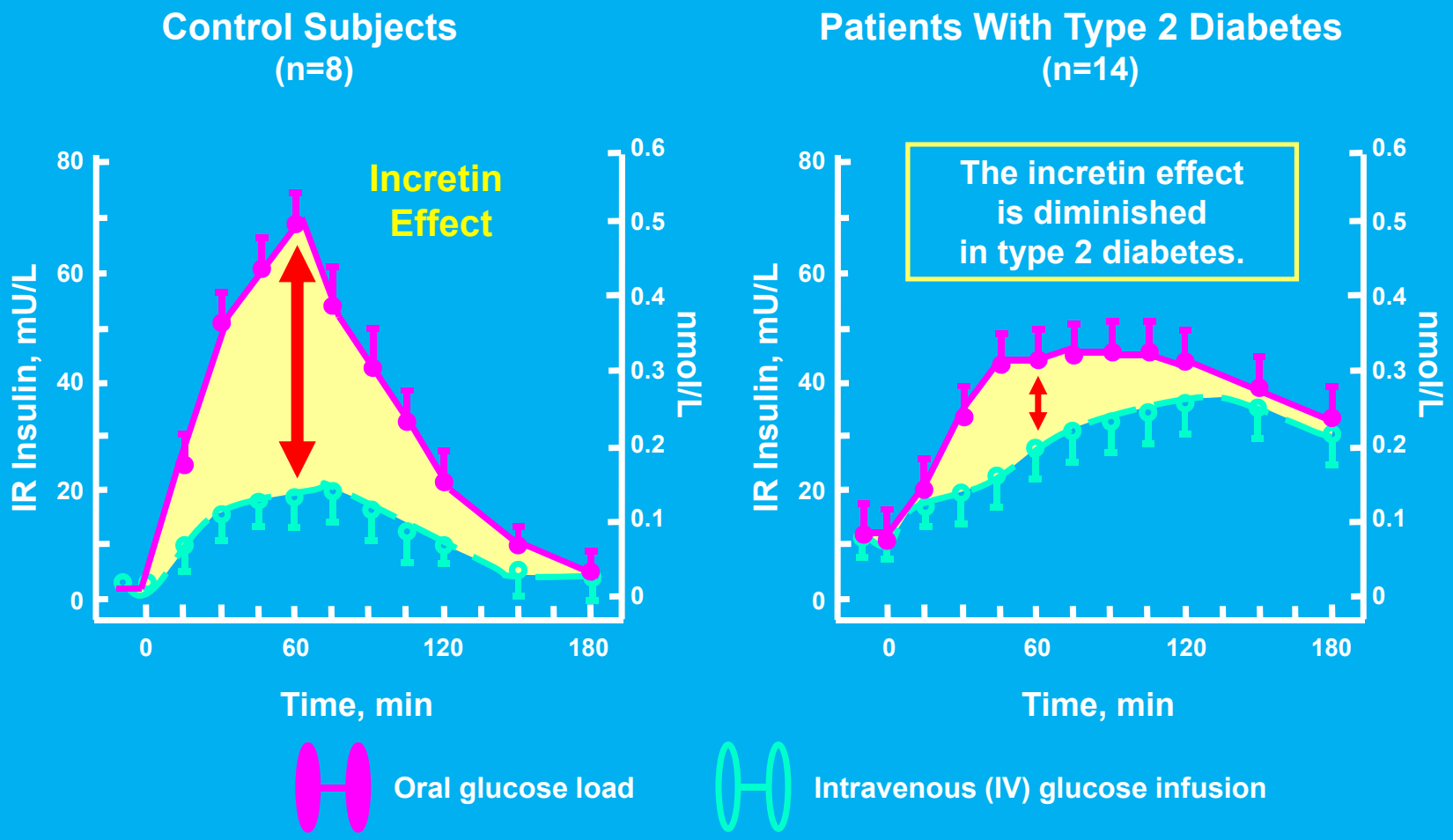
EFFECTS OF GLP-1 BASED THERAPY ON THE HEART

Prof Avraham Karasik

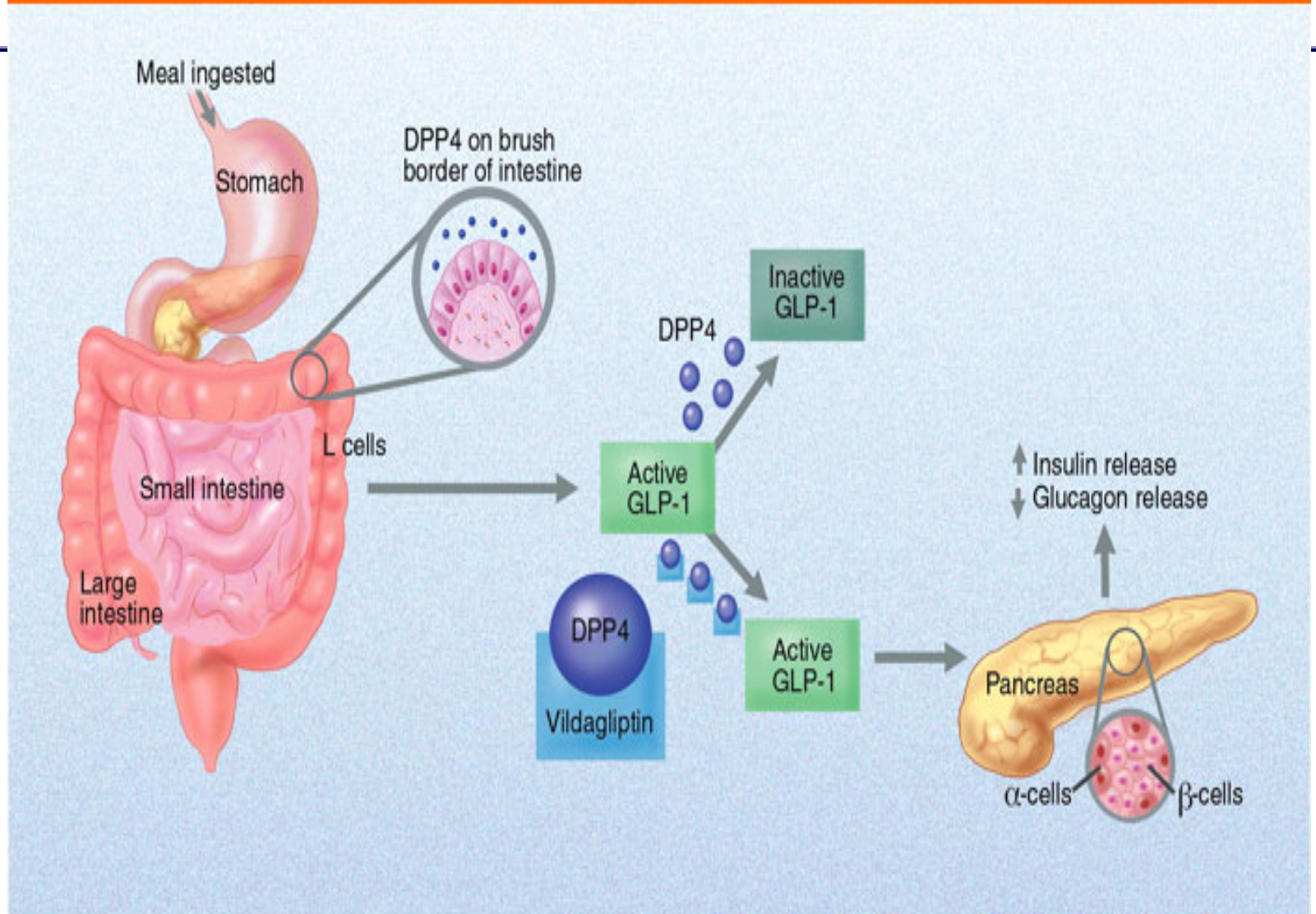
Sheba Medical Center

Tel Aviv University

אפקט האינקרטינים באנשים בריאים ובחולי סוכרת סוג 2



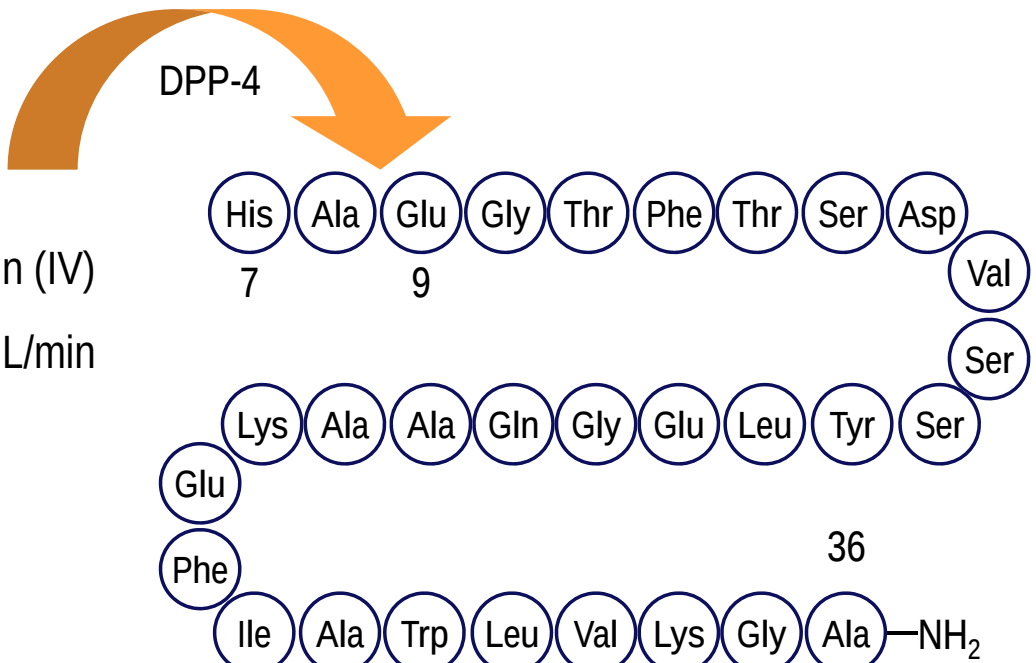
IR=Immune Reactive.


Meal ingested
Stomach
DPP4 on brush border of intestine
L cells
Small intestine
Large intestine
DPP4
Inactive GLP-1
Active GLP-1
DPP4
Vildagliptin
Active GLP-1
Insulin release
Glucagon release
Pancreas
α-cells
β-cells

GLP-1 is Rapidly Degraded by DPP-4

Plasma $t_{1/2}$ = 1–2 min (IV)

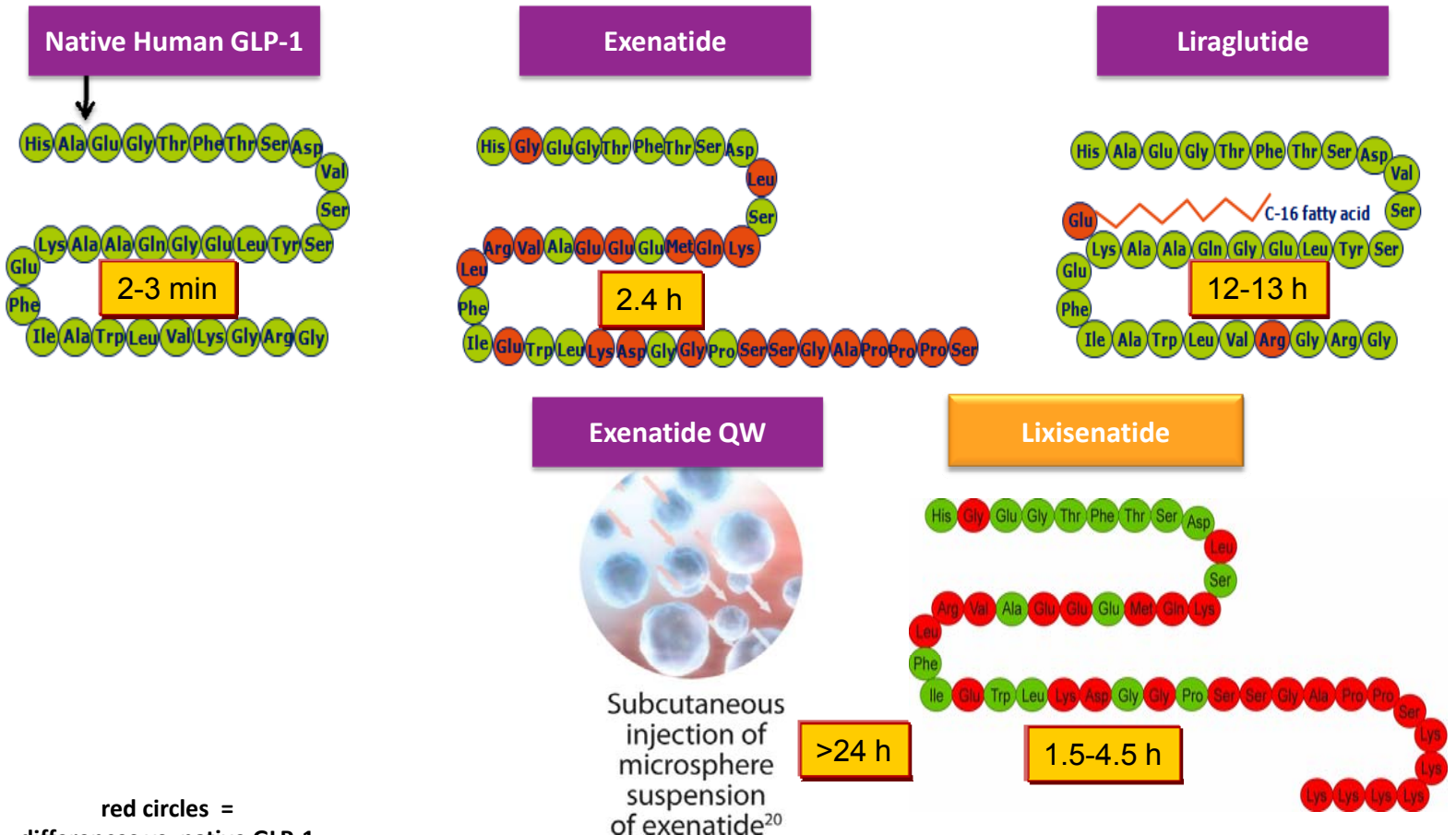
CL = 5–10 L/min



CL=clearance rate;
DPP-4=dipeptidyl peptidase-4;
GLP-1=glucagon-like peptide-1;
IV=intravenously

Rasmussen et al. *Nature Structural Biology* 2003
Vilsbøll et al. *J Clin Endocrinol Metab*. 2003

