L’insulinothérapie en 2018

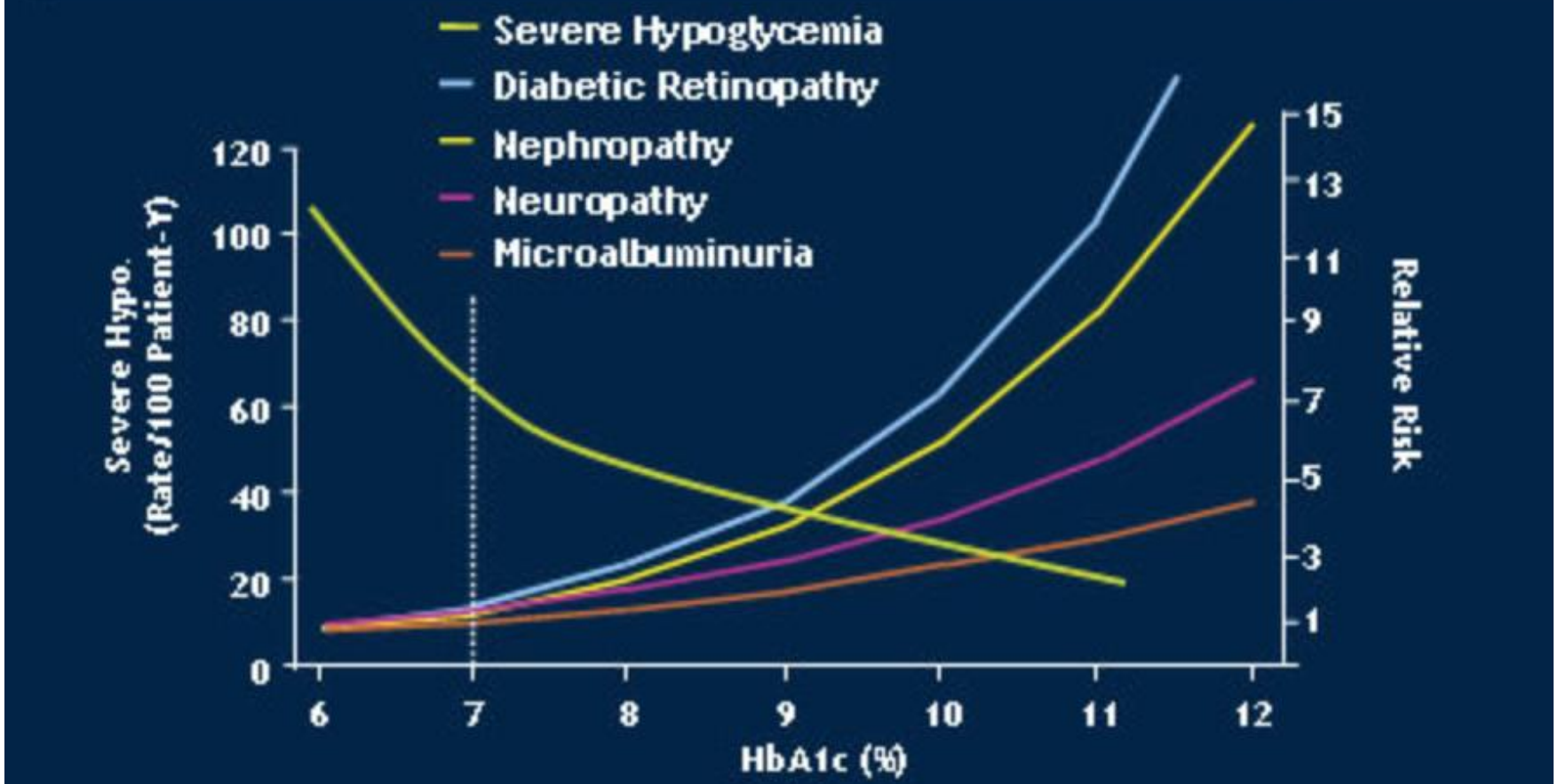
SMAV 2018

Prof. Jean-Christophe Philips
Service de Diabétologie
CHU Liège – CHR East Belgium

Quelles nouveautés ?

- Les nouvelles insulines et nouvelles formulations
- Les associations fixes d’insuline avec un analogue GLP-1

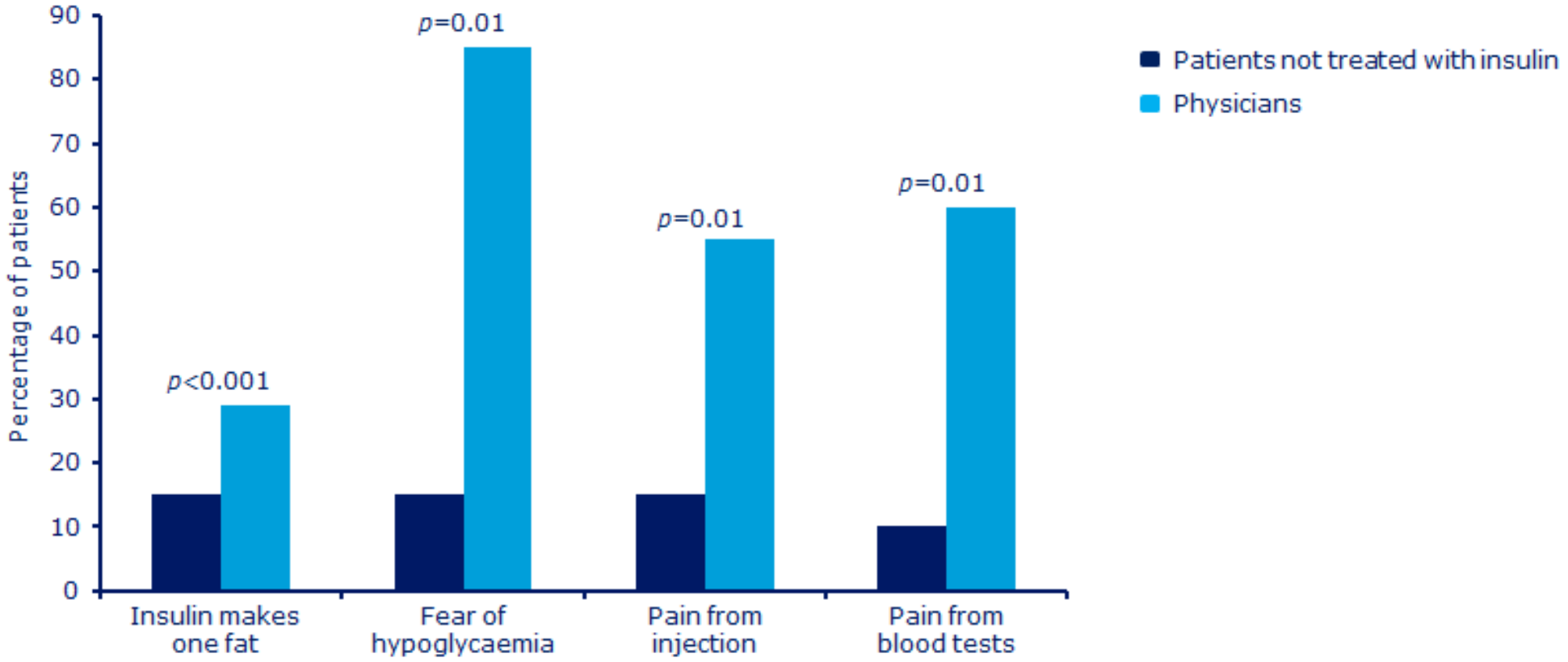
Risk of Progression of Complications: DCCT Study



DCCT = Diabetes Control and Complications Trial.

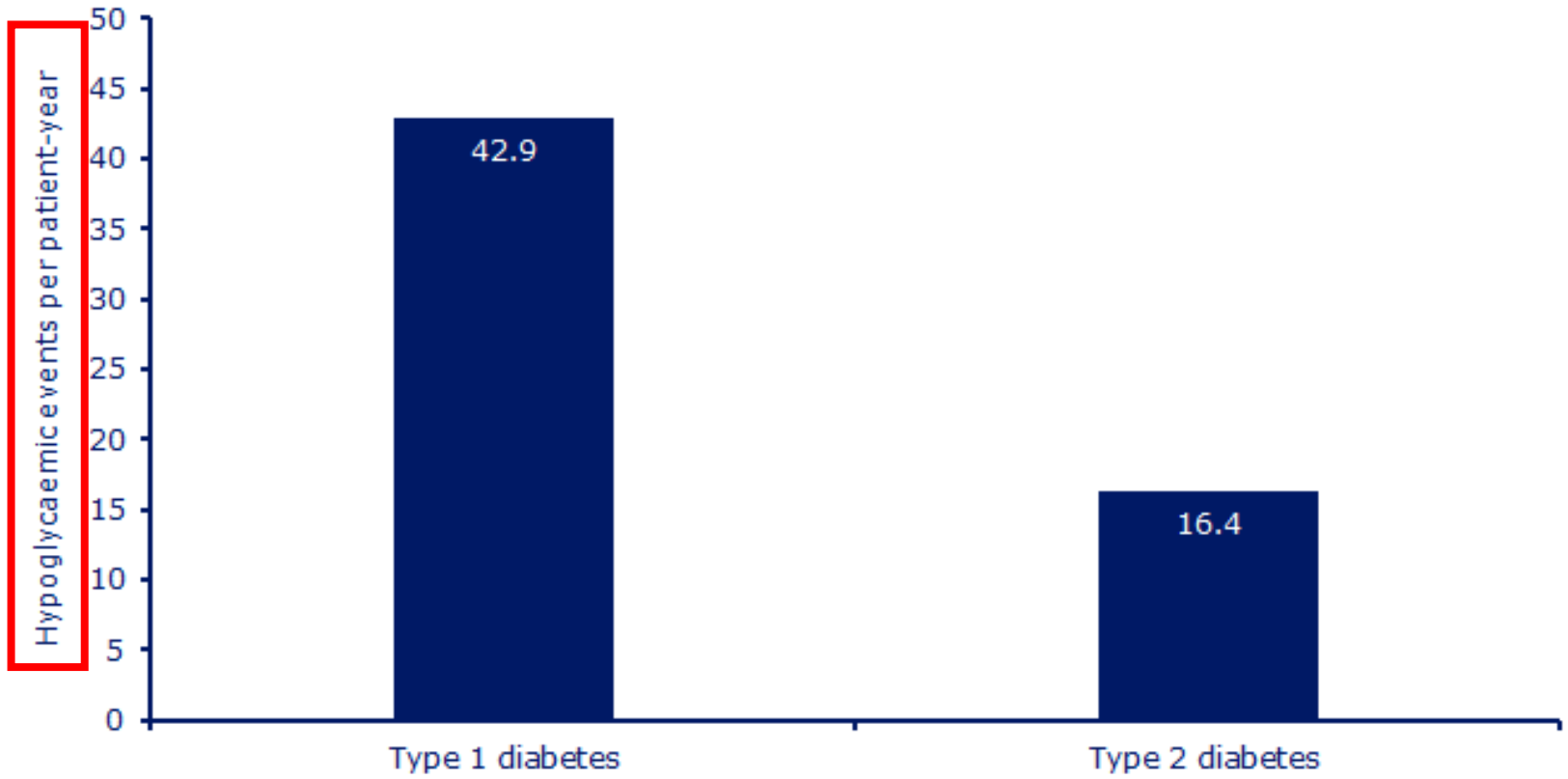
Skyler JS. Endocrinol Metab Clin North Am. 1996;25:243-254. [Evidence Level C]

Qui a peur de quoi en instaurant l'insuline ?



