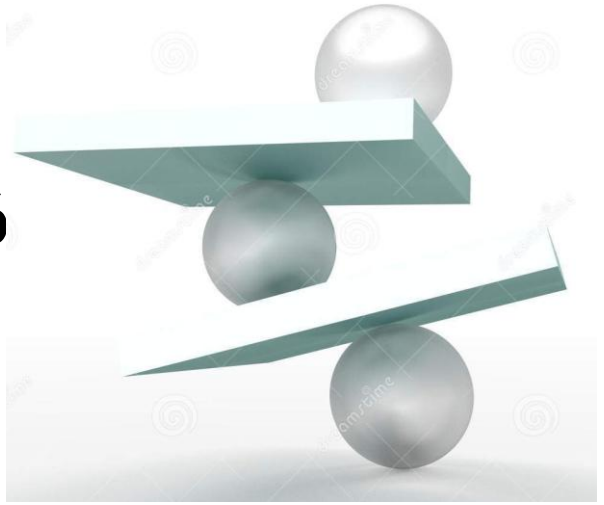
Diabetis inestable: existeix realment?

Eva Aguilera

Servei Endocrinologia i Nutrició



Germans Trias i Pujol
Hospital

DIABETIS INESTABLE, LÀBIL,"*BRITTLE*" DIABETES

Autor	Definició	Any
Woodyatt	Fluctuacions marcades dels nivells de glucèmia sense causa aparent	Anys 30
Molnar	Hiperlabilitat	1964
Tattersall	Alteració constant de la vida del pacient per hipo-hiperglùcèmia	1977
Schade	Alteració de la vida del pacient > 3/setmana per hipo-hiperglucèmies de repetició	1988
Tattersall et al.	Mínim 3 hospitalitzacions per hipo-hiperglucèmia en 2 anys	1991
Gill et al.	Inestabilitat greu del control glucèmic que comporta alteració de la vida i ingressos hospitalaris repetits o perllongats	1996

Adaptat de Gill GV et al. Difficult Diabetes 2001, Blackwell Science Ltd.Oxford

THE CANADIAN MEDICAL ASSOCIATION

LE JOURNAL DE

L'ASSOCIATION MÉDICALE CANADIENNE

APRIL 18, 1964 • VOL. 90, NO. 16

Observations on the Etiology and Therapy of "Brittle" Diabetes

GEORGE D. MOLNAR, M.D., *Rochester, Minn., U.S.A.*

BRITISH MEDICAL JOURNAL

LONDON, SATURDAY 31 AUGUST 1985

Brittle diabetes

Many patients with insulin dependent diabetes spend their lives walking a tightrope between extremes of high and low blood sugar concentrations. Most have abnormally variable values much of the time but stay out of major trouble with an average of only one hypoglycaemic coma every six years and one admission with ketoacidosis every 10. An unlucky or improvident few have their lives and those of their families disrupted by repeated episodes of hypoglycaemia or keto-acidosis. The scale of their instability may be daunting; one of our middle aged patients had 136 hypoglycaemic comas in six years,[1] while a 13 year old girl reported by Pickup *et al* had 50 admissions with ketoacidosis in 18 months.[2] Laymen would regard these as obvious examples of brittle diabetes, terms of avoiding complications were those who had at least one coma each year.[9] Better insulin regimens and home blood glucose monitoring have made it easier for patients to achieve nearly normal concentrations of blood sugar without such alarming side effects, though some patients believe that the best way to avoid complications is to sail as close to the wind as possible keeping their blood sugar on the verge of hypoglycaemia most of the time. In our experience patients with recurrent hypoglycaemia may be of either sex and heterogeneous in age and duration of their disease.[10]

Much recent interest has been shown in patients who lack warning symptoms of hypoglycaemia or an adequate counter-regulatory hormonal response or both. Those who

ROBERT TATTERSALL

Consultant Physician,
University Hospital,
Nottingham NG7 2UH

Possibles causes

- Trastorns digestius-malabsorció (celiaquia)
- Disautonomia (gastroparèsia, hipoglucèmies desapercebudes)
- Defecte d'hormones contrarreguladores:
  - Insuficiència SR
  - Dèficit glucagó (post-pancreatectomia)
  - GH
- Alteracions en l'absorció de la insulina (lipodistròfia)
- Alcohol, fàrmacs psicotròpics
- Alteracions o trastorns conducta, emocionals, psicosocials

Tattersall R et al. Brittle diabetes. BMJ 1985; 291: 555-556
Darias-Garzón R et al. Av Diabetol 2014; 30: 167-172

Journal of Diabetes and Its Complications 30 (2016) 1544–1547

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Brittle diabetes: Psychopathology and personality

Lorenzo Pelizza [a,*], Simona Pupo [b]

In this study, patients with brittle diabetes show no differences in terms of global severity of psychopathological distress and specific symptoms of axis I DSM-IV-TR psychiatric diagnoses in comparison with subjects without brittle diabetes. Differently, individuals with brittle diabetes are more frequently affected by specific DSM-IV-TR cluster B personality disorders

Estratègies terapèutiques

- **Educació diabetològica (dieta, esport, horaris...)**

- **Tecnologies aplicades a la diabetis**

- **Noves insulines**

- **Abordatge psicològic**

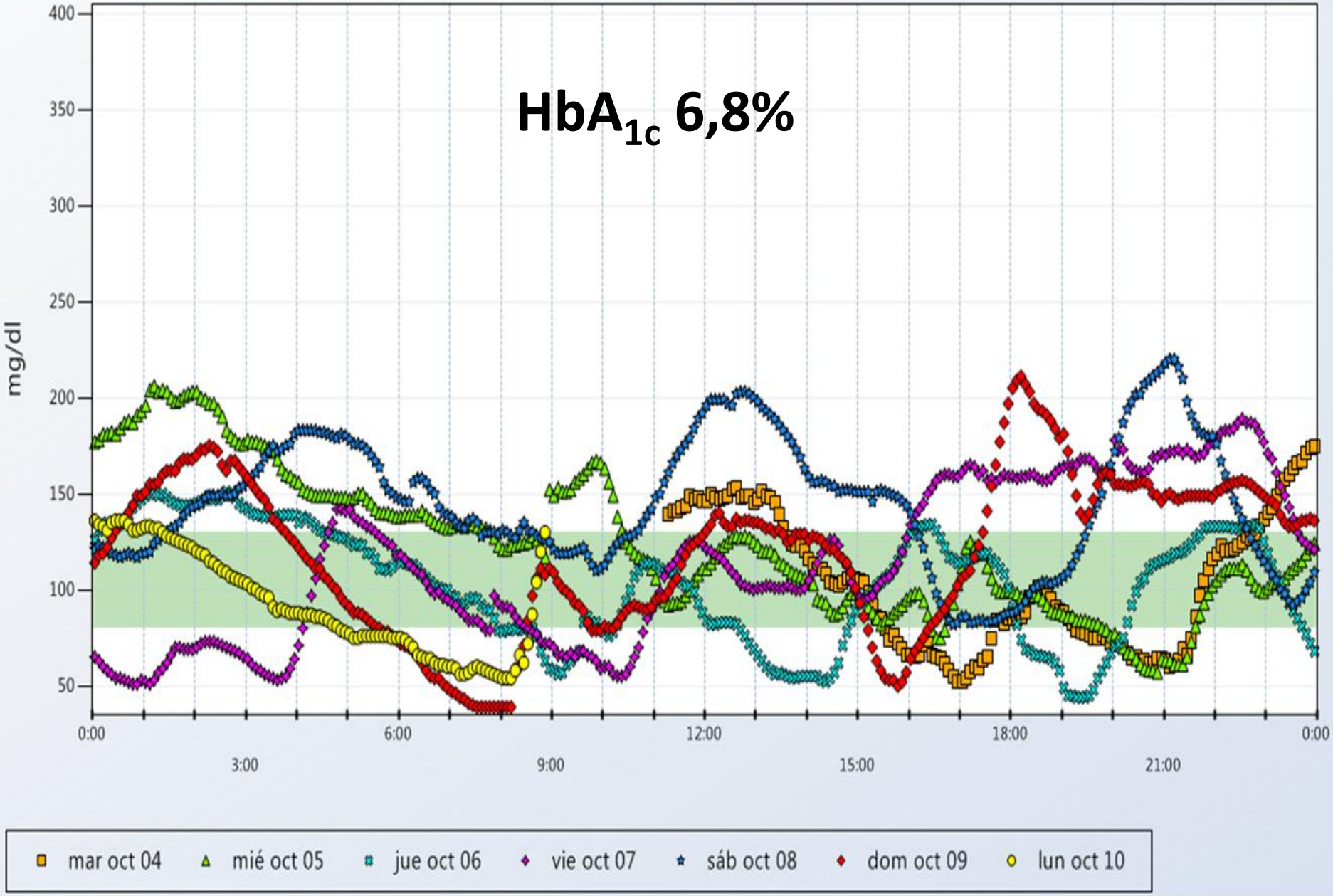
COM IDENTIFICAR LA DIABETIS INESTABLE??