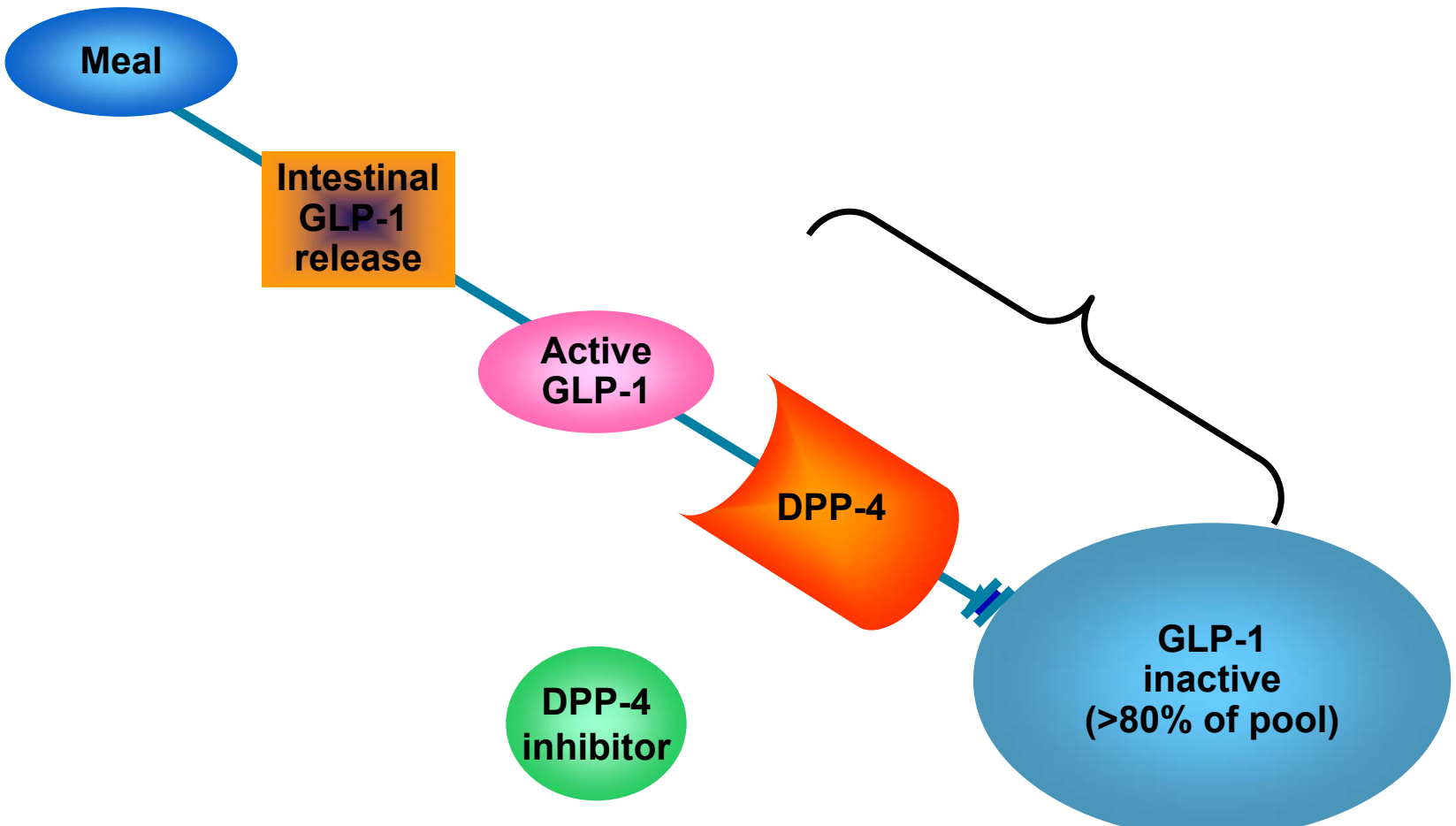
GLP-1R Agonists: 'Similar' Structure to Native Human GLP-1



red circles = differences vs. native GLP-1

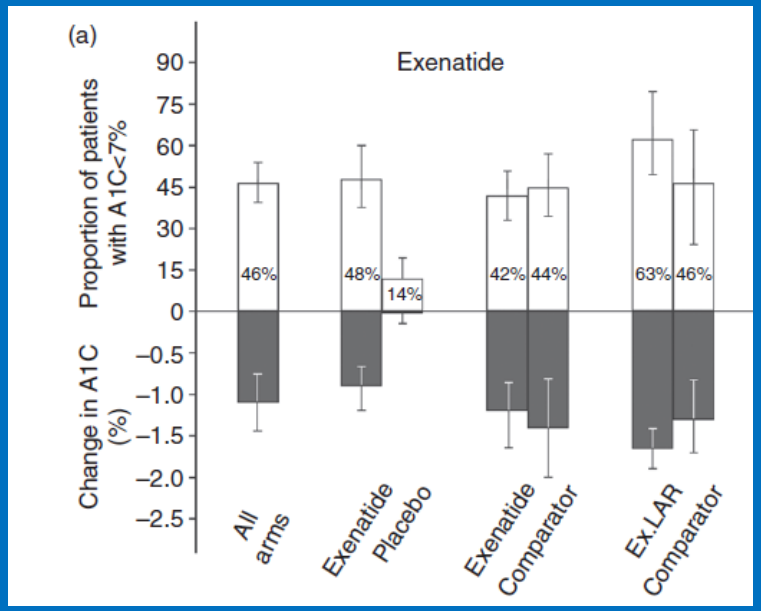
Adapted from Werner U, et al *Regul Pept*. 2010;164:58–64

Inhibition of DPP-4 Increases Active GLP-1

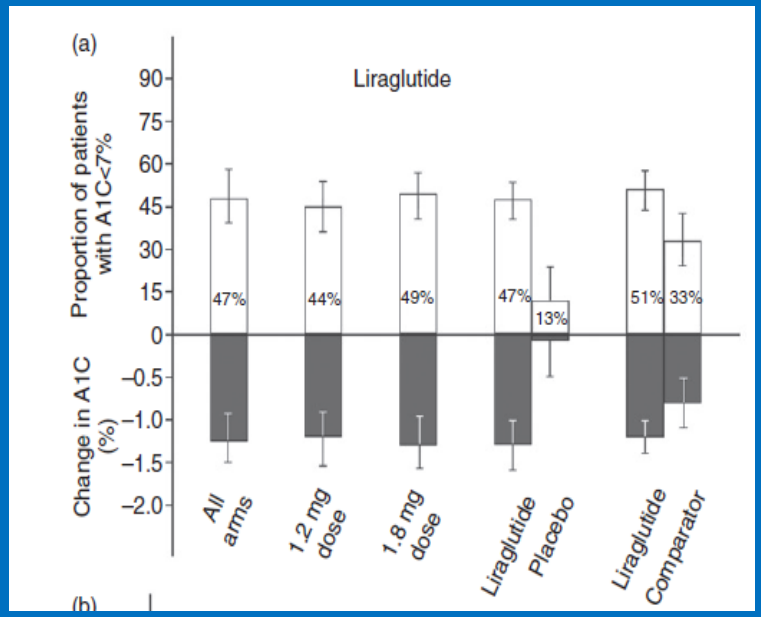


Improved glucose control

Exanatide

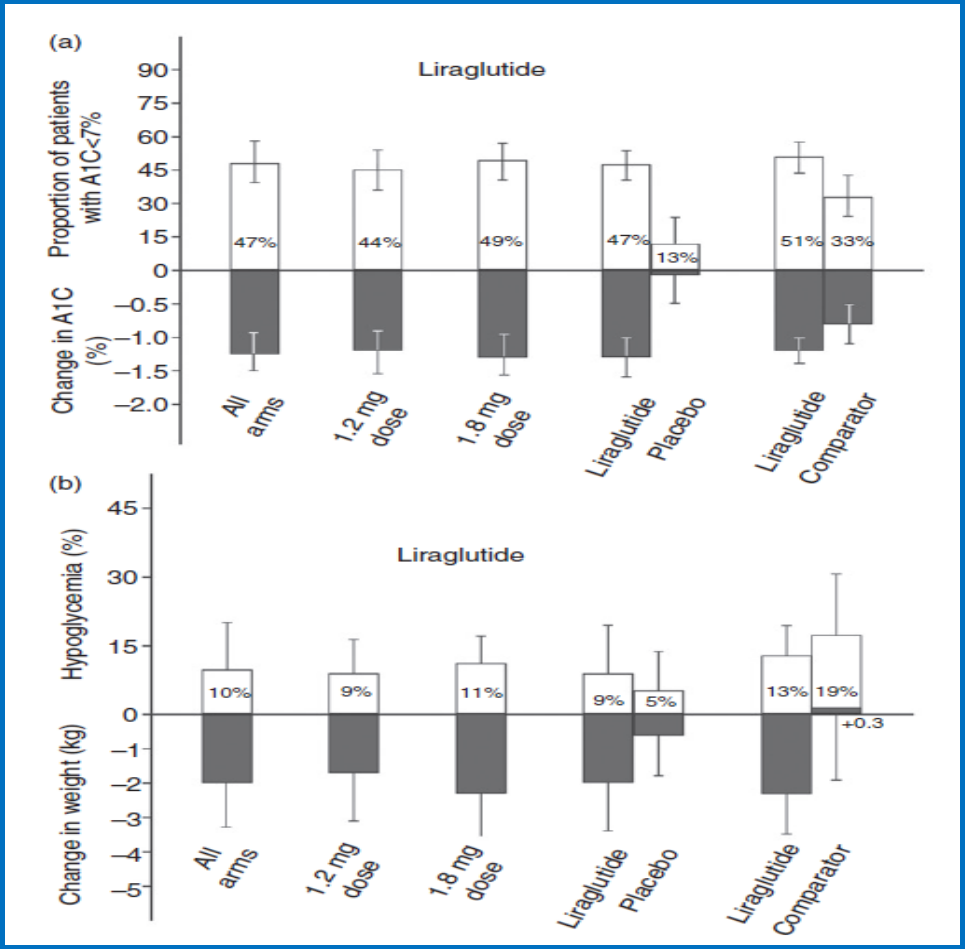


Liraglutide



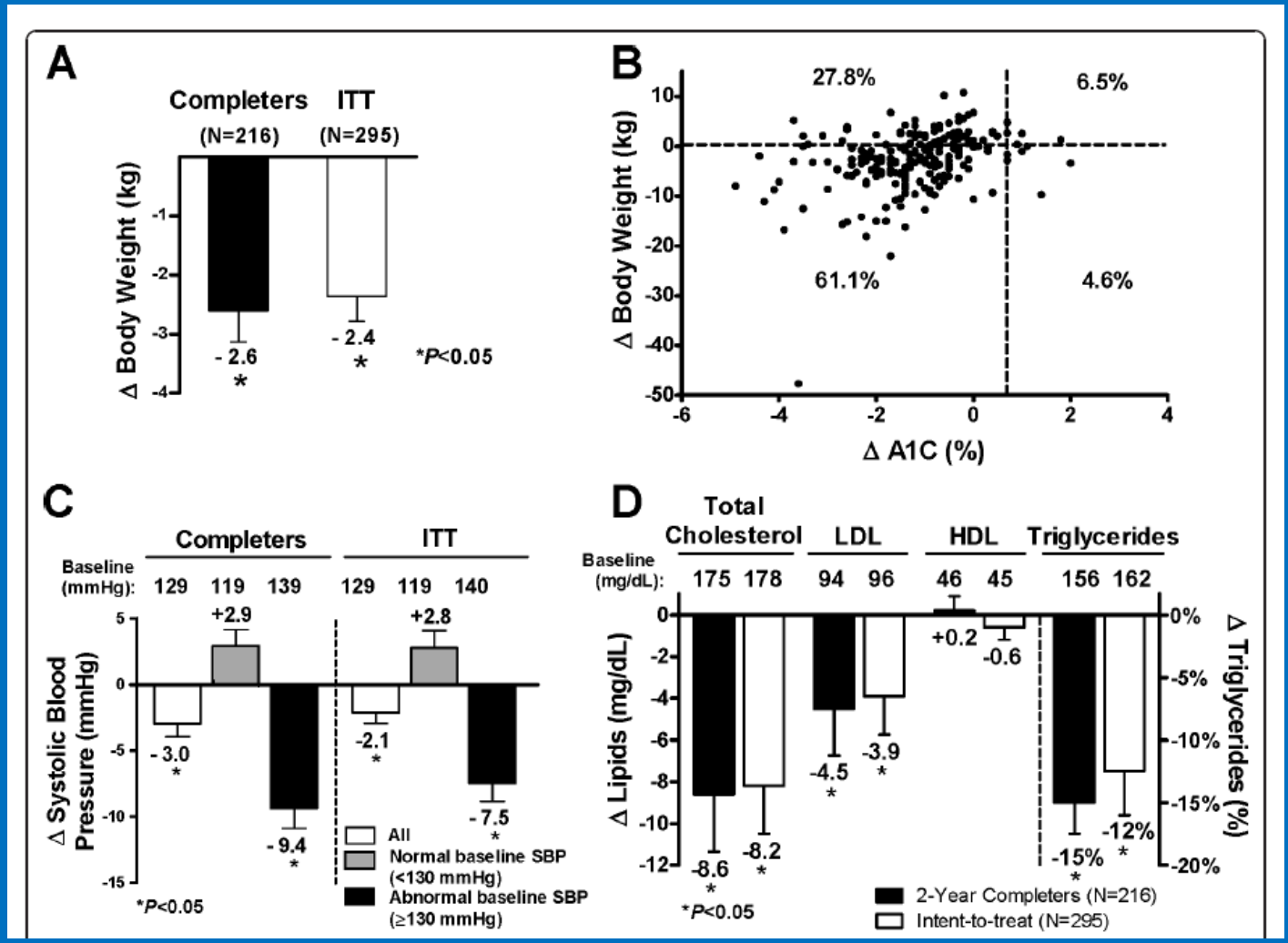
Current Medical Research & Opinion Vol. 27, No. 8, 2011, 1519–1528