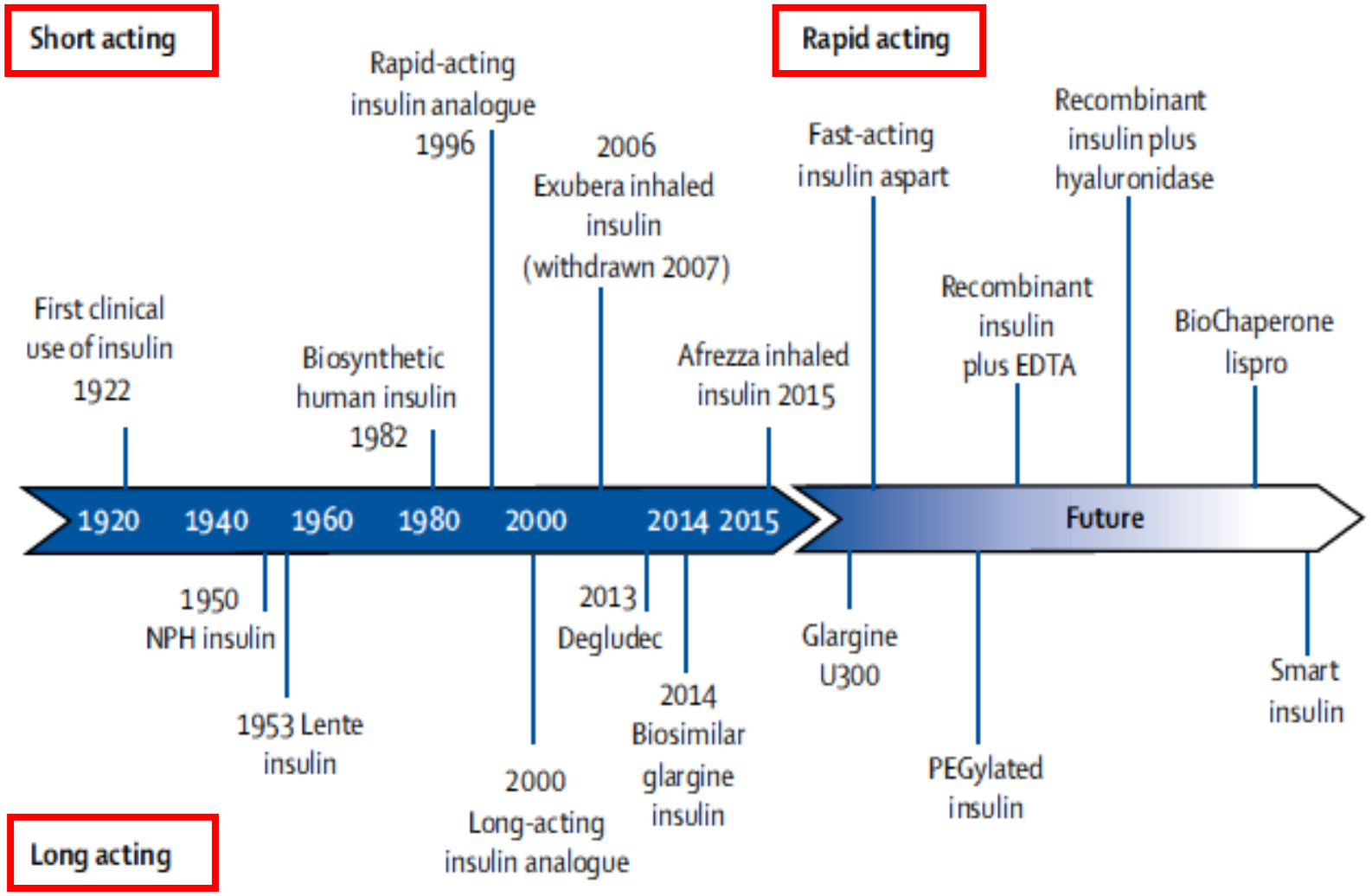
Nakar *et al*. *J Diabetes Complications* 2007;21:220–6

Fréquence des hypos chez les diabétiques



n=267

Donnelly *et al*. *Diabet Med* 2005;22:749–55



*Avivit Cahn, Roberto Miccoli, Angela Dardano, Stefano Del Prato**

Lancet Diabetes Endocrinol
2015; 3: 638–52

Diabetes Care 1

Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Melanie J. Davies,[1,2] David A. D'Alessio,[3] Judith Fradkin,[4] Walter N. Kernan,[5] Chantal Mathieu,[6] Geltrude Mingrone,[7,8] Peter Rossing,[9,10] Apostolos Tsapas,[11] Deborah J. Wexler,[12,13] and John B. Buse[14]

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[6]Clinical and Experimental Endocrinology, UZ Gasthuisberg, KU Leuven, Leuven, Belgium
[7]Department of Internal Medicine, Catholic University, Rome, Italy
[8]Diabetes and Nutritional Sciences, King's College London, London, U.K.
[9]Steno Diabetes Center Copenhagen, Gentofte, Denmark
[10]University of Copenhagen, Copenhagen, Denmark
[11]Second Medical Department, Aristotle University Thessaloniki, Thessaloniki, Greece
[12]Department of Medicine and Diabetes Unit, Massachusetts General Hospital, Boston, MA
[13]Harvard Medical School, Boston, MA
[14]Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, NC

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M.J.D. and J.B.B. were co-chairs for the Consensus Statement Writing Group. D.A.D'A., J.F., W.N.K., and D.J.W. were the writing group members for the American Diabetes Association. C.M., G.M., P.R., and A.T. were writing group members for the European Association for the Study of Diabetes.

This article is being simultaneously published in Diabetes Care and Diabetologia by the American Diabetes Association and the European Association for the Study of Diabetes.

CONSENSUS REPORT

Diabetologia
https://doi.org/10.1007/s00125-018-4729-5

CONSENSUS REPORT

Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Melanie J. Davies[1,2] · David A. D'Alessio[3] · Judith Fradkin[4] · Walter N. Kernan[5] · Chantal Mathieu[6] · Geltrude Mingrone[7,8] · Peter Rossing[9,10] · Apostolos Tsapas[11] · Deborah J. Wexler[12,13] · John B. Buse[14]

Abstract
The American Diabetes Association and the European Association for the Study of Diabetes convened a panel to update the prior position statements, published in 2012 and 2015, on the management of type 2 diabetes in adults. A systematic evaluation of the literature since 2014 informed new recommendations. These include additional focus on lifestyle management and diabetes self-management education and support. For those with obesity, efforts targeting weight loss, including lifestyle, medication and surgical interventions, are recommended. With regards to medication management, for patients with clinical cardiovascular disease, a sodium–glucose cotransporter-2 (SGLT2) inhibitor or a glucagon-like peptide-1 (GLP-1) receptor agonist with proven cardiovascular benefit is recommended. For patients with chronic kidney disease or clinical heart failure and atherosclerotic cardiovascular disease, an SGLT2 inhibitor with proven benefit is recommended. GLP-1 receptor agonists are generally recommended as the first injectable medication.

Keywords Cardiovascular disease · Chronic kidney disease · Costs · Glucose-lowering therapy · Guidelines · Heart failure · Hypoglycaemia · Patient-centred care · Type 2 diabetes mellitus · Weight management

Abbreviations

ARR	Absolute risk reduction
ASCVD	Atherosclerotic cardiovascular disease
CANVAS	Canagliflozin Cardiovascular Assessment Study
CKD	Chronic kidney disease
CVD	Cardiovascular disease
CVOT	Cardiovascular outcomes trial
DKA	Diabetic ketoacidosis
DPP-4	Dipeptidyl peptidase-4
DPP-4i	Dipeptidyl peptidase-4 inhibitor
DSMES	Diabetes self-management education and support
EMPA-REG OUTCOME	Empagliflozin, Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients
ESRD	End-stage renal disease
EXSCEL	Exenatide Study of Cardiovascular Event Lowering
GLP-1	Glucagon-like peptide-1
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
HF	Heart failure
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of of Cardiovascular Outcomes Results
MACE	Major adverse cardiac events
MI	Myocardial infarction
MNT	Medical nutrition therapy
RCT	Randomised clinical trial
SGLT2	Sodium–glucose cotransporter-2

M. J. Davies and J. B. Buse were co-chairs for the Consensus Statement Writing Group. D. A. D'Alessio, J. Fradkin, W. N. Kernan and D. J. Wexler were the writing group members for the ADA. C. Mathieu, G. Mingrone, P. Rossing and A. Tsapas were writing group members for the EASD.

This article is being simultaneously published in *Diabetes Care* and *Diabetologia* by the American Diabetes Association and the European Association for the Study of Diabetes.

✉ Melanie J. Davies
Melanie.davies@uhl-tr.nhs.uk

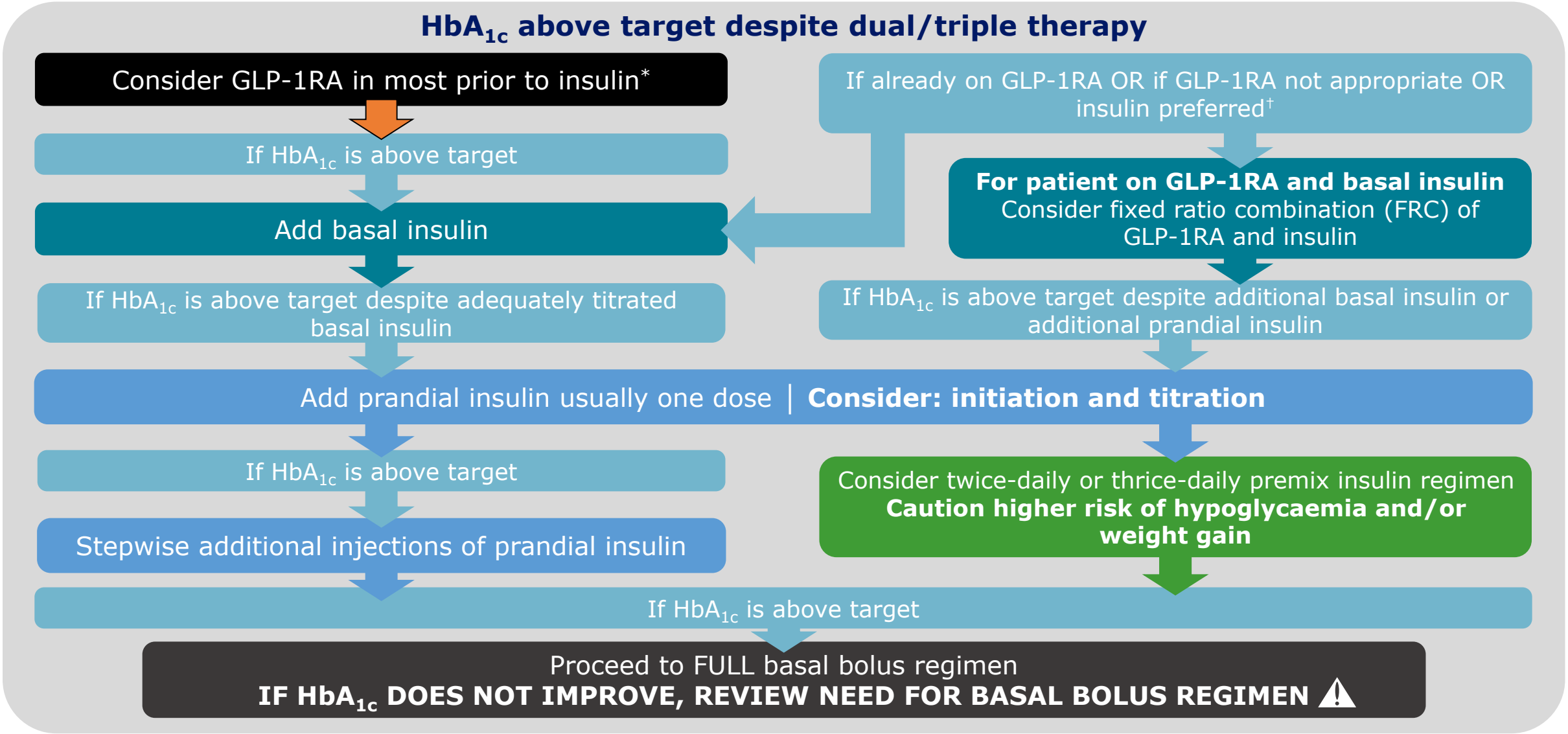
Extended author information available on the last page of the article

Springer

ADA/EASD 2018 Consensus Report

ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes
Davies MJ et al. *Diabetes Care* 2018. Sep; dci180033. https://doi.org/10.2337/dci18-0033;
Davies MJ et al. *Diabetologia* 2018. https://doi.org/10.1007/s00125-018-4729-5

Intensifying to injectable therapies



*Consider choice of GLP-1RA considering patient preference, HbA_{1c} lowering, weight-lowering effect or frequency of injection. If CVD, consider GLP-1RA with proven CVD benefit
†Consider insulin as preferred to GLP-1RA if symptoms of hyperglycaemia are present, or evidence of ongoing catabolism (polyuria, polydipsia or weight loss)
CVD, cardiovascular disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycosylated haemoglobin

Quelles nouveautés ?

