INCONTRI DIABETOLOGI TERNANI

Il Diabete Mellito: le tante "zone d'ombra" di una sindrome complessa ed eterogenea

Diabete Mellito di tipo 1
Terapia insulinica: stato dell'arte

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Terni, 17 Settembre 2022

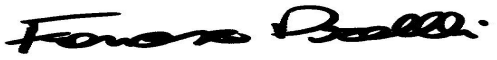
Disclosure

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.).

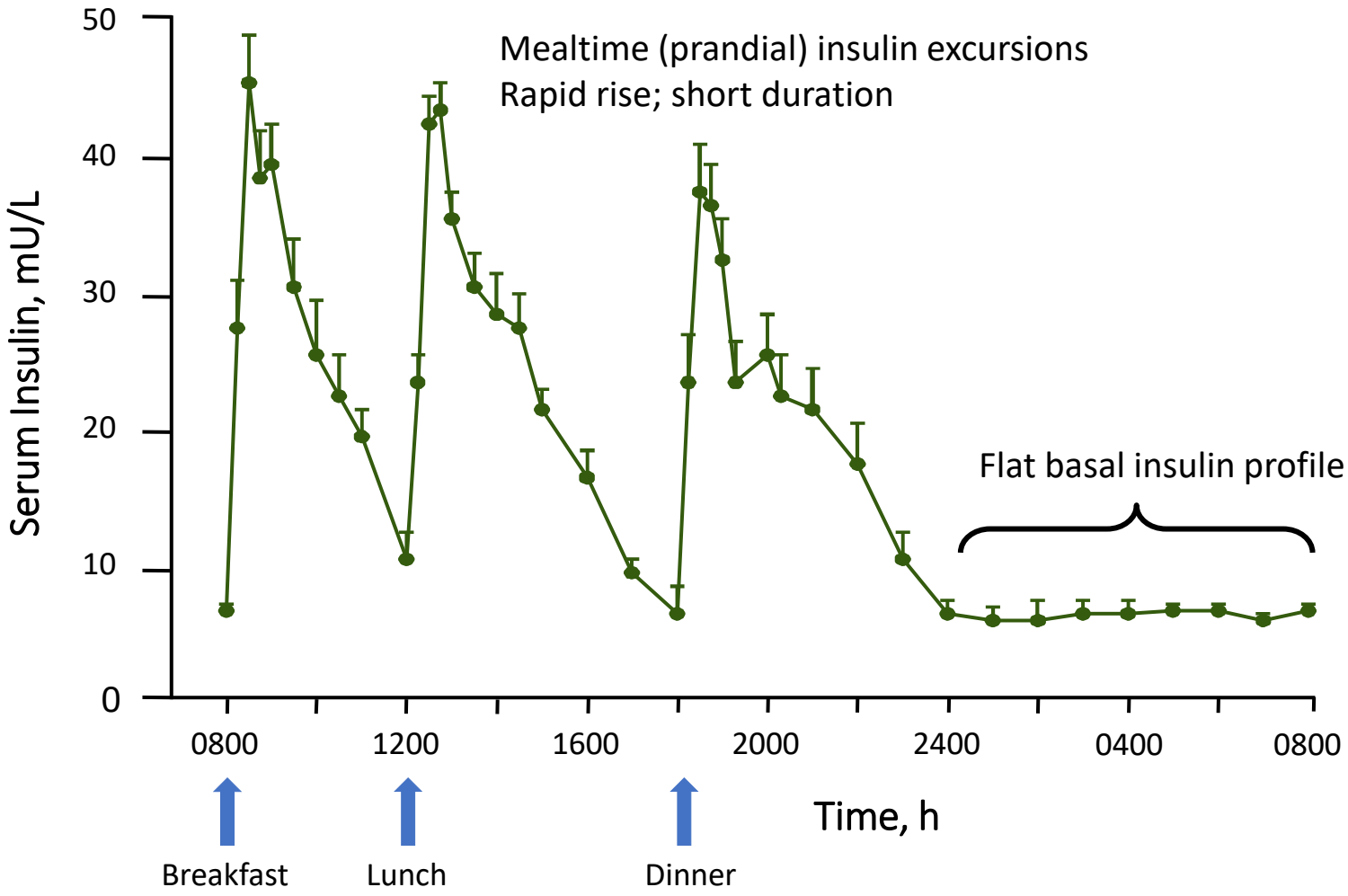
In fede, Francesca Porcellati



What I am NOT going to talk about today….

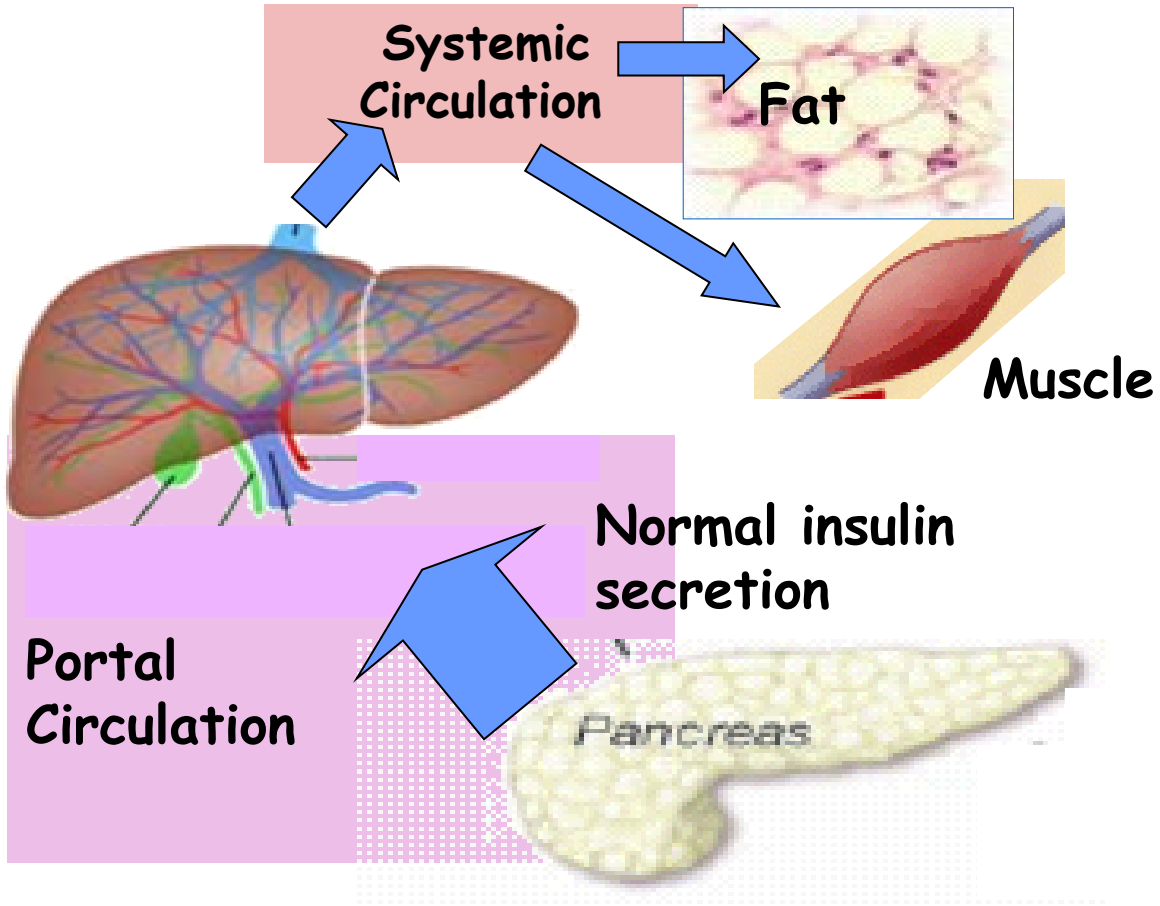
- Clinical guidelines
- Current outcomes in the management of Type 1 DM
- Technology
- Glucose-lowering therapy beyond insulin

