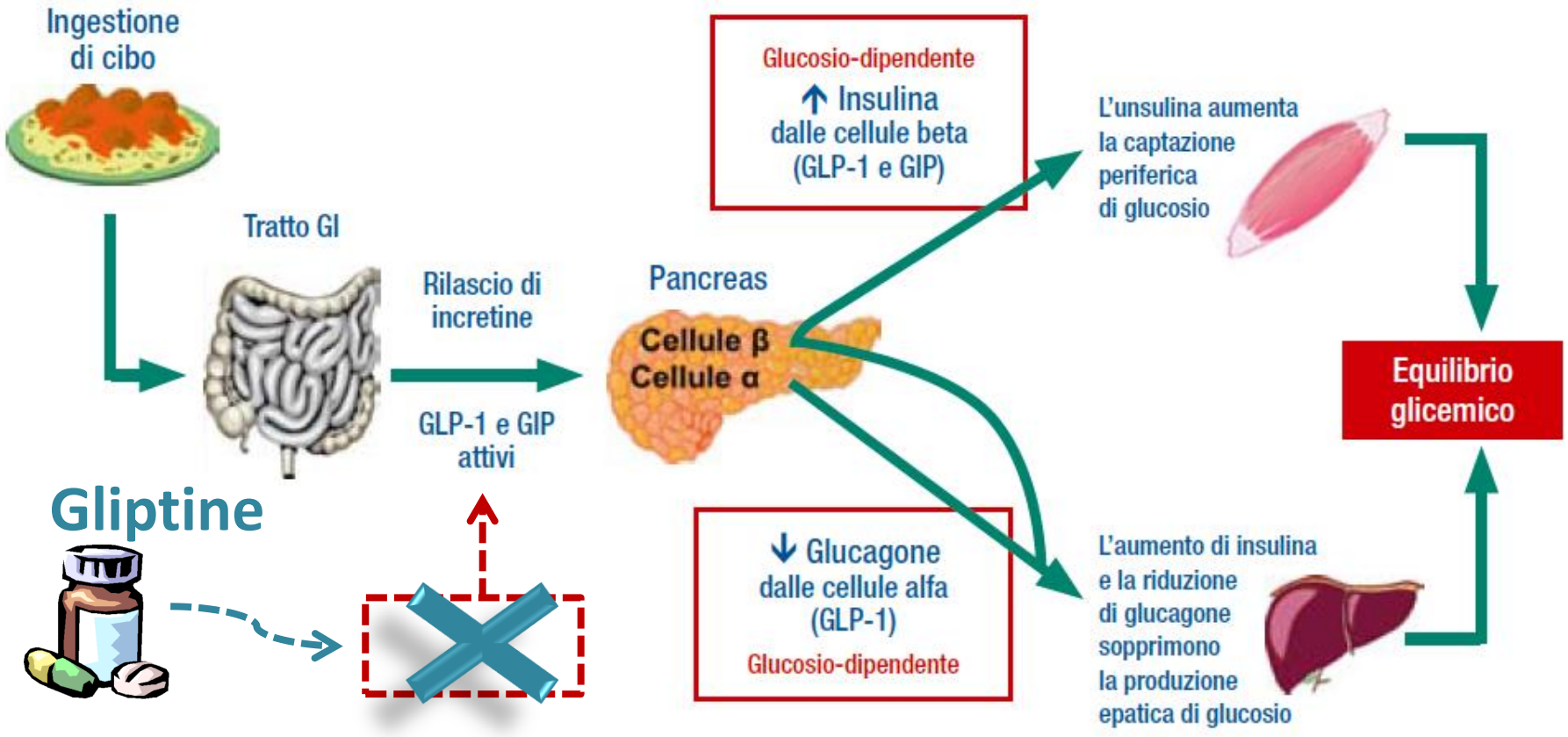
Effetti dei DPP-4 inibitori sul cuore

Dott. Roberta Assaloni
SSD di –diabetologia
AAS2 Bassa Friulana-Isontina

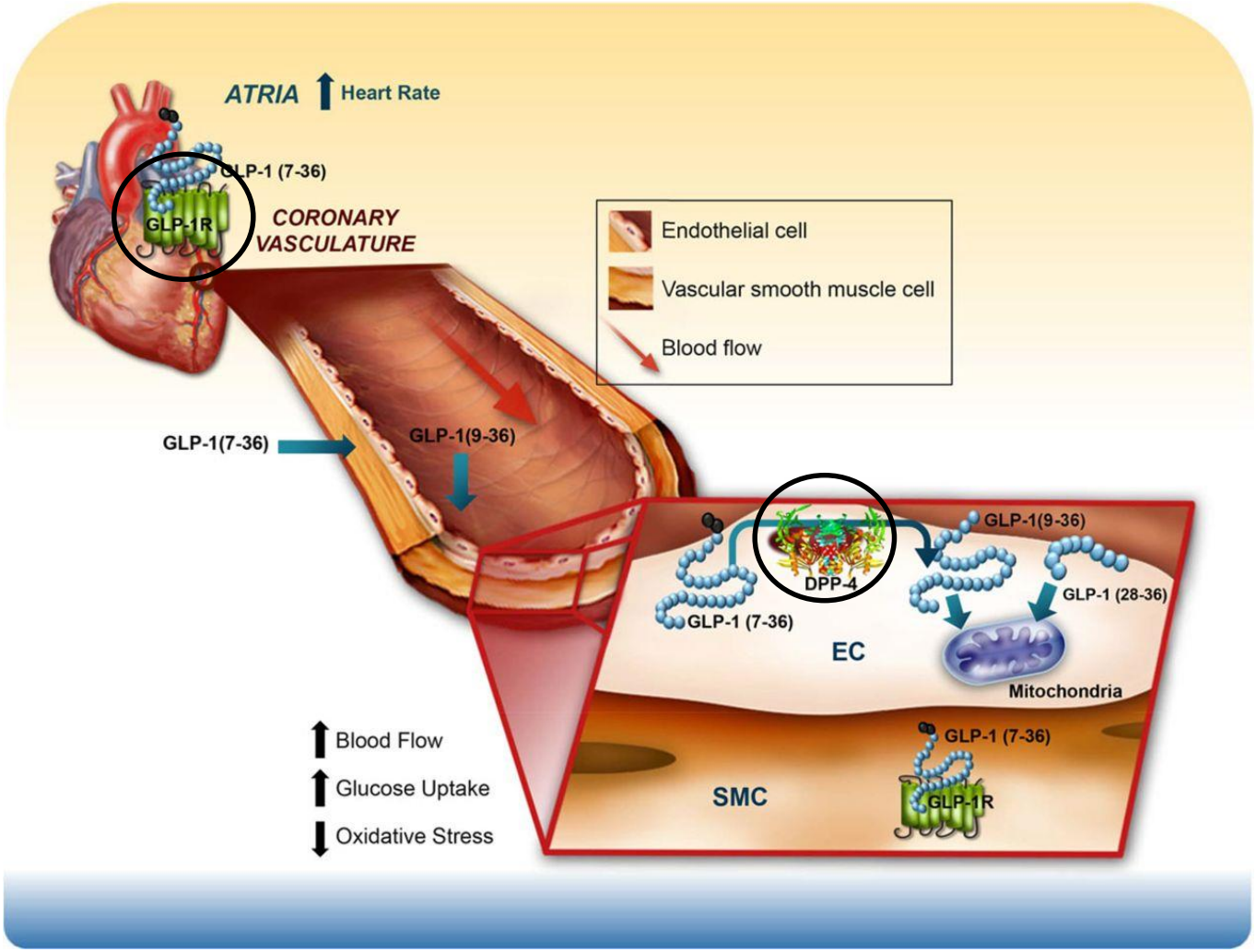
Sistema Incretinico: effetto glicemico



(adattato da Brubaker PL, Drucker DJ. *Minireview: glucagon-like peptides regulate cell proliferation and apoptosis in the pancreas, gut, and central nervous system.* Endocrinology 2004;145:2653-9; Zander M, Madsbad S, Madsen JL, et al. *Effect of 6-week course of glucagon-like peptide 1 on glycaemic control, insulin sensitivity, and beta-cell function in type 2 diabetes: a parallel-group study.* Lancet 2002;359:824-30; Buse JB, Polonsky KS, Burant CF. *Type 2 diabetes mellitus.* In: Larsen PR, Kronenberg HM, Melmed S, et al., eds. *Williams Textbook of Endocrinology.* 10th ed. Philadelphia: WB Saunders Company 2003, pp. 1427-83)

Incretine: effetto diretto sul cuore?

