi:10.3390/cells7100181

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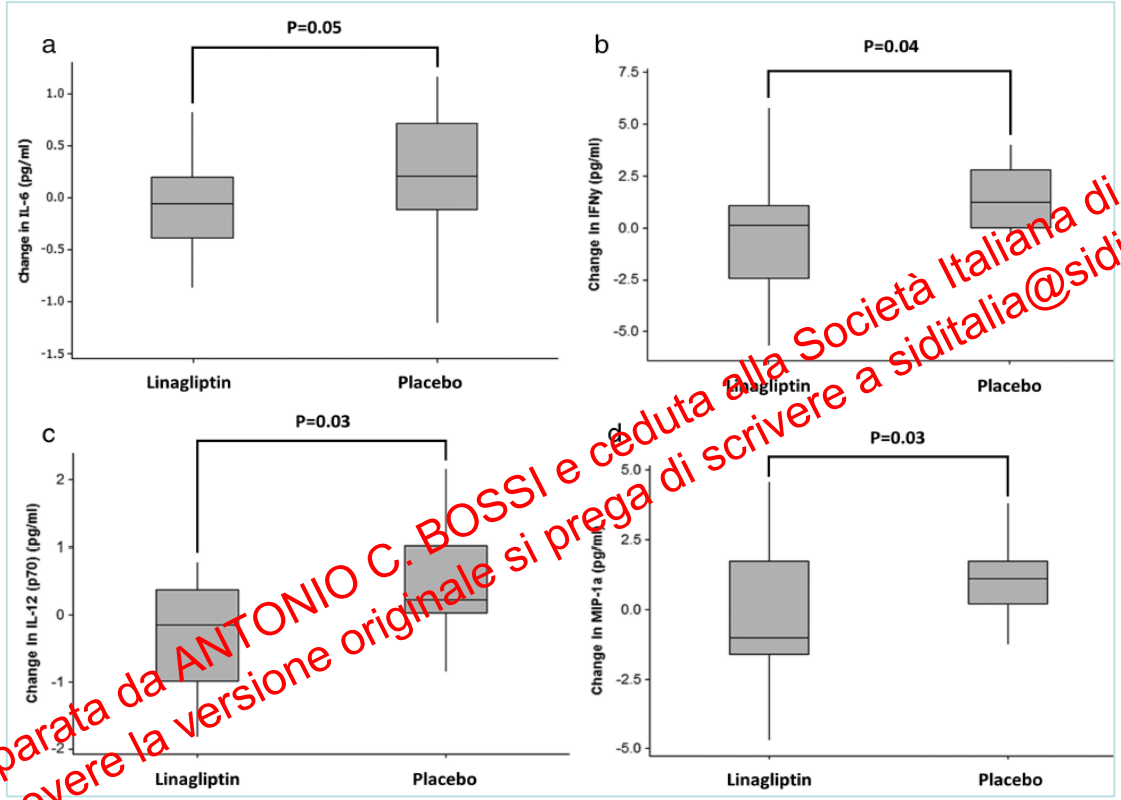
Effect of linagliptin on vascular function: a randomized, placebo-controlled study

IL6



IFNγ

IL12

MMP

Linagliptin tends to improve endothelial and neurovascular microvascular function and is associated with decreased markers of inflammation in T2D patients.
No significant effect on mitochondrial function, macrovascular function, or EPCs.

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D. Baltzis et Al. 2016
J Clin Endocrinol Metab
doi: 10.1210/jc.2016-2655

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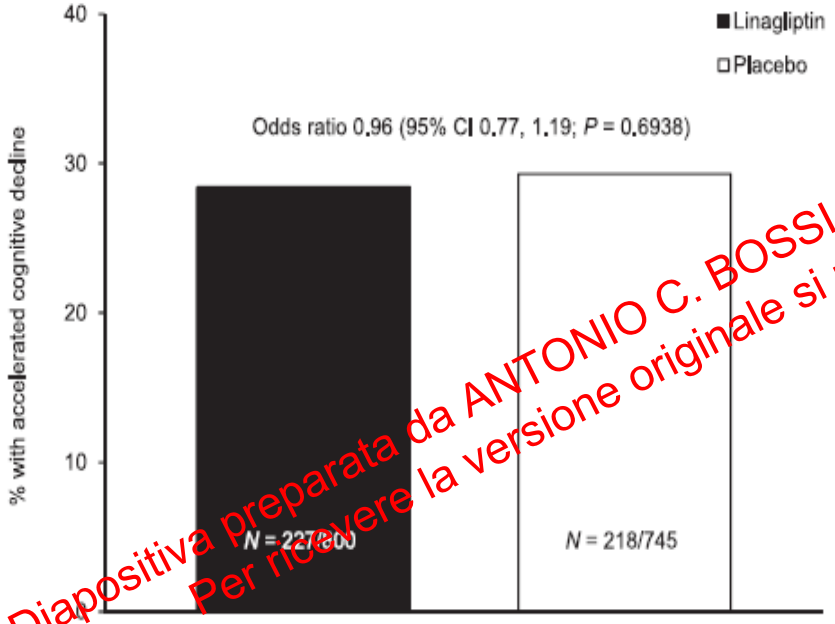
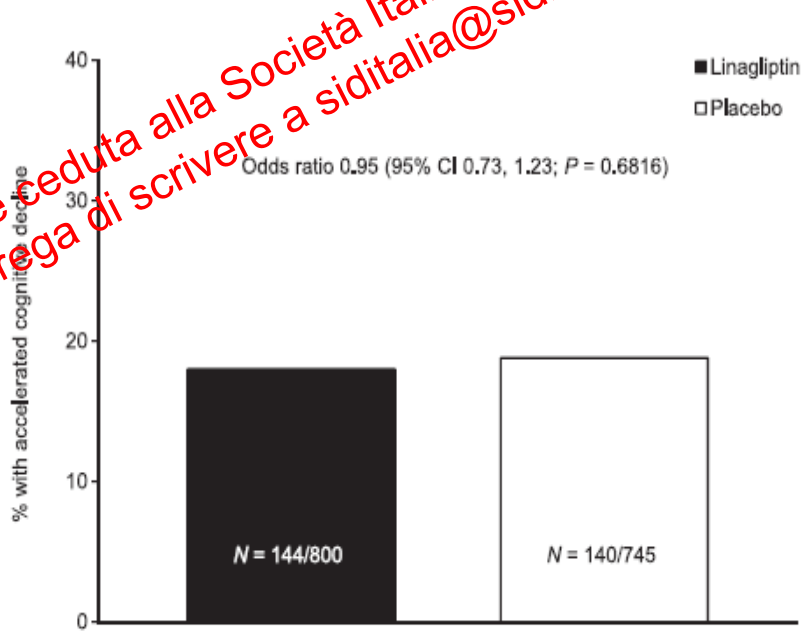
Effect of Linagliptin on Cognitive Performance in Patients With Type 2 Diabetes and Cardiorenal Comorbidities: The CARMELINA Randomized Trial

Geert Jan Biessels,[1] Chloë Verhagen,[1] Jolien Janssen,[1,2] Esther van den Berg,[1,3] Bernard Zinman,[4] Julio Rosenstock,[5] Jyothis T. George,[6] Anna Passera,[7] Sven Schnaidt,[8] and Odd Erik Johansen,[9] on behalf of the CARMELINA investigators





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Diabetes Care, 2019
doi.org/10.2337/dc19-0783

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Oltre il Cardio-Vascolare:
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CONCLUSIONI

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I farmaci DPP4-inibitori possono interferire con la sopravvivenza di pazienti diabetici con alcuni tipi di tumore?