- Les nouvelles insulines et nouvelles formulations
- Les associations fixes d’insuline avec un analogue GLP-1

Randomized Clinical Trial Comparing Basal Insulin Peglispro and Insulin Glargine in Patients With Type 2 Diabetes Mellitus Previously Treated With Basal Insulin: IMAGINE 5

DOI: 10.2337/dc15-1531

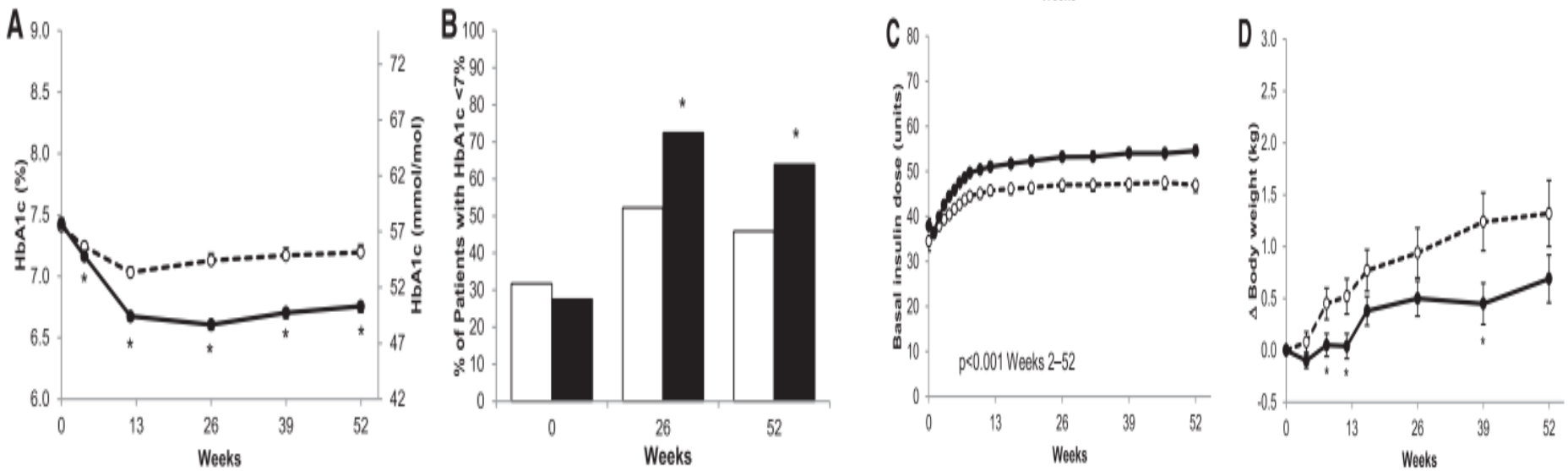
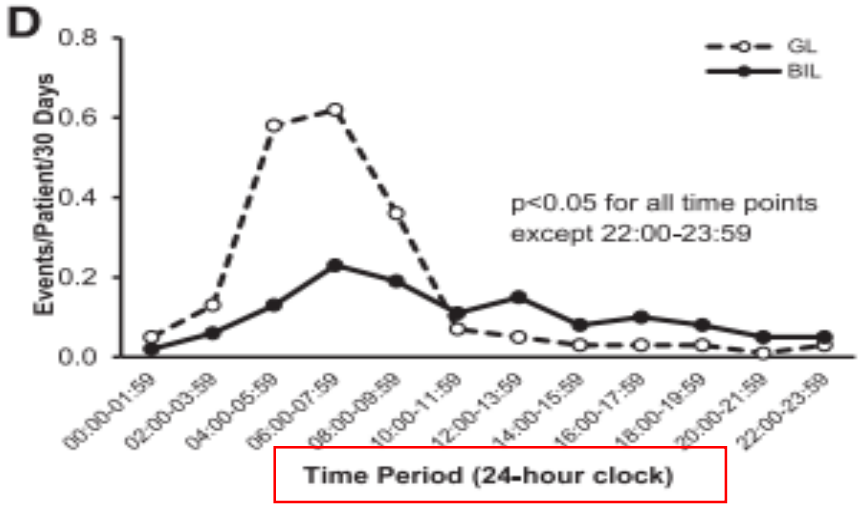


Table 2—Treatment outcomes at baseline and after 26 and 52 weeks of treatment

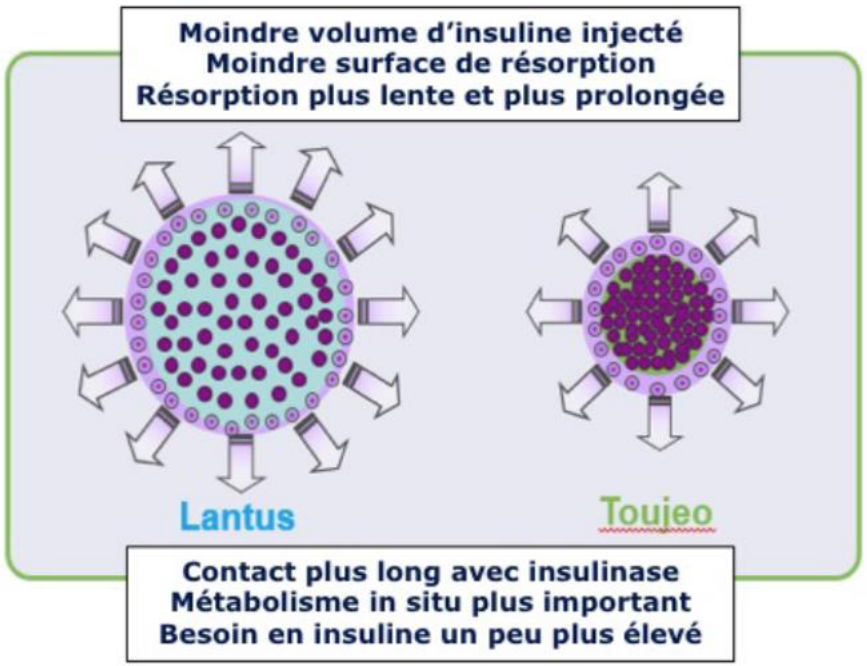
Outcome	Baseline*		26 weeks			52 weeks		
	Glargine (*N* ■ 159)	BIL (*N* ■ 307)	Glargine (*N* ■ 159)	BIL (*N* ■ 307)	*P***	Glargine (*N* ■ 159)	BIL (*N* ■ 307)	*P***
HbA_{1c}, %†	7.41 ± 0.06	7.43 ± 0.05	7.13 ± 0.06	6.60 ± 0.04	<0.001	7.20 ± 0.06	6.75 ± 0.05	<0.001
Change from baseline	—	—	−0.29 ± 0.06	−0.82 ± 0.04		−0.22 ± 0.06	−0.67 ± 0.05	
Total hypoglycemia rate‡‖	1.40 ± 0.30	1.08 ± 0.16	1.98 ± 0.19	1.55 ± 0.13	0.05	1.62 ± 0.15	1.24 ± 0.10	0.03
Total hypoglycemia incidence§	30 (18.9)	51 (16.8)	128 (80.5)	232 (76.3)	0.35	132 (83.0)	244 (80.3)	0.54
Nocturnal hypoglycemia rate‡‖	0.62 ± 0.16	0.53 ± 0.12	1.04 ± 0.15	0.43 ± 0.06	<0.001	0.88 ± 0.14	0.35 ± 0.06	<0.001
Nocturnal hypoglycemia incidence§	18 (11.3)	25 (8.2)	99 (62.3)	140 (46.1)	0.001	107 (67.3)	153 (50.3)	<0.001



LE MÉDICAMENT DU MOIS
Insuline glargine 300 U/mL (Toujeo®)

A.J. SCHEEN (1)