Actions of glucagon-like peptide-1 (GLP-1) and GLP-1 receptor (GLP-1R) agonists on the atria and vasculature.



John R. Ussher, and Daniel J. Drucker Circ Res. 2014;114:1788-1803

American Heart Association

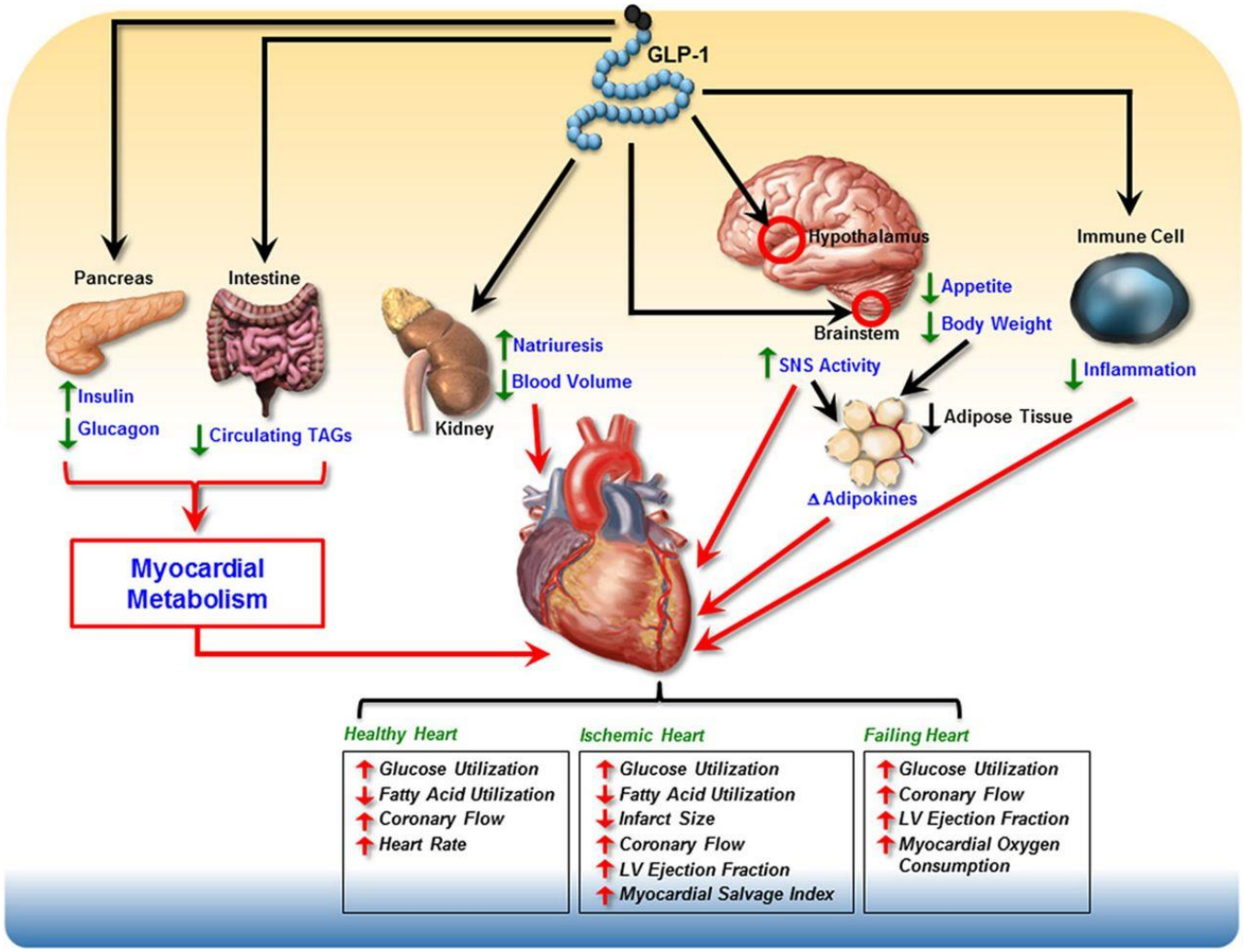
Table. Contrasting Actions of Native GLP-1, GLP-1R Agonists, DPP-4 Inhibitors, and GLP-1(9–36) on the Cardiovascular System and Cardiovascular Risk Factors

	GLP-1R Agonists	GLP-1	DPP-4 Inhibitors	GLP-1(9–36)
LV function	Increased	Increased	Increased	Increased
Heart rate	Increased	Increased	No effect	No effect
Coronary flow	No effect	Increased	No effect	Increased
Infarct size	Decreased	Decreased	Decreased	Decreased
Body weight	Decreased	Decreased	No effect	No effect
Blood pressure	Decreased	Decreased	No effect/decreased	ND

The table depicts the effects of native GLP-1, GLP-1R agonists, GLP-1(9–36), and DPP-4 inhibitors on the parameters important for the cardiovascular system as inferred from available preclinical and limited clinical studies. Scant data from head-to-head clinical trials using these agents limit extrapolation of the available data to human subjects. DPP-4 indicates dipeptidyl peptidase-4; GLP-1R, glucagon-like peptide-1 (GLP-1) receptor; LV, left ventricular; and ND, not determined.

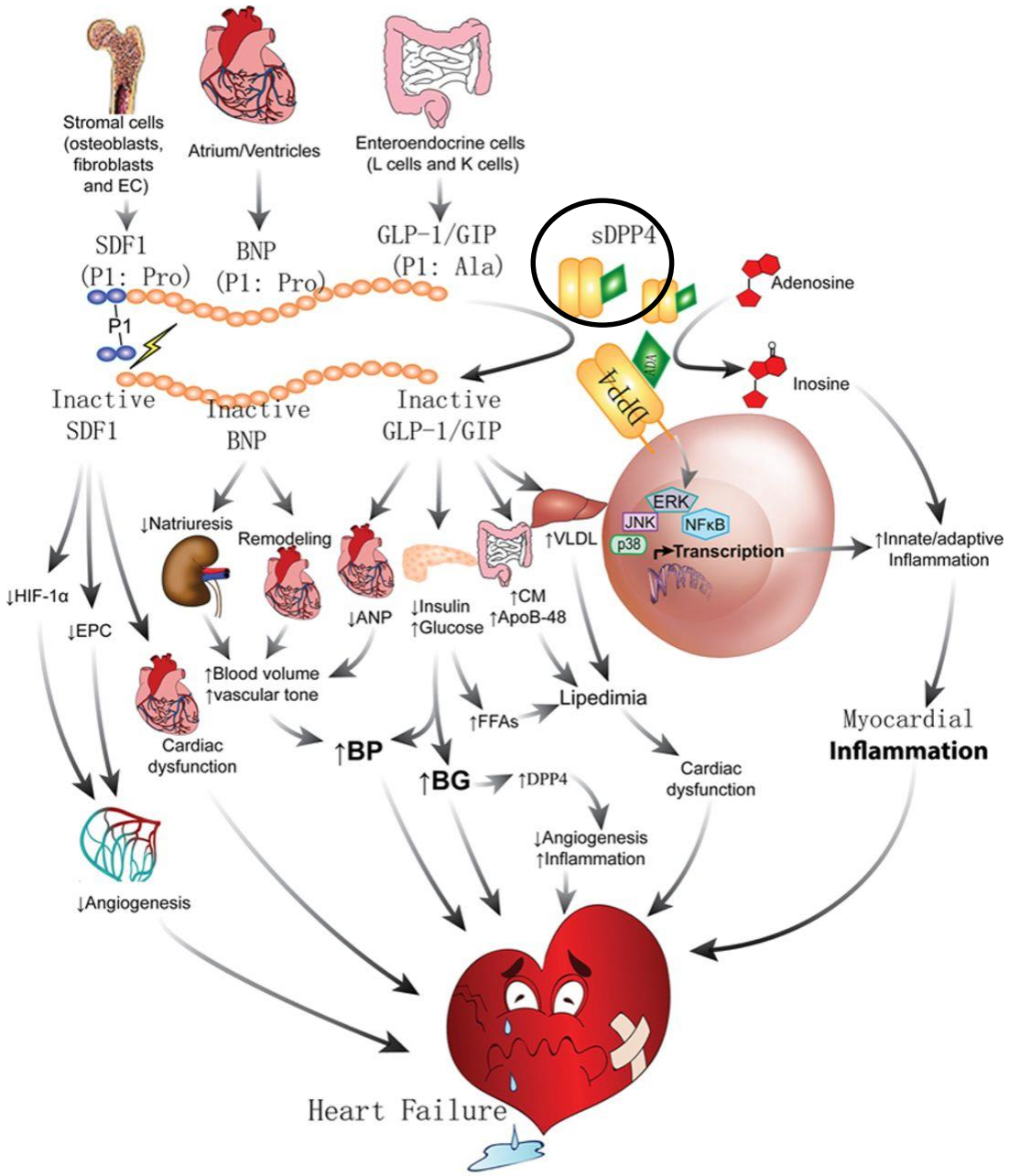
John R. Ussher, and Daniel J. Drucker Circ Res. 2014;114:1788-1803

Potential indirect cardiovascular effects of glucagon-like peptide-1 receptor (GLP-1R) agonists.



