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22-23 giugno 2018



Il pleiotropismo dei DPP-4 inibitori: realtà o fantasie?

Gian Paolo Fadini

Diapositiva preparata da GIAN PAOLO FADINI e ceduta alla Società Italiana di Diabetologia.
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University
of Padua

Venetian Institute of
Molecular Medicine



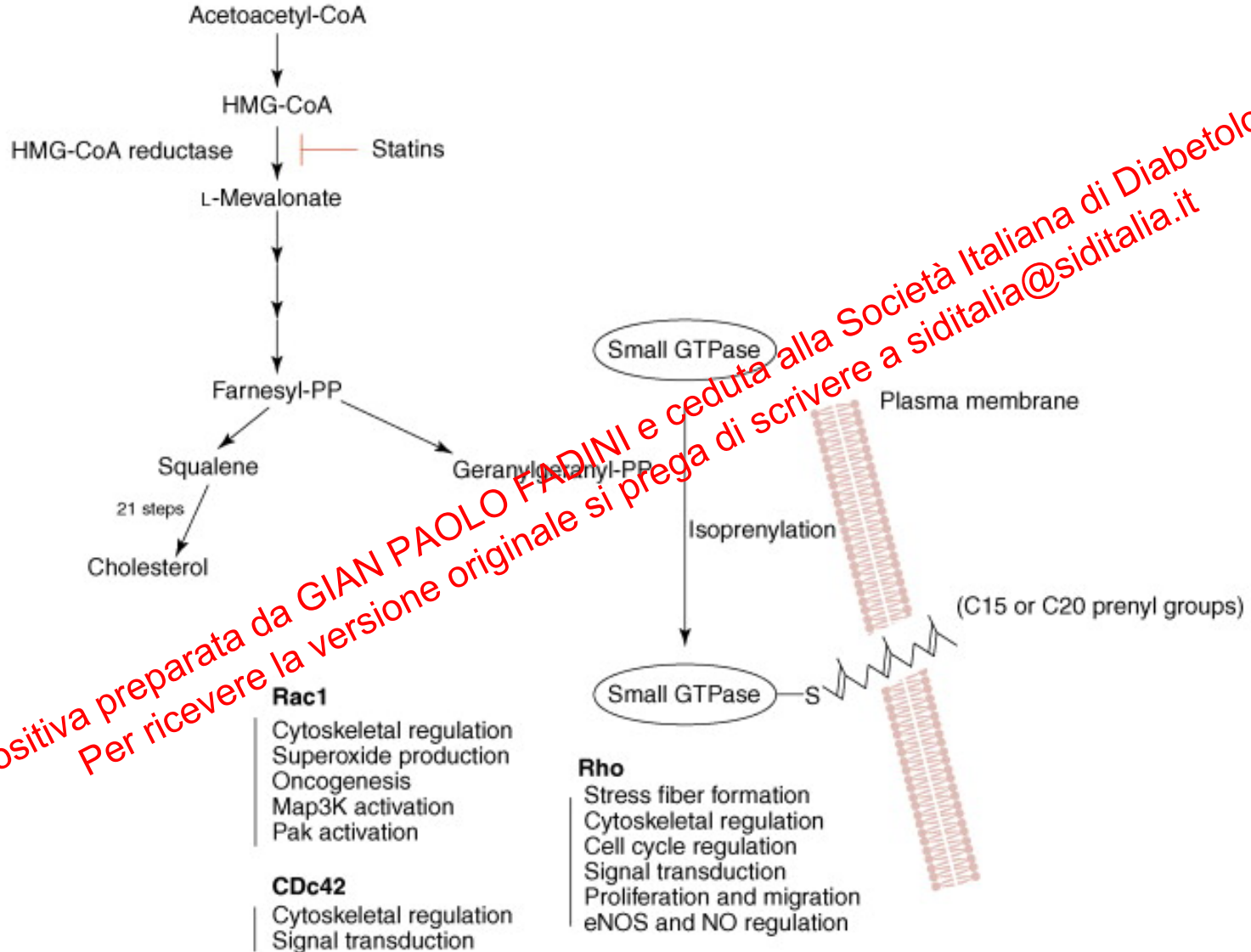
Conflitti di interesse

Gian Paolo Fadini dichiara di aver ricevuto grant, lecture fees o altro supporto da:

- **Abbott**
- **AstraZeneca**
- **Boehringer**
- **Lilly**
- **Merck**
- **Novartis**
- **Novonordisk**
- **Sanofi**

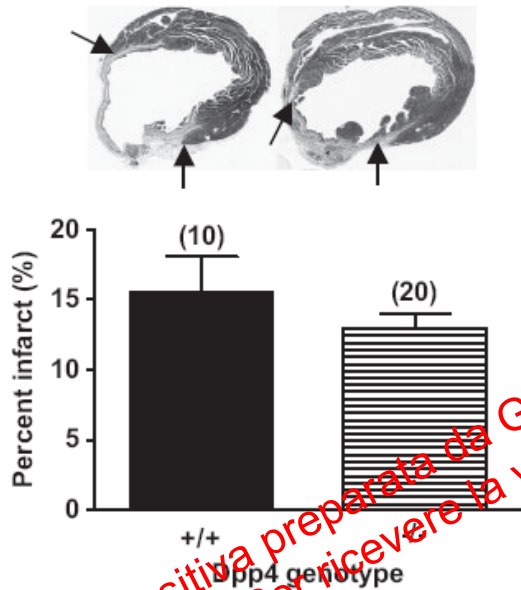
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Statin pleiotrophy

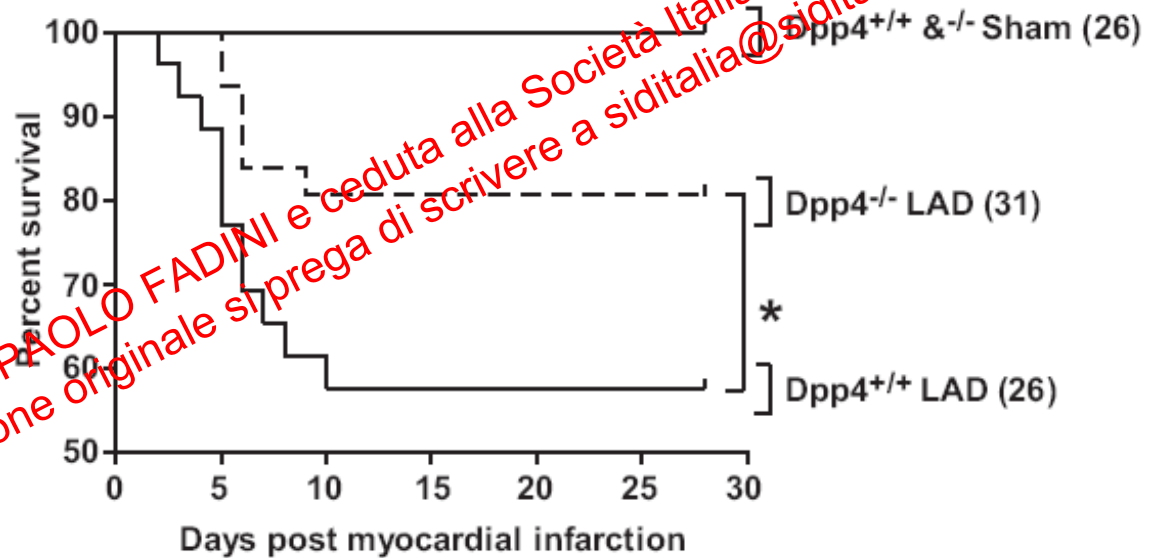


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Genetic Deletion or Pharmacological Inhibition of Dipeptidyl Peptidase-4 Improves Cardiovascular Outcomes After Myocardial Infarction in Mice

