SIMDO

SOCIETÀ
ITALIANA
METABOLISMO
DIABETE
OBESITÀ

XVI CONGRESSO NAZIONALE

29-31marzo 2017

NH Vittorio Veneto

Roma

Presidente del Congresso: ***Vincenzo Provenzano***

ANDREA FONTANELLA M.D, Ph.D, FCCP.
Presidente Nazionale FADOI
Direttore del Dipartimento di Medicina dell'Ospedale del Buon Consiglio-Fatebenefratelli Napoli

Il sottoscritto Andrea Fontanella, ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009, per conto di Fondazione FADOI

dichiara

che negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:
Alfa Wassermann, Bayer, Boehringer-Ingelheim, Bristol Myers Squibb, Daichii Sankyo, Novo Nordisk, Pfizer, Sanofi Aventis.
Il sottoscritto dichiara altresì che detti rapporti non sono tali da poter influenzare l'attività di docenza espletata nell'ambito di codesto evento pregiudicando la finalità esclusiva di educazione/formazione di professionisti.
Il dott. Andrea Fontanella non si trova pertanto in una situazione di conflitto di interessi rispetto all'evento ai sensi e per gli effetti dell'Accordo Stato-Regioni del 5 /01/2009.

SIMDO
SOCIETÀ ITALIANA METABOLISMO DIABETE OBESITÀ

XVI CONGRESSO NAZIONALE

Il mondo delle insuline

Andrea Fontanella

… più che un mondo un universo

Novo Nordisk

	Europe	USA
FIAsp (NN-1218): an ultra-rapid-acting formulation of NovoLog / NovoRapid (insulin aspart).	Phase III clinical trials presented ADA 2016	
Tresiba *(insulin degludec)*: ultra-long acting basal insulin, lasts 42+ hours, with flexible time of dosing. Day-to-day variability is 20%.	launched in 2013	approved in Sep 2015. Expected launch: Q1 2016
Ryzodeg 70/30 (*insulin degludec / insulin aspart):* pre-mixed basal-bolus formulation.	same as above	

Novo Nordisk

From the current R&D pipeline of Novo Nordisk: two more insulin formulations are at a very early phase (Phase I) of clinical trials:

- LAI338 (NN1438) – long-acting basal for daily administration
- LAI287 (NN1436) – long-acting basal intended for **once-weekly** dosing

LILLY

	Europe	USA
Abasaglar / Basaglar (*insulin glargine biosimilar*): cheaper analogue of Sanofi's Lantus	Approved in Sep 2014. Launched in Aug 2015 (UK).	Launch postponed to December 15, 2016 after a patent dispute with Sanofi
ultra-rapid insulin	Phase I clinical trials	

SUSPENDED: PLANS TO RELEASE THEIR NEW BASAL INSULIN PEGLISPRO BECAUSE OF LIVER SAFETY ISSUES IN CLINICAL TRIALS.

SANOFI

	Europe	USA
Toujeo (*insulin glargine U300*, longer-acting version of insulin glargine) – with a goal of converting Lantus users to Toujeo, since the patents for Lantus have expired.	Launched in Aug 2015 (UK)	Launched in Apr 2015
SAR342434: new insulin lispro biosimilar to Lilly's Humalog	Phase III clinical trials	

MANNKIND

	Europe	USA
Afrezza: an ultra-rapid-acting inhaled insulin. Previously marketed by Sanofi.	Phase III clinical trials	launched in Jan 2015

ADOCIA

Type	Insulin	Status
ultra-rapid acting	BioChaperone Lispro – an accelerated version of lispro (Humalog) – in collaboration with Lilly – standard version U100 and concentrated version U200	Clinical trials
rapid acting	Hinsbet U100 and U500 – cost-effective rapid insulin and its concentrated version	Clinical trials
mixed	BioChaperone Combo – mixed basal/bolus, a combination of Lantus and Humalog, mainly for type 2	Clinical trials

BIODEL

Insulin	Status
BIOD-123 – ultra-rapid acting insulin	Phase II clinical trials
BIOD-238 and BIOD-250 – ultra-rapid acting insulin	Phase I clinical trials
BIOD-531 – concentrated bolus/basal – ultra-rapid acting insulin with basal duration of action – primarily for type 2	Phase I clinical trials

BIOCON

Insulin	Status
•Proprietary: new oral insulin IN-105	Phase III clinical trials
•Biosimilar glargine, cheaper version of Lantus (with Mylan) •Recombinant human insulin (rh-insulin)	Phase III clinical trials
•Biosimilar lispro, cheaper version of Humalog •Biosimilar aspart, cheaper version of Novolog	early development, not yet in trials

BASED IN INDIA. DEVELOPS CHEAPER VERSIONS OF INSULINS WHICH PATENTS EXPIRED.

