Réunion d'information pour les pharmaciens

JC Daubresse

17 mars 2022

question1

- Il faut arrêter la metformine quand la créatinine est égale à:
- 55
- 45
- 35
- 25 ml/min

Question 2

- Parmi les insulines suivantes cochez les analogues
- Novorapid
- Fiasp
- NPH humulin
- Lantus

Question 3

- En Europe, la proportion moyenne des patients qui ne sont pas à l'objectif (HbA1c <7%)est de :
- 10%
- 20%
- 30%
- 40%

Type 1 ou type 2 ou autres ?

- On pensera à un type 1 chez un sujet jeune sans trop d'antécédents familiaux, de poids normal , qui maigrit dans le cadre d'un syndrome polyuro-polydipsique
- La glycémie est élevée avec des corps cétoniques et sans insuline, la situation va rapidement se dégrader
- IL y a des auto anticorps
- Mais est-ce toujours si évident?
- Et les autres qui sont secondaires…

Mais rien n'est simple…

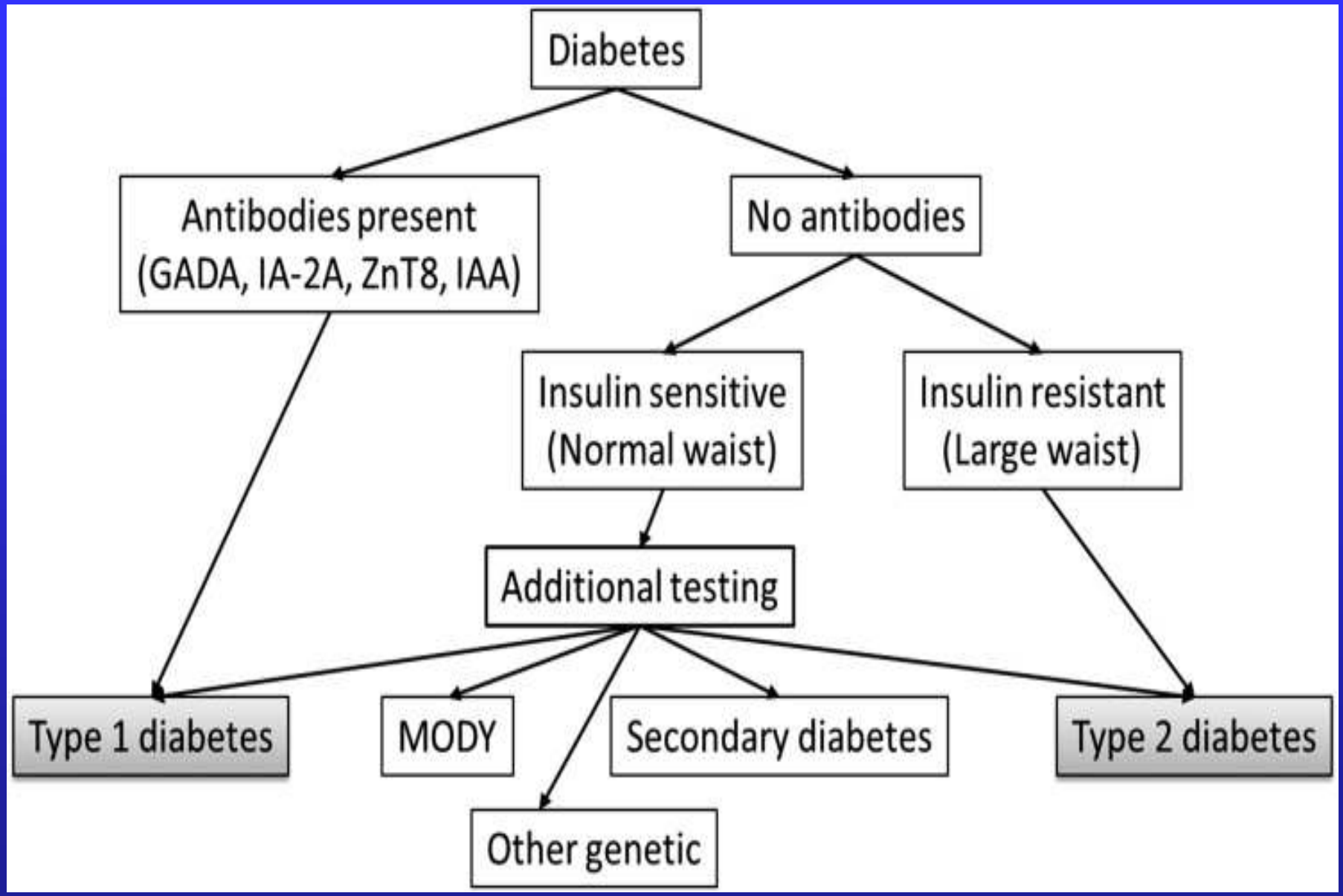
- Avec l'épidémie d'obésité, on trouve des ados type 1 obèses
- Le type 1 peut commencer chez des adultes
- Seulement 90% des types 1 ont au moins un des auto anticorps
- Des types 2 (LADA) et des diabètes gestationnels peuvent présenter des auto anticorps
- IL y a aussi les MODY
- 10% des patients sont mal classés au départ
- Le C peptide est utile mais difficile à interpréter

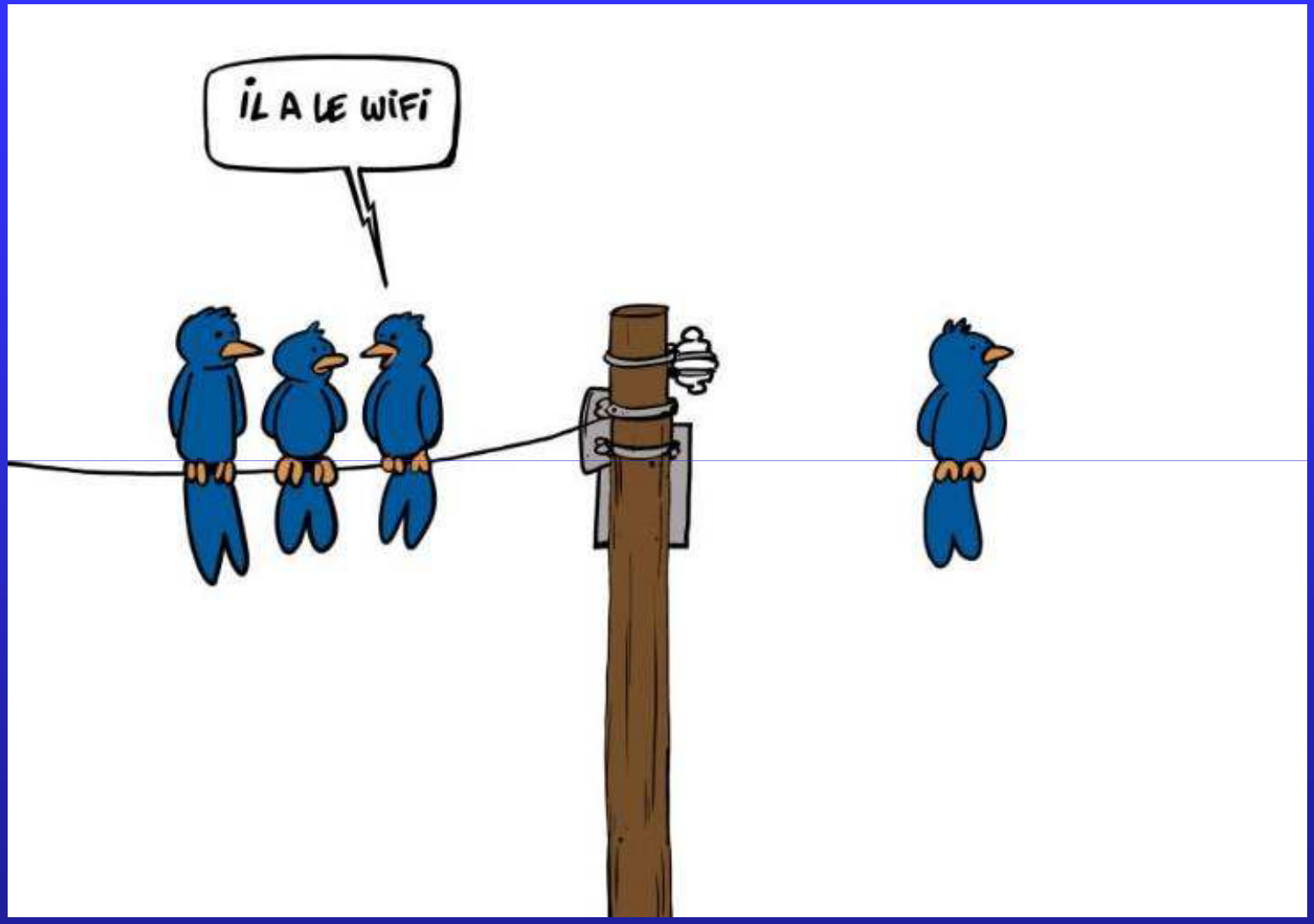
Auto anticorps intéressants pour le diagnostic

- ICA anti îlots
- GAD anti décarboxylase de l'acide glutamique
- IA-2 anti tyrosine phosphatase

IAA anti insuline ou proinsuline

ET bien d'autres…


Diabetes
Antibodies present
(GADA, IA-2A, ZnT8, IAA)
No antibodies
Insulin sensitive
(Normal waist)
Insulin resistant
(Large waist)
Additional testing
Type 1 diabetes
MODY
Secondary diabetes
Type 2 diabetes
Other genetic


İL A LE WiFi

Prise charge de l'hyperglycémie

Que nous disent les recommandations internationales?

- Pour les américains, on commence avec l'hygiène de vie et d'emblée la metformine
- Pour la seconde ligne, toutes les options sont possibles
- En Belgique, nous devons tenir compte des règles INAMI pour la prescription , MEME dans les trajets de soins

Règles de prescription en Belgique

- Toujours commencer par la metformine
- Ensuite grand choix quand l'HbA1c atteint 7%
- Mais souvent demande au MC sauf TdS
- Pour les incrétinomimétiques il faut HbA1c plus que 7.5% et BMI =30
- Pour les insulines d'abord commencer avec les bon marché avant de passer aux analogues

… ne pas vous égarer,

Objectifs thérapeutiques dans le diabète

- Réduire les complications micro vasculaires: Améliorer les taux d'HbA1c
- Réduire le risque CV et HF: nouvelles molécules
- Eviter les hypoglycémies : éducation, nouvelles molécules et Glucagen
- Eviter la prise de poids
- Garder une bonne qualité de vie
- UN traitement pour UNE personne

Agents thérapeutiques oraux

- Metformine
- Sulfamidés
- Glinide
- Glitazone (Actos)
- Gliptines : DPP4 i
- Gliflozines : SGLT2 i
- Associations: Met+Glip; Met+Glif; Glif+Glip
- GLP-1 analogue Semaglutide Rybelsus

Le début de la saga Glucophage

- Galega officinalis est connue depuis le moyen-âge pour traiter le diabète, on en a extrait la galegine, dérivée de la guanidine très toxique puis on a synthétisé la metformine

Metformine (la suite)

- Introduite en 1957 par le laboratoire ARON
- Utilisée essentiellement à l'Ulg
- Action normoglycémiante sans hypoglycémie en agissant surtout pour réduire le débit glucosé hépatique et un peu en augmentant la pénétration intra musculaire du glucose(sensibilisation à l'insuline et action par l'AMPactivated PK)
- Doit subir la 'vague' de l'acidose lactique

Metformine (suite)

- L'étude Cochrane de Salpeter et al. ne montre aucune augmentation du risque d'AL si le produit est utilisé selon les recommandations
- Reprise du brevet par LIPHA puis essais américains de R. De Fronzo qui 'redécouvre' le mode d'action, FDA puis commercialisation par BMS aux USA

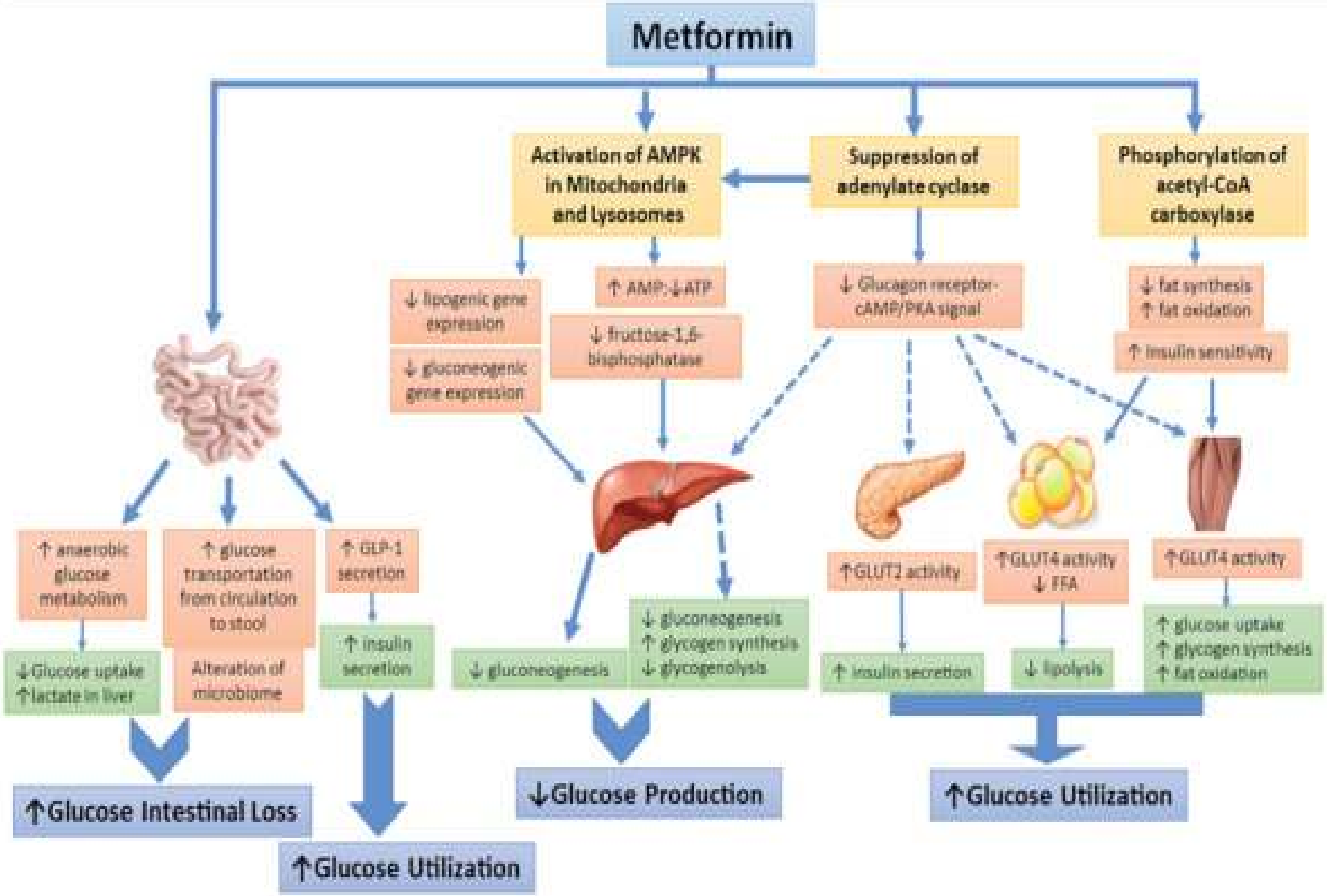
Metformine (suite)

- Etude UKPDS démontre une réduction de la mortalité CV
- Le Glucophage devient la drogue à utiliser en première intention cfr le récent consensus ADA, EASD
- Le prix est ,par ailleurs, très compétitif
- Bref: un parcours sans faute et le marché chinois s'ouvre à Lipha Merck
- 2022 arrêt de la commercialisation du Glucophage…

Le bon usage de la metformine

Holstein et Stumvoll (Diabetologia 2005)

- Pas si IRC : clearance< 30ml/min, réduire la dose de 30à 40 ml/min
- Pas si hypoxie (BPCO et NYHA 3 et 4)
- Arrêter la veille d'une injection d'iode ou de la chirurgie et reprise 48 h après
- Surveiller les taux de vitamine B12
- Il n'y a aucune interaction médicamenteuse connue et… on s'en passe trop souvent