Insulin Replacement Therapy Aims to Recreate the Normal Blood Insulin Profile

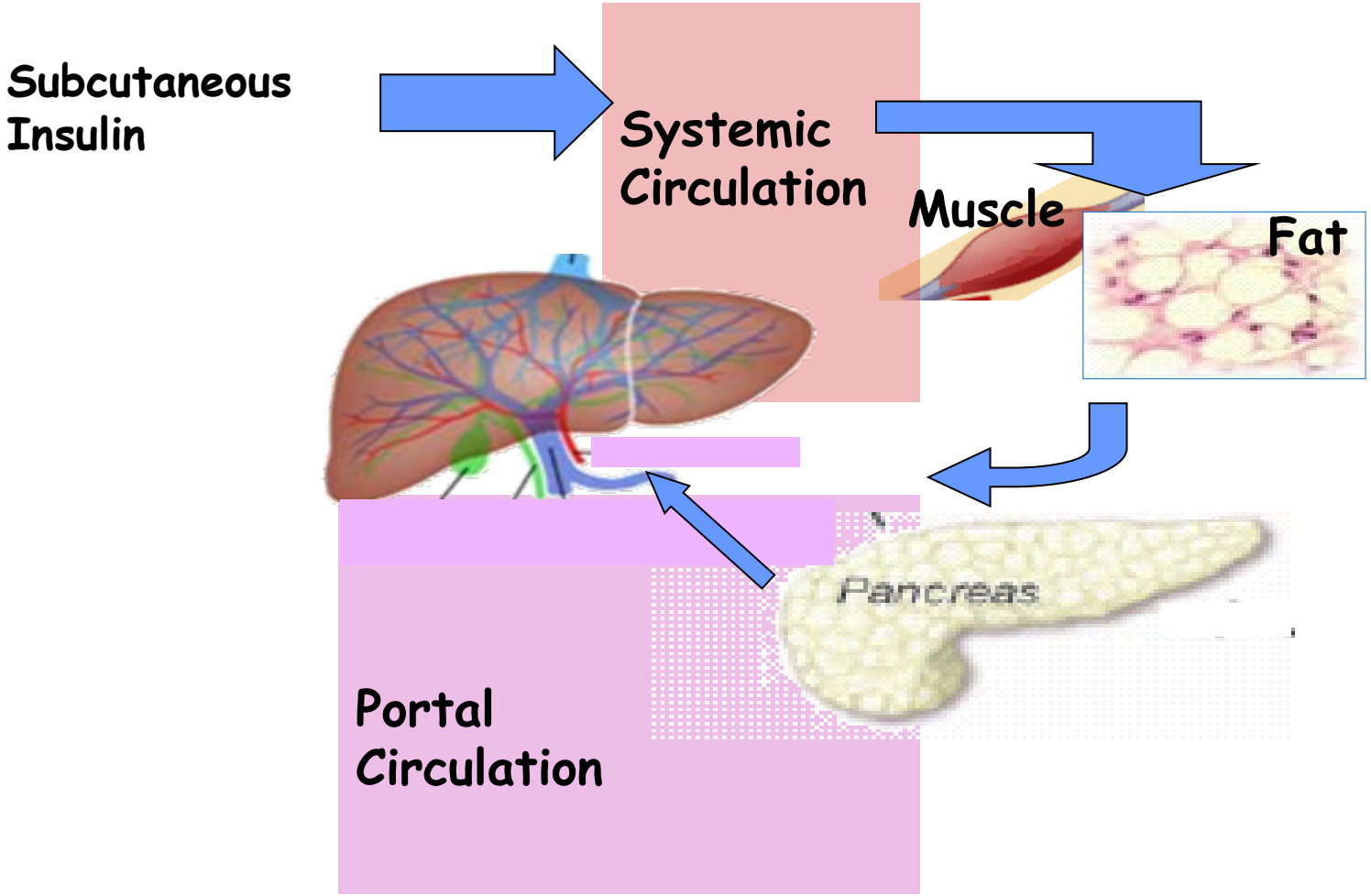


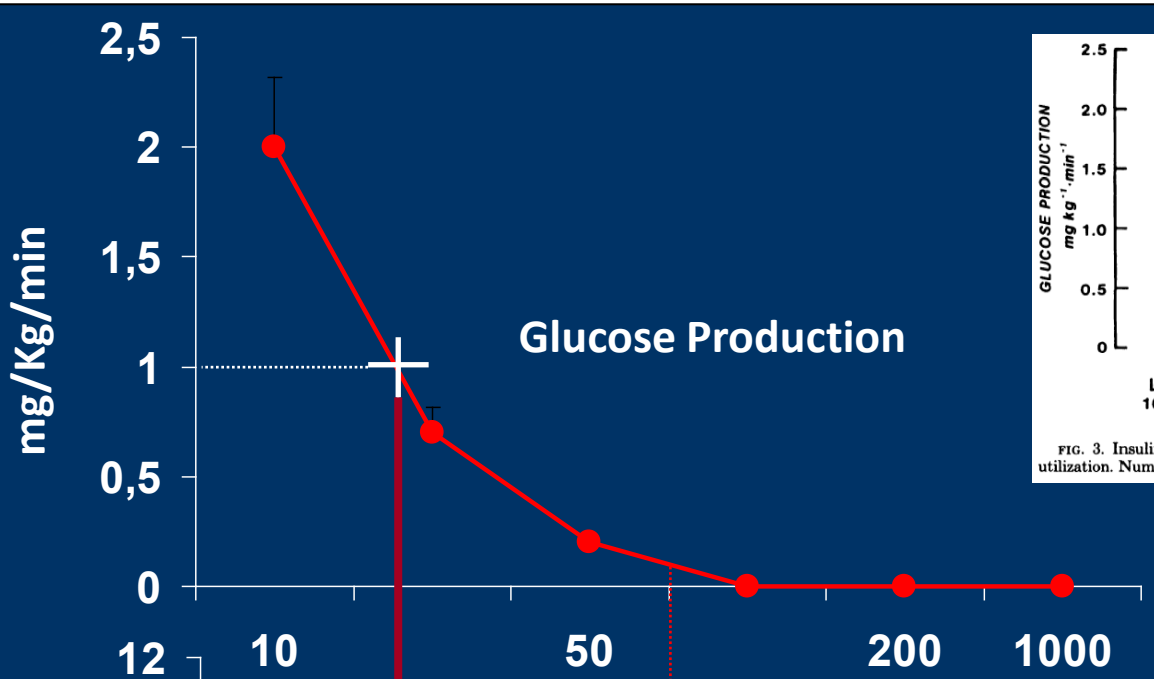
Kruszynska YT, et al. *Diabetologia.* 1987;30:16-21.

IN PHYSIOLOGY



IN DIABETES


Subcutaneous Insulin
Systemic Circulation
Muscle
Fat
Pancreas
Portal Circulation



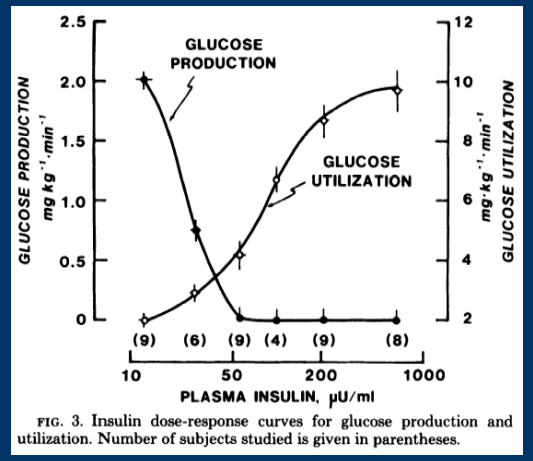
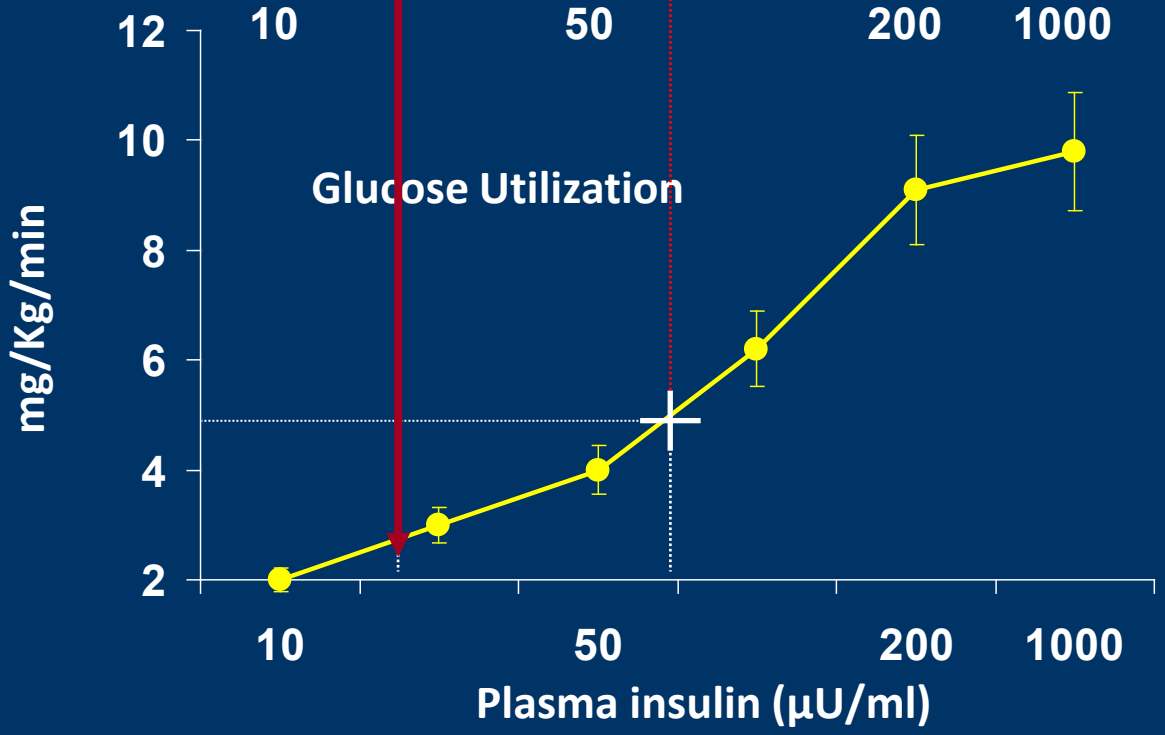


