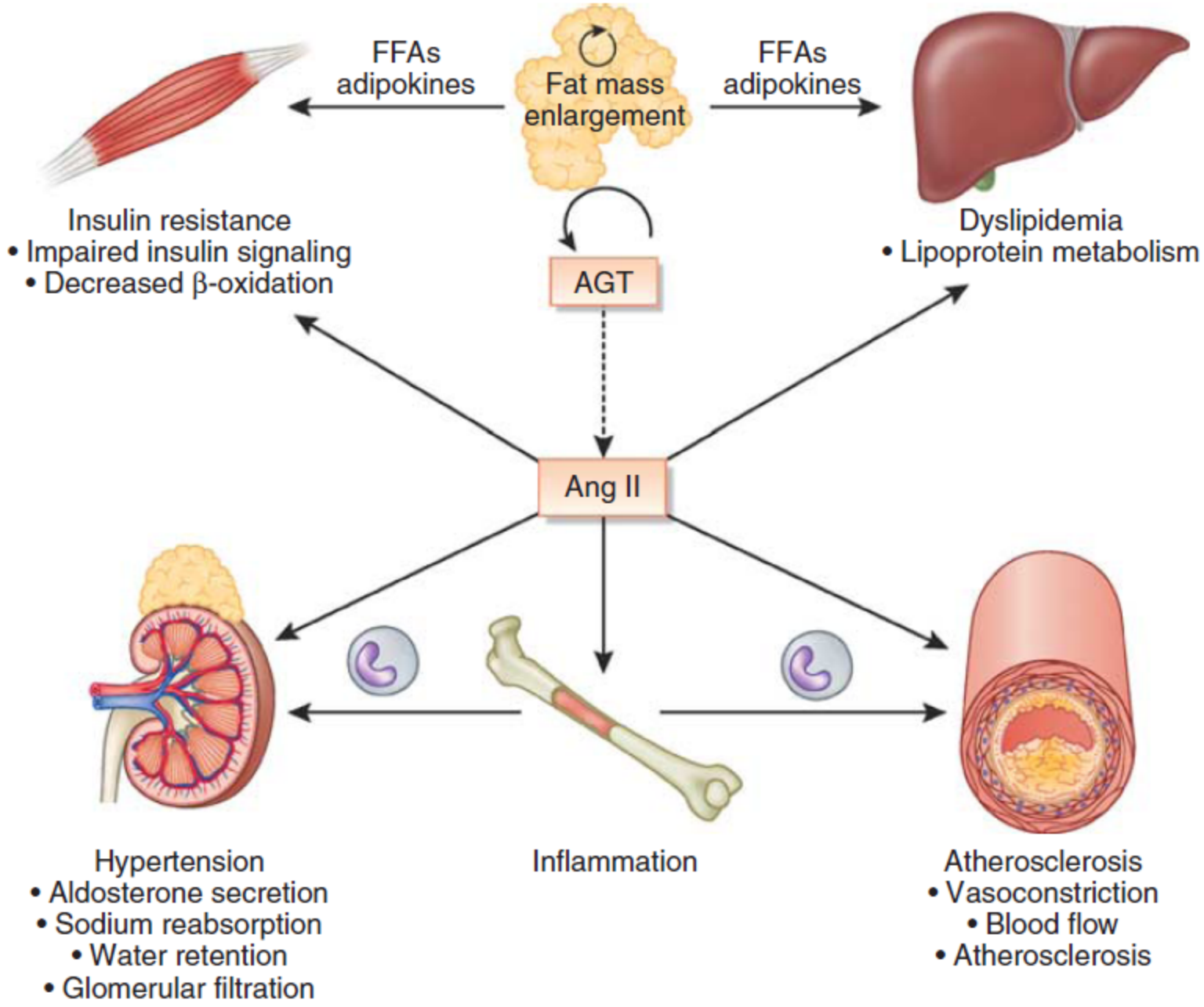
FFAs
adipokines
Fat mass
enlargement
FFAs
adipokines
Insulin resistance
• Impaired insulin signaling
• Decreased β-oxidation
AGT
Dyslipidemia
• Lipoprotein metabolism
Ang II
Hypertension
• Aldosterone secretion
• Sodium reabsorption
• Water retention
• Glomerular filtration
Inflammation
Atherosclerosis
• Vasoconstriction
• Blood flow
• Atherosclerosis

ORIGINAL ARTICLE

# Protective Effects of GLP-1 on Glomerular Endothelium and Its Inhibition by PKCβ Activation in Diabetes

Akira Mima,[1] Junko Hiraoka-Yamomoto,[1] Qian Li,[1] Munehiro Kitada,[1] Chenzhong Li,[1] Pedro Geraldes,[2] Motonobu Matsumoto,[1] Koji Mizutani,[1] Kyoungmin Park,[1] Christopher Cahill,[1] Shin-Ichi Nishikawa,[3] Christian Rask-Madsen,[1] and George L. King[1]

PKCβ INHIBITS GLP-1 ACTION IN DIABETIC NEPHROPATHY

Diabetes Publish Ahead of Print, published online July 23, 2012

Thus, our study has identified mechanisms by which GLP-1 can induce protective actions on the glomerular endothelial cells by inhibiting the signaling pathway of Ang II at phospho–c-Raf(Ser338) via phospho–c-Raf(Ser259). Further, we have demonstrated, in vivo and in vitro, that hyperglycemia can activate PKCβ isoforms, which enhance Ang II toxic effect in glomerular endothelial cells. These studies suggest that effective therapeutic agents could be designed to enhance GLP-1R on the endothelium, which may prevent glomerular endothelial dysfunction and slow the progression of diabetic nephropathy.

ORIGINAL ARTICLE

# Protective Effects of GLP-1 on Glomerular Endothelium and Its Inhibition by PKCβ Activation in Diabetes

Akira Mima,[1] Junko Hiraoka-Yamomoto,[1] Qian Li,[1] Munehiro Kitada,[1] Chenzhong Li,[1] Pedro Geraldes,[2] Motonobu Matsumoto,[1] Koji Mizutani,[1] Kyoungmin Park,[1] Christopher Cahill,[1] Shin-Ichi Nishikawa,[3] Christian Rask-Madsen,[1] and George L. King[1]

PKCβ INHIBITS GLP-1 ACTION IN DIABETIC NEPHROPATHY

These results showed that the renal protective effects of GLP-1 were mediated via the inhibition of Ang II actions on cRaf (Ser259) and diminished by diabetes because of PKCβ activation and the increased degradation of GLP-1R in the glomerular endothelial cells.

Contents lists available at SciVerse ScienceDirect

Microvascular Research

journal homepage: www.elsevier.com/locate/ymvre


# Glucagon-like peptide-1 inhibits angiotensin II-induced mesangial cell damage via protein kinase A

Yuji Ishibashi, Takanori Matsui, Ayako Ojima, Yuri Nishino, Sae Nakashima, Sayaka Maeda, Sho-ichi Yamagishi *

*Department of Pathophysiology and Therapeutics of Diabetic Vascular Complications, Kurume University School of Medicine,*

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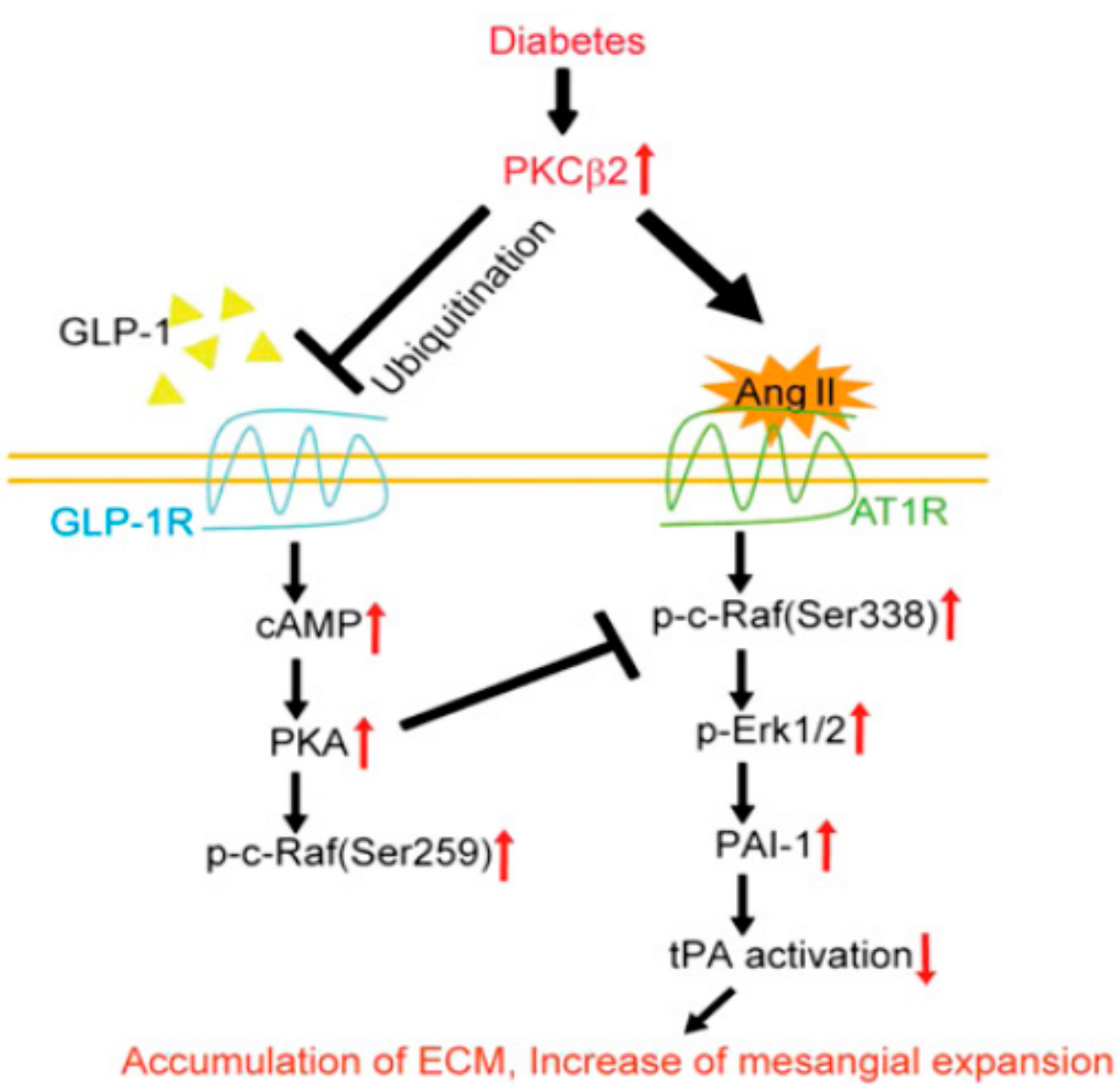
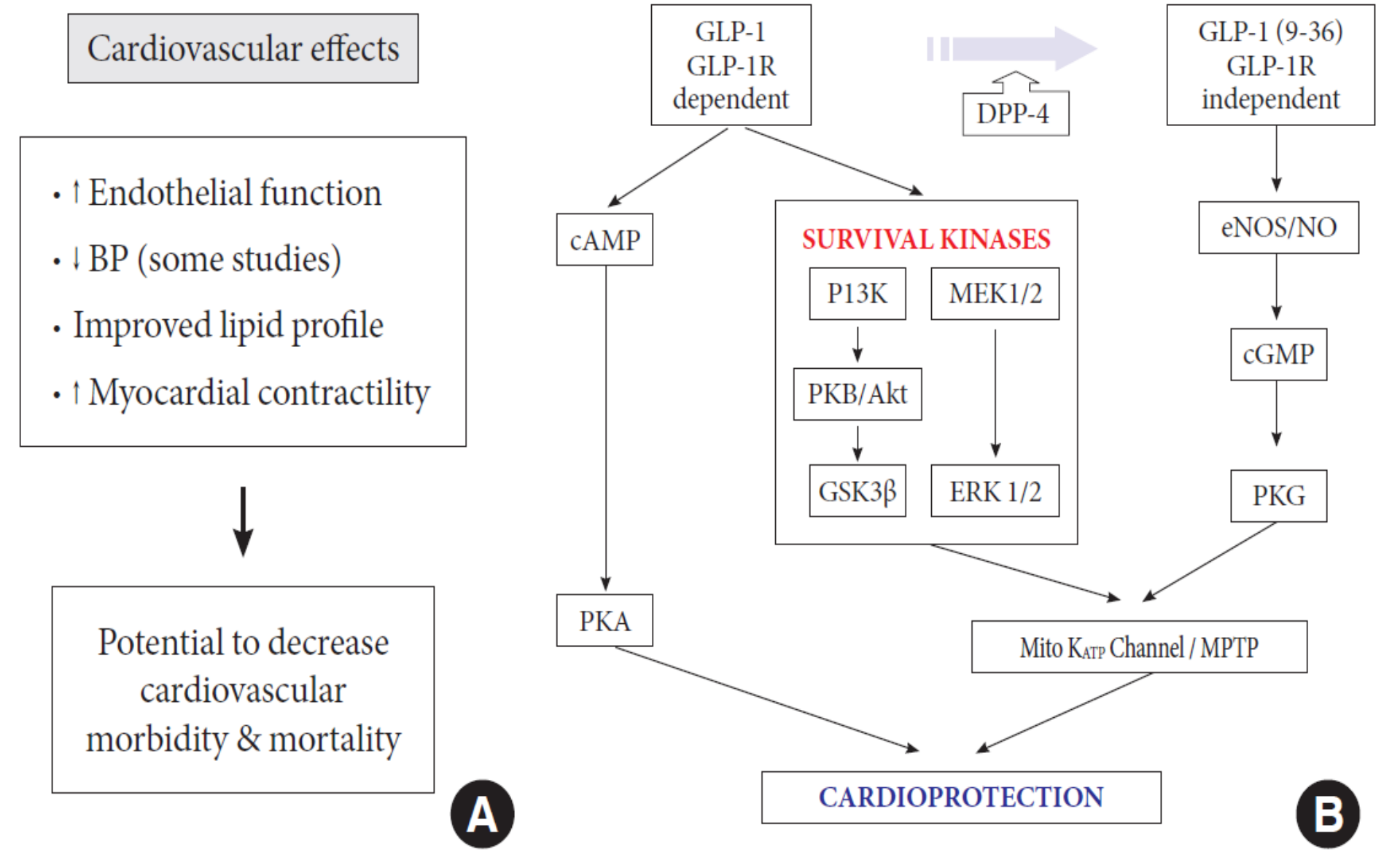
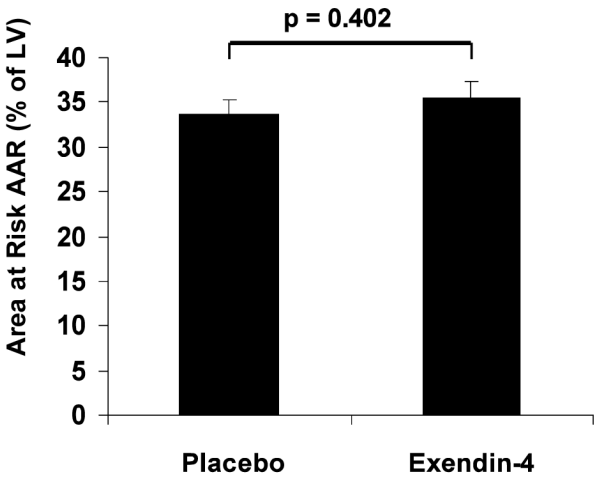
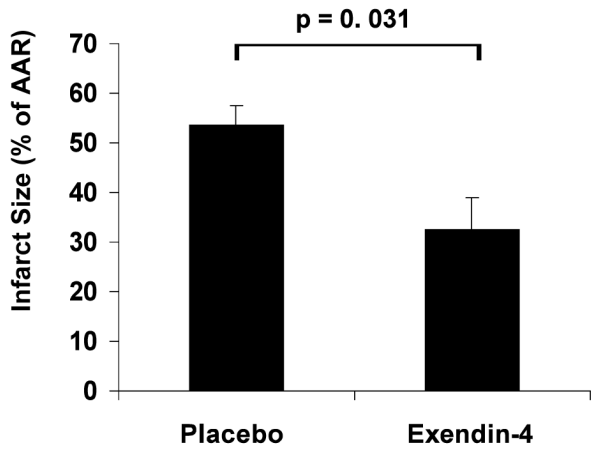
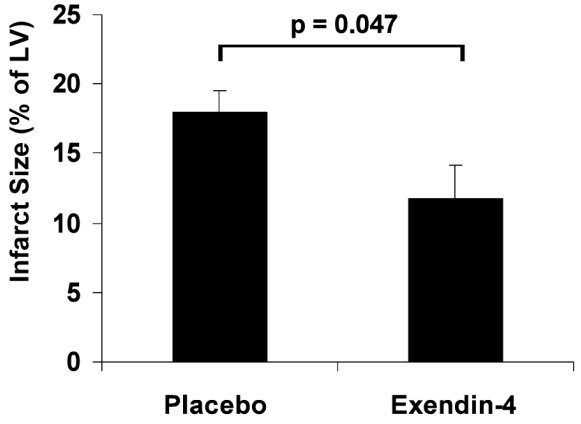