Metformin
Activation of AMPK in Mitochondria and Lysosomes
Suppression of adenylate cyclase
Phosphorylation of acetyl-CoA carboxylase
↓ lipogenic gene expression
↓ gluconeogenic gene expression
↑ AMP:↓ATP
↓ fructose-1,6-bisphosphatase
↓ Glucagon receptor-cAMP/PKA signal
↓ fat synthesis
↑ fat oxidation
↑ insulin sensitivity
↑ anaerobic glucose metabolism
↓Glucose uptake
↑lactate in liver
↑ glucose transportation from circulation to stool
Alteration of microbiome
↑ GLP-1 secretion
↑ insulin secretion
↓ gluconeogenesis
↓ gluconeogenesis
↑ glycogen synthesis
↓ glycogenolysis
↑GLUT2 activity
↑ insulin secretion
↑GLUT4 activity
↓ FFA
↓ lipolysis
↑GLUT4 activity
↑ glucose uptake
↑ glycogen synthesis
↑ fat oxidation
↑Glucose Intestinal Loss
↑Glucose Utilization
↓Glucose Production
↑Glucose Utilization

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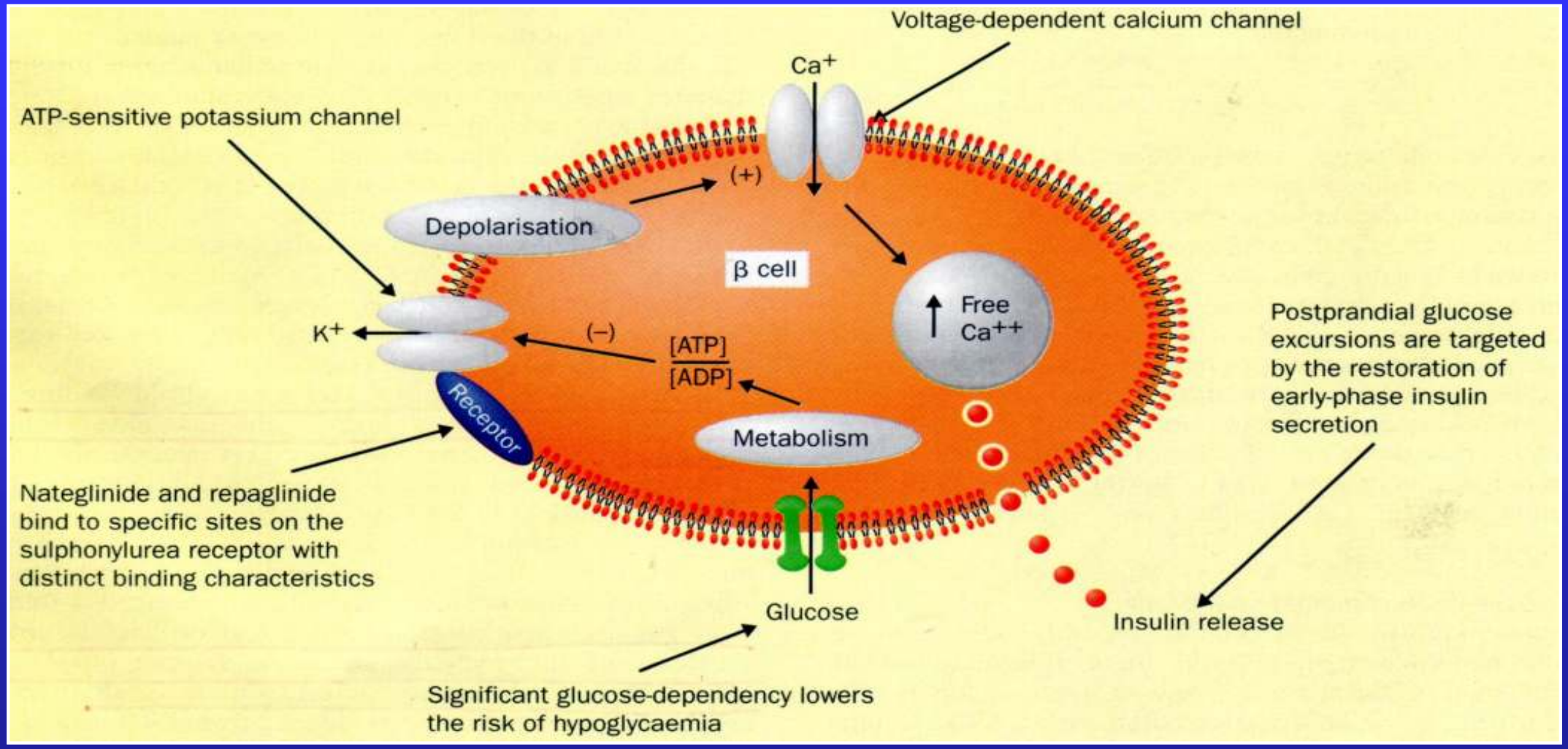

Voltage-dependent calcium channel
Ca+
ATP-sensitive potassium channel
(+)
Depolarisation
β cell
Free
Ca++
K+
(–)
[ATP]
[ADP]
Receptor
Metabolism
Postprandial glucose excursions are targeted by the restoration of early-phase insulin secretion
Nateglinide and repaglinide bind to specific sites on the sulphonylurea receptor with distinct binding characteristics
Glucose
Insulin release
Significant glucose-dependency lowers the risk of hypoglycaemia

Les sulfonylurées et Répaglinide

- Médicaments faciles à prescrire, bon marché avec un effet immédiat, parfois puissant DONC à commencer avec des petites doses
- Risque d' » épuisement de la cellule bèta »???
- Risques d'hypoglycémies réels
- Prise de poids potentiel
- Effets négatifs au plan cardio vasculaire

Sulfonylureas and CV Mortality

Observational trials comparing any sulfonylureas (monotherapy or combination) vs any non-sulfonylurea treatment including insulin

	Sulfonylurea		Non-sulfonylurea		Odds Ratio
Author(s), y	Alive	Deaths	Alive	Deaths	(95% CI)
Evans et al, 2006	5308	373	2248	38	4.16 (2.971 5.83)
Johnson et al, 2005	2899	320	862	61	1.56 (1.17, 2.07)
Schramm et al, 2011	57,757	3942	42,513	827	3.51 (3.25, 3.79)
Schramm et al, 2011	5278	961	2737	169	2.95 (2.49, 3.49)
Sillars et al, 2010	396	137	503	81	2.15 (1.58, 2.91)
Random effects model					**2.72 (1.95, 3.79)**

German CREST Study: Patient Outcomes

Events	Crude HR (95% CI)	*P*-value	PSM HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value
Death	3.3 (2.5-4.3)	<.001	1.4 (0.9-2.3)	.120	2.0 (1.5-2.6)	<.001
MACE	1.9 (1.4-2.4)	<.001	1.4 (0.9-2.2)	.137	1.3 (1.0-1.7)	<.05
T2DM-related hospitalization	3.0 (1.9-4.6)	<.001	4.1 (1.6-10.9)	<.005	2.8 (1.8-4.4)	<.001
Composite outcome*	2.5 (2.1-3.0)	<.001	1.6 (1.2-2.3	<.005	1.8 (1.5-2.1)	<.001

HRs/adjusted HRs reported for SU exposure in comparison with MET exposure.
*Any event, whichever came first.

Berg B, et al. EASD Annual Meeting, 2015. Abstract 130.

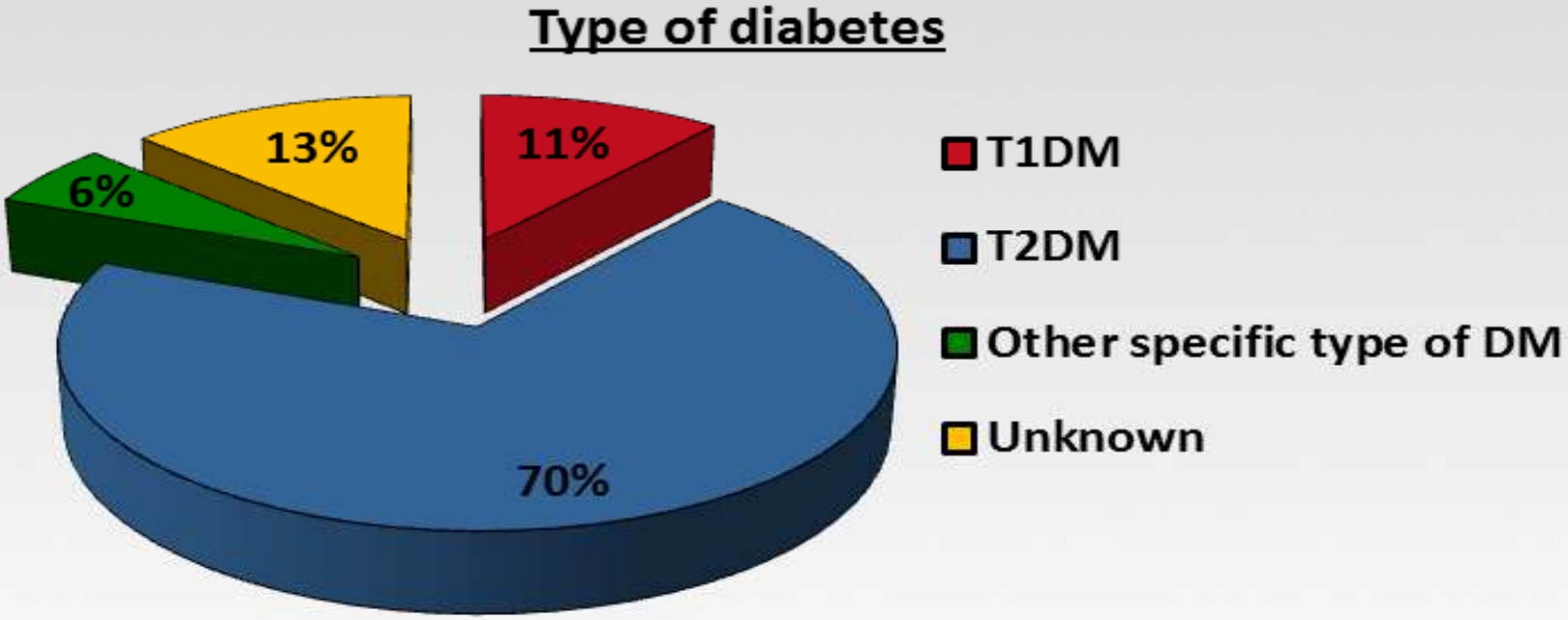
The Hypoglycemia and CV Risk Debate

- Arrhythmogenic?
- Induction of pro-inflammatory, prothrombotic phenotype
- QT prolongation
- Ischemia precipita
- "Dead in bed" phenomenon
  - Hypoglycemia-related arrhythmia leads to sudden death

Laitinen T, et al.[20] Frier BM, et al.[21]

ED Admissions for Hypoglycemia in Diabetes Patients at the Santa Chiara Hospital-Pisa

380 ED admissions from January 1, 2009 to June 30, 2012
N=276 subjects (mean age 69 ± 18 years , 51% male); 92% identified as diabetic



26% of subjects experienced recurrent severe hypoglycemia (≥ 2 admissions)

ED = emergency department; T1DM = type 1 diabetes mellitus

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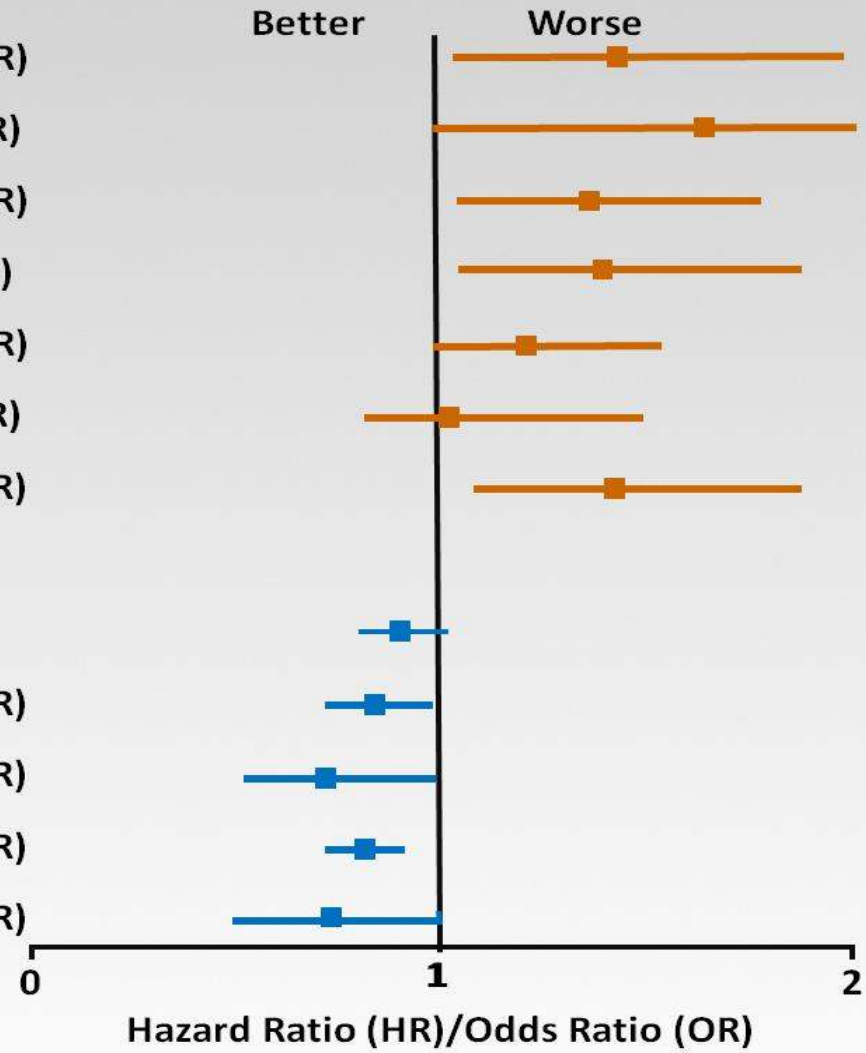
CV Events: Rosiglitazone vs Pioglitazone

Rosiglitazone

Meta-analysis, Nissen et al[a]	Myocardial infarction (OR)
Meta-analysis, Nissen et al[a]	Cardiovascular death (OR)
Meta-analysis, Krall[b]	Myocardial infarction (OR)
Meta-analysis of 42 trials, FDA[c]	Myocardial ischemia (OR)
Data from Nissen and RECORD[d]	Myocardial infarction (OR)
Data from Nissen and RECORD[d]	Cardiovascular death (OR)
Meta-analysis, Singh[e]	Myocardial infarction (HR)

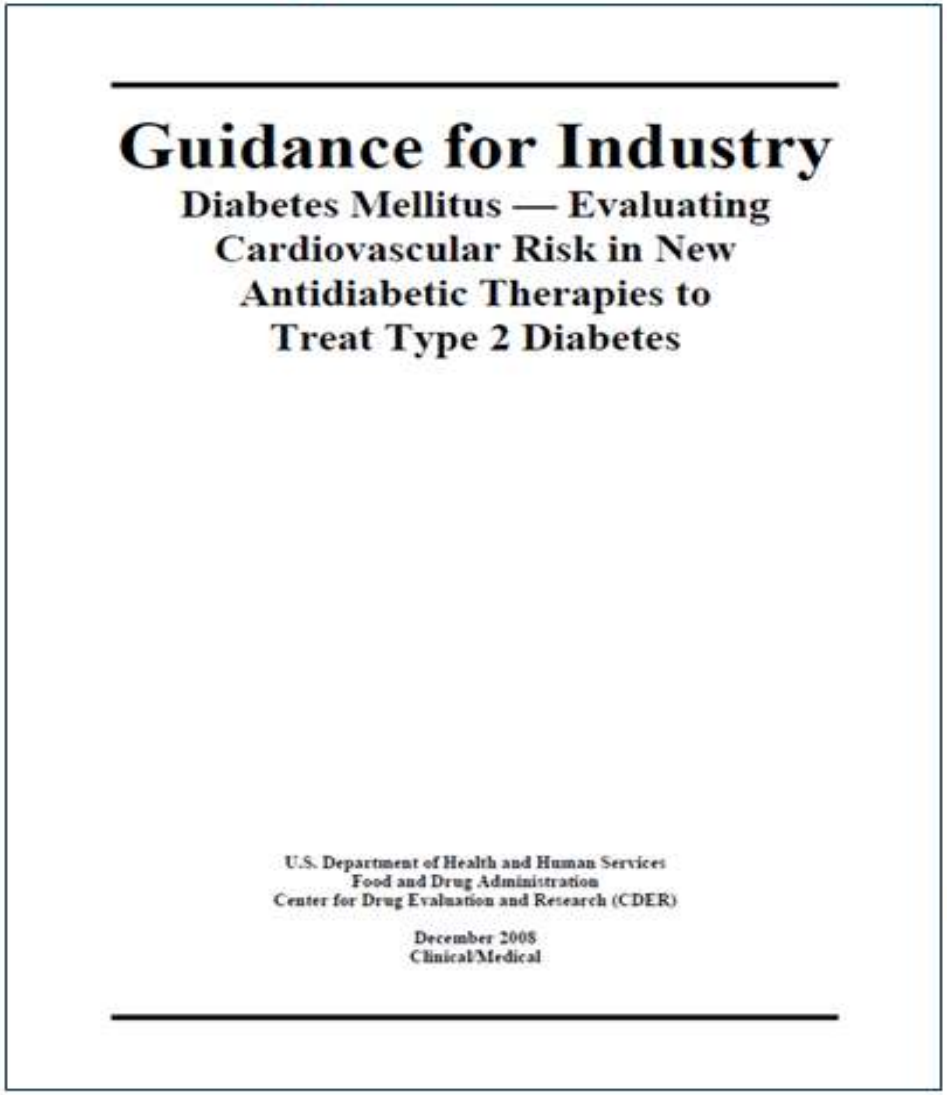
Pioglitazone

PROactive[f]	Primary end point (HR)
PROactive[g]	MI, stroke, and death (HR)
PROactive MI subgroup[h]	Myocardial infarction (HR)
Meta-analysis, Lincoff et al[i]	MI, stroke, and death (HR)
Meta-analysis, FDA 2007[c]	MI, stroke, and death (HR)



a. Nissen SE, et al[4]; b. Krall RL, et al[5]; c. www.fda.gov[6]; d. Bracken MB et al[7]; e. Singh S, et al[8]; f. Diamond G, et al[9]; g. Dormandy JA, et al[10]; h. Erdmann E, et al[11]; i. Lincoff AM, et al.[12]

December 2008 FDA Guidance on Evaluating CV Risk in New Antidiabetic Therapies for T2DM



Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2008
Clinical/Medical

III. RECOMMENDATIONS

To establish the safety of a new antidiabetic therapy to treat type 2 diabetes, sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk. To ensure that a new therapy does not increase cardiovascular risk to an unacceptable extent, the development program for a new type 2 antidiabetic therapy should include the following.

