Prise en charge du diabète de type 2 en 2018

21.11.2018

Dr. Gastaldi

Service de diabétologie endocrinologie

hypertension et nutrition

Hôpitaux Universitaires Genève

Epidémie de diabète

1/3 non diagnostiqué

Les individus souffrant de diabète sucré sont :

≈425 Mio

9 % population mondiale

10% Diabète auto-immun

≈465 000

6.36 % des helvètes*

≈40’000 DT1

≈ 30’000

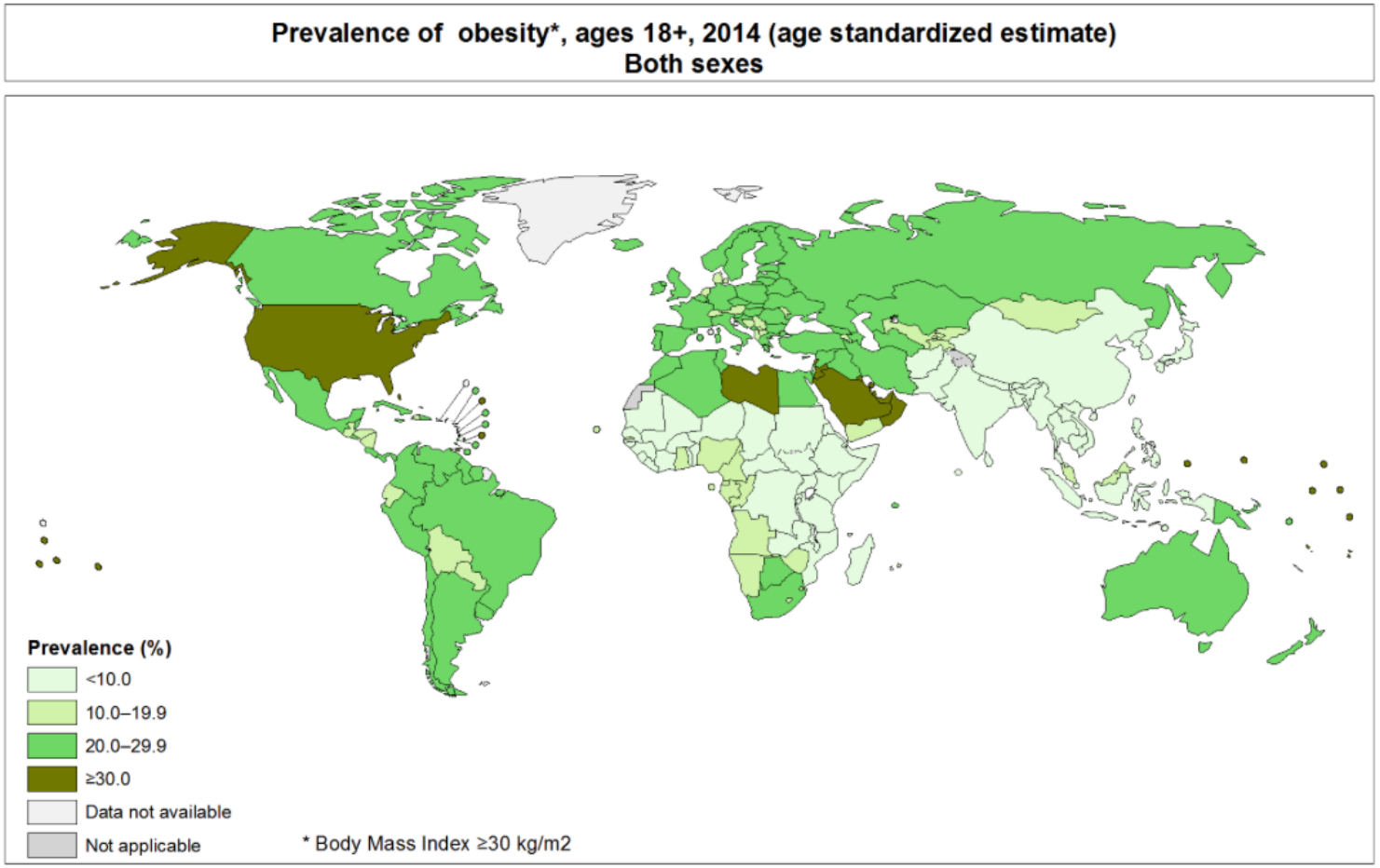
7 % des genevois

≈ 2’500 DT1

PAYS/ TERRITOIRE	Cas de diabète (20-79 ans) en milliers	Cas de diabète non diagnostiqués (20-79 ans) en milliers	Prévalence nationale du diabète (%)	Prévalence comparative du diabète (%)	Décès liés au diabète (20-79 ans)	Coût/personne atteinte de diabète* (USD)
Suisse :	438’000	148’960	7.18 %	5.63%	2487	10.592 USD

*D’après les estimations de l’IDF pour l’année 2012

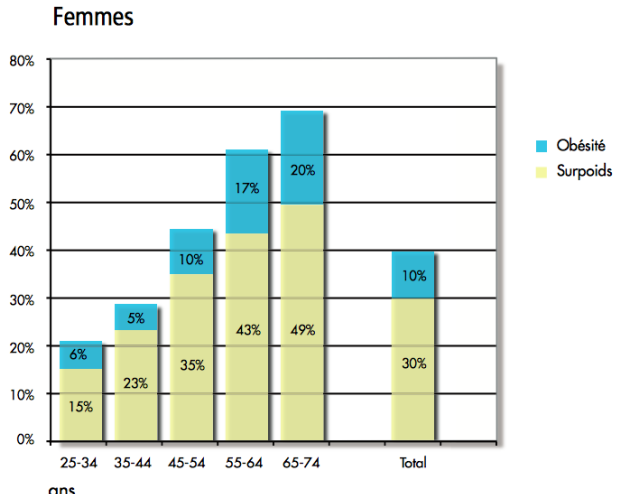
Prevalence of obesity, IDF 2015

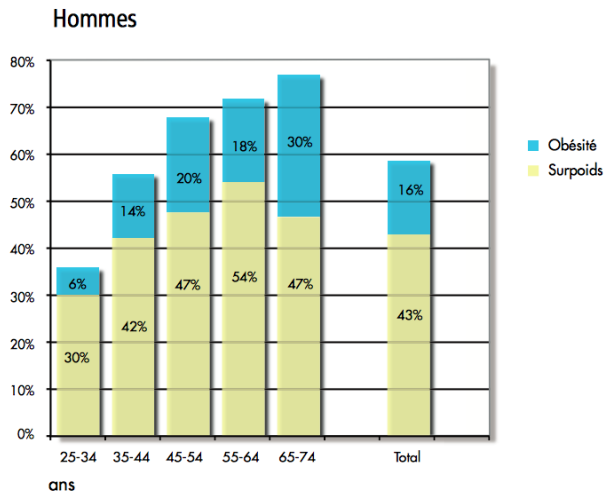


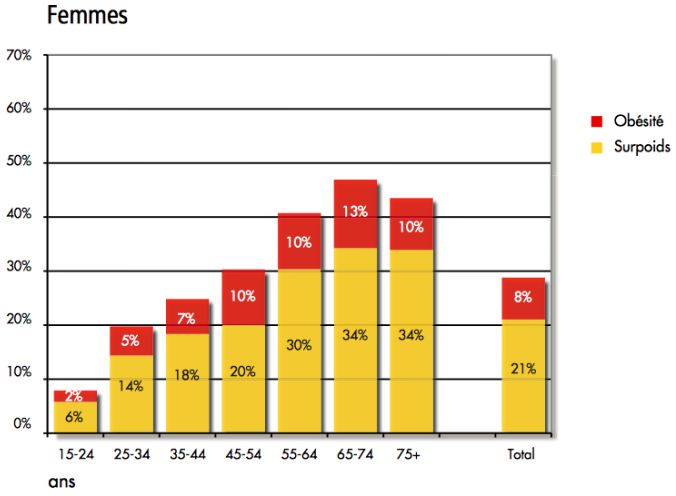
Augmentation spectaculaire dans les pays avec un PIB faible ou moyen, essentiellement en milieu urbain.

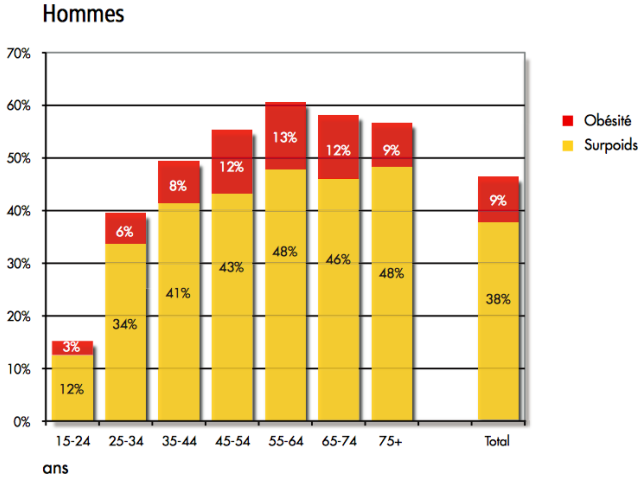
Epidémie d'obésité en Suisse

Enquête Suisse sur la Santé de 2007



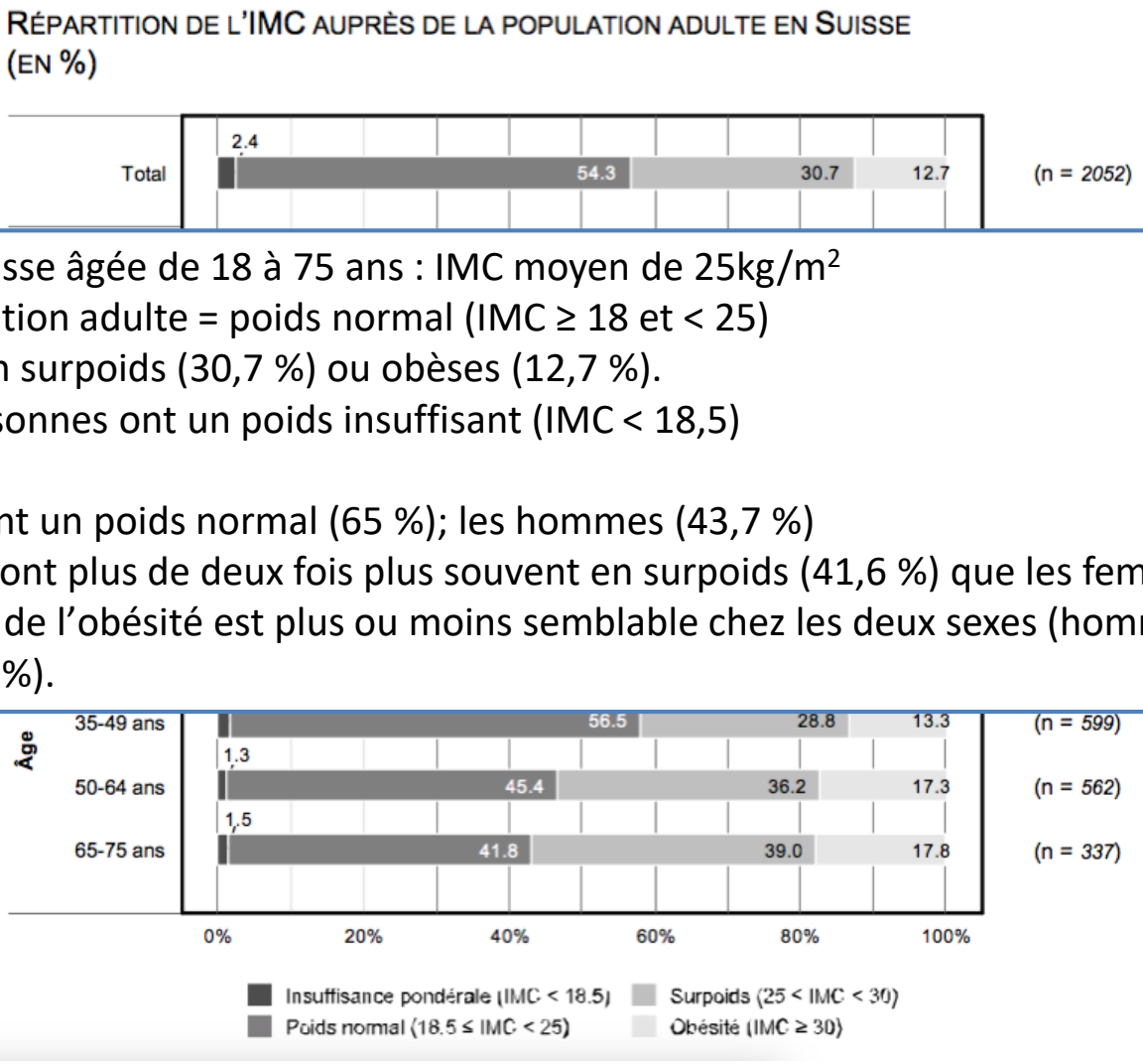






Répartition IMC en Suisse

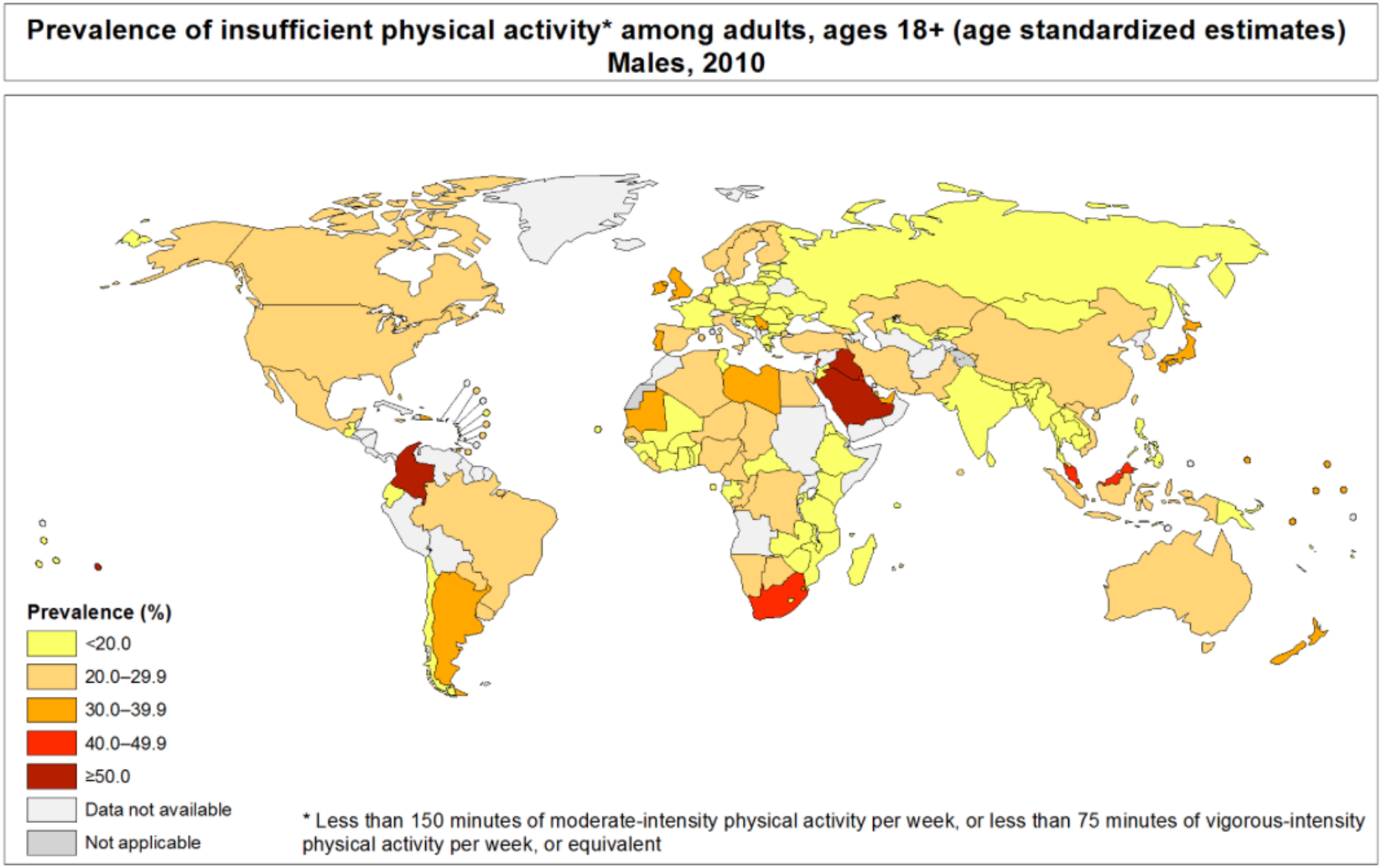
Office fédéral de la sécurité alimentaire et des affaires vétérinaires



Population suisse âgée de 18 à 75 ans : IMC moyen de 25kg/m^2
54,3 % population adulte = poids normal (IMC ≥ 18 et < 25)
43,4 % sont en surpoids (30,7 %) ou obèses (12,7 %).
2,4 % des personnes ont un poids insuffisant (IMC < 18,5)

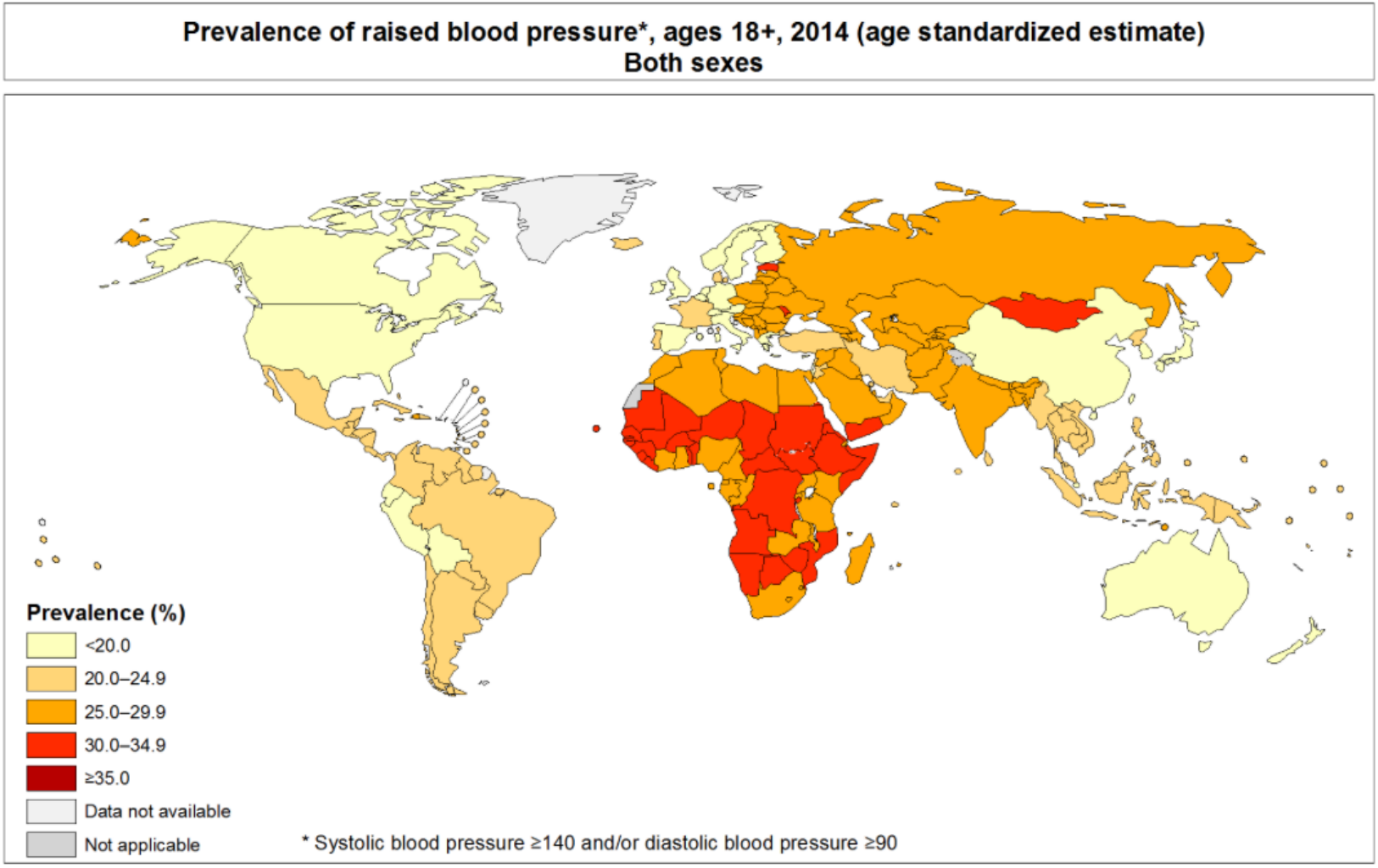
Les femmes ont un poids normal (65 %); les hommes (43,7 %)
Les hommes sont plus de deux fois plus souvent en surpoids (41,6 %) que les femmes (19,6 %).
La prévalence de l'obésité est plus ou moins semblable chez les deux sexes (hommes: 13,9 %, femmes: 11,6 %).