Improved glucose control + weight loss w/o hypoglycemia



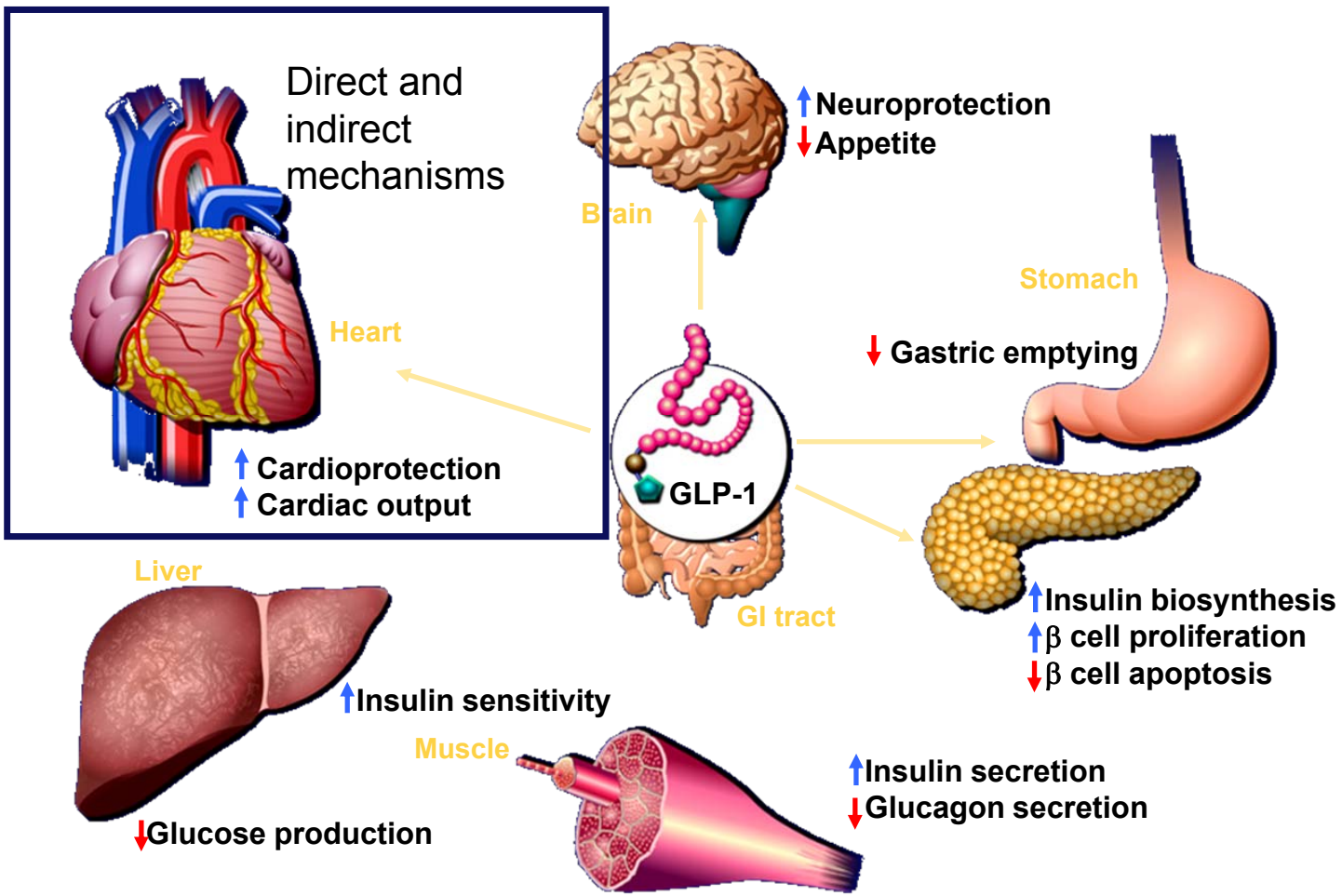
Current Medical Research & Opinion Vol. 27, No. 8, 2011, 1519–1528

Change in metabolic parametes after 2 y therapy with Exanatide ER



Taylor *et al. BMC Endocrine Disorders* 2011, **11**:9

Incretin Actions on Different Target Tissues



Drucker DJ. *Cell Metab*. 2006;3:153-165.

European Heart Journal (2012) 33, 1491–1499
doi:10.1093/eurheartj/ehr309

CLINICAL RESEARCH
Acute coronary syndromes

Exenatide reduces reperfusion injury in patients with ST-segment elevation myocardial infarction

Jacob Lønborg[1]*, Niels Vejlstrup[1], Henning Kelbæk[1], Hans Erik Bøtker[2], Won Yong Kim[2], Anders B. Mathiasen[1], Erik Jørgensen[1], Steffen Helqvist[1], Kari Saunamäki[1], Peter Clemmensen[1], Lene Holmvang[1], Leif Thuesen[2], Lars Romer Krusell[2], Jan S. Jensen[3], Lars Køber[1], Marek Treiman[4], Jens Juul Holst[4], and Thomas Engstrøm[1]

[1]Department of Cardiology, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark; [2]Department of Cardiology, Skejby, Aarhus, Denmark; [3]Department of Cardiology, Gentofte Hospital, Copenhagen, Denmark; and [4]Department of Biomedical Sciences and The Danish National Foundation Research Centre for Heart Arrhythmia, University of Copenhagen, Denmark

Study design

- Patients presenting within 12 h of onset of STEMI
- All underwent pPCI
- Randomised to IV Exenatide for 6 hours or placebo
- Evaluated for Area at risk by cMR in first week
- Evaluated for infarct size by cMR at 3 m
- Evaluated for LVEF by cMR at 3 m

Exenatide decreases infarct size

Infarct size at 3 m plotted against area at risk (by CMR)

All patients

LAD lesion

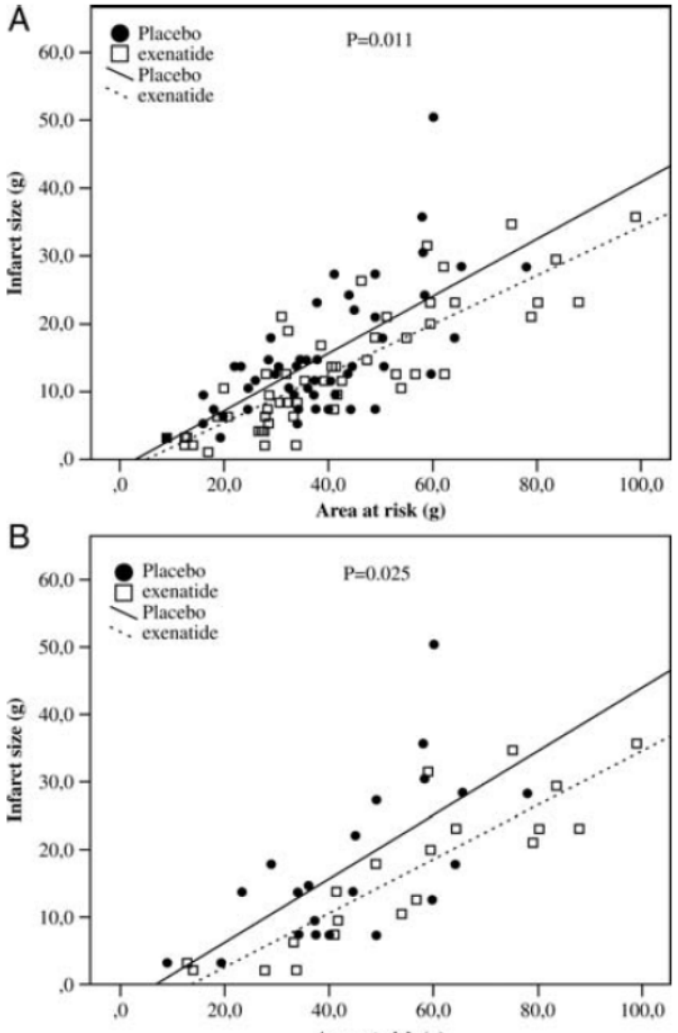
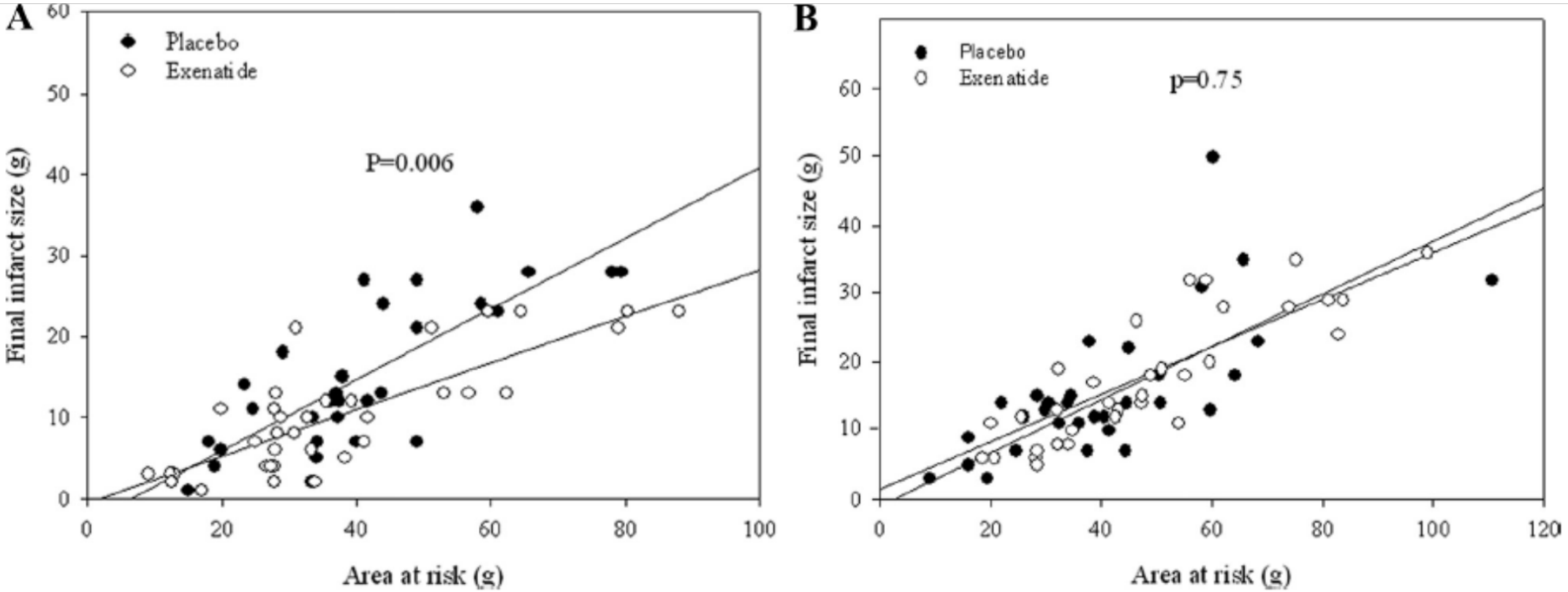


Table 2 Outcomes evaluated with cardiac magnetic resonance

	n	Exenatide	*n*	Placebo	*P*-value
Overall study population					
Salvage index[a]	54	0.71 ± 0.13	51	0.62 ± 0.16	0.003
Infarct size (g)/area at risk (g)	54	0.30 ± 0.15	51	0.39 ± 0.15	0.003
Area at risk (g)	54	42 ± 21	51	39 ± 14	0.43
Final infarct size (g)	60	13 ± 9	57	17 ± 14	0.11
Final infarct size (%LV)	60	11 ± 7	57	12 ± 6	0.33
LVEF 3 months (%)	60	55 ± 9	57	55 ± 11	0.82
Anterior infarct location[b]					
Salvage index[a]	20	0.74 ± 0.11	21	0.62 ± 0.18	0.023
Infarct size (g)/area at risk (g)	20	0.27 ± 0.12	21	0.39 ± 0.19	0.024
Area at risk (g)	20	53 ± 24	21	45 ± 17	0.14
Final infarct size (g)	23	17 ± 11	25	21 ± 19	0.32
Final infarct size (%LV)	23	13 ± 9	25	14 ± 8	0.76
LVEF 3 months (%)	23	55 ± 11	25	51 ± 14	0.27

Effect of exenatide only after short duration of ischemia



<132 min

>132 min

Lonburg Circulation Cardiovas Interven 2012

Administration of High dose GLP-1 is feasible and safe (20ug/24 h for 72 hours)

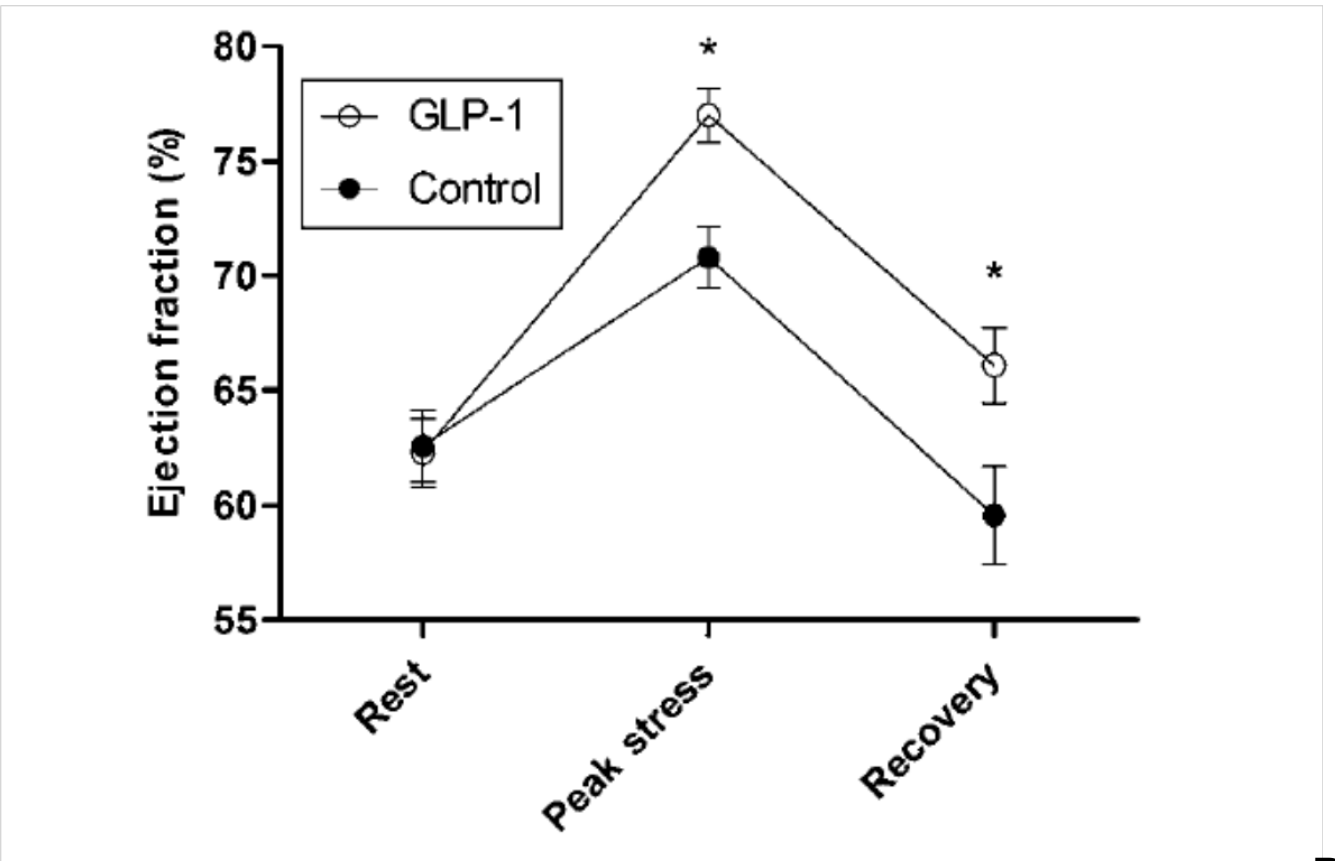
Table 2
Results of side effects and follow-up oral glucose tolerance test of patients included in the safety analysis.

