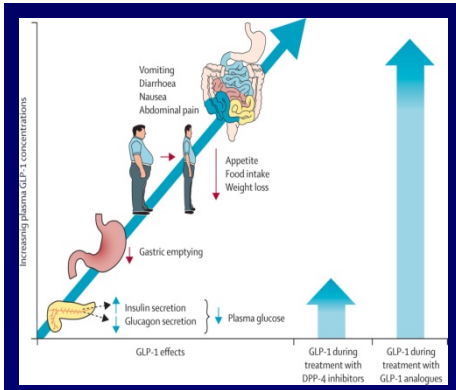

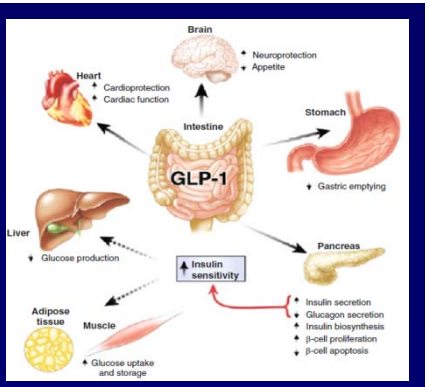

Agonistes des récepteurs du GLP-1 ou inhibiteurs de la DPP-4 : comment orienter le choix du clinicien ?

Professeur André J. Scheen

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Service de Diabétologie, Nutrition & Maladies métaboliques,
Unité de Pharmacologie clinique
CHU Sart Tilman, Liège, Belgique

Conflits d'intérêt (André Scheen)

Conférencier, Membre d'un Conseil scientifique et/ou Investigateur clinique pour les firmes pharmaceutiques suivantes :

AstraZeneca, BMS, Boehringer Ingelheim, Eli Lilly, GSK, Novartis, MSD, NovoNordisk, Sanofi-Aventis, Servier

CHU de Liège

Université de Liège

European Journal of Internal Medicine 23 (2012) 132–136

Contents lists available at SciVerse ScienceDirect

European Journal of Internal Medicine

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Debate

Dipeptidyl peptidase-4 (DPP-4) inhibitors are favourable to Glucagon-Like Peptide-1 (GLP-1) agonists: No

Sten Madsbad *

Department of Endocrinology, Hvidovre University Hospital, 2650 Hvidovre, Denmark

European Journal of Internal Medicine 23 (2012) 126–131

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Debate

Dipeptidylpeptidase-4 (DPP-4) inhibitors are favourable to glucagon-like peptide-1 (GLP-1) receptor agonists: Yes

André J. Scheen *

Division of Diabetes, Nutrition and Metabolic Disorders, University of Liège, Liège, Belgium
Division of Clinical Pharmacology, University of Liège, Liège, Belgium
Department of Medicine, CHU Sart Tilman, Liège, Belgium

Agonistes du GLP-1 R vs inhibiteurs de la DPP-4

Plan de l'exposé

1. Glucagon-like peptide-1 et médicaments « incrétine »
2. Place respective dans le « position statement » ADA-EASD
3. Efficacité comparée (glucose, poids, pression artérielle)
4. Profil de sécurité/tolérance
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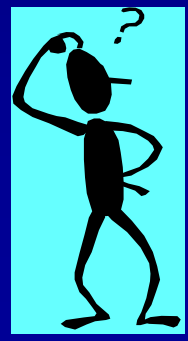
6. Propositions de prescription rationnelle au clinicien



Agonistes du GLP-1 R vs inhibiteurs de la DPP-4

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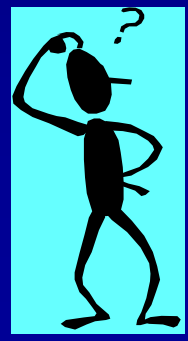
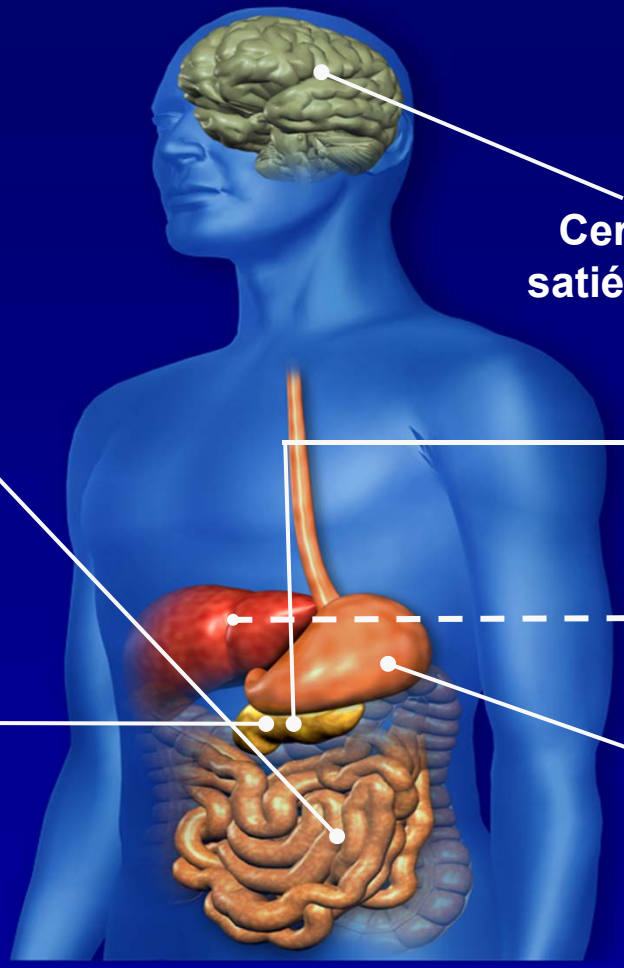


Les effets métaboliques du Glucagon-like Peptide-1 (GLP-1)

GLP-1 sécrété en réponse au repas

↑ Beta-cell response

↓ Beta-cell workload



Cerveau : Favorise la satiété et réduit l'appétit

Cellules alpha :
↓ Sécrétion postprandiale du glucagon

Foie :
↓ Glucagon et ↑ insuline réduisent la production hépatique de glucose

Cellules beta : Augmentation de la sécrétion d'insuline (glucose-dépendante)

Estomac : Ralentit la vidange gastrique

Adapted from Flint A, et al. *J Clin Invest*. 1998;101:515-520.; Adapted from Larsson H, et al. *Acta Physiol Scand*. 1997;160:413-422.; Adapted from Nauck MA, et al. *Diabetologia*. 1996;39:1546-1553.; Adapted from Drucker DJ. *Diabetes.* 1998;47:159-169.

Médicaments centrés sur l'effet incrétine

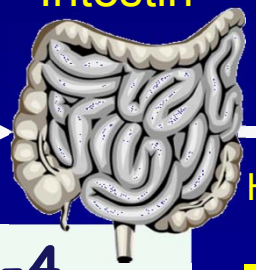
Ingestion d'un repas

GLP-1 R Agonistes
Résistant à la DPP-4
Exénatide, liraglutide

Glucose dépendant
↑ Insuline
par les cellules beta
(GLP-1 & GIP)

L'insuline augmente la captation péripérique du glucose

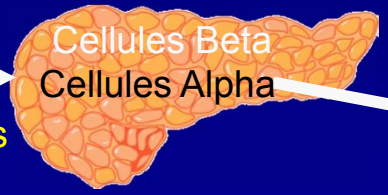
Intestin



Libération d'hormones incrétines

Hormones actives GLP-1 & GIP

Pancreas



Contrôle de la glycémie

DPP-4 Inhibiteurs

Sitagliptine
Vildagliptine
Saxagliptine
Linagliptine

L'enzyme DPP-4 dégrade rapidement les incrétines

↓ Glucagon
par les cellules alpha
(GLP-1)
Glucose dépendant

L'insuline accrue et le glucagon diminué réduisent la production hépatique de glucose

L'effet incrétine est diminué dans le diabète de type 2

Les taux plasmatiques de GLP-1 atteints expliquent les différences d'efficacité et de tolérance des deux approches incrétines

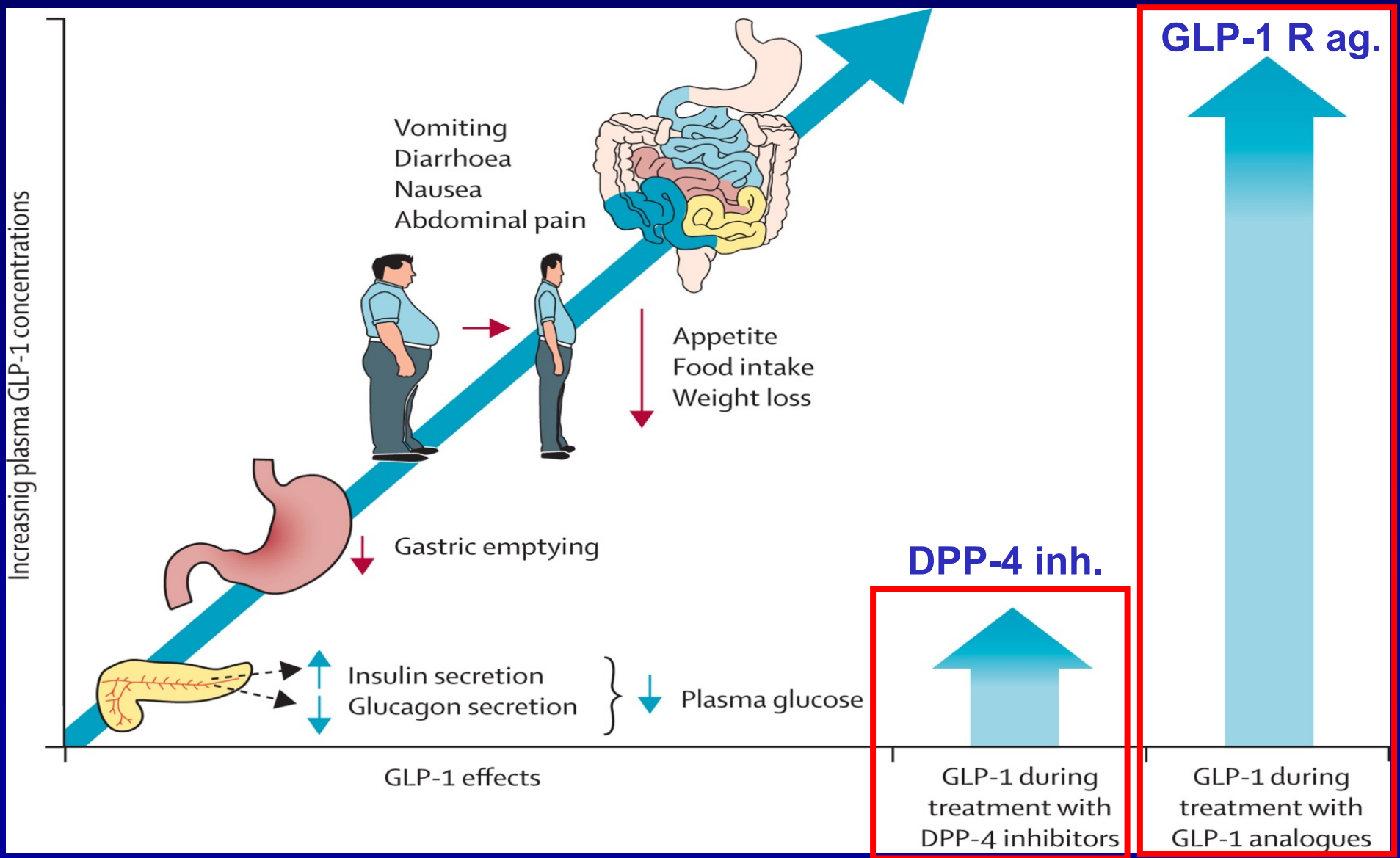


Figure 5.

La DPP-4 a de nombreux substrats !

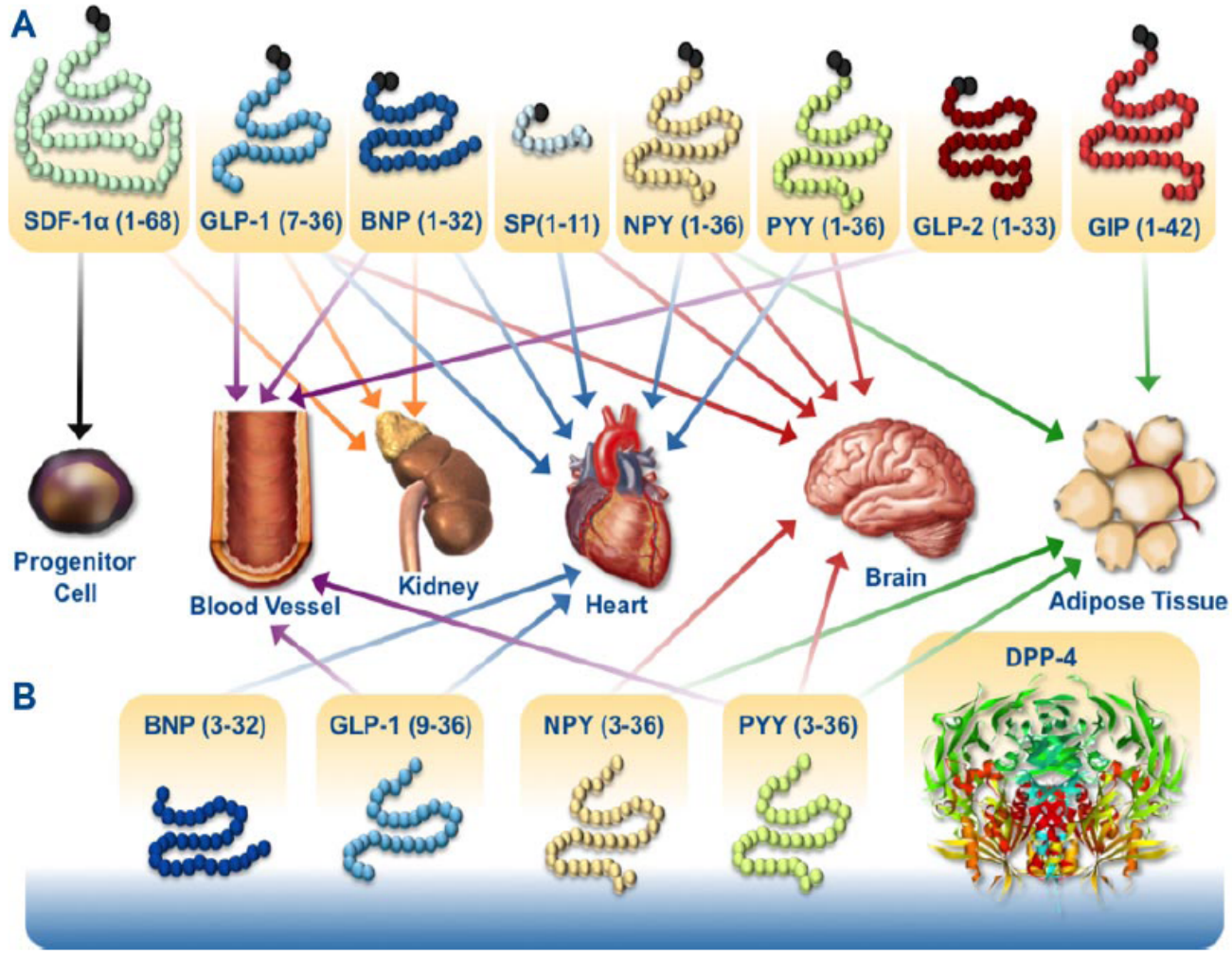


Figure 5. DPP-4 substrates that directly or indirectly regulate cardiovascular function. Multiple DPP-4 substrates have been identified that act on multiple peripheral tissues that influence the cardiovascular system. For a summary of these direct effects on target tissues, refer to Table 1. SP, Substance P.

