Nuevos análogos de insulina basal: ¿ qué aportan a los pacientes ?

Dr. Joan Rosal

Sademi 2015, Punta Umbría

“ Espero que viva lo suficiente …”

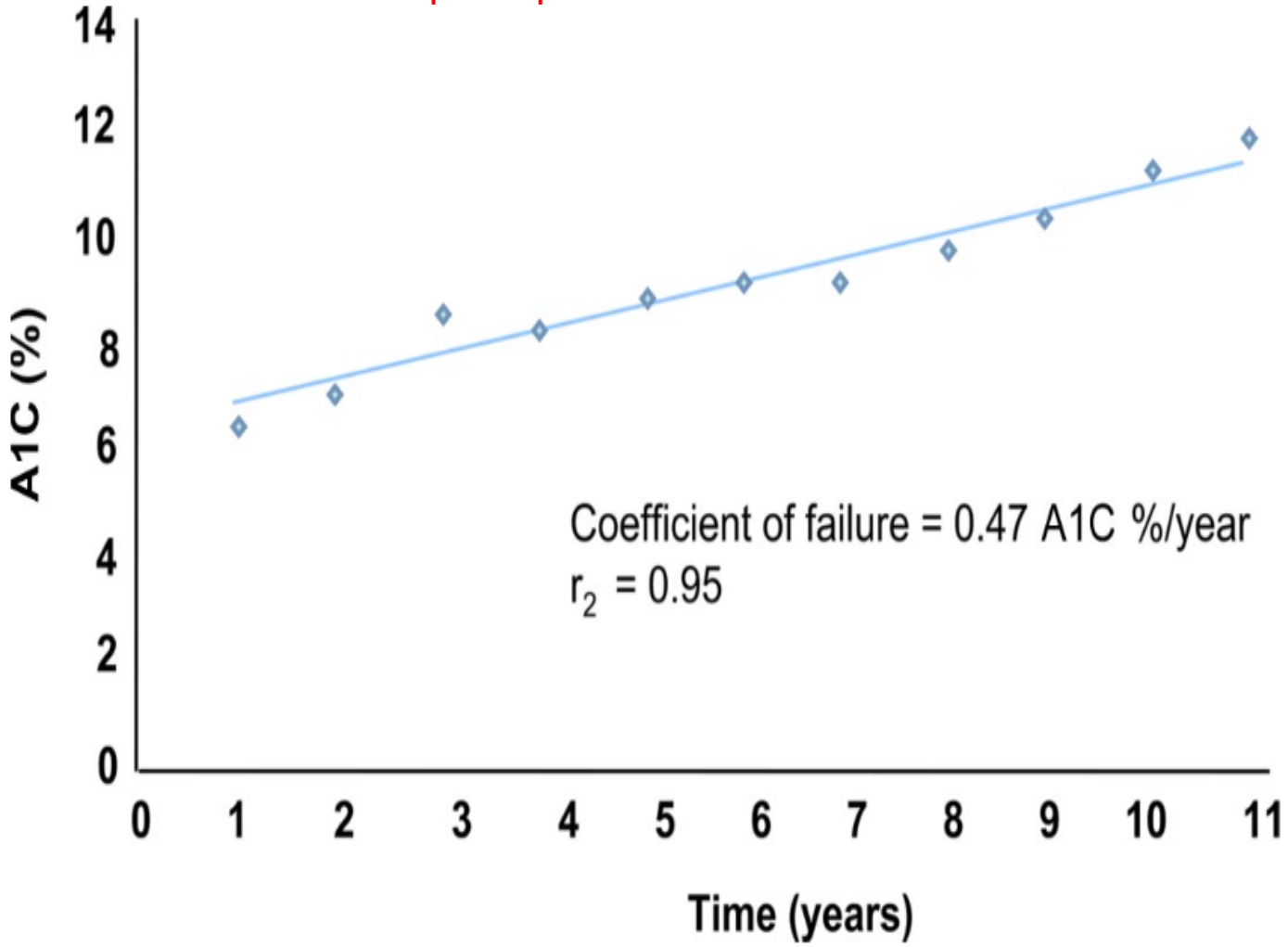


Figure 2—*Illustration of coefficient of β-cell failure over time in relation to A1C (from UKPDS)*

Fonseca VA. Diabetes Care 2009;32 (Suppl 2):S15

OBJETIVOS TTº INSULINA

- - A1c
- Evitar + kg
- Evitar hipoglucemias
- - Variabilidad glucémica (estrés oxidativo, inflamatorio, apoptosis beta)
- Prevención vs Control de daños

Second-Generation Basal Insulin Analogues Compared With Detemir and Glargine

- Equally effective
- Longer duration of action
- Even flatter action profile
- Less variability
- Lower risk for hypoglycemia, especially nocturnal hypoglycemia
- Less weight gain (than glargine)

Borgoño, CA, et al. *Endocrin Metab Clin North Am.* 2012;41:1-24.
Hermansen K, et al. *Diabetes Obes Metab.* 2007;9:209-217.
Owens DR, et al. *Diabetes Metab Res Rev.* 2014;30:104-119.

PRINCIPLES OF THE AACE ALGORITHM FOR THE TREATMENT OF TYPE 2 DIABETES

3) Minimizar el riesgo de hipoglucemia es una prioridad. Se trata de seguridad, adherencia y coste.

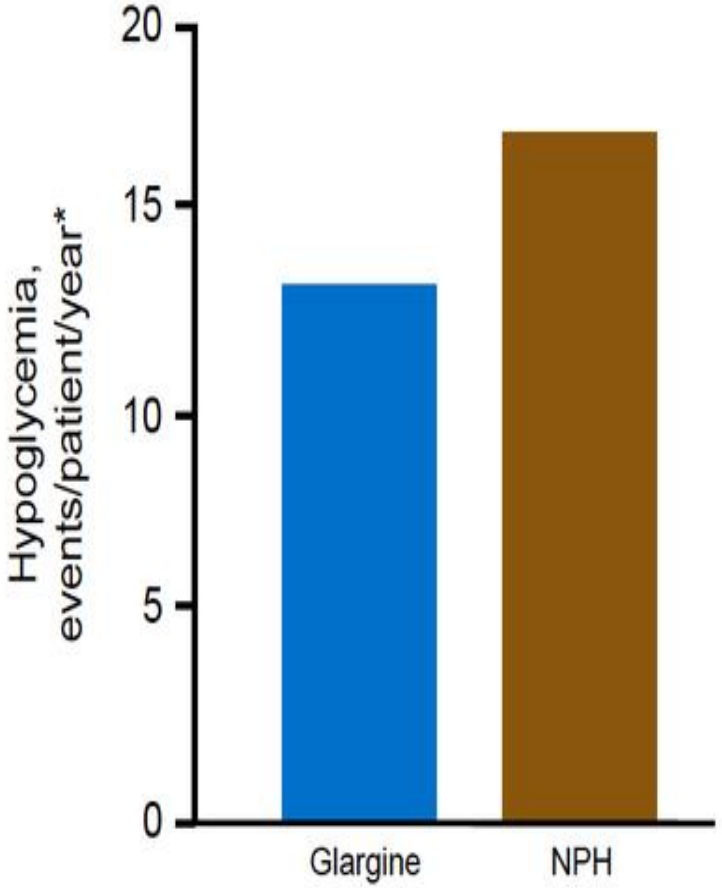
6) … "facilidad de uso"…, como atributo a tener en cuenta para elegir un tratamiento.

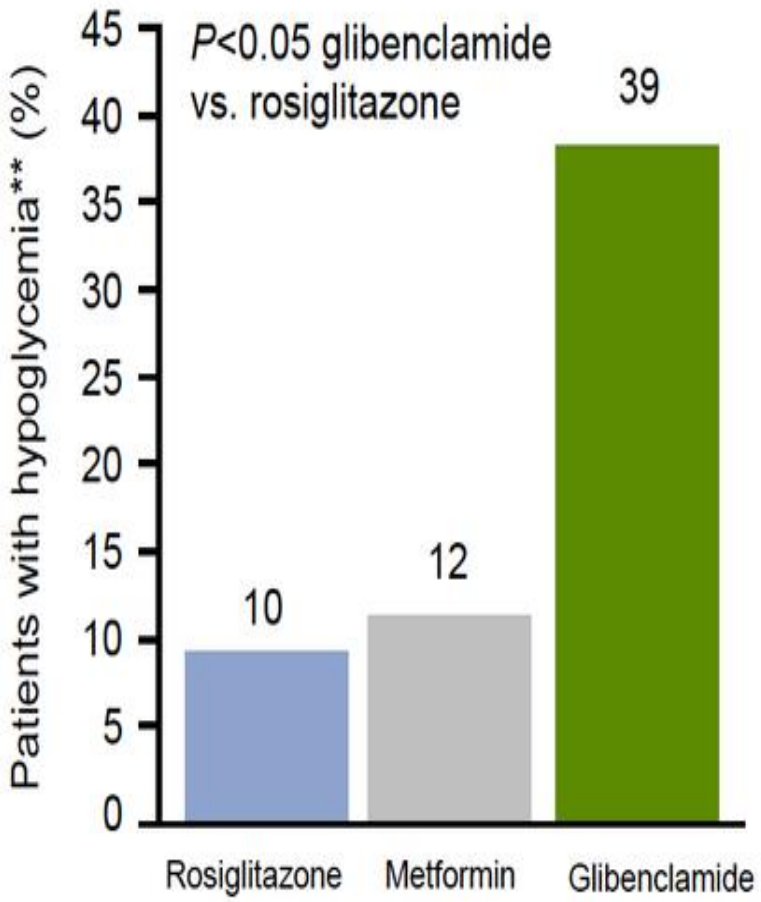
10) Hay que dar mucha más prioridad a la seguridad y eficacia que al coste de adquisición de los medicamentos, que solamente supone una pequeña parte del coste total.

15) Los análogos rápidos son superiores a la insulina regular porque son más predecibles.

16) Los análogos basales son superiores a la NPH por su respuesta plana de 24 horas y mejor reproducibilidad y consistencia (tanto intra como interindividual), lo que implica menor riesgo de hipoglucemas.

Current Treatments Increase Risk of Hypoglycaemia





*All symptomatic hypoglycemic events

**Patients self-reporting (unconfirmed) hypoglycemia

Riddle MC, et al. Diabetes Care 2003;26:3080-3086; Kahn SE, et al. N Engl J Med 2006;355:2427-2443.

MEJOR > BUENO

ANTES (bueno)

- Regular (no tan rápida)
- NPH (no tan lenta)

HOY (mejor)

- Análogos rápidos (lispro, aspart, glulisina)
- Análogos lentos (detemir, glargina)

ÓPTIMO >MEJOR

HOY (mejor)

- Análogos rápidos (lispro, aspart, glulisina)
- Análogos lentos (detemir, glargina)

MAÑANA (óptimo)

- Análogos ultrarápidos (aspart, BIO-123, +hialuronidasa)
- Análogos ultralentos (U-300, DEGLUDEC, PEG-LISPRO)

Class	Mechanism	Advantages	Disadvantages	Costs
Insulin	Activates insulin receptor ↑ peripheral glucose uptake	Universally effective Unlimited efficacy ↓ Microvascular risk	Hypoglycaemia Weight gain Injectable Training requirements 'Stigma'	Variable

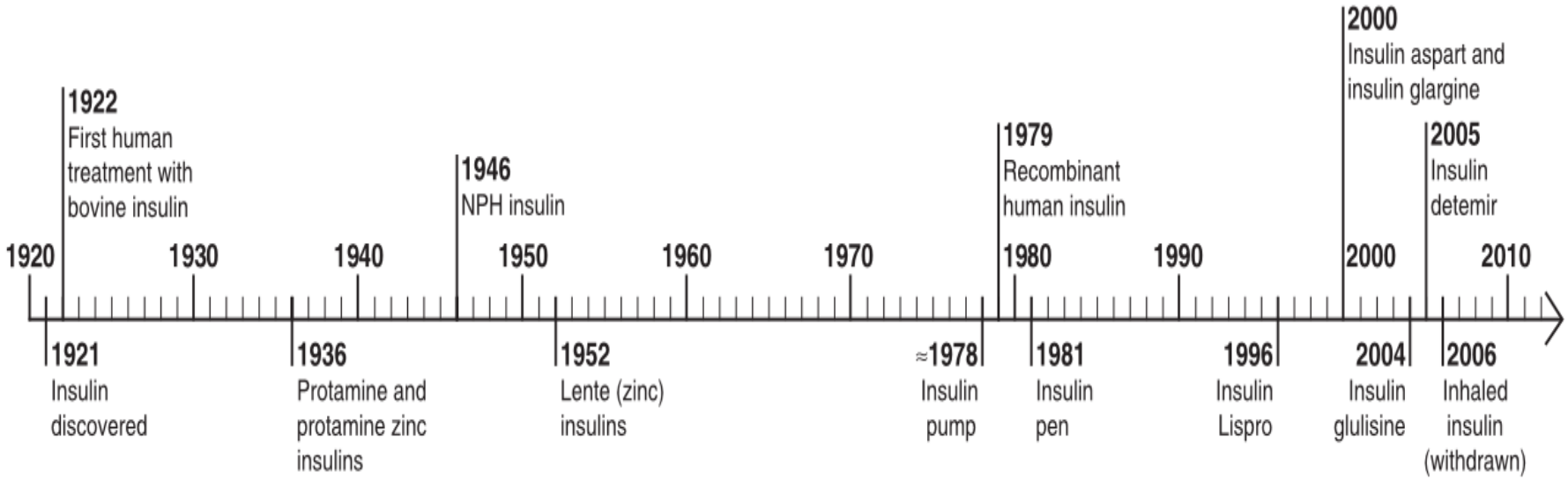
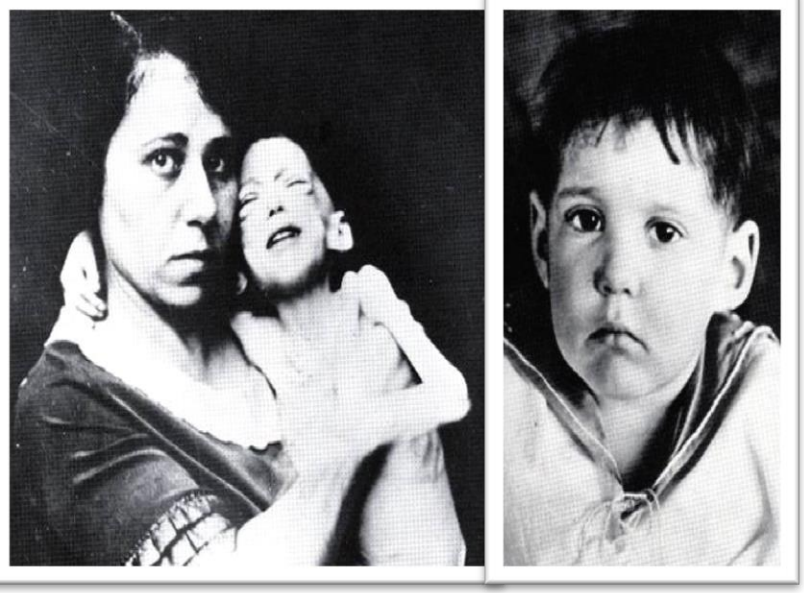


Figure 1. Milestones in insulin development.