FIG. 3. Insulin dose-response curves for glucose production and utilization. Number of subjects studied is given in parentheses.



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

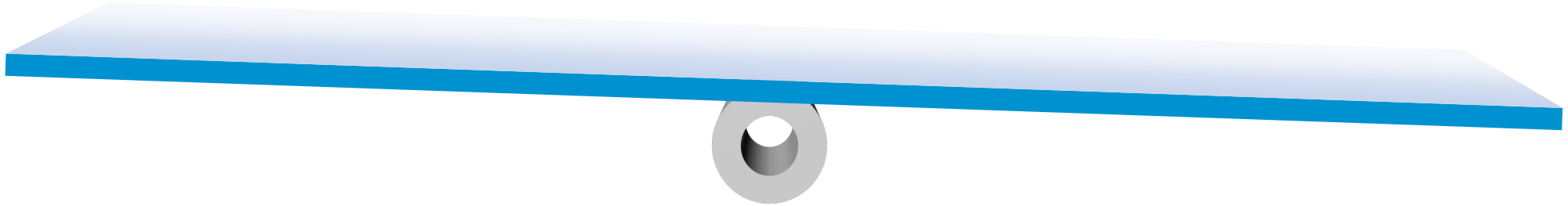
Insulin Therapy: the Need of a Balance

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

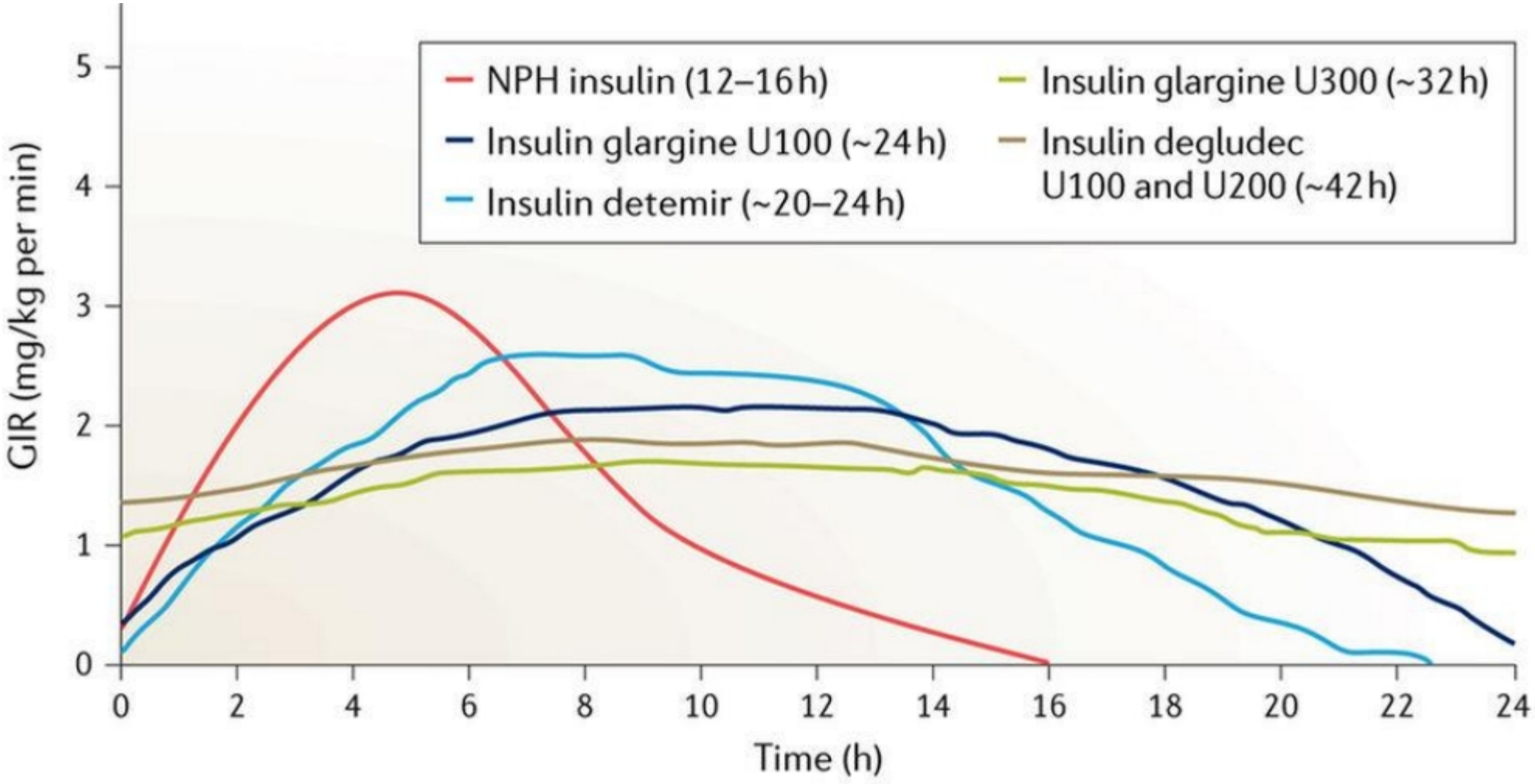
Low risk of hypoglycemia

- 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

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

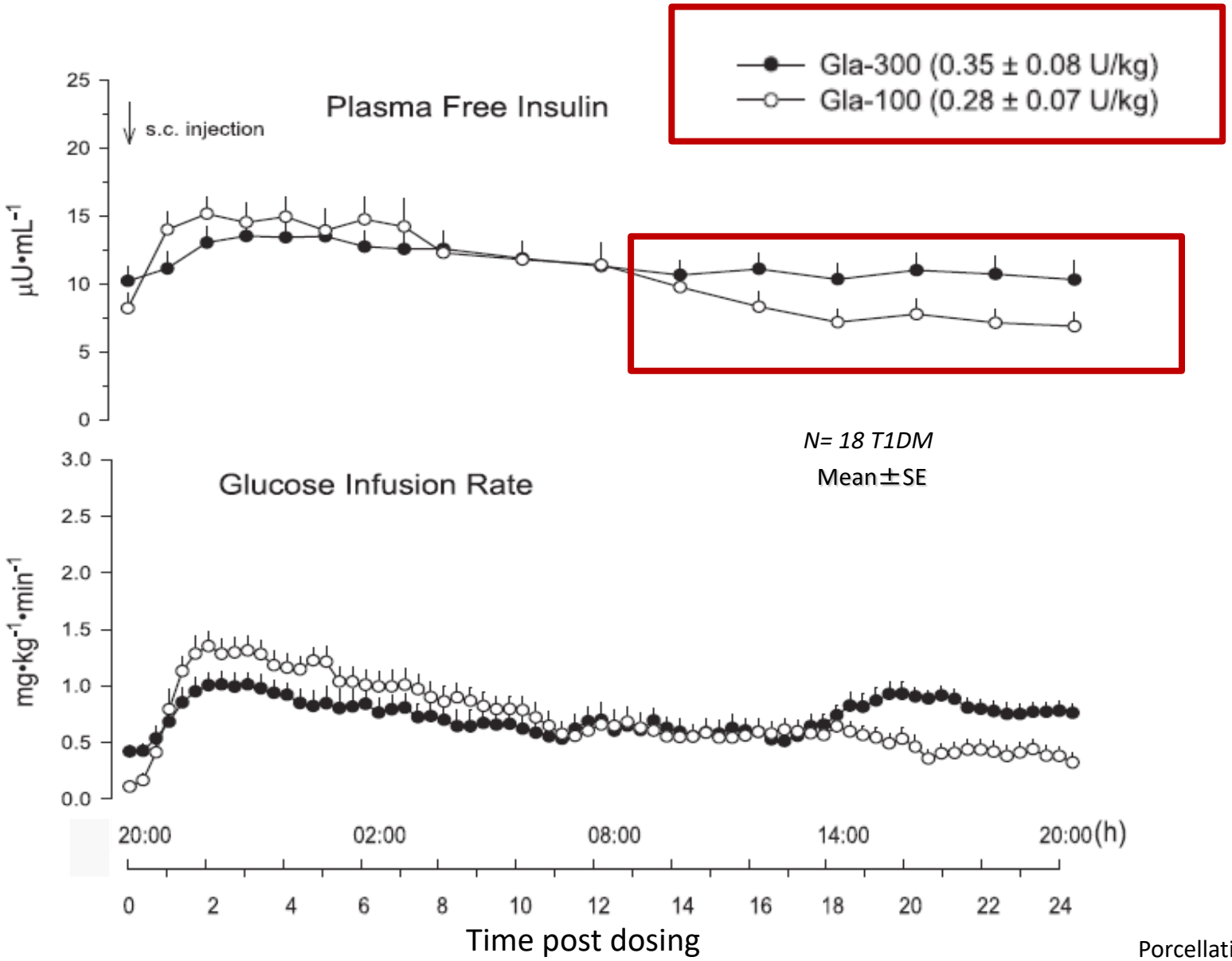
Head-to head Comparisons vs Insulin Glargine 100

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

Pharmacokinetic and Pharmacodynamic Variables

	Gla 300 (0.34U/kg)	IDeg (0.26 U/Kg)	Gla 300/IDeg ratio Point estimate[a] (90% CI)
PK parameters			
FIRI-AUC$_{0\text{-}24\,h}$ [µU•h•mL^{-1}]*	394 (335; 462)	1735 (1405; 2140)	