Diabetes
PKCβ2
Ubiquitination
GLP-1
Ang II
GLP-1R
AT1R
cAMP
p-c-Raf(Ser338)
PKA
p-Erk1/2
p-c-Raf(Ser259)
PAI-1
tPA activation
Accumulation of ECM, Increase of mesangial expansion

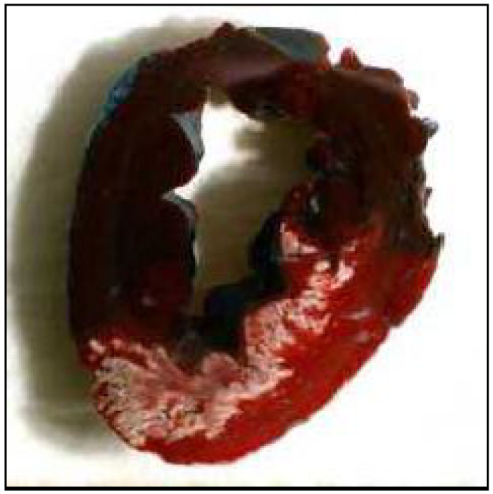

Cardiovascular effects
• ↑ Endothelial function
• ↓ BP (some studies)
• Improved lipid profile
• ↑ Myocardial contractility
Potential to decrease cardiovascular morbidity & mortality
A
GLP-1
GLP-1R
dependent
DPP-4
GLP-1 (9-36)
GLP-1R
independent
cAMP
SURVIVAL KINASES
P13K
MEK1/2
PKB/Akt
GSK3β
ERK 1/2
eNOS/NO
cGMP
PKG
PKA
Mito KATP Channel / MPTP
CARDIOPROTECTION
B

# Exendin-4 Reduces Infarct Size



Placebo

Exendin-4

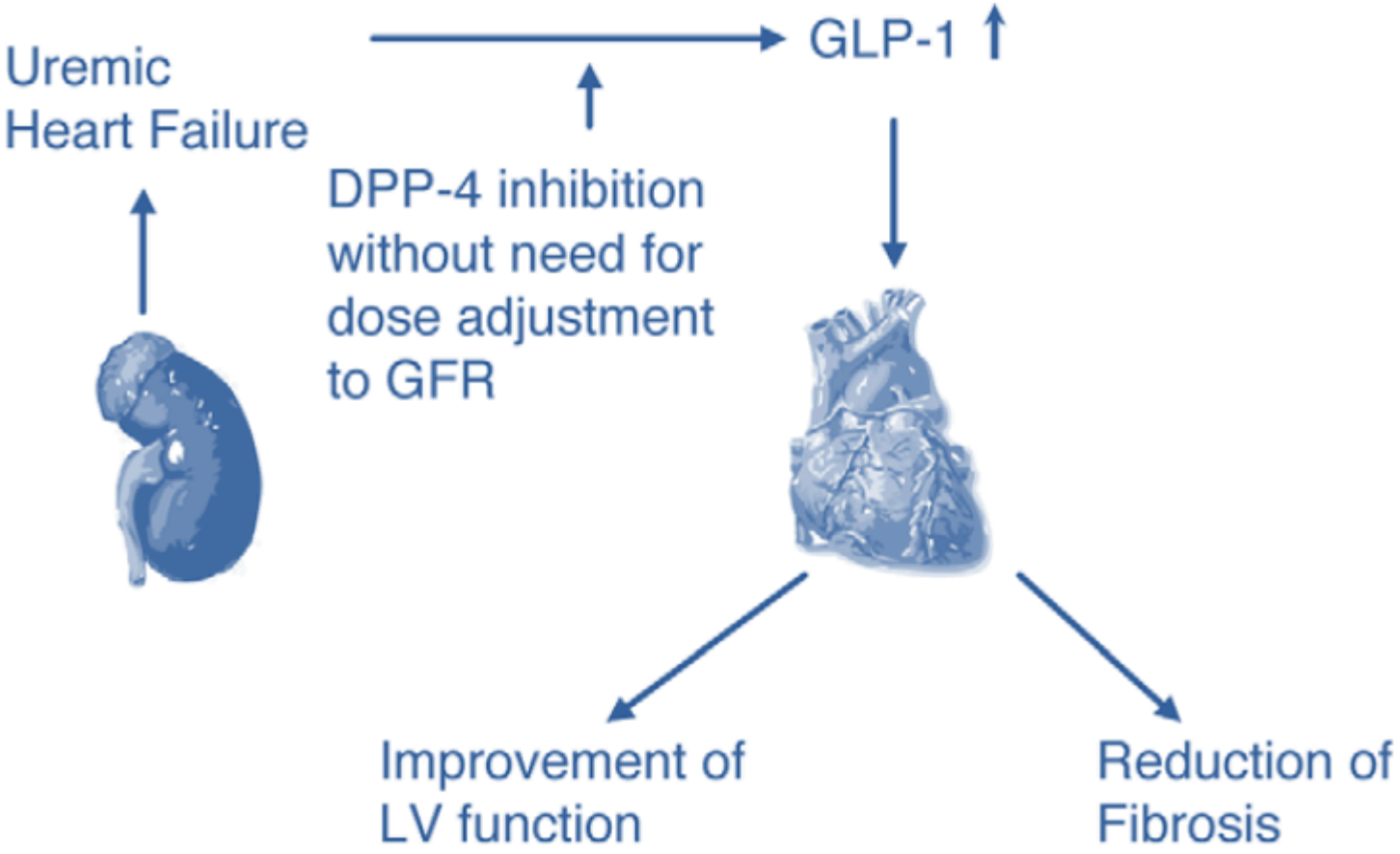
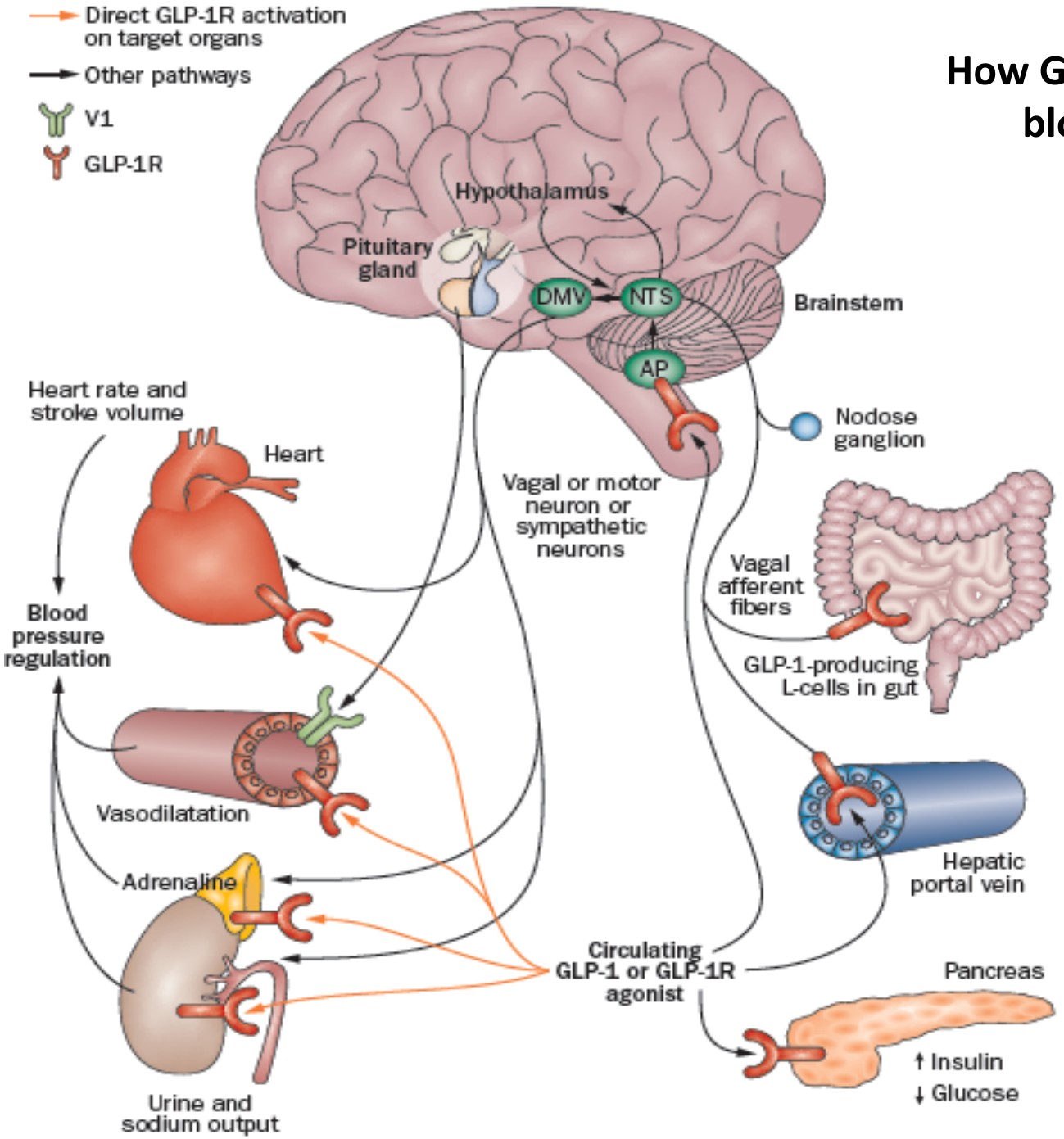
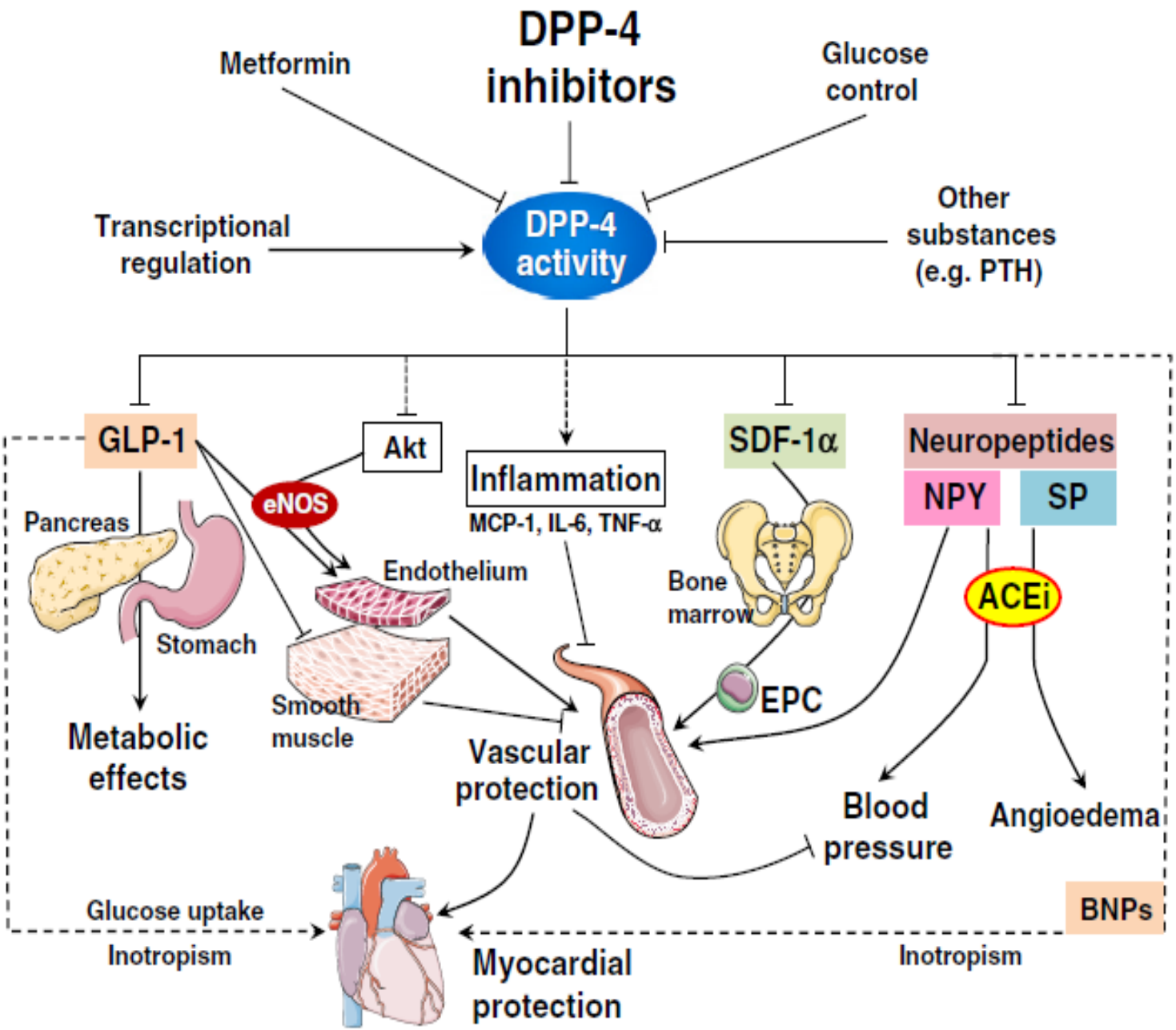