A. No, non modificano la prognosi della malattia oncologica
B. Si, peggiorano l'evoluzione della malattia oncologica
C. Si, migliorano l'evoluzione della malattia oncologica
D. L'aumento della sopravvivenza in alcuni tipi di tumore è maggiore associando DPP4-i e metformina

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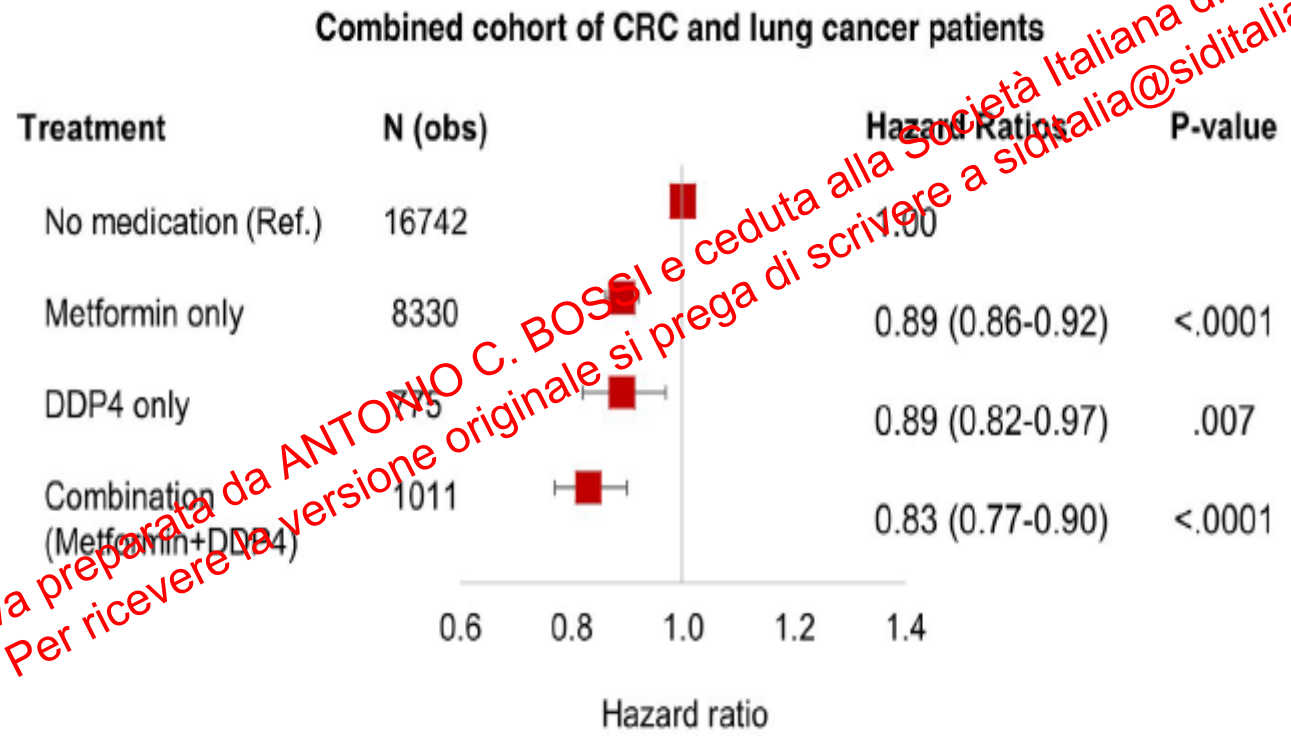
Dipeptidyl peptidase 4 inhibitors as novel agents in improving survival in diabetic patients with colorectal cancer and lung cancer: A Surveillance Epidemiology and Endpoint Research Medicare study



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Centro Studi Aterosclerosi

Bishnoi R et Al. Cancer Med, 2019
DOI: 10.1002/cam4.2278

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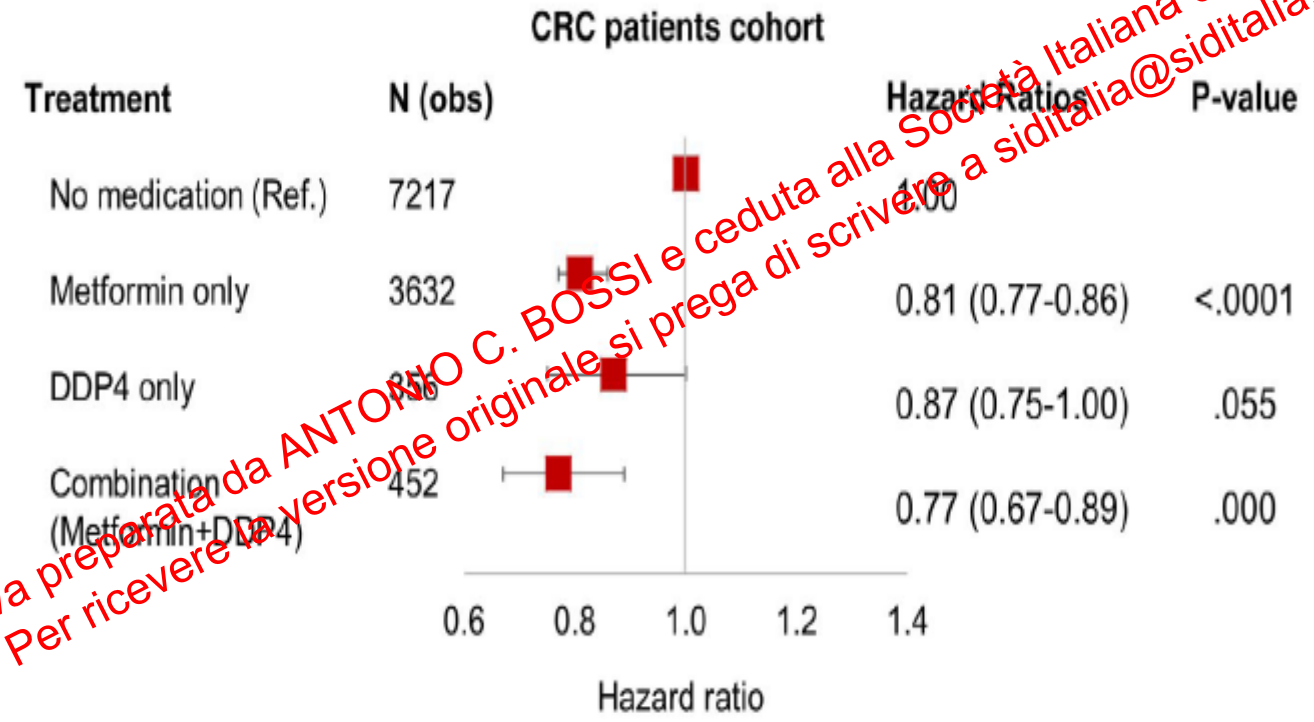
Dipeptidyl peptidase 4 inhibitors as novel agents in improving survival in diabetic patients with colorectal cancer and lung cancer: A Surveillance Epidemiology and Endpoint Research Medicare study