FIRI-AUC$_{0\text{-}12\,h}$ [µU•h•mL^{-1}]*	208 (179; 243)	922 (752; 1131)	
FIRI-AUC$_{12\text{-}24\,h}$ [µU•h•mL^{-1}]*	184 (155; 220)	809 (648; 1010)	
PD parameters			
GIR-AUC$_{0\text{-}24\,h}$ [mg•kg^{-1}]*	1121 (951;1322)	1087 (883; 1327)	1.04 (0.91; 1.18)
GIR-AUC$_{0\text{-}12\,h}$ [mg•kg^{-1}]*	486 (341; 693)	489 (374; 641)	0.99 (0.70; 1.40)
GIR-AUC$_{12\text{-}24\,h}$ [mg•kg^{-1}]*	573 (482; 681)	514 (350; 755)	1.11 (0.84; 1.47)

Data are geometric mean (95% CI)* (N=22). [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;*

Lucidi P . et al., Diabetes Care 2021

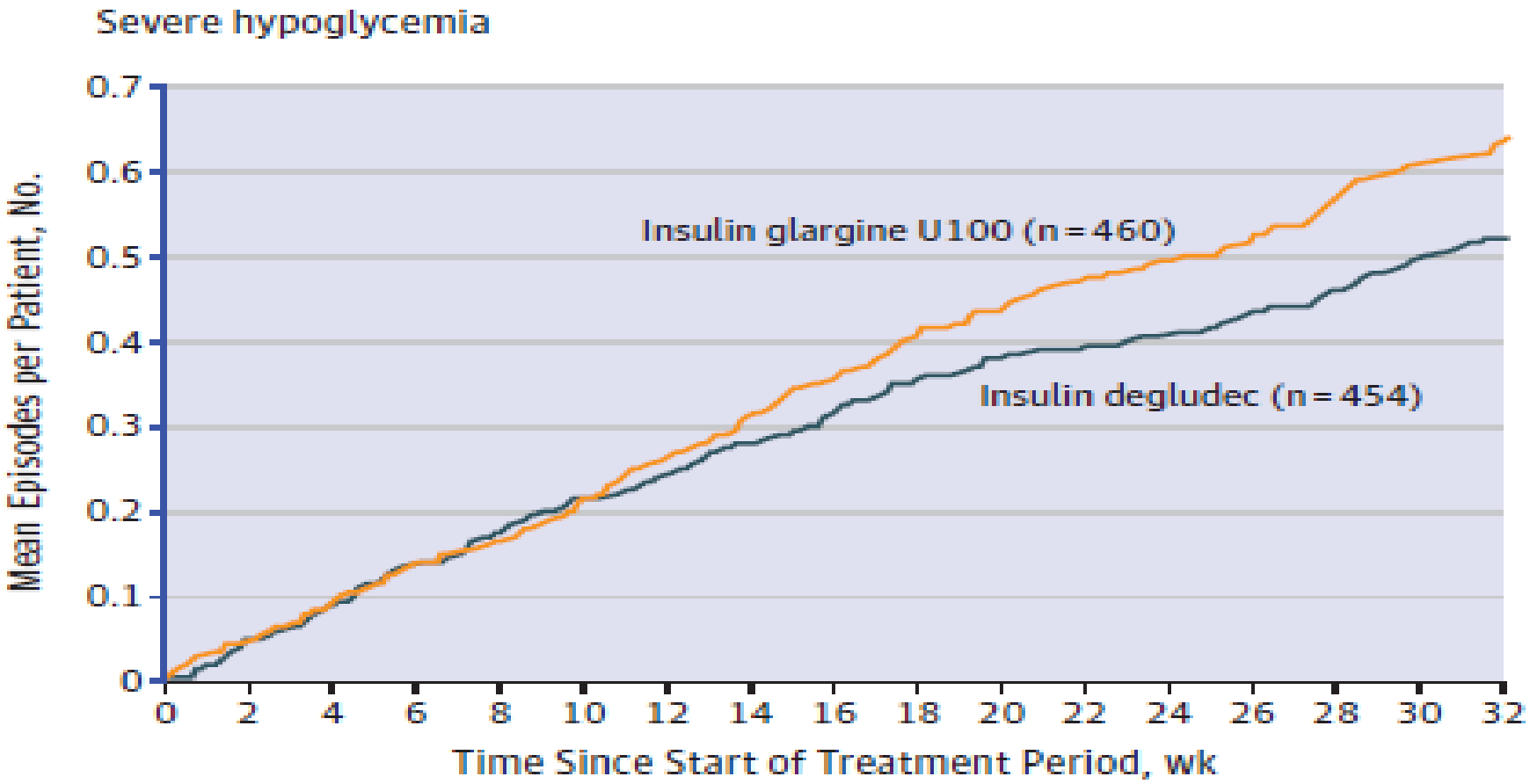
From PK-PD Studies to Clinical Outcomes

	Glargine 300	Degludec
Hypoglycemia reduction vs Glargine 100	✓	✓
Similar efficacy vs Glargine 100	✓	✓
Flexibility	✓	✓
Safe insulin titration	✓	✓
Once daily injection in all subjects	✓	✓
Insulin doses vs Glargine 100	↑	=
Comparable weight change vs Glargine 100	✓	✓