Prevalence of sedentarity, IDF 2015



http://gamapserver.who.int/mapLibrary/app/searchResults.aspx

Prevalence of HTA, IDF 2015

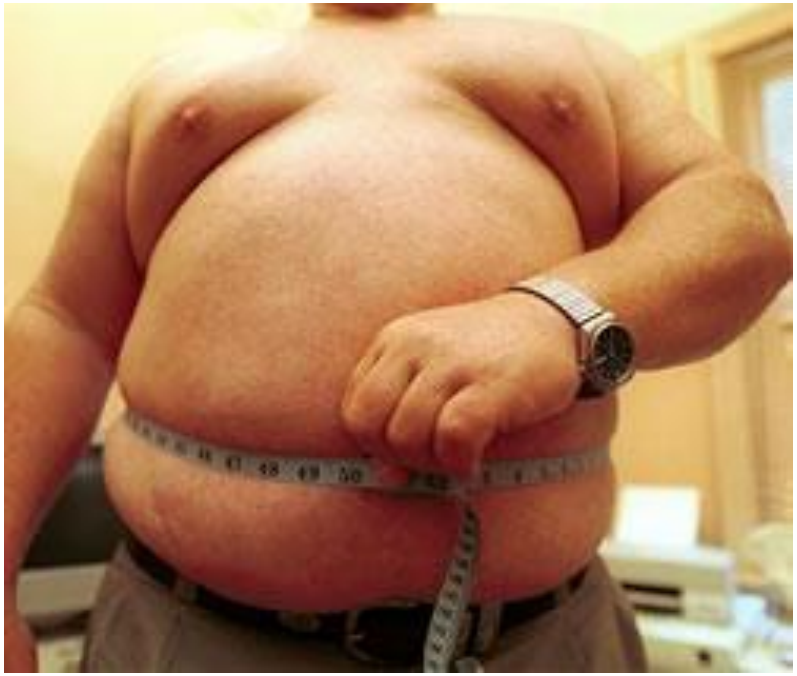


http://gamapserver.who.int/mapLibrary/app/searchResults.aspx

Syndrome métabolique

diabète, hypertension, sucharge pondérale, dyslipidémie

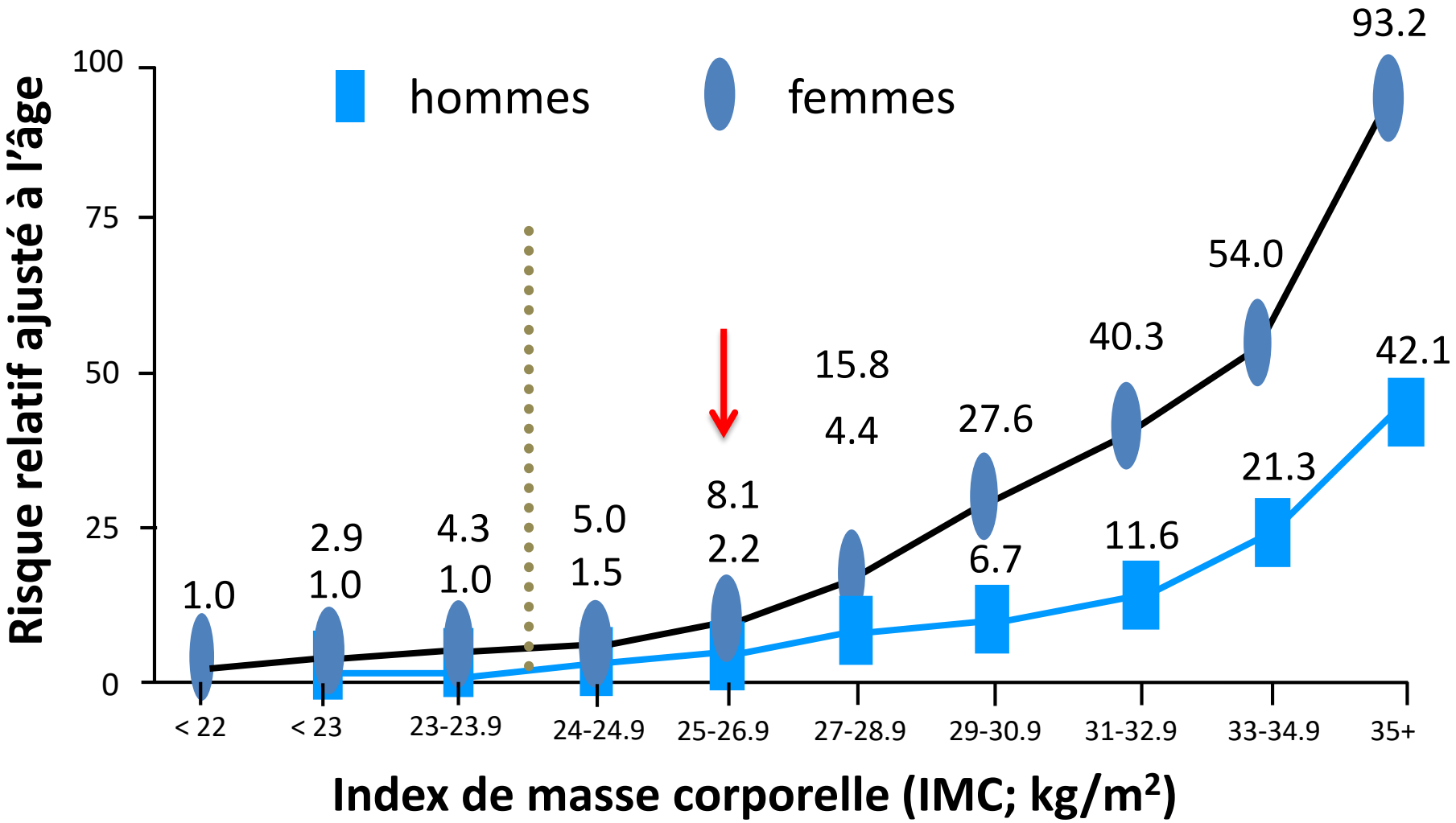
80% des diabétiques de type 2 souffrent de surpoids ou d'obésité
50% des diabétiques de type 2 souffrent d'obésité



Diabésité

25% de la population mondiale

Diabète de Type 2 et IMC



Chan J, et al. *Diabetes Care.* 1994;17:961-969.

Colditz G, et al. *Ann Intern Med.* 1995;122:481-486.

Physiologie intégrative

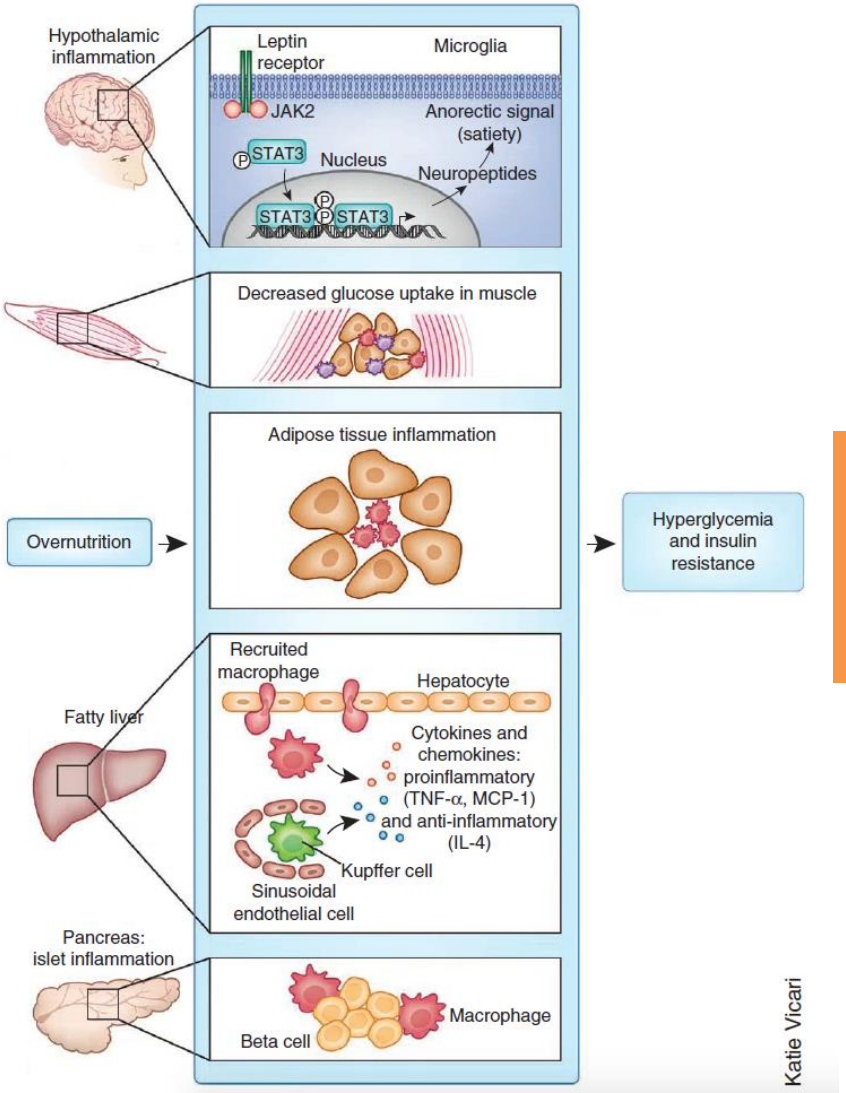
ALIMENTATION Déséquilibrée

SNC

Muscle

Foie

Pancréas



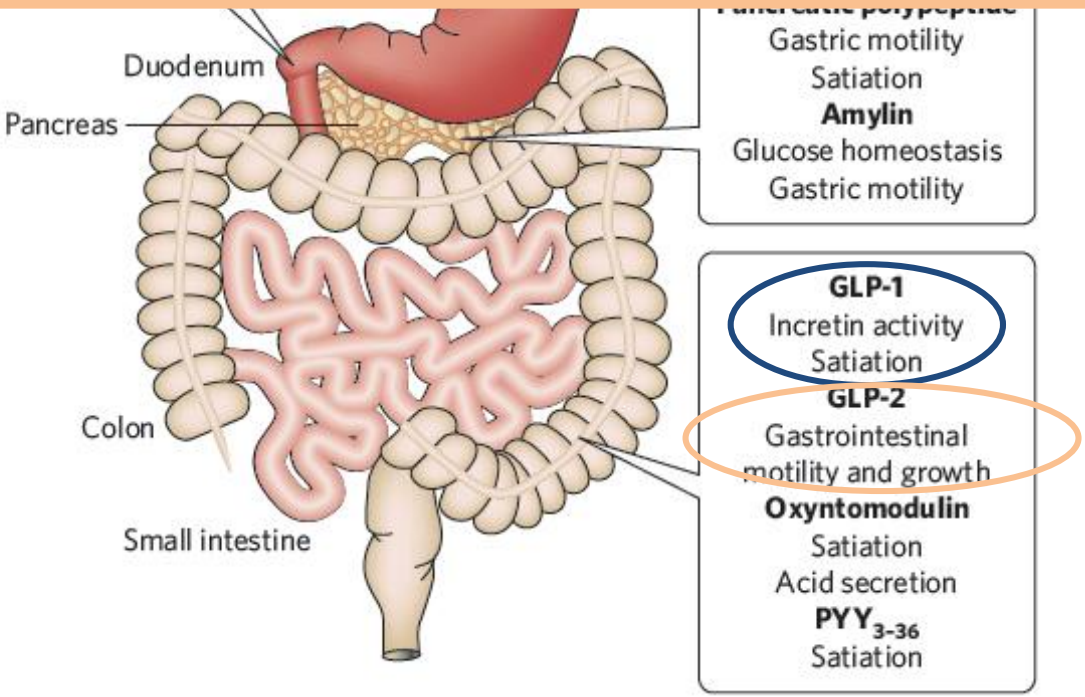
Hyperglycémie Résistance à l'insuline

Nature reviews endocrinology, vol 10, 2014

Hormones de l'axe entéro-insulaire

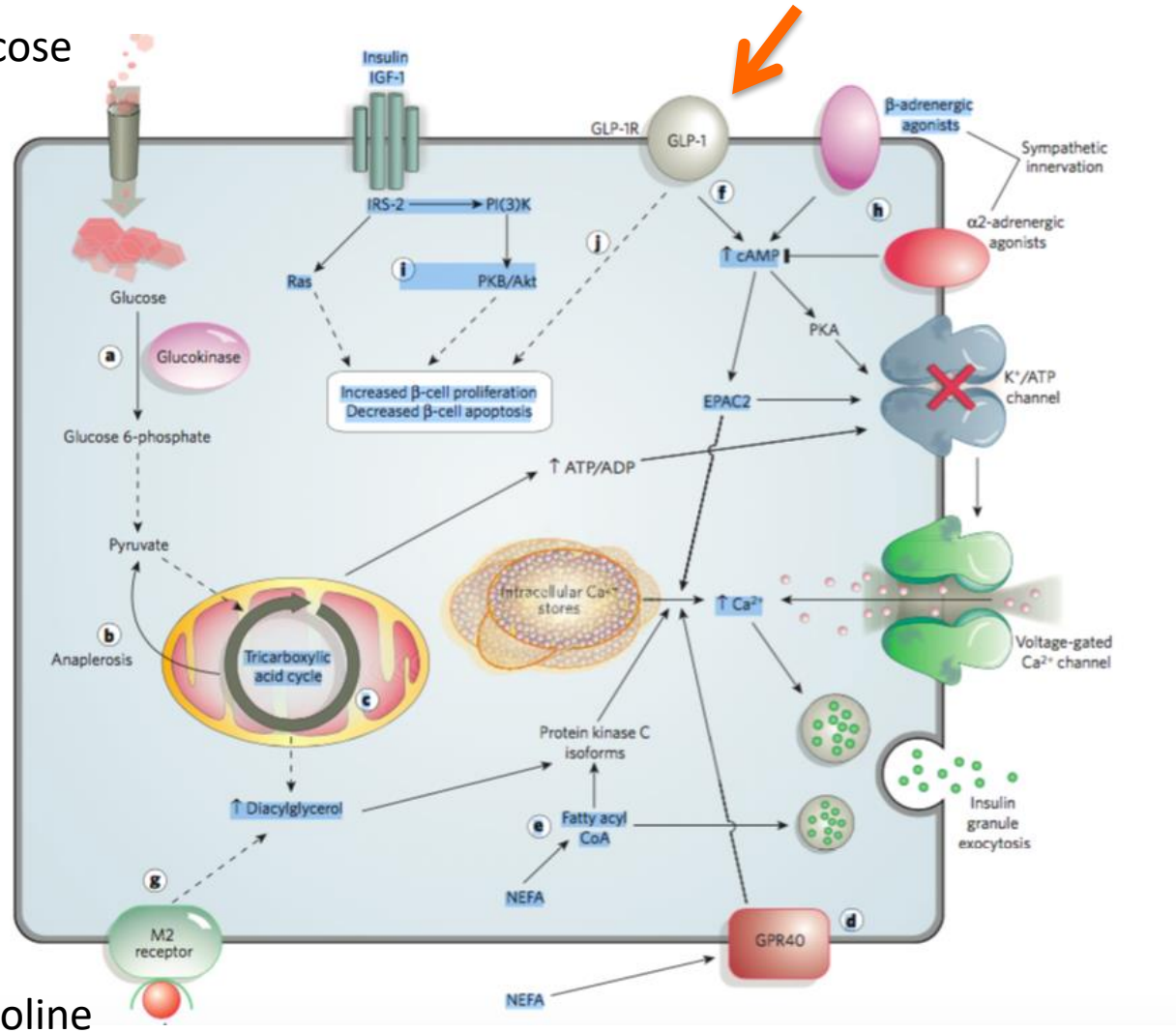
GLP-1[1]
- Libéré principalement par les cellules L de l'iléum et du colon
- Agit notamment sur: les cellules β et α du pancréas, le tractus gastro-intestinal, le SNC, le cœur

GIP[1]
- Libéré principalement par les cellules K du duodénum et du jéjunum
- Agit notamment sur: les cellules β du pancréas, les adipocytes, les cellules souches neurales[4], les ostéoblastes



Sécrétion d'insuline par la cellule β

Glucose

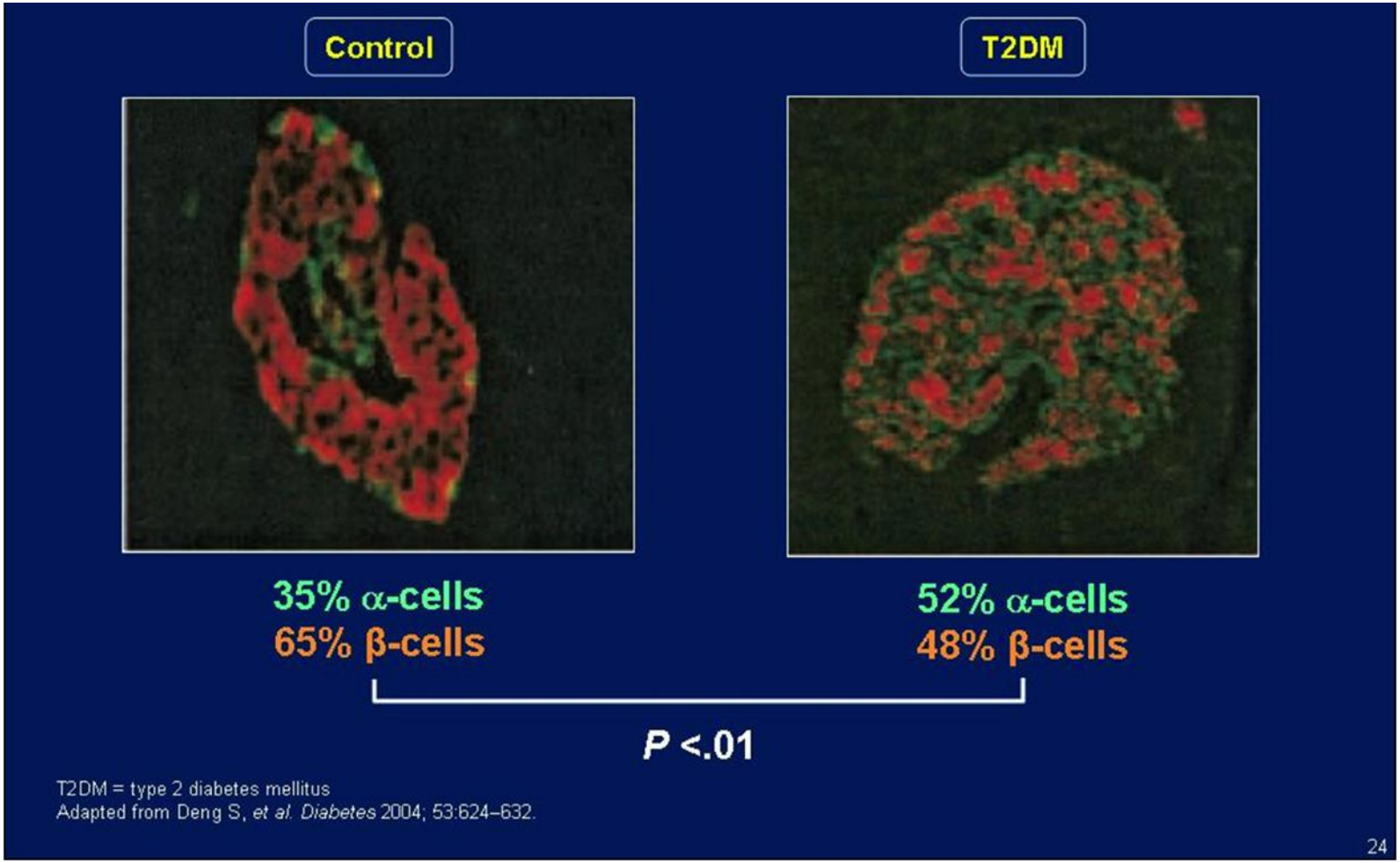


Acétylcholine

S. Kahn et al. Nature 2006

Dysfonction of β and α cells

T2D : a Bi-functional disease



Conséquences du diabète de type 2

Paramètre	Caractéristique du diabète
Sécrétion d'insuline:	altérée
- Réponse rapide:	absente
- Effet de l'incrétine:	réduit
Glucagon:	hypersécrétion
Masse de cellules bêta:	réduit
Appétit/poids:	augmenté
Vidange gastrique:	normale/accélérée?
Sensibilité à l'insuline:	résistance