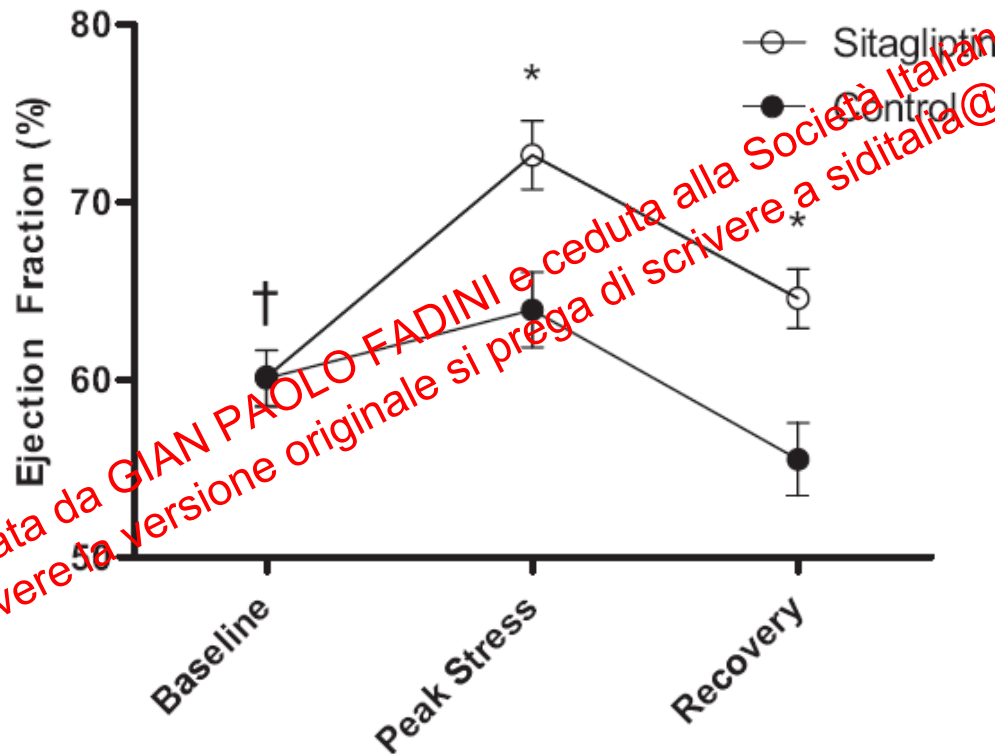


Similar infarct area



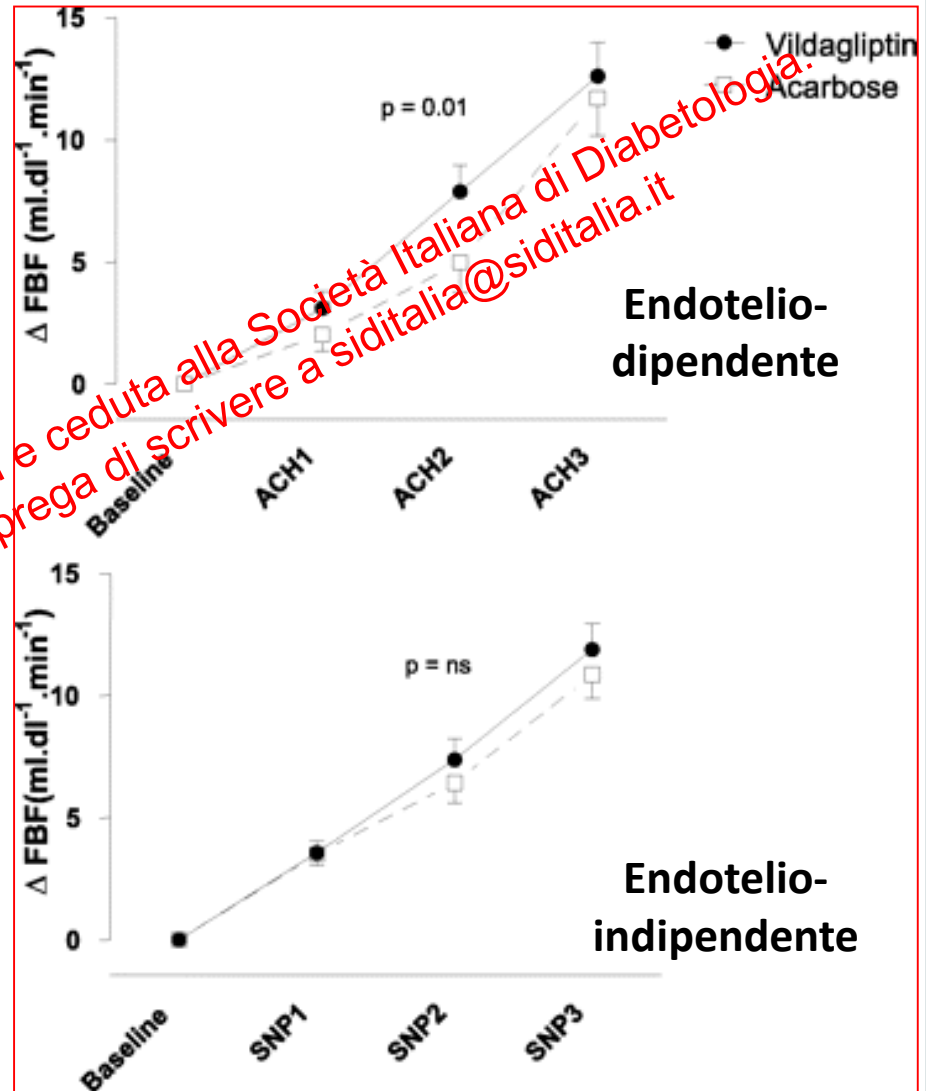
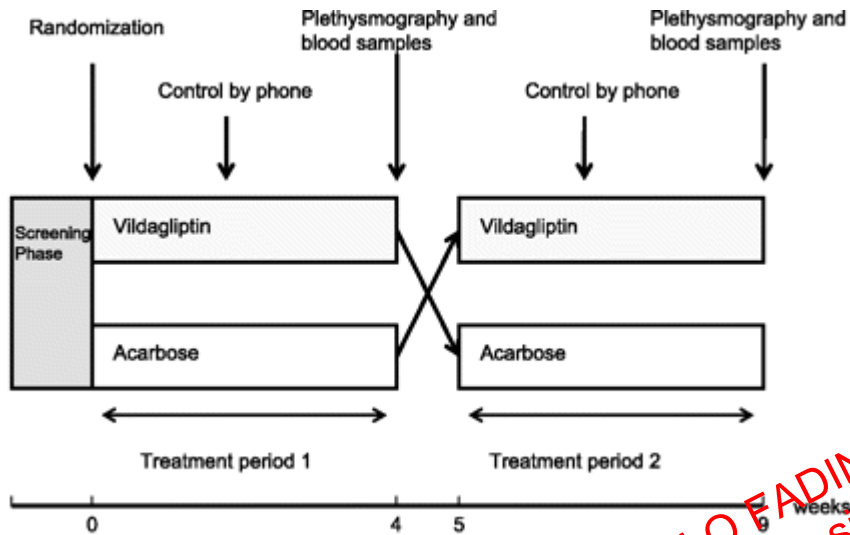
Improved survival

DPP-4 Inhibition by Sitagliptin Improves the Myocardial Response to Dobutamine Stress and Mitigates Stunning



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Vildagliptin improves endothelium-dependent vasodilatation in type 2 diabetes



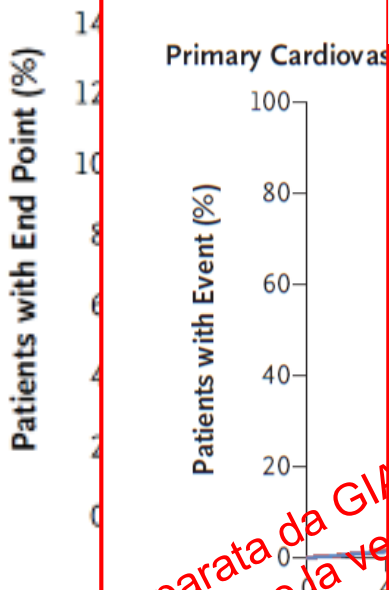
DPP4i CVOTs

SAVOR – 16k pts – 2.1 yr f-up

Primary End Point

TECOS – 14k pts – 3.0 yr f-up

EXAMINE– 5.3k pts – 1.5 yr f-up



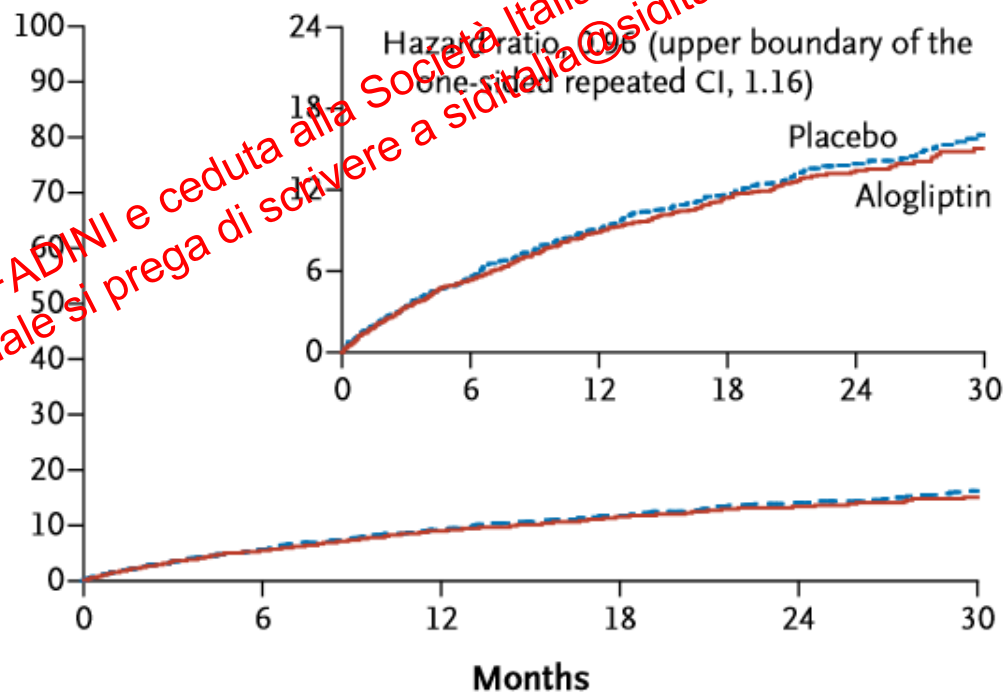
No. at Risk

Placebo
Saxagliptin

No. at Risk

Sitagliptin 7332 71
Placebo 7339 71

Cumulative Incidence of Primary End-Point Events (%)