UOC Malattie Endocrine
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Centro Studi Aterosclerosi

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DOI: 10.1002/cam4.2278

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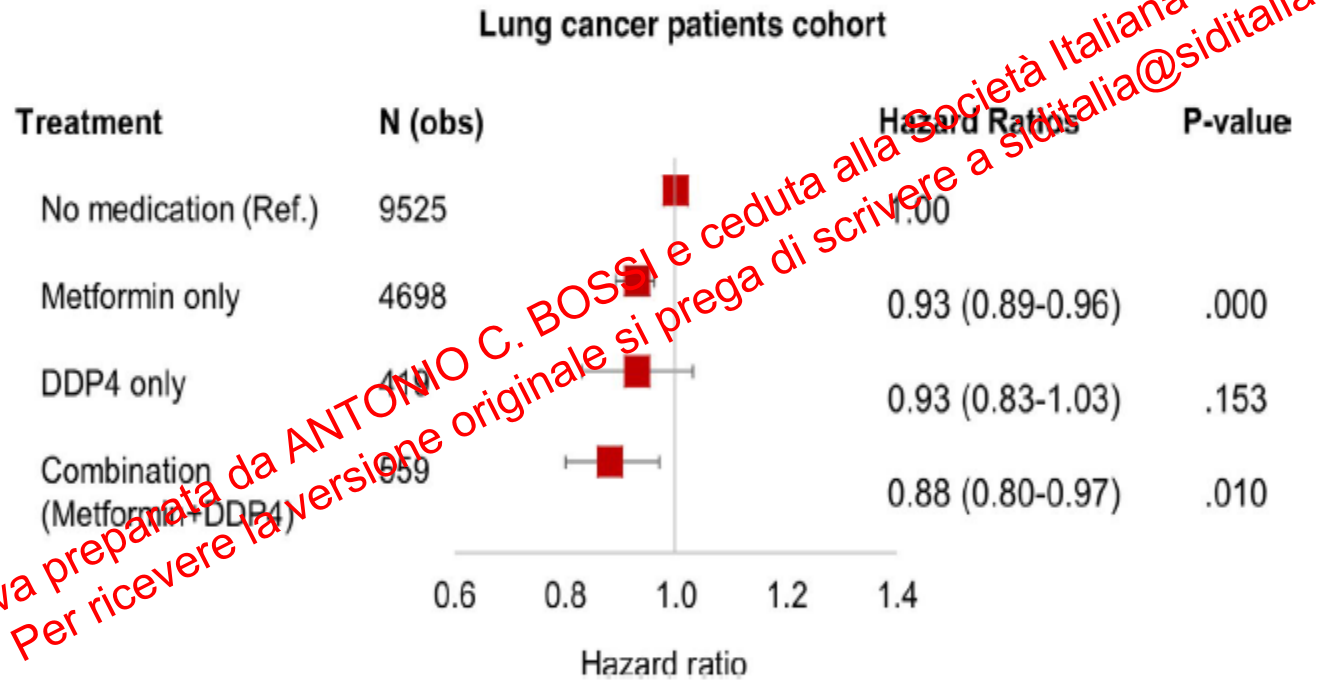

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Bishnoi R et Al. Cancer Med, 2019
DOI: 10.1002/cam4.2278

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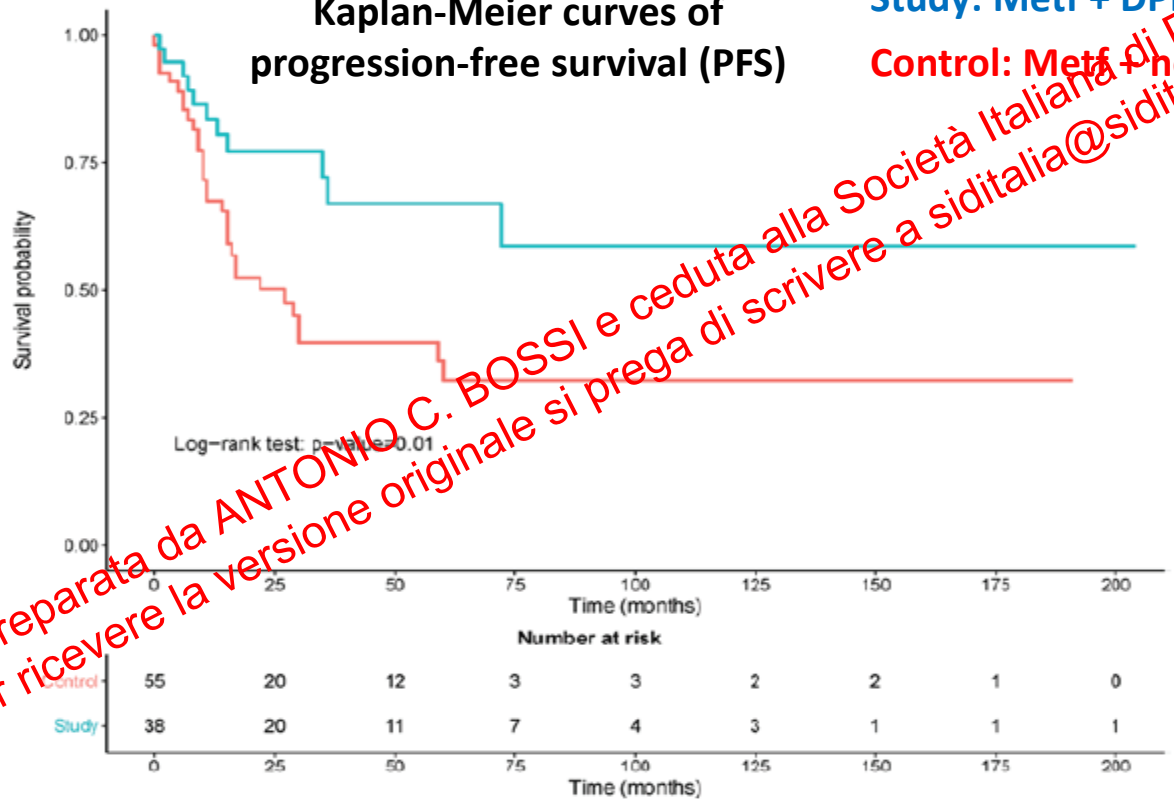
A multi-center retrospective analysis of the effect of DPP4 inhibitors on progression-free survival in advanced airway and colorectal cancers