Modifié d'après: Drucker DJ u. Nauck MA. Lancet . 2006;368:1696-1705

Les complications du diabète

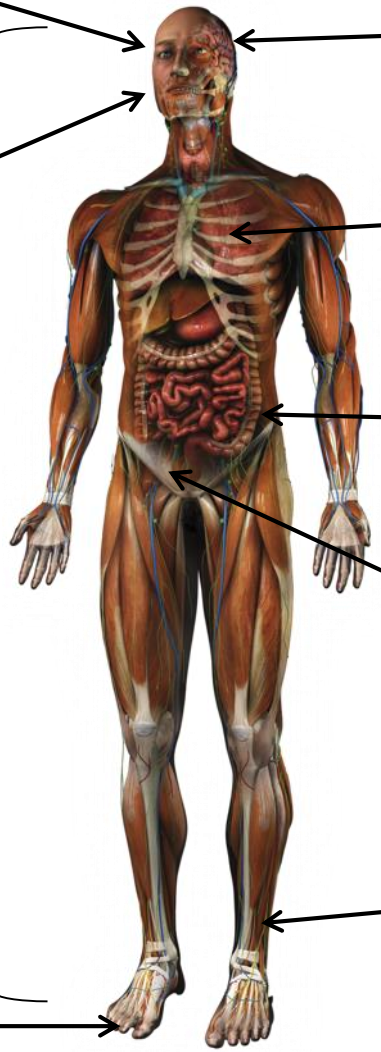
Source: International Diabetes Federation. Diabetes Atlas, 5th Ed. www.diabetesatlas.org (accessed June 2012).

Rétinopathie
(caused by microvascular damage)

Complications périodontales
(caused by microvascular damage)

Neuropathie
(diabetic neuropathy can cause impotence, problems with digestion and urination, and pain/loss of feeling in the extremities)

Pied diabétique (ulcères et plaies)
(caused by diabetic neuropathy and blood vessel damage, leading to amputation)



AVC

Cardiopathie ischémique

Néphropathie
(caused by microvascular damage)

Complications liées à la grossesse

Insuffisance Artérielle des Memb. Inf. (IAMI)

Risque de cancer associé au diabète et à l'obésité

Worldwide burden of cancer attributable to diabetes and high body-mass index: a comparative risk assessment

Jonathan Pearson-Stuttard, Bin Zhou, Vasilis Kontis, James Bentham, Marc J Gunter, Majid Ezzati

Summary

Background Diabetes and high body-mass index (BMI) are associated with increased risk of several cancers, and are increasing in prevalence in most countries. We estimated the cancer incidence attributable to diabetes and high BMI as individual risk factors and in combination, by country and sex.

Lancet Diabetes Endocrinol 2017
Published Online
November 28, 2017
http://dx.doi.org/10.1016/

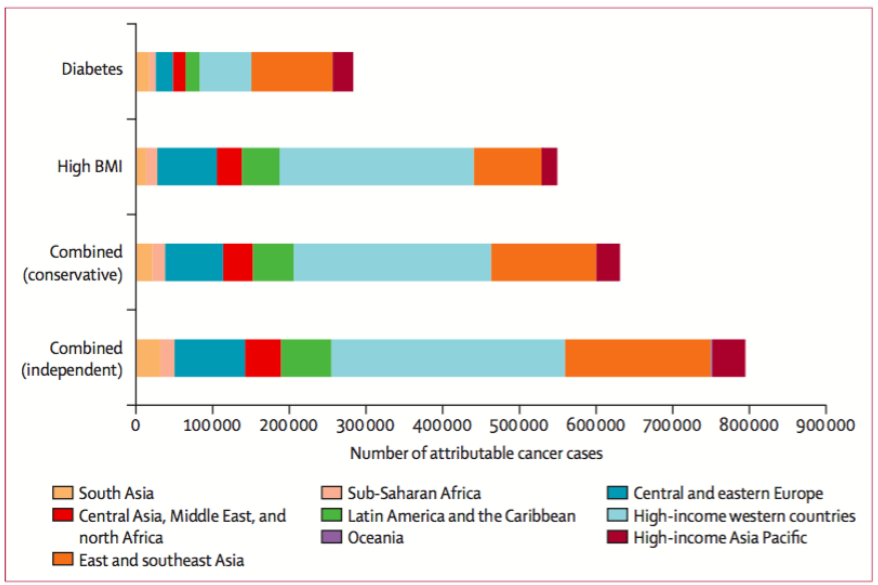


Figure 1: **Global cancer cases in 2012 attributable to diabetes and high BMI, individually and combined, in the conservative and independent scenarios, by region**
BMI=body-mass index.

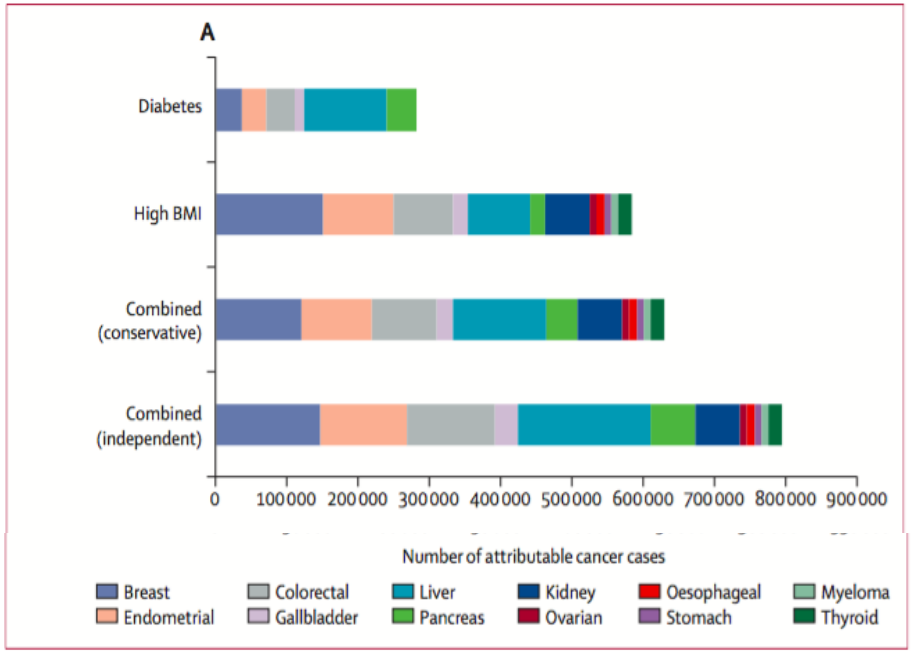


Figure 2: **Global site-specific cancer cases in 2012**

6% of all incident cancers are related to the combined effects of diabetes and high BMI (792 600 cases).

- 59 ans, homme divorcé
- Diabète de type 2 depuis 7 ans
- IMC 29.4 kg/m^2
- HbA1c 8,0%
- Traitement actuel :
  - Metformine
  - Gliclazide

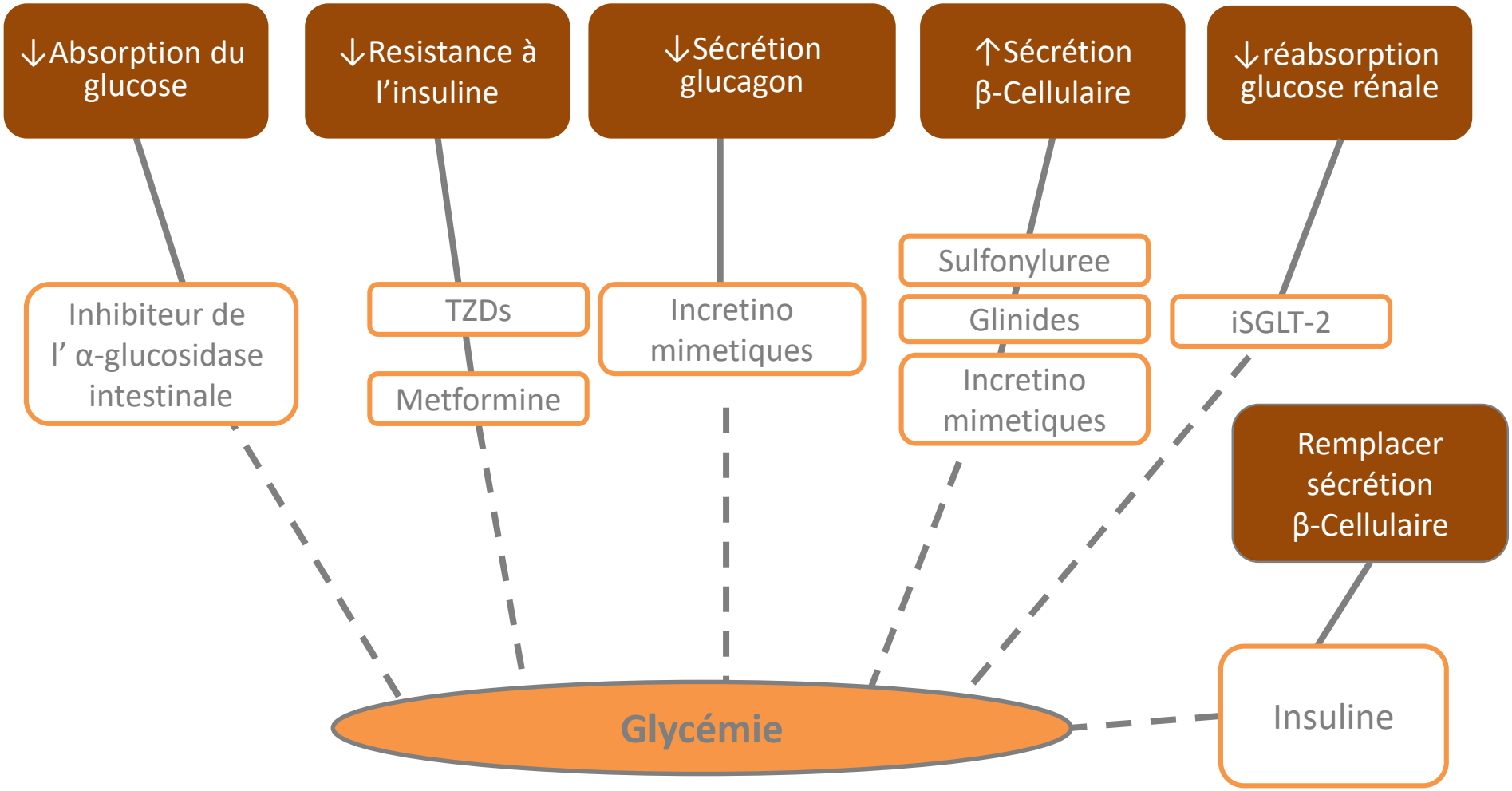
Son traitement ne suffit plus...

Quel traitement choisir maintenant ?

CAS	2
Age	59 ans
Polyurie, polydipsie	++
Perte de poids	+(2%)
Social	+ (vit seul)
Tb. Cognitif	⃠
Orthostatisme (TA)	⃠
Glycémie (horaire)	**15 mmol/L 13h30**
Corps cétoniques	-
HbA1c	8.9%

Si transition vers les injectables ? Lesquels choisir ?

Les options thérapeutiques



Traitements de base

+

150 min

L'alimentation, l'activité physique et **l'éduction thérapeutique** sont la base du traitement du diabète de type 2

Inertie clinique et adhésion thérapeutique

Clinical Care/Education/Nutrition/Psychosocial Research
ORIGINAL ARTICLE

Clinical Inertia in People With Type 2 Diabetes

A retrospective cohort study of more than 80,000 people

KAMLESH KHUNTI, MD[1]
MICHAEL L. WOLDEN, MSC[2]
BRIAN LARSEN THORSTED, MSC[2]
MARC ANDERSEN, PHD[3]
MELANIE J. DAVIES, MD[1]

≥7.5% (≥ 58 mmol/mol) while the patient is already receiving at least two OADs, further intensification of treatment, including the use of insulin, is recommended (6,7).

Khunti et al. Diab. Ob. Metab 2012

Solve study: 41% HbA1c > 9%
22% HbA1c > 10%

Efficacité de la thérapie nutritionnelle sur l'équilibre glycémique et métabolique

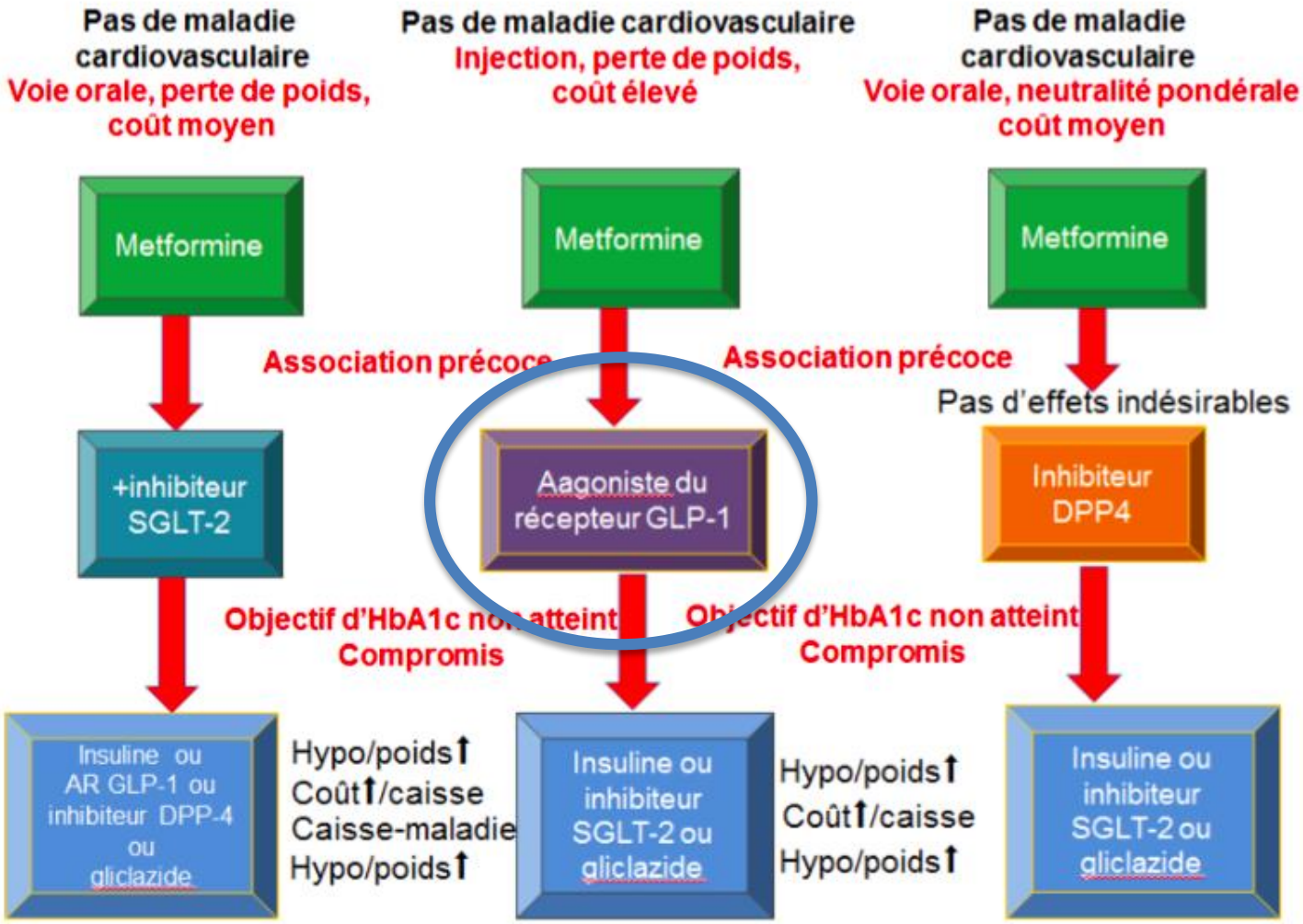
- ↘ 0.3 to 1% de l'HbA1c chez patients avec DT1
  - DAFNE Study Group. Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: Dose Adjustment For Normal Eating (DAFNE) randomised controlled trial. BMJ 2002;325:746
  - Rossi MC, Nicolucci A, Di Bartolo P, et al. Diabetes Interactive Diary: a new telemedicine system enabling flexible diet and insulin therapy while improving quality of life: an open-label, international, multicenter, randomized study. Diabetes Care 2010;33:109–115
  - Laurenzi A, Bolla AM, Panigoni G, et al. Effects of carbohydrate counting on glucose control and quality of life over 24 weeks in adult patients with type 1 diabetes on continuous subcutaneous insulin infusion: a randomized, prospective clinical trial (GIOCAR). Diabetes Care 2011;34:823–827
  - Kulkarni K, Castle G, Gregory R, et al.; The Diabetes Care and Education Dietetic Practice Group. Nutrition Practice Guidelines for type 1 diabetes mellitus positively affect dietitian practices and patient outcomes. J Am Diet Assoc 1998; 98:62–70

- ↘ 0.5 to 2% de l'HbA1c chez patients avec DT2
  - UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352: 854–865
  - Andrews RC, Cooper AR, Montgomery AA, et al. Diet or diet plus physical activity versus usual care in patients with newly diagnosed type 2 diabetes: the Early ACTID randomised controlled trial. Lancet 2011;378:129–139
  - Rickheim PL, Weaver TW, Flader JL, Kendall DM. Assessment of group versus individual diabetes education:a randomized study. Diabetes Care 2002; 25:269–274
  - Franz MJ, Monk A, Barry B, et al. Effectiveness of medical nutrition therapy provided by dietitians in the management of non-insulin-dependent diabetes mellitus: a randomized, controlled clinical trial. J Am Diet Assoc 1995;95:1009–1017