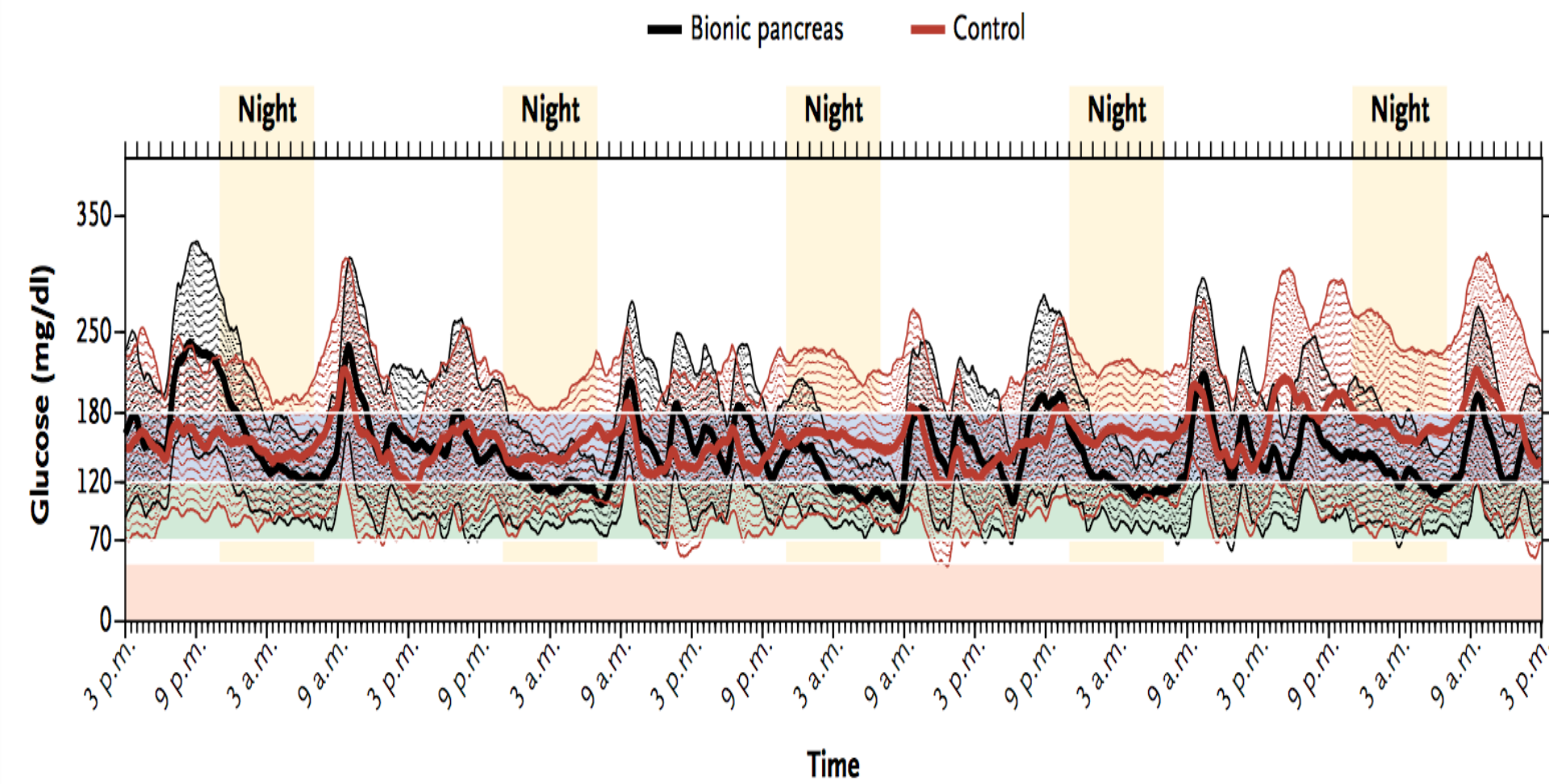
15 de diciembre de 1922

15 de febrero de 1923

Banting y Best

Páncreas biónico

2014

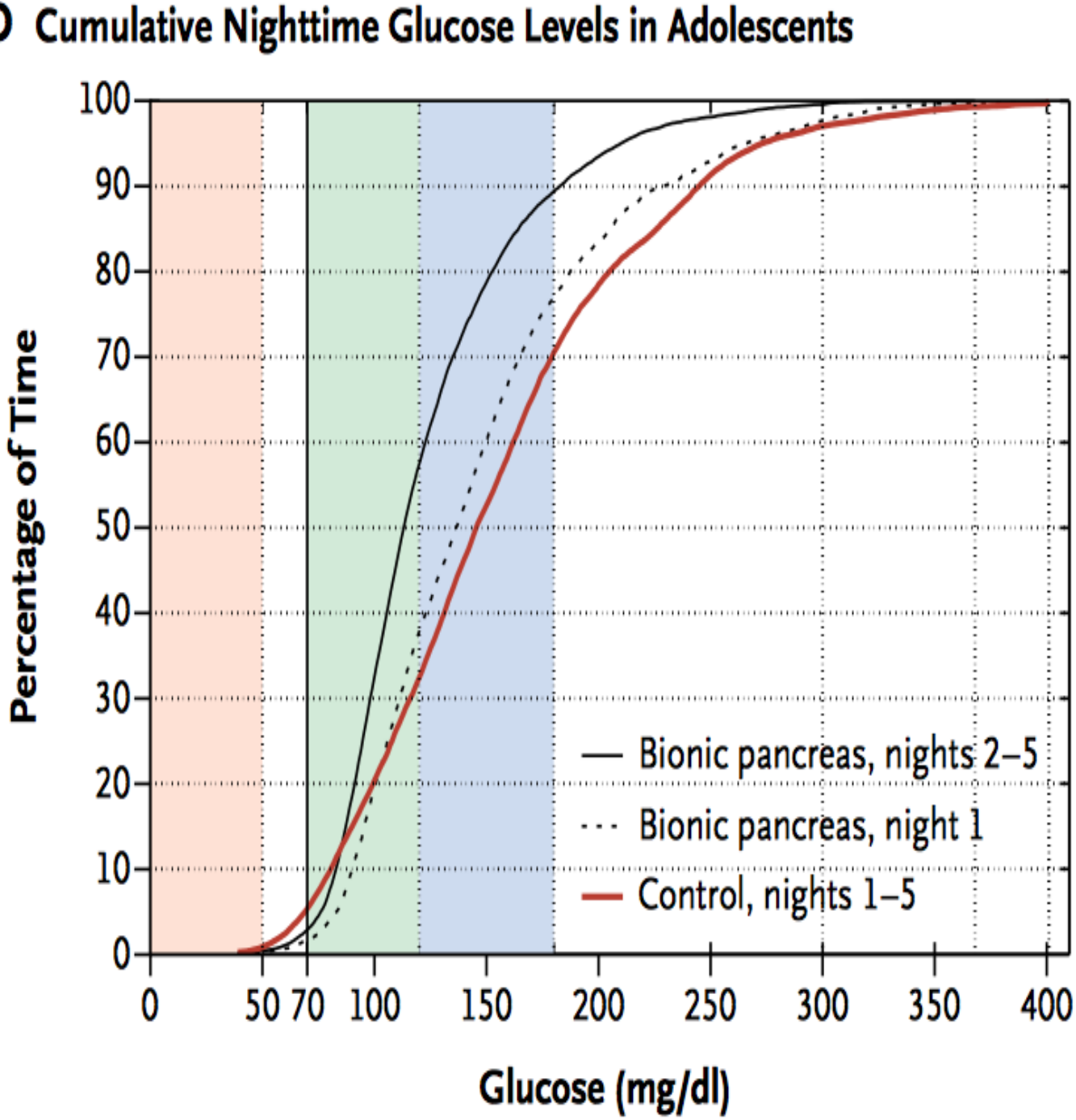


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

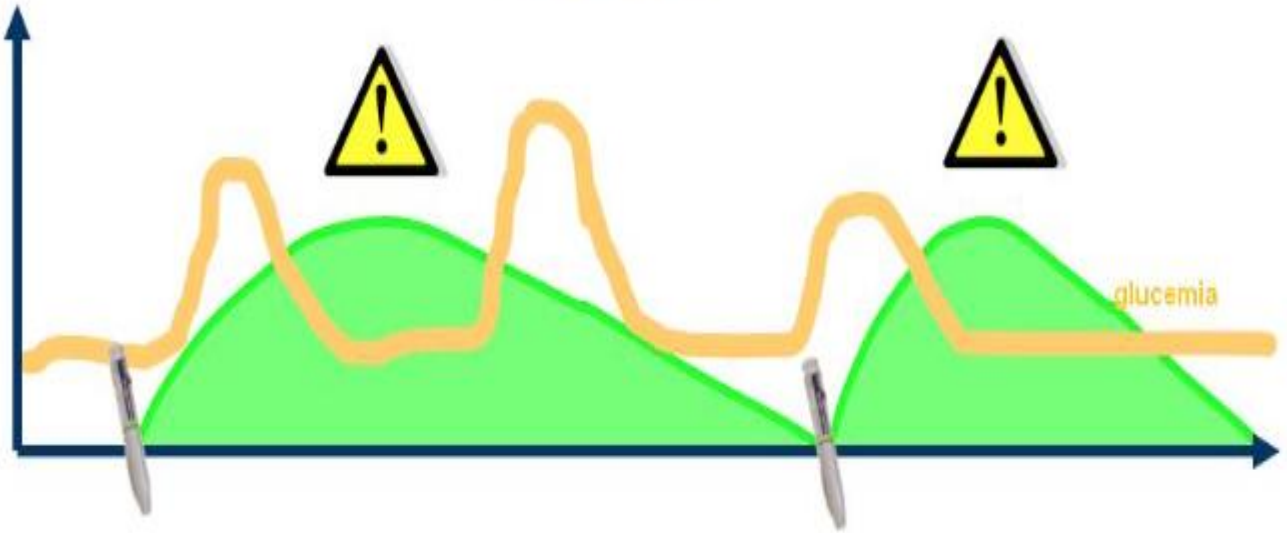
Outpatient Glycemic Control with a Bionic Pancreas in Type 1 Diabetes

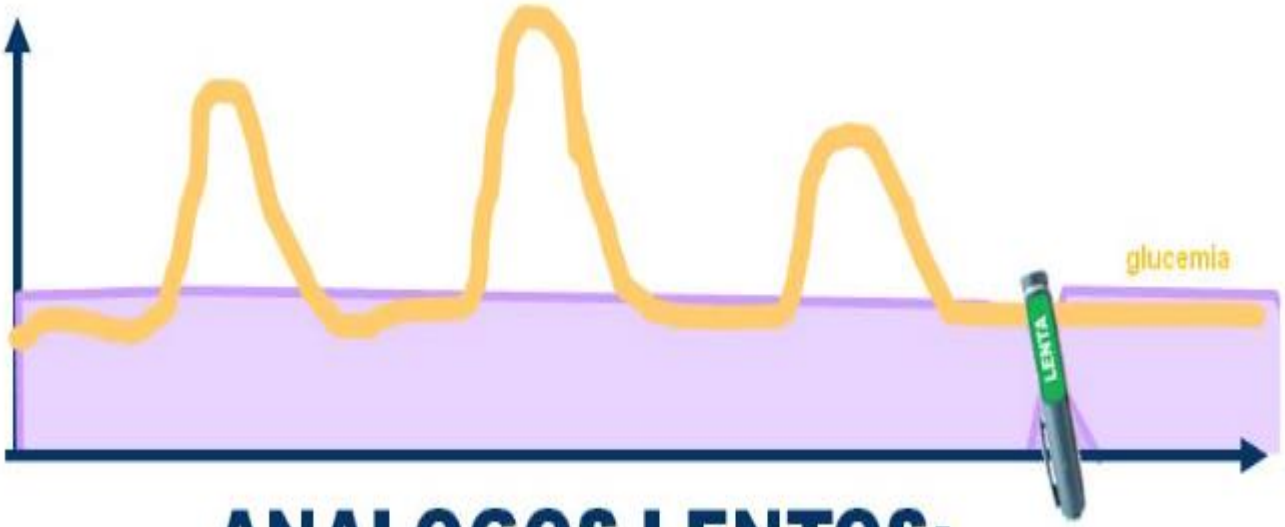
NEJM, 2014; 371: 313-25



NEJM, 2014; 371: 313-25

NPH

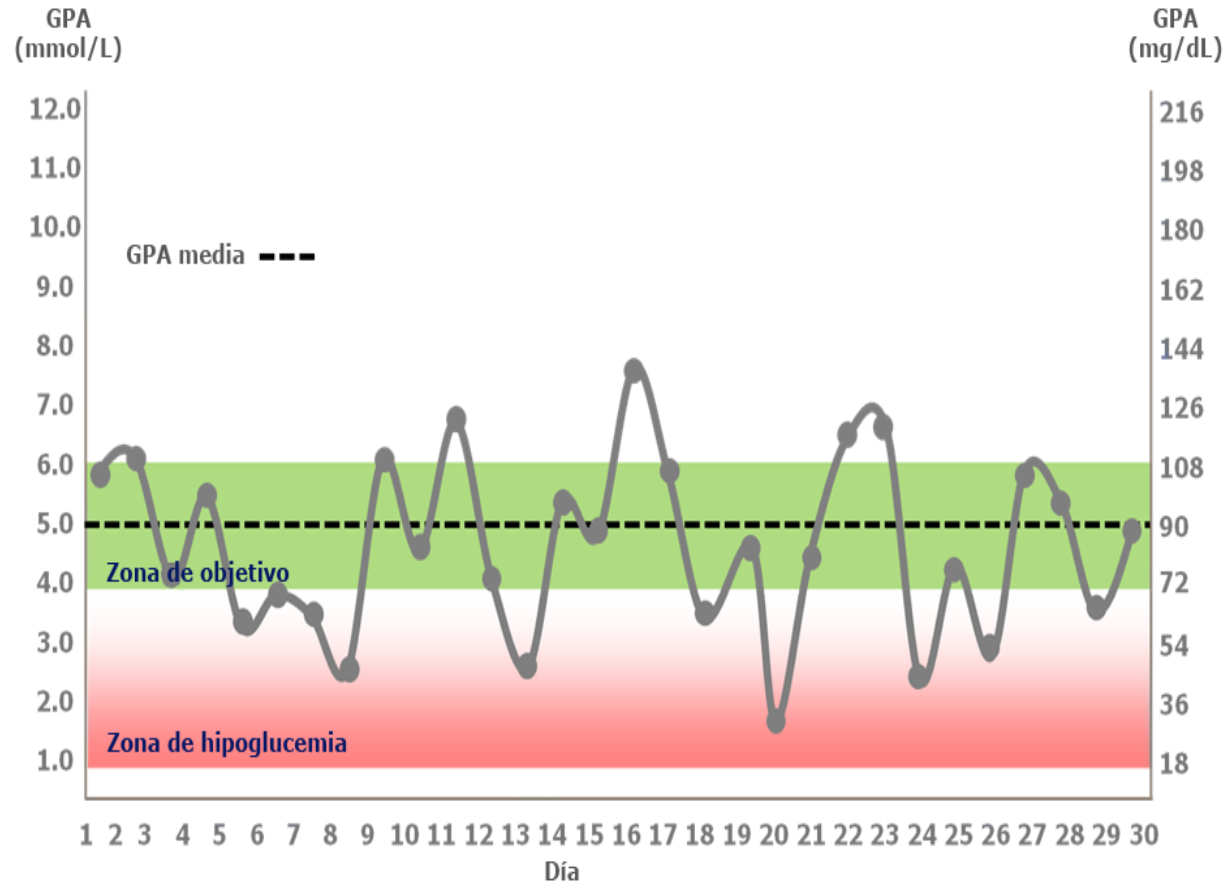




ANALOGOS LENTOS:

INSULINAS EN EL TRATAMIENTO DE LA DM2

Variabilidad glucemia y riesgo de hipoglucemia

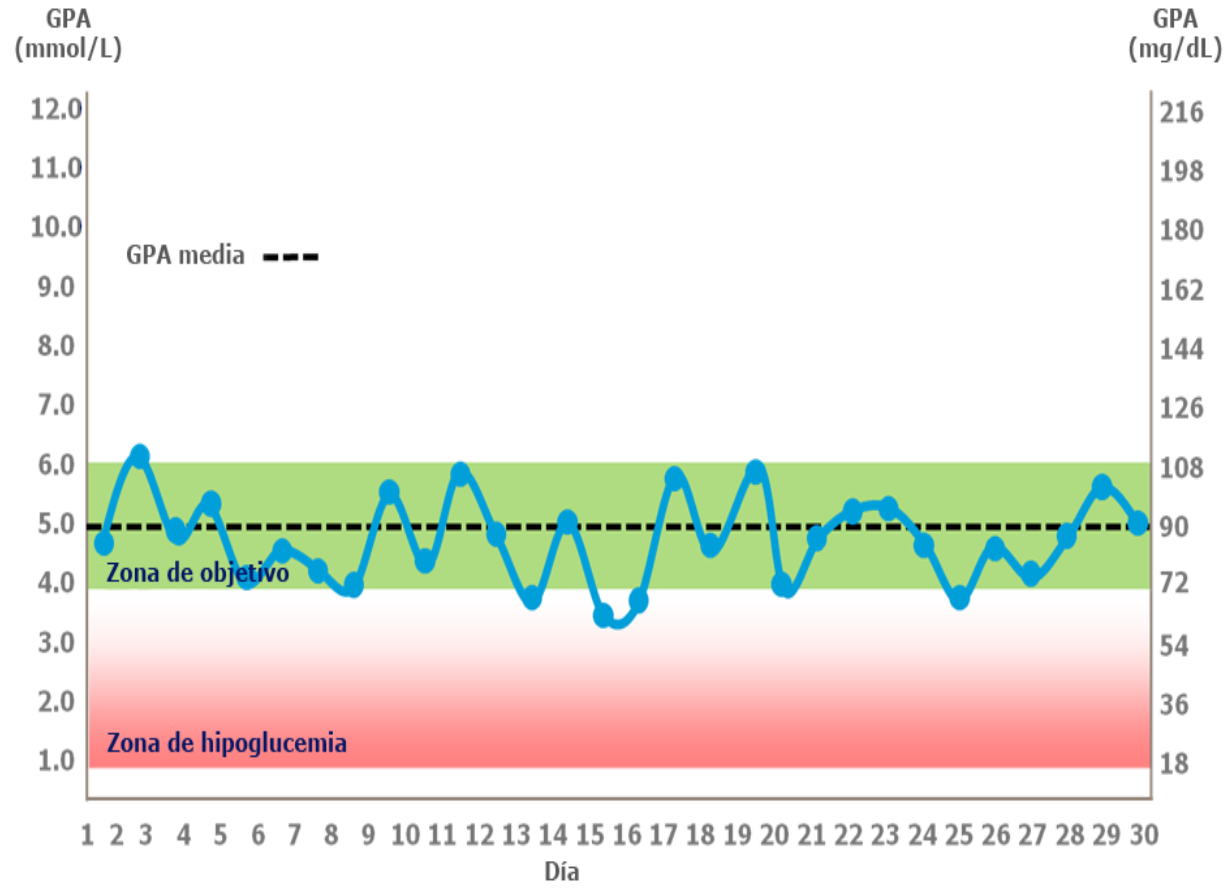


Adaptado de: Kovatchev et al. 2006

Kovatchev et al. Evaluation of a New Measure of Blood Glucose Variability in Diabetes. Diabetes Care 2006;29:2433–8

