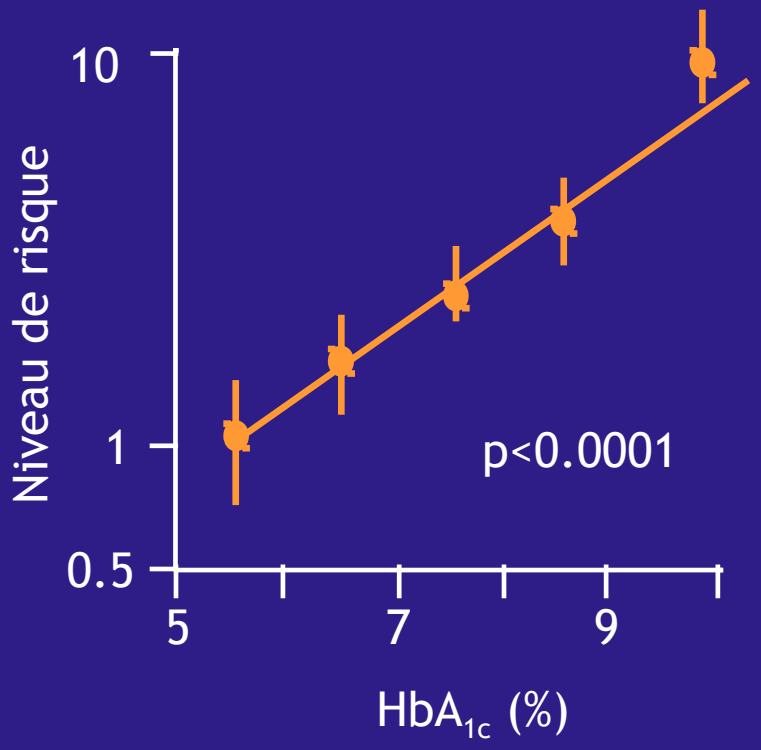
Corrélation épidémiologique entre le contrôle glycémique et le risque de complications

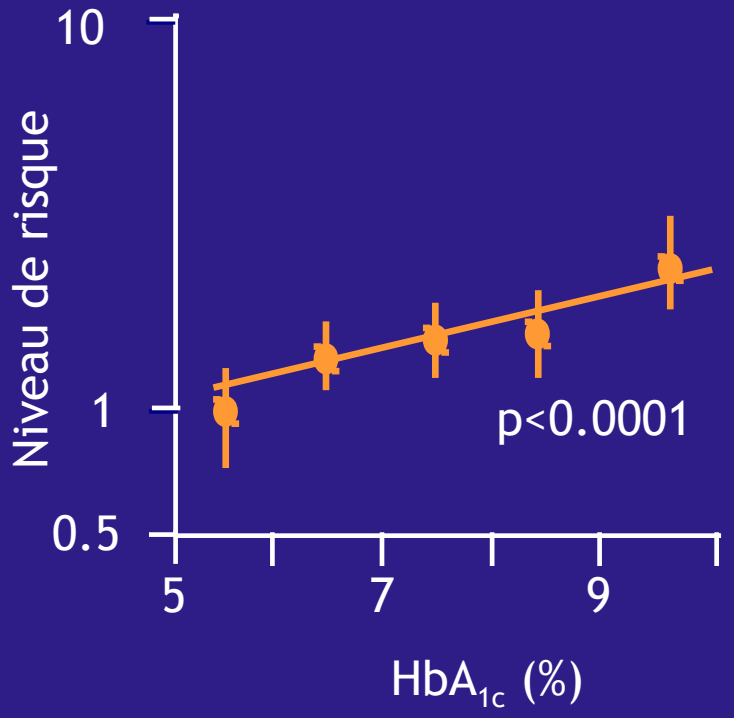
Endpoints microvasculaires

37% réduction du risque par 1% de diminution en HbA_{1c}



IM fatal et non-fatal

14% réduction du risque par 1% de diminution en HbA_{1c}



IM = Infarctus du Myocarde .

Stratton I, et al. BMJ 2000;321:405—12.

Glycaemic targets for the management of type 2 diabetes

- Glycaemic targets for the management of people with type 2 diabetes as recommended by various organisations[1–5]

Organisation	HbA_{1c} (%)	FPG (mmol/L)	PPG (mmol/L)
ADA-EASD[1]	**<7**	**–**	**–**
IDF-Europe[2]	**<6.5**	**<6.0 (<110*)**	**<8.0 (<145*)**
AACE[3]	**≤6.5**	**<6.1 (<110*)**	**<7.8 (<140*)**
NICE[4]	**<6.5****	**–**	**<8.5 (<153*)**
DDG[5]	**<6.5**	**–**	**–**

*mg/dL

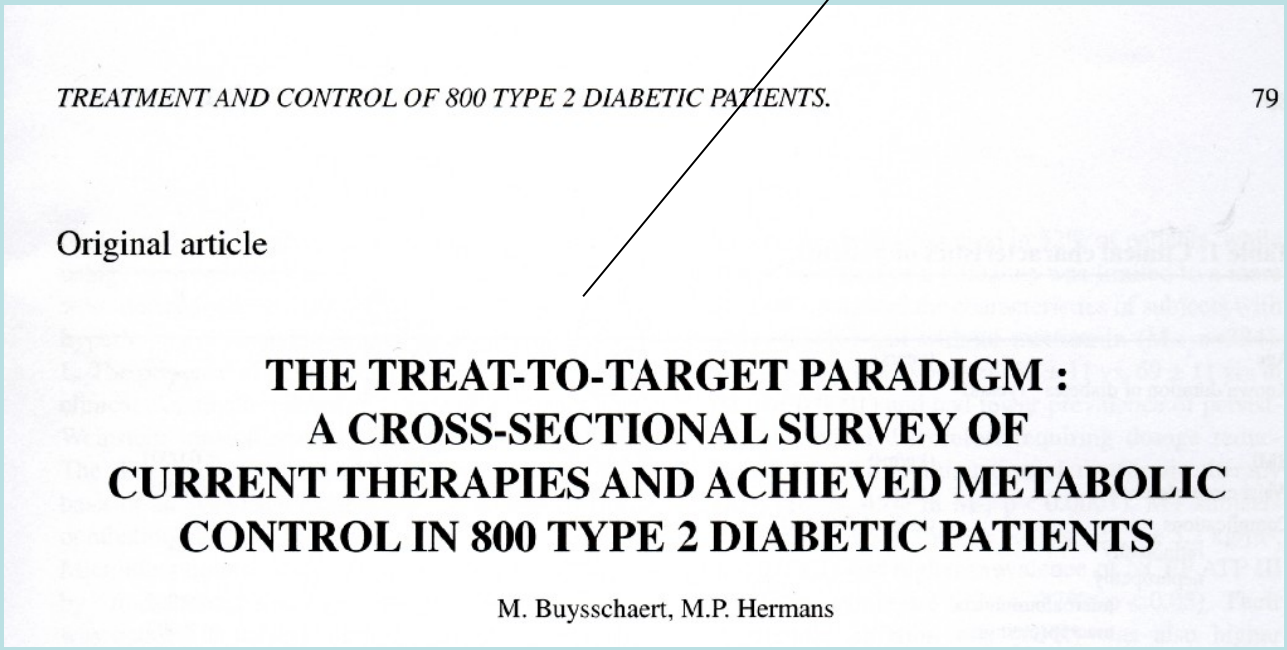
**<7.5% for people receiving ≥2 oral glucose-lowering drugs or those requiring insulin

FPG, fasting plasma glucose; PPG, postprandial glucose; ADA, American Diabetes Association; IDF, International Diabetes Federation; AACE, American Association of Clinical Endocrinologists; NICE, National Institute of Clinical Excellence; DDG, Deutschen Diabetes-Gesellschaft (German Diabetes Association)

1. Nathan DM, et al. Diabetologia. 2009;52:17-30. 2. IDF. Global Guidelines 2005. 3. Rodbard HW, et al. Endocr Pract. 2007;13(Suppl. 1):1-68. 4. NICE clinical guideline 87. Quick reference guide. May 2009. 5. Matthaei S, et al. German Diabetes Association guidelines. October 2008.

HbA1c : 7.9 ±1.6 %

Patients avec HbA1c < 7% : 30%



Original article

THE TREAT-TO-TARGET PARADIGM : A CROSS-SECTIONAL SURVEY OF CURRENT THERAPIES AND ACHIEVED METABOLIC CONTROL IN 800 TYPE 2 DIABETIC PATIENTS

M. Buysschaert, M.P. Hermans

Acta Clinica Belgica, 2005

Original article

METABOLIC (GLYCAEMIC, LIPIDIC) AND BLOOD PRESSURE CONTROL IN 101 TYPE 2 DIABETIC PATIENTS ON FIRST ADMISSION TO DIABETES CENTRES

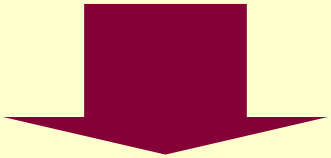
D. Lienart[1], V. Preumont[1,2], O. Alexopoulou[1], J. Donckier[2], A. Colson[1], M.P. Hermans[1], M. Buysschaert[1]

Key words : type 2 diabetes, general practionners, diabetes centres, HbA1c

HbA1c: 8.8 ±2.3%

Acta Clinica Belgica,2006

Key challenge of type 2 diabetes: outcome

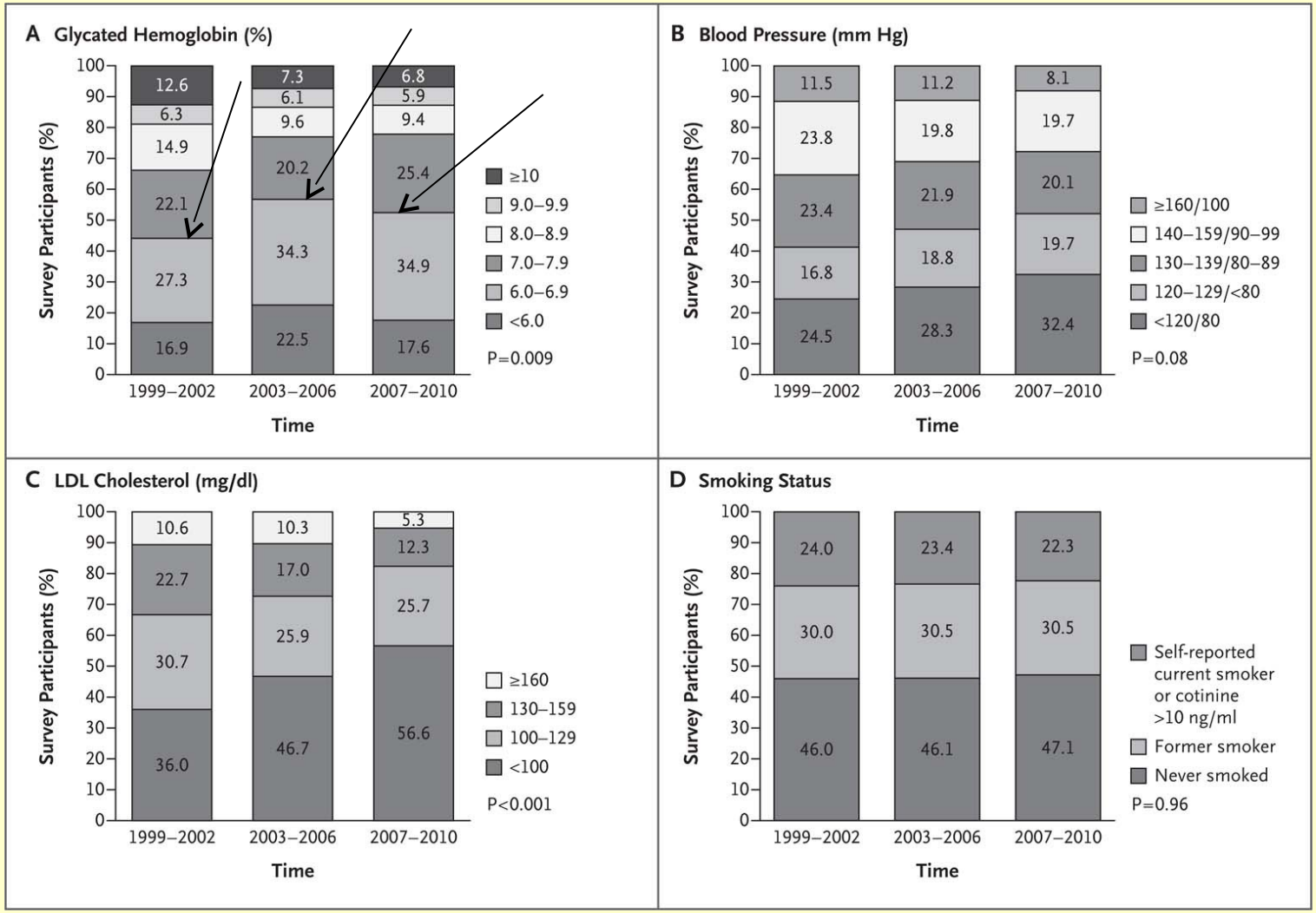


43% of patients
do not
achieve glycaemic targets
(HbA_{1c}<7%)

Ford *et al* (NHANES). *Diabetes Care* 2008;31:102–4

BY/ELB/11/209/462

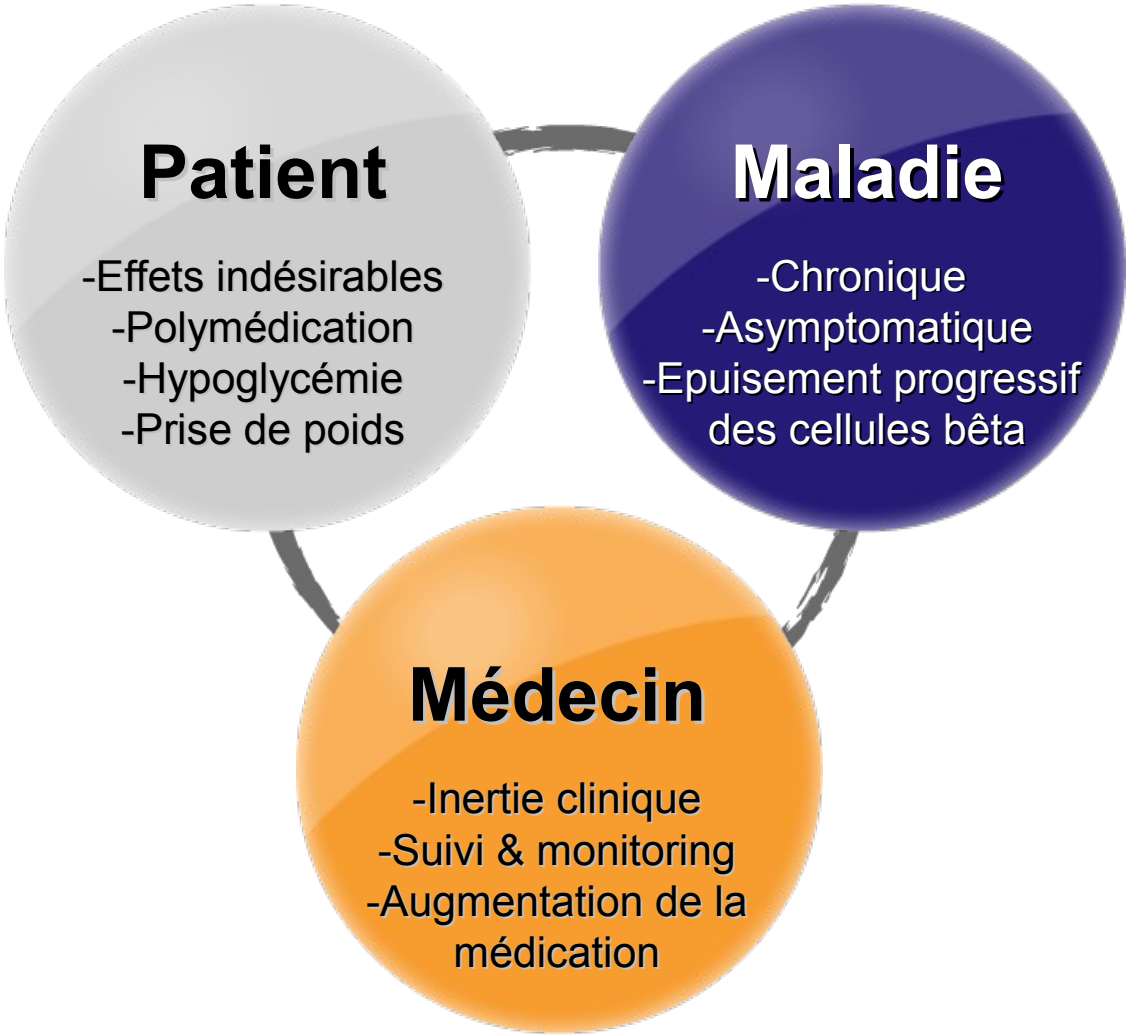
Distribution of Risk Factors for Microvascular and Macrovascular Complications among U.S. Adults with Diabetes, 1999–2010.