For new clinical studies in the planning stage:

- Sponsors should establish an independent cardiovascular endpoints committee to prospectively adjudicate, in a blinded fashion, cardiovascular events during all phase 2 and phase 3 trials. These events should include cardiovascular mortality, myocardial infarction, and stroke, and can include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possibly other endpoints.

- Sponsors should ensure that phase 2 and phase 3 clinical trials are appropriately designed and conducted so that a meta-analysis can be performed at the time of completion of these studies that appropriately accounts for important study design features and patient or study level covariates. To obtain sufficient endpoints to allow a meaningful estimate of risk, the phase 2 and phase 3 programs should include patients at higher risk of cardiovascular events, such as patients with relatively advanced disease, elderly patients, and patients with some degree of renal impairment. Because these types of patients are likely to be treated with the antidiabetic agent, if approved, this population is more appropriate than a younger and healthier population for assessment of other aspects of the test drug's safety.

- Sponsors also should provide a protocol describing the statistical methods for the proposed meta-analysis, including the endpoints that will be assessed. At this time, we believe it would be reasonable to include in a meta-analysis all placebo-controlled trials, add-on trials (i.e., drug versus placebo, each added to standard therapy), and active-

FDA.org

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The incretin story

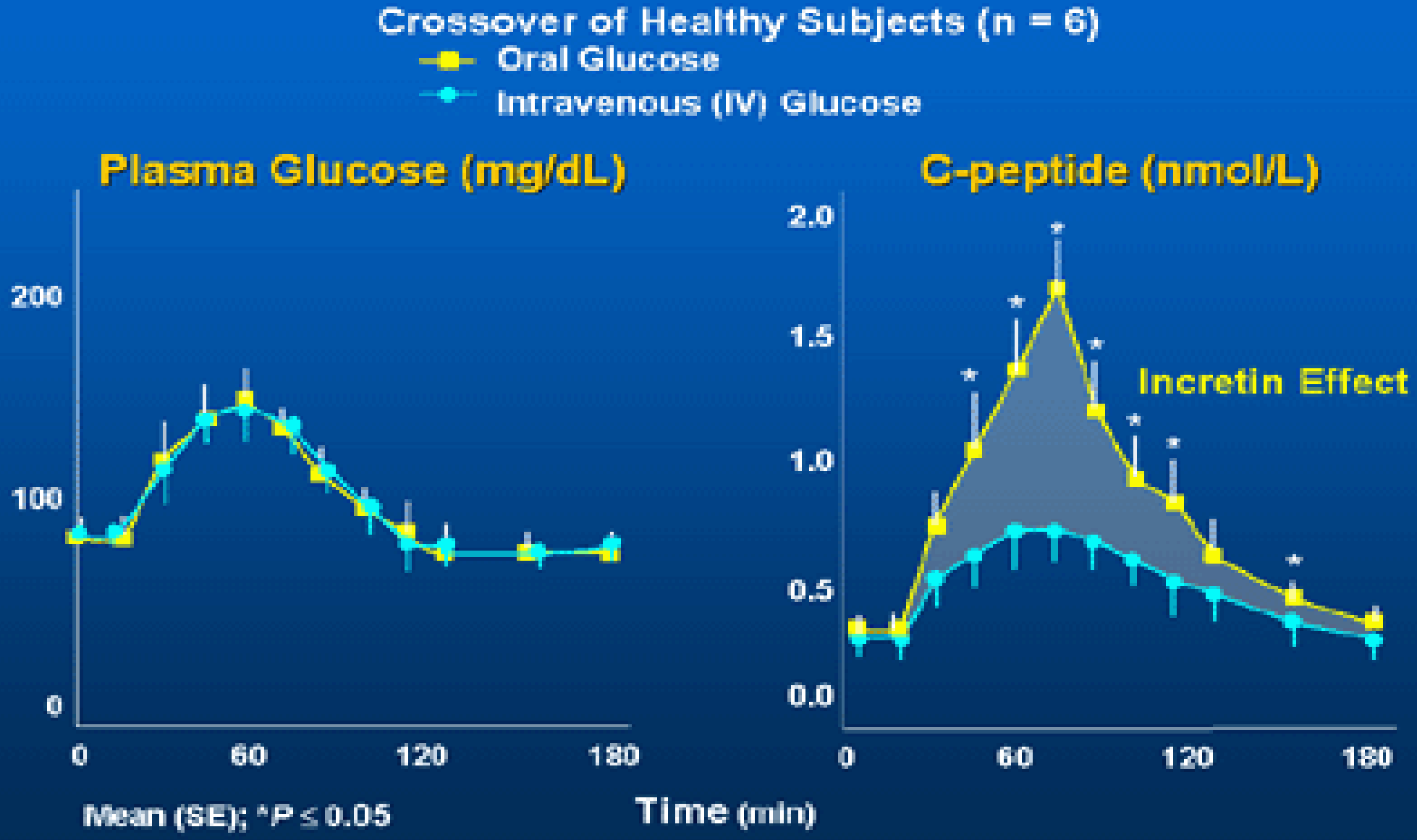
- 1902 Bayliss et Starling suggèrent que la muqueuse intestinale contient un stimulant de la sécrétion EXOCRINE du pancréas= sécrétine
- 1932 L pharmacien La Barre (Ulb) montre qu'un extrait de l'intestin grèle proximal donne de l'hypoglycémie
- 1940 Léon remet tout en question mais en 1970 , on isole le GIP, le GLP-1 et l'histoire recommence avec des applications à l'homme

The incretin story

- GLP-1 = glucagon like peptide-1
- GIP = Glucose dependent insulinotropic peptide

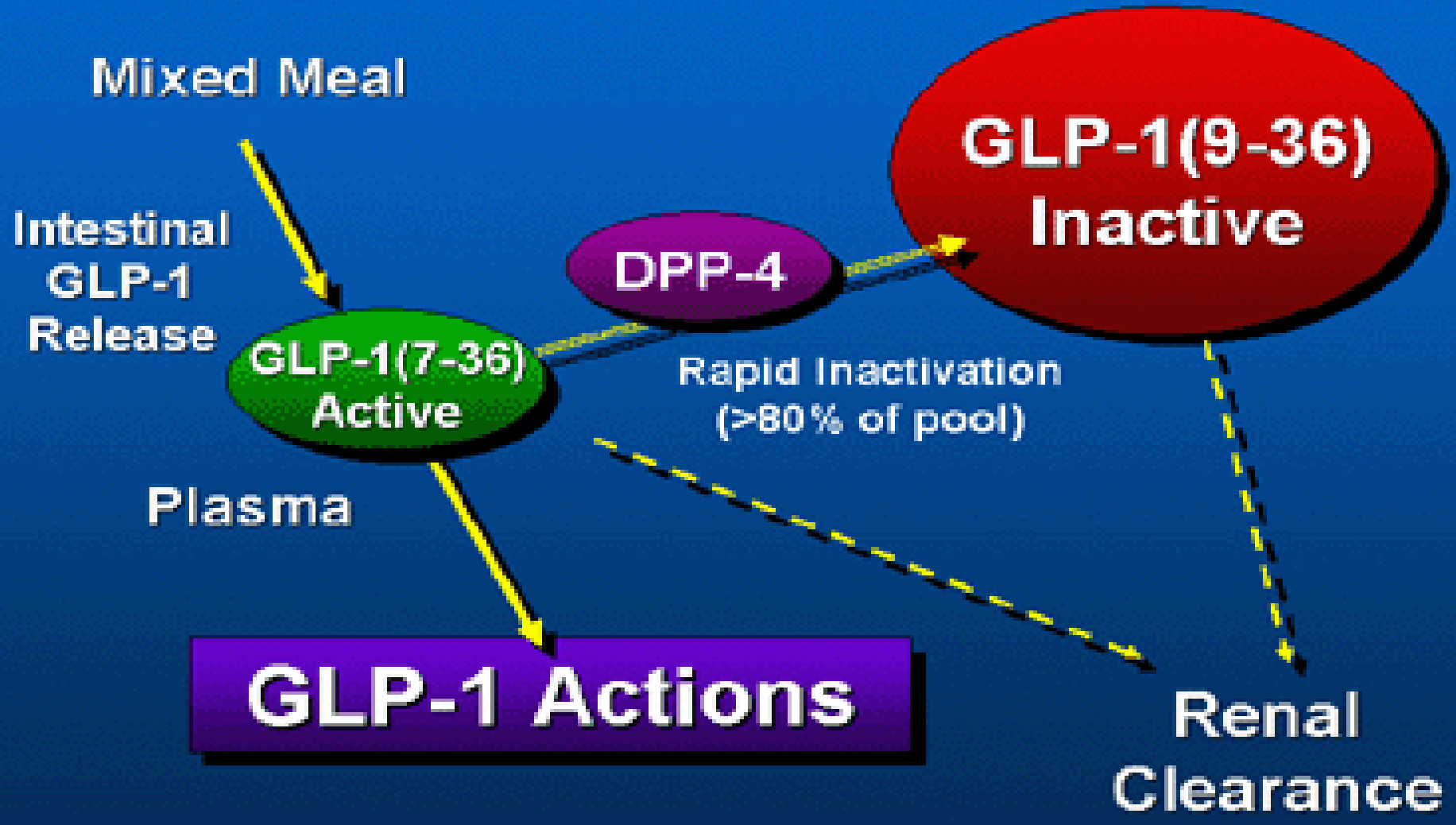
Ce sont 2 peptides qui stimulent la sécrétion d'insuline de manière gluco-dépendante, c'est –à-dire que l'effet disparaît quand la glycémie se normalise, donc sans risque d'hypoglycémie!

The Incretin Effect
Beta-Cell Response to Oral vs IV Glucose



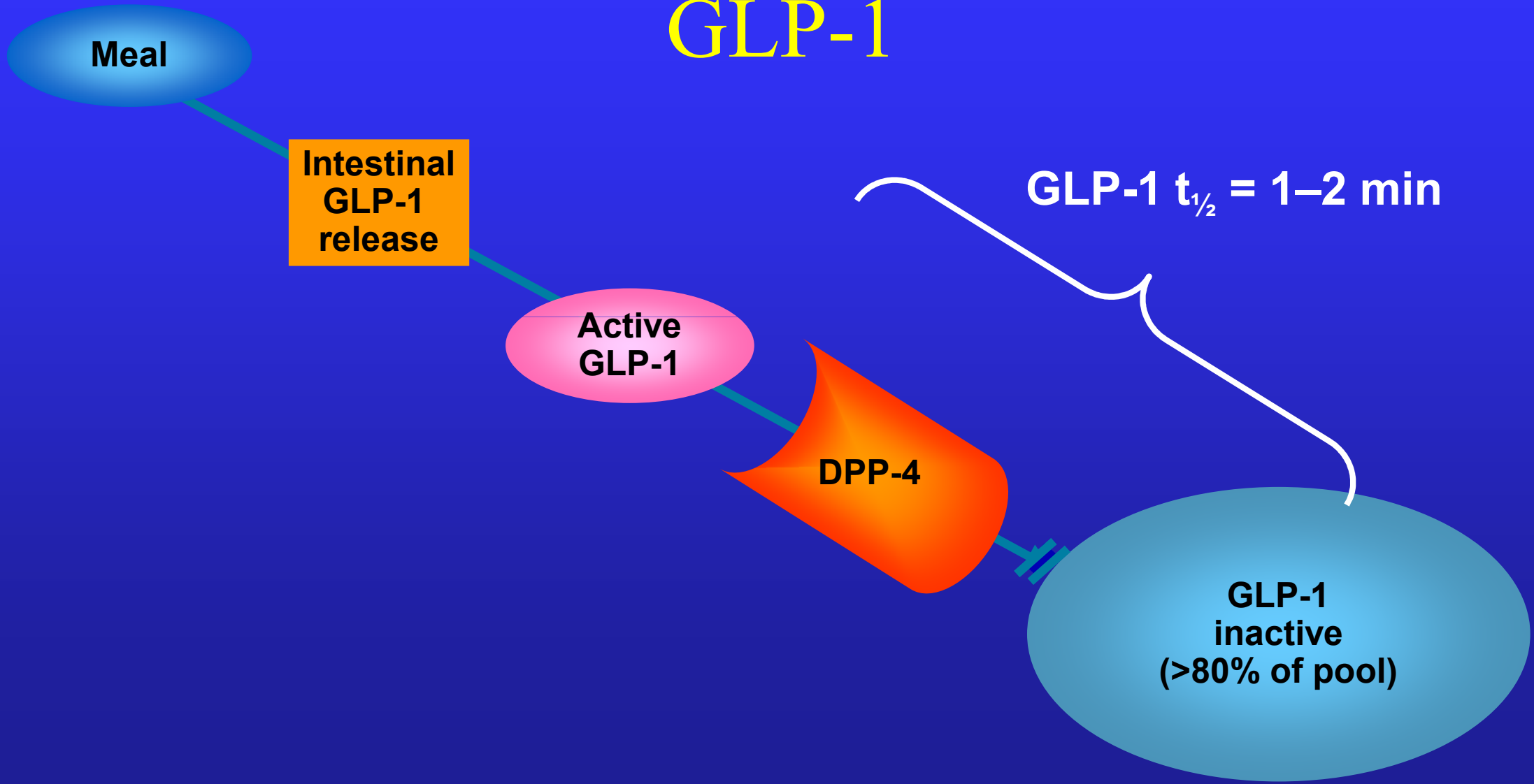
Data from Nauck MA et al. *J Clin Endocrinol Metab.* 1986;63:492-8.