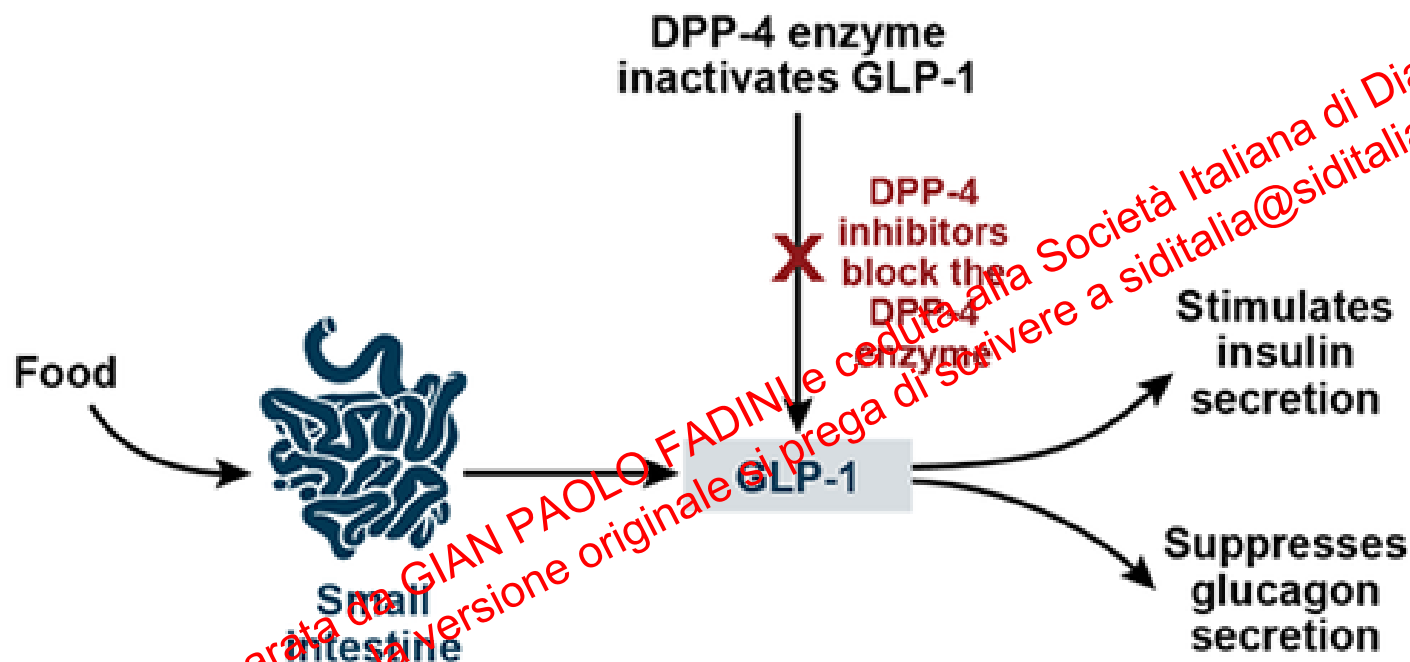


No. at Risk

Placebo	2679	2299	1891	1375	805	286
Alogliptin	2701	2316	1899	1394	821	296

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DPP-4i: meccanismo d'azione

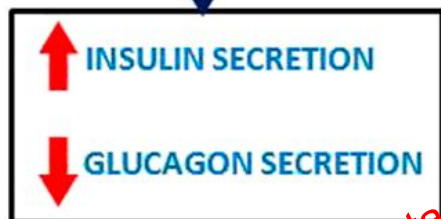


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DPP-4i: meccanismo d'azione

CLASSICAL MECHANISM

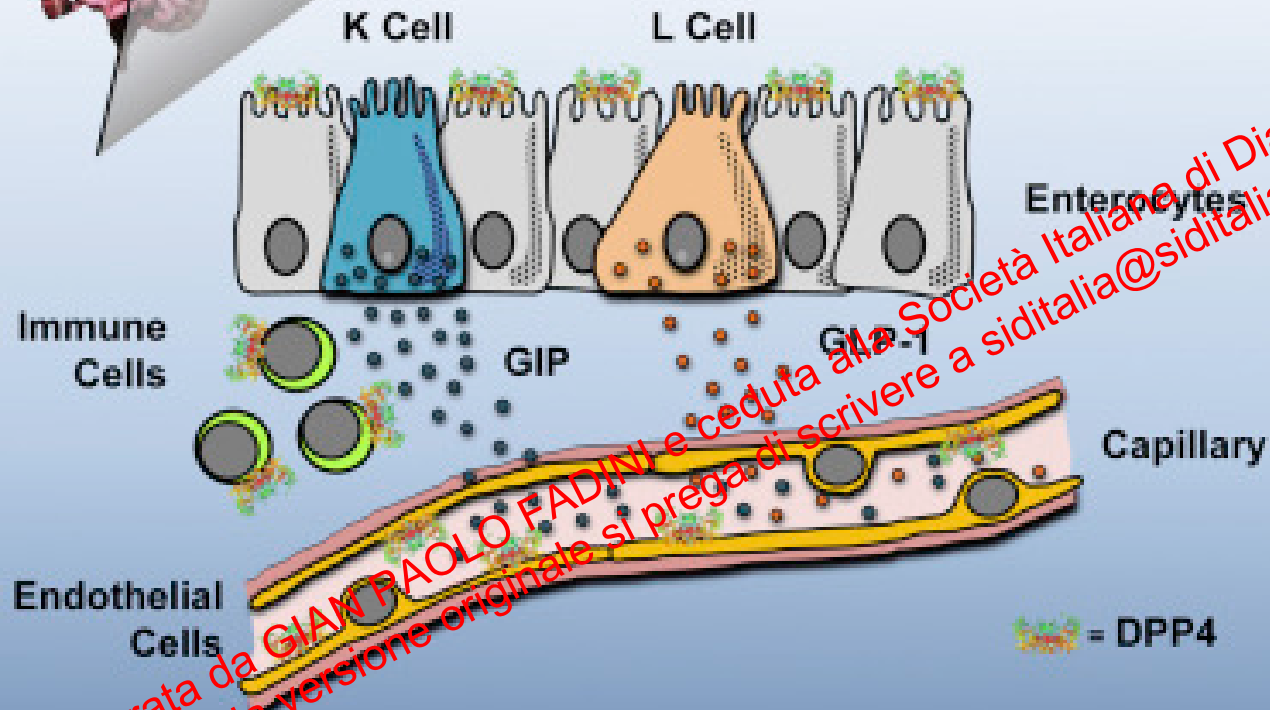
**DPP-4 INHIBITION IN
PERIPHERAL PLASMA
PREVENTS INACTIVATION
OF CIRCULATING GLP-1 IN
PERIPHERAL PLASMA**



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Mouse gut

Selective pharmacological inhibition of **enteric DPP4** improves **glucose control** under both euglycemic and insulin-resistant conditions

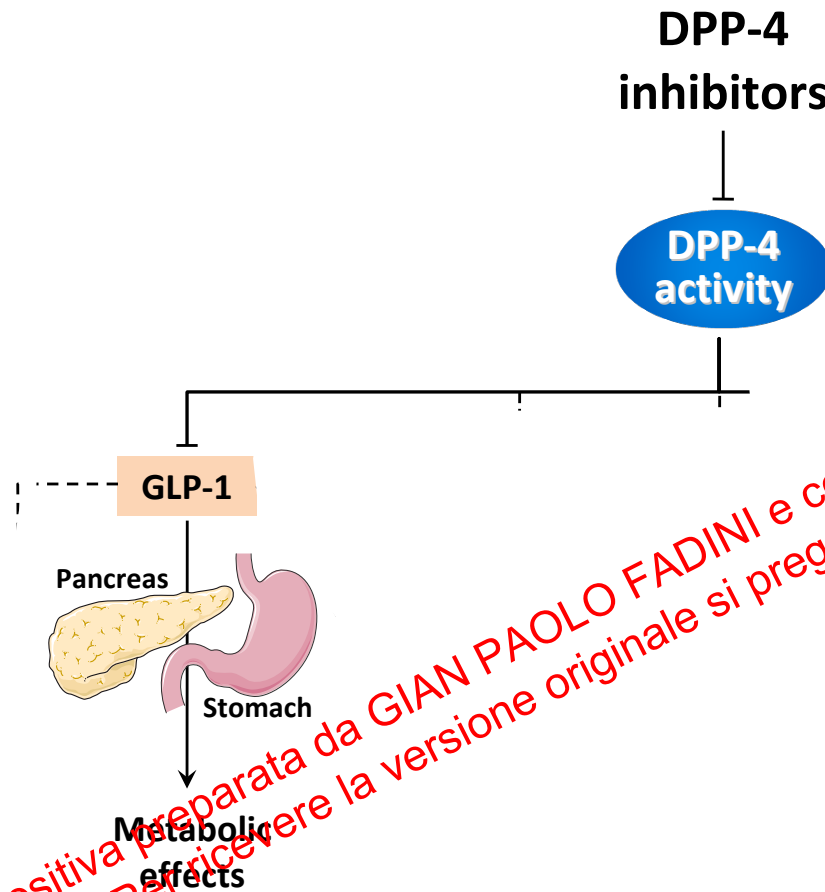


Enterocyte DPP4
No role in incretin degradation or glucose control

Hematopoietic cell DPP4
Cleaves GIP

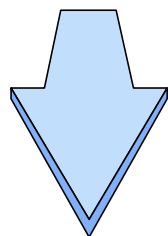
Endothelial cell DPP4
Cleaves GIP and GLP-1 and contributes to glucoregulation in insulin-resistant states

Pleiotropismo dei DPP-4i



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DPP-4 pleiotrophy



**A major regulator of
stem cell egress
from the bone
marrow**

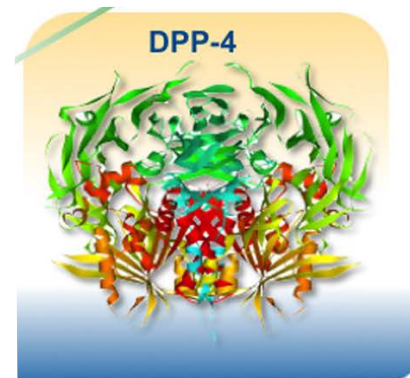
Sitagliptin

Linagliptin

Saxagliptin

Vildagliptin

**Increase
stem/progenitor cells**



The balance between damage and repair

Endothelial damage

Risk factors



Apoptosis

Detachment of
mature ECs

Editorial

Bone Marrow Takes Center Stage in Cardiovascular Disease

Filip K. Swirski, Matthias Nahrendorf

Circ Res 2016

Editorial

A Look at the Bone Marrow Predicts the Global Outcome

Gian Paolo Fadini

Circ Res 2015

Editorial

Task for Today: Complete the Puzzle of Circulating Stem Cells and the Atherosclerotic Burden