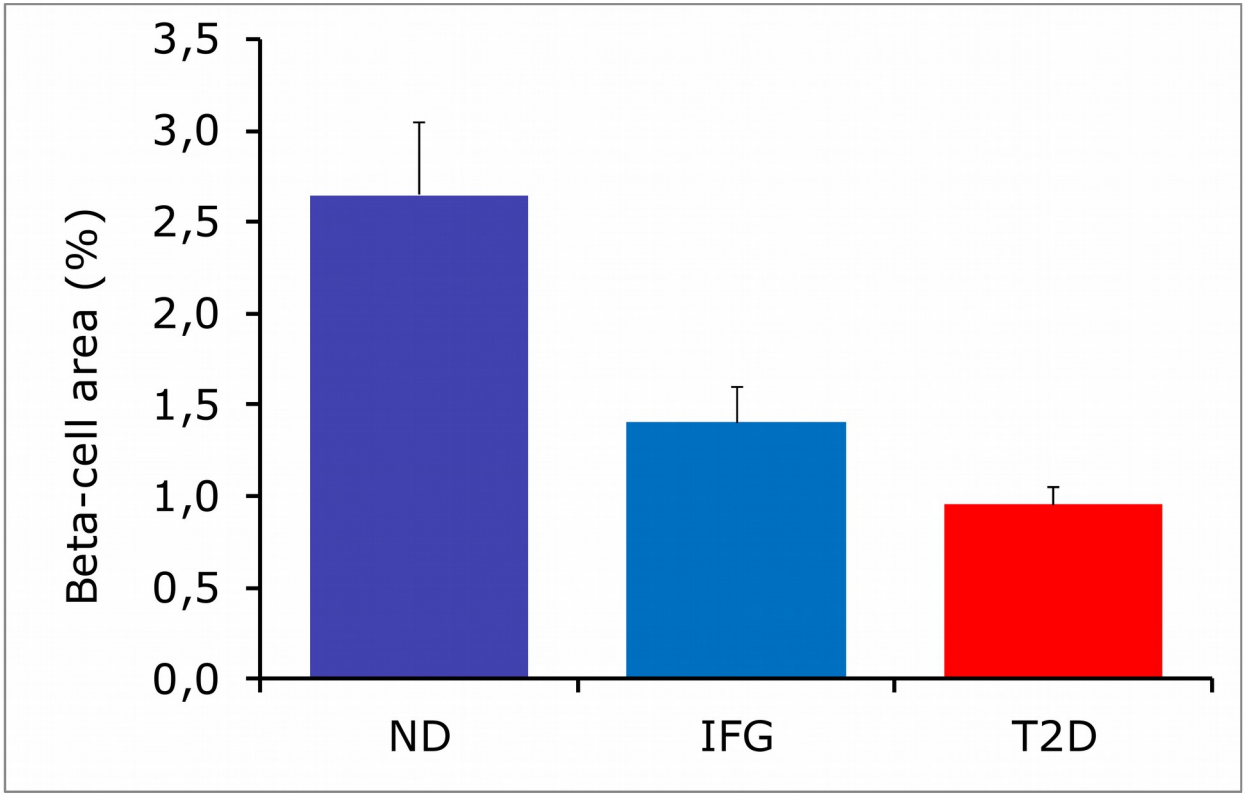
Ali MK et al. N Engl J Med 2013;368:1613-1624

Barrières pour un bon contrôle

Barrières à 3 niveaux différents



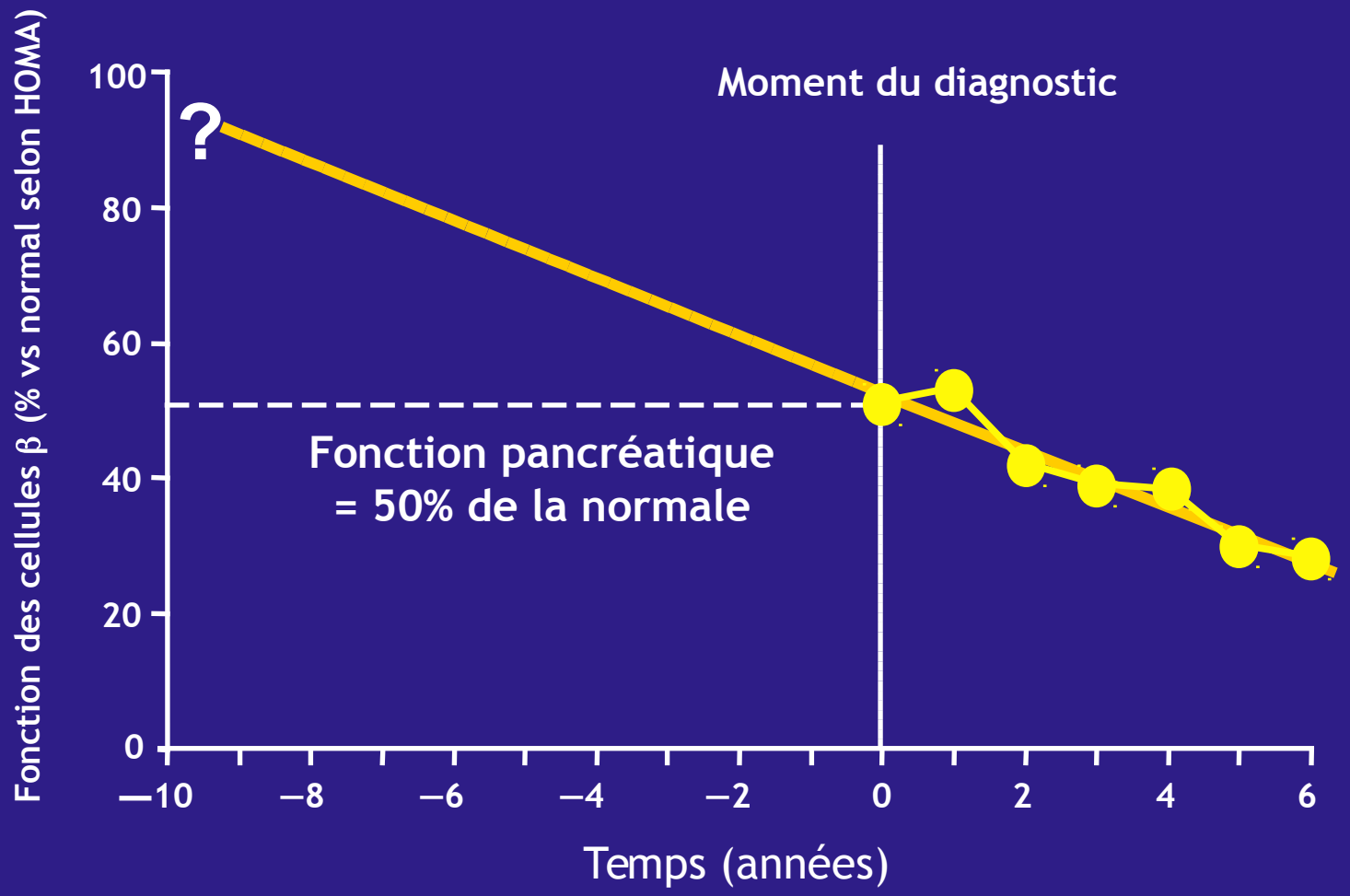
Réduction de la masse Beta-cellulaire chez les patients DT2



ND, non diabetic; IFG, impaired fasting glucose

Matveyenko *et al. DOM* 2008;10(Suppl. 4):23–31

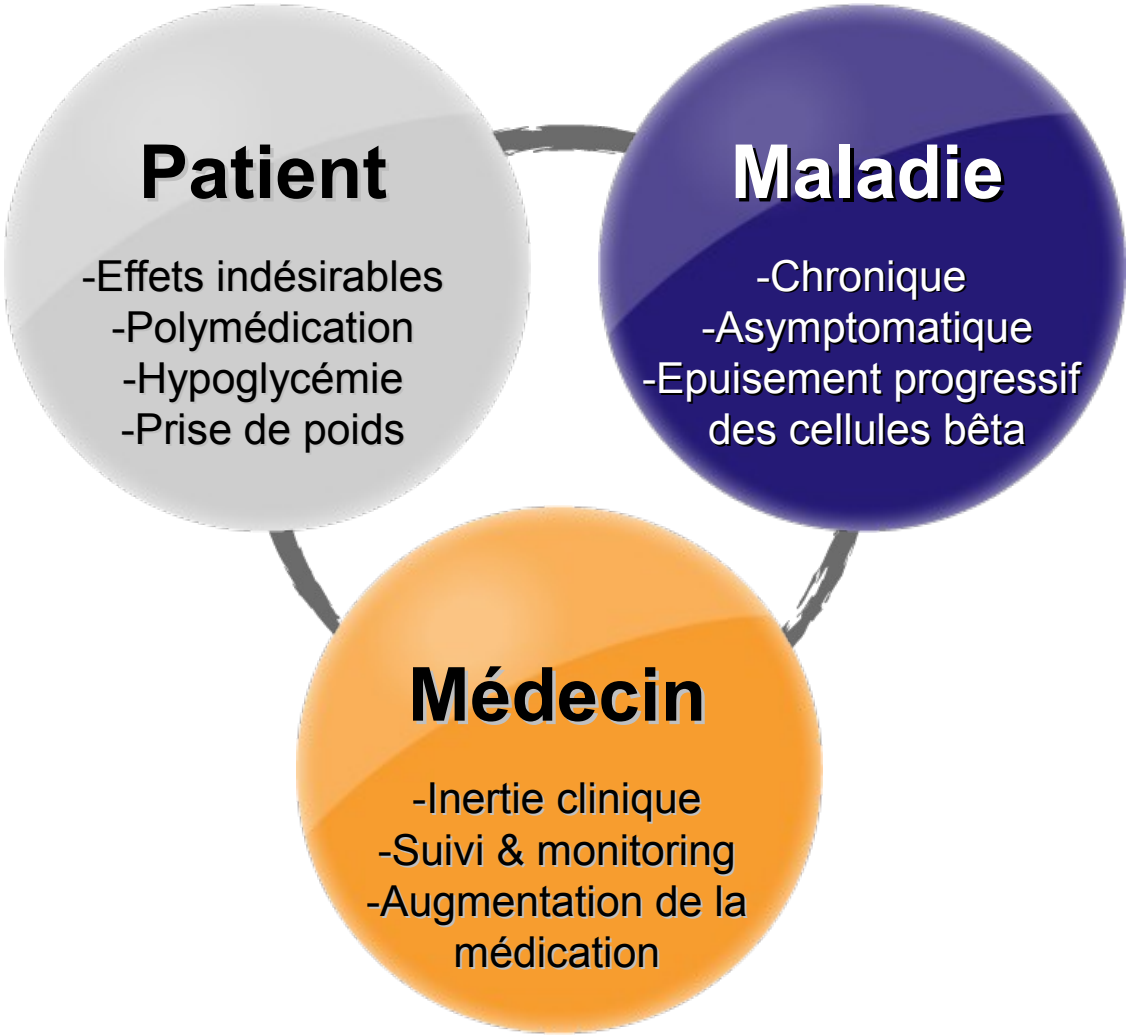
Le déclin de la fonction des cellules β détermine la nature progressive du DT2



HOMA = homeostasis model assessment.
UKPDS Group. Diabetes 1995;44:1249—58.
D'après Holman RR. Diabetes Res Clin Pract 1998;40(suppl 1):S21—5.

Barrières pour un bon contrôle

Barrières à 3 niveaux différents



Barrières pour un bon contrôle

Les effets indésirables ont un impact négatif sur la compliance

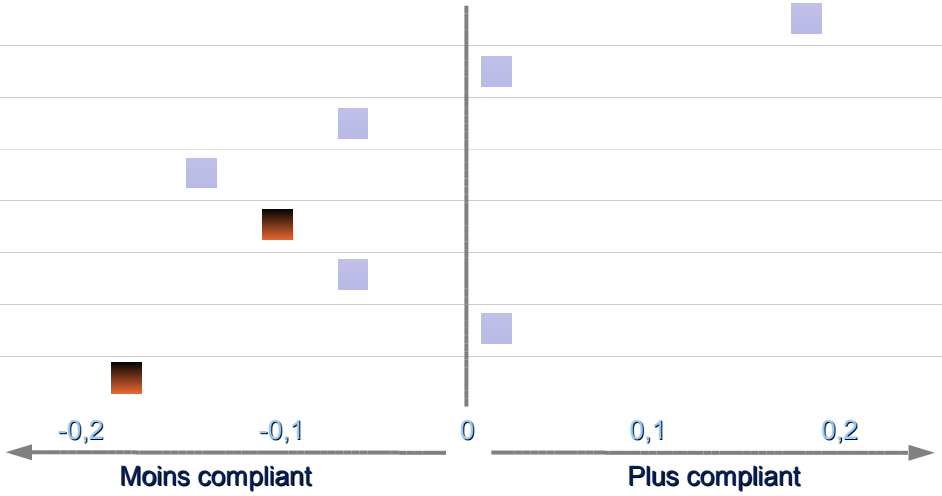
Patient

- Environ un tiers des patients diabétiques, recevant des AD oraux, ont mentionné avoir ressenti des effets indésirables liés au traitement.
- Cette perception était significativement associée à une non-adhérence aux antidiabétiques.

Analyse de régression linéaire (n = 445)

Méthodologie : questionnaire remis aux patients diabétiques de type 2 sous antidiabétiques oraux

Variable	B	Valeur p
Âge		< 0,05
Comorbidité		
Durée de la maladie		
Score de symptôme de dépression		< 0,001
Multi-thérapie		
Facteur ethnique		
Revenus		
Effets indésirables ressentis		< 0,01



Un patient diabétique de type 2 prend en moyenne 6,3 médicaments différents*

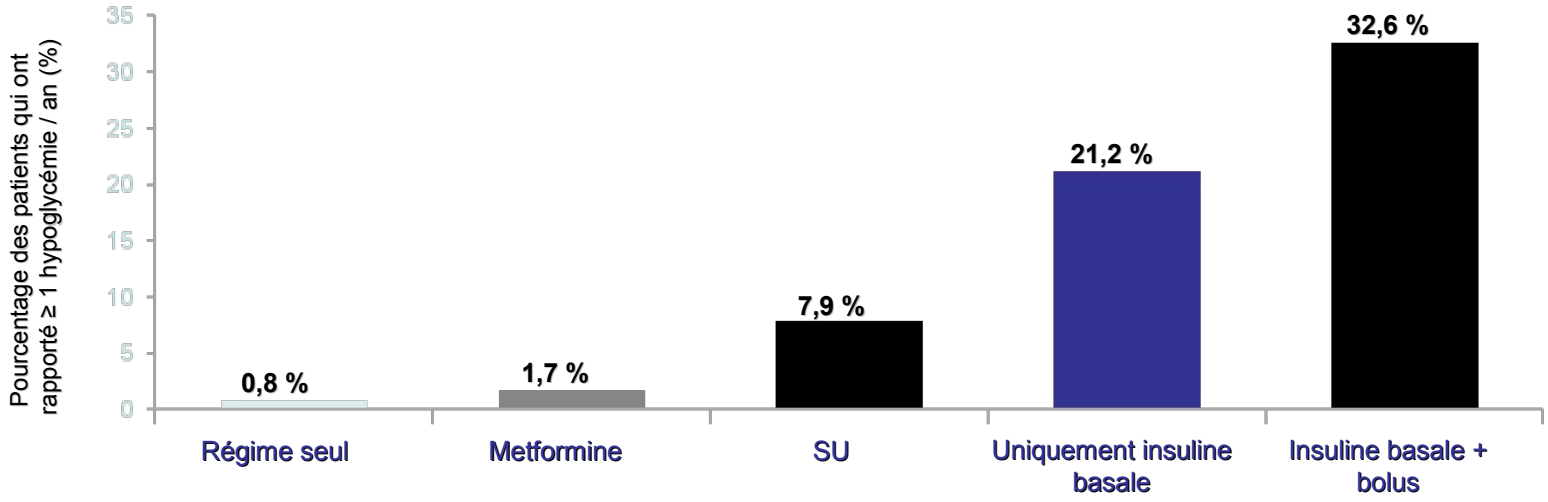
Revue adaptée d'après Chao J, et al. Clin Ther. 2007;29:177-180. *Paquot N Rev Med Liège 2010; 65: 326-310.

Barrières pour un bon contrôle

Patient

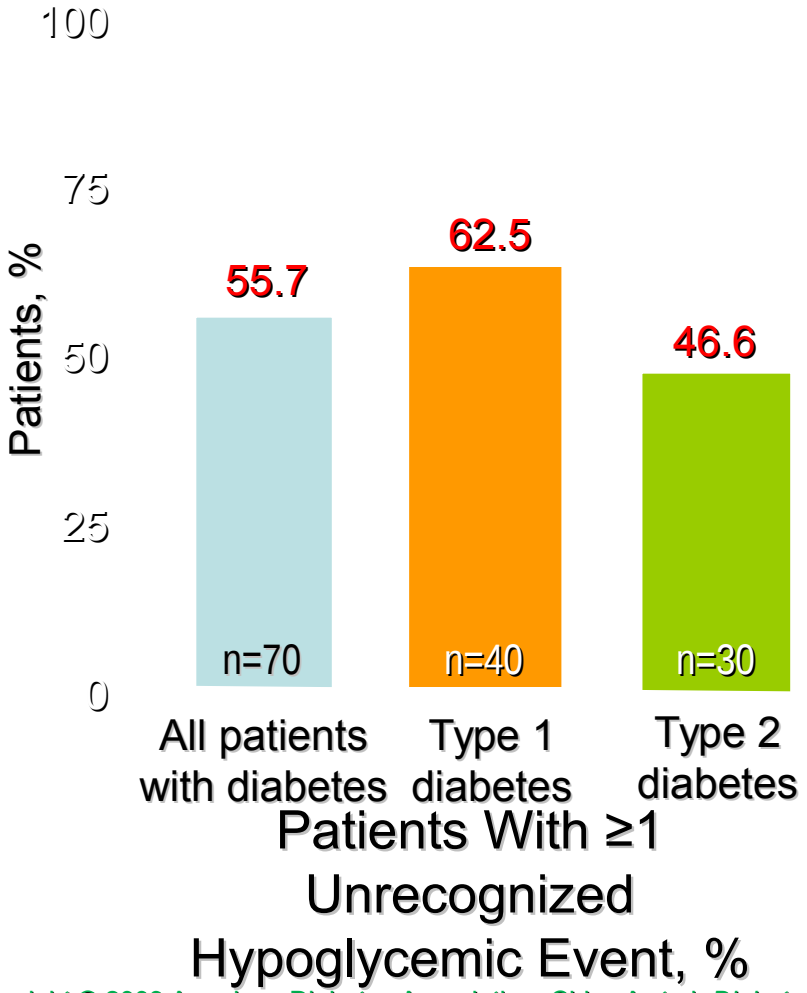
Hypoglycémies associées au traitement

- % patients ayant, par an, au moins 1 hypoglycémie liée au traitement.
- Patients diabétiques de type 2 de l'étude UKPDS.
- Les épisodes hypoglycémiques rapportés ont été classés comme transitoires, temporairement invalidants, besoin d'aide d'une tierce personne, besoin d'assistance médicale.
- Pour tous les traitements, la différence significative se situe au niveau < 0,0001.



Wright AD et al (2006) J Diabetes Complicat 20; 395-401.