	Exenatide ($n=22$)	Placebo ($n=21$)	P value
Nausea (%)	11 (50)	4 (19)	0.033
Need for anti-emetics (%)	9 (41)	1 (5)	0.005
Hypoglycaemic episode (%)	6 (27)	3 (14)	0.46
Hyperglycaemic episode (%)	2 (9)	5 (24)	0.24
	($n=18$)[a]	($n=16$)[a]	
OGTT (%)			0.55
Normal glucose regulation	5 (28)	6 (38)	
Abnormal glucose regulation	12 (67)	7 (44)	
Impaired fasting glucose	12 (67)	7 (44)	
Impaired glucose tolerance	5 (28)	3 (19)	
Diabetes	1 (6)	3 (19)	

OGTT = oral glucose tolerance test.
[a] 3 patients in the exenatide group and 2 patients in the placebo group refused OGTT.

Bernink. Int J Cardiol 2013

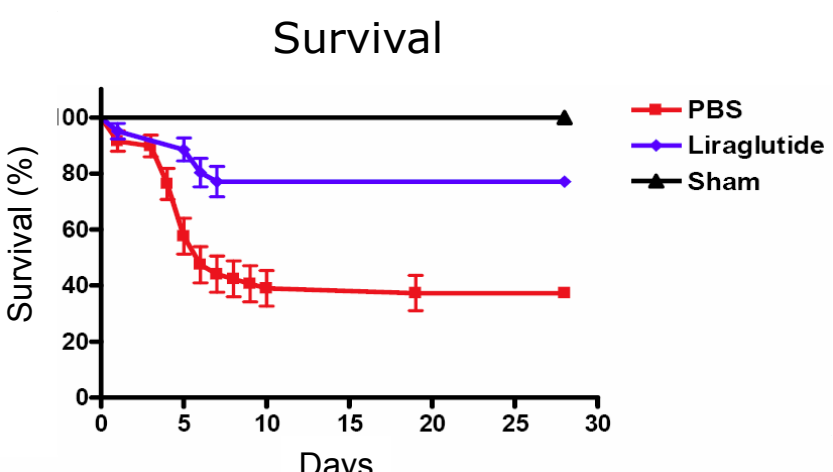
GLP-1 infusion improves LVEF during dobutamine stress echocardiography

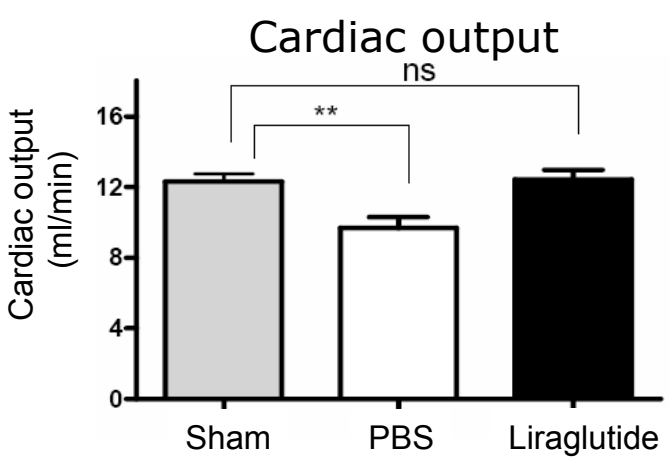


Read PA Heart 2011

Liraglutide: beneficial effect in a mouse myocardial infarction model

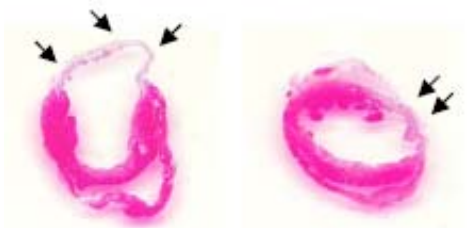
- In a mouse model of myocardial infarction, a 7-day course of liraglutide:
  - Induced a cardioprotective gene expression profile
  - Reduced infarct size and cardiac rupture
  - Improved survival versus placebo (80% versus 40%, respectively; *p*=0.0001)



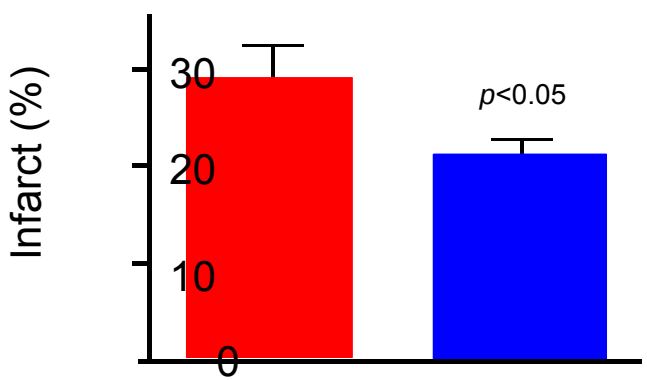


Noyan-Ashraf *et al. Diabetes* 2008:57(Suppl.1). Oral Presentation 190.

Pre-treatment with liraglutide reduces infarct size



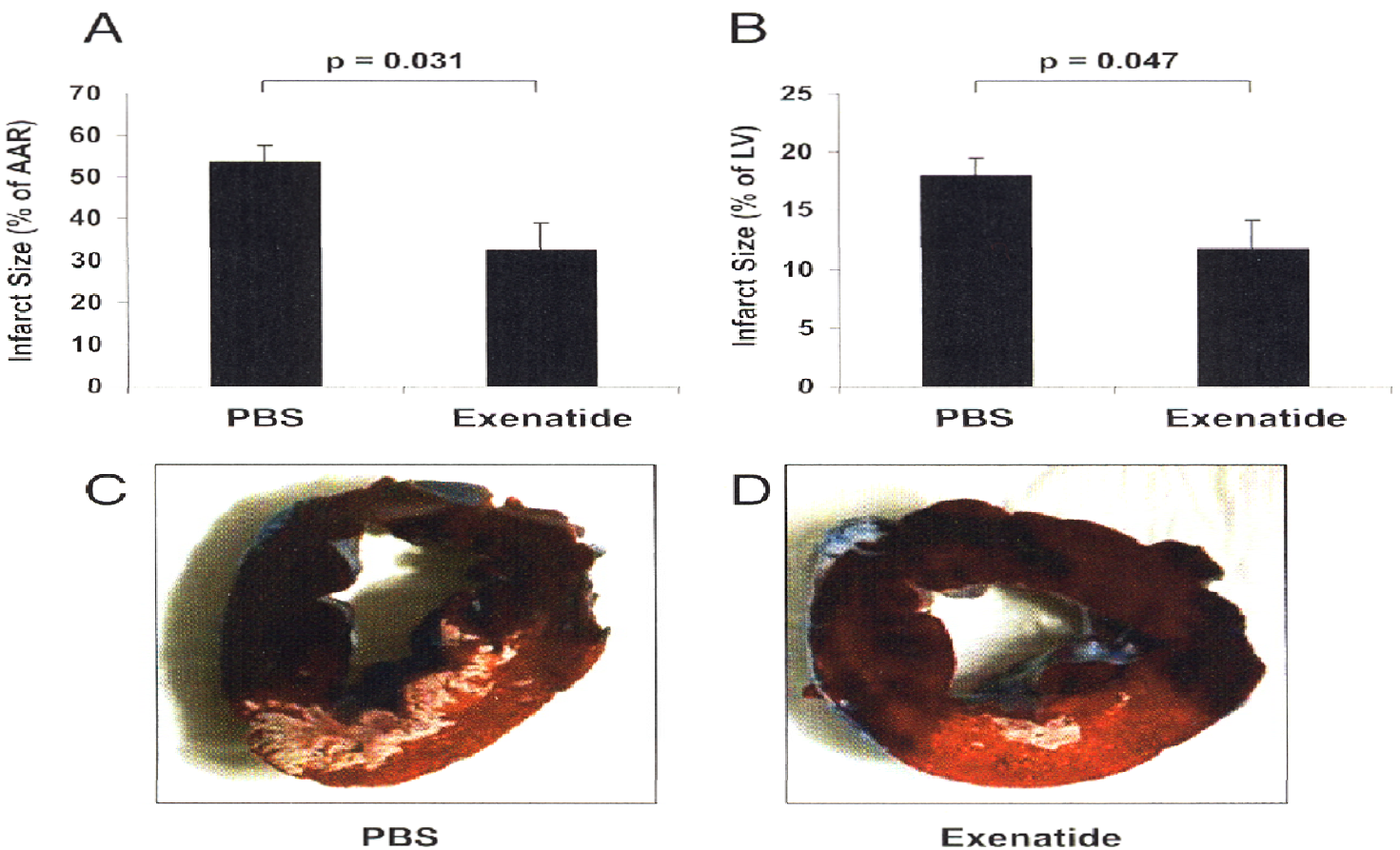
Arrows represent extent of infarct



Liraglutide
Placebo

Noyan-Ashraf *et al. Diabetes* 2009;

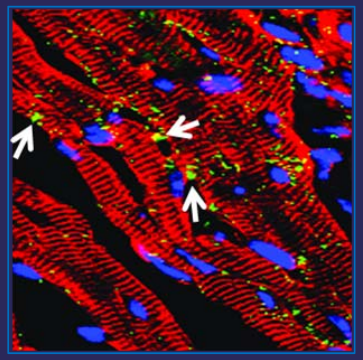
Myocardial Infarction and Exenatide in Dogs



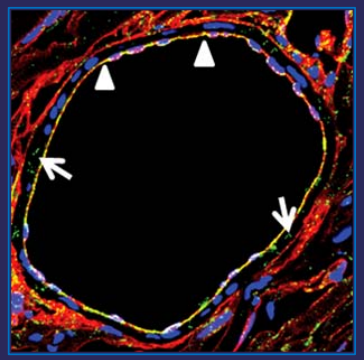
Timmers et al. 2009; J Am Coll Cardio

GLP-1 Receptors are Present in Cardiovascular Tissues

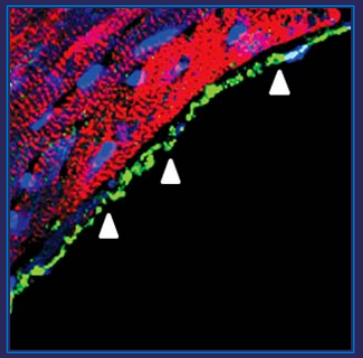
Cardiomyocytes



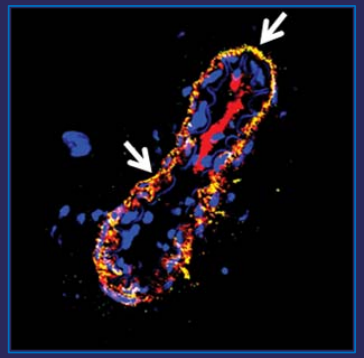
Microvascular endothelium;
Coronary smooth muscle



Endocardium



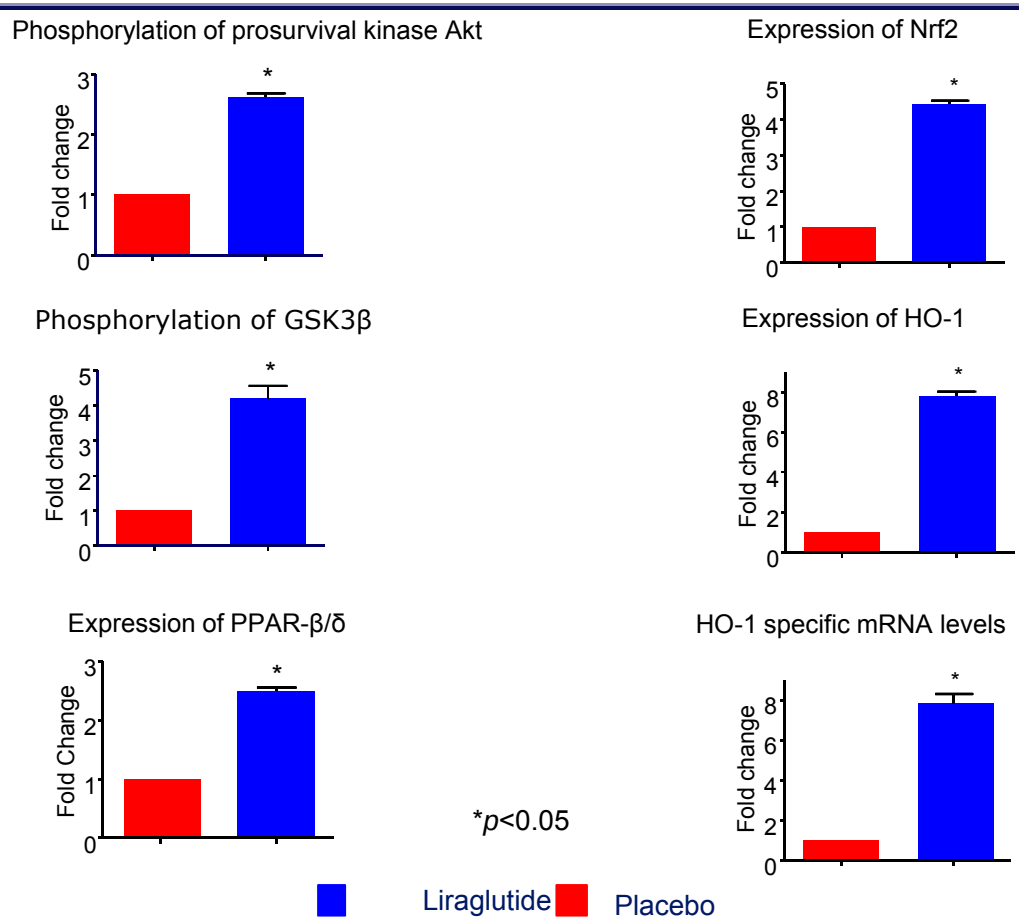
Mesenteric artery
(medial smooth muscle cells)