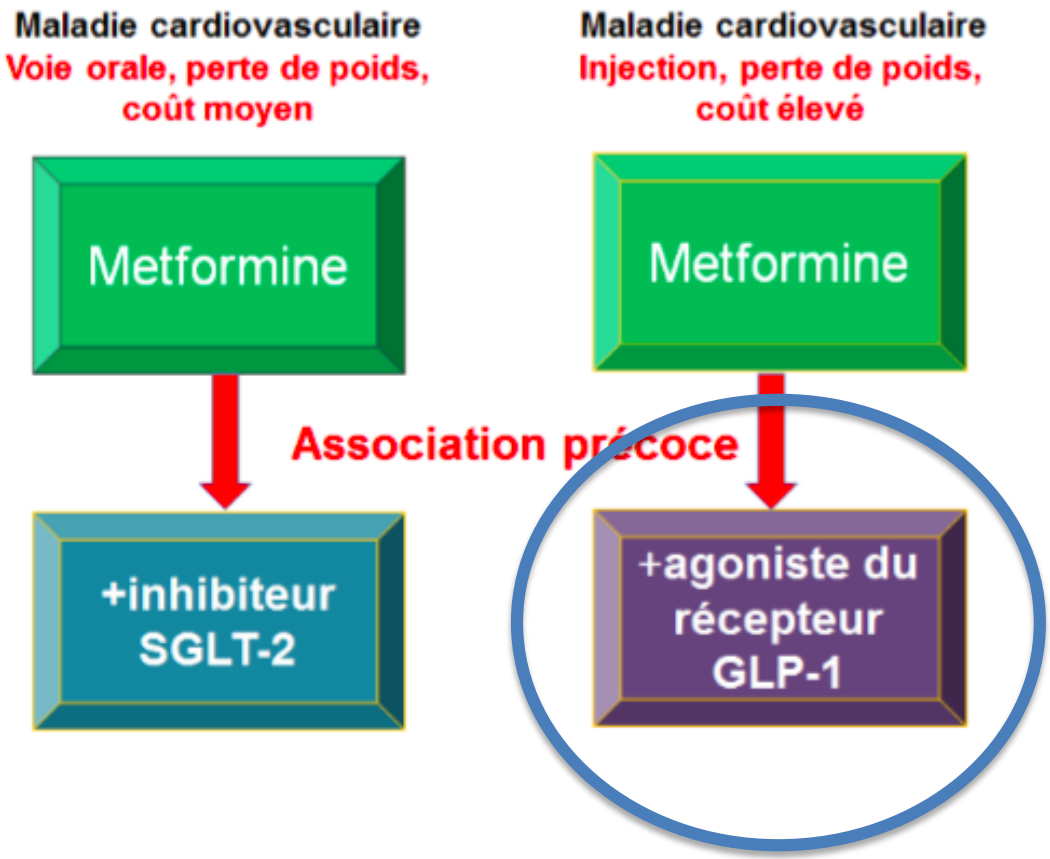
- ↘ Triglycérides : 11-31%
- ↘ LDL cholestérol de 7-22%
- ↘ Cholestérol total de 7-21%

(Evert et al, 2013, S3824)

Recommandations SSED



Recommandations SSED



Anti-diabétique disponibles sur le marché suisse

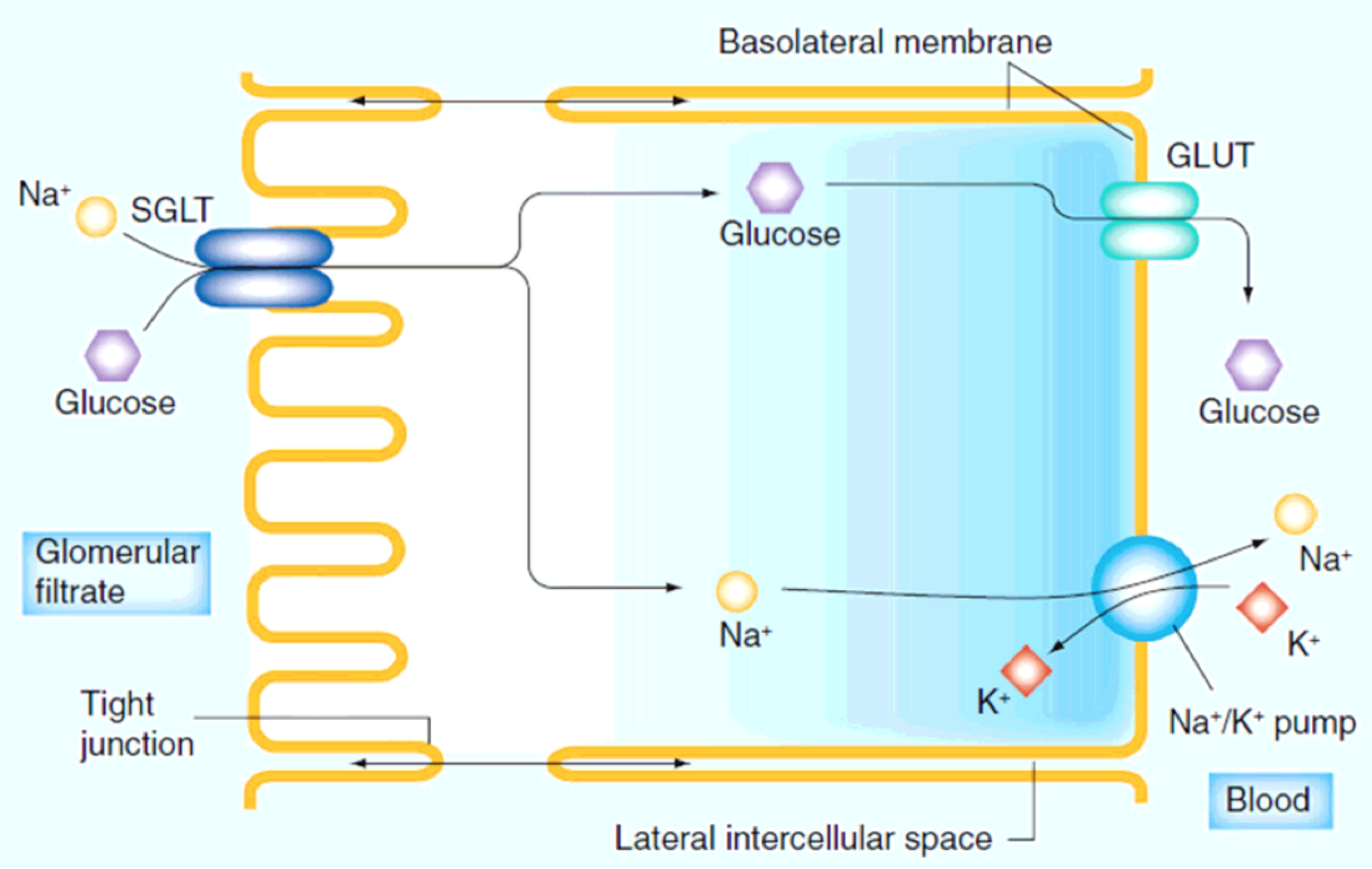
DPP-4-Inhibitors		
Alogliptin	Vipidia®	Vipdomet®
Linagliptin	Trajenta®	Jentadueto®
Saxagliptin	Onglyza®	Kombiglyze® XR*
Sitagliptin	Januvia®, Xelevia®	Janumet®, -XR*, Velmetia®
Vildagliptin	Galvus®	Galvumet®

Sulfonylurea		
Gliclazide	Diamicron® or Generika	
Glibenclamide	Daonil®/Semi-Daonil® or Generics	Glucovance®/- mite
Glimepiride	Amaryl® or Generics	

Physiologie rénale et DT2

- Reins organes clés de l'homéostasie du glucose
  - Production: 15-55g glucose/24h (glycogénolyse)
  - Utilisation: 25-35gr/24h (10% glucose total/24h)
  - Réabsorption du glucose : **180 g de glucose filtré et réabsorbé/24h par reins** **(180l/j** (5.5mmol/l = 100mg/dl)
- Na-Glu co-transporteur 1 et 2 **(SGLT-2)**

Physiologie rénale et DT2



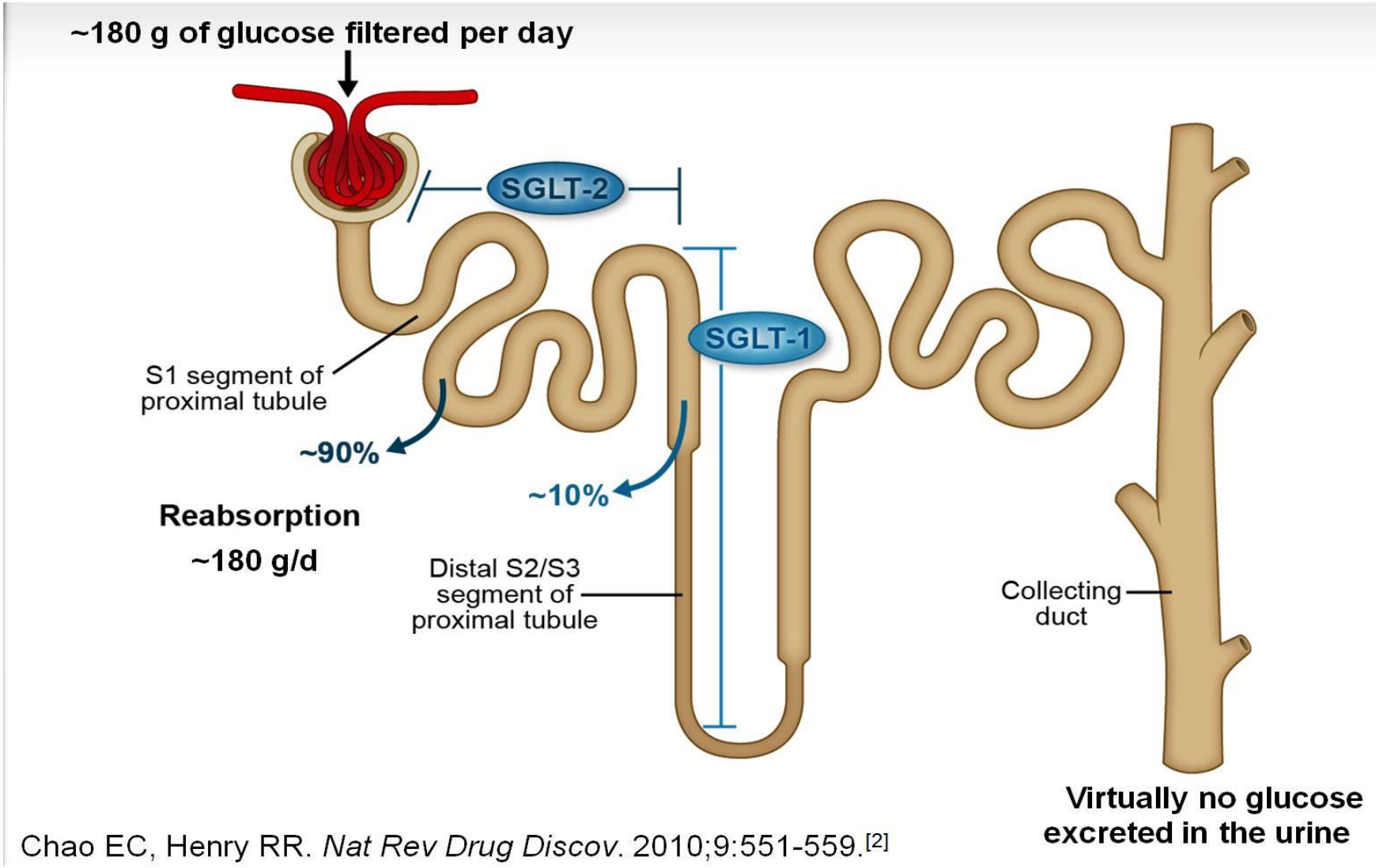
Seuil de glucosurie : 11 mmol/l (non diabétique)

Glucosurie rénale familiale: mutation de SGLT-2

→ mutation + sévère perte 100gr glucose par jour dans les urines

En cas de DT2 : la néoglucogenèse rénale 40% et hépatique 60% (à jeun et post-prandial,

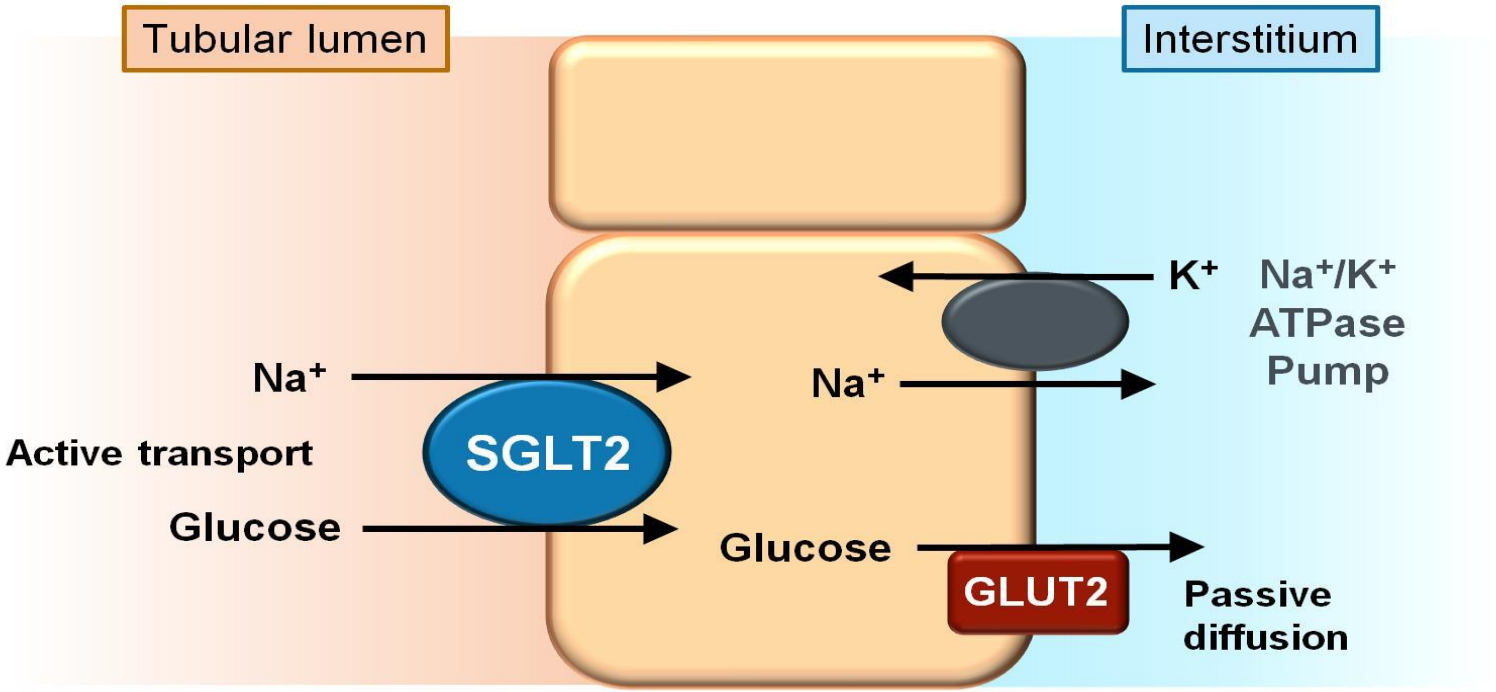
Homéostasie du glucose et rôle des reins



Chao EC, Henry RR. *Nat Rev Drug Discov*. 2010;9:551-559.[2]

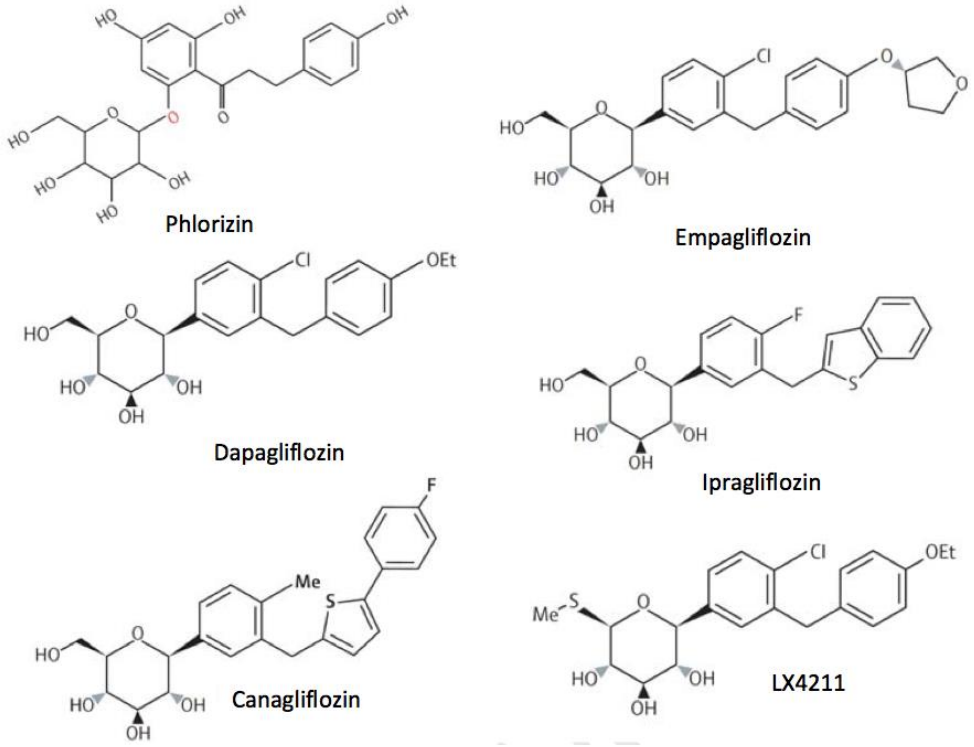
SGLT2

Cellular Glucose Homeostasis



Nair S, Wilding JP. *J Clin Endocrinol Metab*. 2010;95:34-42.[3]

iSGLT2



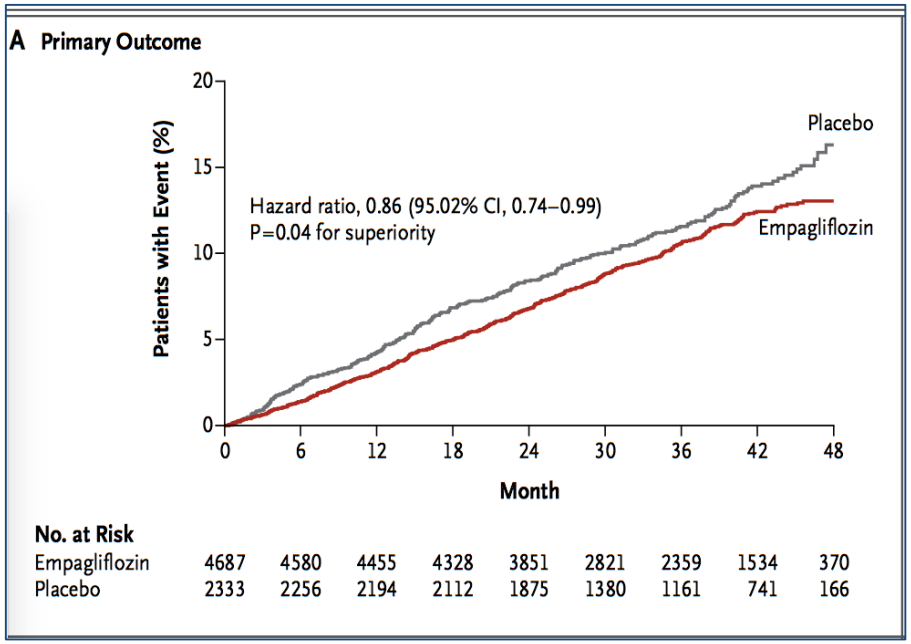
Action rénale
Pas d'hypoglycémie
Bénéfique sur le risque CV
Perte pondérale