**Figure 4. Influence of DPP-4 inhibition on cardiac impairment in the setting of uremia.**

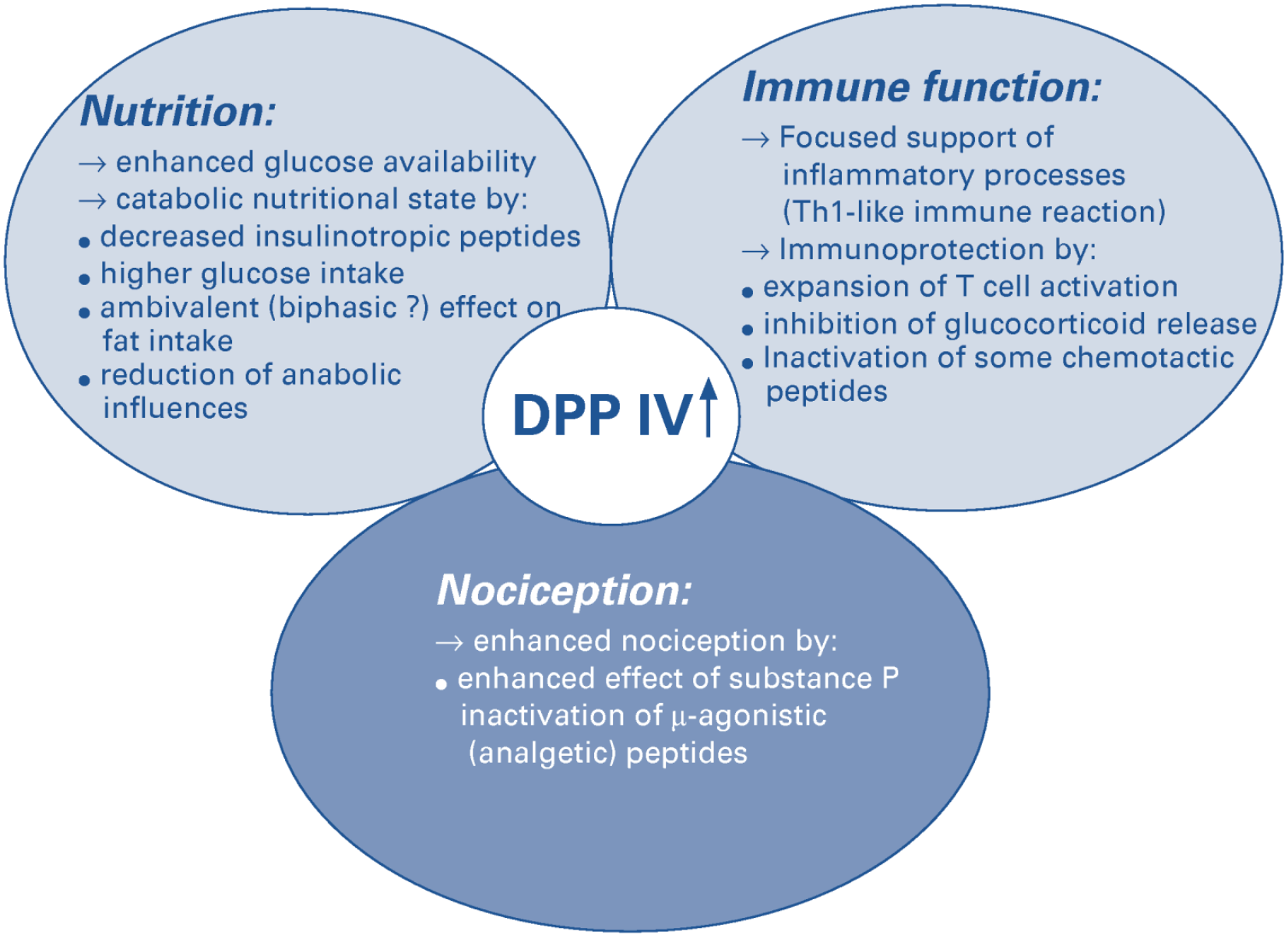
doi:10.1371/journal.pone.0027861.g004

# How GLP-1 might regulate blood pressure ?






Fadini G. et al 2011


Nutrition:
→ enhanced glucose availability
→ catabolic nutritional state by:
• decreased insulinotropic peptides
• higher glucose intake
• ambivalent (biphasic ?) effect on fat intake
• reduction of anabolic influences
Immune function:
→ Focused support of inflammatory processes (Th1-like immune reaction)
→ Immunoprotection by:
• expansion of T cell activation
• inhibition of glucocorticoid release
• Inactivation of some chemotactic peptides
DPP IV↑
Nociception:
→ enhanced nociception by:
• enhanced effect of substance P
inactivation of μ-agonistic (analgetic) peptides

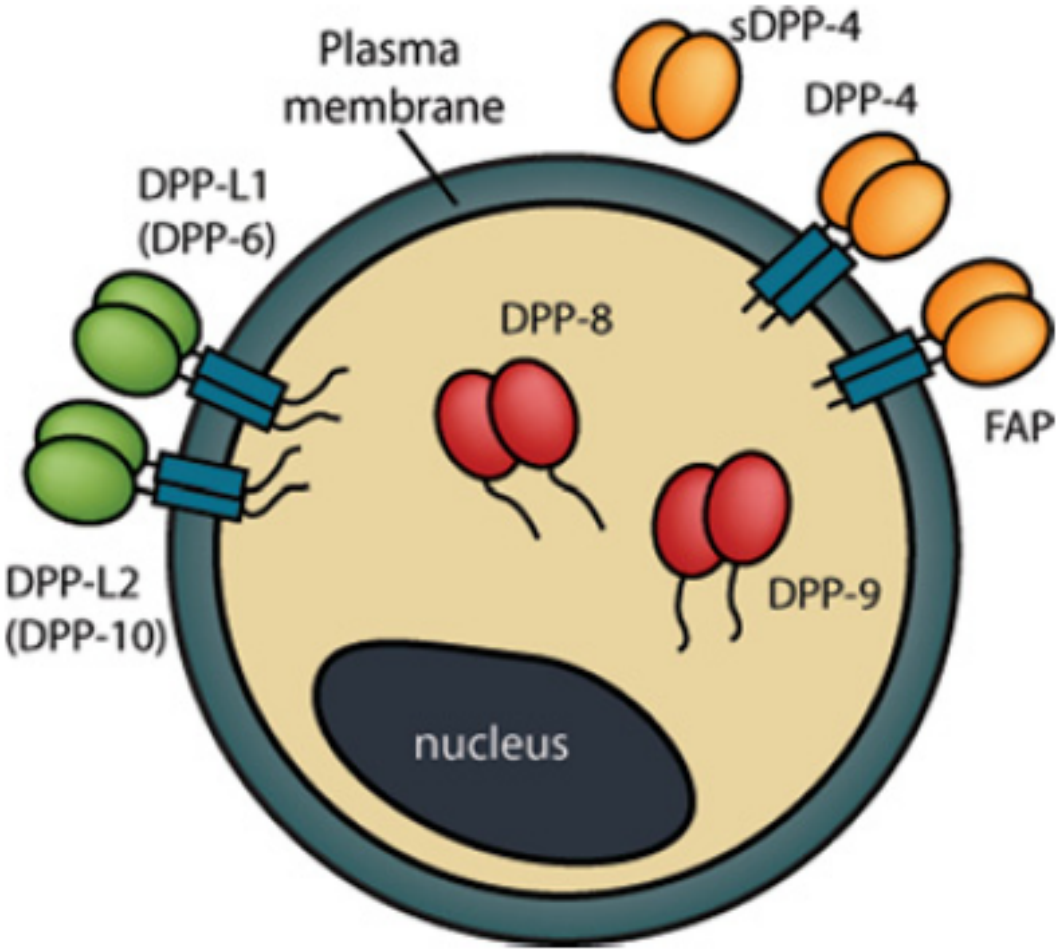



**Figure 4** **Cellular localization of the six members of the *DPP-4* gene family**

sDPP-4, soluble form of DPP-4.

# The role of incretins in salt-sensitive hypertension: the potential use of dipeptidyl peptidase-IV inhibitors

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Tel: +81 87 891 2125; fax: +81 87 891 2126;
e-mail: akira@kms.ac.jp

**Current Opinion in Nephrology and Hypertension** 2011, 20:476–481


**Purpose of review**

Incretin mimetics, such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), as well as dipeptidyl peptidase-IV (DPP-IV) inhibitors, are used in the treatment of type 2 diabetes mellitus (T2DM). In addition to stimulating insulin secretion from pancreatic β cells, incretins have apparent extrapancreatic functions beyond glycemic control. This review summarizes the recent findings regarding the blood-pressure-lowering effects of incretins and DPP-IV inhibitors in patients who are obese, diabetic, or have metabolic syndrome.

**Recent findings**

Clinical studies have indicated that GLP-1 and its analogues lower blood pressure in patients with T2DM, particularly in patients with moderate-to-severe hypertension. DPP-IV inhibitors also appear to elicit a similar blood-pressure-lowering effect. In animal models of salt-sensitive hypertension, incretins appear to induce their antihypertensive effects by inhibiting the proximal tubular sodium reabsorption, and thereby increasing urinary excretion of sodium. These data suggest that the local actions of incretins may be via their key role in regulating natriuresis and lowering blood pressure.

**Summary**

Incretin mimetics and DPP-IV inhibitors are a novel class of antihypertensive drugs with natriuretic properties. They can be used in the treatment of salt-sensitive hypertension, which is characterized by edema.

**Keywords**

dipeptidyl peptidase-IV inhibitor, glucagon-like peptide-1, incretin, natriuresis, salt-sensitive hypertension

Curr Opin Nephrol Hypertens 20:476–481

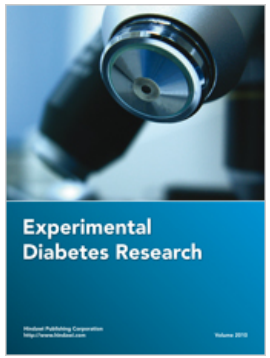
1062-4821

## Key points

- Incretin mimetics, such as GLP-1 analogues, mediate antihypertensive effects in patients with type 2 diabetes mellitus.
- GLP-1 facilitates urinary excretion of sodium in proximal tubules.
- Dipeptidyl peptidase-IV (DPP-IV) inhibition decreases sodium re-uptake in the proximal tubule through inhibition of NHE-3 activity. However, the antihypertensive effect of DPP-IV inhibitors has not been fully characterized by clinical trials.
- The patient populations (e.g. obese, diabetic, and metabolic syndrome) in which incretin mimetics most effectively lower blood pressure merit further investigation.