GLP-1 Secretion and Metabolism

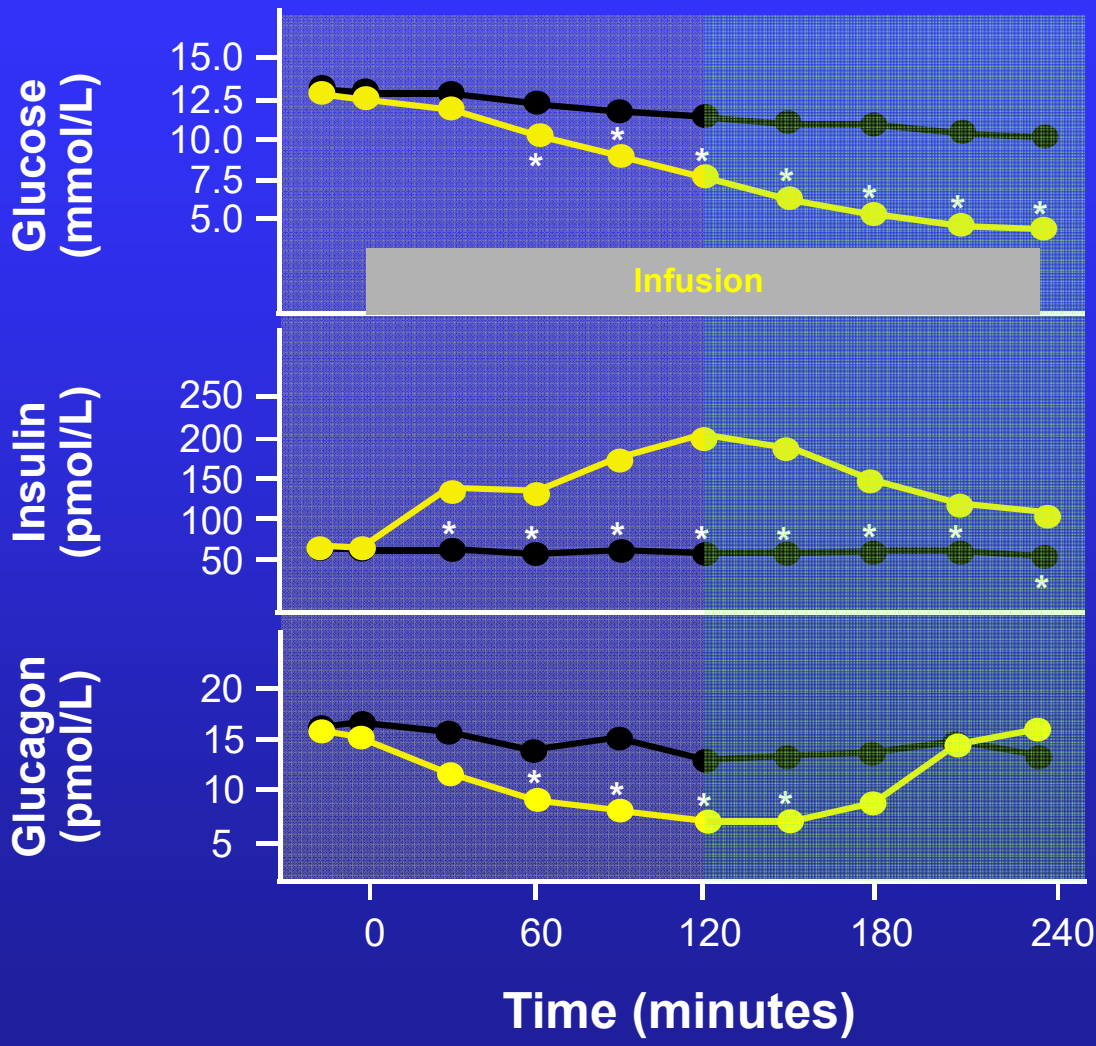


Adapted from Deacon et al. *Diabetes*. 1995;44:1126.

Inhibition of DPP-4 Increases Active GLP-1



Effects of GLP-1 on Insulin and Glucagon Shown to Be Glucose Dependent in Type 2 Diabetes



With hyperglycemia GLP-1 stimulated insulin and suppressed glucagon.

When glucose levels approached normal, insulin levels declined and glucagon was no longer suppressed.

N=10 patients with type 2 diabetes. Patients were studied on two occasions. A regular meal and drug schedule was allowed for one day between the experiments with GLP-1 and placebo.

***p<0.05 GLP-1 vs. placebo**

Adapted from Nauck MA et al *Diabetologia* 1993;36:741–744.

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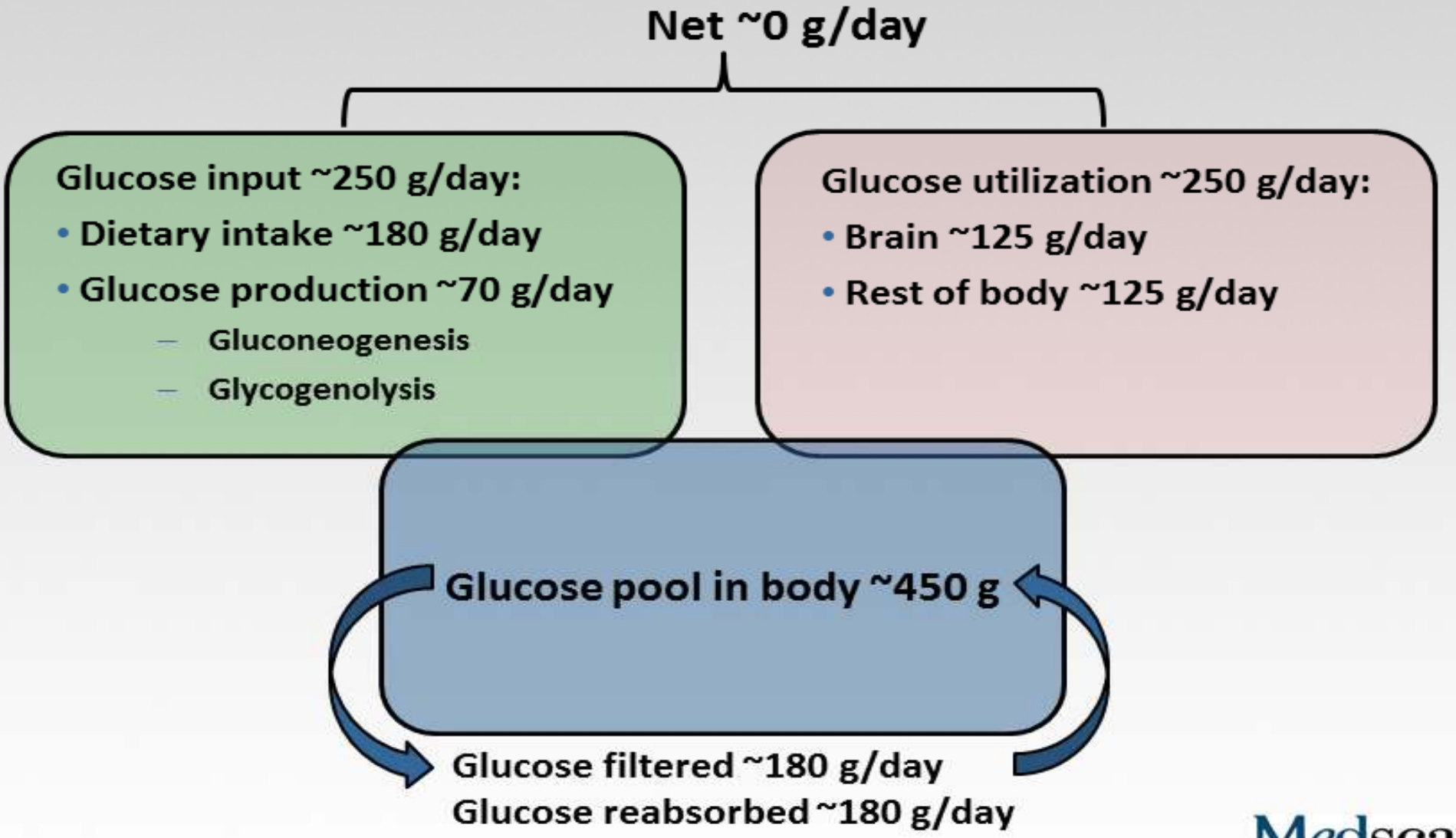
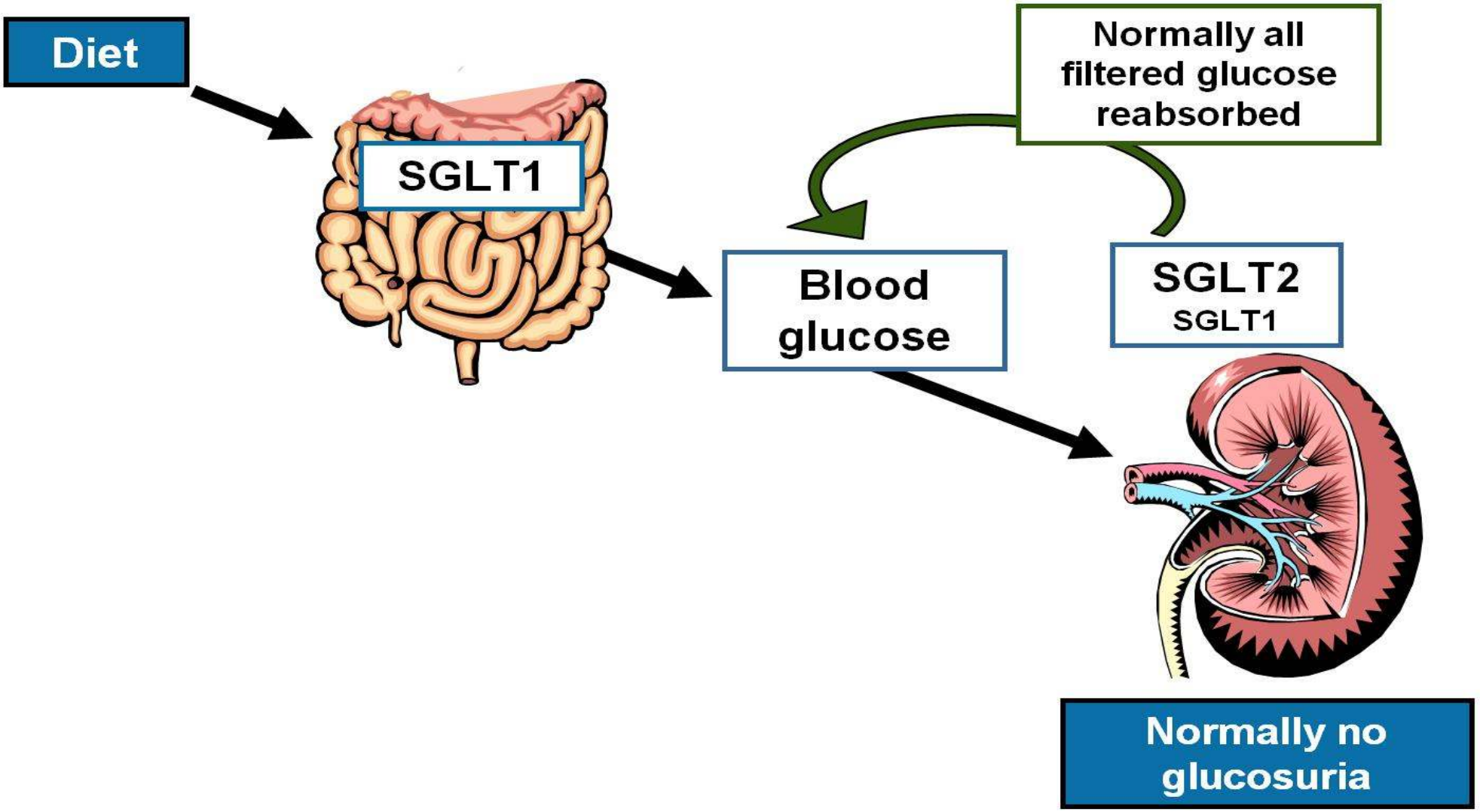
The Kidney Filters and Reabsorbs a Large Proportion of the Glucose Present in the Body



Medscape EDUCATION

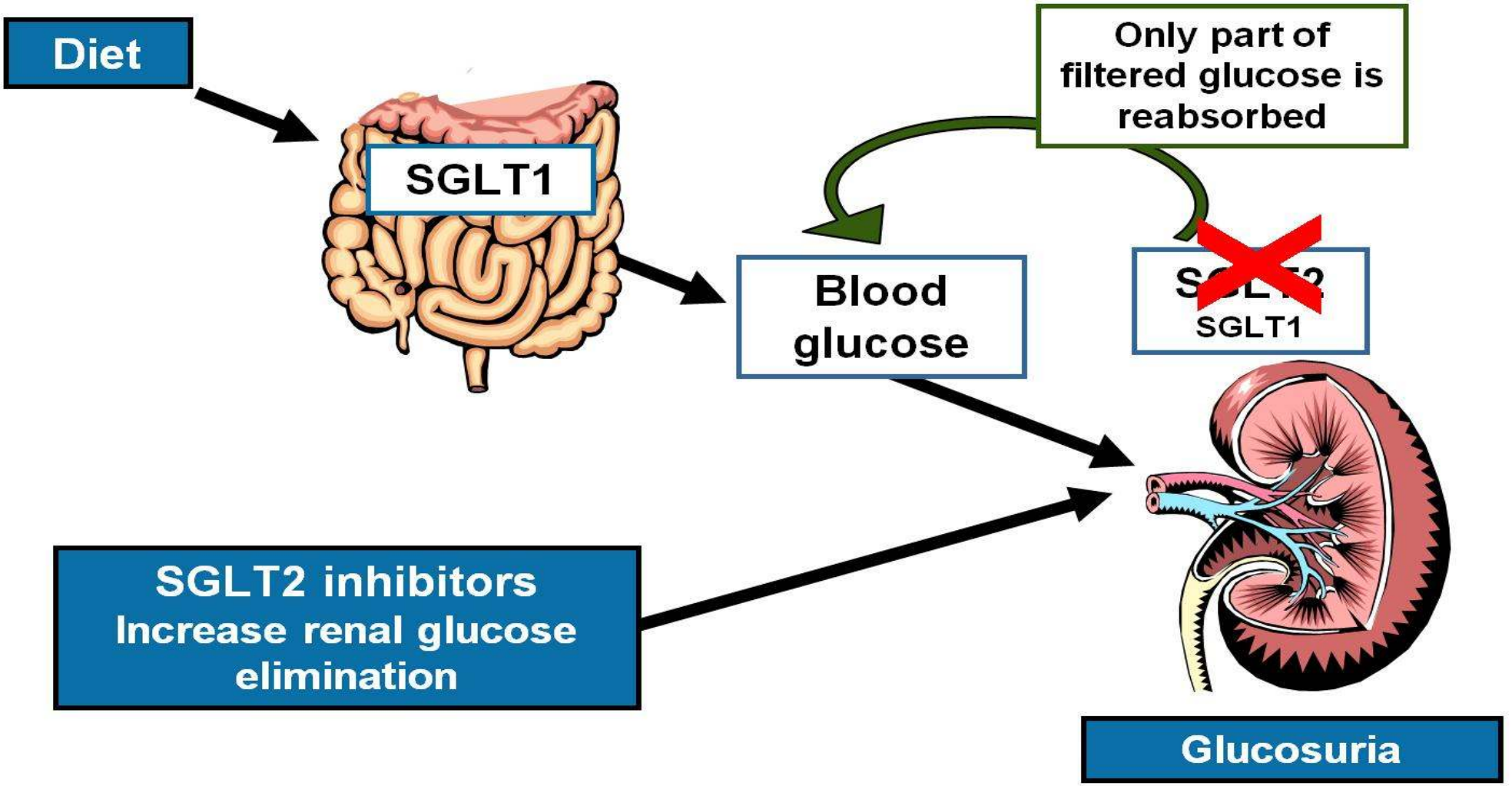
Wright EM, et al. *J Int Med.* 2007;261:32-43.

Sodium Glucose Cotransporters



Courtesy of Clifford J. Bailey.

SGLT2 Inhibitors



Courtesy of Clifford J. Bailey.