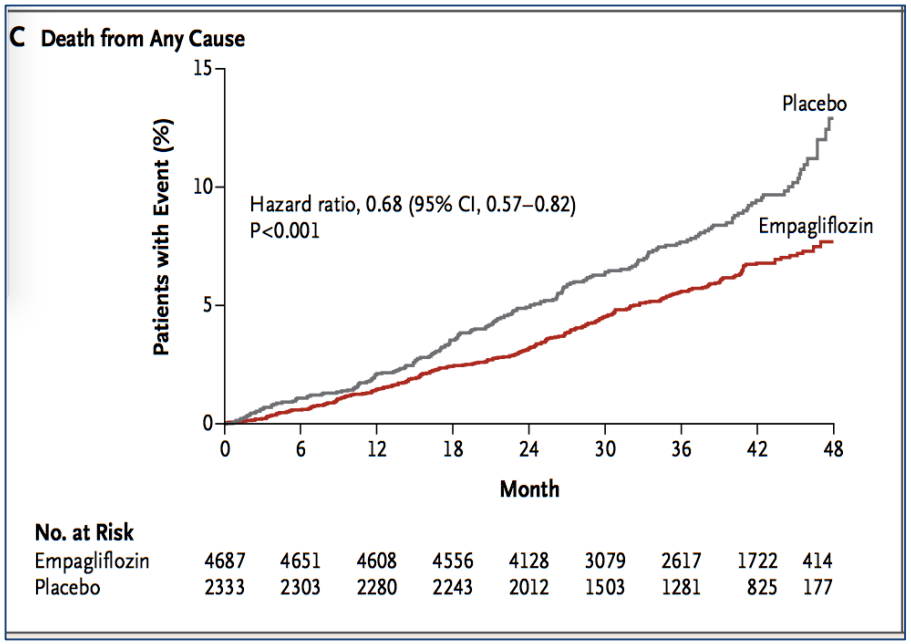
Action indépendante

iSGLT2

DCI	Mécanismes cellulaires	Actions physiologiques principales	Avantages	Désavantages
Dapagliflozin (Forxiga: 5 ou 10mg 1x/j) Canagliflozin (Invokana 100mg ou 300mg 1x/j) Empagliflozine (jardiance 10mg 1x/j) Ipragliflozine	Inhibe le récepteur SGLT-2	Limite la réabsorption du glucose par les reins	➢Diminution du poids (viscéral) ➢Pas d'Hypo ➢Diminution TA ➢Réduction RCV (empagliflozine, canagliflozine) ➢Amélioration masse/fonction des cellules béta (non)	Efficacité diminuée en cas de clairance < 60ml/min STOP si < 45ml/min ➢IVRS ➢Vaginite, Balanite ➢Acidocétose

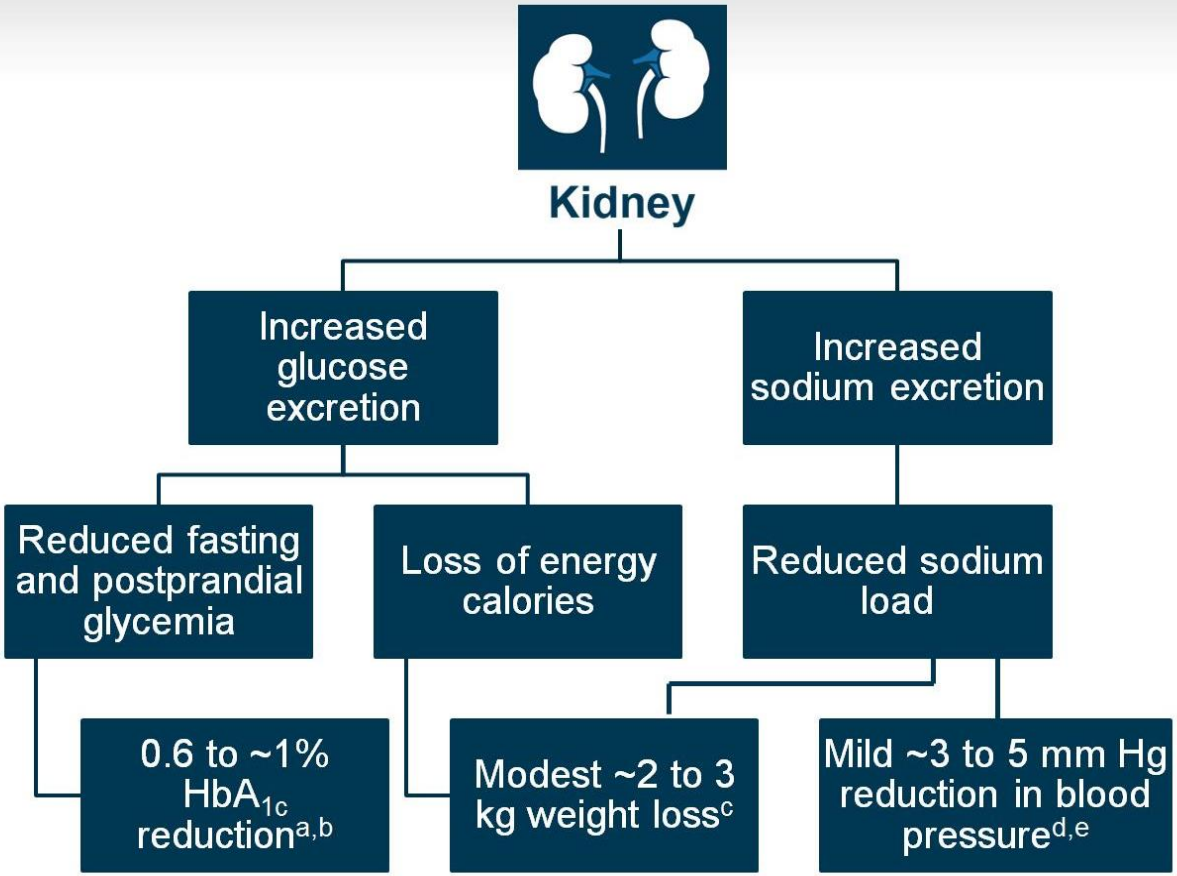
Empa-REG





N ENGL J MED 373;22 NEJM.ORG NOVEMBER 26, 2015

Effets métaboliques des iSGLT-2



a. Wilding JP, et al. *Diabetes Obes Metab*. 2014;16:124-136[5]; b. Forst T, et al. *Diabetes Obes Metab*. 2014. 16:467-477[6]; c. Valentine V. *Clin Diabetes*. 2012;30:151-155[9]; d. Rosenstock J, et al. *Diabetes Obes Metab*. 2014;15:1154-1160[7]; e. Goring S, et al. *Diabetes Obes Metab*. 2014;16:433-442.[8]

Caractéristiques RA-GLP-1 disponibles en Suisse

	Médicament journaliers			Médicaments hebdomadaires		
	Exenatide[1]	Lixisenatide[2]	Liraglutide[3]	Dulaglutide[4]	Exenatide[5]	Semaglutide[6]
Administration	2x par jour	1x par jour		1x par semaine		
Stylo	multi-dose	multi-dose	multi-dose	mono-dose	mono-dose	Multi-dose
Aiguille	pas inclue	Pas inclue	pas inclue	intégrée, invisible	inclue	inclue
Demi-vie	2.4 h	3-4 h	13 h	4.7 j	> 24 h	6.8-7.6 j
Prix jour	**CHF 4.2**	**CHF 4.2**	**CHF 7.5/5**	**CHF 6.2**	**CHF 4.9**	**CHF 2.8/5.6**
Nb doses par stylo	60 x 10 mcg	14 x 0.2 mg	10 x 1.8 mg	1 x 1.5 mg	1 x 2 mg	4 x 0.5mg 2 x 1mg






Informations professionnelles: 1. Byetta® ; 2. Lyxumia®; 3. Victoza®; 4. Trulicity® ; 5. Bydrueon®; 6. Ozempic http://www.swissmedicinfo.ch

* Public price, according to official price, checked on 12 nov. 2018

Titration lors de l'introduction

Semagluditde (Ozempic) :
La dose initiale 0,25 mg une fois par semaine.
Après 4 semaines de traitement, la dose devrait être augmentée à 0,5 mg par sem.
Après au moins 4 semaines à une dose de 0,5 mg par sem., la dose peut être augmentée à 1 mg une fois par semaine

Liraglutide (Victoza):
Afin d'améliorer la tolérance gastro-intestinale, le traitement avec Victoza doit être instauré chez tous les patients avec une dose de 0.6 mg/j pendant au moins une semaine, puis augmentée à 1.2 mg.
Après au moins une semaine supplémentaire, la dose peut être portée à 1.8 mg selon la réponse clinique. Des doses journalières supérieures à 1.8 mg ne sont pas recommandées

Dulaglutide (Trulicity):
le traitement est initié à la dose de 0.75mg ou 1.5mg 1x/sem.

Exenatide (Byduréon):
Le traitement est de 2mg 1x/sem

Titration lors de l’introduction

Lyxumia:
le traitement est initié à la dose de 10 µg de Lyxumia, une fois par jour, pendant 14 jours. Dose d'entretien: une dose fixe de Lyxumia de 20 µg, une fois par jour, à partir du 15ème jour.

Exenatide (Byetta):
le traitement est initié à la dose de 5 µg 2x par jour pendant 7-14 jours puis le dosage peut être augmenté selon tolérance à 2x 10ug par jour

Etudes cliniques agonistes R GLP-1

Semaglutide : 5 études incluant 7'215 patients diabétiques de type 2

Lixisenatide : 10 études

Table 6 Phase 3 GETGOAL Trials with Lixisenatide[66-64]

Trial	Study drug	Lixisenatide outcomes vs comparator drugs
GETGOAL-Mono	Lixisenatide 1-stop AM vs 2-stop AM vs placebo; 12-week study	HbA_{1c}: –0.66% 1-stop vs –0.54% 2-stop Achieved HbA_{1c} goal (<7%): 46.5% 1-stop vs 52.2% 2-stop Decrease in body weight: –2 kg in both groups Symptomatic hypoglycemia: 1.7% in lixisenatide groups vs 1.4% in placebo groups Significant improvements in HbA_{1c}, 2-hr PPG, FPG vs placebo
GETGOAL-F1	Lixisenatide 1-stop AM vs 2-stop AM; all concurrently taking metformin; 24-week study	HbA_{1c}: –0.9% vs –0.8% vs –0.4% Improved FPG: –0.5 vs –0.6 vs +0.1 mmol/L Body weight: –2.6 kg vs –2.7 kg vs –1.6 kg Symptomatic hypoglycemia: 1.9% vs 2.5% vs 0.6%
GETGOAL-S	Lixisenatide 2-stop AM vs placebo; all concurrently taking sulfonylurea; 24-week study	HbA_{1c}: –1.1% mean significant diffe Significant 2-hr postprandial glucos Body weight: –1.12 kg vs –1.02 kg GI adverse effects: 52.6% vs 29.4% Symptomatic hypoglycemia: 17.1% No cases of severe symptomatic hy either group
GETGOAL-L	Lixisenatide 2-stop AM vs placebo; all concurrently taking basal insulin	HbA_{1c} reduction: –0.4% difference v Symptomatic hypoglycemia: 28% vs Severe hypoglycemia: 1.2% vs 0%
GETGOAL-P	Lixisenatide 2-stop AM vs placebo; all concurrently taking pioglitazone; 24-week study	HbA_{1c} reduction: –0.56% differenc Significantly improved FPG: –0.84 v Small decrease body weight w/ loss insignificant increase w/ placebo Symptomatic hypoglycemia: 3.4% v episodes
GETGOAL-X	Lixisenatide 2-stop AM vs exenatide 10 mcg twice daily; all concurrently taking metformin; 24-week study	Noninferiority in HbA_{1c} reduction vs FPG reduction was comparable Weight loss: –2.8 kg vs –3.6 kg Serious adverse events: 2.8% vs 2.2 Significantly reduced symptomatic h vs 7.0% Significantly less nausea events: 24
GETGOAL-M	Lixisenatide 2-stop AM or PM vs placebo; all concurrently taking metformin; 24-week study (similar to GETGOAL-F1)	Significant HbA_{1c} reduction: –0.36% placebo Significant reduction in 2-hr PPG vs No difference in weight loss Nausea: 16.3% vs 2.6% Symptomatic hypoglycemia: 5.6% v No severe symptomatic hypoglycem
GETGOAL-Mono JAPAN LTS	Lixisenatide 1-stop AM vs 2-stop AM; 52-week study with primary and point on safety measures	Nausea: 59% vs 36.4% Symptomatic hypoglycemia: 0% vs HbA_{1c}, FPG, body weight reduced fro
GETGOAL-L-ASIA	Lixisenatide 2-stop AM vs placebo; all concurrently taking basal insulin; 24-week study (similar to GETGOAL-S)	HbA_{1c} reduction: –0.88% vs placebo Significant improvement in 2-hr pos Nausea and vomiting: 10.2% vs 1.9 Symptomatic hypoglycemia: 42.9% No severe hypoglycemia
GETGOAL-M-ASIA	Lixisenatide 2-stop AM vs placebo; all concurrently taking metformin ± sulfonylurea; 24-week study	HbA_{1c} reduction: –0.57% significant Superior to placebo in lowering 2-h glucose Body weight in lixisenatide group tr

AM indicates morning administration; FPG, fasting plasma glucose; GI, gastrointesti
hemoglobin; PM, evening administration; PPG, postprandial plasma glucose.

Exenatide : 6 études

Table 2 Phase 3 DURATION Trials with Exenatide ER[16-22]

Trial	Study drug	Exenatide ER outcomes vs comparator drugs
DURATION-1	Exenatide ER 2 mg vs exenatide 10 mcg twice daily	Greater HbA_{1c} reduction: –1.9% vs –1.5% Greater reduction in lipid profile, total cholesterol, triglycer Better glucose control, body weight reduction, systolic bl pressure reduction Reduced nausea
DURATION-2	Exenatide ER vs pioglitazone vs sitagliptin; all agents taken with metformin	Greater HbA_{1c} reduction w/ exenatide ER: –1.5% vs –0.9 vs –1.2% Greater weight loss: –2.3 kg vs –0.8 kg vs +2.8 kg Less nausea (5% vs 10.8% vs 9.6%) No hypoglycemia w/ exenatide ER
DURATION-3	Exenatide ER vs insulin glargine, titrated to goal <100 mg/dL	Greater HbA_{1c} reduction w/ exenatide ER: –1.5% vs –1. 3 × lower hypoglycemia rate w/ exenatide ER
DURATION-4	Exenatide ER vs metformin vs pioglitazone vs sitagliptin; all in treatment-naïve patients	HbA_{1c} reduction: –1.53% vs 1.48% vs 1.63% vs 1.15% Weight loss: –2.0 kg vs –2.0 kg vs +1.5 kg vs –0.8 kg Nausea & diarrhea: 11.3% and 10.9% w/ exenatide ER No major hypoglycemia occurred
DURATION-5	Exenatide ER vs exenatide; this is similar to DURATION-1	At 24 weeks, greater HbA_{1c} reduction: –1.6% vs –0.9% Greater fasting glucose reduction: –35 mg/dL vs –12 mg Similar weight reduction, adverse effects
DURATION-6	Exenatide ER vs liraglutide	Greater HbA_{1c} reduction w/ liraglutide: –1.48% vs –1.28% More patients reached goal w/ liraglutide: 60% vs 53% Greater weight loss w/ liraglutide

ER indicates extended-release; HbA_{1c}, glycated hemoglobin.

Liraglutide : 6 études

Table 3 Phase 3 LEAD Trials with Liraglutide[28-33]

Trial	Study drug	Liraglutide outcomes vs comparator drugs
LEAD-1	Liraglutide 1.2 mg & 1.8 mg once daily vs rosiglitazone 4 mg once daily; all concurrently taking sulfonylurea	Significant HbA_{1c} reduction w/ liraglutide 1.2 mg & 1.8 mg: 1.1% vs –0.4% w/ rosiglitazone 4 mg Significant decrease in FPG & PPG w/ liraglutide vs rosiglitazone Minor hypoglycemia, <10%; nausea, <11%; vomiting, <5%; diarrhea, <8%
LEAD-2	Liraglutide 1.2 mg & 1.8 mg vs glimepiride 4 mg; all concurrently taking metformin	Noninferior HbA_{1c} reduction in liraglutide groups: mean decrease, –1% Body weight –2.8 kg w/ 1.8-mg liraglutide vs +1.0 kg w/ glimepiride Less hypoglycemic events in liraglutide groups: 3% vs 17% w/ glimepiride Increased nausea in liraglutide groups
LEAD-3	Liraglutide 1.2 mg & 1.8 mg once daily vs glimepiride 8 mg once daily	HbA_{1c} reductions: –0.84% & –1.23% w/ liraglutide 1.2 mg & 1.8 mg vs 0.51% w/ glimepiride 8 mg No major hypoglycemic events Significantly less minor hypoglycemia: 8% & 12% vs 24%
LEAD-4	Liraglutide 1.2 mg & 1.8 mg vs placebo; all concurrently taking metformin and rosiglitazone	HbA_{1c} reduction: –1.5% vs –0.5% Significant FPG and PPG reductions w/ 1.2-mg & 1.8-mg liraglutide Body weight reductions: –1.0 kg & –2.0 kg w/ liraglutide 1.2 mg & 1.8 mg vs +0.6-kg weight gain w/ placebo Systolic BP reductions: –6.7 mm Hg & –5.6 mm Hg w/ liraglutide 1.2 mg & 1.8 mg vs –1.1 mm Hg w/ placebo Minor hypoglycemia: 7.9% & 9% vs 5.1% No major hypoglycemic events
LEAD-5	Liraglutide 1.8 mg vs insulin glargine; all concurrently taking metformin and glimepiride	Significantly greater HbA_{1c} reduction: –1.33% vs –1.09% Significantly greater weight loss w/ liraglutide: –1.39 kg vs +3.43 kg Systolic BP reduction: –4 mm Hg vs +0.5 mm Hg Major & minor hypoglycemia rates: 0.06 & 1.2 vs 0 & 1.3 events/patient annually
LEAD-6	Liraglutide 1.8 mg vs exenatide 10 µg twice daily, all concurrently taking metformin and sulfonylurea	Significant HbA_{1c} reduction: –1.12% vs –0.79% Greater FPG reduction vs exenatide Weight loss: 3.24 kg vs 2.87 kg (difference not significant) Significantly less minor hypoglycemia w/ liraglutide: 25.5% vs 33.6% 2 patients taking exenatide & sulfonylurea had major hypoglycemia Less nausea w/ liraglutide

BP indicates blood pressure; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; PPG, postprandial glucose.

