CONGRESSO CONGIUNTO SID-AMD-SIEDP-ANIED-OSDI LIGURIA PIEMONTE VALLE D'AOSTA

L'ULTIMA CONNESSIONE... E QUINDI USCIMMO A RIVEDER LE STELLE

LA STORIA DELL'INSULINA: DALLA FARMACOCINETICA ALLA OSSERVAZIONE CLINICA

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22-23 OTTOBRE 2021

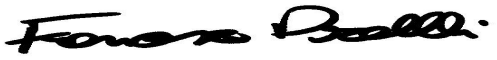
Disclosure

La sottoscritta Dr.ssa Francesca Porcellati dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Eli-Lilly
- Mundipharma
- MSD
- Novo-Nordisk
- Sanofi

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

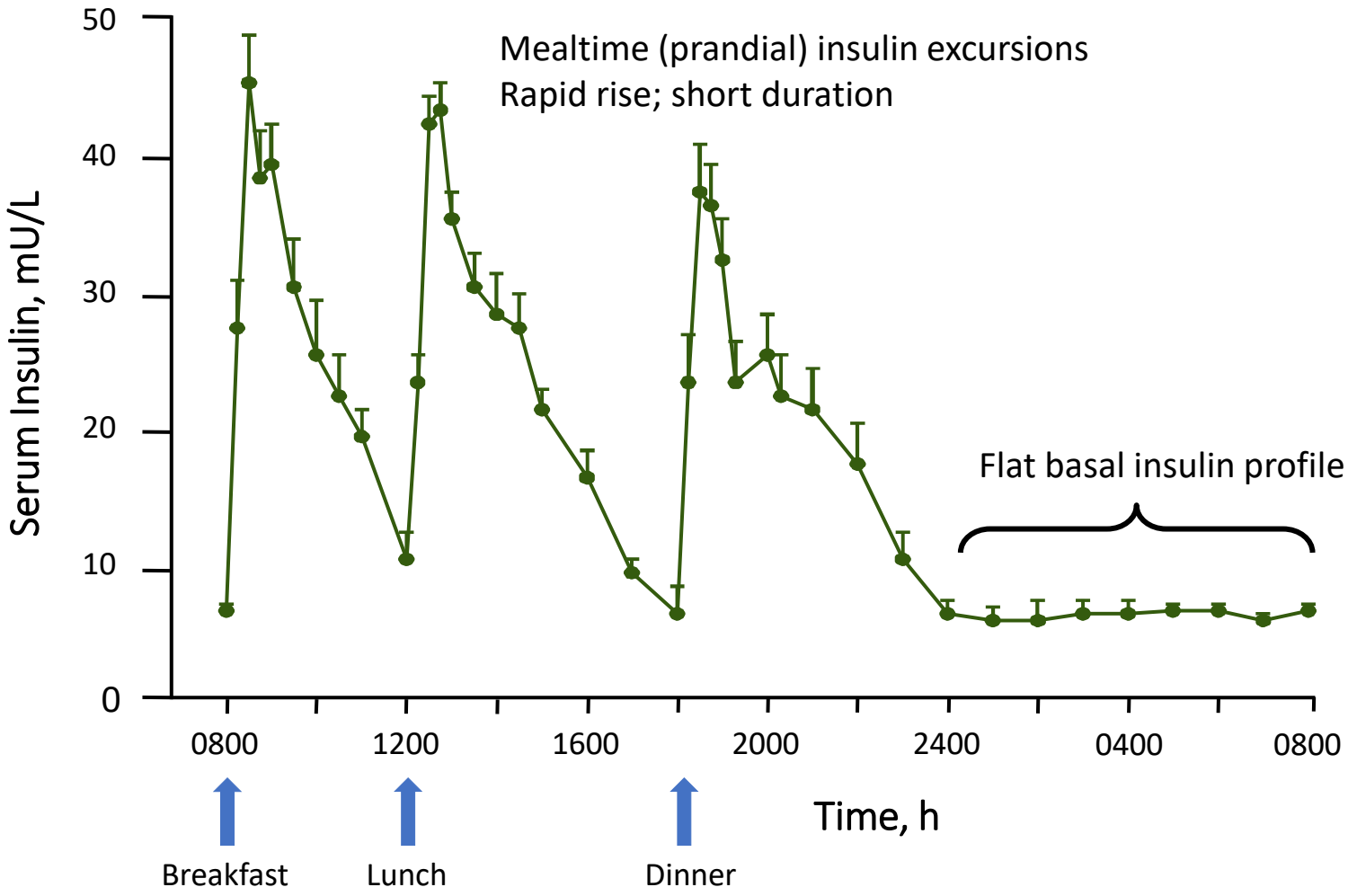
In fede, Francesca Porcellati



AGENDA

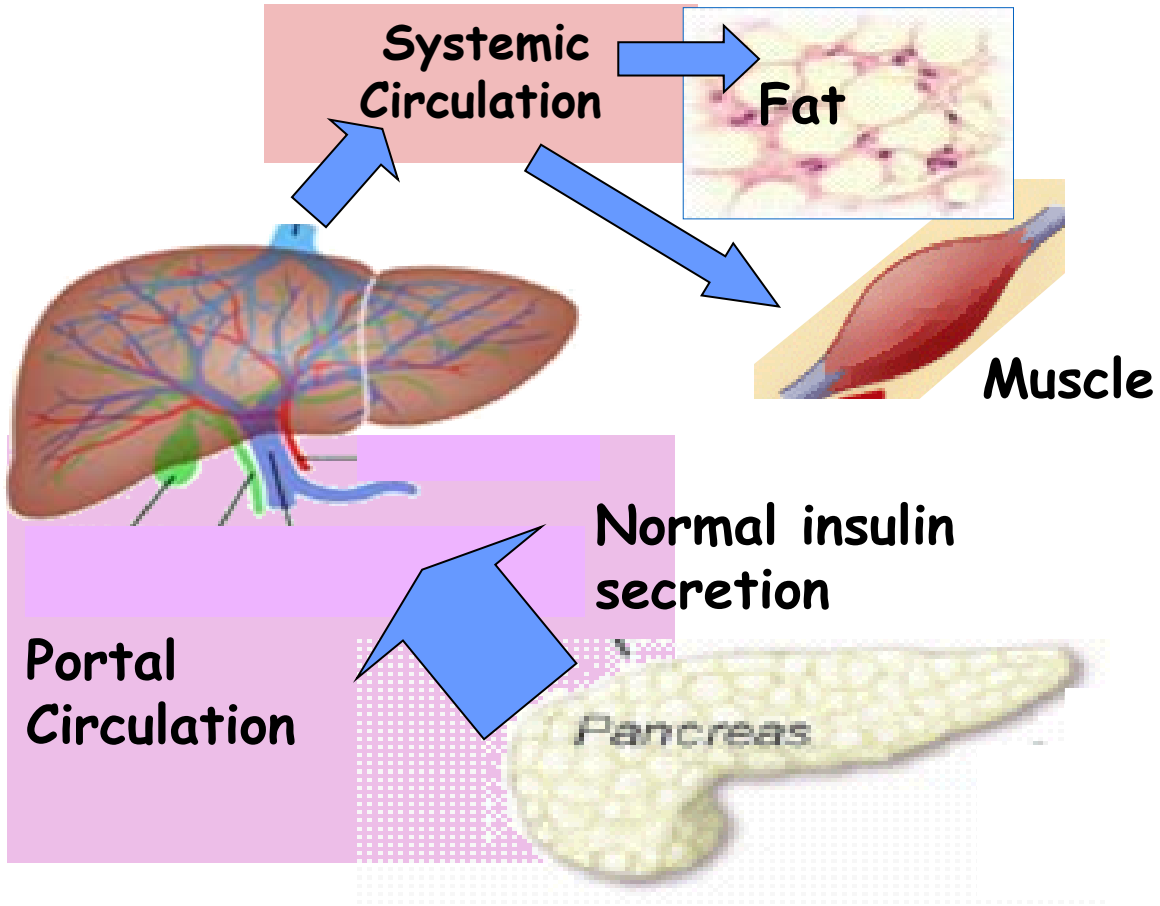
- The challenge of insulin substitution in Type 1 Diabetes
- Basal insulin: the physiology and evolution of its replacement
  - Long-acting insulin analogs: first and second generation
  - Clinical benefits
- The Need for Faster Insulin
- From PK to clinical application
- Conclusion

Insulin Replacement Therapy Aims to Recreate the Normal Blood Insulin Profile

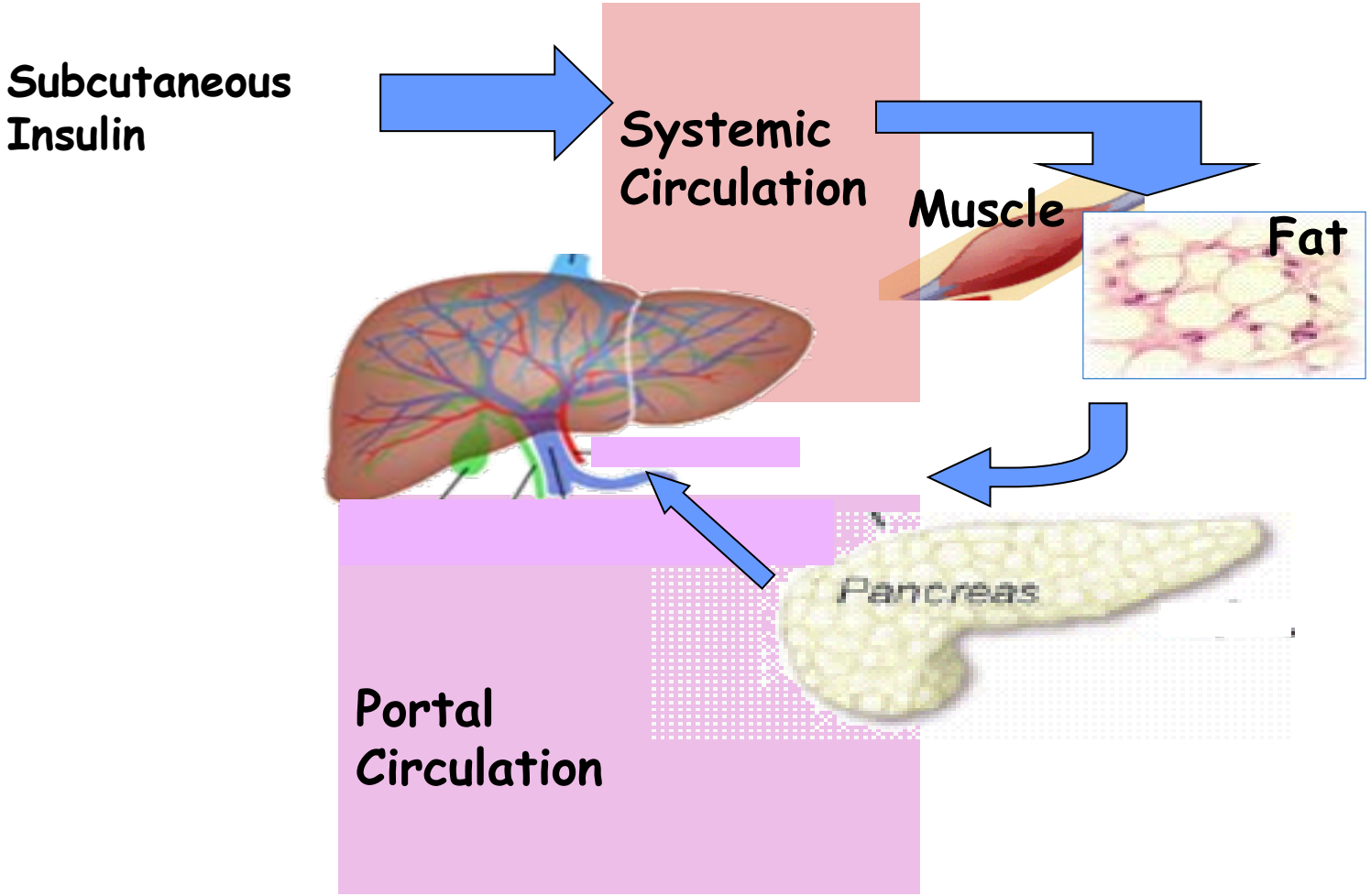


Kruszynska YT, et al. *Diabetologia.* 1987;30:16-21.

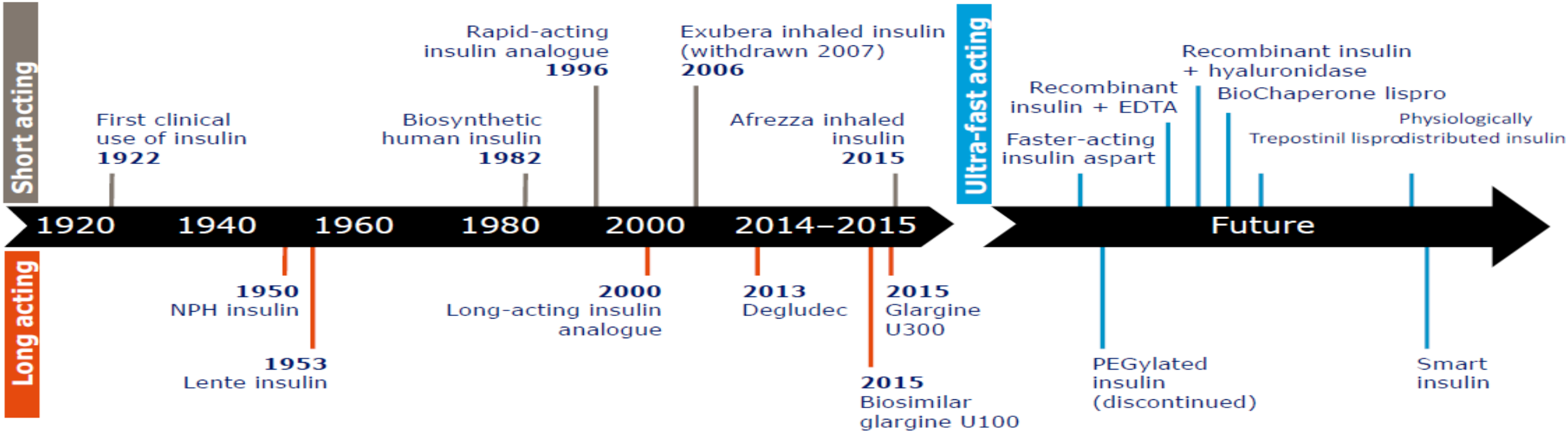
IN PHYSIOLOGY



IN DIABETES


Subcutaneous Insulin
Systemic Circulation
Muscle
Fat
Pancreas
Portal Circulation

The Long Road of Insulin Substitution



Adapted from Cahn A et al. *Lancet Diabetes Endocrinol* 2015;3:638–652.