MERCK

Insulin	Status
MK-2640 ("Smart Insulin"): Glucose-responsive insulin which starts and stops working depending on glucose levels. Expected launch: 2021 or later. Previously known as "L-490".	Phase I clinical trials
insulin glargine biosimilar (generic Lantus)	Phase III clinical trials

OTHER COMPANIES

Company	Insulin type	Status
Generex	insulin oral, insulin buccal (Oral-lyn, Oralgen)	launched in United Arab Emirates and India, awaiting approval or Phase III trials in several other markets
Halozyme	ultra-rapid acting: Insulin-PH20 & Analog-PH20	Phase II clinical trials
Oramed	insulin oral	Phase II clinical trials for T1D in Israel. An orally ingestible insulin capsule.

SUMMARY

Market trends:

new ultra-rapid acting insulins to replace Humalog and Novolog (patents expired), important for pump users and real-time artificial pancreas;

new attempts to create oral insulin, as ingestible capsules;

cheaper versions of Lantus and other insulins with expired patents;

new basal insulins with longer action, more important for type 2 diabetes;

mixed formulations for type 2 market: mixed basal/bolus and other mixed medications;

exploration of non-insulin drugs for glucose control in type 1 diabetes.

Annals of Internal Medicine

CLINICAL GUIDELINE

Pharmacologic Therapy for Type 2 Diabetes: Synopsis of the 2017 American Diabetes Association Standards of Medical Care in Diabetes

James J. Chamberlain, MD; William H. Herman, MD, MPH; Sandra Leal, PharmD; Andrew S. Rhinehart, MD; Jay H. Shubrook, DO; Neil Skolnik, MD; and Rita Rastogi Kalyani, MD, MHS

James J. Chamberlain, et al. *Ann Intern Med.* 14 March 2017.

Table 2. Median Cost of Insulins in the United States, Calculated as the AWP per 1000 Units of Specified Dosage Form/Product*

Compounds	Dosage Form/Product	Median AWP Package Price (Range), $†
Rapid-acting analogues		
Lispro	U-100 vial	306
	U-100 3 mL cartridges	306 (306-379)
	U-100 prefilled pen; U-200 prefilled pen	394
Aspart	U-100 vial	306
	U-100 3 mL cartridges	380
	U-100 prefilled pen	395
Glulisine	U-100 vial	283
	U-100 prefilled pen	365
Inhaled insulin	Inhalation cartridges	557 (453-754)
Short-acting		
Human regular	U-100 vial	165
Intermediate-acting		
Human NPH	U-100 vial	165
	U-100 prefilled pen	350
Concentrated human regular insulin		
U-500 human regular insulin	U-500 vial	165
	U-500 prefilled pen	213
Basal analogues		
Glargine	U-100 vial; U-100 prefilled pen; U-300 prefilled pen	298
Detemir	U-100 vial; U-100 prefilled pen	323
Degludec	U-100 prefilled pen; U-200 prefilled pen	355
Premixed products		
NPH/regular 70/30	U-100 vial	165
	U-100 prefilled pen	350
Lispro 50/50	U-100 vial	317
	U-100 prefilled pen	394
Lispro 75/25	U-100 vial	317
	U-100 prefilled pen	394
Aspart 70/30	U-100 vial	318
	U-100 prefilled pen	395

AWP = average wholesale price; NPH = neutral protamine Hagedorn.
* Adapted from reference 9 and the American Diabetes Association.
† AWP listed alone when only 1 product and/or price.

James J. Chamberlain, et al. *Ann Intern Med.* 14 March 2017.