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- GLP-1 agoniste Semaglutide Rybelsus

Agents thérapeutiques injectables

- Insulines rapides, ultra rapides, lentes, ultralentes
- Incrétinomimétiques: GLP-1 analogues
- Double GLP-1 + GIP : Tirzepatide
- Association insuline retard + GLP-1 analogues

Insulines rapides

- Actrapid
- Regular
- Insuman rapid solostar
- Apidra solostar
- Humalog KP
- Novorapid FT
- Fiasp FT
- Lyumjev KP

Insulines »intermédiaires »

- Insulatard
- Humuline NPH
- Insuman basal Solostar

Insulines « retard »

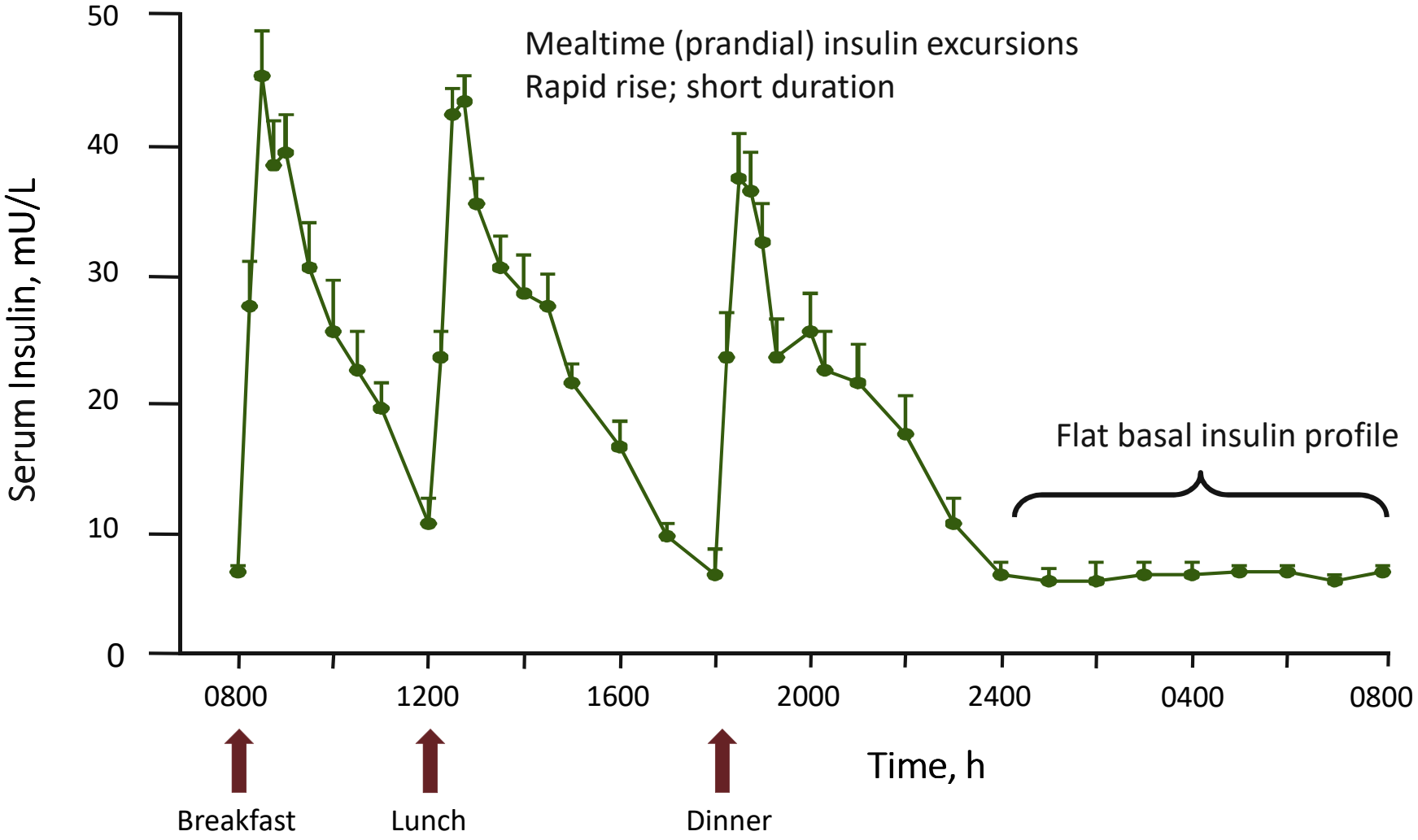
• Lantus	solostar
• Abasaglar	KP
• Levemir	FP
• Toujéo 300	Solo et double star
• Tresiba	Flex touch (2)

Insulines « combinées »

- Ce sont des mélanges d'analogues et d'analogues protaminés
- Novomix 30 50 70 FP

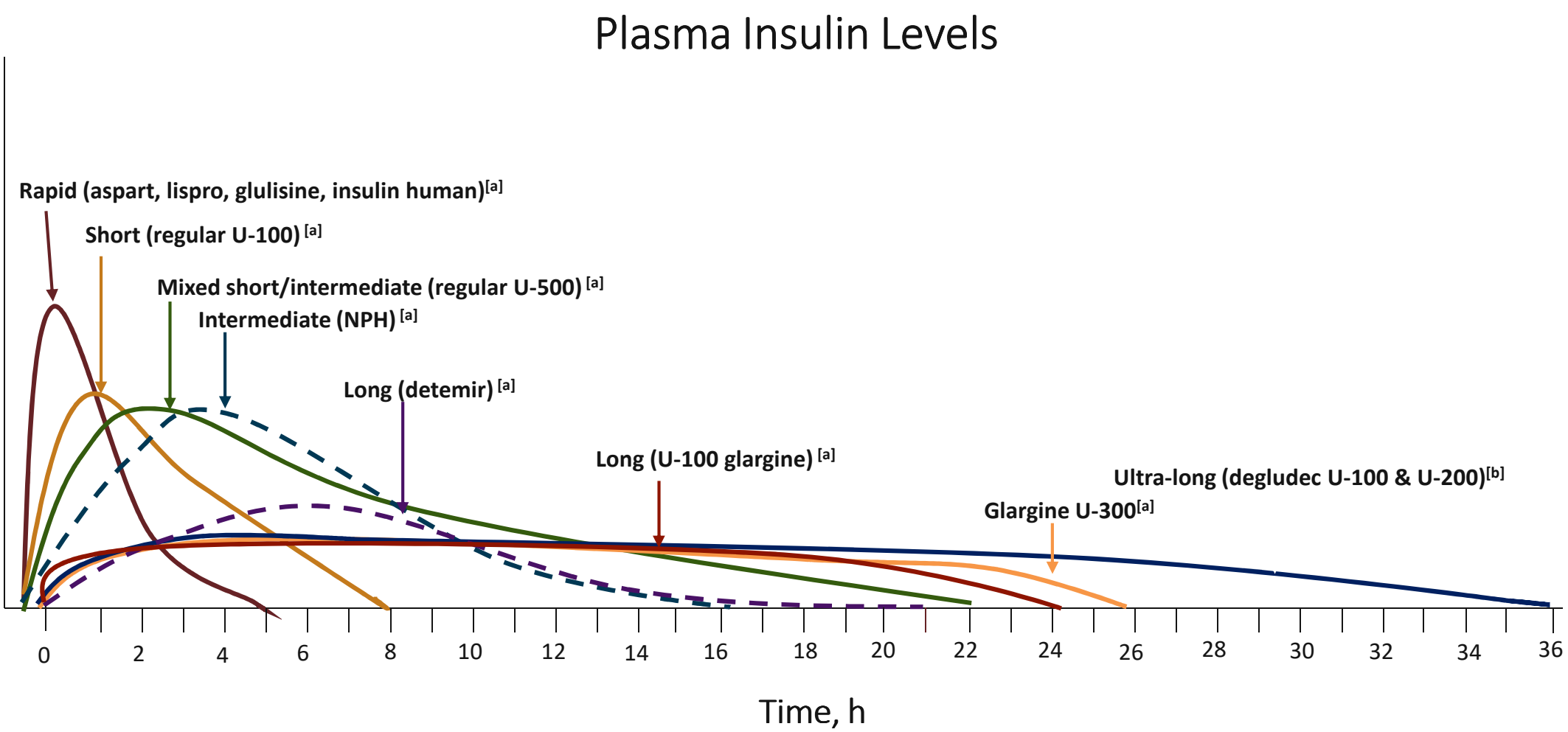
- Humalog mix 25 50 KP

Insulin Replacement Therapy Aims to Recreate the Normal Blood Insulin Profile



Kruszynska YT, et al. *Diabetologia.* 1987;30:16-21.

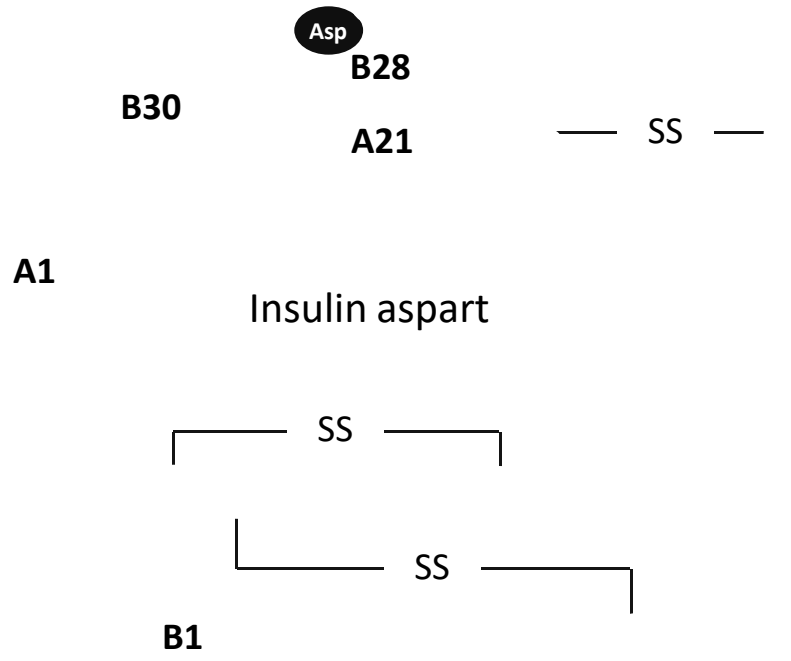
PK Profile of Insulin Replacement Therapy (Schematic Representation)



a. Hirsh IB. *N Engl J Med*. 2005;352:174-183; b. Haahr H, et al. *Clin Pharmacokinet.* 2014;53:787-800.

Faster-Acting Insulin Aspart: A New Formulation of Insulin Aspart

- Insulin aspart: reduced strength of the insulin dimer leading to fast absorption[a]
- Faster-acting insulin aspart is a new formulation of insulin aspart, which contains 2 excipients, nicotinamide and arginine[b]
  - Nicotinamide acts as an absorption modifier; arginine acts as a stabilizing agent
  - Both ingredients are "generally recognized as safe" by the FDA
  - The excipients result in a stable formulation and faster initial absorption after SC injection



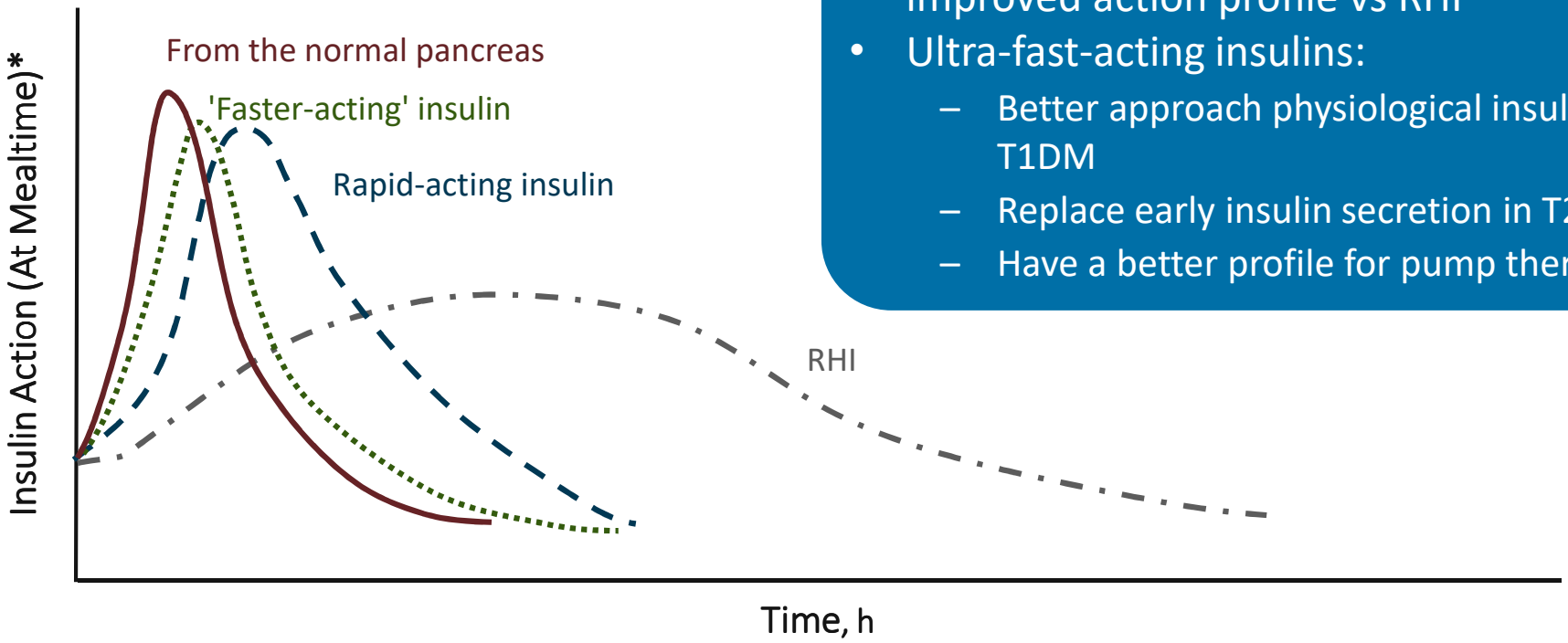
Nicotinamide: absorption modifier

L-Arginine: added for stability

a. Brange J, et al. *Diabetes Care*. 1990;13:923-954.
b. Heise T, et al. *Diabetes Obes Metab*. 2015;17:682-688.

Figure courtesy of Tim Heise, MD.

Ultra-Fast-Acting Insulin: Approaching a More Exact Physiological Insulin Profile

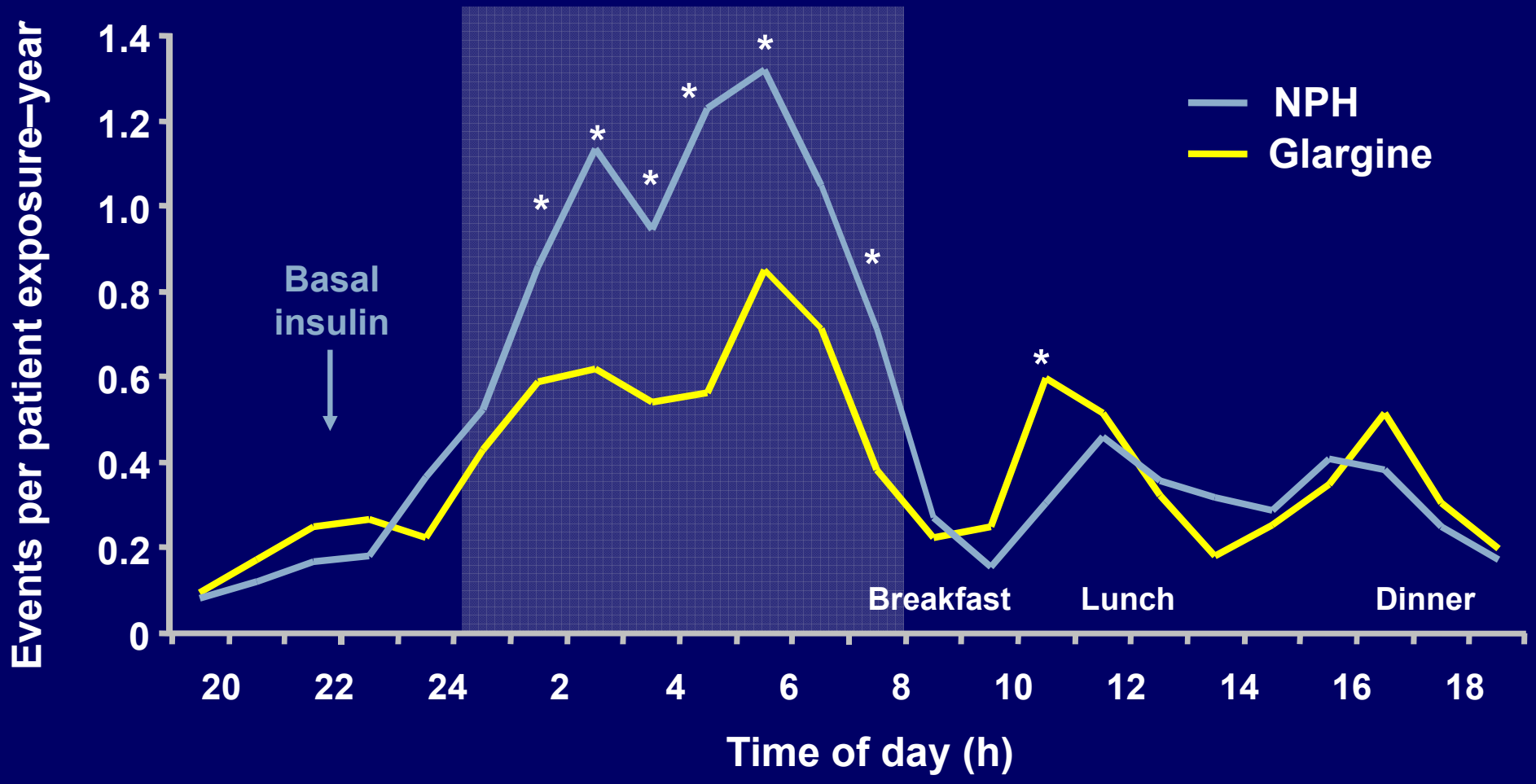


- First-generation rapid-acting insulins had improved action profile vs RHI
- Ultra-fast-acting insulins:
  - Better approach physiological insulin secretion in T1DM
  - Replace early insulin secretion in T2DM
  - Have a better profile for pump therapy

*Schematic representation.

