Analoghi GLP-1 e DPP-IV inibitori : una terapia cost-effective ?

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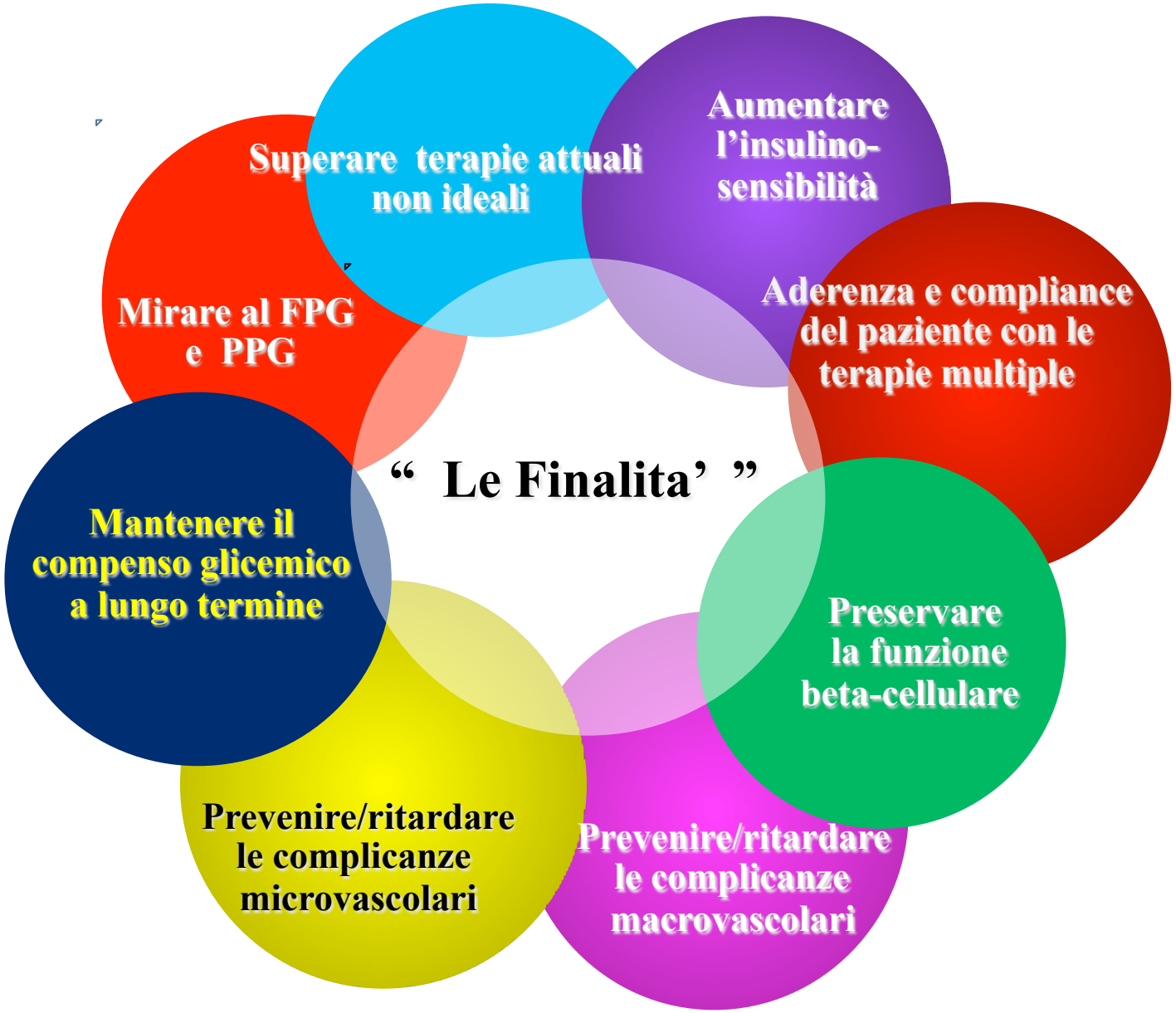
Ospedale dei Pellegrini – Napoli

Finalita’ della Terapia del Diabete Mellito di Tipo 2:



Obiettivi per un trattamento ottimale

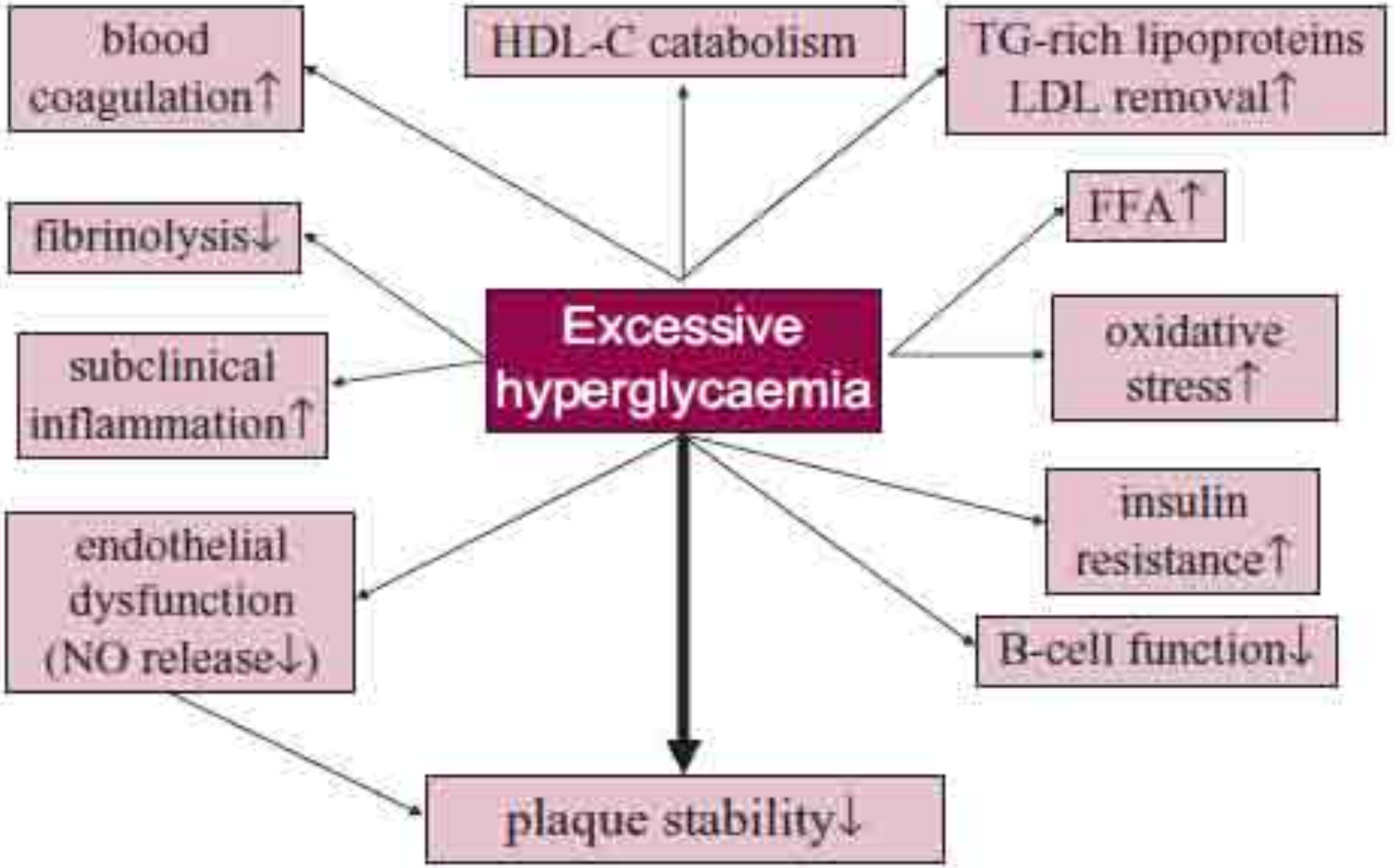
- **L'approccio terapeutico ideale dovrebbe soddisfare tutti i seguenti aspetti :**

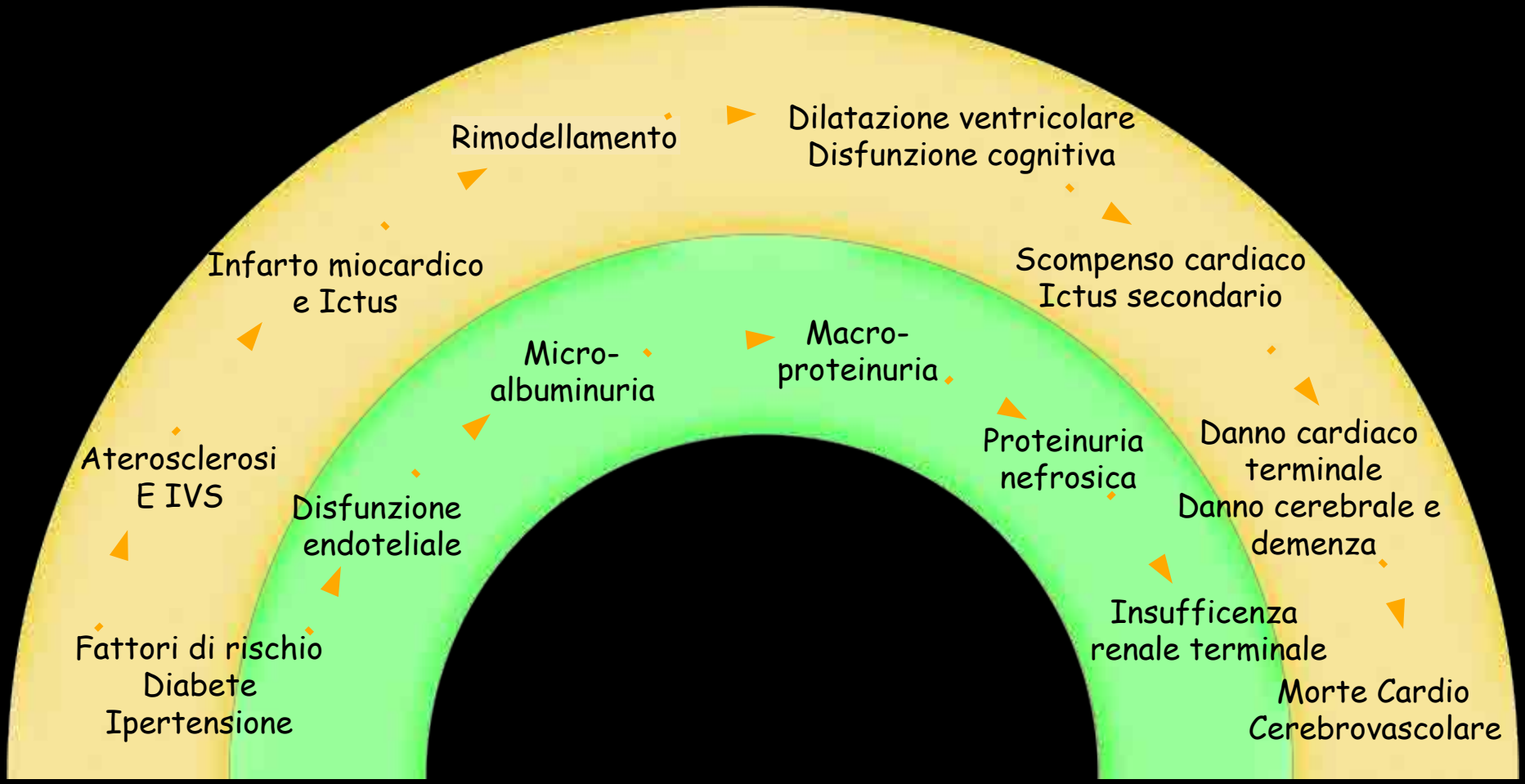
- efficacia clinica a lungo termine
- basso rischio di ipoglicemie
- preservazione della funzionalità beta cellulare
- effetto neutrale o di riduzione sul peso corporeo
- effetto protettivo sul rischio cardiovascolare
- buon profilo di sicurezza e tollerabilità
- regime di trattamento semplice e flessibile

UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; 352: 837-53
Kahn SE, et al. for the ADOPT Study Group. N Engl J Med 2006; 35: 2427-43

Glucotoxicity

- High glucose levels are toxic for two main pathogenetic defects of type 2 diabetes
  - Beta-cell function
  - Insulin action in peripheral tissues
- High chronic hyperglycaemia damages vascular tissues resulting in
  - Microvascular complications
  - Macroangiopathy of diabetes


blood coagulation↑
HDL-C catabolism
TG-rich lipoproteins LDL removal↑
fibrinolysis↓
FFA↑
subclinical inflammation↑
Excessive hyperglycaemia
oxidative stress↑
insulin resistance↑
endothelial dysfunction (NO release↓)
B-cell function↓
plaque stability↓



Obiettivo: prevenire, arrestare, ridurre il danno d'organo che è lo step intermedio tra esposizione ai fattori di rischio ed eventi

PARADIGM SHIFT TO MOVE :

BEYOND GLYCEMIC CONTROL

as new anti-diabetic therapies are developed

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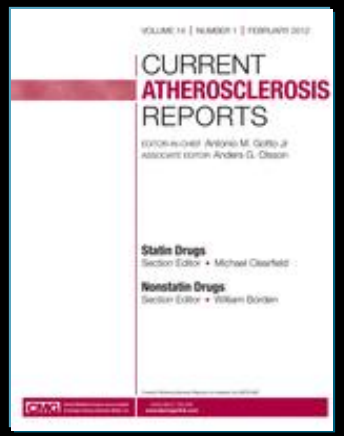
Baylor College of Medicine,
Houston, TX, USA

Curr Atheroscler Rep (2011) 13:115–122
DOI 10.1007/s11883-010-0153-0



Determinanti dell' HbA1c

HbA_{1c} = Glicemia a digiuno (FPG) + Glicemia Postprandiale (PPG)

FPG influenzata da:

- Produzione di glucosio epatico
- Sensibilità epatica all'insulina
- Esercizio durante il giorno precedente
- Pasto dalla sera precedente
- Alcool
- Apnea ostruttiva del sonno
- Ipoglicemia notturna

PPG influenzata da:

- Glicemia pre-pandiale
- Carico di glucosio al pasto
- Livello di incretine
- Secrezione di insulina
- Sensibilità all'insulina nei tessuti periferici
- Diminuzione nell'eliminazione di glucagone

Current Therapies Glycemic Efficacy

Drug	Average A1c Reduction
Meglitidines	0.5-1.5%
Biguanides	1-2%
Sulfonylureas	1-2%
TZDs	1-1.5%
Alpha-glucosidase inhibitors	0.5-1%
DPP-4s	0.5-1%
GLP-1s	1-1.5%
Amylin Agonists	0.5-1%

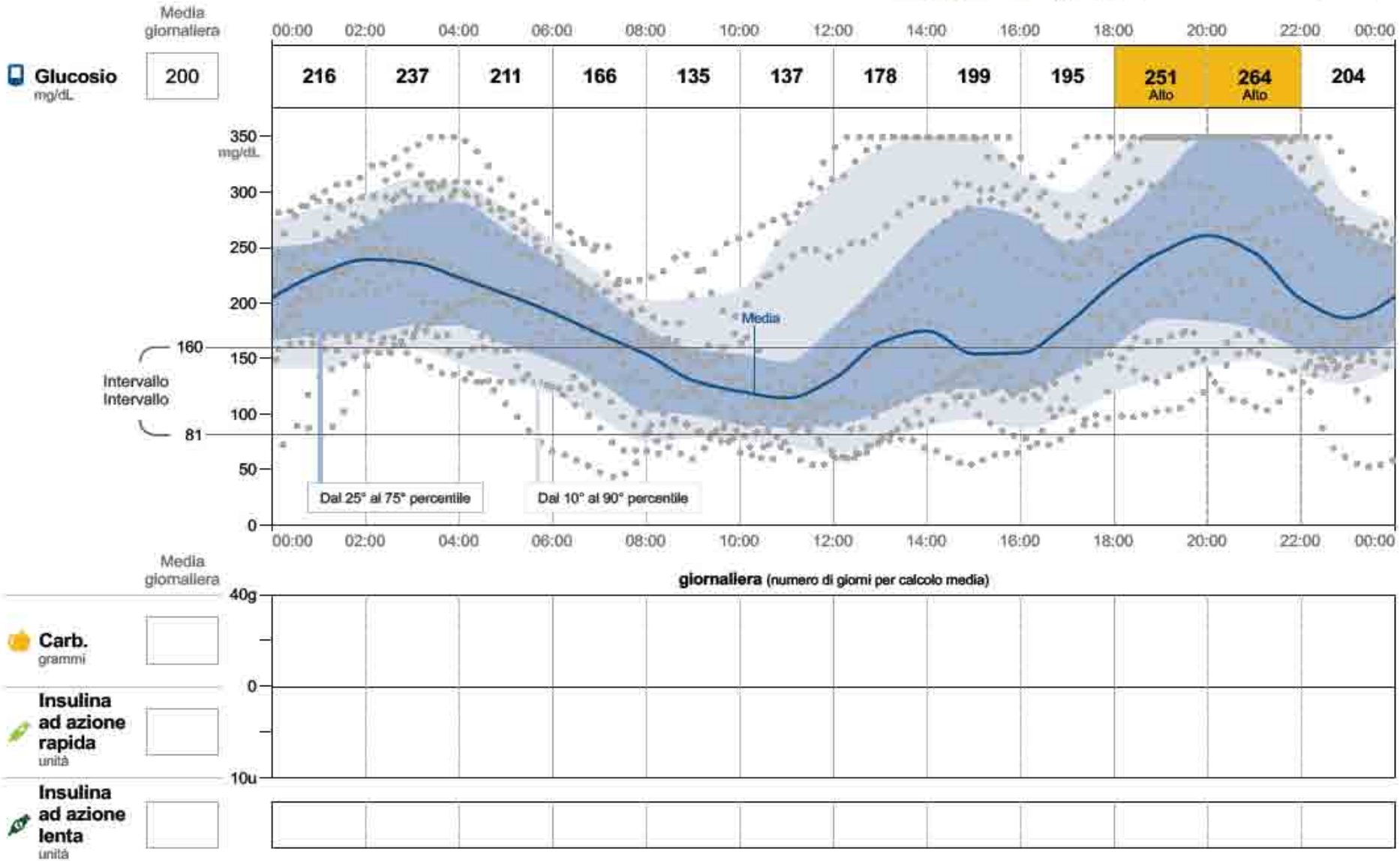
* SGLT2s average A1c reduction = 0.5 – 1 %

1. PL detail-document. Drugs for type 2 diabetes. Pharmacist's Letter/Prescriber's Letter. Oct 2014.
2. ADA. Diabetes care. Diabetes Care 2012;34(suppl 1):S18. Table 10.

Andamento giornaliero (con valori del glucosio)

12 febbraio 2016 - 25 febbraio 2016 (14 giorni)

A1c stimata 8,6% o 70 mmol/mol



Istantanea

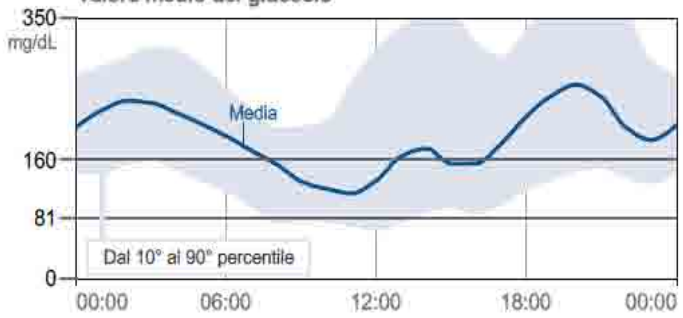
12 febbraio 2016 - 25 febbraio 2016 (14 giorni)

Glucosio

A1c stimata 8,6% o 70 mmol/mol

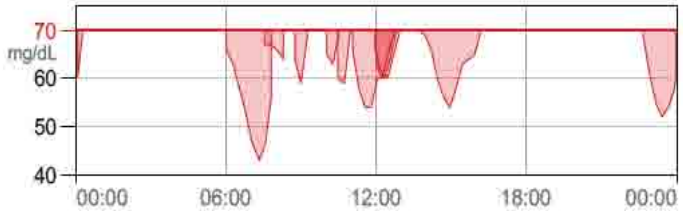
GLUCOSIO MEDIO	**200**	mg/dL
% sopra intervallo	62	%
% nell'intervallo	31	%
% sotto intervallo	7	%

Valore medio del glucosio



EVENTI DI GLUCOSIO BASSO	**9**	
Durata media	103	Min

Eventi di glucosio basso



Uso del sensore

DATI SENSORE ACQUISITI	**97**	%
Scansioni giornaliere	6	

Dati sensore acquisiti

Carb. registrati

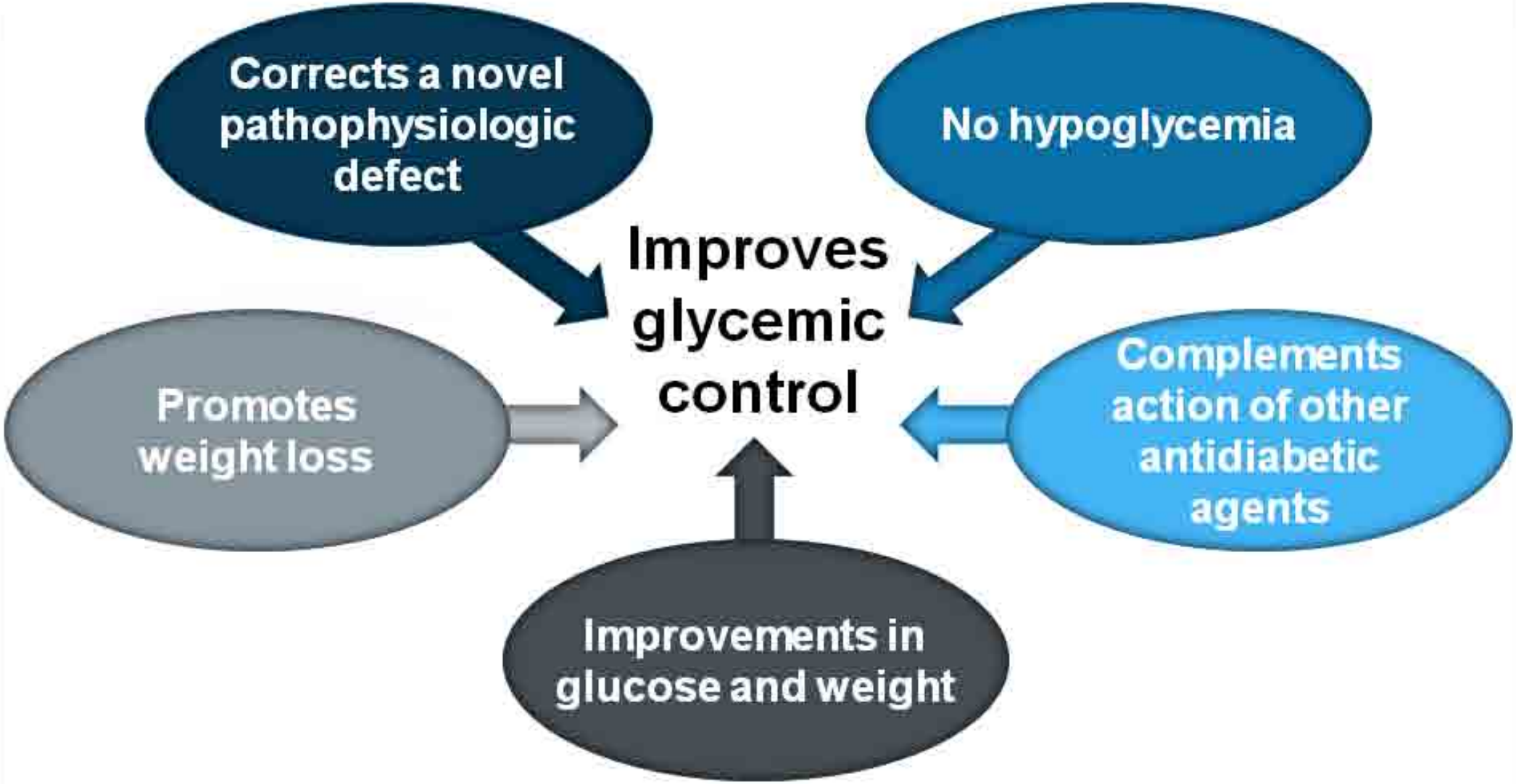
CARB. GIORNALIERI	grammi/ giorno

Insulina registrata

Insulina ad azione rapida	unità/ giorno
Insulina ad azione lenta	unità/ giorno
INSULINA GIORNALIERA TOTALE	unità/ giorno

FONTE: FreeStyle Libre 2.1.2
FreeStyle Libre 1.0

Individualizing Therapy: Factors to Consider



DeFronzo RA. *Diabetes*. 2009;58:773-795.