Kaplan-Meier curves of progression-free survival (PFS)

Study: Metf + DPP4-i

Control: Metf + non-DPP4-i



UOC Malattie Endocrine
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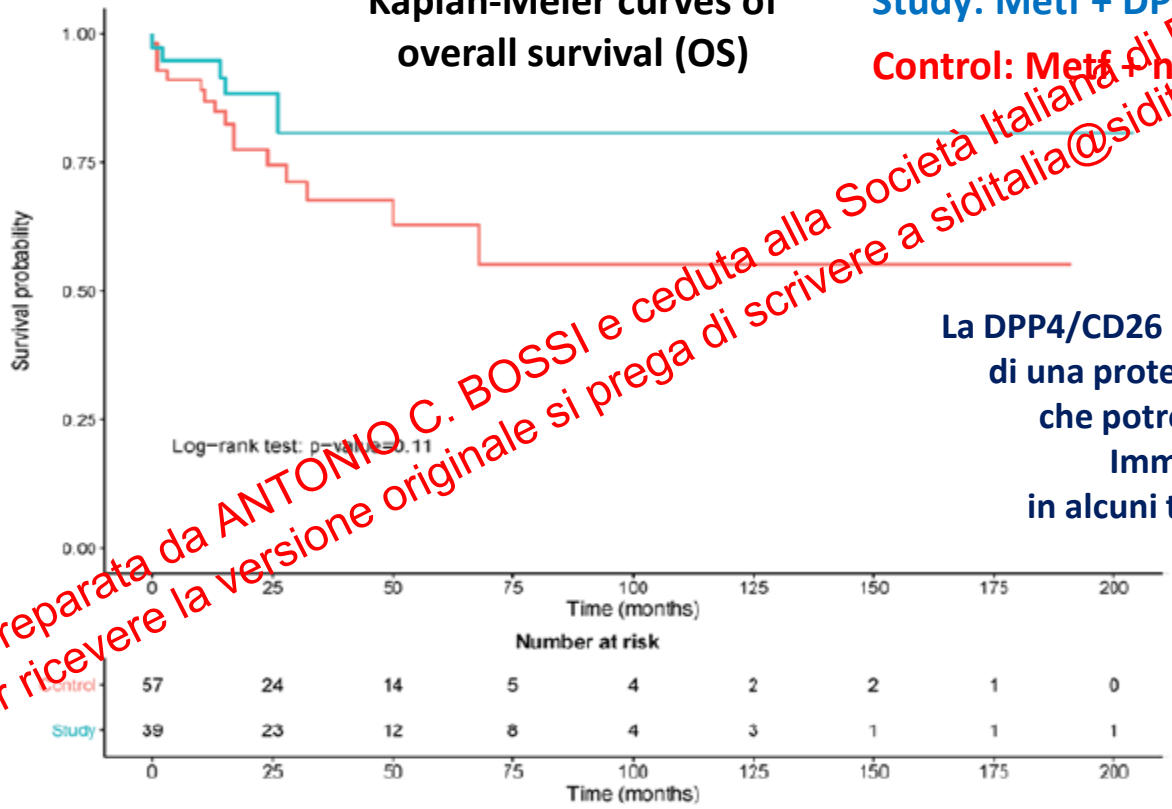
Centro Studi Aterosclerosi

Ali A et Al.
Molecular and Clinical Oncology
10: 118-124, 2019

Sistema Socio Sanitario
Regione Lombardia
ASST Bergamo Ovest

A multi-center retrospective analysis of the effect of DPP4 inhibitors on progression-free survival in advanced airway and colorectal cancers

Kaplan-Meier curves of overall survival (OS)



Study: Metf + DPP4-i

Control: Metf + non-DPP4-i

La DPP4/CD26 cellulare è parte di una proteina di superficie che potrebbe agire come Immunomodulatore in alcuni tipi di neoplasia.

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Centro Studi Aterosclerosi

Ali A et Al.
Molecular and Clinical Oncology
10: 118-124, 2019

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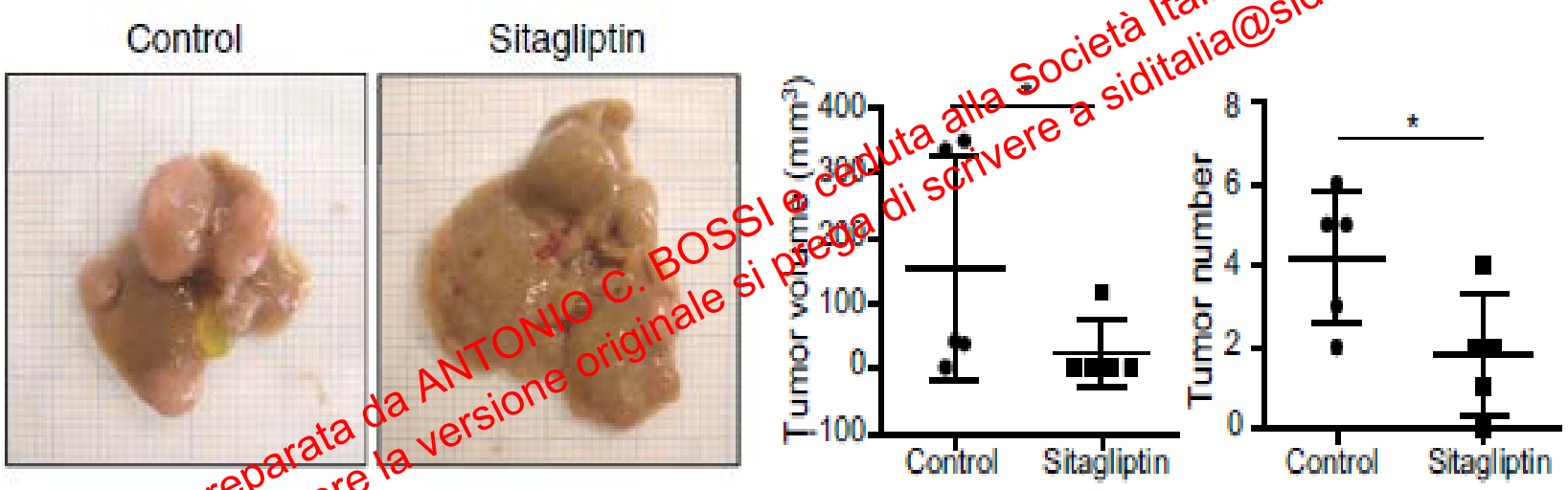
cmgh
CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

ORIGINAL RESEARCH

Dipeptidyl Peptidase 4 Inhibitors Reduce Hepatocellular Carcinoma by Activating Lymphocyte Chemotaxis in Mice



The liver of control mice at 18 weeks of age showed **multiple liver tumors**, whereas the liver of mice administered with **sitagliptin** showed significantly **smaller and fewer liver tumors** (n = 5 for each group). *P < .05.