John R. Ussher, and Daniel J. Drucker Circ Res. 2014;114:1788-1803

American Heart Association.



Role of dipeptidyl peptidase-4 (DPP4) inhibition in heart failure: DPP4 may affect heart failure through both catalytic dependent and independent pathways.

American Heart Association.

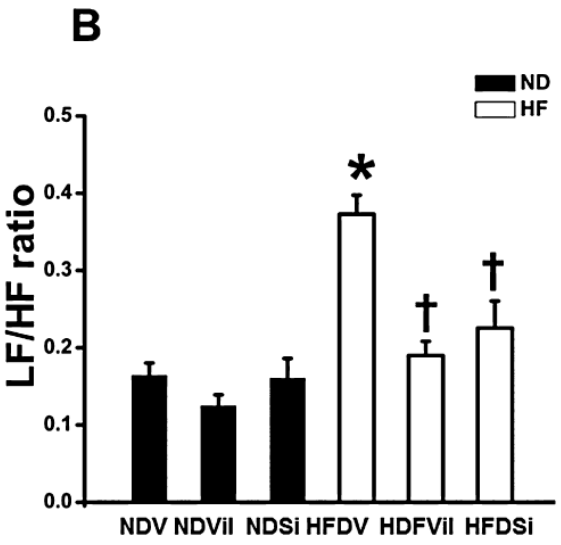
Jixin Zhong et al. Circ Heart Fail. 2015;8:819-825

BJP British Journal of Pharmacology

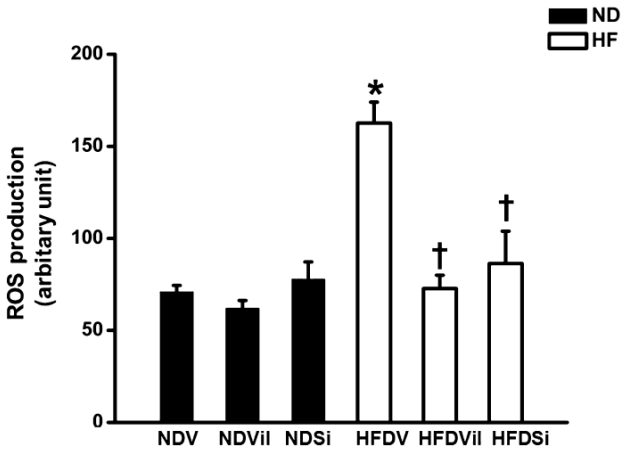
RESEARCH PAPER

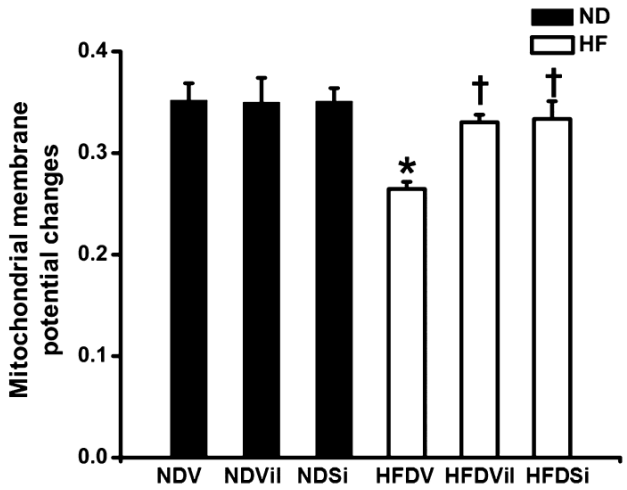
Effects of vildagliptin versus sitagliptin, on cardiac function, heart rate variability and mitochondrial function in obese insulin-resistant rats

Nattayaporn Apaijai[1], Hiranya Pintana[1], Siriporn C Chattipakorn[1,2] and Nipon Chattipakorn[1,3]



In HFD rats, vildagliptin and sitagliptin restored the LF/HF ratio, in comparison with the vehicle. **P* < 0.05 versus NDV, †*P* < 0.05 versus HFDV.





British Journal of Pharmacology (2013) **169** 1048–10576

Cardiovascular Research (2016) **111**, 338–347
doi:10.1093/cvr/cvw182

Dipeptidyl peptidase-4 inhibitor improved exercise capacity and mitochondrial biogenesis in mice with heart failure via activation of glucagon-like peptide-1 receptor signalling

Shingo Takada[1†], Yoshihiro Masaki[1†], Shintaro Kinugawa[1]*, Junichi Matsumoto[1], Takaaki Furihata[1], Wataru Mizushima[1], Tomoyasu Kadoguchi[1], Arata Fukushima[1], Tsuneaki Homma[1], Masashige Takahashi[1], Shinichi Harashima[2], Shouji Matsushima[1], Takashi Yokota[1], Shinya Tanaka[3], Koichi Okita[4], and Hiroyuki Tsutsui[1]

The citrate synthase activity, mitochondrial oxidative phosphorylation capacity, supercomplex formation, and their quantity were reduced in the skeletal muscle from the MI mice, and these decreases were normalized in the MIþMK-0626 group, in association with the improvement of mitochondrial biogenesis

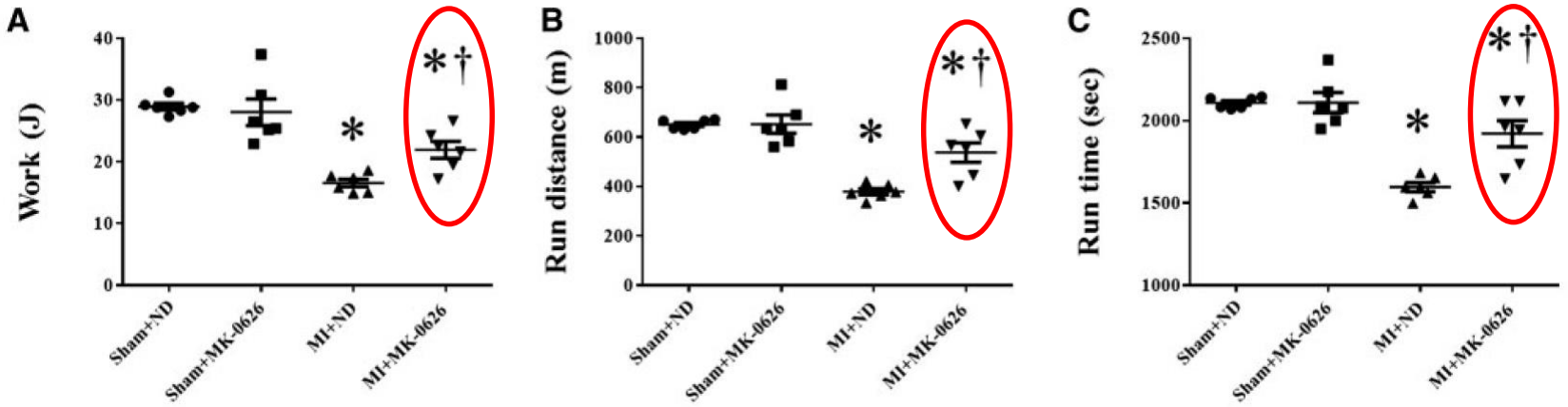


Table. Experimental Evidence Supporting Beneficial Effects of DPP4 Inhibition in Heart Failure

Reference	Major Findings	Disease	Subject	Duration	Dose
Vyas et al[42]	Saxagliptin improved glucose tolerance but not survival in a transgenic murine model of dilated cardiomyopathy	Dilated cardiomyopathy	Mouse	≤7 wk	10 mg/kg per d
Gomez et al[43]	Sitagliptin reserved the GFR, modulated stroke volume and heart rate, and potentiated the positive inotropic effect	Overpacing-induced heart failure	Pig	3 wk	30 mg/kg per d
Shigeta et al[41]	Both vildagliptin and genetic DPP4 disruption reversed diabetic diastolic left ventricular dysfunction and pressure-overload–induced left ventricular dysfunction	Heart failure	Rat	4 wk	30 mg/kg per d
Takahashi et al[44]	Vildagliptin increased GLP-1 levels. It also improved cardiac dysfunction, TAC-induced left ventricular enlargement and overall survival in the TAC mice at day 28	Heart failure	Mice	28 d	10 mg/kg per d
Bostick et al[45]	MK0626 improved western diet–induced insulin resistance and diastolic relaxation, accompanied by reduced myocardial oxidant stress and fibrosis	Diastolic dysfunction	Mouse	16 wk	33 mg/kg in diet (≈ 10 mg/kg per d)
Miyoshi et al[46]	Vildagliptin attenuated the β-adrenergic stimulation–induced cardiac hypertrophy as well as cardiomyocyte hypertrophy and perivascular fibrosis	Cardiac hypertrophy	Rat	7 d	30 mg/kg per d

DPP4, dipeptidyl peptidase-4; GFR, glomerular filtration rate; GLP-1, glucagon-like peptide-1; and TAC, T-cell α chemoattractant.