INSULINAS EN EL TRATAMIENTO DE LA DM2

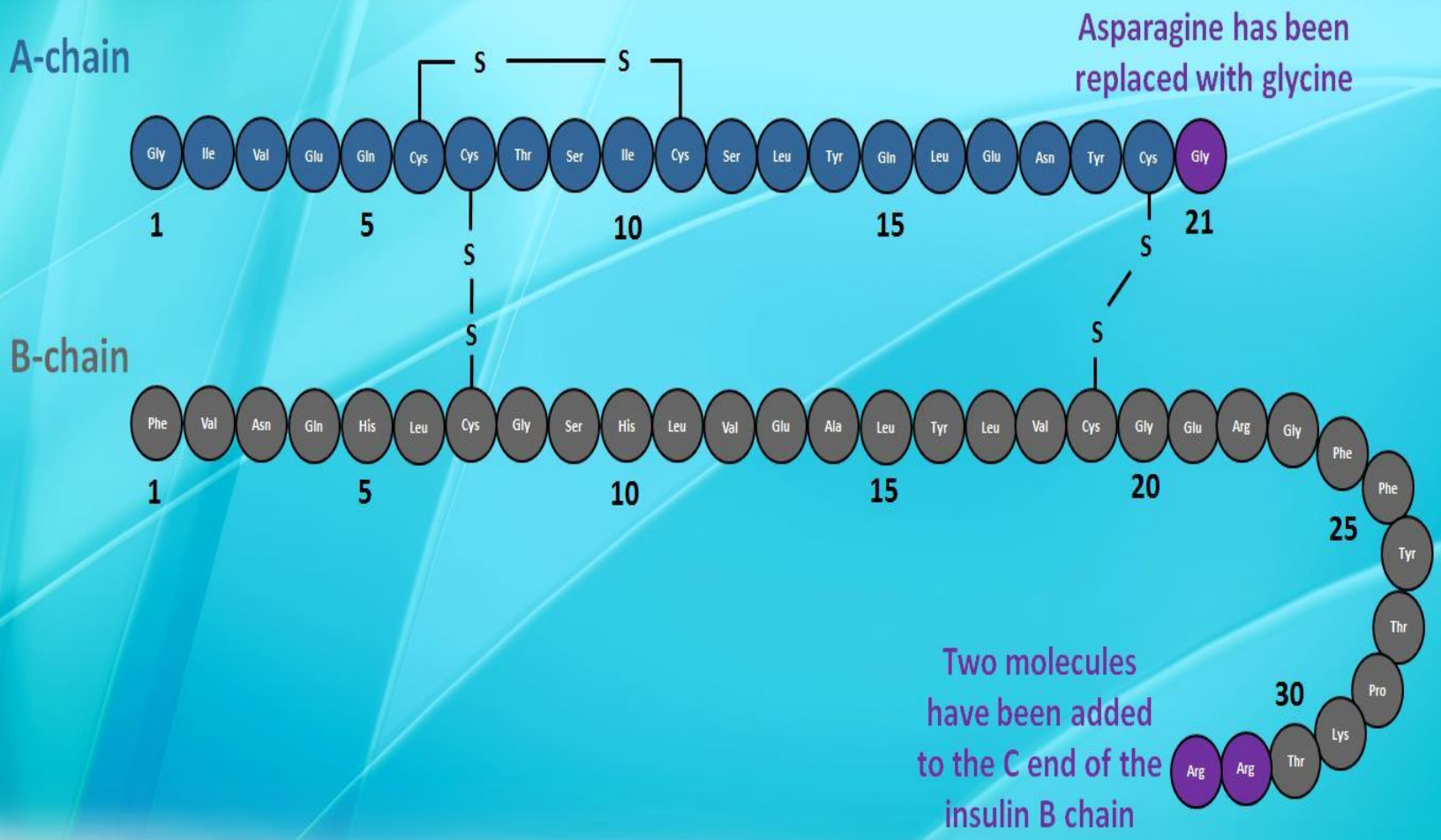
Variabilidad glucemia y riesgo de hipoglucemia



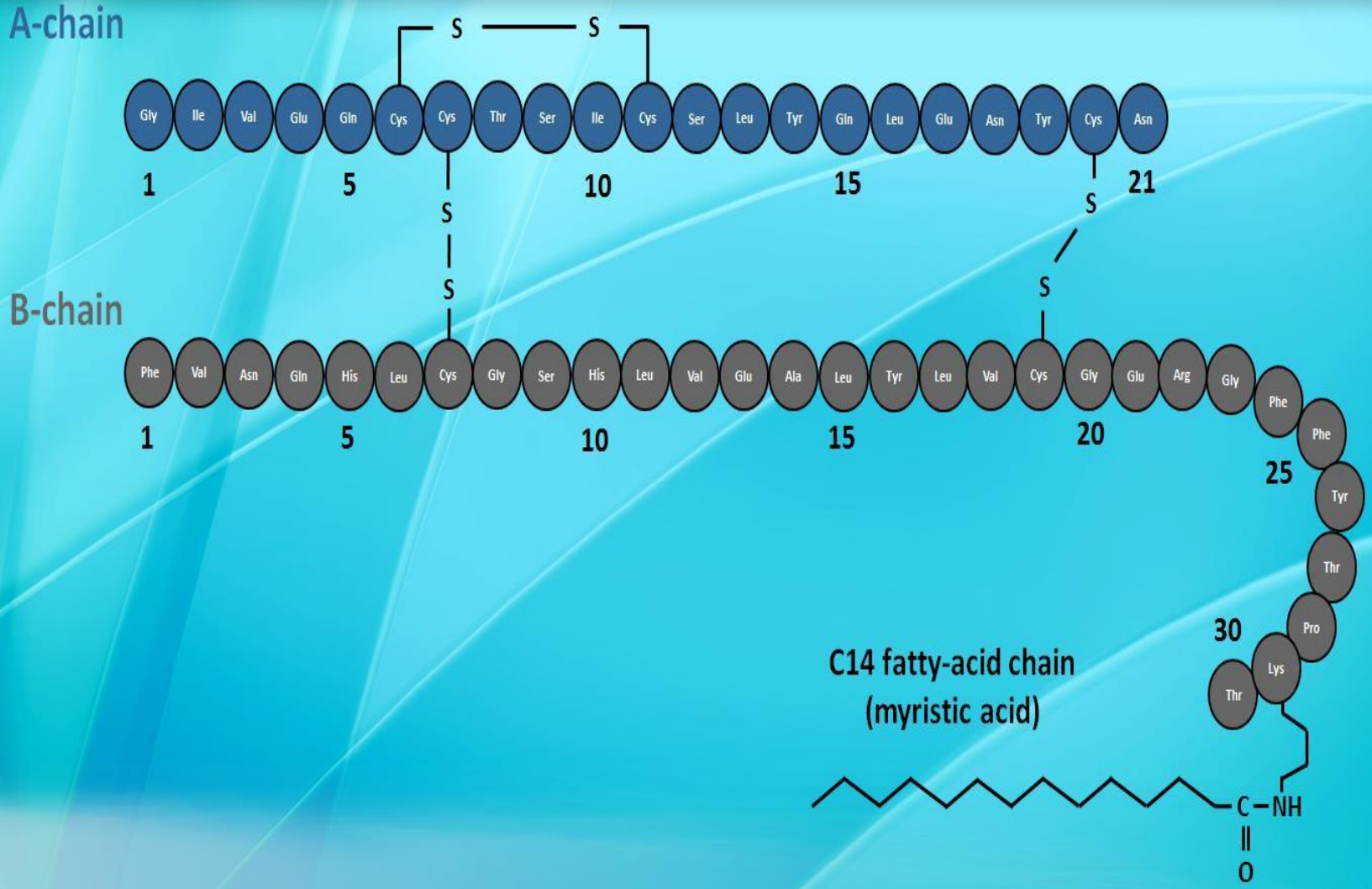
Adaptado de: Kovatchev et al. 2006

Kovatchev et al. Evaluation of a New Measure of Blood Glucose Variability in Diabetes. Diabetes Care 2006;29:2433–8

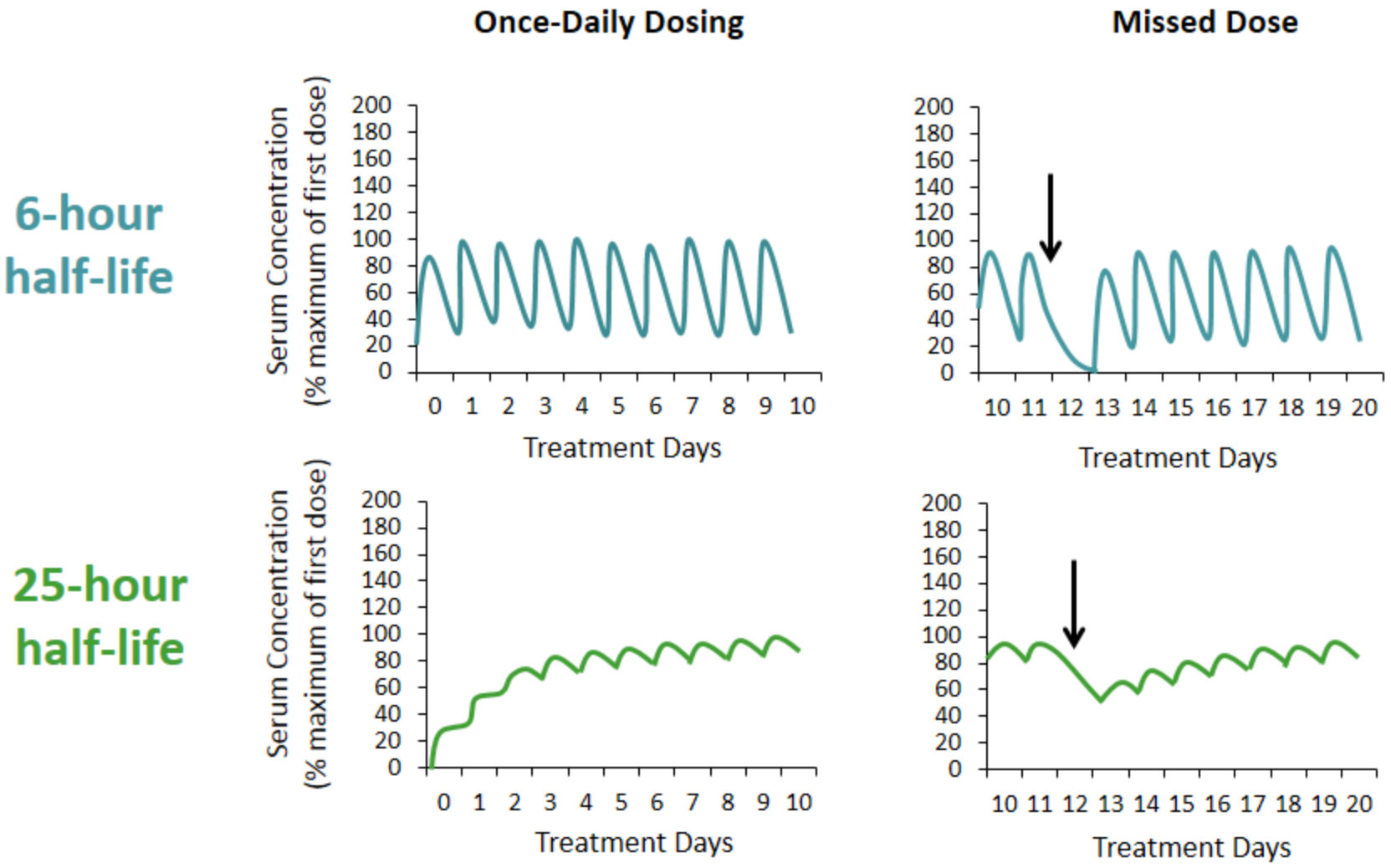
Insulin Glargine



Insulin Detemir



Lower Impact of Missed Dose With Basal Insulins



Adapted from Heise T, et al. *Endocr Pract.* 2014;20:75-83.

Insulin Analogs—Are They Worth It? Yes!

George Grunberger

Diabetes Care 2014;37:1767–1770 | DOI: 10.2337/dc14-0031

Table 1—A1C and hypoglycemia outcomes in 64 comparisons between analog and human insulins in randomized control trials

			ΔA1C (%) [mmol/mol] analog minus regular or NPH			Hypoglycemia*		
Comparison	No. of studies	No. of subjects	Range	No. of significant studies*	Weighted mean	Overall	Nocturnal	Severe†
Type 1 diabetes								
Analog vs. regular‡[a]	17	6,002	(−0.50 to +0.51) [−5.5 to +5.6]	↑4/17	(−0.03) [−0.3]	↓3/16 ↑2/16	↓6/7	↓2/15
Basal vs. NPH§[b]	12	4,770	(−0.40 to +0.05) [−4.4 to +0.5]	↑2/12	(−0.08) [−0.9]	↓4/12	↓6/12	↓2/8
Both analogs vs. NPH/regular‖[c]	3	674	(−0.50 to +0.10) [−5.5 to +1.1]	↑1/3	(−0.23) [−2.5]	↓1/3	↓2/3	↓1/3
Analog vs. regular¶ in pumps[d]	7	445	(−0.53 to +0.03) [−5.8 to +0.3]	↑5/8	(−0.16) [−1.7]	↓2/7	↓1/2	0/5
Type 2 diabetes								
Analog vs. regular#[e]	9	3,507	(−0.52 to +0.03) [−5.7 to +0.3]	↑2/9	(−0.08) [−0.9]	↓1/9 ↑1/9	↓2/4	0/4
Basal vs. NPH**[f]	14	5,742	(−0.34 to +0.21) [−3.7 to +2.3]	↑1/14	(−0.01) [−0.1]	↓6/14	↓10/14	↓1/9
Both analogs vs. NPH/regular††[g]	1	394	Only 1 study	0/1	(−0.07) [−0.8]	0/1	0/1	0/1

Insulin Analogs—Is There a Compelling Case to Use Them? No!

Mayer B. Davidson

Diabetes Care 2014;37:1771–1774 | DOI: 10.2337/dc13-2915

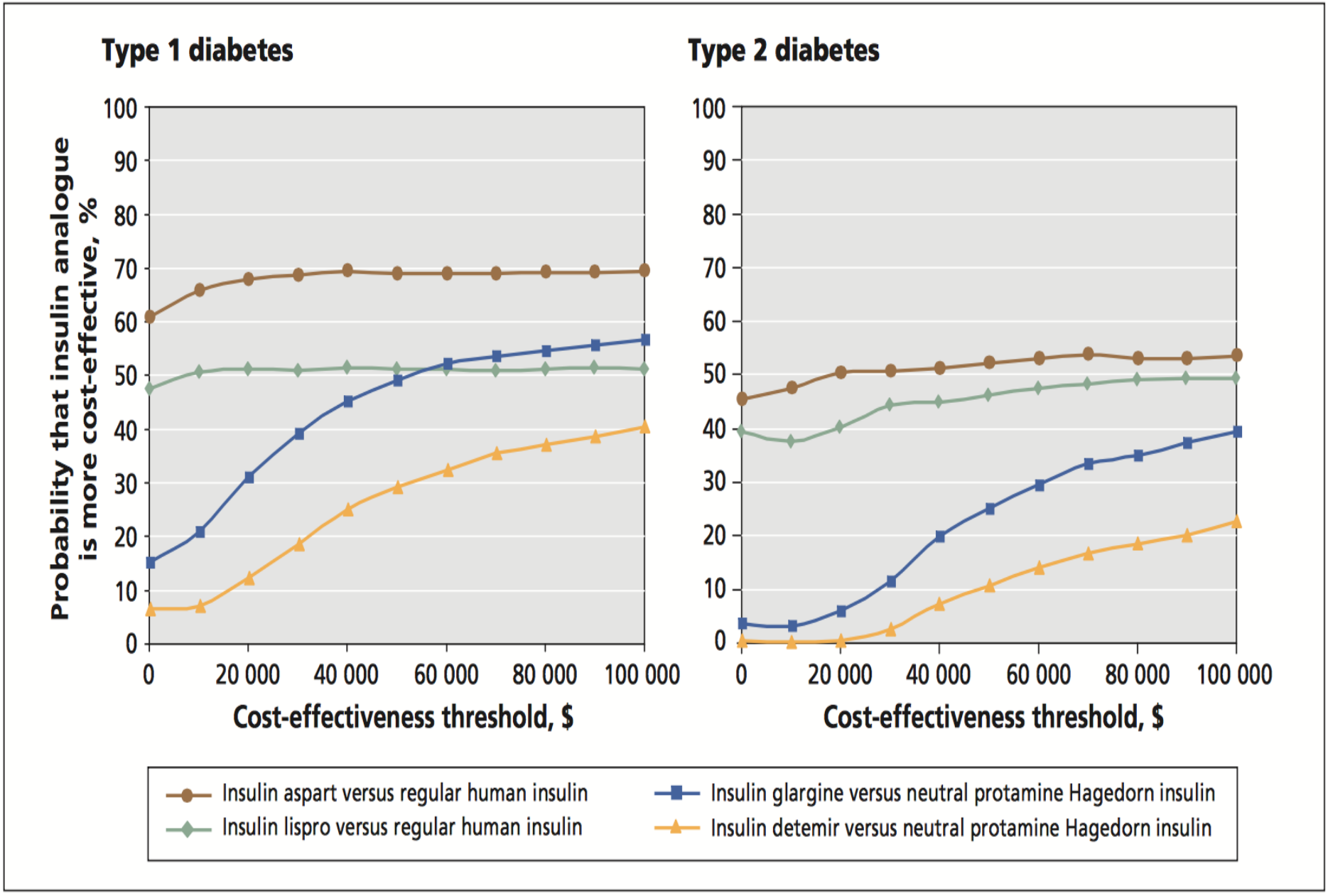


Figure 2: Cost-effectiveness acceptability curves of insulin analogues for the treatment of type 1 and type 2 diabetes mellitus in adults, by treatment comparison. Costs are in 2007 Canadian dollars.