D'où les effets pléiotropes des inhibiteurs de la DPP-4, en partie indépendants du GLP-1

Complexité des effets potentiels dont l'importance clinique dans les effets observés ou attendus (CV) reste à démontrer

Ussher JR & Drucker DJ. Endocr Rev 2012, 33, 187-215

Différences entre analogues du GLP-1 (exénatide, liraglutide) et inhibiteurs de la DPP-4 (gliptines)

Propriétés/effets	GLP-1 analogues	Inhibiteurs de la DPP-4
Mécanisme de stimulation de l'insulino-sécrétion exclusivement via GLP-1	Oui	Non connu
Abaissement de l'HbA1c	Oui (-1,0-1,4 %)	Oui (- 0,7-0,8%)
Hypoglycémie	Non	Non
Contre-régulation à l'hypoglycémie par le glucagon maintenue	Oui	Non testée
Inhibition de la vidange gastrique	Oui (exénatide)	Marginale
Effet sur le poids corporel	Perte de poids	Neutralité pondérale
Manifestations indésirables	Nausées, vomissement Pancréatite (?)	Néant Pancréatite (?)
Administration	Sous-cutanée	Orale

Agonistes du GLP-1 R vs inhibiteurs de la DPP-4

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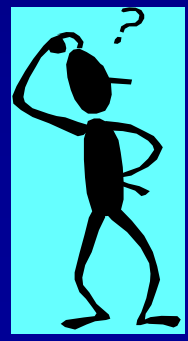


Reviews/Consensus Reports/ADA Statements

POSITION STATEMENT

Diabetes Care Publish Ahead of Print, published online April 19, 2012

Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach

Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

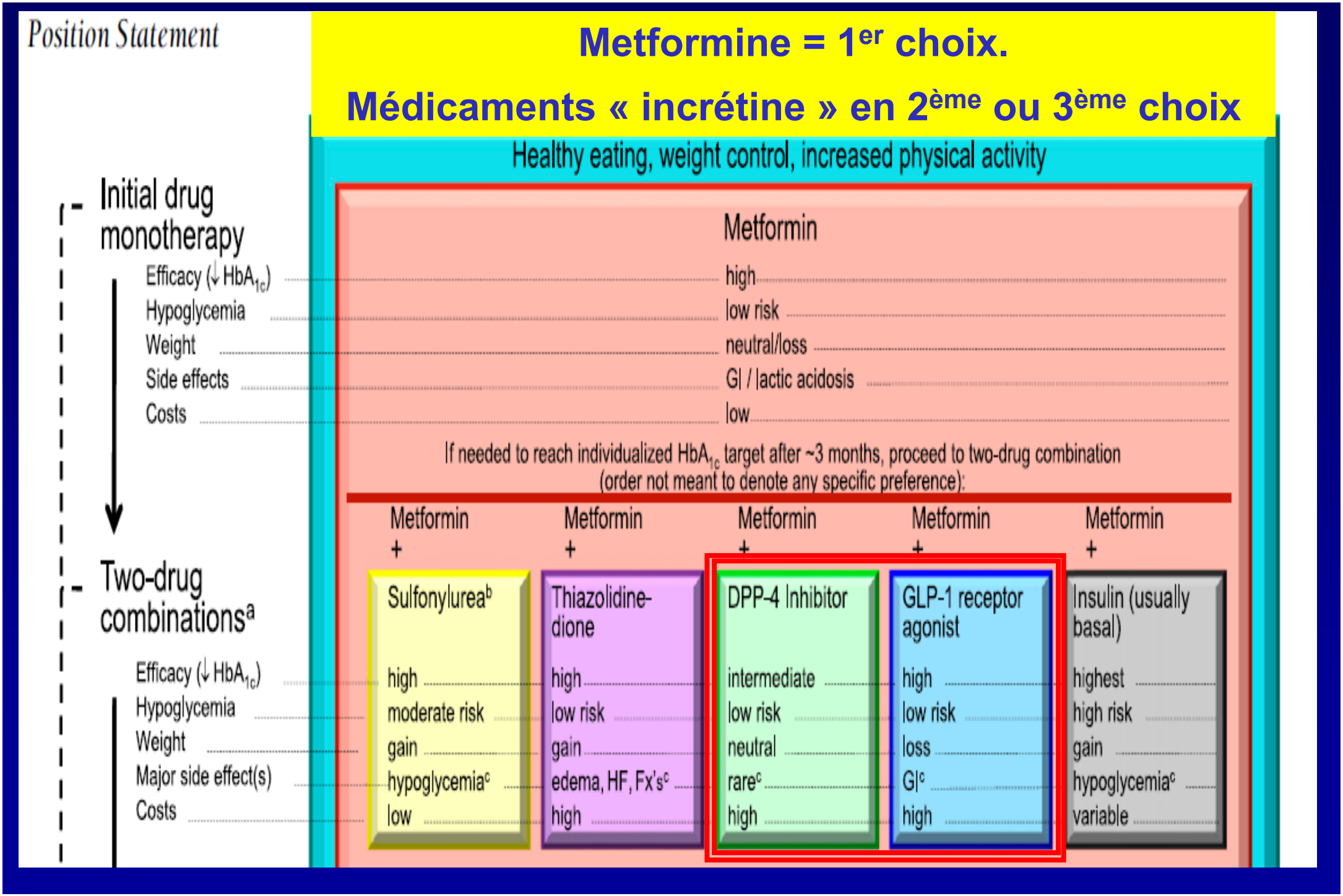
Silvio E. Inzucchi, MD[1]
Richard M. Bergenstal, MD[2]
John B. Buse, MD, PhD[3]
Michaela Diamant, MD, PhD[4]
Ele Ferrannini, MD[5]
Michael Nauck, MD[6]
Anne L. Peters, MD[7]
Apostolos Tsapas, MD, PhD[8]
Richard Wender, MD[9]
David R. Matthews, MD, DPhil[10,11,12]

Diabetologia
DOI 10.1007/s00125-012-2534-0

POSITION STATEMENT

Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

S. E. Inzucchi · R. M. Bergenstal · J. B. Buse · M. Diamant · E. Ferrannini · M. Nauck · A. L. Peters · A. Tsapas · R. Wender · D. R. Matthews


Position Statement
Metformine = 1er choix.
Médicaments « incrétine » en 2ème ou 3ème choix
Healthy eating, weight control, increased physical activity
Initial drug monotherapy
Efficacy (↓ HbA1c)
Hypoglycemia
Weight
Side effects
Costs
Metformin
high
low risk
neutral/loss
GI / lactic acidosis
low
If needed to reach individualized HbA1c target after ~3 months, proceed to two-drug combination (order not meant to denote any specific preference):
Two-drug combinations[a]
Efficacy (↓ HbA1c)
Hypoglycemia
Weight
Major side effect(s)
Costs
Metformin + Sulfonylurea[b]
high
moderate risk
gain
hypoglycemia[c]
low
Metformin + Thiazolidine-dione
high
low risk
gain
edema, HF, Fx's[c]
high
Metformin + DPP-4 Inhibitor
intermediate
low risk
neutral
rare[c]
high
Metformin + GLP-1 receptor agonist
high
low risk
loss
GI[c]
high
Metformin + Insulin (usually basal)
highest
high risk
gain
hypoglycemia[c]
variable

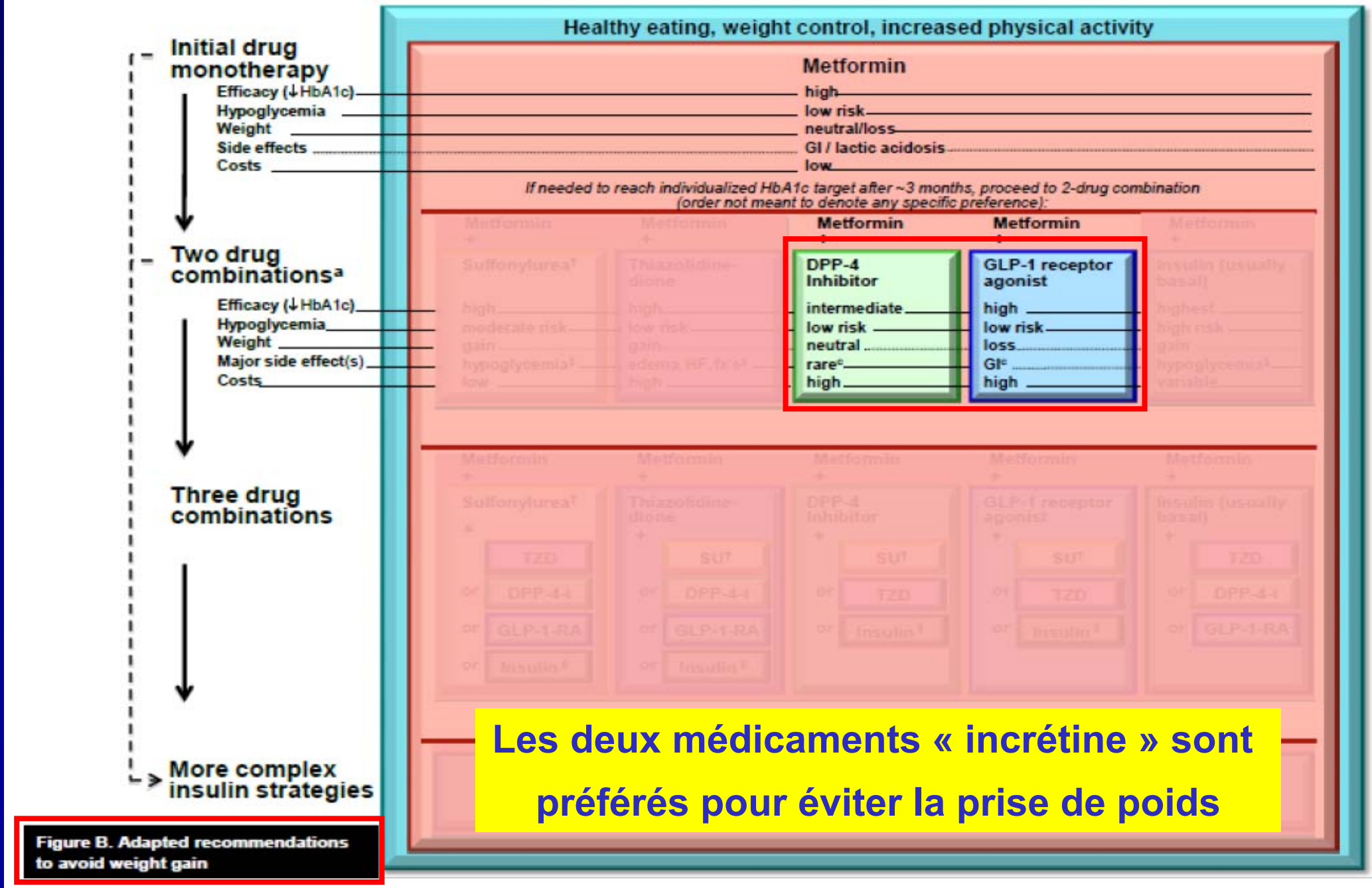


Figure B. Adapted recommendations to avoid weight gain

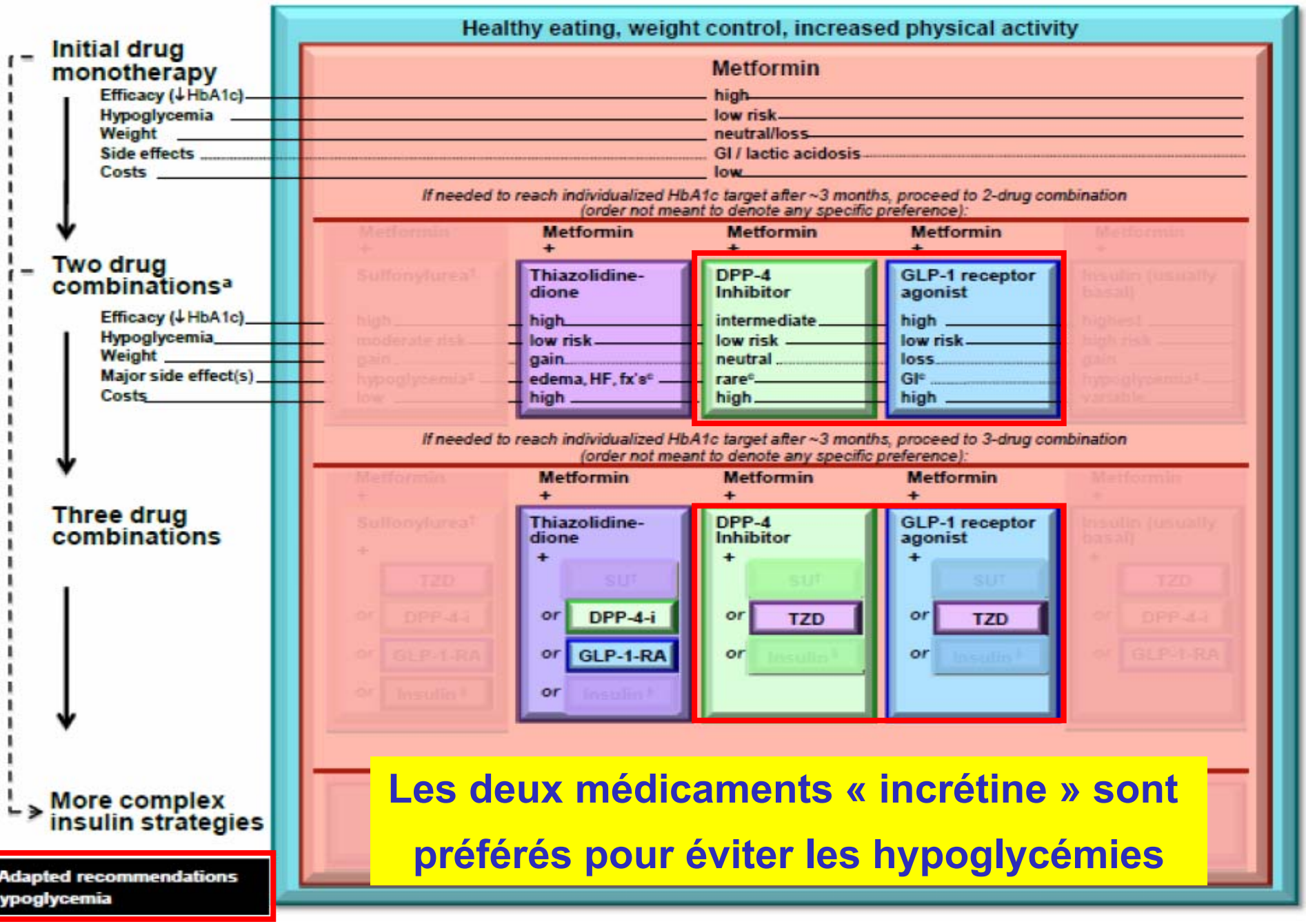


Figure A. Adapted recommendations to avoid hypoglycemia

Les deux médicaments « incrétine » sont préférés pour éviter les hypoglycémies

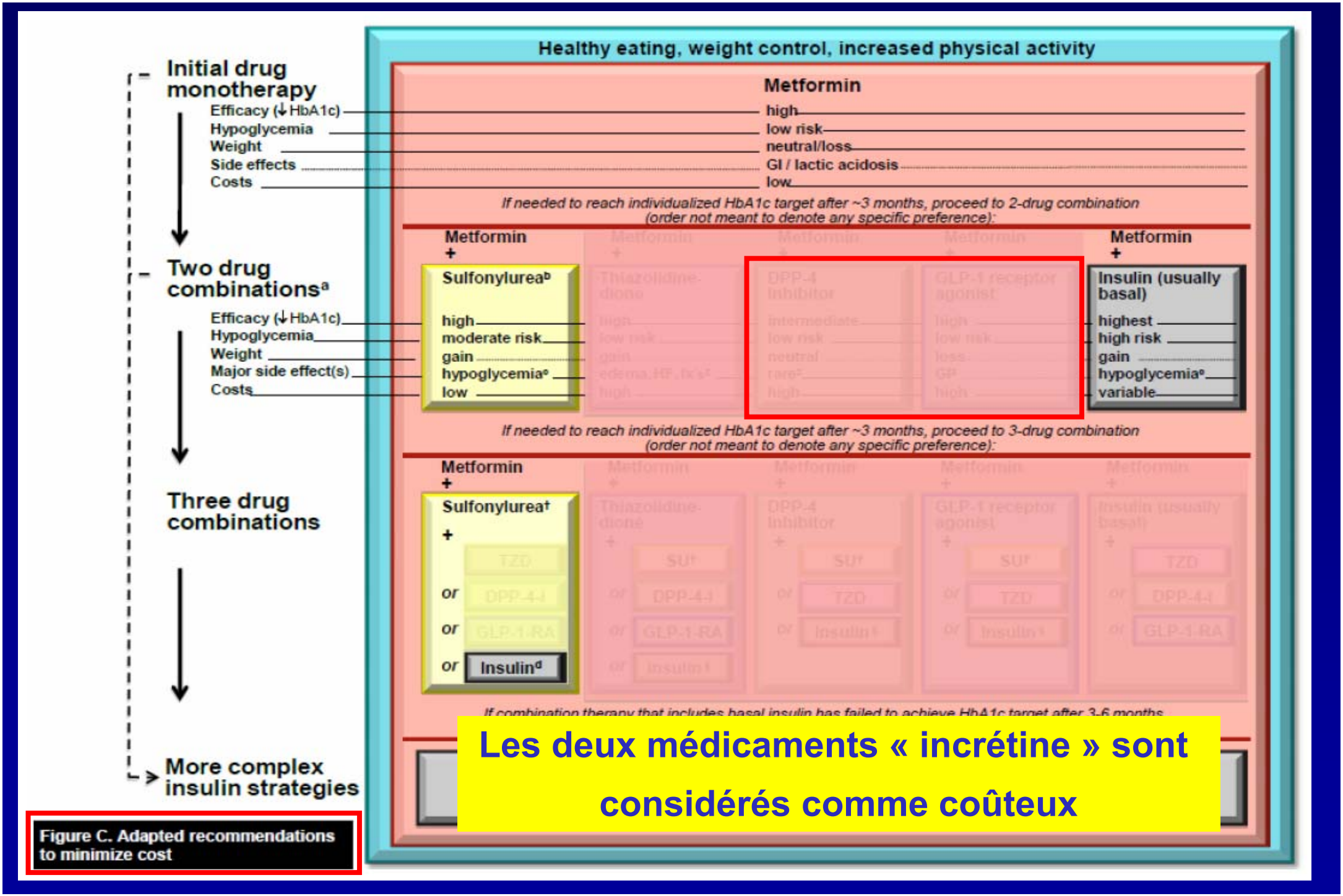


Figure C. Adapted recommendations to minimize cost

Agonistes du GLP-1 R vs inhibiteurs de la DPP-4

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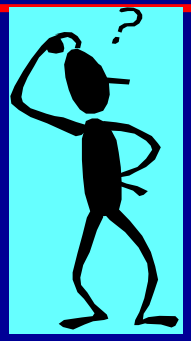