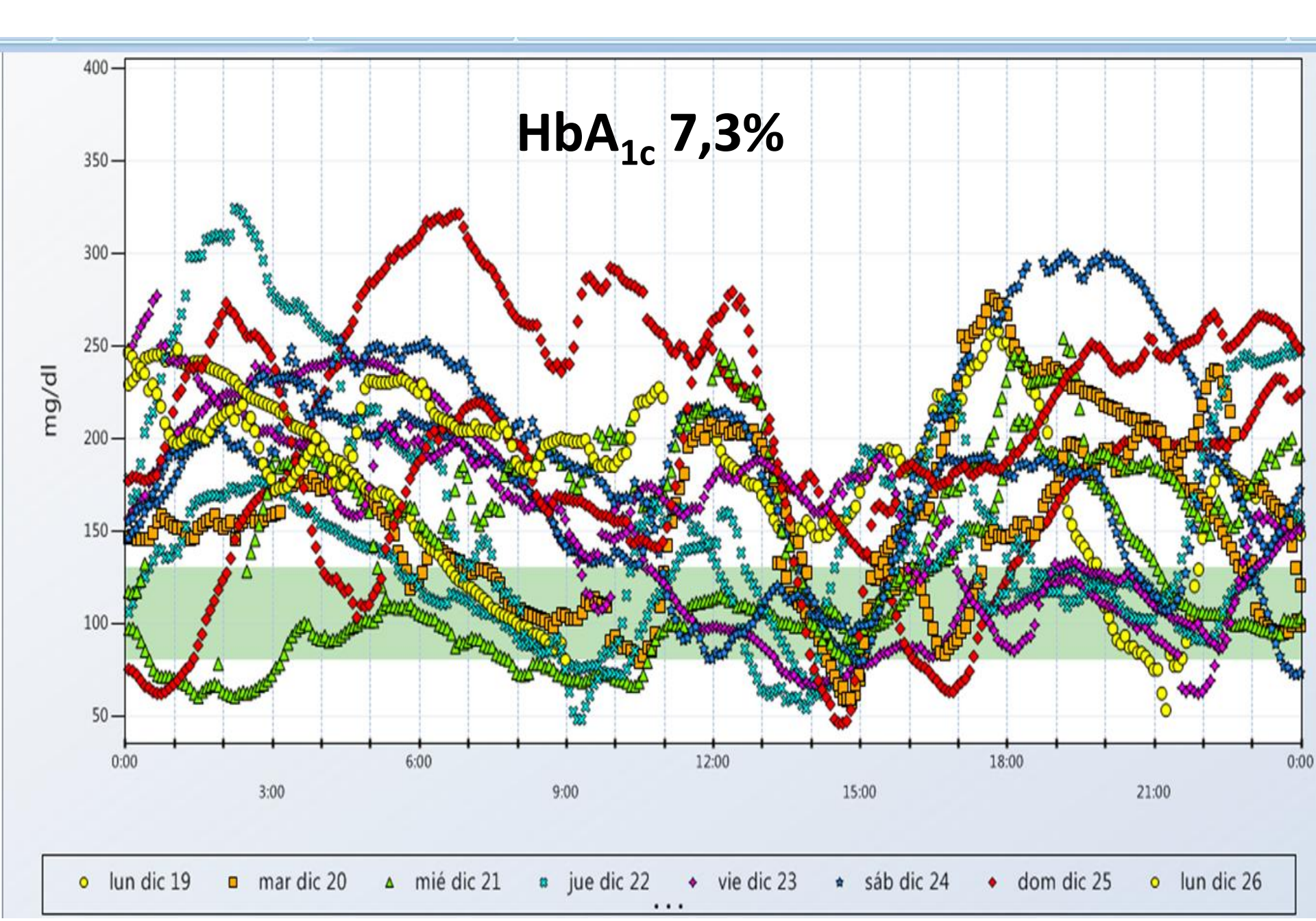
HbA_{1c}

-HbA_{1c}: S'utilitza habitualment per a monitoritzar el control glucèmic

- No aporta dades completes sobre:

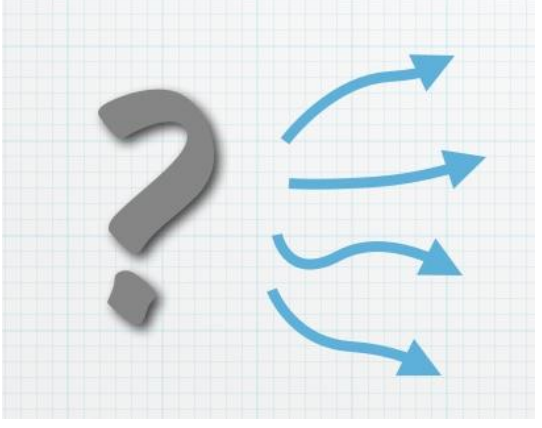
- **Freqüència i duració hipoglucèmies**
- **Magnitud de les fluctuacions de glucèmia**


HbA1c 6,8%
mg/dl
400
350
300
250
200
150
100
50
0:00
3:00
6:00
9:00
12:00
15:00
18:00
21:00
0:00
mar oct 04
mié oct 05
jue oct 06
vie oct 07
sáb oct 08
dom oct 09
lun oct 10


HbA1c 7,3%
400
350
300
250
200
150
100
50
mg/dl
0:00
3:00
6:00
9:00
12:00
15:00
18:00
21:00
0:00
lun dic 19
mar dic 20
mié dic 21
jue dic 22
vie dic 23
sáb dic 24
dom dic 25
lun dic 26

Variabilitat glucèmica

- **Importància determinació variabilitat glucèmica:**
  - **Predicció d'hipoglucèmies greus en DM1**
  - **Relació amb estrés oxidatiu**
  - **Relació amb complicacions microvasculars i macrovasculars**
- **També en DM2 (valoració pre-intensificació tractament per a determinar resultats, ISCI)**
- **Mètodes??**



De Vries JH. Diabetes 2013; 62:1405-8
Reznik Y et al. Lancet 2014; 384:1265-72
Inzucchi SE et al. Diab Res Cli Pract 2015;110: 234-40

Mesura variabilitat glucèmica

- **SD (desviació estàndar): Medida de dispersió**
- **MAGE (*Mean amplitude glycaemic excursions*) Medició excursions glucèmiques post-prandials**
- **MAG (*Mean absolute glucose*)**
- **MOOD (*Mean of Daily Differences*)**
- **CV: Coeficient de variació**
- **HBGI (*High blood glucose index*)**
- **LBGI (*Low blood glucose index*)**

Descàrrega dades

GLUCEMIA

RESULTADOS EVALUADOS	FRECUENCIA/DIA	PROMEDIO		
		TOTAL	ANTES DE COMIDAS	DESPUÉS DE COMIDAS
54	3.9 (3.9)	134 mg/dL	150 mg/dL	132 mg/dL

VALOR MÍNIMO	INTERVALO OBJETIVO % +		Nº HIPOS	DESVIACIÓN ESTÁNDAR	HBGI	LBGI
52 mg/dL	SUPERIOR A	37%	5	63 mg/dL	4.6	2.9
VALOR MÁXIMO	DENTRO	43%	UMBRAL HIPO			
324 mg/dL	INFERIOR A	20%	60 mg/dL			

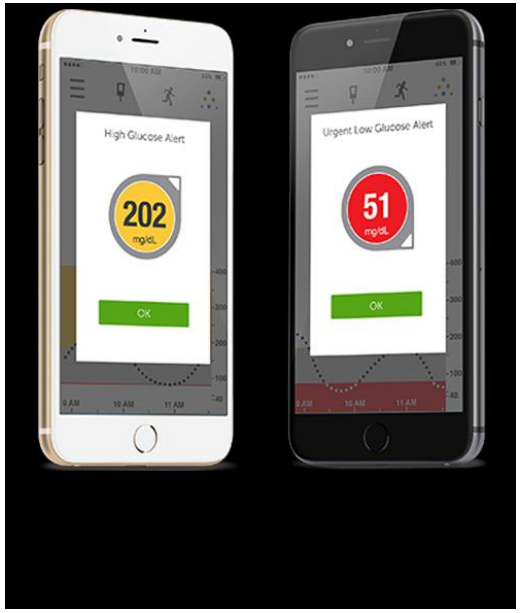
BOLO INSULINA

RESULTADOS EVALUADOS	FRECUENCIA/DIA	PROMEDIO UI/DÍA	VALOR MÍNIMO	VALOR MÁXIMO
29	2.9	10.6	1	9

INGESTAS

RESULTADOS EVALUADOS	FRECUENCIA/DIA	PROMEDIO HC/DÍA	VALOR MÍNIMO HC	VALOR MÁXIMO HC
22	2.2	95.4	11	73

Tecnologia i variabilitat glucèmica



Calculadors de bolus

Monitorització continua glucèmia

Teràpia bomba+sensor

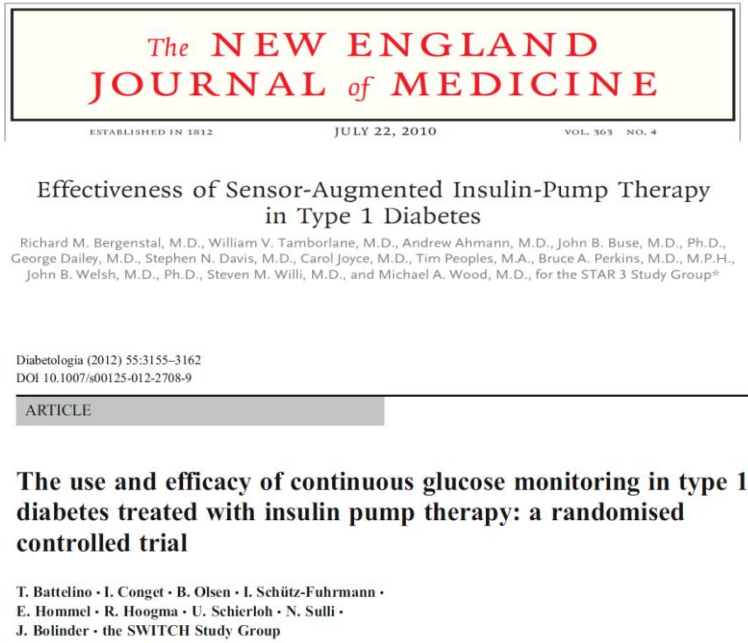
- **MCG real time vs. glucèmia capilar:**
  - **Milloria control metabòlic**
  - **Disminució hipoglucèmies**

- **MCG retrospectius:**
  - **No clars beneficis**

Langendam M et al. Cochrane Database Syst Tev. 2012; 18: 1: CD008101
Pickup JC. BMJ 2011; 343: d3805
Wong JC. Diabetes Care 2014; 37: 2702-2709

- **Milloria control metabòlic sense augment hipoglucèmies**

- **Asociat a l´ús estricte del sensor**



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 22, 2010 VOL. 363 NO. 4

Effectiveness of Sensor-Augmented Insulin-Pump Therapy in Type 1 Diabetes

Richard M. Bergenstal, M.D., William V. Tamborlane, M.D., Andrew Ahmann, M.D., John B. Buse, M.D., Ph.D., George Dailey, M.D., Stephen N. Davis, M.D., Carol Joyce, M.D., Tim Peoples, M.A., Bruce A. Perkins, M.D., M.P.H., John B. Welsh, M.D., Ph.D., Steven M. Willi, M.D., and Michael A. Wood, M.D., for the STAR 3 Study Group*

Diabetologia (2012) 55:3155–3162
DOI 10.1007/s00125-012-2708-9

ARTICLE

The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial

T. Battelino · I. Conget · B. Olsen · I. Schütz-Fuhrmann · E. Hommel · R. Hoogma · U. Schierloh · N. Sulli · J. Bolinder · the SWITCH Study Group

MDI+MCG

Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections

The DIAMOND Randomized Clinical Trial

Roy W. Beck, MD, PhD[1]; Tonya Riddlesworth, PhD[1]; Katrina Ruedy, MSPH[1]; et al

» Author Affiliations

JAMA. 2017;317(4):371-378. doi:10.1001/jama.2016.19975

Continuous Glucose Monitoring vs Conventional Therapy for Glycemic Control in Adults With Type 1 Diabetes Treated With Multiple Daily Insulin Injections

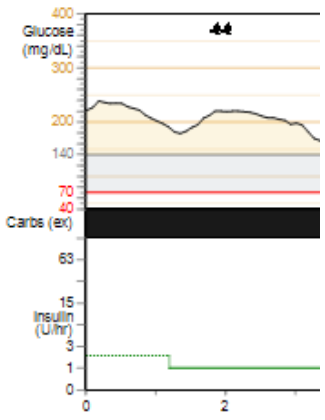
The GOLD Randomized Clinical Trial

Marcus Lind, MD, PhD[1,2]; William Polonsky, PhD[3]; Irl B. Hirsch, MD[4]; et al

» Author Affiliations

JAMA. 2017;317(4):379-387. doi:10.1001/jama.2016.19976

ISCI+MCG (suspensió predictiva hipoglucèmia)