Cameron CG. CMAJ 2009; 180(4):40

Management of Hyperglycemia in Type 2 Diabetes, 2015:
A Patient-Centered Approach

Update to a Position Statement of the ADA an EASD

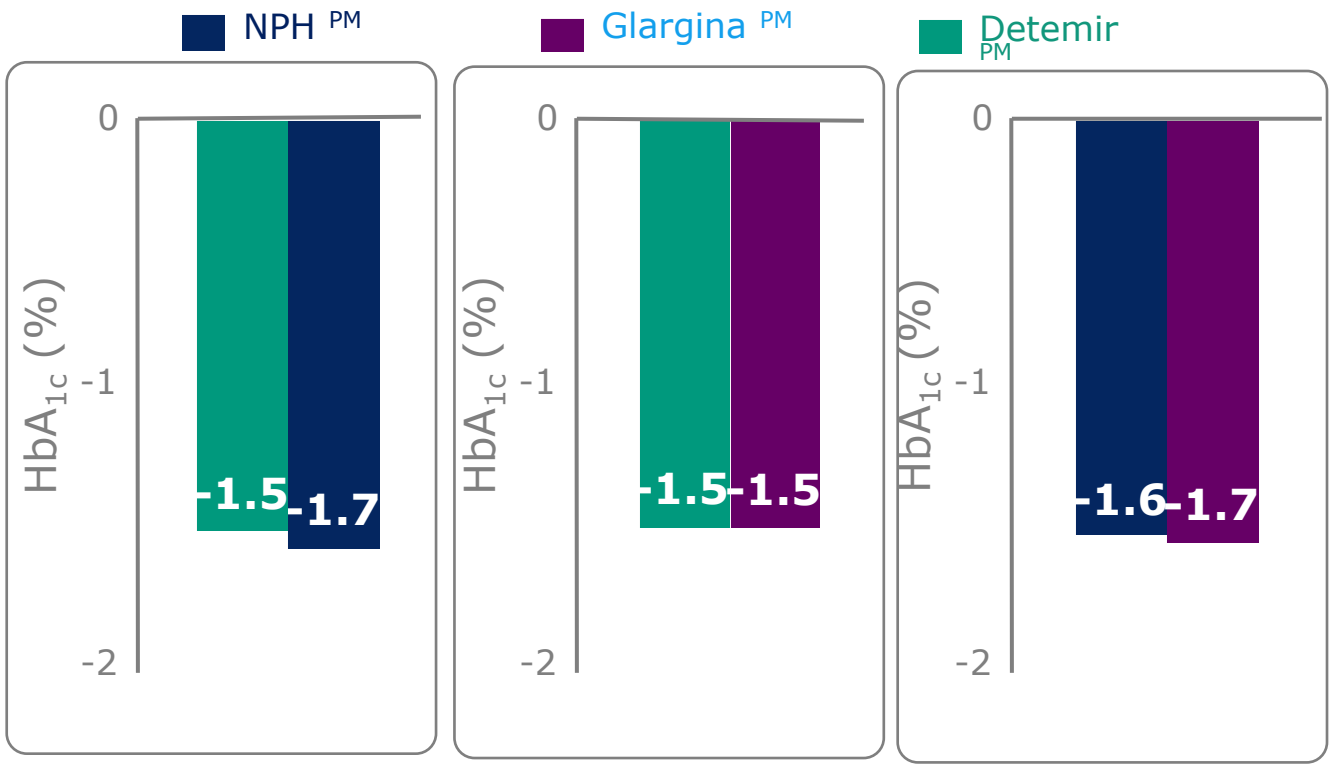
* Regular human insulin and human NPH-Regular premixed formula- tions (70/30) are less costly alternatives to rapid-acting insulin analogs and premixed insulin analogs, respectively, but their pharmacodynamic profiles make them suboptimal for the coverage of postprandial glucose excursions.

* Finally, cost can be an important consideration in drug selection. As the prices of newer medications continue to increase, practitioners should take into account patient (and societal) resources and determine when less costly, generic products might be appropriately used.

Inzucchi et al. Diabetes Care 2015; 38:140-9

INSULINAS EN EL TRATAMIENTO DE LA DM2

Insulinas basales en DM2

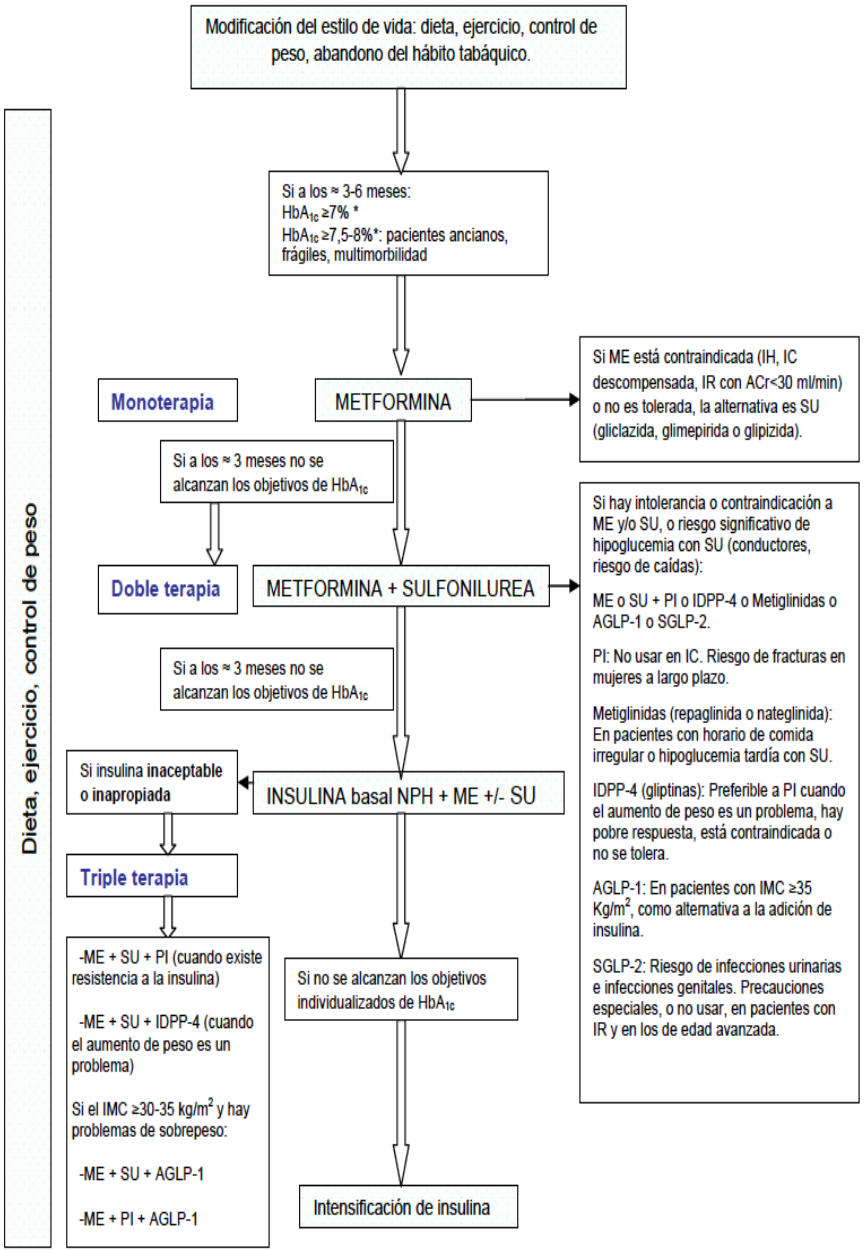


Adaptado de: Philis-Tsimikas et al. 2006[1] Adaptado de: Rosenstock et al. 2008[2] Adaptado de: Riddle et al. 2003[3]

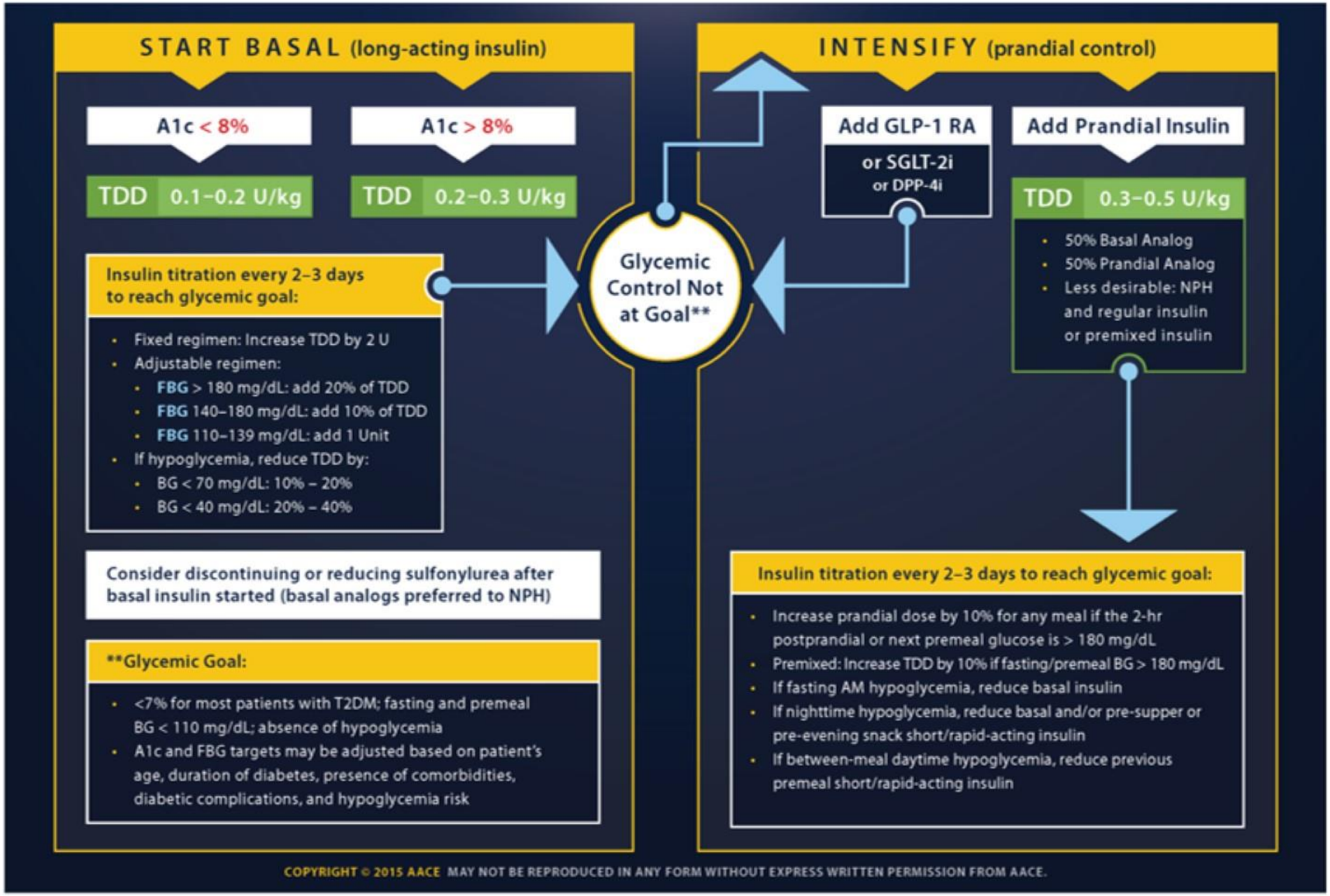
1.Philis-Tsimikas A et al. Comparision of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes. Clin Ther 2006; 28: 1569-1581. 2. Rosenstock et al. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes *Diabetologia* 2008; 51(3):408-16. 3.Riddle *et al.* The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care 2003;26:3080–3086

ALGORITMO DEL TRATAMIENTO DE LA DM2.

(Junio, 2014)



Algorithm for Adding/Intensifying Insulin



Garber AJ, et al. *Endocr Pract.* 2015;21(4):e1-e10.[1]

INDICACIÓN (restricción) DE ANÁLOGOS

- DM1
- DM2 + insulinopenia grave (bolo-basal)
- DM2 + hipoglucemias (basal)

Second-Generation Basal Insulin Analogues

- Introduced to the market or at an advanced stage of clinical testing
- Each has a unique mechanism of protraction:
  - **Degludec**—multihexamer chain (>5000 kDa)[a]
  - **PEGylated lispro**—PEG attached to lispro creates large hydrodynamic size (71-98 kDa)[b]
  - **Glargine U300**—3-fold concentrated insulin with a depot surface area half the size of glargine 100[c]
- Molecular size/depot surface influences the rate of absorption and clearance

a. Wang F, et al. *Diabetes Metab Syndr Obes.* 2012;5:191-204.
b. Sinha VP, et al. ADA 2012. Poster 1063-P.
c. Maorino MI, et al. *Expert Opin Biol Ther.* 2014;14:799-808.

Second-Generation Basal Insulin Analogues

Degludec, PEGLispro, and Gla-300 have improved PK and PD profiles

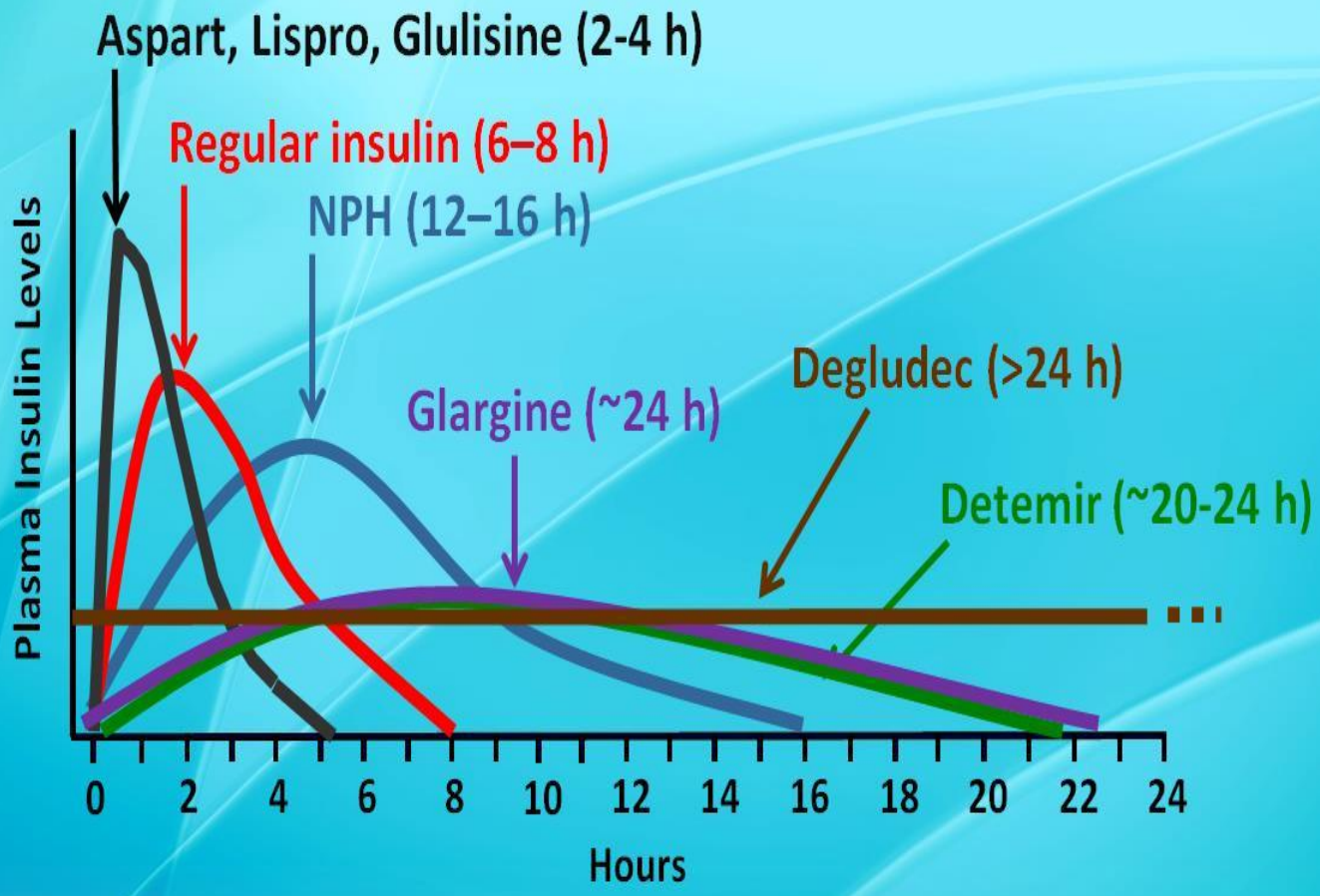
→ Provide ≥24 hours of insulin coverage

→ Flexible dosage timing

→ Make treatment simpler and more convenient

Borgoño, CA, et al. *Endocrin Metab Clin North Am.* 2012;41:1-24.
Owens DR, et al. *Diabetes Metab Res Rev.* 2014;30:104-119.