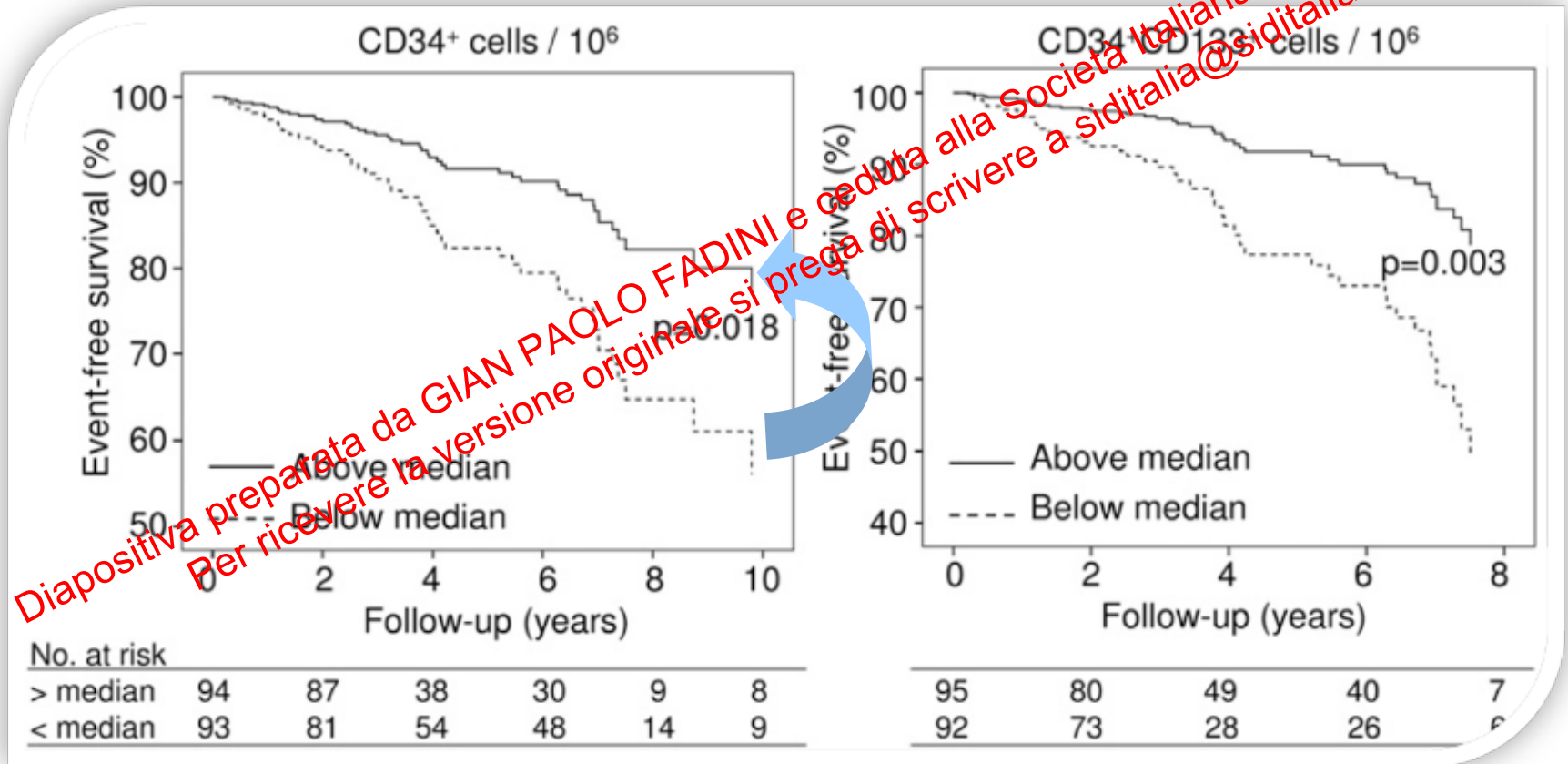
Gian Paolo Fadini

Circ Res 2016

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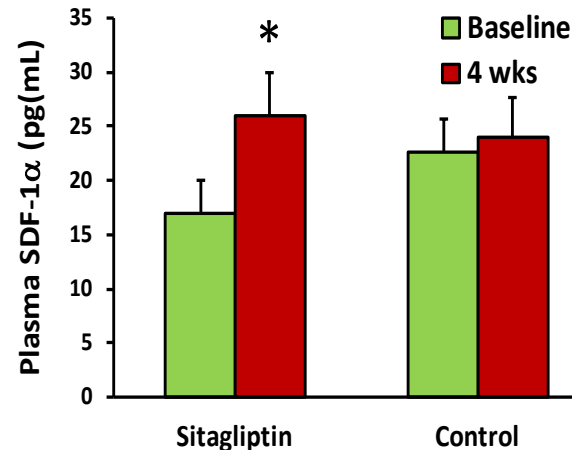
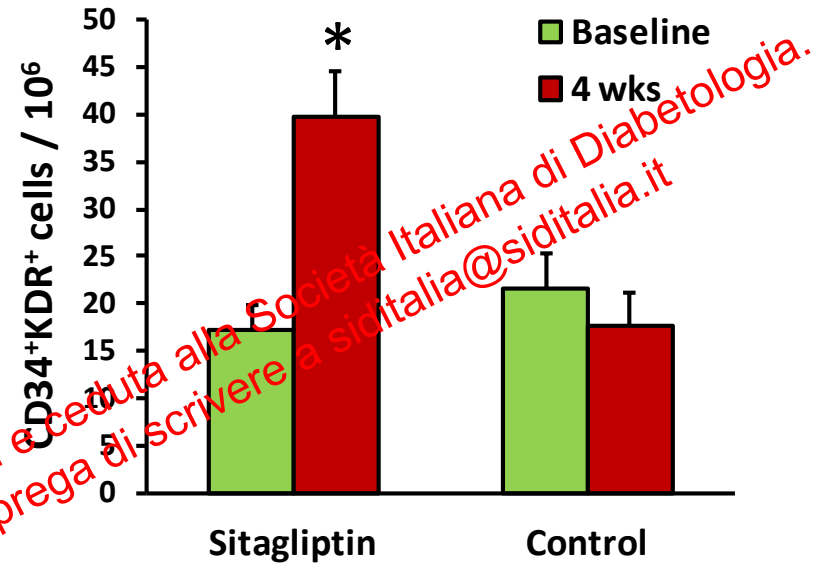
Long-term Prediction of Cardiovascular Outcomes by Circulating CD34⁺ and CD34⁺CD133⁺ Stem Cells in Patients With Type 2 Diabetes

DOI: 10.2337/dc16-1755



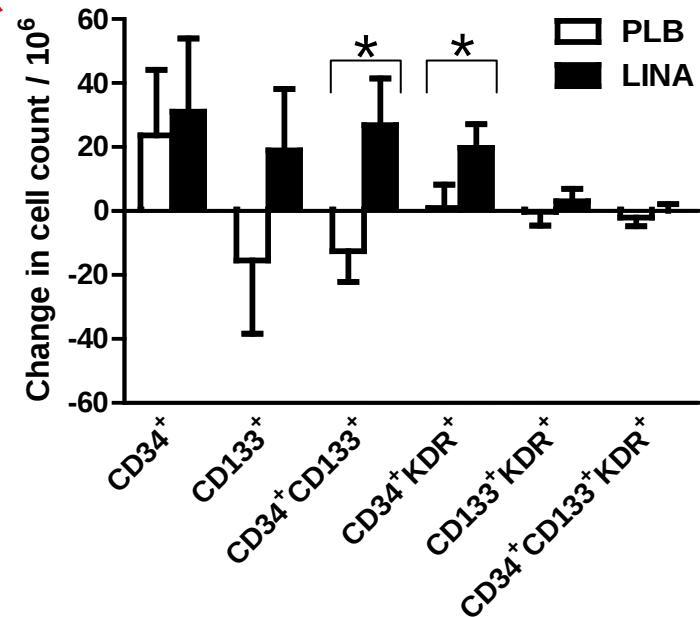
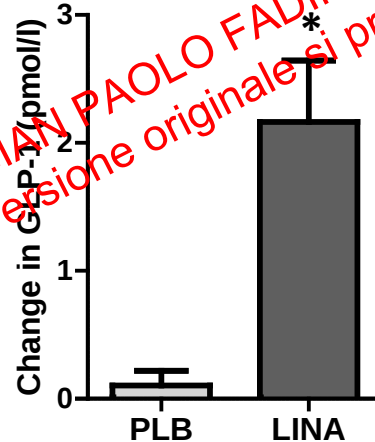
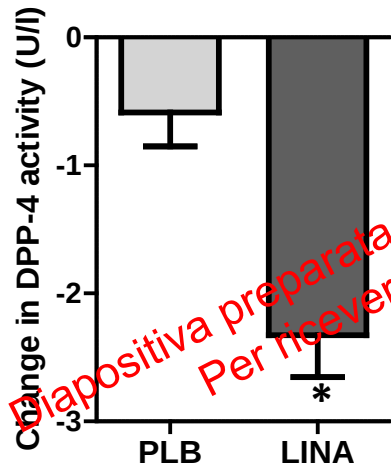
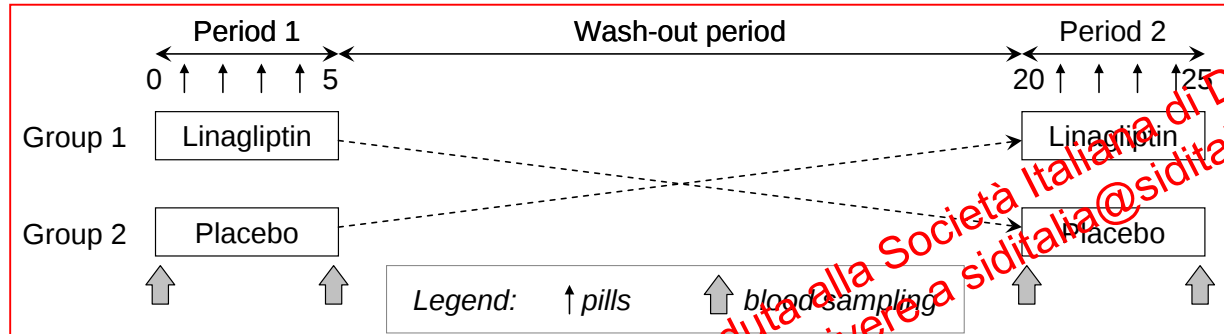
Sitagliptin increases circulating EPCs in T2D

A controlled, non-randomized clinical trial comparing 4-week sitagliptin (n=16) versus no additional treatment (n=16) on top of metformin and/or secretagogues in type 2 diabetic patients.

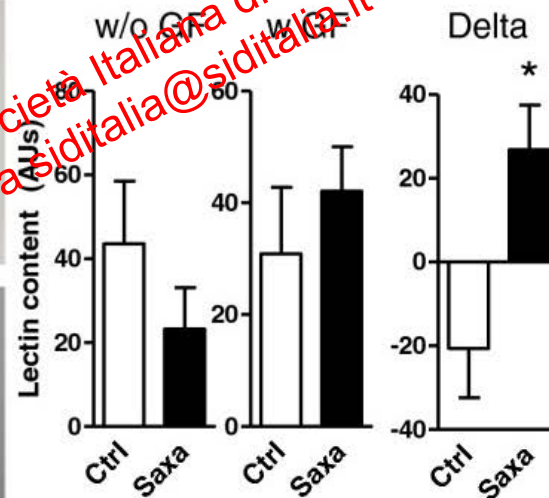
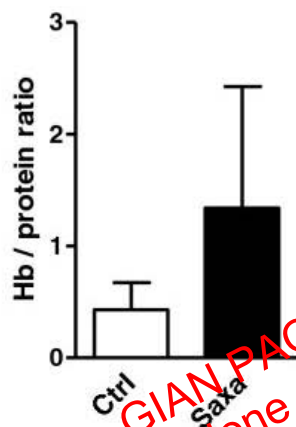
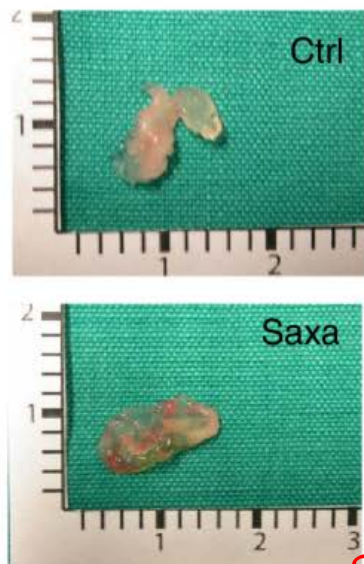


Rapid effect of Linagliptin on circulating EPCs in T2D

A randomized placebo-controlled cross-over trial to test the effects of 4-day linagliptin therapy on circulating EPCs in T2D