*Review Article*

# Strategies to Reverse Endothelial Progenitor Cell Dysfunction in Diabetes




**Alessandra Petrelli,[1,2] Raffaele Di Fenza,[2] Michele Carvello,[3] Francesca Gatti,[1] Antonio Secchi,[4] and Paolo Fiorina[1,2]**

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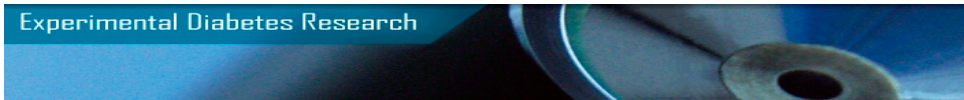
Hindawi Publishing Corporation
Experimental Diabetes Research
Volume 2012, Article ID 471823, 9 pages
doi:10.1155/2012/471823

Bone-marrow-derived cells-mediated postnatal vasculogenesis has been reported as the main responsible for the regulation of vascular homeostasis in adults. Since their discovery, endothelial progenitor cells have been depicted as mediators of postnatal vasculogenesis for their peculiar phenotype (partially staminal and partially endothelial), their ability to differentiate in endothelial cell line and to be incorporated into the vessels wall during ischemia/damage. Diabetes mellitus, a condition characterized by cardiovascular disease, nephropathy, and micro- and macroangiopathy, showed a dysfunction of endothelial progenitor cells. Herein, we review the mechanisms involved in diabetes-related dysfunction of endothelial progenitor cells, highlighting how hyperglycemia affects the different steps of endothelial progenitor cells lifetime (i.e., bone marrow mobilization, trafficking into the bloodstream, differentiation in endothelial cells, and homing in damaged tissues/organs). Finally, we review preclinical and clinical strategies that aim to revert diabetes-induced dysfunction of endothelial progenitor cells as a means of finding new strategies to prevent diabetic complications.



# The Oral Dipeptidyl Peptidase-4 Inhibitor Sitagliptin Increases Circulating Endothelial Progenitor Cells in Patients With Type 2 Diabetes

## Possible role of stromal-derived factor-1α

GIAN PAOLO FADINI, MD
ELISA BOSCARO, BSC
MATTIA ALBIERO, PHD
LISA MENEGAZZO, BSC
VERA FRISON, MD
SAULA DE KREUTZENBERG, MD, PHD
CARLO AGOSTINI, MD
ANTONIO TIENGO, MD
ANGELO AVOGARO, MD, PHD

**OBJECTIVE** — Vasculoprotective endothelial progenitor cells (EPCs) are regulated by stromal-derived factor-1α (SDF-1α) and are reduced in type 2 diabetes. Because SDF-1α is a substrate of dipeptidyl-peptidase-4 (DPP-4), we investigated whether the DPP-4 inhibitor sitagliptin modulates EPC levels in type 2 diabetic patients.

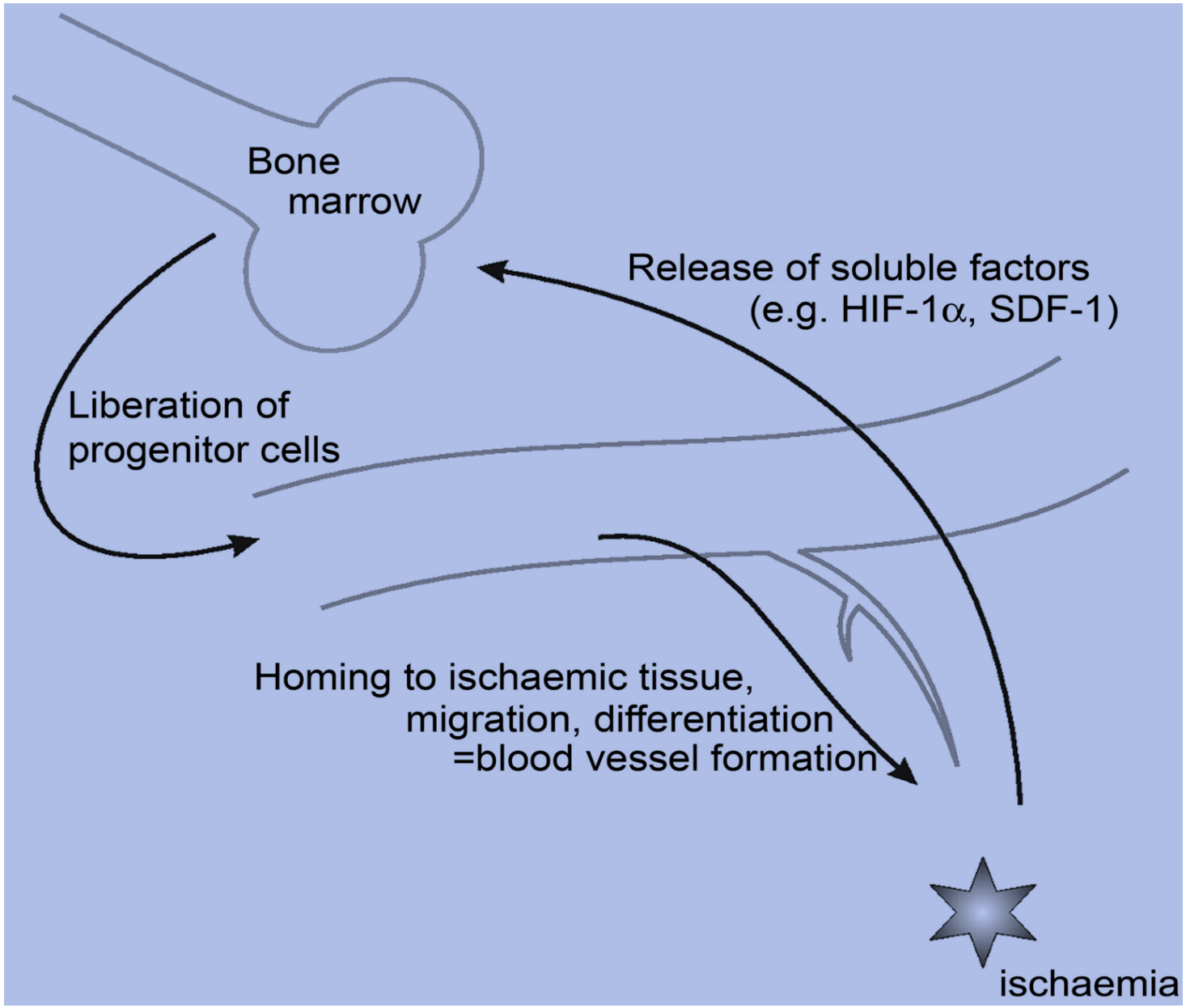
**RESEARCH DESIGN AND METHODS** — This was a controlled, nonrandomized clinical trial comparing 4-week sitagliptin ($n = 16$) versus no additional treatment ($n = 16$) in addition to metformin and/or secretagogues in type 2 diabetic patients. We determined circulating EPC levels and plasma concentrations of SDF-1α, monocyte chemoattractant protein-1 (MCP-1), vascular endothelial growth factor (VEGF), and nitrites/nitrates.

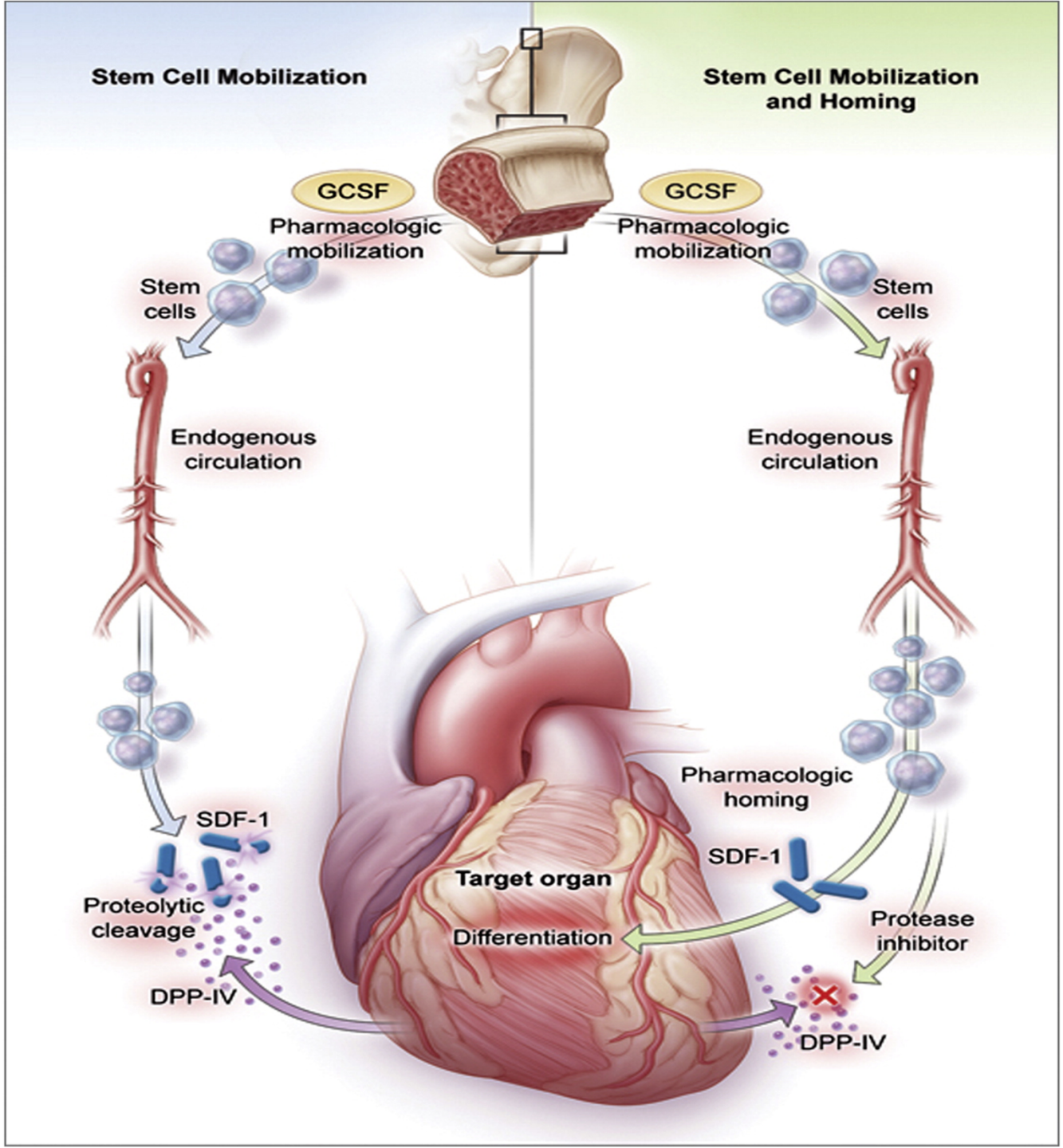
**RESULTS** — There was no difference in clinical baseline data between the sitagliptin and control arms. After 4 weeks, as compared with control subjects, patients receiving sitagliptin showed a significant increase in EPCs and SDF-1α and a decrease in MCP-1.

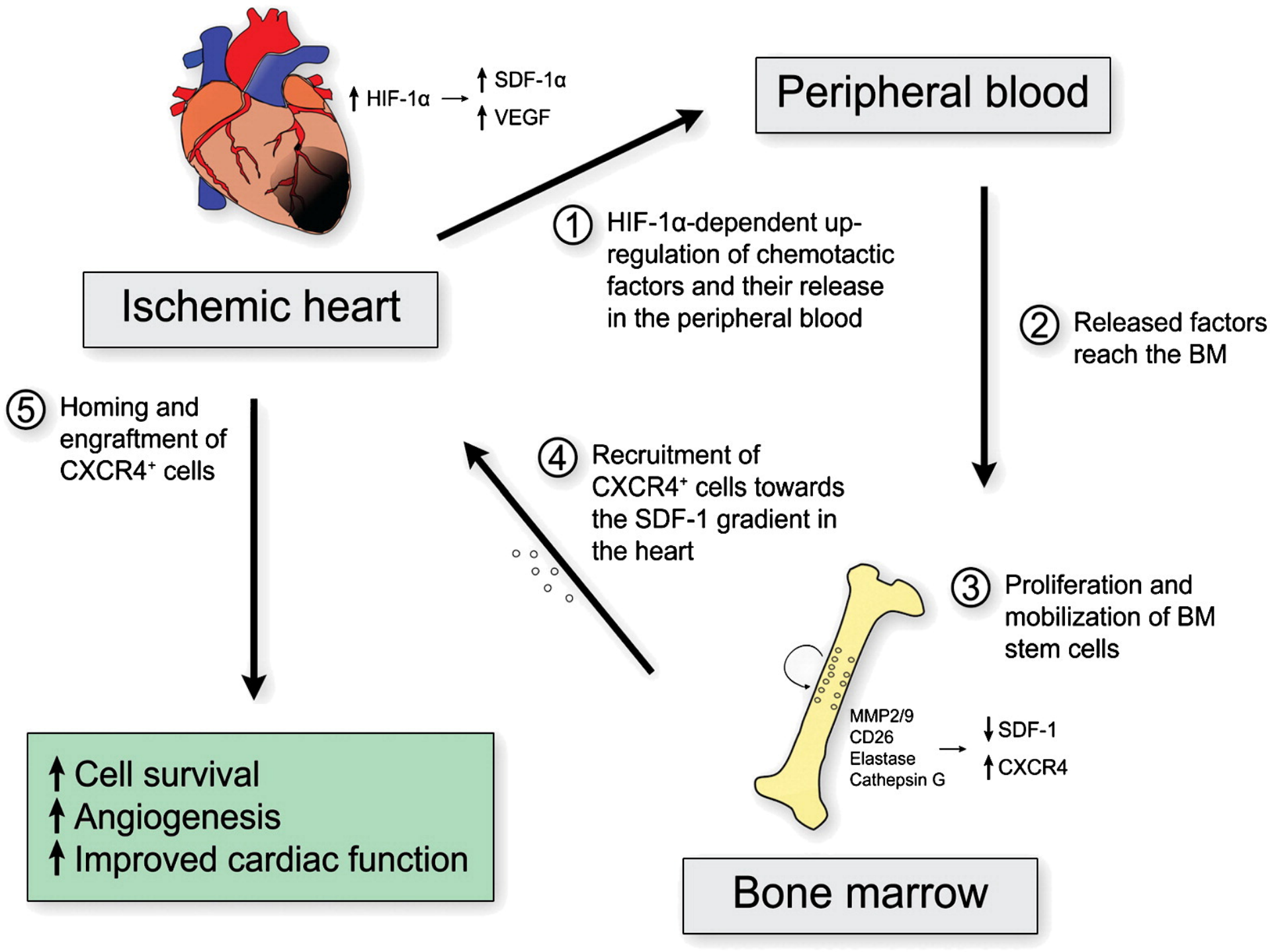
**CONCLUSIONS** — Sitagliptin increases circulating EPCs in type 2 diabetic patients with concomitant upregulation of SDF-1α. This ancillary effect of DPP-4 inhibition might have potential favorable cardiovascular implications.