GLP-1-Receptor; green
Vascular/cardiac smooth muscle; red
Nuclei: blue

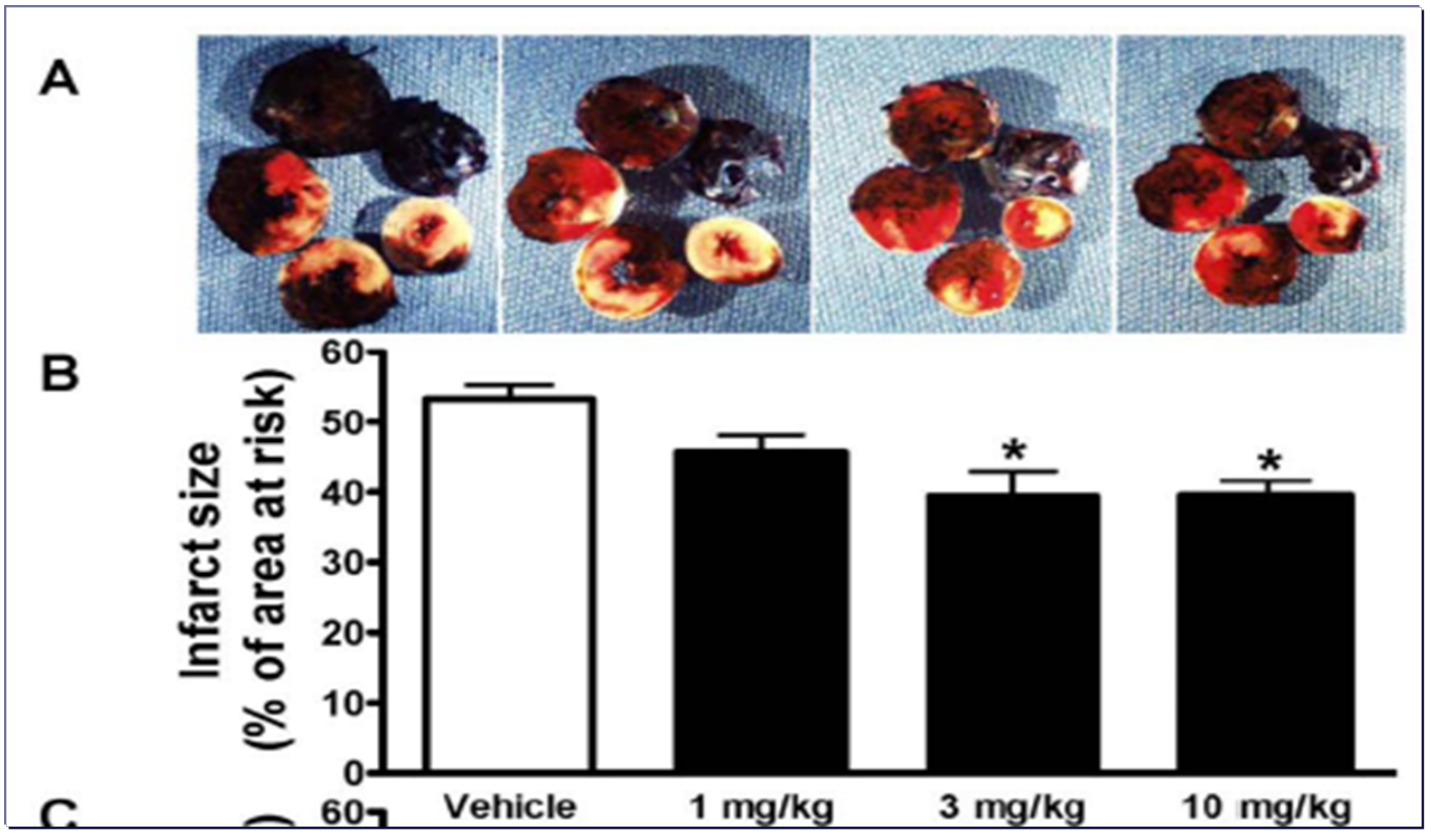
Ban et al; Circulation 2008

Treatment with liraglutide activates pro-survival pathways in the heart



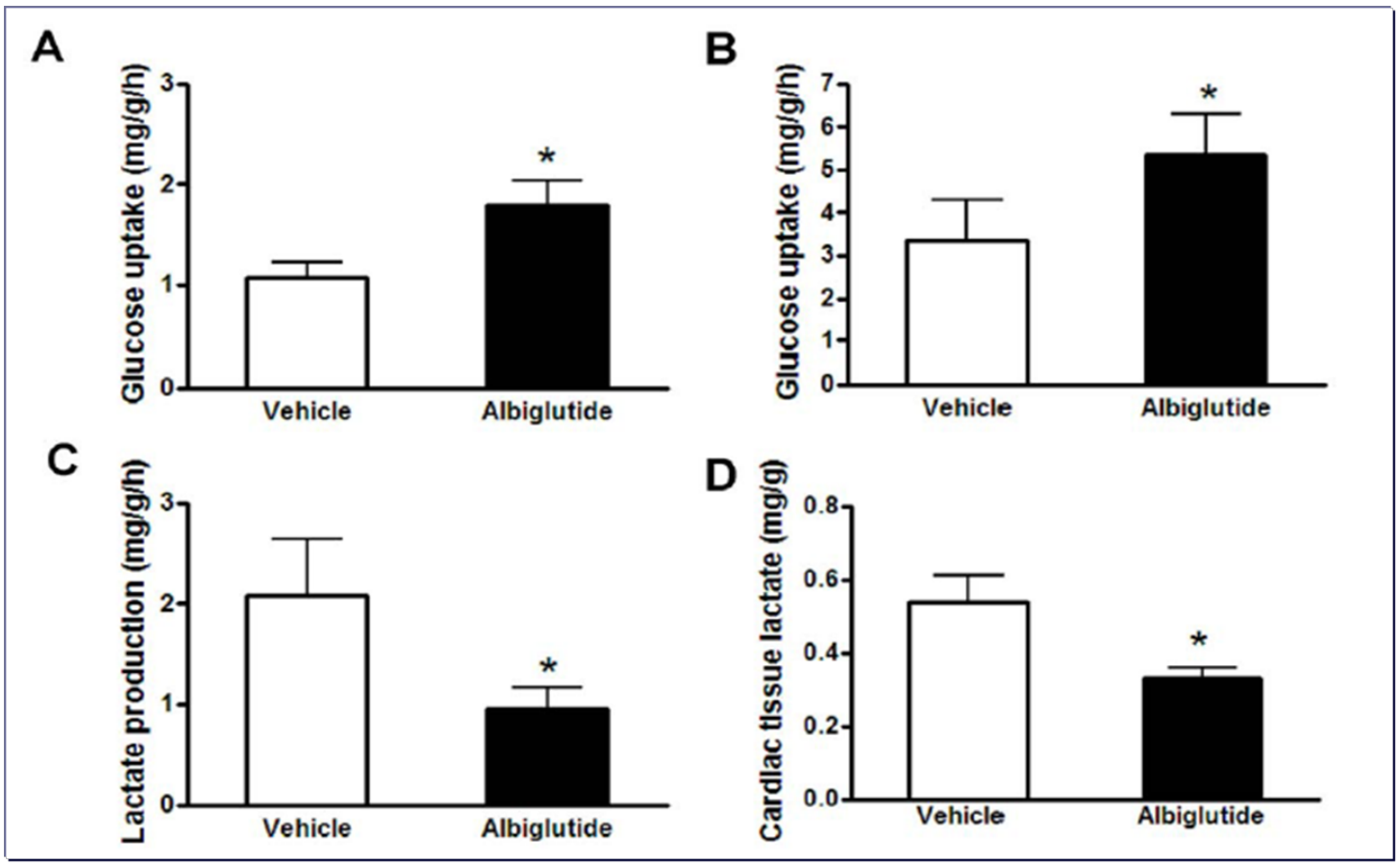
Noyan-Ashraf *et al*. *Diabetes* 2009;58:975–83. GSK3, glycogen synthase kinase 3; HO-1, heme-oxygenase-1; Nrf2; nuclear factor erythroid-2 related factor 2; PPAR; peroxisome proliferator activated receptor

Albiglutide, a Long Lasting Glucagon-Like Peptide-1 Analog, Protects the Rat Heart against Ischemia/ Reperfusion Injury: Evidence for Improving CardiacMetabolic Efficiency