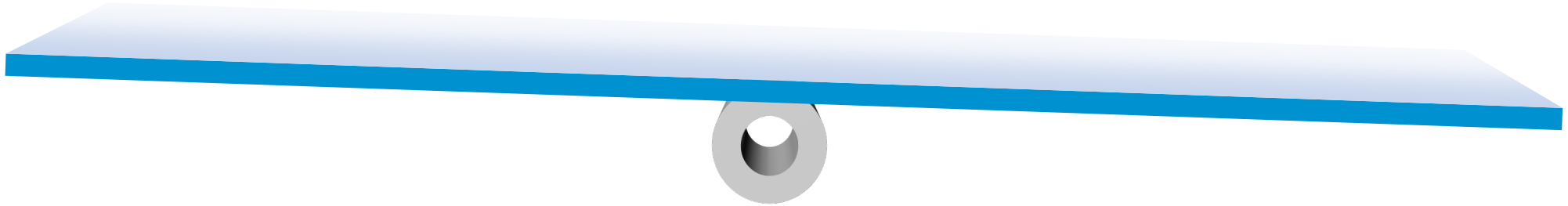
Insulin Therapy: the Need of a Balance

Timely, effective and stable glycemic control

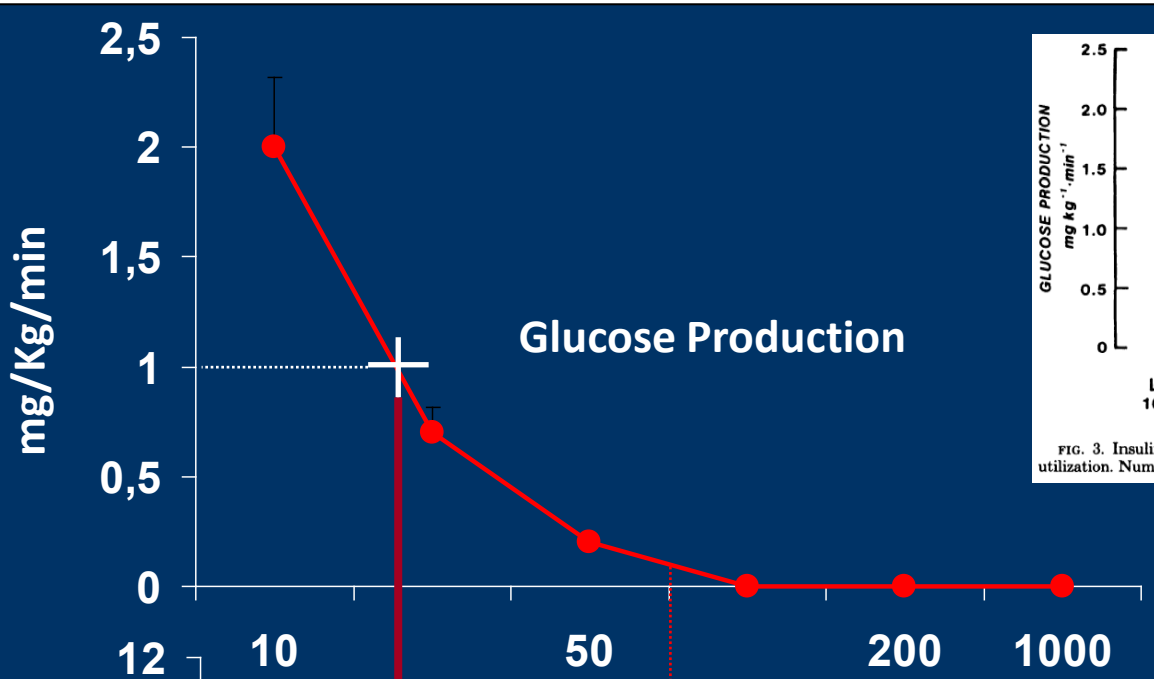
- Improved achievement of HbA1c targets
- Prevention of complications and lower healthcare utilization
- Less restrictive regimens may improve adherence and quality of life

Low risk of hypoglycemia

- Reduced fear of hypoglycemia
- May allow for optimal dose titration and improved glycemic control
- May improve adherence
- May result in reduced morbidity and healthcare resource utilization



Pogach L, Aron D. JAMA. 2010;26;303(20):2076–2077; Khunti K, et al. Diabetes Obes Metab. 2016;18(9):907–915; Riddle M, et al. Diabetes Technol Ther. 2016;18(4):252–257; Peyrot M, et al. Diabet Med. 2012;29:682–9; Davies MJ, et al. Diabet Med. 2013;30(5):512–524; Willis WD, et al. Expert Rev Pharmacoecon Outcomes Res. 2013;13(1):123–130; Ahrén B. Vasc Health Risk Manag. 2013;9:155–163



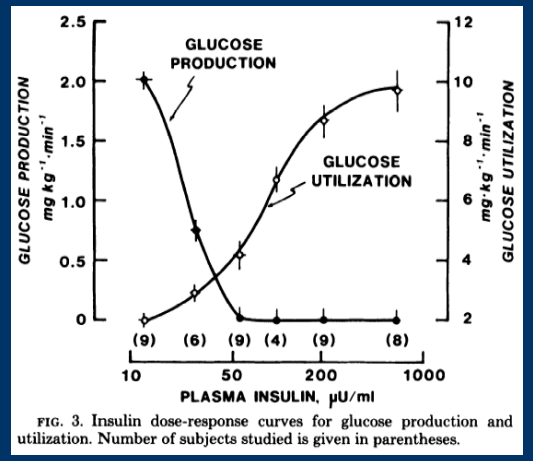
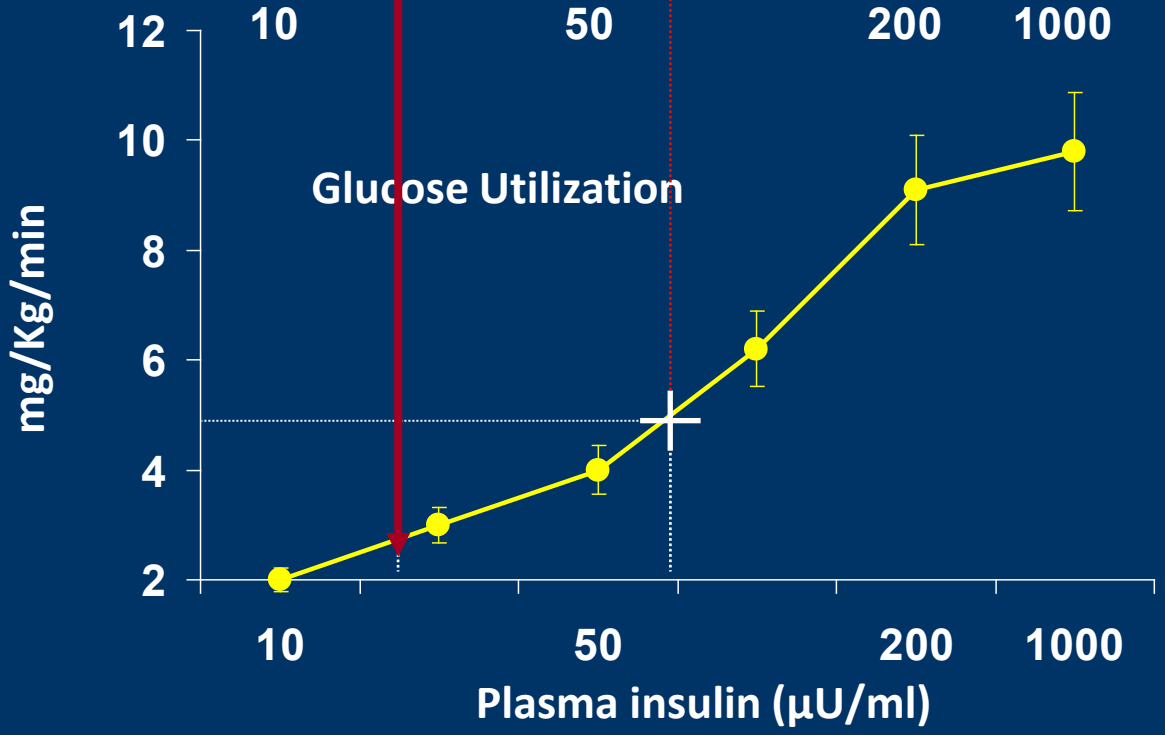
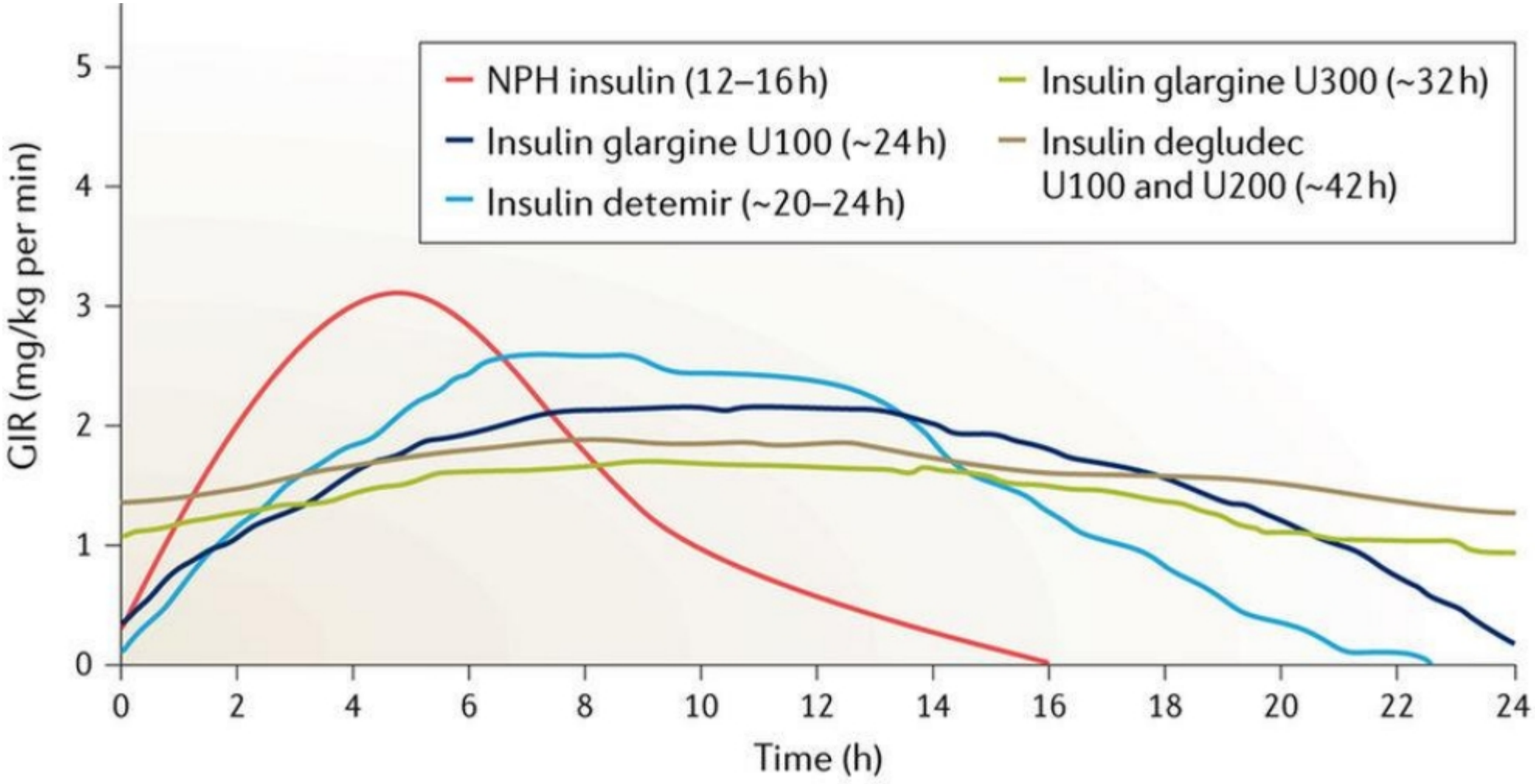


FIG. 3. Insulin dose-response curves for glucose production and utilization. Number of subjects studied is given in parentheses.



Rizza RA et al. Am J Physiol 240: E630-E639, 1981

The Need to Achieve a Physiological Insulin-action Profile

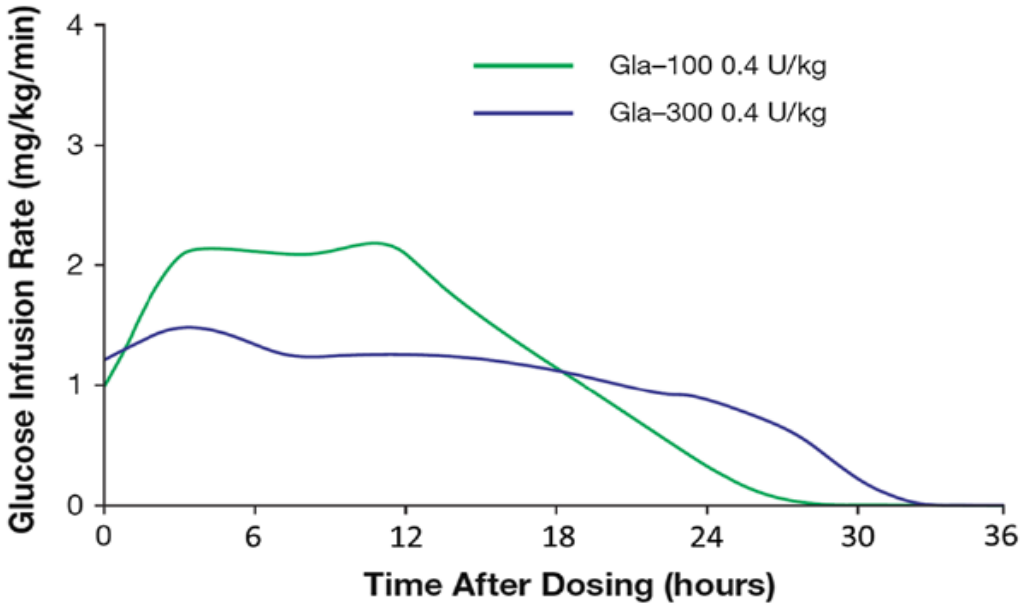


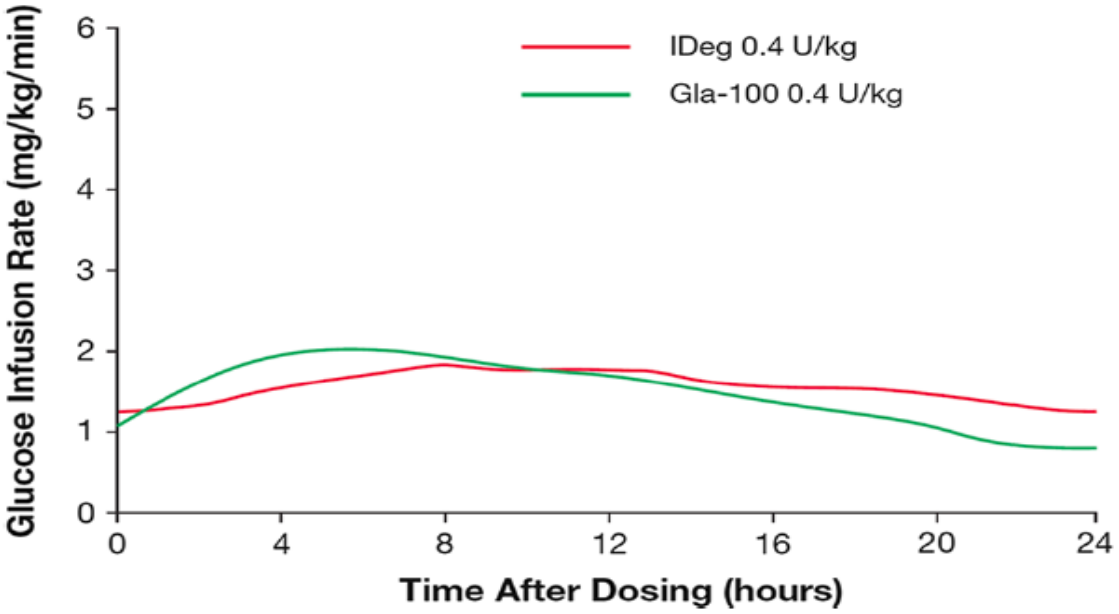
Mathieu, et al. Nature Reviews 2017; 13: 385-399

Care must be taken when interpreting the curves, as experimental settings in which the data were gathered differed between studies

Insulin Effect: First vs Second Generation of Basal Insulin Analogues

Glucose infusion rate profiles of Gla-300 and IDeg compared with Gla-100





Becker RH, et al. Diabetes Care. 2015;38:637-643; US FDA. Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA; Heise T, et al. Diabetes. 2012;61(suppl 1):A91 [abstract 349-OR].