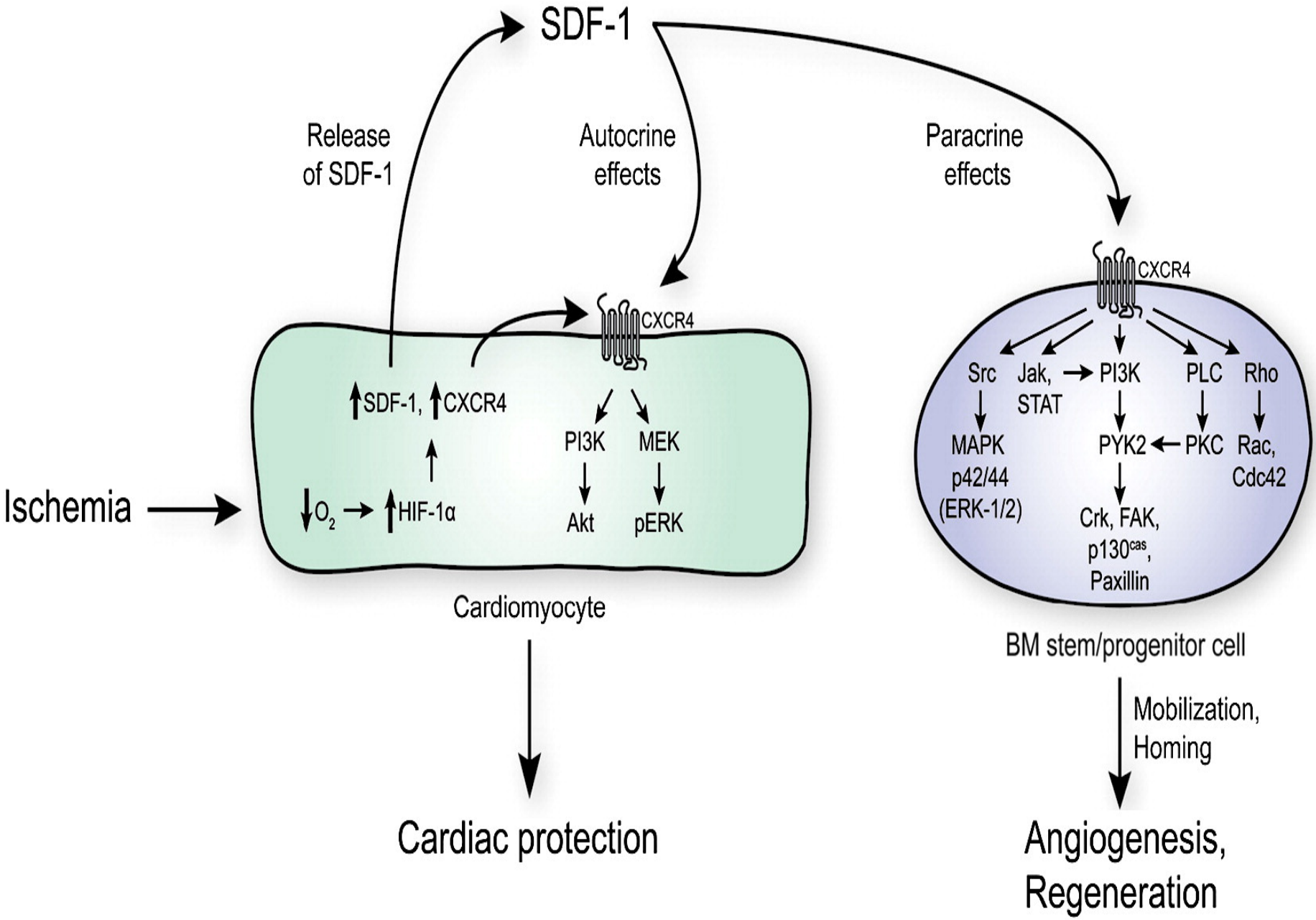
*Diabetes Care* 33:1607–1609, 2010

# Ischaemia-induced vasculogenesis




Stem Cell Mobilization
Stem Cell Mobilization and Homing
GCSF
Pharmacologic mobilization
GCSF
Pharmacologic mobilization
Stem cells
Stem cells
Endogenous circulation
Endogenous circulation
SDF-1
Proteolytic cleavage
DPP-IV
Target organ
Differentiation
Pharmacologic homing
SDF-1
Protease inhibitor
DPP-IV


↑ HIF-1α → ↑ SDF-1α ↑ VEGF
Peripheral blood
Ischemic heart
① HIF-1α-dependent up-regulation of chemotactic factors and their release in the peripheral blood
② Released factors reach the BM
③ Proliferation and mobilization of BM stem cells
④ Recruitment of CXCR4⁺ cells towards the SDF-1 gradient in the heart
⑤ Homing and engraftment of CXCR4⁺ cells
MMP2/9
CD26
Elastase
Cathepsin G
↓ SDF-1
↑ CXCR4
Bone marrow
↑ Cell survival
↑ Angiogenesis
↑ Improved cardiac function


SDF-1
Release of SDF-1
Autocrine effects
Paracrine effects
CXCR4
CXCR4
SDF-1, CXCR4
PI3K
MEK
Ischemia
O2
HIF-1α
Akt
pERK
Cardiomyocyte
Src
Jak, STAT
PI3K
PLC
Rho
MAPK p42/44 (ERK-1/2)
PYK2
PKC
Rac, Cdc42
Crk, FAK, p130cas, Paxillin
BM stem/progenitor cell
Mobilization, Homing
Cardiac protection
Angiogenesis, Regeneration

# Ongoing CV Outcome Trials With GLP-1 Analogues

- LEADER trial with liraglutide
  - ~9000 patients with type 2 diabetes
  - MACE endpoints (CV death, myocardial infarction, stroke)
  - Start September 2010, 42-60 months follow-up → first results ~2016
- EXSCEL trial with exenatide LAR (once-weekly injection)
  - ~9500 patients with type 2 diabetes
  - Composite endpoint of primary CV events
  - Start June 2010, average 5.5 yrs follow-up → results ~2017

**Table 1.** Ongoing clinical cardiovascular outcomes trials of DPP-4 inhibitors in type 2 diabetes.

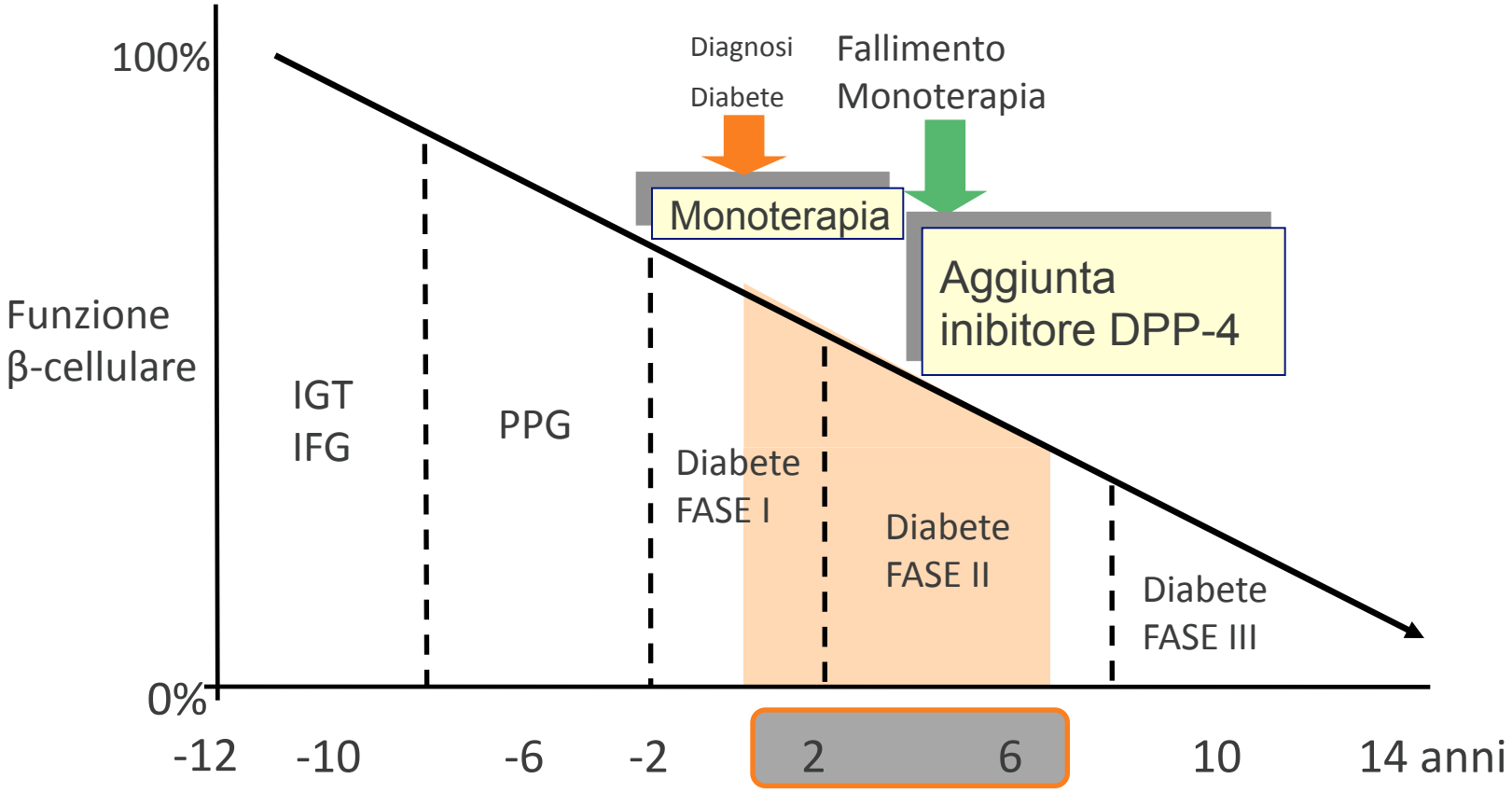
| Study name | Drug | Estimated enrolment | Estimated duration | Major inclusion criteria | Primary outcome |
|---|---|---|---|---|---|
| TECOS[34]<br>Sitagliptin Cardiovascular Outcome Study | Sitagliptin | 14,000 | December 2008–December 2014 | T2DM<br>HbA1c 6.5–8.0<br>%Pre-existing CV disease | Time to first confirmed CV event (composite defined as CV-related death, non-fatal MI, non-fatal stroke, or unstable angina requiring hospitalisation) |
| EXAMINE[35]<br>Cardiovascular Outcome Study of Alogliptin in Subjects with Type 2 Diabetes and Acute Coronary Syndrome | Alogliptin | 5400 | September 2009–May 2014 | T2DM<br>HbA1c 6.5–11% on monotherapy or combination anti-hyperglycaemic therapy (non-insulin)<br>HbA1c of 7–11% if the anti-hyperglycaemic regimen includes insulin<br>Diagnosis of acute coronary syndrome 15–90 days prior to randomization | Time from randomisation to the occurrence of the primary major cardiac event (composite defined as CV death, non-fatal MI or non-fatal stroke) |
| SAVOR-TIMI 53[36]<br>Does Saxagliptin Reduce the Risk of Cardiovascular Events When Used Alone or Added to Other Diabetes Medications? | Saxagliptin | 16,500 | May 2010–April 2014 | T2DM<br>HbA1c ≥6.5%<br>High CV risk (established CV disease and/or multiple risk factors) | Time to first CV event (composite defined as CV death, non-fatal MI or non-fatal ischaemic stroke) |
| CAROLINA[37]<br>Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients with Type 2 Diabetes | Linagliptin | 6000 | October 2010–September 2018 | T2DM<br>HbA1c 6.5–8.5% if treatment naïve or mono/dual therapy with metformin and/or AGI<br>HbA1c 6.5–7.5% if treatment with sulfonylurea/meglitinide in mono/dual with metformin or AGI<br>Pre-existing CV disease or specified diabetes end organ damage or<br>≥2 CV risk factors or age >70 | Time to the first CV event (composite of CV death, non-fatal MI, non-fatal stroke or hospitalisation for unstable angina) |

T2DM: type 2 diabetes mellitus; CV: cardiovascular; MI: myocardial infarction; AGI: alpha-glucosidase inhibitor.