The New Paradigm

1. Metformin
2. Sulfonylureas/Glinides
3. TZDs (Pioglitazone)
4. α-glucosidase-inhibitors
5. DPP4-inhibitors

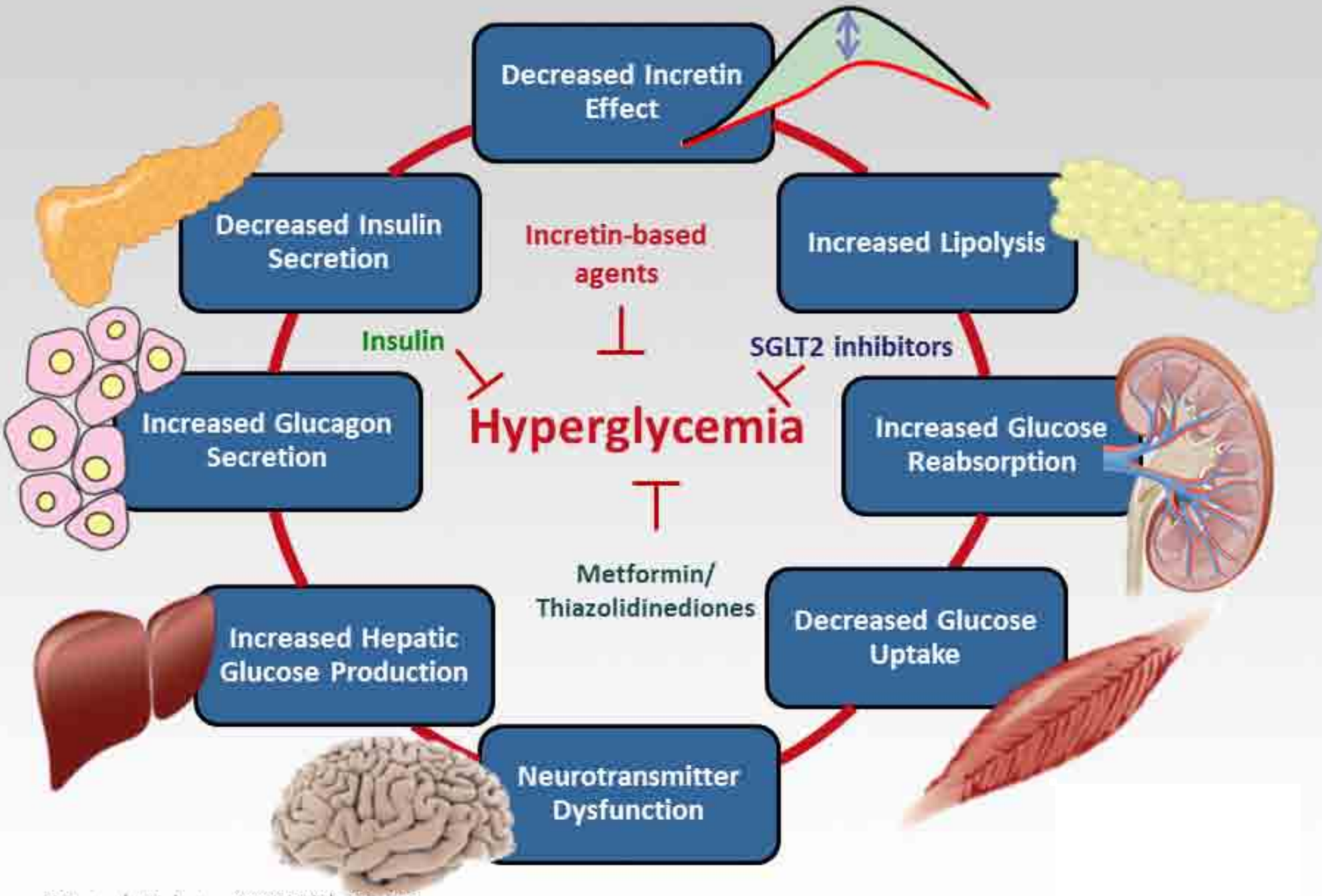
Oral agents

6. GLP1-agonists
7. Insulins

injections

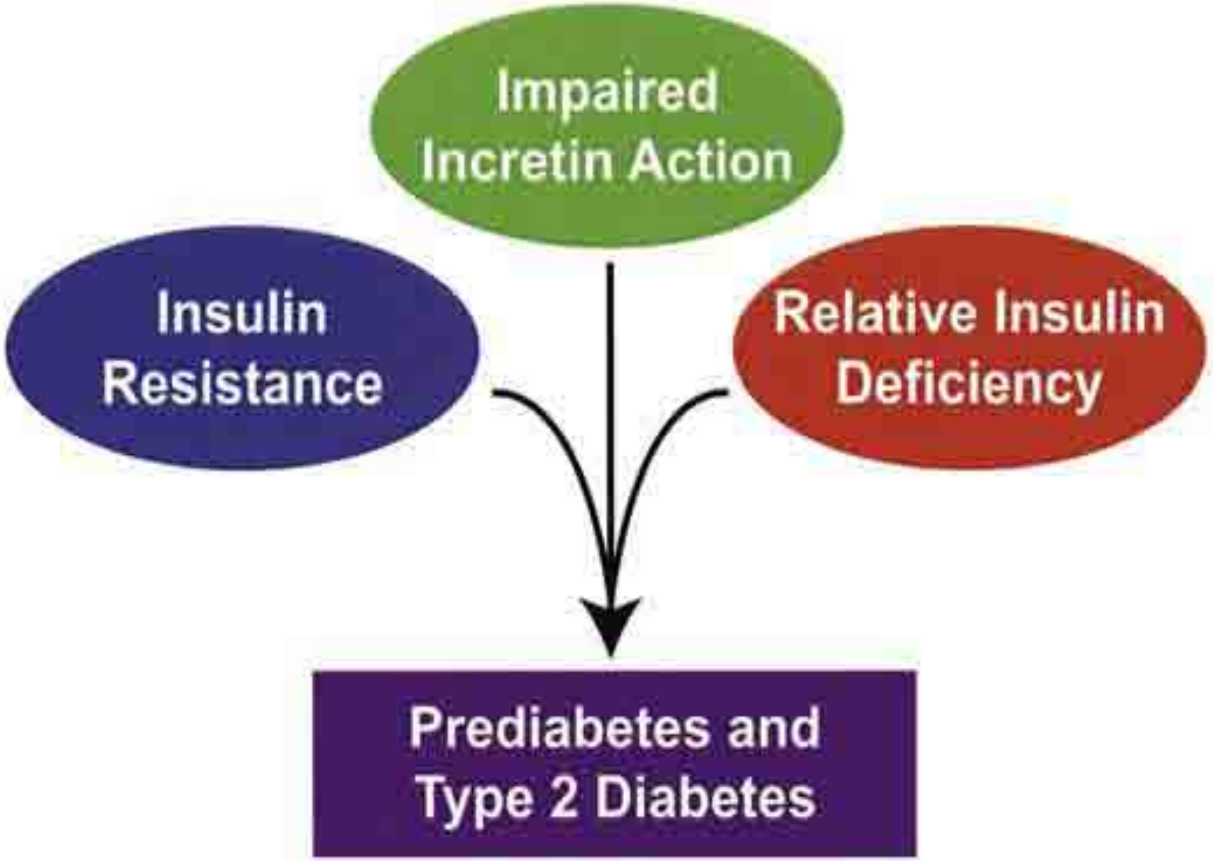
8. Coming-up : SGLT2-inhibitors

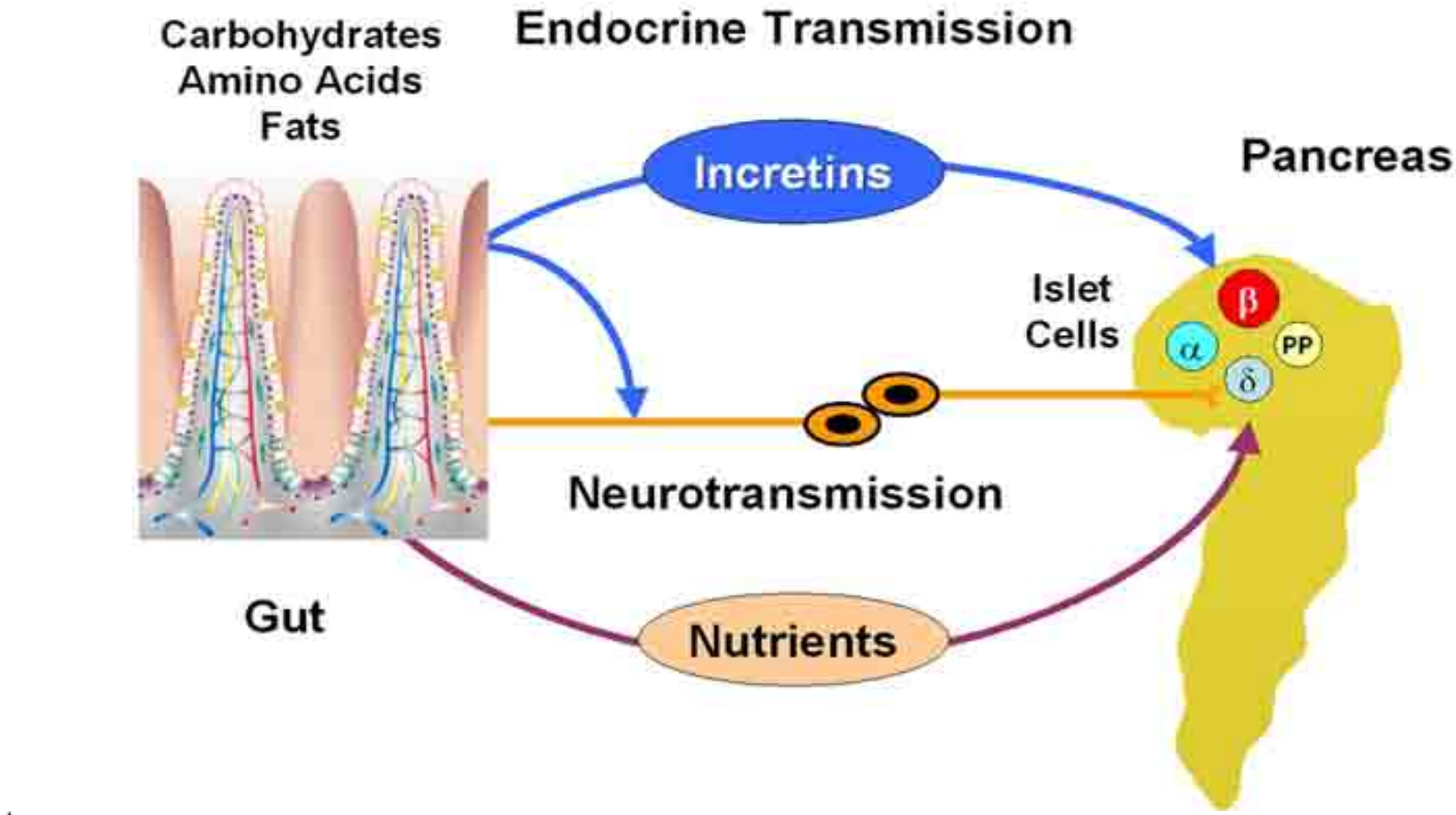
Pathophysiological Pathways in T2DM

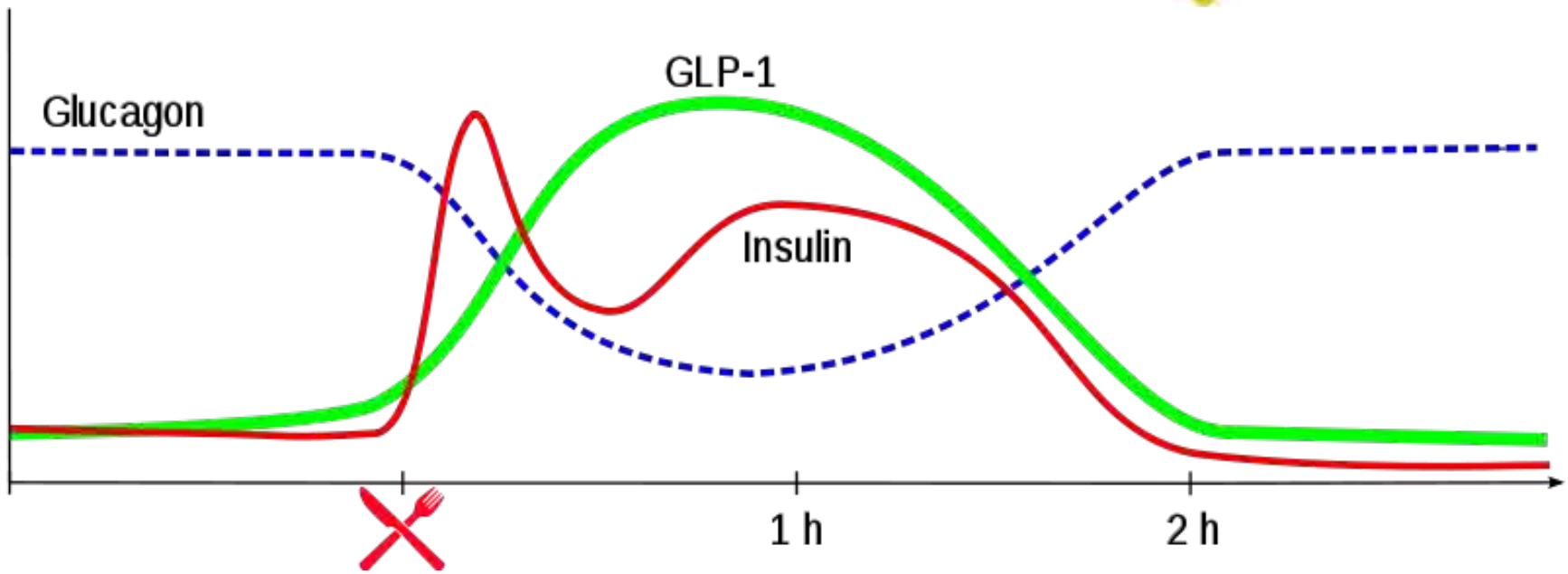


DeFronzo RA, et al. *Diabetes*. 2009;58(4):773-795.

Redefining Pathophysiology of Type 2 Diabetes




Carbohydrates
Amino Acids
Fats
Endocrine Transmission
Incretins
Pancreas
Islet
Cells
β
α
PP
δ
Neurotransmission
Gut
Nutrients


GLP-1
Glucagon
Insulin
1 h
2 h

Review Article

Diabetes is predominantly an intestinal disease

Debmalya Sanyal
KPC Medical College, Kolkata, West Bengal, India

ABSTRACT

Diabetes mellitus (DM) is a chronic, progressive, medically incurable disease and is poorly controlled in a vast majority, in spite of tremendous advancements in pharmacotherapy. Altered gut microbiome can predict diabetes. There is strong and consistent evidence regarding role of the gut and many gut hormones like incretins in energy and glucose homeostasis. Incretin group of agents including glucagon-like peptide (GLP-1) receptor agonists and dipeptidyl peptidase IV (DPP-IV) inhibitors are efficacious therapeutic agents in diabetes treatment. A growing body of evidence, however, appears to indicate that type 2 DM (T2DM) may be an operable intestinal illness—a novel revolutionary concept about an old disease. This may facilitate research that can better clarify our understanding of the etiology of the disease and provide a new opportunity to develop new and more effective therapies. Future research should focus on an approach to bypass the bypass, that is, to replace the gastric bypass by equally effective but less invasive treatments for majority of diabetics.

Key words: Bariatric surgery, gut microbiota, type 2 diabetes, gastric inhibitory polypeptide, GLP-1

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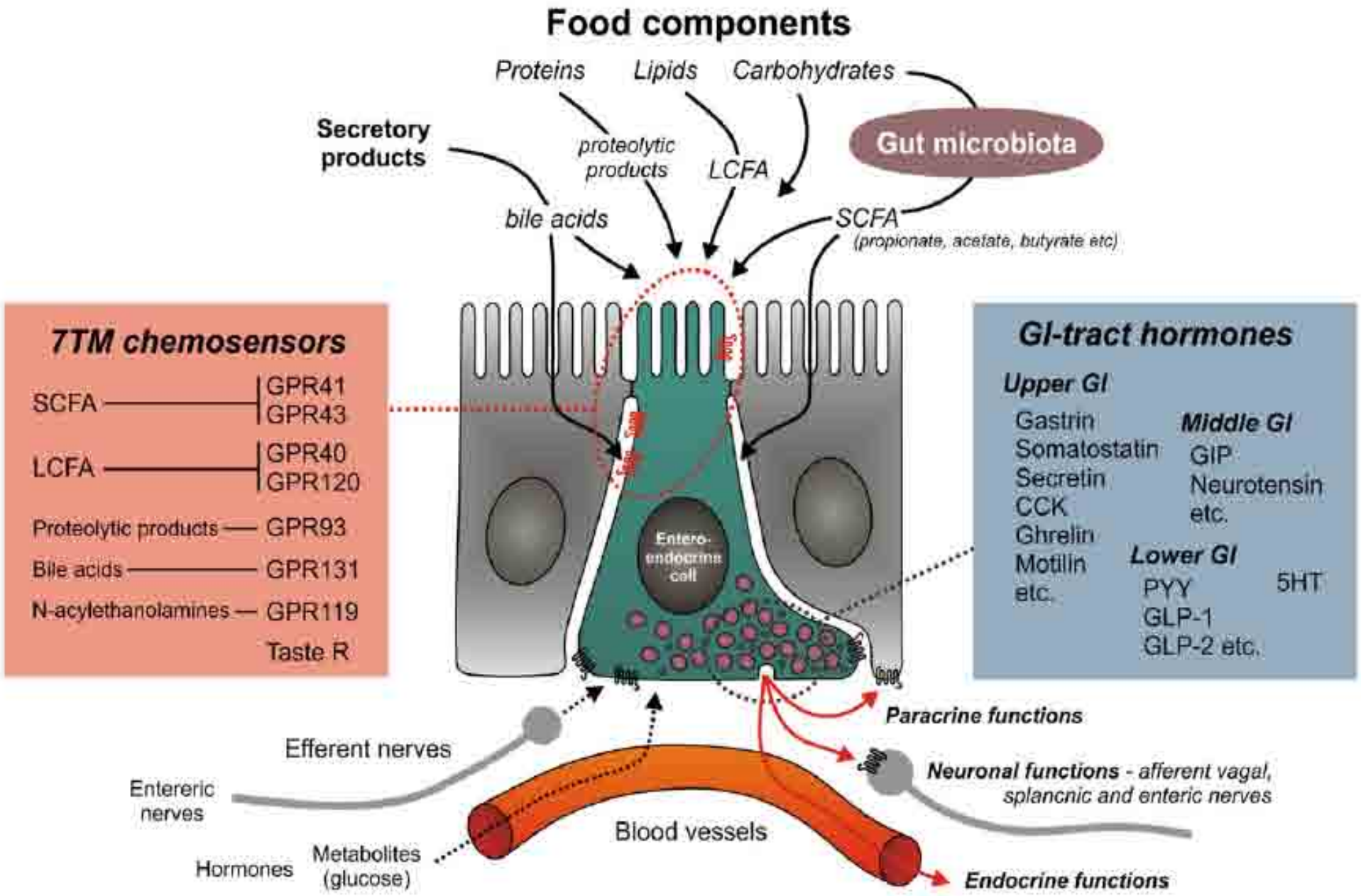
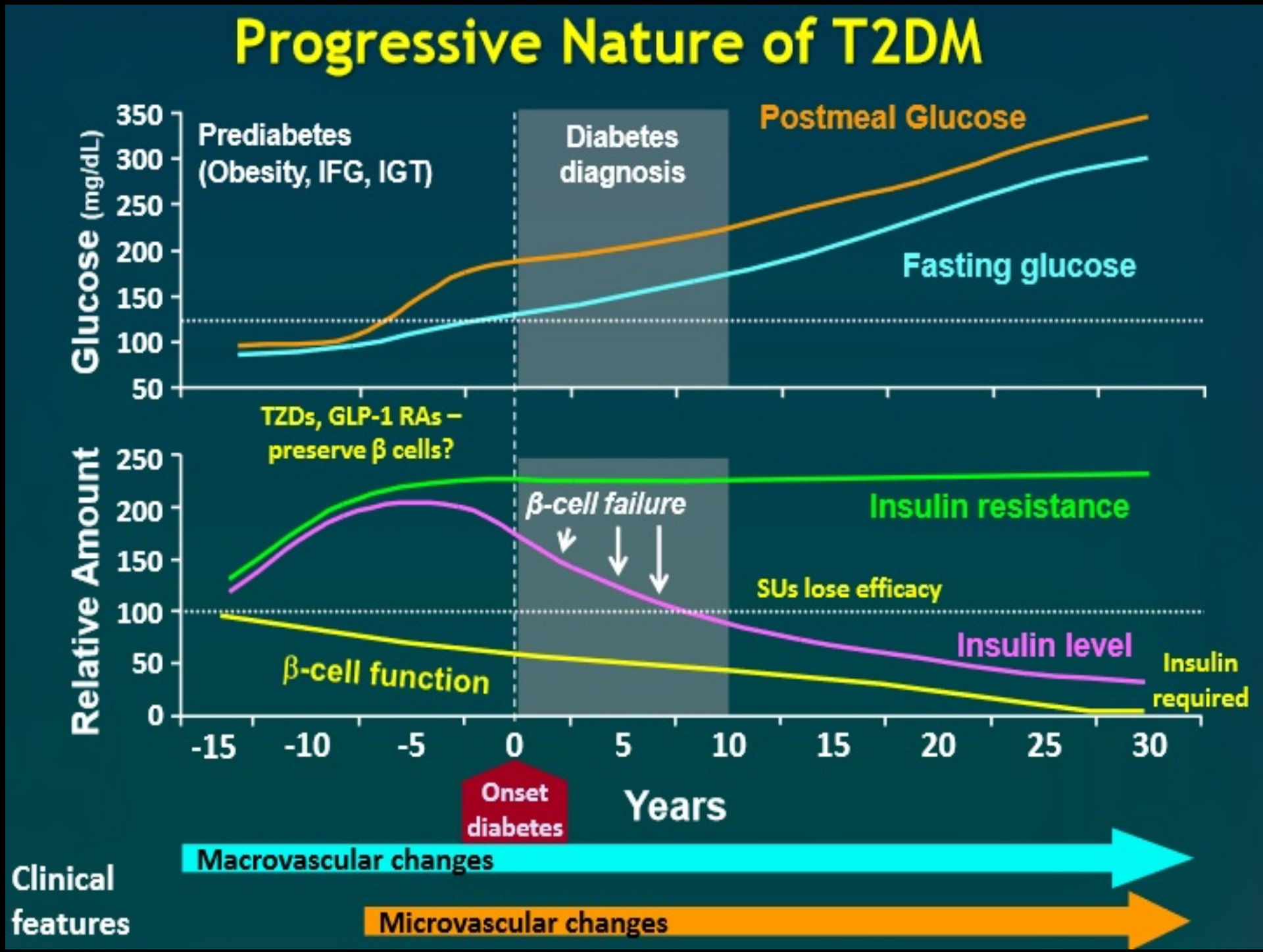
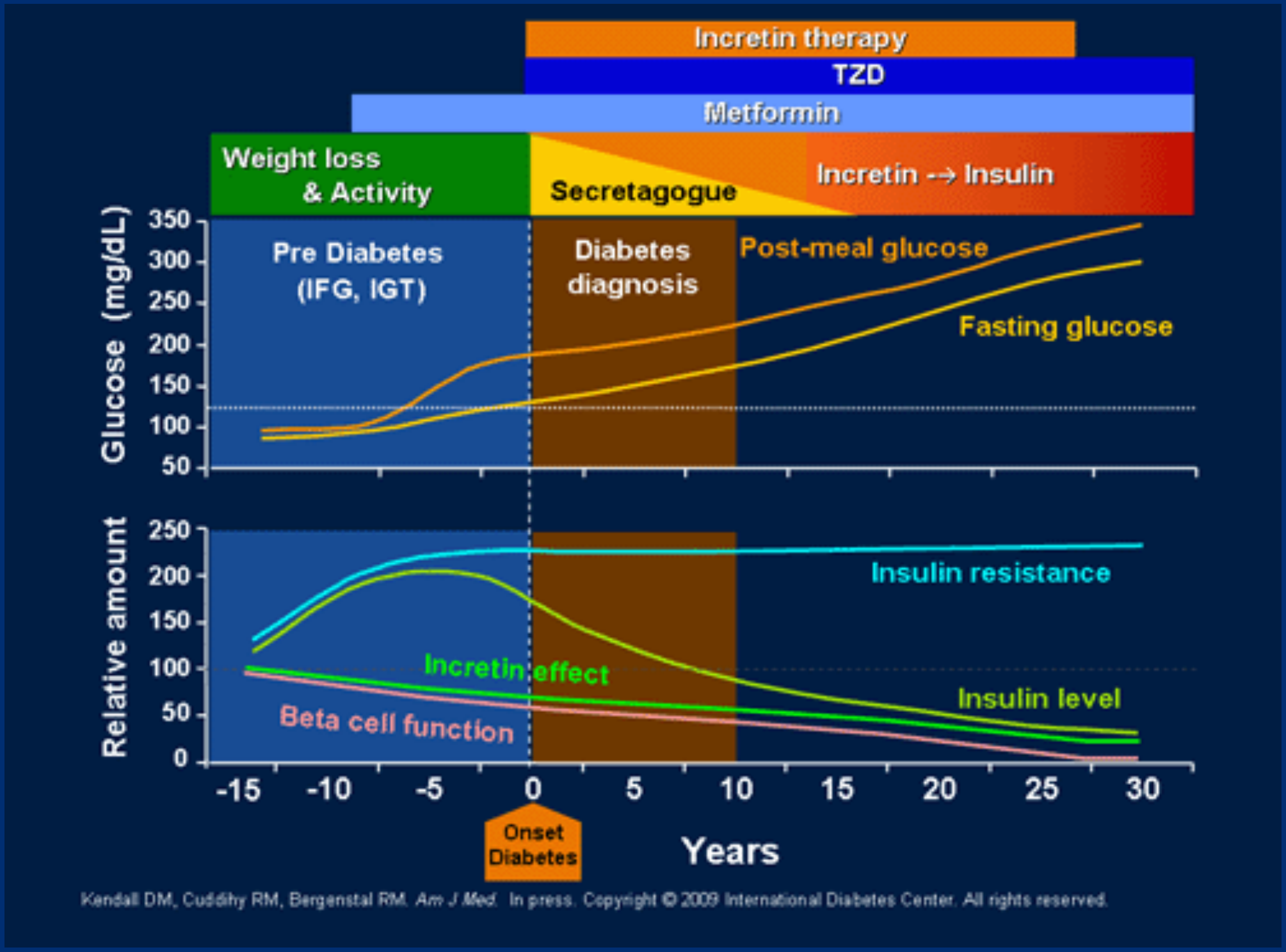
Indian Journal of Endocrinology and Metabolism