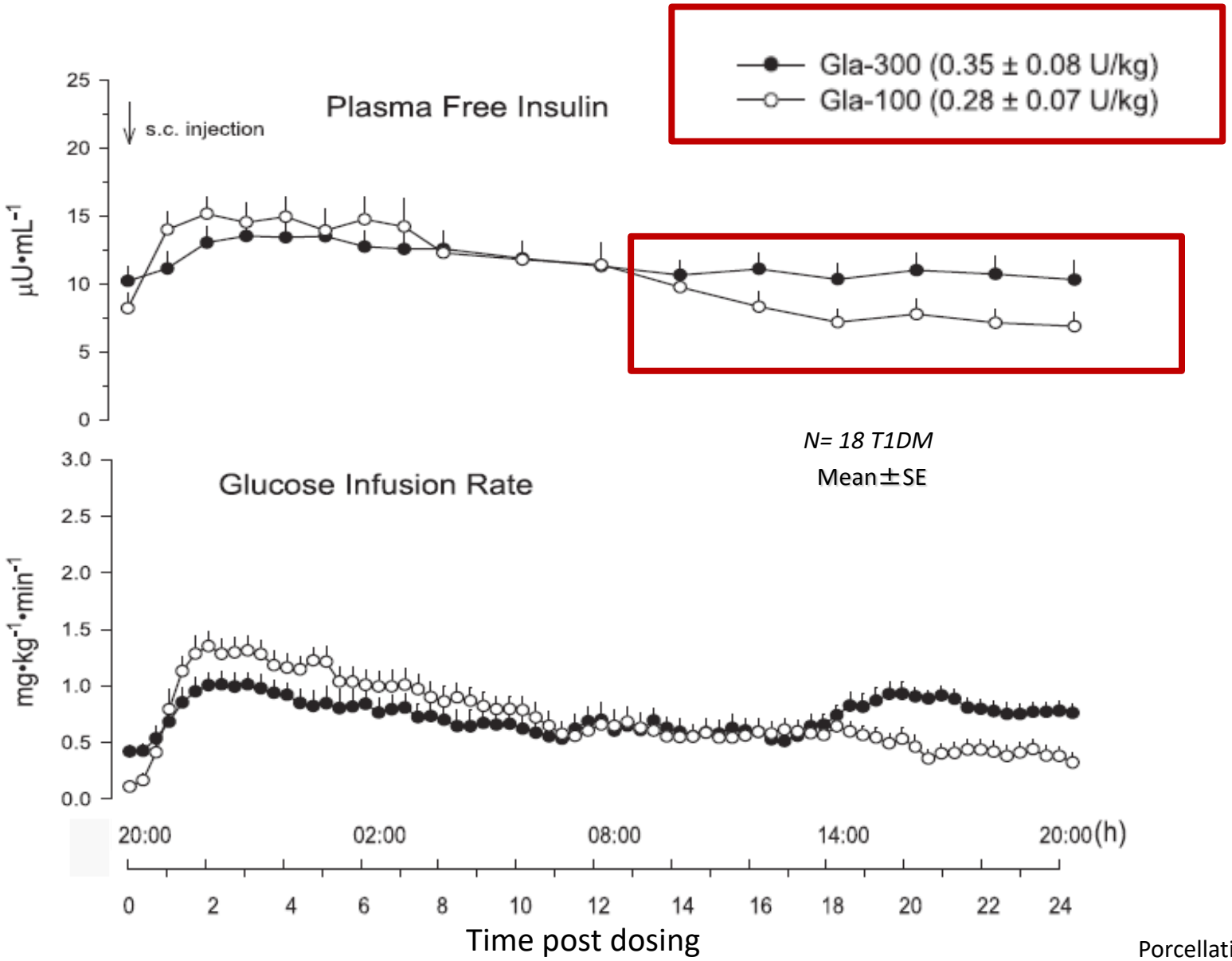
Head-to head Comparisons vs Insulin Glargine 100

T1 DM studies, 0.4U/kg

	Glargine U-300[1]	Degludec[2]
Onset of action	ND	ND
Peak of action	Flat	Flat
Duration of action	<36 hours	<42 hours
Half-Life	~ 19 hours	~ 25 hours
Time to Steady State	3-4 days	2-3 days

1. Becker RH, et al. *Diabetes Care*. 2015;38:637-643.
2. Heise T, et al. *Diabetes Obes Metab*. 2012;14(10):944-950.

PK-PD of Gla-300 and Gla-100 at Clinical Doses



Porcellati F. et al., Diabetes Care 2019

Pharmacokinetic and Pharmacodynamic Variables

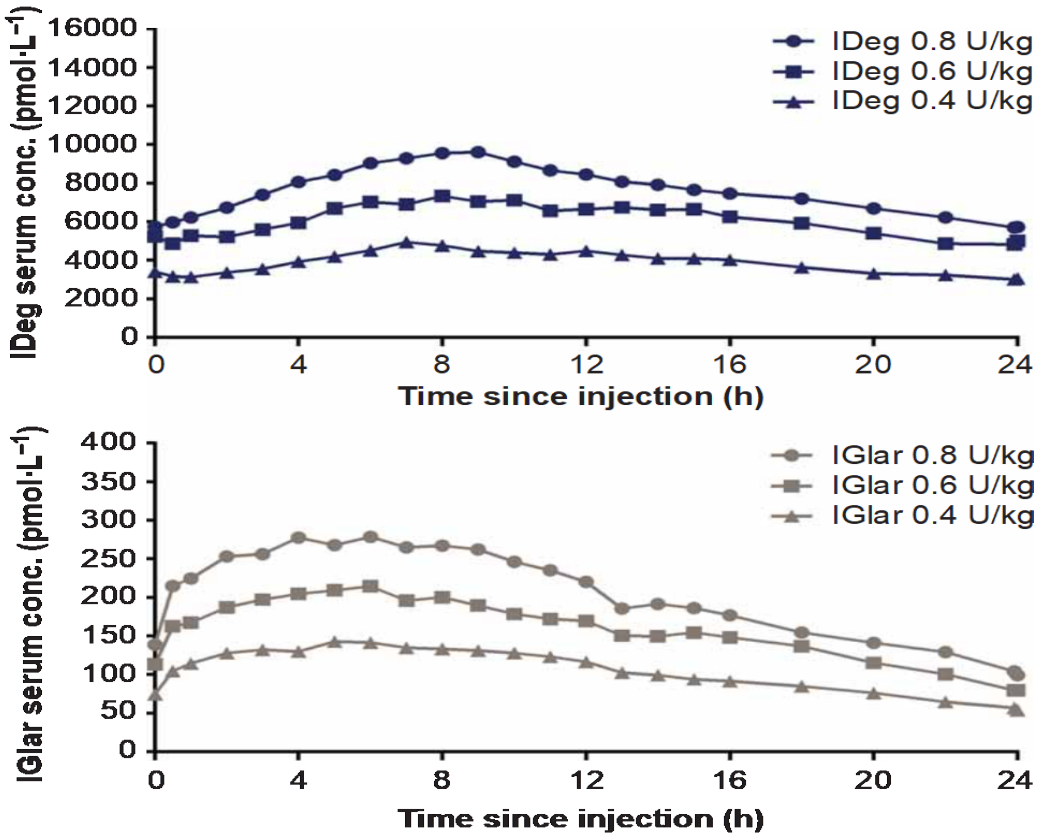
	Gla 300 (0.35 U/kg)	Gla 100 (0.28 U/Kg)	Gla 300/Gla 100 ratio Point estimate[a] (90% CI)
PK parameters			
FIRI-AUC$_{0\text{-}24\,h}$ [µU•h•mL^{-1}]*	257 (208; 317)	231 (182; 294)	1.11 (1.03; 1.20)
FIRI-AUC$_{0\text{-}12\,h}$ [µU•h•mL^{-1}]*	139 (115; 168)	145 (116; 181)	0.96 (0.89; 1.04)
FIRI-AUC$_{12\text{-}24\,h}$ [µU•h•mL^{-1}]*	116 (91; 148)	84 (63; 113)	1.38 (1.21; 1.56)
PD parameters			
GIR-AUC$_{0\text{-}24\,h}$ [mg•kg^{-1}]*	981 (803;1198)	950 (758; 1190)	1.03 (0.88; 1.21)
GIR-AUC$_{0\text{-}12\,h}$ [mg•kg^{-1}]*	464 (345; 613)	604 (476; 766)	0.77 (0.62; 0.95)
GIR-AUC$_{12\text{-}24\,h}$ [mg•kg^{-1}]*	482 (394;590)	314 (228; 433)	1.53 (1.23; 1.92)

Data are geometric mean (95% CI). [a]Point estimates of treatment ratios with 90% confidence intervals (CIs) were calculated using a linear mixed effects model based on log-transformed data and re-transformations;*

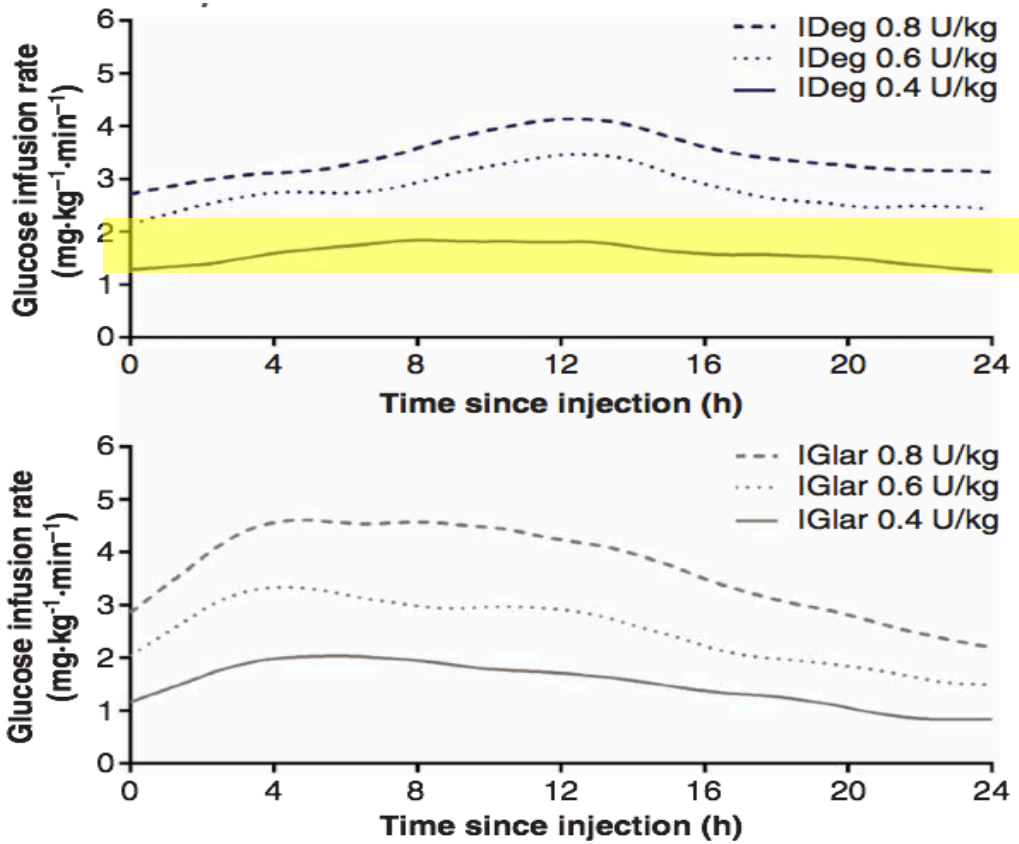
Porcellati F. et al., Diabetes Care 2019

PK-PD of insulin degludec in Type 1 diabetes at steady-state – comparison with glargine U100

Based on 22 patients per dose level for degludec and 22 patients per dose level for Gla-100
At steady state on Day 8



Pharmacokinetic profiles



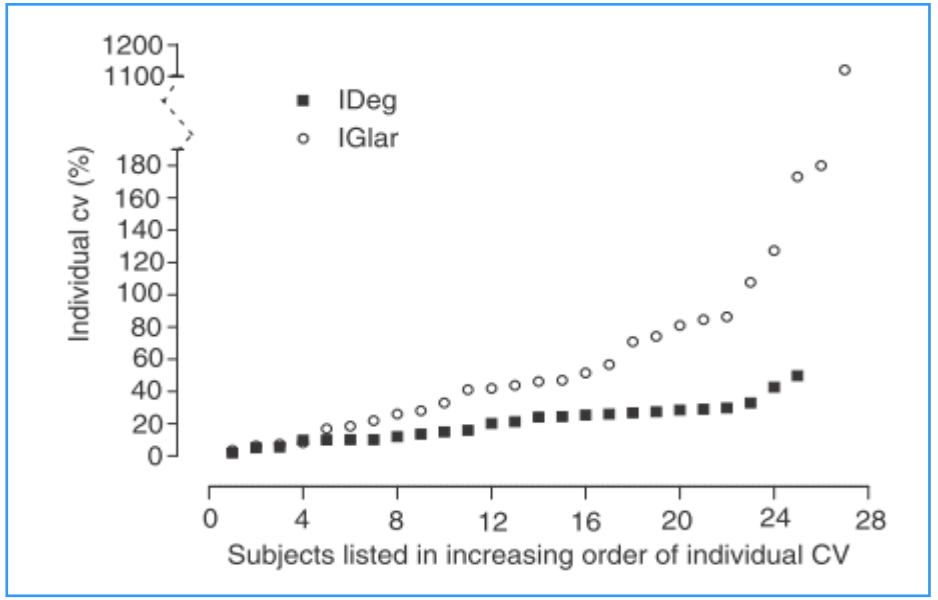
Pharmacodynamic profiles

Randomized, single-center, double-blind, two-period, crossover, multiple dose euglycemic glucose clamp trial

Heise et al. Expert Opin Drug Metab Toxicol. 2015;18:1-9.