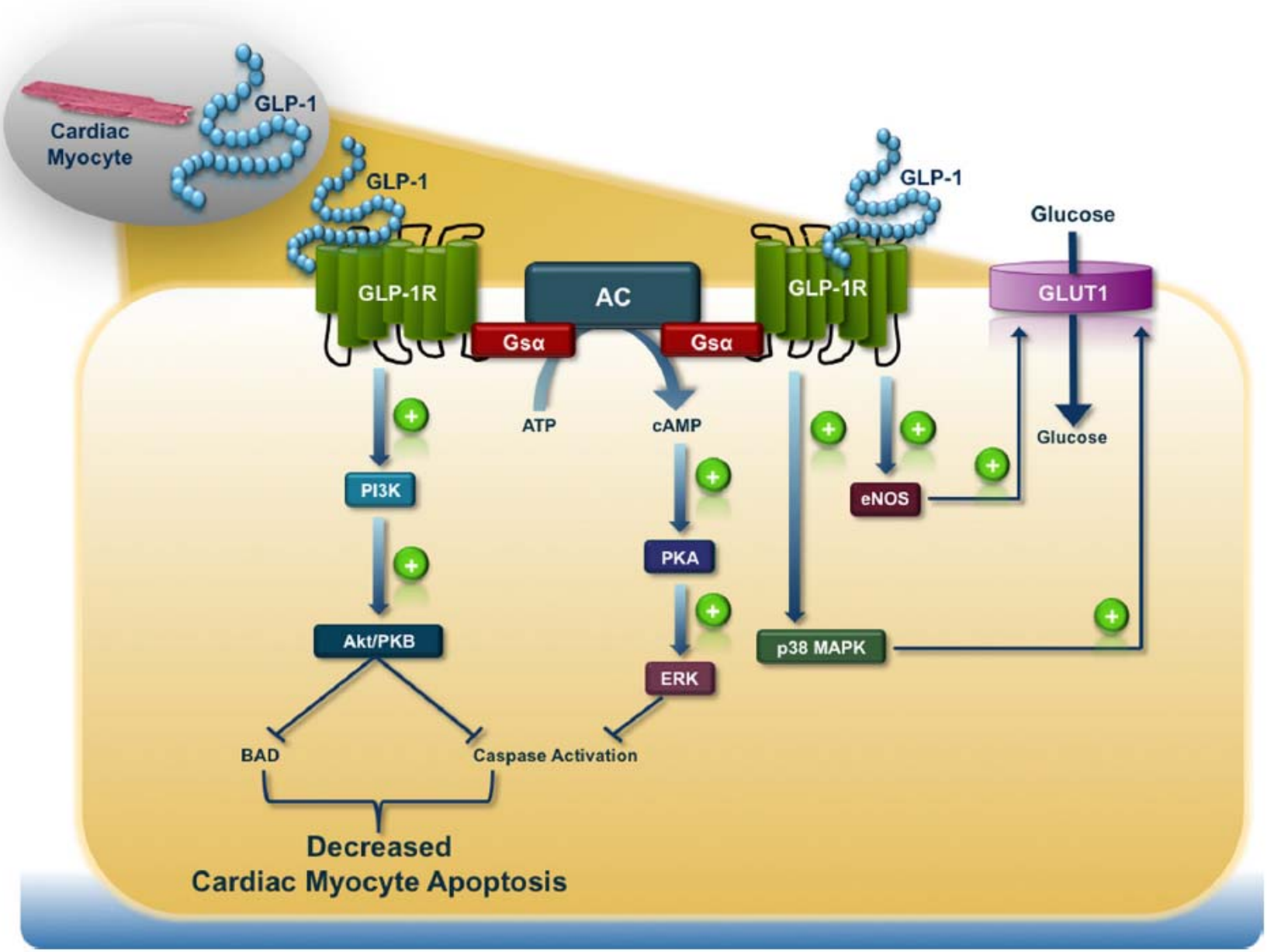


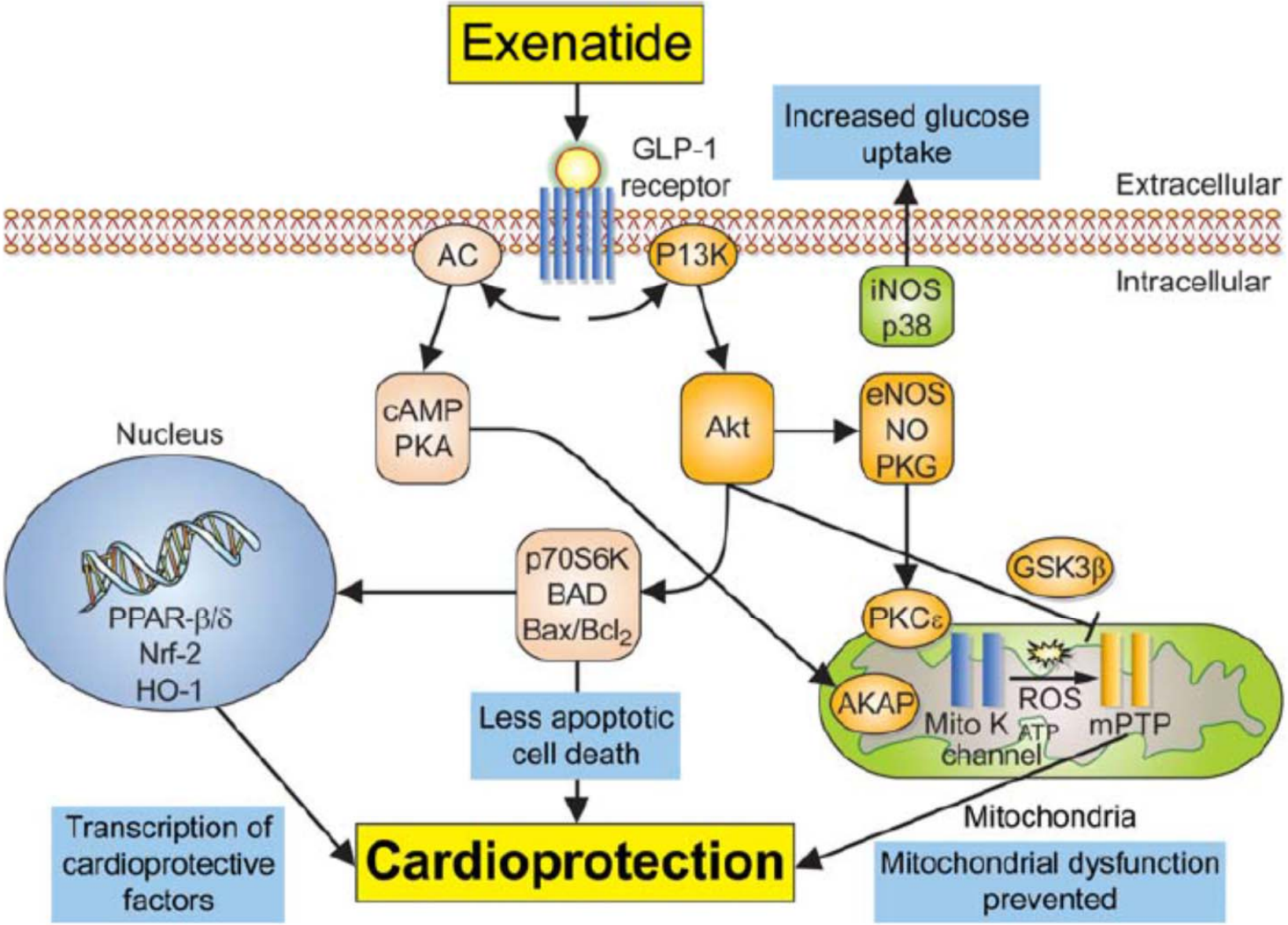
Weike Bao; PLoS ONE,2011

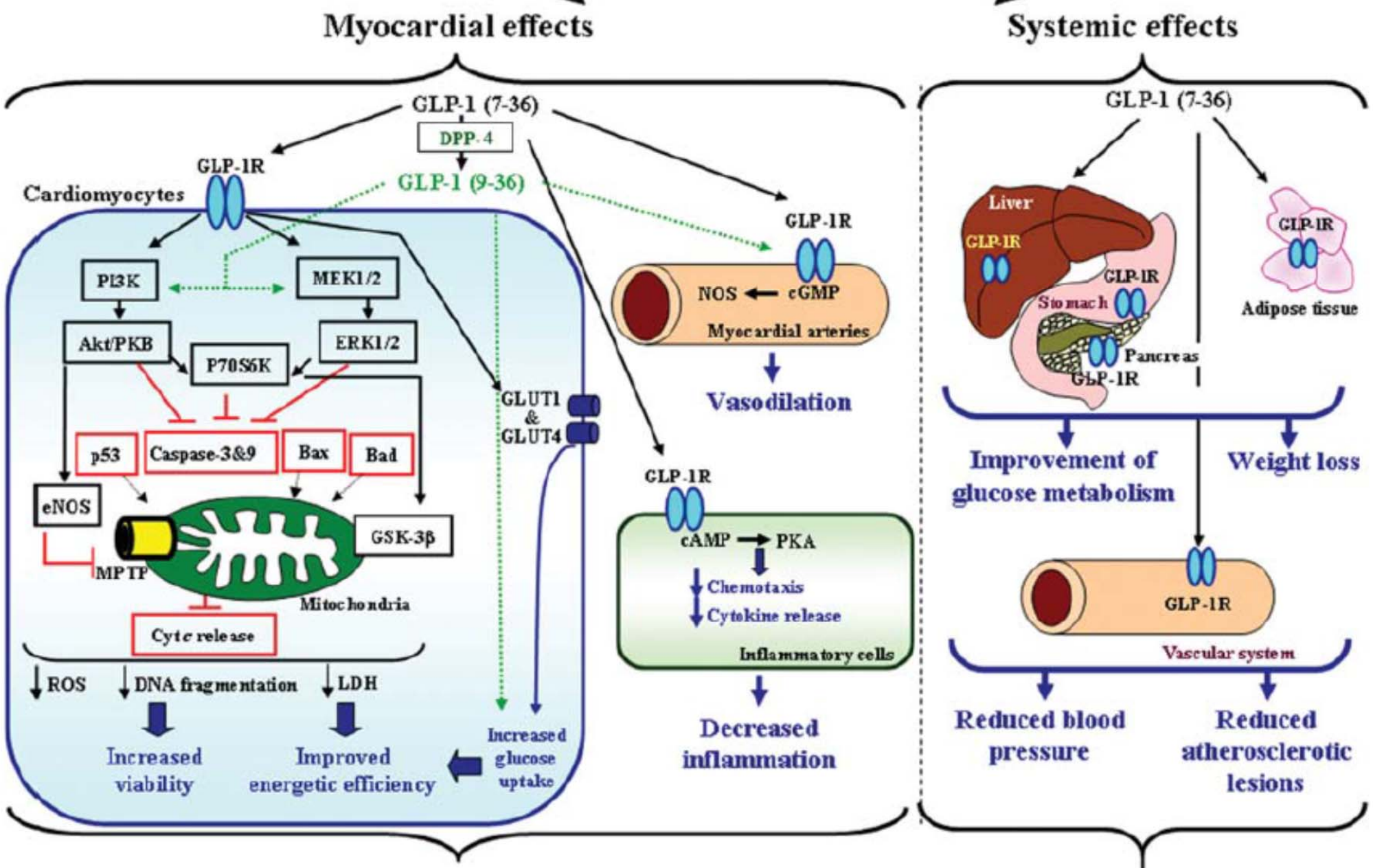
Cardiac glucose metabolism in vivo and ex vivo



Weike Bao; PLoS ONE,2011

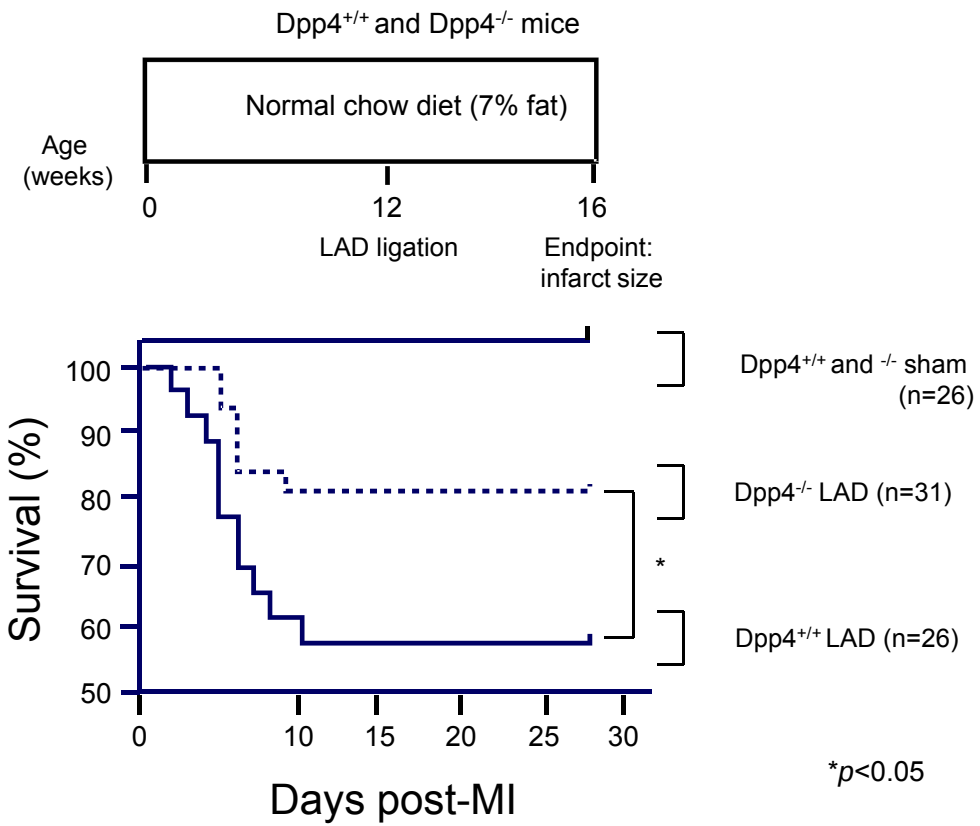

Cardiac Myocyte
GLP-1
GLP-1
GLP-1
GLP-1R
AC
GLP-1R
Gsα
Gsα
Glucose
GLUT1
ATP
cAMP
Glucose
PI3K
eNOS
PKA
Akt/PKB
p38 MAPK
ERK
BAD
Caspase Activation
Decreased
Cardiac Myocyte Apoptosis

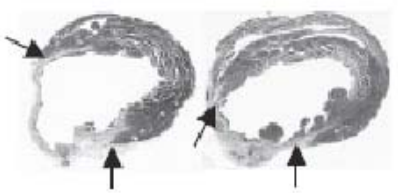

Exenatide
GLP-1 receptor
Increased glucose uptake
Extracellular
Intracellular
AC
P13K
iNOS
p38
cAMP
PKA
Akt
eNOS
NO
PKG
Nucleus
PPAR-β/δ
Nrf-2
HO-1
p70S6K
BAD
Bax/Bcl2
GSK3β
PKCε
AKAP
Mito K ATP channel
ROS
mPTP
Mitochondria
Less apoptotic cell death
Transcription of cardioprotective factors
Cardioprotection
Mitochondrial dysfunction prevented

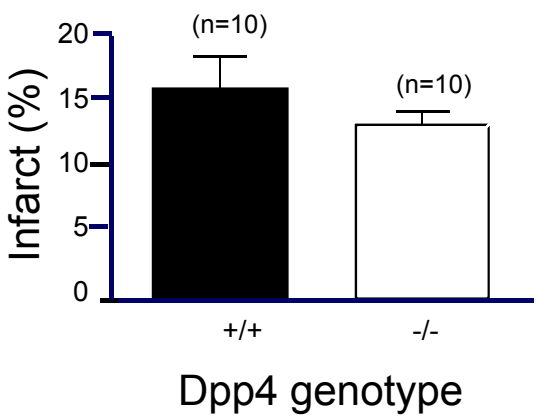

Myocardial effects
Systemic effects
GLP-1 (7-36)
DPP-4
GLP-1 (9-36)
GLP-1R
Cardiomyocytes
PI3K
MEK1/2
Akt/PKB
P70S6K
ERK1/2
p53
Caspase-3&9
Bax
Bad
eNOS
GSK-3β
MPTP
Mitochondria
Cyt c release
ROS
DNA fragmentation
LDH
Increased viability
Improved energetic efficiency
GLUT1 & GLUT4
Increased glucose uptake
NOS
cGMP
Myocardial arteries
Vasodilation
cAMP
PKA
Chemotaxis
Cytokine release
Inflammatory cells
Decreased inflammation
Liver
Stomach
Pancreas
Adipose tissue
Improvement of glucose metabolism
Weight loss
Vascular system
Reduced blood pressure
Reduced atherosclerotic lesions

Genetic and pharmacological inhibition of Dpp4

Mice lacking Dpp4 have improved outcomes after experimental MI

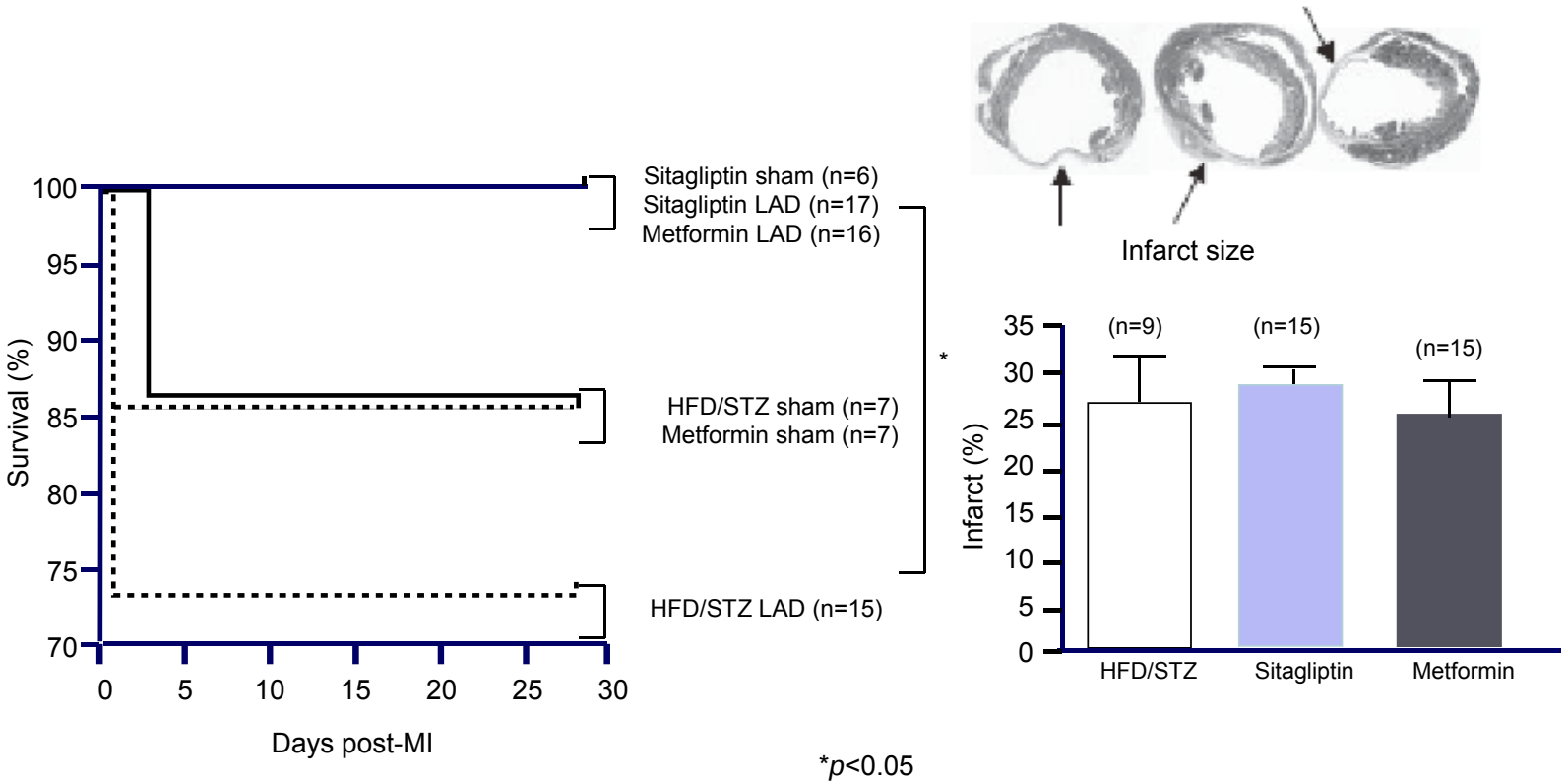






Sauve *et al*. *Diabetes* 2010;59:1063–73. MI, myocardial infarction; LAD, left anterior descending artery

Diabetic mice treated with a Dpp4 inhibitor have improved outcomes after experimental MI

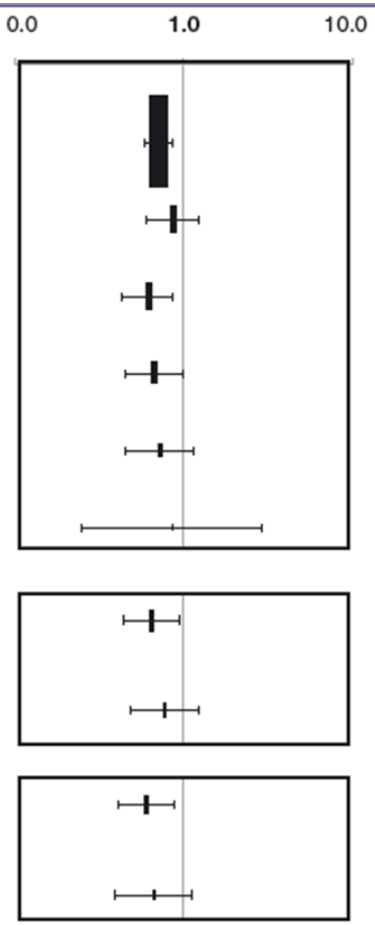


Sauve *et al*. *Diabetes* 2010;59:1063–73. MI, myocardial infarction; HFD/STZ, high-fat-fed streptozotocin-treated

Dipeptidyl peptidase-4 inhibitors and cardiovascular risk: a meta-analysis of randomized clinical trials