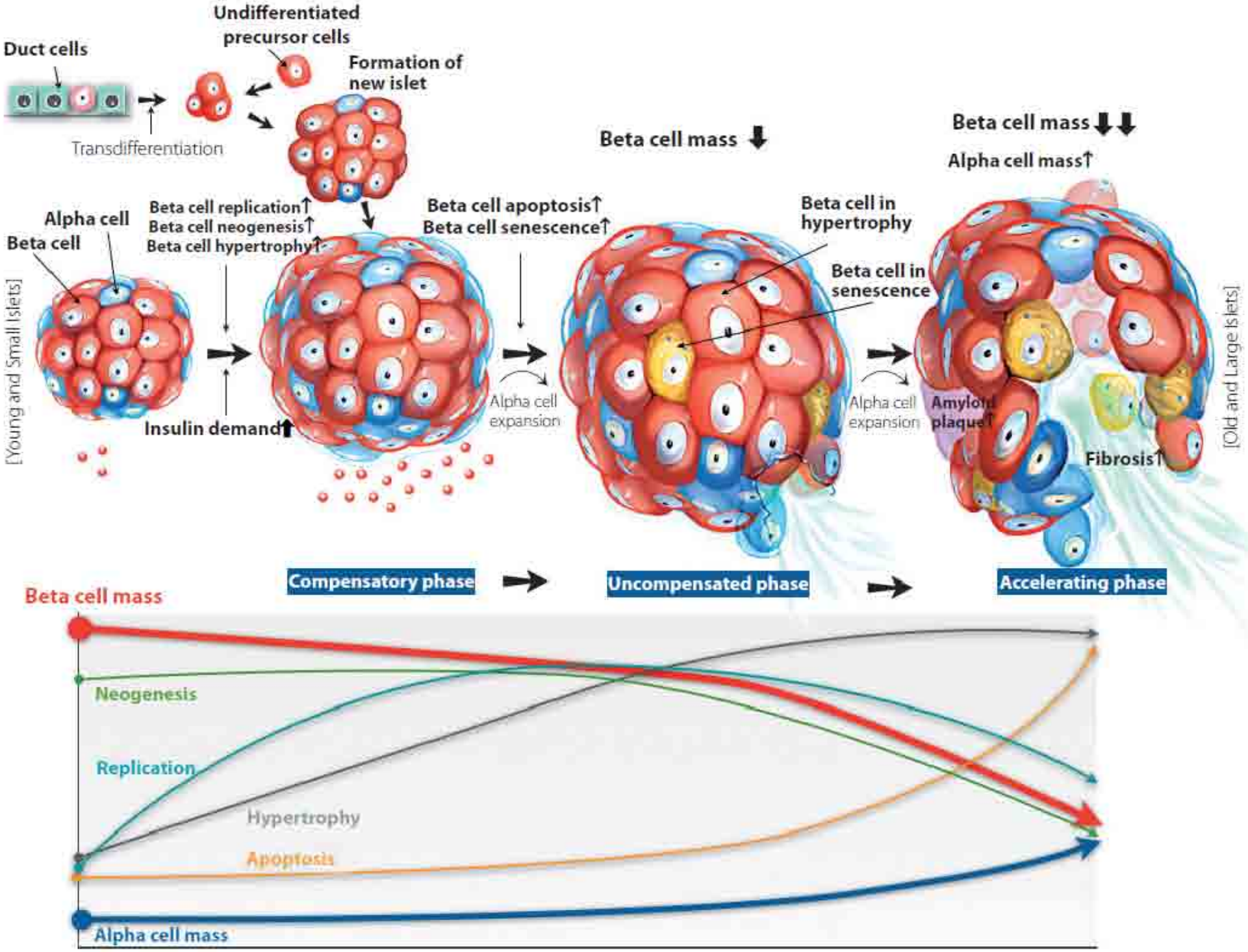
Sensory and Secretory Functions of Enteroendocrine Cells of the Gut

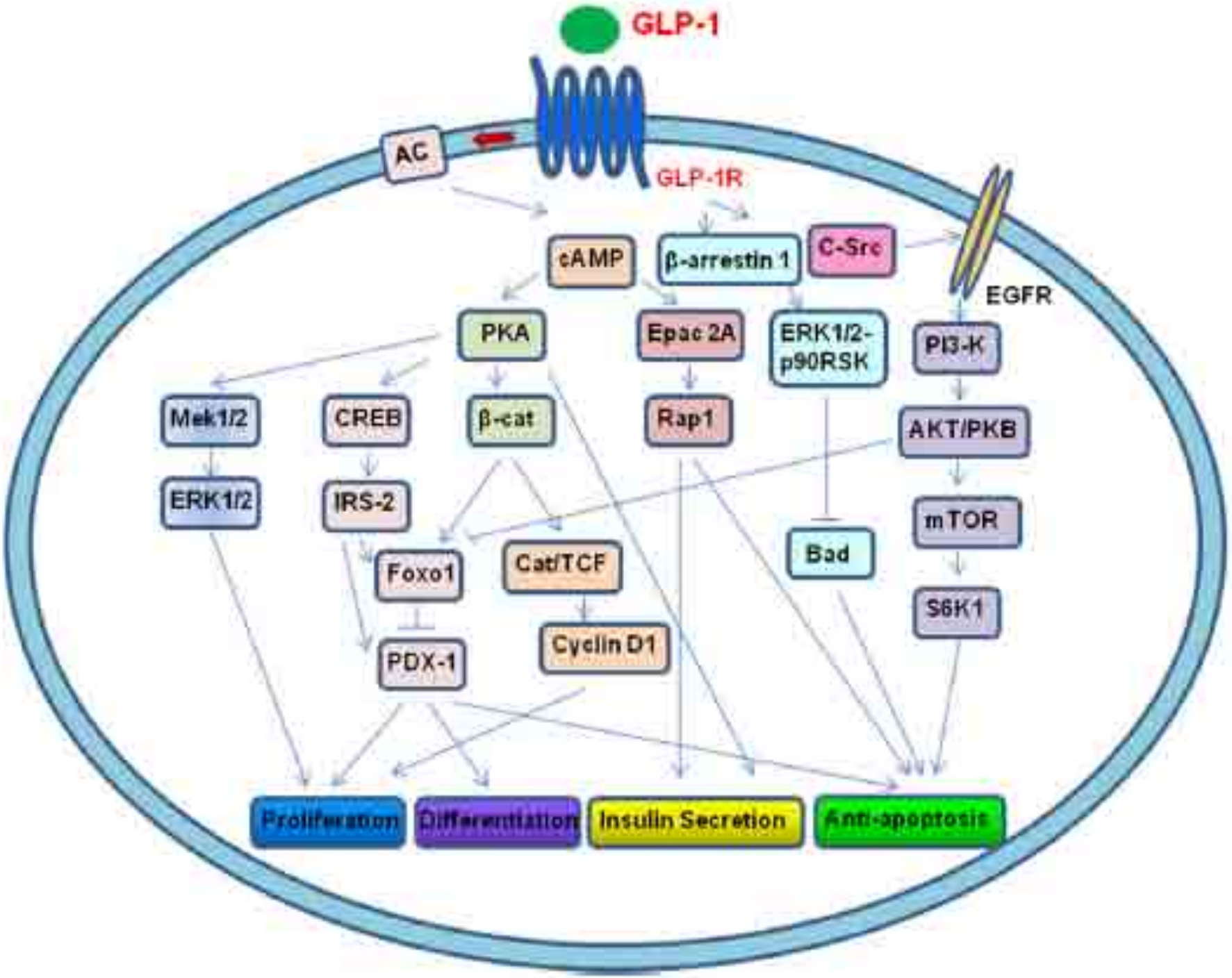



Progressive Nature of T2DM
Glucose (mg/dL)
350
300
250
200
150
100
50
Prediabetes
(Obesity, IFG, IGT)
Diabetes
diagnosis
Postmeal Glucose
Fasting glucose
TZDs, GLP-1 RAs –
preserve β cells?
Relative Amount
250
200
150
100
50
0
β-cell failure
Insulin resistance
SUs lose efficacy
Insulin level
β-cell function
Insulin
required
-15
-10
-5
0
5
10
15
20
25
30
Onset
diabetes
Years
Clinical
features
Macrovascular changes
Microvascular changes

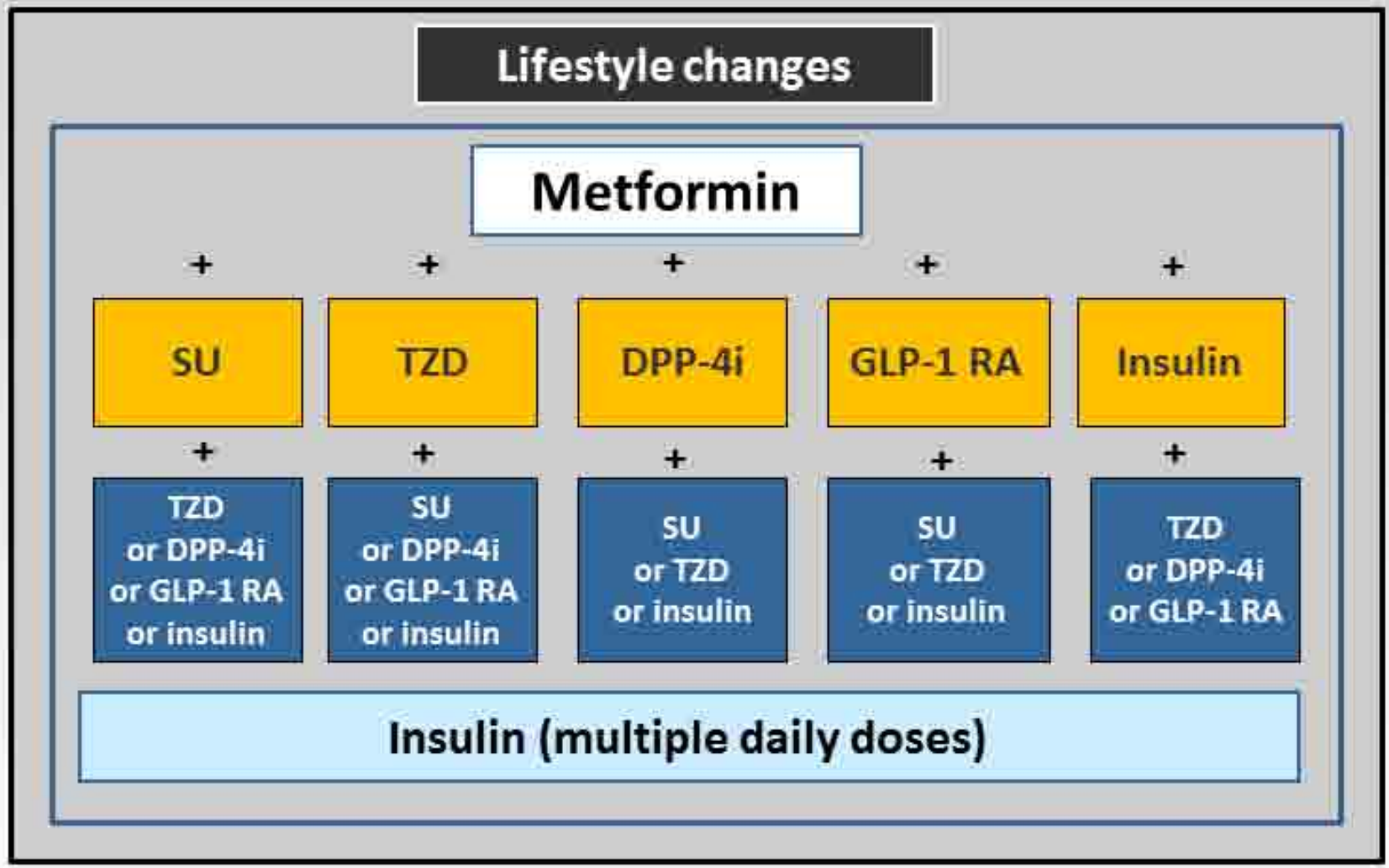


Kendall DM, Cuddihy RM, Bergenstal RM. *Am J Med.* In press.


Duct cells
Undifferentiated precursor cells
Formation of new islet
Transdifferentiation
Beta cell mass ⬇
Beta cell mass ⬇⬇
Alpha cell mass↑
Alpha cell
Beta cell
Beta cell replication↑
Beta cell neogenesis↑
Beta cell hypertrophy↑
Beta cell apoptosis↑
Beta cell senescence↑
Beta cell in hypertrophy
Beta cell in senescence
[Young and Small Islets]
Insulin demand⬆
Alpha cell expansion
Alpha cell expansion
Amyloid plaque↑
Fibrosis↑
[Old and Large Islets]
Compensatory phase
Uncompensated phase
Accelerating phase
Beta cell mass
Neogenesis
Replication
Hypertrophy
Apoptosis
Alpha cell mass


GLP-1
AC
GLP-1R
cAMP
β-arrestin 1
C-Src
EGFR
PKA
Epac 2A
ERK1/2-
p90RSK
PI3-K
Mek1/2
CREB
β-cat
Rap1
AKT/PKB
ERK1/2
IRS-2
mTOR
Foxo1
Cat/TCF
Bad
S6K1
PDX-1
Cyclin D1
Proliferation
Differentiation
Insulin Secretion
Anti-apoptosis

ADA/EASD Position Statement on the Management of Hyperglycemia in T2DM: General Recommendations



AACE/ACE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM

2016

TASK FORCE

Alan J. Garber, MD, PhD, FACE, *Chair*

Martin J. Abrahamson, MD
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Guillermo Umpierrez, MD, FACP, FACE

GLYCEMIC CONTROL ALGORITHM

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

MONOTHERAPY*

- ✓ Metformin
- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥ 7.5%

DUAL THERAPY*

MET or other 1st-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ! Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*

MET or other 1st-line agent + 2nd-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ! TZD
- ! Basal insulin
- ✓ DPP-4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

Entry A1C > 9.0%

SYMPTOMS

NO	YES
DUAL Therapy OR TRIPLE Therapy	INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN

Refer to Insulin Algorithm

LEGEND

- ✓ Few adverse events and/or possible benefits
- ! Use with caution

* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation

PROGRESSION OF DISEASE

ALGORITHM FOR ADDING/INTENSIFYING INSULIN

START BASAL (Long-Acting Insulin)

A1C < 8%

TDD 0.1–0.2 U/kg

A1C > 8%

TDD 0.2–0.3 U/kg

Insulin titration every 2–3 days to reach glycemic goal:

- Fixed regimen: Increase TDD by 2 U
- Adjustable regimen:
  - **FBG** > 180 mg/dL: add 20% of TDD
  - **FBG** 140–180 mg/dL: add 10% of TDD
  - **FBG** 110–139 mg/dL: add 1 unit
- If hypoglycemia, reduce TDD by:
  - **BG** < 70 mg/dL: 10% – 20%
  - **BG** < 40 mg/dL: 20% – 40%

Consider discontinuing or reducing sulfonylurea after starting basal insulin (basal analogs preferred to NPH)

***Glycemic Goal:**

- <7% for most patients with T2D; fasting and premeal BG < 110 mg/dL; absence of hypoglycemia
- A1C and FBG targets may be adjusted based on patient's age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk

Glycemic Control Not at Goal*

INTENSIFY (Prandial Control)

Add GLP-1 RA

Or SGLT-2i
Or DPP-4i

Add Prandial Insulin

Basal Plus 1, Plus 2, Plus 3

- Begin prandial insulin before largest meal
- If not at goal, progress to injections before 2 or 3 meals

- Start: 10% of basal dose or 5 units

Basal Bolus

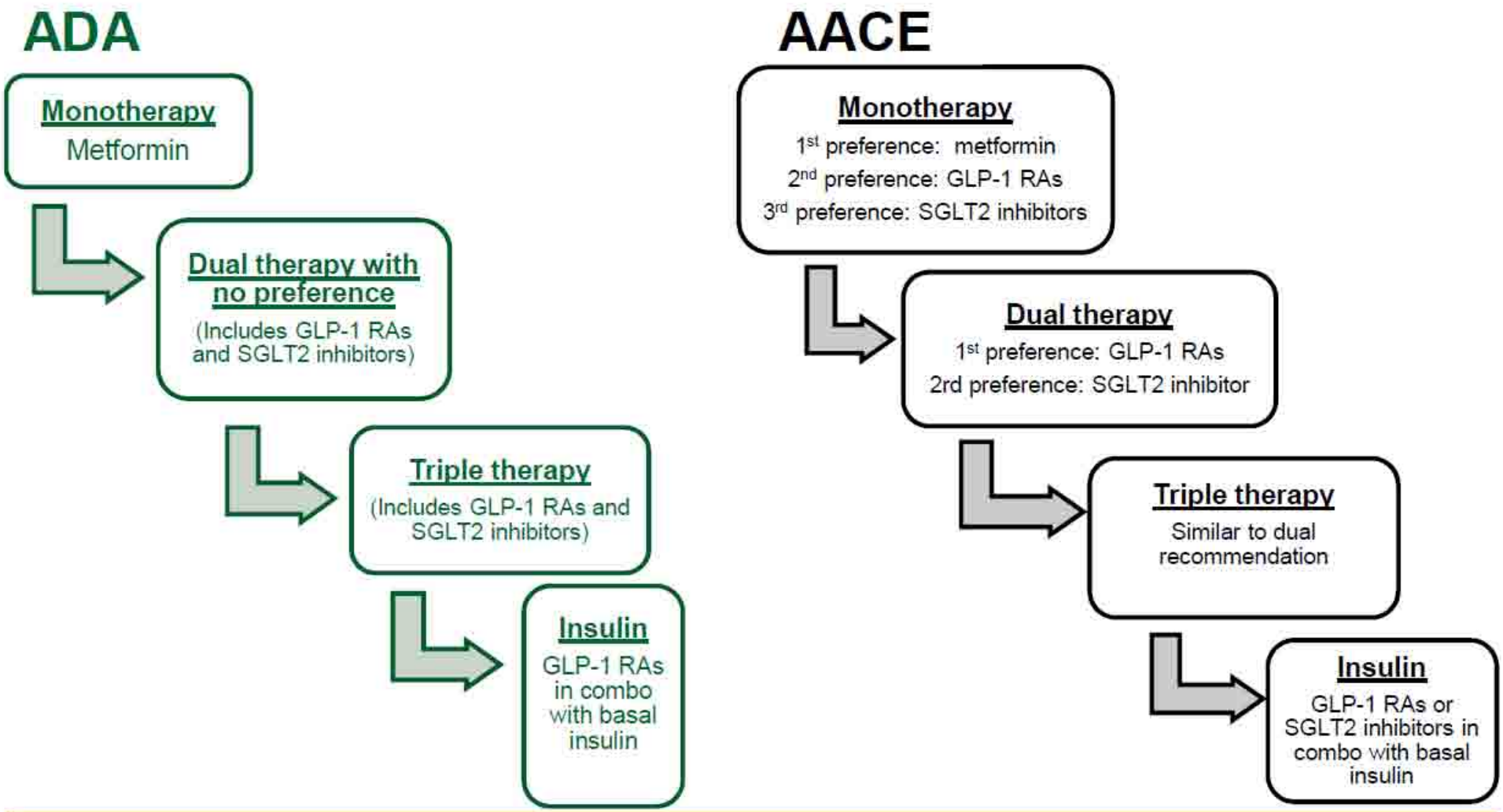
- Begin prandial insulin before each meal
- 50% Basal / 50% Prandial TDD 0.3–0.5 U/kg

- Start: 50% of TDD in three doses before meals

Insulin titration every 2–3 days to reach glycemic goal:

- Increase prandial dose by 10% or 1-2 units if 2-h postprandial or next premeal glucose consistently > 140 mg/dL
- If hypoglycemia, reduce TDD basal and/or prandial insulin by:
  - BG consistently < 70 mg/dL: 10% - 20%
  - Severe hypoglycemia (requiring assistance from another person) or BG < 40 mg/dL: 20% - 40%

Comparison of 2015 ADA & AACE/ACE Medication Recommendations for Type 2 DM (GLP-1 RAs and SGLT2 Inhibitors Place in Therapy)



AACE = American Association of Clinical Endocrinologists
ACE = American College of Endocrinology

Diabetes Care. 2015: 38:140-149
*Endocr Pract.*2015;21:438-447.