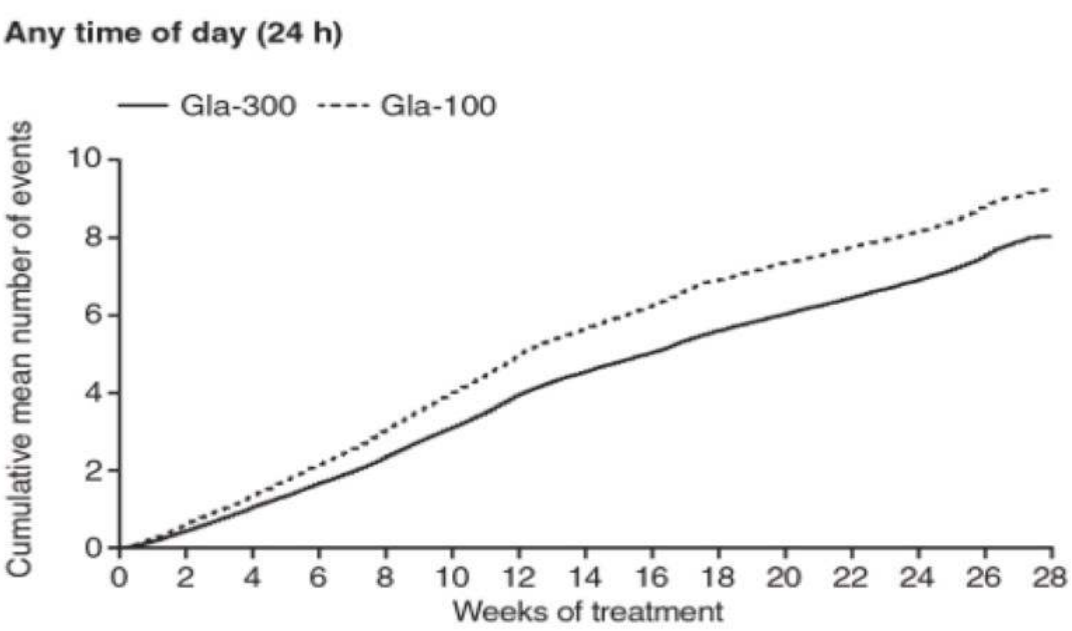
Home PD. *Diabetes Obes Metab.* 2015;17:1011-1020.

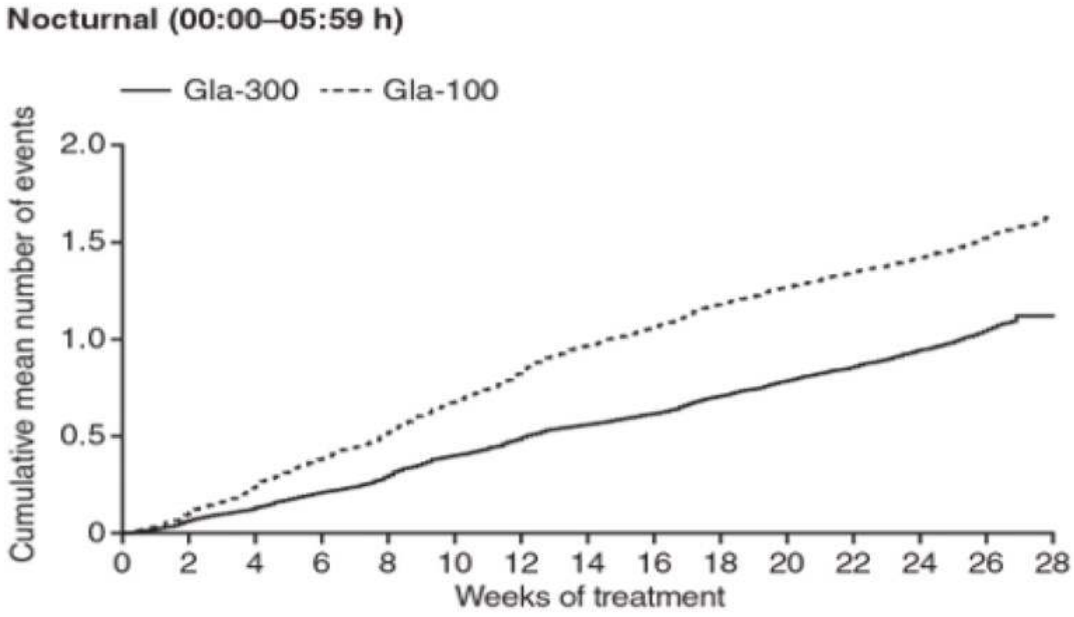
Symptomatic Hypoglycaemic Events: Insulin Glargine vs NPH Insulin



Hypoglycaemia defined as plasma glucose ≤72 mg/dL.
*P<0.05 vs insulin glargine.
NPH=neutral protamine Hagedorn.
Adapted from Riddle M et al. *Diabetes Care.* 2003;26:3080-3086. Used with permission.

EDITION I to III Meta-Analysis: Severe or Confirmed Hypoglycemia ≤ 3.9 mmol/L (70 mg/dL)

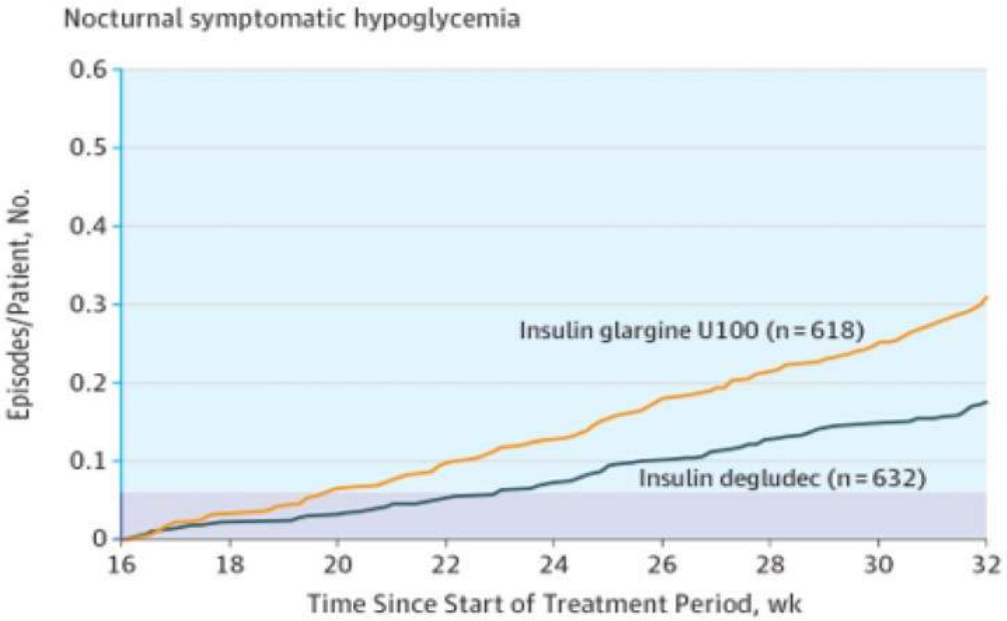




Ritzel R, et al., *Diabetes Obes Metab*, 2015;17:859–67. © 2015 The Authors. Diabetes, Obesity and Metabolism published by John Wiley & Sons Ltd.

SWITCH 2: Nocturnal Symptomatic Hypoglycemia - IDeg Significantly Reduced Nocturnal Symptomatic Hypoglycemia vs IGlar U100

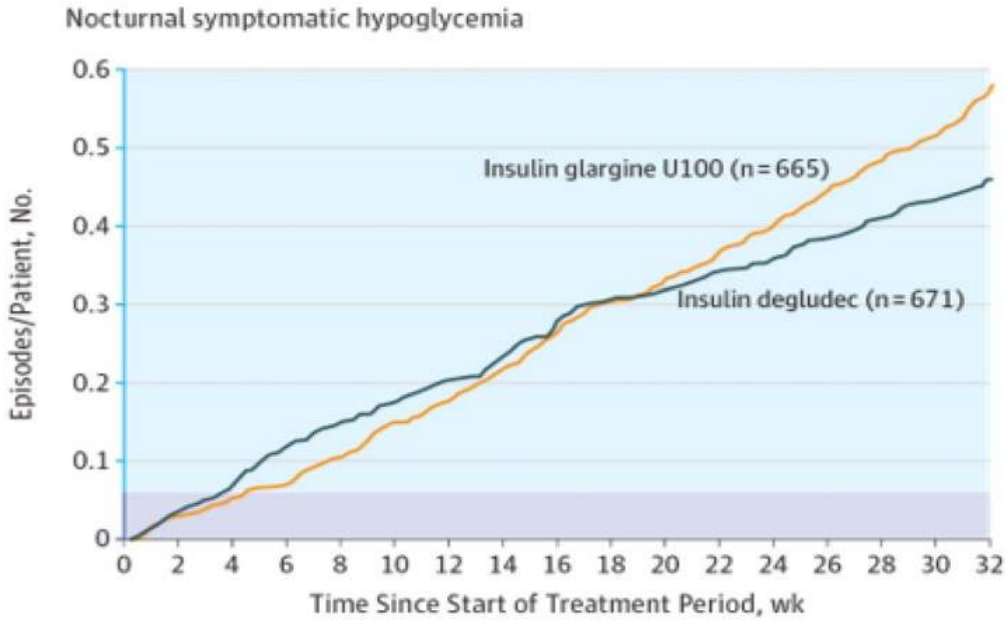
Maintenance Period



No. of patients treated for 1 year with IDeg vs IGlar U100 to experience **1** fewer event:

3

Full Treatment Period



No. of patients treated for 1 year with IDeg vs IGlar U100 to experience **1** fewer event:

5

En résumé…

- Commencer l'insuline plus tôt
- Utiliser des algorithmes faciles
- Impliquer le patient à l'auto injection et à recourir aux stylos
- Commencer avec une injection au coucher
- Utiliser l'auto contrôle glycémique au lever (FFF)
- Inscrire le patient dans un trajet de soins en utilisant les facilités du réseau local multidisciplinaire

Agents thérapeutiques injectables

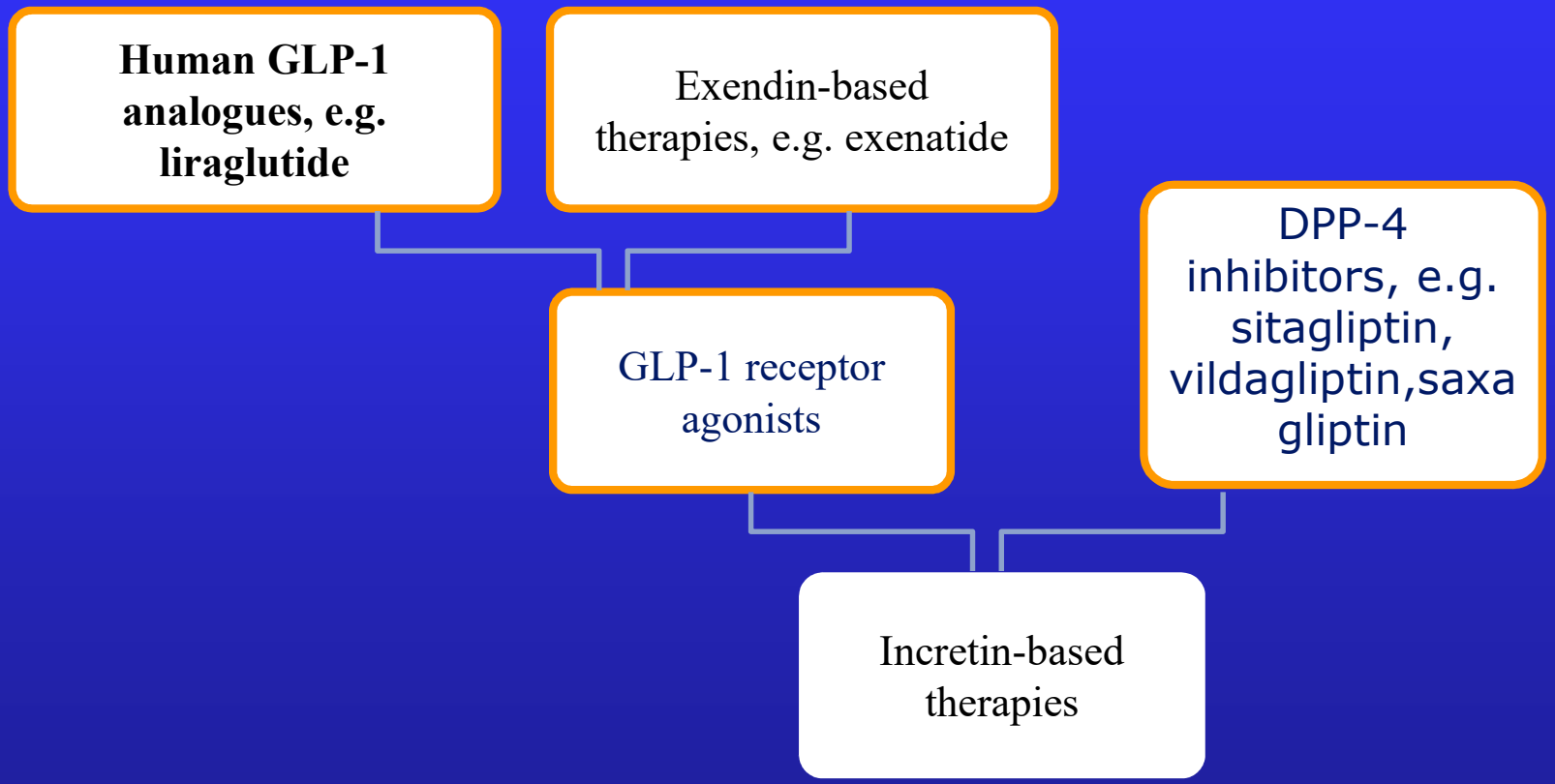
- Insulines rapides, ultra rapides, lentes, ultralentes
- Incrétinomimétiques: GLP-1 analogues
- Double GLP-1 + GIP : Tirzepatide
- Association insuline retard + GLP-1 analogues

Development of Exenatide: An Incretin Mimetic

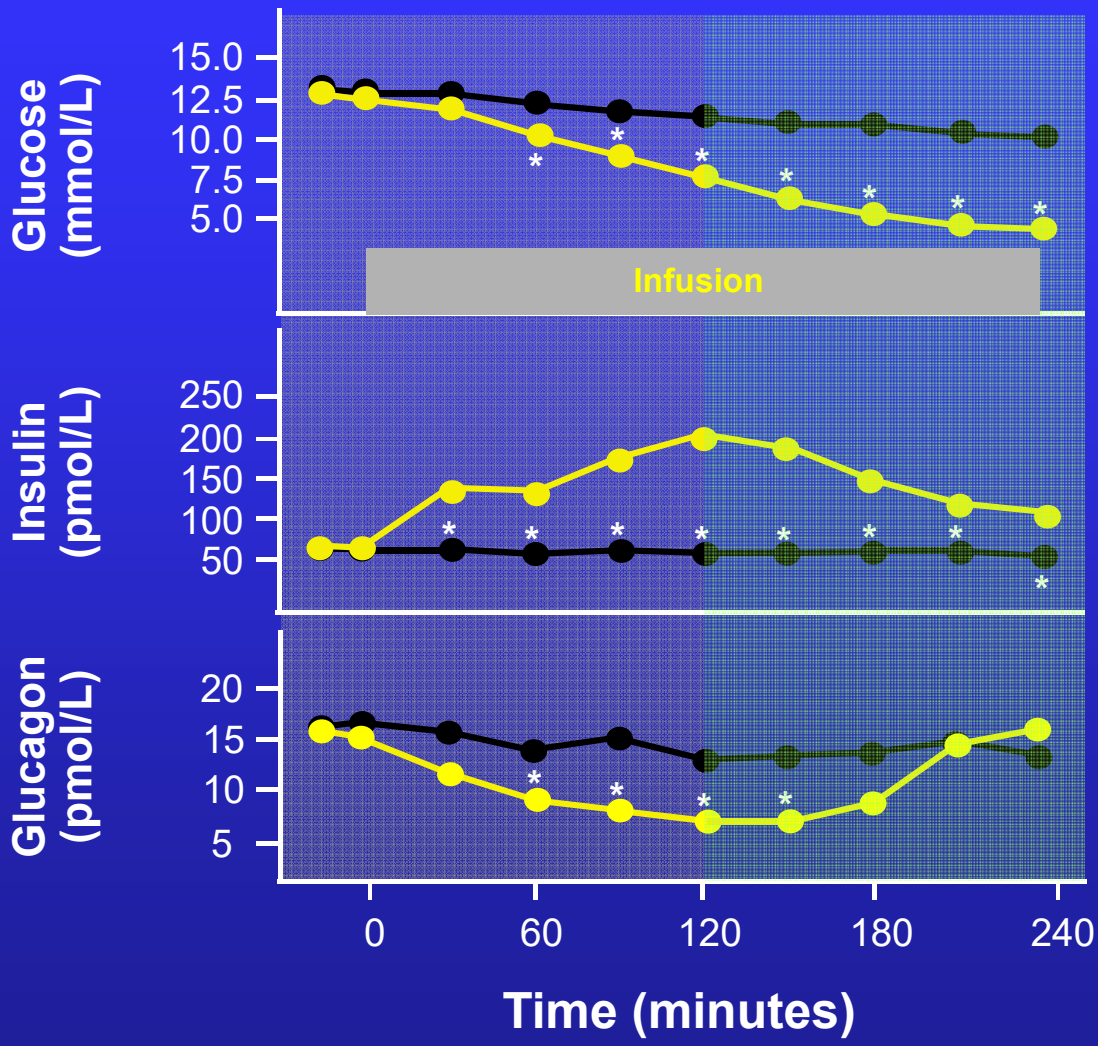
Exenatide (Exendin-4)

- Synthetic version of salivary protein found in the Gila monster
- Approximately 50% identity with human GLP-1
- Resistant to DPP-4 inactivation

The family of incretin-based therapies



Effects of GLP-1 on Insulin and Glucagon Shown to Be Glucose Dependent in Type 2 Diabetes



With hyperglycemia GLP-1 stimulated insulin and suppressed glucagon.