Albiglutide : 8 études

Table 4 Phase 3 HARMONY Trials with Albiglutide[39-46]

Trial	Study drug	Albiglutide outcomes vs comparator drugs
HARMONY-1	Albiglutide 30 mg vs placebo	HbA_{1c}: –0.8% vs –0.1% Hyperglycemia events: 24.4% vs 47.7% No significant differences in weight change All GI events: 31.3% vs 29.8% Diarrhea: 11.3% vs 8.0% Nausea: 10.7% vs 11.3% Vomiting: 4% vs 4%
HARMONY-2	Albiglutide 30 mg vs albiglutide 50 mg vs placebo	HbA_{1c}: –0.84% vs –1.04% No significant changes in weight w/ 2 albiglutide doses Similar nausea, diarrhea, vomiting, hypoglycemia rate in all groups, including placebo
HARMONY-3	Albiglutide 30 mg vs sitagliptin 100 mg vs glimepiride 2 mg vs placebo; all concurrently taking metformin	HbA_{1c}: –0.9% vs –0.4% vs –0.3% (vs placebo) Weight change: –1.21 kg vs –0.86 kg vs +1.17 kg vs –1.0 kg Hyperglycemia rates: 25.8% vs 36.4% vs 32.7% vs 59.2% Diarrhea: 12.9% vs 8.6% vs 10.9% (vs placebo) Nausea: 10.3% vs 6.2% vs 10.9% (vs placebo)
HARMONY-4	Albiglutide vs insulin glargine titrated to fasting plasma glucose goal of 100 mg/dL	HbA_{1c}: –0.7% vs –0.8% Weight change: –1.0 kg vs +1.5 kg Hypoglycemia: 17.5% vs 27.4%
HARMONY-5	Albiglutide 30 mg titrated up to 50 mg vs pioglitazone 30 mg titrated up to 50 mg; all concurrently taking metformin ± glimepiride 4 mg	HbA_{1c} reduction: –0.87% vs placebo HbA_{1c} +0.25 vs pioglitazone; not meeting noninferiority criteria Hypoglycemia: 14% vs 25% vs 14% Weight change: –0.42 kg vs +4.4 kg vs –0.4 kg
HARMONY-6	Albiglutide 30 mg titrated up to 50 mg vs insulin lispro 3 × daily adjusted per glucose level	HbA_{1c}: –0.82% vs –0.66% Weight change: –7.3 kg vs +0.81 kg Severe hypoglycemia: 0 vs 2 events Nausea: 11.2% vs 1.4% Vomiting: 6.7% vs 1.4% Injection-site reaction: 9.5% vs 5.3%
HARMONY-7	Albiglutide 30 mg titrated up to 50 mg vs liraglutide 0.6 mg titrated up to 1.8 mg; all concurrently taking metformin ± sulfonylurea ± thiazolidinedione	HbA_{1c}: –0.78% vs –0.99% Injection-site reaction: 12.9% vs 5.4% GI adverse effects: 35.9% vs 49%
HARMONY-8	Albiglutide vs sitagliptin with GFR >60 mL/min, GFR 30-59 mL/min, GFR 15-29 mL/min; all ± oral diabetes drugs	HbA_{1c}: –0.83% vs –0.52% Time to hyperglycemic rescue longer w/ albiglutide All adverse events: 51.7% vs 25.2% Diarrhea: 10% vs 6.5% Nausea: 4.8% vs 3.3% Vomiting: 1.6% vs 1.2% Hypoglycemia: 24.1% vs 15.9% (sulfonylurea: 22.5% vs 14.2%; no sulfonylurea: 4% vs 4%) Weight change: –0.79 kg vs –0.19 kg

GFR indicates glomerular filtration rate; GI, gastrointestinal; HbA_{1c}, glycated hemoglobin.

Am Health Drug Benefits. 2017 Jun; 10(4): 178–188.

Analogues du GLP-1

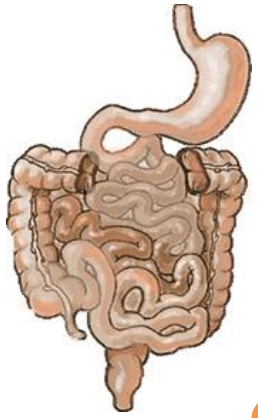
Principe actif	Nom de marque	Date de mise sur le marché européen	Essais cliniques
Exanatide	Byetta	Nov. 2006	AMIGO
Exenatide XR	Bydurèon	Juin 2011	DURATION
Liraglutide	Victoza	Juin 2009	LEAD
Dulaglutide	Trulicity	2014	AWARD
Lixisenatide	Lyxumia	Fev. 2013	Getgoal
Albiglutide	Eperzam	Janv. 2014	HARMONY
Semaglutide	Ozempic	Sept. 2018	SUSTAIN

Effets métaboliques des incrétines

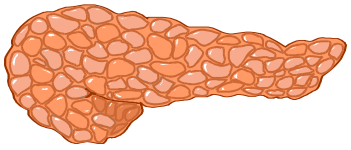
Molécule d'exendin-4(salive du Gila monster)
Homologie de 53% en acides aminés avec GLP-1 natif mais qui active le récepteur humain des GLP-1 aussi bien que le GLP-1 humain.

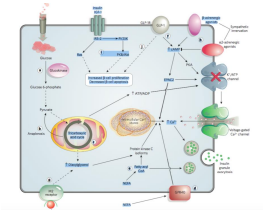
Incrétine : GLP-1 et DPP4

Repas

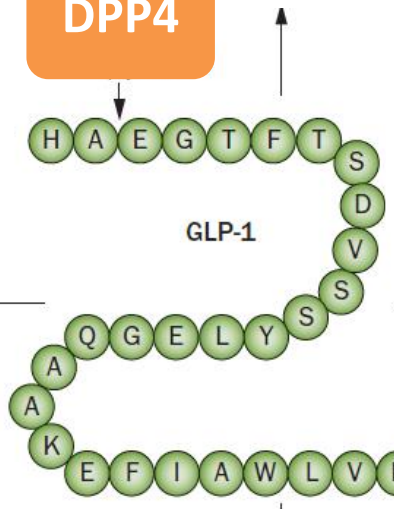


GLP-1





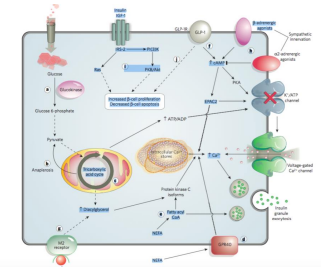
DPP4

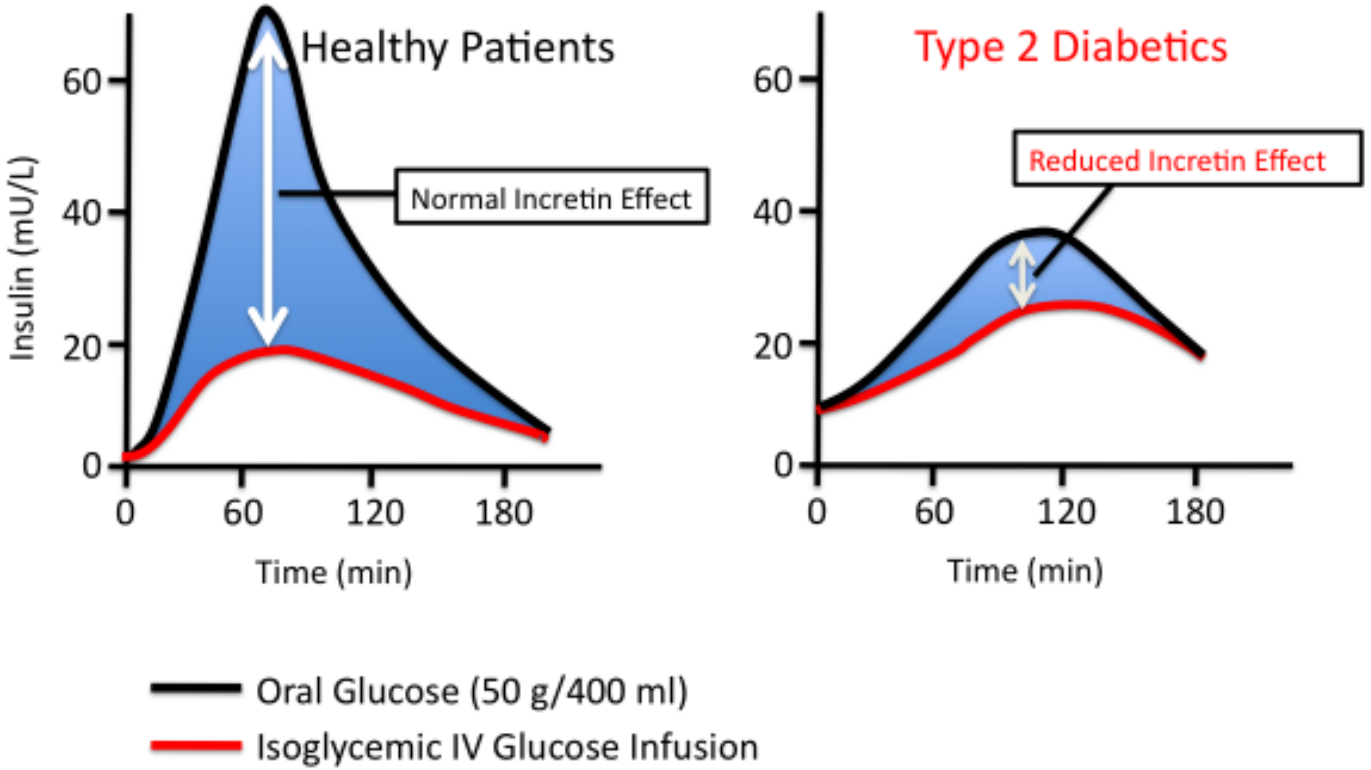


GLP-1 actif

GLP-1 inactivé par les DPP-4

Effet incrétine et diabète de type 2





Augmentation de l'insulinémie secondaire à l'injection orale de glucose

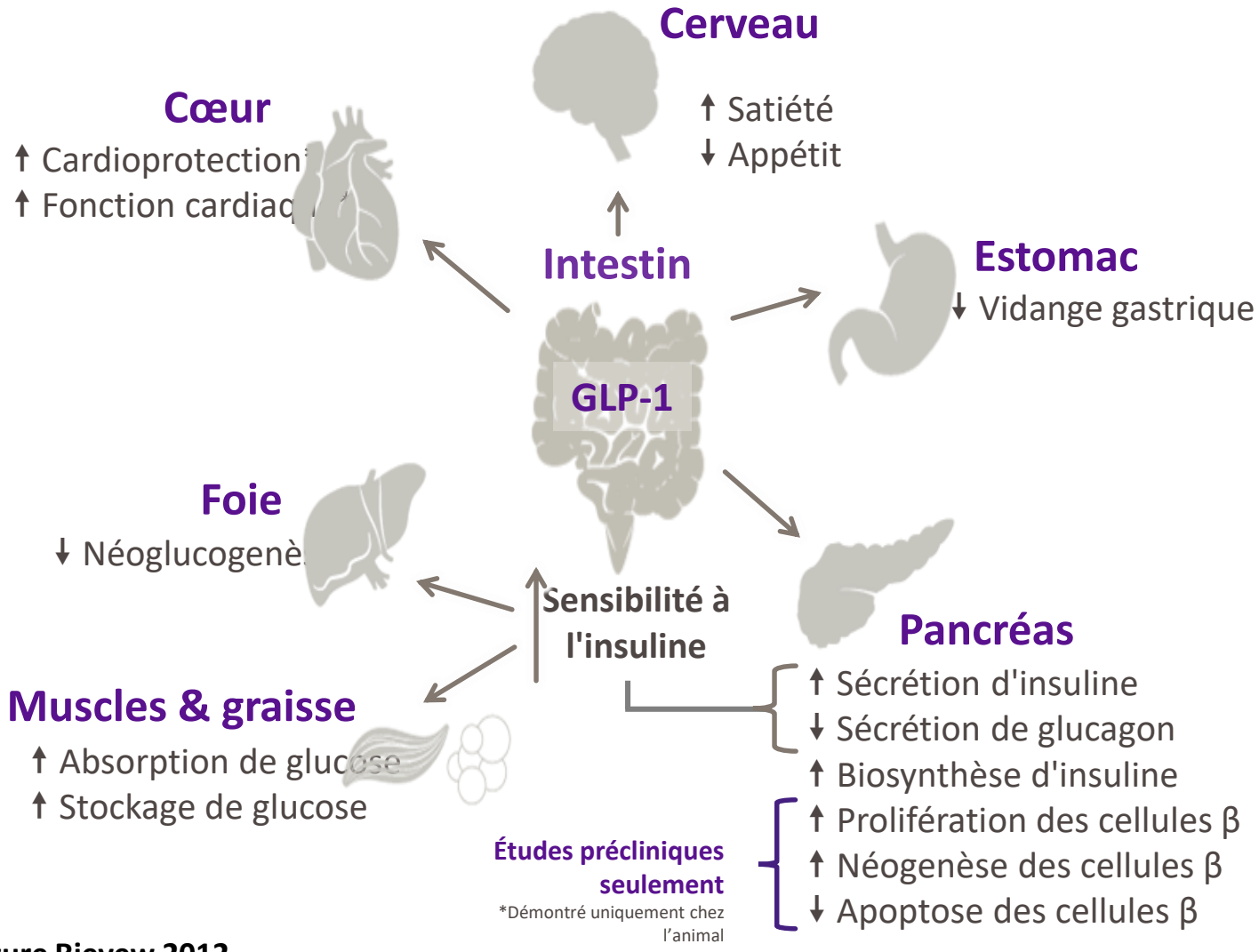
Nauck M et al. Diabetologia 1986

Potentiel des thérapies à base d'incrétine

- L'effet incrétine est dû aux hormones GLP-1 et GIP, qui sont libérées par le tractus intestinal lors de l'absorption d'aliments.
  - GLP-1 et GIP améliorent la sécrétion d'insuline glucose-dépendante des cellules β du pancréas
  - Le GLP-1 supprime la sécrétion de glucagon par les cellules α du pancréas, qui est dépendant du glucose.
- Comme l'effet incrétine du diabète de type 2 est moins prononcé, il existe un potentiel thérapeutique pour les médicaments qui rétablissent cet effet.

Drucker DJ et al. Diabetes Care 2003;26:2929-40. Baggio LL et al. Gastroenterology 2007;132:2131-57. Drucker DJ. Exp Opin Investig Drugs 2003;12:87-100

Effets pléiotropiques du GLP-1



Meier JJ, Nature Rievew 2012

Baggio LL, Drucker DJ. *Gastroenterol.* 2007;132(6):2131-2157.

Effets pléiotropiques du GLP-1

Les incrétines sont des hormones intestinales qui augmentent la sécrétion d'insuline postprandiale[1] et:

- jouent un rôle essentiel dans la régulation de l'homéostasie glucidique dans la physiologie normale[1] ↑ sécrétion de l'insuline ↓ sécrétion de glucagon
- sont sécrétées par des cellules situées principalement dans l'intestin grêle, mais se retrouvent également dans le gros intestin, les cellules pancréatiques a et le système nerveux central[2]
- sont libérées en réaction aux repas, pour augmenter la sécrétion d'insuline en réponse aux nutriments[1,3]
- sont responsables de l'effet incrétine, ce qui représente 50-70% de la libération totale d'insuline suite à l'administration orale de glucose[3,4]
- ↓ vidange gastrique, ↑ contractilité gastrique

1. Aronoff SL, et al. Diabetes Spectr. 2004;17(3):183-190.
2. Nauck MA. Am J Med. 2011;124(Suppl1):S3-S18.
3. Kim W, Egan JM, et al. Pharmacol Rev. 2008;60(4):470-512.
4. Baggio LL, et al. Gastroenterology. 2007;132(6):2131-2157
5. Drucker DJ, Cell Metab 2006

Intérêts des analogues du GLP-1

Paramètre	Conséquences du diabète	Effets du GLP-1
Sécrétion d'insuline:	altérée	augmenté
- Réponse rapide:	absente	rétablie
- Effet de l'incrétine:	réduit	remplacé
Glucagon:	hypersécrétion	inhibition
Masse de cellules bêta:	réduit	augmentée (essais expérimentaux sur les animaux)
Appétit/poids:	augmenté	réduit
Vidange gastrique:	normale/accélérée?	ralentie
Sensibilité à l'insuline:	résistance	absence d'effet immédiat

1. Aronoff SL, et al. Diabetes Spectr. 2004;17(3):183-190.
2. Nauck MA. Am J Med. 2011;124(Suppl1):S3-S18.
3. Kim W, Egan JM, et al. Pharmacol Rev. 2008;60(4):470-512.
4. Baggio LL, et al. Gastroenterology. 2007;132(6):2131-2157
5. Drucker DJ, Cell Metab 2006

Amélioration de l'HbA1c

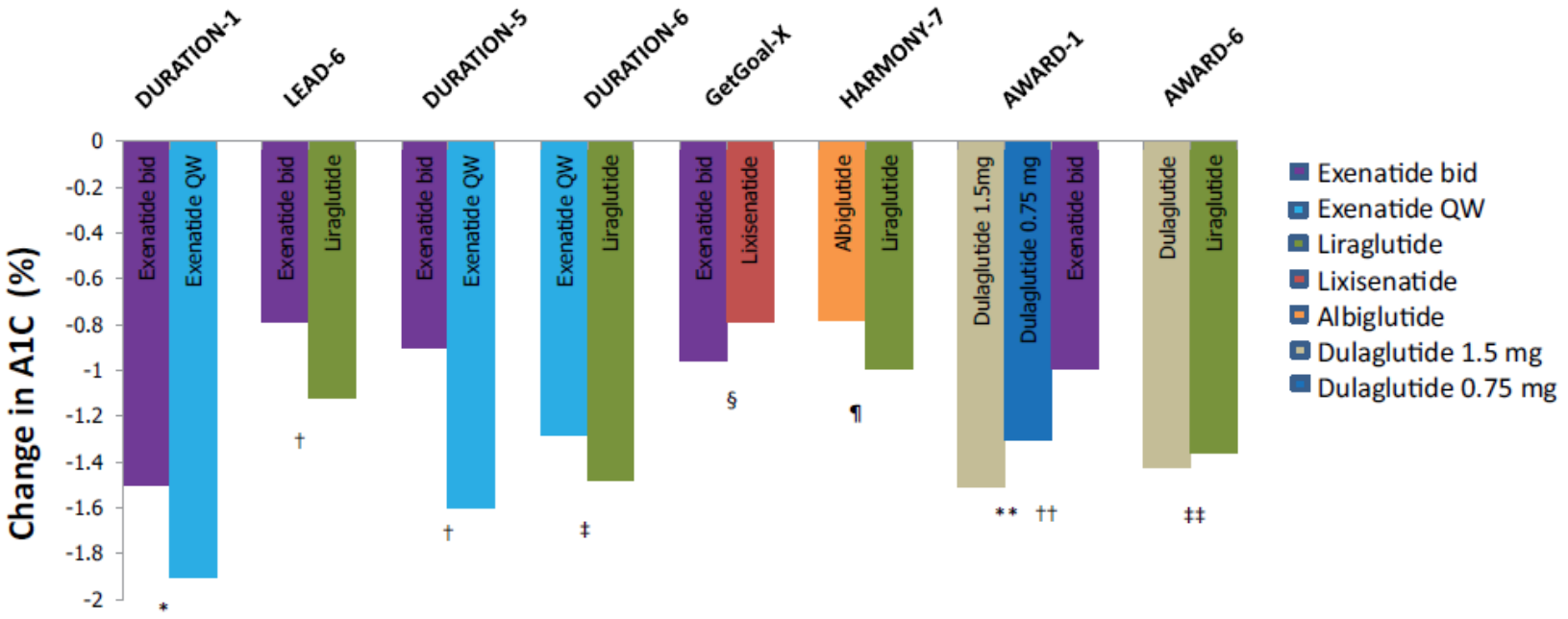


Figure 1. Changes in A1C values with glucagon-like peptide 1 receptor agonists (GLP-1 RAs) in head-to-head clinical studies.