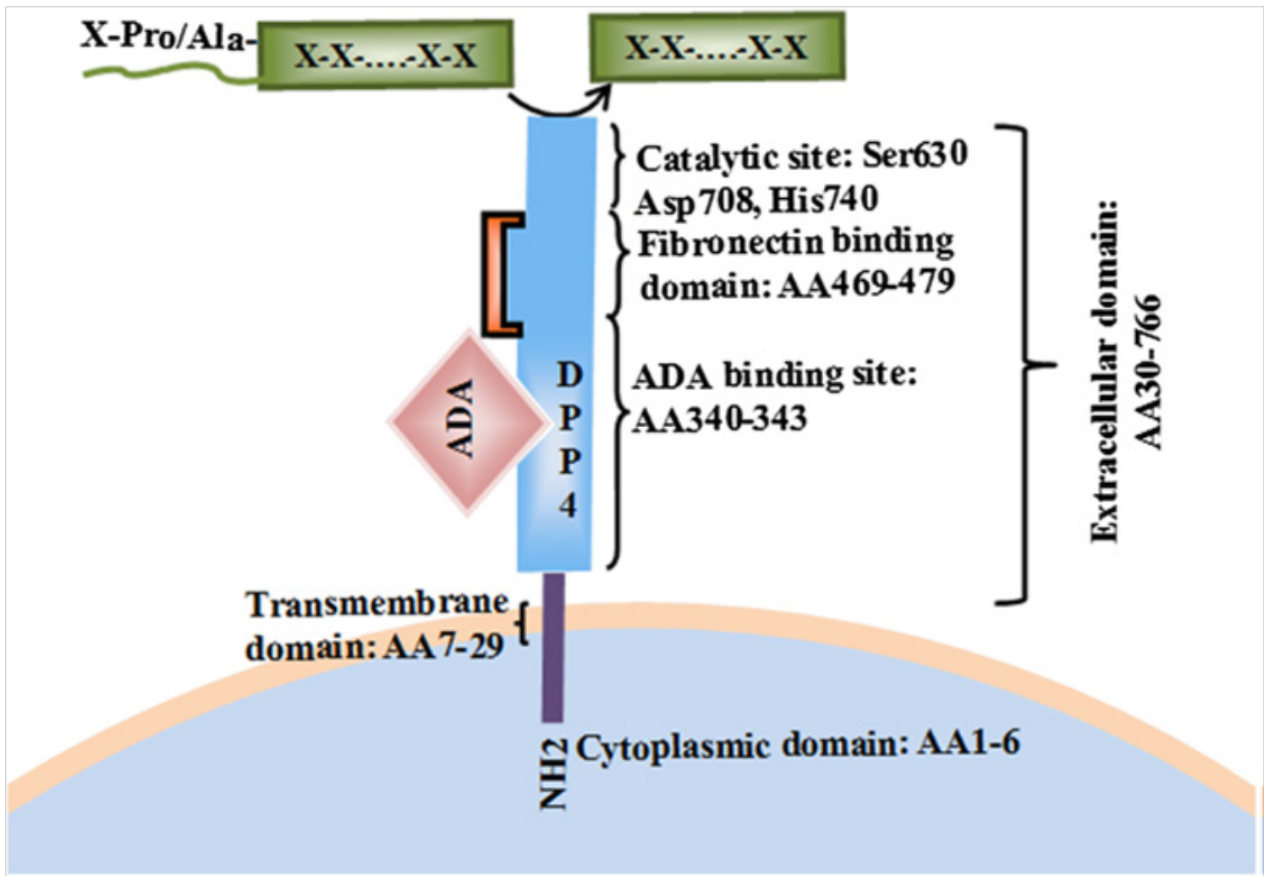
M. Monami[1], B. Ahrén[2], I. Dicembrini[3] & E. Mannucci[4]

	# trials	# trials with events	# events (*DPP4i*)	# events (*Comparator*)	MH-OR [95%, CI]	p	Kendall's tau	p
MACE	**70**	**63**	**263**	**232**	**0.71[0.59;0.86]**	**<0.001**	**0.04**	**0.64**
Sitagliptin	27	24	77	67	0.86[0.60;1.24]	0.430	0.04	0.80
Vildagliptin	16	15	75	74	0.61[0.43;0.86]	0.005	0.03	0.89
Saxagliptin	13	12	62	46	0.67[0.45;0.99]	0.047	0.36	0.10
Linagliptin	9	8	37	41	0.72[0.45;1.16]	0.18	0.00	1.00
Alogliptin	5	4	12	4	0.86[0.25;2.93]	0.81	0.30	0.15
AMI	**62**	**41**	**61**	**59**	**0.64[0.44;0.94]**	**0.023**	**-0.13**	**0.27**
Stroke	**63**	**29**	**41**	**33**	**0.77[0.48;1.24]**	**0.290**	**-0.24**	**0.14**
Mortality	**53**	**30**	**50**	**51**	**0.60[0.41;0.88]**	**0.008**	**0.13**	**0.28**
CV Mortality	**48**	**20**	**26**	**26**	**0.67[0.39;1.14]**	**0.140**	**0.05**	**0.76**

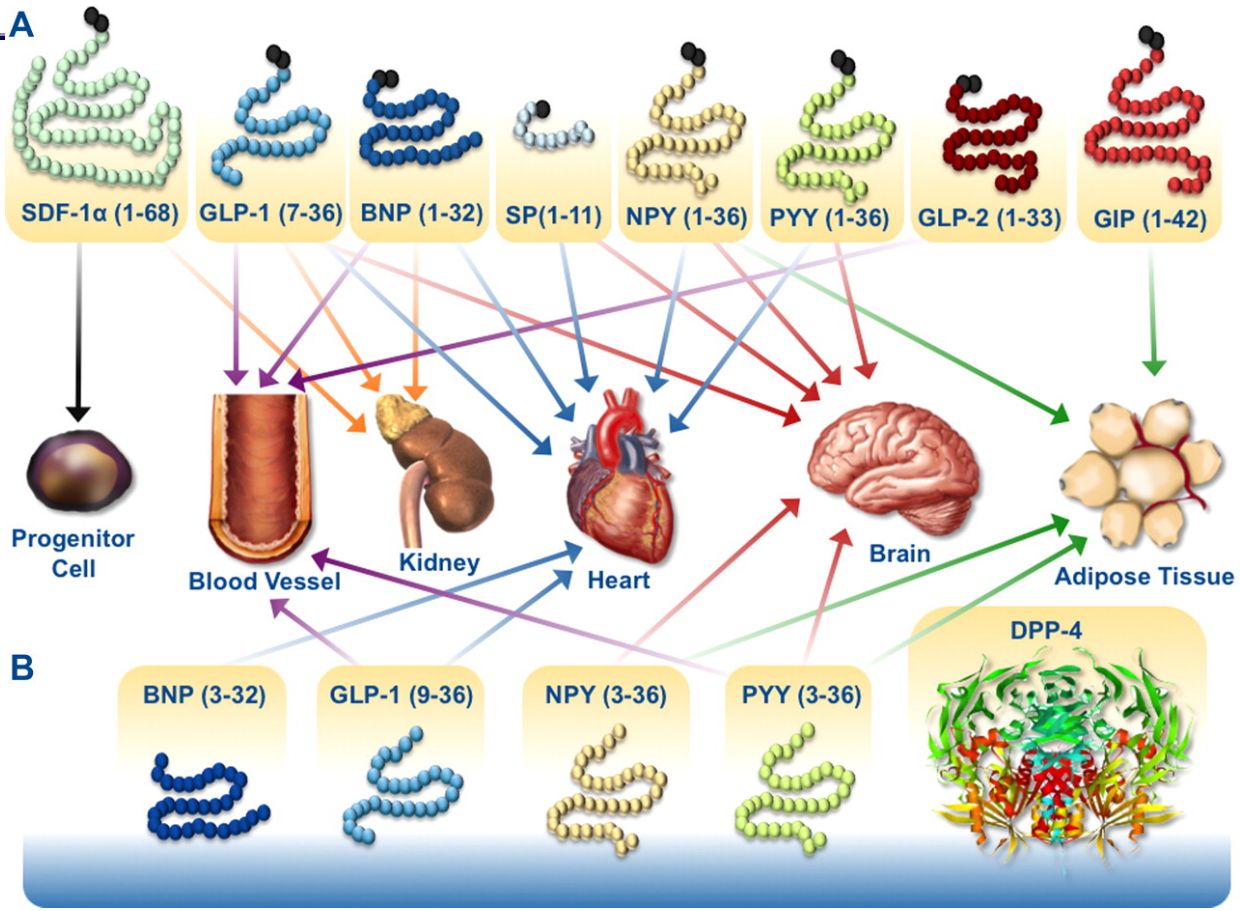


Diabetes, Obesity and Metabolism 2012.

Structure of DPP-4/ CD 26

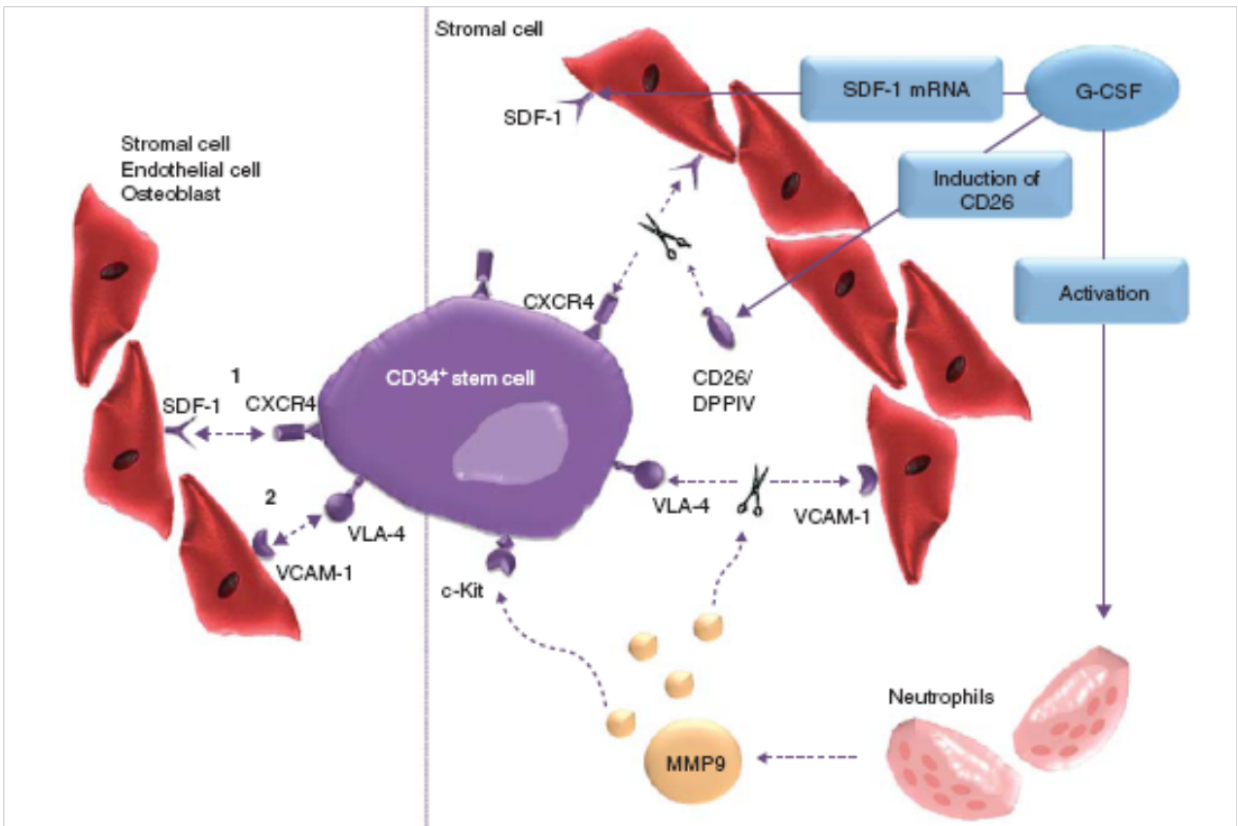


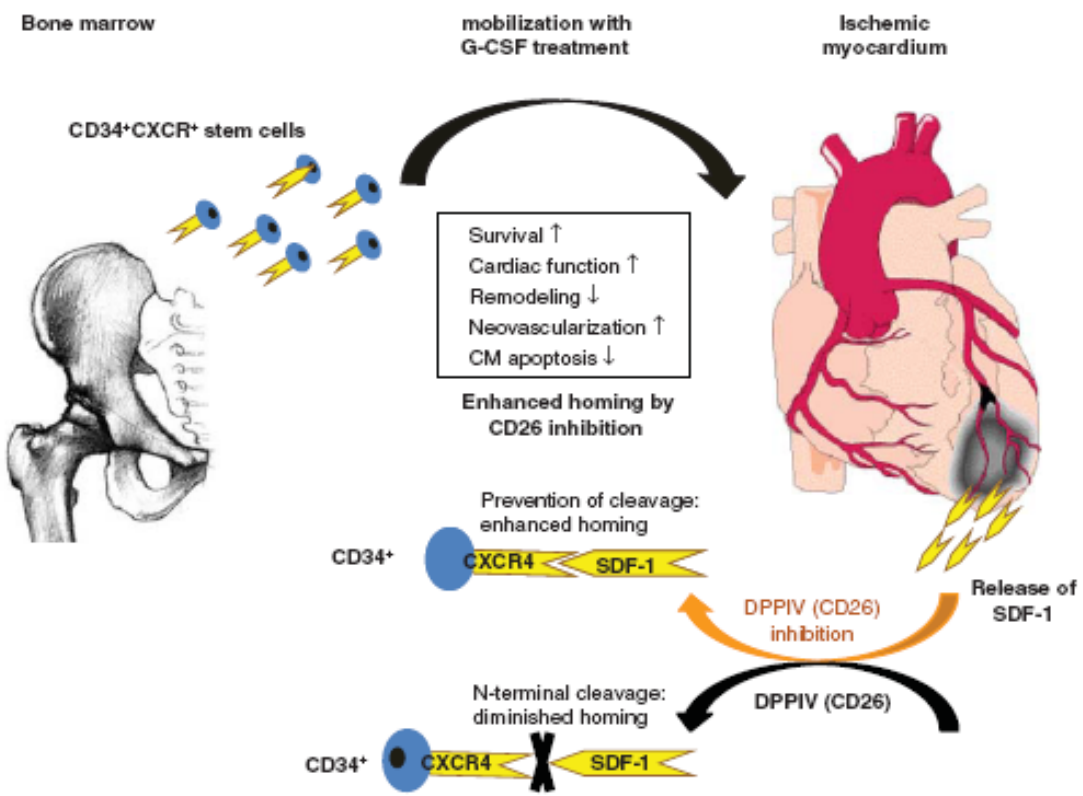
DPP-4 substrates that directly or indirectly regulate cardiovascular function.