Gliptines versus GLP-1 agonistes en addition à la metformine

	Number of patients	Study duration (weeks)	Baseline HbA_{1c}	Reduction in HbA_{1c}*	Reduction in bodyweight (kg)*
DPP-4 inhibitors					
100 mg sitagliptin once daily					
Charbonnel et al (2006)[8]	464	24	7·96%	−0·67%	−0·70
Scott et al (2008)[9]	94	18	7·70%	−0·73%	−0·40
Nauck et al (2007)[10]	588	52	7·40%	−0·67%	−1·50
Bergenstal et al (2009)[4]	166	26	8·50%	−1·00%	−0·90
Pratley et al (2010)[6]	219	26	8·5%	−0·90%	−0·96
50 mg vildagliptin twice daily					
Ferrannini et al (2009)[12]	1396	52	7·30%	−0·44%	−0·20
5 mg saxagliptin once daily					
De Fronzo et al (2009)[13]	191	24	8·10%	−0·68%	−0·87
GLP-1 agonists					
10 µg exenatide twice daily					
De Fronzo et al (2005)[11]	113	30	8·18%	−0·78%	−2·8
Drucker et al (2008)[3]†	147	30	8·30%	−1·50%	−3·6
Buse et al (2009)[7]‡	231	26	8·20%	−0·79%	−2·87
2 mg exenatide (longacting release) once weekly					
Drucker et al (2008)[3]§	148	30	8·30%	−1·90%	−3·70
Bergenstal et al (2009)[4]	160	26	8·50%	−1·55%	−2·70
1·2 mg liraglutide once daily					
Nauck et al (2009)[7]	100	26	8·30%	−1·10%	−2·60
Pratley et al (2010)[6]	221	26	8·4%	−1·24%	−2·86
1·8 mg liraglutide once daily					
Nauck et al (2009)[7]	100	26	8·40%	−1·00%	−2·80
Buse et al (2009)[7]‡	233	26	8·20%	−1·12%	−3·24
Pratley et al (2010)[6]	218	26	8·4%	−1·50%	−3·38

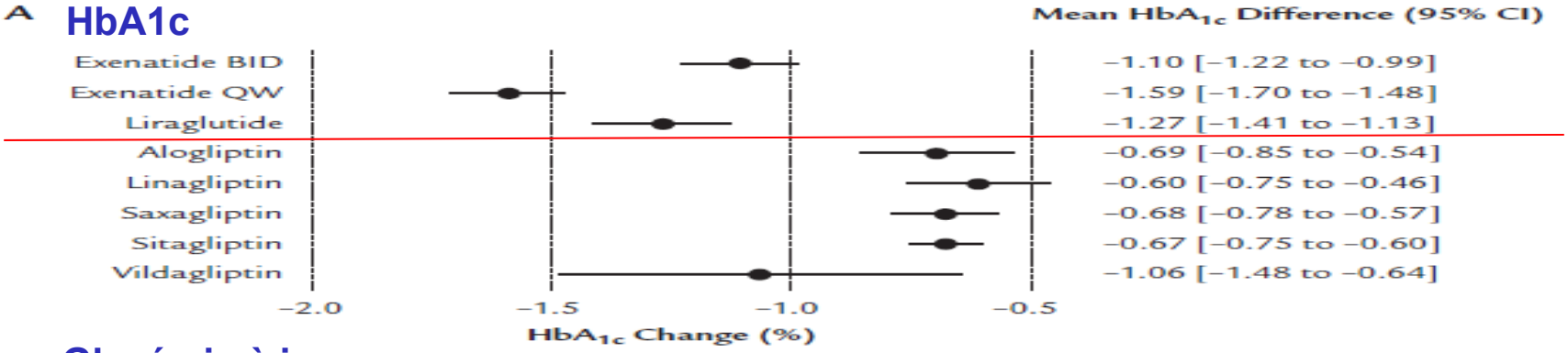
Scheen AJ & Radermecker RP. Lancet 2010, 375, 1410-1412.

Clinical Therapeutics/Volume 34, Number 6, 2012

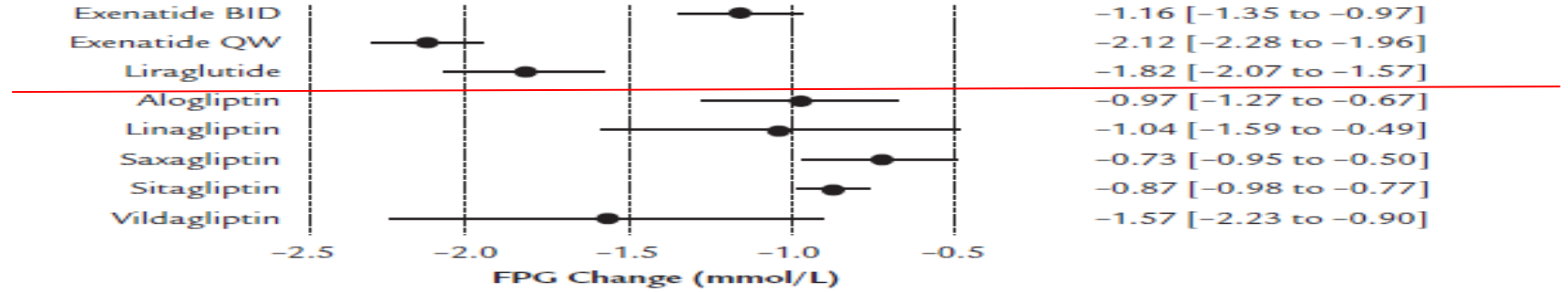
Efficacy of GLP-1 Receptor Agonists and DPP-4 Inhibitors: Meta-Analysis and Systematic Review

Vanita R. Aroda, MD[1]; Robert R. Henry, MD[2]; Jenny Han, MS[3]; Wenying Huang, PhD[3]; Mary Beth DeYoung, PhD[3]; Tamara Darsow, PhD[3*]; and Byron J. Hoogwerf, MD[4]

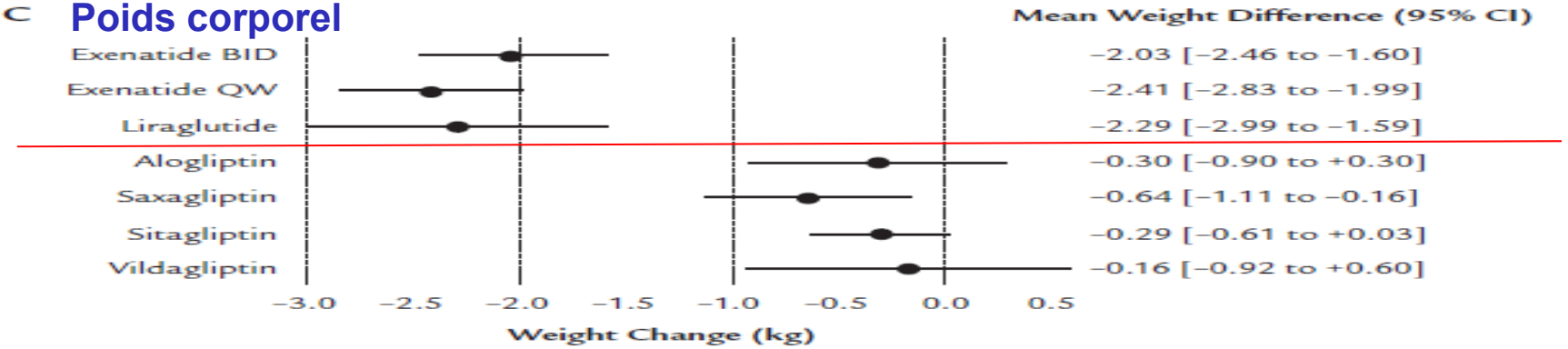
A HbA1c



B Glycémie à jeun



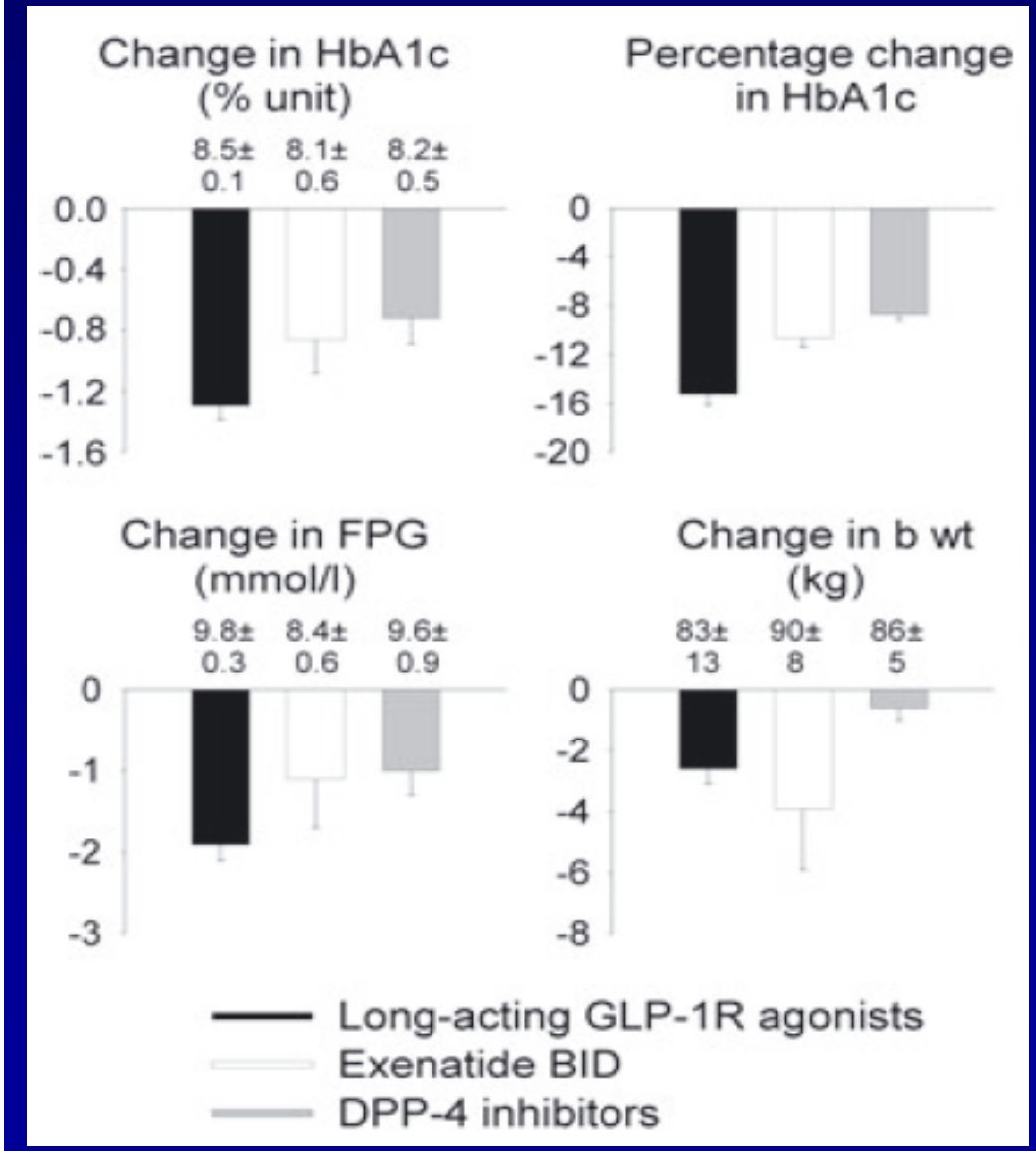
C Poids corporel



Glycaemic efficacy of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors as add-on therapy to metformin in subjects with type 2 diabetes—a review and meta analysis

C. F. Deacon[1], E. Mannucci[2] & B. Ahrén[3]

Diabetes, Obesity and Metabolism 14: 762–767, 2012.



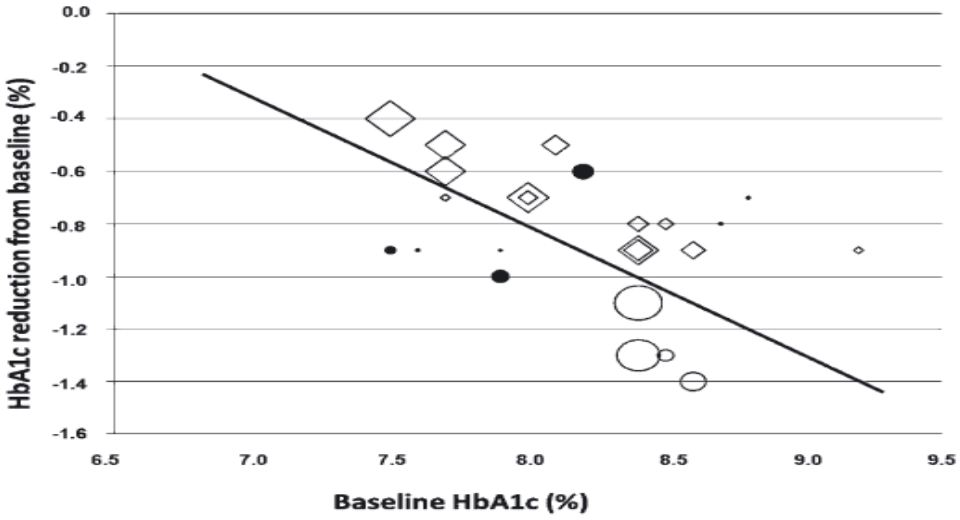
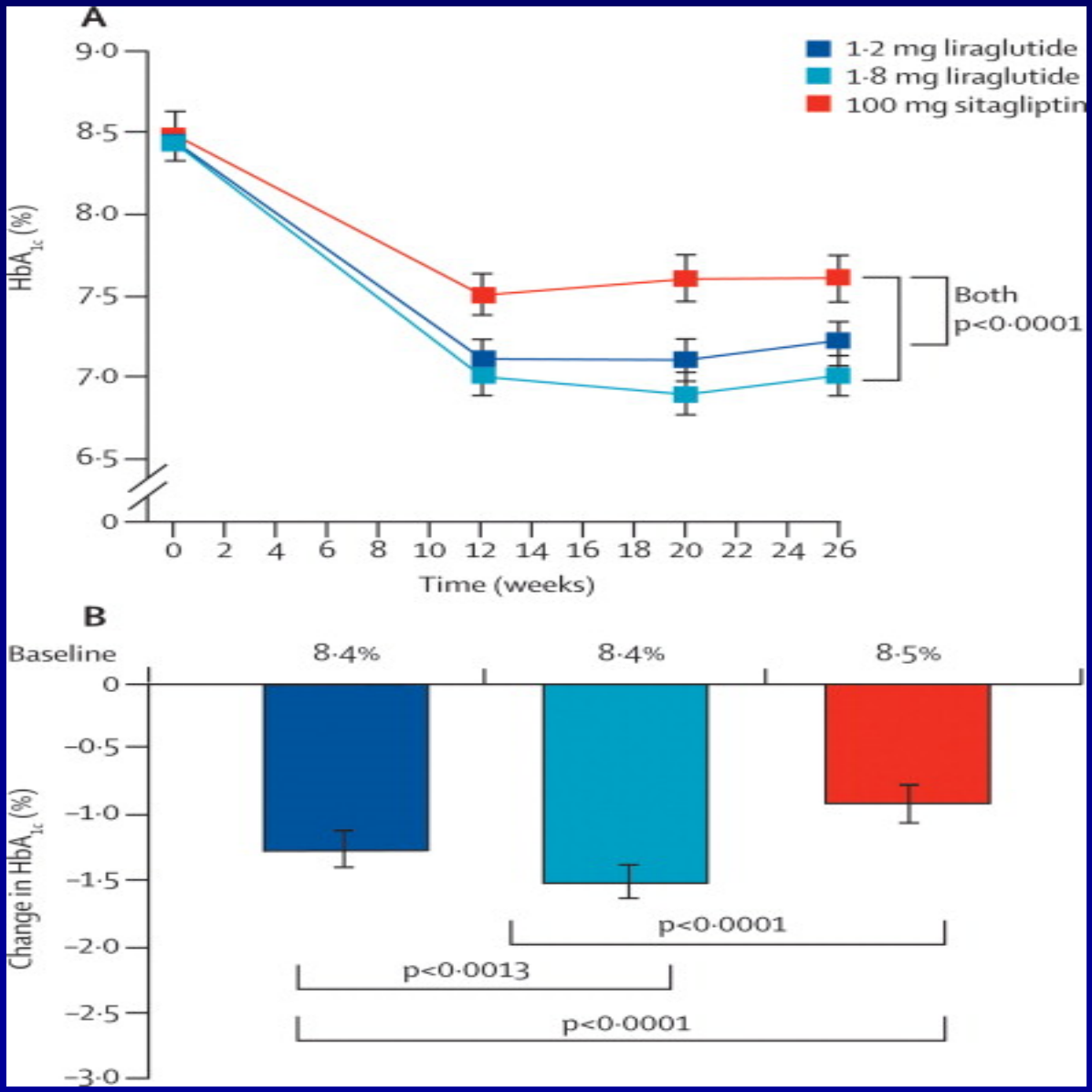


Figure 2. Relation between baseline HbA1c and change in HbA1c following 16–30 week treatment with incretin-based therapy as add-on to metformin in subjects with type 2 diabetes. Open circles show long-acting glucagon-like peptide-1 (GLP-1) receptor agonists, closed circles exenatide BID and squares dipeptidyl peptidase-4 (DPP-4) inhibitors. Trial size illustrated by size of symbol.