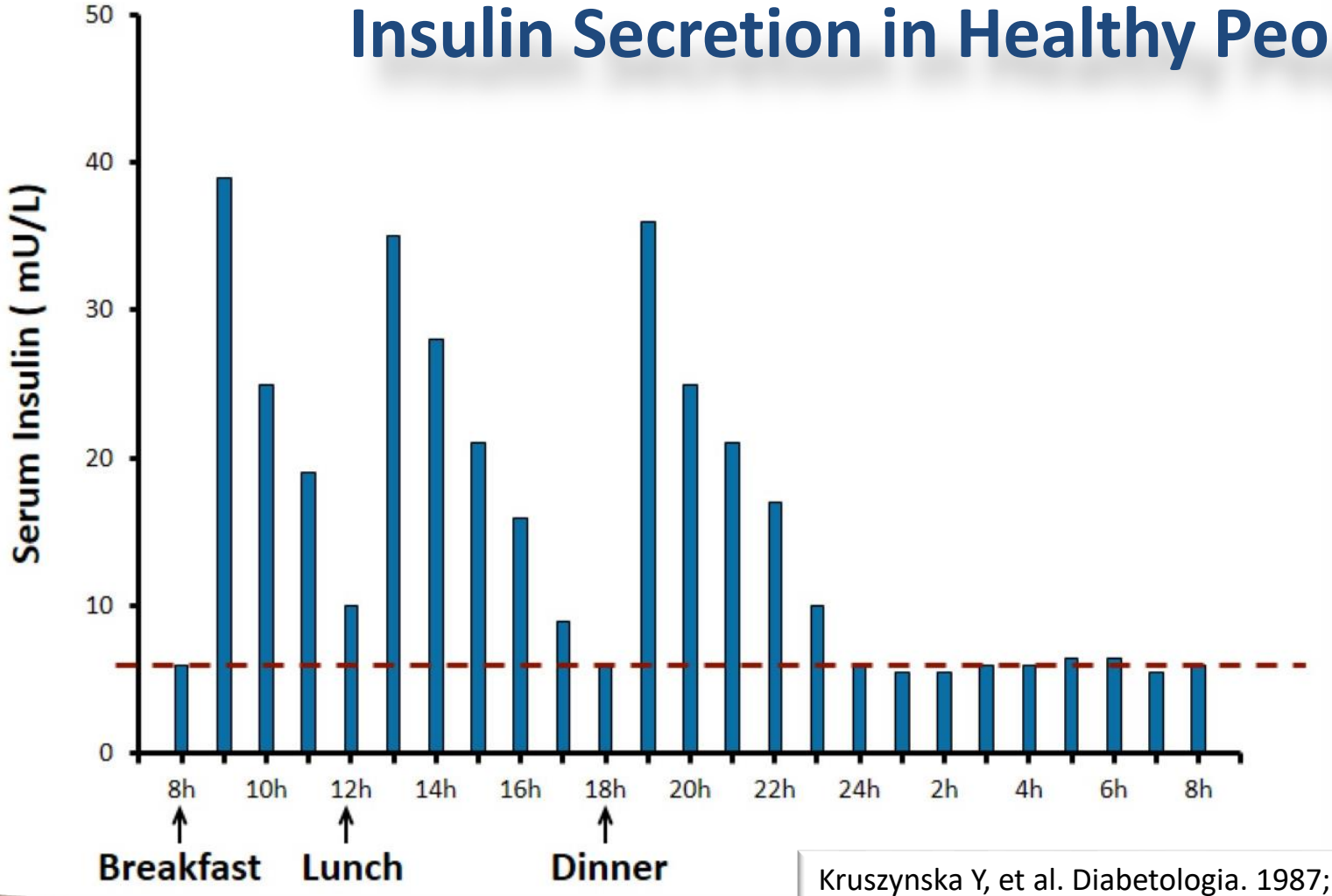
Open source insulin

As a part of do-it-yourself movement, there is an initiative to create an open-source protocol for insulin.

the Open Insulin project team is made up of roughly 50 self-described "hackers and tinkerers" who proudly point out they are all "bio-curious" — with a mix of genetic engineering, software, biochemistry and biotech experience. [..]
"People across the world are going without insulin because it's so expensive, and we need to do something about that," Anthony says. "Maybe someday, what we're doing here could lead to a do-it-yourself insulin factory."
— Biohackers Creating Open-Source Insulin