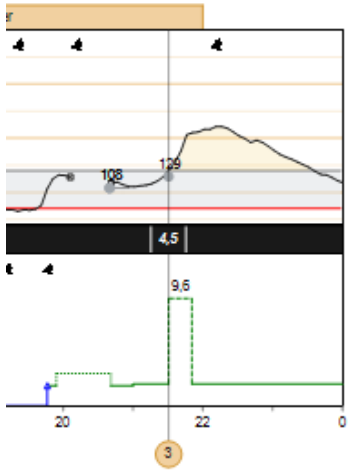
DIABETES TECHNOLOGY & THERAPEUTICS
Volume 18, Number 10, 2016
Mary Ann Liebert, Inc.
DOI: 10.1089/dia.2016.0216

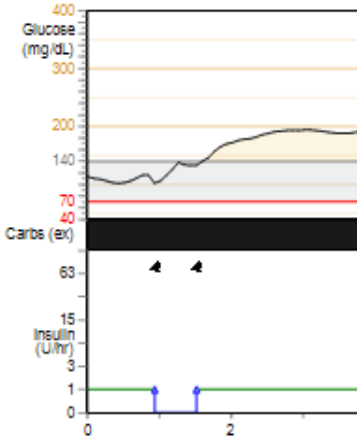
DTT

ORIGINAL ARTICLE

Effectiveness of Automated Insulin Management Features of the MiniMed® 640G Sensor-Augmented Insulin Pump

Alex Zhong, MS,[1] Pratik Choudhary, MD,[2] Chantal McMahon, PhD,[1] Pratik Agrawal, MS,[1] John B. Welsh, MD, PhD,[1] Toni L. Cordero, PhD,[1] and Francine R. Kaufman, MD[1]





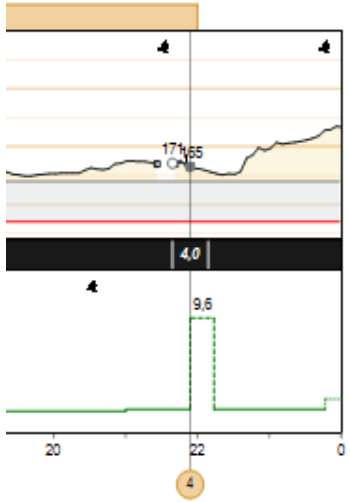
DIABETES TECHNOLOGY & THERAPEUTICS
Volume 18, Number 5, 2016
Mary Ann Liebert, Inc.
DOI: 10.1089/dia.2015.0324

DTT

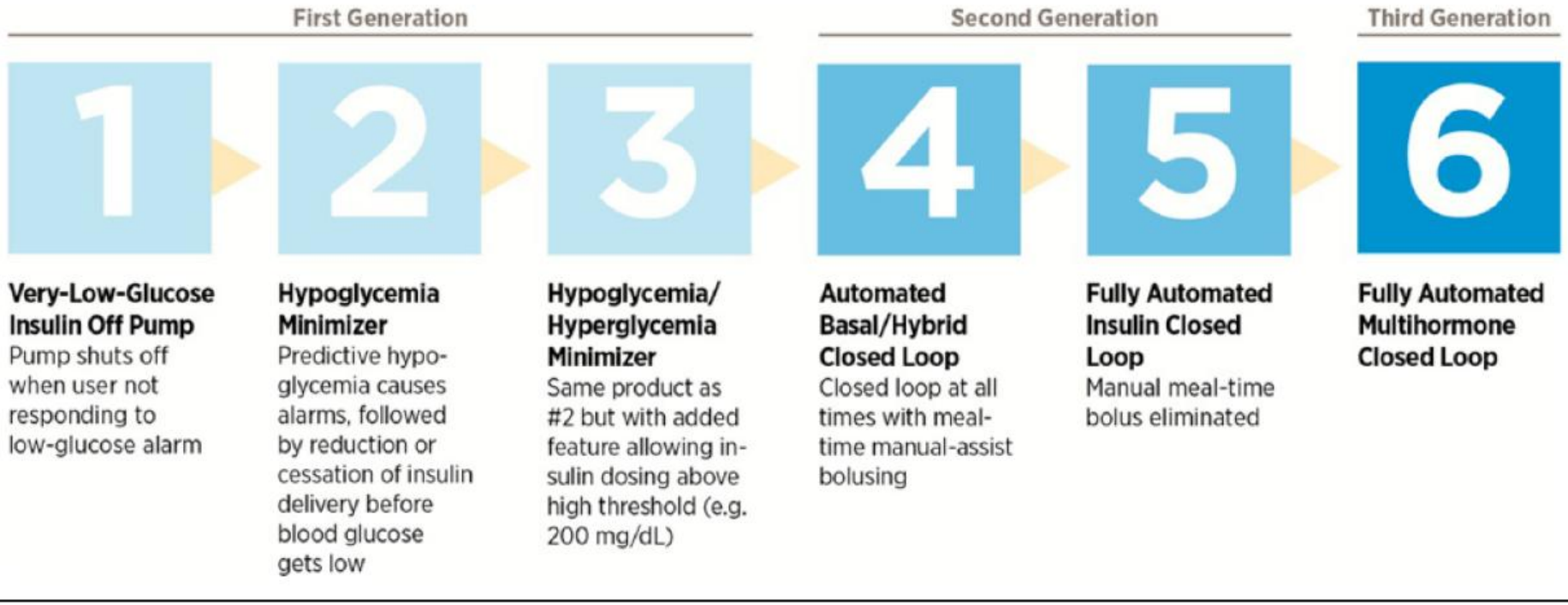
ORIGINAL ARTICLE

Hypoglycemia Prevention and User Acceptance of an Insulin Pump System with Predictive Low Glucose Management

Pratik Choudhary, MD,[1] Birthe S. Olsen, MD,[2] Ignacio Conget, MD,[3] John B. Welsh, MD, PhD,[4] Linda Vorrink, MSc,[5] and John J. Shin, PhD[4]

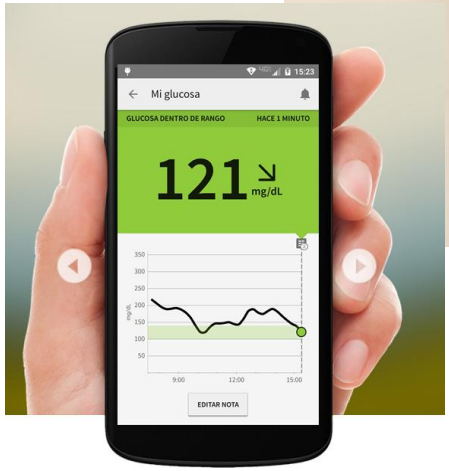


Pàncrees artificial: Sistemes de nansa tancada



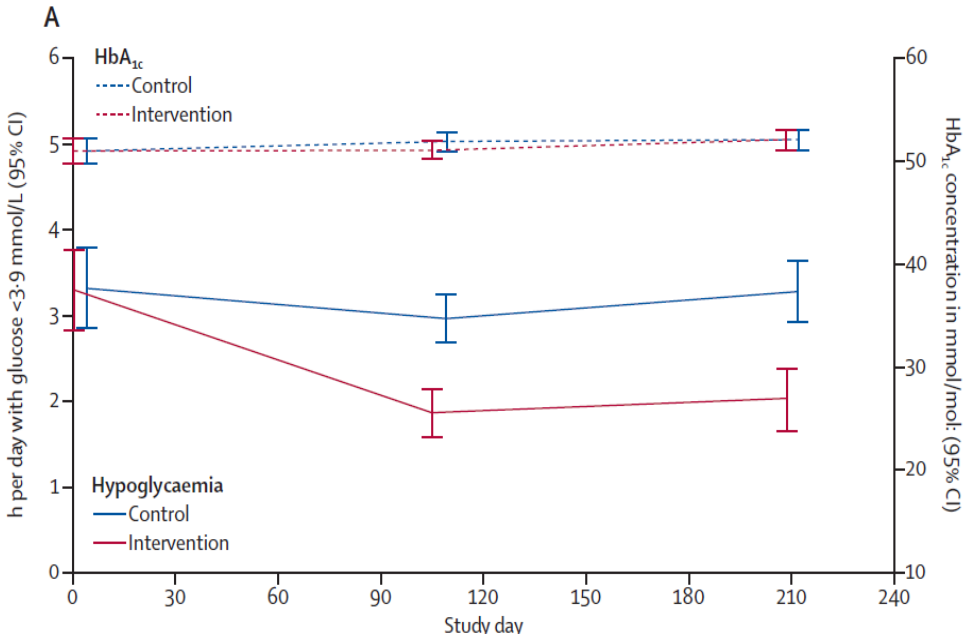
Trevitt S et al. J Diabetes Sci Technol. 2016;10(3):714-23

Flash Glucose monitoring



Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial

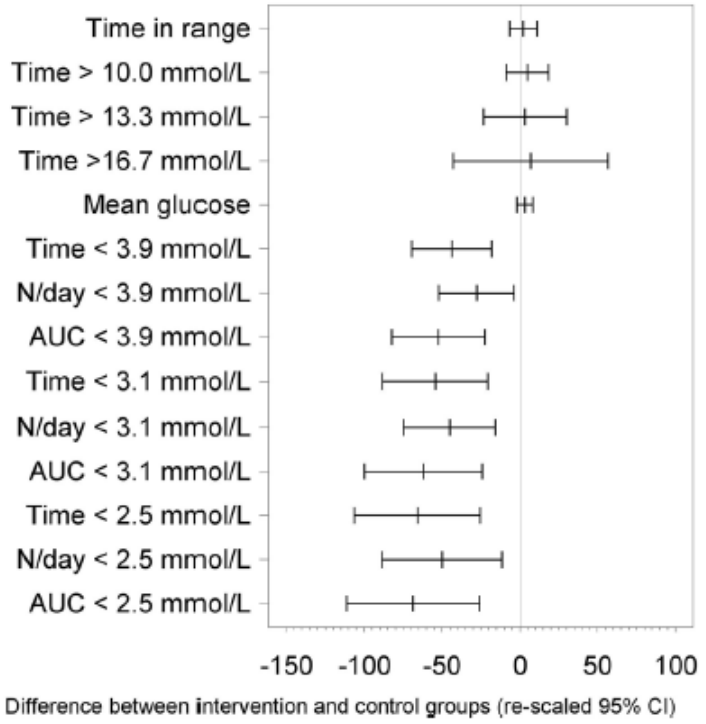
Jan Bolinder, Ramiro Antuna, Petronella Geelhoed-Duijvestijn, Jens Kröger, Raimund Weitgasser



www.thelancet.com **Published online September 12, 2016**

Flash Glucose-Sensing Technology as a Replacement for Blood Glucose Monitoring for the Management of Insulin-Treated Type 2 Diabetes: a Multicenter, Open-Label Randomized Controlled Trial