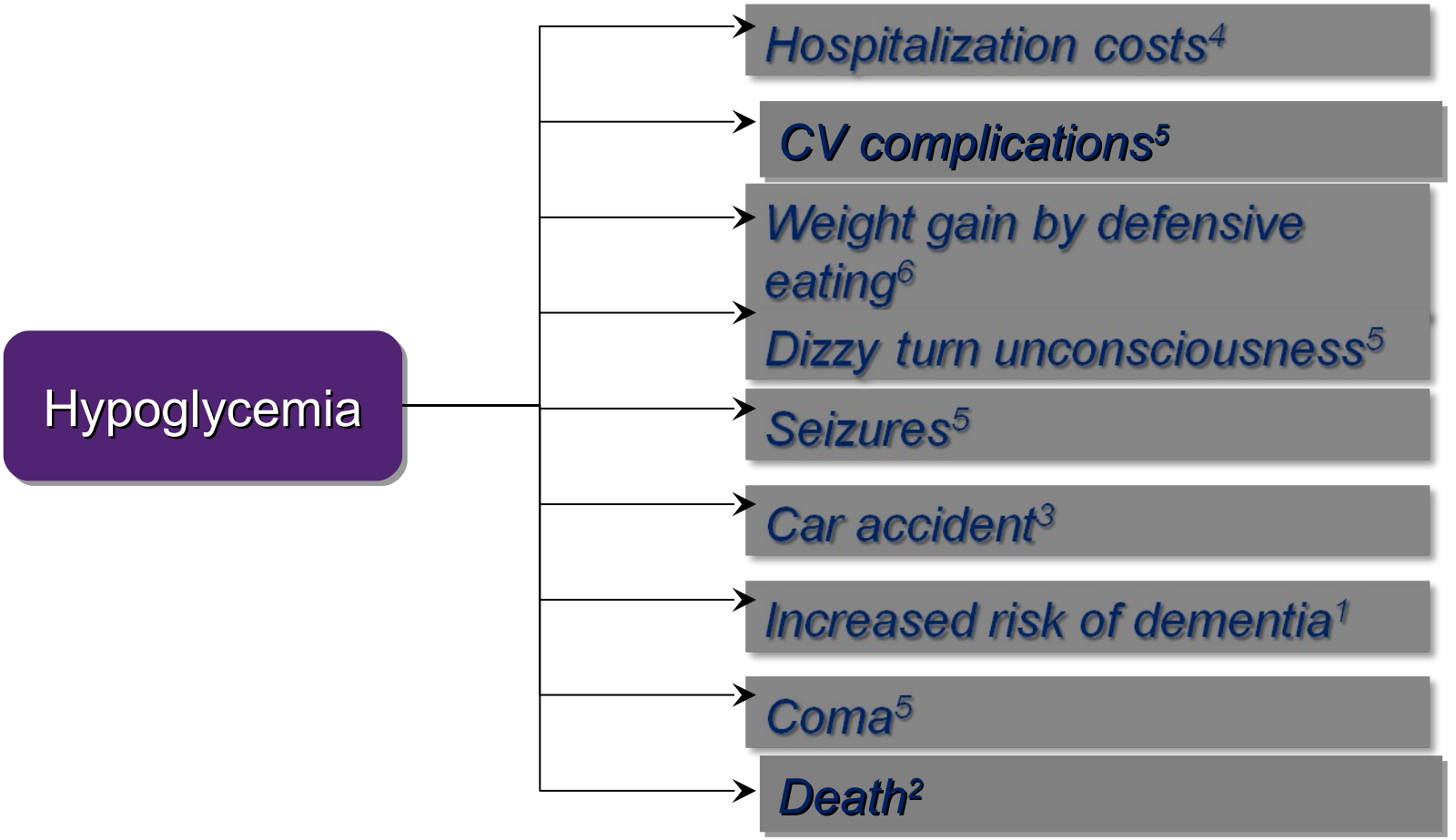
Asymptomatic Episodes of Hypoglycemia May Go Unreported



- In a cohort of patients with diabetes, more than 50% had asymptomatic (unrecognized) hypoglycemia, as identified by continuous glucose monitoring[1]
- Other researchers have reported similar findings[2,3]

1. Copyright © 2003 American Diabetes Association. Chico A et al. *Diabetes Care*. 2003;26(4):1153–1157. Reprinted with permission from *The American Diabetes Association*.
2. Weber KK et al. *Exp Clin Endocrinol Diabetes*. 2007;115:491–494.
3. Zick R et al. *Diab Technol Ther*. 2007;9:483–492.

Hypoglycemia – understimated consequences



1. Whitmer RA et al JAMA 2009, 301:1565; 2. Zammitt NN et al Diabetes Care 2005, 28:2948; 3. Canadian Diabetes Association's Clinical Practice Guidelines for Diabetes and Private and Commercial Driving. Canadian Journal Of Diabetes. 2003;27:128; 4. Jönsson L et al. Cost of Hypoglycemia in Patients with Type 2 Diabetes in Sweden. Value In Health. 2006; 9: 193-198; 5. Barnett AH, CMRO 2010;26: 1333; 6. Foley J & Jordan J, Vascular Health Risk Management, 2010 6:541-548

Table 3—*Five-year mortality risk*

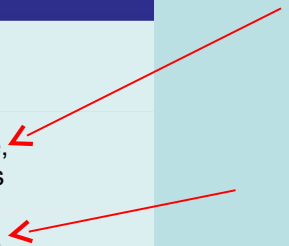
	OR	95% CI	*P* value
Age	1.047	1.027–1.066	<0.001
Male sex	1.716	1.135–2.596	0.011
Type 1 diabetes	0.836	0.410–1.706	0.623
Diabetes duration	1.006	0.985–1.027	0.595
HbA_{1c}	1.127	0.965–1.316	0.131
CCI	1.437	1.323–1.561	<0.001
Hypoglycemia			
Mild	1.564	0.986–2.481	0.468
Severe	3.381	1.547–7.388	0.005

OR for 5-year [illegible] was adjusted for age, sex, diabetes type and duration, HbA_{1c}, CCI, and hypoglycemia history. Unless otherwise specified, all measures were obtained at baseline.

McCoy et al, Diabetes Care, 2012

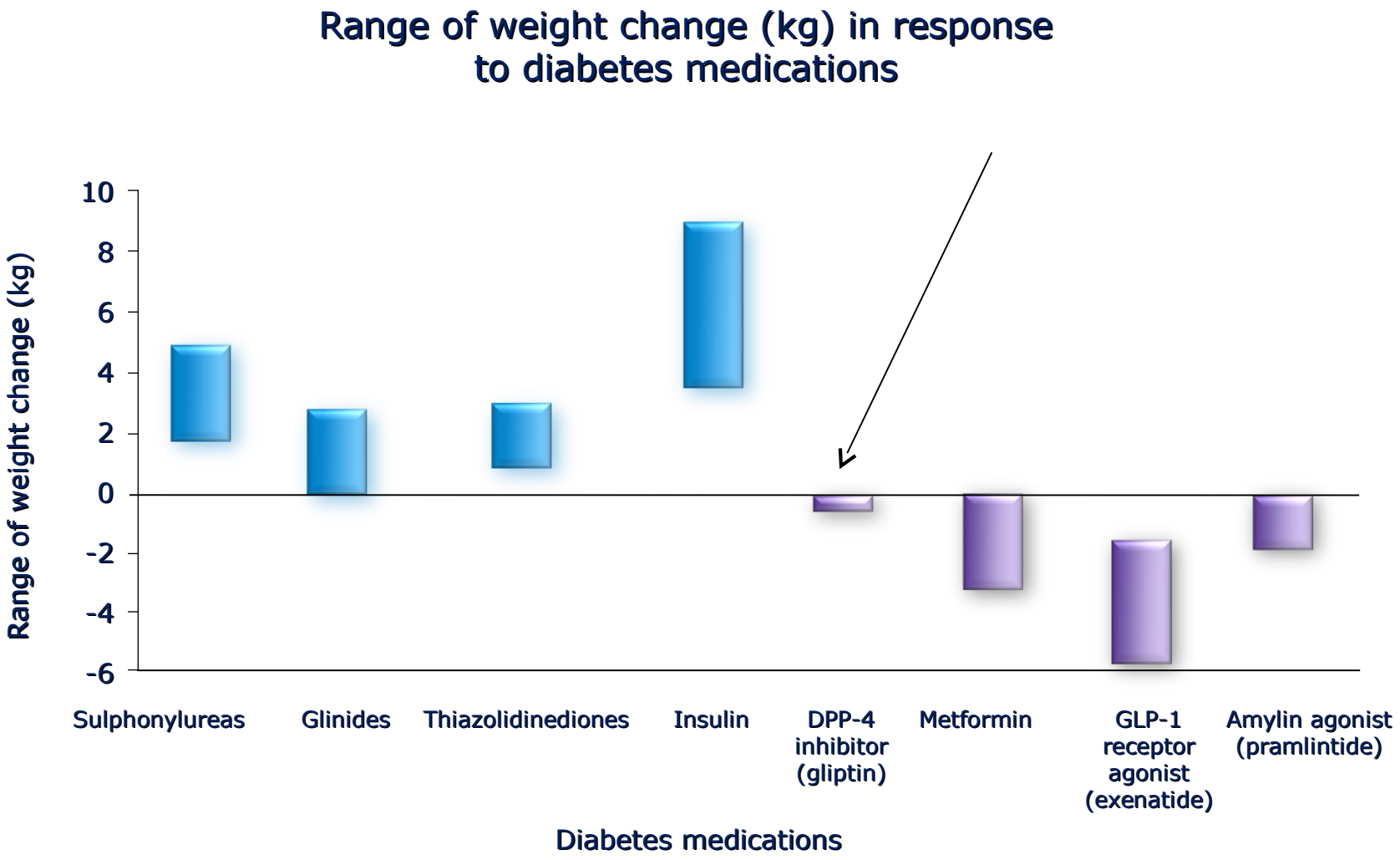
Antidiabétiques oraux disponibles

	Effet sur l'insulino-résistance	Effet sur l'insulino-sécrétion	Effet sur le poids	Risque d'hypo-glycémies	Importants effets indésirables
Metformine	↓	↔	↔	-	Troubles GI
Sulfamidés	↔	↑	↑	↑	Hypoglycémie, prise de poids
Glinides	↔	↑	↑	↑	Hypoglycémie, prise de poids
Thiazolidinediones	↓	-	↑	-	Prise de poids, rétention aqueuse
Inhibiteurs de la DPP-4	↔	↑	↔	-	Pas de tendance significative



Inzucchi et al. Diabetes Care. 2012;35:1364-1379.
ADA Standards of medical care, Dabetes care 35, S11-S63, 2012

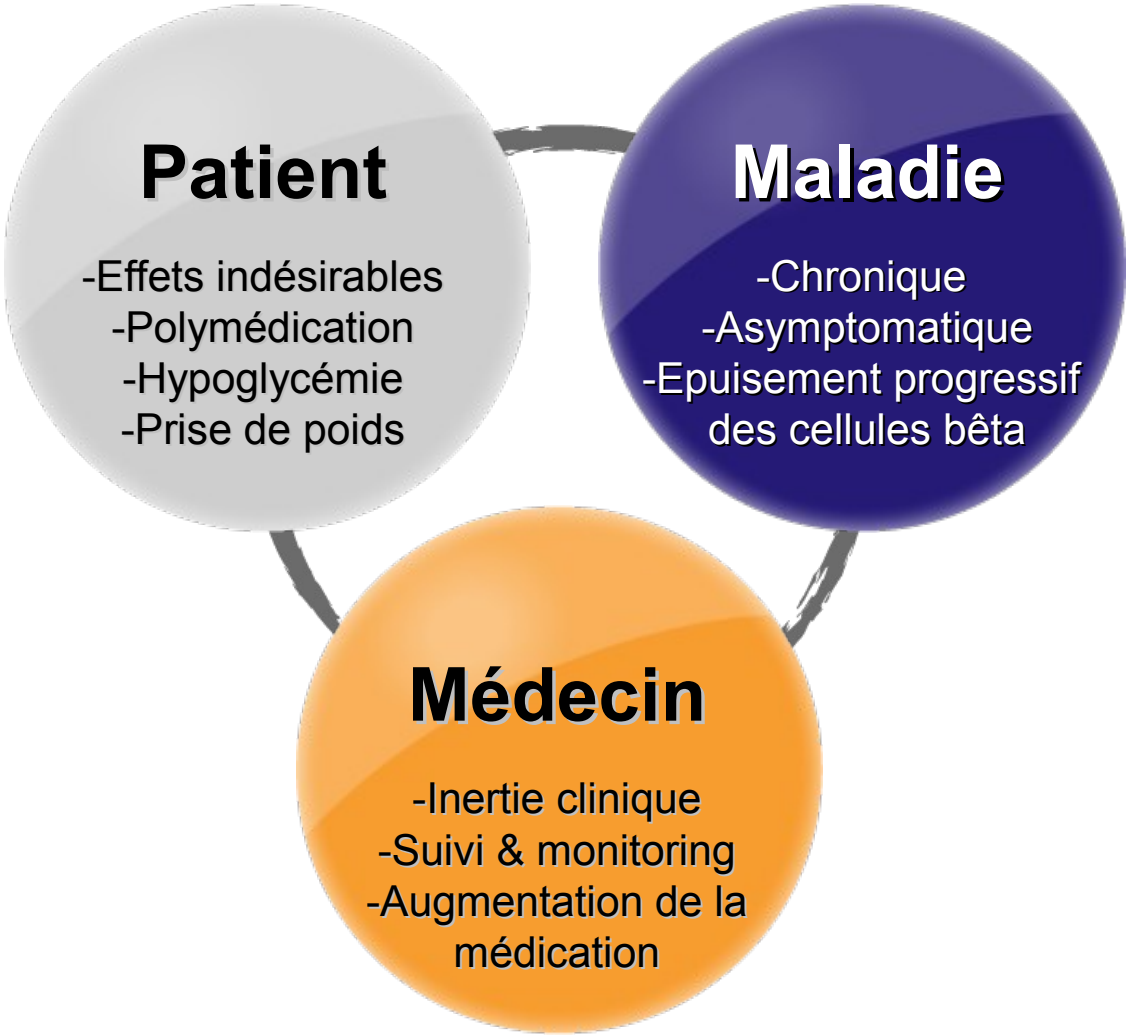
OTHER CONSIDERATIONS



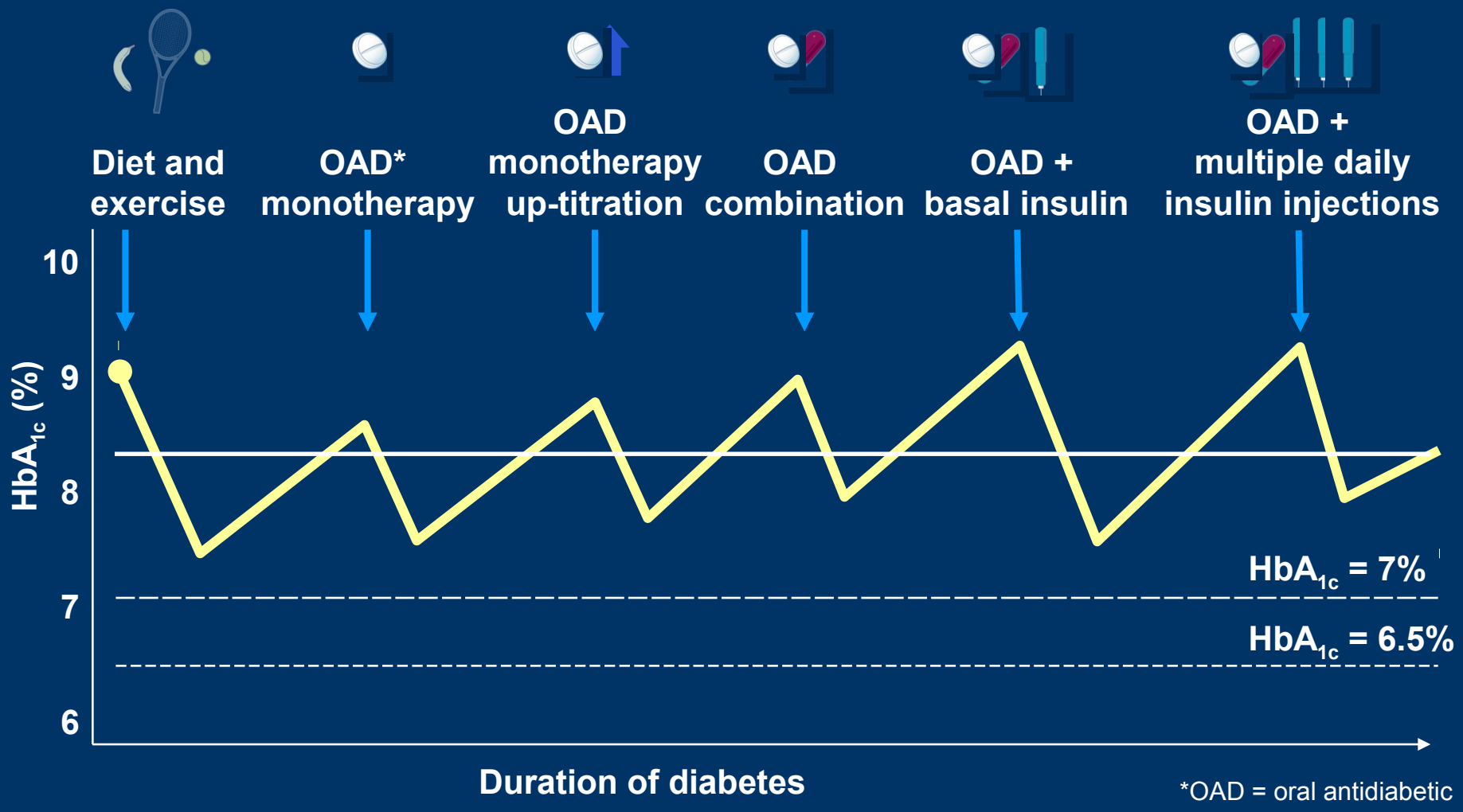
Mitri J, Hamdy O. Expert Opin Drug Saf. 2009;8:573-84

Barrières pour un bon contrôle

Barrières à 3 niveaux différents



Conservative management of glycemia: traditional stepwise approach



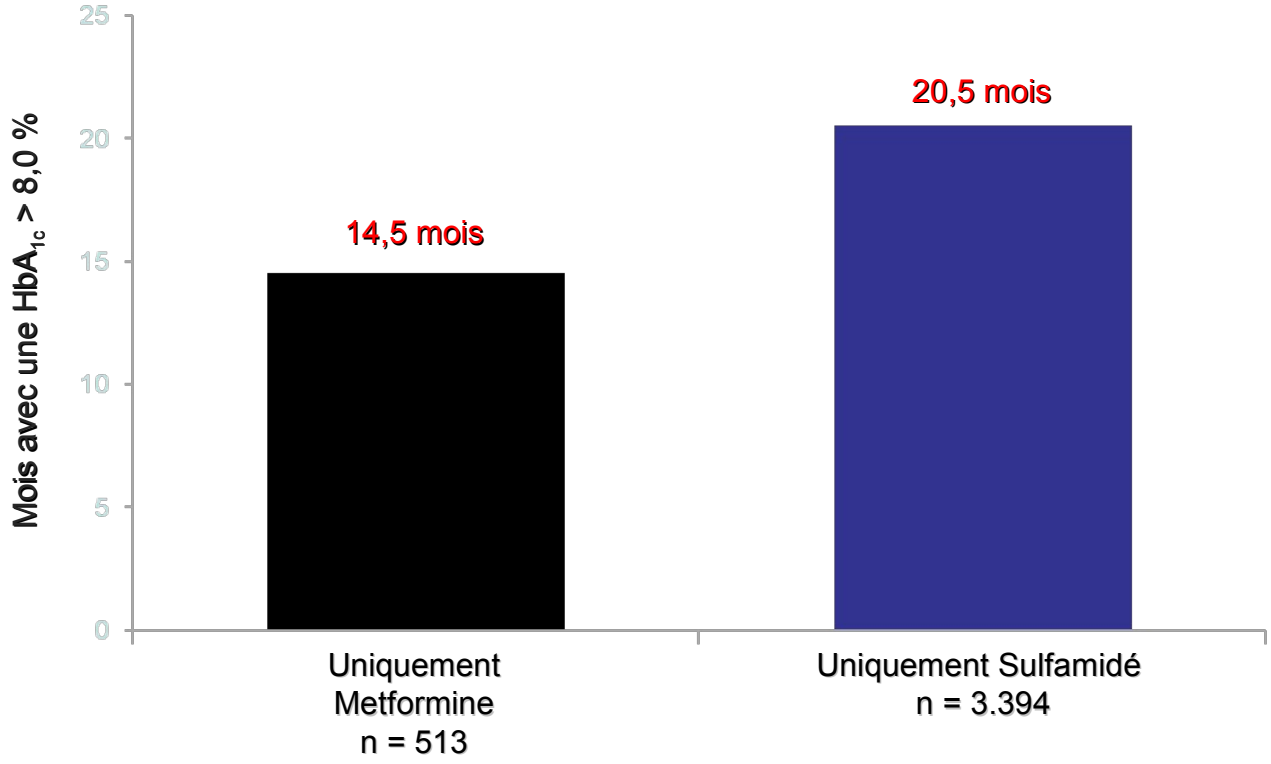
Campbell IW. *Br J Cardiol* 2000; 7:625–631.