GIT
↓Gastric emptying
↑Acid secretion
↓GI motility

Brain
↓Apetite
↑Satiety
↑Energy expenditure

Heart
↓Blood pressure
↑Heart rate
↑Myocardial contractility
↑Cardioprotection

GLP-1
or
GLP-1R AGONISTS

Pancreas
↑Insulin secretion
↓Glucagon secretion
↑Insulin biosynthesis
↑ß-cell survival
↑ß-cell proliferation

↑Insulin sensitivity

Kidney
↑Natriuresis

Liver
↓Hepatic glucose production

Adipose tissue
↑Lyposis
↑FFA synthesis
↑Glucose uptake

Muscle
↑Glycogen synthesis
↑Glucose oxidation

Effetti degli Inibitori del DPP-4 in pazienti con DM2

Prevengono la degradazione del GLP-1 [1,2]
Migliorano la secrezione insulinica [1,2]
Riducono i livelli di glucagone [1,2]
Riducono la glicemia post-prandiale [2,3]
Riducono la glicemia a digiuno [4,5]
Riducono l'HbA1c [4,5]

- **Non ritardano lo svuotamento gastrico** [2]
- **Sono neutri sul peso** [5,6]

1. Herman GA, et al. J Clin Endocrinol Metab. 2006; 91:4612-4619; 2. Vella A, et al. Diabetes. 2007;56:1475-1480; 3. Aschner P, et al. Diabetes Care. 2006;29:2632-2637; 4. Pi-Sunyer FX, et al. Diabetes Res Clin Pract. 2007;76:132-138; 5. Zerilli T and Pyon EY. Clin Ther. 2007;29(12):2614-2634; 6. Bolli G, et al. Diabetes Obes Metab. 2008;10:82-90.

DPP-4 Inhibitors

- Mechanism of action[a]
  - Inhibits DPP-4 activity, thus increasing postprandial GLP-1 and GIP concentrations
- Physiologic action[a]
  - Increase insulin secretion
  - Decrease glucagon secretion
- Modest glucose-lowering effect[a]
- HbA_{1c} reduction by 0.5% to 0.9%[a]
- Weight-neutral[a]
- Efficacy: higher potency when combined with metformin[b]
- No GI adverse effects[b]
- Dosing adjustments for renal dysfunction EXCEPT linagliptin[b]

a. Garber AJ, et al. *Endocr Pract*. 2013;19:1-48.[3]
b. Deacon CF, Holst JJ. *Expert Opin Pharmacother*. 2013;14:2047-2058.[24]

Journal of Diabetes

REVIEW ARTICLE

Dipeptidyl peptidase-4 inhibitors: Multitarget drugs, not only antidiabetes drugs

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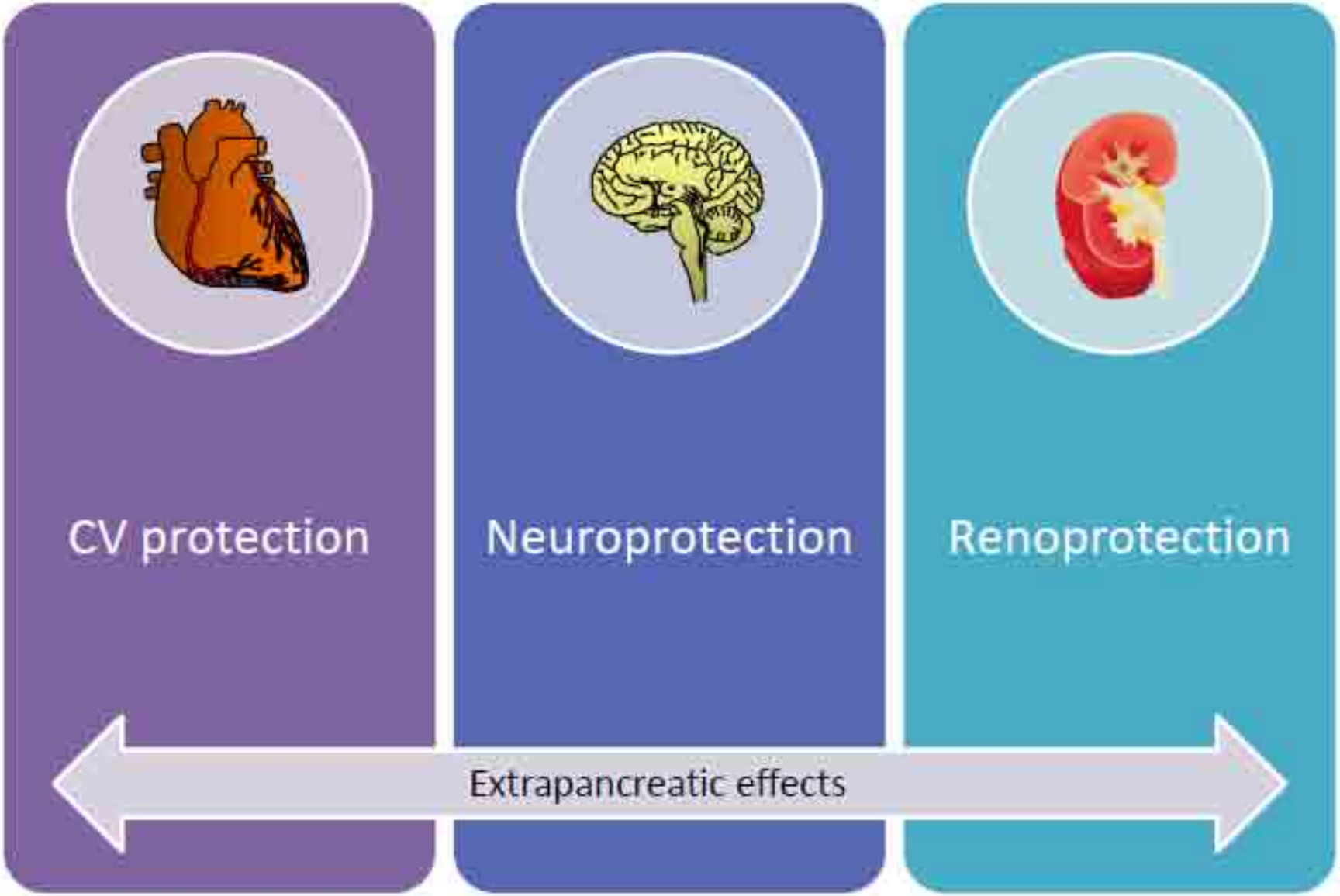
doi: 10.1111/1753-0407.12063

Abstract

Dipeptidyl peptidase (DPP)-4 inhibitors are a new class of antidiabetic agents that reduce blood glucose by preventing the degradation of the endogenous incretin hormones glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide. Protection by DPP-4 inhibitors of β-cell function has been demonstrated in patients with type 2 diabetes. Because DPP-4 is an enzyme widely expressed in humans, DPP-4 inhibitors are speculated to be multitarget agents. However, other potential therapeutic benefits of DPP-4 inhibitors remain unknown. Recently, some therapeutic effects of DPP-4 inhibitors, such as immune regulation, cardiovascular protection, and anti-inflammatory effects, have been observed. This article provides a systematic and comprehensive review of current research into the newly found effects and mechanism of action of DPP-4 inhibitors in a therapeutic context.

Keywords: anti-inflammatory, cardiovascular protection, dipeptidyl peptidase-4 inhibitors, immunomodulatory.

What is there beyond glycemic control?



Physiological Properties and Clinical Implications

DPPIV is highly expressed on endothelial and epithelial cells, and lymphocytes.[8-10] It is also present in plasma in its soluble form.[11] DPPIV is involved in the regulation of several important physiological processes.[12-14]

- Immune system
- Inflammation
- CNS
- Endocrine functions
- Bone marrow mobilization
- Cancer growth
- Cell adhesion
- Glucose hemostasis
- Sepsis/severe infection

8. Hegan, M., *et al.*, *Adv. Exp. Med. Biol.*, **421**, 109-116 (1997).
9. De Meester, *et al.*, *Immunol. Today*, **20**, 367-373 (1999).
10. Kahne, T., *et al.*, Int. *J. Mol. Med.*, **4**, 3-15 (1999).
11. Durinx, C., *et al.*, *Eur. J. Biochem.*, 267, 5608-5613 (2000).
12. Gorrell, M.D., *Clinical Science*, **108**, 277-292 (2005).
13. Aertgeets, K., *et al.*, *Protein Sci.*, **13**, 412-421 (2004).
14. Busek, P., *et al.*, Int. *J. Biochem. Cell Bio.*, **36**, 408-421 (2004).

Mannucci , E. et al

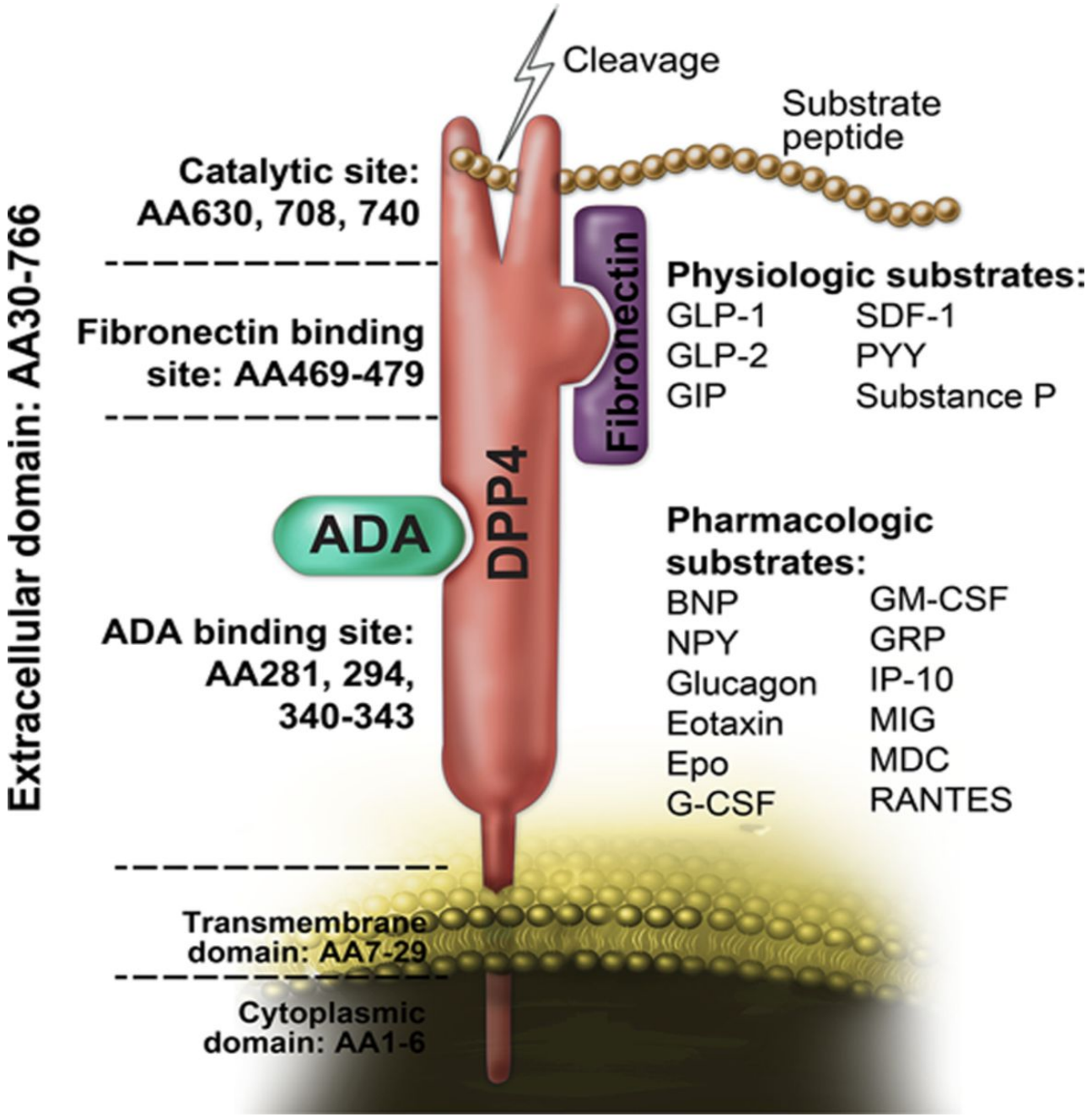
Hyperglycaemia increases Dipeptidyl Peptidase IV activity in diabetes mellitus

CONCLUSIONS/INTERPRETATION:

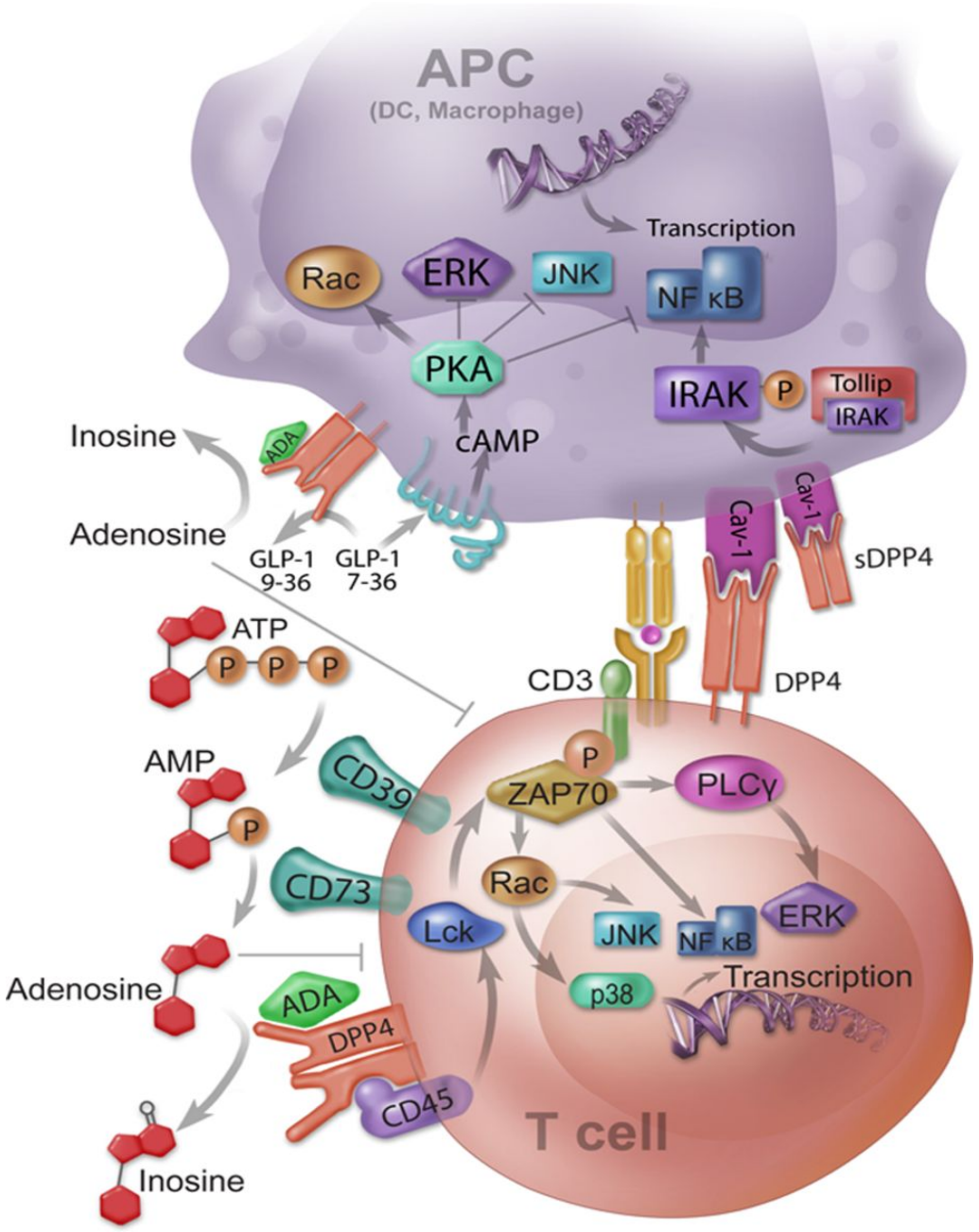
Chronic hyperglycaemia induces a significant increase in DPP-IV activity in type 1 and type 2 diabetes. This phenomenon could contribute to the reduction in circulating active glucagon-like peptide-1 and to the consequent postprandial hyperglycaemia in type 2 diabetic patients with poor metabolic control .

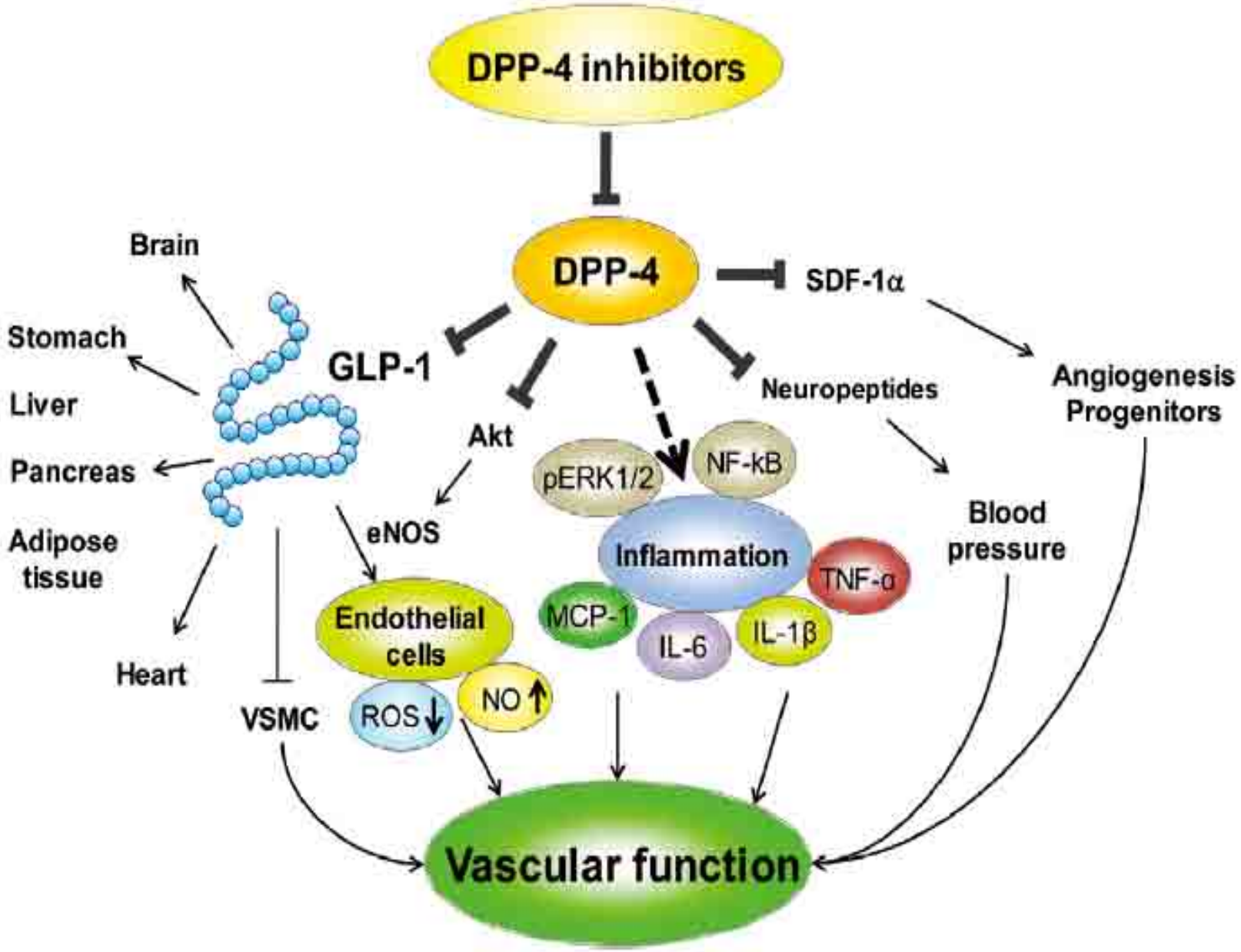
Diabetologia 48: 1168–1172, 2005

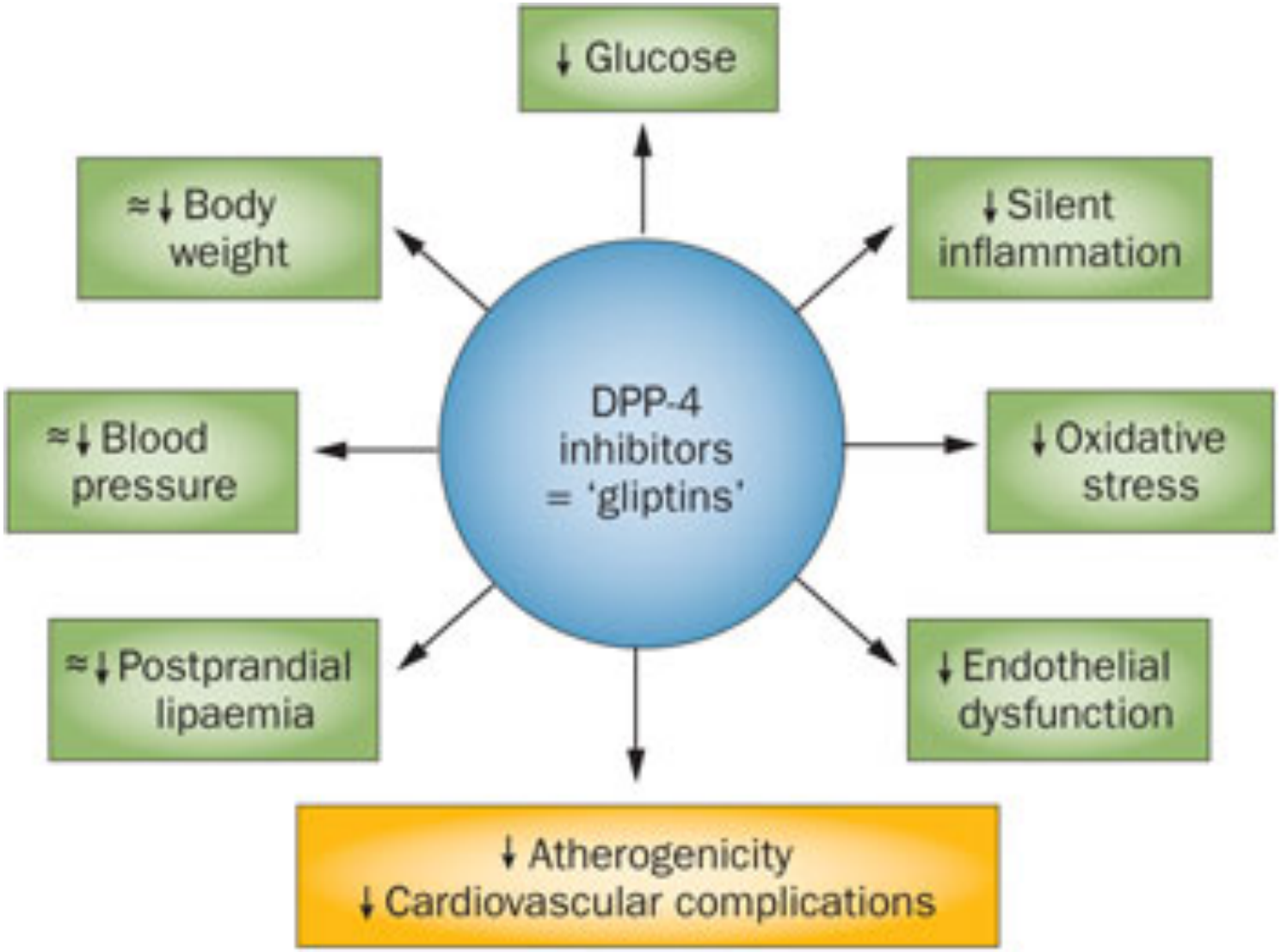
Dipeptidyl peptidase-4 (DPP4) functions and structure