Jixin Zhong et al. Circ Heart Fail. 2015;8:819-825

DPP-4i sono tutti uguali?

Table 2
Pharmacodynamics and pharmacokinetics of marketed DPP-4 inhibitors.

Inhibitor	Chemistry	Compound $t_{1/2}$(h)	Dosing	Metabolism	Elimination	DPP-4 inhibition[a]
Sitagliptin [31]	β-Amino acid based (triazolepyrazine compound)	8–24	100 mg qd	Not appreciably metabolized	Renal (~79% unchanged as parent drug)	Max ~ 97%; >80% 24 h postdose
Vildagliptin [32–34]	Cyanopyrrolidine	1.5–4.5	50 mg bid	Hydrolysed to inactive metabolite (P450 enzyme independent)	–	Max ~ 95%; >80% 12 h postdose
Saxagliptin [35–36]	Cyanopyrrolidine (hydroxyadamantyl compound)	2–4 (Parent) 3–7 (Metabolite)	5 mg qd	Hepatically metabolized to active metabolite (via P450 3A4/5)	Renal (12–29% as parent drug, 21–52% as metabolite)	Max ~ 80%; >70% 24 h postdose
Alogliptin [37]	Modified pyrimidinedione/ quinazolinone-based compound	12–21	25 mg qd	Not appreciably metabolized	Renal (>70% unchanged as parent drug)	Max ~ 90%; >75% 24 h postdose
Linagliptin [38]	Xanthine based	10–40	5 mg qd (Anticipated)	Not appreciably metabolized	Biliary (>70% unchanged as parent drug), <6% via kidney	Max ~ 80%; >70% 24 h postdose

[a] DPP-4 activity measured in human plasma *ex vivo*; not corrected for sample dilution in the assay.

Table 3
Selectivity of marketed drugs against various DPP enzymes.

Inhibitor	Selectivity	DPP-2	FAPα	DPP-8	DPP-9
Sitagliptin [43,100]	High	>1,00,000	>10,000	48,000	>1,00,000
Vildagliptin [34,41]	Moderate	>5,00,000	>10,000	>100	>30
Saxagliptin [43,45]	Moderate	>6000	>1000	>400	>75
Alogliptin [44,147]	High	>10,000	>10,000	>10,000	>10,000
Linagliptin [29]	Moderate	>1,00,000	89	40,000	>10,000

FAPα, fibroblast activation protein-α.

Patel B.D. et al. European Journal of Medicinal Chemistry 74 (2014) 574e605

JACC: HEART FAILURE
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http://dx.doi.org/10.1016/j.jchf.2017.08.004

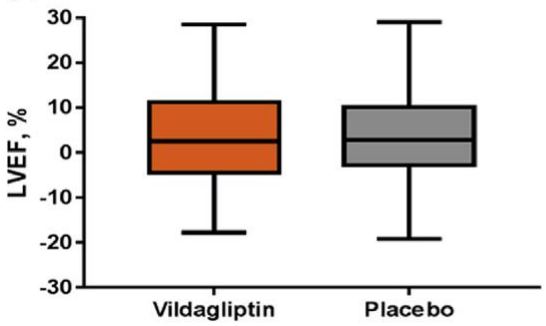
CLINICAL RESEARCH

Effects of Vildagliptin on Ventricular Function in Patients With Type 2 Diabetes Mellitus and Heart Failure

A Randomized Placebo-Controlled Trial

Studio randomizzato 52 sett di trattamento con vildagliptin
128 trattati vs 126 controlli

A



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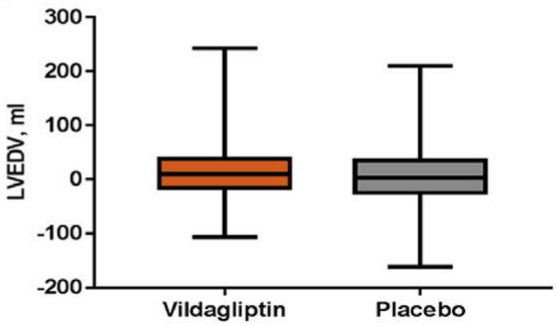


Scopo dello studio:

Valutare la sicurezza di vildagliptin nei pazienti con scompenso cardiaco (Classe NYHA I-III) e ridotta frazione di eiezione ventricolare sinistra (<0,40).

End point primario:

Modificazione rispetto al basale della **frazione di eiezione ventricolare** valutata mediante ecocardiografia

Conclusioni:

Rispetto al placebo, la terapia con vildagliptin **non ha mostrato un effetto significativo sulla frazione di eiezione ventricolare**, essendoci una differenza di 0,62 (IC 2,21-3,44; p = 0.667) che rientrava nel margine predefinito di non inferiorità (−3,5%), ma ha determinato un **aumento dei volumi del ventricolo sinistro**.

L'aumento del volume ventricolare sinistro è associato ad una prognosi clinica peggiore, compresa la mortalità, nello scompenso

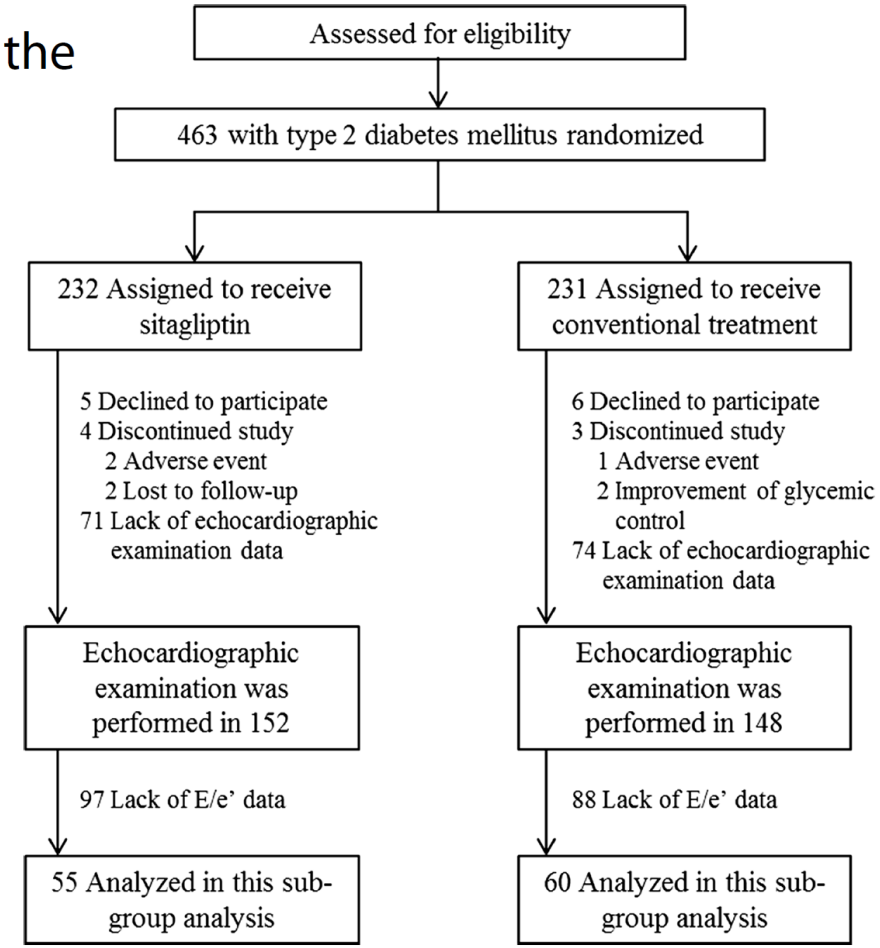
Yamada et al. Cardiovasc Diabetol (2017) 16:63
DOI 10.1186/s12933-017-0546-2