When glucose levels approached normal, insulin levels declined and glucagon was no longer suppressed.

N=10 patients with type 2 diabetes. Patients were studied on two occasions. A regular meal and drug schedule was allowed for one day between the experiments with GLP-1 and placebo.

***p<0.05 GLP-1 vs. placebo**

Adapted from Nauck MA et al *Diabetologia* 1993;36:741–744.

Agents thérapeutiques injectables

- Insulines rapides, ultra rapides, lentes, ultralentes
- Incrétinomimétiques: GLP-1 analogues
- Double GLP-1 + GIP : Tirzepatide
- Association insuline retard + GLP-1 analogues

Mecanism of Action

Glucagon-like peptide-1 receptor agonism

Central nervous system

- ↑ Satiety
- ↑ Nausea
- ↓ Food intake
- ↓ Body weight

Pancreas

- ↑ Insulin
- ↓ Glucagon

Stomach

- ↓ Gastric emptying

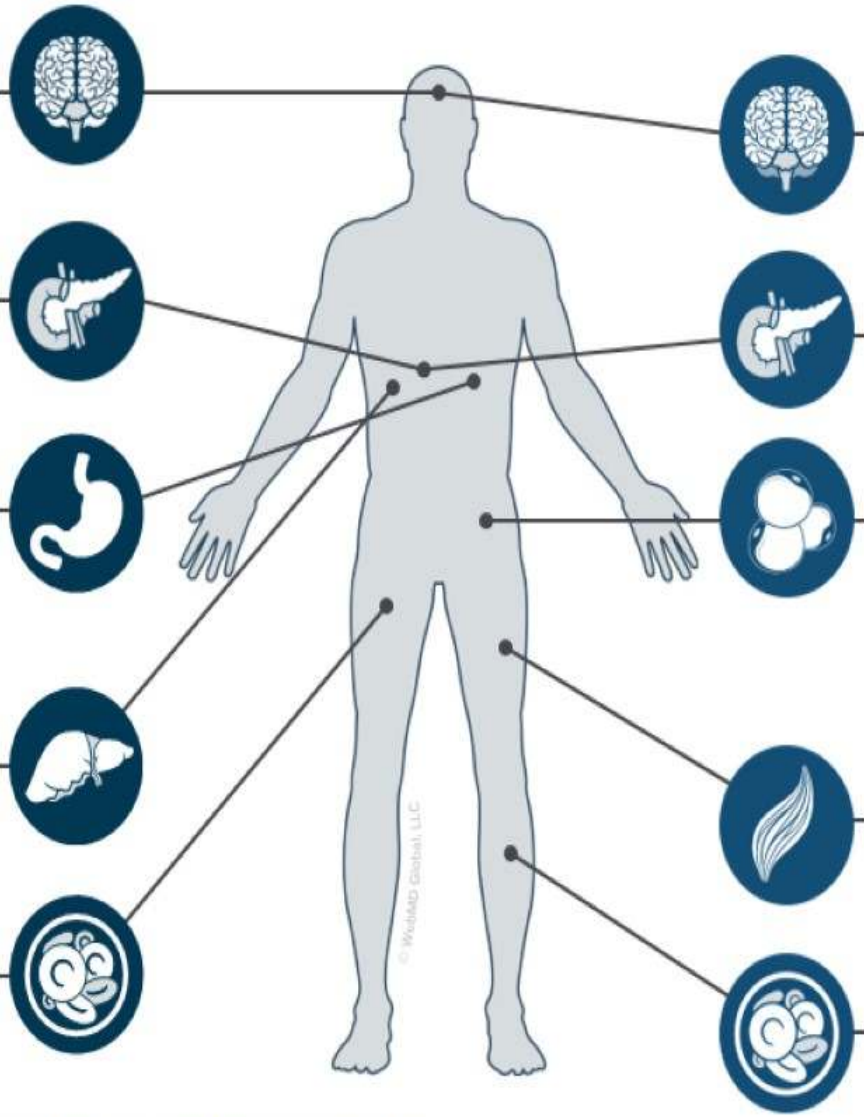
Indirect action

Liver

- ↑ Insulin sensitivity
- ↓ Hepatic glucose production
- ↓ Ectopic lipid accumulation

Systemic

- ↓ Hyperglycemia



Glucose-dependent insulinotropic polypeptide receptor agonism

Central nervous system

- ↓ Nausea
- ↓ Food intake
- ↓ Body weight

Pancreas

- ↑ Insulin
- ↑ Glucagon

Adipose tissue

- ↑ Insulin sensitivity
- ↑ Lipid buffering capacity
- ↑ Blood flow
- ↑ Storage capacity
- ↓ Proinflammatory immune cell infiltration

Skeletal Muscle

- ↑ Insulin sensitivity
- ↑ Metabolic flexibility
- ↓ Ectopic lipid accumulation

Systemic

- ↓ Hyperglycemia
- ↓ Dietary triglyceride

Baggio LL, et al. Gastroenterol 2007;132:2131-57; Niswender KD. Postgrad Med 2011;123:27-37.

Agents thérapeutiques injectables

- Insulines rapides, ultra rapides, lentes, ultralentes
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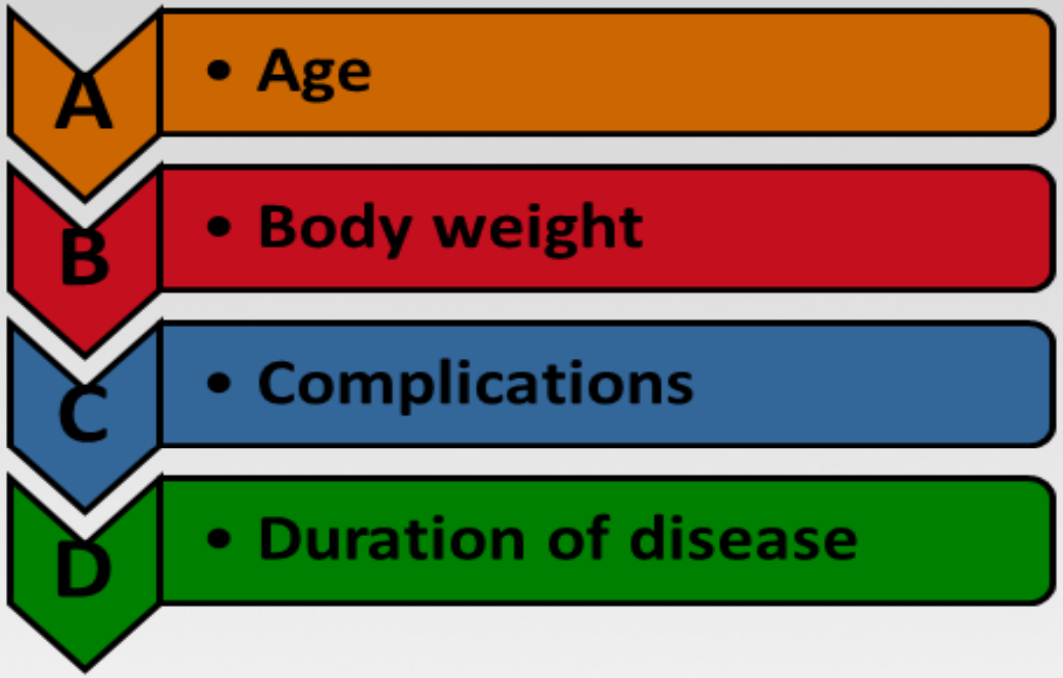
- Association insuline retard + GLP-1 analogues

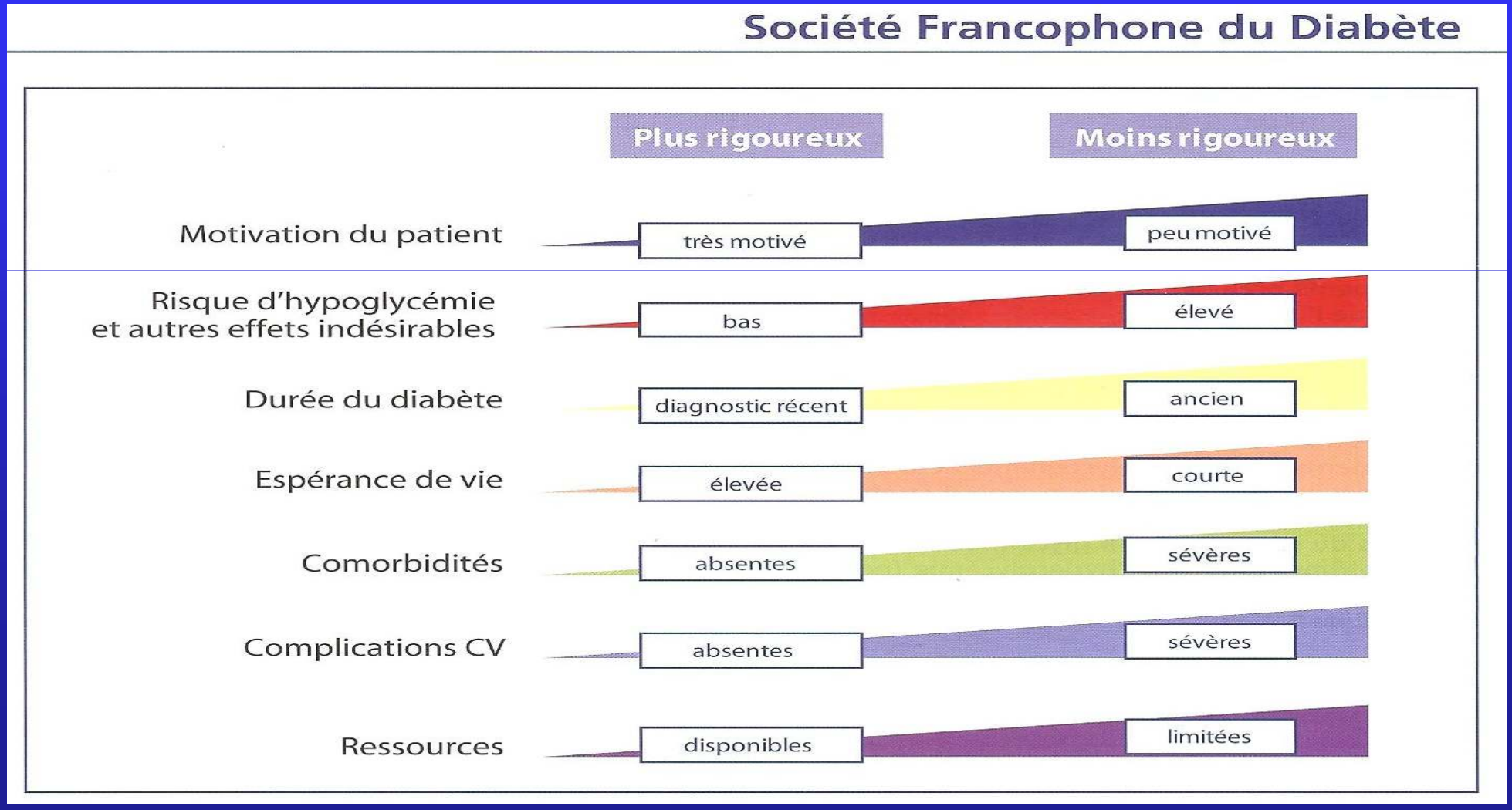
ABCs of Individualization in Patients With T2DM: Factors to Consider When Selecting a Glycemic Target



- HbA1c < 7.0% for most; individualization is key
  - Tighter targets (6.0%-6.5%) for younger, healthier patients
  - Looser targets (7.5%-8.0%) for older patients, those with comorbidities, and those prone to hypoglycemia

Inzucchi SE, et al. *Diabetologia*. 2012;55(6):1577-1596.

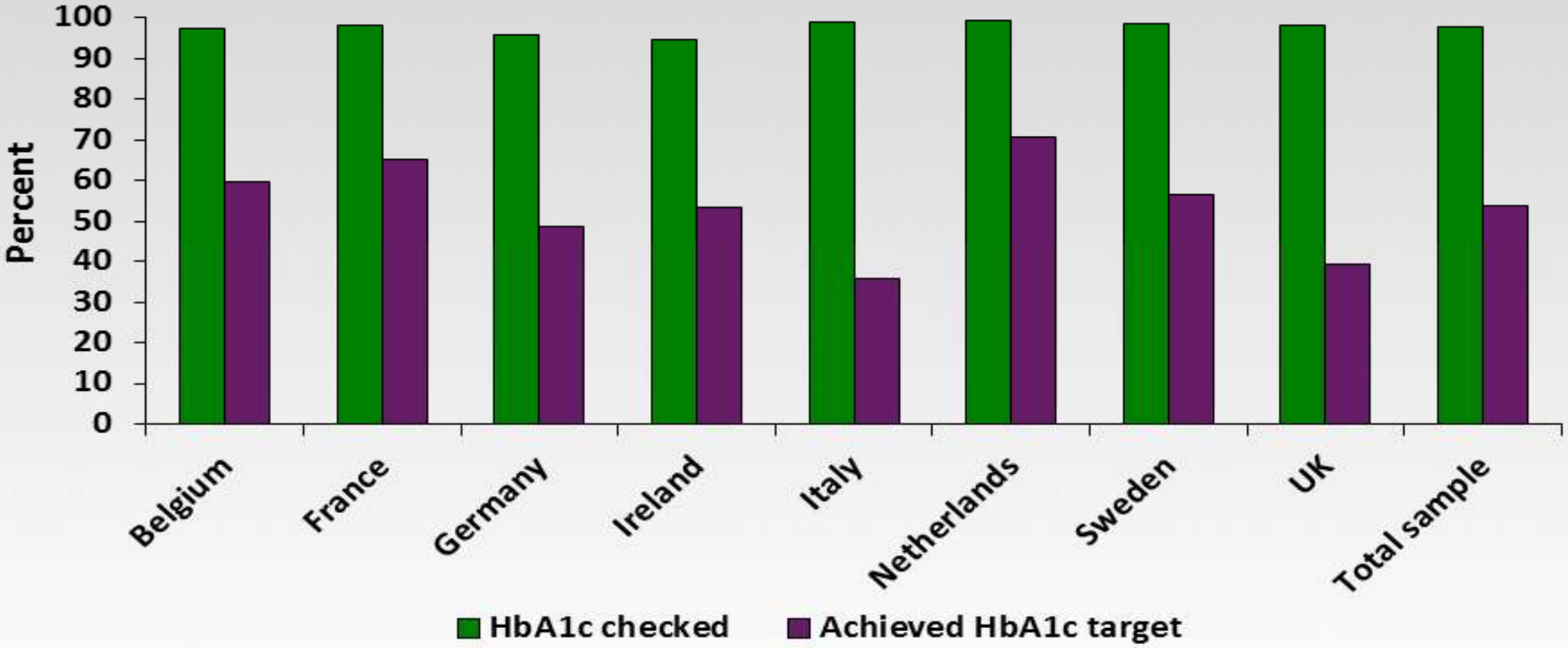
Comment individualiser le traitement?



A Significant Proportion of T2D Patients Fail to Reach Target HbA1c Despite Advances in Treatment

GUIDANCE Study: 7597 T2D patients

Gap exists between checking HbA1C and achieving target HbA1C <7%



GUIDANCE = Guideline Adherence to Enhance Care

LIPID & METABOLIC

Stone MA, et al. *Diabetes Care*. 2013;36(9):2628-2638.