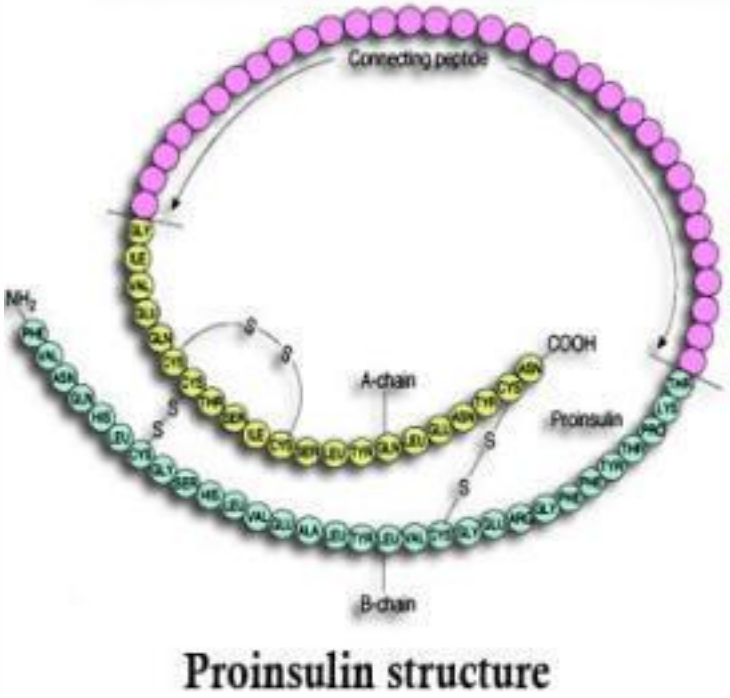
Lo scopo è ottenere questo !!!

Insulin Secretion in Healthy People



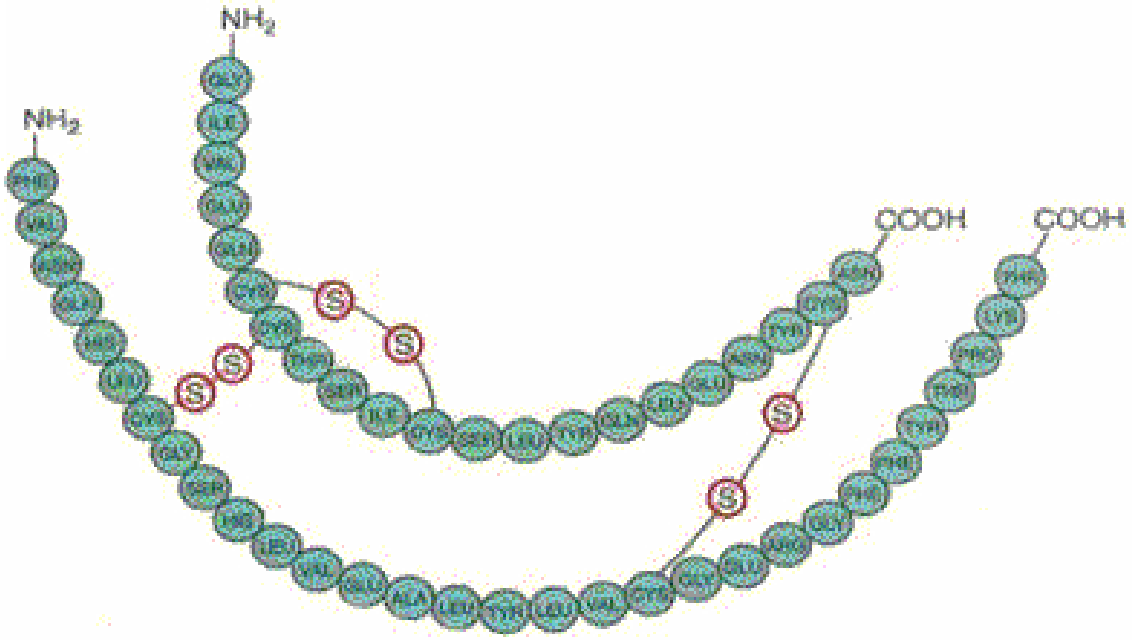
Kruszynska Y, et al. Diabetologia. 1987; 30: 16-21.

Struttura dell'insulina



Proinsulin structure

L'insulina umana è stato il primo farmaco biologico creato mediante tecnologia del DNA ricombinante nel 1982



Krämer I and Sauer T. Br J Diabetes Vasc Dis 2010; 10(4): 163-71

Ovvero come imitare la Natura e la sua perfezione

FARMACI BIOLOGICI sono macromolecole (es. proteine, glicoproteine o polisaccaridi) ottenuti mediante procedimenti di produzione diversi dalla sintesi chimica, utilizzando processi estrattivi da fonti biologiche (es. colture di cellule procariotiche o eucariotiche non modificate, plasma).