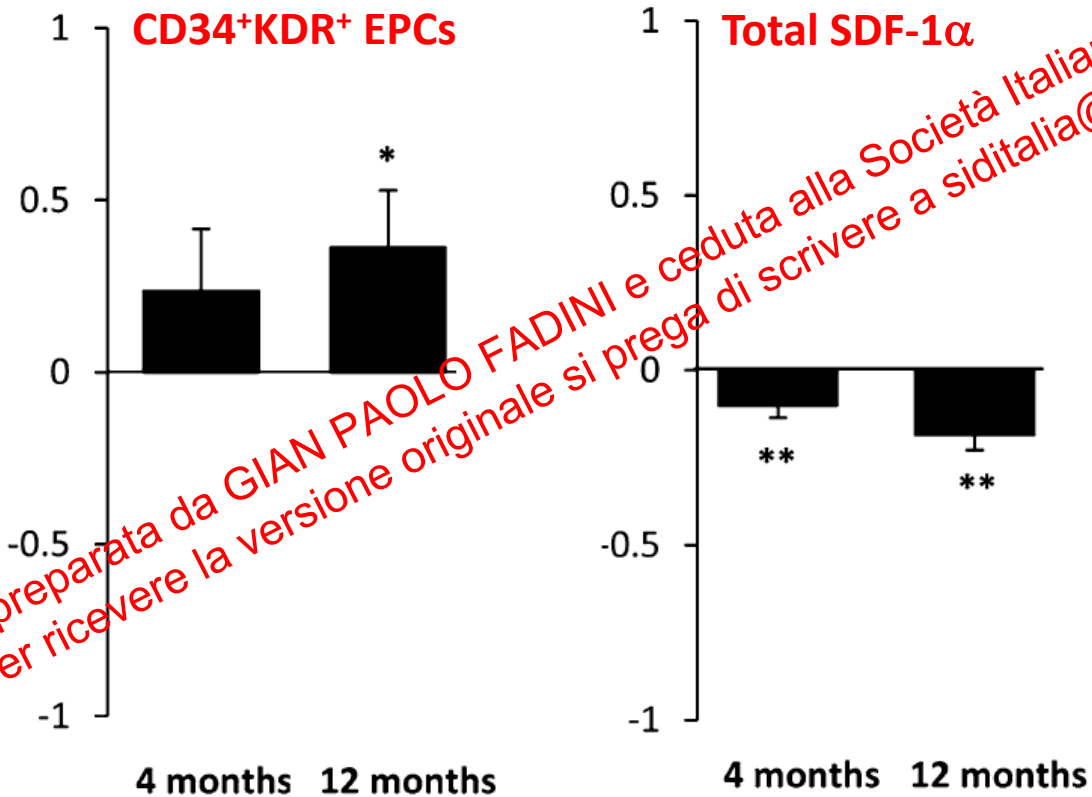
DPP-4i saxagliptin improves function of EPCs



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Vildagliptin but not glibenclamide increases EPCs

Glibenclamide substrated effect (β -coefficient)



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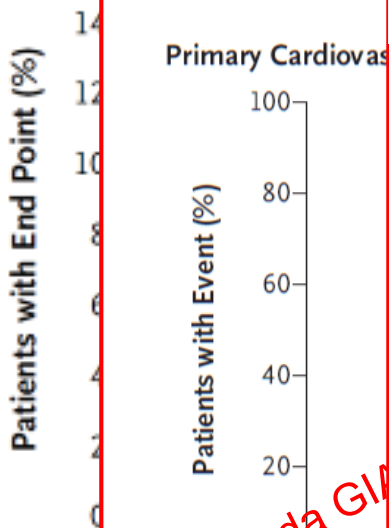
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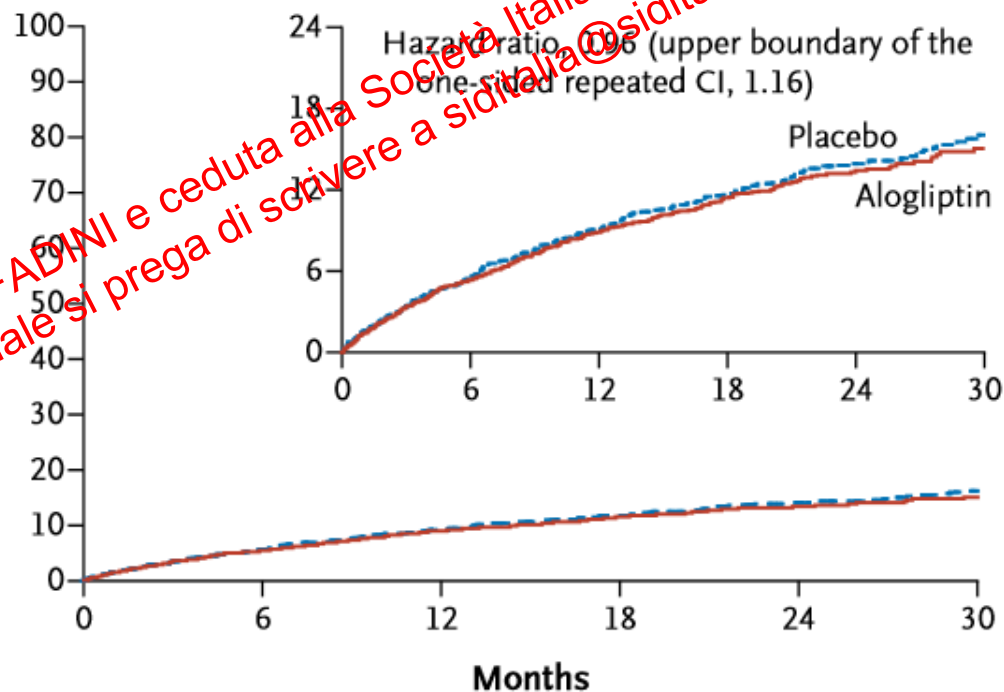
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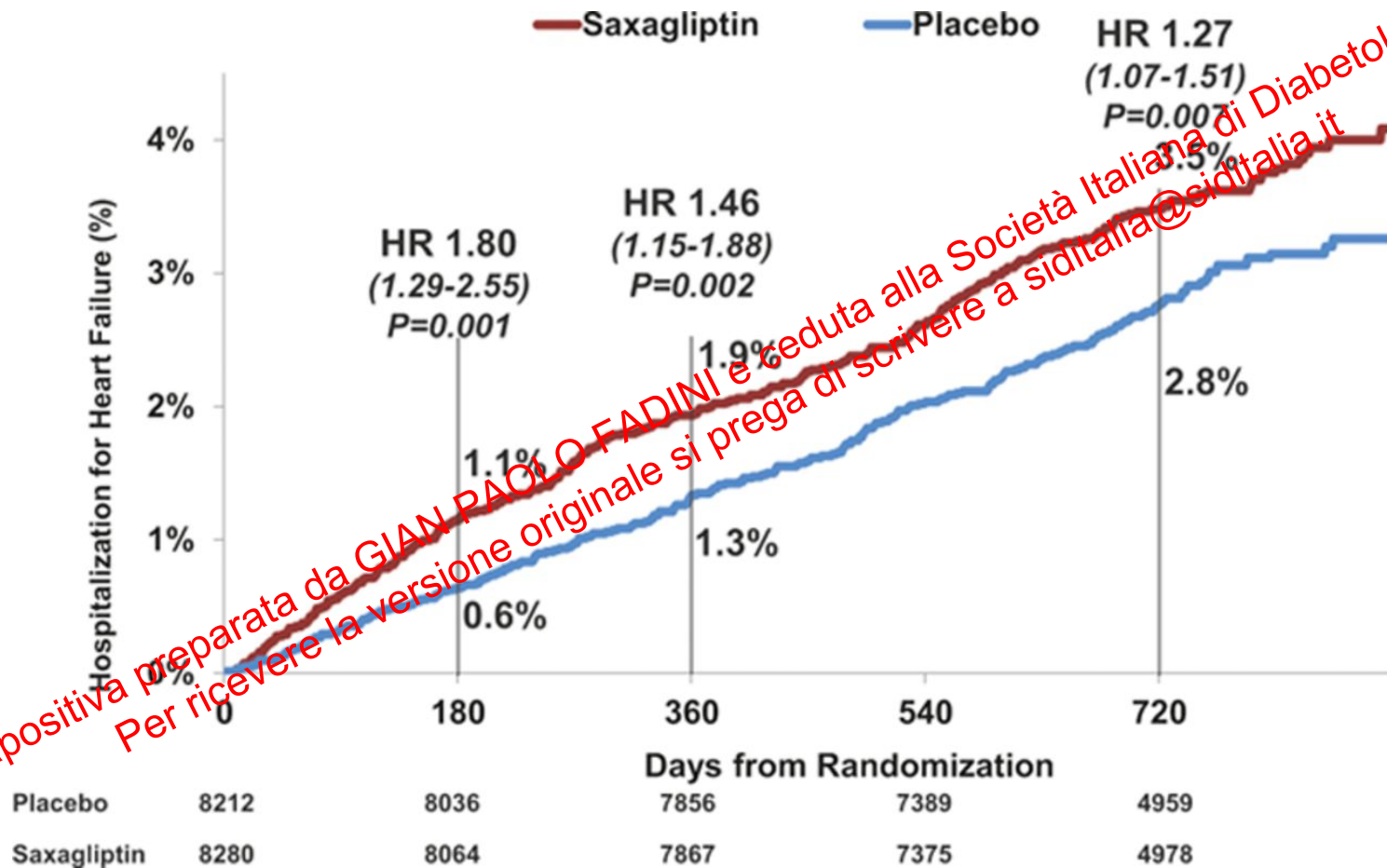
Cumulative Incidence of Primary End-Point Events (%)



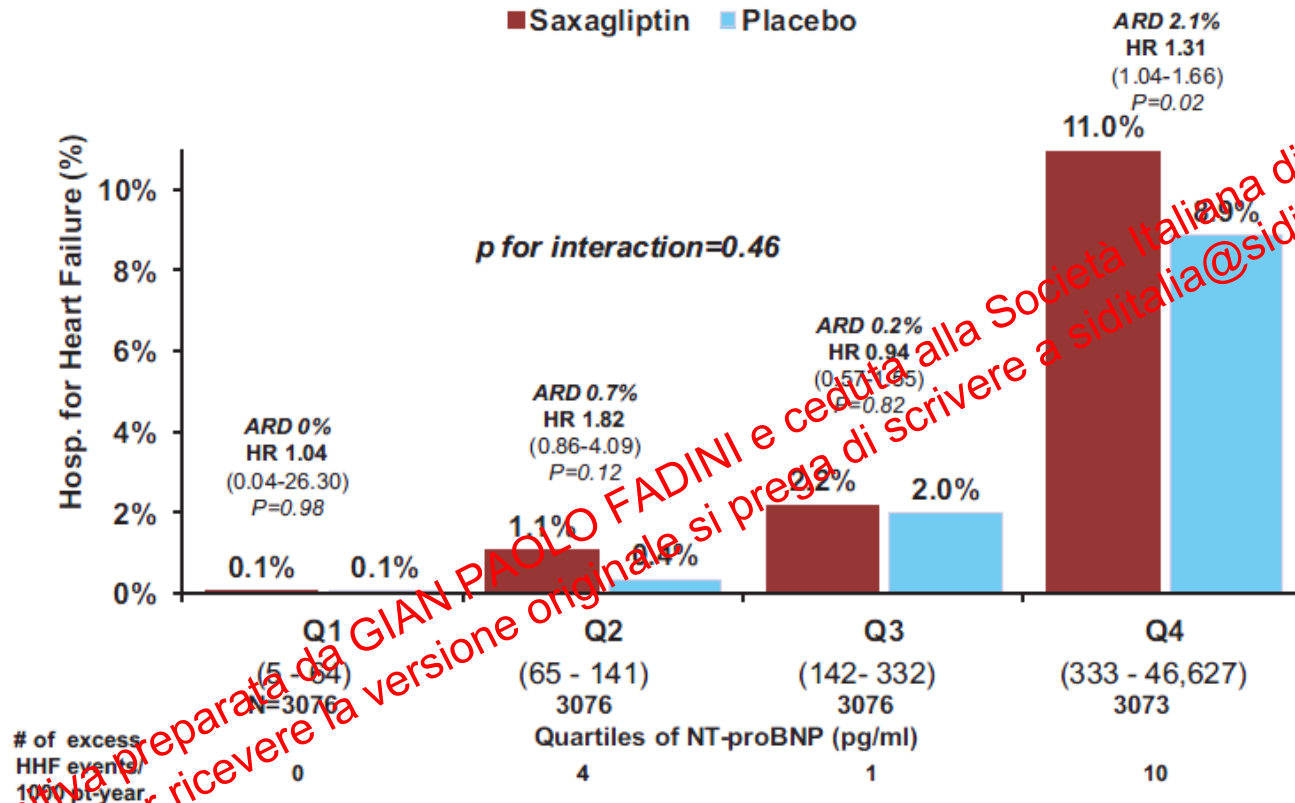
No. at Risk

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Risk of hospitalization for heart failure in the SAVOR trial