Cardiovascular Diabetology

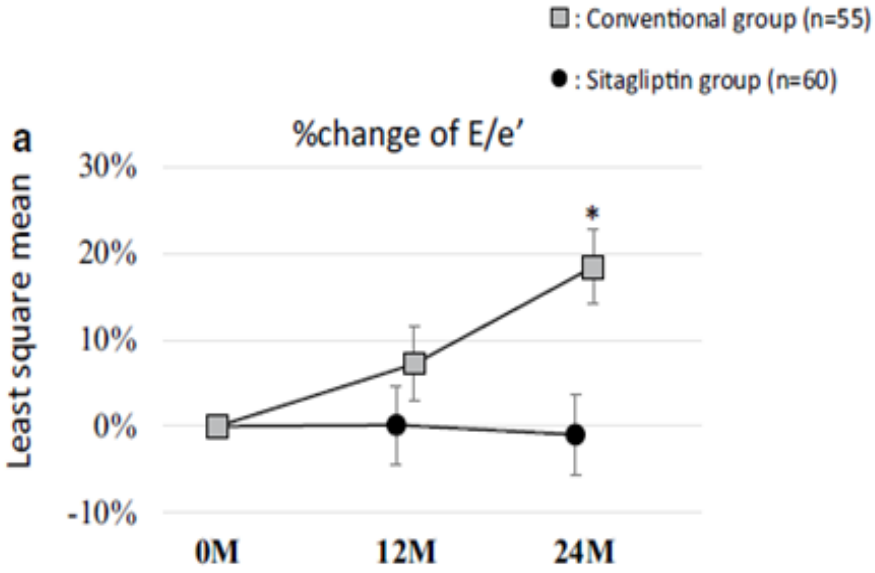
ORIGINAL INVESTIGATION Open Access

Effect of sitagliptin on the echocardiographic parameters of left ventricular diastolic function in patients with type 2 diabetes: a subgroup analysis of the PROLOGUE study

PROLOGUE Multicenter, randomized, prospective, open-label, blindedendpoint trial carried out at 48 institutions in Japan to evaluate the inhibitory effect of sitagliptin on the progression of atherosclerosis based on carotid-artery intima-media thickness (IMT)



- Sotto analisi dello studio PROLOGUE condotta per valutare l'effetto di sitagliptin sui parametri ecocardiografici della funzione diastolica in pazienti con diabete di tipo 2
- Le alterazioni metaboliche e il diabete sono strettamente associati con la disfunzione diastolica come la cardiomiopatia diabetica e vi è evidenza che I pazienti con diabete ed un aumentato E/e'* hanno una mortalità più elevata
- Dei 463 pazienti partecipanti allo studio, sono stati inclusi nell'analisi 115 pazienti (55 nel gruppo sitagliptin e 60 nel gruppo in trattamento convenzionale) che avevano dati ecocardiografici completi al basale e dopo 12 e 24 mesi.



L'aggiunta di sitagliptin al regime antidiabetico convenzionale per 24 mesi ha attenuato l'esacerbazione della disfunzione diastolica indipendentemente da altre variabili cliniche quali la pressione arteriosa e il controllo glicemico

Circulation
Cardiovascular Imaging

American Heart Association.

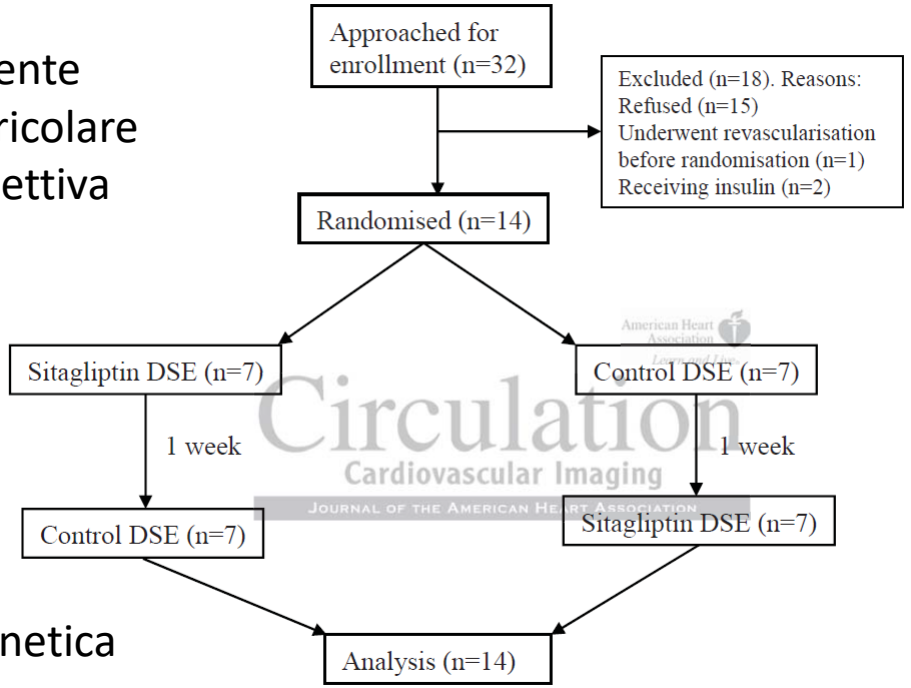
DPP-4 Inhibition by Sitagliptin Improves the Myocardial Response to Dobutamine Stress and Mitigates Stunning in a Pilot Study of Patients with Coronary Artery Disease

Philip A. Read, Fakhar Z. Khan, Patrick M. Heck, Stephen P. Hoole and David P. Dutka

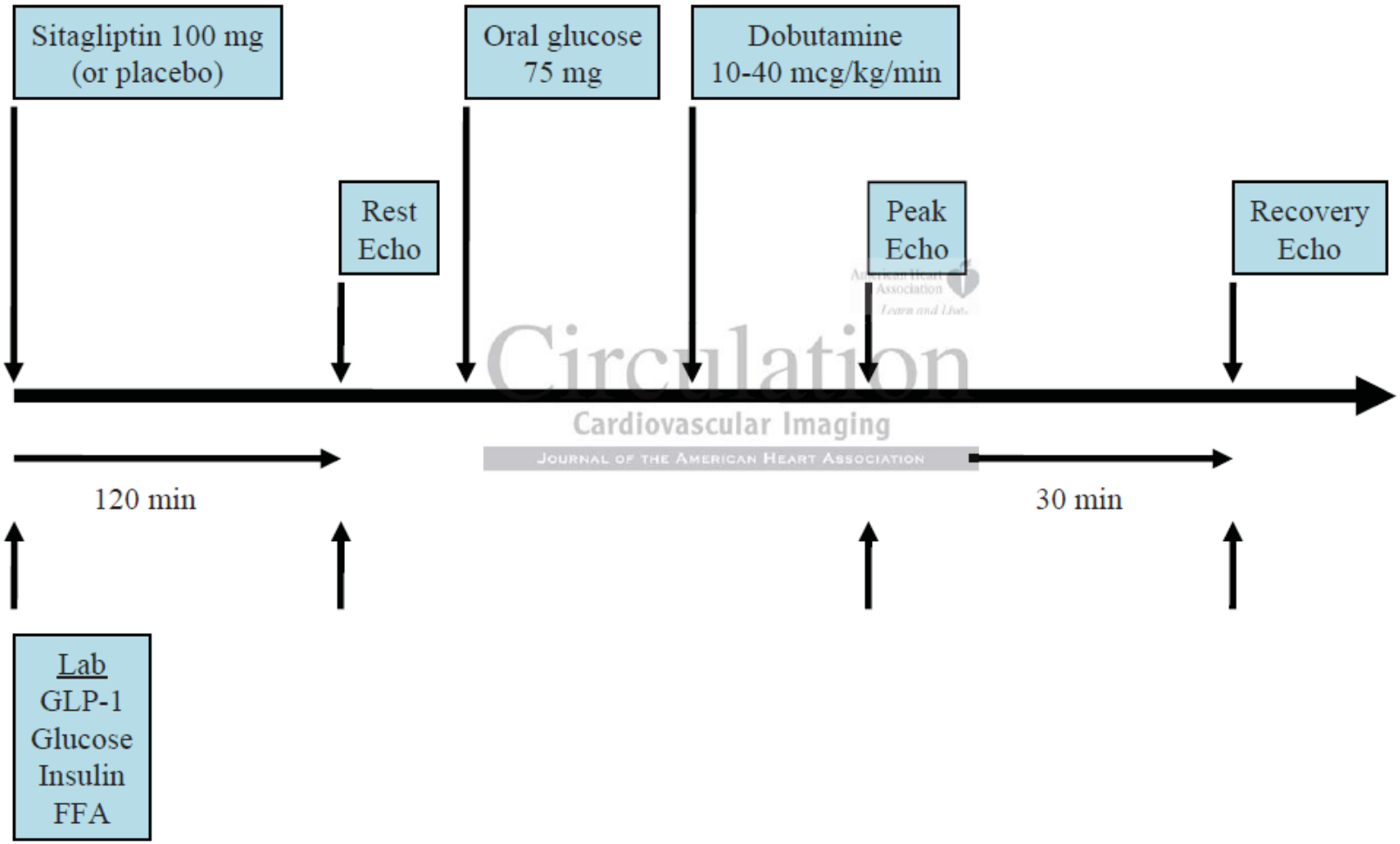
Circ Cardiovasc Imaging. published online January 14, 2010;
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