Medscape EDUCATION

Multiple Barriers to Effective T2D Treatment Exist

- Weight gain, either from lifestyle or antidiabetic medication[a]
- Rates and fear of hypoglycemia due to use of certain classes of antidiabetic therapies[b]
- Poor adherence to therapy[c]
- Clinical inertia around the progressive nature of T2D and eventual requirement for insulin[d,e]

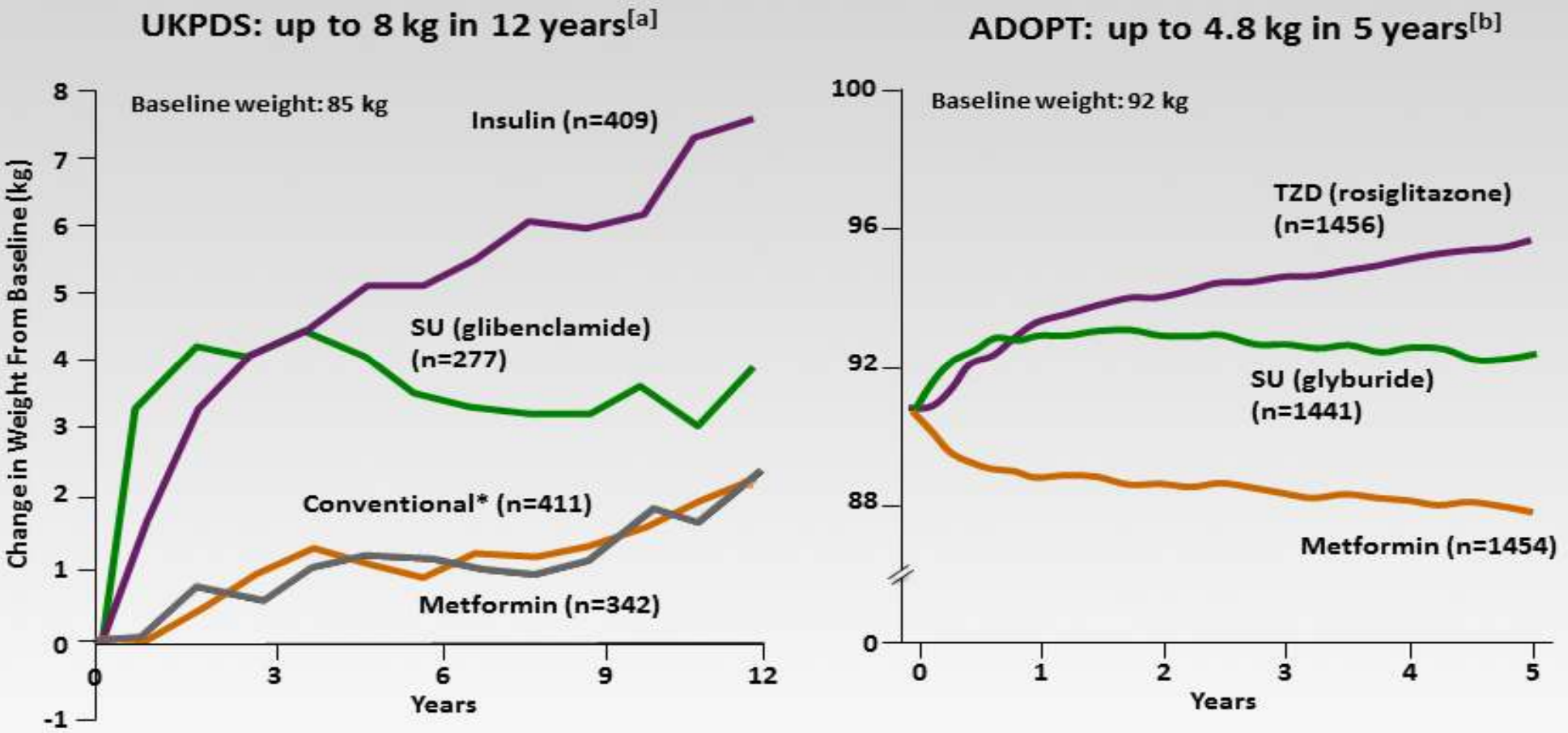
a. UKPDS Group. *Lancet.* 1998;352(9131):854-865.
b. Amiel SA, et al. *Diabet Med.* 2008;25(3):245-254.
c. Guisasola AF. *Diabetes Obes Metab.* 2008;10(Suppl 1):25-32.
d. Weyer C, et al. *J Clin Invest.* 1999;104(6):787-794.
e. Khunti K, et al. *Diabetes Care.* 2013;36(11):3411-3417.

ADVANCE Study: Association Between Severe Hypoglycemia and Cardiovascular Outcomes

Event	Patients With Severe Hypoglycemia (%)	Patients Without Severe Hypoglycemia (%)	Adjusted HR (95% CI)
Major macrovascular events	15.9	10.2	3.5 (2.4-5.2)
Major microvascular events	11.5	10.1	2.2 (1.4-3.5)
Death from any cause	19.5	9.0	3.3 (2.3-4.7)
Cardiovascular disease	9.5	4.8	3.8 (2.4-6.1)
Noncardiovascular disease	10.0	4.3	2.8 (1.6-4.8)

Zoungas S, et al. *N Engl J Med.* 2010;363(15):1410-1418.

Many Current Antihyperglycemic Agents Result in Weight Gain Over Time



ADOPT = A Diabetes Outcome Progression Trial; TZD = thiazolidinedione
*Conventional treatment = diet initially, then SUs, insulin, and/or metformin if fasting plasma glucose >15 mmol/L.

LIPID & METABOLIC

a. UKPDS Group. *Lancet.* 1998;352(9131):854-865.
b. Kahn SE, et al. *N Engl J Med.* 2006;355(23):2427-2443.

Medscape EDUCATION

Rates of Nonadherence and Associated Outcomes Among People With T2D

- 13%-64% of oral agent users and 19%-46% of insulin users are nonadherent.[a-c]
- Medication nonadherence is associated with adverse outcomes.[c]

Outcome	Adherent Patients	Nonadherent Patients	*P* Value
All-cause mortality (%)	4.0	5.9	<.001
All-cause hospitalization (%)	19.2	23.2	<.001
Mean systolic BP (mm Hg)	131.4	132.1	.09
Mean diastolic BP (mm Hg)	74.2	75.8	<.001
LDL-C (mm/dL)	85.5	98.2	<.001
HbA1c (%)	7.7	8.1	<.001

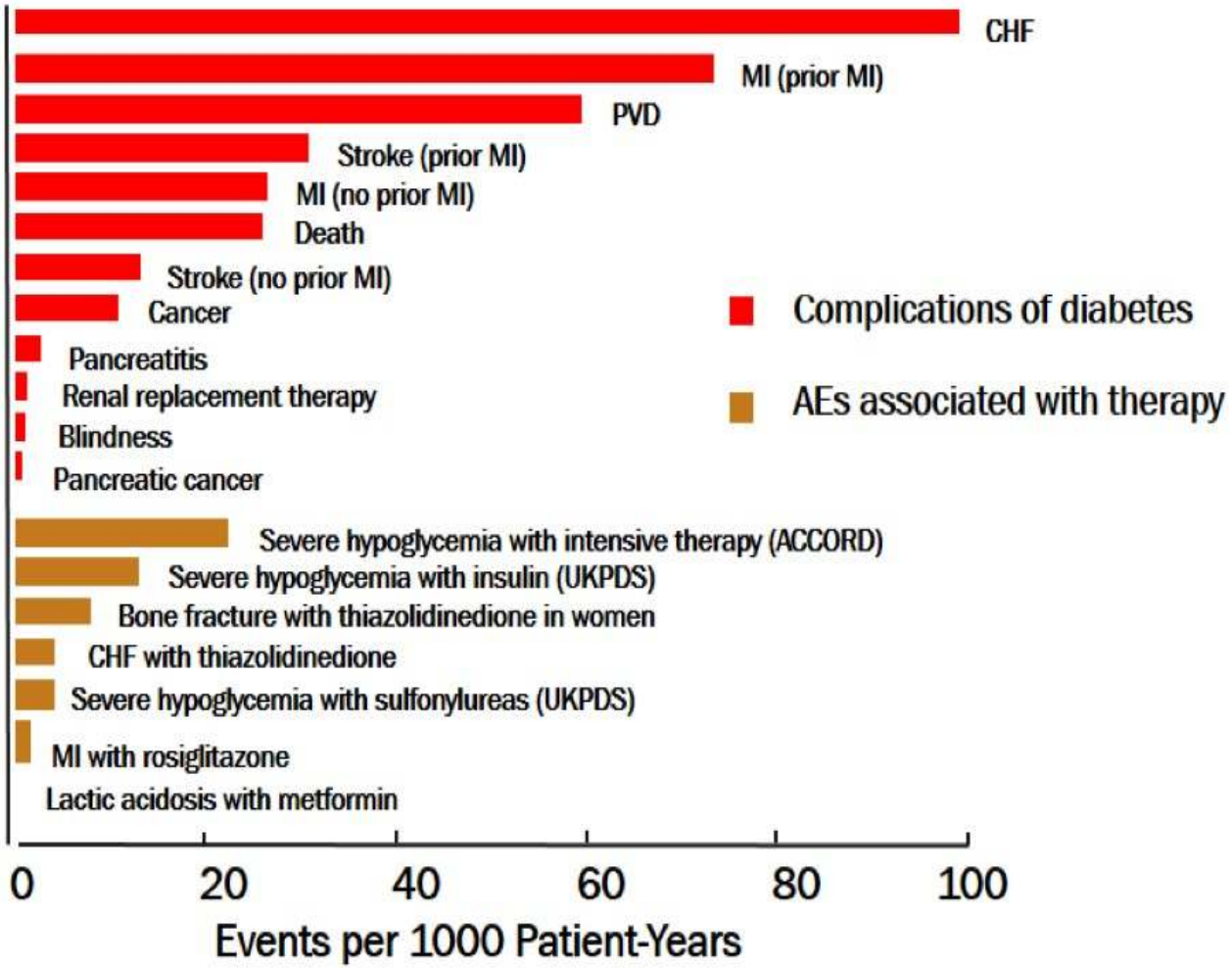
BP = blood pressure; LDL-C = low-density lipoprotein-cholesterol

a. Lee WC, et al. *Manag Care Interface.* 2006;19(7):31-41.
b. Cramer JA. *Diabetes Care.* 2004;27(5):1218-1224.
c. Ho PM, et al. *Arch Intern Med.* 2006;166(17):1836-1841.

Résumé des effets cardio vasculaires des différentes molécules

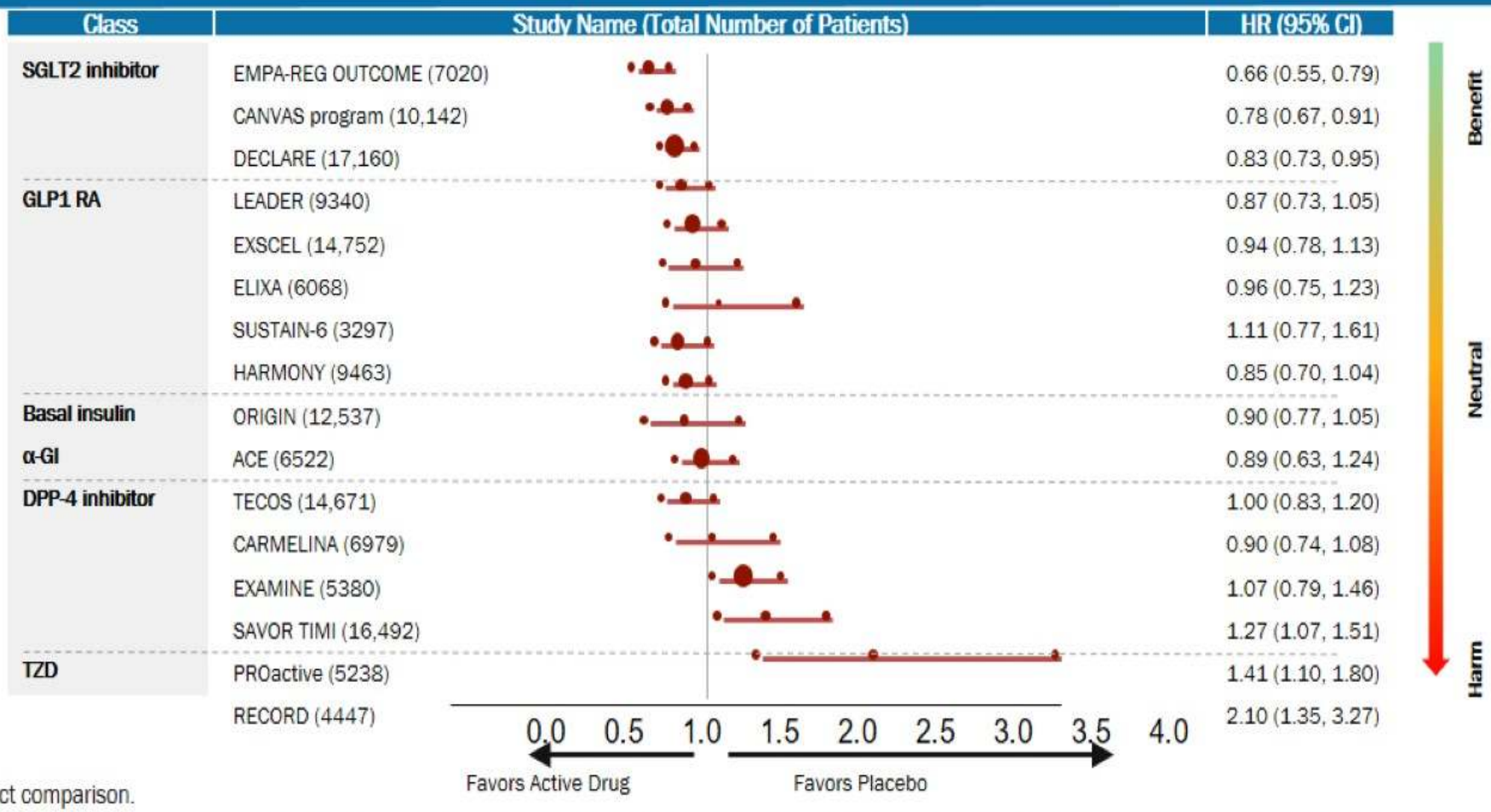
• Metformine	Favorable
• Sulfamidés	Défavorables
• Glinide (novonorm)	?
• Actos	Légèrement favorable
• Inhibiteurs de DPP4	Neutres
• Gliflozines	Très favorables
• Agonistes GLP-1	Très favorables
• Insuline	Neutre

Absolute Risks of Diabetes and its Therapy



Bailey CJ. *Clin Pharmacol Therap*. 2015;98:185-195. Slide courtesy of Clifford J. Bailey, PhD.

HF Effects of Glucose-Lowering Drugs Are Class/Molecule-Specific



Not intended for direct comparison.

Zinman B, et al. *N Engl J Med.* 2015;373:2117-2128; Rosenstock J, et al. *JAMA.* 2019;321:69-79; Neal B, et al. *N Engl J Med.* 2017;377:644-657; Wiviott SD, et al. *N Engl J Med.* 2019;380:347-357; Marso SP, et al. *N Engl J Med.* 2016;375: 311;Holman RR, et al. *N Engl J Med.* 2017;377:1228-1239; Pfeffer MA, et al. *N Engl J Med.* 2015;373:2247-2257; Marso SP, et al. *N Engl J Med.* 2016;375:1834-1844; Hernandez AF, et al. *Lancet.* 2018;392:1519-1529; ORIGIN Trial Investigators. *N Engl J Med.* 2012;367:309-318; Holman RR, et al. *Lancet Diabetes Endocrinol.* 2017;5:877-886; Green JB, et al. *N Engl J Med.* 2015;373:232-242; Zannad F, et al. *Lancet.* 2015;385:2067-2076; Scirica BM, et al. *N Engl J Med.* 2013;369:1317-1326; Erdmann E, et al. *Diabetes Care.* 2007;30:2773-2778; Home PD, et al. *Lancet.* 2009;373:2125-2135.


SERAIT-CE TROP DE DEMANDER DE PARLER D'AUTRE CHOSE QUE DE FOOT, PENDANT 45 MINUTES?...
TOUTE UNE MI-TEMPS?...

Les conventions hospitalières pour diabétiques

- Convention d'autocontrôle adultes
- Convention enfants
- Convention pompes
- Convention pied diabétique

Autres conventions hospitalières

- Enfants diabétiques
- Patients traités par pompes à insuline
- Patients suivis pour lésions du pied

Convention d'autocontrôle glycémique

- > 16 ans et DMG
- Groupe A: Type 1 ou pancréatectomisés, mucoviscidose ou MODY à 3 piqûres

- Groupe B : Type 2 à 3 injections, diabète gestationnel à l'insuline, diabétiques transplantés ou dialysés à l'insuline

Convention d'autocontrôle glycémique

- Groupe C: Type 2 à 2 injections plus multimorbidité
- Diabétiques transplantés ou dialysés sans insuline
- Diabète gestationnel sans insuline
- Femmes diabétiques souhaitant une grossesse sans insuline

Convention capteurs glycémiques

- Type 1
- Pancréatectomisés ou Cpeptide négatifs
- Mucoviscidose sous insuline ou ADO
- MODY 3 injections
- Insulinomes et autres hypoglycémies sévères

Merci pour votre attention