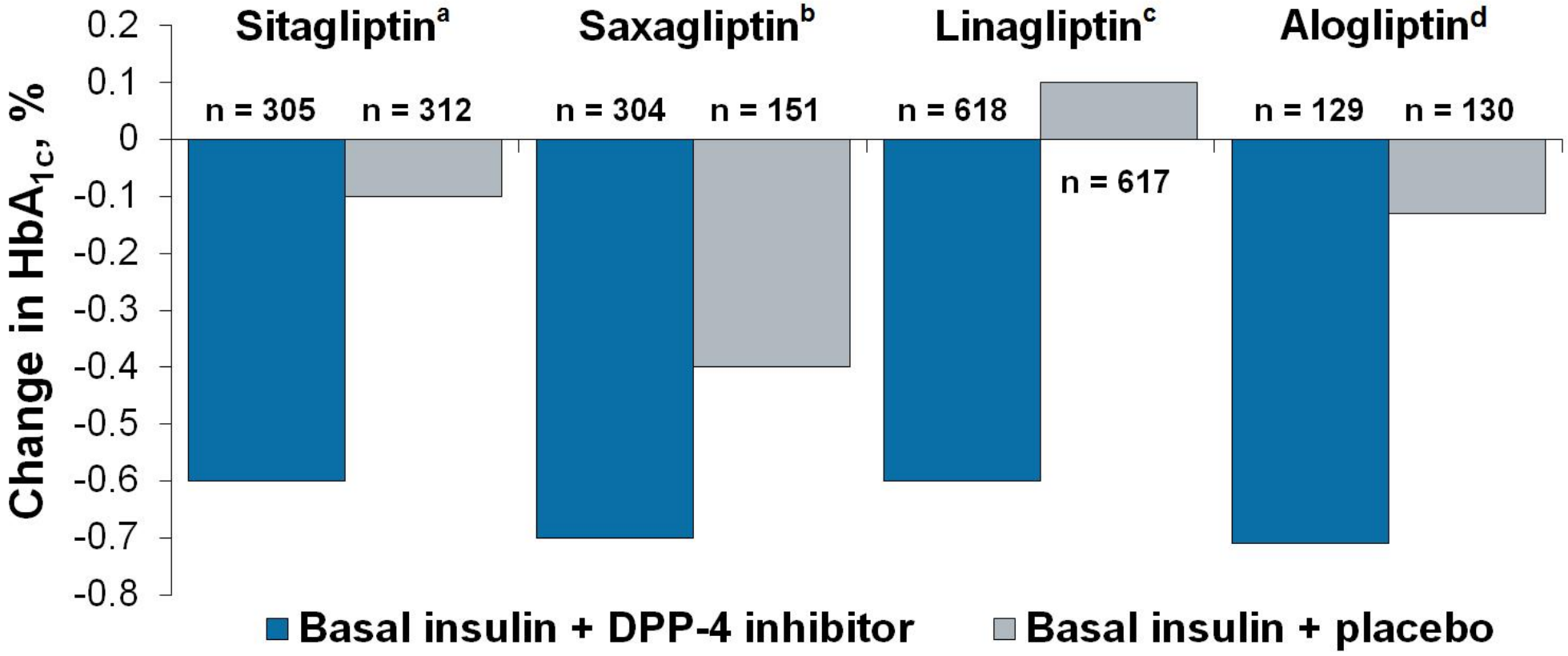
Mechanisms by which dipeptidyl peptidase-4 (DPP4) modulates immune response of relevance to cardiovascular disease



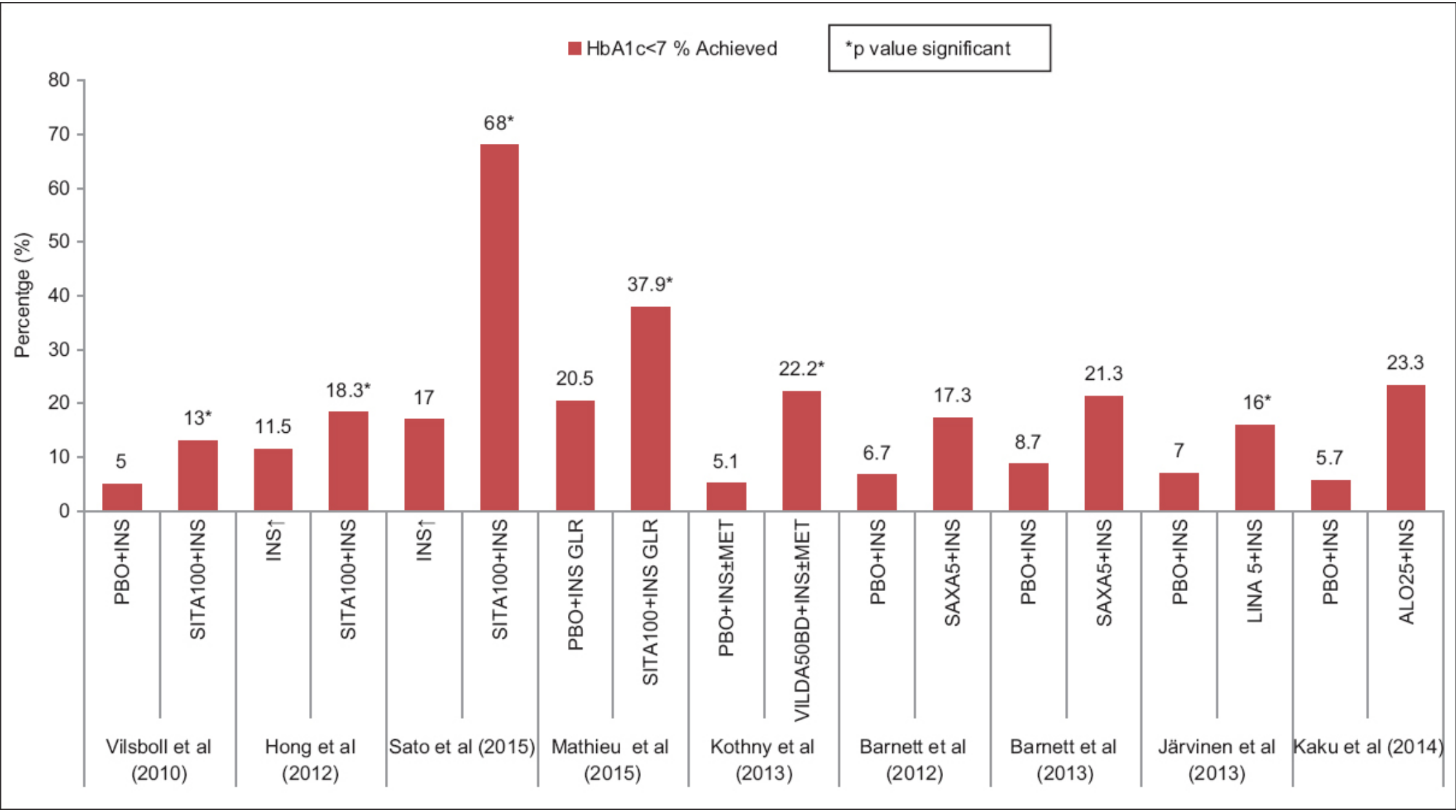

DPP-4 inhibitors
DPP-4
SDF-1α
Brain
Stomach
Liver
Pancreas
Adipose tissue
Heart
GLP-1
Akt
eNOS
Endothelial cells
NO
ROS
VSMC
pERK1/2
NF-kB
Inflammation
TNF-α
MCP-1
IL-6
IL-1β
Neuropeptides
Blood pressure
Angiogenesis Progenitors
Vascular function


↓ Glucose
≈↓ Body weight
↓ Silent inflammation
DPP-4 inhibitors = 'gliptins'
≈↓ Blood pressure
↓ Oxidative stress
≈↓ Postprandial lipaemia
↓ Endothelial dysfunction
↓ Atherogenicity
↓ Cardiovascular complications

DPP-4 Inhibitors as Add-on Therapy to Basal Insulin (With or Without Oral Agents)



a. Vilsbøll T, et al. *Diabetes Obes Metab*. 2010;12:167-177[25]; b. Barnett AH, et al. *Curr Med Res Opin*. 2012;28:513-523[26]; c. TRADJENTA® PI 2013[27]; d. Rosenstock J, et al. *Diabetes Obes Metab*. 2009;11:1145-1152.[28]


HbA1c<7 % Achieved
*p value significant
Percentge (%)
80
70
60
50
40
30
20
10
0
5
13*
11.5
18.3*
17
68*
20.5
37.9*
5.1
22.2*
6.7
17.3
8.7
21.3
7
16*
5.7
23.3
PBO+INS
SITA100+INS
INS↑
SITA100+INS
INS↑
SITA100+INS
PBO+INS GLR
SITA100+INS GLR
PBO+INS±MET
VILDA50BD+INS±MET
PBO+INS
SAXA5+INS
PBO+INS
SAXA5+INS
PBO+INS
LINA 5+INS
PBO+INS
ALO25+INS
Vilsboll et al (2010)
Hong et al (2012)
Sato et al (2015)
Mathieu et al (2015)
Kothny et al (2013)
Barnett et al (2012)
Barnett et al (2013)
Järvinen et al (2013)
Kaku et al (2014)

Rationale for Combination of Basal Insulin plus a GLP-1 Agonist

Basal insulin analogues

- Suppress hepatic glucose production
- Control nocturnal and FPG
- Improve β-cell function
- Weight *re*-gain ~1–3 kg
- Less hypoglycemia risk vs NPH
- Simple titration algorithms available
- Avoid clinical inertia

GLP-1 receptor agonists

- Differential impacts on both FPG,PPG
- Improve insulin release and sensitivity to insulin
- Decrease gastric emptying
- No independent increase in hypoglycaemia
- Weight loss ~1–3 kg
- Simple to use

Complementary and potentially synergistic effects

Optimise HbA_{1c} control, safely

World Journal of Diabetes

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.4239/wjd.v5.i1.40

World J Diabetes 2014 February 15; 5(1): 40-51
ISSN 1948-9358 (online)

REVIEW

Insulin plus incretin: A glucose-lowering strategy for type 2-diabetes

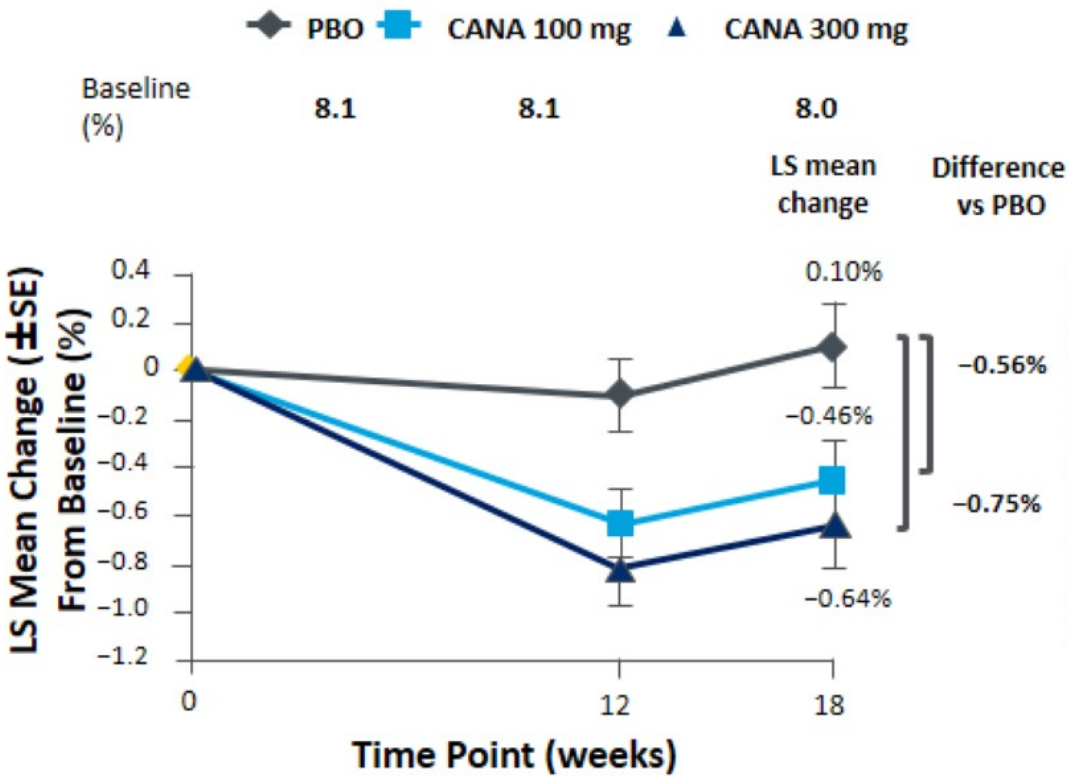
Bo Ahrén

Bo Ahrén, Department of Clinical Sciences Lund, Lund University, 221 84 Lund, Sweden
Author contributions: Ahrén B designed and wrote the article.
Correspondence to: Dr. Bo Ahrén, Professor, Department of Clinical Sciences Lund, Lund University, B11 BMC, 221 84 Lund, Sweden. bo.ahren@med.lu.se

Core tip: Incretin therapy (glucagon-like peptide-1 receptor agonists or dipeptidyl peptidase-4 inhibitors) combined with insulin therapy is a glucose-lowering strategy in type 2 diabetes. The combination allows a complementary mode of mechanistic action and, as demonstrated in several clinical trials, is glucose-lowering in association with limited risk for hypoglycemia and weight gain. The combination is a promising strategy in patients in whom metformin with either incretin therapy or basal insulin is insufficient for adequate glycemic control. This article reviews the background and clinical studies on this combination.

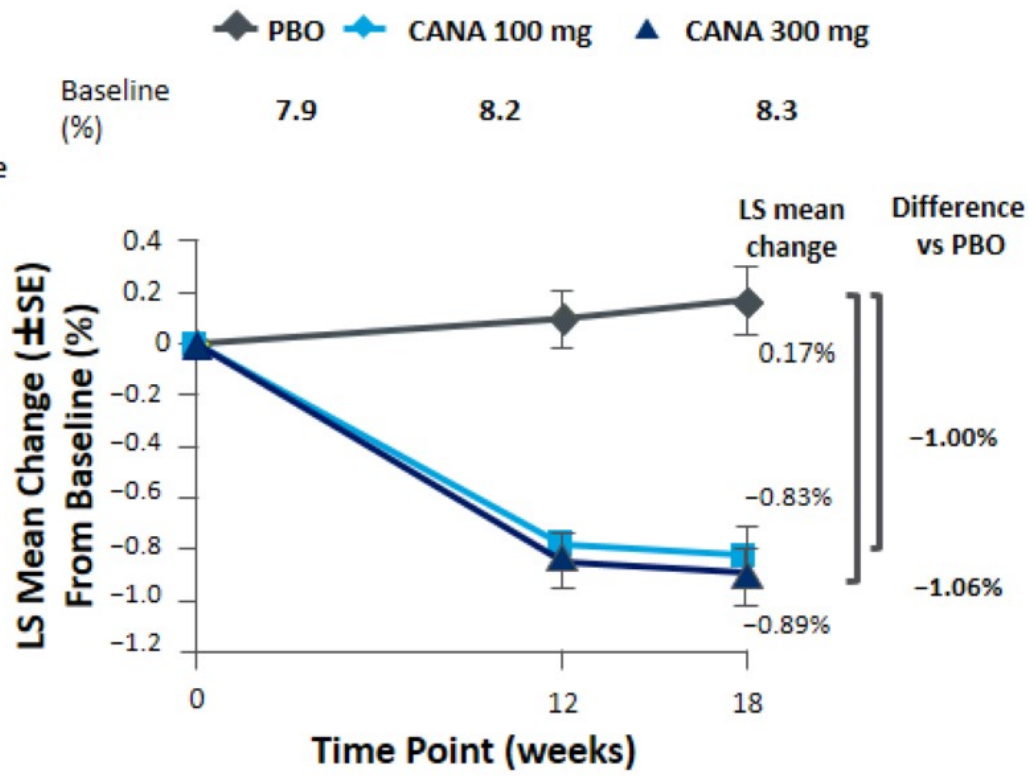
Canagliflozin Add-on to DPP-4 Inhibitors or GLP-1 RAs With or Without Other OADs in T2DM

Change in HbA1c in DPP-4 Subset



Proportion of subjects who achieved HbA1c <7.0% in DPP-4 inhibitor subset:
21.8% (CANA 100 mg), 34.3% (CANA 300 mg), and 14.6% (PBO)

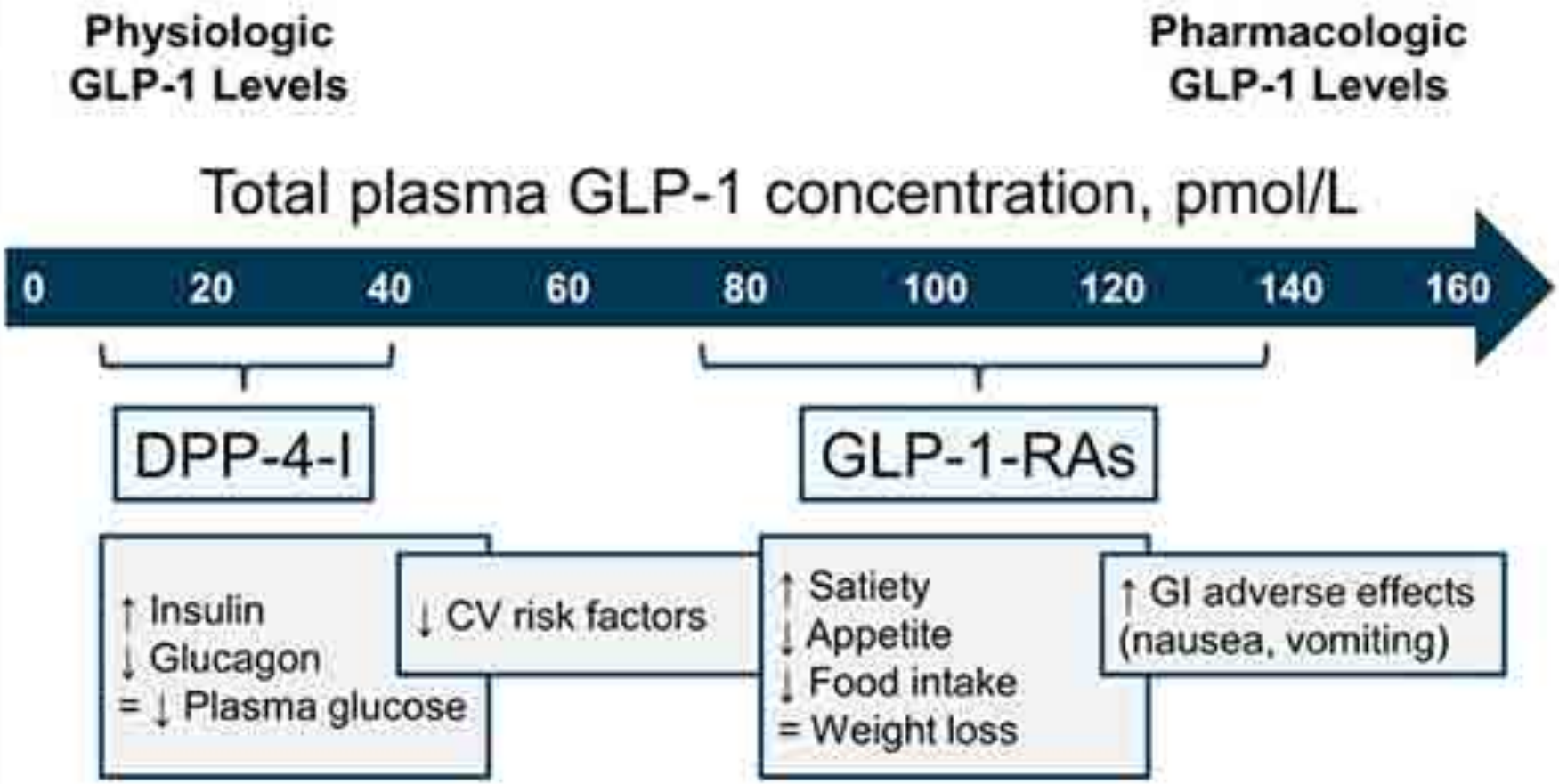
Change in HbA1c in GLP-1 RA Subset



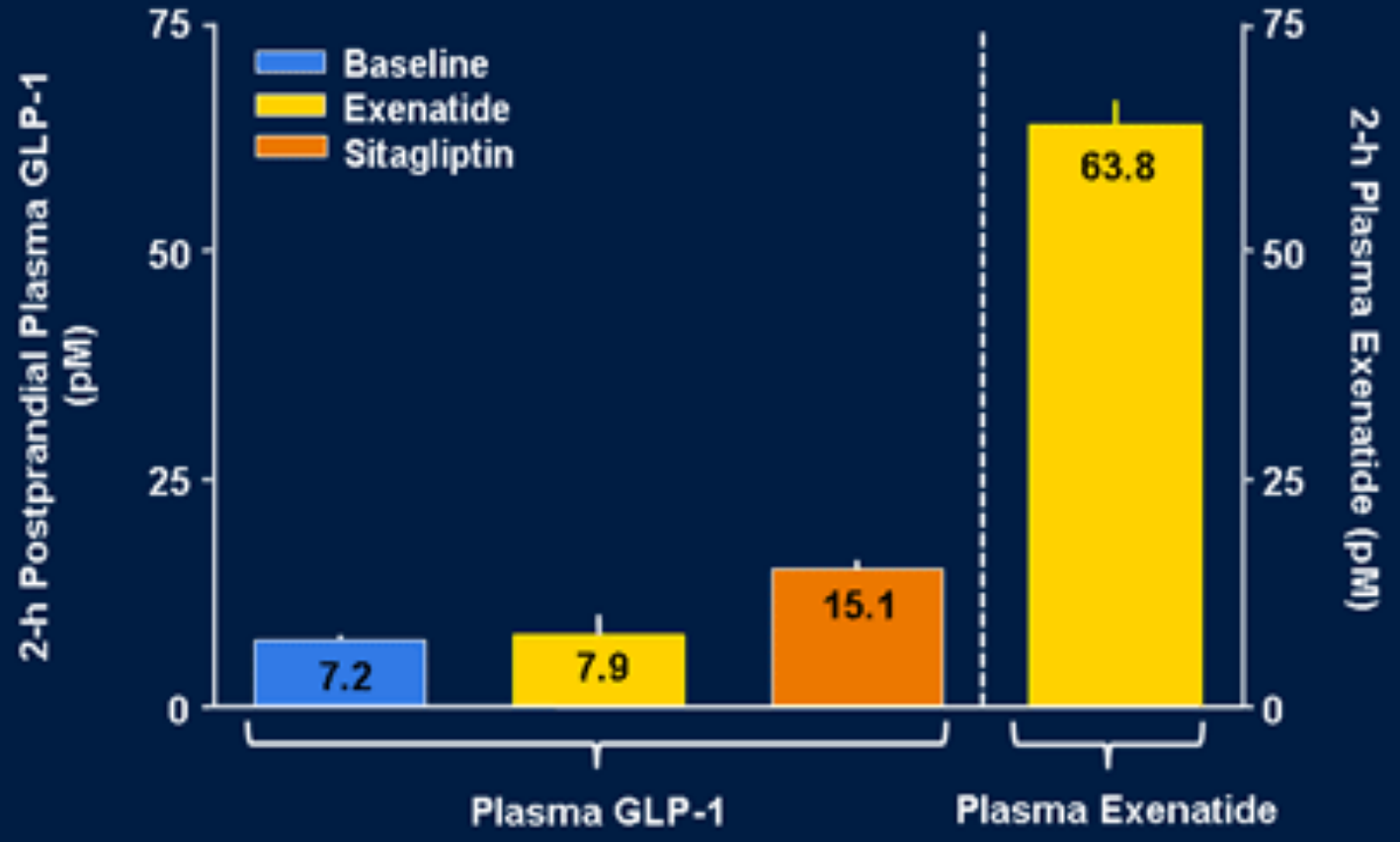
Proportion of subjects who achieved HbA1c <7.0% in GLP-1 RA subset:
29.4% (CANA 100 mg), 34.5% (CANA 300 mg), and 6.9% (PBO)

Meininger GA, et al. EASD 2013. Poster presentation.

Dose-Related Effects of GLP-1



Postprandial Plasma Levels of Exenatide Exceeded Physiologic Levels of GLP-1



Patients with T2DM; Evaluable population, n=61 for all treatment groups; Mean ± SE
2-week post-treatment concentration data

DeFronzo RA, et al. *Curr Med Res Opin.* 2008;24(10):2943-2952.

Summary of the Clinical Effects of Glucagon-like Peptide–1 (GLP-1) Receptor Agonists and Dipeptidyl Peptidase–4 (DPP-4) Inhibitors.