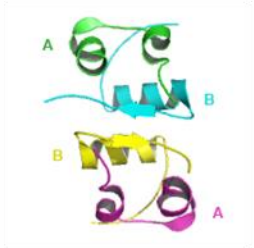
FARMACI BIOTECNOLOGICI sono una sottocategoria di farmaci biologici a struttura macromolecolare (proteine, glicoproteine) ottenuti mediante processi di estrazione e purificazione a partire da substrati cellulari/animali che hanno subito un procedimento di ingegnerizzazione genetica (inserzione del gene di interesse) o modifica (fusione cellulare, linee continue, monoclonali) di varia entità.

http://www.sifact.it/joomla/images/img/congresso/2014/relazioni/Canonico.pdf

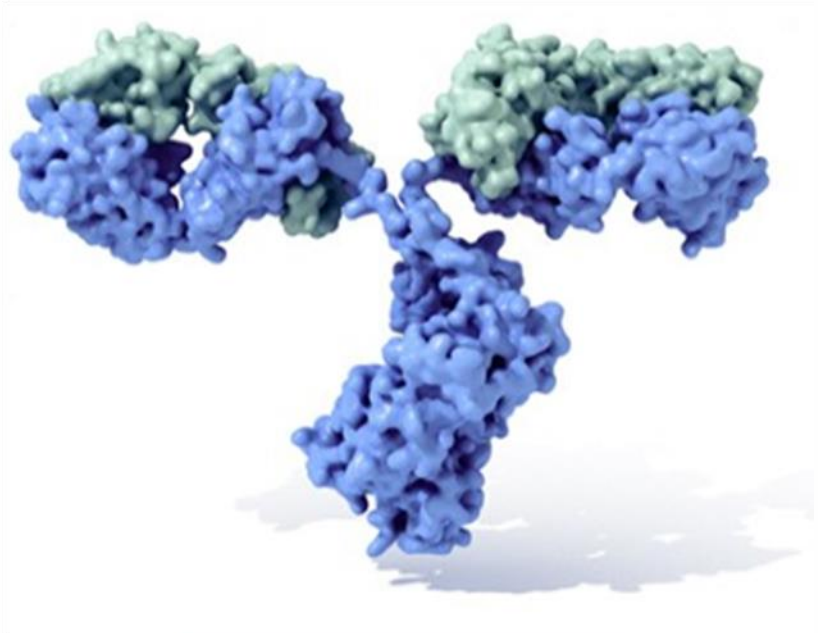
I farmaci biologici sono più complessi delle molecole di piccole dimensioni

Aspirin

Insulin



Monoclonal Antibody



Small Chemical Molecule	Simple Biologic	Complex Biologic
MW = 180 Da 0 amino acids	MW = ~5800 Da 51 amino acids	MW = ~150,000 Da >1000 amino acids

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM315764.pdf MW=Molecular Weight

… ma imitare la struttura molecolare potrebbe non essere sufficiente considerando che anche i percorsi sono differenti…