Thomas Haak · Hélène Hanaire · Ramzi Ajjan · Norbert Hermanns · Jean-Pierre Riveline · Gerry Rayman

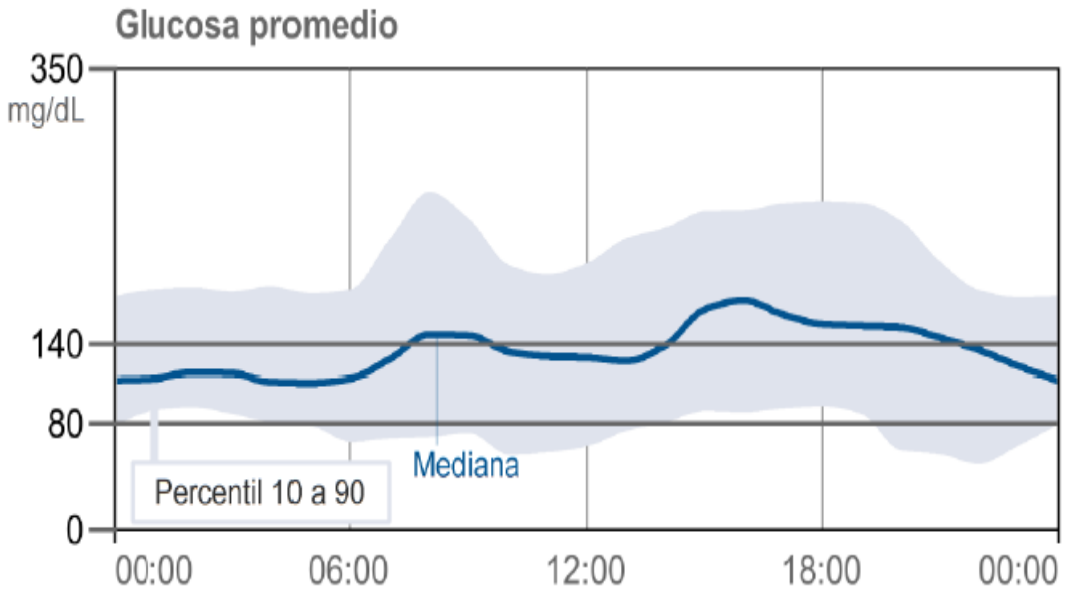


Diabetes Ther (2017) 8:55–73

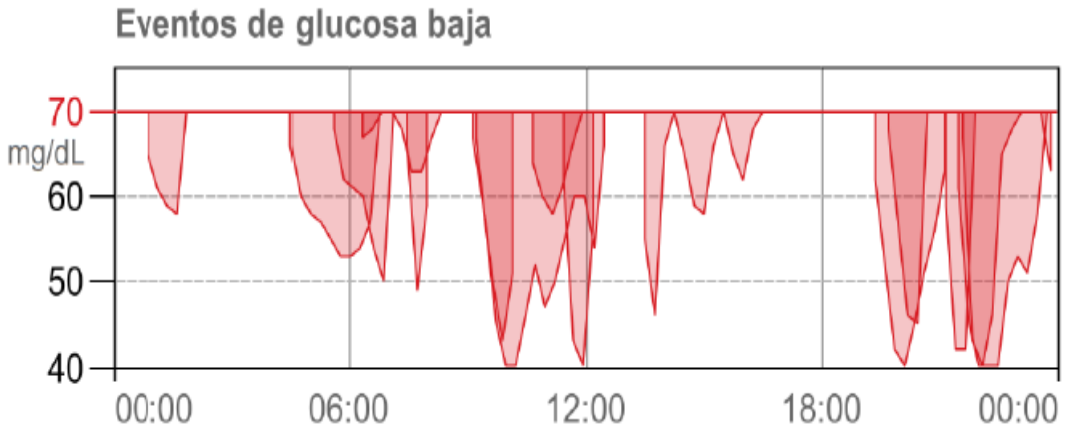
Glucosa

A1c estimado 6,5% o 48 mmol/mol

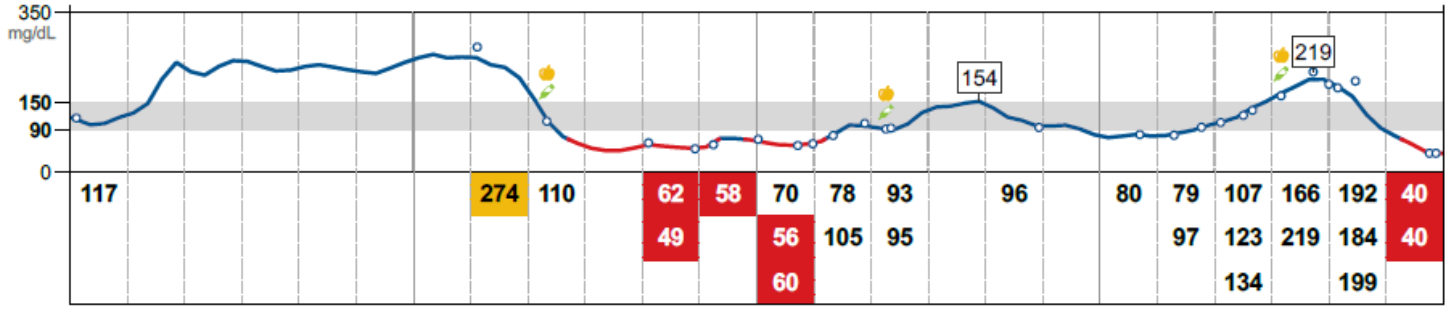
GLUCOSA PROMEDIO	**140**	mg/dL
% por encima del objetivo	**44**	%
% en el objetivo	**42**	%
% por debajo del objetivo	**14**	%



EVENTOS DE GLUCOSA BAJA	**15**	
Duración promedio	**116**	Min



mié 17 de feb



Glucosa mg/dL

117	274	110	62	58	70	78	93	96	80	79	107	166	192	40
			49		56	105	95			97	123	219	184	40
					60						134		199	

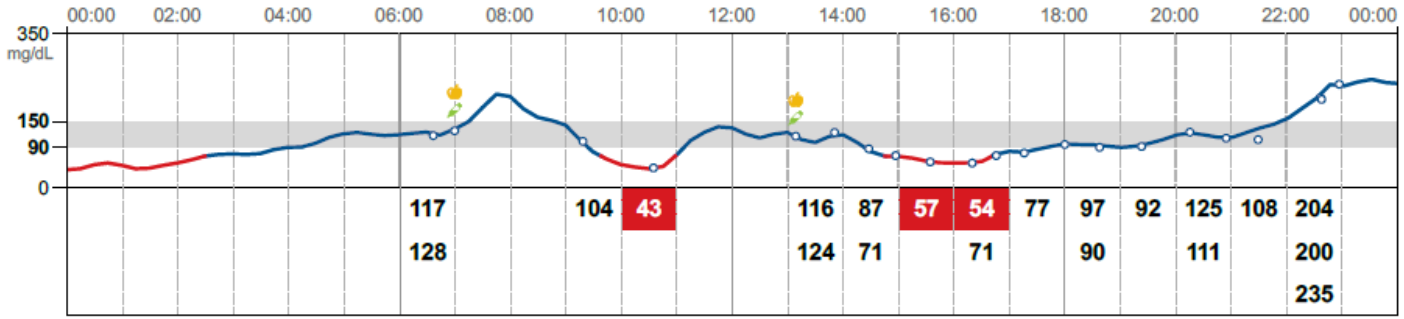
Carb. gramos

							50						50			

Insulina de acción rápida

		10.0					12.0						14.0			

jue 18 de feb



Glucosa mg/dL

117	104	43	116	87	57	54	77	97	92	125	108	204
128			124	71		71		90		111		200
												235

Carb. gramos

	51			50												

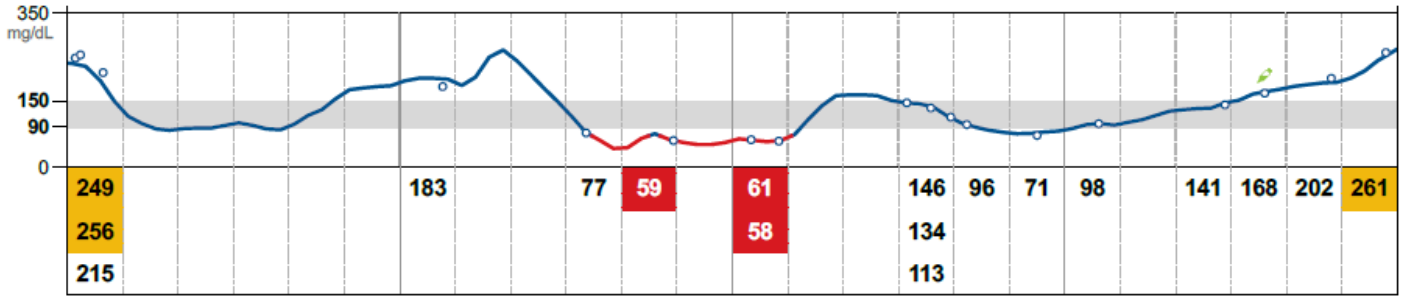
Insulina de acción rápida Unidades

	11,0															

Notas

▸ Ejercicio

vie 19 de feb



Glucosa mg/dL

249	183	77	59	61	146	96	71	98	141	168	202	261
256				58	134							
215					113							

Insulina de acción rápida Unidades

											2,0					

Accuracy and Longevity of an Implantable Continuous Glucose Sensor in the PRECISE Study: A 180-Day, Prospective, Multicenter, Pivotal Trial

Jort Kropff[1], Pratik Choudhary[2], Sankalpa Neupane[3], Katharine Barnard[4], Steve C. Bain[5], Christoph Kapitza[6], Thomas Forst[7], Manuela Link[8], Andrew Dehennis[9] **and** J. Hans DeVries[1]

Author Affiliations

Corresponding author: Jort Kropff, j.kropff@amc.nl.