DPP-4 Inhibitors (sitagliptin, alogliptin, saxaglitpin, vildagliptin)	GLP-1 Receptor Agonists (exenatide, liraglutide, taspoglutide)
• HbA_{1c} reduction 0.5–1.0% • Weight neutral • Oral administration • No significant GI side effects • Low rates of hypoglycemia • Improved meal-related insulin secretion, reduced glucagon release • Can reduce dose and use in renal insufficiency	• HbA_{1c} reduction 0.6–1.5% • Significant and sustained weight loss generally observed • Injected therapy (once daily, twice daily, once weekly) • GI side effects most common (nausea, diarrhea particularly with initiation) • Low rates of hypoglycemia • Multiple mechanisms of action — ↑ Insulin secretion, ↓ glucagon release — Reduced food intake, slowing of gastric emptying — Weight loss

GI = gastrointestinal; HbA_{1c} = hemoglobin A_{1c}; ↑ = increased; ↓ = decreased.

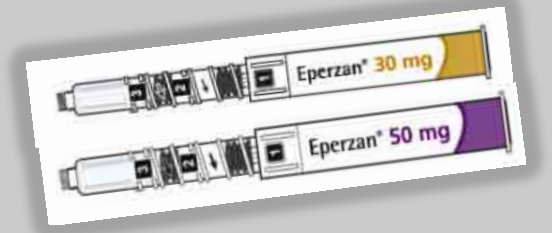
SOMMINISTRAZIONE DEL FARMACO E DISPOSITIVI

Exenatide BID

Due penne preriempite (5 µg e 10 µg)[1]
L'ago (29-31 gauge) necessita di attacco prima dell'uso[1]

Liraglutide

Una penna preriempita; ogni penna rilascia 0,6, 1,2 e 1,8 mg[2]
Un ago di ≥32 gauge necessita di attacco prima dell'uso[2]



Albiglutide

Due penne preriempite; 30 mg (penna dorata) o 50 mg (penna viola)[3]
Necessita di ricostituzione
L'ago necessita di attacco prima dell'uso[3]

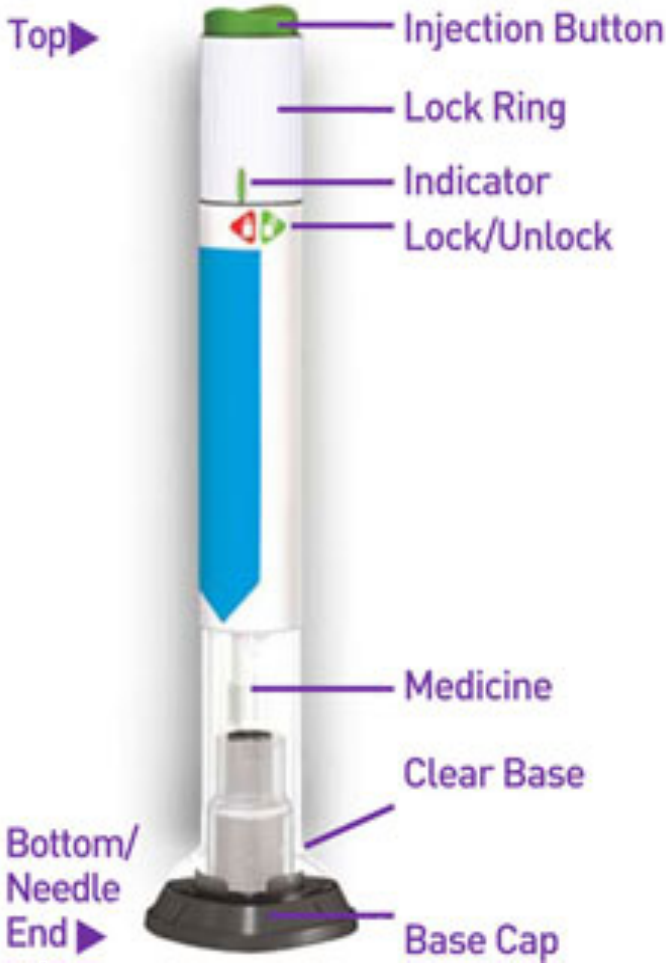
Lixisenatide

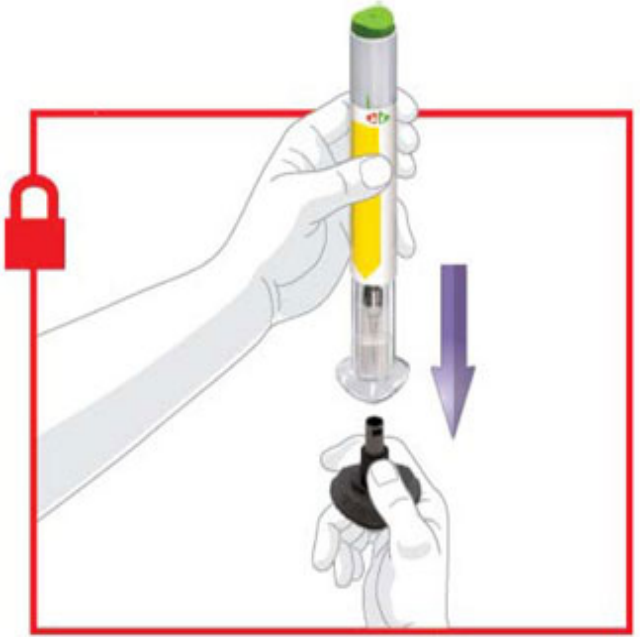
Due penne preriempite; ciascuna dose contiene 10 µg (penna verde) o 20 µg (penna viola)[4]
L'ago (29-32 gauge) necessita di attacco prima dell'uso[4]

Exenatide QW

Polvere e siringa; necessita di ricostituzione[5]
Un ago di 23 gauge necessita di attacco prima dell'uso[5]

Dulaglutide Semi-finished Syringe (SFS)





Dulaglutide Prefilled Syringe (PFS)

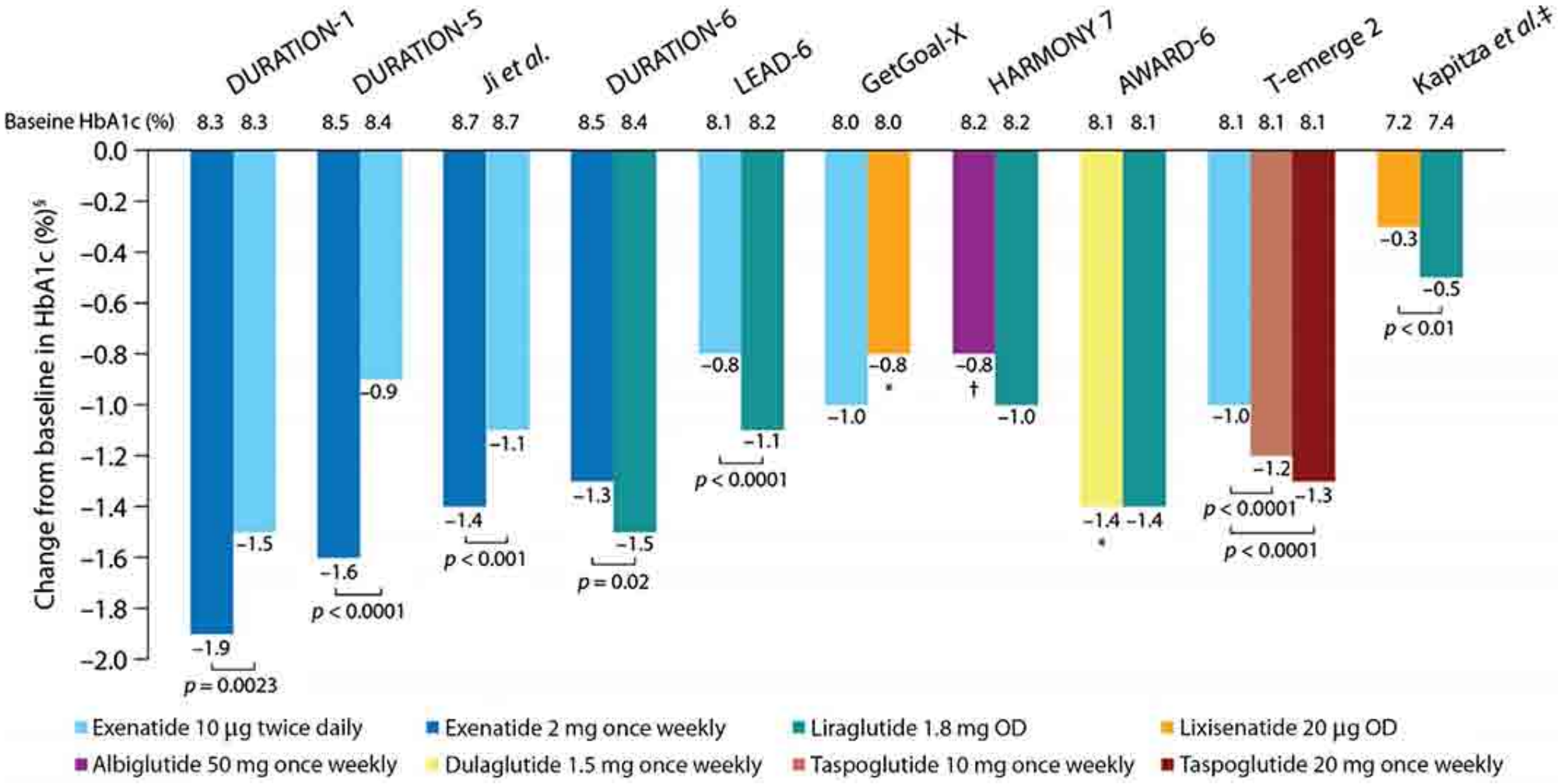
Depiction of Dulaglutide Semi-finished Syringe (SFS), Single-Use Pen (SUP) and Prefilled Syringe (PFS)

CARATTERISTICHE DELLA PENNA MONOUSO

- Pronta all'uso
- Dispositivo di piccole dimensioni
- Step per l'utilizzo: **rimuovere il cappuccio, posizionare e sbloccare, iniettare**
- Fornisce conferma dell'avvenuta somministrazione di dose
- Processo di iniezione <5 secondi
- Dopo l'iniezione, l'ago si retrae automaticamente
- Ago nascosto
- Ago di piccolo calibro

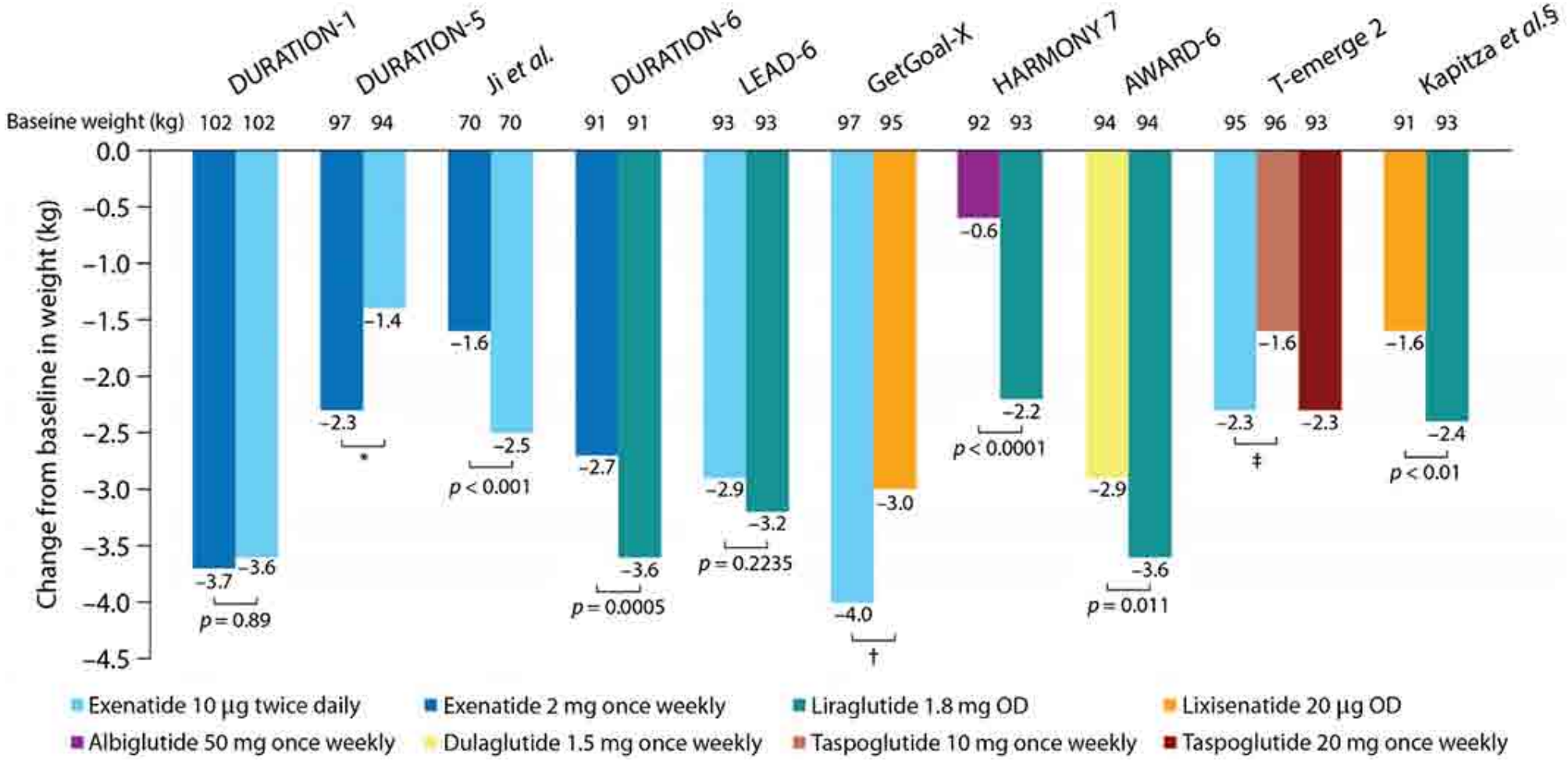
Matfin G, et al. Presentato all'American Diabetes Association 74th Scientific Sessions; 13-17 giugno, 2014 San Francisco, CA. Poster 122-LB

Review of head-to-head comparisons of glucagon-like peptide-1 receptor agonists



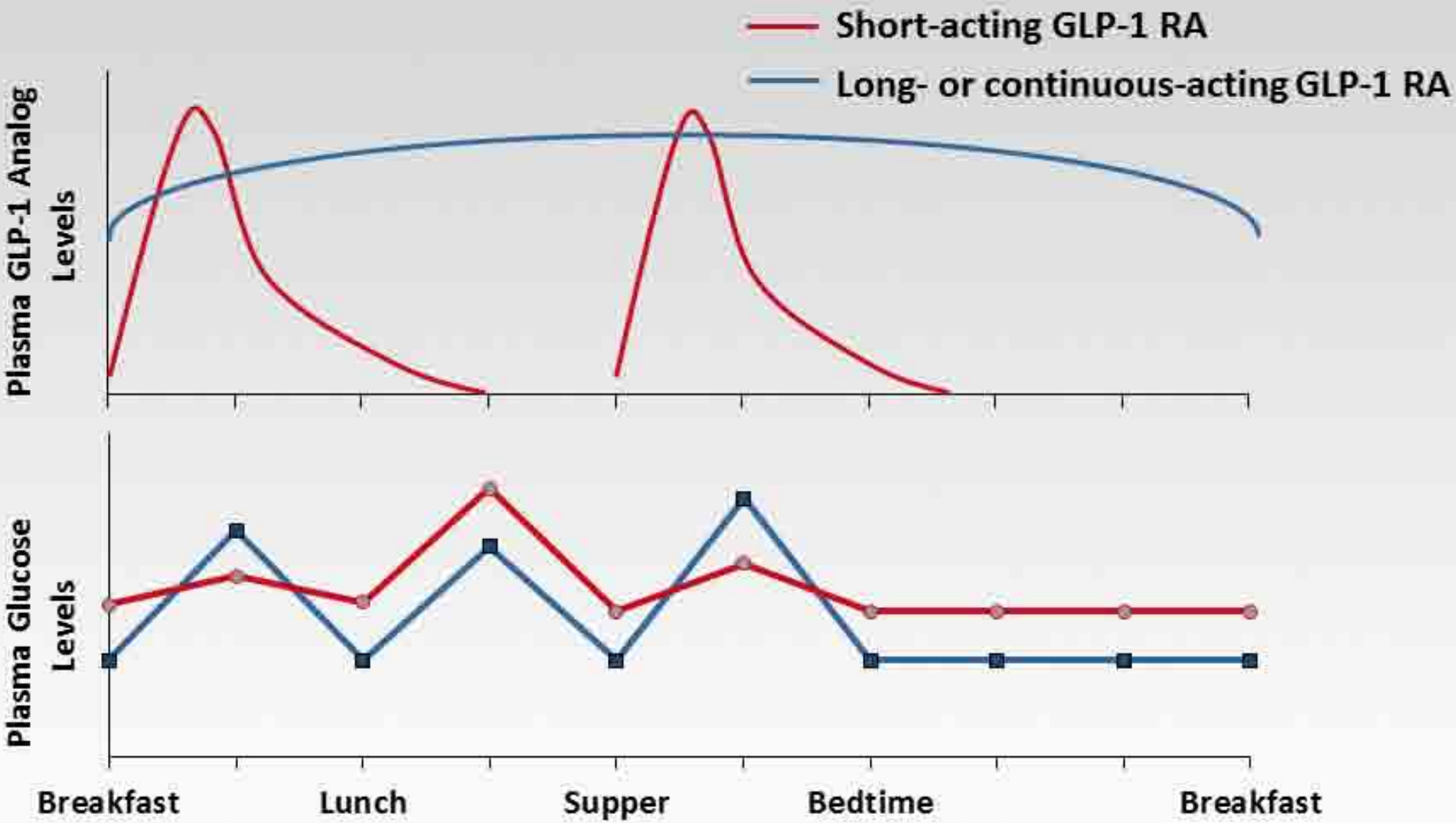
Diabetes, Obesity and Metabolism
Volume 18, Issue 4, pages 317-332, 29 DEC 2015 DOI: 10.1111/dom.12596
http://onlinelibrary.wiley.com/doi/10.1111/dom.12596/full#dom12596-fig-0002

Review of head-to-head comparisons of glucagon-like peptide-1 receptor agonists



Diabetes, Obesity and Metabolism
Volume 18, Issue 4, pages 317-332, 29 DEC 2015 DOI: 10.1111/dom.12596
http://onlinelibrary.wiley.com/doi/10.1111/dom.12596/full#dom12596-fig-0004

Differences in GLP-1 and Plasma Glucose Concentrations With Short- vs Continuous-Acting GLP-1 RAs



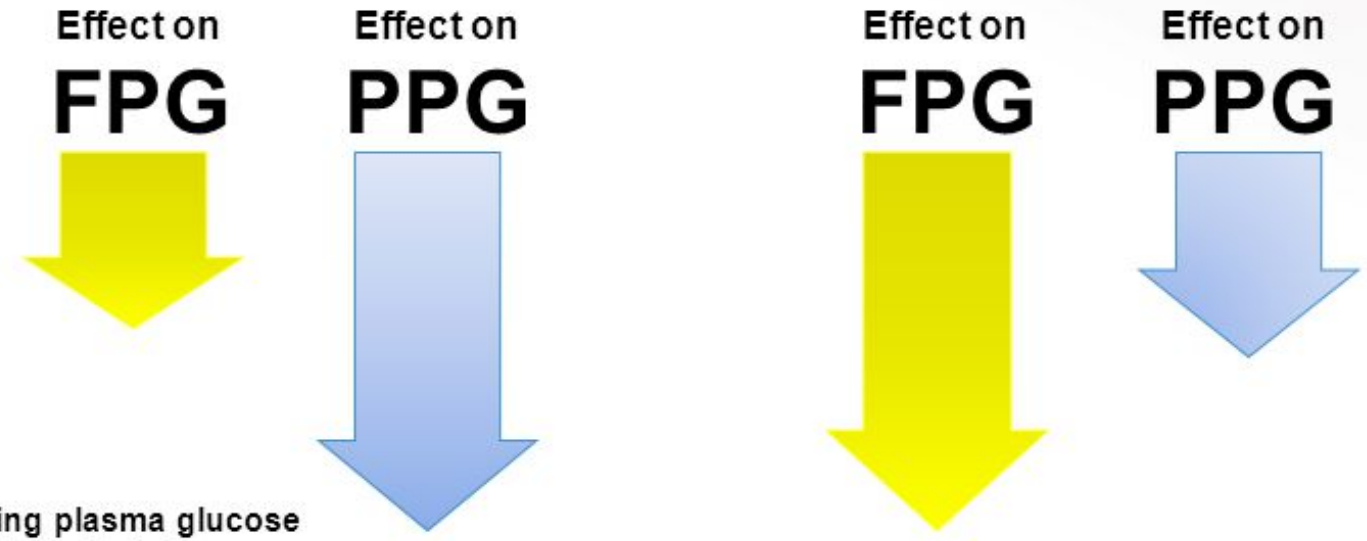
Choice of GLP-1 receptor agonist: short acting versus long acting

The pharmacological profile and half-life of a GLP-1 receptor agonist influences its effects on postprandial and basal (fasting) glycaemia

SHORT ACTING
GLP-1 receptor agonists
eg. Lixisenatide OD, Exenatide BD

or

LONG ACTING
GLP-1 receptor agonists
eg. Liraglutide OD, Exenatide QW



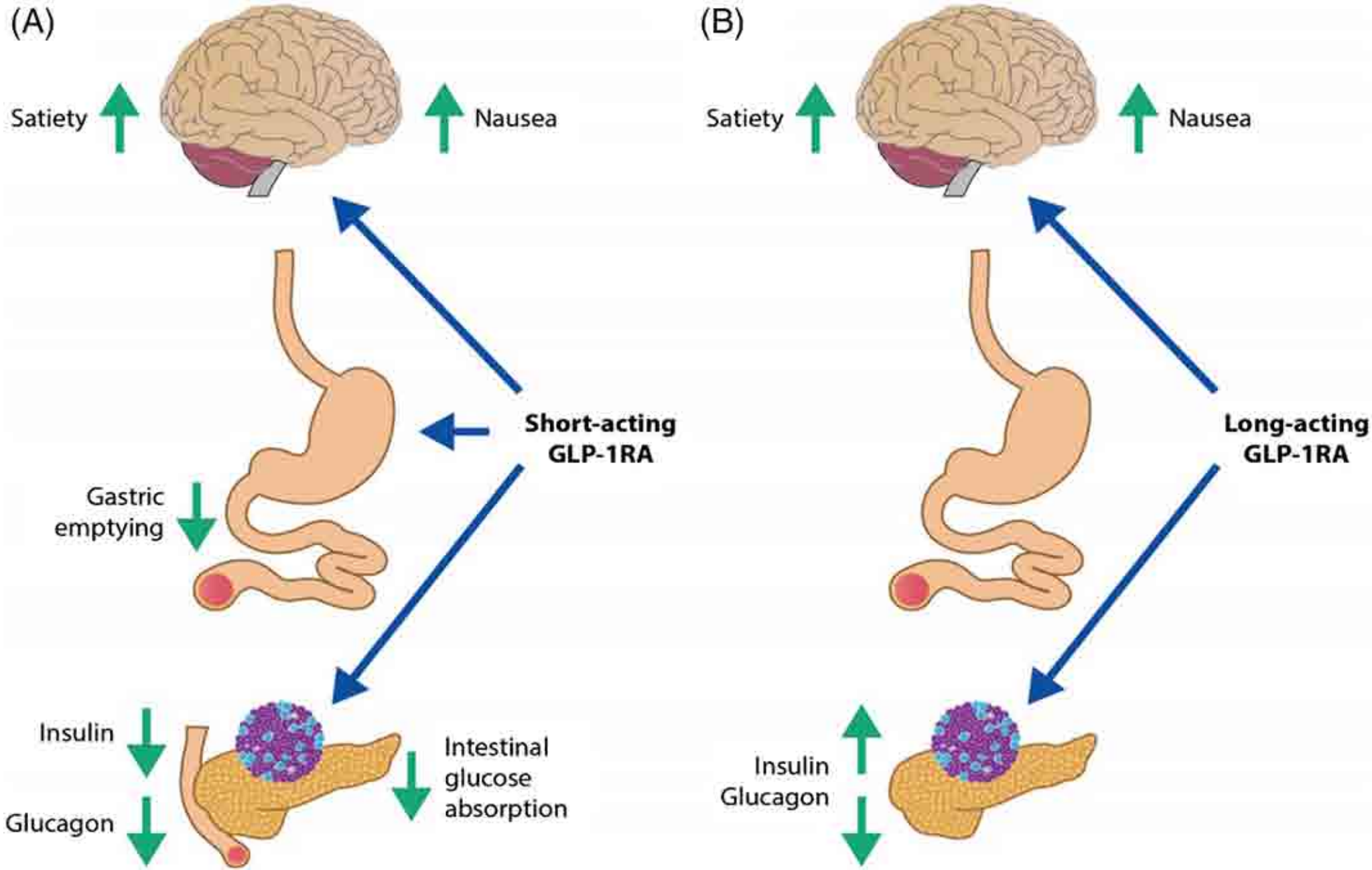
FPG = fasting plasma glucose
PPG = postprandial glucose

Fineman MS et al. Diabetes Obes Metab 2012;14:675-88

Tabella I. Elementi caratterizzanti exenatide O.W. rispetto il b.i.d. (da Madsbad et al., 2011, mod.).