Variability of Insulin Degludec and Glargine U100 in Type 1 Diabetes

	Deg	Gla	*p* value
	Within-subject CV (%)		
AUC $_{GIR, 0-24}$	20	82	*p< 0.0001*
AUC $_{GIR, 2-24}$	22	92	*p< 0.0001*
GIR $_{max}$	18	60	*p< 0.0001*



Three replicates- Steady state dose study

Heise T et al. Diabetes Obesity and Metabolism, 2012

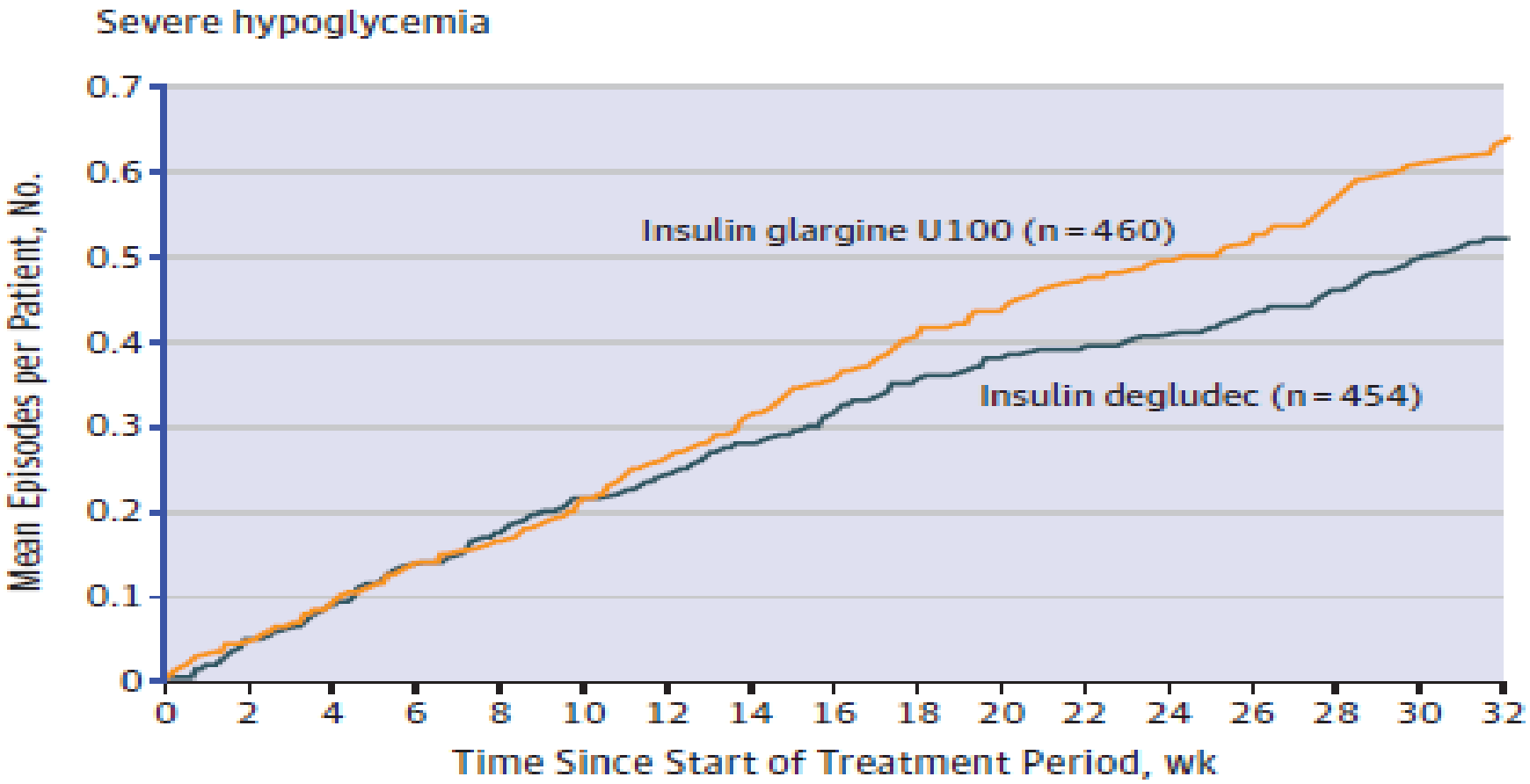
From PK/PD Characteristic to Potential Clinical Benefit

Characteristic	Potential clinical benefit
• Flat PK profile, with sustained and consistent insulin exposure over 24 hours • Flat PD profile with duration of action ≥ 24 hours • Physiological regulation of glucose metabolism with less suppression of endogenous glucose production during night and more during afternoon	• Reduced risk of hypoglycemia • Consistent BG control over 24 hours • Once-daily injection • Flexible injection timing • Lower risk of nocturnal/morning hypoglycemia, favouring better pre-dinner BG control
• Low within-subject, between-day variability in insulin exposure (PK) and action (PD)	• Facilitates insulin titration • Lower risk of hypoglycemia

Becker R.H.A. et al., Diabetes Obes. Metab. 2015, Becker R.H.A. et al., Diabetes Care, 2015, Home PD et al. Diabetes Care. 2015, RM Bergenstal et al., Diabetes Care, 2017, Porcellati F. et al., 77th American Diabetes Association Scientific Session; Heise et al. Expert Opin Drug Metab Toxicol. 2015;18:1-9; Heise T et al. Diabetes Obesity and Metabolism, 2012

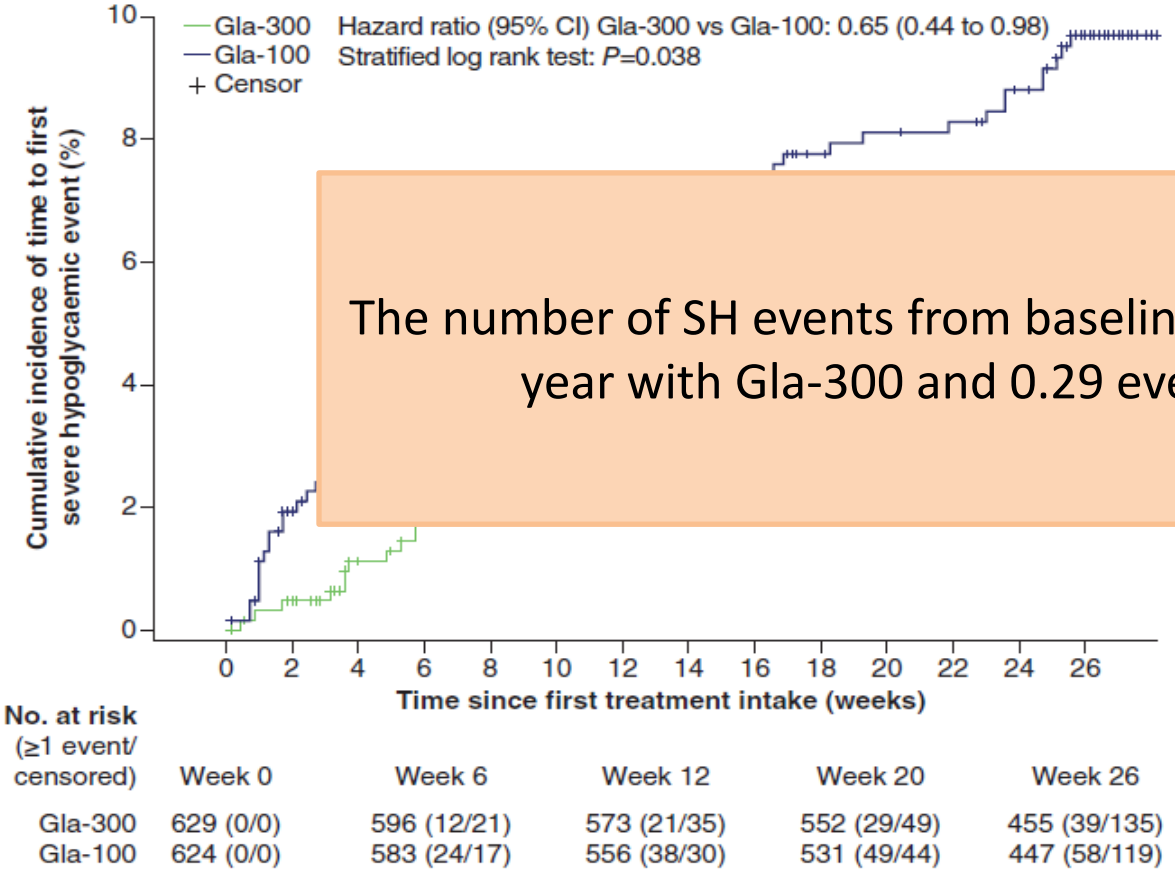
SWITCH 1 Trial: Rate for Episodes of Severe Hypoglycemia Significantly Lower with Insulin Degludec vs Insulin Glargine 100

Cumulative Rates of Hypoglycemia per Patient

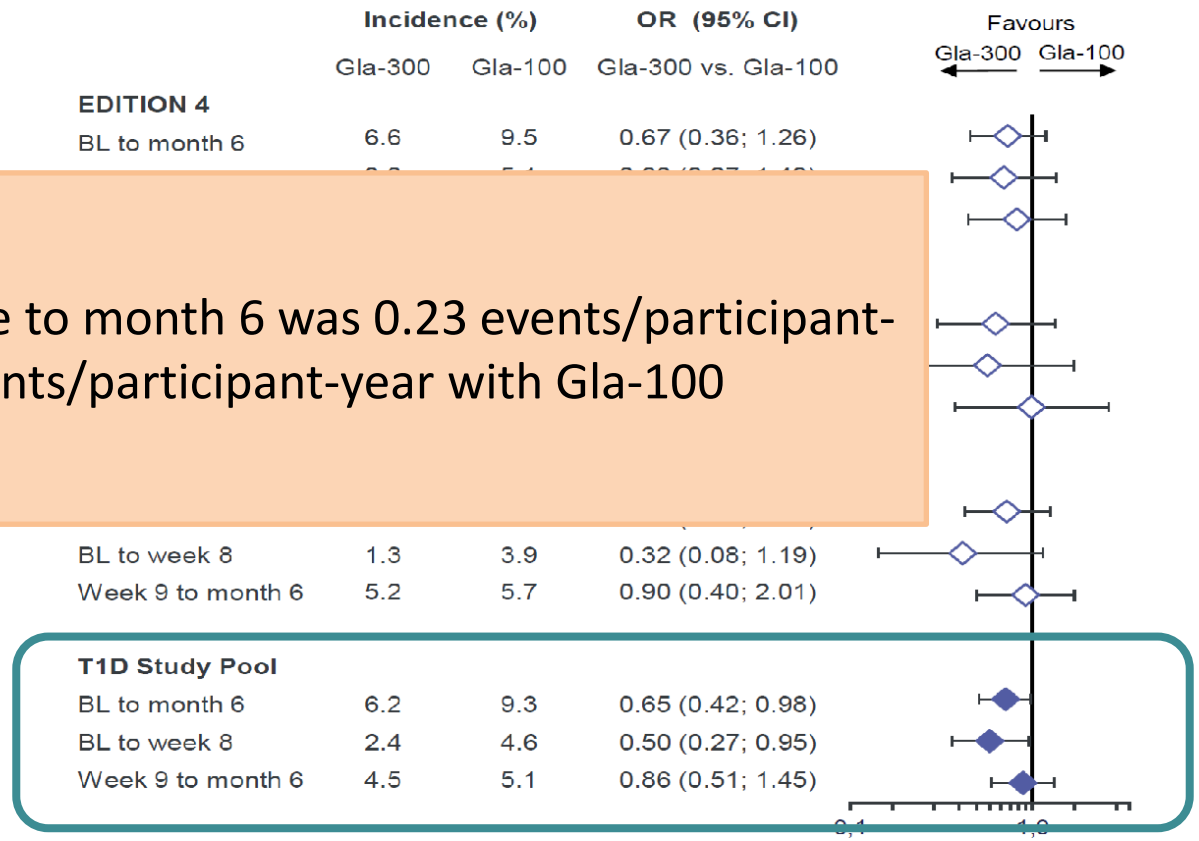


Lane W. et al. JAMA. 2017;318:33-44

Lower Percentage of Patients with ≥1 Severe Hypoglycemic Event with Gla-300 vs. Gla-100



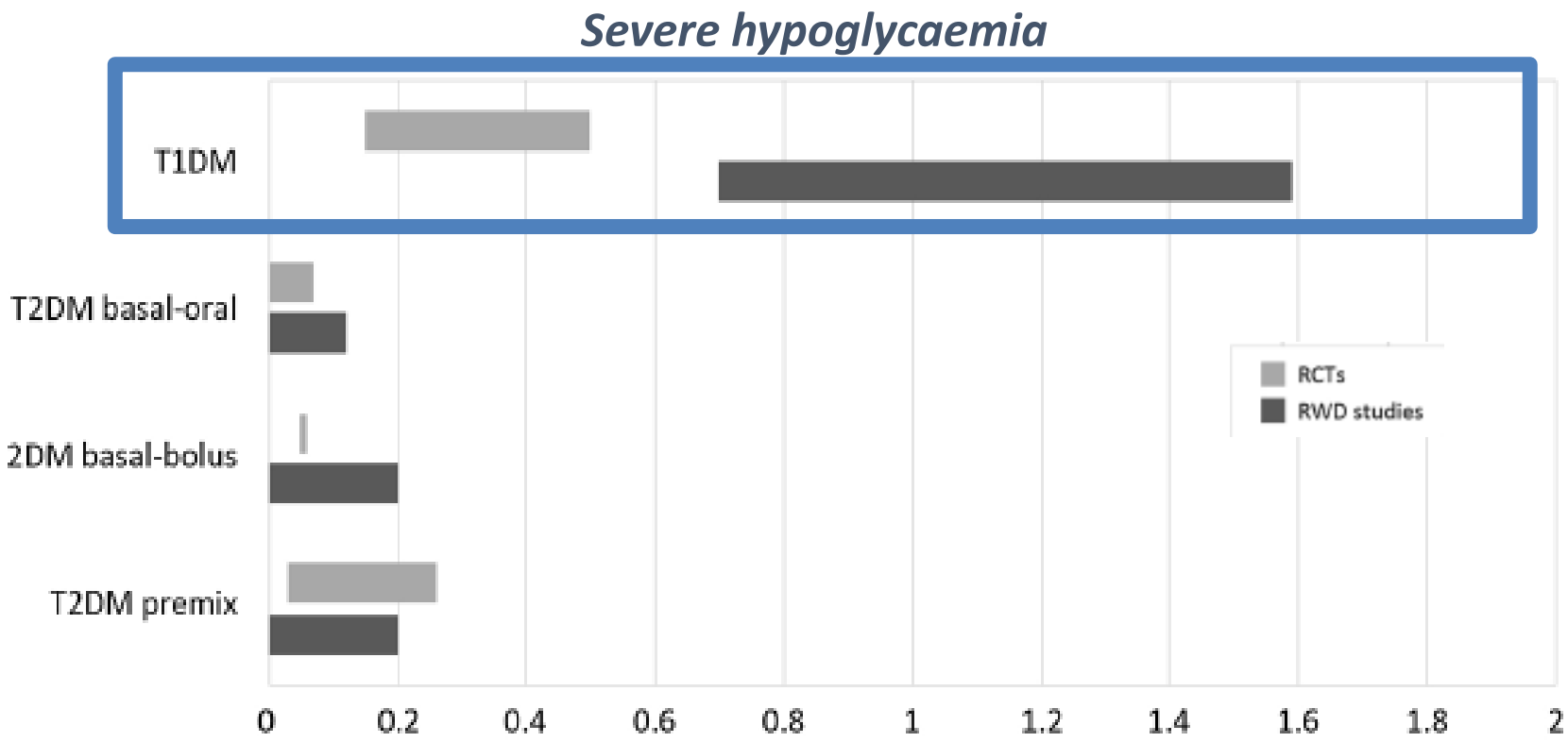
The number of SH events from baseline to month 6 was 0.23 events/participant-year with Gla-300 and 0.29 events/participant-year with Gla-100



BL, baseline; W, weeks since first injection; OR, Odds ratio; OR based on logistic model with treatment as fixed effect, and by adding study as fixed effect for the T1D study pool; cumulative incidences curves were calculated using Kaplan-Meier estimates; Hazard ratio estimated using a Cox proportional hazard model with treatment group and study as fixed effects; Log-rank test stratified by study

Danne T. et al., Diabetes Obes Metab. 2020.