Diabetes Care 2017 Jan; 40(1): 63-68. https://doi.org/10.2337/dc16-1525

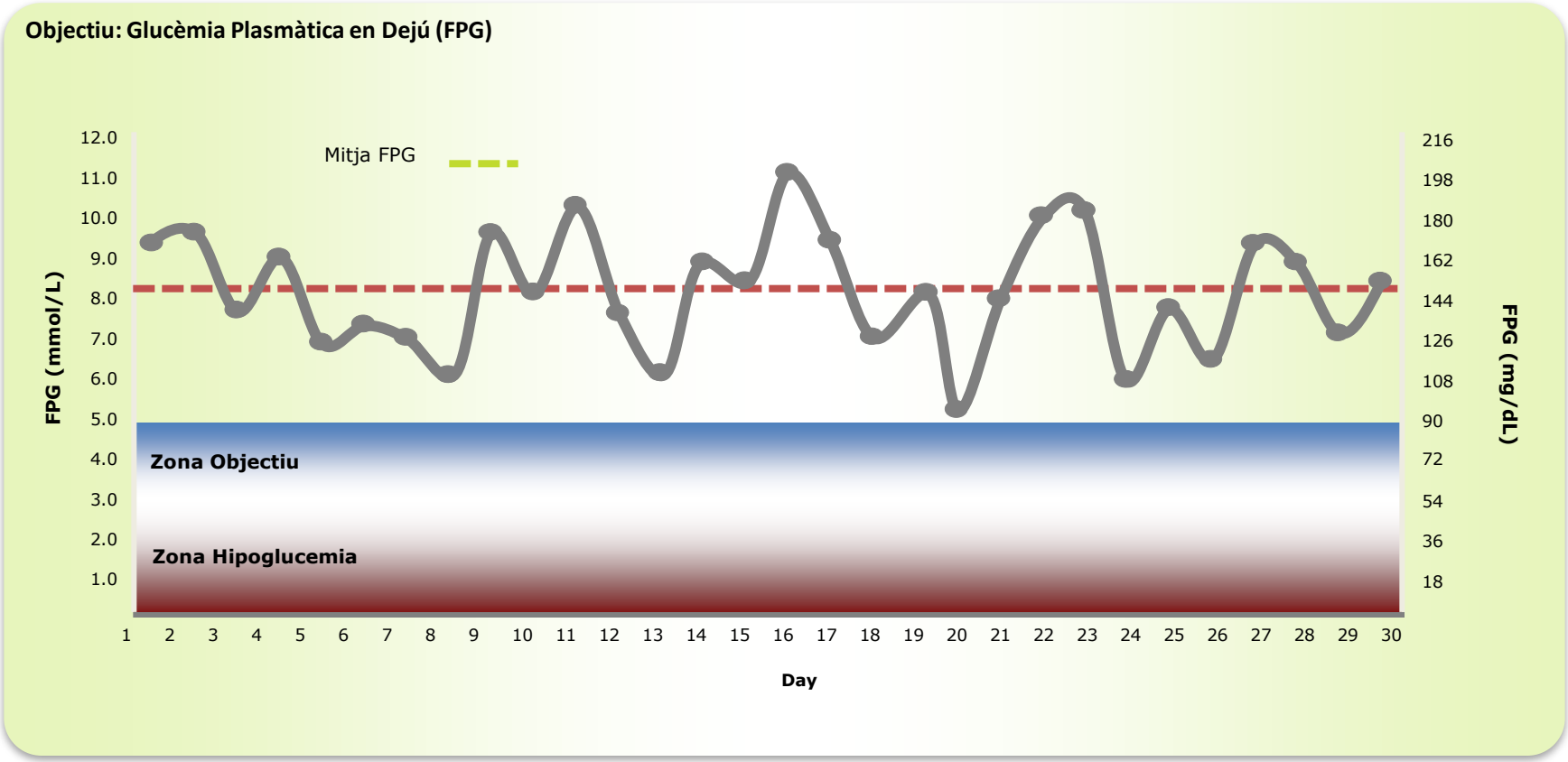
Anàlegs acció lenta

Análogos					
Insulina detemir	Levemir 100 U/ml, solución inyectable en una pluma precargada (Flexpen)	813576.9	5 plumas precargadas de 3 ml	Flexpen	Novo Nordisk A/S
	Levemir 100 U/ml, solución inyectable en una pluma precargada (Innolet)	656056.3	5 plumas precargadas de 3 ml	Innolet	Novo Nordisk A/S
Insulina glargina	Lantus Solostar 100 unidades/ml solución inyectable en pluma precargada	700603.9	5 plumas precargadas de 3 ml	Solostar	Sanofi Aventis Deutschland Gmbh
	Lantus 100 unidades/ml solución inyectable en un cartucho	901579.4	5 cartuchos de 3 ml	N/A	Sanofi Aventis Deutschland Gmbh
	Lantus 100 unidades/ml solución inyectable en un vial	831453.9	1 vial de 10 ml	N/A	Sanofi Aventis Deutschland Gmbh
	Abasaglar 100 unidades/ml solución inyectable en pluma precargada	706364.3	5 plumas precargadas de 3 ml	KwikPen	Eli Lilly Regional Operations Gmbh
	Toujeo 300 unidades/ml solución inyectable en pluma precargada	706414.5	3 plumas precargadas de 1,5 ml	SoloStar	Sanofi Aventis Deutschland Gmbh
Insulina degludec	Tresiba 100 U/ml solución inyectable	697408.7	5 plumas precargadas de 3 ml	FlexTouch	Novo Nordisk A/S

Noves insulines basals: Objetius

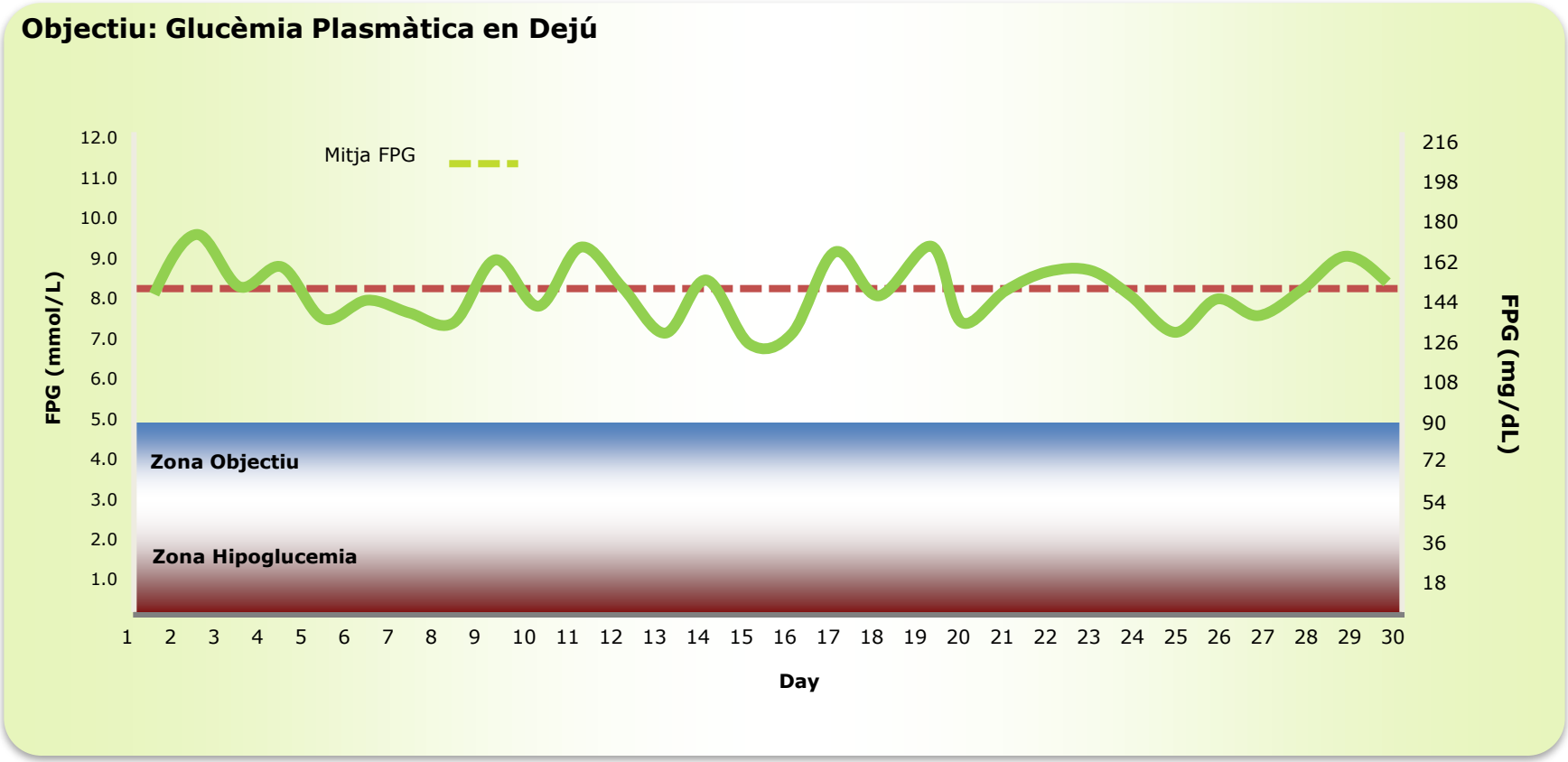
- Més duració acció → Control glicèmia en dejú
- Perfil de acció pla → Menor risc hipoglucèmies
- Menor variabilitat → Més facilitat per ajust dosis d'insulina

Variabilitat i control de la glucèmia en dejú (FPG)



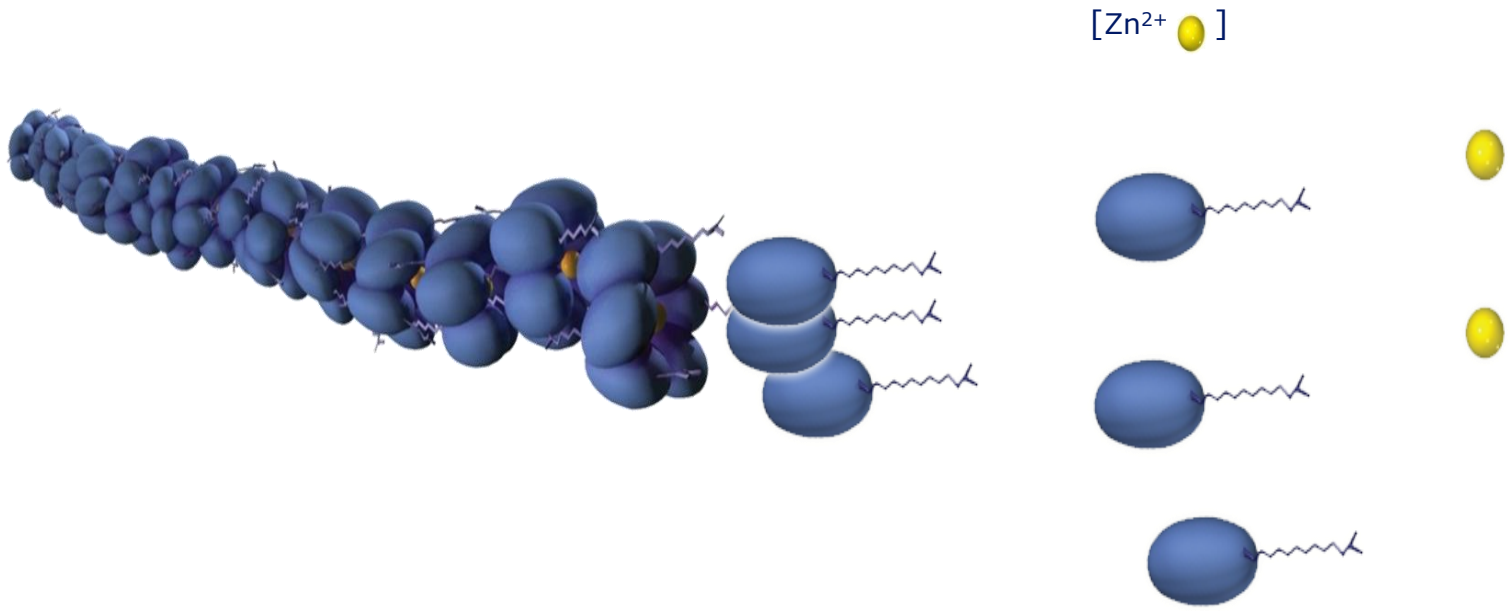
*Hypothetical patient

Variabilitat i control de la glucèmia en dejú (FPG)