Riduzione dell'HbA_{1c}: maggiore
Riduzione di FPG: maggiore
Riduzione di PPG: minore
Aumento dell'insulina a digiuno: maggiore
Diminuzione di glucagone a digiuno: maggiore
Perdita di peso: equivalente
Effetto sullo svuotamento gastrico: diminuito
Nausea: diminuita
Ipoglicemia associata: diminuita

Madsbad S, Kielgast U, Asmar M, et al. An overview of once-weekly glucagon-like peptide-1 receptor agonists--available efficacy and safety data and perspectives for the future. Diabetes Obes Metab 2011;13:394-407.


(A)
Satiety
Nausea
Short-acting
GLP-1RA
Gastric
emptying
Insulin
Glucagon
Intestinal
glucose
absorption
(B)
Satiety
Nausea
Long-acting
GLP-1RA
Insulin
Glucagon

MAYO CLINIC

Five-Year Efficacy and Safety Data of Exenatide Once Weekly: Long-term Results From the DURATION-1 Randomized Clinical Trial

Carol H. Wysham, MD; Leigh A. MacConell, PhD; David G. Maggs, MD; Ming Zhou, PhD; Peter S. Griffin, BA; and Michael E. Trautmann, MD

Abstract

Objective: To evaluate the 5-year efficacy and safety of once weekly exenatide.

Patients and Methods: The Diabetes Therapy Utilization: Researching Changes in A1C, Weight and Other Factors Through Intervention with Exenatide Once Weekly (DURATION-1) randomized clinical trial consisted of a 30-week controlled phase (2 mg of exenatide once weekly vs 10 μg of exenatide twice daily) with an open-ended uncontrolled extension (once weekly exenatide only) in patients with type 2 diabetes mellitus on background glucose-lowering therapies (April 15, 2006, through February 21, 2012). At week 30, patients initially receiving 10 μg of exenatide twice daily switched to 2 mg of exenatide once weekly. Study end points included changes from baseline in hemoglobin A_{1c}, fasting plasma glucose, weight, lipids, and blood pressure. Long-term safety data included adverse events, liver and renal function, and heart rate.

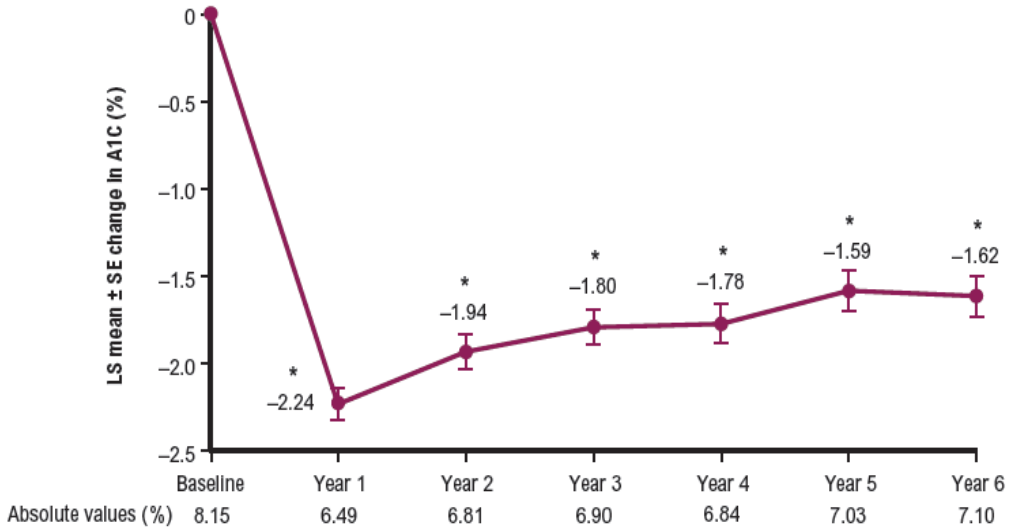
Results: Of 258 extension-phase patients, 153 (59.3%) completed 5 years of treatment. Hemoglobin A_{1c} levels were significantly and durably reduced from baseline (least-squares mean, −1.6%; 95% CI, −1.8% to −1.4%; vs −1.9% for exenatide once weekly at week 30), and 65 (43.9%) of 148 patients achieved hemoglobin A_{1c} levels of less than 7.0%. Significant improvements in fasting plasma glucose level (−28.8 mg/dL; 95% CI, −36.2 to −21.5 mg/dL), weight (−3.0 kg; 95% CI, −4.6 to −1.3 kg), lipids, and diastolic blood pressure were observed, with minimal heart rate increase. Frequencies of nausea and injection-site reactions or nodules were decreased vs the initial 30-week controlled phase. Minor hypoglycemia occurred predominantly with sulfonylurea use, and no major hypoglycemia or new safety signals were observed.

Conclusion: Long-term once weekly exenatide treatment was generally well tolerated with sustained glycemic improvement, weight reduction, and improved markers of cardiovascular risk in patients with type 2 diabetes.

Trial Registration: clinicaltrials.gov Identifier: NCT00308139

DURATION-1 Extension: Efficacy and Tolerability of Exenatide Once Weekly (QW) Over 6 Years in Patients with T2DM

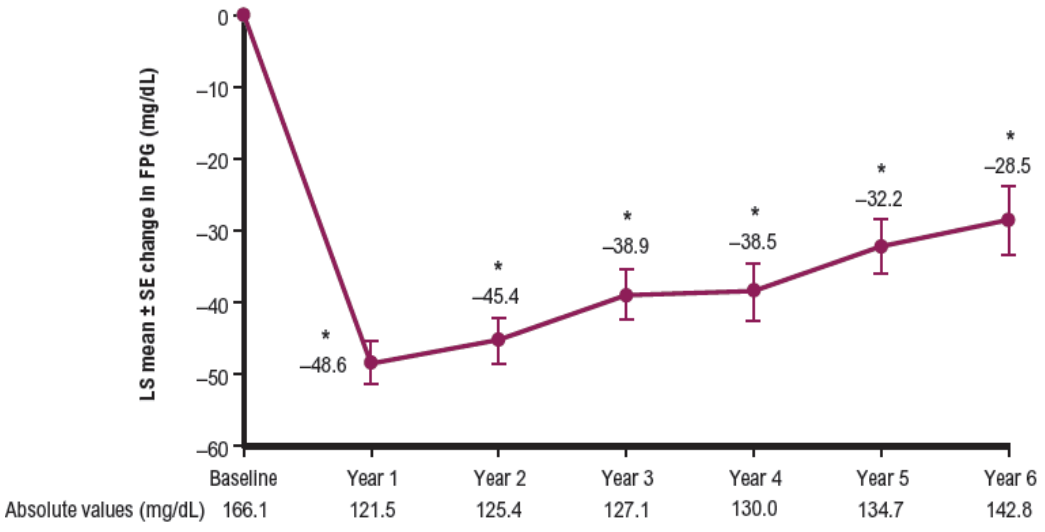
Figure 2. Change in A1C over time (LOCF) in the 6-year completer population (N=127 at all timepoints)



LOCF, last observation carried forward; LS, least squares; SE, standard error.

*P<0.05 for change from baseline.

Figure 4. Change in FPG over time (LOCF) in the 6-year completer population (N=127 at all timepoints)

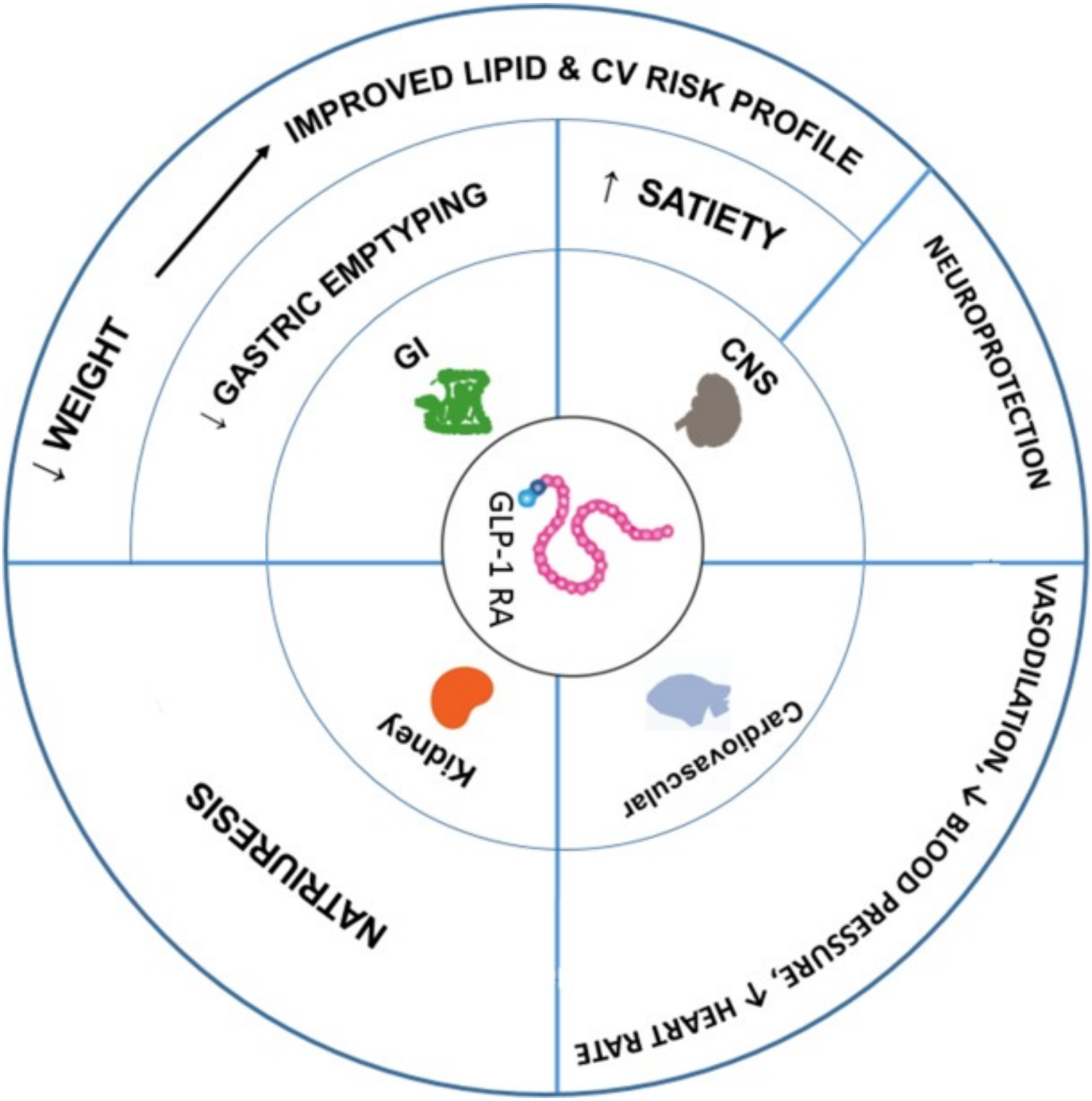


FPG, fasting plasma glucose; LOCF, last observation carried forward; LS, least squares; SE, standard error.

*P<0.05 for change from baseline.

- **Glycemic parameters (A1C and FPG) and body weight were all significantly reduced from baseline with exenatide QW over 6 years (P<0.05)**
- **Almost half of all patients achieved the ADA-recommended A1C target <7.0% at 6 years**
- **No major hypoglycemia was reported; most minor hypoglycemia occurred with concomitant sulfonylurea treatment**
- **Nausea, which was the most common adverse event in the first 30 weeks of DURATION-1, decreased over time**

Henry R, et al. ADA Scientific Sessions 2014; Sat., June 14 11:30 – 1:30PM, Poster 964-P

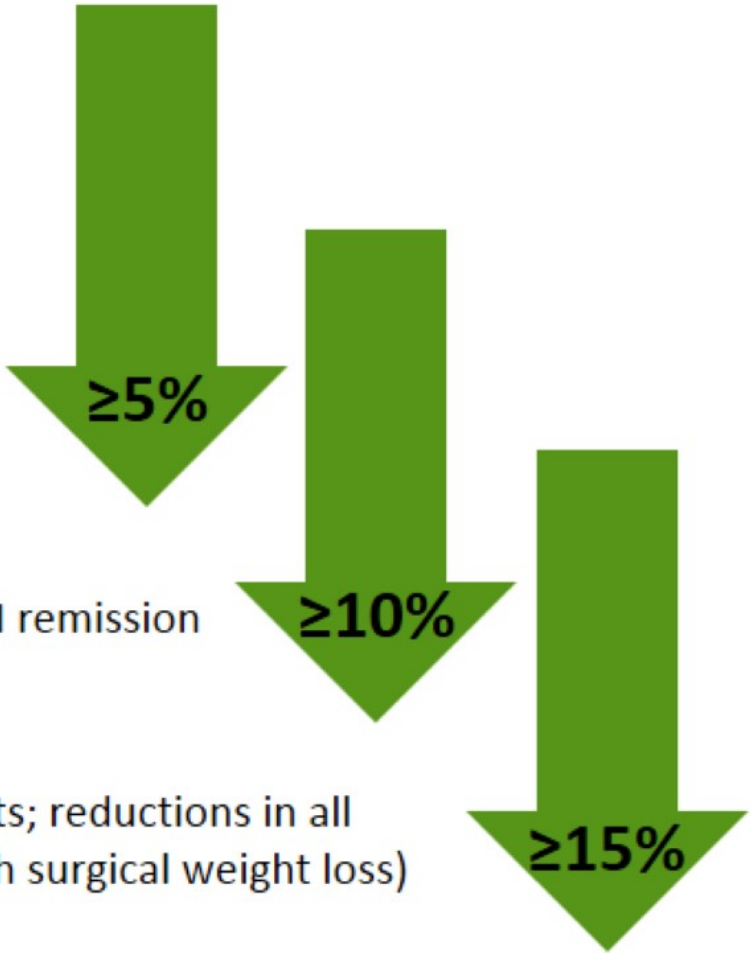

IMPROVED LIPID & CV RISK PROFILE
↓ WEIGHT
↓ GASTRIC EMPTYPING
↑ SATIETY
NEUROPROTECTION
GI
CNS
GLP-1 RA
Kidney
Cardiovascular
NATRIURESIS
VASODILATION, ↓ BLOOD PRESSURE, ↓ HEART RATE

GLP-1 Receptor Agonists: Cardiometabolic Effects

GLP-1 Agent	SBP, mm Hg	DBP, mm Hg	LDL, mg/dL	TG, mg/dL
Exenatide twice daily	↓ 0 – 9.4	↓ 0 – 2.7	↓ 12	↓ 16 - 44
Liraglutide daily	↓ 2.0 – 6.7	↓ 0 – 1.7	↓ 8 - 17	↓ 16 - 34
Exenatide once weekly	↓ 4.7	↓ 1.7	↓ 5	↓ 25

Blonde L, et al[39]; Drucker DJ, et al[27]; Klonoff DC, et al[28]; Apovian CM, et al[29]; Zinman B, et al[36]; Buse JB, et al[38]; Bergenstal RM, et al[31]; Verge D, et al.[40]

Weight Loss, Metabolic, and Other Health Benefits



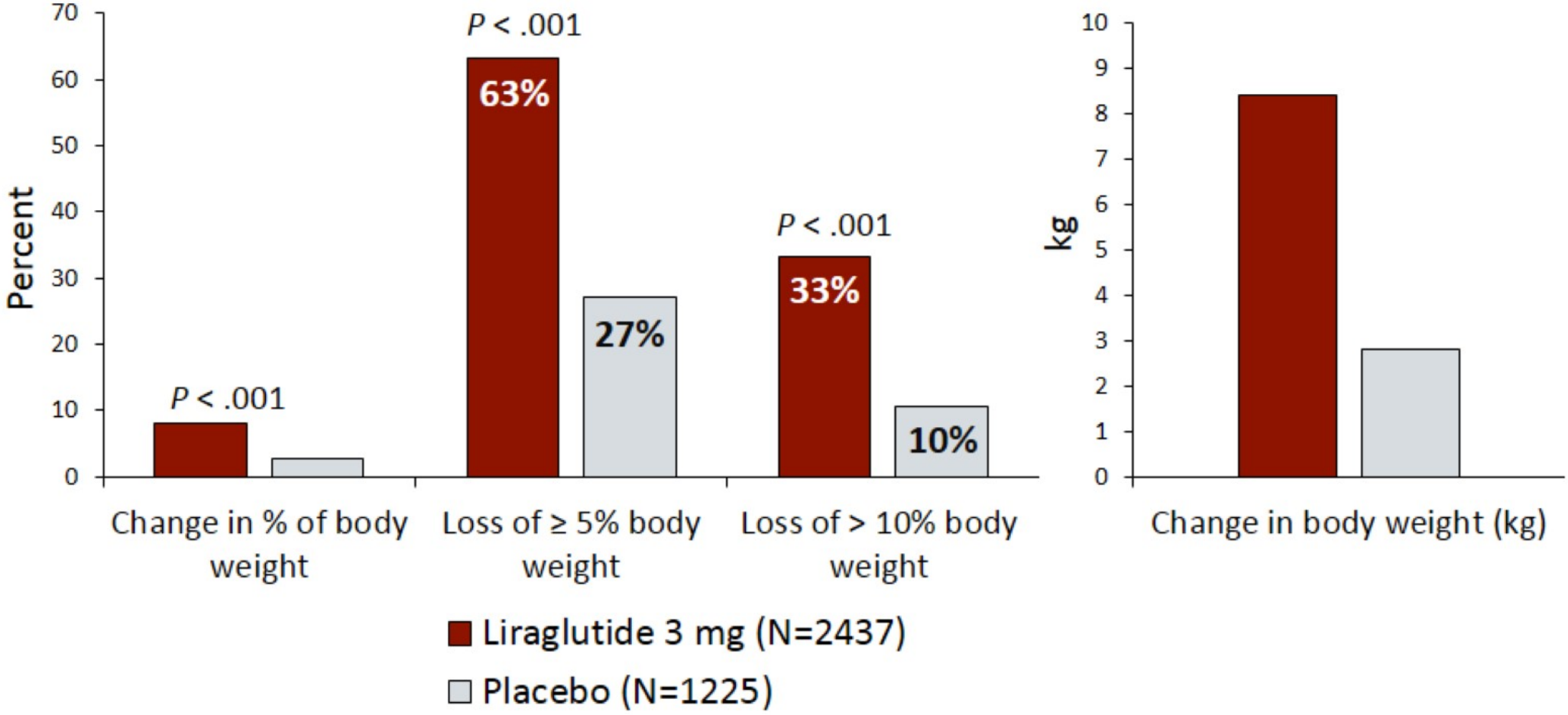
Blackburn G. *Obes Res*. 1995;3(suppl 2):211s-216s.
Foster GD, et al. *Arch Intern Med*. 2009;169:1619-1626.
Greg EW, et al. *JAMA*. 2012;308:2489-2496.
Sjostrom L, et al. *J Intern Med*.2013;273:219-234.
Christou NV,et al. *Surg Obes Relat Dis*. 2008;4:691-695
Wing RR, et al. *J Urol*. 2010;184:1005-1010.

Liraglutide Approval for Weight Management

- FDA approval: 23 December, 2014
- EMA approval: 22 January, 2015
- Health Canada approval: 26 February, 2015
- Indicated as an adjunct to diet and exercise to help manage weight in adults who are:
  - Obese (30 kg/m2 or greater)
  - Overweight (have a BMI between 27 and 30 kg/m2) and have weight-related complications such as diabetes, abnormally high levels of fats in the blood, high blood pressure, or obstructive sleep apnea

http://www.ema.europa.eu/ema/

SCALE Obesity and Prediabetes: Effect of Liraglutide on Weight at 56 Weeks



Pi-Sunyer X, et al. *N Engl J Med*. 2015;373:11-22.

La Farmacoeconomia si propone di

Aiutare a selezionare i farmaci correlando il beneficio al costo

non ridurre contemporaneamente il livello dell'assistenza terapeutica

tener presente che il farmaco non è solo un costo, ma anche un investimento di carattere socio-economico

Valutazione dell'efficacia clinica di un medicamento

Mediante sperimentazioni cliniche controllate (RCT) che confrontano il farmaco innovativo con un altro di riferimento o con il placebo

→ Efficacy

Efficacy:

Valutazione dell'efficacia clinica registrata su pazienti (campione di popolazione) arruolati in una sperimentazione clinica

Studi sulla popolazione

→ **Effectiveness**

Effectiveness:

Valutazione dell'efficacia clinica registrata su popolazione nelle normali condizioni di impiego

CRITERI PER LA VALUTAZIONE EFFICACY - EFFECTIVENESS

Outcome

- **TARGET SECONDARI**
  (Surrogate endpoints)
  - normalizzazione di un parametro coinvolto nel processo fisiopatologico di una malattia
  - Es.: ↓ Px Arteriosa
    ↓ Aggr. Piastrinica

- **TARGET PRIMARI**
  (Hard endopoints)
  - prolungamento della vita
  - miglioramento della qualità di vita
  - prevenzione o riduzione dell'incidenza di uno specifico esito patologico

Gli Outcomes sono gli esiti o le conseguenze cliniche di una terapia

Tipi di Outcome

prolungamento della vita

miglioramento della qualità di vita

prevenzione / riduzione
di un'esito patologico

normalizzazione di un parametro
indicatore di una malattia

Esempi di outcome:

anni di vita guadagnati

riduzione attacchi epilettici

giorni liberi da attacchi asmatici

diminuzione di complicanze

vite salvate

Evaluation of the long-term cost-effectiveness of liraglutide therapy for patients with type 2 diabetes

Econ. 2016 Feb;19(2):121-34

Ronan Roussel,

Abstract

Objectives:

The present study aimed to compare the projected long-term clinical and cost implications associated with liraglutide, sitagliptin and glimepiride in patients with type 2 diabetes mellitus failing to achieve glycemic control on metformin monotherapy in France.

Methods:

Clinical input data for the modeling analysis were taken from two randomized, controlled trials (LIRA-DPP4 and LEAD-2). Long-term (patient lifetime) projections of clinical outcomes and direct costs (2013 Euros;E) were made using a validated computer simulation model of type 2 diabetes. Costs were taken from published France-specific sources. Future costs and clinical benefits were discounted at 3% annually. Sensitivity analyses were performed.