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Centro Studi Aterosclerosi

Mod. from: Nishina S et Al.
Cell Mol Gastroenterol Hepatol
2019;7:115–134;

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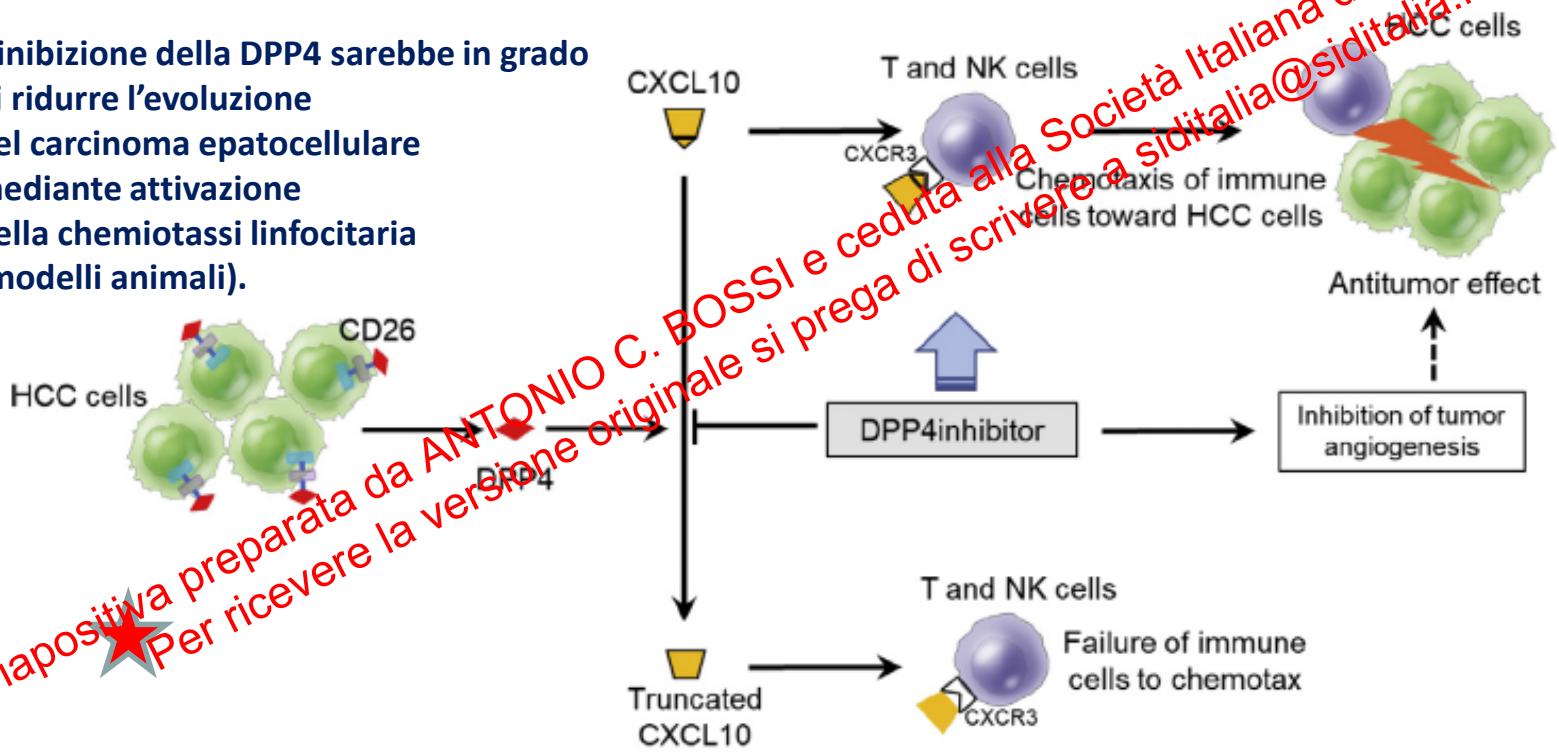
1)Glucagone, in grado di contrastare possibili ipoglicemie
2)Tireoglobulina, glicoproteina dimerica sintetizzata dalle cellule epiteliali che rivestono i follicoli tiroidei
3)SDF-1 (Stromal cell Derived Factor-1) in grado di promuovere l'arteriogenesi

cmgh
CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

ORIGINAL RESEARCH

Dipeptidyl Peptidase 4 Inhibitors Reduce Hepatocellular Carcinoma by Activating Lymphocyte Chemotaxis in Mice

L'inibizione della DPP4 sarebbe in grado di ridurre l'evoluzione del carcinoma epatocellulare mediante attivazione della chemiotassi linfocitaria (modelli animali).



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Nishina S et Al.
Cell Mol Gastroenterol Hepatol
2019;7:115–134;

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Nationwide Trends in Pancreatitis and Pancreatic Cancer Risk Among Patients With Newly Diagnosed Type 2 Diabetes Receiving Dipeptidyl Peptidase-4 Inhibitors

Minyoung Lee,[1] Jiyu Sun,[2] Minkyung Han,[3] Yongin Cho,[1] Ji-Yeon Lee,[1] Chung Mo Nam,[4] and Eun Seok Kang[1,5]

Table 2—HRs for pancreatitis and pancreatic cancer associated with DPP-4i use

Exposure group	Events	PYs	Incidence rate*	Crude HR (95% CI) 0d time lag	*P*	6-month time lag	*P*
Pancreatitis							
DPP-4i use	156	14,545	1,073	1.18 (0.99–1.40)	0.062	1.15 (0.95–1.41)	0.153
Nonuse	928	99,289	935	1.00 (reference)		1.00 (reference)	
Pancreatic cancer							
DPP-4i use	35	14,827	236	1.32 (0.92–1.90)	0.130	1.55 (1.02–2.35)	0.038
Nonuse	202	100,838	200	1.00 (reference)		1.00 (reference)	

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Diabetes Care, 2019
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Table 3—Risks for pancreatitis and pancreatic cancer associated with DPP-4i use by time since the initial prescription