*Hypothetical patient

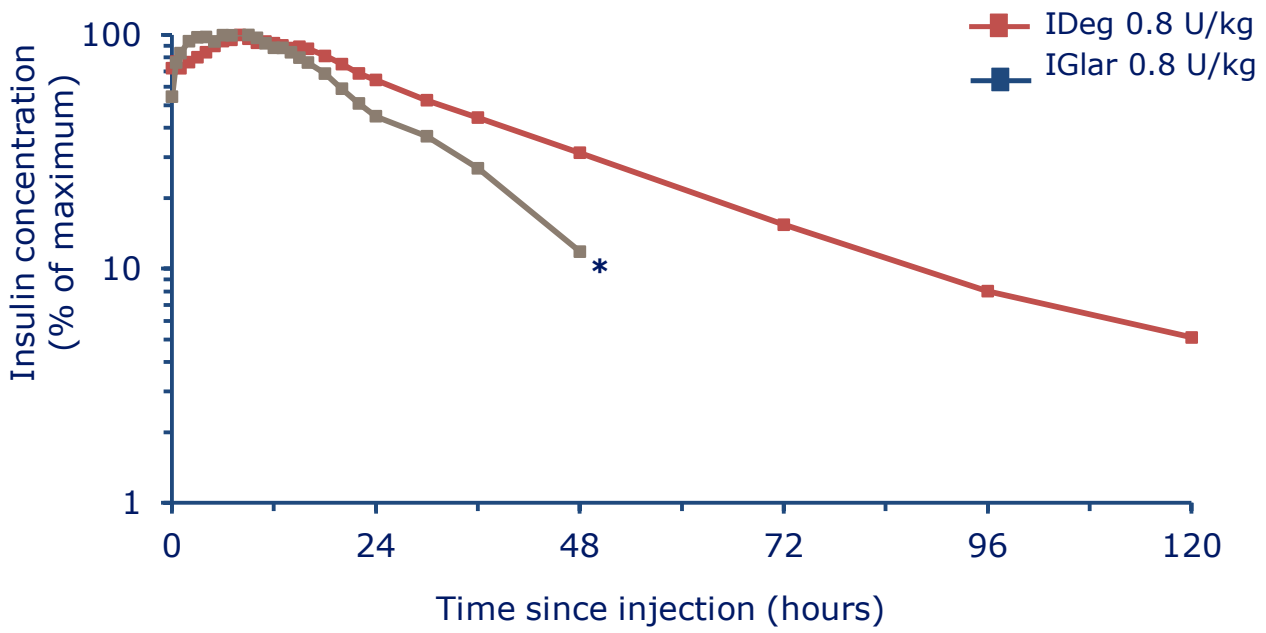
Degludec: Multihexàmers



Liberació lenta monòmers

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

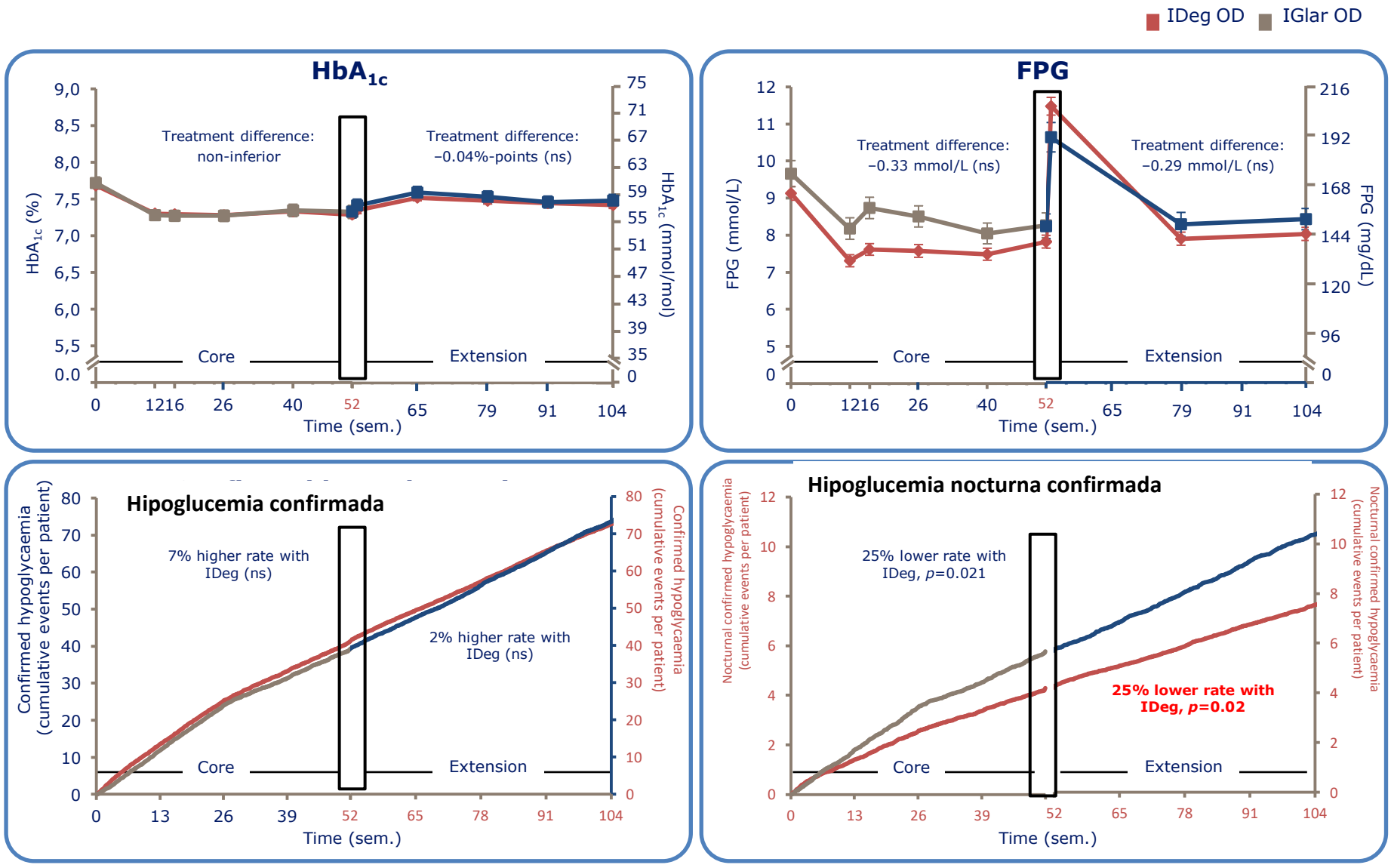
Degludec: Vida mitja



	IDeg			IGlar		
	0.4 U/kg	0.6 U/kg	0.8 U/kg	0.4 U/kg	0.6 U/kg	0.8 U/kg
Vida Media (hours)	25.9	27.0	23.6	11.5	12.9	11.9
Media (vida media)	**25.4**			**12.1**		

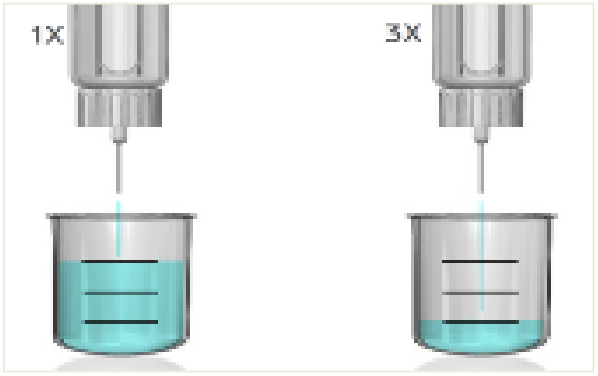
*Heise *et al. Diabetes* 2011;60(Suppl. 1):LB11; Heise *et al. Diabetologia* 2011;54(Suppl. 1):S425

DM1: Estudi BEGIN



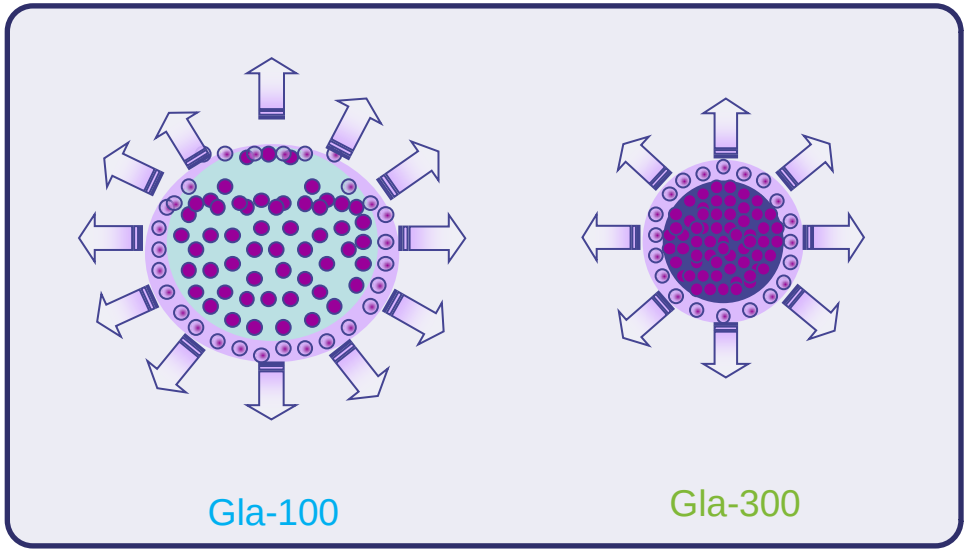
Heller *et al. Lancet* 2012;379:1489–97; Bode *et al. Diabet Med* 2013;30:1293–7