EDITION and BEGIN trials

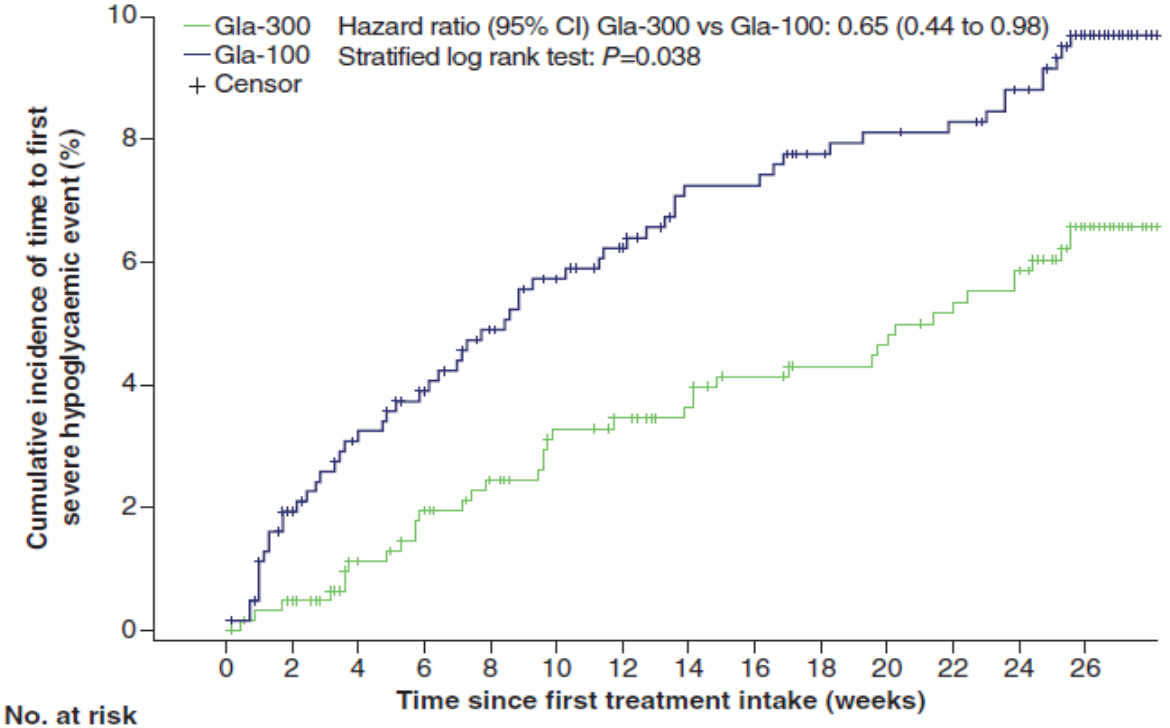
SWITCH 1 Trial: Rate for Episodes of Severe Hypoglycemia Significantly Lower with Insulin Degludec vs Insulin Glargine 100

Cumulative Rates of Hypoglycemia per Patient



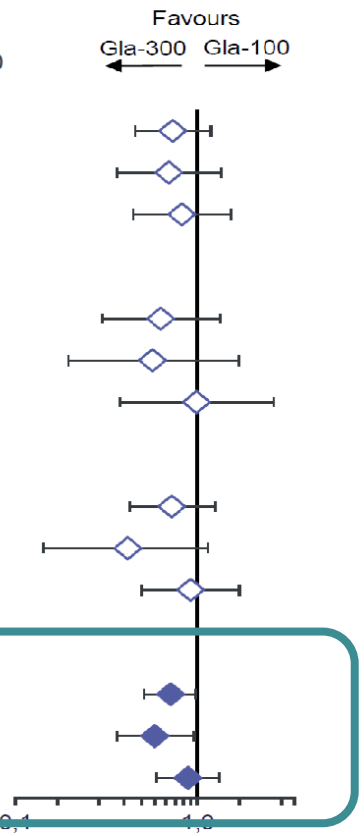
Lane W. et al. JAMA. 2017;318:33-44

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



No. at risk (≥1 event/ censored)	Week 0	Week 6	Week 12	Week 20	Week 26
Gla-300	629 (0/0)	596 (12/21)	573 (21/35)	552 (29/49)	455 (39/135)
Gla-100	624 (0/0)	583 (24/17)	556 (38/30)	531 (49/44)	447 (58/119)

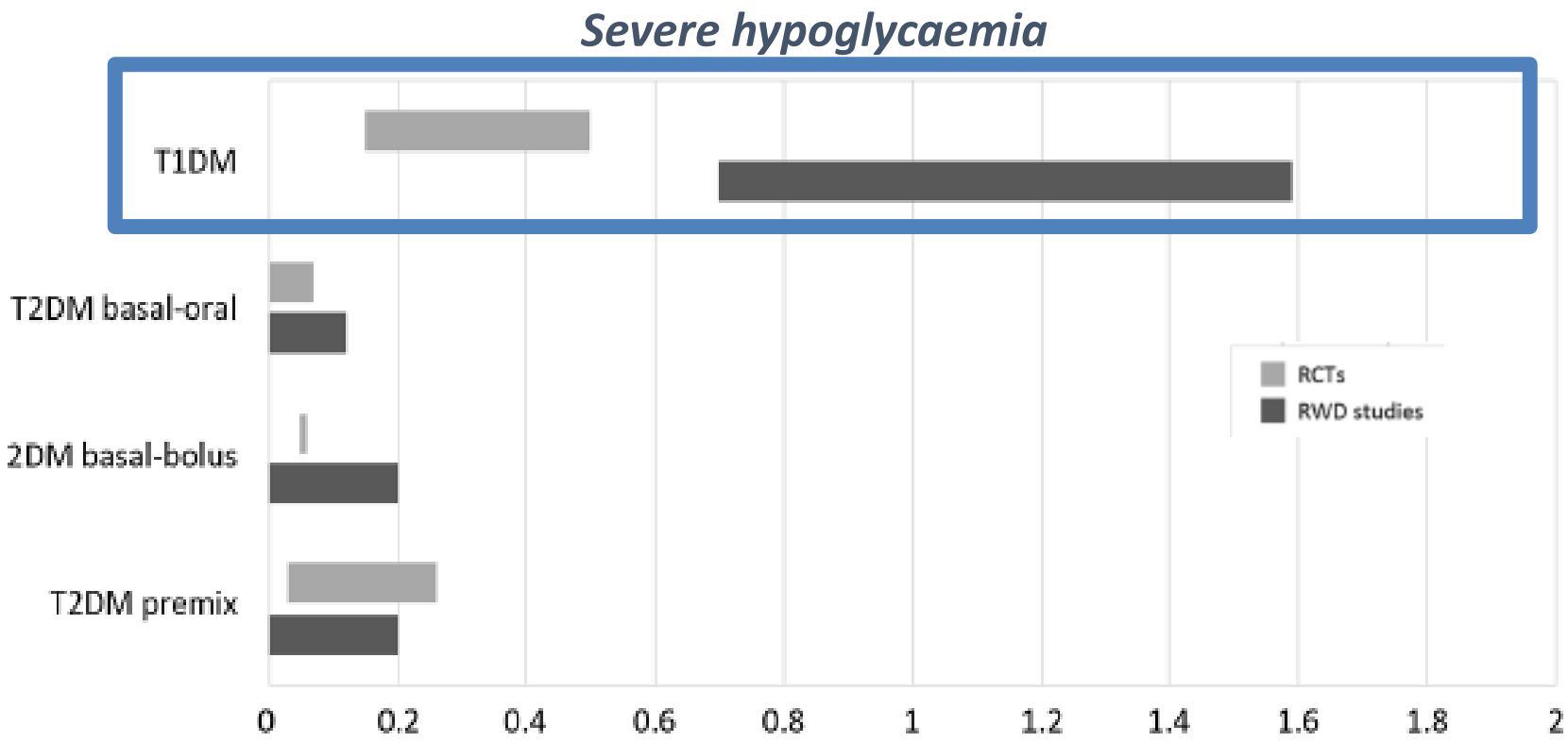
	Incidence (%)		OR (95% CI)
	Gla-300	Gla-100	Gla-300 vs. Gla-100
EDITION 4			
BL to month 6	6.6	9.5	0.67 (0.36; 1.26)
BL to week 8	3.3	5.1	0.63 (0.27; 1.49)
Week 9 to month 6	4.0	5.1	0.78 (0.35; 1.75)
EDITION JP 1			
BL to month 6	5.7	9.9	0.55 (0.21; 1.46)
BL to week 8	2.5	5.0	0.48 (0.12; 1.98)
Week 9 to month 6	4.1	4.1	0.99 (0.28; 3.52)
EDITION JUNIOR			
BL to month 6	6.0	8.8	0.66 (0.33; 1.35)
BL to week 8	1.3	3.9	0.32 (0.08; 1.19)
Week 9 to month 6	5.2	5.7	0.90 (0.40; 2.01)
T1D Study Pool			
BL to month 6	6.2	9.3	0.65 (0.42; 0.98)
BL to week 8	2.4	4.6	0.50 (0.27; 0.95)
Week 9 to month 6	4.5	5.1	0.86 (0.51; 1.45)



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.