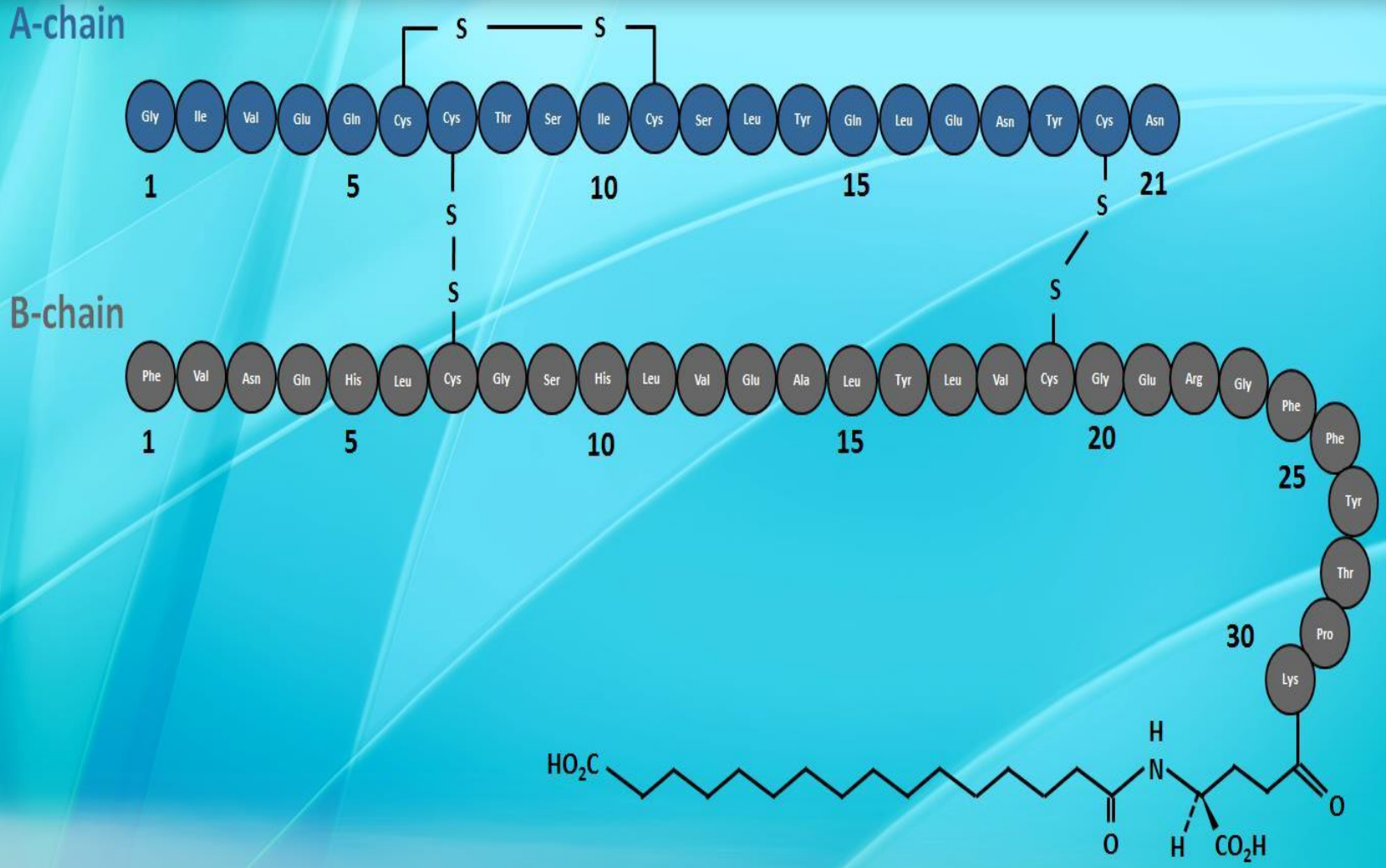
Rapid- and Long-acting Insulin Profiles



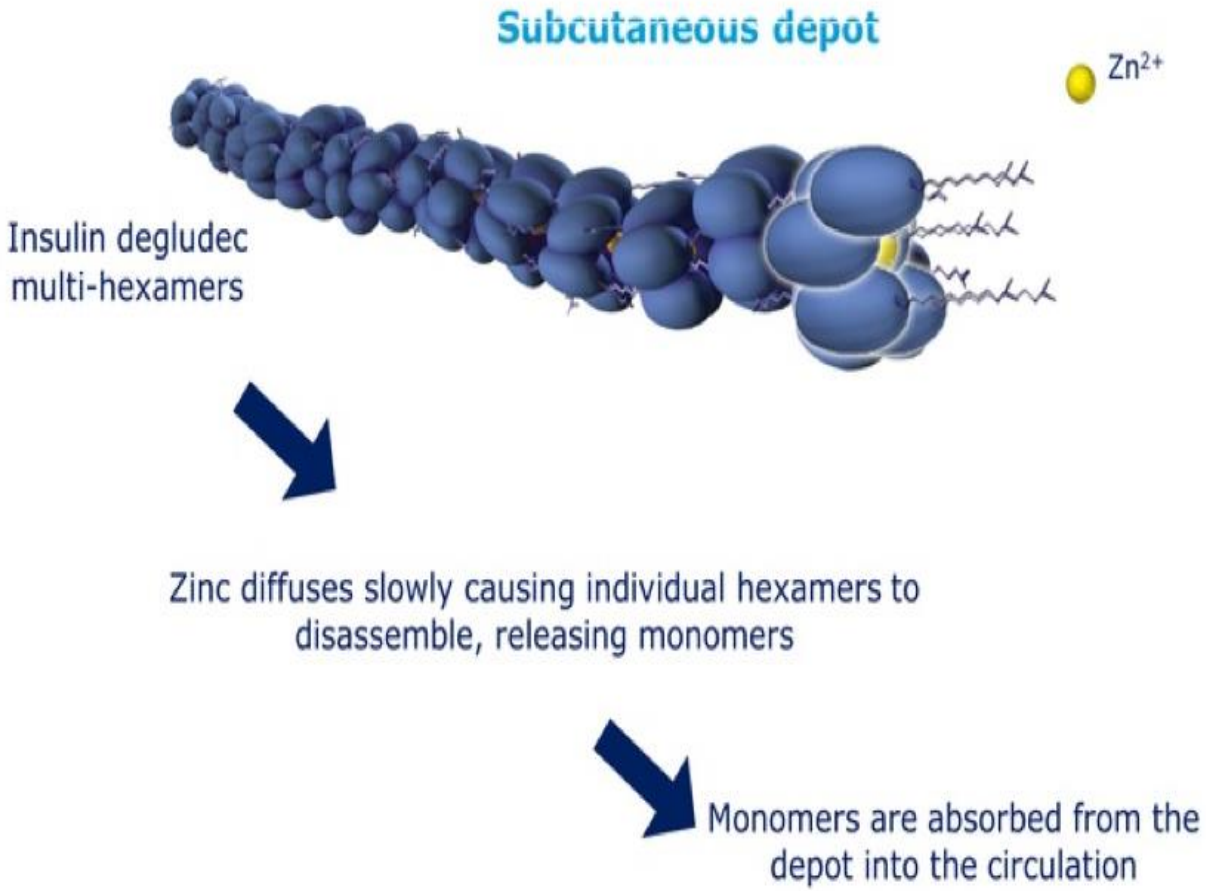
DEGLUDEC

- - Variabilidad intraindividual (x 4)
- = A1c, aunque mejores basales
- - Hipo nocturnas
- + Flexibilidad horaria
- Posible co-formulación 30:70 con aspart
- 100 U/mL y 200 U/mL, = farmacodin.

Insulin Degludec

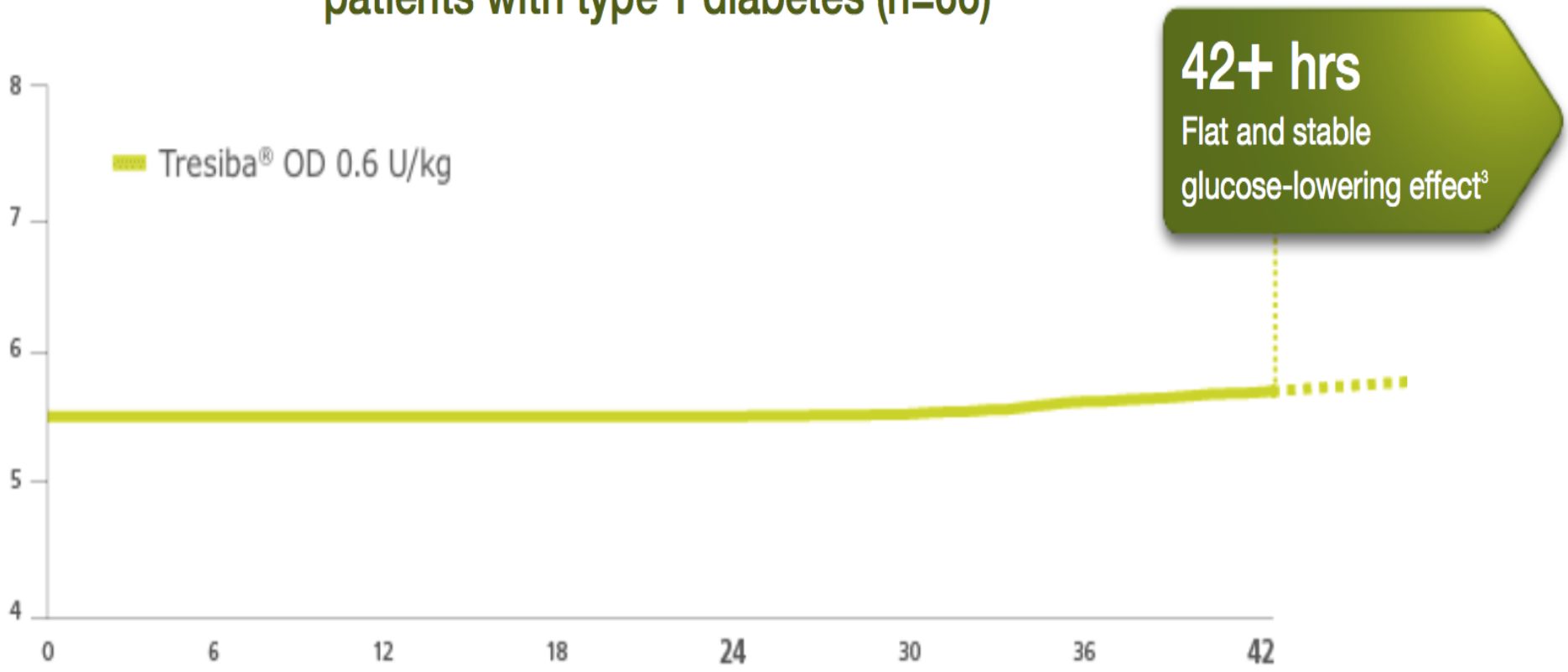


Insulin degludec: slow release from subcutaneous depot

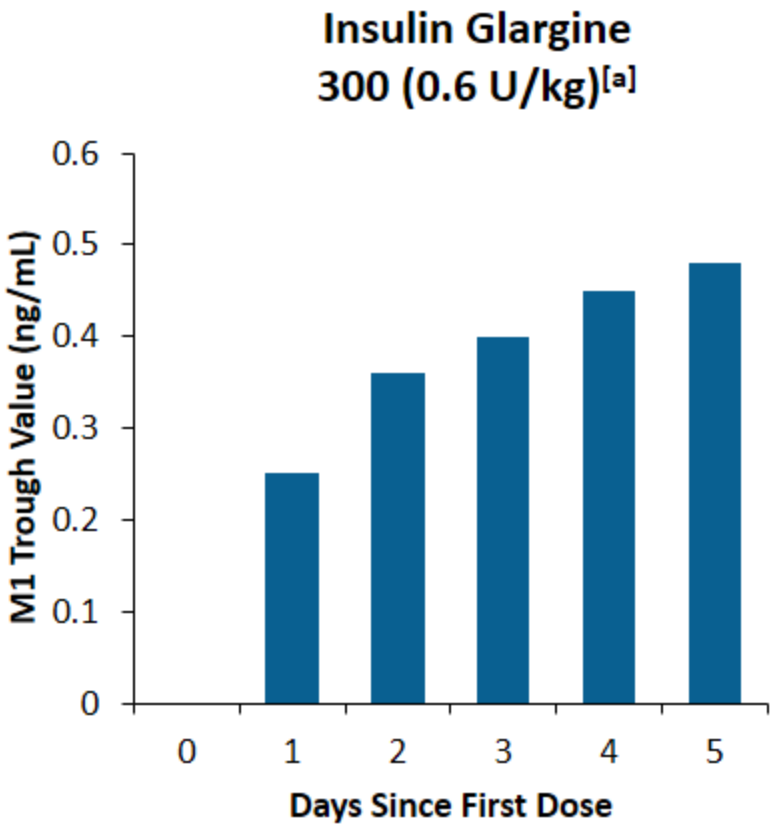


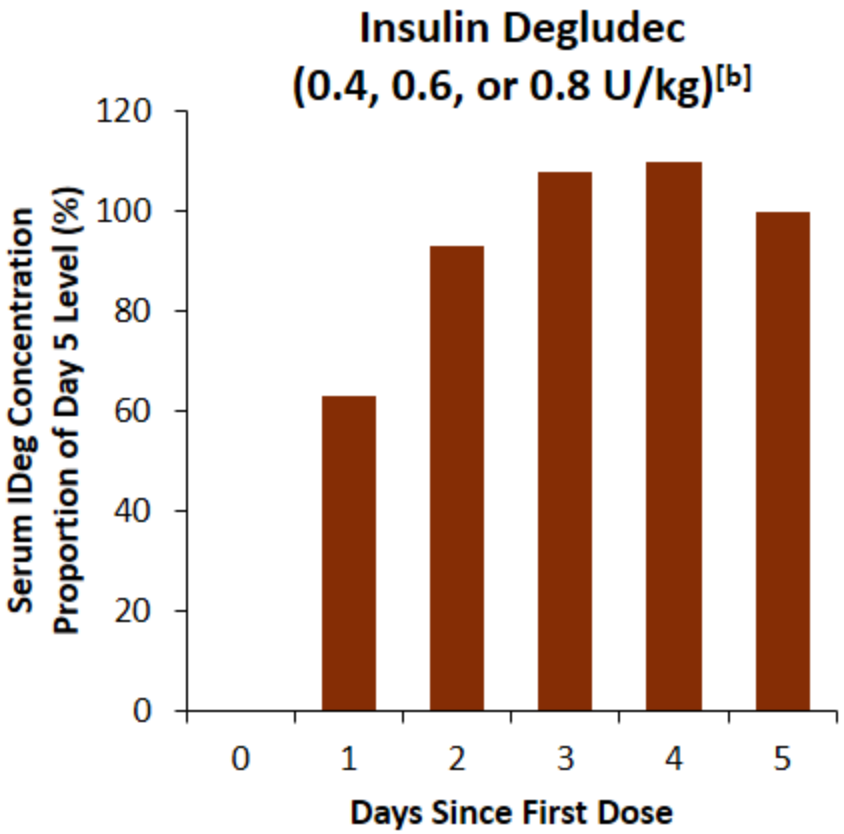
Jonassen *et al. Pharm Res* 2012;29:2104–14

Mean glucose profile in a 42-hour clamp study in patients with type 1 diabetes (n=66)[6]