Figure 1. Changes in HbA1c (in unit and as percent of baseline level), fasting glucose and body weight following 16–30 week treatment with long-acting glucagon-like peptide-1 (GLP-1) receptor agonists (7 studies; 1556 patients), exenatide BID (6 studies, 505 patients) or dipeptidyl peptidase-4 (DPP-4) inhibitors (14 studies, 3744 patients) as add-on to metformin in subjects with type 2 diabetes. Baseline HbA1c, fasting glucose and body weight indicated above respective column. Means ± standard deviation are shown. For statistical analysis, see Result section.

Liraglutide *versus* sitagliptine

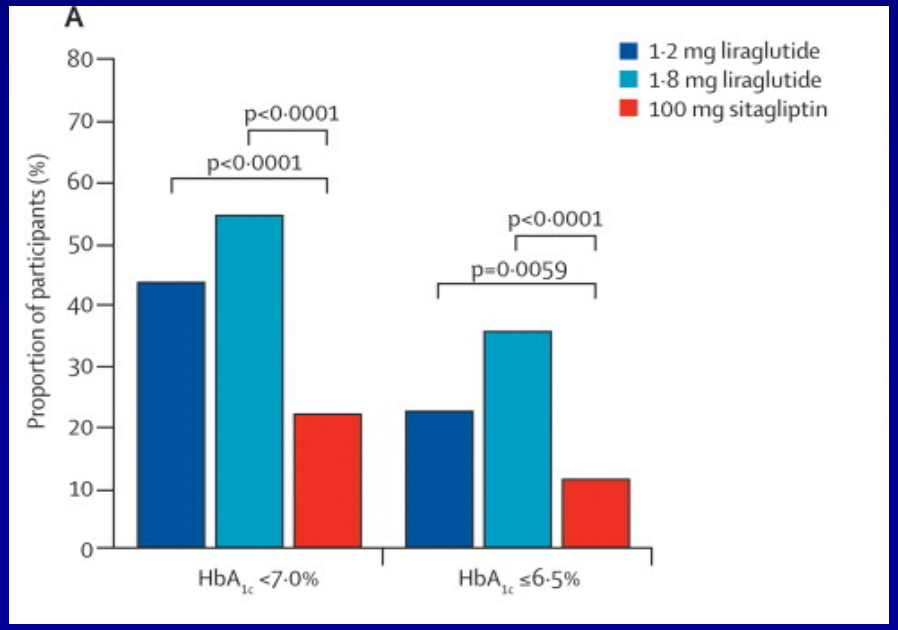


Efficacité sur le critère d'évaluation principal = réduction HbA1c

Sita 100 : - 0,90 (1,03-0,77)

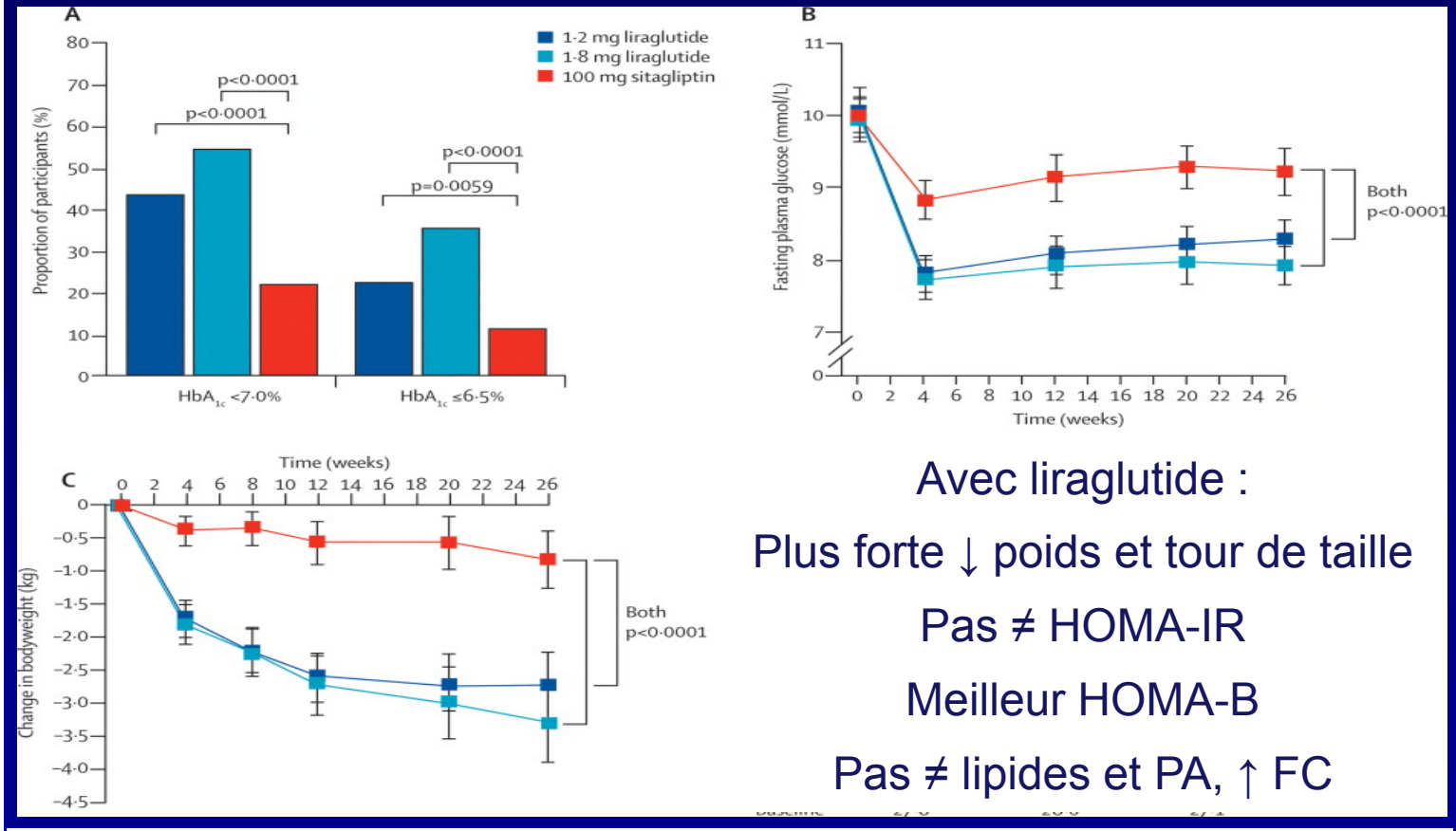
Lira 1,2 : - 1,24 (1,37-1,11)

Lira 1,8 : - 1,50 (1,63-1,37)



Pratley RE et al. Lancet 2010; 375: 1447-56

Liraglutide *versus* sitagliptine



Avec liraglutide :

Plus forte ↓ poids et tour de taille

Pas ≠ HOMA-IR

Meilleur HOMA-B

Pas ≠ lipides et PA, ↑ FC

	Mean change from baseline		
	1·2 mg liraglutide (n=221)	1·8 mg liraglutide (n=218)	100 mg sitagliptin (n=219)
Vital signs			
Systolic blood pressure (mm Hg)	−0·55 (−2·30 to 1·19)	−0·72 (−2·47 to 1·03)	−0·94 (−2·69 to 0·81)
Diastolic blood pressure (mm Hg)	−0·71 (−1·88 to 0·46)	0·07 (−1·10 to 1·23)	−1·78 (−2·95 to −0·61)
Heart rate (beats per min)	2·32 (1·17 to 3·48)	3·94 (2·79 to 5·08)	−0·64 (−1·79 to 0·52)

Hypoglycémies : rares (5 % des patients) et pas de différence entre liraglutide et sitagliptine

(1 seule hypo sévère avec lira 1,2 mg)

Pratley RE et al.

Lancet 2010; 375: 1447-56

Pas encore d'études sur des critères d'évaluation clinique

Méta-analyses des essais avec événements cardio-vasculaires

DPP-4 inhibiteurs

18 essais ≥ 24 semaines

N=4998 vs n=3546

Evénements CV majeurs (MACE)

RR vs comparateur (placebo ou actif)

RR : 0,48 (0,31-0,75) p = 0,001

RR vs placebo

RR : 1,05 (0,39-2,82) p = 0,92

Patil HR et al.

Am J Med 2012, 110, 826-33.

GLP-1 R agonistes

20 essais ≥ 12 semaines

N=6490 vs n=3995

Evénements CV majeurs (MACE)

RR vs comparateur (placebo ou actif)

RR : 0,74 (0,50-1,08) p = 0,12

RR vs placebo

RR : 0,46 (0,25-0,83) p = 0,009

Monami et al.

Exp Diabetes Res 2011, 215764

European Journal of Internal Medicine 23 (2012) 132–136

Contents lists available at SciVerse ScienceDirect

European Journal of Internal Medicine

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

Debate

Dipeptidyl peptidase-4 (DPP-4) inhibitors are favourable to Glucagon-Like Peptide-1 (GLP-1) agonists: No

Sten Madsbad *

Department of Endocrinology, Hvidovre University Hospital, 2650 Hvidovre, Denmark

Table 1
Comparison between DPP-4 inhibitors and GLP-1 receptor agonists.

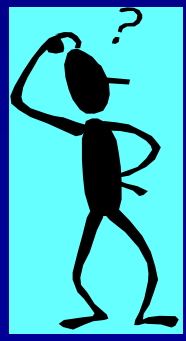
Characteristics/action	GLP-1 receptor agonists	DPP-4 inhibitors
Mode of administration	Injectable	Oral
Incretin action	GLP-1	GLP-1 and GIP
Effect on HbA1c	++	+
Effect on weight	++	−
Effect on insulin secretion	++	+
Effect on glucagon secretion	++	+
Effect on gastric emptying	++	−
Effect on appetite	++	−
Gastrointestinal side effects	++	−
Effect on systolic BT	++	+
Effect on lipids	++	+
Potential immunogenicity	++	−

Globalement, meilleure efficacité des agonistes GLP-1 même si parfois résultats hétérogènes … mais à quel prix ?

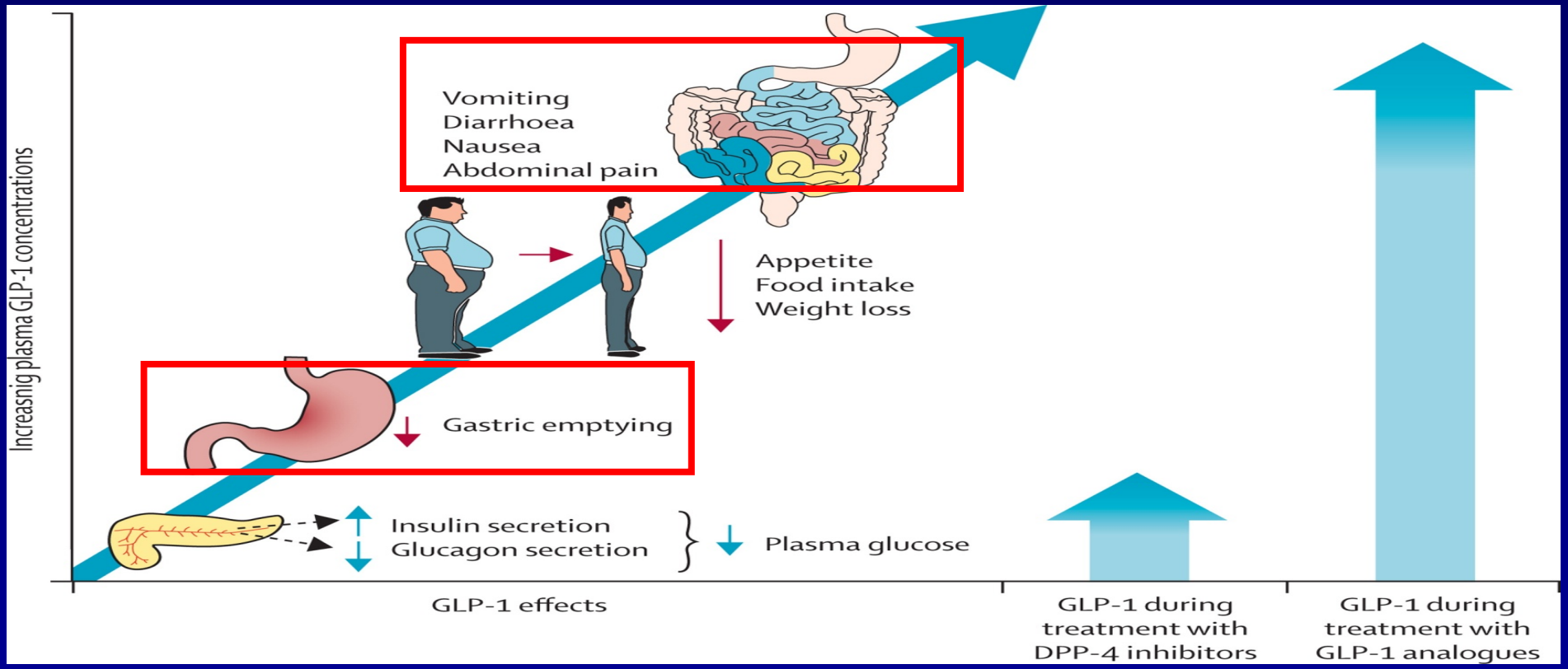
Agonistes du GLP-1 R vs inhibiteurs de la DPP-4

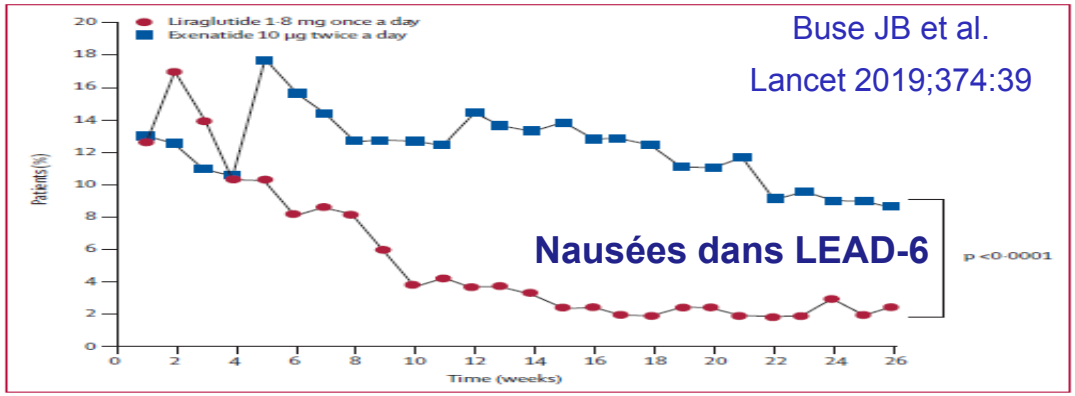
Plan de l'exposé

1. Glucagon-like peptide-1 et médicaments « incrétine »
2. Place respective dans le « position statement » ADA-EASD
3. Efficacité comparée (glucose, poids, pression artérielle)
4. Profil de sécurité/tolérance
5. Facilité d'administration/ coût
6. Propositions de prescription rationnelle au clinicien



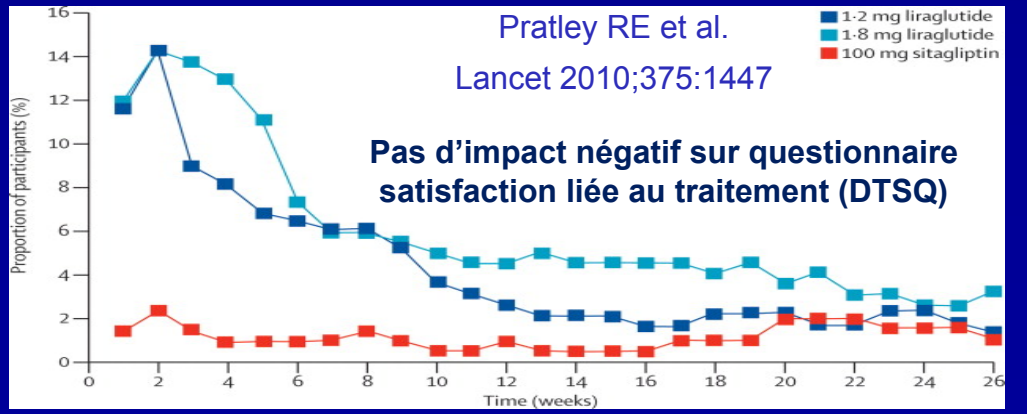
Les effets négatifs du GLP-1 sur la vidange gastrique dépendent des taux plasmatiques atteints (quasi nuls avec inhibiteurs de la DPP-4)





Buse JB et al.