**Table 1.** Present landscape of phase III and IV cardiovascular outcomes trials assessing safety and efficacy of drugs for type 2 diabetes mellitus.

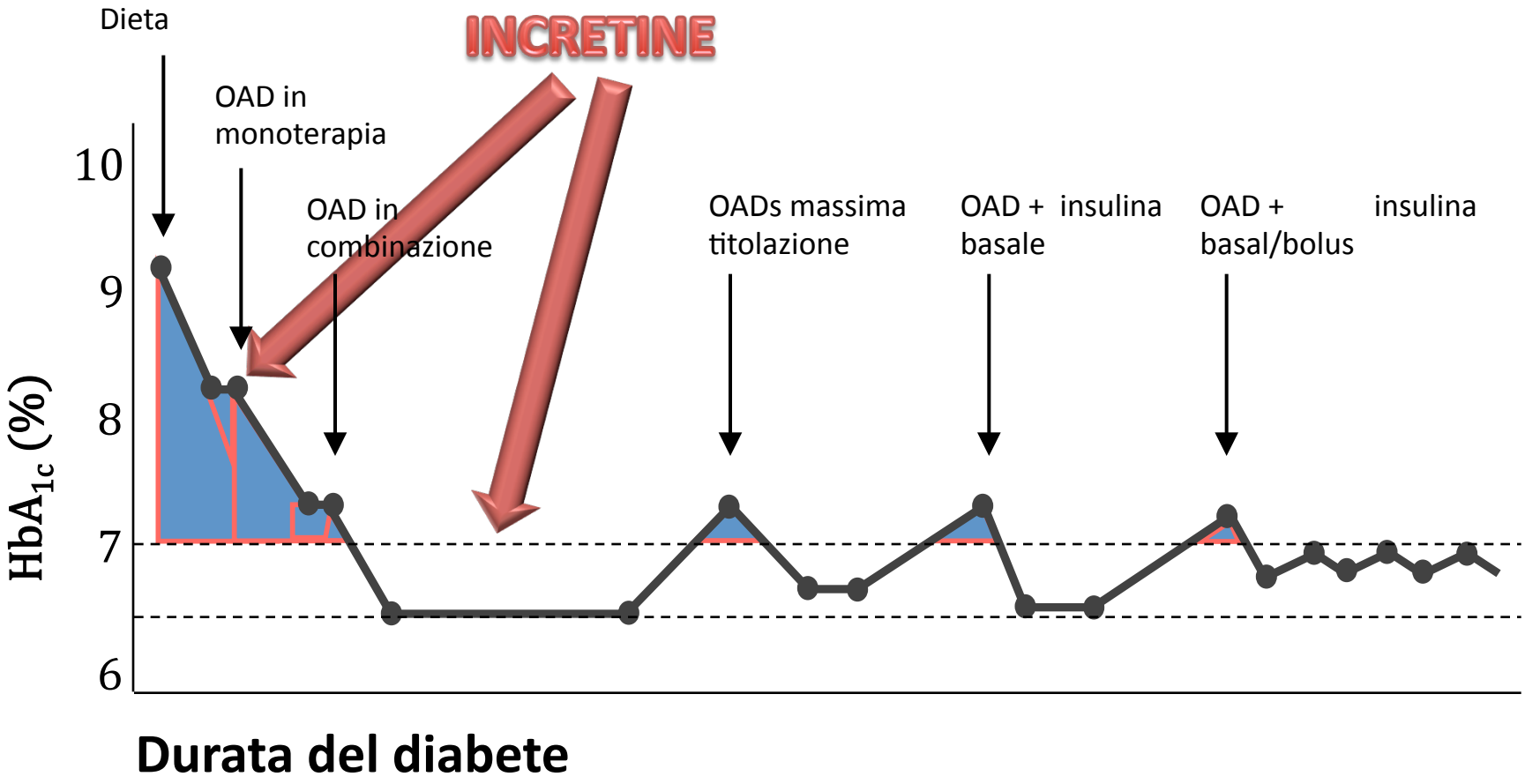
| Trial | Start month | Drug | Sample Size | ClinicalTrials.gov identifier |
|---|---|---|---|---|
| ORIGIN | 09/2003 | Insulin glargine | 12,500 | NCT00069784 |
| TECOS | 12/2008 | Sitagliptin | 14,000 | NCT00790205 |
| ACE | 02/2009 | Acarbose | 7500 | NCT00829660 |
| EXAMINE | 09/2009 | Alogliptin | 5400 | NCT00968708 |
| CANVAS | 11/2009 | Canagliflozin | 4300 | NCT01032629 |
| AleCardio | 02/2010 | Aleglitazar | 7000 | NCT01042769 |
| SAVOR TIMI-53 | 04/2010 | Saxagliptin | 16,500 | NCT01107886 |
| ELIXA | 06/2010 | Lixisenatide | 6000 | NCT01147250 |
| EXSCEL | 06/2010 | Exenatide LAR | 9500 | NCT01144338 |
| C-SCADE 8 | 07/2010 | Empagliflozin | 7000 | NCT01131676 |
| CAROLINA | 10/2010 | Linagliptin | 6000 | NCT01243424 |
| LEADER | 11/2010 | Liraglutide | 8750 | NCT01179048 |
| REWIND | 07/2011 | Dulaglutide | 9600 | NCT01394952 |
| CV Outcomes with ITCA 650 | 01/2012 | Exenatide ITCA 650 | 2000 | NCT01455896 |

# Prima si inizia e meglio è !




QUANDO?: appena il pz non è più a target di $HbA_{1c}$ ($HbA_{1c}$ >7,5%)

# Diabete di tipo 2 - la nuova sfida: Vincere l'inerzia terapeutica




Del Prato S et al. Int J Clin Pract 2005; **59**: 1345–1355.

Cobble *Diabetology & Metabolic Syndrome* 2012, **4**:8
http://www.dmsjournal.com/content/4/1/8

DIABETOLOGY &
METABOLIC SYNDROME

REVIEW Open Access

# Differentiating among incretin-based therapies in the management of patients with type 2 diabetes mellitus

Michael Cobble

**Abstract**

The glucagon-like peptide-1 receptor (GLP-1R) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors have become important options for the management of patients with type 2 diabetes mellitus. While the GLP-1R agonists and DPP-4 inhibitors act on the incretin system to regulate glucose homeostasis, there are important clinical differences among the five agents currently available in the U.S. For example, the GLP-1R agonists require subcutaneous administration, produce pharmacological levels of GLP-1 activity, promote weight loss, have a more robust glucose-lowering effect, and have a higher incidence of adverse gastrointestinal effects. In contrast, the DPP-4 inhibitors are taken orally, increase the half-life of endogenous GLP-1, are weight neutral, and are more commonly associated with nasopharyngitis. Differences in efficacy, safety, tolerability, and cost among the incretin-based therapies are important to consider in the primary care management of patients with type 2 diabetes mellitus.

**Keywords:** type 2 diabetes, exenatide, liraglutide, sitagliptin, saxagliptin, linagliptin, efficacy, safety

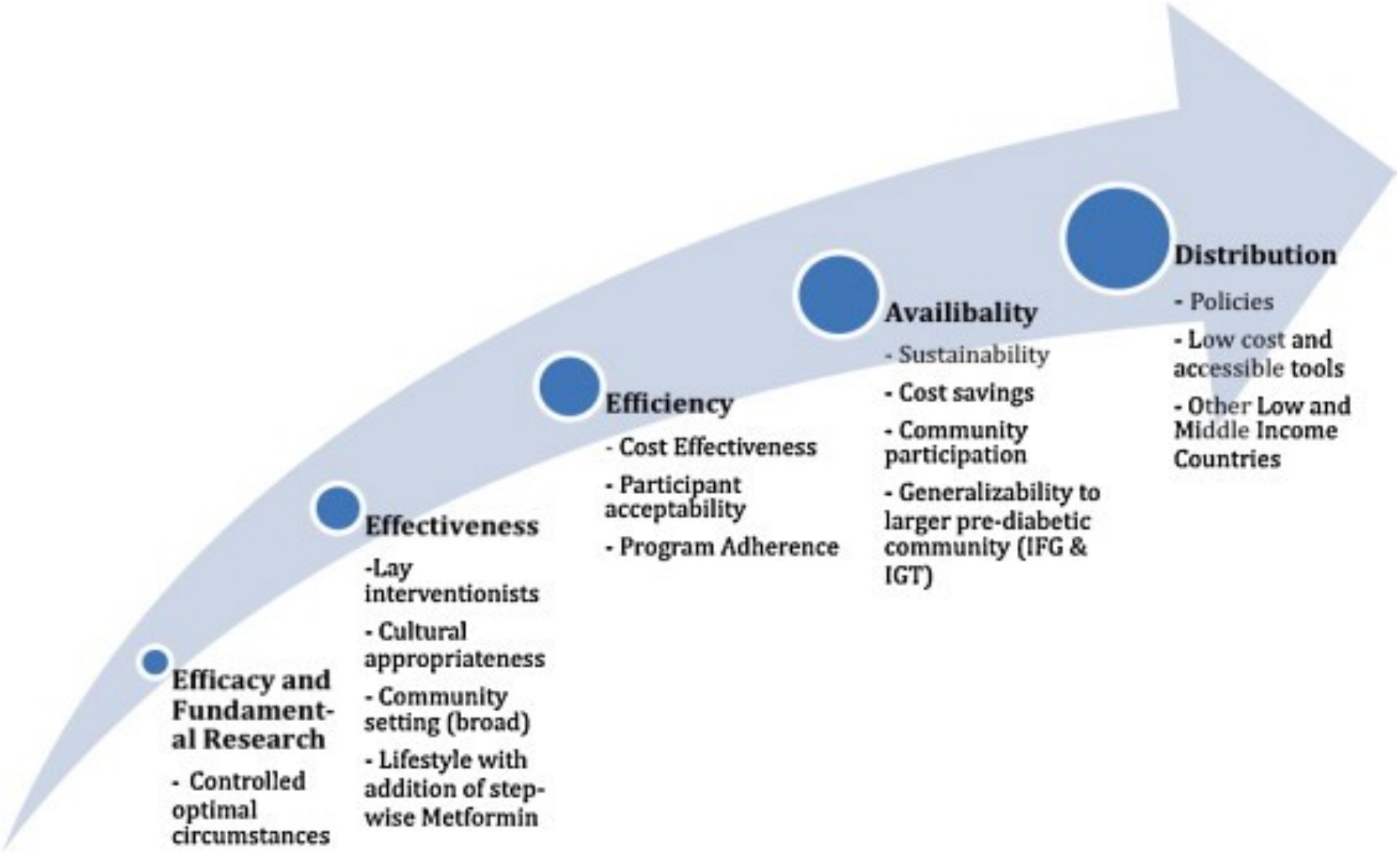
**Table 1 Comparison of GLP-1R agonists and DPP-4 inhibitors.**

| | GLP-1R Agonists | DPP-4 Inhibitors |
|---|---|---|
| Agents currently available in U.S. with dosing information (normal renal function)[31-35] | • Exenatide 5-10 mcg SC BID<br>• Liraglutide 1.2-1.8 mg QD | • Sitagliptin 100 mg PO QD<br>• Saxagliptin 2.5-5 mg PO QD<br>• Linagliptin 5 mg PO QD |
| **Benefits** | | |
| Reduction in A1C level*[22-24,26,29,36-45] | 0.5%-1.5% | 0.5%-0.9% |
| Reduction in fasting plasma glucose*[29,39-41,49-51] | ↓7 to 74 mg/dL | ↓11 to 29 mg/dL |
| Reduction in postprandial glucose*[9,27,51,54,55] | ↓41 to 47 mg/dL | ↓49 to 68 mg/dL |
| Weight effect [14,22,24,26,29,37,39-41,44,45,49,50,52,60] | ↓1-4 kg | ↓0.9 to ↑1.4 kg |
| Effect on triglycerides [24,29,36,37,39,41,49,60,62] | ↓12-40 mg/dL | ↑16 mg/dL to ↓35 mg/dL |
| Reduction in systolic blood pressure [13,14,24,29,36,37,39,41,49,60,62] | ↓1-7 mm Hg | 0 to ↓3.9 mm Hg |
| May improve markers of pancreatic β-cell function (such as homeostasis model assessment-β-cell function, fasting insulin, fasting proinsulin to insulin ratio, fasting C-peptide)[8,13,22-24,26,30] | ✓ | ✓ |
| **Disadvantages** | | |
| Incidence of mild/moderate hypoglycemia**[9,10,24,26,36-39,41,43-45,52,55,64] | 0%-12% | 0%-4% |
| Nausea [13,33-35] | 26%-28% | 0-1% |
| Hypersensitivity reactions [33-35] | Rare (exenatide) | ✓ |
| Antibody formation [31-35,79,80] | 30-67% E; 8% L | NR |

*As monotherapy or as add-on therapy.

**Generally included asymptomatic hypoglycemia or symptomatic hypoglycemia with blood glucose < 55 mg/dL not requiring third-party assistance.