	All subjects				Subjects without insulin use			
DPP-4i exposure category	Events	PYs	Adjusted HR	95% CI	Events	PYs	Adjusted HR	95% CI
Pancreatitis								
No use	928	99,289	1.00 (reference)	—	897	97,829	1.00 (reference)	—
<3 months	33	2,206	1.32	1.01–1.75	31	2,178	1.29	0.96–1.72
3 to <6 months	16	1,875	1.09	0.71–1.66	16	1,852	1.06	0.69–1.65
6 to <12 months	35	3,028	1.39	1.01–1.90	35	2,988	1.43	1.04–1.96
≥12 months	72	7437	1.19	0.93–1.52	69	7,330	1.18	0.92–1.51
Pancreatic cancer								
No use	202	100,838	1.00 (reference)	—	194	99,307	1.00 (reference)	—
<3 months	7	2,236	1.93	1.17–3.21	7	2,206	1.86	1.10–3.13
3 to <6 months	4	1,900	1.39	0.57–3.42	4	1,876	1.13	0.42–3.08
6 to <12 months	8	3,074	2.00	1.01–3.96	7	3,032	2.04	1.03–4.04
≥12 months	16	7,617	1.95	1.16–3.29	15	7,506	1.86	1.09–3.17

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Nationwide Trends in Pancreatitis and Pancreatic Cancer Risk Among Patients With Newly Diagnosed Type 2 Diabetes Receiving Dipeptidyl Peptidase-4 Inhibitors

Minyoung Lee,[1] Jiyu Sun,[2] Minkyung Han,[3] Yongin Cho,[1] Ji-Yeon Lee,[1] Chung Mo Nam,[4] and Eun Seok Kang[1,5]

…DPP-4i use was associated with increased risks of pancreatitis and pancreatic cancer in patients with newly diagnosed T2DM.

The risk was not affected by potential confounding risk factors.

However, **considering the absence of trend according to exposure duration of DPP-4i** and limited follow-up duration in the current study, **the chances of reverse causality cannot be excluded**.

…physicians should develop better strategies to **monitor the DPP-4i use** in clinical settings, **particularly in patients with newly diagnosed T2DM**.

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Diabetes Care, 2019
doi.org/10.2337/dc18-2195

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Oltre il Cardio-Vascolare:
potenziali effetti sistemici dei DPP4-inibitori

AGENDA

POTENZIALI ATTIVITA' DEI DPP4-INIBITORI:

- **a livello RENALE**
- **a livello ENDOTELIALE – EPC – ANGIOGENESI - MCI**
- **a livello TUMORALE**
- **a livello IBD – BP**
- **a livello ANTIFIBROTICO**

CONCLUSIONI

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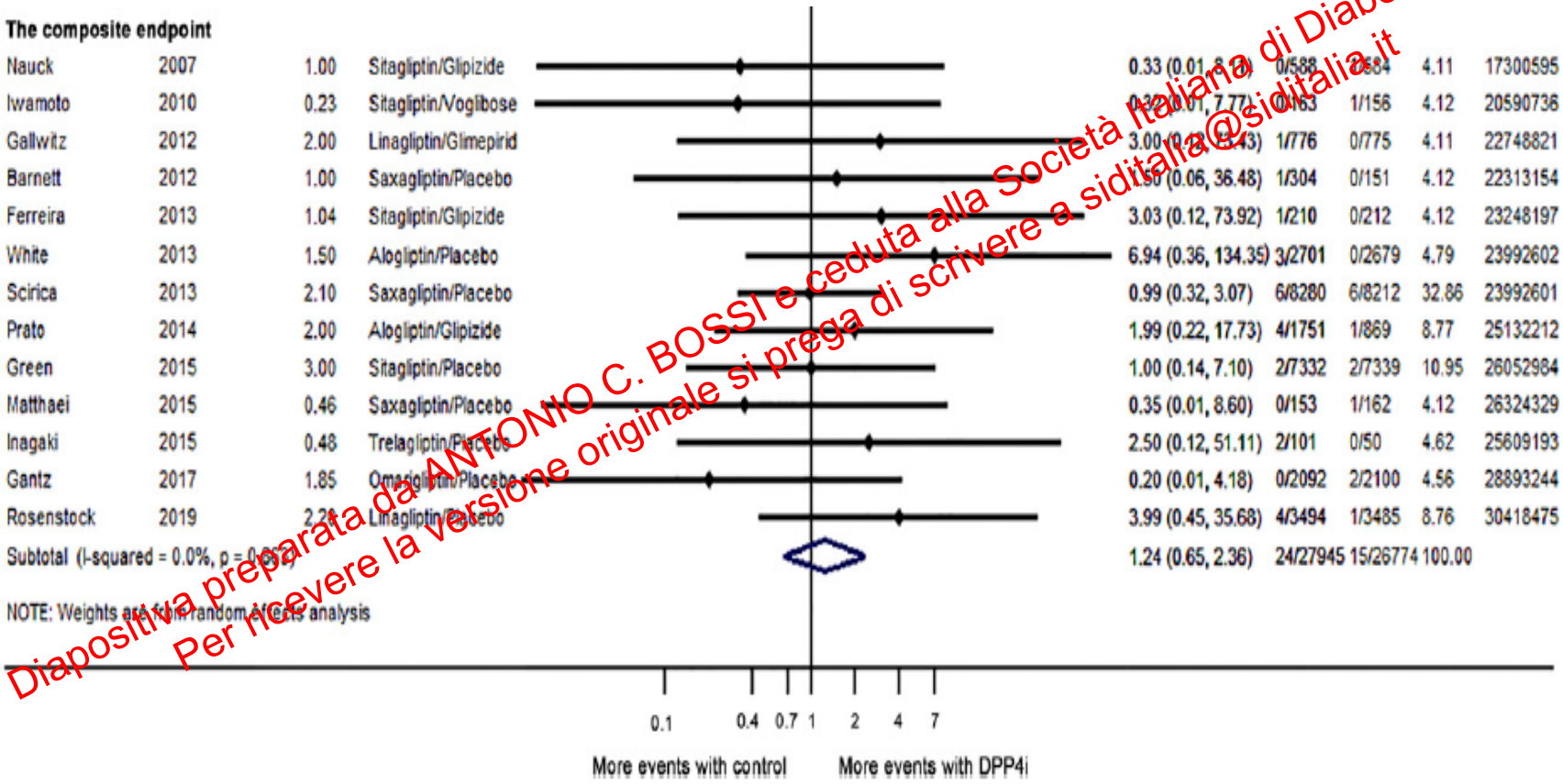
Dipeptidyl Peptidase 4 Inhibitors and Risk of Inflammatory Bowel Disease Among Patients With Type 2 Diabetes: A Meta-analysis of Randomized Controlled Trials

Guangyao Li,[1,2] Matthew J. Crowley,[3,4] Huilin Tang,[5] Jeff Y. Yang,[6,7] Robert S. Sandler,[6,7] and Tiansheng Wang[7]

IBD: Inflammatory Bowel Disease + Chron's diasease + Ulcerative colitis



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Diabetes Care 2019
doi.org/10.2337/dc18-1578