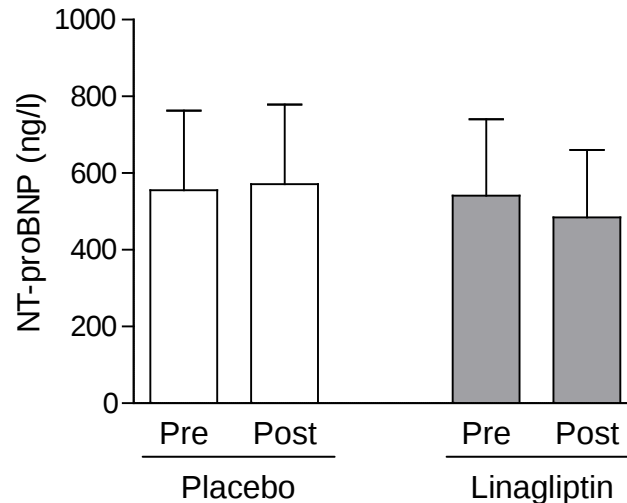
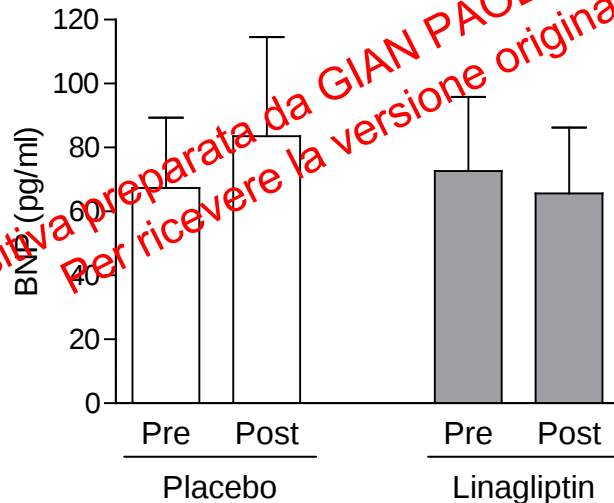
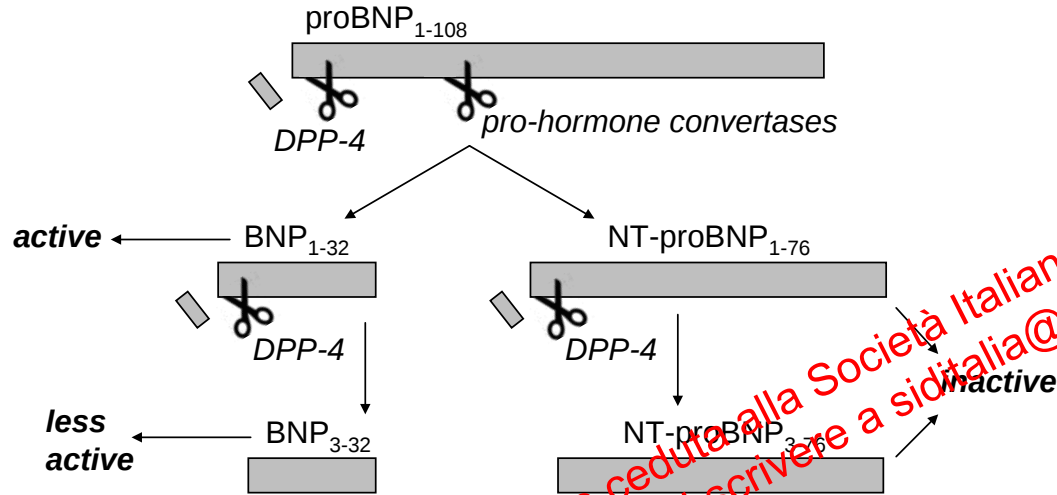


SAVOR-TIMI: Sorprese



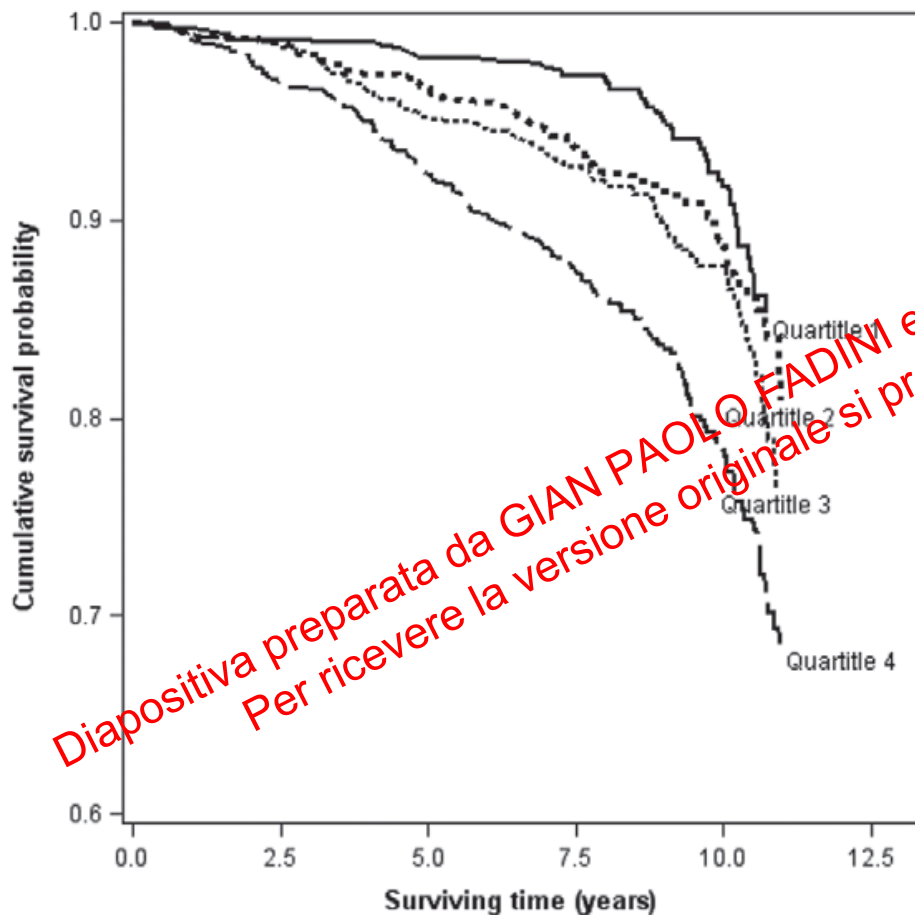
The absolute risk excess for heart failure with saxagliptin was greatest in the highest NT-proBNP quartile (2.1%)

DPP-4i e BNP



DPP-4 pleiotropy

Stromal Cell–Derived Factor 1 as a Biomarker of Heart Failure and Mortality Risk



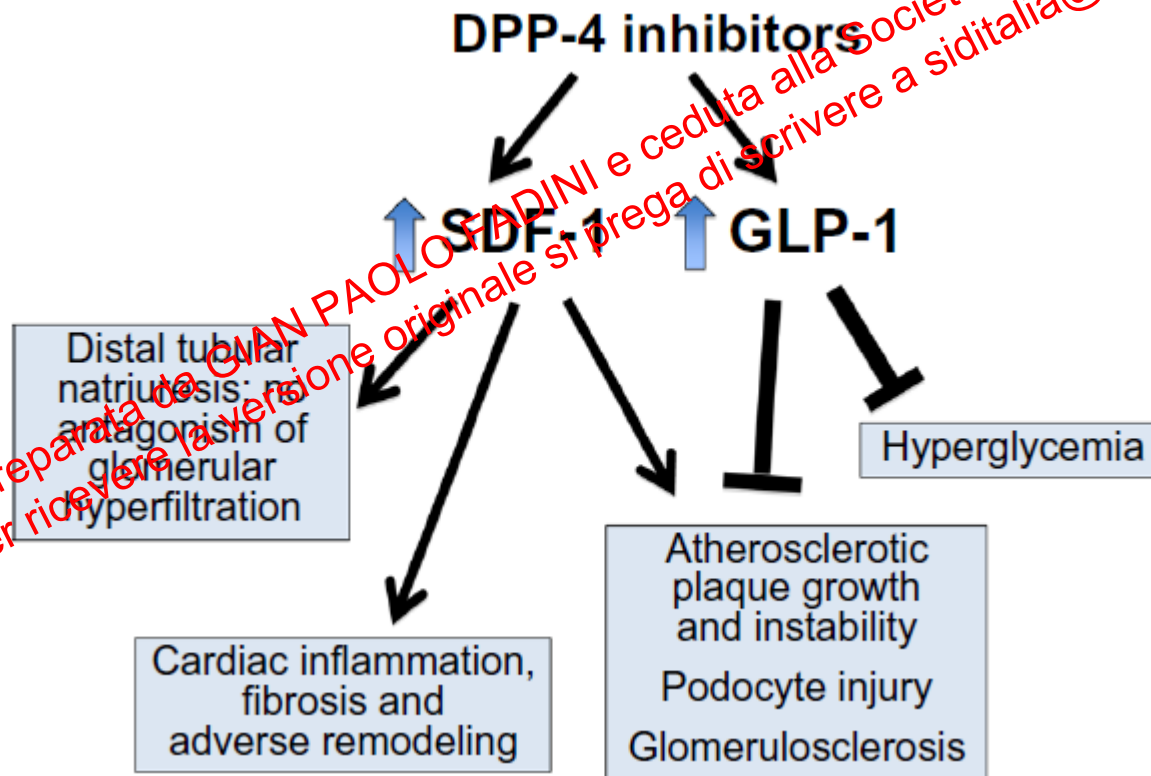
After adjusting for clinical risk factors, SDF-1 levels were associated with heart failure ($P=0.04$) but not with CVD ($P=0.39$) or myocardial infarction ($P=0.10$).