Barrières pour un bon contrôle

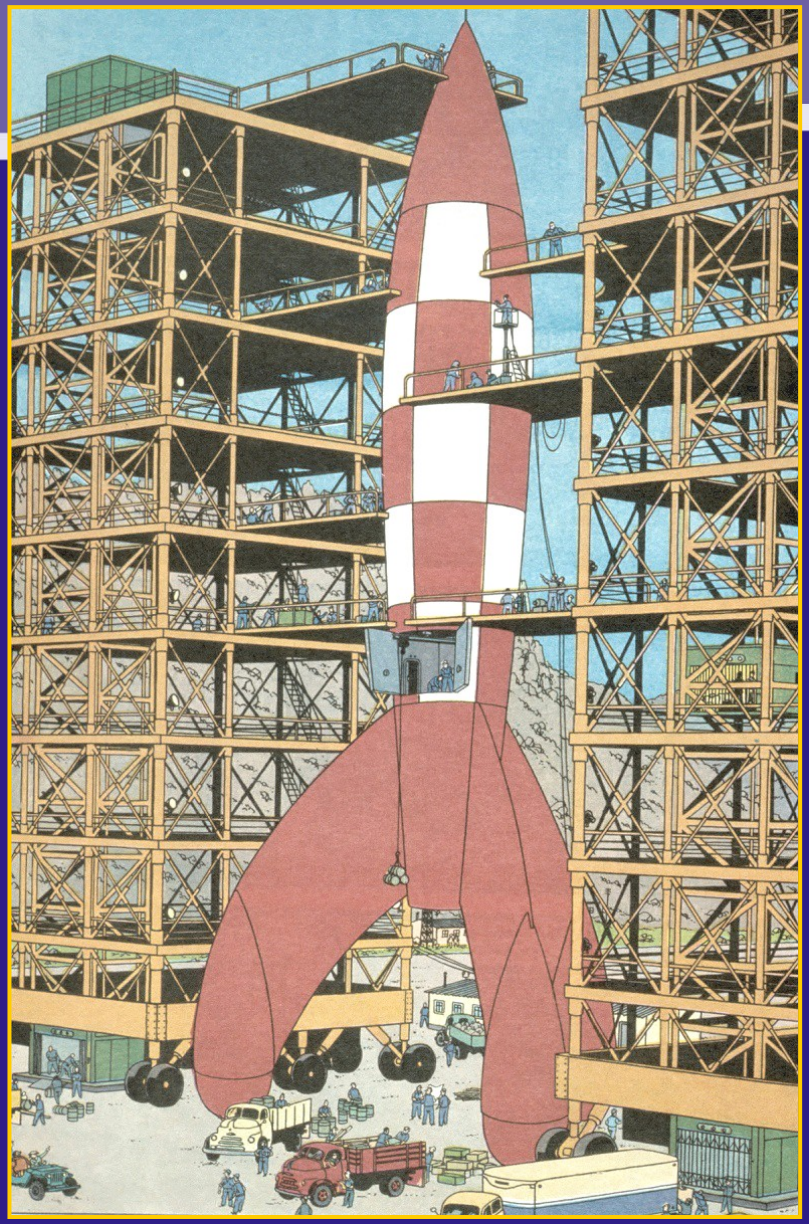
Inertie clinique fréquente entre monothérapie et association

Médecin

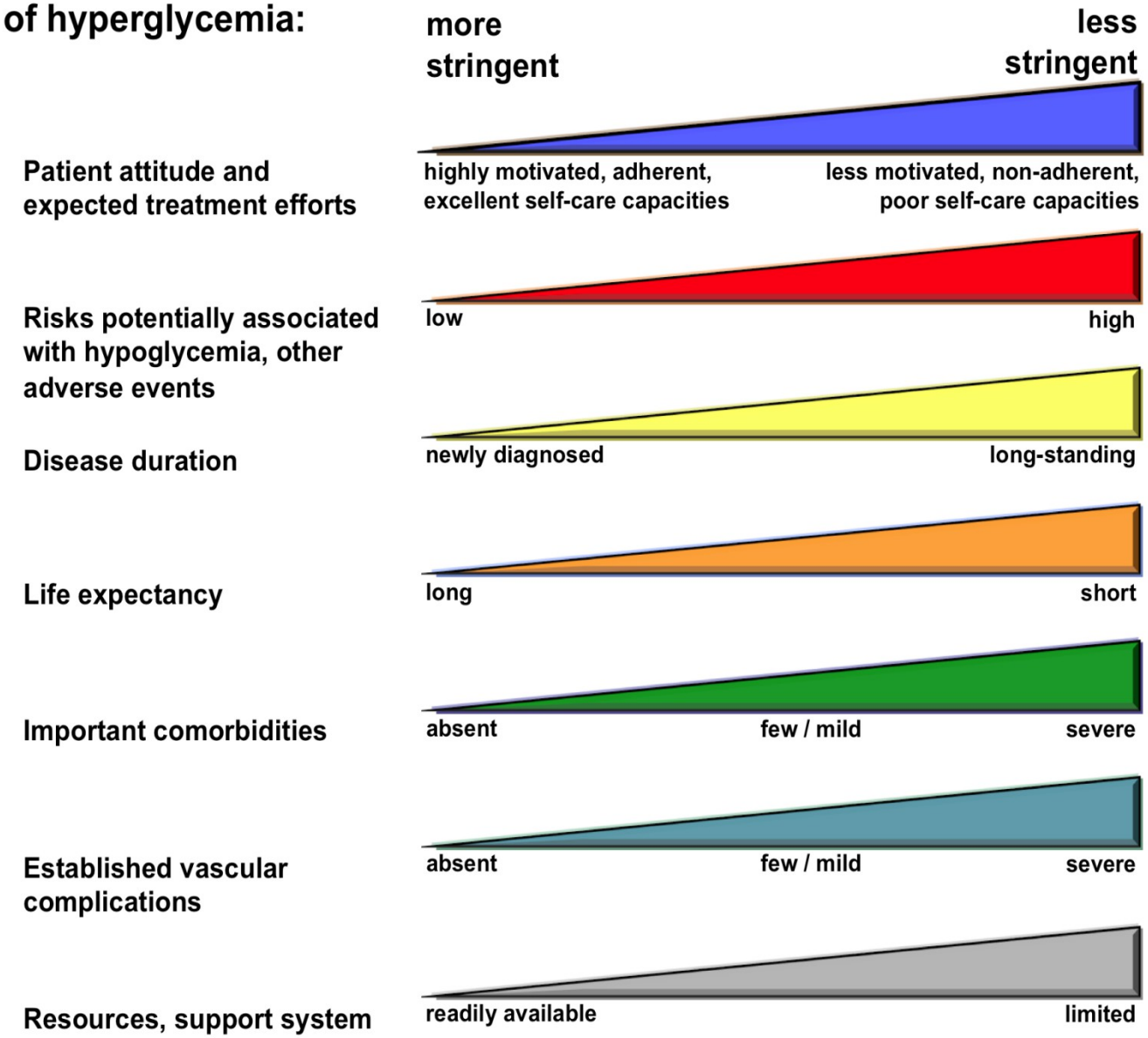
Délai entre la monothérapie initiale avec une HbA_{1c} > 8,0 % et passage / ajout d'une thérapie (mois)



Adapté d'après Brown JB, et al. Diabetes Care. 2004;27:1535-1540.



Approach to management of hyperglycemia:



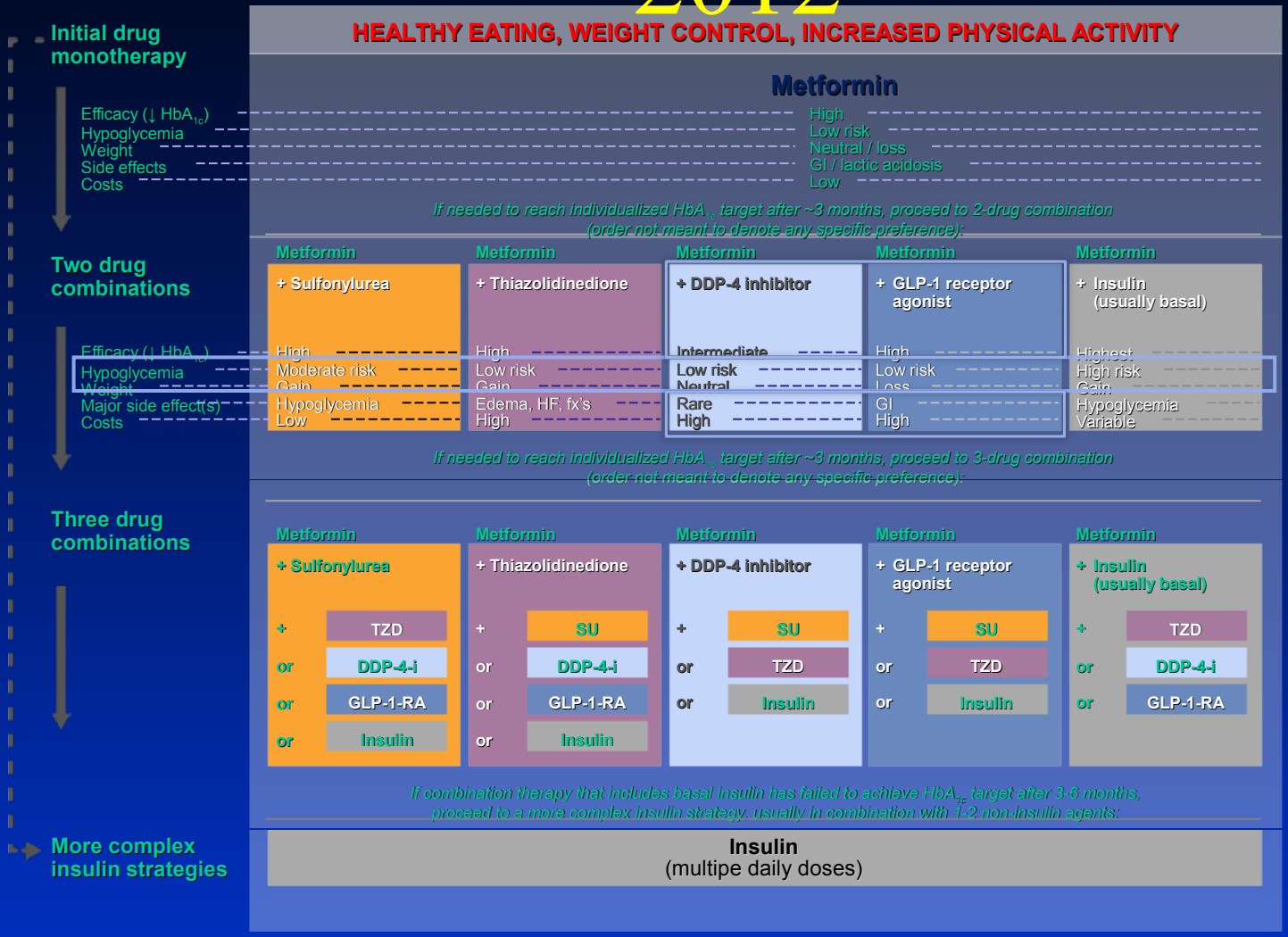
Diabetes Care, Diabetologia. 19 April 2012 [Epub ahead of print]
(Adapted with permission from: Ismail-Beigi F, et al. *Ann Intern Med* 2011;154:554)

Recommandations ADA/ EASD

Trajenta (linagliptin)

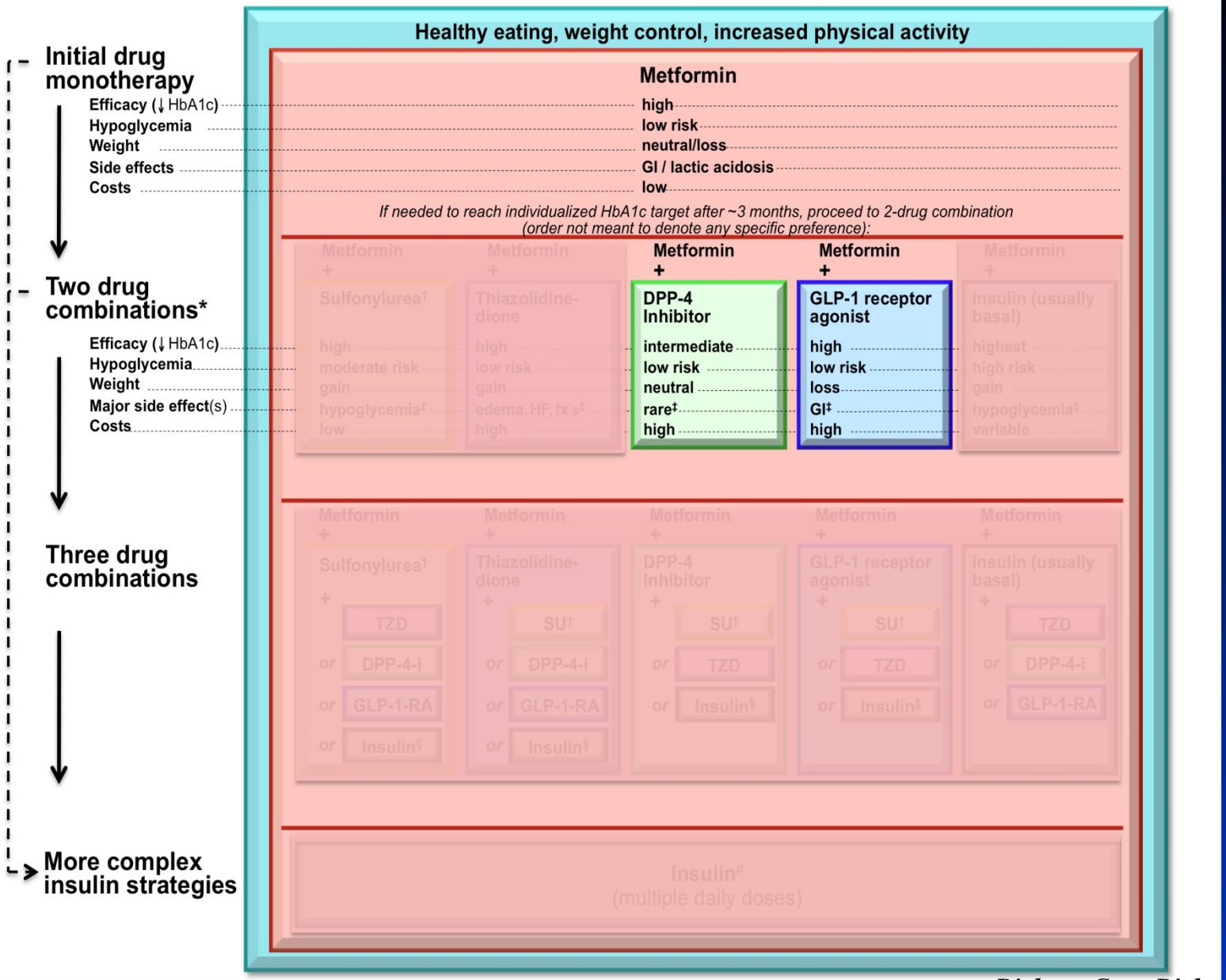
DPP-4 comme 2e choix après la metformine

2012



Adapté d'après Inzucchi et al. Diabetes Care 2012;35:1364-1379.