InRange study: comparison of second-generation BI analogues in T1D using TIR as the primary endpoint

ATTD 2022

27–30 April

Abstract LB009/ #1015

12-week, multicentre, randomized, active-controlled, parallel-group, open-label study

Primary endpoint	Main secondary endpoint	Hypoglycaemia and safety profile
Non-inferiority for glycaemic control (% TIR)	**Non-inferiority for glycaemic variability** (total glucose CV)	**Similar occurrences of hypoglycaemia, with no unexpected safety findings**

Gla-300 is non-inferior to IDeg-100 in people with T1D in terms of glycaemic control (TIR), and in terms of glycaemic variability, with no difference in occurrences of hypoglycaemia or safety profiles

BI, basal insulin; CV, coefficient of variation; Gla-300, insulin glargine 300 U/mL; IDeg-100, insulin degludec 100 U/mL; MDI, multiple daily injections; RCT, randomised controlled trial; T1D, type 1 diabetes; TIR, time in range

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
- Highe
- Shift v
- Frequ
- …….
- ……..

Glargine 300

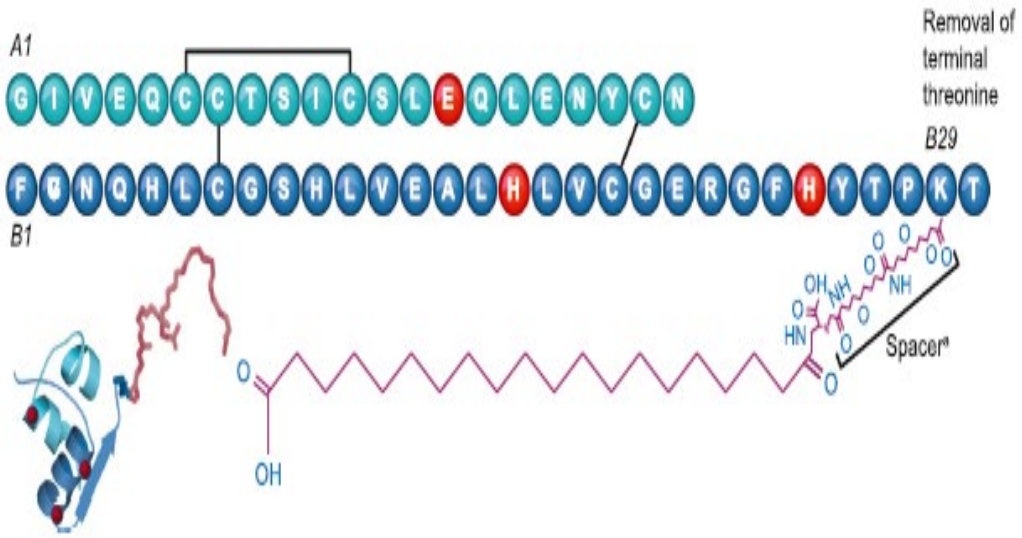
- Higher insulin sensitivity
- Lower insulin requirement (e.g. LADA, long diabetes duration etc. etc.)
- Lower prandial insulin requirements
- ……..
- ……..

Basal insulin dose adjusted according to the relationship between bedtime BG and morning FBS

↓ rapid-acting insulin requirement

Not “1 to 1 unit switch” from other BI

Basal Weekly Insulins: the Way of the Future



- Acylated insulin: 20-carbon fatty diacid sidechain
- High albumin binding
- Reduced enzymatic degradation
- Reduced insulin receptor-mediated clearance
- Time-action profile (t½ = approx. 8 days) supports once-weekly dosing in humans
- Currently in Phase 3 Trials

Insulin-naïve T2D

ONWARDS 1
Insulin naïve T2D

- Insulin icodec + non-insulin anti-diabetic drugs
- IGlar U100 + non-insulin anti-diabetic drugs

ONWARDS 3
Insulin naïve T2D

- Insulin icodec + non-insulin anti-diabetic drugs
- IDeg + non-insulin anti-diabetic drugs

ONWARDS 5
RCT with real world elements
Insulin naïve T2D

- Insulin icodec with DoseGuide
- Once Daily basal insulin analogues

Insulin-experienced T2D

ONWARDS 2
Basal switch T2D

- Insulin icodec + non-insulin anti-diabetic drugs
- IDeg + non-insulin anti-diabetic drugs

ONWARDS 4
Basal switch T2D

- Insulin icodec + IAsp ± non-insulin anti-diabetic drugs
- IGlar U100 + IAsp ± non-insulin anti-diabetic drugs

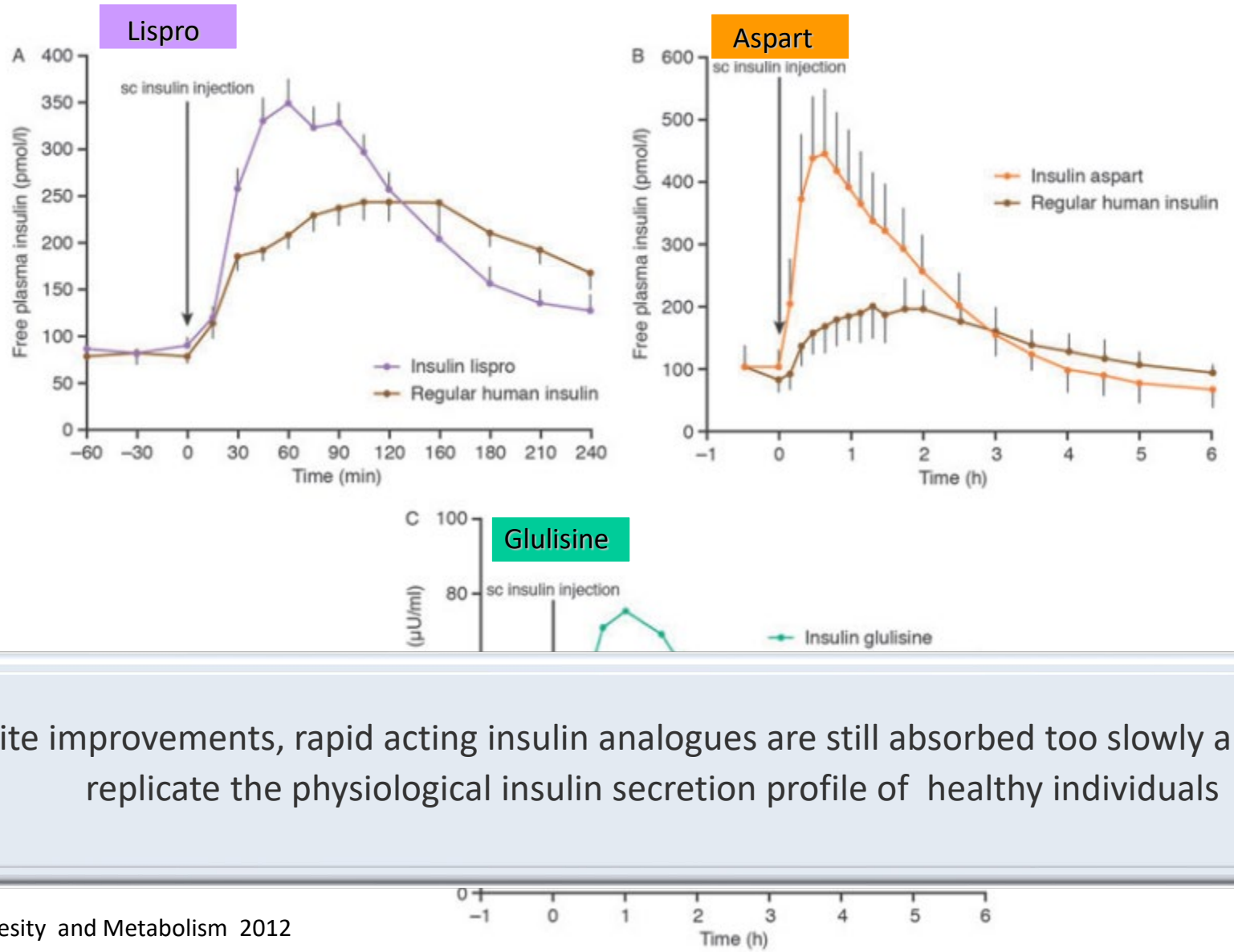
T1D

ONWARDS 6
Basal-bolus T1D

- Insulin icodec + IAsp
- IDeg + IAsp

Rosenstock J , Del Prato S, Metabolism Clinical and Experimental 2022;
Moyers J et al. Preclinical Characterization of Once Weekly Basal Insulin Fc (BIFJournal of the Endocrine Society, Volume 5, Issue Supplement_1, April-May 2021, Page A442, https://doi.org/10.1210/jendso/bvab048.903