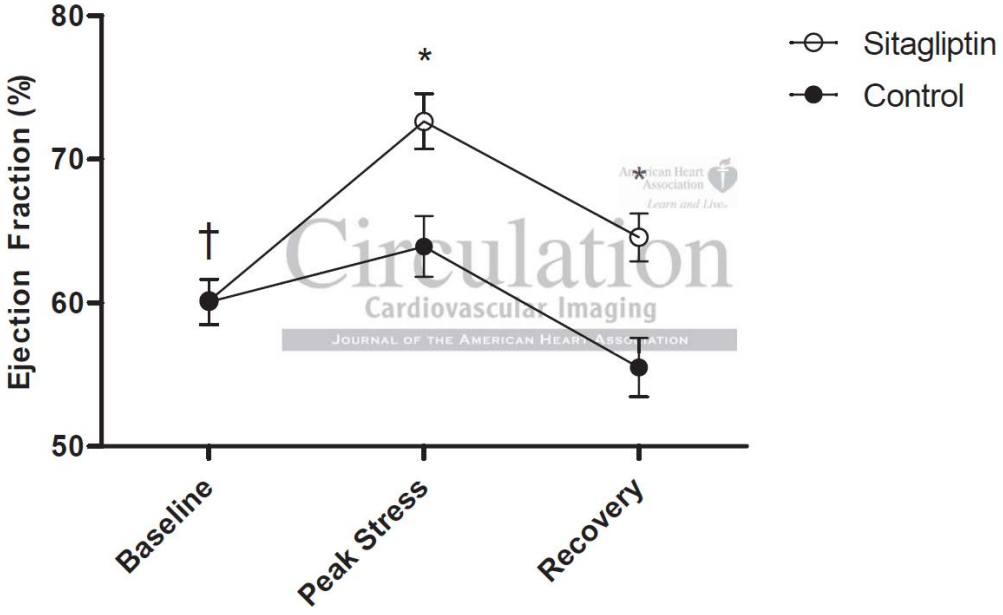
Print ISSN: 1941-9651. Online ISSN: 1942-0080

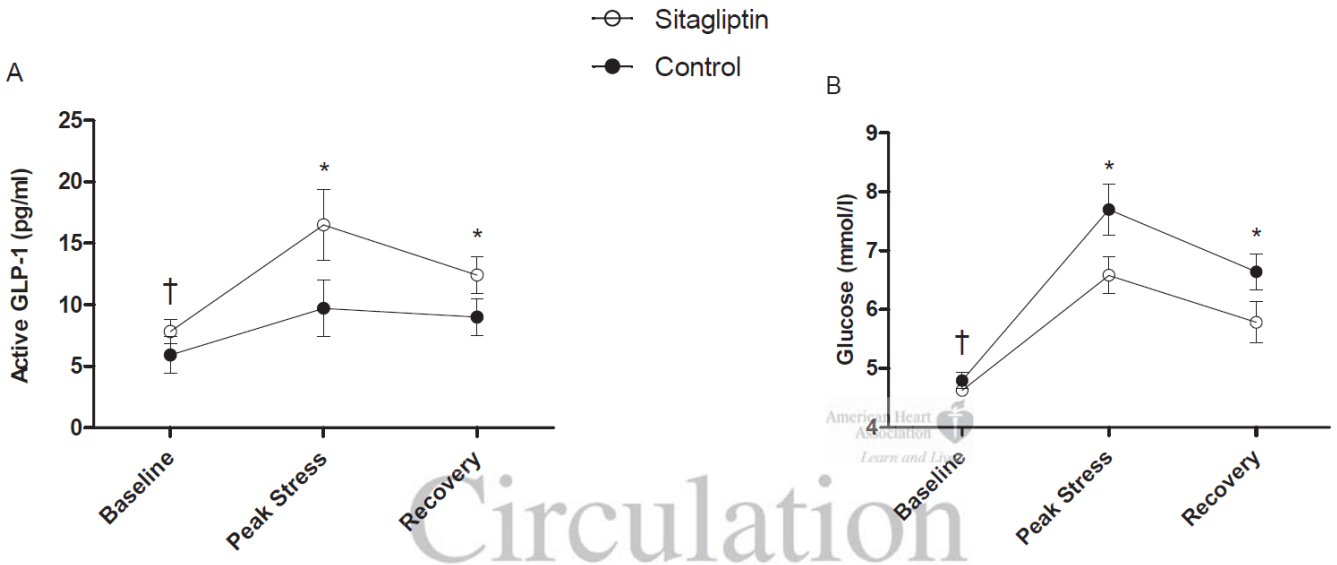
Pazienti con malattia coronarica con recente coronarografia e normale funzione ventricolare sinistra in attesa di rivascolarizzazione elettiva



Criteri di esclusione: anormalità della cinetica LV a riposo, una storia di MI nei 3 mesi precedenti, anomalie di conduzione , cardiopatie valvolari e diabete insulino-dip