Novel Basal Insulins Reach Steady State After 3-4 Days

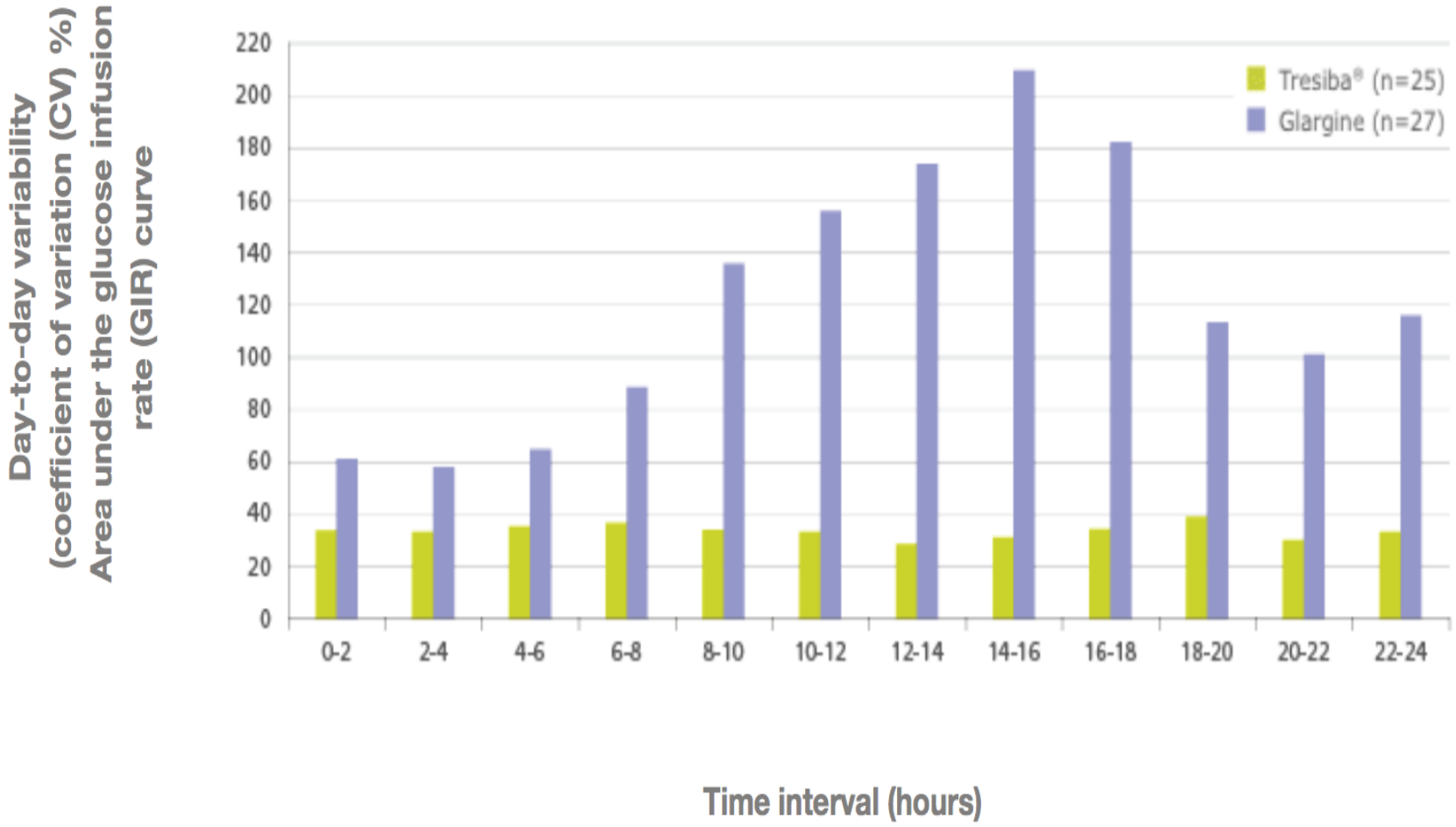




Dosage should not be adjusted more than every 3-4 days after initiation.

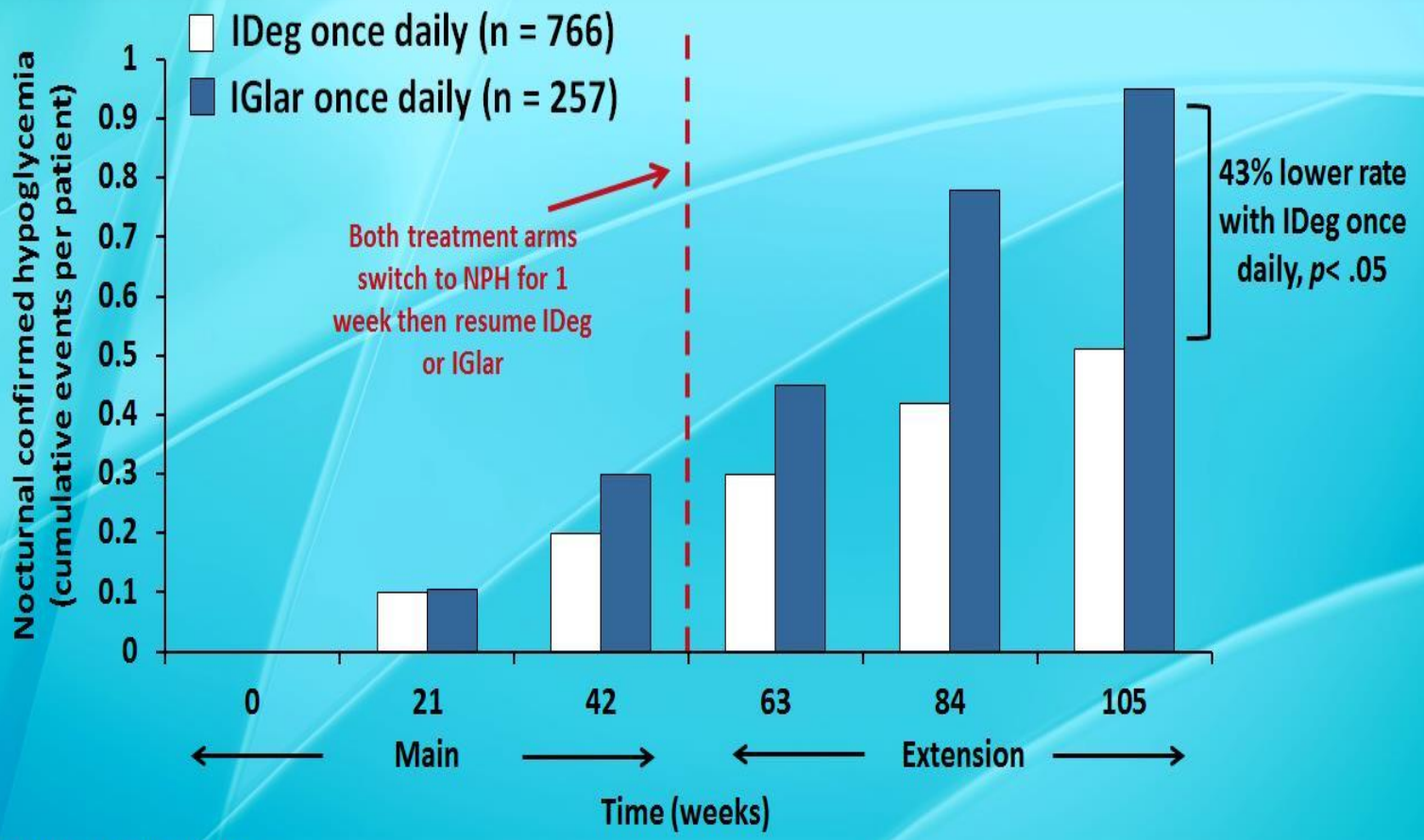
a. Steinstraesser A, et al. *Diabetes Obes Metab.* 2014;16:873-876.
b. Heise T, et al. *Diabetes.* 2012;61(Suppl 1):A259. Abstract 1013-P.

Within-patient variation in glucose-lowering effect over 24 hours, calculated at two-hourly intervals in patients with type 1 diabetes[5]



* CV, coefficient variation

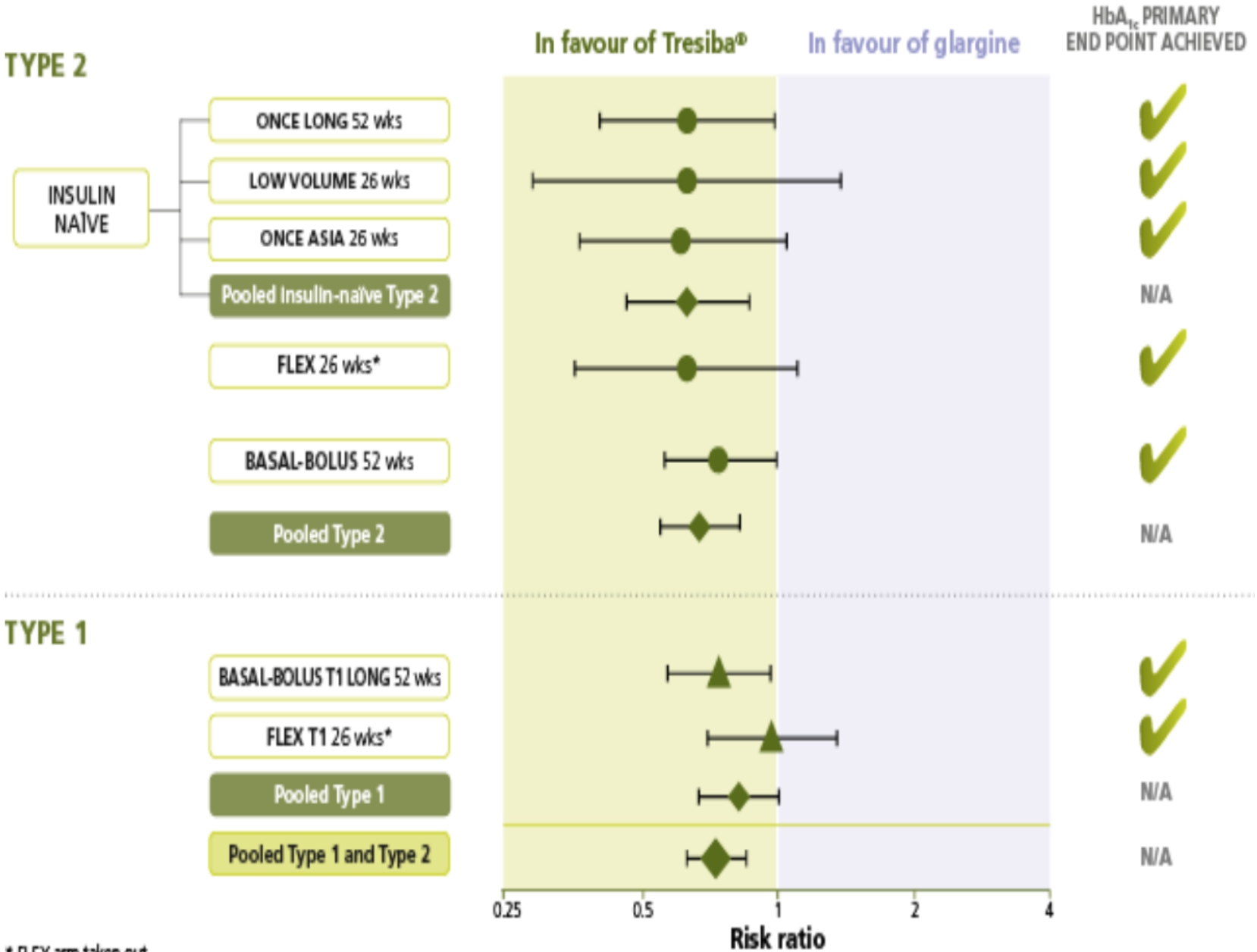
BEGIN Once Long Trial: Nocturnal Confirmed Hypoglycemia



IDeg = insulin degludec; IGlar = insulin glargine

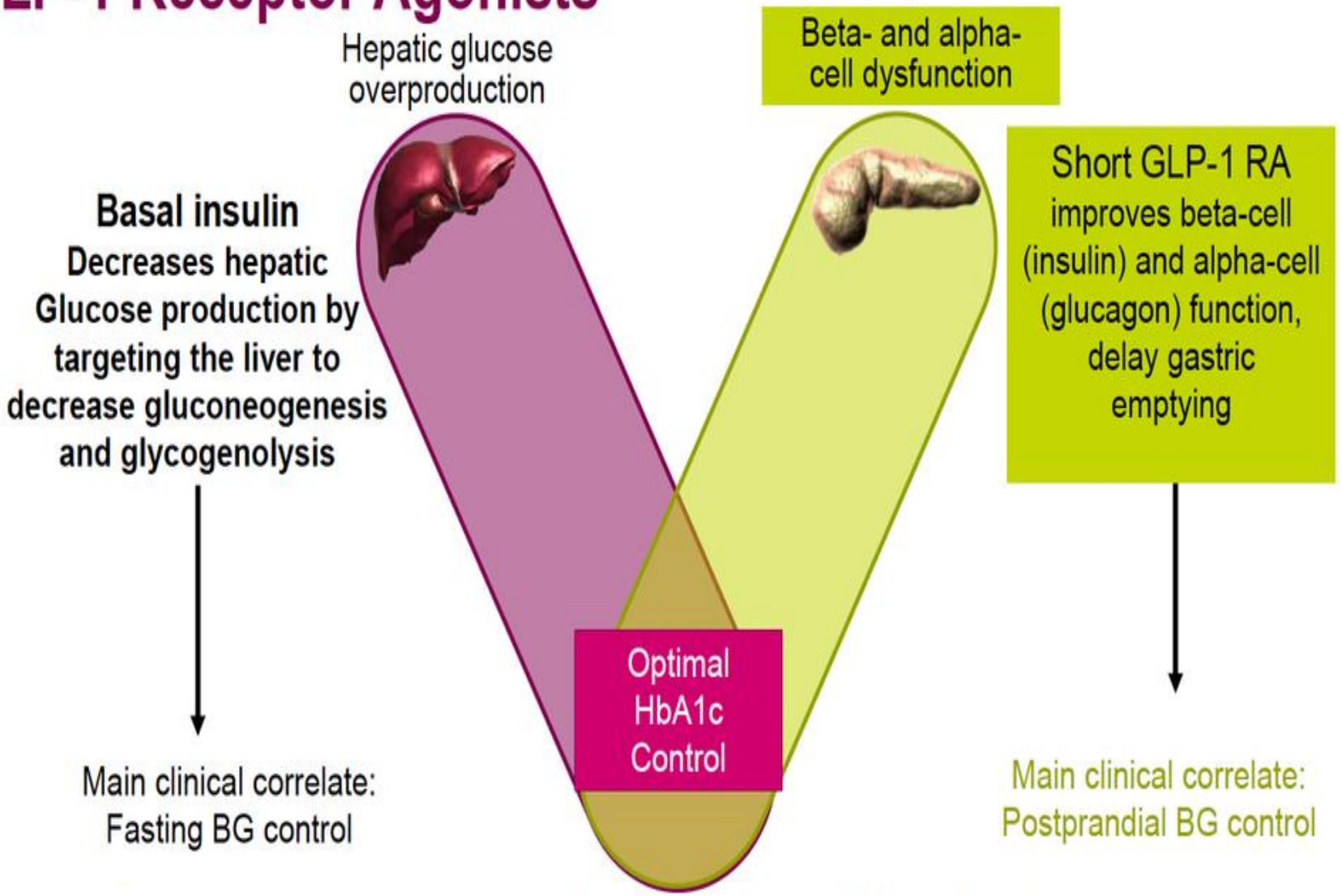
Zinman B, et al. *Diabetes Care.* 2012;35:2464-2471; Rodbard HW, et al. *Diabet Med.* 2013;30(11):1298-1304.

Nocturnal confirmed hypoglycaemia meta-analysis: Tresiba® vs glargine[17]



* FLEX arm taken out

Complementary Actions of Basal Insulin and GLP-1 Receptor Agonists



Baggio LL and Drucker DJ. Gastroenterology 2007;132:2131-2157; Wang Z, et al. Diabetes Care 2010;33:1555-1560; Holst JJ. Physiol Rev 2007;87:1409-1439.