Ussher J R , Drucker D J Endocrine Reviews 2012;33:187-215

ENDOCRINE REVIEWS

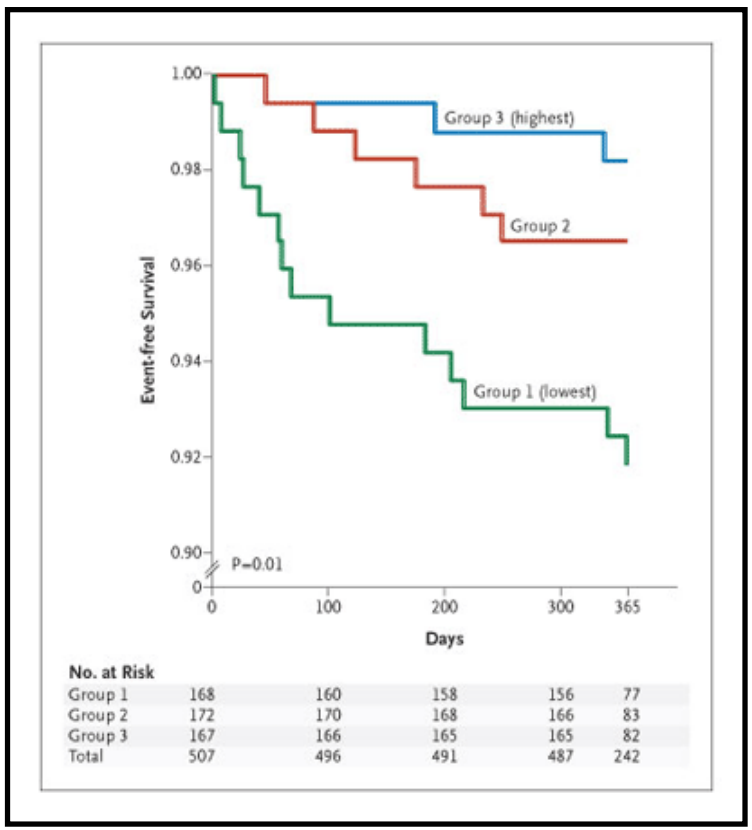

Stromal cell
SDF-1 mRNA
G-CSF
SDF-1
Induction of CD26
Stromal cell
Endothelial cell
Osteoblast
Activation
CXCR4
CD34+ stem cell
CD26/ DPPIV
1
SDF-1
CXCR4
VLA-4
VCAM-1
2
VLA-4
VCAM-1
c-Kit
Neutrophils
MMP9


Bone marrow
mobilization with
G-CSF treatment
Ischemic
myocardium
CD34+CXCR+ stem cells
Survival ↑
Cardiac function ↑
Remodeling ↓
Neovascularization ↑
CM apoptosis ↓
Enhanced homing by
CD26 inhibition
Prevention of cleavage:
enhanced homing
CD34+
CXCR4
SDF-1
Release of
SDF-1
DPPIV (CD26)
inhibition
DPPIV (CD26)
N-terminal cleavage:
diminished homing
CD34+
CXCR4
SDF-1

EPCs predicts the occurrence of cardiovascular events and death

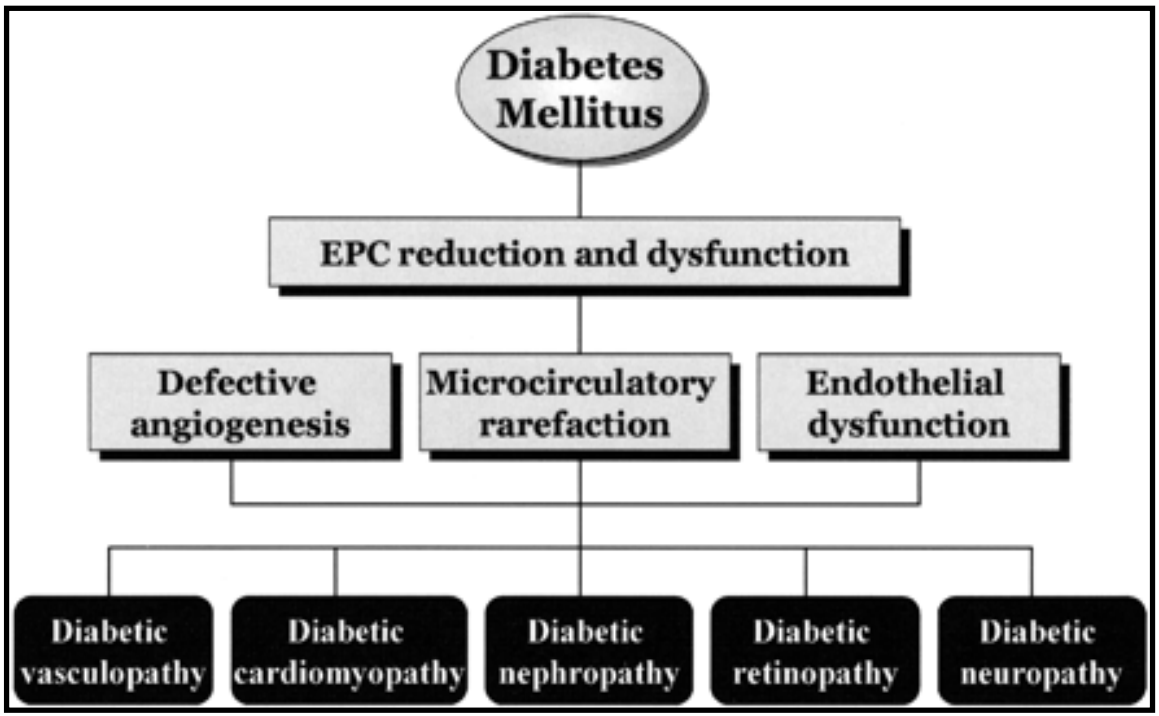
The level of circulating EPCs:

- May help to identify patients at high CV risk (Werner et al N *Engl J Med*. 2005)
- Reduced EPCs are considered a novel pathogenic mechanism of vascular disease (Fadini *Diabetes care* 2007)



Cumulative Event-free Survival in an Analysis of Death from Cardiovascular Causes at 12 Months, According to Levels of EPC at the Time of Enrollment

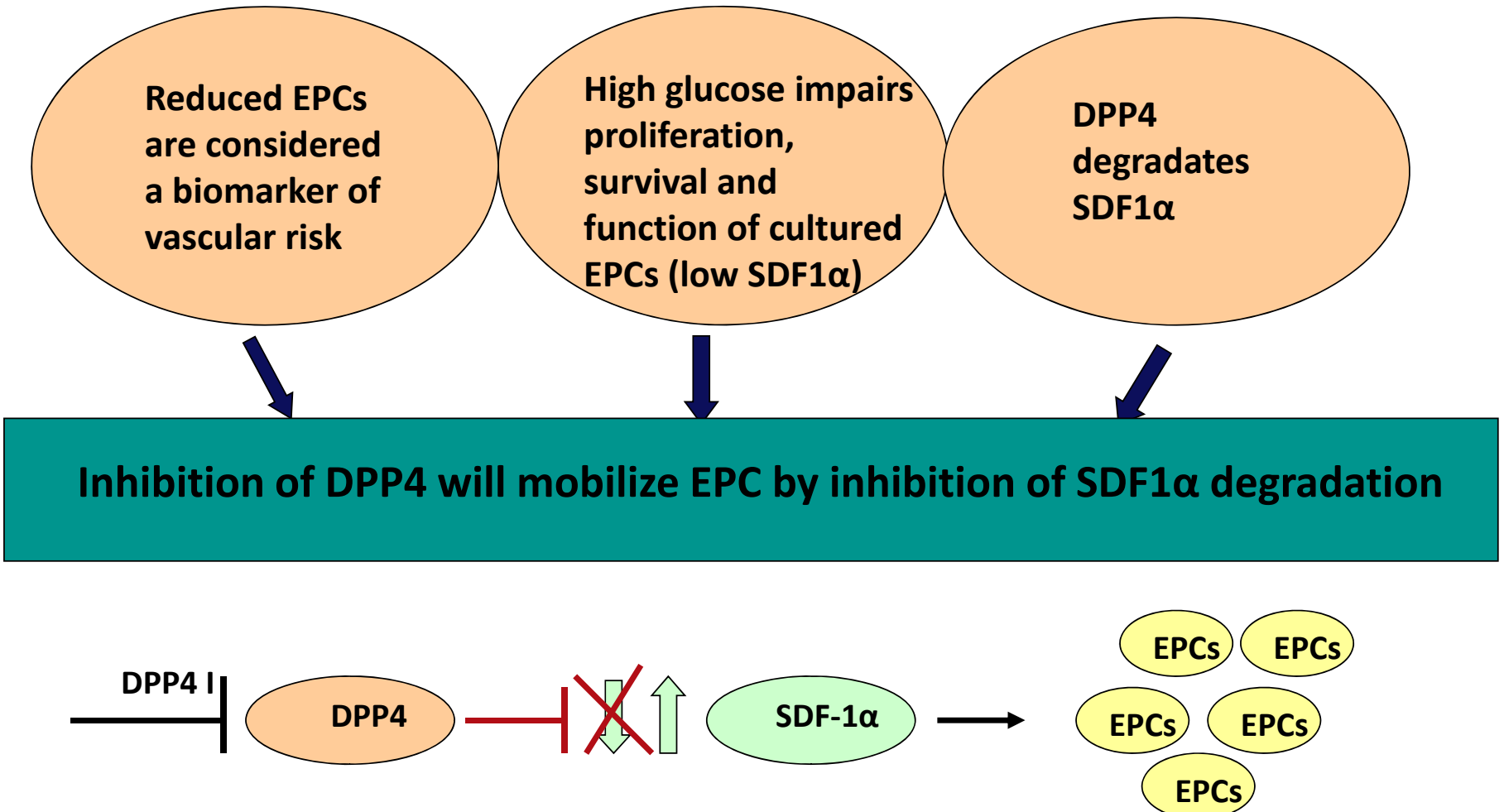
Significance of EPCs in subjects with diabetes



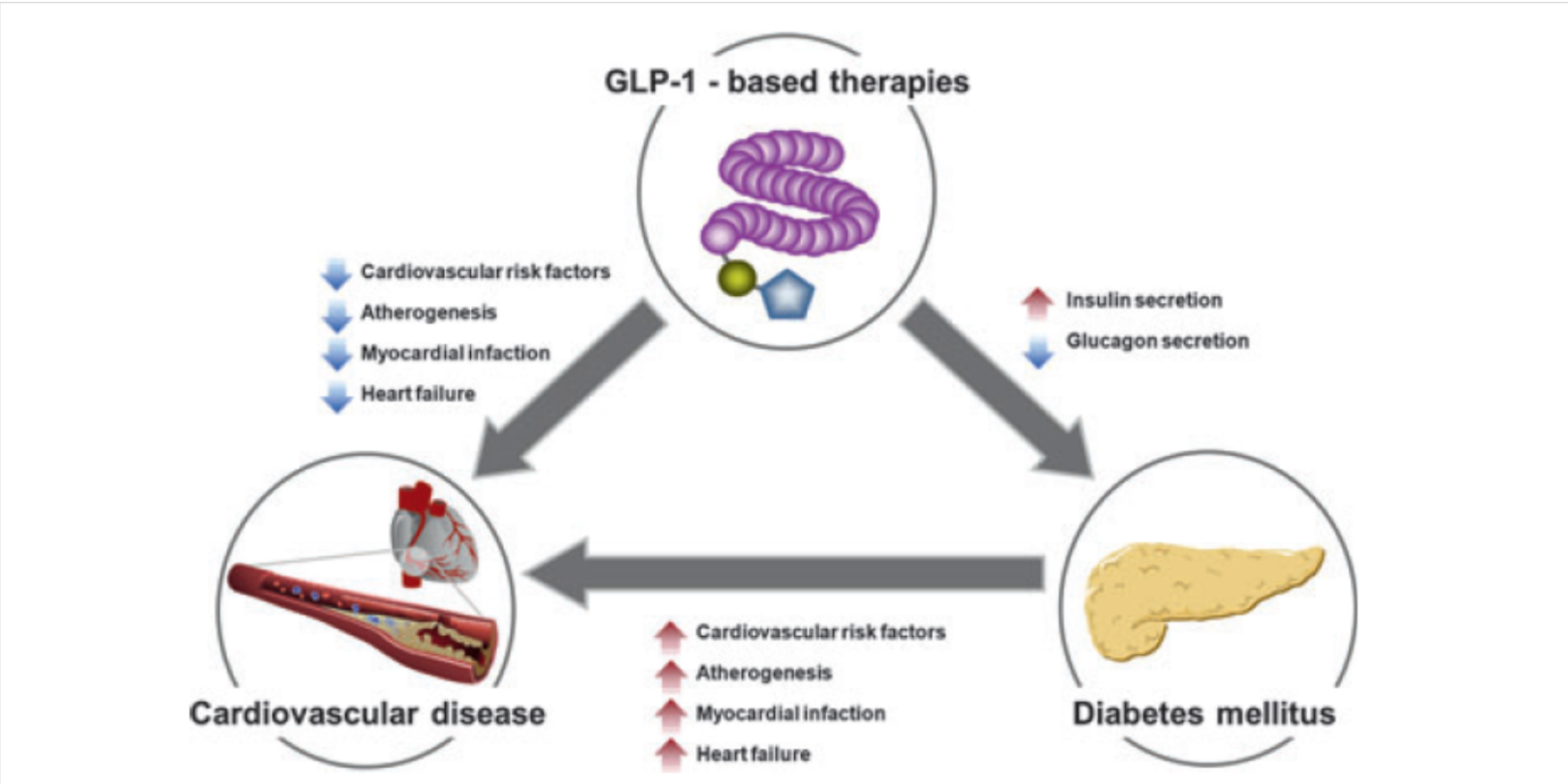
Fadini et al.,*Diabetes Care* , 2007

A major feature of early stage of atherosclerotic process and can predict CVD in human *(*Suwaidi et al., *circulation 2000)*

Hypothesis


Reduced EPCs are considered a biomarker of vascular risk
High glucose impairs proliferation, survival and function of cultured EPCs (low SDF1α)
DPP4 degradates SDF1α
Inhibition of DPP4 will mobilize EPC by inhibition of SDF1α degradation
DPP4 I
DPP4
SDF-1α
EPCs
EPCs
EPCs
EPCs
EPCs

GLP-1 based therapies are interesting options to treat CVD in type II DM Patients



Future Outcome CV studies with DPP4i and GLP1A

	Sitagliptin	Saxagliptin	Vildagliptin	Linagliptin	Liraglutide	Exenetide
Study Name	**TECOS**	SAVOR- TIMI 53	NA	CAROLINA	LEADER	EXSCEL
Comparator	**Placebo**	Placebo	NA	Glimepiride	Placebo	Placebo
Patients	**CV risk**	CV risk	NA	CV risk	CV risk	CV risk
Size	**14000**	16500	NA	6000	9341	9500
End point	**CV Morbidity & Mortality**	CV Morbidity & Mortality	NA	CV Morbidity & Mortality	CV Morbidity & Mortality	CV Morbidity & Mortality
Start Study	**2008**	2010	NA	2010	2010	2010