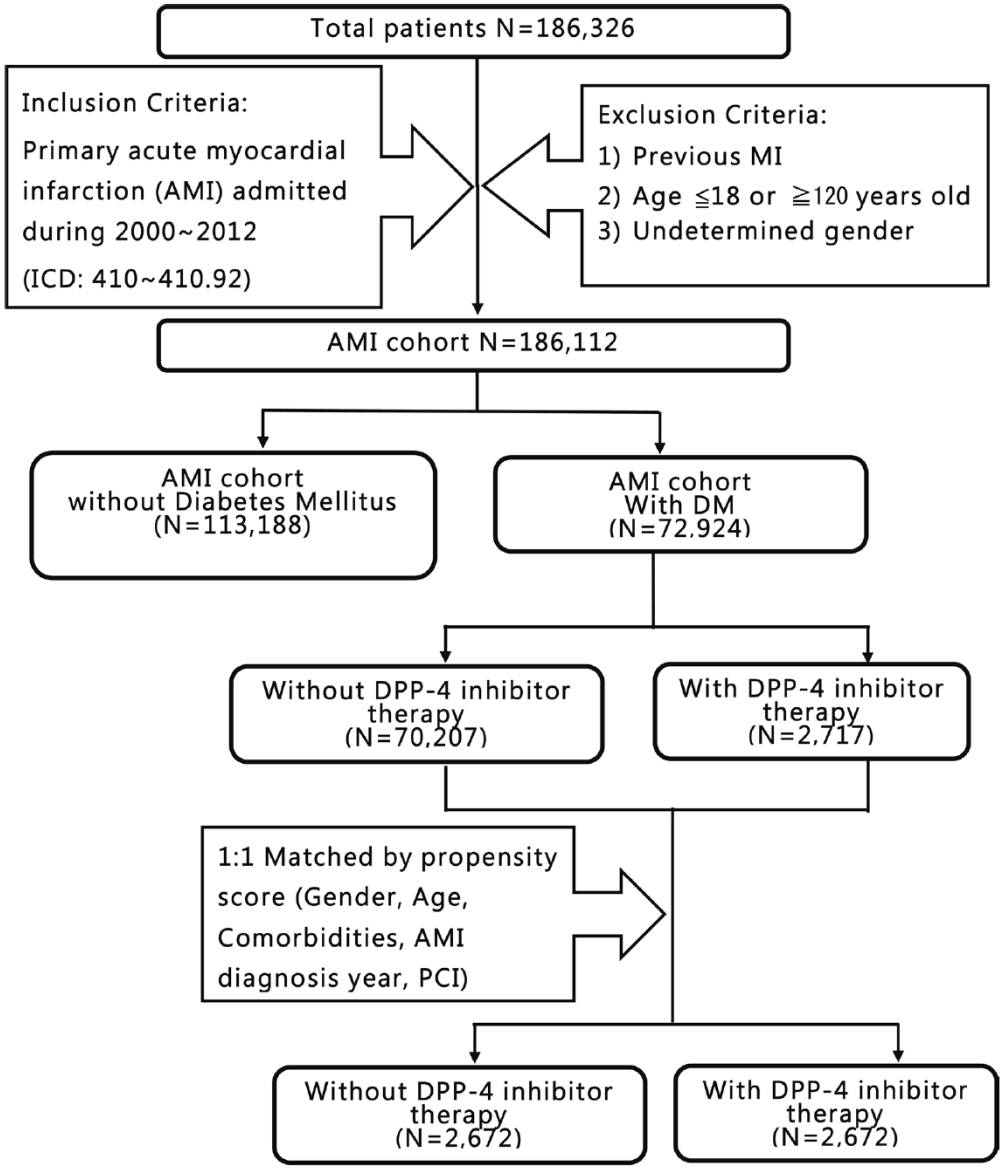


ORIGINAL INVESTIGATION Open Access

The impact of DPP-4 inhibitors on long-term survival among diabetic patients after first acute myocardial infarction

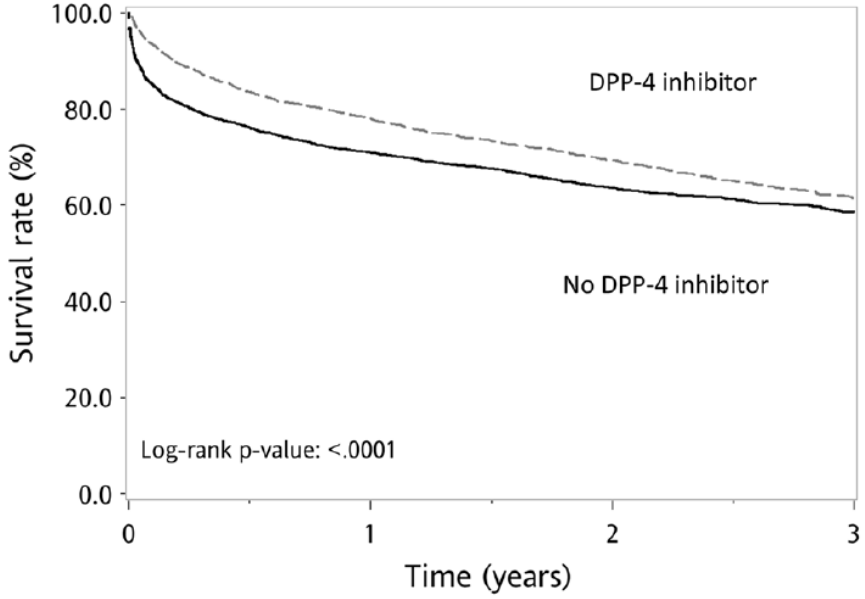
Mei-Tzu Wang[1†], Sheng-Che Lin[1†], Pei-Ling Tang[1], Wang-Ting Hung[1], Chin-Chang Cheng[1,2,3], Jin-Shiou Yang[3], Hong-Tai Chang[1], Chun-Peng Liu[1,3], Guang-Yuan Mar[1] and Wei-Chun Huang[1,2,3,4*]

There were 186,326 patients in Taiwan between January 2000 and December 2012 with a primary diagnosis of acute myocardial infarction (AMI) (ICD codes: 410–410.92).
From this group, patients were excluded who had a previous admission for AMI, who were ≤18 or ≥120 years old, and whose gender was undetermined.
Among the remaining 186,112 cases with a primary diagnosis AMI, 72,924 cases had diabetes mellitus and underwent propensity score matching to controls to minimize baseline differences between the two groups.
2672 AMI patients with DPP-4i and 2672 matched controls were, therefore, included in our final analysis.


Total patients N=186,326
Inclusion Criteria:
Primary acute myocardial infarction (AMI) admitted during 2000~2012
(ICD: 410~410.92)
Exclusion Criteria:
1) Previous MI
2) Age ≦18 or ≧120 years old
3) Undetermined gender
AMI cohort N=186,112
AMI cohort without Diabetes Mellitus (N=113,188)
AMI cohort With DM (N=72,924)
Without DPP-4 inhibitor therapy (N=70,207)
With DPP-4 inhibitor therapy (N=2,717)
1:1 Matched by propensity score (Gender, Age, Comorbidities, AMI diagnosis year, PCI)
Without DPP-4 inhibitor therapy (N=2,672)
With DPP-4 inhibitor therapy (N=2,672)

a

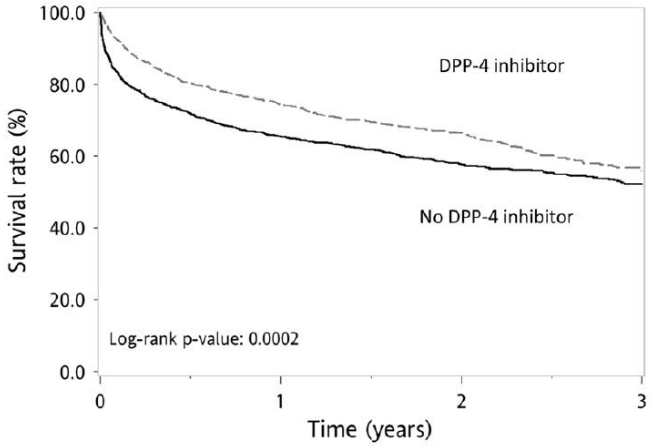
Survival Curve of AMI Patients with Diabetes mellitus



No. at Risk				
No DPP-4 inhibitor	2672	1884	942	405
DPP-4 inhibitor	2672	2071	1038	424

b

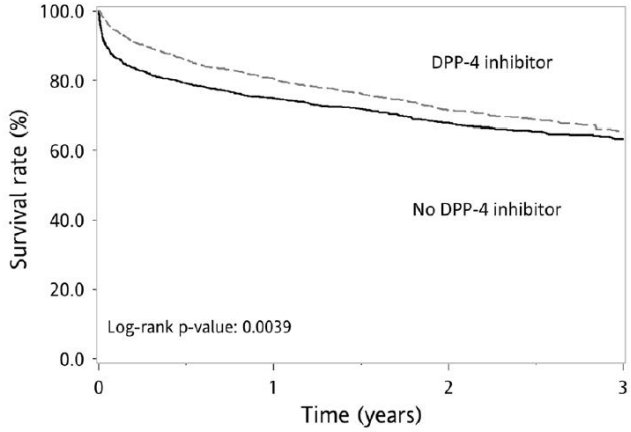
Survival Curve of AMI Patients with Diabetes mellitus (Female)



No. at Risk				
No DPP-4 inhibitor	1098	714	365	160
DPP-4 inhibitor	1098	814	425	179

c

Survival Curve of AMI Patients with Diabetes mellitus (Male)



No. at Risk				
No DPP-4 inhibitor	1574	1170	577	245
DPP-4 inhibitor	1574	1257	613	245

Table 2 Cox proportional hazard regression analysis on mortality of diabetic patients after first acute myocardial infarction