Lancet 2019;374:39



Pratley RE et al.

Lancet 2010;375:1447

Pas d'impact négatif sur questionnaire satisfaction liée au traitement (DTSQ)

Comparaison des profils de sécurité/tolérance

	DPP-4 inhibiteurs	GLP-1 agonistes
Hypoglycémie	Non (sauf si avec SU)	Non (sauf si avec SU)
Poids	Neutre (ou faible perte)	Diminution (en moyenne modérée)
Effets indésirables	Infections respiratoires (?)	Nausées, vomissements Réactions au site d'injection Immunogénicité
Sécurité CV	A priori bonne Etudes en cours	A priori bonne Etudes en cours
Question en suspens	Pancréatite ? Cancer pancréas ??	Pancréatite ? Cancer pancréas ??

Grands essais de sécurité/efficacité cardio-vasculaire
Essais de non-infériorité/supériorité vs placebo
(sauf CAROLINA versus glimépiride)

	DPP-4 inhibiteurs
Sitagliptine	TECOS (n≈14.000)
Vildagliptine	-
Saxagliptine	SAVOR-TIMI53 (n≈16.500)
Linagliptine	CAROLINA (n≈6.000)
Alogliptine	EXAMINE (n≈5.400)

	GLP-1 R agonistes
Exénatide	-
Exénatide retard	EXSCEL (n≈9.500)
Liraglutide	LEADER (n≈8.750)
Lixisénatide	ELIXA (n≈6.000)
Dulaglutide	REWIND (n≈9.600)

Agonistes du GLP-1 R vs inhibiteurs de la DPP-4

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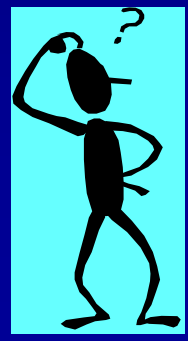

Facilité d'administration

Inhibiteurs DPP-4 : 1 comprimé par jour (2/j pour vildagliptine)

Agonistes des récepteurs du GLP-1

- Exénatide : 2 injections sc par jour
- Liraglutide, lixisénatide : 1 injection sc par jour
- Exénatide retard, dulaglutide… : 1 injection sc par semaine

Coût de la thérapie

Inhibiteurs DPP-4 : ≈ 1,50 Euros/jour

Agonistes des récepteurs du GLP-1

- Exénatide (2x10 µg/j) : ≈ 3,60 Euros/jour
- Liraglutide (1,2 mg/j) : ≈ 3,60 Euros/jour /jour

Coût au moins x 2

Agonistes du GLP-1 R vs inhibiteurs de la DPP-4

Plan de l'exposé

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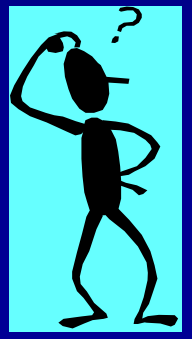


European Journal of Internal Medicine 23 (2012) 126–131

Contents lists available at SciVerse ScienceDirect

European Journal of Internal Medicine

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

Debate

Dipeptidylpeptidase-4 (DPP-4) inhibitors are favourable to glucagon-like peptide-1 (GLP-1) receptor agonists: Yes

André J. Scheen *

Division of Diabetes, Nutrition and Metabolic Disorders, University of Liège, Liège, Belgium
Division of Clinical Pharmacology, University of Liège, Liège, Belgium
Department of Medicine, CHU Sart Tilman, Liège, Belgium

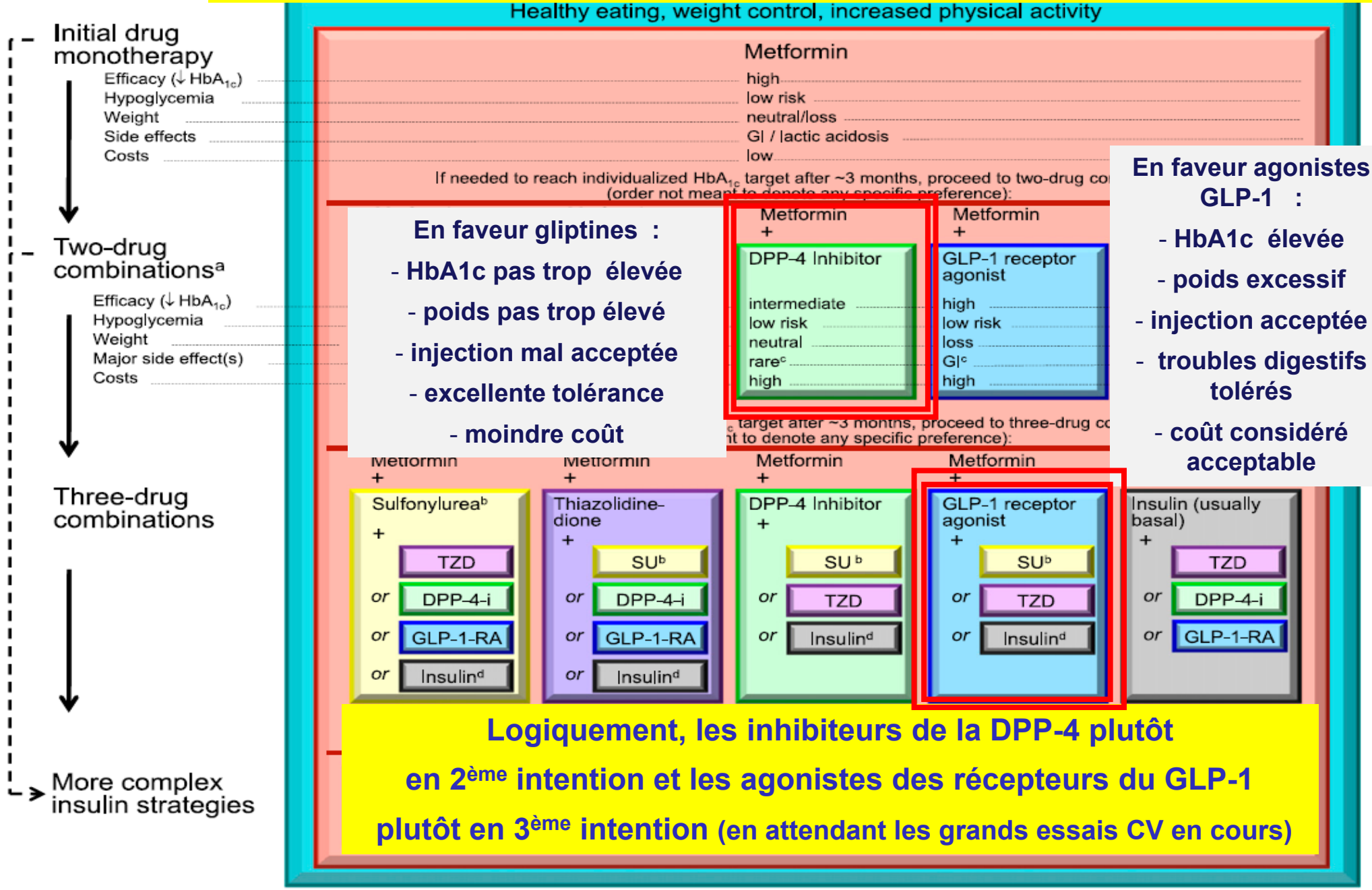
5. Which incretin-based therapy is the most favourable? Is it really a good question?

Only long-term trials with hard clinical outcomes would allow the demonstration of a clear superiority of one pharmacological class over another, but results of such trials are not available yet (and direct comparison trials would not be available in a near future). To my opinion, both types of therapies have a place in the management of T2DM, considering the individual profile of the patient, so that the question of whether DPP-4 inhibitors may be more favourable than GLP-1 receptor agonists (or vice versa) is probably a useless question from a practical clinical point of view.

A patient-centered approach ! (ADA-EASD Position Statement)

Position Statement

Choix multiples : fonction des caractéristiques/objectifs



En faveur gliptines :

- **HbA1c pas trop élevée**
- **poids pas trop élevé**
- **injection mal acceptée**
- **excellente tolérance**
- **moindre coût**

En faveur agonistes GLP-1 :

- **HbA1c élevée**
- **poids excessif**
- **injection acceptée**
- **troubles digestifs tolérés**
- **coût considéré acceptable**

Logiquement, les inhibiteurs de la DPP-4 plutôt en 2ème intention et les agonistes des récepteurs du GLP-1 plutôt en 3ème intention (en attendant les grands essais CV en cours)

Position Statement

Choix multiples : fonction des caractéristiques/objectifs

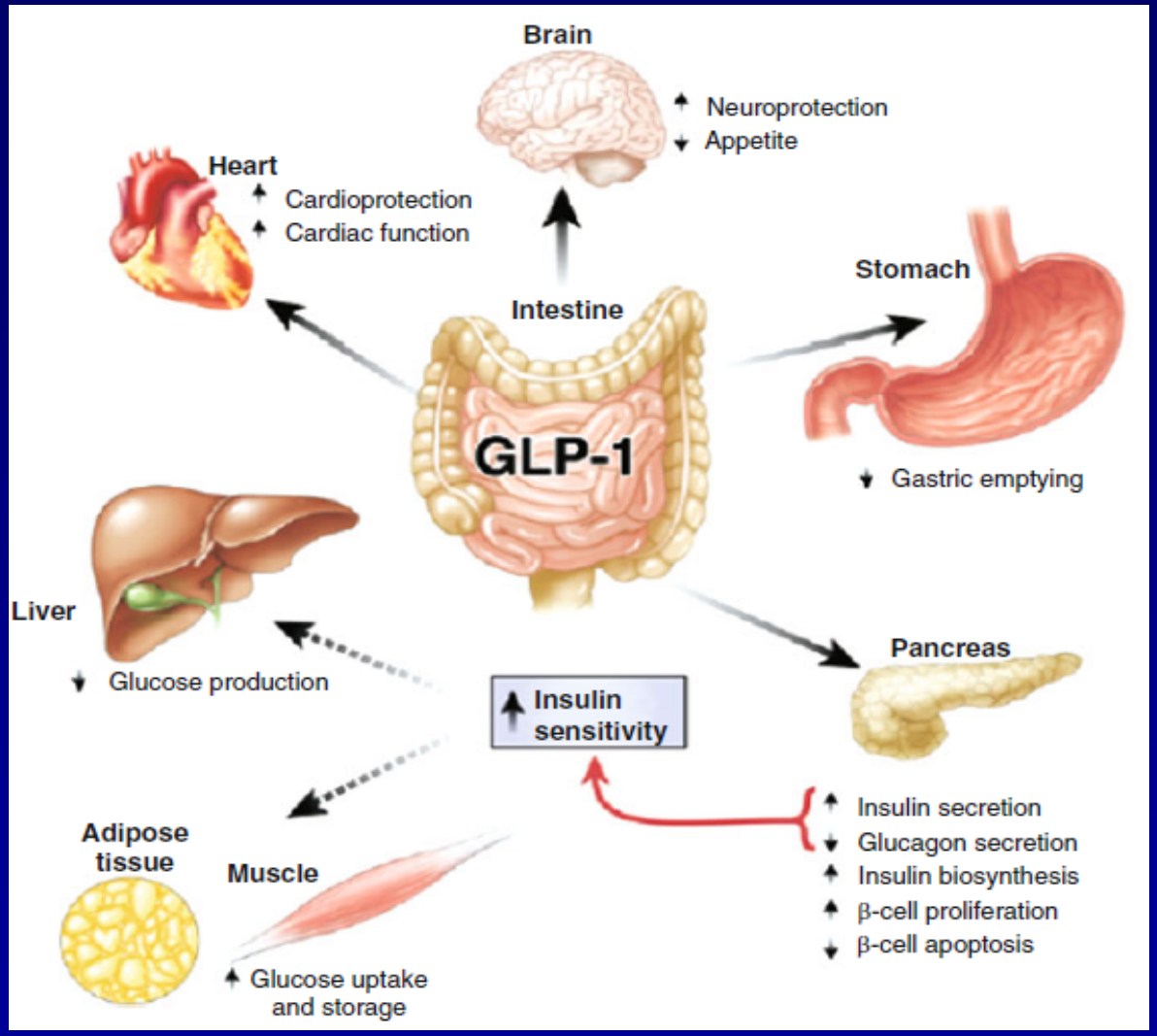
En faveur gliptines :

- **HbA1c pas trop élevée**
- **poids pas trop élevé**
- **injection mal acceptée**
- **excellente tolérance**
- **moindre coût**

En faveur agonistes GLP-1 :

- **HbA1c élevée**
- **poids excessif**
- **injection acceptée**
- **troubles digestifs tolérés**
- **coût considéré acceptable**

Pour une médecine personnalisée centrée sur le patient !



Merci pour votre attention

Rôle du GLP-1 dans le contrôle de la glycémie

Figure 1.

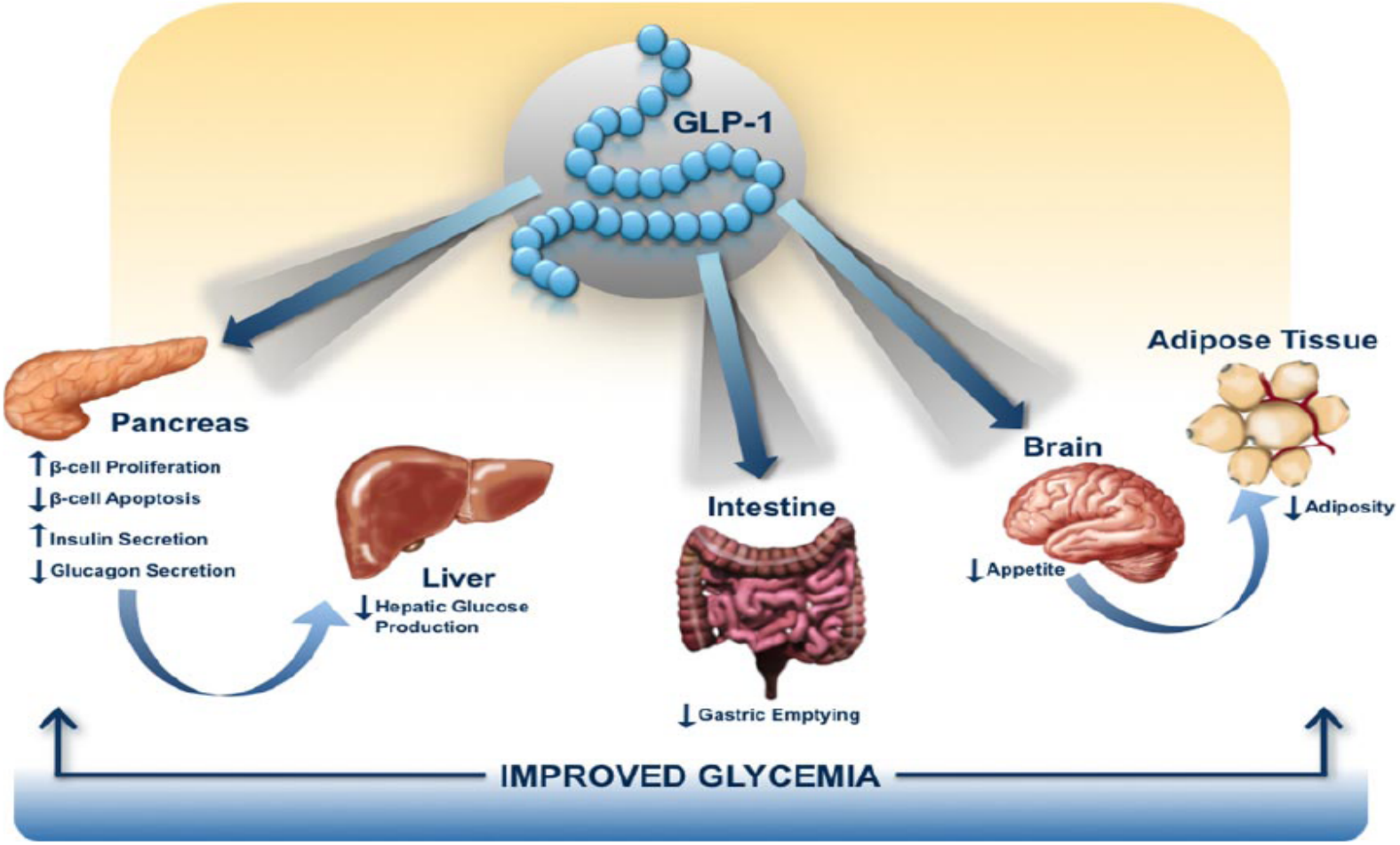


Figure 1. GLP-1 targets multiple organs to improve glucose control in T2DM. GLP-1 acts directly and indirectly on several peripheral tissues that contribute to lowering of blood glucose levels. These include potent effects on the pancreatic β-cell to stimulate insulin secretion, inhibition of α-cell glucagon secretion that reduces hepatic glucose production, a decrease in gastric motility, and a reduction in appetite that contributes to weight loss, reduced levels of adipocytokines, and decreased inflammation.