	IDegLira (n=833)	Degludec (n=413)	Liraglutida (n=414)
Reducción en GPA (26 semanas)	-1,9%	-1,4%*	-1,3%*
Reducción en GPA (26 semanas)	-3,6 mmol/l	-3,6 mmol/l	-1,8 mmol/l*
Proporción que alcanza HbA1c <7,0%	81%	65%*	60%*
Cambio en peso corporal	-0,5 kg	+1,6 kg*	-3,0 kg*

*P<0,0001 frente a IDegLira

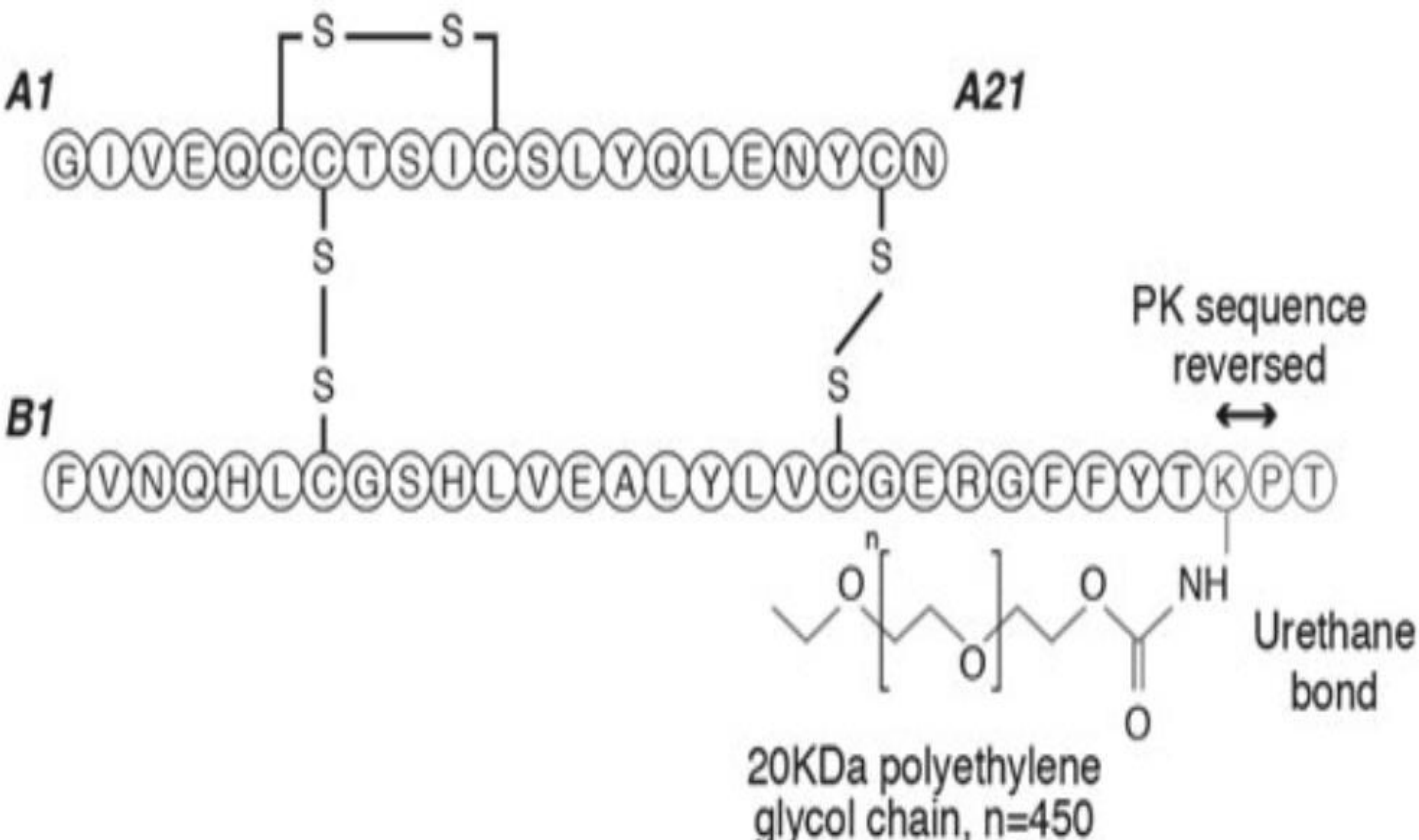
Tabla 2. Eficacia de una combinación en dosis fijas de degludec y liraglutida en comparación con cada uno de los componentes por sí solo

Datos de Gough SC, et al.[53] *GPA = glucosa plasmática en ayunas; HbA1c = hemoglobina glucosilada; SD = desviación estándar. Diferencia calculada del tratamiento con IDegLira frente a degludec: -2,22 kg (intervalo de confianza de 95%: -2,64 a -1,80,* P *<0,0001); IDegLira frente a liraglutida: 2,44 kg (intervalo de confianza de 95%: 2,02 a 2,86,* P*<0,0001).*

PEG-LYSPR (Bil)

Gran tamaño hidrodinámico (extracción hepática, < eliminación renal, retraso absorción, duración > 36h)

- > duración
- < variabilidad, hipo nocturnas, ganancia peso
- > TG, ALT, esteato (RNM), hipo severa en DM1


A1
A21
GIVEQCCTSICSLYQLENYCN
S
S
S
S
S
S
PK sequence reversed
B1
FVNQHLCGSHLVEALYLVCGERGFFYTKPT
n
O
O
O
O
NH
Urethane bond
20KDa polyethylene glycol chain, n=450

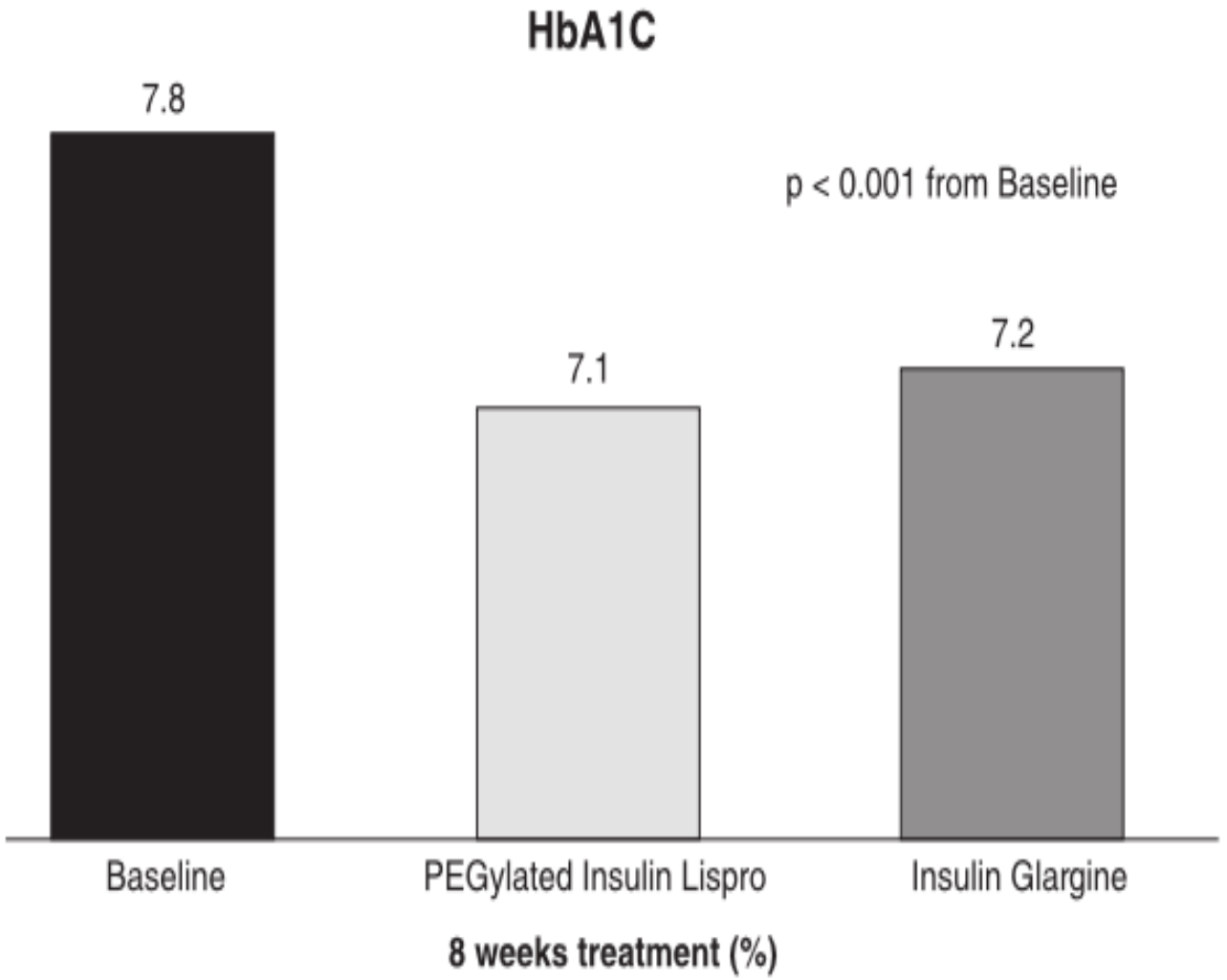


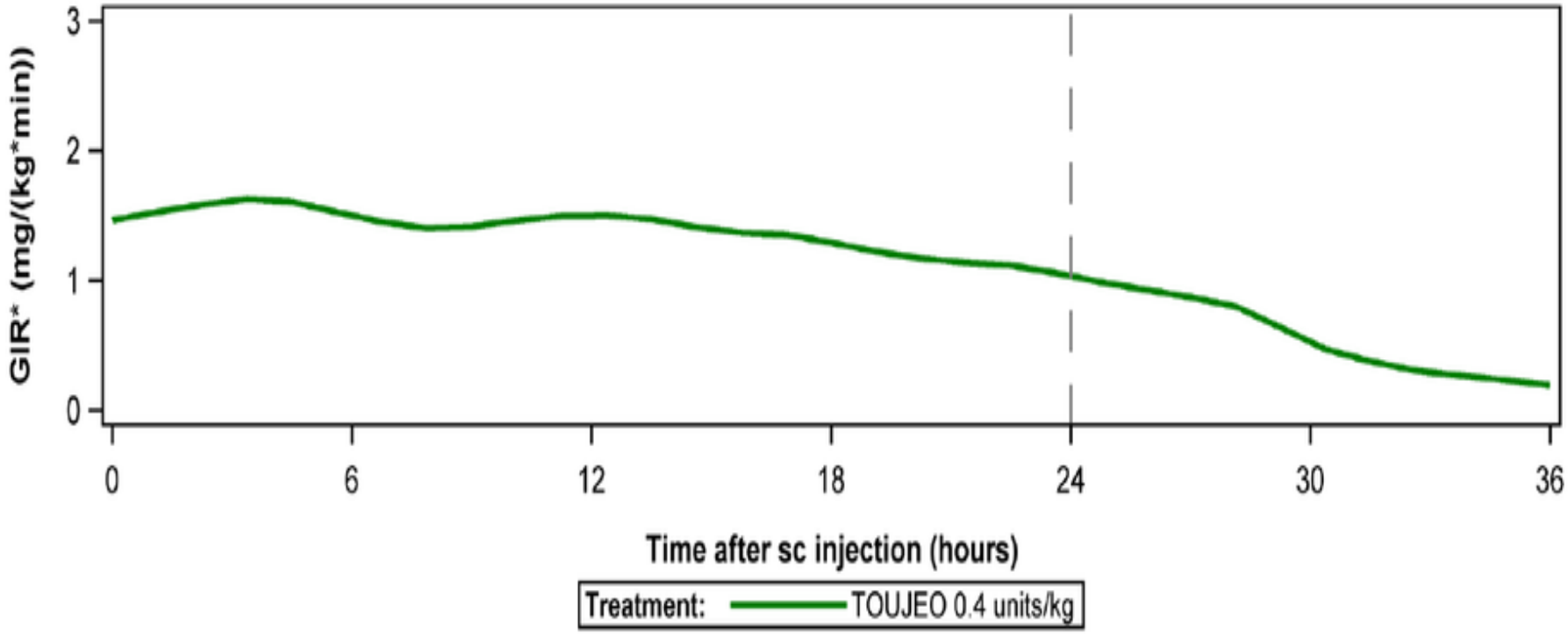
Figure 1. Glycaemic control with PEGylated insulin lispro compared with insulin glargine in patients with T1DM. Adapted from data in table 2, from

Patients Who Will Benefit From High-Dose Insulins

- Many T2DM patients are overweight and require large amounts of insulin
- Novel high-dose insulin analogues provide effective glycemic control, with less weight gain and a low risk for hypoglycemia
- They are of particular benefit for patients who need >4 units of insulin per day

Owens DR, et al. *Diabetes Metab Res Rev.* 2014;30:104-119.
Riddle MC, et al. *Diabetes Care.* 2014;37:2755-2762.
Yki-Järvinen H, et al. *Diabetes Care.* 2014;37:3235-3243.

Figure 1: Glucose infusion rate in Patients with type 1 diabetes in multiple dose administration of TOUJEO



* Glucose infusion rate

Glucose infusion rate: determined as amount of glucose infused to maintain constant plasma glucose levels.

Trials With Gla-300—EDITION 1 and 2

EDITION 1[a]

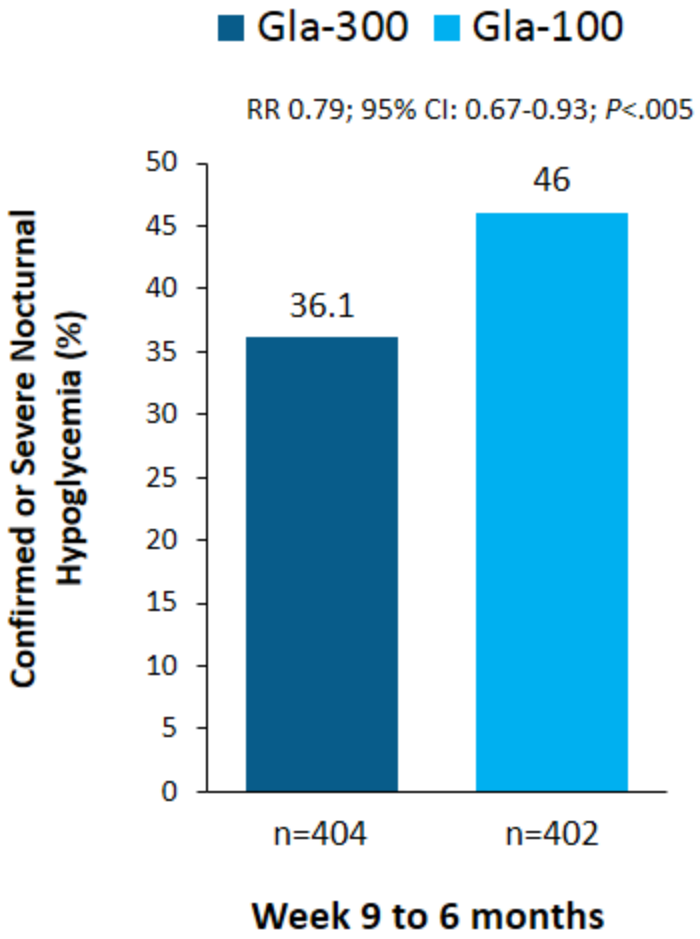
- 6-month, multicenter, open-label, parallel-group, phase 3a study
- 807 participants, mean age 60 years, T2DM duration 16 years, BMI 36.6 kg/m^2, HbA1c 8.15%
- Patients taking basal insulin (≥42 U/day) plus mealtime insulin
- Randomly assigned to receive 300 U/mL or 100 U/mL glargine

EDITION 2[b]

- 6-month, multicenter, open-label, parallel-group, phase 3a study
- 811 participants, mean age 58 years, T2DM duration >12 years, BMI 34.8 kg/m^2, HbA1c 8.24%
- Patients taking basal insulin (≥64 U/day) plus oral antihyperglycemic agent
- Randomly assigned to receive 300 U/mL or 100 U/mL glargine

a. Yki-Järvinen H, et al. *Diabetes Care.* 2014;37:3235-3243.
b. Riddle MC, et al. *Diabetes Care.* 2014;37:2755-2762.

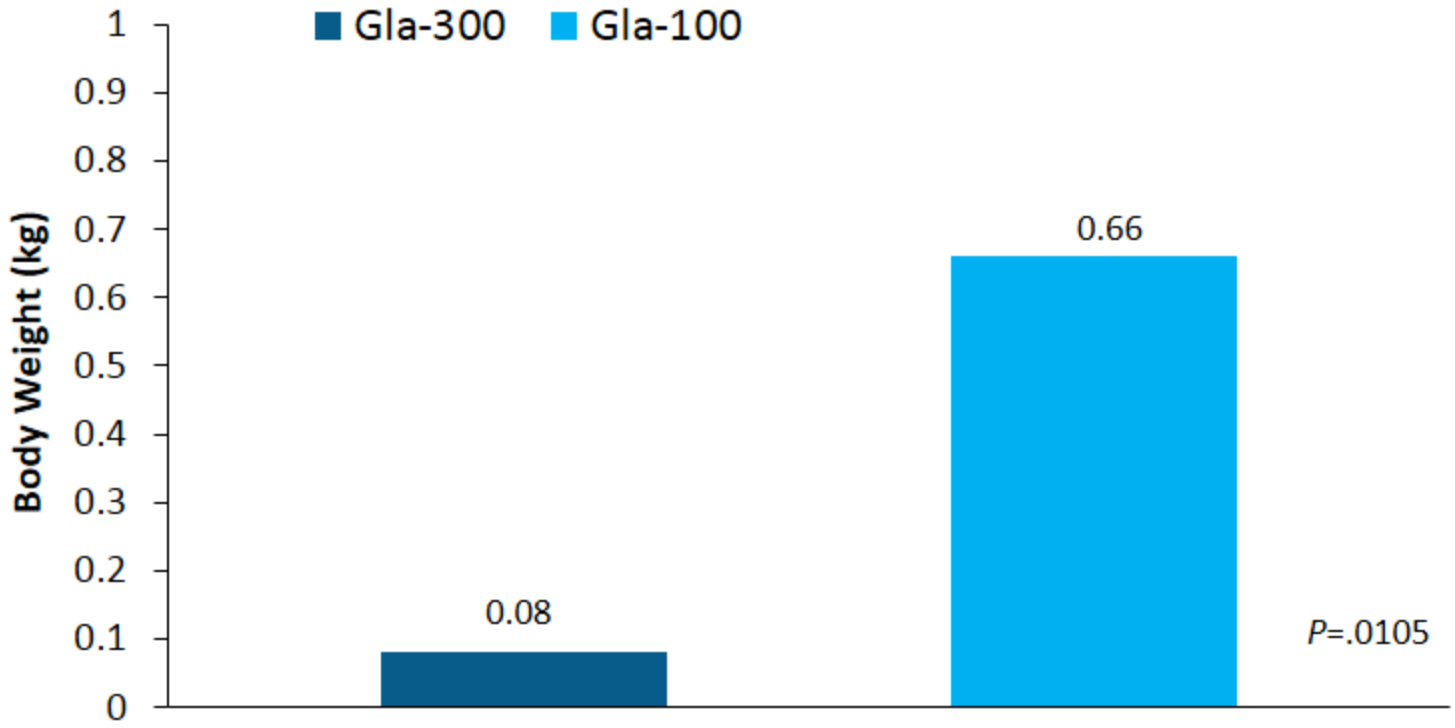
EDITION 1—Less Nocturnal Hypoglycemia With Gla-300



- Consistently lower rates of nocturnal hypoglycemia with Gla-300 compared with Gla-100
- Lower rates of other categories of hypoglycemia
- Lower hypoglycemia rates also in the first 8 weeks of treatment

Riddle MC, et al. *Diabetes Care.* 2014;37:2755-2762.