BID, twice daily; NR, not reported; PO, orally; QD, once daily; SC, subcutaneously


Efficacy and Fundamental Research
- Controlled optimal circumstances
Effectiveness
-Lay interventionists
- Cultural appropriateness
- Community setting (broad)
- Lifestyle with addition of step-wise Metformin
Efficiency
- Cost Effectiveness
- Participant acceptability
- Program Adherence
Availibality
- Sustainability
- Cost savings
- Community participation
- Generalizability to larger pre-diabetic community (IFG & IGT)
Distribution
- Policies
- Low cost and accessible tools
- Other Low and Middle Income Countries

(a)


(b)

$$\text{VALUE} = \frac{\text{Cost}}{\text{Outcome}}$$

(c)

**Direct Medical Costs**
- Technology itself
  - e.g., physician time, lab tests
- Health care
  - e.g., complications of diabetes
  - e.g., side-effects of technology

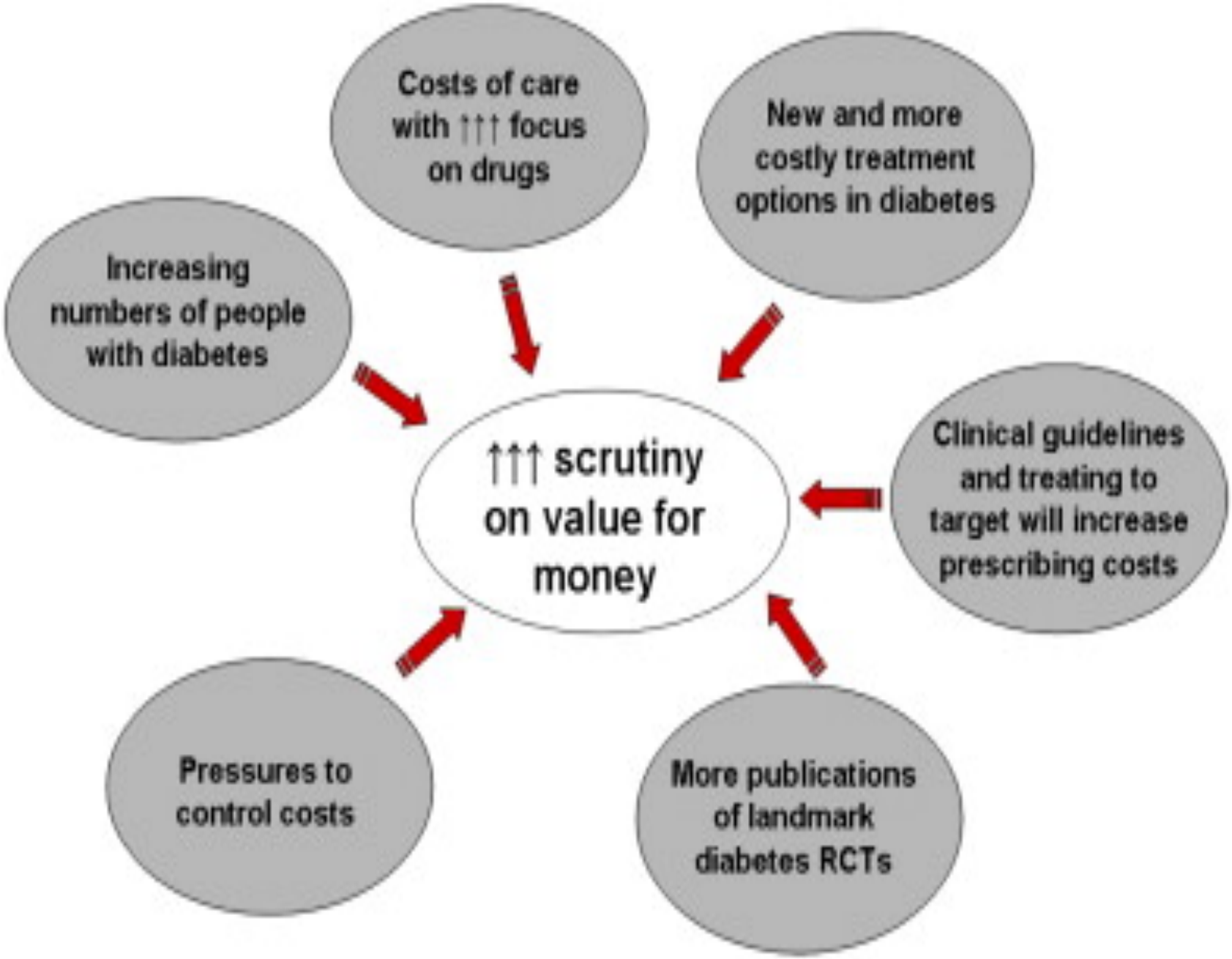
**Direct Non-medical Costs**
- Incurred by patient
  - e.g., exercise equipment, special diet, carer

**Indirect Costs**
- Lost productivity due to **illness**
- Lost productivity due to **death**

**Intangible Costs**
- Reduced HRQOL

*Health System Perspective*

*Societal Perspective*


Costs of care with ↑↑↑ focus on drugs
New and more costly treatment options in diabetes
Increasing numbers of people with diabetes
↑↑↑ scrutiny on value for money
Clinical guidelines and treating to target will increase prescribing costs
Pressures to control costs
More publications of landmark diabetes RCTs

Strict BP control better than less strict control

Primary & secondary prevention very cost effective

Medicines to reduce both weight & $HbA_{1c}$ cost effective versus conventional interventions

Individual drugs to reduce individual risk factors show wide variation in cost effectiveness

Newer medicines produce high ICERs and deserve further scrutiny

More attention needed on sensitivity analyses and testing for uncertainty in modelled analyses

**Cost-effective use of resources**

**Further research???**

Journal of Medical Economics 2012, 1–10

1369-6998
doi:10.3111/13696998.2012.716111

Article JME-2012-0080/716111


Original article

# Long-term clinical and economic outcomes associated with liraglutide versus sitagliptin therapy when added to metformin in the treatment of type 2 diabetes: a CORE Diabetes Model analysis

## Results

### Liraglutide 1.8 mg and 1.2 mg vs sitagliptin: Life expectancy, quality-adjusted life expectancy, and cost-effectiveness

Table 4. Base case cost-effectiveness results.

| | liraglutide 1.8 + MET | liraglutide 1.2 +MET | sitagliptin +MET | Difference liraglutide 1.8 vs sitagliptin | Difference liraglutide 1.2 vs sitagliptin |
|---|---|---|---|---|---|
| Life expectancy* (years) | 13.189 | 13.003 | 12.84 | 0.348 | 0.163 |
| Quality adjusted life expectancy (years)* | 8.979 | 8.825 | 8.624 | 0.356 | 0.201 |
| Total treatment costs (US$) | 89,502 | 81,444 | 76,262 | 13,241 | 5182 |
| ICER (US$ per QALY) | | N/A | | 37,234 | 25,742 |

*The life expectancy and quality-adjusted life expectancy are discounted at 3% per annum over 35 years.

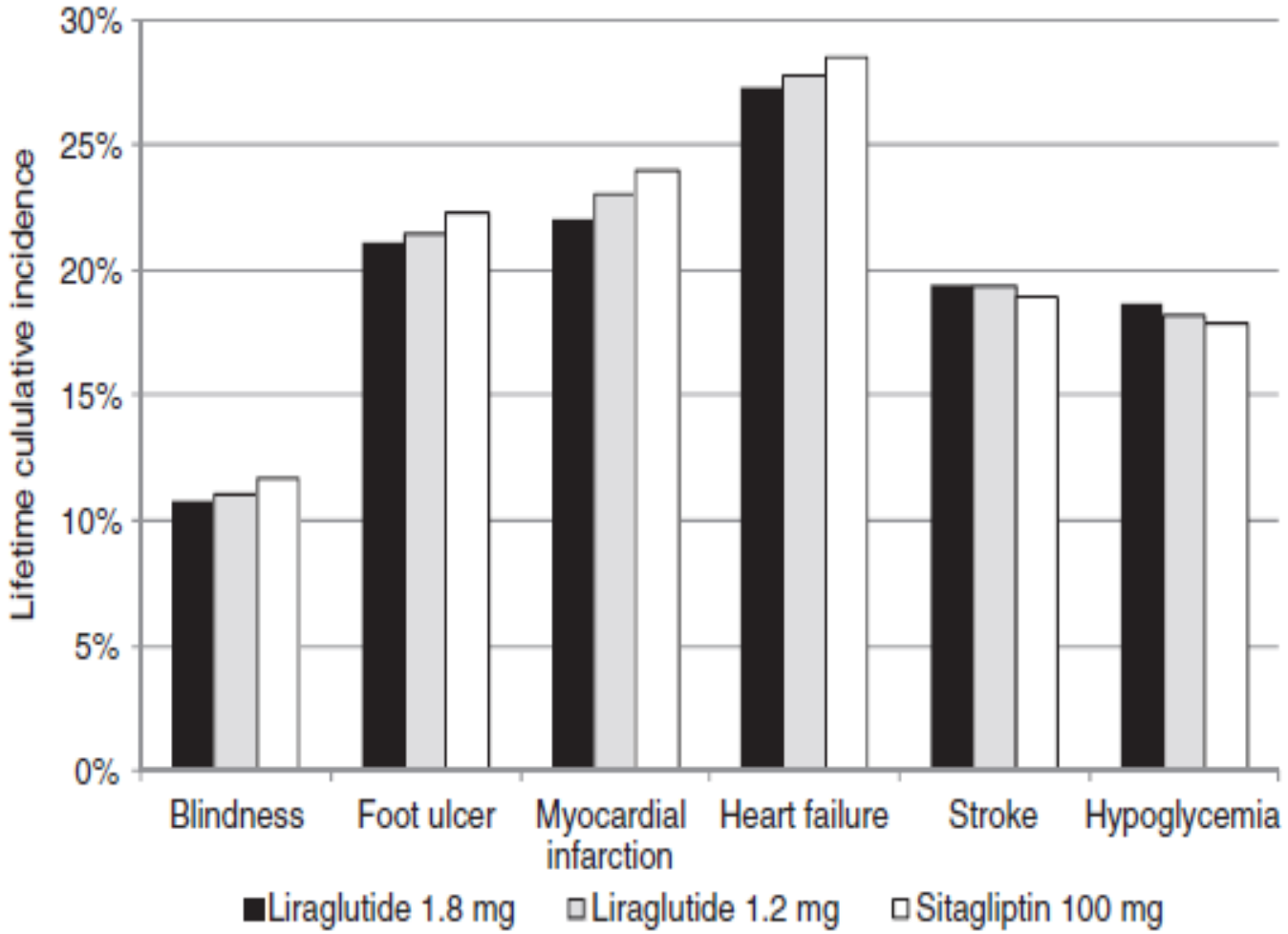



Figure 1. 35-year cumulative incidence of diabetes complications.

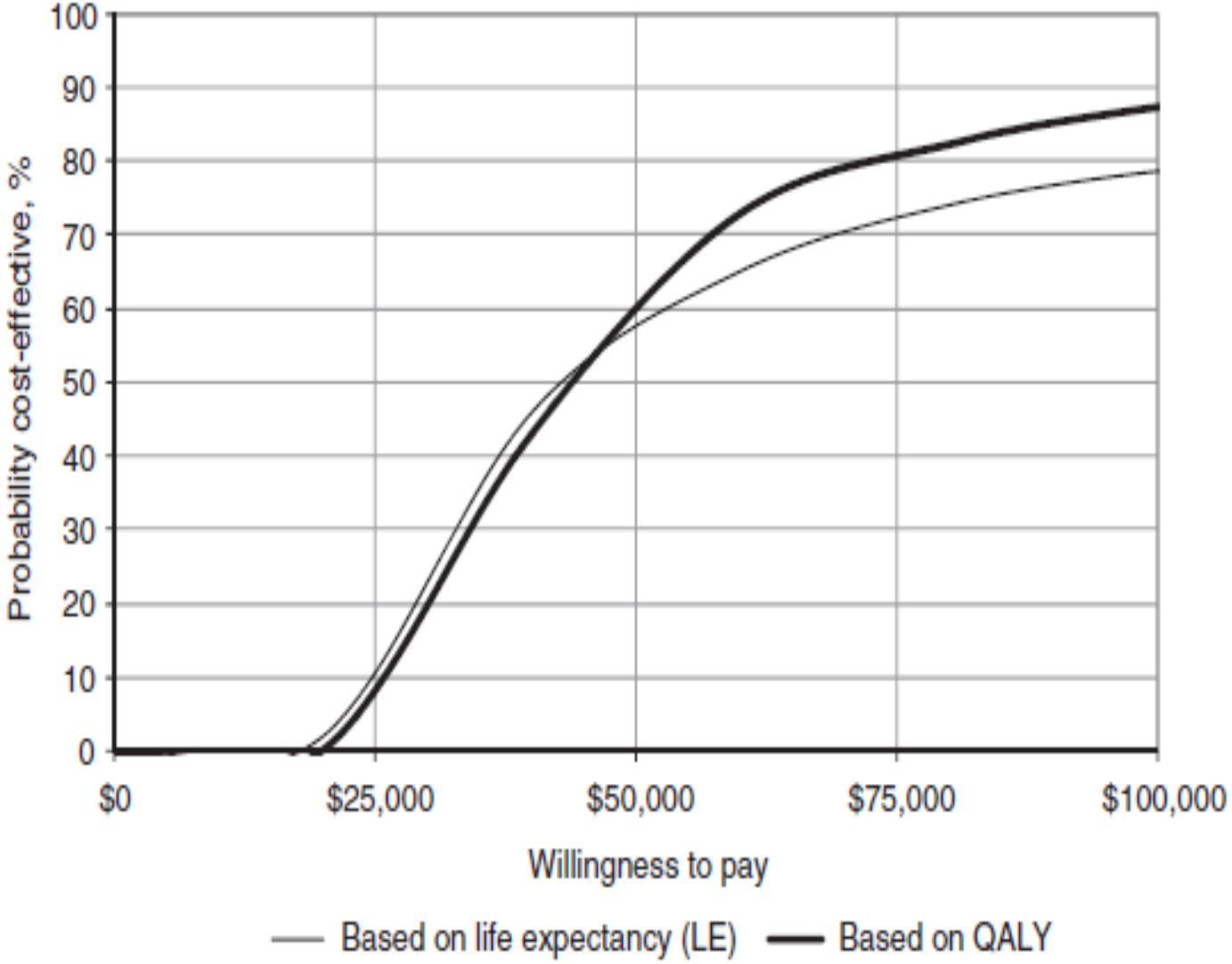



Figure 2. Cost-effectiveness acceptability curve for liraglutide 1.8 mg vs sitagliptin.