Rev Med Liège 2016; 71 : 2 : 101-107



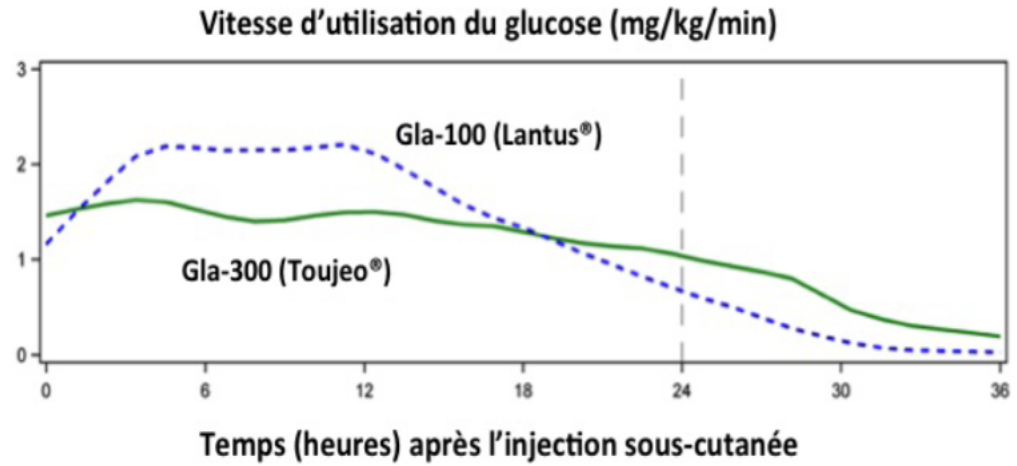
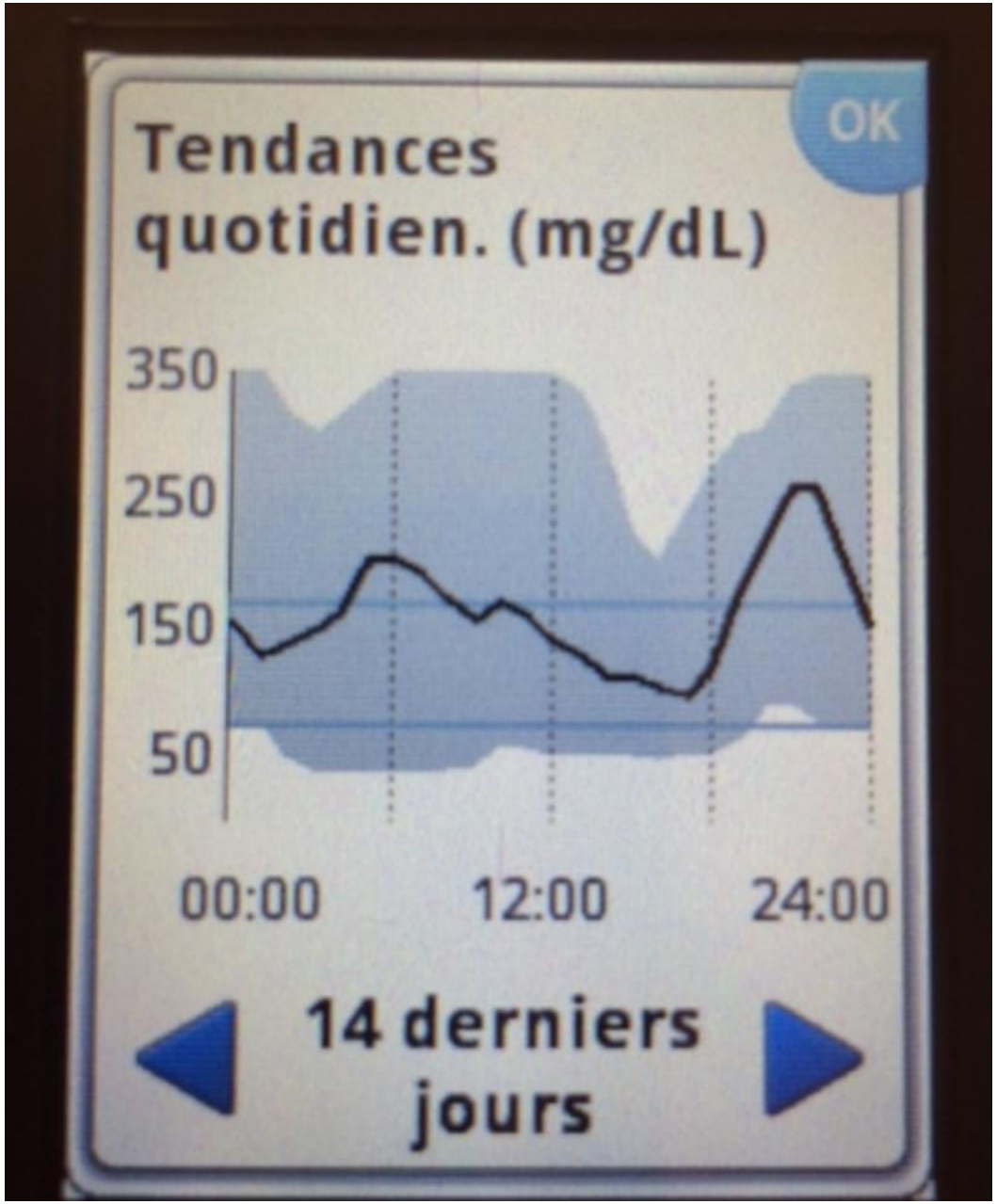
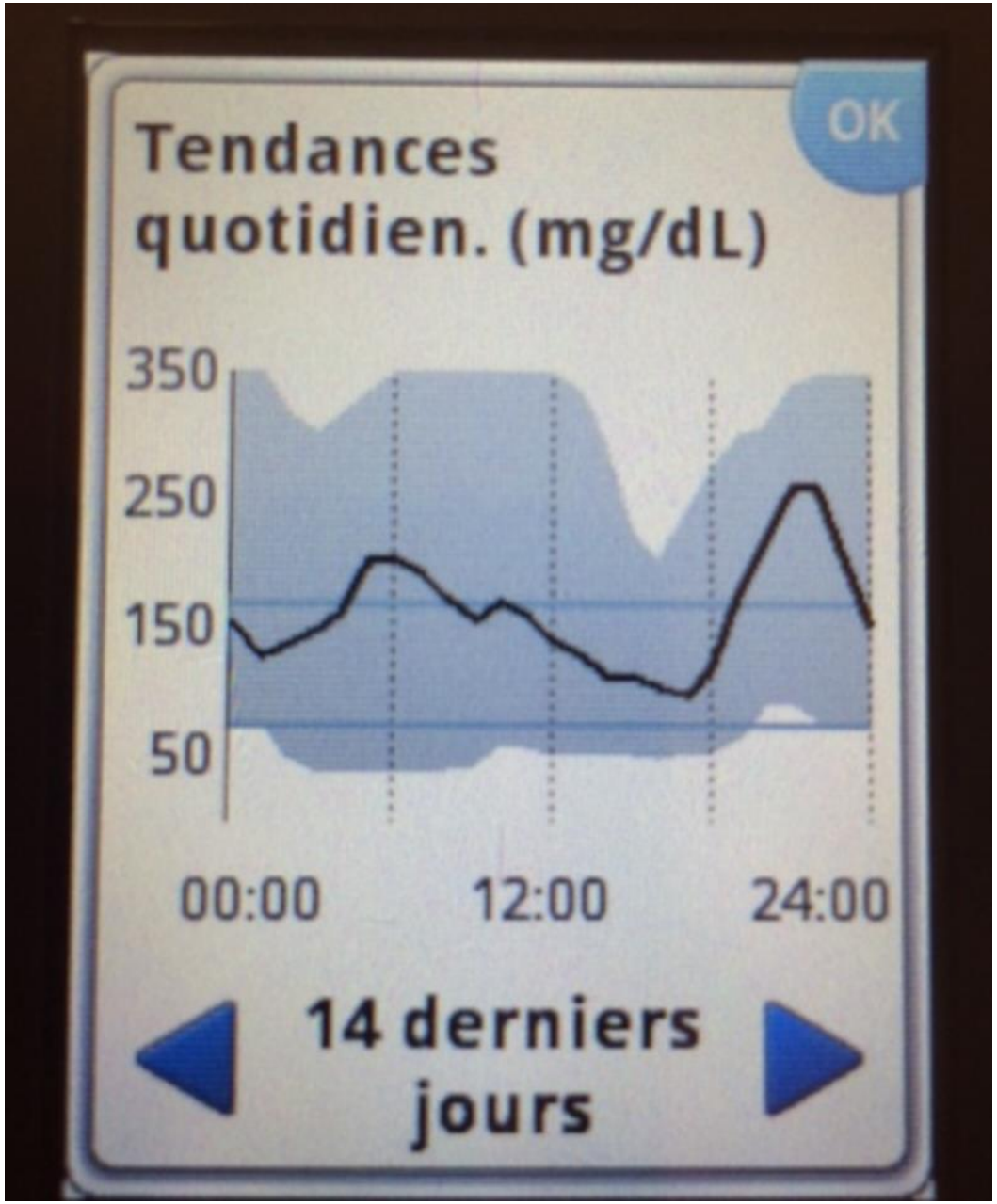


Figure 2. Profil pharmacodynamique de l'insuline Gla-300 (en vert) et de l'insuline Gla-100 (en bleu) chez des patients diabétiques de type 1 dans une étude de clamp euglycémique de 36 heures. L'action métabolique de l'insuline est déterminée par la quantité de glucose perfusée (valeurs moyennes horaires) pour maintenir une glycémie constante après l'injection sous-cutanée de 0,4 U/kg d'insuline glargine. Adapté de la référence Becker et coll. (14).

Toujeo: intérêt DT1 ?

- Mal équilibrés et/ou hypo (nocturnes) sévères ou fréquentes
- « brittle diabetes »
- Switch lantus (1 ou 2 fois), levemir (1 ou 2 fois)
- Dose basale > 40 U , bien équilibrés
- « Douleur » site injection insuline basale, quelle qu'elle soit


Tendances quotidien. (mg/dL)
OK
350
250
150
50
00:00
12:00
24:00
14 derniers jours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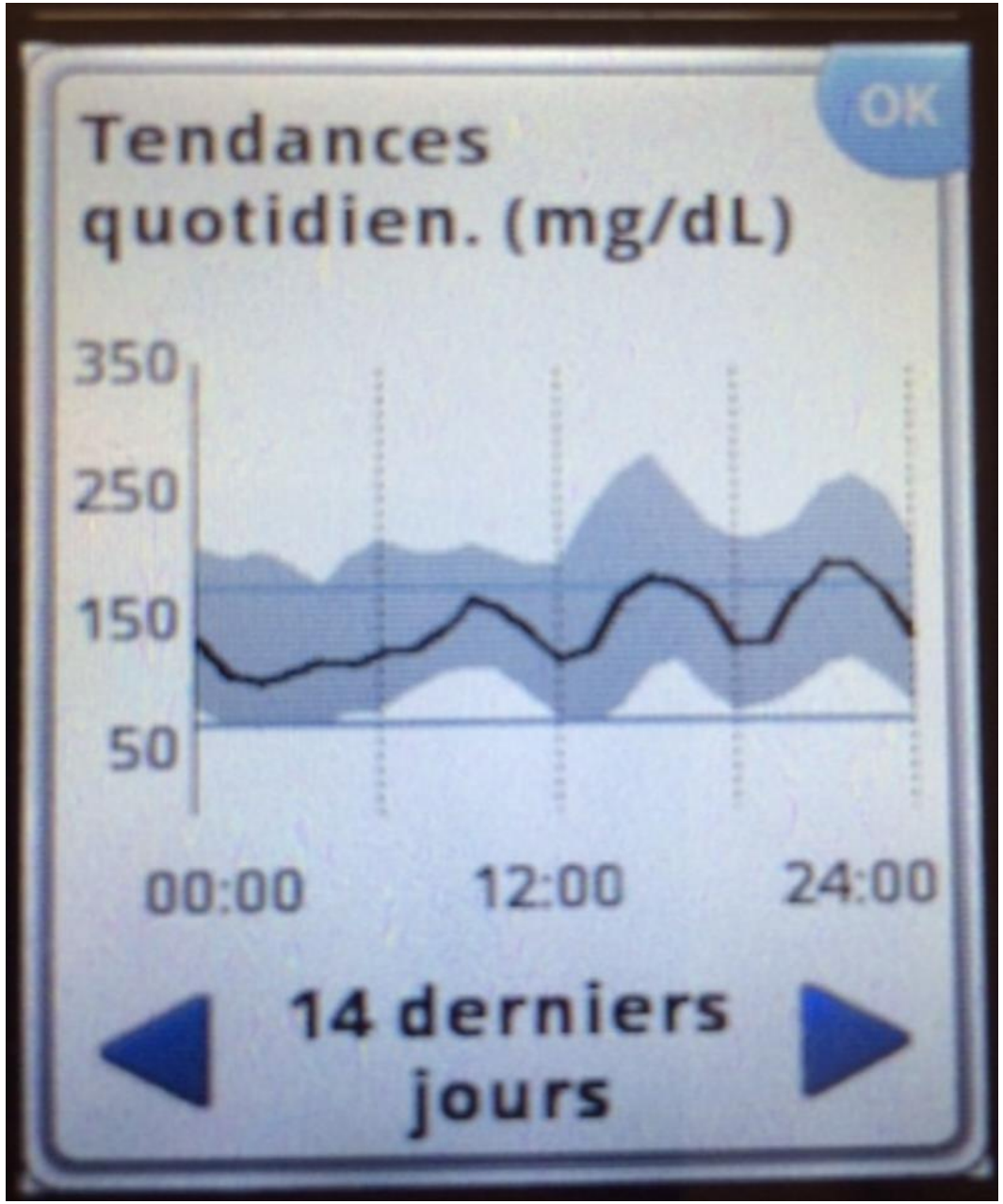
jours


OK
Tendances
quotidien. (mg/dL)
350
250
150
50
00:00
12:00
24:00
14 derniers
jours

Toujeo: intérêt dans DT2

- « idem » DT1

+

- Passage ADO + une basale (puis GLP-1 si nécessaire..)