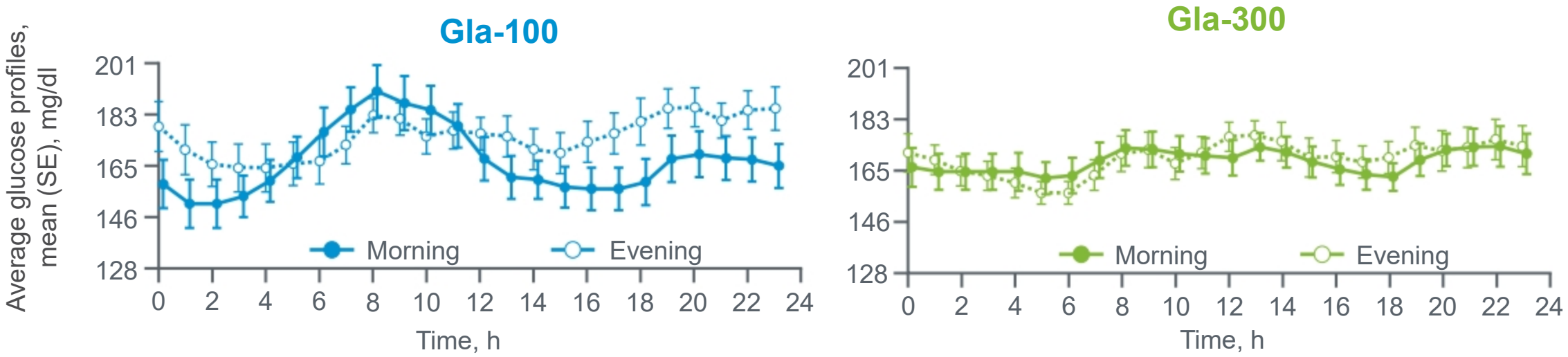
Hypoglycaemia Events Rates: Real World Data Studies versus Randomized Controlled Trial



Elliott L. Diabetes Ther (2016) 7:45–60.

24-hour glucose profile of AM vs PM administration of Gla 100 or Gla-300 in T1DM

Smoother 24 hr glucose profiles with Gla-300, irrespective of injection time



Average 24-h glucose profiles during the last 2 weeks of each treatment period

A 16-week, exploratory, open-label, parallel-group, two-period crossover study designed to compare glucose control in patients with T1DM (N=59) receiving Gla-300 or Gla-100 in morning or evening, in combination with prandial insulin

Bergenstal RM, et al. Diabetes Care 2017;40:554–60

Clinical Observation

Clinical Observation

Degludec

- Robust “dawn” and “dusk” phenomenon
- High BG variability
- Lower insulin sensitivity
- Higher insulin requirements
- Shift workers
- Frequent travellers
- …….
- ……..

↓ rapid-acting insulin requirement

Clinical Observation

Degludec

- Robust “dawn” and “dusk” phenomenon
- High BG variability
- Lower insulin sensitivity
- Higher insulin requirements
- Shift workers
- Frequent travellers
- …….
- ……..

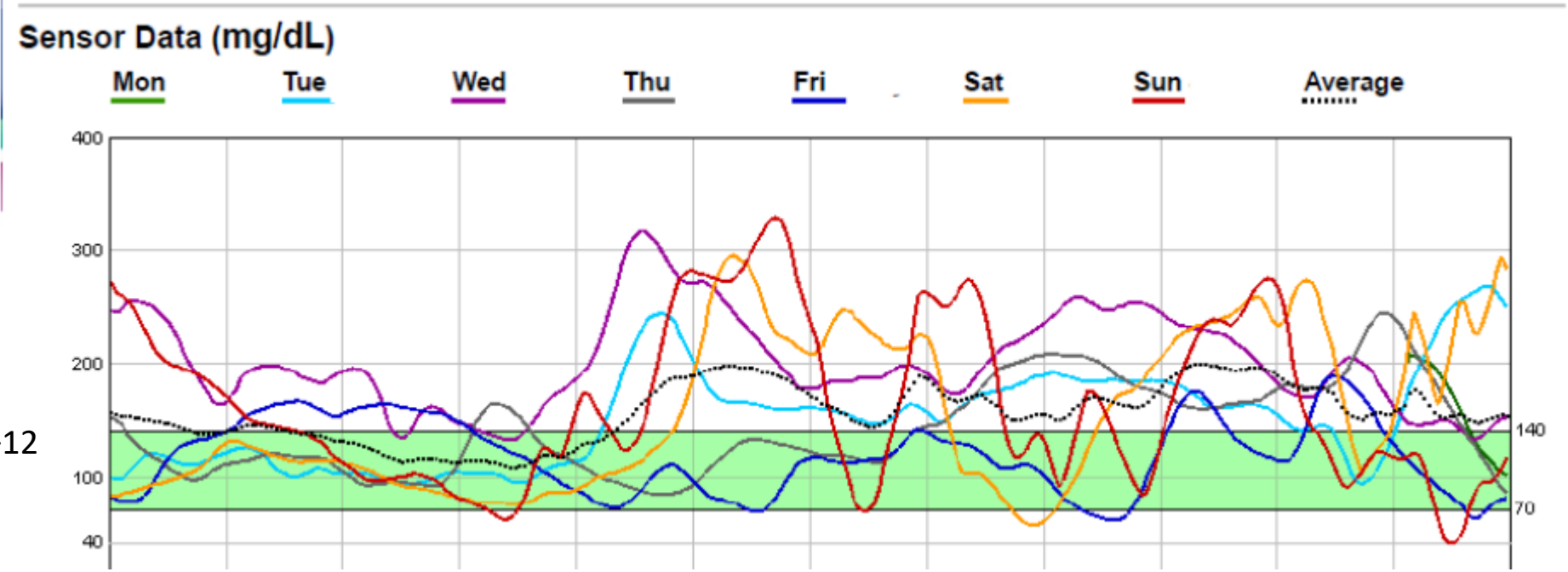
↓ rapid-acting insulin requirement

Glargine 300

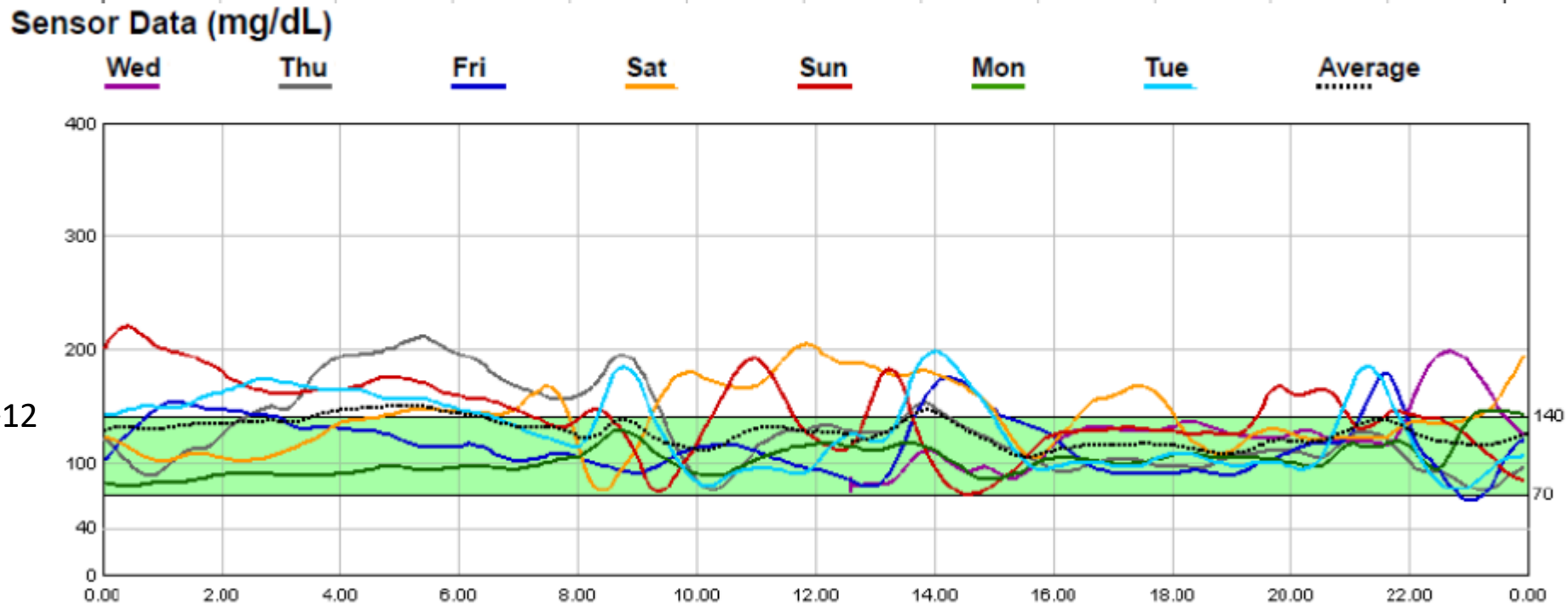
- Higher insulin sensitivity
- Lower insulin requirement (e.g. LADA, long diabetes duration etc. etc.)
- Lower prandial insulin requirements
- When smooth titration is needed
- When faster dose adaptation is needed
- ……
- ……..

Not “1 to 1 unit switch” from other BI

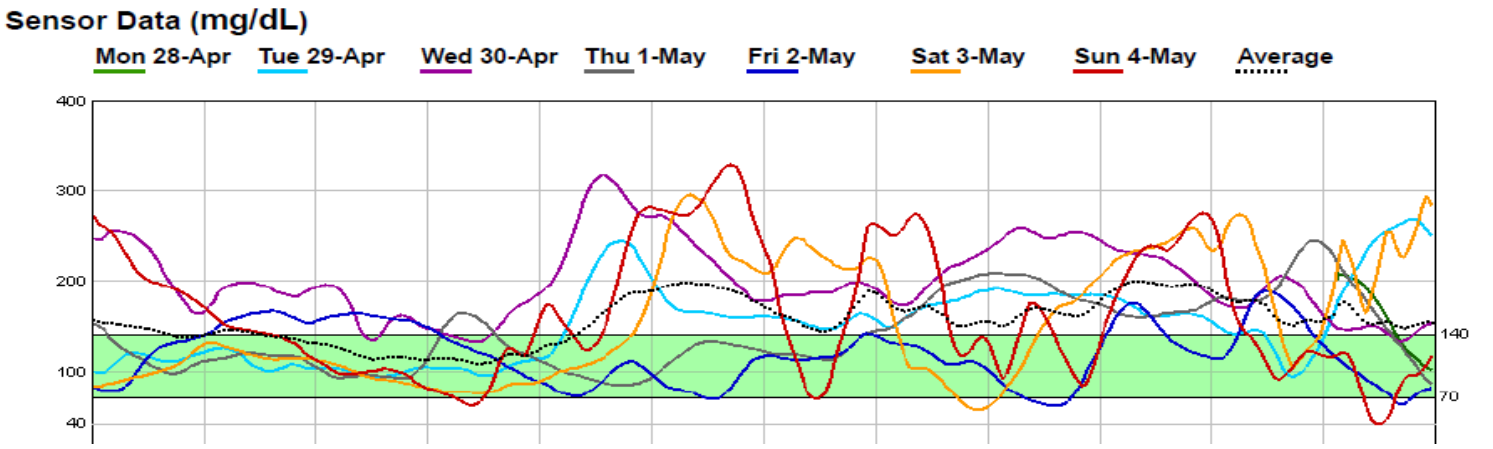
Glargine 100
28 U
Lispro 8+12+12



Degludec
28 U
Lispro 5+8+12

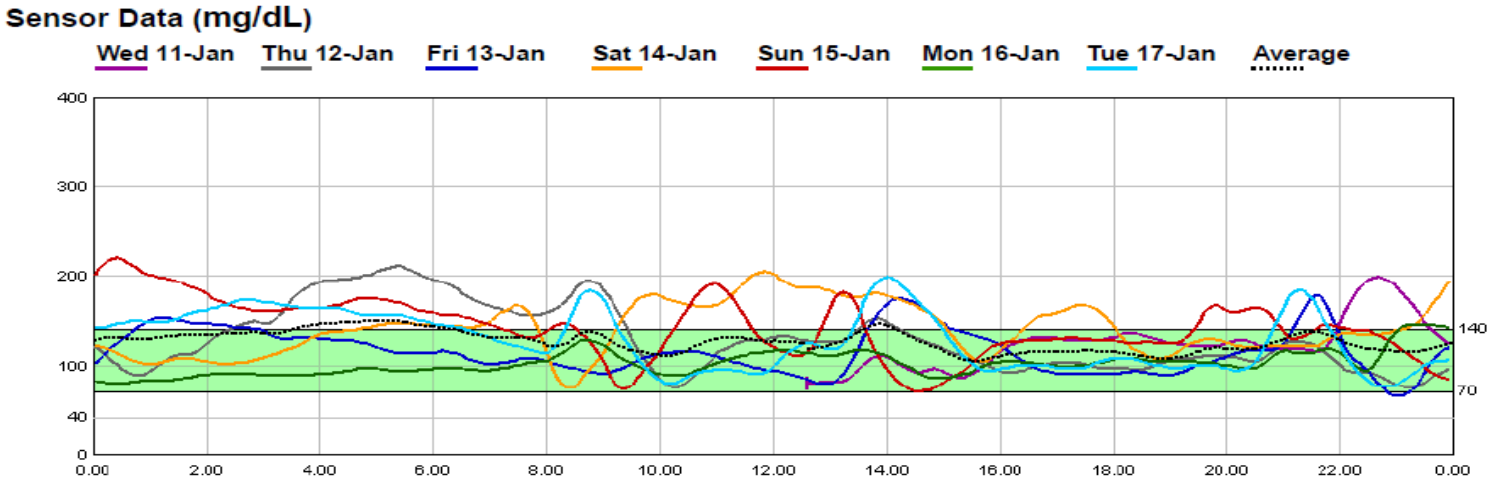


R. 32 anni, ingegnere.
Esordio acuto del DT1 a 16 anni, familiarità per DT1 (padre)
Controllo metabolico non adeguato negli anni successive all'esordio.
Malattia celiaca
Assenti complicanze