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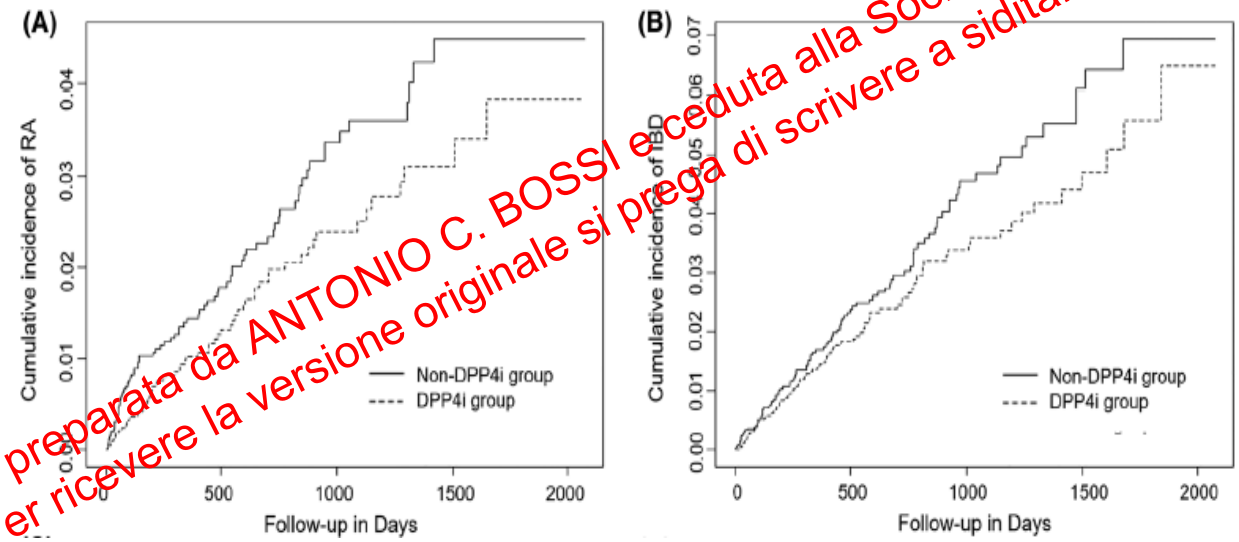
Dipeptidyl peptidase-4 inhibitors lower the risk of autoimmune disease in patients with type 2 diabetes mellitus: A nationwide population-based cohort study

BJCP — BRITISH PHARMACOLOGICAL SOCIETY

	DPP4i group (*n* = 497 619)			Non-DPP4i group (*n* = 643 165)				
All patients	Cases	Person-years	Incidence (per 1000 person-years)	Cases	Person-years	Incidence (per 1000 person-years)	HR	(95% CI)
Rheumatoid arthritis	65	775 741	0.08	120	1 138 608	0.11	0.67	(0.49–0.92)
Inflammatory bowel disease	100	775 672	0.13	175	1 138 499	0.15	0.94	(0.72–1.24)



Kaplan–Meier curves for cumulative incidence of autoimmune disease.
A, Rheumatoid arthritis (RA); B, inflammatory bowel diseases (IBD);

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Seong JM, Yee J, Gwak HS.
Br J Clin Pharmacol. 2019; 85:1719–1727.

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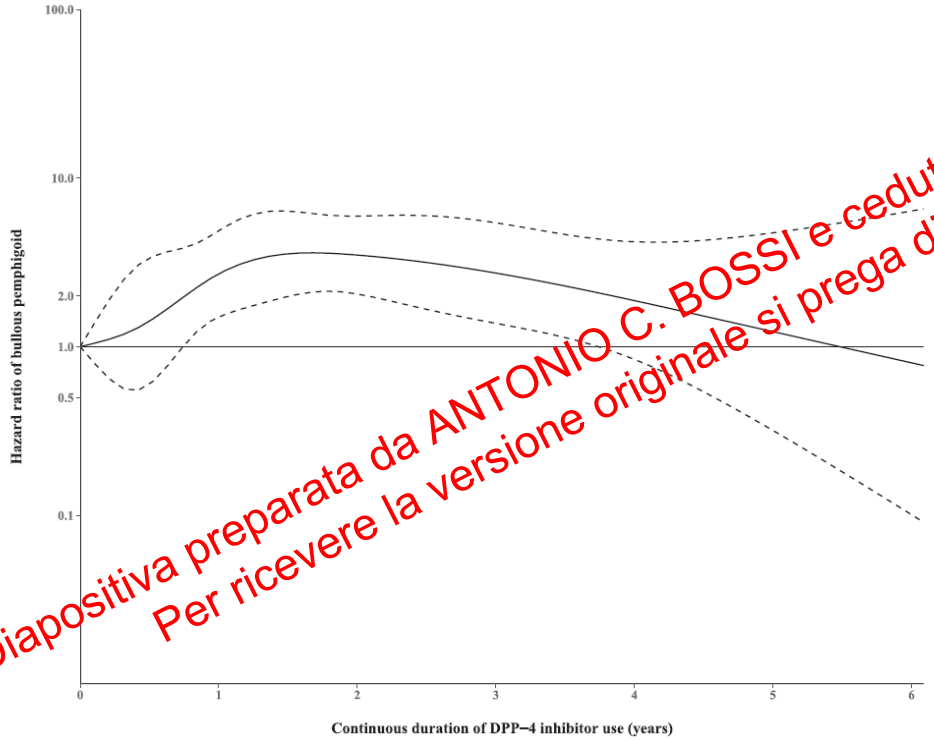
Dipeptidyl Peptidase 4 Inhibitors and the Risk of Bullous Pemphigoid Among Patients With Type 2 Diabetes

Antonios Douros,[1,2,3] Julie Rouette,[4] Hui Yin,[1] Oriana Hoi Yun Yu,[1,5] Kristian B. Filion,[1,2,4] and Laurent Azoulay[1,4,6]



During 711,311 person-years of follow-up, 150 patients were newly diagnosed with BP (crude incidence rate, 21.1 per 100,000 person-years). **Current use of DPP-4 inhibitors was associated with an increased risk of BP** (47.3 vs. 20.0 per 100,000 person-years; **HR 2.21** [95% CI 1.45–3.38]).

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CONCLUSIONI

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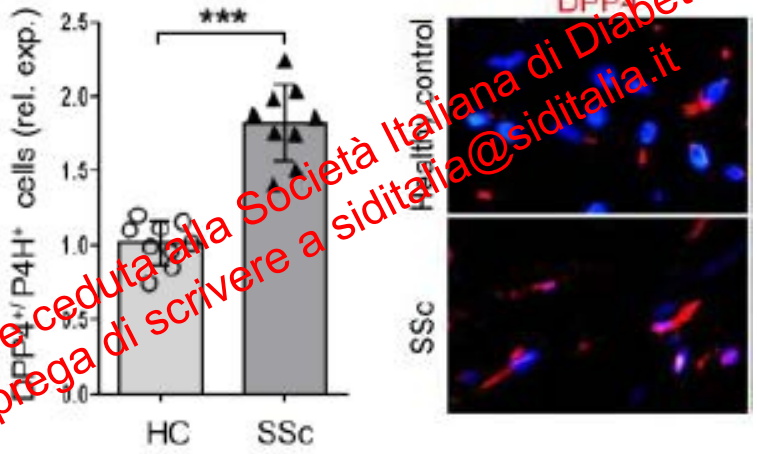
Dipeptidyl-peptidase-4 as a marker of activated fibroblasts and a potential target for the treatment of fibrosis in Systemic Sclerosis (SSc)

DPP4 expression is increased in SSc and murine models of SSc.