Glargina U-300



Gla-100 Gla-300

Reducció del volum d`inyecció



Superficie de precipitat més petita

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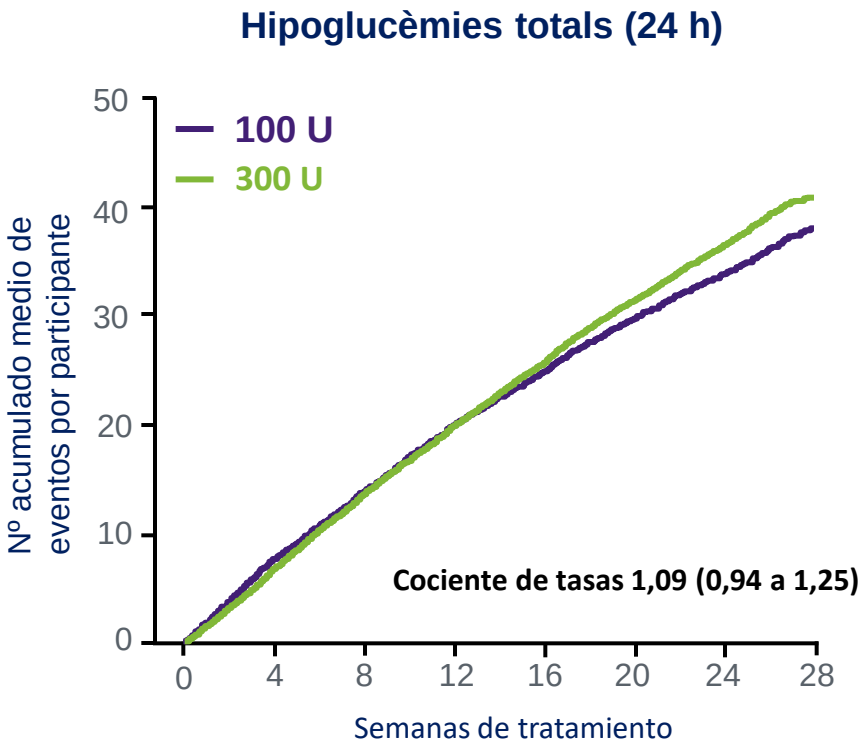
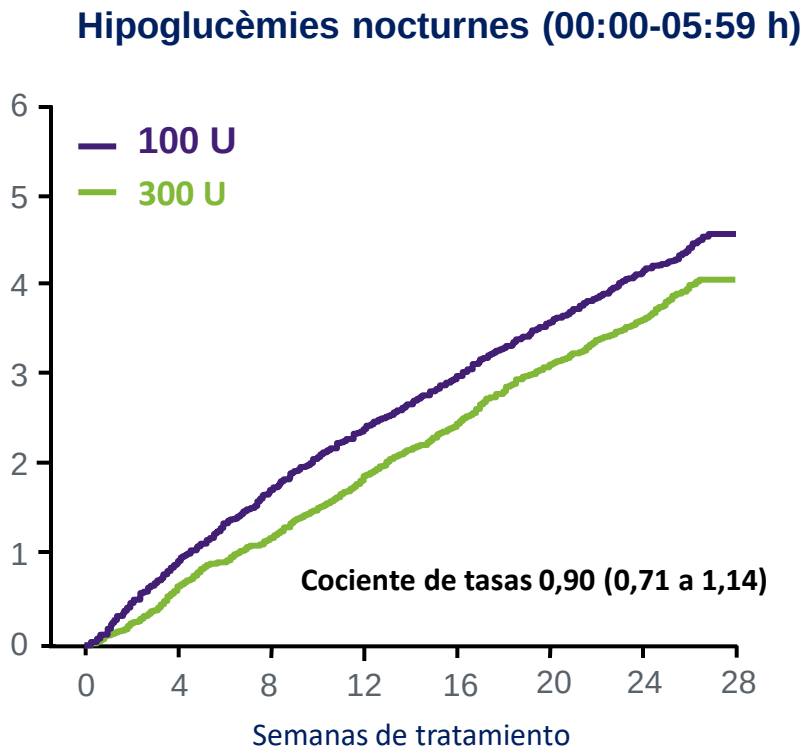
Glargina 300 U EMEA Summary of Product Characteristics. 2015.

DM1: Edition 4





Home PD, et al. Diabetes Care 2015

Insulin degludec: four times lower pharmacodynamic variability than insulin glargine under steady-state conditions in type 1 diabetes

T. Heise[1], L. Hermanski[1], L. Nosek[1], A. Feldman[1], S. Rasmussen[2] & H. Haahr[3]

Diabetes, Obesity and Metabolism 14: 859–864, 2012.

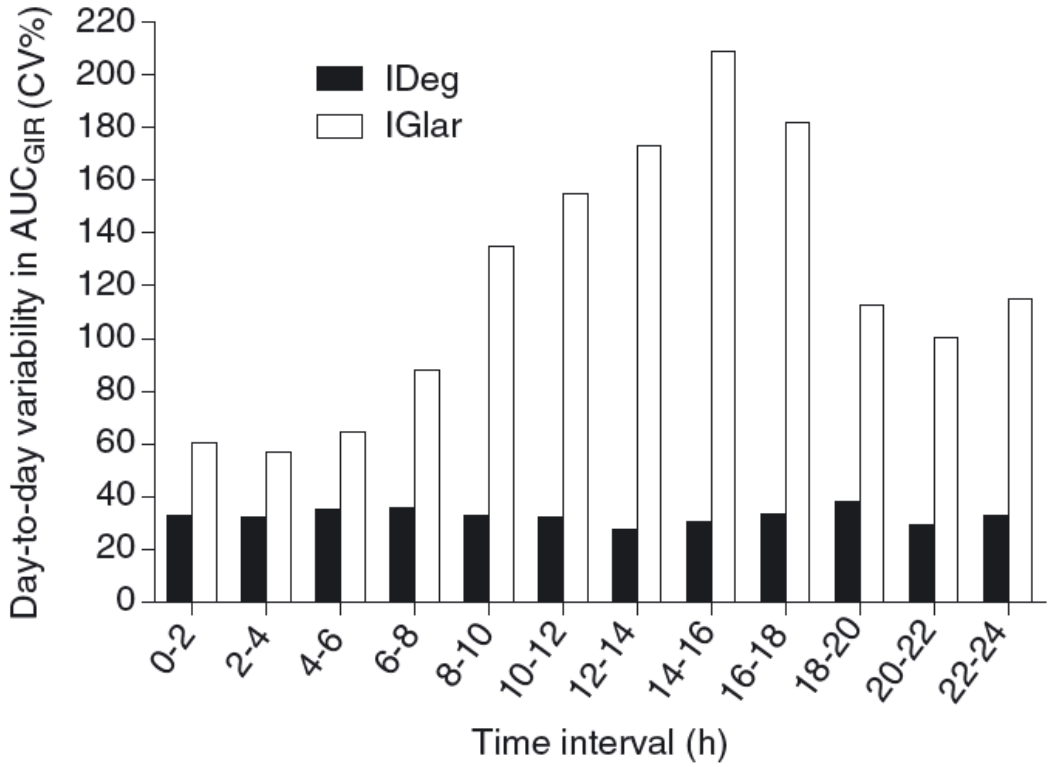


Figure 2. Day-to-day variability in glucose-lowering effect over 24 h at steady state.

Comparison of glycemic variability in Japanese patients with type 1 diabetes receiving insulin degludec versus insulin glargine using continuous glucose monitoring: A randomized, cross-over, pilot study

Yoshiko Onda [a], *Rimei Nishimura* [a,b,*], *Kiyotaka Ando* [a], *Hiroshi Takahashi* [a], *Daisuke Tsujino* [a], *Kazunori Utsunomiya* [a]

DIABETES RESEARCH AND CLINICAL PRACTICE 120 (2016) 149–155

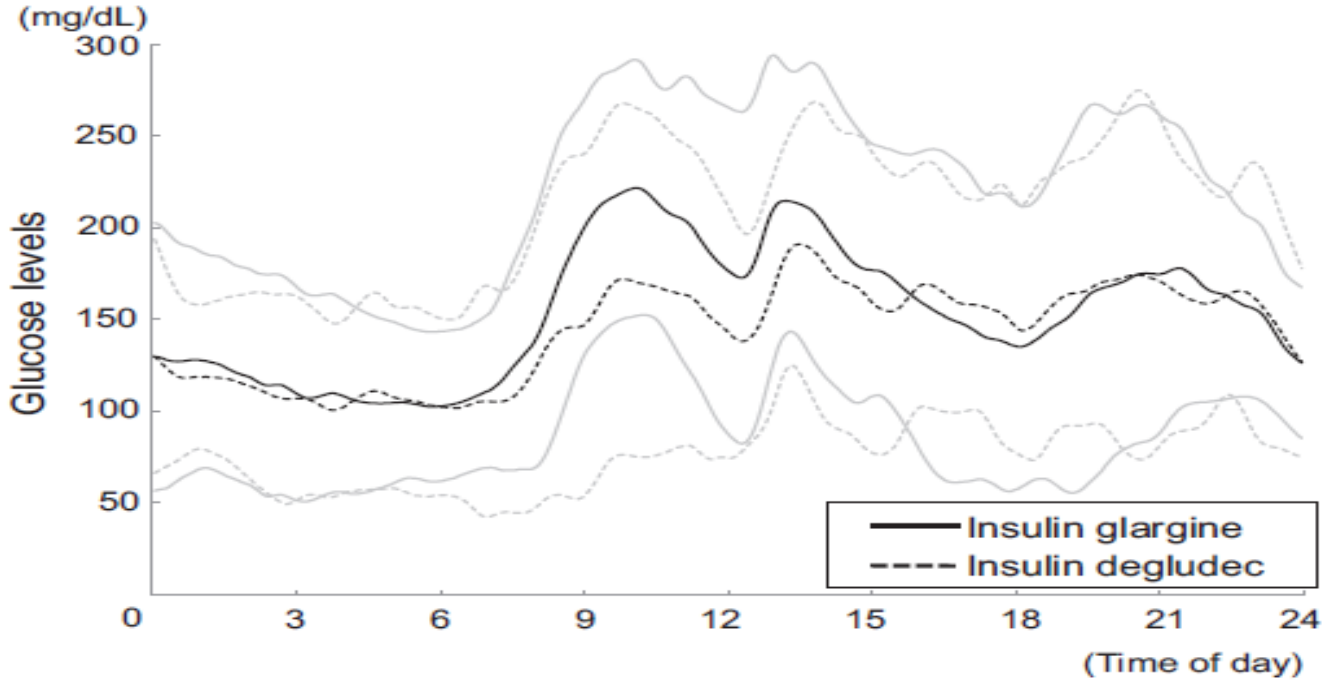


Fig. 1 – 24-h glucose variations in patients receiving insulin degludec and insulin glargine ($n = 13$). Curves are expressed as means ± standard deviations.