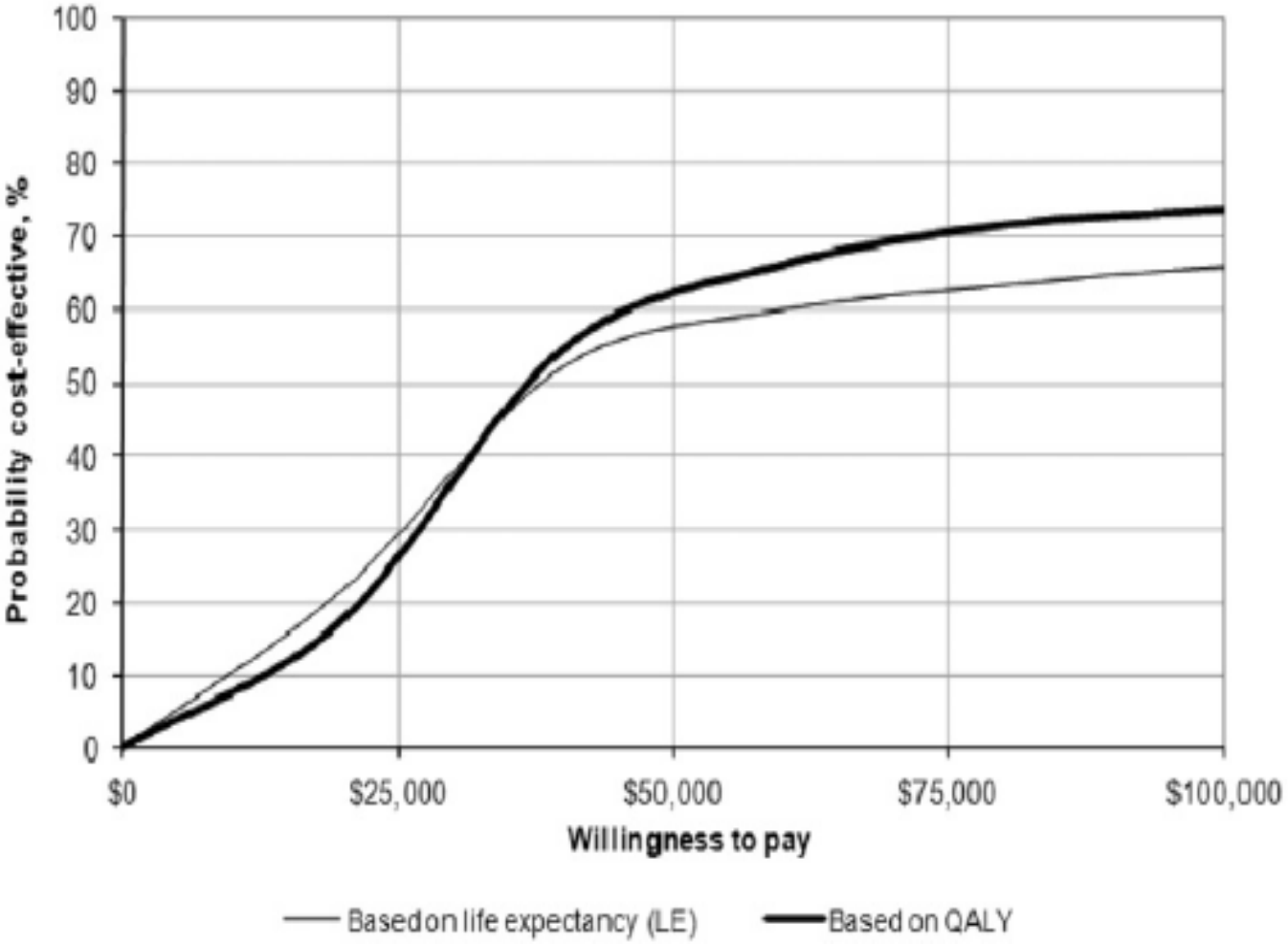



Figure 3. Cost-effectiveness acceptability curve for liraglutide 1.2 mg vs sitagliptin.

## Conclusions

Despite these limitations, there is sufficient evidence that liraglutide 1.2 mg and 1.8 mg, with improved efficacy profiles over sitagliptin, could improve patient care while being cost-effective treatments in type 2 diabetes patients in the US setting.

DIABETICMedicine

DOI: 10.1111/j.1464-5491.2011.03429.x

Article: Health Economics

# Cost–utility analysis of liraglutide compared with sulphonylurea or sitagliptin, all as add-on to metformin monotherapy in Type 2 diabetes mellitus

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*Accepted 19 August 2011*

## Abstract

**Aim** To investigate the cost-effectiveness of liraglutide as add-on to metformin vs. glimepiride or sitagliptin in patients with Type 2 diabetes uncontrolled with first-line metformin.

**Methods** Data were sourced from a clinical trial comparing liraglutide vs. glimepiride, both in combination with metformin, and a clinical trial comparing liraglutide vs. sitagliptin, both as add-on to metformin. Only the subgroup of patients in whom liraglutide was added to metformin monotherapy was included in the cost–utility analysis. The CORE Diabetes Model was used to simulate outcomes and costs with liraglutide 1.2 and 1.8 mg vs. glimepiride and vs. sitagliptin over patients' lifetimes. Treatment effects were taken directly from the trials. Costs and outcomes were discounted at 3.5% per annum and costs were accounted from a third-party payer (UK National Health System) perspective.

**Results** Treatment with liraglutide 1.2 and 1.8 mg resulted, respectively, in mean increases in quality-adjusted life expectancy of 0.32 ± 0.15 and 0.28 ± 0.14 quality-adjusted life years vs. glimepiride, and 0.19 ± 0.15 and 0.31 ± 0.15 quality-adjusted life years vs. sitagliptin, and was associated with higher costs of £3003 ± £678 and £4688 ± £639 vs. glimepiride, and £1842 ± £751 and £3224 ± £683 vs. sitagliptin, over a patient's lifetime. Both liraglutide doses were cost-effective, with incremental cost-effectiveness ratios of £9449 and £16 501 per quality-adjusted life year gained vs. glimepiride, and £9851 and £10 465 per quality-adjusted life year gained vs. sitagliptin, respectively.

**Conclusions** Liraglutide, added to metformin monotherapy, is a cost-effective option for the treatment of Type 2 diabetes in a UK setting.

Diabet. Med. 29, 313–320 (2012)

**Keywords** cost-effectiveness, liraglutide, Type 2 diabetes, UK

**Abbreviations** NICE, National Institute for Health and Clinical Excellence; QALY, quality-adjusted life year

In conclusion, this study investigated the cost–utility, in a UK setting, of liraglutide vs. glimepiride or sitagliptin (all added to metformin monotherapy), scenarios intended to simulate likely clinical practice in real life. The results suggest that liraglutide added to metformin monotherapy leads to improvements in quality adjusted-life expectancy and is a cost-effective option for the treatment of Type 2 diabetes in this setting.

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1369-6998
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Article 0044.R1/703633


Original article

# Willingness to pay for diabetes drug therapy in type 2 diabetes patients: based on LEAD clinical programme results

Table 2. Main results from the meta-analysis.

| Variable | Liraglutide 1.2 mg ($n=898$) | Rosiglitazone 4 mg ($n=232$) | Glimepiride* 4–8 mg ($n=492$) | Insulin glargine** ($n=234$) | Exenatide 20 μg ($n=231$) |
|---|---|---|---|---|---|
| Change in $HbA_{1c}$ at 26 weeks (%)† | –1.01 | –0.35 | –0.71 | –0.98 | –0.82 |
| Change in systolic blood pressure at 26 weeks (mmHg) | –2.57 | –0.35 | 0.41 | 1.64 | –3.89 |
| Weight change at 26 weeks (kg) | –1.52 | 1.94 | 1.04 | 1.57 | –2.29 |
| Hypoglycaemia event rate | 0.284 | 0.134 | 1.365 | 1.403 | 2.669 |
| Blood glucose measure (tests per day) | 0.77 | 0.77 | 0.77 | 1.63 | 0.77 |
| Nausea (% of patients) | 4.1 | 0.2 | 0.8 | 0.1 | 12.2 |

*Glimepiride 4 mg/day (LEAD 2), 8 mg/day (LEAD 3); **Insulin glargine dose variable dependent on patient's clinical requirements; †$HbA_{1c}$ in DCCT aligned units (%).

Table 3. Willingness to pay (WTP) for liraglutide 1.2 mg per day compared with other standard therapies (€ per day).

| Variable | WTP for liraglutide 1.2 mg per day versus other glucose lowering treatments, € per day | | | |
|---|---|---|---|---|
| | Rosiglitazone 4 mg | Glimepiride* 4–8 mg | Insulin glargine** | Exenatide 20 μg |
| Change in $HbA_{1c}$ at 26 weeks (%)† | 0.95 | 0.43 | 0.04 | 0.27 |
| Change in systolic blood pressure at 26 weeks (mmHg) | 0.34 | 0.46 | 0.65 | −0.20 |
| Change in body weight at 26 weeks (kg) | 2.70 | 1.87 | 2.35 | −0.46 |
| Minor hypoglycaemia event rate (minor + major per patient per year) | 0.00 | 0.03 | 0.03 | 0.07 |
| Administration | −1.30 | −0.82 | 0.00 | 1.04 |
| Blood glucose measure (tests per day) | 0.00 | 0.00 | 0.33 | 0.00 |
| Nausea (% of patients) | −0.04 | −0.03 | −0.04 | 0.08 |
| **Total** | **2.64** | **1.94** | **3.36** | **0.81** |

*Glimepiride 4 mg/day (LEAD 2), 8 mg/day (LEAD 3): **Insulin glargine dose variable dependent on patient's clinical requirements: †$HbA_{1c}$ in DCCT aligned units (%).

The positive values mean that treatment with liraglutide is preferred to the alternative, i.e., the willingness to pay for liraglutide is positive. The negative values imply a willingness to pay to avoid, i.e., the alternative treatment is preferred to liraglutide when looking at that parameter.

## Conclusions

Results from this analysis suggest that people with type 2 diabetes may place considerably more value on liraglutide than other standard treatments. The main motivations driving the WTP were decrease in weight compared with rosiglitazone, glimepiride, and insulin glargine, and administration frequency compared with exenatide.

# LIFESTYLE MODIFICATION

## A1C 6.5 – 7.5%**

*Monotherapy*

MET † | DPP4 [1] | GLP-1 | TZD [2] | AGI [3]

2 - 3 Mos.***

*Dual Therapy*

| | | |
|---|---|---|
| MET | + | GLP-1 or DPP4 [1] |
| | | TZD [2] |
| | | Glinide or SU [5] |
| TZD | + | GLP-1 or DPP4 [1] |
| MET | + | Colesevelam |
| | | AGI [3] |

2 - 3 Mos.***

*Triple Therapy*

| | | |
|---|---|---|
| MET + GLP-1 or DPP4 [1] | + | TZD [2] |
| | | Glinide or SU [4,7] |

2 - 3 Mos.***

**INSULIN ± Other Agent(s) [6]**

## A1C 7.6 – 9.0%

*Dual Therapy* [8]

| | | |
|---|---|---|
| MET | + | GLP-1 or DPP4 [1] or TZD [2] |
| | | SU or Glinide [4,5] |

2 - 3 Mos.***

*Triple Therapy* [9]

| | | | |
|---|---|---|---|
| MET | + | GLP-1 or DPP4 [1] | + TZD [2] |
| | | GLP-1 or DPP4 [1] | + SU [7] |
| | | TZD [2] | |

2 - 3 Mos.***

**INSULIN ± Other Agent(s) [6]**

## A1C > 9.0%

*Drug Naive* / *Under Treatment*

*Symptoms* / *No Symptoms*

**INSULIN ± Other Agent(s) [6]**

| | | | |
|---|---|---|---|
| MET | + | GLP-1 or DPP4 [1] | ± SU [7] |
| | | TZD [2] | |
| | | GLP-1 or DPP4 [1] | ± TZD [2] |

**INSULIN ± Other Agent(s) [6]**


**AACE/ACE Algorithm for Glycemic Control Committee**

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* May not be appropriate for all patients

** For patients with diabetes and A1C < 6.5%, pharmacologic Rx may be considered

*** If A1C goal not achieved safely

† Preferred initial agent

1 DPP4 if ↑ PPG and ↑ FPG or GLP-1 if ↑↑ PPG

2 TZD if metabolic syndrome and/or nonalcoholic fatty liver disease (NAFLD)

3 AGI if ↑ PPG

4 Glinide if ↑ PPG or SU if ↑ FPG

5 Low-dose secretagogue recommended

6 a) Discontinue insulin secretagogue with multidose insulin
b) Can use pramlintide with prandial insulin

7 Decrease secretagogue by 50% when added to GLP-1 or DPP-4

8 If A1C < 8.5%, combination Rx with agents that cause hypoglycemia should be used with caution

9 If A1C > 8.5%, in patients on Dual Therapy, insulin should be considered

# Grazie per l’attenzione !

S.S.