- Passage prémixées « hautes doses » vers toujeo + humalog 200

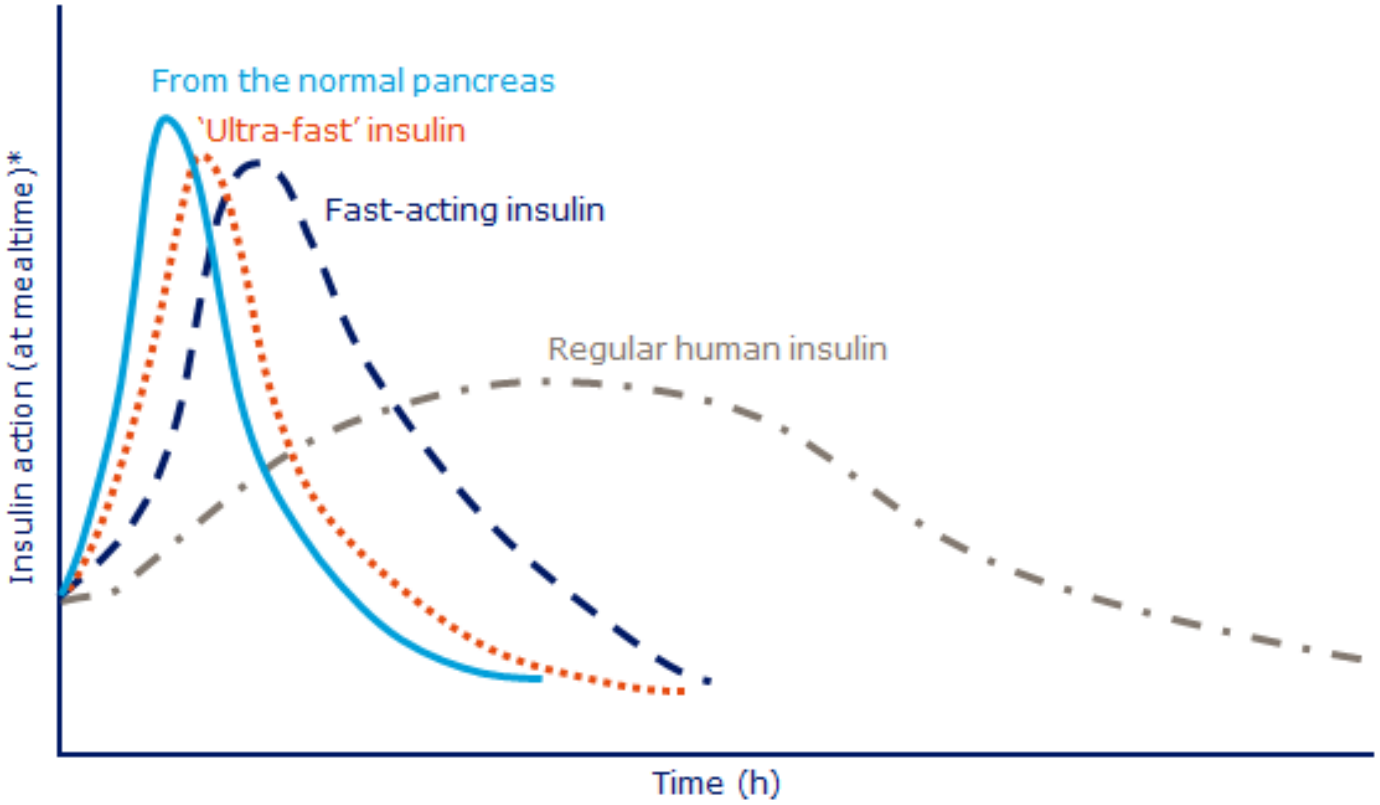
- Résultats TRES satisfaisants avec Toujeo + gliflozine…

Humalog 200 UI/ml

- Pas de modification des caractéristiques pharmaco-dynamiques/cinétiques

- Confort d’injection pour certains patients

Ultra-fast insulin: approaching a physiological insulin profile even further



Ultra-fast insulin should:

- Better approach physiological insulin secretion in type 1 diabetes
- Replace early insulin secretion in type 2 diabetes
- Have a better profile for pump therapy

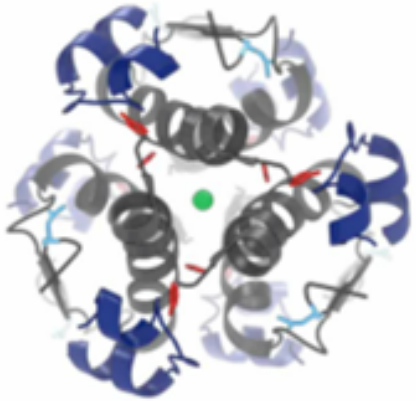
Faster aspart is being developed with the objective of achieving an increased early absorption compared to insulin aspart

*Schematic representation
Faster aspart, fast-acting insulin aspart

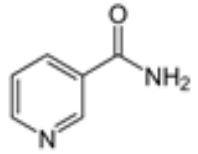
Adapted from Home. *Diabetes Obes Metab* 2015;17:1011–20

Faster Insulin ASPart

Insulin aspart hexamer

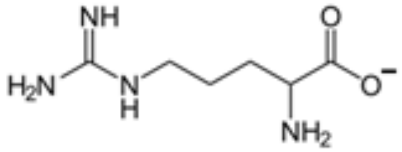


NA: absorption modifier



One of two forms of vitamin B3

L-arginine: added for stability



Naturally occurring amino acid

Insulin aspart monomer

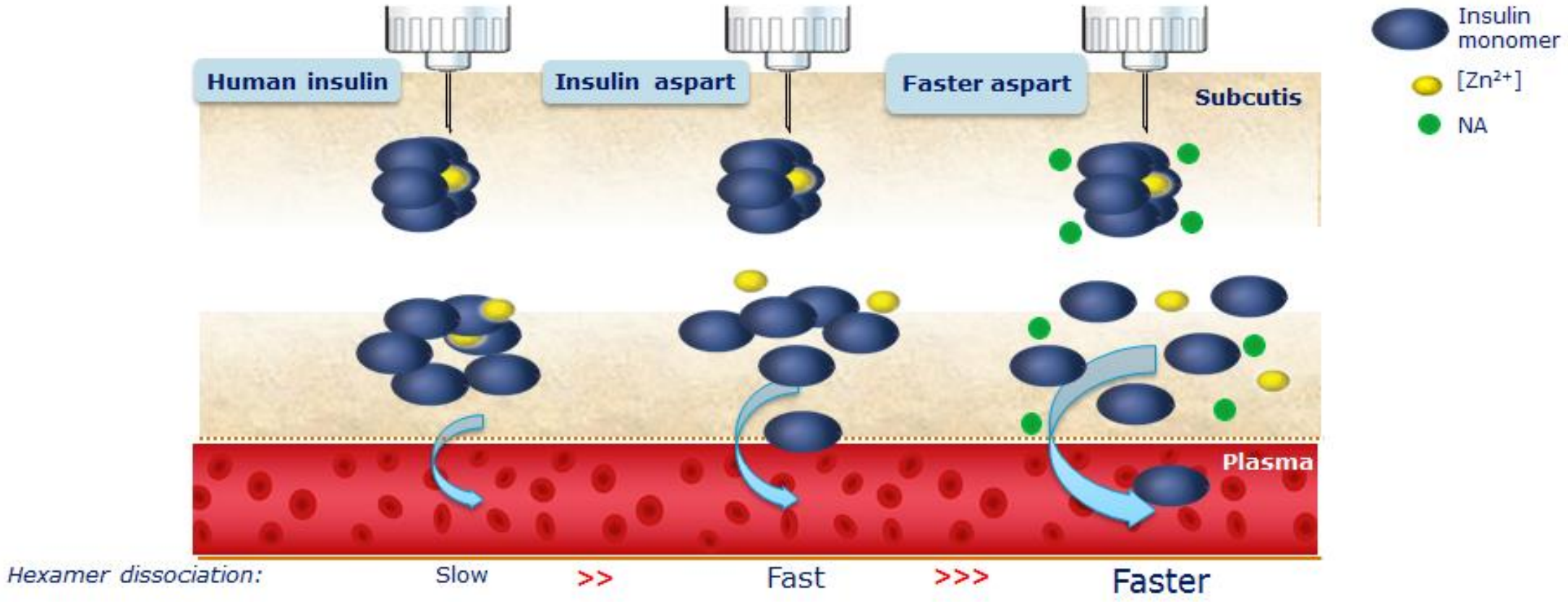
Zinc stabilises the multimeric state

Le nicotinamide, aussi connue sous le nom de niacinamide, est un dérivé de l'acide nicotinique. Le nicotinamide est une vitamine hydrosoluble et fait partie du groupe de vitamines B. Wikipédia

Faster aspart, fast-acting insulin aspart; NA, niacinamide

FDA. Inactive ingredient search for approved drug products database. www.accessdata.fda.gov/scripts/cder/iig/index.cfm

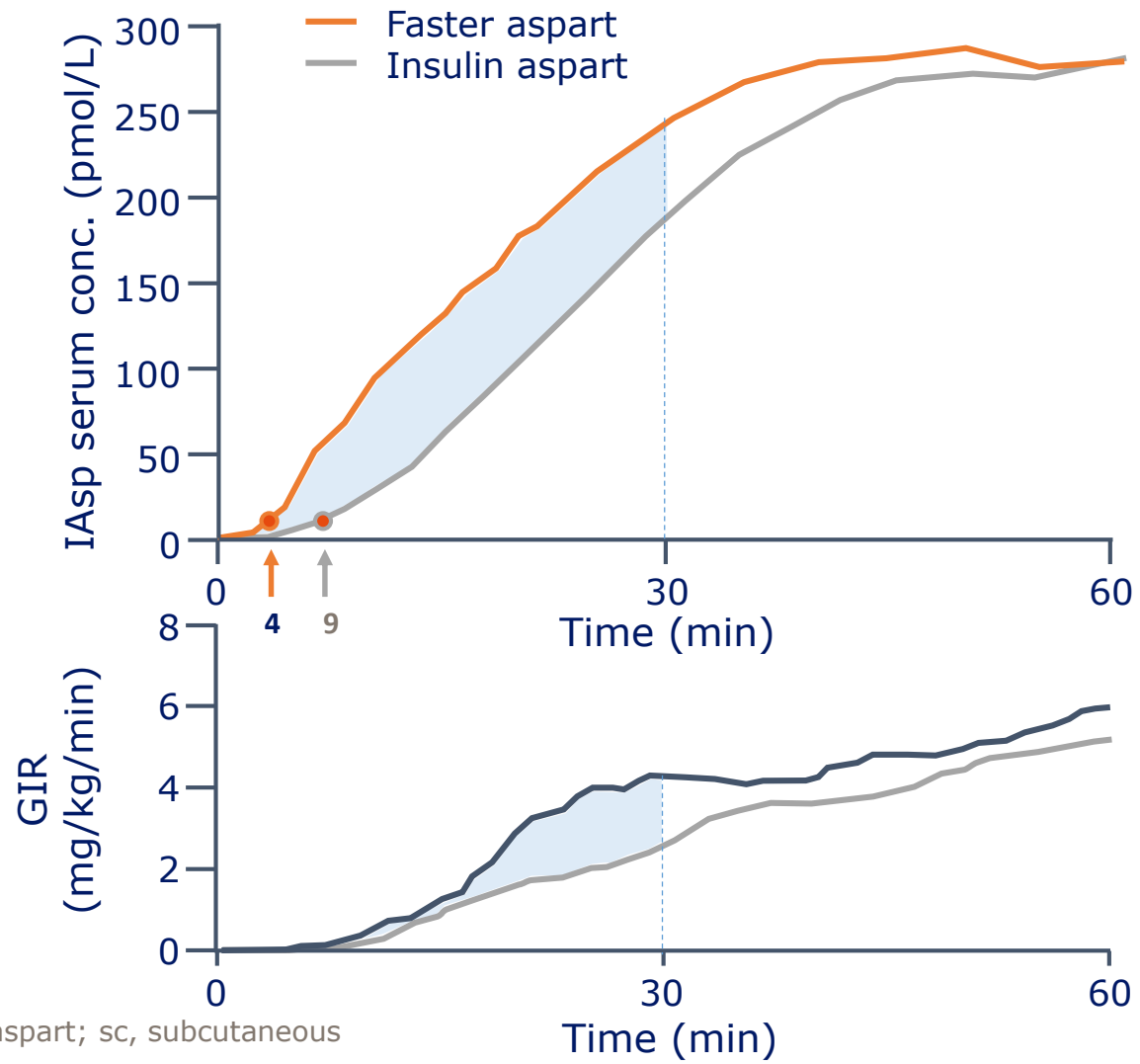
Fiasp: faster dissociation of hexamers into monomers