Adapted Recommendations: When Goal is to Avoid Weight Gain

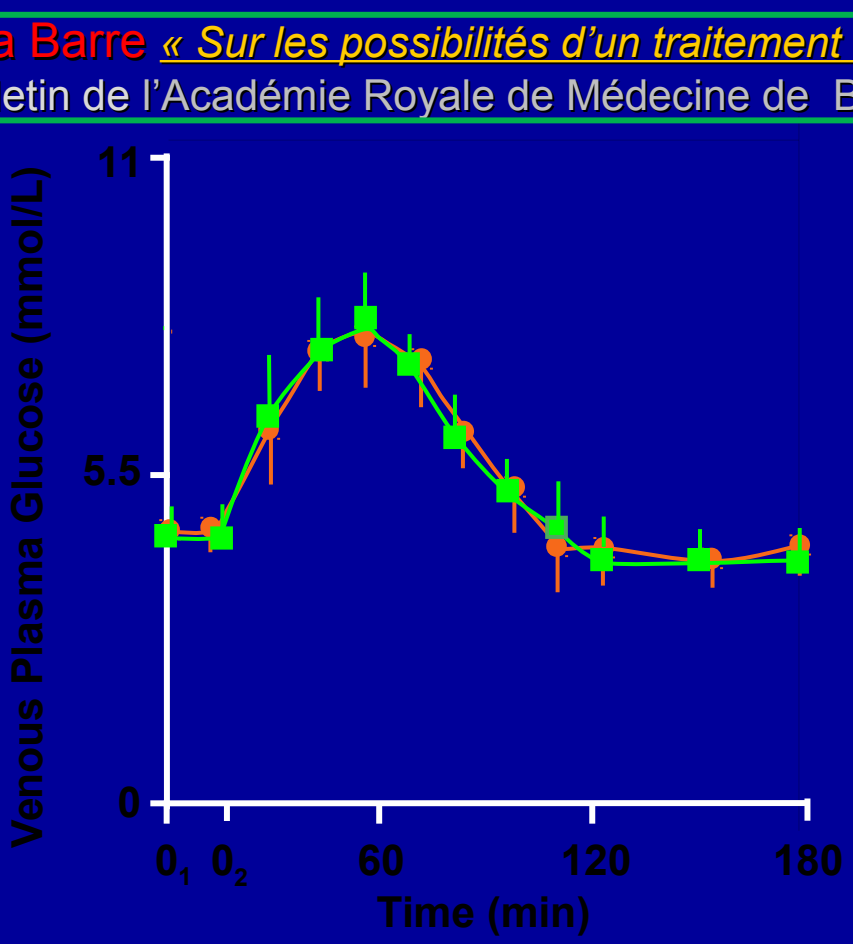


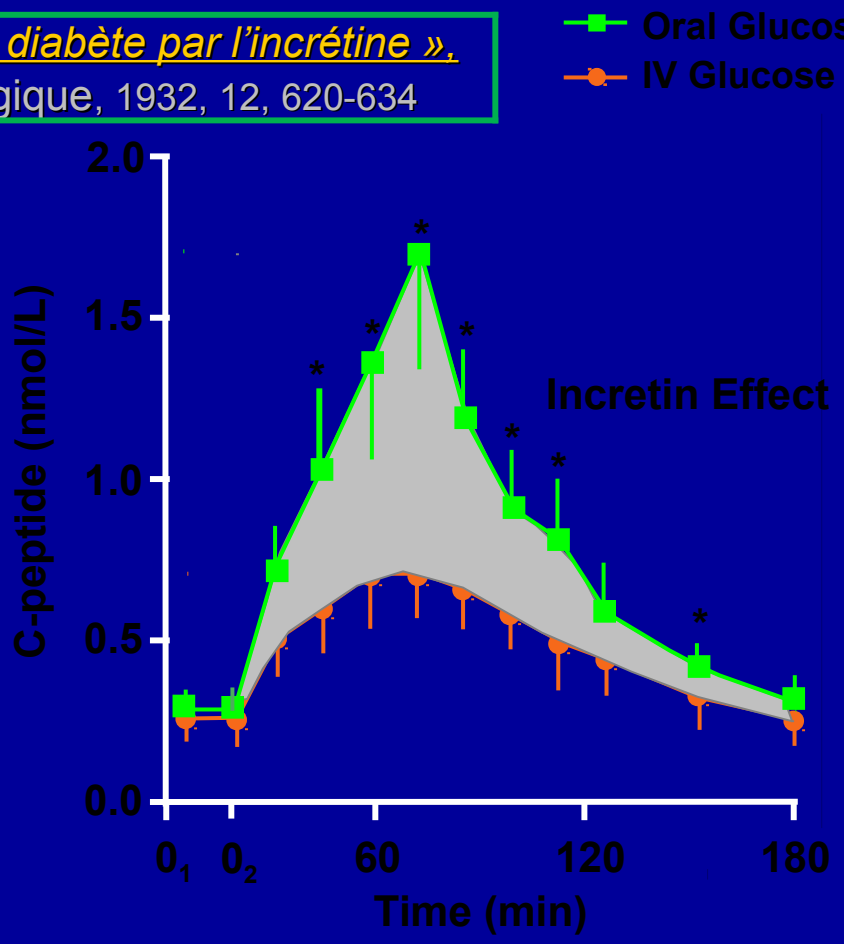
Diabetes Care, Diabetologia. 19 April 2012 [Epub ahead of print]

TR/ELB/05/2012/236

The Incretin Effect Demonstrates the Response to Oral vs IV Glucose[1]

La Barre *« Sur les possibilités d'un traitement du diabète par l'incrétine »,*
Bulletin de l'Académie Royale de Médecine de Belgique, 1932, 12, 620-634





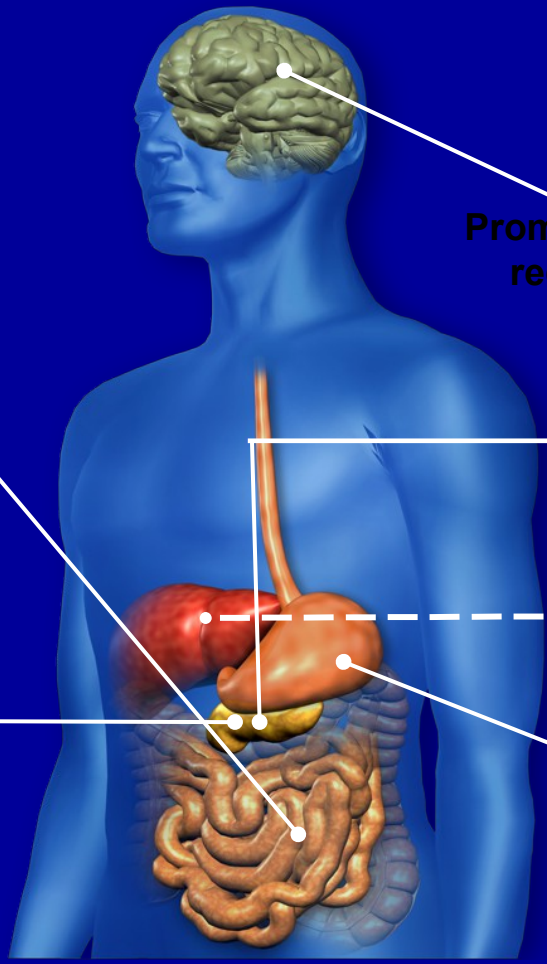
Mean ± SE; n = 6; *p≤0.05; 0_1-0_2 = glucose infusion time.

1. Nauck MA, et al. *J Clin Endocrinol Metab.* 1986;63:492–498.

INCRETINS

Glucagon-like peptide 1 [GLP-1]	Gastric inhibitory polypeptide [GIP]
L cells Glucose dependant Inactivation by DPP-4 Reduced secretion in diabetes	K cells Glucose dependant Inactivation by DPP-4 Normal secretion and reduced effect in diabetes

GLP-1 Effects in Humans: Understanding the Glucoregulatory Role of Incretins[1–4]



GLP-1 secreted upon the ingestion of food

↑ Beta-cell response

↓ Beta-cell workload

Promotes satiety and reduces appetite

Alpha cells:
↓ Postprandial glucagon secretion

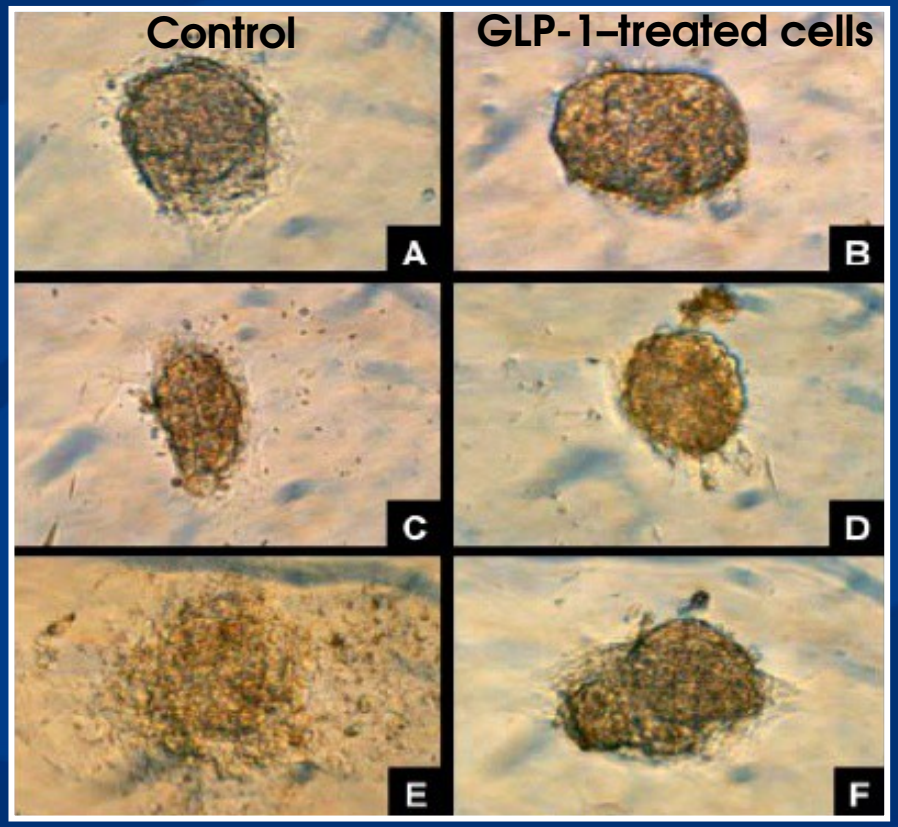
Liver:
↓ Glucagon reduces hepatic glucose output

Beta cells:
Enhances glucose-dependent insulin secretion

Stomach:
Helps regulate gastric emptying

1. Adapted from Flint A, et al. *J Clin Invest*. 1998;101:515–520. 2. Adapted from Larsson H, et al. *Acta Physiol Scand*. 1997;160:413–422.
3. Adapted from Nauck MA, et al. *Diabetologia*. 1996;39:1546–1553. 4. Adapted from Drucker DJ. *Diabetes*. 1998;47:159–169.

GLP-1 Preserved Morphology of Human Islet Cells *In Vitro*

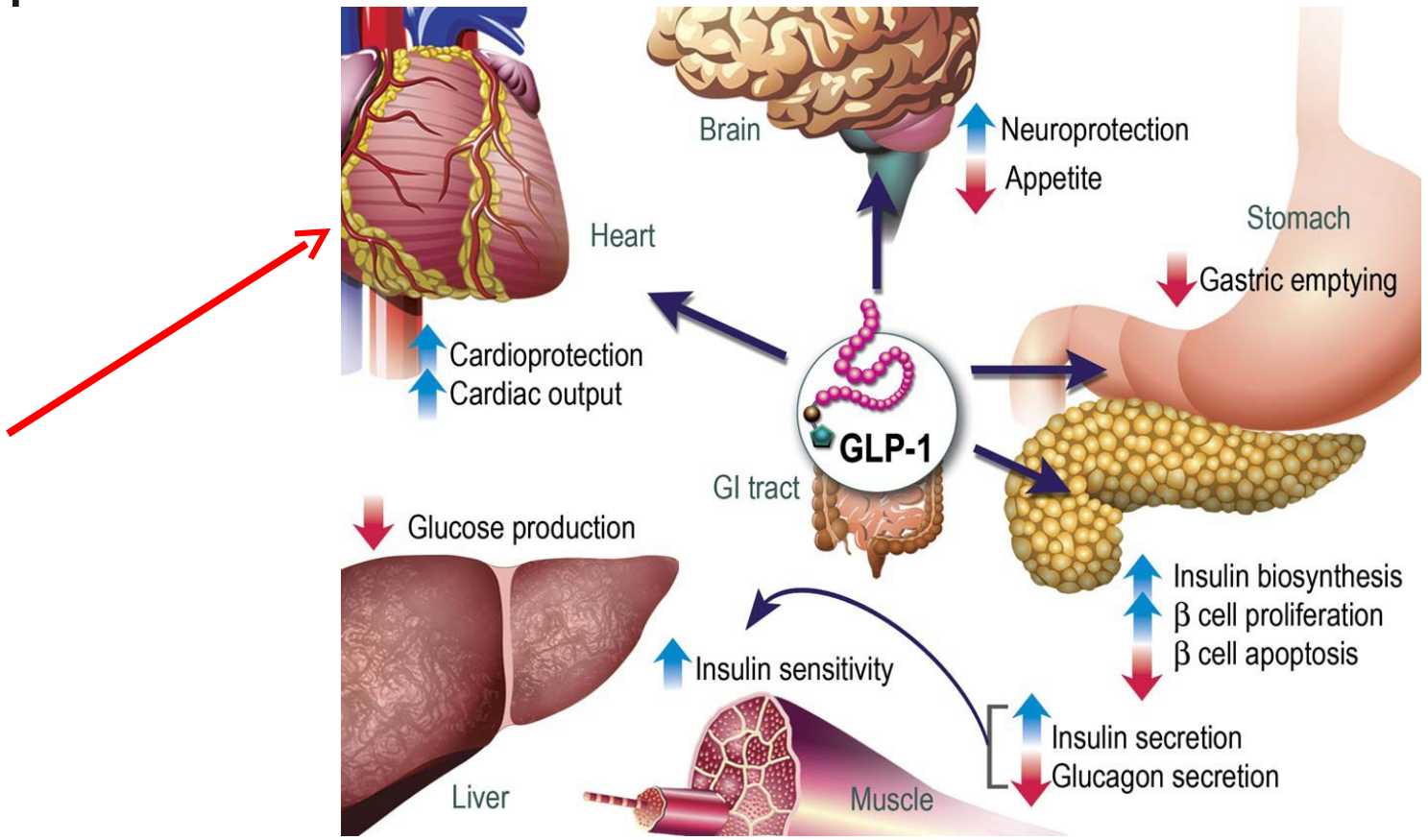


Islets treated with GLP-1 in culture were able to maintain their integrity for a longer period of time.

09-Aug-2008-JAN-2007-BE-1263-SS

Adapted from Farilla L et al *Endocrinology* 2003;144:5149–5158.

GLP-1 actions in the heart



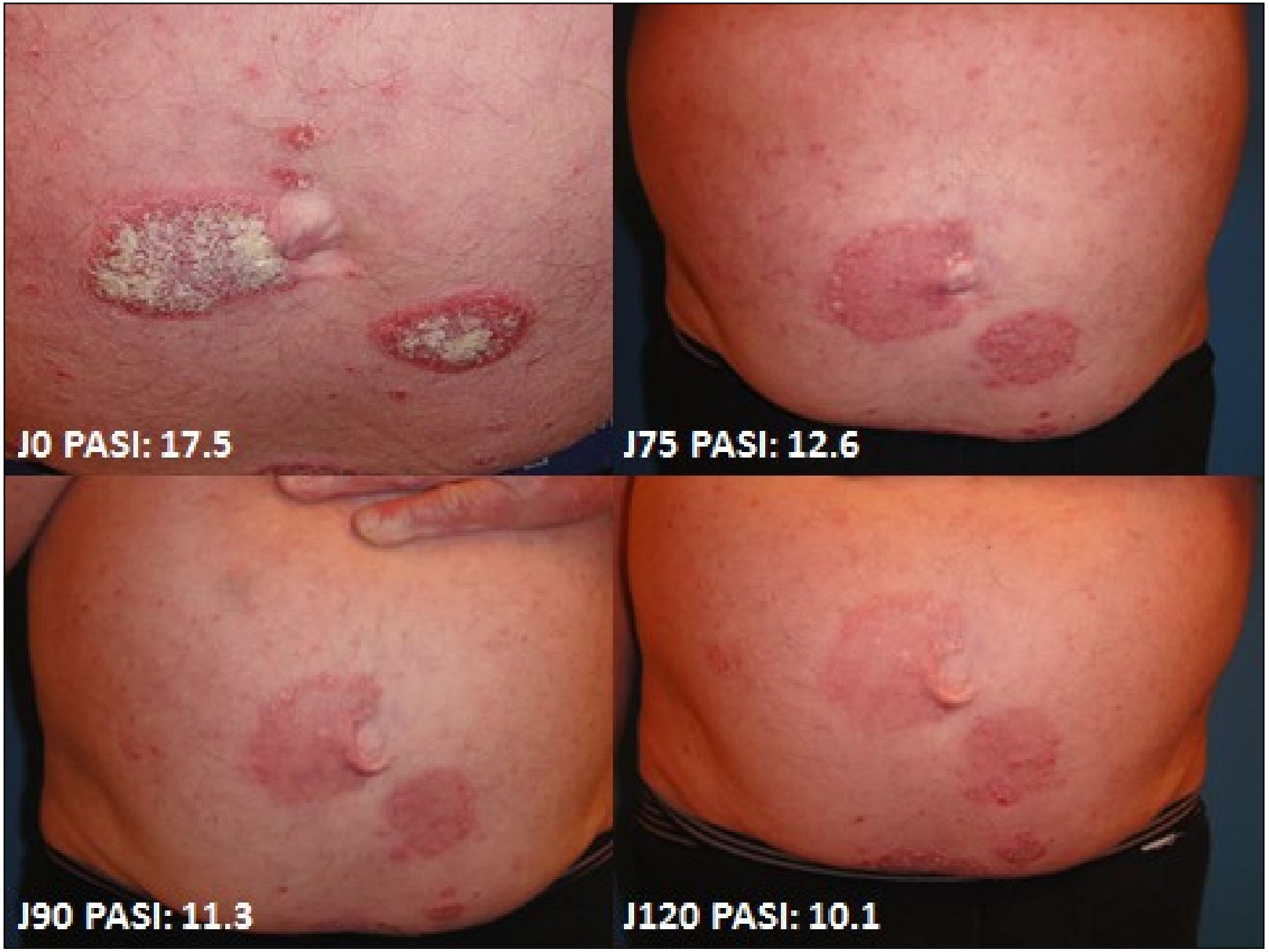
CELL METABOLISM 3, 153–165, MARCH 2006. The biology of incretin hormones Review
Daniel J. Drucker

Diabetologia (2011) 54:2741–2744
DOI 10.1007/s00125-011-2297-z

COMMENTARY

Glucagon-like peptide-1 (GLP-1) receptor agonists, obesity and psoriasis: diabetes meets dermatology