The Continuing Quest for Better Subcutaneously Administered Prandial Insulins



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

Aspects of Self-Reported Diabetes Management in 2016–2018

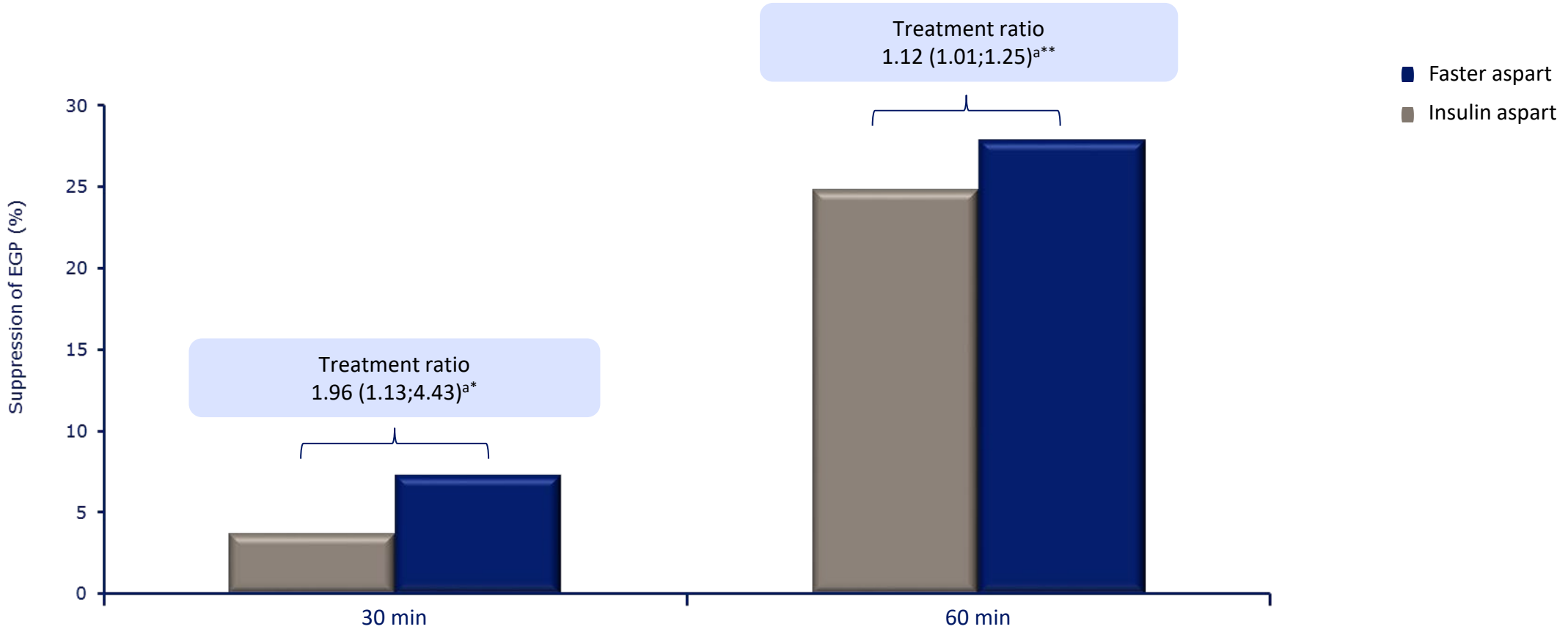
	Overall, N=11,007	*6–12 years old, N=1312*	*13–17 years old, N=3179*	*18–25 years old, N=2440*	*26–49 years old, N=2122*	*≥50 years old, N=1953*
Insulin use						
Timing of insulin bolus, *n* (%)						
At least several minutes before the meal	2671 (24)	359 (27)	626 (20)	419 (17)	544 (26)	723 (37)
Immediately 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: Suppression of EGP

41 people with T1 DM received identical s.c. single faster aspart and IAsp doses (individualized for each participant), together with a standardized mixed meal



Two-fold greater suppression of EGP in the first 30 min with faster aspart vs. insulin aspart

*p=0.017; **p=0.040 [a]Treatment ratio, 95% CI. Full analysis set CI, confidence interval; EGP, endogenous glucose production; faster aspart, fast-acting insulin aspart

Basu *et al. Diabetes Obes Metab* 2018;doi: 10.1111/dom.13270; Pieber *et al. Diabetologia* 2017;60(Suppl 1):690-P

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

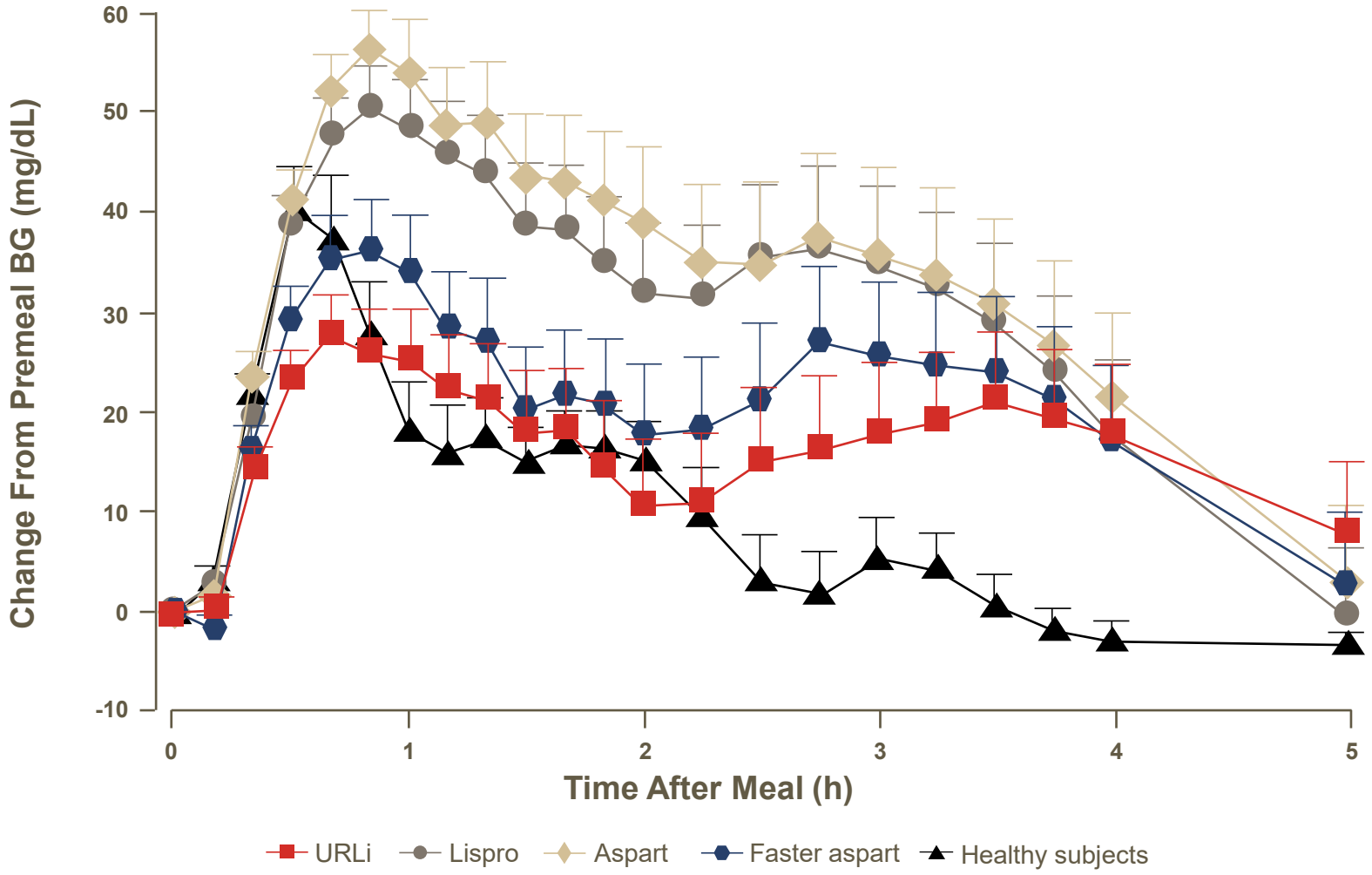
Faster Aspart…..which patients and conditions would benefit most