Faster aspart, fast-acting insulin aspart; NA, niacinamide; Zn, zinc

Compared with insulin aspart, faster aspart has:

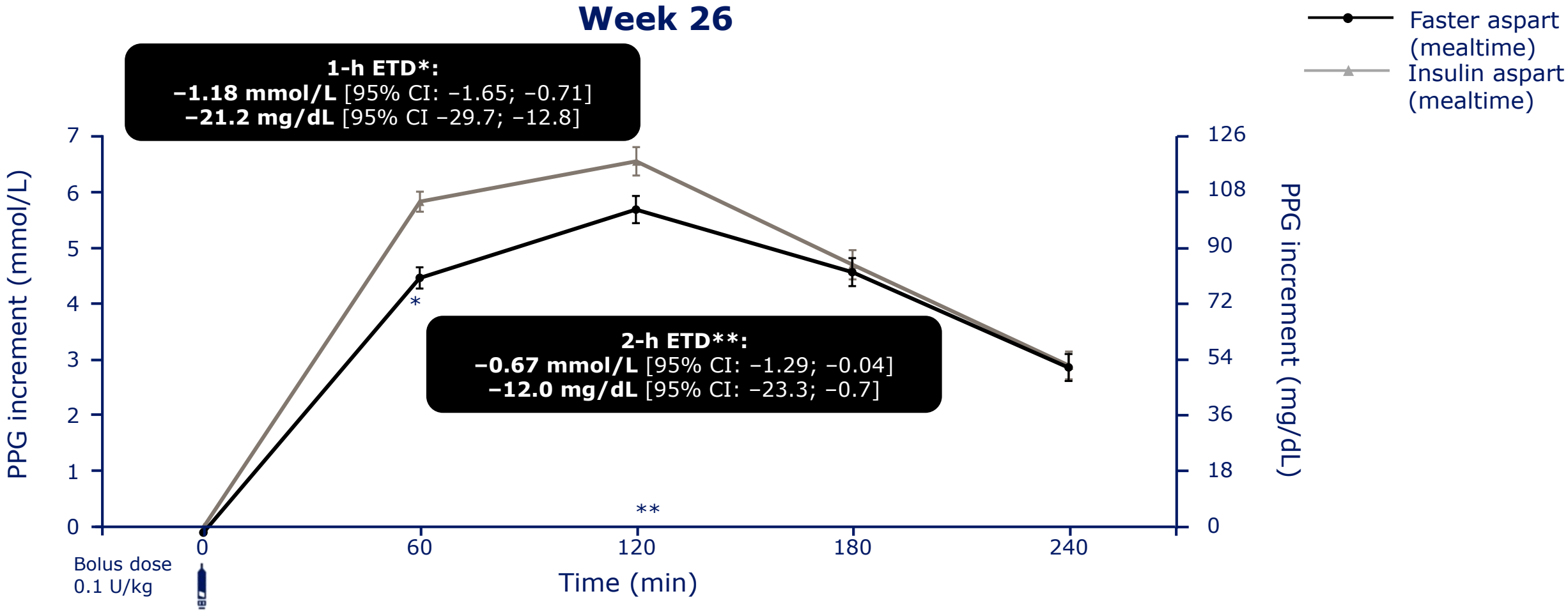
- Twice as fast onset of appearance in the bloodstream
- Two-fold higher insulin exposure within the first 30 min
- 74% greater insulin action within the first 30 min



Pooled analysis of NN1218 trials 3887, 3888, 3889, 3891, 3921, 3978.
Faster aspart, fast-acting insulin aspart; GIR, glucose infusion rate; IAsp, insulin aspart; sc, subcutaneous
Heise *et al. Clin Pharmacokinet* 2017;56:551–9

onset 1: PPG increment at week 26

Standardised meal test: mealtime comparison



Error bars: ± standard error (mean).*$p<0.0001$; **$p=0.0375$.
P-values are 2-sided. ETD represents PPG changes from baseline estimates. Changes from baseline in PPG increments were analysed based on an ANOVA model.
[a]Compared with mealtime insulin aspart.
ANOVA, analysis of variance; CI, confidence interval; ETD, estimated treatment difference (faster aspart–insulin aspart); PPG, postprandial plasma glucose

Russell-Jones *et al. Diabetes Care* 2017;doi:10.2337/dc16-1771

FlexTouch®

Main characteristics of FlexTouch®

No push-button extension

End-of-dose click

Very low dose force[3]

Accurate and consistent dosing from 1–80 U[4]

Easy touch button[1–3]

1. Oyer *et al. Expert Opin Drug Deliv* 2011;8:1259–69; 2. Bailey *et al. Curr Med Res Opin* 2011;27:2043–52; 3. Hemmingsen *et al. Diabetes Technol Ther* 2011;13:1207–11; 4. Wielandt *et al. J Diabetes Sci Technol* 2011;5:1195–9

Arrivées des insulines ULTRA-rapides…

- Hyperglycémie post-prandiale reste un enjeu majeur et difficile à maîtriser dans prise en charge DT1 et DT2
- Fiasp a démontré son intérêt et sa sécurité dans DT1, DT2 et pompe
- Exposer le patient à son insuline rapide 9,5 min plus tôt si SC et 12 min si pompe – quel réel impact à court et long terme ?
- L'utilisation du FSL nous aidera à vérifier ces données
- Nouveau stylo à expérimenter
- A nous de voir….

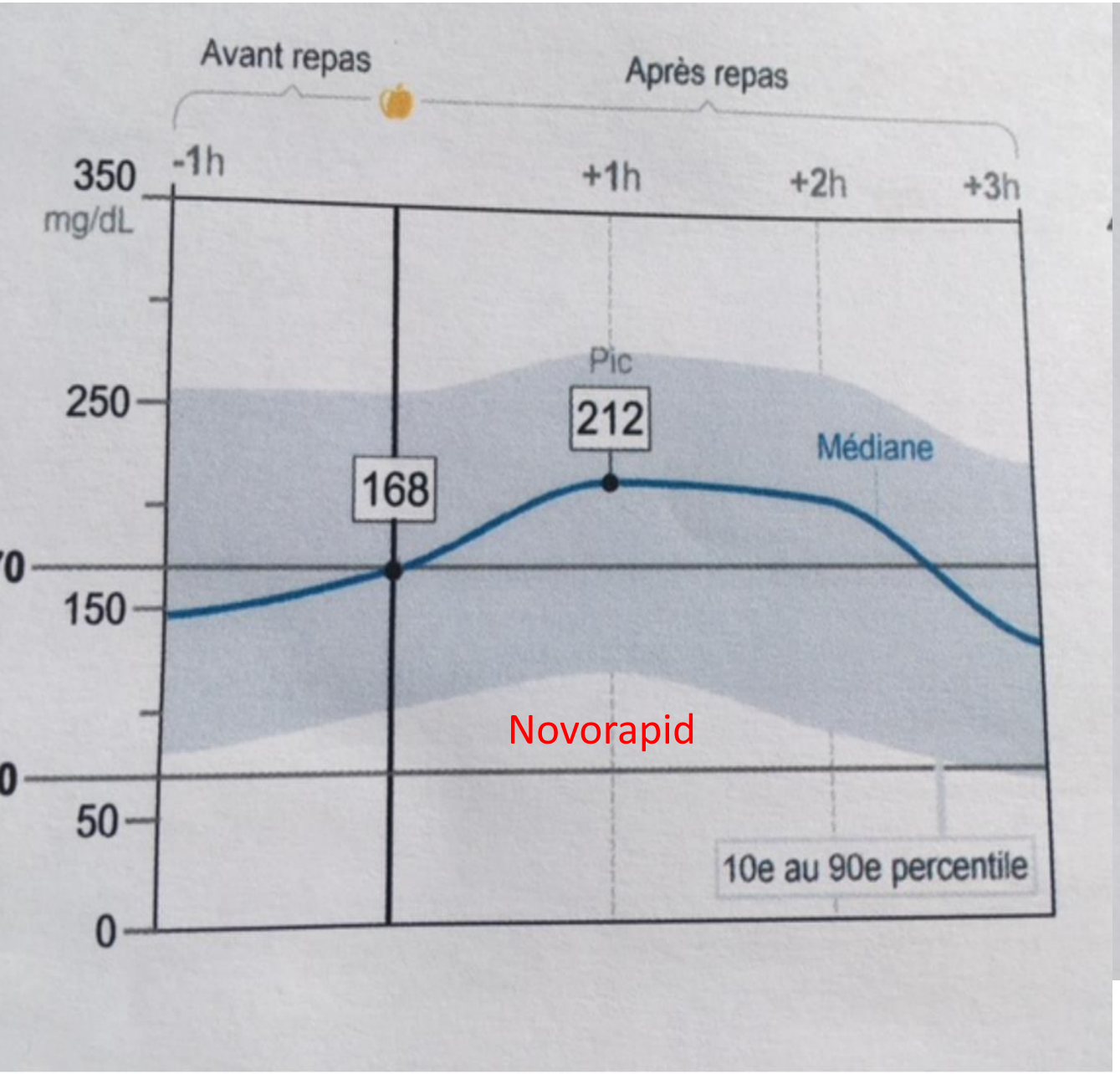
Fiasp®:
First experience in Belgium and clinical implications