The association was attenuated after adjustment for high-density lipoprotein-cholesterol



Have dipeptidyl peptidase-4 inhibitors ameliorated the vascular complications of type 2 diabetes in large-scale trials? The potential confounding effect of stem-cell chemokines

Milton Packer*



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COMMENTARY

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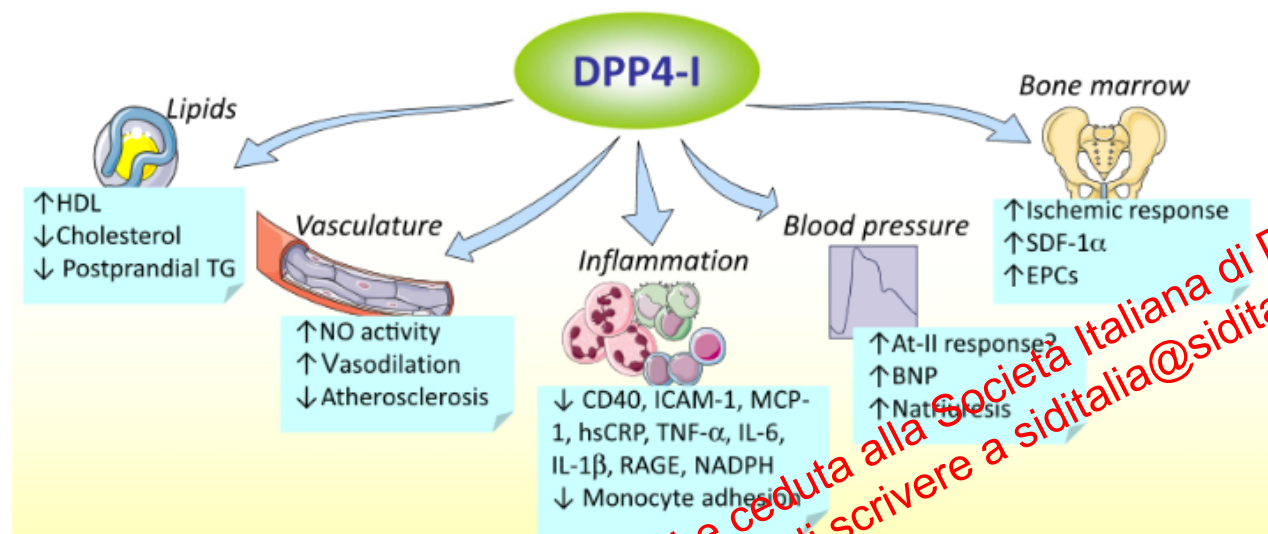
How to interpret the role of SDF-1 α on diabetic complications during therapy with DPP-4 inhibitors

Gian Paolo Fadini*  and Angelo Avogaro

“DPP-4 inhibition increases the concentrations of biologically active/intact SDF-1 α , whereas in studies showing an inverse association between SDF-1 α concentrations and adverse cardiovascular outcomes, total (mostly cleaved and biologically inactive) SDF-1 α was measured”

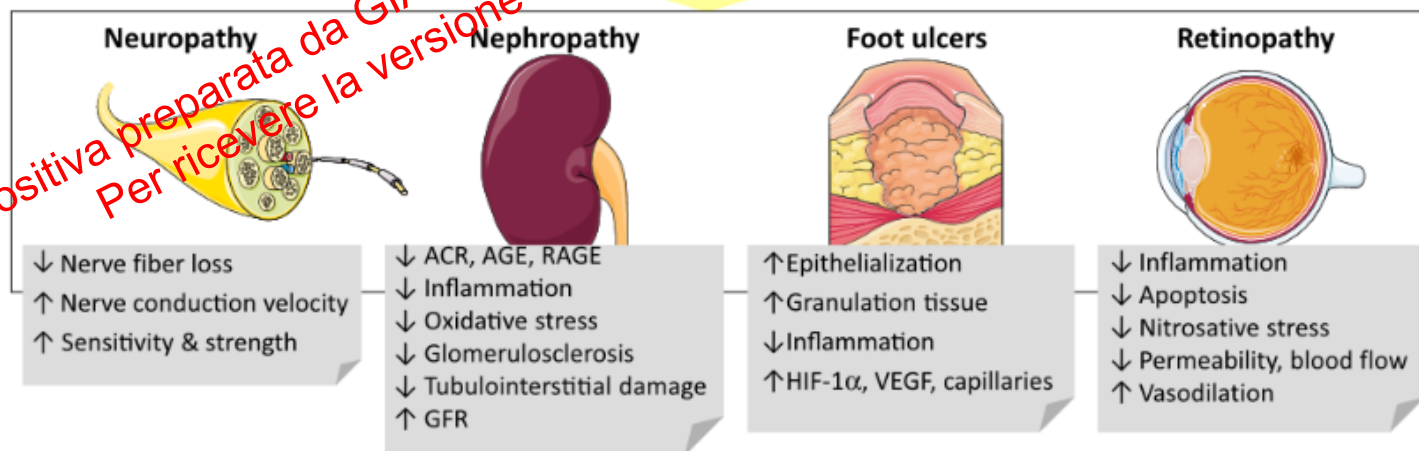
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Dedica da GIUSEPPE PAOLO FADINI e ceduta alla Società Italiana di Diabetologia.

DPP-4i e microangiopatia



↑ **GLP-1**

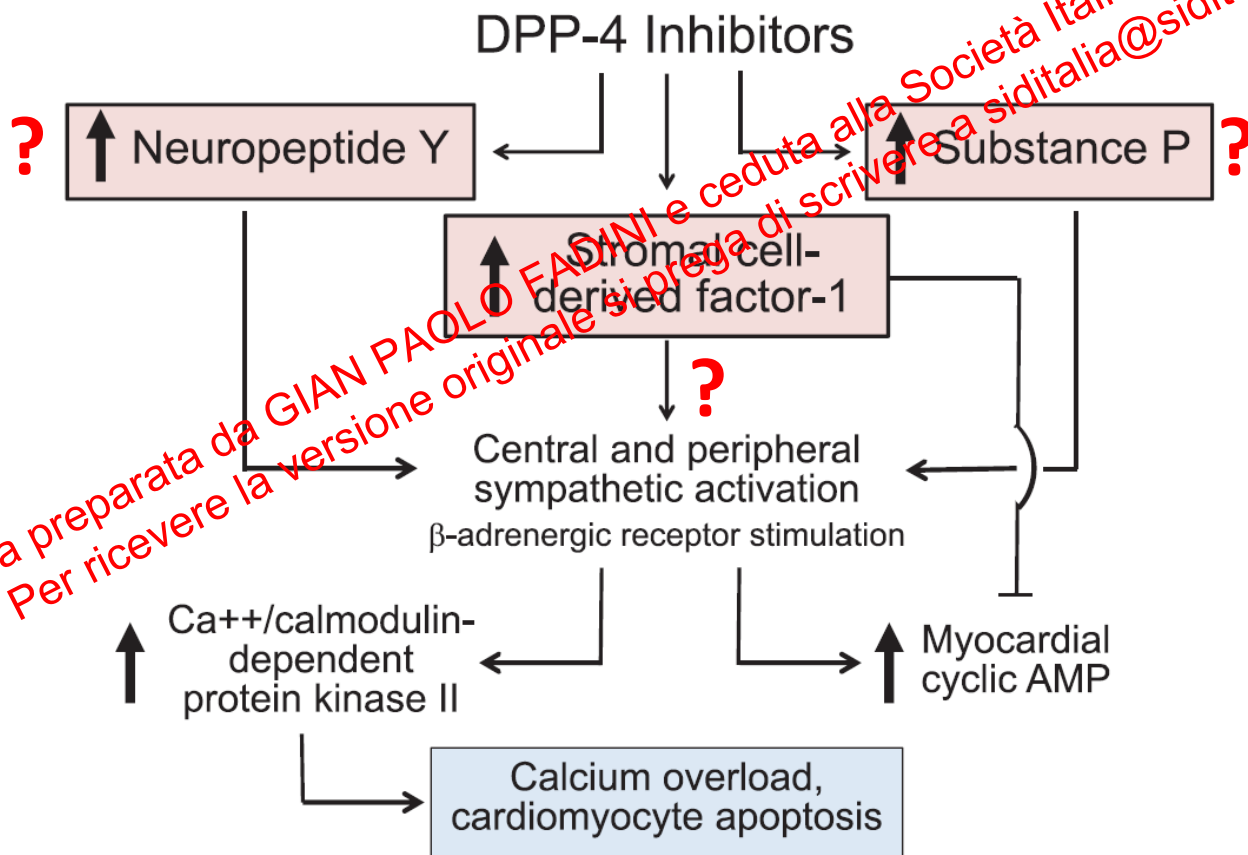
↓ **HbA1c**



New Hypotheses in Clinical Medicine

Do DPP-4 Inhibitors Cause Heart Failure Events by Promoting Adrenergically Mediated Cardiotoxicity? Clues From Laboratory Models and Clinical Trials