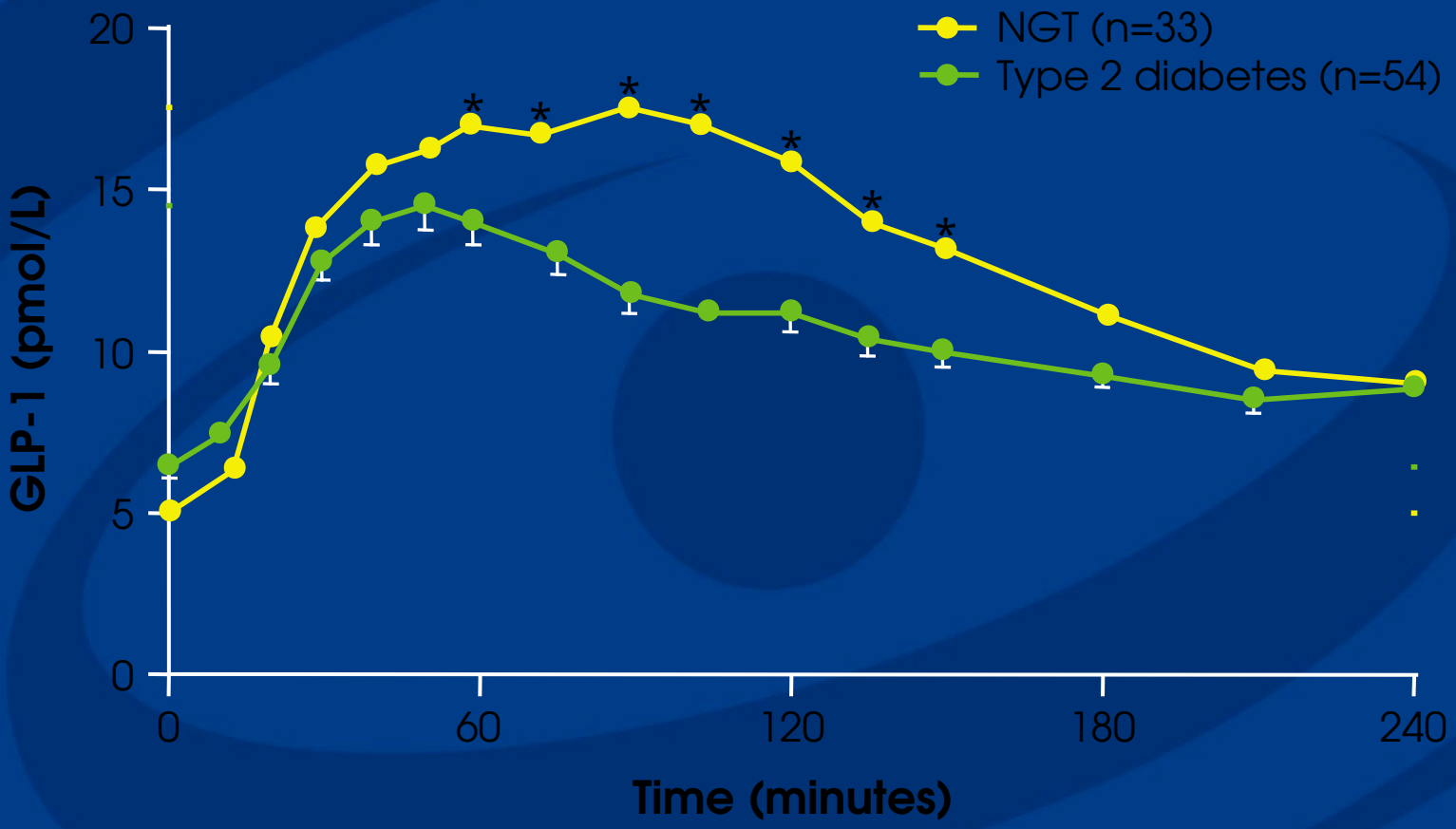
D. J. Drucker · C. F. Rosen



Preumont, Baeck, Dumoutier et Buysschaert, SFD,2013

Meal Test Study

GLP-1 Levels Decreased in Type 2 Diabetes



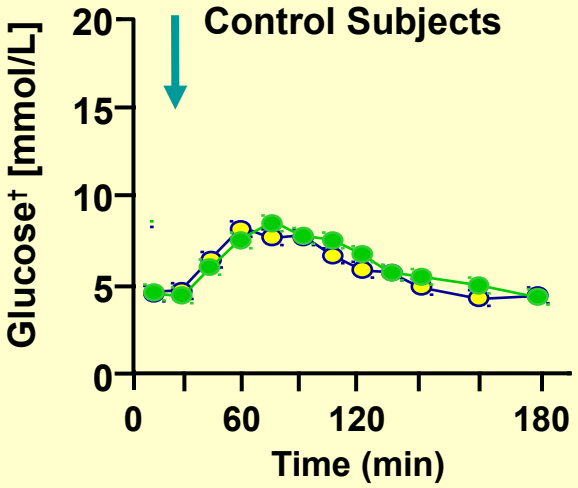
*p<0.05, type 2 diabetes vs. NGT

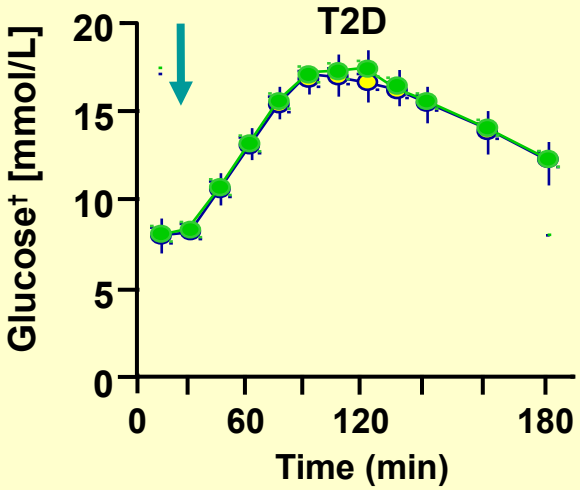
Meal started at time 0 and finished at 10–15 minutes.

Adapted from Toft-Nielsen M-B et al *J Clin Endocrinol Metab* 2001;86:3717–3723.

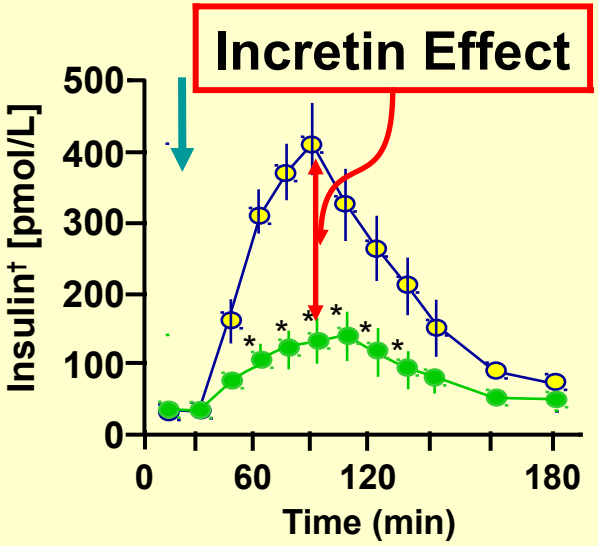
09-Aug-2008-JAN-2007-BE-1263-SS

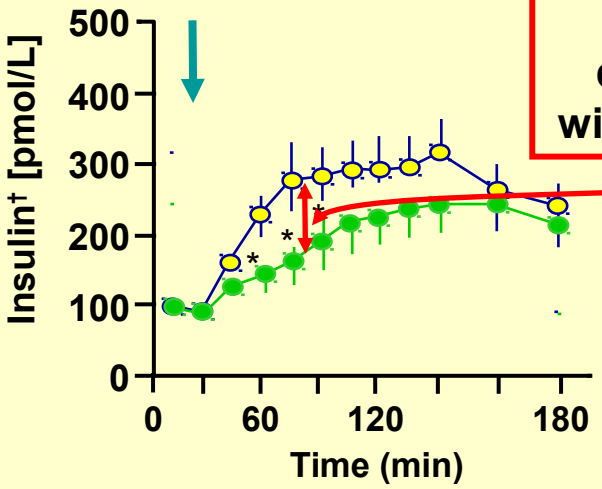
Incretin Effect





Oral glucose
Intravenous glucose





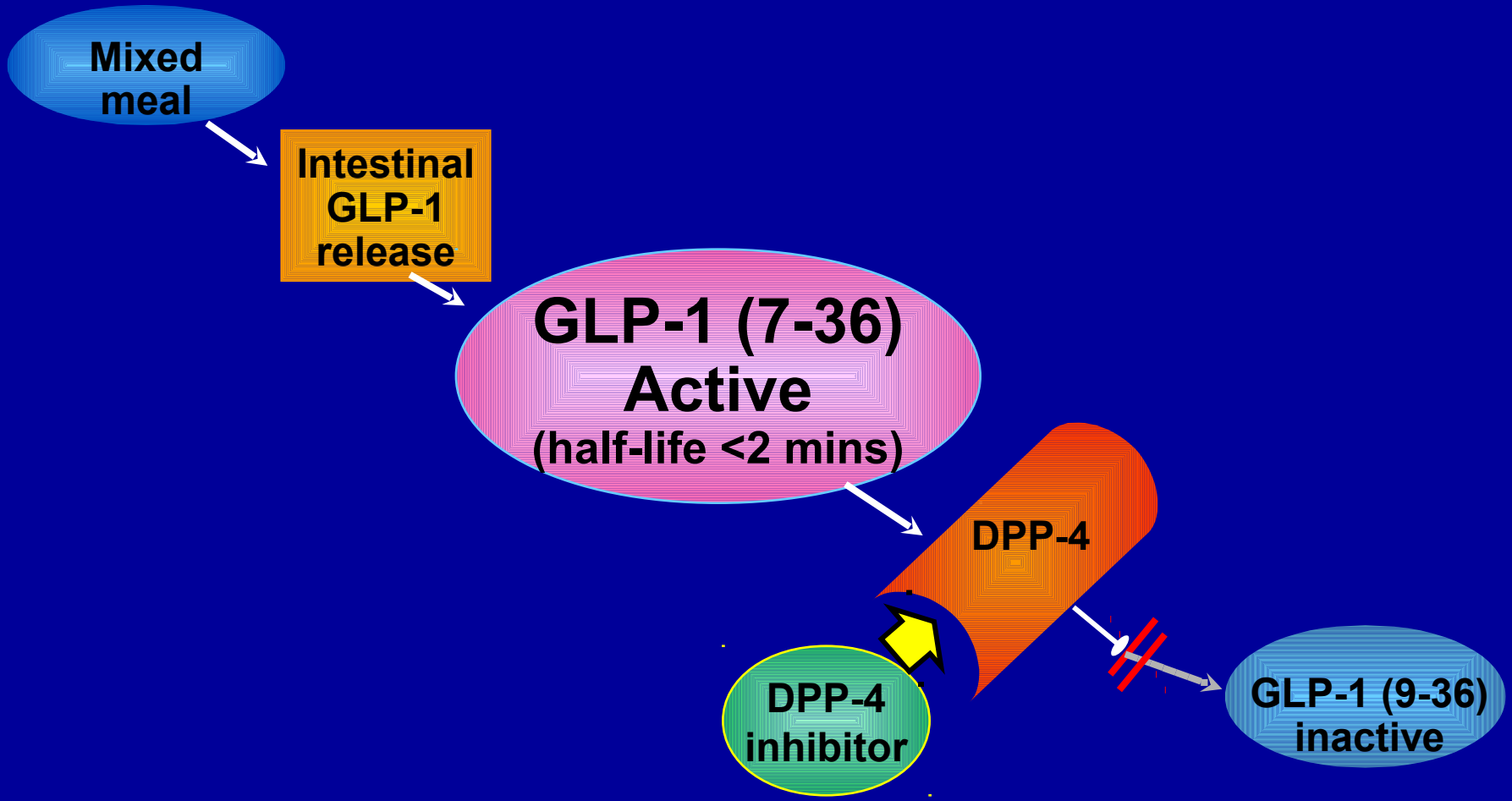
The incretin effect is diminished in patients with type 2 diabetes (T2D)

*p<.05; †Plasma

Adapted from Nauck MA, et al. *Diabetologia.* 1986;29:46-52.

BY/ELB/11/2009/462

Rapid Inactivation (1–2 minutes) of GLP-1



DPP-4: Dipeptidyl peptidase-4.

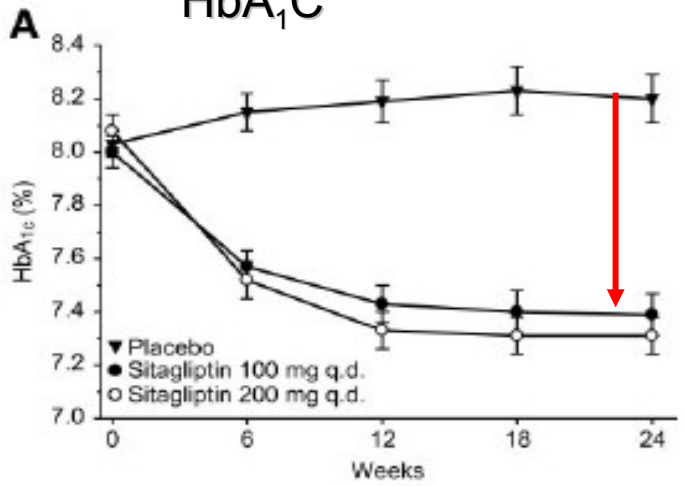
Adapted from Drucker DJ *Expert Opin Invest Drugs* 2003;12(1):87–100; Ahrén B *Curr Diab Rep* 2003;3:365–372.

Diabète de type 2 sans traitement

Sitagliptine

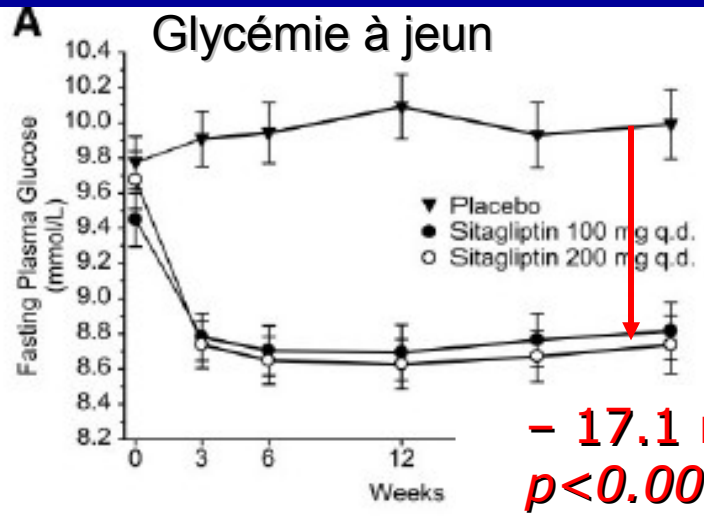
Sitagliptine 100/200 mg *vs.* placebo
24 semaines