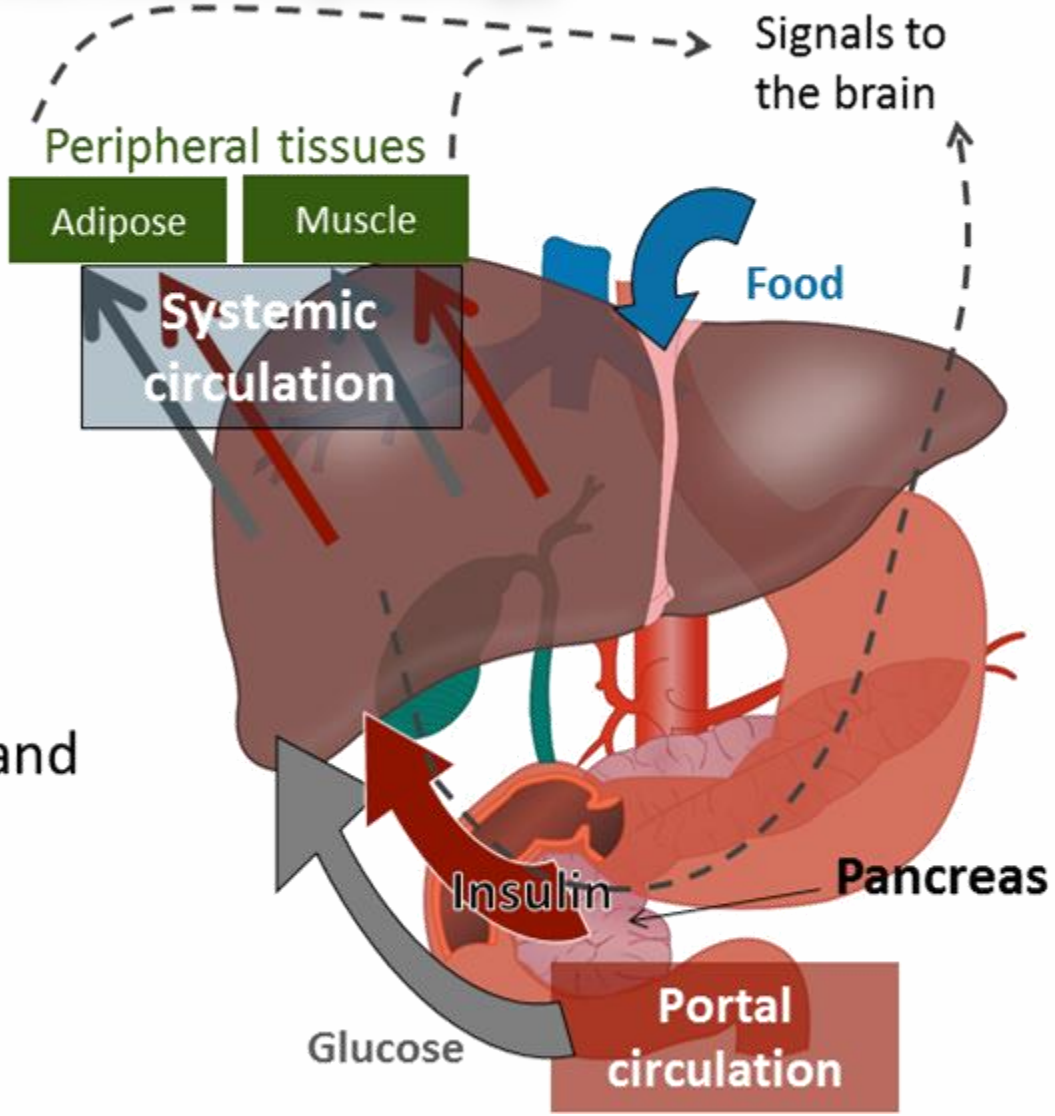
Insulin Distribution in Normal Physiology

Physiologic insulin secretion:

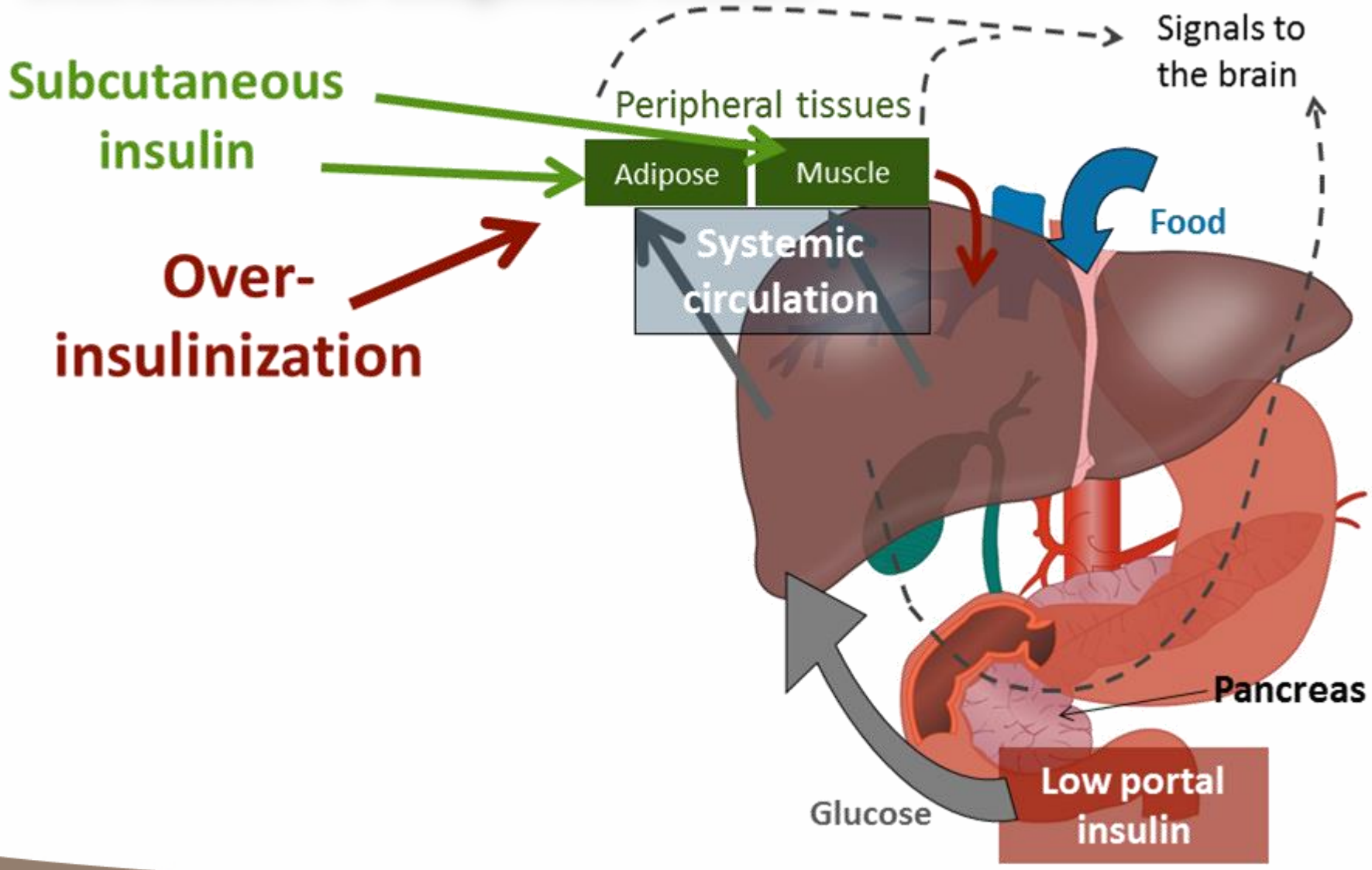
1. Suppresses hepatic glucose production