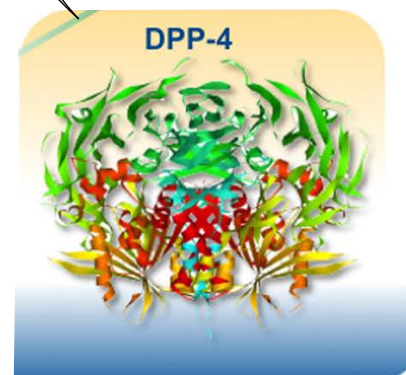
Milton Packer



DPP-4 pleiotrophy



**Sympathetic
overactivity**

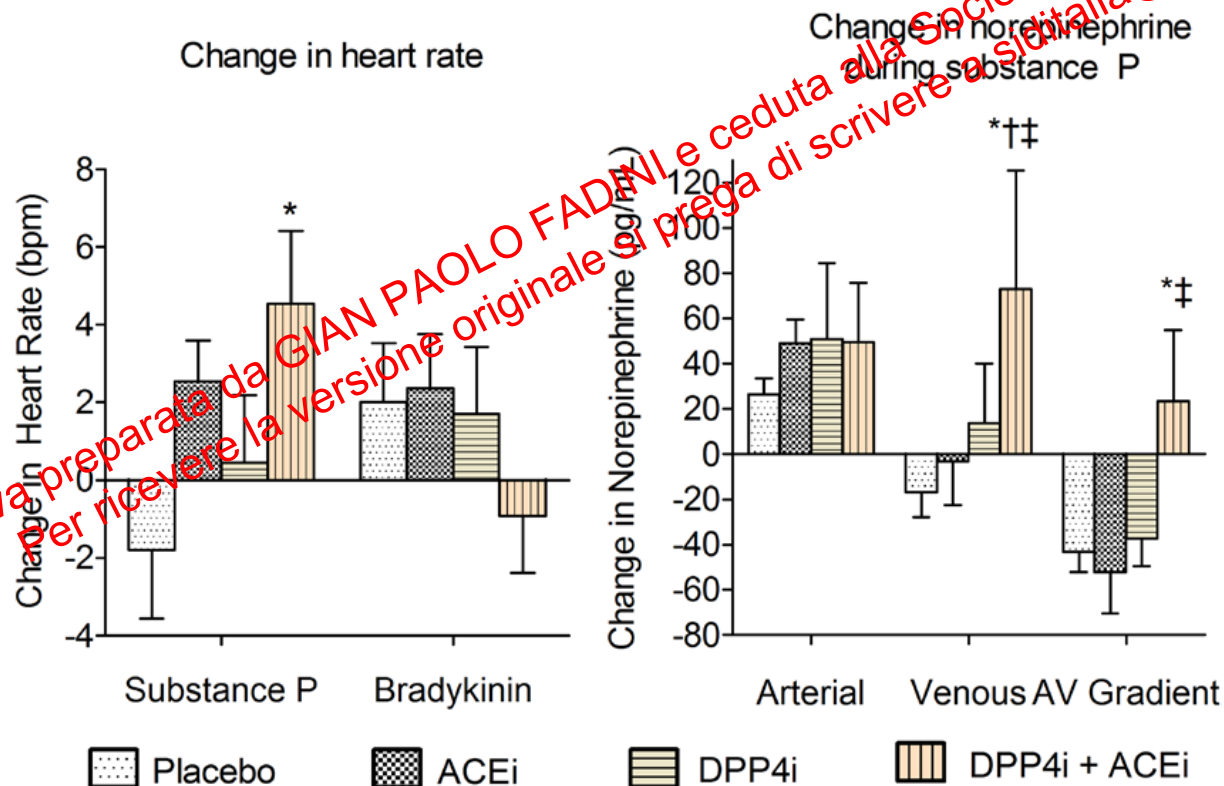


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Clinical Trial

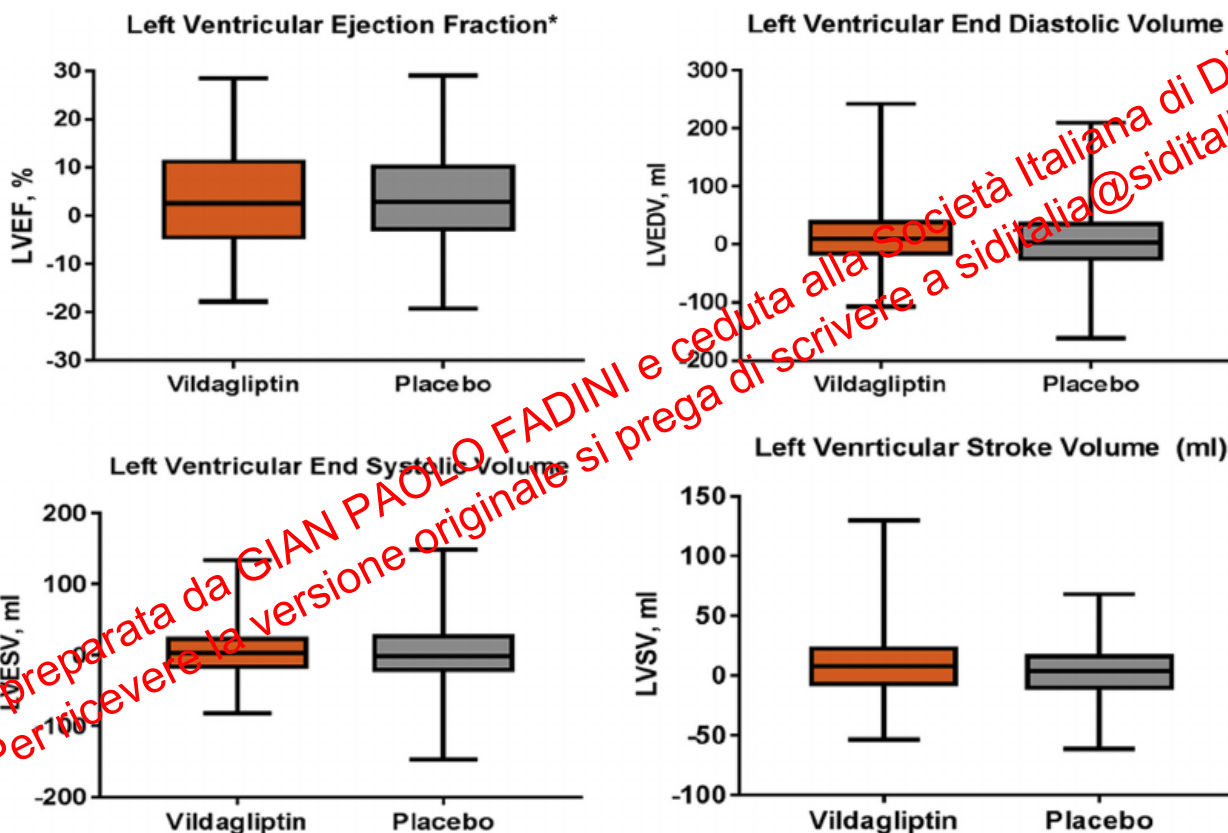
Substance P Increases Sympathetic Activity During Combined Angiotensin-Converting Enzyme and Dipeptidyl Peptidase-4 Inhibition

Jessica K. Devin, Mias Pretorius, Hui Nian, Chang Yu, Frederic T. Billings, Nancy J. Brown



254 patients with T2D and heart failure NYHA I-III and EF <40%

Randomized to vildagliptin vs placebo (about 30% discontinuation)



LV-EDV increased more with vildagliptin by 17.1 ml (95% CI: 4.6 to 29.5 ml; p=0.007)

LV-ESV increased more with vildagliptin by 9.4 ml (95% CI: 0.49 to 19.4 ml; p=0.062)

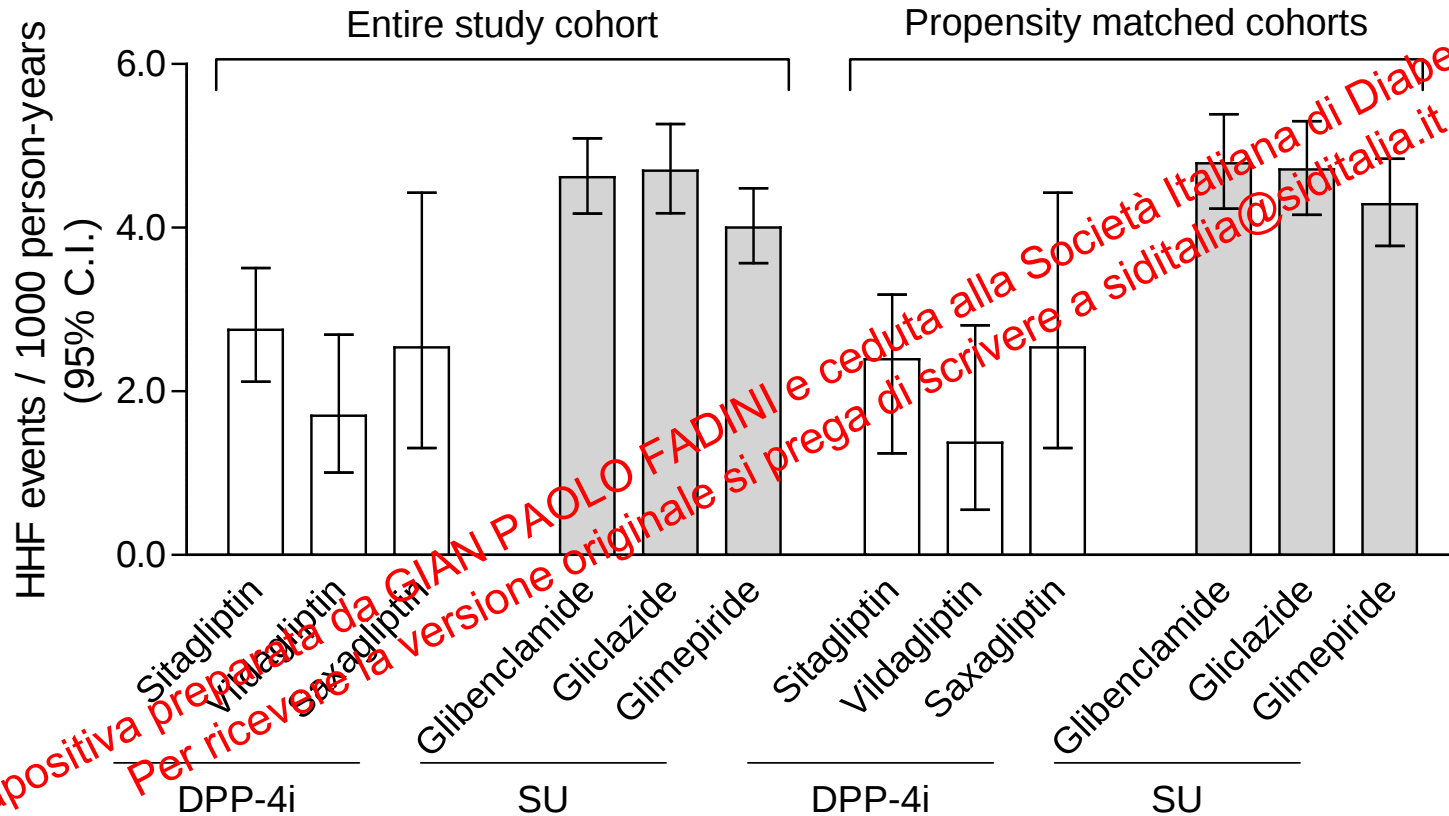
Risk of hospitalization for heart failure in patients with type 2 diabetes newly treated with DPP-4 inhibitors or other oral glucose-lowering medications: a retrospective registry study on 127,555 patients from the Nationwide OsMed Health-DB Database

Table 4 Results of the Cox proportional hazard multiple regression analysis in the whole study population including hospitalization episodes with a primary or secondary HF diagnosis

Variable	Before propensity matching		After propensity matching	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Glucose-lowering medications				
Sulphonylureas (reference)	1.000		1.000	
Glitazones	0.978 (0.807–1.183)	0.277	0.777 (0.635–0.950)	0.014
DPP-4 inhibitors	0.751 (0.630–0.895)	0.001	0.642 (0.510–0.808)	<0.001

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Risk of HF by DPP-4i molecule in teh OsMED database



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Conclusions



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