HbA$_1$C



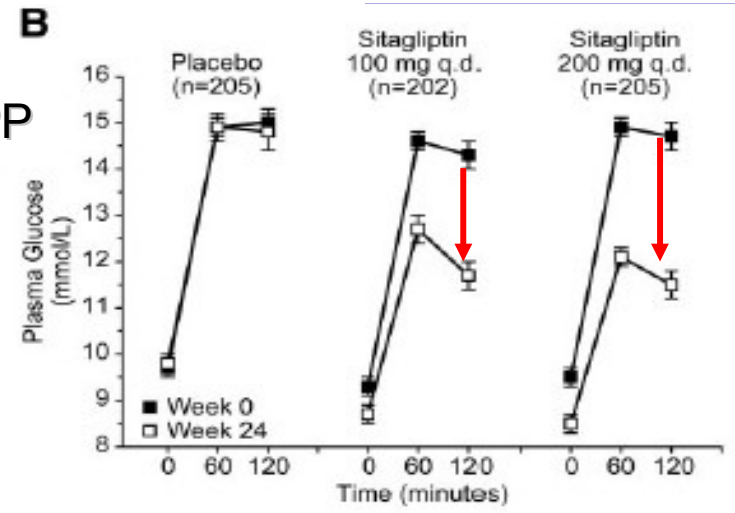
– 0.79 % (100mg)
p≤0.001 vs. placebo

Glycémie à jeun



– 17.1 mg/dl (100 mg)
p<0.001 vs. placebo

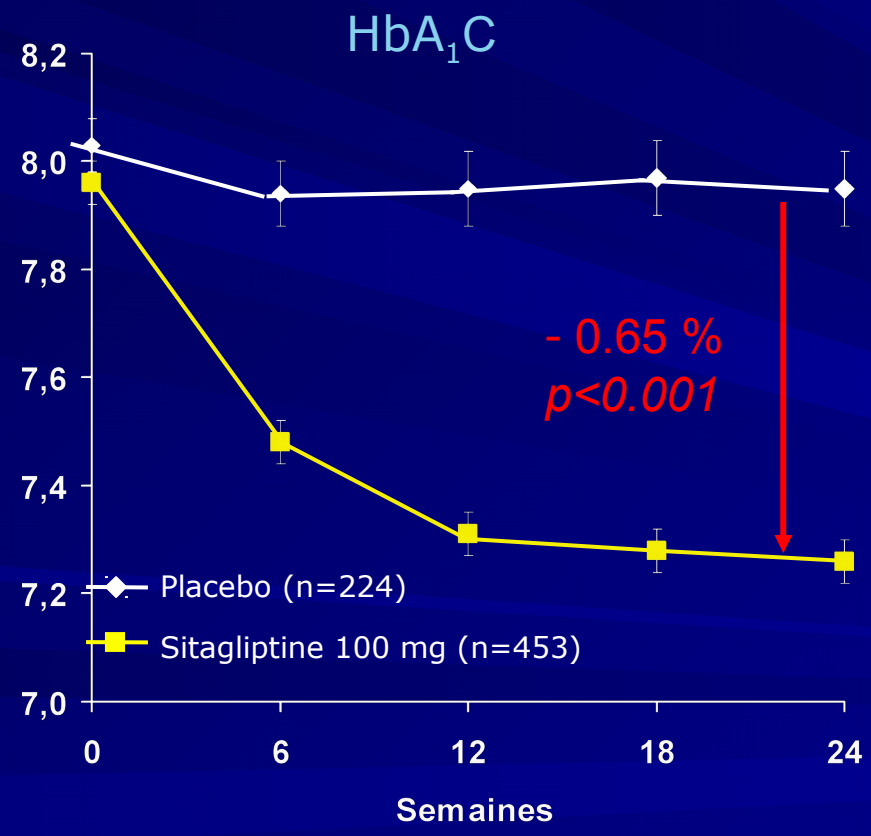
Glycémie PP

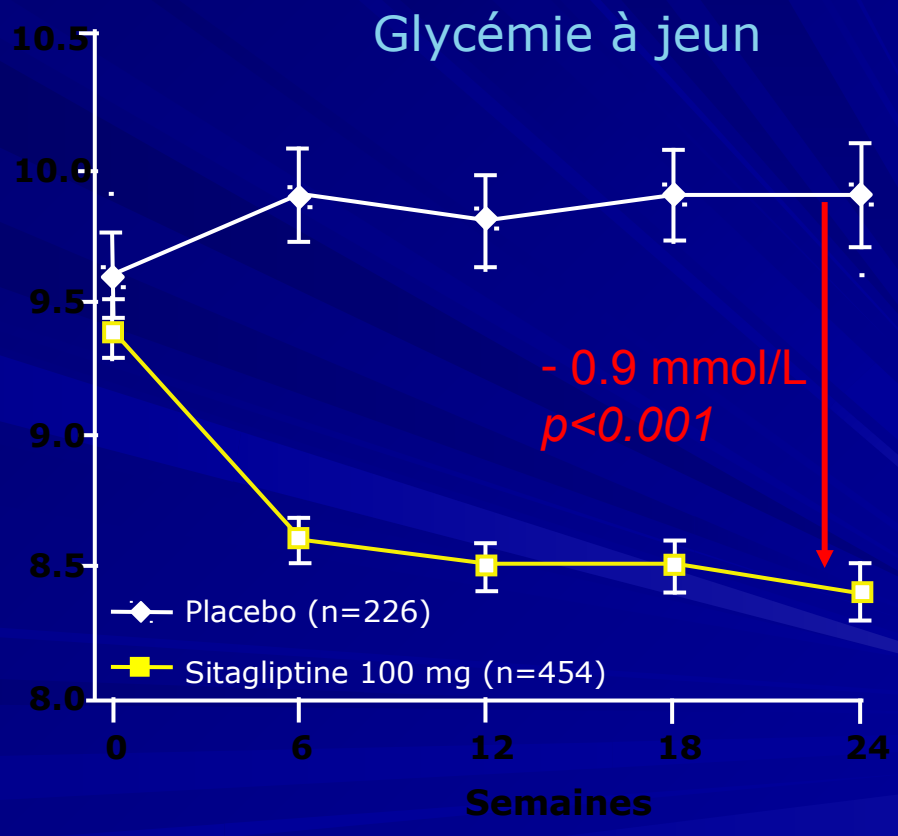


Aschner *et al*. Diabetes Care 2006; 29: 2632-2637

Sitagliptine + Metformine

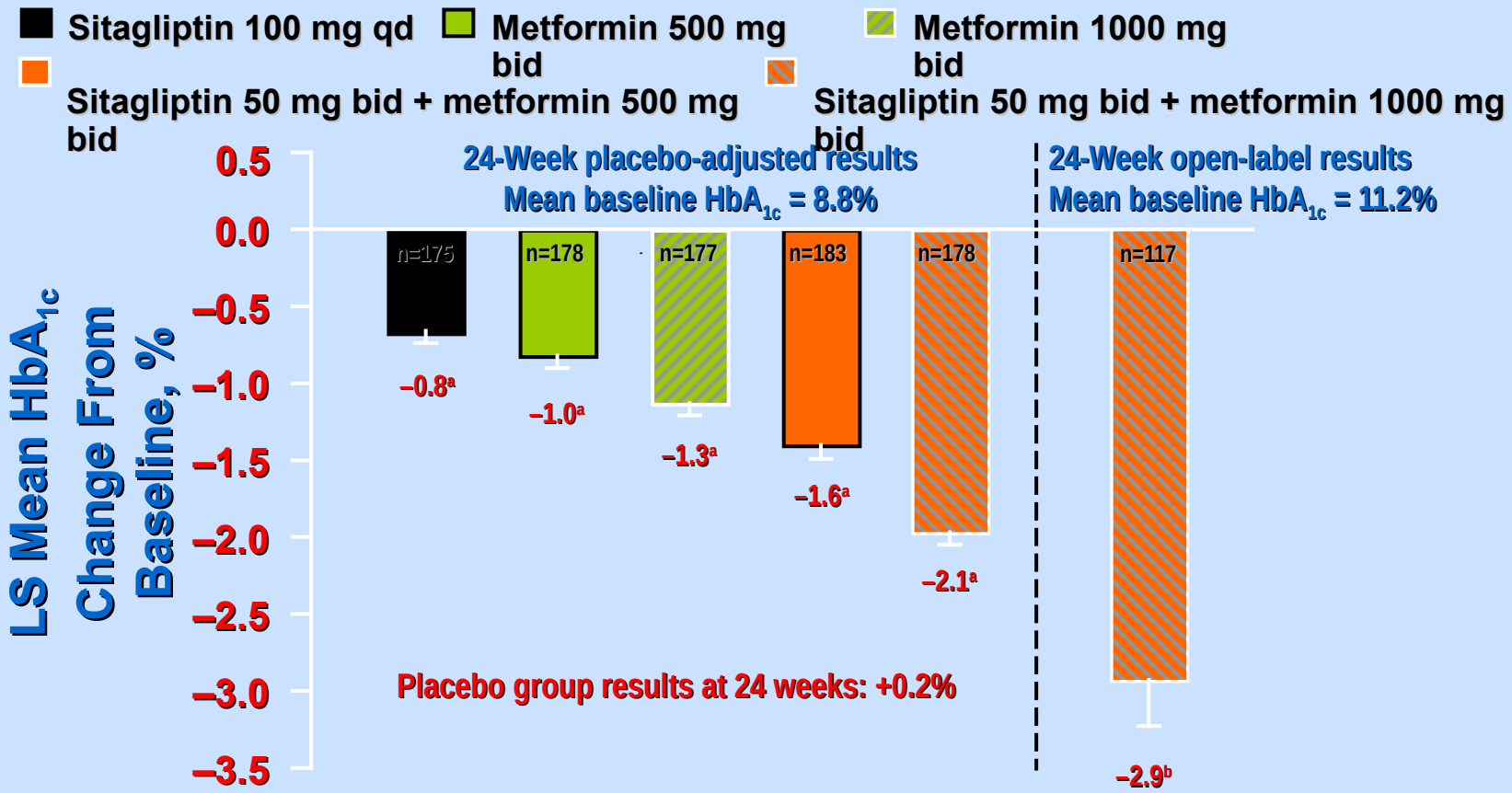
Sitagliptine + Metformine *vs.*
Metformine + Placebo
24 semaines





Charbonnel *et al*. Diabetes Care 2006; 29: 2368-2643

Initial Combination Therapy With Sitagliptin Plus Metformin Provided HbA_{1c} Reductions at 24 Weeks[1]



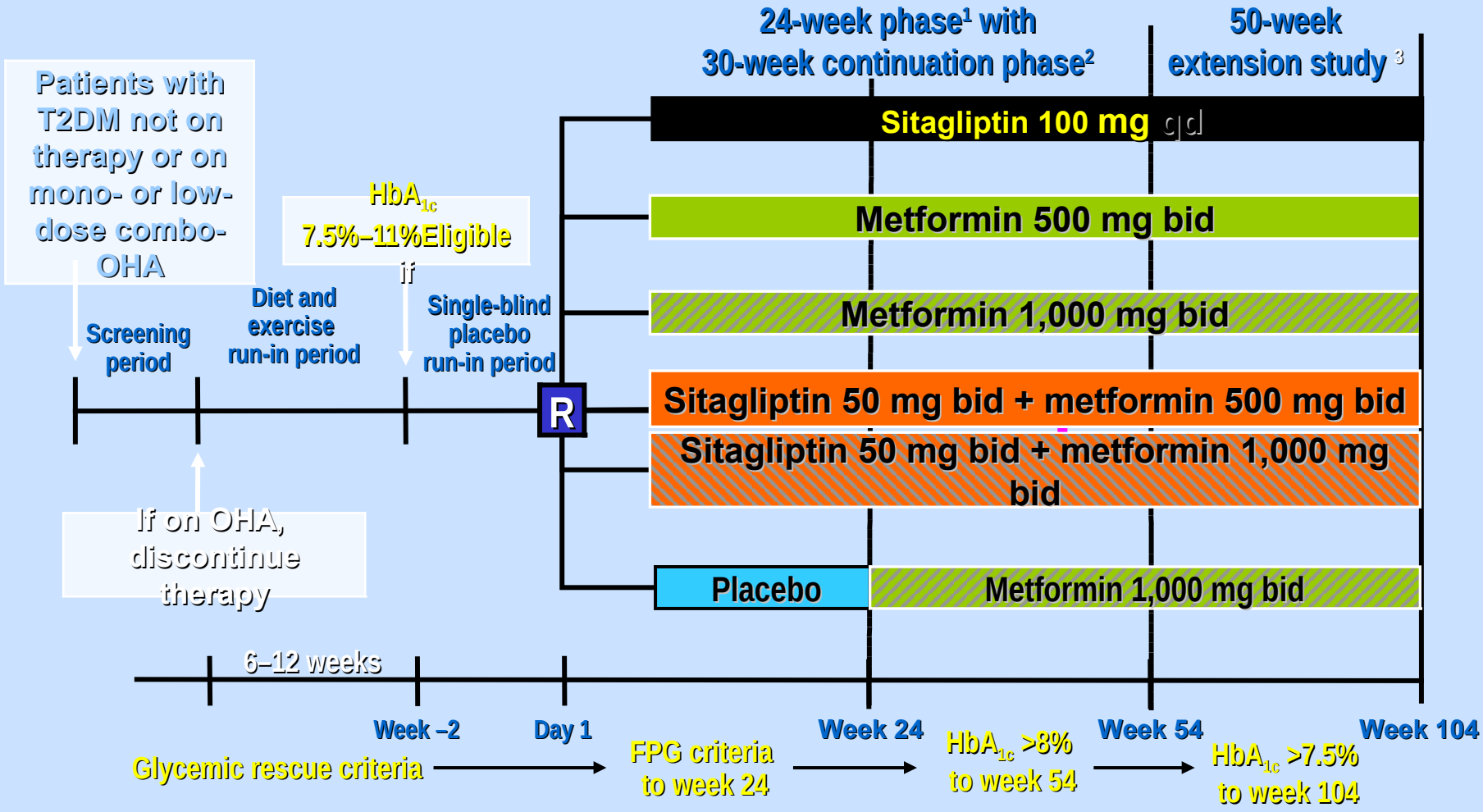
APT=all-patients-treated; bid=twice daily; LS=least-squares; qd=once daily.

[a]$P \leq 0.001$ vs placebo.

[b]LS mean change from baseline without adjustment for placebo.

1. Goldstein BJ et al. *Diabetes Care*. 2007;30(8):1979–1987. Please note: Dr. Goldstein is currently a Merck employee but was not at the time this study was conducted or when the publication was written.

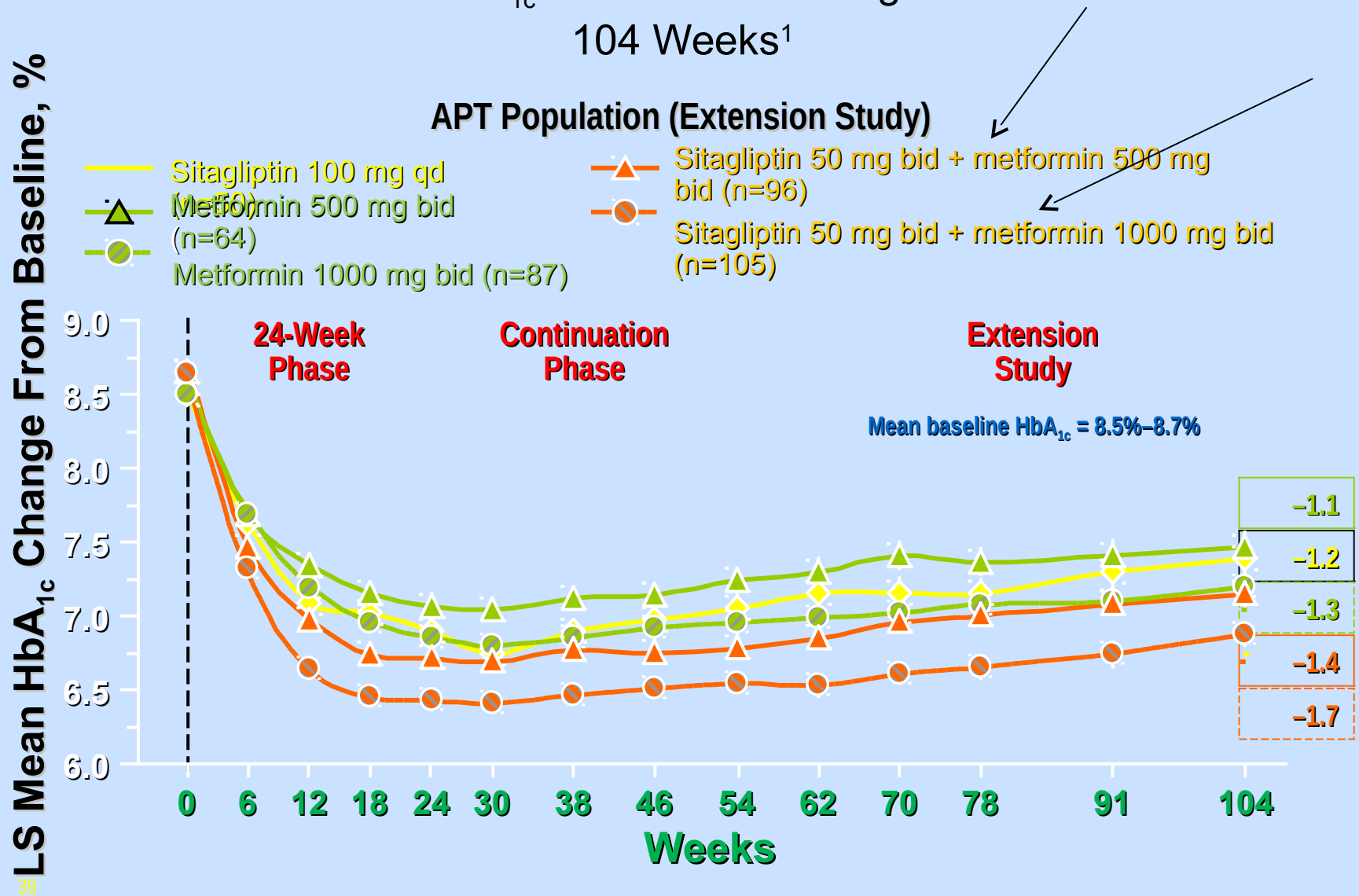
Initial Combination Therapy With Sitagliptin Plus Metformin



bid=twice daily; FPG=fasting plasma glucose; OHA=oral antihyperglycemic agent; qd=once daily; R=randomization; T2DM=type 2 diabetes mellitus.

1. Goldstein B et al. *Diabetes Care*. 2007;30(8):1979–1987.
2. Williams-Herman D et al. *Curr Med Res Opin*. 2009;25(3):569–583.
3. Williams-Herman D et al. *Diabetes Obes Metab*. 2010;12(5):442–451.

Initial Combination Therapy With Sitagliptin Plus Metformin Provided HbA_{1c} Reductions Through 104 Weeks[1]



APT=all-patients-treated; bid=twice daily; LS=least-squares; qd=once daily.

1. Used with permission: Williams-Herman D et al. *Diabetes Obes Metab*. 2010;12(5):442–451.

Initial Combination Therapy With Sitagliptin Plus Metformin: Body Weight at 104 Weeks[1,a]

APT Population (Extension Study)

	Sitagliptin 100 mg qd n=50	Metformin 500 mg bid n=59	Metformin 1000 mg bid n=81	Sitagliptin 50 mg bid + Metformin 500 mg bid n=94	Sitagliptin 50 mg bid + Metformin 1000 mg bid n=100
LS mean change in weight from baseline, kg (95% CI)	0.5 (–0.7, 1.7)	–0.8 (–1.9, 0.3)	–2.4[b] (–3.3, –1.5)	0.0 (–0.8, 0.9)	–1.2[b] (–2.0, –0.3)

APT=all-patients-treated; bid=twice daily; CI=confidence interval; LS=least-squares; qd=once daily.
[a]Results include only randomized patients who entered the extension study, had not received glycemic rescue therapy through week 54, took at least 1 dose of study medication after week 54, and had at least 1 post-54-week A1C measurement.
[b]95% confidence interval for LS mean change from baseline excluded "0."
1. Williams-Herman D et al. *Diabetes Obes Metab*. 2010;12(5):442–451.

The AE Profile of Sitagliptin Plus Metformin Therapy Was Similar to Those of Either Agent Alone Over 104 Weeks[1,a]

Patients, n (%)	Sitagliptin 100 mg qd (n=179)	Metformin 500 mg bid (n=182)	Metformin 1000 mg bid (n=182)	Sitagliptin 50 mg + metformin 500 mg bid (n=190)	Sitagliptin 50 mg + metformin 1000 mg bid (n=182)
One or more AEs	108 (60)	117 (64)	135 (74)	135 (71)	137 (75)
Drug-related AEs	17 (10)	27 (15)	35 (19)	33 (17)	37 (20)
Serious AEs	13 (7)	7 (4)	9 (5)	12 (6)	11 (6)
Discontinued due to AEs	5 (3)	8 (4)	7 (4)	6 (3)	4 (2)
Discontinued due to serious AEs	4 (2)	5 (3)	1 (1)	1 (1)	0 (0)
Deaths	0 (0)	1 (1)	0 (0)	1 (1)	1 (1)

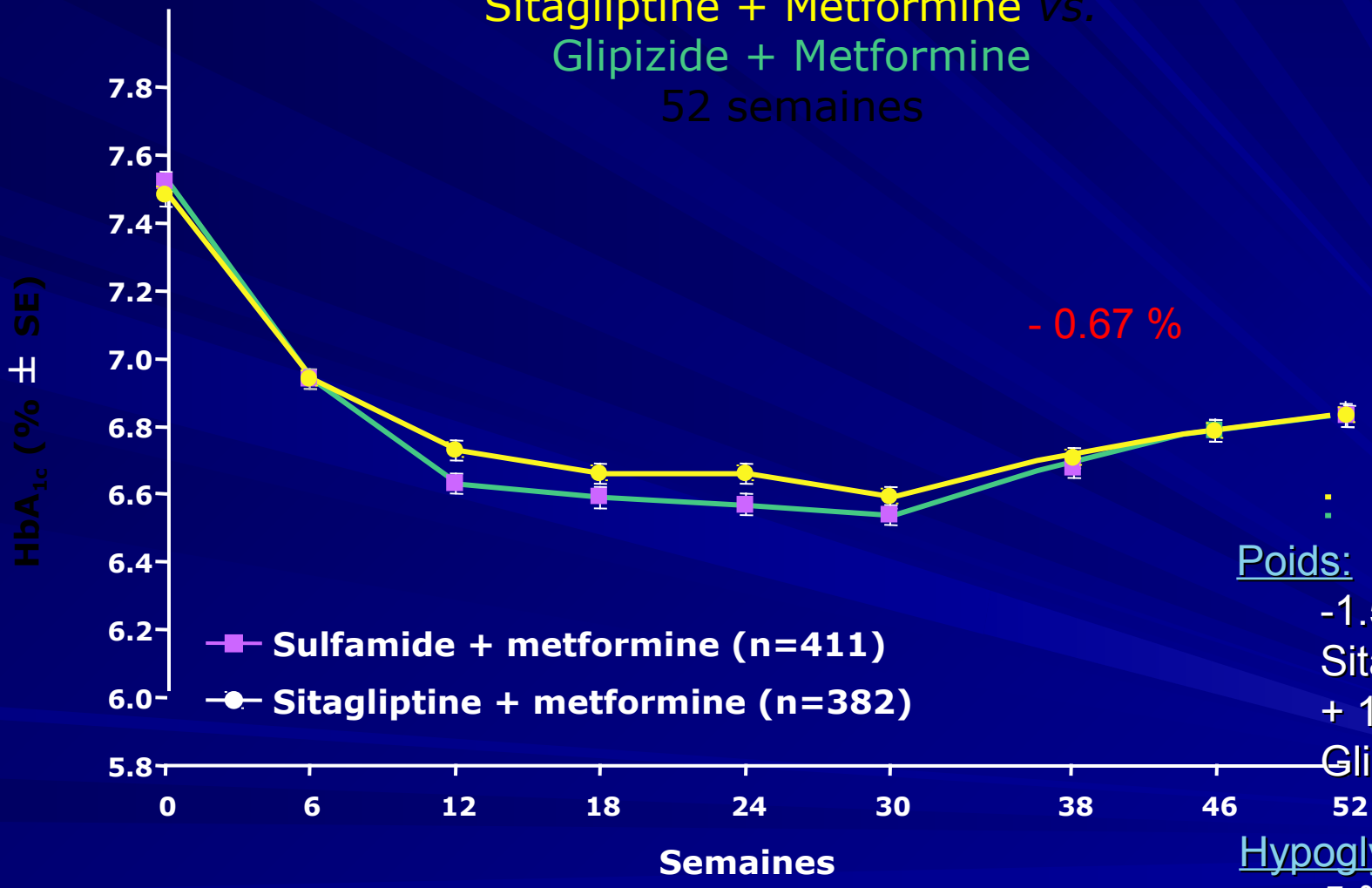
AE=adverse event; bid=twice daily; qd=daily.