Degludec is superior to glargine in terms of daily glycemic variability in people with type 1 diabetes mellitus

Chiho Yamamoto[1)], Hideaki Miyoshi[1)], Yutaka Fujiwara[2)], Reina Kameda[1)], Mei Ichiyama[1)], Hiroshi Nomoto[1)], Hiraku Kameda[1)], Akinobu Nakamura[1)] and Tatsuya Atsumi[1)]

Endocrine Journal 2016, **63** (1), 53-60

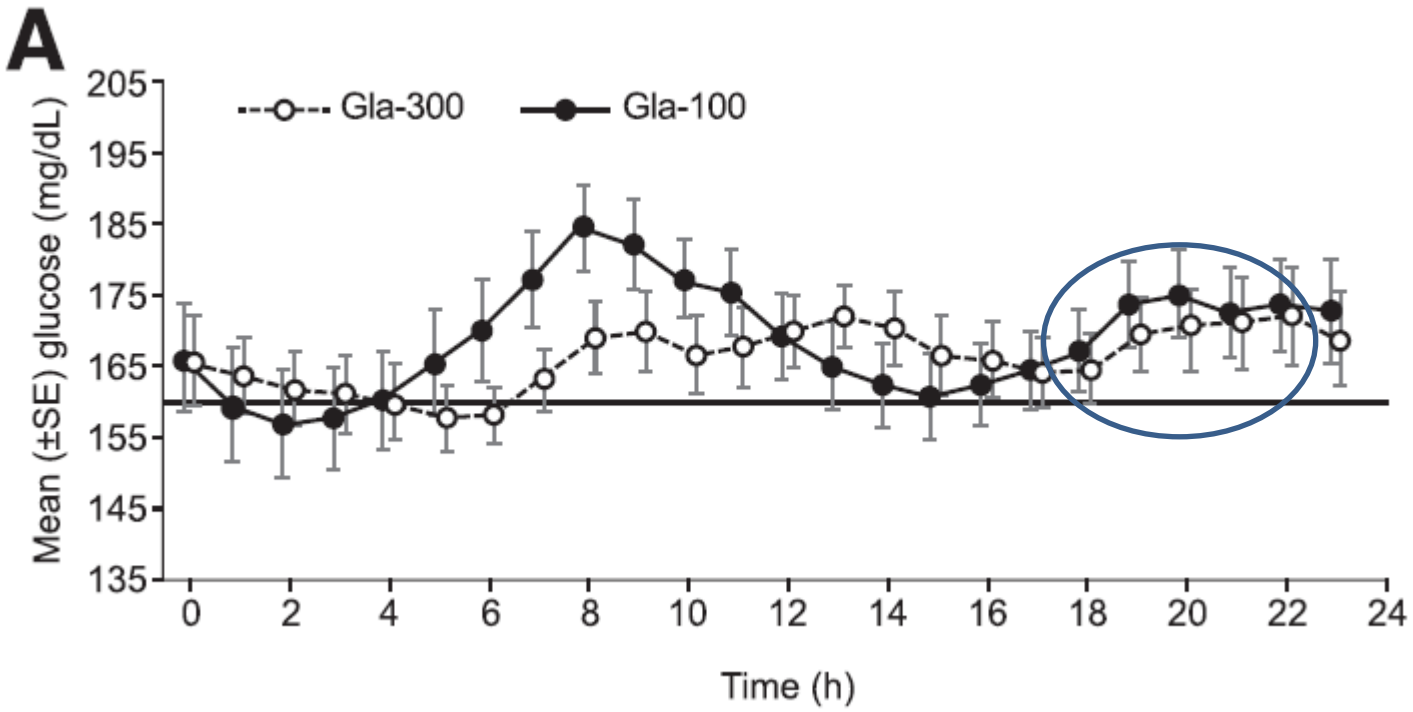
Table 2 Comparison of 3 days' CGM data of 21 participants between Gla and Deg

	Gla	*Deg*	*p* value
24-h mean glucose levels (mg/dL)	153.9 ± 31.8	153.6 ± 26.2	0.959
MAGE (mg/dL)			
24-h	144.4 ± 56.6	121.7 ± 42.2	0.028
early morning	41.8 ± 32.6	28.7 ± 11.4	0.048
24-h SD values glucose levels (mg/dL)	51.6 ± 18.1	43.7 ± 13.7	0.031
AUC <70 (mg/dL·h)			
24-h	0.8 ± 1.1	0.2 ± 0.5	0.046
Nighttime	0.5 ± 0.9	0.2 ± 0.3	0.090
Daytime	0.6 ± 1.0	0.2 ± 0.3	0.040
24-h AUC >180 (mg/dL·h)	17.0 ± 16.7	14.0 ± 13.6	0.321
MODD (mg/dL)			
24-h	50.2 ± 16.2	44.1 ± 10.2	0.084
Early morning	51.2 ± 28.2	38.7 ± 18.0	0.089
Insulin dose (U/kg)			
Twice a day			
Basal insulin	0.27 ± 0.10	0.20 ± 0.07	<0.001
Bolus insulin	0.48 ± 0.28	0.49 ± 0.28	0.785
Once a day			
Basal insulin	0.21 ± 0.04	0.15 ± 0.05	0.007
Bolus insulin	0.38 ± 0.11	0.36 ± 0.10	0.609

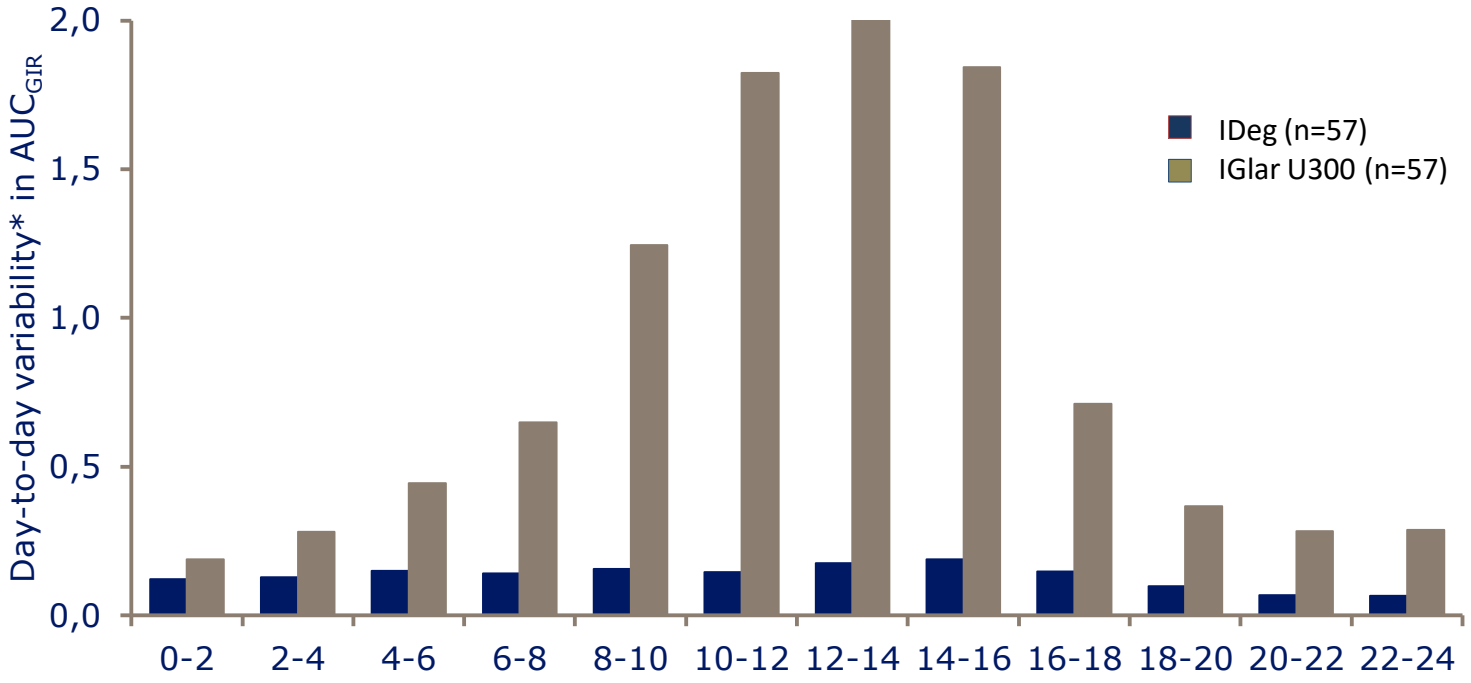
Comparison of Insulin Glargine 300 U/mL and 100 U/mL in Adults With Type 1 Diabetes: Continuous Glucose Monitoring Profiles and Variability Using Morning or Evening Injections

Richard M. Bergenstal,[1] Timothy S. Bailey,[2] David Rodbard,[3] Monika Ziemen,[4] Hailing Guo,[5] Isabel Muehlen-Bartmer,[4] and Andrew J. Ahmann[6]

Diabetes Care Publish Ahead of Print, published online January 23, 2017



Insulin degludec: Four-times lower pharmacodynamic within-patient variability compared to insulin glargine U300 in type 1 diabetes



Heise et al. Presented at Diabetes Technology Meeting, 16th Annual Scientific Sessions, 10–12 November 2016, Bethesda, MD, USA

INSULIN GLARGINE 300 U/ML (GLA-300) PROVIDES MORE STABLE AND MORE EVENLY DISTRIBUTED STEADY-STATE PHARMACODYNAMIC/ PHARMACOKINETIC PROFILES COMPARED WITH INSULIN DEGLUDEC IN TYPE 1 DIABETES (T1DM)

ATTD
Advanced Technologies & Treatments for Diabetes
15-18 FEBRUARY, 2017 I PARIS, FRANCE

T. Bailey[1], *R. Dahmen*[2], *J. Pettus*[3], *R. Roussel*[4], *K. Bergmann*[2], *M. Maroccia*[5], *N. Nassr*[2], *O. Klein*[6], *G. Bolli*[7], *T. Heise*[6]

Conclusions: This PK/PD analysis supports a superior glucodynamic profile of Gla-300 versus IDeg1 at a dose clinically relevant for T1DM (0.4 U/kg/day), in terms of within-day variability. An overall more stable and more evenly distributed insulin exposure over the dosing interval was observed at both dose levels under Gla-300.

EXISTEIX LA DIABETIS INESTABLE?

SI

NO TOT ÉS NEGATIU:

- **En l'actualitat disposem de sistemes de monitorització de la glucèmia que ens permeten conéixer la variabilitat glucèmica**

- **Els nous anàlegs d'insulina d'acció lenta presenten un perfil d'acció més perllongat i menor variabilitat**

- **Si no consecució d'objectius amb teràpia bolus-basal: tractament amb sensor+/-ISCI**

- **Futur proper: Sistemes de nansa tancada**

Moltes gràcies