En moyenne : réduction de 1.0 à 1.6%

Maximum : - 1.8%
Ozempic

Modifications du poids

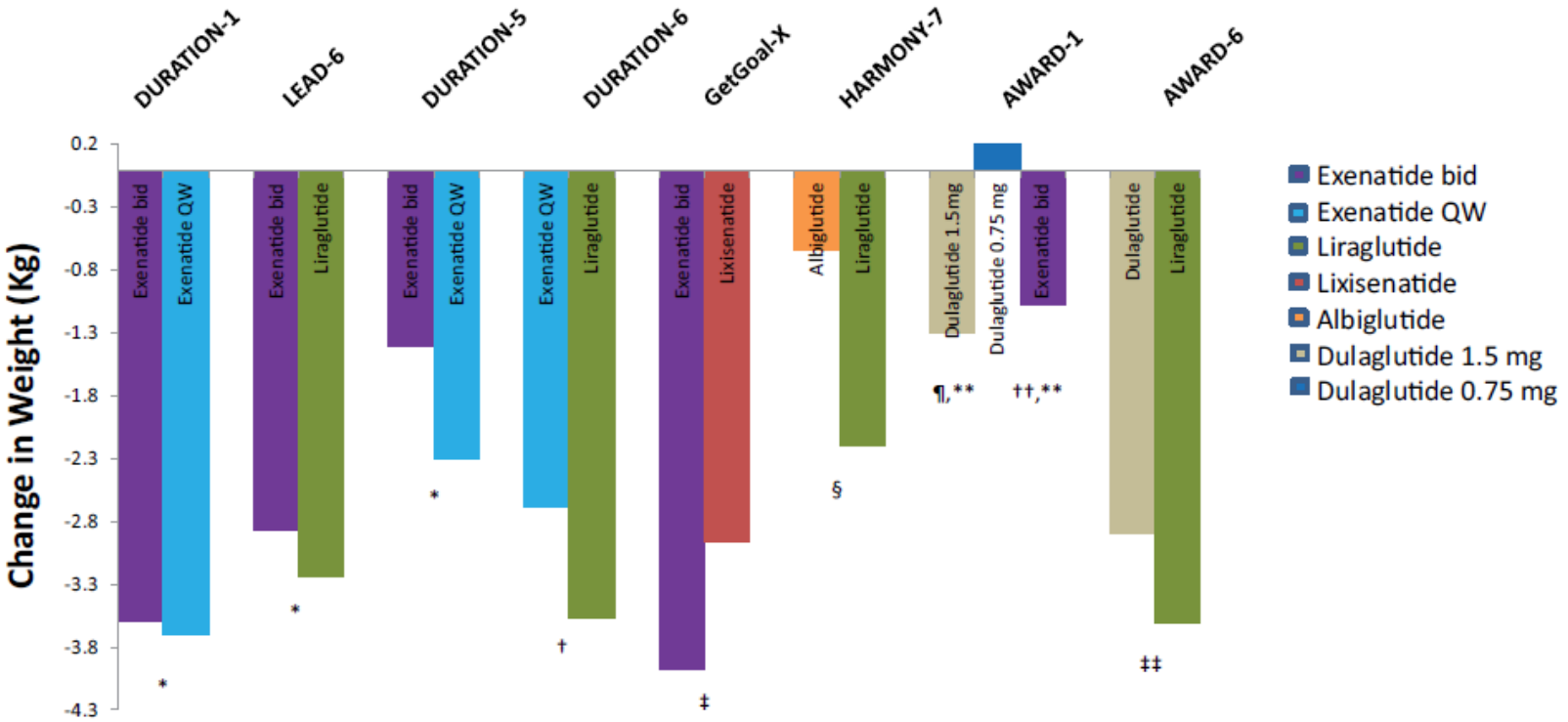


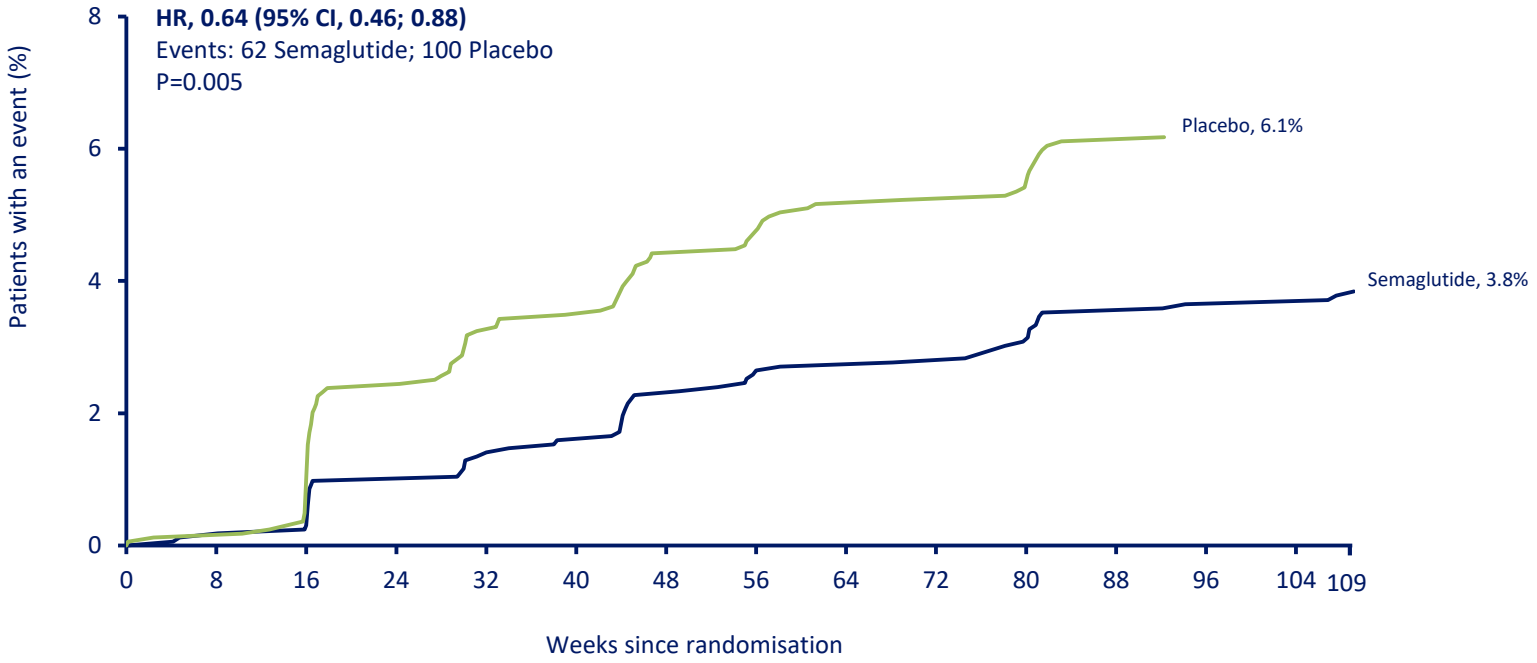
Figure 2. Changes in weight with glucagon-like peptide 1 receptor agonists (GLP-1 RAs) in head-to-head clinical studies.

En moyenne : 3 et 5 kg de perte pondérale

Maximum : - 6.1kg
Ozempic

Quelles sont les autres indications à l'introduction d'un GLP-1 analogue

New or worsening nephropathy



Number of patients at risk

Semaglutide	**1648**	**1630**	**1605**	**1580**	**1563**	**1541**	**1525**	**1518**
Placebo	1649	1629	1570	1545	1518	1498	1471	1465

New or worsening nephropathy = Persistent macroalbuminuria, Persistent doubling of serum creatinine level and creatinine clearance per MDRD <45 ml/min/1.73m2, Need for continuous renal-replacement therapy

Supplementary Figure 5B. Kaplan Meier plot for time from randomisation to first EAC-confirmed new or worsening nephropathy using 'in-trial' data from subjects in the full analysis set. HR is from a proportional hazard model. CI, confidence interval; EAC, (external) event adjudication committee; HR, hazard ratio.
Marso *et al. NEJM* [in press]

Table S6. Baseline Characteristics (Expanded)

Renal function (N, %)	Semaglutide 0.5 mg (n=826)	Semaglutide 1.0 mg (n=822)	Placebo 0.5 mg (n=824)	Placebo 1.0 mg (n=825)	Total (N=3297)
Normal (eGFR ≥90)	247 (29.9)	246 (29.9)	245 (29.7)	252 (30.5)	990 (30.0)
Mild renal impairment (eGFR 60 – <90)	329 (39.8)	357 (43.4)	336 (40.8)	346 (41.9)	1368 (41.5)
Moderate renal impairment (eGFR 30 – <60)	229 (27.7)	194 (23.6)	215 (26.1)	194 (23.5)	832 (25.2)
Severe renal impairment (eGFR 15 – <30)	20 (2.4)	21 (2.6)	25 (3.0)	29 (3.5)	95 (2.9)
End-stage renal disease (eGFR <15)	1 (0.1)	4 (0.5)	3 (0.4)	4 (0.5)	12 (0.4)

Renal function is based on estimated glomerular filtration rate (MDRD) (ml/min/1.73 m^2). [a]Means and standard deviations;

[b]Geometric means and coefficients of variation; [c]Number of patients (N) and percentage (%).

Baseline Characteristics According to Renal Fonction

28.5% of patients have an eGFR <60

Marso SP et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes N Engl J Med 2016;375:1834–44_Annexe p.80.

Change from baseline to the end of treatment in eGFR

- The largest decreases in eGFR were in subjects with normal renal function or mild renal impairment
  - The decrease in eGFR was significantly lower with semaglutide 1.0 mg vs placebo among subjects with moderate renal impairment (p<0.05)
  - There was no significant difference between either dose of semaglutide vs placebo within any other subgroup

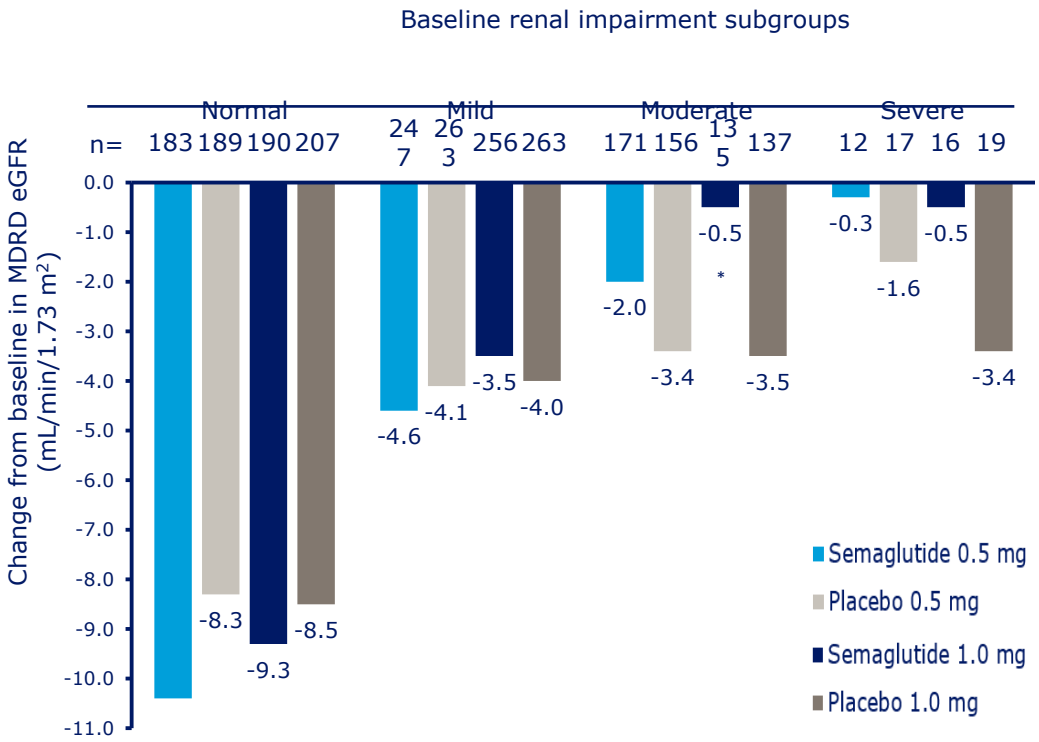


Figure 2. Change from baseline to the end of treatment in eGFR, stratified by baseline renal function in the SUSTAIN 6 trial. *p<0.05 vs placebo. Renal function categories based on MDRD eGFR: normal function (≥90 mL/min/1.73 m²); mild impairment (≥60 to <90 mL/min/1.73 m²); moderate impairment (≥30 to <60 mL/min/1.73 m²); or severe impairment (<30 mL/min/1.73 m²). Data are group geometric means from observed 'in-trial' data using a mixed model for repeated measurements with interaction between randomized treatment and subgroup as fixed factors and baseline value as covariate, all interacting with visit. Descriptive means (mL/min/1.73 m²) without analysis: semaglutide 0.5 mg (–9.6, –4.8, –2.1, –4.1); placebo 0.5 mg (–7.4, –4.2, –4.8, –4.1); semaglutide 1.0 mg (–8.6, –3.2, –2.4, –0.5); and placebo 1.0 mg
(–6.5, –5.6, –4.2, –2.6) with normal renal function or mild, moderate or severe impairment, respectively. eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

LEADER Renal

The NEW ENGLAND JOURNAL of MEDICINE

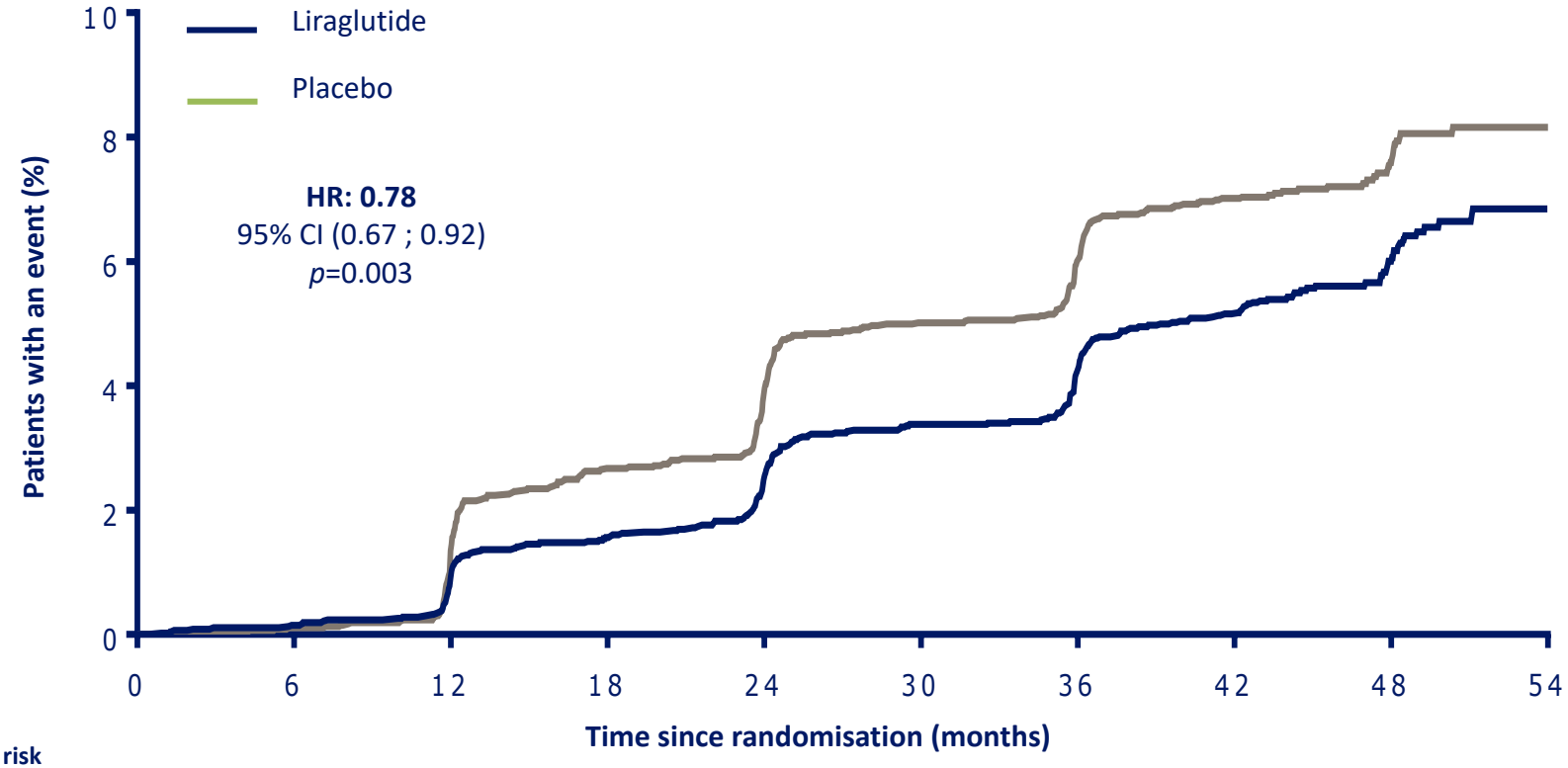
ORIGINAL ARTICLE

Liraglutide and Renal Outcomes in Type 2 Diabetes

Johannes F.E. Mann, M.D., David D. Ørsted, M.D., Ph.D.,
Kirstine Brown-Frandsen, M.D., Steven P. Marso, M.D.,
Neil R. Poulter, F.Med.Sci., Søren Rasmussen, Ph.D., Karen Tornøe, M.D., Ph.D.,
Bernard Zinman, M.D., and John B. Buse, M.D., Ph.D.,
for the LEADER Steering Committee and Investigators*

Composite renal outcome

Macroalbuminuria, doubling of serum creatinine,* ESRD, renal death (N=605)

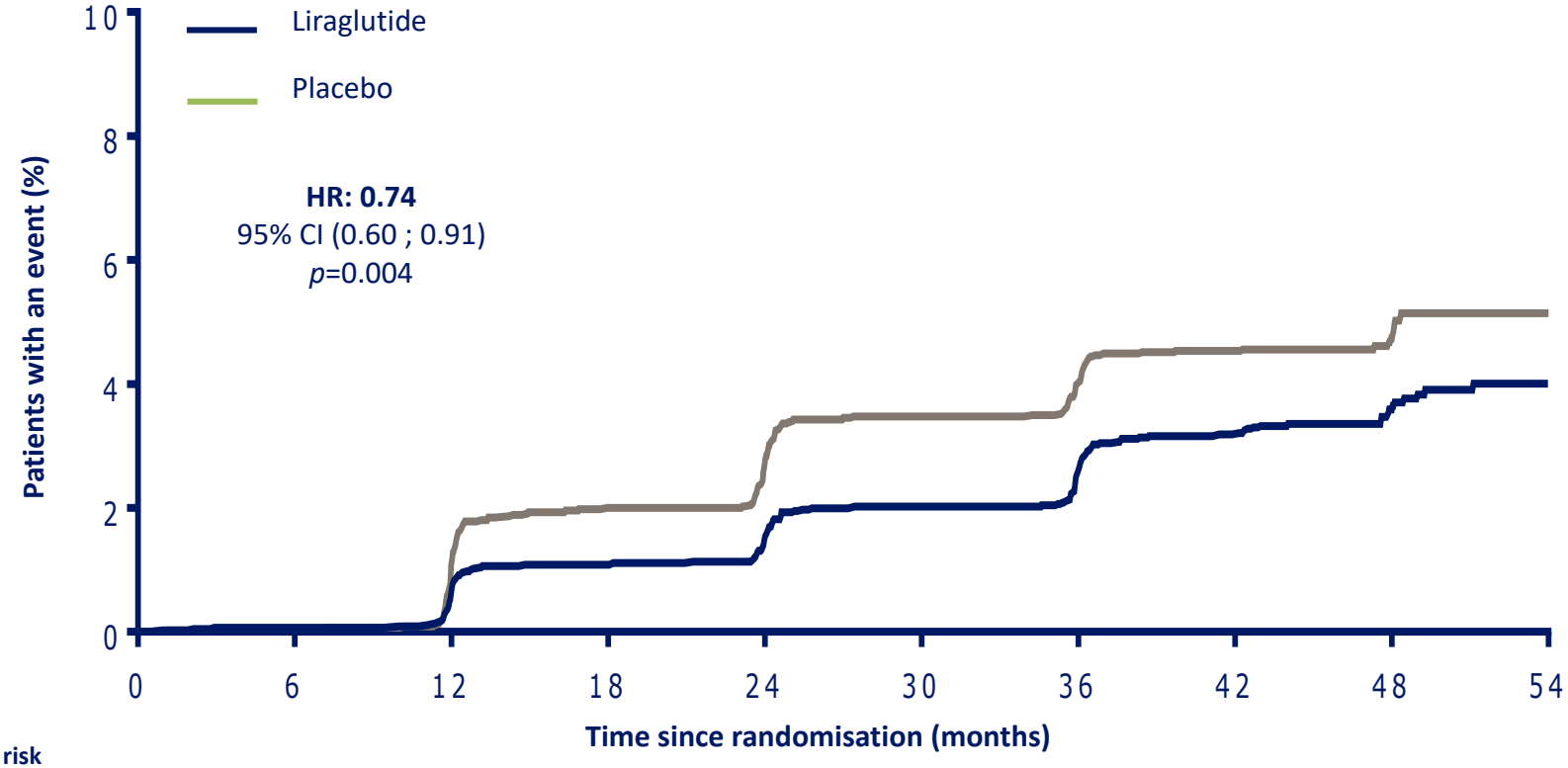


No. at risk										
Liraglutide	4668	4635	4561	4492	4400	4304	4210	4114	1632	454
Placebo	4672	4643	4540	4428	4316	4196	4094	3990	1613	433