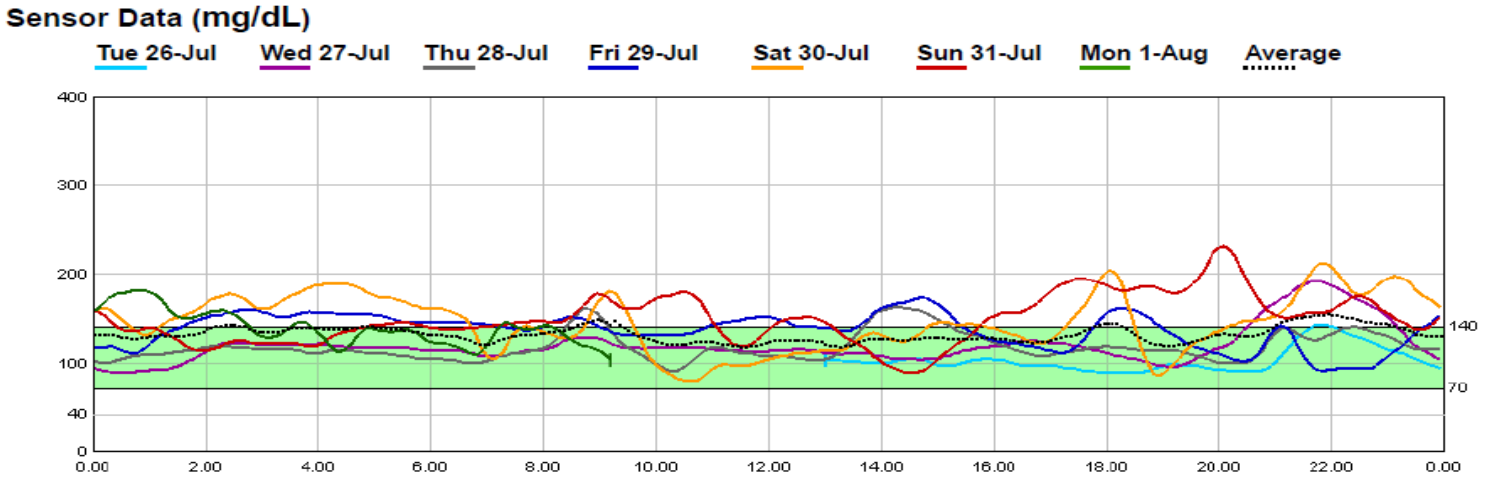


A1c: 8.4%

Gla 100 10 U
Aspart 2+5+5



A1c: 7.4%
Gla 300 12 U
Aspart 3+6+4



A1c: 6.7

Silvia 56 anni, , T1 dall'età di 3.
Controllo glicemico non sempre adeguato.
Elevate frequenza di ipoglicemia, lipodistrofia in zona perimobelicale
Assenti complicanze
Tiroidectomia per Mt. di Basedow 15 anni orsono.

The Use of FPG to Titrate Basal Insulin in T1DM is Necessary but NOT Sufficient

F, D, O+

DATA	COLAZIONE prima glicemia	U	dopo glicemia	U	PRANZO prima glicemia	U	dopo glicemia	U	ORE 16.30 glicemia	U	CENA prima glicemia	U	dopo glicemia	U	NOTE
4/4	226	30m 2.5			167	4	220	+1	160		159	5	120		
5/4	115	2.0			144	4	189		201	+1	124	4	177		snack
6/4	299	2.0	+Ex		127	3.5	162		171	+1	135	4	109		
7/4	92	2.5			131	3.5	193	+1	131		156	4	205	+1	u R
8/4	144	2.0			143	4	205	+1	167	+1	135	3,5	129		
9/4	101	2,5			102	3.0	167		183	+1	127	3,5	50	+	ECHO
10/4	284	3.0			128	3.5	149		158	+1	161	4	147		

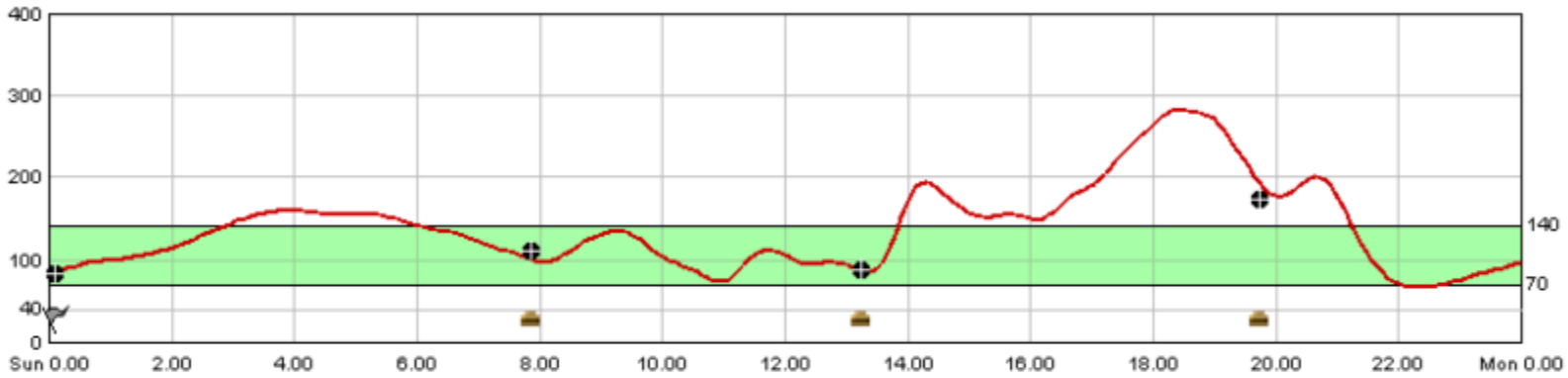
The Use of FPG to Titrate Basal Insulin in T1DM is Necessary but NOT Sufficient

F, D, O+

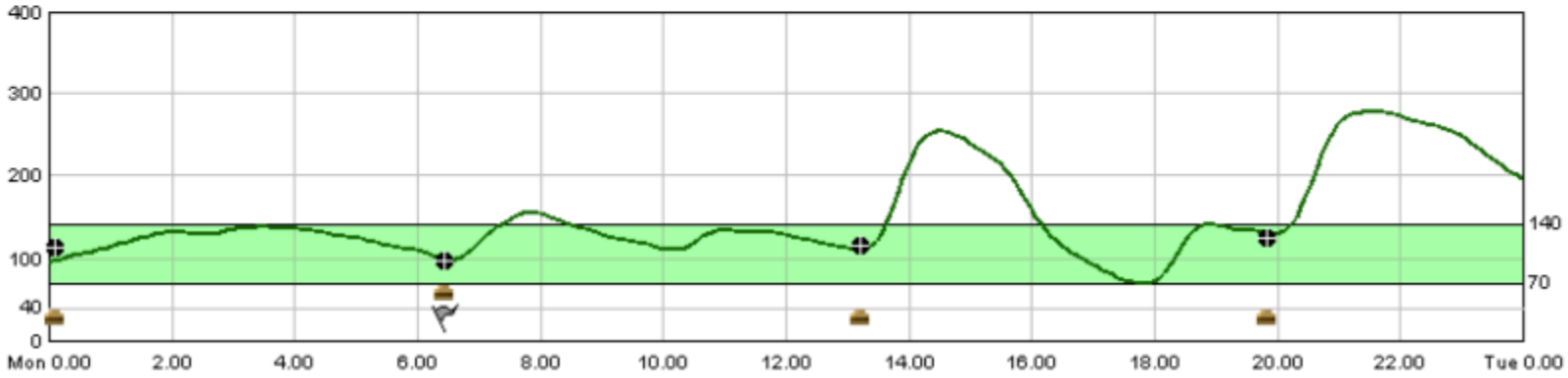
DATA	COLAZIONE prima glicemia	U	COLAZIONE dopo glicemia	U	PRANZO prima glicemia	U	PRANZO dopo glicemia	U	ORE 16.30 glicemia	U	CENA prima glicemia	U	CENA dopo glicemia	U	NOTE
4/4	226	30m 2.5			167	4	220	+1	160		159	5	120		
5/4	115	3.0			144	4	189		201	+1	124	4	177		snack
6/4	299	3.0	+Ex		127	3.5	162		171	+1	135	4	109		
7/4	92	2.5			131	3.5	193	+1	131		156	4	205	+1	U R
8/4	144	2.0			143	4	205	+1	167	+1	135	3,5	129		
9/4	101	2.5			102	3.0	167		183	+1	127	3,5	50		+ ECO
10/4	284	3.0			128	3.5	149		158	+1	161	4	147		

Basal insulin should not be titrated just based on the FBS; it should be adjusted based on the relationship of the bedtime BG to the morning FBS