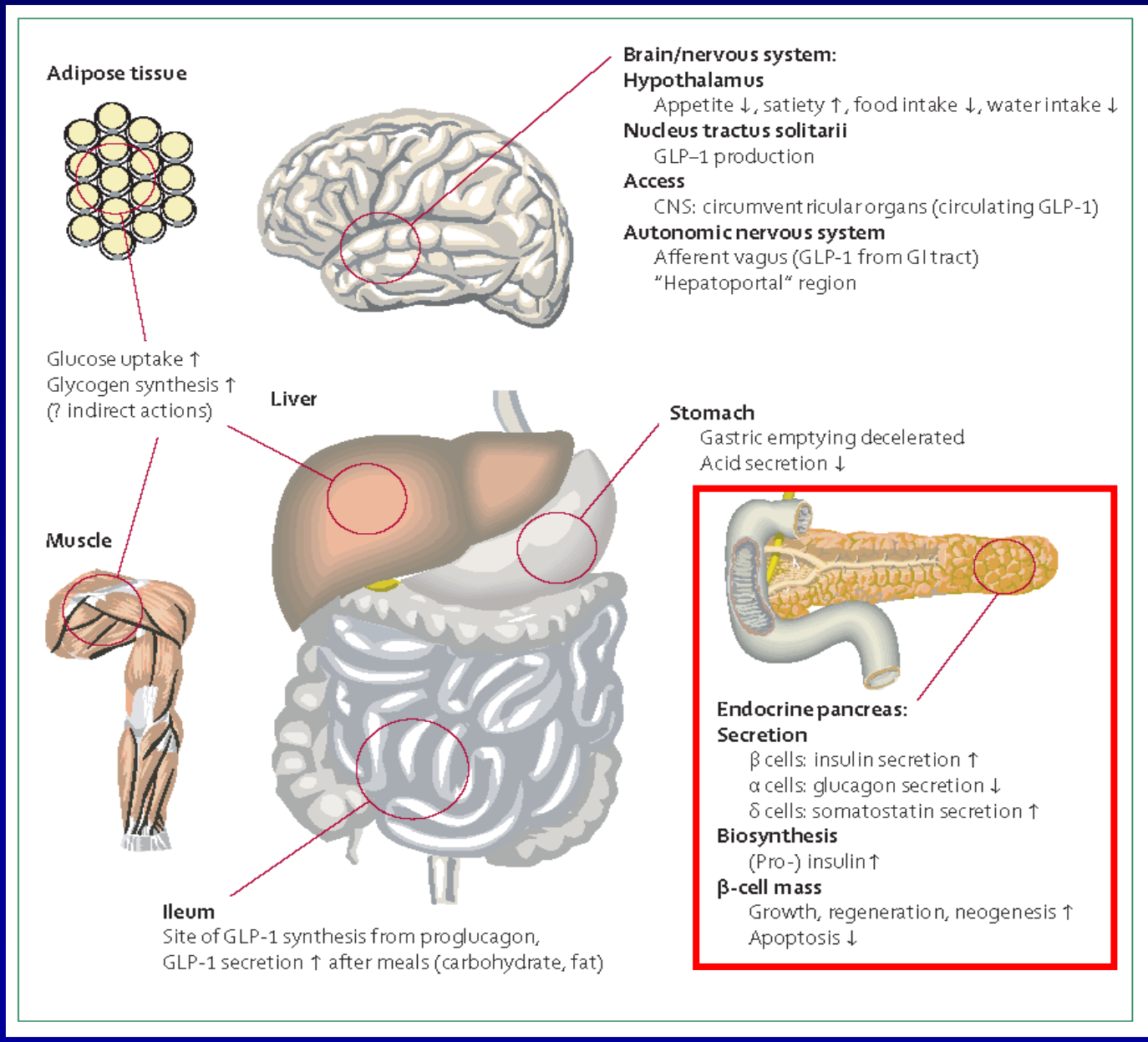
Effets extra-pancréatiques du GLP-1

Effets métaboliques indirects

(via ↑ insuline et ↓ glucagon)

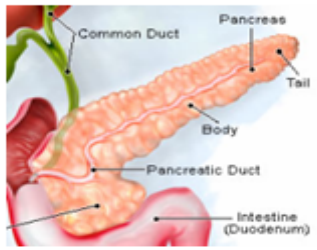
1) Foie
2) Muscle
3) Tissu adipeux

Drucker, Lancet 2006; 368: 1696–705

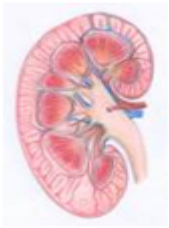


Effets extra-pancréatiques du GLP-1

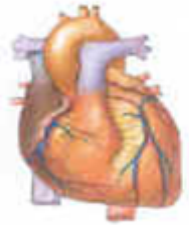
- glucose-dependent insulin secretion/synthesis
- beta-cell mass (animals)
- glucagon secretion



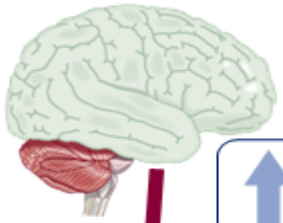
GLP-1



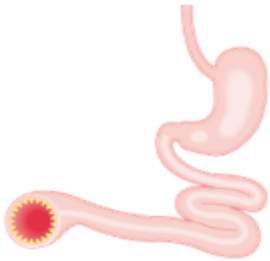
- Diuresis and sodium excretion



- Glucose uptake
- Activation of anti-apoptotic kinases
- Endothelial function



- Satiety



- Food intake
- Gastric emptying

Greeve et al. Emerging cardiovascular actions of the incretin hormone glucagon-like peptide-1: potential therapeutic benefits beyond glycaemic control ? Br J Pharmacol 2009; 157: 1340- 51.

Cardiovascular Biology of the Incretin System

John R. Ussher and Daniel J. Drucker

Endocrine Reviews, April 2012, 33(2):0000–0000

Figure 3.

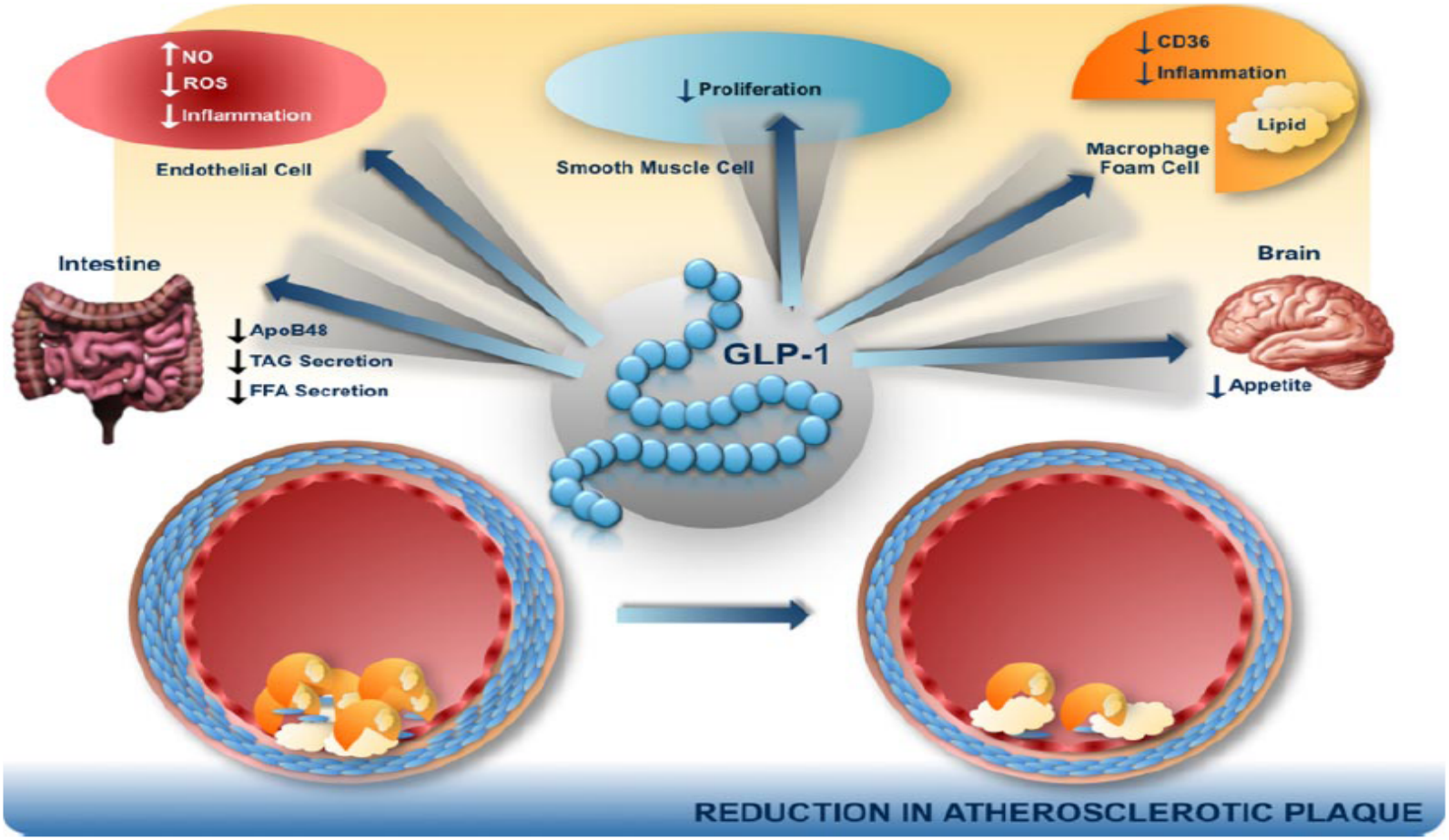


Figure 3. Antiatherosclerotic potential of GLP-1 action. The direct actions of GLP-1 on blood vessels and macrophages and on the regulation of plasma lipid profiles may impact the development and/or progression of atherosclerotic plaques.

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Department of Medicine, CHU Sart Tilman, Liège, Belgium

Table 1

Head-to-head trials comparing a DPP-4 inhibitor and a GLP-1 receptor agonist in T2DM patients already treated with metformin (= or > 1500 mg/day).

Reference	Duration (wks)	Intervention (mg/day) [a]	n	Baseline HbA1c (%)	Δ HbA1c (%)	HbA1c <7% (% pts)	FPG (mmol/l)	Δ BW (kg)	SBP/DBP mmHg	HR bpm	LDL-C mmol/l	HDL-C mmol/l	Tg mmol/l
DeFronzo et al. (2008) [18]	2	Sitagliptin 100	61 [b]	8.5	NA	NA	−0.83 [c]	−0.3	NA	NA	NA	NA	NA [d]
		Exenatide 2x 5 μg → 2×10 μg	61 [b]	8.5	NA	NA	−1.06	−0.8	NA	NA	NA	NA	NA
Bergenstal et al. (2010) [19]	26	Sitagliptin 100	166	8.5	−0.9	30	−0.9	−0.8	+0.3/NA	NA	+0.04	+0.05	−0.10
		Exenatide 2 mg once weekly sc	160	8.6	−1.5	59	−1.8	−2.3	−3.7/NA	NA	−0.03	+0.05	−0.10
Wysham et al. (2011) [21]	52	Shift from sitagliptin to exenatide (26–52 wks)	116	7.5	−0.31	+17	−0.7	−1.1	−2.7/−0.4	NA	−0.09	−0.01	+0.03
Pratley et al. (2010) [20]	26	Sitagliptin 100	219	8.5	−0.9	21	−0.83	−0.96	−1.78/−0.94	−0.64	+0.13	0	−0.40
		Liraglutide 1.2	225	8.4	−1.24	44	−1.87	−2.86	−0.55/−0.71	+2.32	+0.08	0	−0.19
		Liraglutide 1.8	221	8.4	−1.50	55	−2.14	−3.38	−0.72/+0.07	+3.94	+0.05	0	−0.43
Pratley et al. (2011) [22]	52	Sitagliptin 100	151	8.5	−0.88	27	NA	−1.16	−1.03/−1.47	+0.09	+0.17	+0.01	−0.23
		Liraglutide 1.2	135	8.4	−1.29	50	NA	−2.78	−0.37/−0.53	+1.72	+0.09	+0.01	−0.10
		Liraglutide 1.8	150	8.4	−1.51	63	NA	−3.68	−2.55/−0.87	+3.09	+0.09	+0.02	−0.32

Δ: change versus baseline. NA: not available. FPG: fasting plasma glucose. BW: body weight. SBP: systolic blood pressure. DBP: diastolic blood pressure. HR: heart rate. LDL-C: LDL cholesterol. HDL-C: HDL cholesterol. Tg: triglycerides.

(a) Except for exenatide.

(b) Cross-over short-term trial.

(c) 2 h-postprandial glucose also available: significantly lower with exenatide compared to sitagliptin (7.39 mmol/l versus 11.56 mmol/l, $p<0.0001$).

(d) Postprandial triglycerides also available: reduction with both incretin-based therapies but 10% greater reduction with exenatide ($p=0.0118$).

Incretin-based therapy: how do incretin mimetics and DPP-4 inhibitors fit into treatment algorithms for type 2 diabetic patients?