EDITION 2—Less Weight Gain With Gla-300



Gla-300 achieves glycemic control with a lower risk for nocturnal hypoglycemia and significantly less weight gain than Gla-100

Yki-Järvinen H, et al. *Diabetes Care.* 2014;37:3235-3243.

ADA. BOSTON, 9 DE JUNIO

- € >500% insulinas en 10 años (USA)
- U-300
- Degludec, sobretodo asociado a lira (vs. glargina): A_1c 1.8% vs. 1.1%, <A_1c-7% (71% vs. 47%), -1.4kg vs. +1.8kg, -57% hipo)
- Peg-lispro (n:2800, DM2, -kg, -A_1c 0.3%)
- Ins. Semanales (labs, AB-101)

LAS SEIS “P”

- Patofisiología
- Potencia
- Pluses (kg, TA)
- Precauciones (hipo)
- Practicidades
- Precio

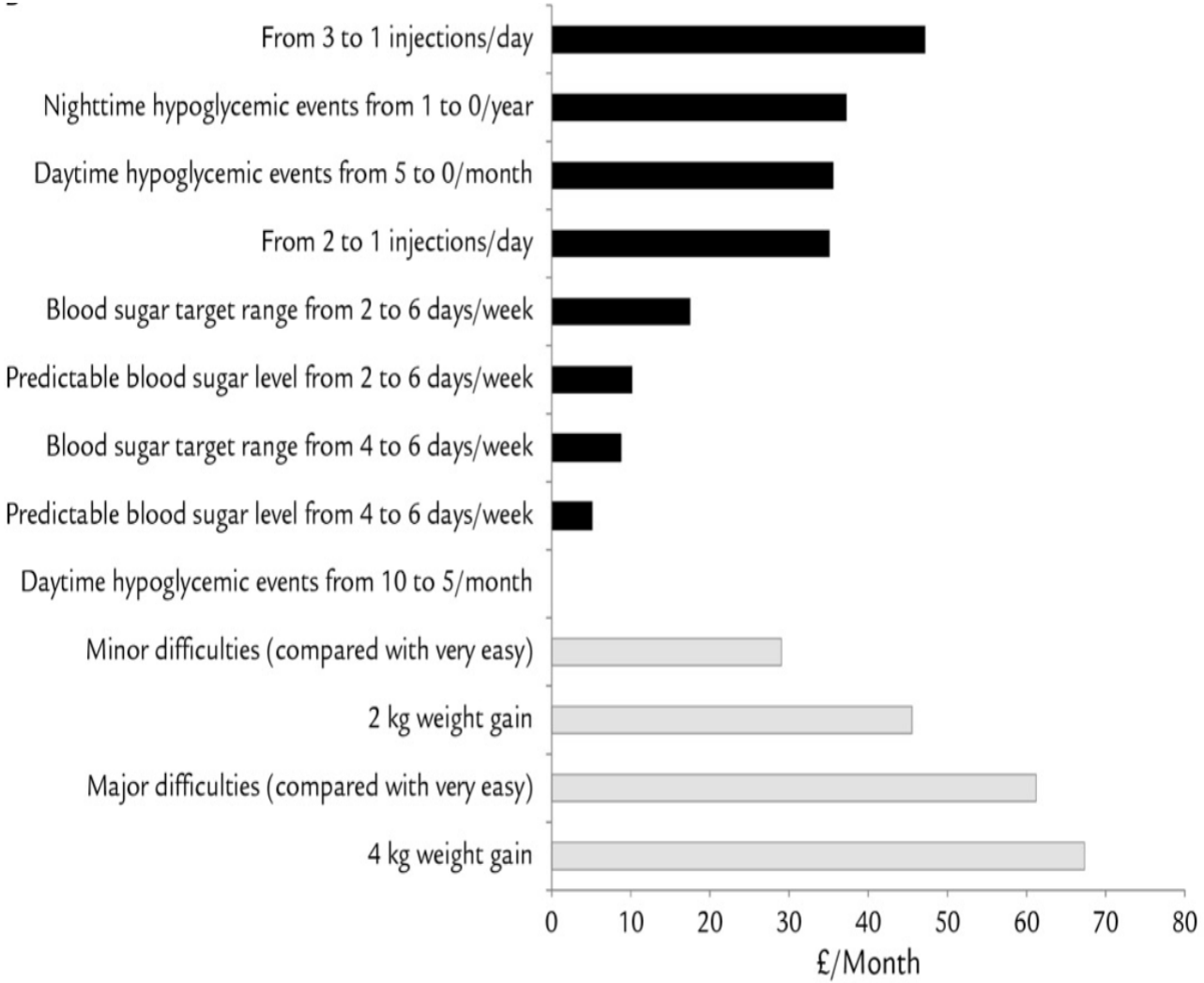
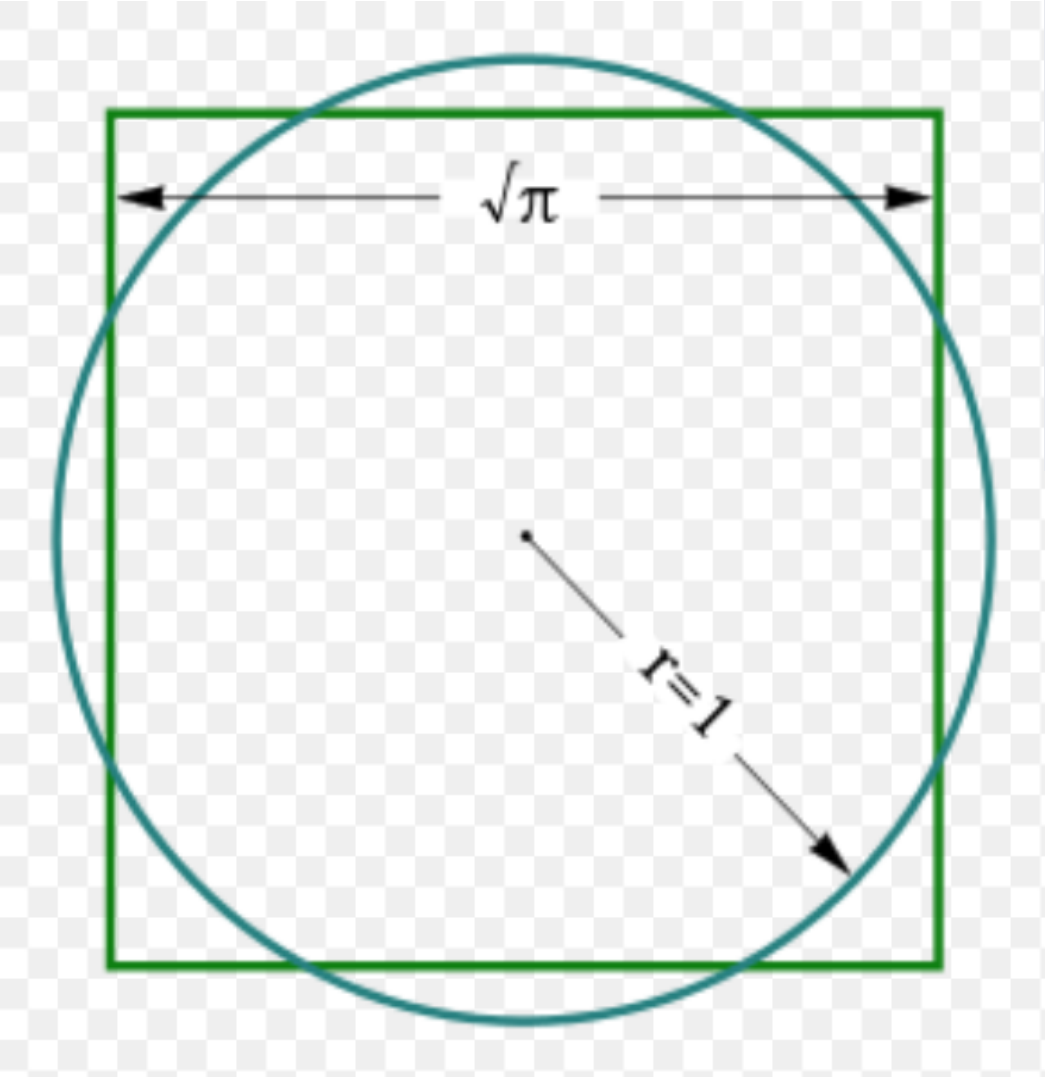


Figure. Comparison of insulin treatment attributes based on willingness to pay (WTP) calculations from a survey

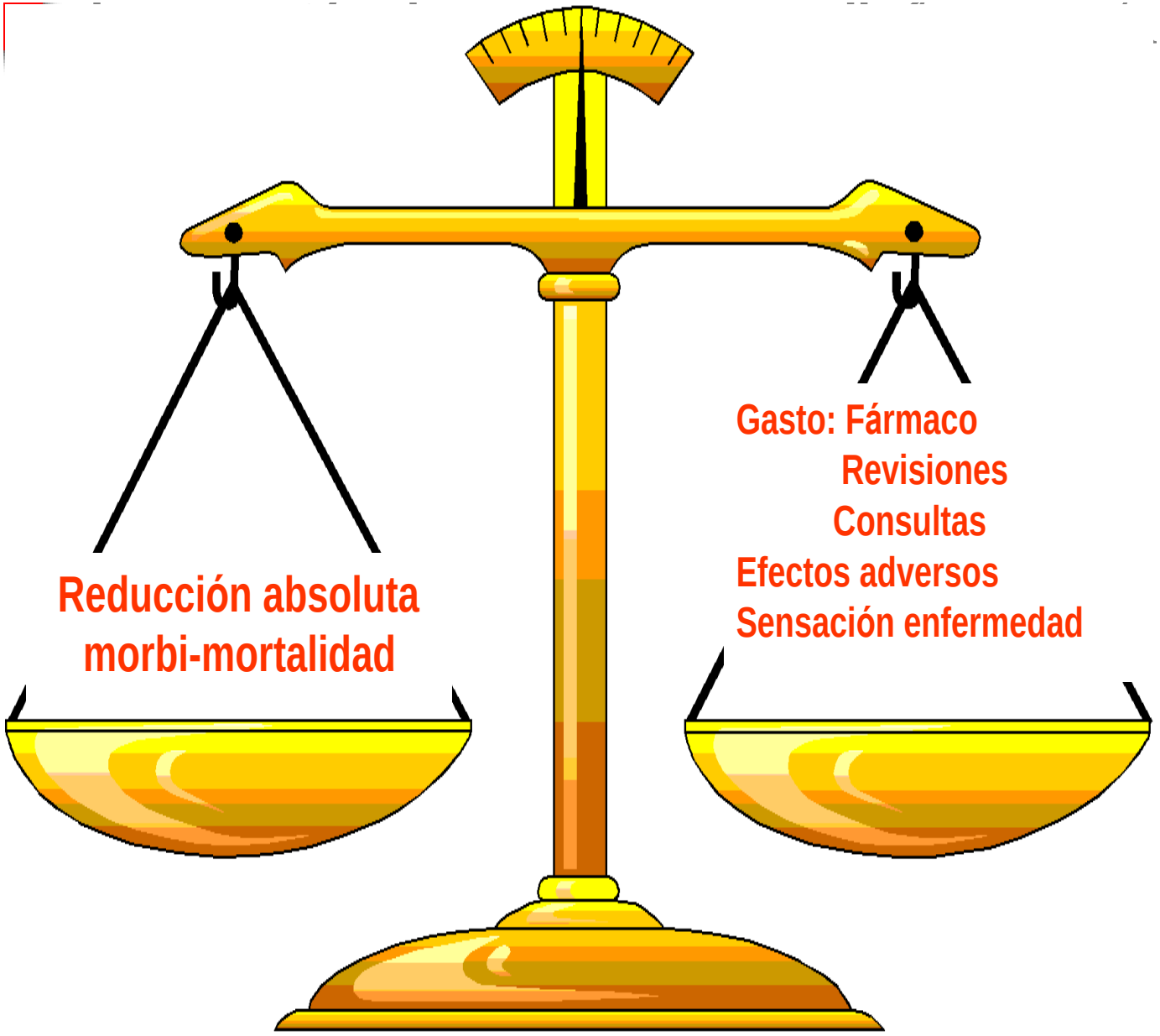


or type 2 diabetes. With the exception of rapid-acting insulin analogues in type 1 diabetes, routine use of insulin analogues, especially long-acting analogues in type 2 diabetes, is unlikely to represent an efficient use of finite health care resources.

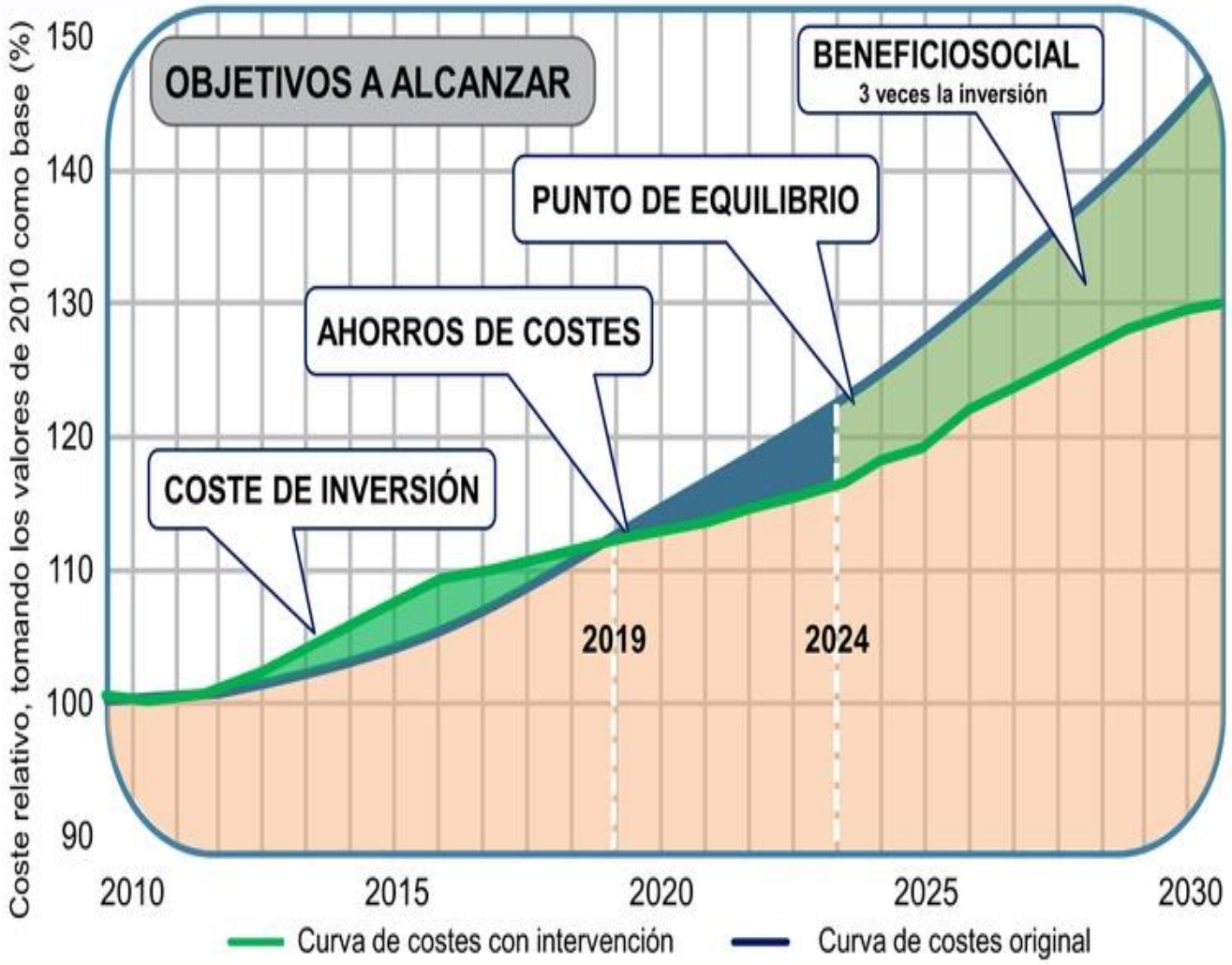
COSTES EN DM2:

- Directos (adquisición)
- Complicaciones crónicas
- Hipoglucemias

- ¡ Miedo a hipoglucemias !


Reducción absoluta
morbi-mortalidad
Gasto: Fármaco
Revisiones
Consultas
Efectos adversos
Sensación enfermedad

El coste del control intensivo de la glucemia: ¿podemos afrontarlo?



Simulación usando la información del modelo de diabetes de UKPDS y CORE

Insulina