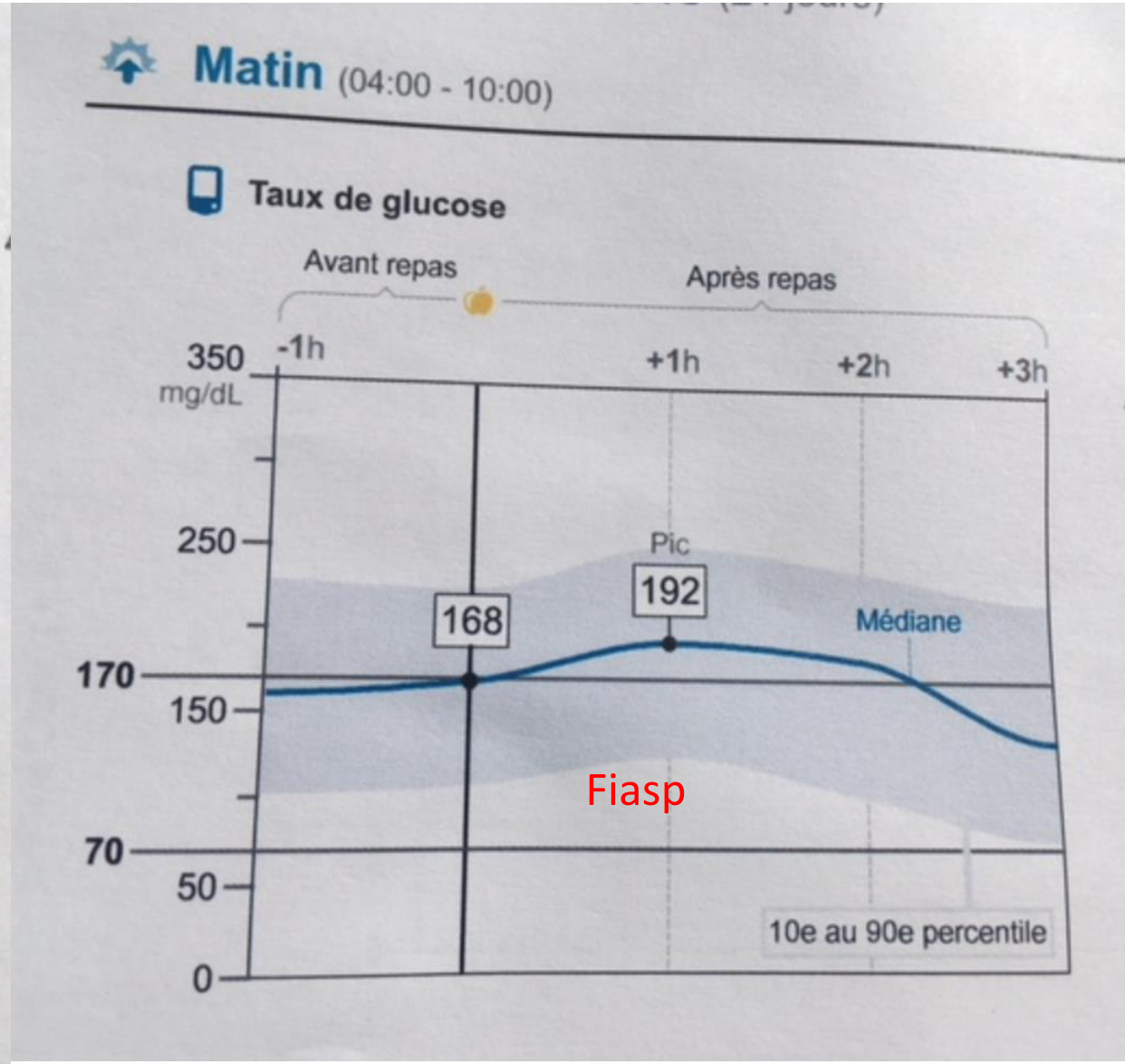
Launch symposium 13-9-18

Prof JC Philips

CHU Liège

novo nordisk


Avant repas
Après repas
350
mg/dL
-1h
+1h
+2h
+3h
250
150
50
0
Pic
212
168
Médiane
10e au 90e percentile
Novorapid


Matin (04:00 - 10:00)
Taux de glucose
Avant repas
Après repas
350
mg/dL
-1h
+1h
+2h
+3h
250
170
150
70
50
0
Pic
192
168
Médiane
10e au 90e percentile
Fiasp

My conclusions after this (little) experience…

- Starting Fiasp® is easy and safe:

No increase hypo, unit-to-unit, injection right before meal

- Some (but not all) patients have objective and positive changes with Fiasp regarding FSL data (esp. after meals)
- What about a potential effect on HbA1c ?
- Patients satisfaction is....very high !
- Flextouch® Pen is highly appreciated
- Some patients feel « less guilty » with fewer hyperglycaemic events

Quelles nouveautés ?

- Les nouvelles insulines et nouvelles formulations
- Les associations fixes d’insuline avec un analogue GLP-1

=

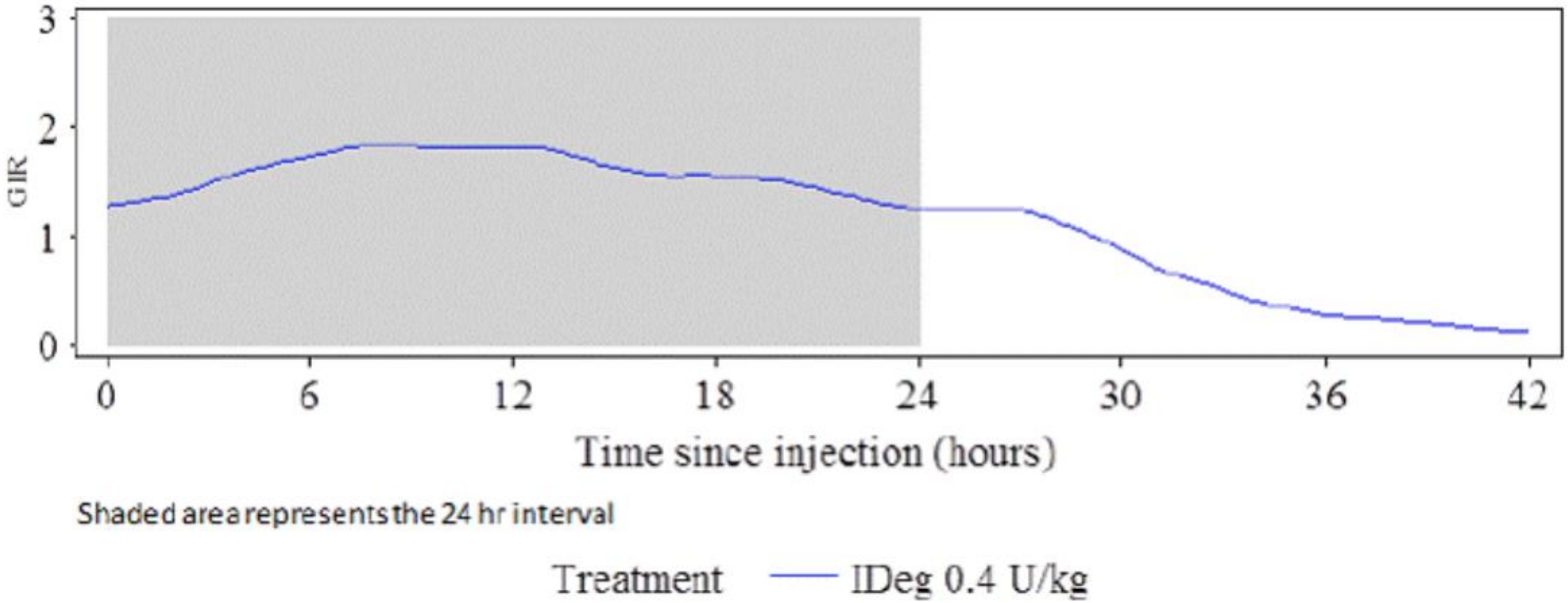
TRESIBA®
insulin degludec injection 100 U/mL, 200 U/mL

+

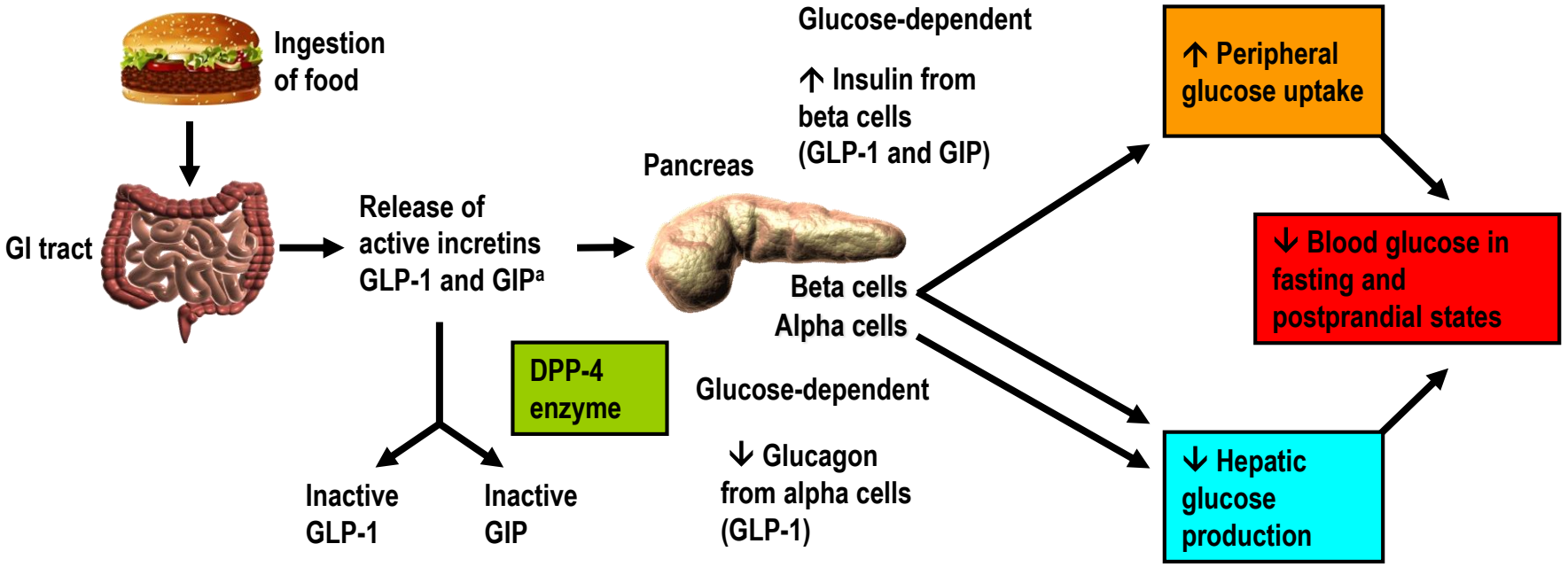
VICTOZA®
liraglutide injection 1.2 mg | 1.8 mg