M. Nauck, Prof. Dr. med. [a,*], U. Smith, MD, PhD [b]

Best Practice & Research Clinical Endocrinology & Metabolism 23 (2009) 513–523

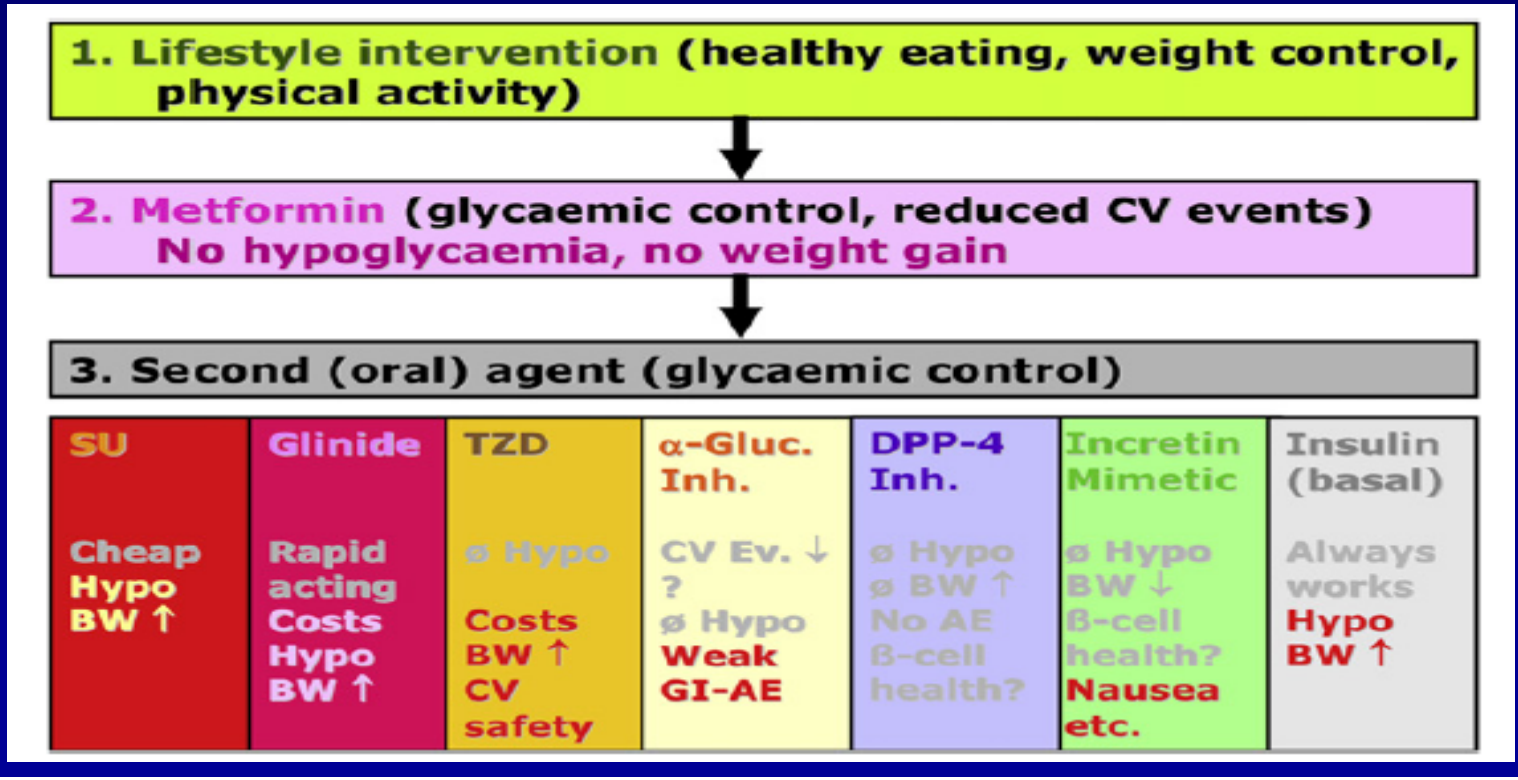


Fig. 1. Treatment algorithm for initiating anti-hyperglycaemic treatment in patients with type 2 diabetes. This algorithm is based on the 'stepped approach' to respond to disease progression. In contrast to recommendations issued by the ADA and EASD, the present algorithm lists all available drug classes including incretin-based medications. Abbreviations: CV: cardiovascular; SU: sulfonylurea; hypo: hypoglycaemia; TZD: thiazolidinediones; Gluc.: Glucosidase; DPP-4: Dipeptidyl peptidase-4; BW: body weight; Ev.: events; AE: adverse events.

Review Article

Choosing between GLP-1 Receptor Agonists and DPP-4 Inhibitors: A Pharmacological Perspective

Dominique Xavier Brown and Marc Evans

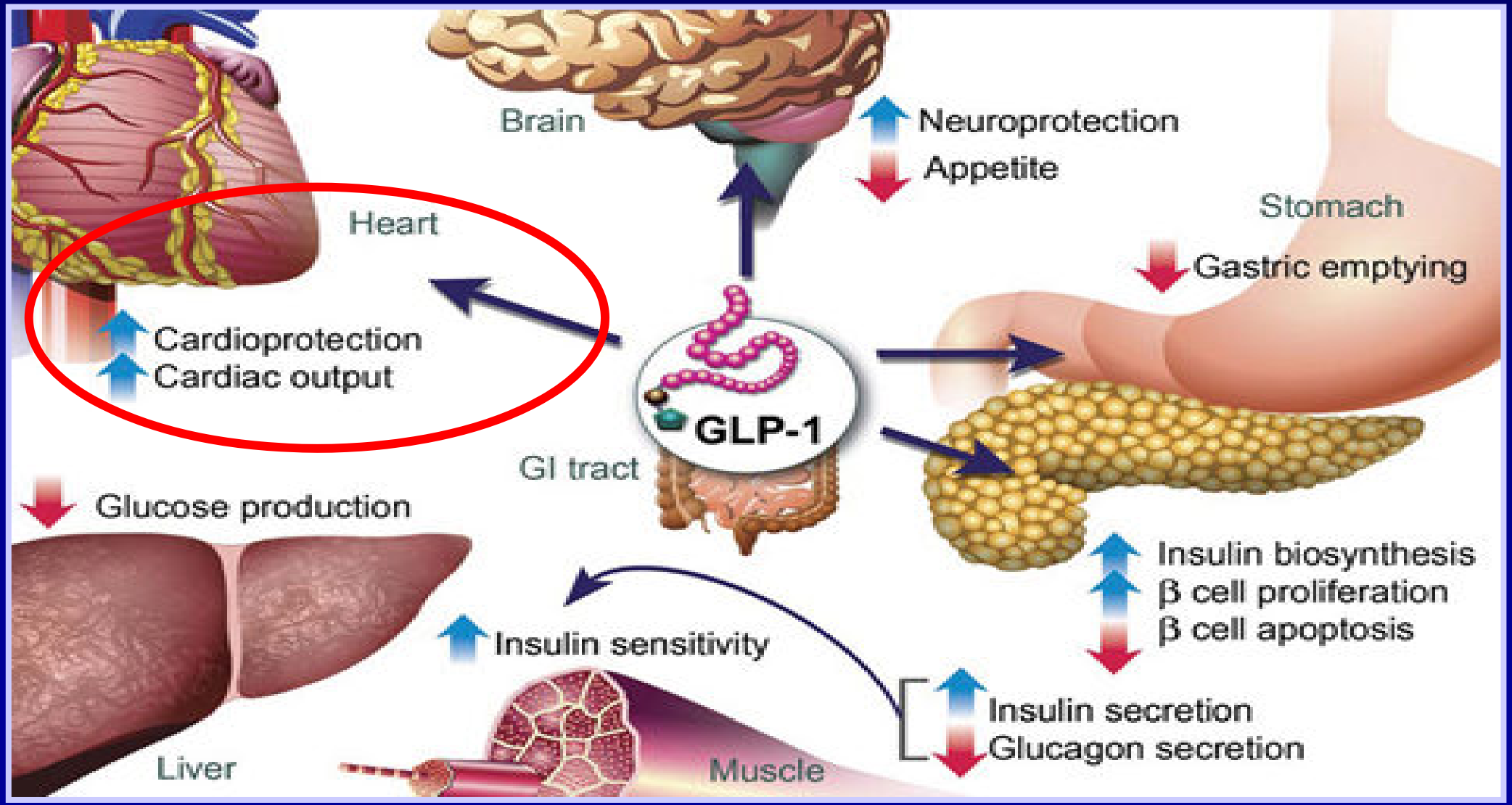
Journal of Nutrition and Metabolism
Volume 2012, Article ID 381713, 10 pages
doi:10.1155/2012/381713

In recent years the incretin therapies have provided a new treatment option for patients with type 2 diabetes mellitus (T2DM). The incretin therapies focus on the increasing levels of the two incretin hormones, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). This results in increased glucose dependent insulin synthesis and release. GLP-1 receptor agonists such as liraglutide and exenatide exert an intrinsic biological effect on GLP-1 receptors directly stimulating the release of insulin from pancreatic beta cells. DPP-4 inhibitors such as sitagliptin and linagliptin prevent the inactivation of endogenous GLP-1 and GIP through competitive inhibition of the DPP-4 enzyme. Both incretin therapies have good safety and tolerability profiles and interact minimally with a number of medications commonly prescribed in T2DM. This paper focuses on the pharmacological basis by which the incretin therapies function and how this knowledge can inform and benefit clinical decisions. Each individual incretin agent has benefits and pitfalls relating to aspects such as glycaemic and nonglycaemic efficacy, safety and tolerability, ease of administration, and cost. Overall, a personalized medicine approach has been found to be favourable, tailoring the incretin agent to benefit and suit patient's needs such as renal impairment (RI) or hepatic impairment (HI).

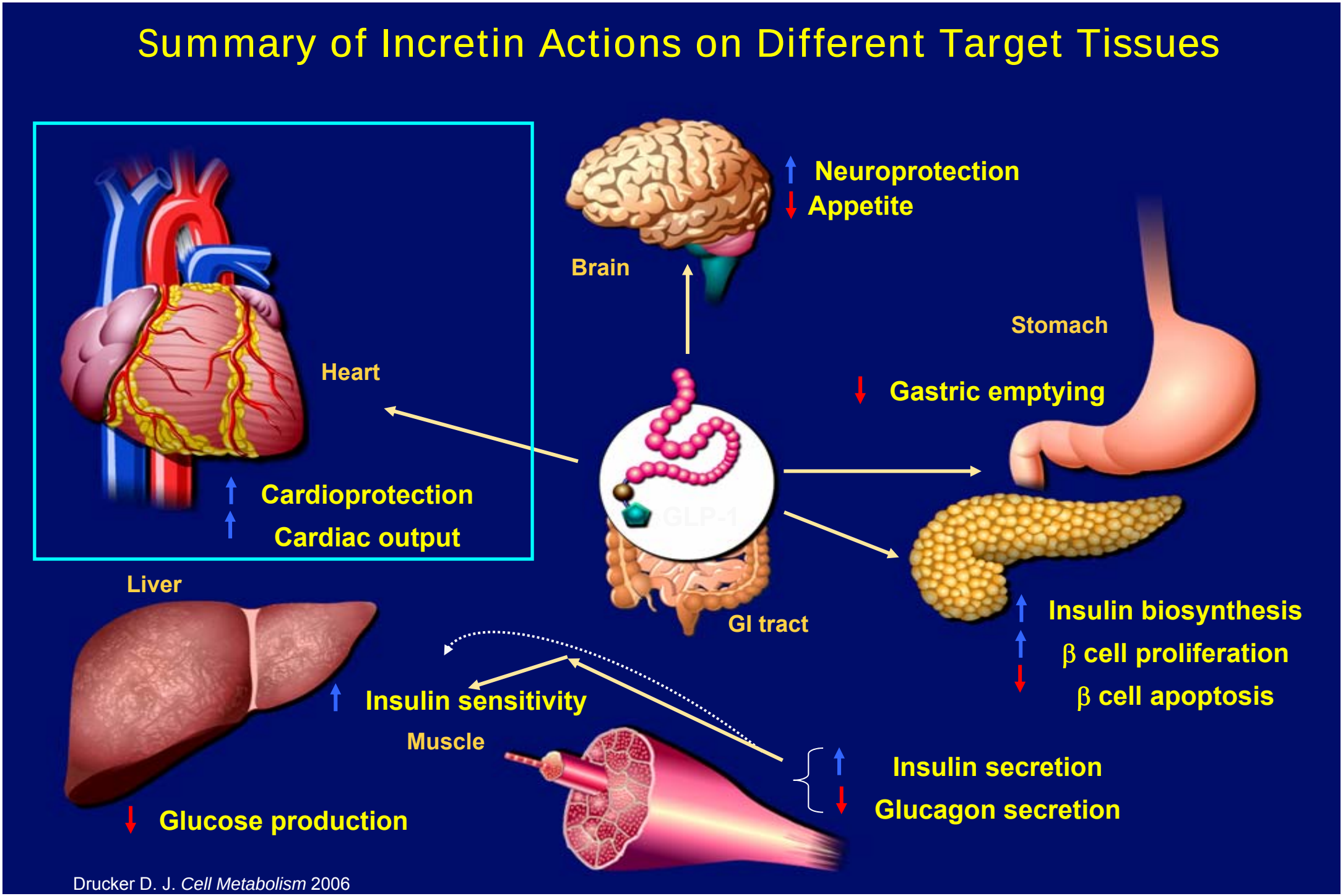
The Extrapancreatic Effects of Glucagon-Like Peptide-1 and Related Peptides

J Clin Endocrinol Metab, June 2009, 94(6):1843–1852

Rania Abu-Hamdah, Atoosa Rabiee, Graydon S. Meneilly, Richard P. Shannon, Dana K. Andersen, and Dariush Elahi

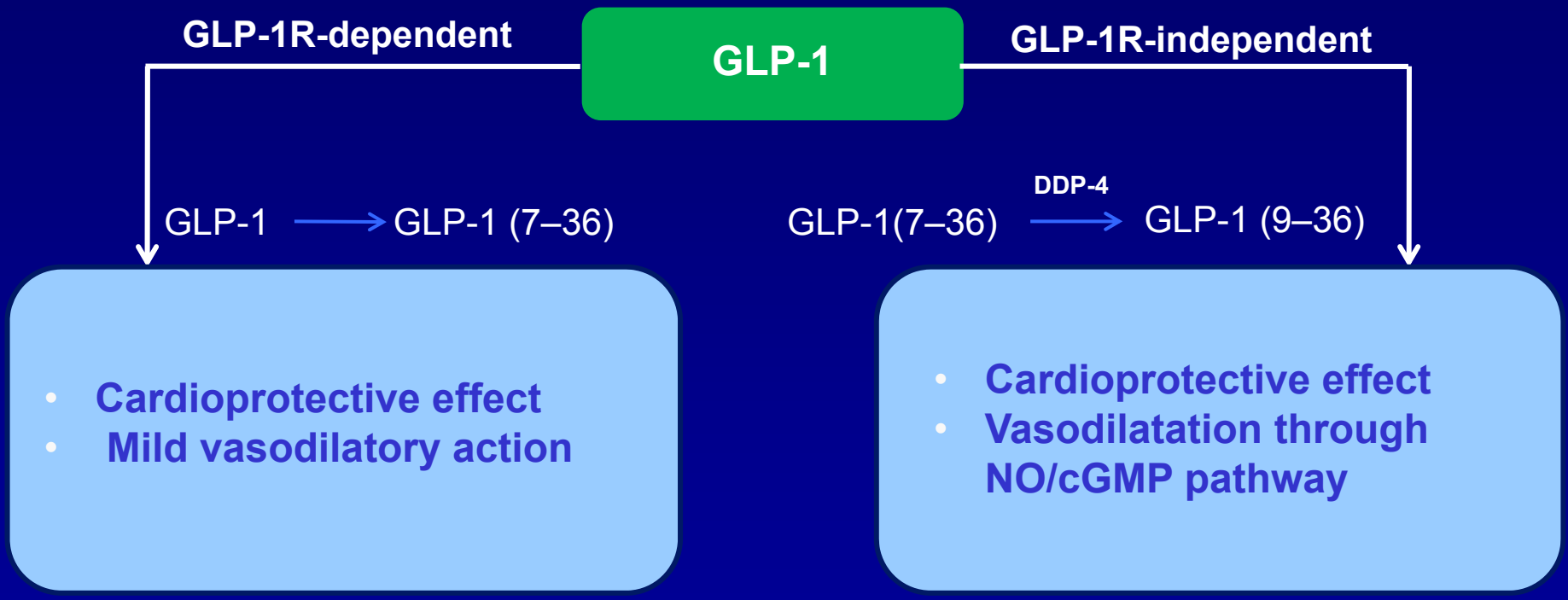


Summary of Incretin Actions on Different Target Tissues



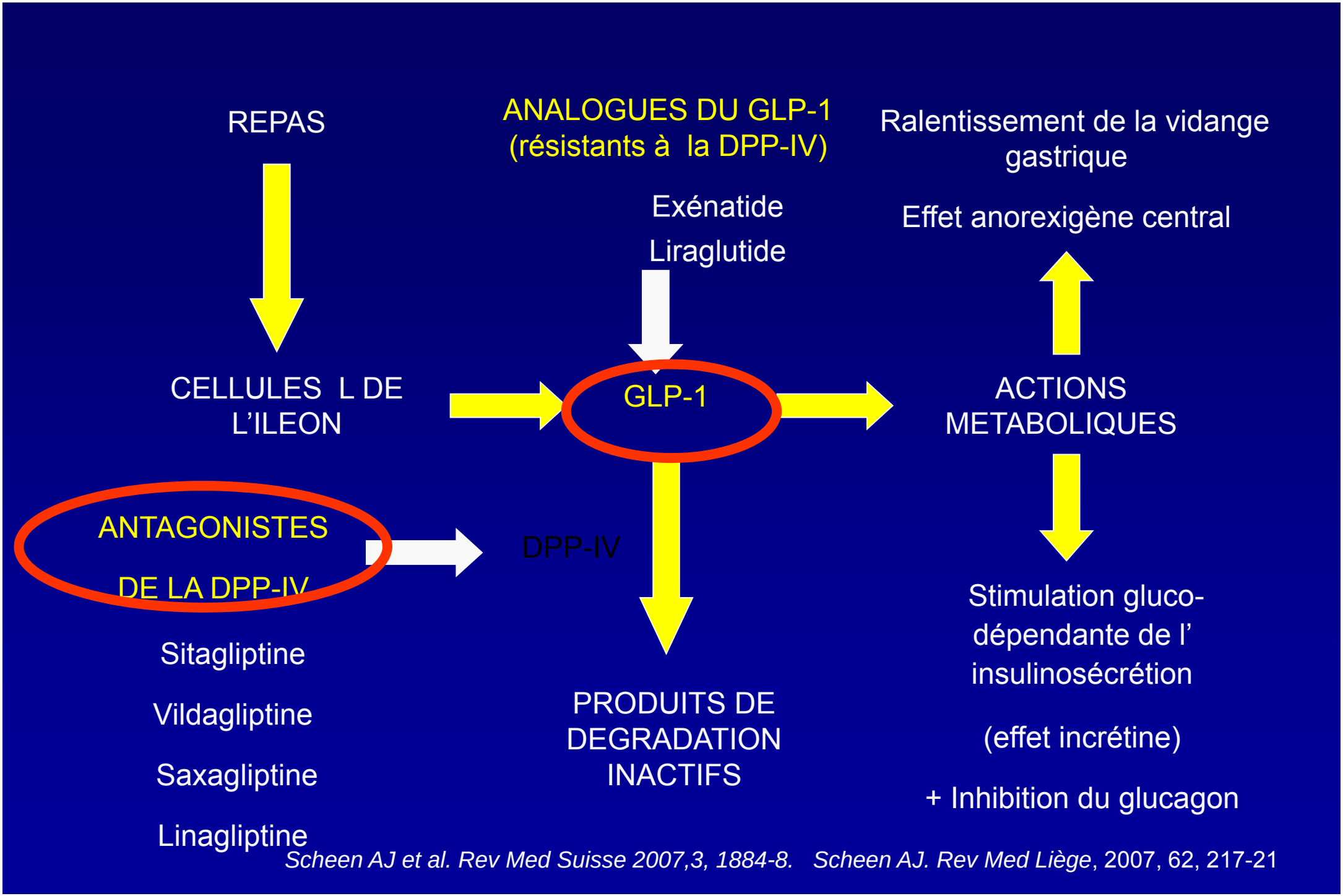
Drucker D. J. *Cell Metabolism* 2006

Potential Cardioprotective Effects of GLP-1



Cardioprotective and vasodilatory actions of GLP 1 receptor are mediated through both GLP 1 receptor dependent and independent pathways

Ban K *et al. Circulation* 2008;117:2340–50.