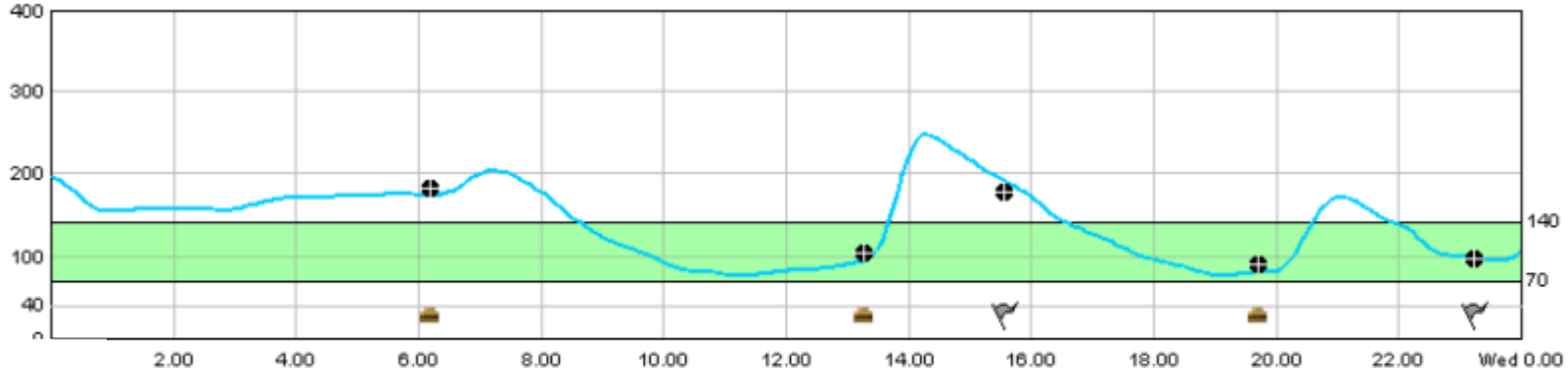
Sun 14-Feb (mg/dL) Sensor



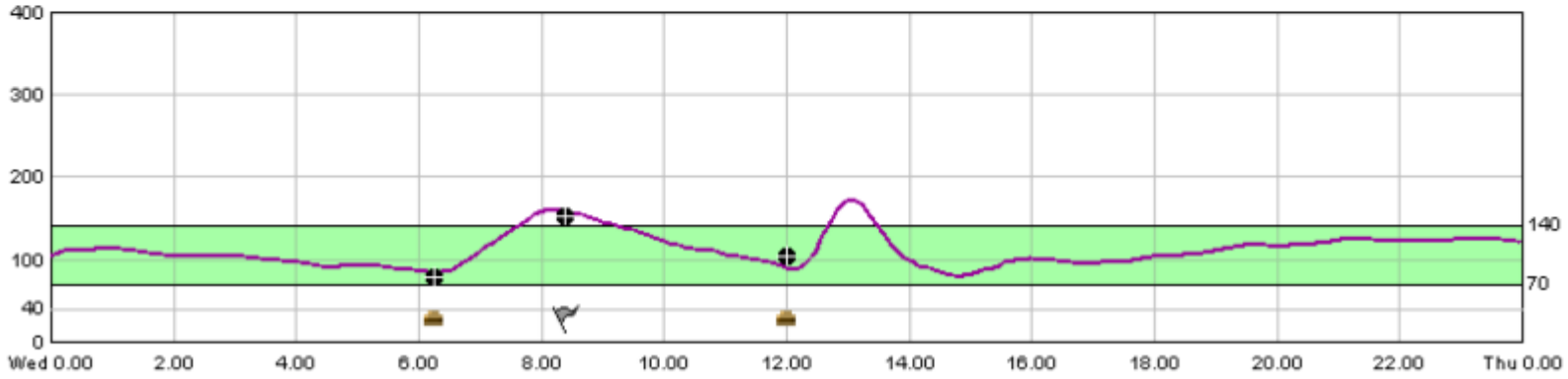
Mon 15-Feb (mg/dL) Sensor

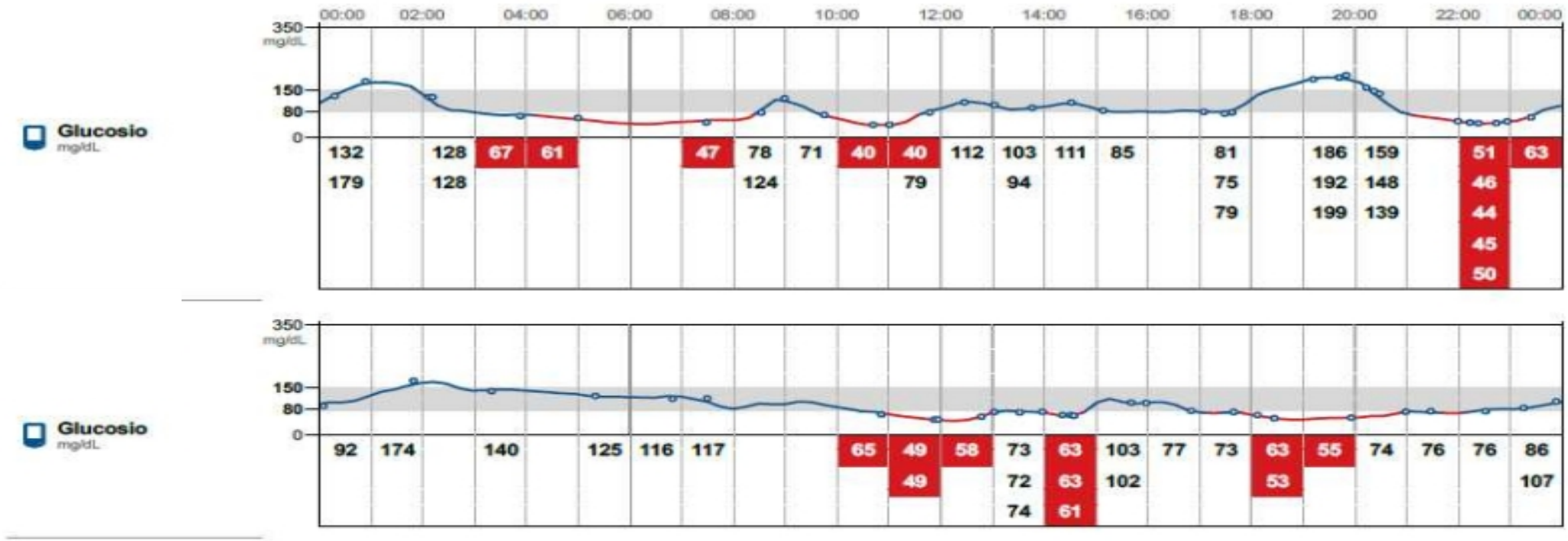


Tue 16-Feb (mg/dL) Sensor



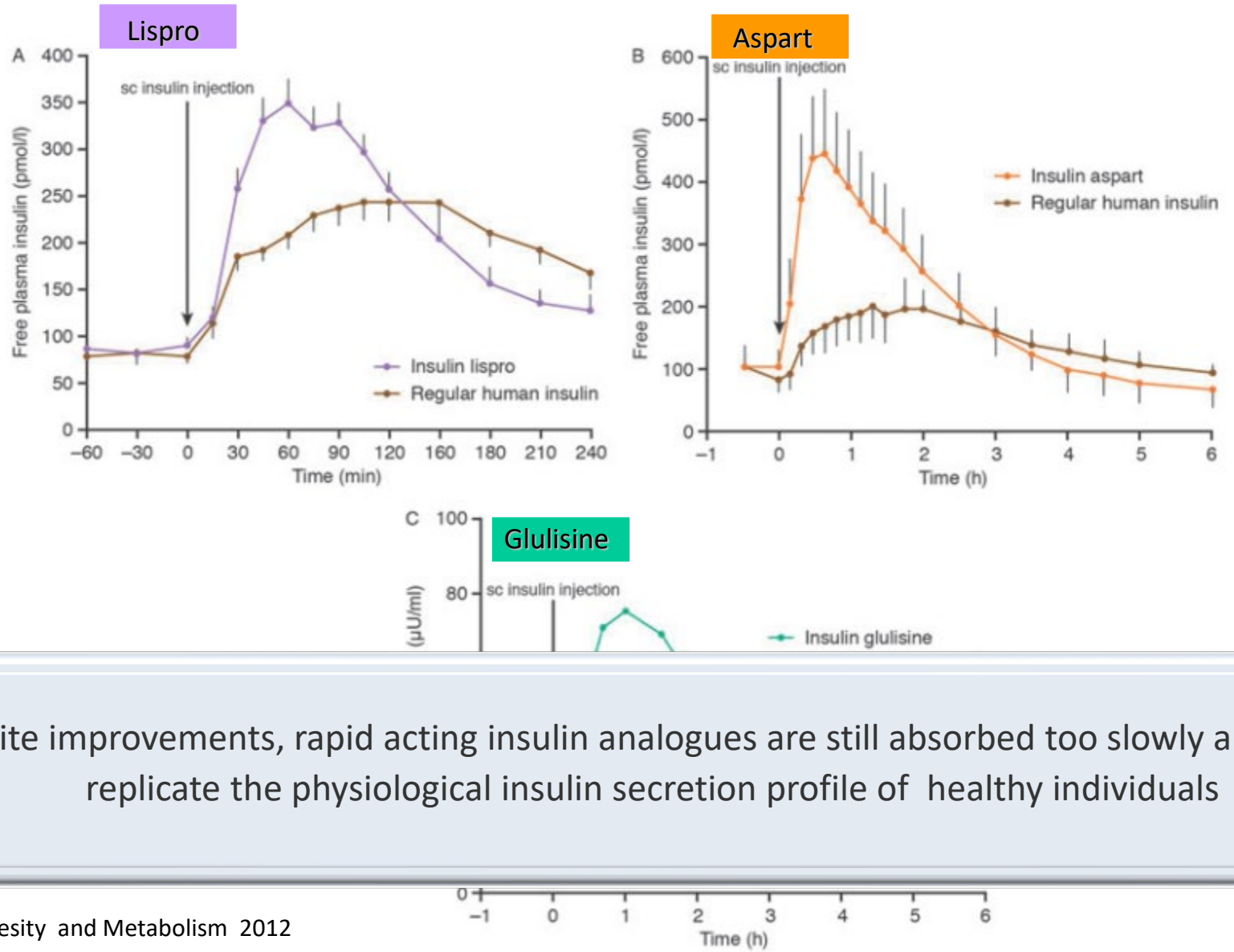
Wed 17-Feb (mg/dL) Sensor





The problem here it is not basal insulin but the rapid one!

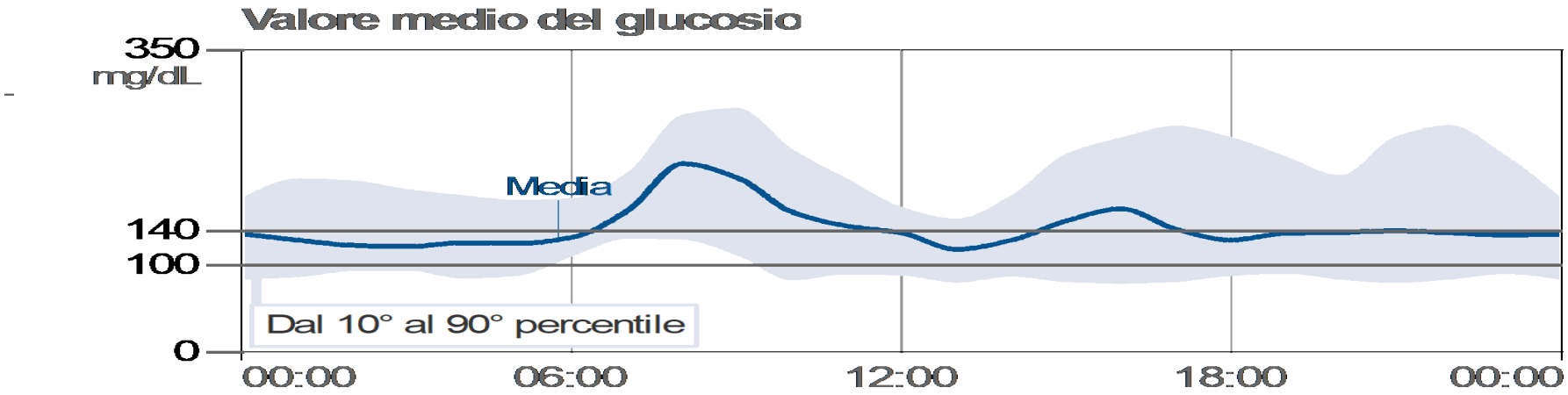
Pharmacokinetics of Rapid Acting Analogs Compared to that of Regular Insulin

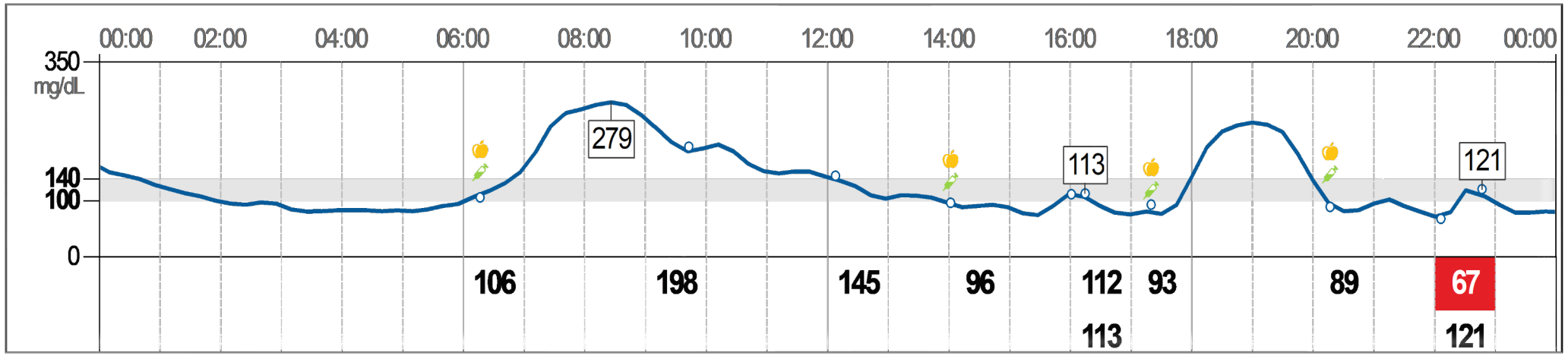


Despite improvements, rapid acting insulin analogues are still absorbed too slowly and do not replicate the physiological insulin secretion profile of healthy individuals

Home P, Diabetes Obesity and Metabolism 2012

Sofia: il risveglio prima della scuola





Breakfast meal-time insulin has a dual task in dealing with the breakfast calorie load and correcting "relative" basal hypoinsulinaemia (i.e. higher insulin requirements at dawn)

Aspects of Self-Reported Diabetes Management in 2016–2018

	Overall, N=11,007	*6–12 years old, N=1312*	*13–17 years old, N=3179*	*18–25 years old, N=2440*	*26–49 years old, N=2122*	*≥50 years old, N=1953*
Insulin use						
Timing of insulin bolus, *n* (%)						
At least several minutes before the meal	2671 (24)	359 (27)	626 (20)	419 (17)	544 (26)	723 (37)
Immediately before the meal	4822 (44)	579 (44)	1491 (47)	1009 (41)	944 (44)	798 (41)
During the meal	1178 (11)	105 (8)	351 (11)	339 (14)	262 (12)	121 (6)
After the meal	2336 (21)	269 (21)	711 (22)	673 (28)	372 (18)	311 (16)

T1D Exchange

Foster NC et al, DTT, 2019

Faster Aspart vs. Insulin Aspart: PK-PD Findings

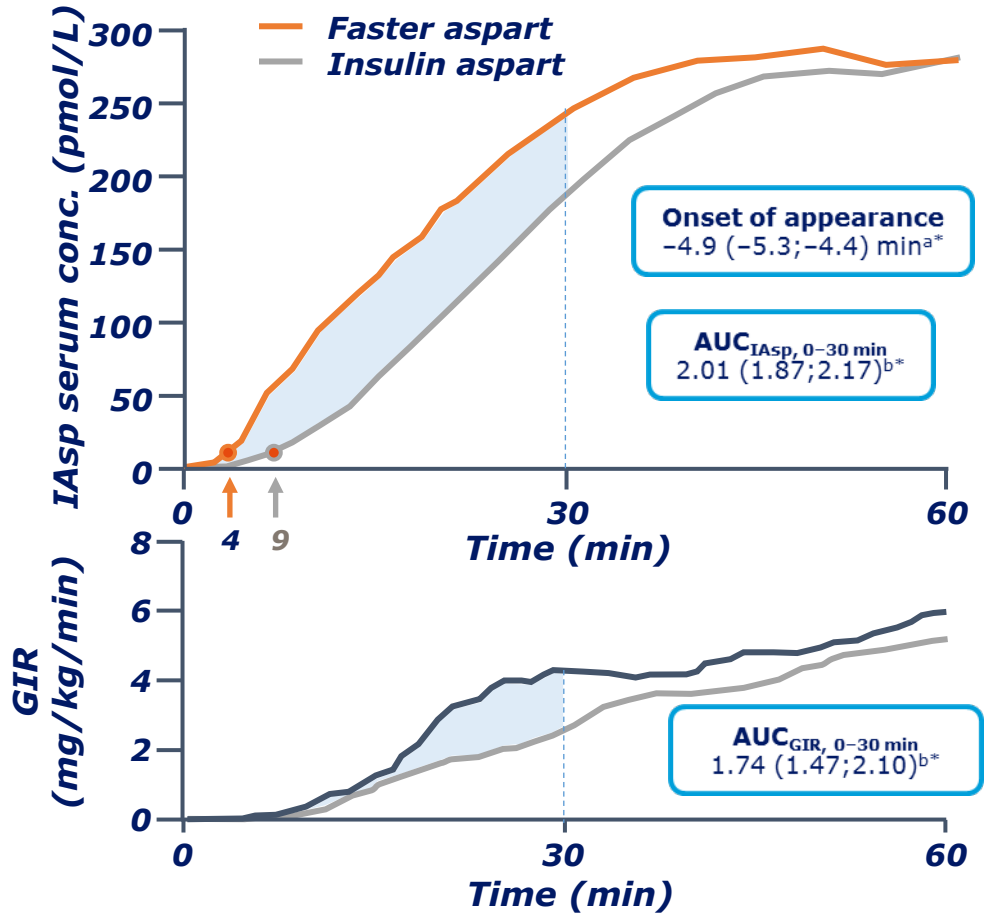
Pooled analysis of six clinical pharmacology trials in adult subjects with type 1 diabetes

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
**p<0.001; [a]Treatment difference, 95% CI; ; [b]Treatment ratio, 95% CI*

Heise et al. Clin Pharmacokinet 2017;56:551–9

Faster Aspart vs Insulin Aspart in Onset Programme: Summary

- Smaller but significant reductions in PPG increment (T1D and T2D), and HbA_{1c} (T1D) without increasing the risk of hypoglycemia
- In CSII studies has proven to be non-inferior with regards to change from baseline in HbA_{1c} and to be superior with regard to change from baseline in 1-h PPG increment (meal test)
- Increased flexibility of mealtime dosing (immediate pre-meal injection, but also the option of post-meal injection) without compromising glycemic control

Faster aspart, fast-acting insulin aspart; PPG, postprandial plasma glucose; sc, subcutaneous; T1D, type 1 diabetes; T2D, type 2 diabetes

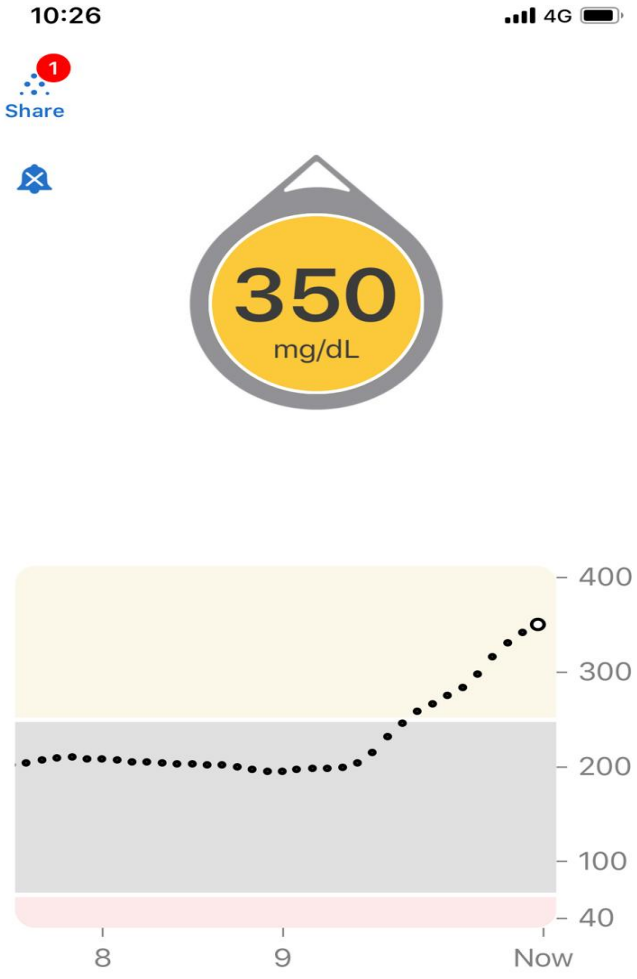
1. Buckley et al. Diabetes Technol Ther 2016;18(Suppl. 1):A116; 2. Heise et al. Diabet Obes Metab 2015;17:682–8; 3. Russell-Jones et al. Diabetes Care 2017;doi:10.2337/dc16-1771;
4. Bowering et al. Diabetes Care 2017;doi:10.2337/dc16-1770; 5. Home et al. Diabet Med 2000;17:762–71