TRESIBA®

insulin degludec injection 100 U/mL, 200 U/mL



Incretin system: mechanisms for improving glycemic control

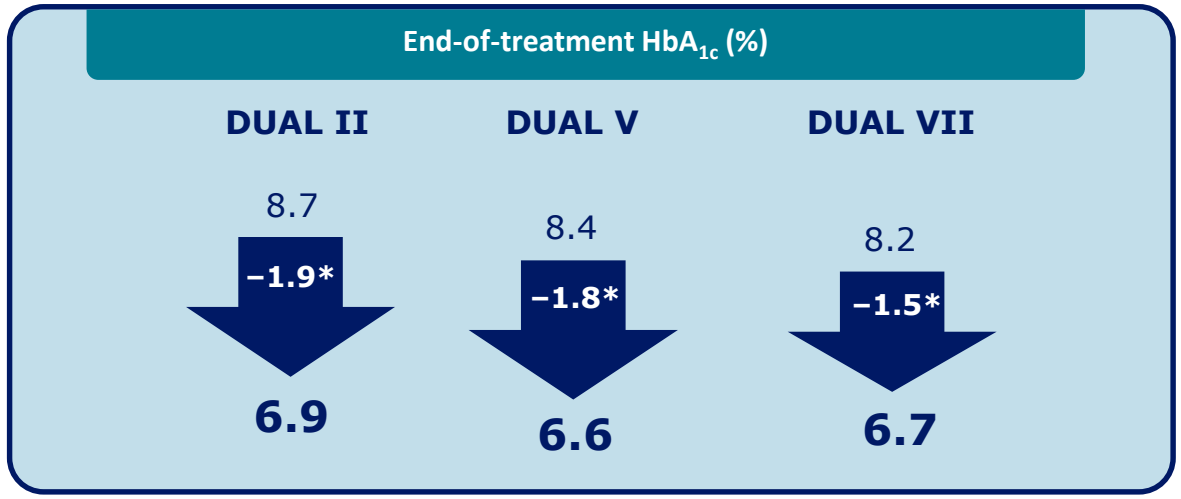


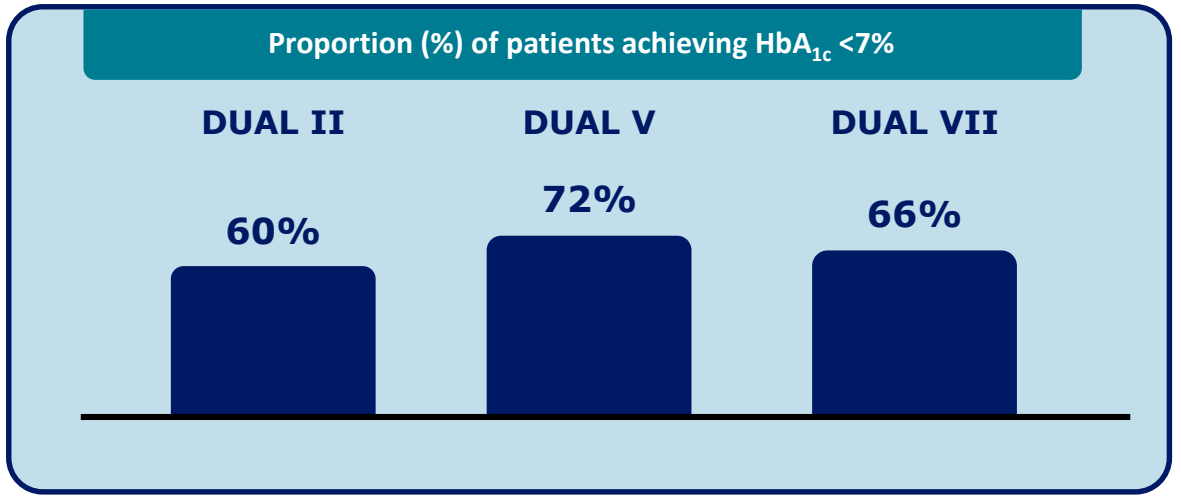
VICTOZA®

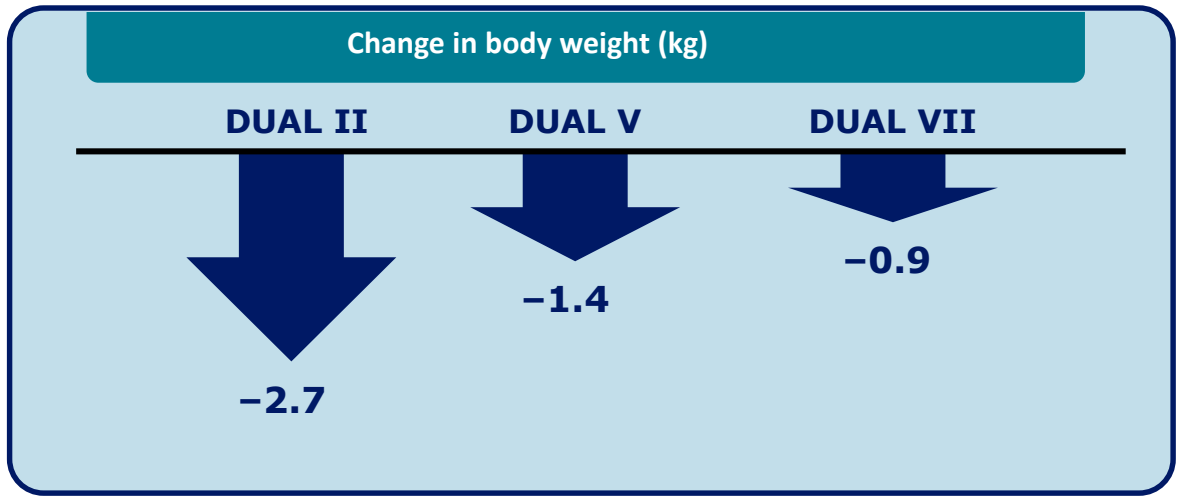
liraglutide injection 1.2 mg | 1.8 mg

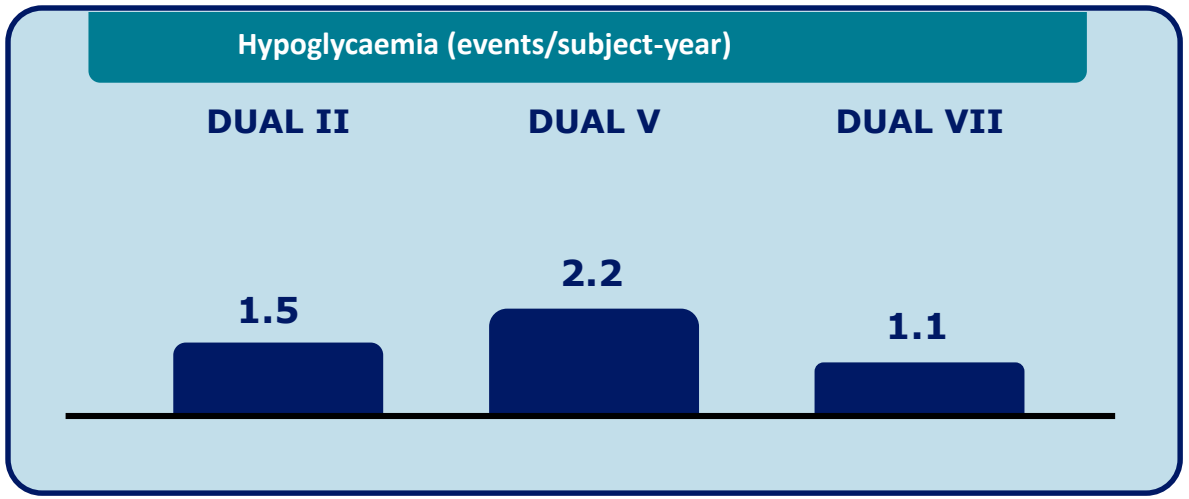
Xultophy chez patients mal équilibrés sous insuline basale

Summary of key clinical findings from DUAL II, V and VII









*change in HbA_{1c} from baseline to week 26

Buse et al. *Diabetes Care* 2014;37:2926–33; Lingvay et al. *JAMA* 2016;315:898-907; Billings et al. *Diabetes Care* 2018;41(5):1009-1016

Xultophy® : Usage pratique

* De préférence au même moment chaque jour. Un intervalle minimum de 8 heures entre deux injections devra toujours être respecté.

1. SPC Xultophy® June 2018; 2. Lingvay *et al. JAMA* 2016;315:898-907

Xultophy® : Initiation

- Pour vos patients diabétiques de type 2 non contrôlés sous insuline basale, la dose initiale recommandée est de 16 doses unitaires de Xultophy® une fois par jour.

- Le traitement par insuline basale doit être arrêté avant de commencer le traitement par Xultophy®.

Xultophy® : Titration

- La dose de Xultophy® doit être ajustée en fonction des besoins individuels du patient.
- Dans le cadre du programme d'études cliniques sur Xultophy® les patients ont ajusté la dose de Xultophy® deux fois par semaine en fonction de leur glycémie à jeun (moyenne des 3 jours précédents).


SULIQUA SoloStar 3 ml
100 units/ml + 50 mcg/ml
SULIQUA SoloStar 3 ml
100 units/ml + 33 mcg/ml

Suliqua® (EU)

=


Lantus® SoloStar®
100 Unités/ml - 100 Units/ml
Solution injectable en stylo prérempli
Solution for injection in a pre-filled pen
insuline glargine / insulin glargine
Rx


Lyxumia 10mcg
lixisenatide
Lyxumia 20mcg
lixisenatide

Conditions de remboursement Suliqua et Xultophy

Pour vos patients diabétiques de type 2*

- **Insuffisamment contrôlés (HbA_{1c} > 7,5%)**

ET

- **Avec un Indice de Masse Corporel (IMC) ≥ 30 kg/m²**

ET

- **Sous un traitement préalable d'au moins 3 mois par insuline basale + au minimum de la metformine**

Dans le trajet de soin

↓

Sans attestation

Indiquez "TSD" sur la prescription

Hors trajet de soin

↓

Avec attestation

- Première demande valable pendant 1 an
- Renouvellement si :
  - HbA_{1c} < 7%
  - Diminution HbA_{1c} ≥ 1%

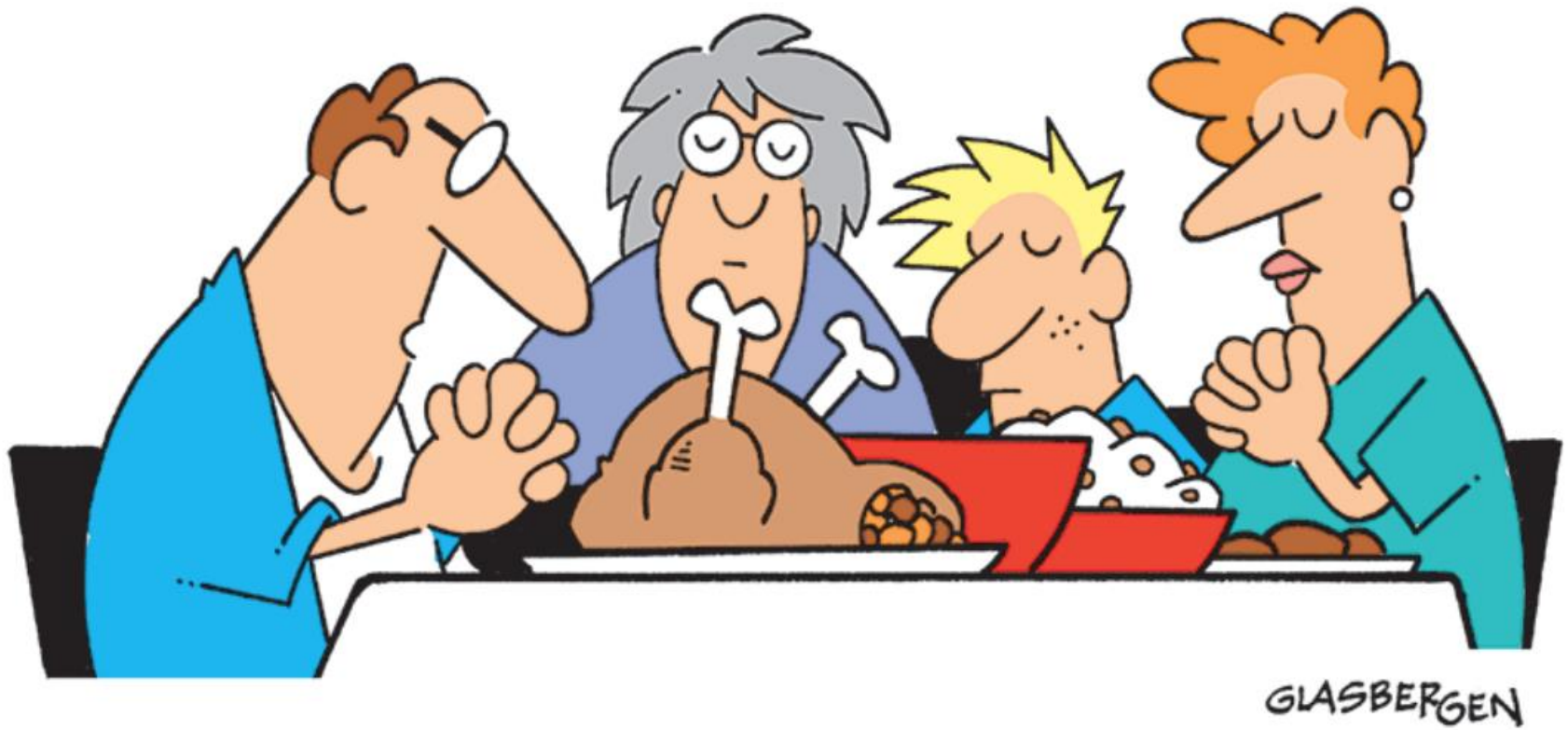
*www.inami.be consulté le 1er septembre 2018

Le FUTUR ?

- Autres voies que injection sous-cutanée (orale, cutanée, inhalée) ?
- Insuline avec passage hépatique prédominant ?
- Insulines encore plus rapides et plus lentes: objectif = ↓ hypos
- Smart insuline ?

CONCLUSIONS

- L’insulinothérapie est facilitée (mais ne doit pas être retardée!) avec l’usage des analogues GLP-1
- Schémas insuliniques sont tous efficaces si titration adéquate
- Recherche permanente de nouvelles insulines se rapprochant de la sécrétion physiologique normale
- L’association d’insuline basale et d’analogues GLP-1 prometteuse dans DT2
- TDS et CD nous offrent un large choix de possibilités
- Ne (RE)TARDEZ PAS et lancez vous !



"Lord, make us grateful for the cholesterol, diabetes, high blood pressure, weight gain and indigestion we are about to receive . "