*And eGFR ≤45 mL/min/1.73 m^2 per MDRD. The cumulative incidences were estimated with the use of the Kaplan–Meier method and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months because less than 10% of the patients had an observation time beyond 54 months. CI, confidence interval; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HR, hazard ratio; MDRD, modification of diet in renal disease

Mann JFE et al. *N Engl J Med* 2017;377:839–848. doi:10.1056/NEJMoa1616011

New onset of persistent macroalbuminuria



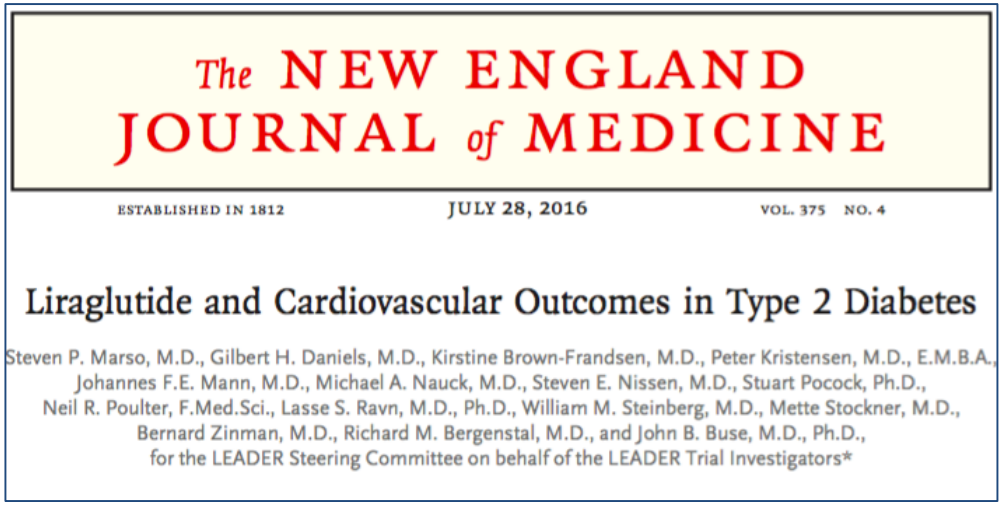
No. at risk										
Liraglutide	4668	4638	4570	4508	4437	4353	4268	4182	1662	461
Placebo	4672	4646	4551	4455	4359	4252	4162	4073	1642	442

Full analysis set. EAC-confirmed index events from randomisation to follow-up. The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months because less than 10% of the patients had an observation time beyond 54 months. Macroalbuminuria was defined as urine albumin >300 mg/g creatinine.

CI, confidence interval; EAC, event adjudication committee; HR, hazard ratio

Mann JFE et al. *N Engl J Med* 2017;377:839–848. doi:10.1056/NEJMoa1616011

GLP-1 et Mortalité cardiovasculaire



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 28, 2016 VOL. 375 NO. 4

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

Le critère primaire était un composite associant les décès CV, les infarctus du myocarde non fatals et les AVC non fatals.

→ Bénéfice cardiovasculaire avec le liraglutide
66 patients durant **3 ans** → réduction 1 év. CV
98 patients durant **3 ans** → **réduction** un décès

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Steven P. Marso, M.D., Stephen C. Bain, M.D., Agostino Consoli, M.D., Freddy G. Eliaschewitz, M.D., Esteban Jódar, M.D., Lawrence A. Leiter, M.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Julio Rosenstock, M.D., Jochen Seufert, M.D., Ph.D., Mark L. Warren, M.D., Vincent Woo, M.D., Oluf Hansen, M.Sc., Anders G. Holst, M.D., Ph.D., Jonas Pettersson, M.D., Ph.D., and Tina Vilsbøll, M.D., D.M.Sc., for the SUSTAIN-6 Investigators*

ABSTRACT

Cardiovascular safety and benefits of GLP-1 receptor agonists

Table 2. Overview of cardiovascular outcome trials in the glucagon-like peptide-1 receptor agonist class.

Glucagon-like peptide-1 receptor agonist	Cardiovascular outcome trial	Estimated enrollment	Study start date	Study completion date	URL
Lixisenatide	Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 (ELIXA)	6076	June 2010	February 2015 Results published	https://clinicaltrials.gov/ct2/show/NCT01147250
Liraglutide	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results – A Long Term Evaluation (LEADER®)	9340	August 2010	December 2015 Results published	https://clinicaltrials.gov/ct2/show/NCT01179048
Semaglutide	Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN™ 6)	3297	February 2013	January 2016 Results published	https://clinicaltrials.gov/ct2/show/NCT01720446
ITCA 650	A Study to Evaluate Cardiovascular Outcomes in Patients With Type 2 Diabetes Treated With ITCA 650 (FREEDOM-CVO)	4000	March 2013	April 2016	https://clinicaltrials.gov/ct2/show/NCT01455896
Exenatide Once-weekly	Exenatide Study of Cardiovascular Event Lowering Trial (EXSCEL)	14000	June 2010	April 2018	https://clinicaltrials.gov/ct2/show/NCT01144338
Albiglutide	Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus (HARMONY)	9400	July 2015	May 2019	https://clinicaltrials.gov/ct2/show/NCT02465515
Dulaglutide	Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND)	9622	July 2011	July 2018	https://clinicaltrials.gov/ct2/show/NCT01394952

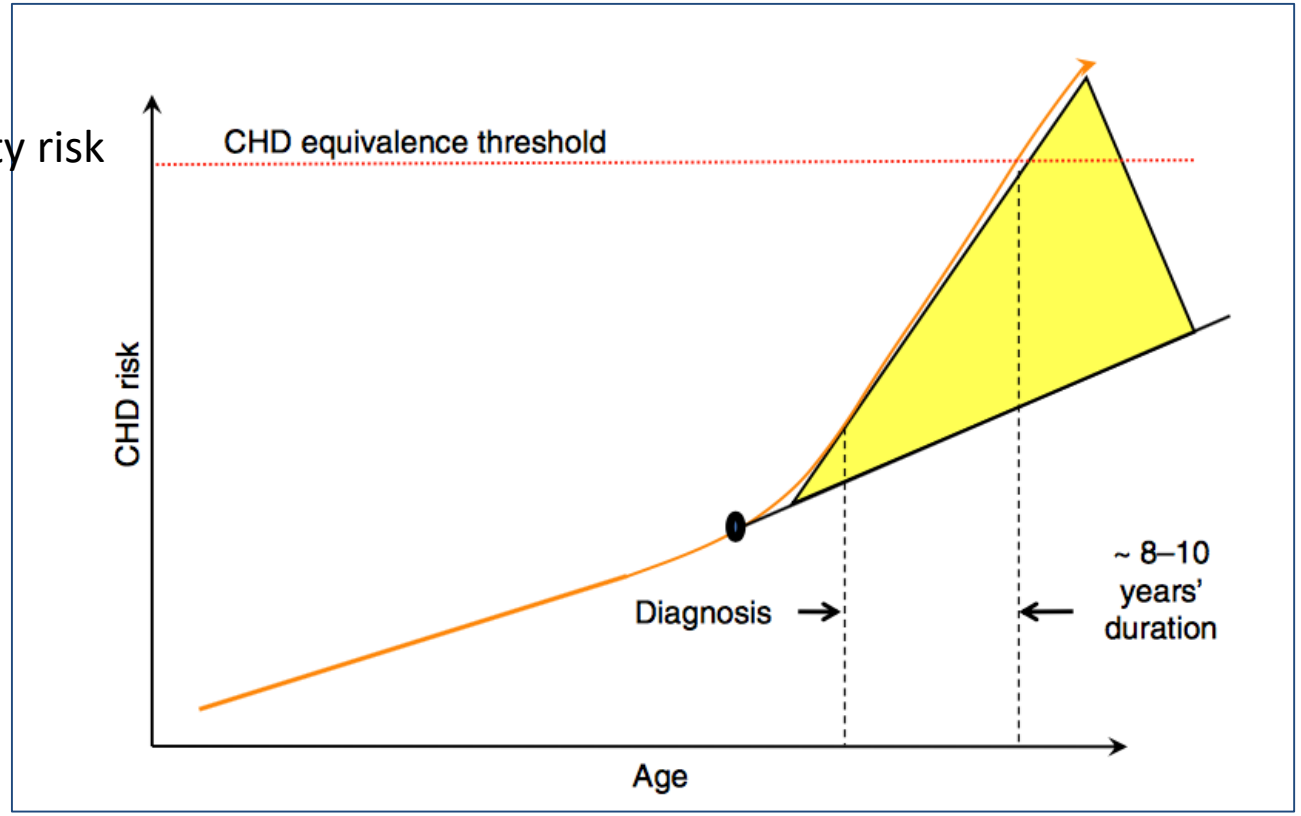
Expert Opinion on Drug Safety, VOL. 16, NO. 3, 351–363, 2017

Aspects pratiques

- Pas de risque d'hypoglycémie
- Risque d'hypoglycémie faible si associé à l'insuline ou sulfonylurée
- Cavea : si IRC (< 30ml/min) hormis pour Semaglutide et Liraglutide
- Cavea : insuffisance hépatique

Risque cardiovasculaire et facteurs déterminants dans le diabète de type 2

6-8% Mortality risk (per year)



CVD risk at the point of diabetes diagnosis is largely determined By conventional CVD risk factors. After 8-10 years'duration patients have attained a CHD risk equivalent state.
After 10 years of T2D duration the CHD risk is higher

Sattar N. Diabetologia (2013) 56:686–695

T2D and CVD risk factors

modifiable vs unmodifiable

- Obesity
- Nutrition
- Sedentarity
- **Genetic**
- **Age/gender**
- Smocke (1cig/jour)
- High blood pressure
  - (>140/90mmHg)
- LDL cholesterol
- HDL cholesterol
  - (M: <1mmol/l, F: < 1.3mmol/l)
- **CVD heredity**
- Emerging CVD factors:
  - Triglyceride (TG)
  - HDL
  - Pro-thrombotic state
  - Pro-inflammatory state

Metabolic syndrome

Glycemia > 6.0 mmol/l

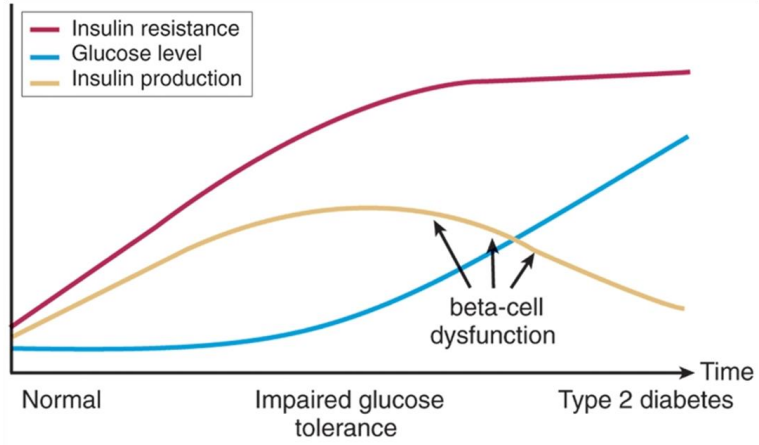
Abdominal circum. (M >102; F >88cm)

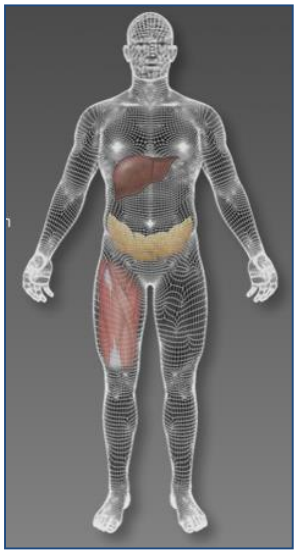
TG > 1.7mmol/l

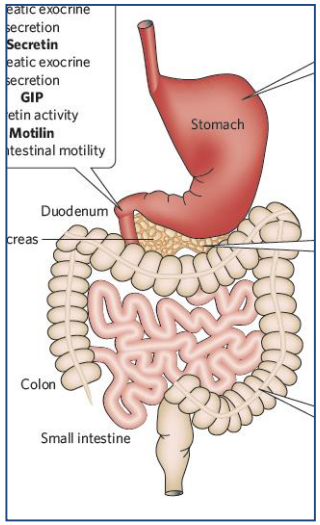
HTA >130/85mmHg

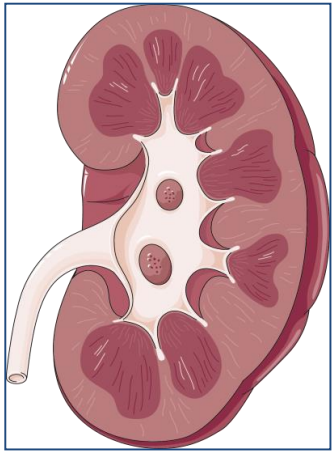
Diabetes (HYPERGLYCEMIA)

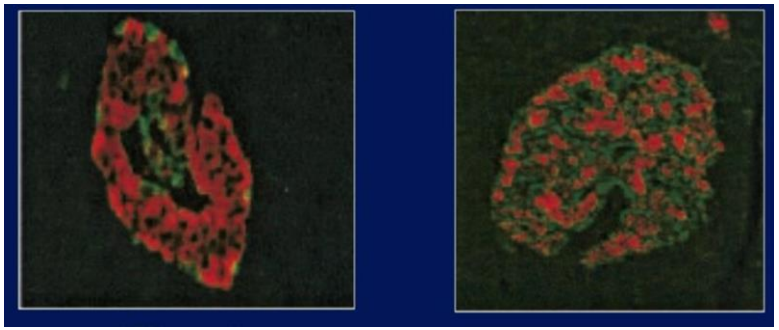
Actions des antidiabétiques oraux











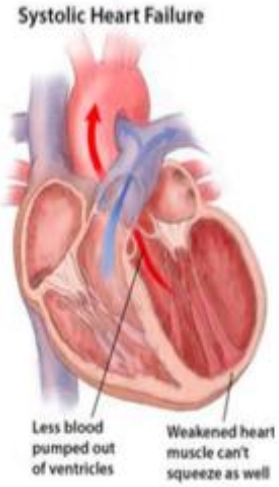
4th clinical question: Asymptomatic Heart Failure?

581 Patients >60 years with T2D
and no none heart failure in primary care

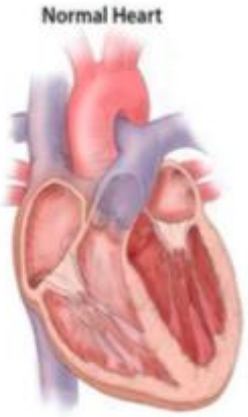
HFpEF: 22.9%
HFrEF: 4.8%
} **27.6%**

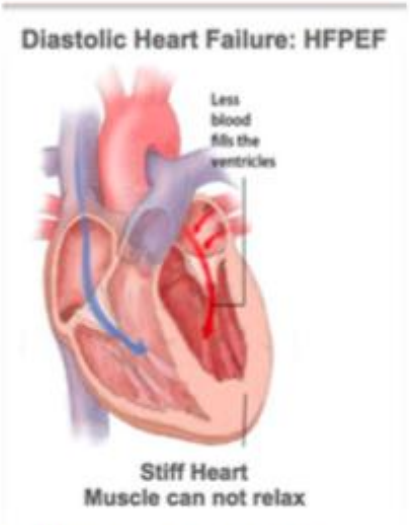
Asymptomatic, diagnosed with echocardiography

~25% of Patients >60 years have asymptomatic heart failure



HFrEF: 4.8%





HFpEF: 22.9%

Diabetologia. 2012 Aug; 55(8): 2154–2162

Swiss recommendations 2016

Swiss Society of Endocrinology and Diabetology

1. Insulin Deficiency?

~25% of all patients

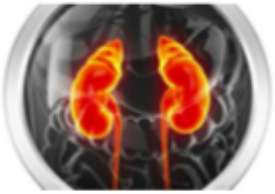
→ Basal Insulin
- Premixed-Insulin
- Basal Insulin + GLP-1 RA (Xultophy®)

or

Basal Bolus

2. eGFR < 30 ml/min?

2.4% of all patients



DPP-4 Inhibitors → Basal Insulin

~25% e-GFR < 60

6.1%: e-GFR 30-45
13.9%: e-GFR 45-60

3. Cardiovascular Disease?

yes

~20-25% of all patients
(~50% asymptomatic)

- Metformin+ SGLT2 I. → + DPP-4 I. or Gliclazide or Basal Insulin
- Metformin+ GLP-1 RA → + Gliclazide or Basal Insulin

no

- Metformin+ SGLT2 I.
- or
- Metformin+ GLP-1 RA
- or
- Metformin + DPP-4 I. → + Gliclazide or Basal Insulin

4. Heart Failure?

~ 10% of all patients
(~25% asymptomatic)

Metformin+ SGLT2 I. → + DPP-4 I. → Basal Insulin

www.sgedssed.ch

Résumé ADO

Il existe un nombre conséquent d'Anti-Diabétiques (AD) avec de multiples spécificités.

Dans le DT2, la metformine reste le traitement de première ligne.

En cas d'indication à l'association d'un ou plusieurs ADO le choix doit prendre en compte la physiopathologie, le risque cardiovasculaire, le risque d'hypoglycémie, l'influence sur le poids, la tolérance, les coûts et le degré de vulnérabilité.

Les buts premiers du contrôle glycémique sont la diminution des complications micro et macro vasculaires et la réduction de la mortalité cardio-vasculaire tout en évitant les décompensations aigues (hyperglycémie. Décomp. Acidocétosique et/ou hyperosmolaire).

Les patients insuffisamment contrôlés sur le plan glycémique, tensionnel ou présentant une micro-albuminurie sont à haut risque d'altération de la fonction rénale.

L'existence d'une IRC double le risque d'événement cardiovasculaire et la mortalité chez les patients souffrant d'un DT2.

La fonction rénale est déterminante sur le choix des anti-diabétiques et **leur renouvellement .**

Le risque cardiovasculaire et la présence d'antécédents cardiovasculaire sont déterminant sur le choix thérapeutiques (metformine + gliflozine ou analogue GLP-1)

L'insuffisance cardiaque asymptomatique est à rechercher activement et est déterminante sur le choix thérapeutique (gliflozines)