Induction of DPP4 by TGF-β.

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Soare A et Al.
Arthritis and Rheumatology, 2019
doi: 10.1002/art.41058

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Dipeptidyl-peptidase-4 as a marker of activated fibroblasts and a potential target for the treatment of fibrosis in Systemic Sclerosis

Pharmacological inhibition of DPP4 induces the regression of bleomycin- and cGvHD-induced experimental fibrosis.

DPP4 characterizes a population of activated fibroblasts and **regulates TGF-β-induced fibroblast activation**.

Inhibition of DPP4 exerts potent anti-fibrotic effects in well tolerated doses.

These results may have direct translational implications as DPP4 inhibitors are already in clinical use for diabetes.

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Mod. from: Soare A et Al.
Arthritis and Rheumatology, 2019
doi: 10.1002/art.41058

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Hepatology Research

Combined effect of a farnesoid X receptor agonist and dipeptidyl peptidase-4 inhibitor on hepatic fibrosis

The farnesoid X receptor agonist **obeticholic acid** (OCA) ameliorates the histological features of NASH. Satisfactory antifibrotic effects have not yet been reported. Here, were investigated the combined effects of OCA + a dipeptidyl peptidase-4 inhibitor (sitagliptin) on **hepatic fibrogenesis** in a rat model of **NASH**. Treatment with OCA + sitagliptin synergistically affected hepatic fibrogenesis by **counteracting endotoxemia induced by intestinal barrier dysfunction** and **suppressing Ac-HSC (activated hepatic stellate cells) proliferation**.

UOC Malattie Endocrine
Centro Regionale Diabete
Centro Studi Aterosclerosi

Shimozato N et Al.
Hepatology Research 2019
doi: 10.1111/hepr.13385

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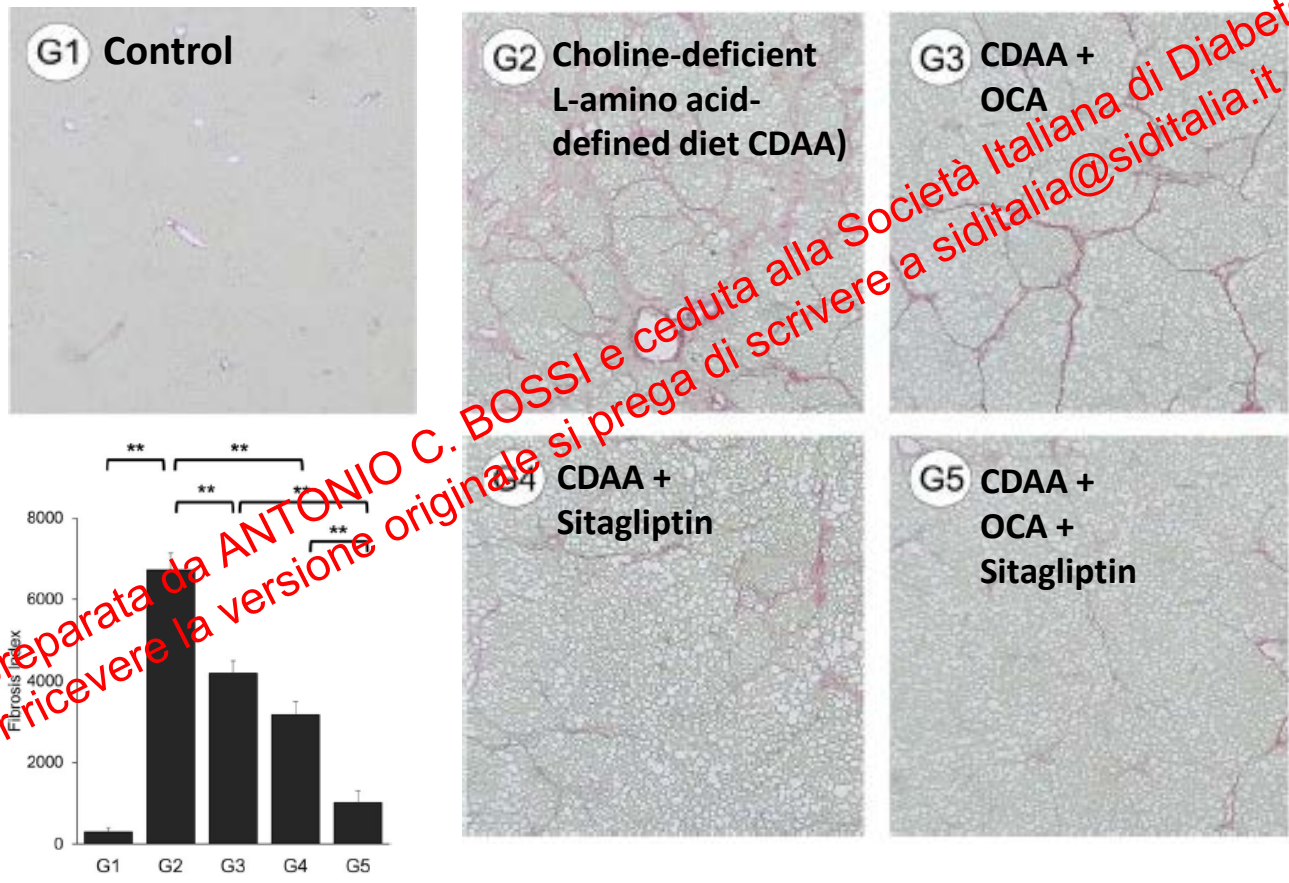
Hepatology Research

Combined effect of a farnesoid X receptor agonist and dipeptidyl peptidase-4 inhibitor on hepatic fibrosis



UOC Malattie Endocrine
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Shimozato N et Al.
Hepatology Research 2019
doi: 10.1111/hepr.13385

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CONCLUSIONI

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- **In programmi di sorveglianza post-marketing a lungo termine, l'utilizzo degli inibitori DPP4 rivela:**
  - Una efficacia ipoglicemizzante intermedia, con basso rischio di ipoglicemia ed effetto neutro sul peso corporeo

- **Lo studio PERS&O è un trial definibile come:**
  - Retrospettivo, osservazionale, monocentrico, "real-world"

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Gestione del rischio globale del diabetico di tipo 2:

un ruolo per i DPP4?

Oltre il Cardio-Vascolare: potenziali effetti sistemici

Antonio C. Rossi - Treviglio (BG)

GRAZIE per la Vostra Attenzione!!!

9 novembre 2019

Milano

Hilton Milan