[a]Results include all study-blind randomized patients who took at least 1 dose of study medication.

1. Williams-Herman D et al. *Diabetes Obes Metab*. 2010;12(5):442–451.

Sitagliptine *vs.* Sulfamides

Sitagliptine + Metformine *vs.*
Glipizide + Metformine
52 semaines



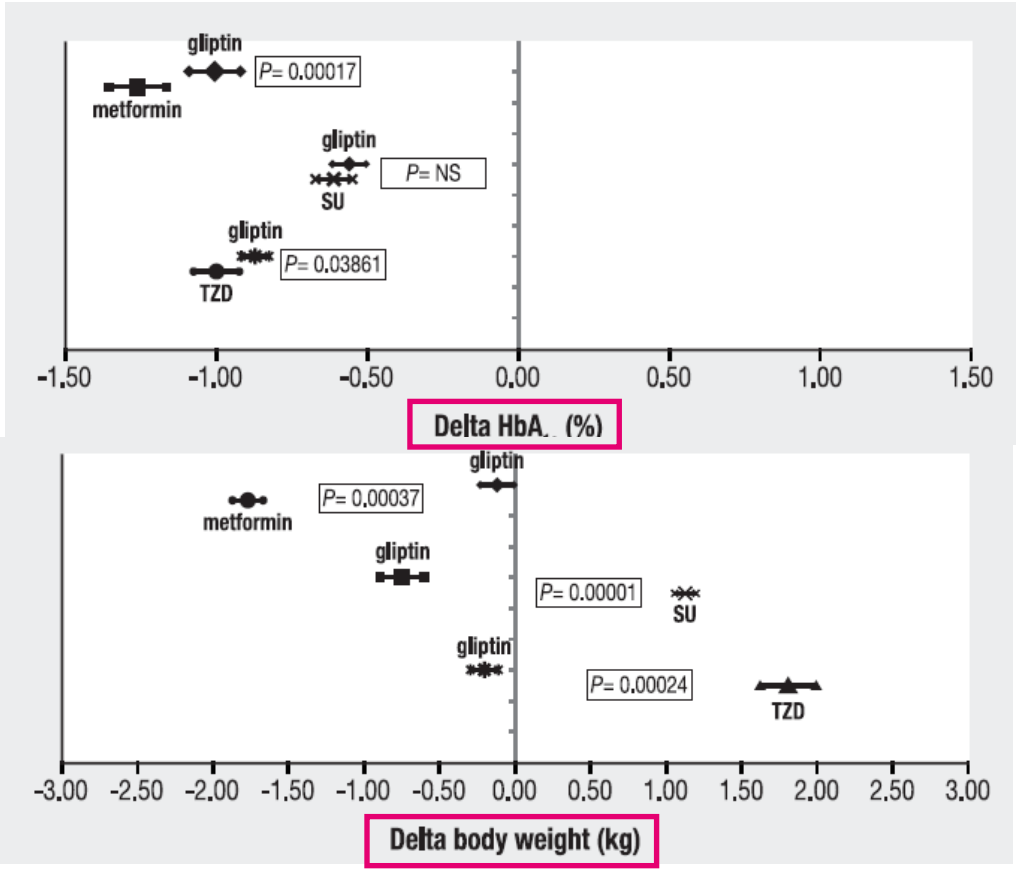
Poids:
-1.5 kg
Sitagliptine
+ 1.1 kg
Glipizide

Hypoglycémies:
5 %
Sitagliptine
32 %

Nauck *et al.* Diabetes Obes Metab 2007; 9: 194–205

Comparative efficacy of DPP4i's vs oral antidiabetic drugs

Head to head trials in drug naive and metformin-treated patients



Mean changes in HbA1c

Mean changes in body weight

- **Metformin** : greater reduction in HbA1c and weight
- **SU** : no significant difference in HbA1c but **greater weight gain and higher incidence of hypo's, more "escape" with secondary increase in HbA1c**
- **TZD** : slightly greater reduction in HbA1c but **greater weight gain**
- **DPP4i's** : **No expected differences in efficacy in the class (shown for saxa vs sitagliptin)**

Scheen AJ, Diabetes & Metabolism, available on line, march 2012

Méta-analyse inhibiteurs de la DPP-4

Risque moindre d'hypoglycémie avec les inhibiteurs de la DPP-4 en bithérapie

Molécules	Nombre d'études	RR pour l'hypoglycémie
Sulfamidés	2	2,63 (0,76; 9,13)
Glinide	2	7,92 (1,45; 43,21)
Inhibiteurs de la DPP-4	8	0,67 (0,30; 1,50)
Tous les médicaments*	19	1,43 (0,89; 2,30)

Bithérapie = metformine + SU / glinide / inhibiteurs DPP-4 / autres OAD

* SU, glinide, TZD, AGI, inhibiteur de la DPP-4, GLP-1
Phung OJ, et al. *JAMA*. 2010;303:1410-1418

Summary: A Case for Use of Sitagliptin as Add-on to Metformin in Place of Sulfonylureas

- Use of DPP-4 inhibitors following metformin therapy is supported by the ADA /EASD algorithm as an option for patient treatment.[1]
- Hypoglycemia is a barrier to glycemic control.[2,3]
- In comparison to sulfonylureas, sitagliptin provided similar efficacy in reducing HbA_{1c} in patients uncontrolled on metformin, but with no weight gain and fewer reported hypoglycemic episodes.[4-7]

1. Rodbard HW et al. *Endocr Pract*. 2009;15(6):540–559.
2. Pollack MF et al. *Diabetes Res Clin Pract*. 2010;87: 204–210.
3. Álvarez Guisasola F et al. *Diabetes Obes Metab*. 2008;10(suppl 1):25–32.
4. Nauck MA et al. *Diabetes Obes Metab*. 2007;9(2):194–205.
5. Seck T et al. *Int J Clin Pract*. 2010;64(5):562–576.
6. Seck TL et al. *Diab Res Clin Pract*. 2011;doi:10.1016/j.diabres.2011.03.006.
7. Arechavaleta R et al. *Diabetes Obes Metab*. 2011;13:160–168.


Pendant ce temps, à Shanghaï...
J'ai une bonne nouvelle à vous annoncer : mon fils va guérir !... Le professeur Fan Se-Yeng a découvert le remède au terrible poison qui rend fou !...
Vrai ?... Oh ! que je suis heureux !

Sitagliptin Pooled Safety Analysis: Design[1]

19 double-blind, randomized, controlled clinical studies up to 2 years in duration

- Sitagliptin as monotherapy
- Sitagliptin in initial combination with metformin (MET) or pioglitazone (PIO)
- Sitagliptin in combination with MET, PIO, sulfonylurea (SU) (±MET), MET + rosiglitazone (ROSI), or insulin (±MET)
- Patients included in the non-exposed group received the following: placebo, MET, PIO, SU (±MET), ROSI (±MET), or insulin (±MET)

Population (N=10,246)

- Sitagliptin 100 mg/day group (n=5429)
  - 1805 patients were treated for at least 1 year
  - 584 patients were treated for 2 years
  - Mean duration of exposure was 282 days
- Non-exposed group (n=4817)
  - 1320 patients were treated for at least 1 year
  - 470 patients were treated for 2 years
  - Mean duration of exposure was 259 days

[a]Studies with results available as of July 2009.

1. Williams-Herman D et al. *BMC Endocr Disord*. 2010;10:7.

Sitagliptin Pooled Safety Analysis: Summary of Adverse Experiences[1]

	Incidence Rate per 100 Patient-Years		
	Sitagliptin n=5429	Non-exposed n=4817	Between-Groups Difference (95% CI)[a]
1 or more AEs	153.5	162.6	–7.6 (–15.6, 0.3)
Drug-related AEs[b]	20.0	26.8	–6.4 (–8.7, –4.1)
Serious AEs	7.8	7.9	–0.1 (–1.3, 1.1)
Serious drug-related AEs[b]	0.4	0.3	0.1 (–0.1, 0.4)
Died	0.3	0.5	–0.2 (–0.5, 0.1)
Discontinued due to AEs	4.8	5.2	–0.5 (–1.5, 0.4)
Discontinued due to drug-related AEs[b]	1.7	2.3	–0.5 (–1.1, 0.1)
Discontinued due to serious AEs	1.7	1.7	–0.0 (–0.6, 0.5)
Discontinued due to serious drug-related AEs[b]	0.2	0.1	0.1 (–0.1, 0.3)

AE=adverse experience; CI=confidence interval.

[a]Between-groups difference and 95% CI based on stratified analysis. Positive differences indicate that the incidence rate for the sitagliptin group was higher than the incidence rate for the non-exposed group. "0.0" and "–0.0" represent rounding for values that were slightly greater and slightly less than zero, respectively.

[b]Considered by the investigator to be drug related.

1. Williams-Herman D et al. *BMC Endocr Disord*. 2010;10:7.

Sitagliptin Pooled Analysis: No Difference in Incidence of Pancreatitis Between Sitagliptin and Non-exposed Groups[1]

	Incidence Rate per 100 Patient-Years		
Adverse Experience	Sitagliptin n=5,429	Non-exposed n=4,817	Between-Groups Difference, (95% CI)[a]
Pancreatitis	0.08	0.10	–0.02 (–0.20, 0.14)
Chronic pancreatitis	0.04	0.03	0.02 (–0.11, 0.13)

- Preclinical and clinical trial data[a] with sitagliptin to date do not indicate an increased risk of pancreatitis in patients with type 2 diabetes treated with sitagliptin.

CI=confidence interval.
[a]Data available through July 2009.
1. Engel SS et al. *Int J Clin Pract*. 2010;6497):984–990.

Data from D Cohen, BMJ, june 2013…

Sitagliptin Pooled Safety Analysis: Malignant and Non-malignant Neoplasms[1]

Adverse Experience	n / Patient-Years of Exposure (incidence rate per 100 patient-years)		
	Sitagliptin n=5429	Non-exposed n=4817	Between-Groups Difference (95% CI)[a]
Any malignancy	46/4690 (1.0)	40/3930 (1.0)	–0.0 (–0.5, 0.4)

- Incidences of malignancies were similarly low for both treatment groups.
  - The most common malignancies were basal cell carcinoma, breast cancer (women), and prostate cancer (men).
- The incidence of non-malignant neoplasms was higher in the sitagliptin group than in the non-exposed group (1.3 per 100 PY vs 0.7 per 100 PY).
  - The most common non-malignant events were uterine leiomyoma and lipoma (women).

CI=confidence interval; PY=patient years.

[a]Betweendrug and 95% CI based on stratified analysis. Positive differences indicate that the incidence rate for the sitagliptin group was higher than the incidence rate for the non-exposed group. "0.0" and "–0.0" represent rounding for values that were slightly greater and slightly less than zero, respectively.

1. Williams-Herman D et al. *BMC Endocr Disord*. 2010;10:7.

Sitagliptin CV Pooled Safety Analysis: No Difference in MACE[a] Between Sitagliptin and Nonexposed Groups[1,b]

	Sitagliptin (n=7,726)	Nonexposed (n=6,885)
Cumulative exposure, PY	6,157	5,114
MACE, n	40	38
Incidence rate per 100 PY	0.65	0.74
RR (95% CI)	0.83 (0.53, 1.30)	

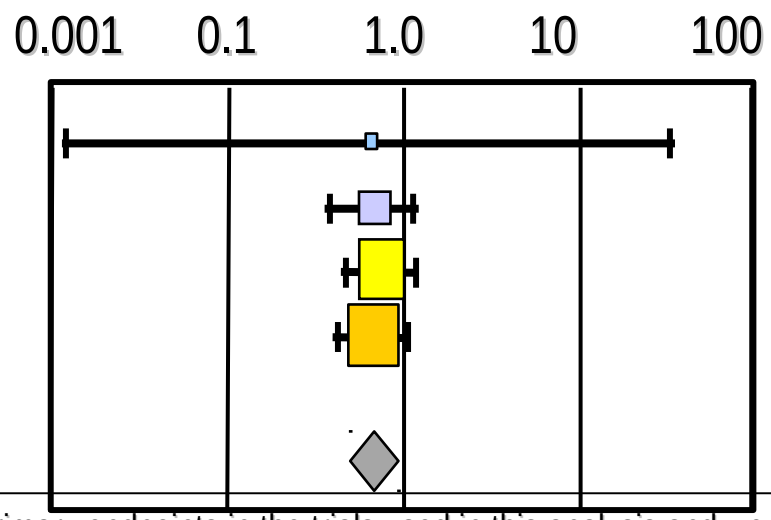
- A total of 78 patients experienced at least 1 MACE-related event

[a]MACE was comprised of ischemic events and cardiovascular deaths.
[b]13,462 of the 14,611 patients contributed to the primary analysis after exclusion of 4 studies with no events.
CI=confidence interval; MACE=major adverse cardiovascular events; PY= patient-years; RR=adjusted incidence rate ratio.
1. Engel S et al. *Cardiovascular Diabetology.* 2013;12:3.

Meta-analysis of Clinical Trials With DPP-4 Inhibitors: No Evidence of Increased Risk of MACE Associated With Treatment[1]

Meta-analysis performed including all randomized clinical trials with a duration of ≥24 weeks, enrolling patients with type 2 diabetes, comparing DPP-4 inhibitors with either placebo or active drugs[a].

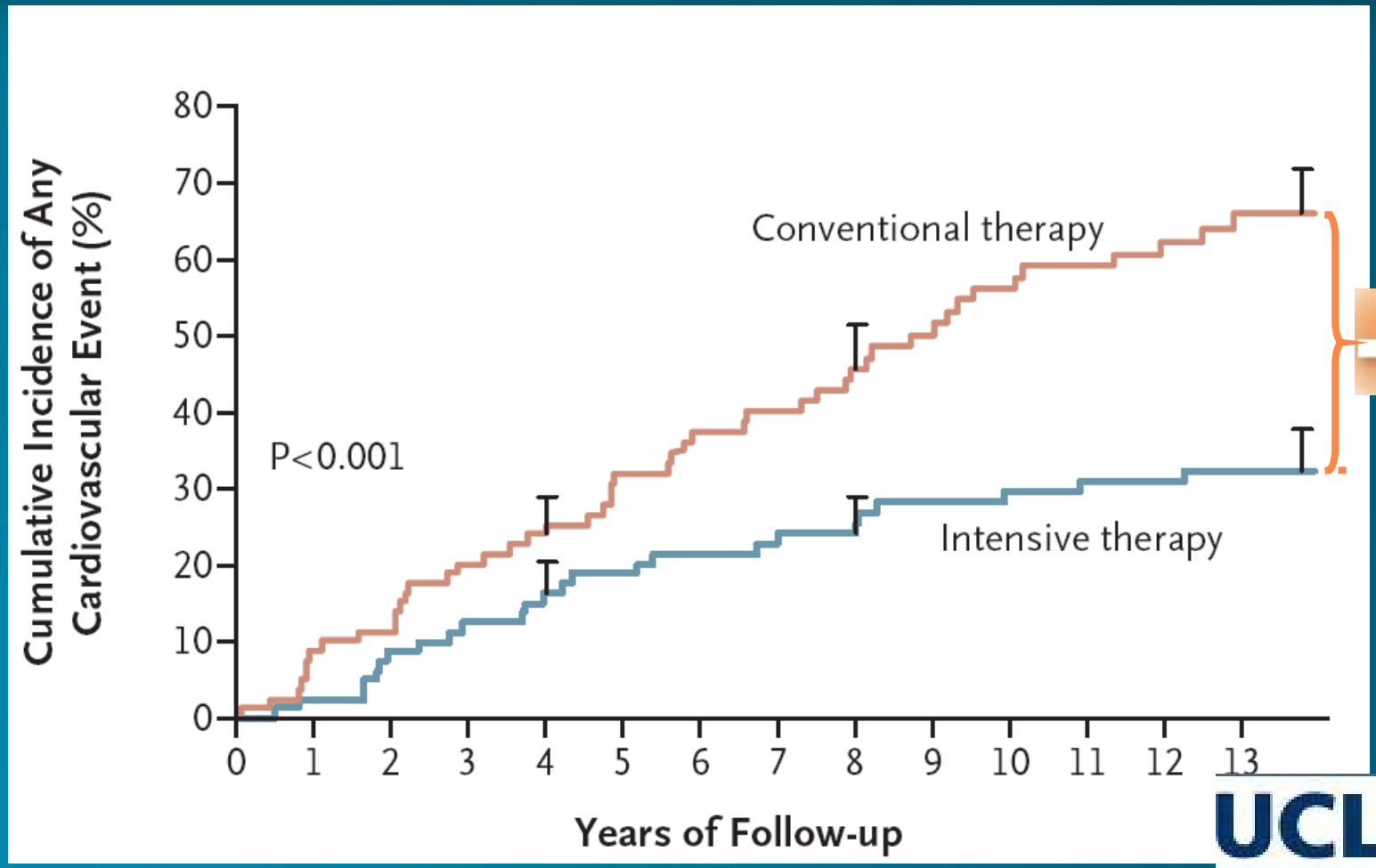
Drugs	Major Cardiovascular Events: MH-OR (95% CI)	*P*	# Trials
Alogliptin	0.630 [0.012, 33.048]	0.819	2
Saxagliptin	0.655 [0.382, 1.123]	0.124	8
Sitagliptin	0.740 [0.479, 1.147]	0.173	18
Vildaglptin	0.666 [0.428, 1.036]	0.072	12
OVERALL	0.689 [0.528, 0.899]	0.006	43



This meta-analysis has several limitations. Cardiovascular events were not primary endpoints in the trials used in this analysis and were only reported as AEs. Also, the short duration of trials included in this analysis do not allow for any conclusions about the long-term safety of DPP-4 inhibitors to be made.

AE=adverse event; CI=confidence interval; DPP-4=dipeptidyl peptidase-4; MH-OR=Mantel–Haenzel odds ratio.
[a]Comparators were: acarbose, GLP-1R agonists, metformin, sulfonylureas, thiazolidinediones, and placebo.
1. Monami M et al. *Curr Med Res Opin*. 2011; 27:57–64.

STENO-2 FOLLOW-UP: résultats après 13.3 années



Gæde P. et al. New Eng J Med 2008, 358 (6): 580-591.

UCL Université catholique de Louvain