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

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

URLi: Greater Reduction in PPG in People with T1D

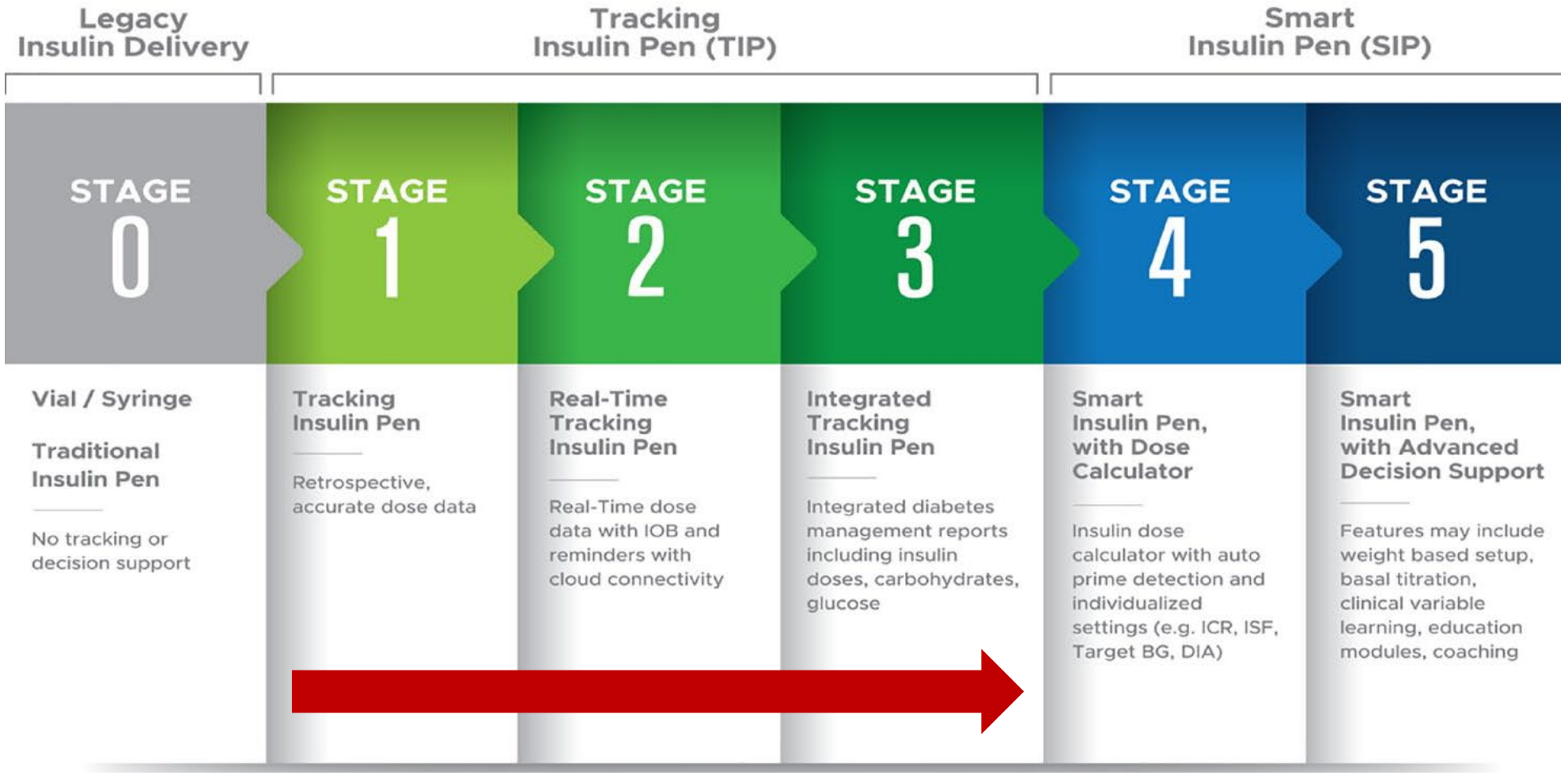
Improvement in PPG excursions with URLi was statistically significant vs insulin lispro and insulin aspart



Data are presented as mean+SE.
Heise T, et al. *Diabetes.* 2019;68(suppl 1):1112-P.

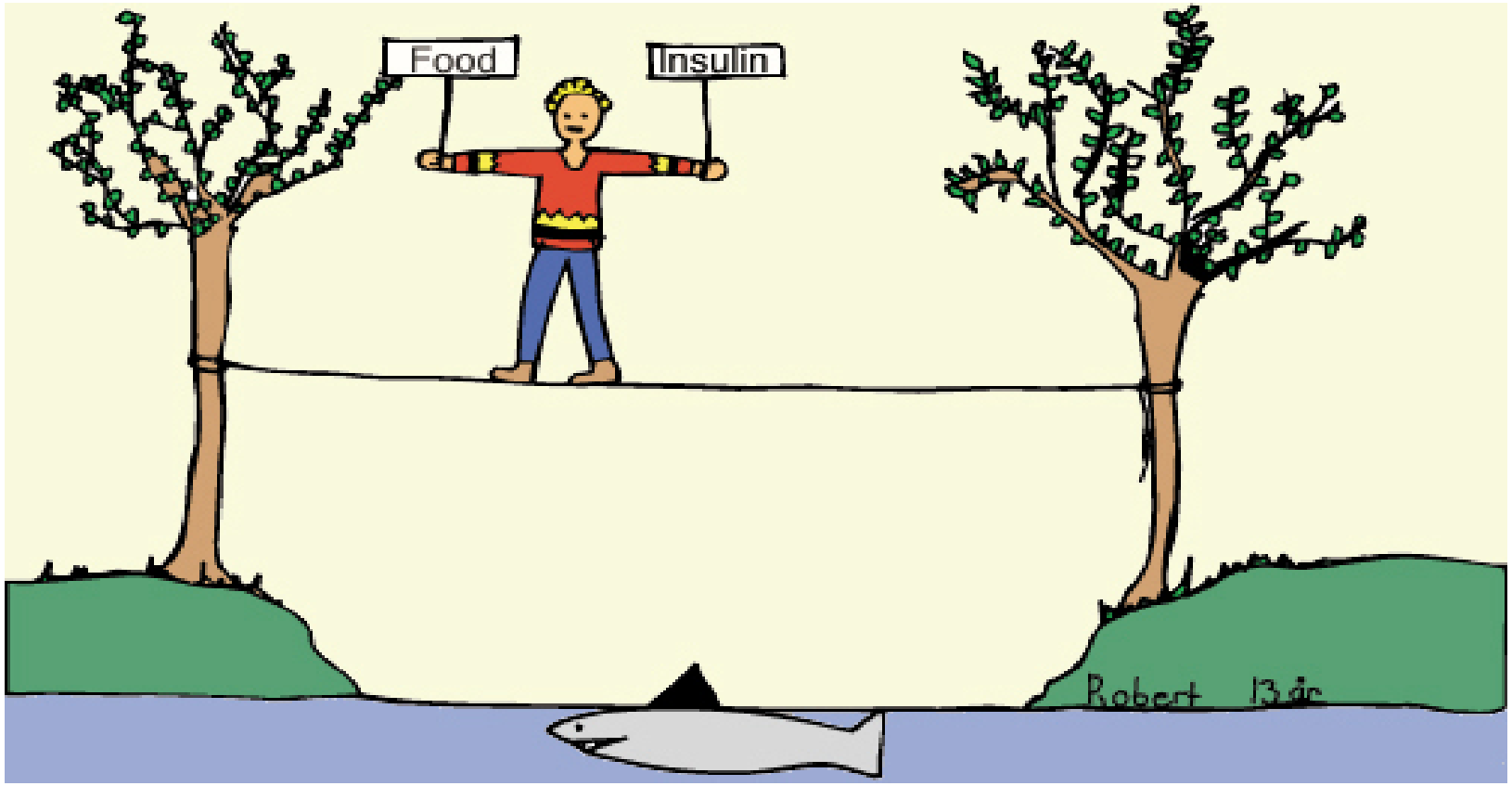
URLi vs Lispro: P<.05 to AUC (0-3 hours; 0-4 hours); P<.01 Δ BG 2 hours; P<.001 to AUC (0-1 hour; 0-2 hours) and Δ BG 1 hour;
URLi vs Aspart: P<.001 to AUC (0-1 hour; 0-2 hours; 0-3 hours) and Δ BG 1 and 2 hours.

Insulin Pen Roadmap



Structured Education

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



Grazie per l’attenzione