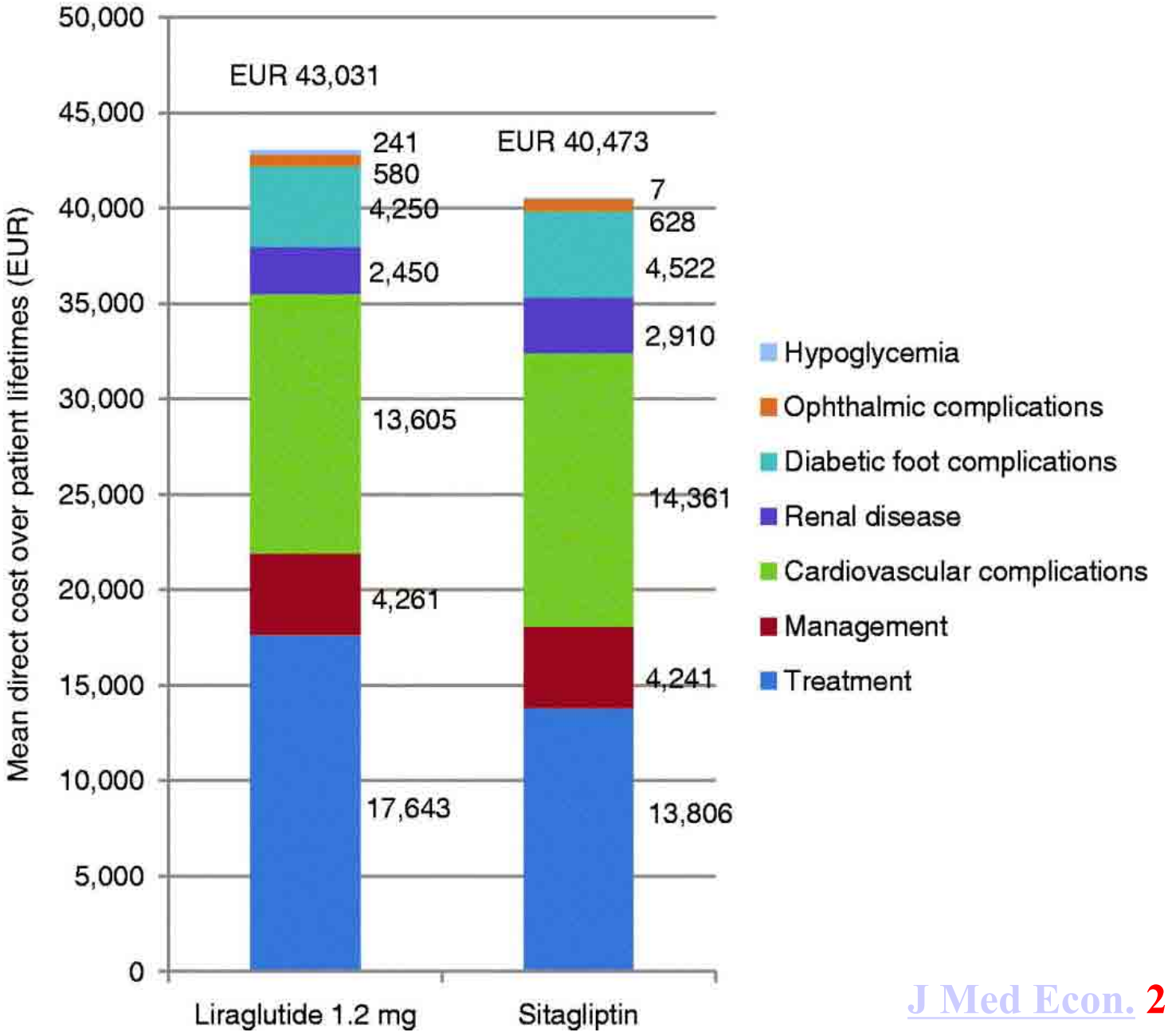
Results:

Liraglutide was associated with an increase in quality-adjusted life expectancy of 0.25 quality-adjusted life years (QALYs) and an increase in mean direct healthcare costs of E 2558 per patient compared with sitagliptin. In the comparison with glimepiride, liraglutide was associated with an increase in quality-adjusted life expectancy of 0.23 QALYs and an increase in direct costs of E 4695. Based on these estimates, liraglutide was associated with an incremental cost-effectiveness ratio (ICER) of E 10,275 per QALY gained vs sitagliptin and E 20,709 per QALY gained vs glimepiride in France.

Conclusion:

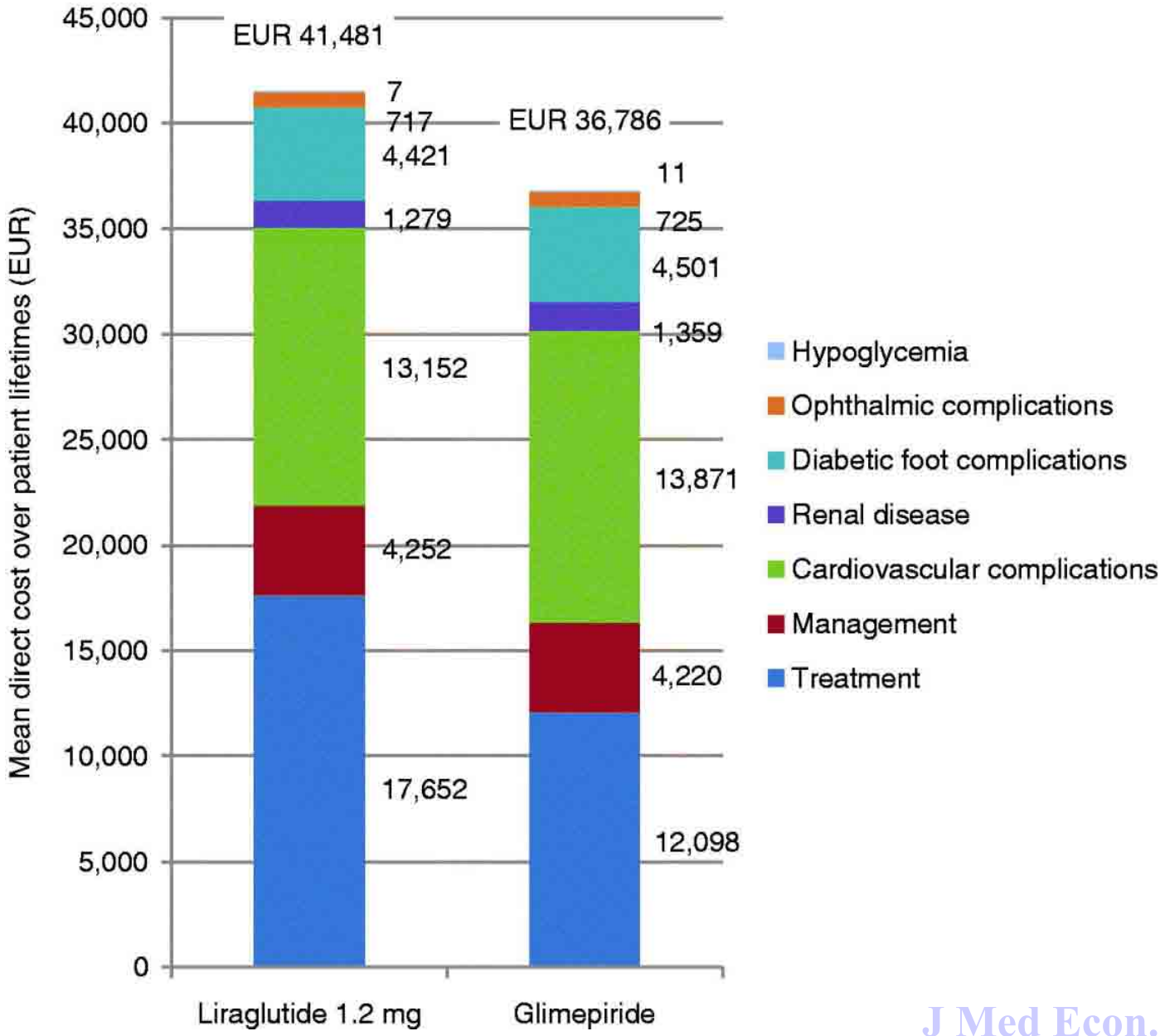
Calculated ICERs for both comparisons fell below the commonly quoted willingness-to-pay threshold of E 30,000 per QALY gained. Therefore, liraglutide is likely to be cost-effective vs sitagliptin and glimepiride from a healthcare payer perspective in France.

Mean direct costs associated with liraglutide 1.2 and sitagliptin over patient lifetimes.



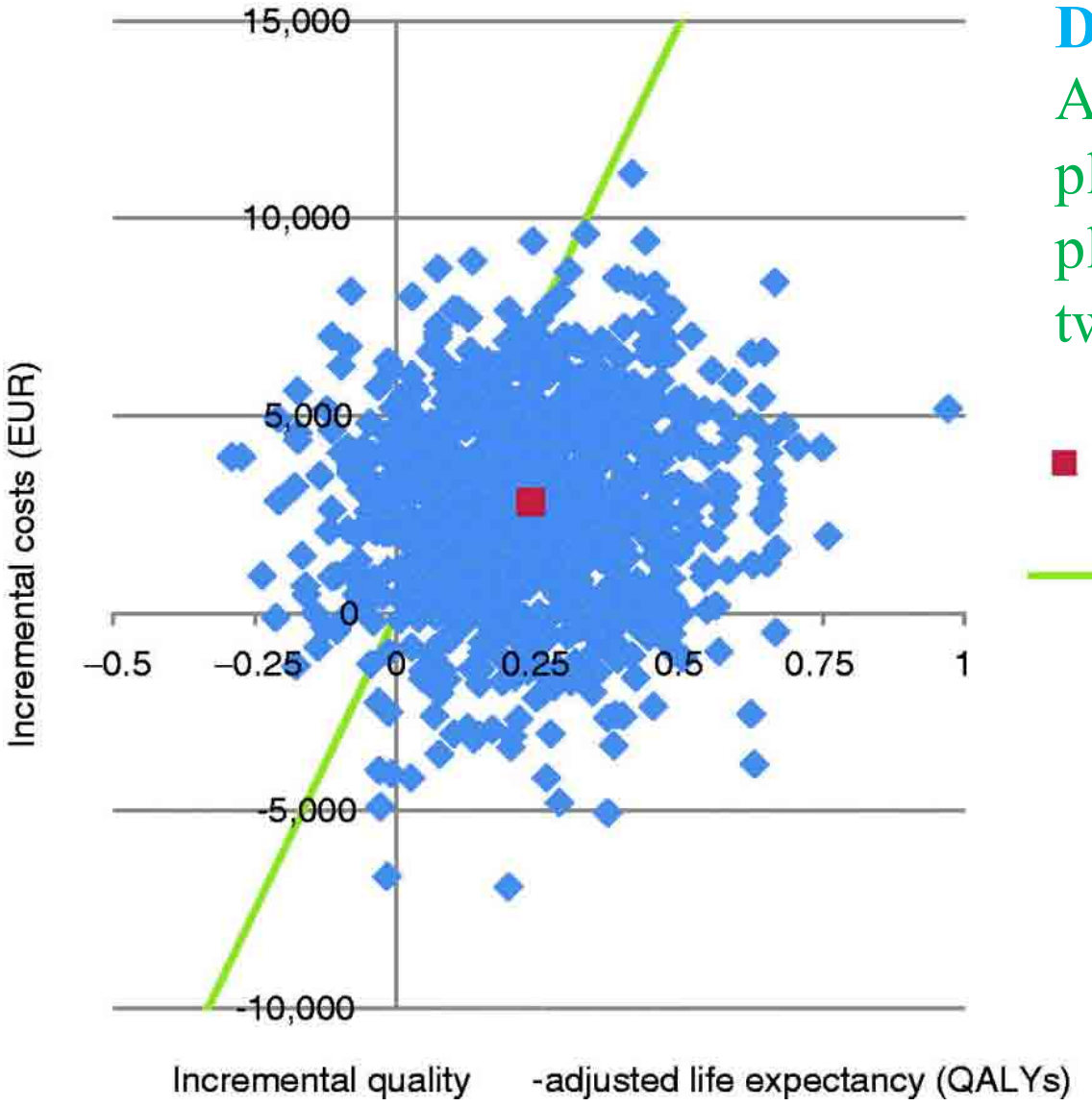
J Med Econ. 2016 Feb;19(2):121-34

Mean direct costs associated with liraglutide 1.2 mg and glimepiride over patient lifetimes; QALYs, quality-adjusted life years.



J Med Econ. 2016 Feb;19(2):121-34

Liraglutide vs sitagliptin: Cost-effectiveness scatterplot for the probabilistic sensitivity analyses. QALY, quality-adjusted life year.



Definition of Scatter Plot

A scatter plot is a graph made by plotting ordered pairs in a coordinate plane to show the correlation between two sets of data

JME Journal of Medical Economics

J Med Econ. 2016 Feb;19(2):121-34

Liraglutide vs glimepiride: Cost-effectiveness scatterplot for the probabilistic sensitivity analyses. QALY, quality-adjusted life year.

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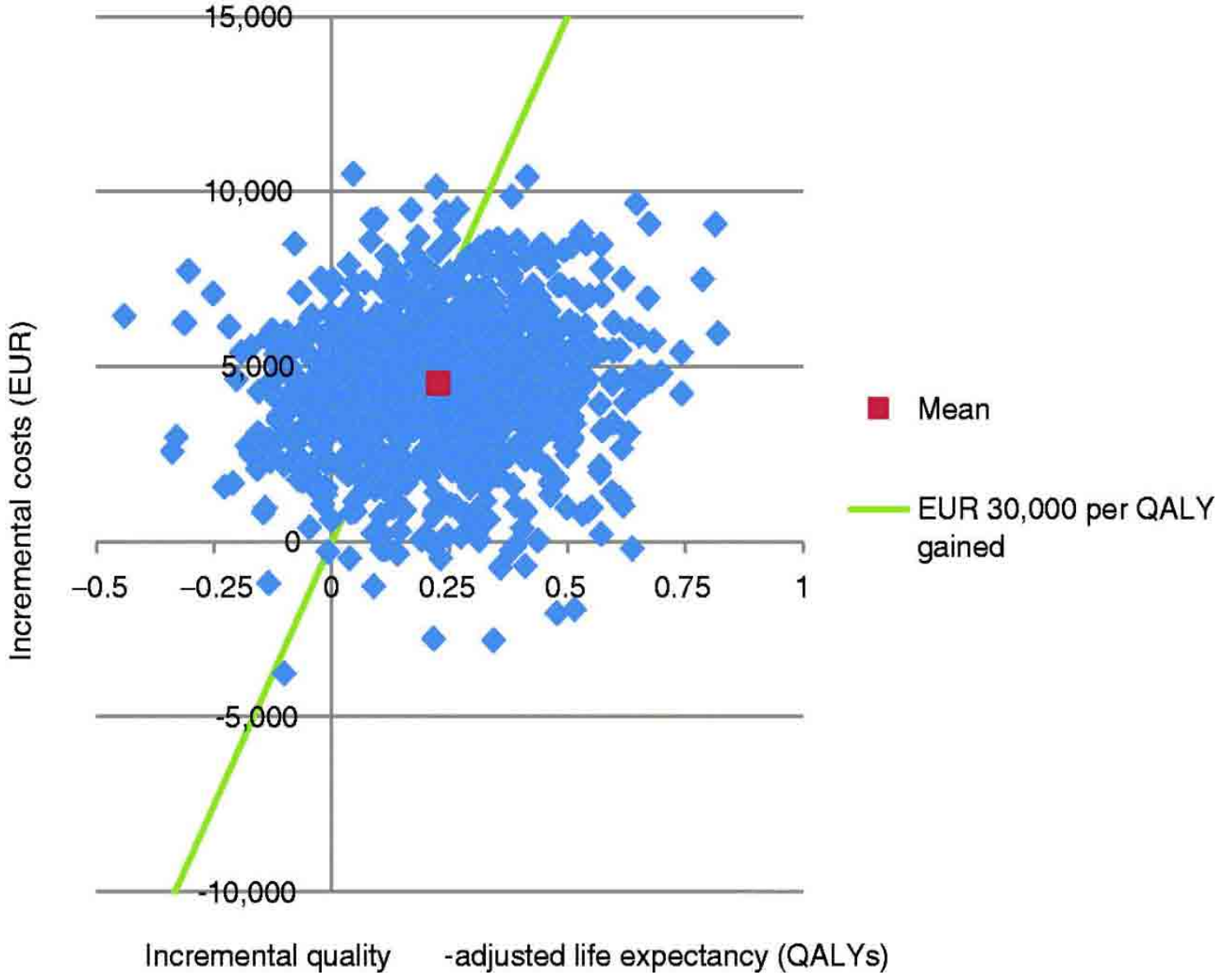
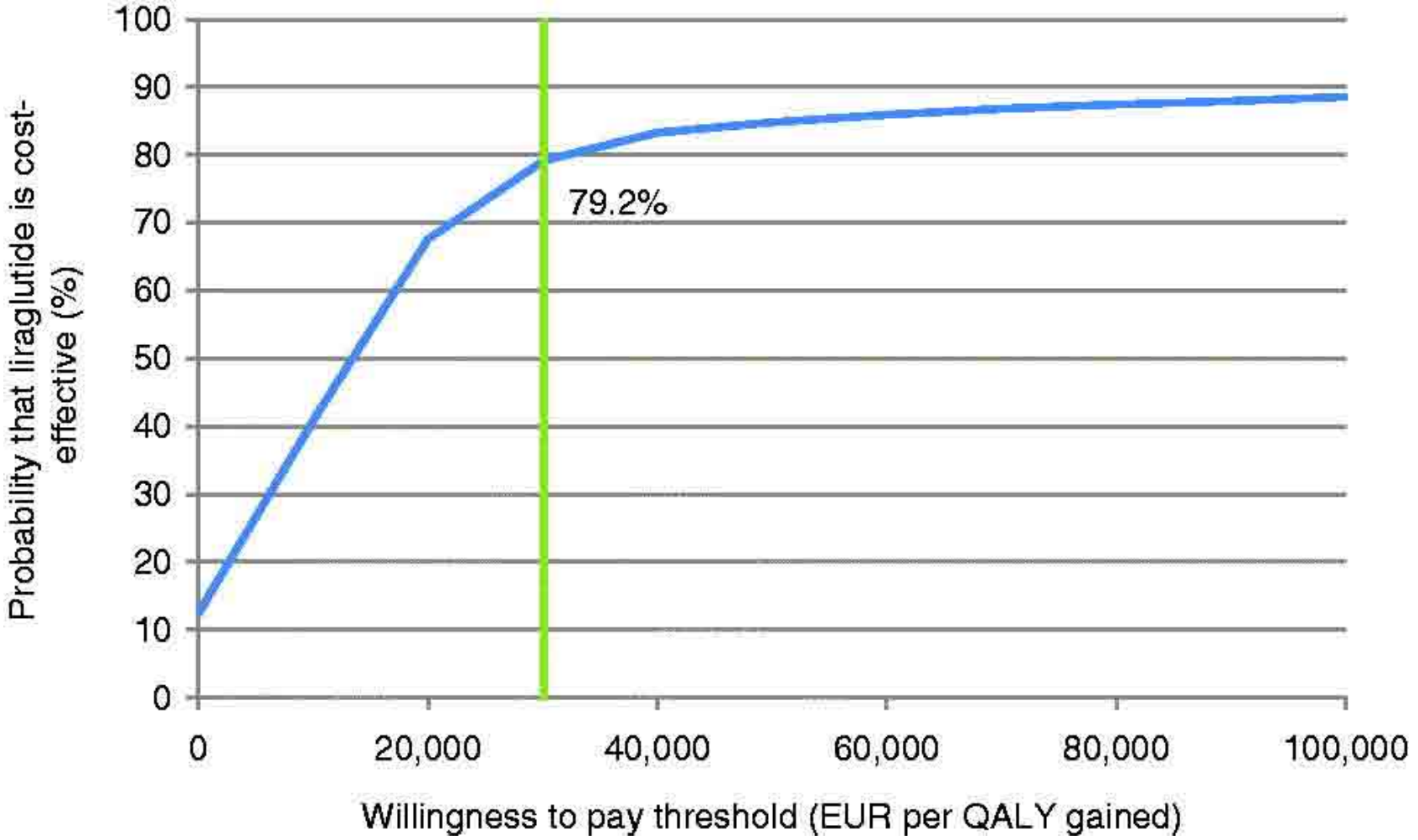


JME
Journal of Medical Economics

Liraglutide vs sitagliptin: Cost-effectiveness acceptability curve for the probabilistic sensitivity analysis. QALY, quality-adjusted life year.



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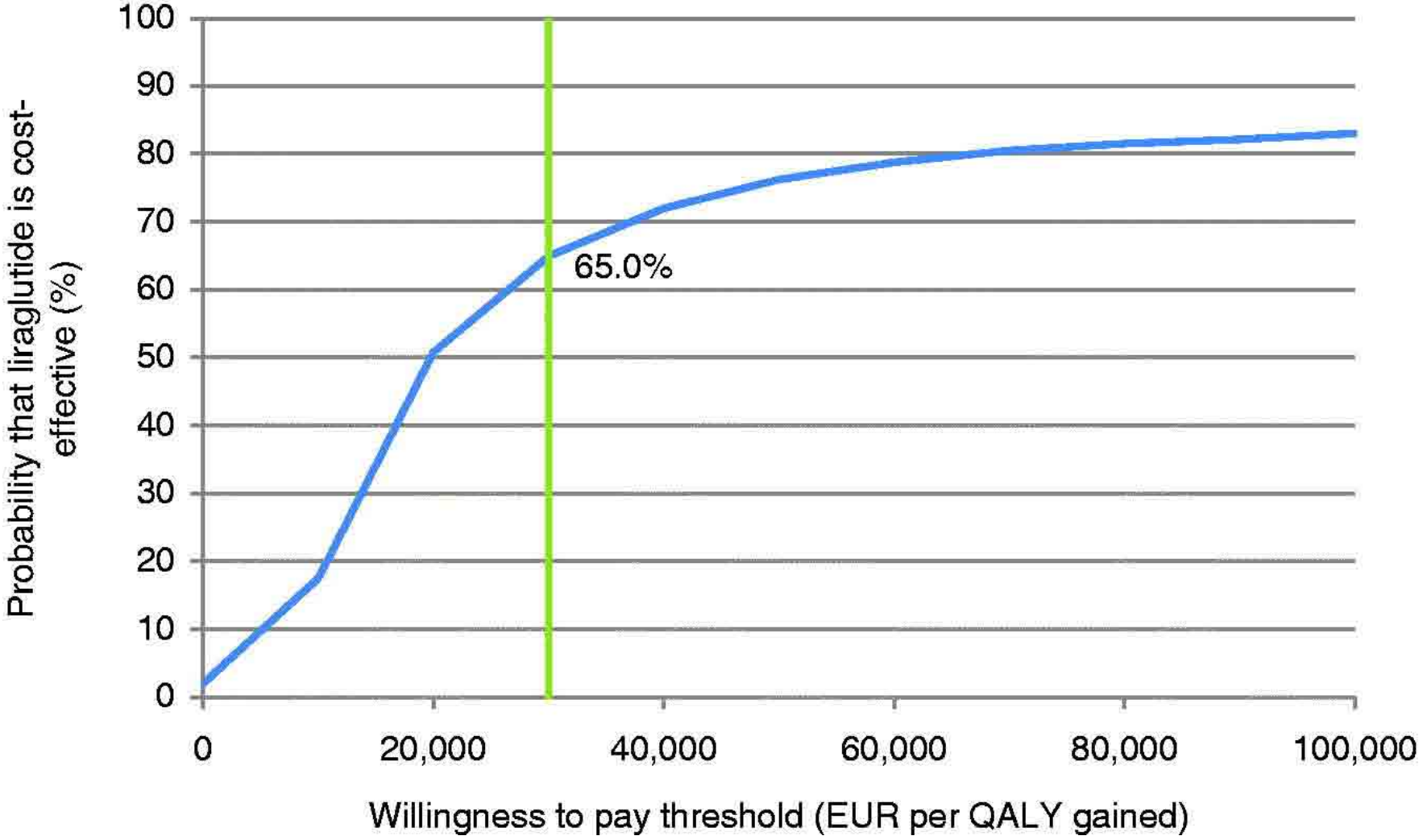

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PharmacoEconomics (2015) 33:581–597
DOI 10.1007/s40273-015-0266-y

SYSTEMATIC REVIEW

Cost Effectiveness of Dipeptidyl Peptidase-4 Inhibitors for Type 2 Diabetes

Jinsong Geng · Hao Yu · Yiwei Mao · Peng Zhang · Yingyao Chen

PharmacoEconomics

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Key Points for Decision Makers

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a new class of antidiabetic drugs used to treat type 2 diabetes mellitus, which is the most common form of diabetes and one of the key risk factors for cardiovascular disease and mortality.

In patients with type 2 diabetes who do not achieve glycemic targets with antidiabetic monotherapy, add-on treatment with DPP-4 inhibitors may represent a cost-effective option compared with sulfonylureas and insulin.

Whether add-on DPP-4 inhibitor therapy is cost-effective compared with thiazolidinediones remains uncertain.

DPP-4 inhibitors may be an attractive treatment option from a payer perspective. High-quality cost-effectiveness analyses that utilize long-term follow-up data and have no conflicts of interests are still needed.

Grazie per l’attenzione !