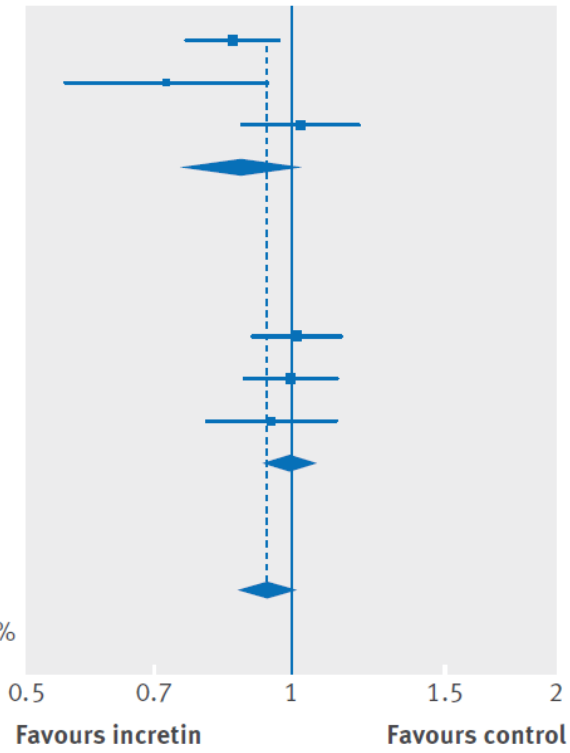
Characteristics (all, N = 5344)	HR (95% CI)
Sex (male vs female)	0.98 (0.89–1.07)
Age (65 ≤ age < 75 vs age <65)	1.71 (1.5–1.96)***
Age (age ≥75 vs age <65)	2.51 (2.2–2.85)***
Hypertension (yes vs no)	1.2 (1.06–1.37)**
Peripheral vascular disease (yes vs no)	1.57 (1.34–1.84)***
Heart failure (yes vs no)	1.35 (1.23–1.49)***
End stage renal disease (yes vs no)	1.76 (1.51–2.06)***
Cerebrovascular disease (yes vs no)	1.33 (1.21–1.47)***
Chronic obstructive pulmonary disease (yes vs no)	1.33 (1.16–1.52)***
Percutaneous coronary intervention (yes vs no)	0.54 (0.49–0.6)***
Any antiplatelet (yes vs no)	0.58 (0.49–0.7)***
ACEI or ARB (yes vs no)	0.72 (0.65–0.8)***
β-Blocker (yes vs no)	0.79 (0.71–0.87)***
Heparin or low molecular weight heparin (yes vs no)	1.02 (0.91–1.15)
α-Glucosidase (yes vs no)	0.95 (0.83–1.08)
Glinides (yes vs no)	1.05 (0.94–1.18)
Metformin (yes vs no)	0.77 (0.68–0.86)***
Sulfonylureas (yes vs no)	0.91 (0.82–1.01)
Thiazolidinedione (yes vs no)	0.79 (0.59–1.04)
DPP-4 inhibitor (yes vs no)	0.86 (0.78–0.95)**

** P < 0.01, *** P < 0.001

This nationwide study showed that DPP-4i therapy improved the long-term survival of diabetic patients after first AMI, regardless of gender.
Furthermore, DPP-4i therapy was shown to be especially beneficial in patients
without peripheral vascular disease, ESRD, or COPD.

Incretin based treatments and mortality in patients with type 2 diabetes: systematic review and meta-analysis

Study/subgroup	No of events/total: Incretin	No of events/total: Control	Odds ratio M-H (95% CI)	Weight (%)	Odds ratio M-H (95% CI)
GLP-1 agonists					
Marso 2016 (LEADER)	608/4668	694/4672		21	0.86 (0.76 to 0.97)
Marso 2016 (SUSTAIN-6)	108/1648	146/1649		8	0.72 (0.56 to 0.94)
Pfeffer 2015 (ELIXA)	397/3034	389/3034		16	1.02 (0.88 to 1.19)
Subtotal	1113/9350	1229/9355		45	0.88 (0.74 to 1.04)
Test for heterogeneity: τ^2=0.01, χ^2=6.22, df=2, P=0.04, I^2=68%					
Test for overall effect: z=1.50, P=0.13					
DPP-4 inhibitors					
Green 2015 (TECOS)	609/7332	602/7339		20	1.01 (0.90 to 1.14)
Scirica 2013 (SAVOR-TIMI 53)	613/8280	609/8212		21	1.00 (0.81 to 1.12)
White 2013 (EXAMINE)	305/2701	316/3679		14	0.95 (0.81 to 1.13)
Subtotal	1527/18 313	1527/18 230		55	0.99 (0.92 to 1.07)
Test for heterogeneity: τ^2=0.00, χ^2=0.37, df=2, P=0.83, I^2=0%					
Test for overall effect: z=0.13, P=0.89					
Total (95% CI)	2640/27 663	2756/27 585		100	0.94 (0.87 to 1.03)
Test for heterogeneity: τ^2=0.01, χ^2=10.01, df=5, P=0.07, I^2=50%					
Test for overall effect: z=1.37, P=0.17					
Test for subgroup differences: χ^2=1.74, df=1, P=0.19, I^2=43%					



Results suggested the possibility of a mortality benefit with GLP-1 agonists but not DPP-4 inhibitors, but the subgroup hypothesis had low credibility. Sensitivity analyses showed no important differences in the estimates of effects.

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Dipeptidyl peptidase-4 inhibitors and risk of heart failure in type 2 diabetes: systematic review and meta-analysis of randomised and observational studies

Study	No of events/total: DPP-4 inhibitors	No of events/total: Control	Peto odds ratio Fixed (95% CI)	Weight (%)	Peto odds ratio Fixed (95% CI)
Arjona Ferreira 2013a	0/210	4/212		5.8	0.13 (0.02 to 0.96)
Arjona Ferreira 2013b	2/64	2/65		5.7	1.02 (0.14 to 7.38)
Bosi 2011	2/404	1/399		4.4	1.93 (0.20 to 18.58)
Ferrannini 2009	2/1389	2/1383		5.8	1.00 (0.14 to 7.08)
Fonseca 2013	0/157	0/156		-	Not estimable
Garber 2007	1/304	1/158		2.6	0.49 (0.03 to 9.22)
Henry 2014	2/691	0/693		2.9	7.42 (0.46 to 118.77)
Iwamoto 2010	1/290	0/73		0.9	3.50 (0.03 to 464.78)
NCT00094770 2009	2/588	1/584		4.4	1.94 (0.20 to 18.65)
NCT00103857 2009	1/372	0/364		1.5	7.23 (0.14 to 364.55)
NCT00121641 2011	1/306	0/95		1.1	3.71 (0.04 to 372.46)
NCT00121667 2011	3/564	2/179		5.3	0.42 (0.05 to 3.26)
NCT00286442 2011	1/423	0/104		0.9	3.48 (0.03 to 478.41)
NCT00286468 2011	1/401	0/99		0.9	3.48 (0.03 to 475.96)
NCT00295633 2009	0/381	1/184		1.3	0.05 (0.00 to 3.04)
NCT00327015 2009	0/643	2/328		2.6	0.05 (0.00 to 0.97)
NCT00395343 2009	0/322	2/319		2.9	0.13 (0.01 to 2.14)
NCT00482729 2009	1/625	0/621		1.5	7.34 (0.15 to 370.02)
NCT00575588 2010	1/428	1/430		2.9	1.00 (0.06 to 16.09)
NCT00614939 2010	1/85	0/85		1.5	7.39 (0.15 to 372.38)
NCT00622284 2011	3/776	2/775		7.3	1.49 (0.26 to 8.63)
NCT00642278 2013	0/65	1/386		0.7	0.31 (0.00 to 82.44)
NCT00707993 2013	1/222	1/219		2.9	0.99 (0.06 to 15.82)
NCT00757588 2011	2/304	0/151		2.6	4.48 (0.24 to 85.32)
NCT00798161 2011	1/428	0/363		1.4	6.35 (0.12 to 324.20)
NCT00838903 2014	1/302	1/408		2.8	1.36 (0.08 to 22.44)
NCT00856284 2013	3/1751	1/878		5.2	1.46 (0.18 to 11.67)
NCT00954447 2012	3/631	2/630		7.3	1.49 (0.26 to 8.63)
NCT01006603 2013	1/359	3/359		5.8	0.37 (0.05 to 2.61)
NCT01189890 2013	0/241	1/236		1.5	0.13 (0.00 to 6.68)
NCT01263483 2011	0/155	1/75		1.3	0.05 (0.00 to 3.05)
NCT01289990 2014	1/223	0/676		1.1	56.34 (0.60 to 5268.88)
Pratley 2009	3/397	0/97		2.7	3.49 (0.20 to 60.57)
Pratley 2014	0/442	0/326		-	Not estimable
Rosenstock 2006	0/175	0/178		-	Not estimable
Rosenstock 2010	0/327	0/163		-	Not estimable
Seino 2012	1/188	0/100		1.3	4.63 (0.08 to 283.93)
Yang 2015	0/68	1/40		1.4	0.07 (0.00 to 3.89)
Total (95% CI)	42/15 701	33/12 591		100.0	0.97 (0.61 to 1.56)

Test for heterogeneity: χ^2=32.27, df=33, P=0.50, I^2=0%

Test for overall effect: z=0.11, P=0.91

0.01 0.1 1 10 100

Favours DPP-4 inhibitors Favours control

The relative effect of DPP-4 inhibitors on the risk of heart failure in patients with type 2 diabetes is uncertain, given the relatively short follow-up and low quality of evidence

Dove le possibili indicazioni per usufruire delle potenzialità del farmaco