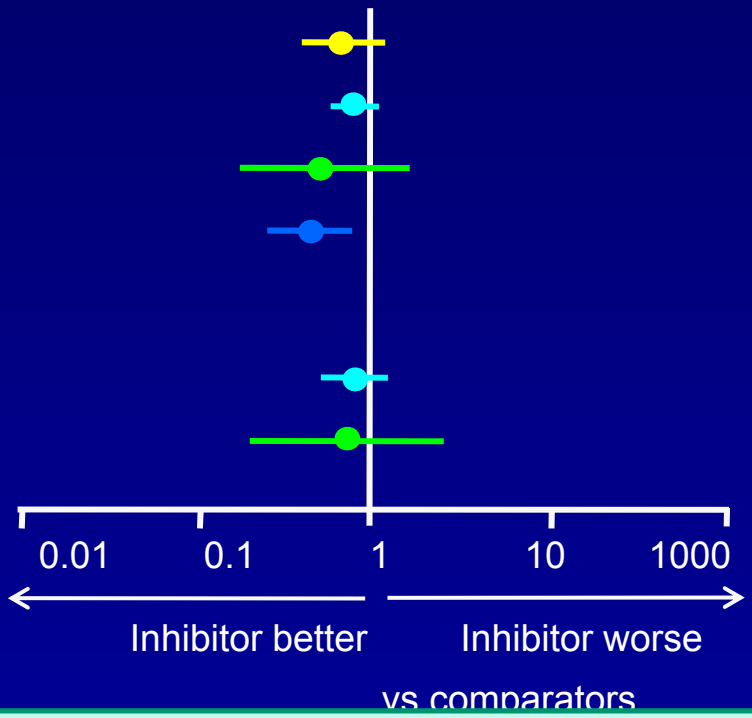


Scheen AJ et al. Rev Med Suisse 2007,3, 1884-8. *Scheen AJ. Rev Med Liège*, 2007, 62, 217-21

Sécurité cardiovasculaire des inhibiteurs de la DPP-4

Incidence

	DPP-4 Inhibitor	vs Comparator
Pooled analysis		
Sitagliptin (100 mg qd)	0.6%	0.9%
Vildagliptin (50 mg bid)	1.32%	1.64%
Alogliptin (25 mg qd)	0.28%	0.50%
Saxagliptin (2.5-100 mg qd)	0.7%	1.4%
Elevated CV risk*		
Vildagliptin (50 mg bid)	3.72%	5.08%
Alogliptin (25 mg qd)	0.46%	0.60%



* Vildagliptin: Patients with previous history of CCV events

Alogliptin: Defined as diabetes + 2 of the following: presence of cardiac, cerebral or peripheral vascular disease, >65 yr old, dislipidaemia, hypertension, current smoking

Méta-analyse

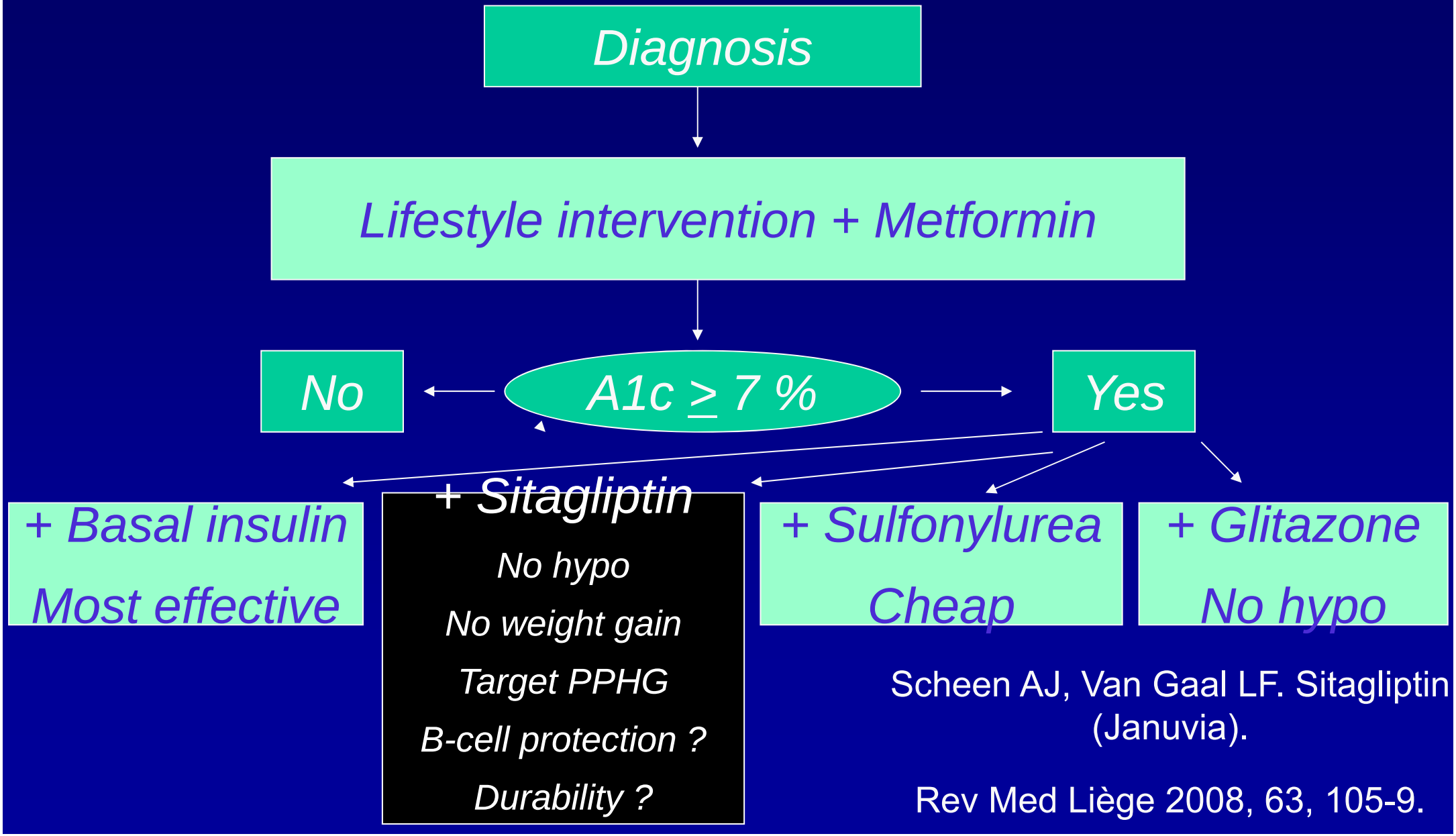
Evénements CV : RR = 0.76 [0.46-1.28]

Décès toute cause : RR = 0.78 [0.40-1.51]

Schweizer et al; Diabetes Obes Metab, 2010; White et al; ADA 2010, Poster 391-P
Williams Herman et al; BMC Endocr Disord 2010; Frederich et al; Postgrad Med 2010

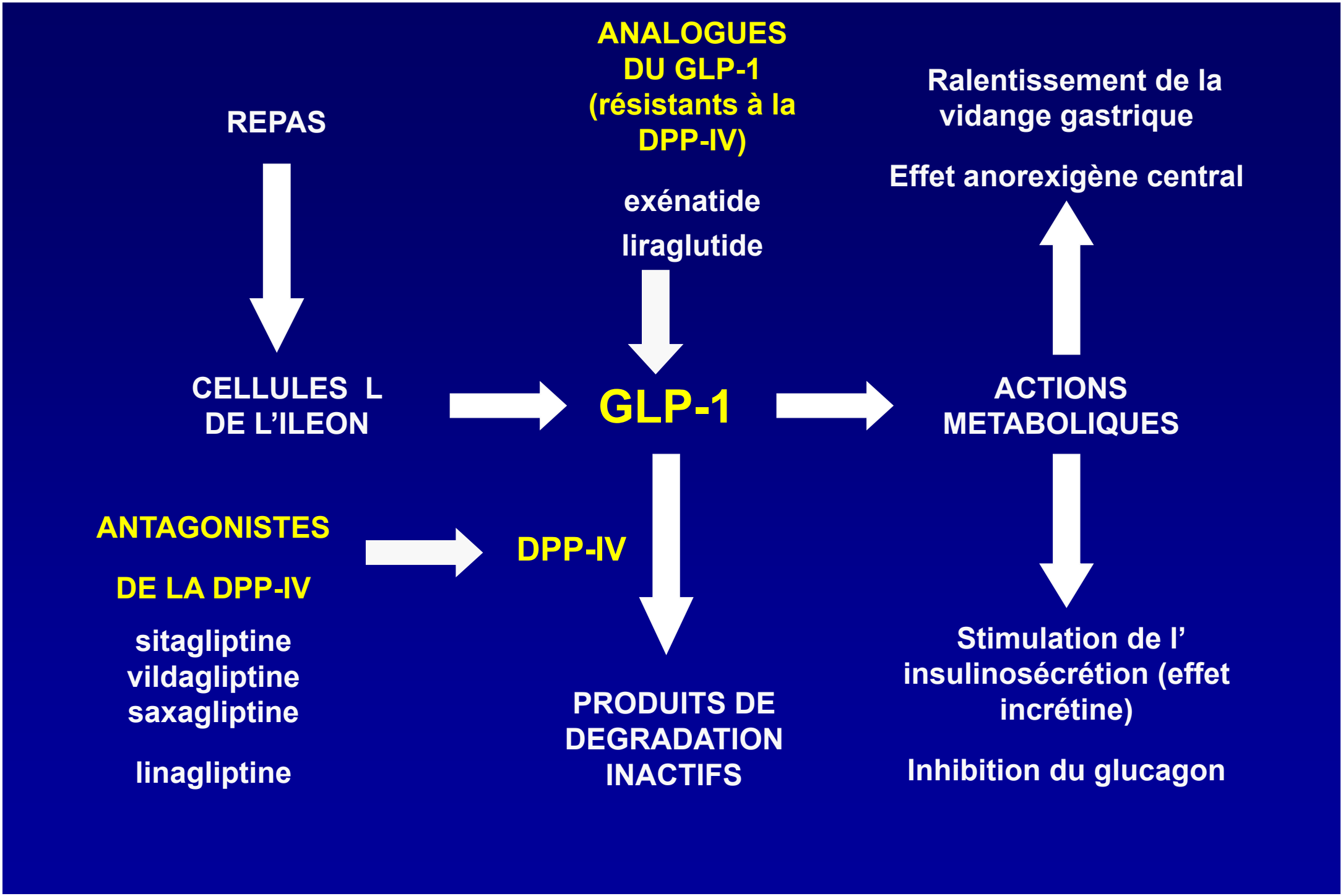
Monami M et al. Nutr Metab Cardiovasc Dis.2010;20:224-35.

Algorithm for the metabolic management of type 2 diabetes

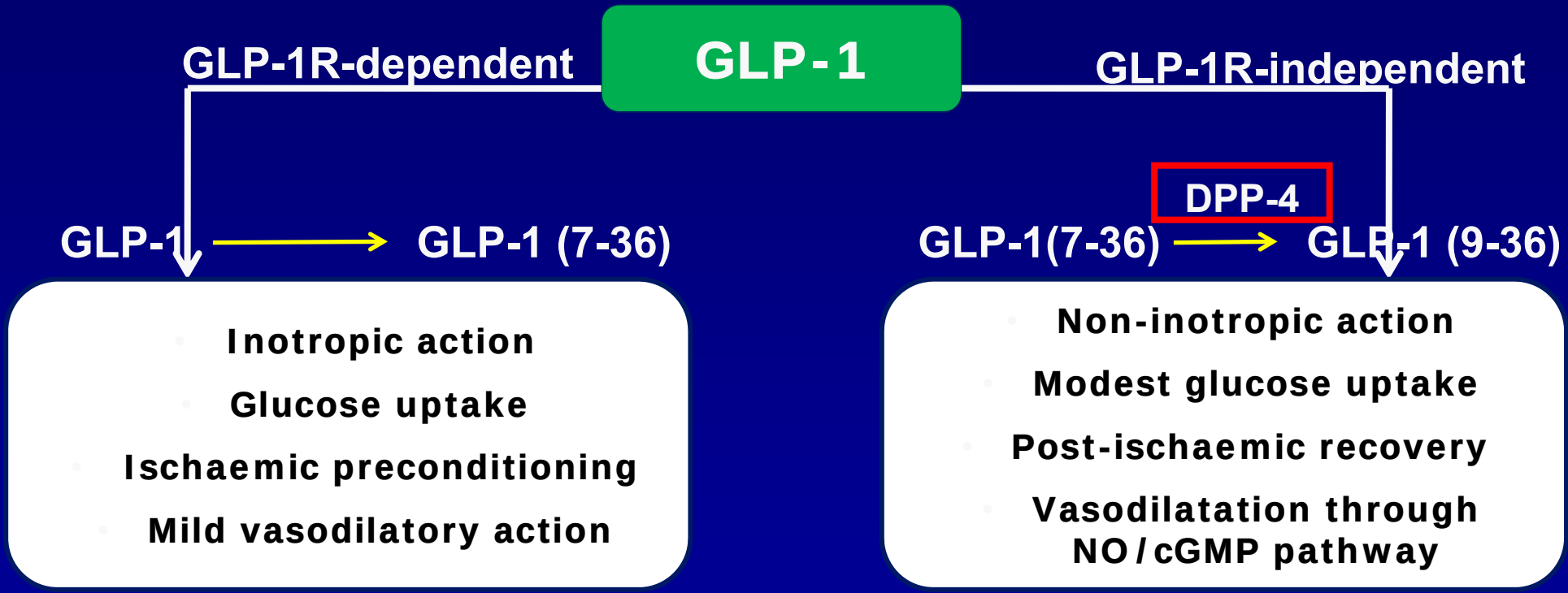


Scheen AJ, Van Gaal LF. Sitagliptin (Januvia).

Rev Med Liège 2008, 63, 105-9.


REPAS
ANALOGUES DU GLP-1 (résistants à la DPP-IV)
exénatide
liraglutide
Ralentissement de la vidange gastrique
Effet anorexigène central
CELLULES L DE L'ILEON
GLP-1
ACTIONS METABOLIQUES
ANTAGONISTES DE LA DPP-IV
sitagliptine
vildagliptine
saxagliptine
linagliptine
DPP-IV
PRODUITS DE DEGRADATION INACTIFS
Stimulation de l' insulinosécrétion (effet incrétine)
Inhibition du glucagon

Le GLP-1 exerce des effets médiés par le récepteur du GLP-1 mais aussi indépendants de ce récepteur



Ban *et al. Circulation* 2008;117:2340–50

Quid si échec d'une bithérapie (orale) ?