…..which patients and conditions would benefit most

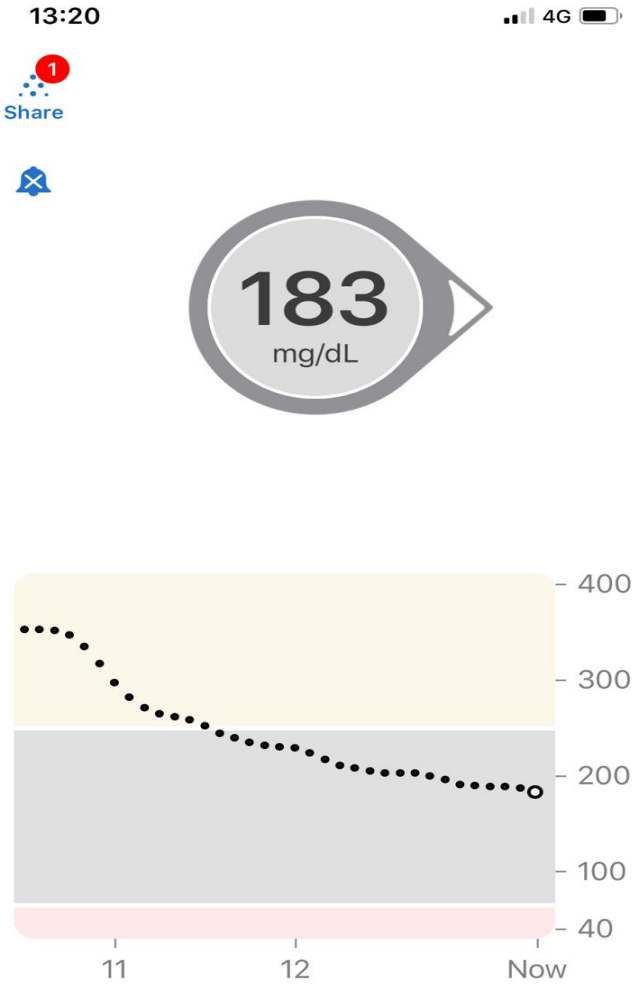
- Marked post-breakfast hyperglycaemia
- Dawn phenomenon
- IR
- Individuals on corticosteroids
- Snaks
- Correction bolus
- Meals with a high content of refined carbohydrates
- High glycemic index meals
- Hospital treatment
- ……..
- ……

Owens D.R. Diabetes Obes Metab. 2020, modified

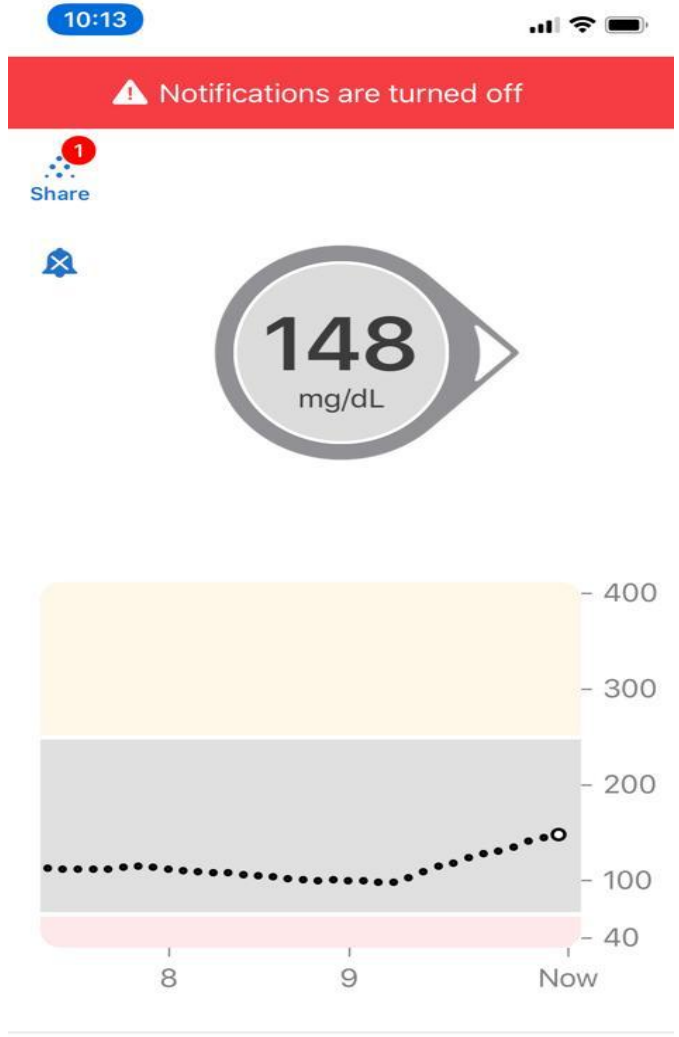
Lorenzo



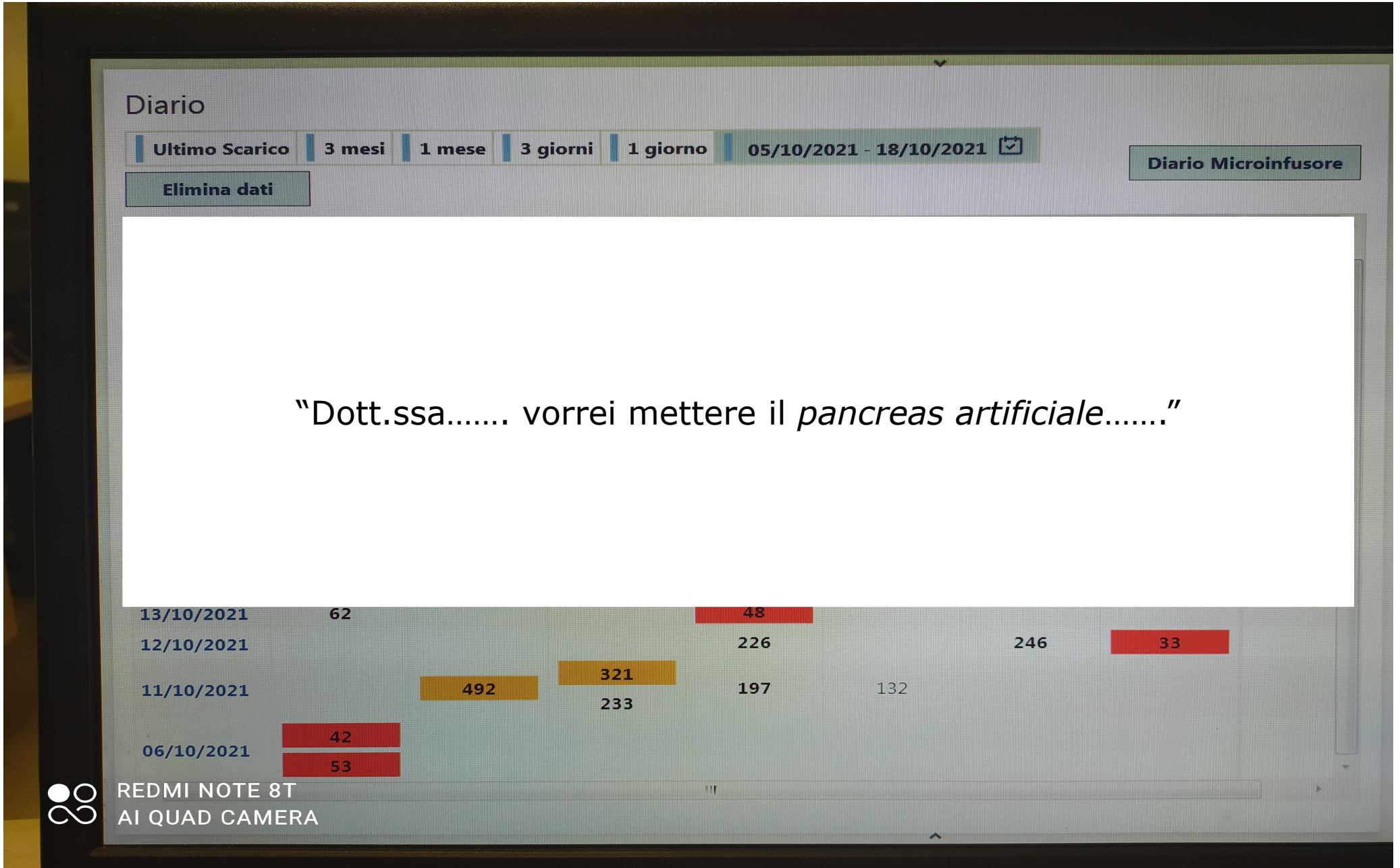
5 U di Aspart 15’ prima di colazione



L’iperglicemia persiste fino al pranzo, nonostante correzione



5 U di Faster Aspart 15’ prima di colazione


Diario
Ultimo Scarico
3 mesi
1 mese
3 giorni
1 giorno
05/10/2021 - 18/10/2021
Diario Microinfusore
Elimina dati
"Dott.ssa……. vorrei mettere il *pancreas artificiale*……."
13/10/2021
62
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11/10/2021
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132
06/10/2021
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REDMI NOTE 8T
AI QUAD CAMERA

Structured Education

- Lfestyle management
- Technology use and interpretation
- SBGM
- Hypoglycemia prevention
- Insulin injection technique
- Insulin dose management

CONCLUSION

- Over the years, many changes in insulin therapy have occurred, including new insulin formulations, new delivery systems and additional therapeutic tactics, with improvement in quality of life and assistance of persons with diabetes.

- However, without education, motivation and engagement of patients even the “ideal” insulin and the “perfect” system to monitor blood glucose, will not translate into efficacy and safety

The NEW ENGLAND JOURNAL of MEDICINE

NEJM.ORG

One Hundred Years of Insulin for Some

Amy Moran-Thomas, Ph.D.

N ENGL J MED 385;4 NEJM.ORG JULY 22, 2021

There is not one story of insulin; there are many. As a young child, Mr. J. lost his mother to what was presumed to be type 1 diabetes. He recalled taking whatever kinds of insulin he could get for his own type 1 diabetes growing up, thanks to the generosity of his neighbors and extended family. But after going ple's experiences living with diabetes in Belize. Statistics on type 1 diabetes weren't being kept in the country at the time, as is the case in many overstretched health systems, so Mr. J.'s and Ms. C.'s dilemmas — like their deaths — weren't registered as part of global diabetes figures.

As the story is often told, 100 creas, and numerous therapeutics that have hugely increased chances for survival.

But these narratives often eclipse more uneasy stories: Mr. J.'s and Ms. C.'s situations give a glimpse into struggles happening every day throughout the world.[1-3] Patients without other options inject expired or suboptimal types

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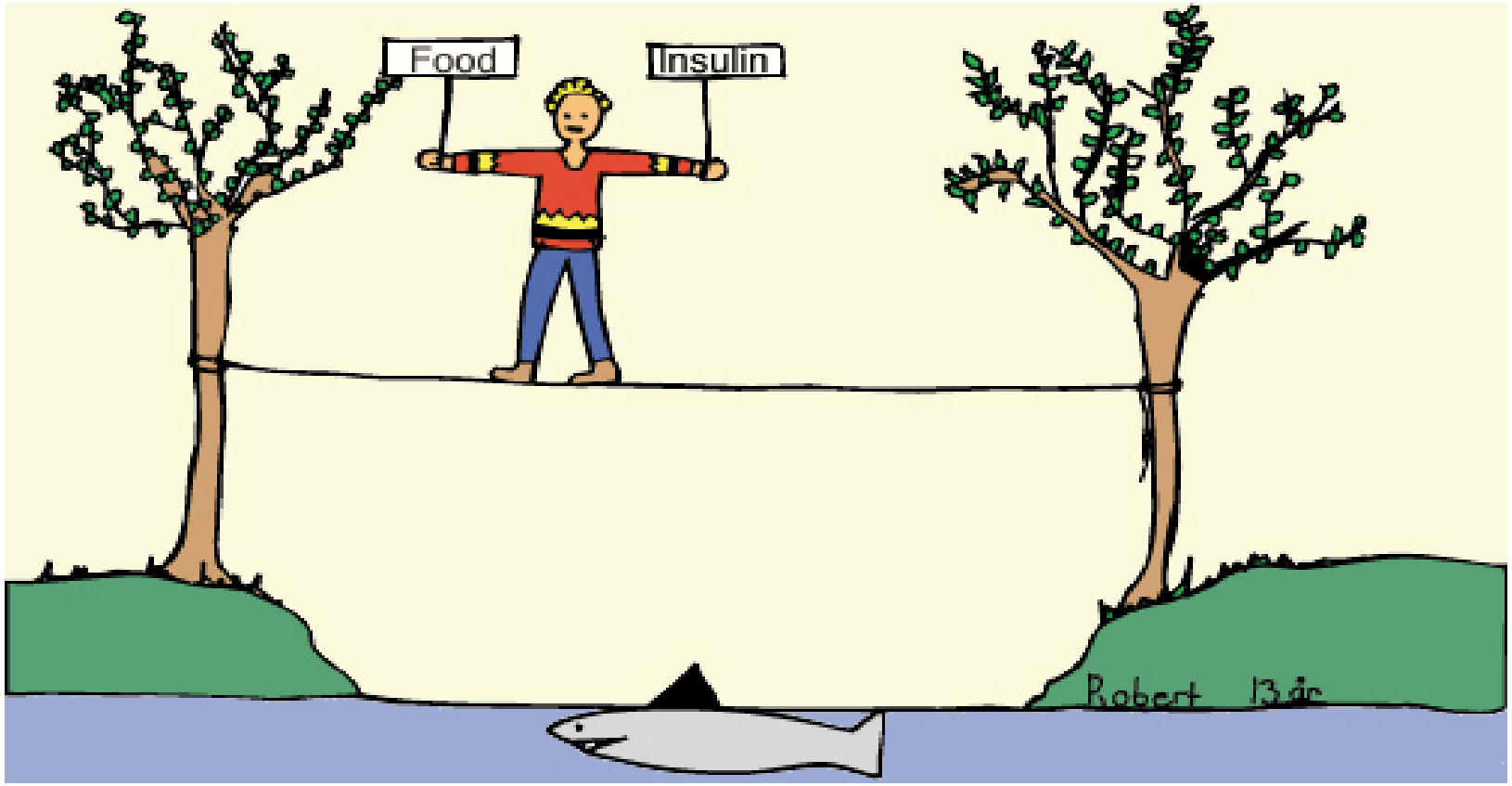
“Me and diabetes”



Grazie per l’attenzione

Back up