then

2. Facilitates peripheral glucose uptake with suppressed lipolysis and lipogenesis

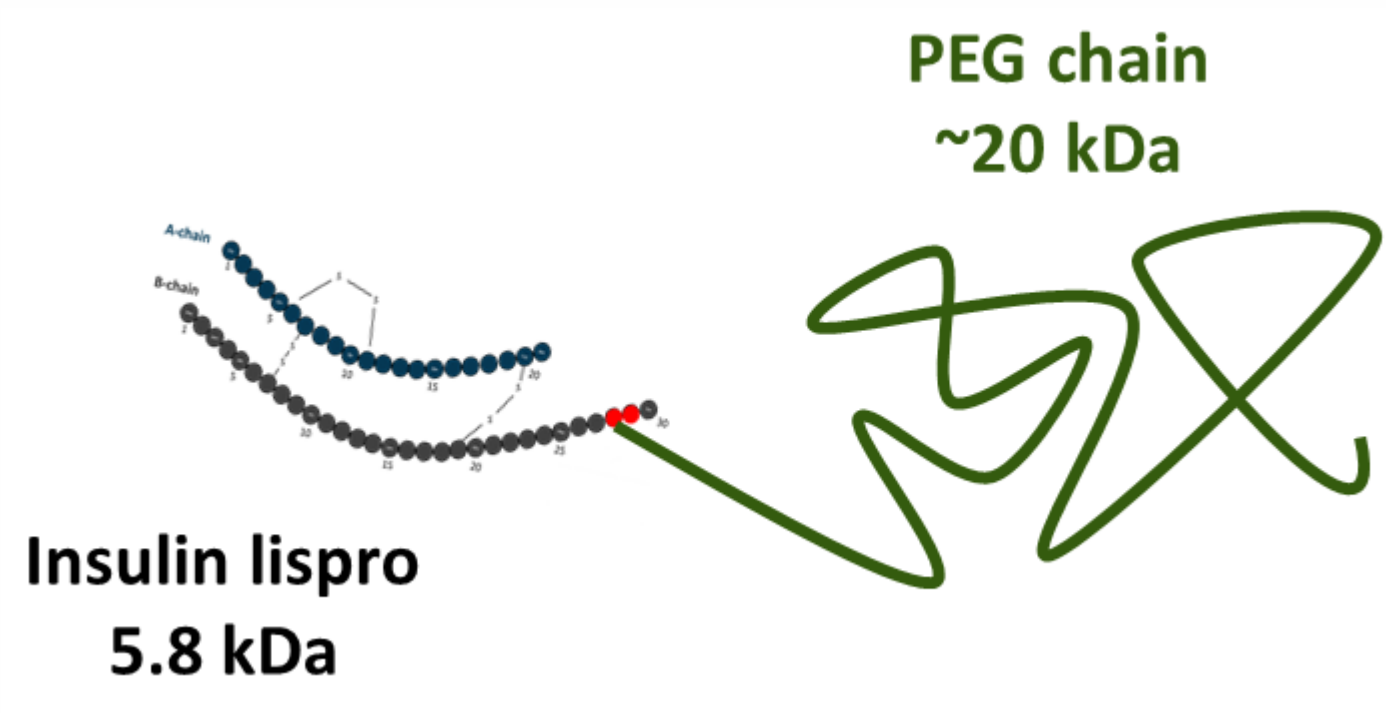


Distribution of Exogenous Insulin



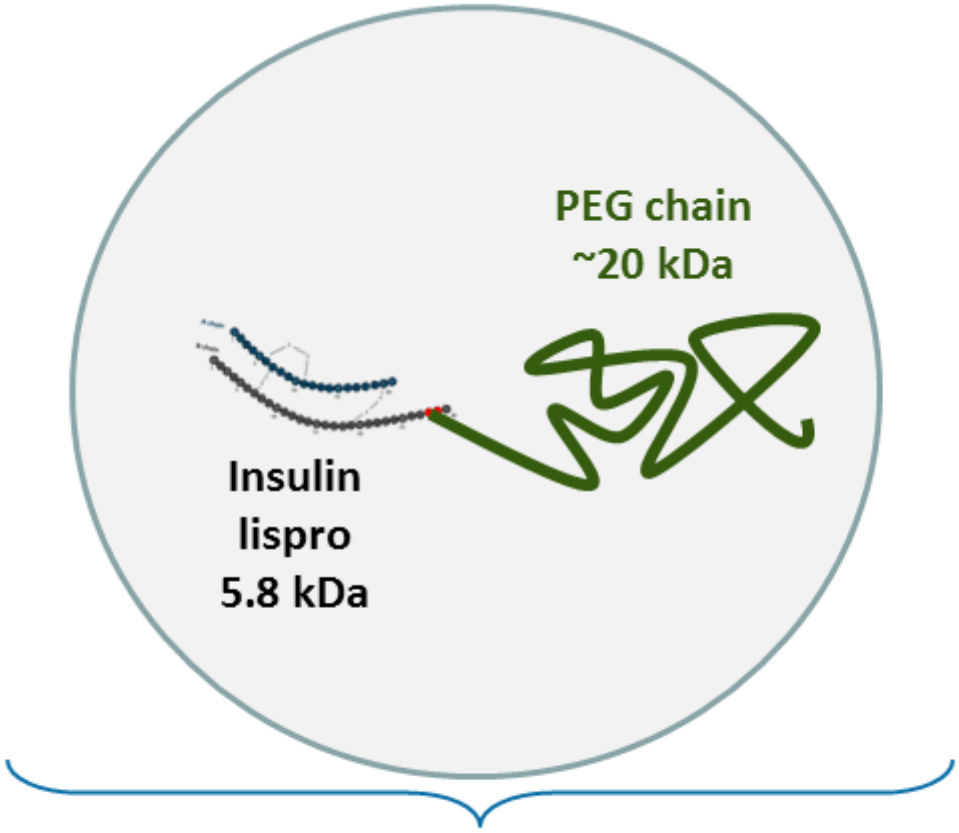
Come imitare il percorso e andare dal centro alla periferia?

PEGylated Lispro (Peglispro) **Insulina epatoselettiva ?**



Hansen RJ et al. Diabetes. 2012; 61 (suppl 1): A228

Hydrodynamic Characteristics



Hydrodynamic diameter of PEGylated lispro
(7.9 ± 0.5 nm) is about 4 times larger than lispro alone

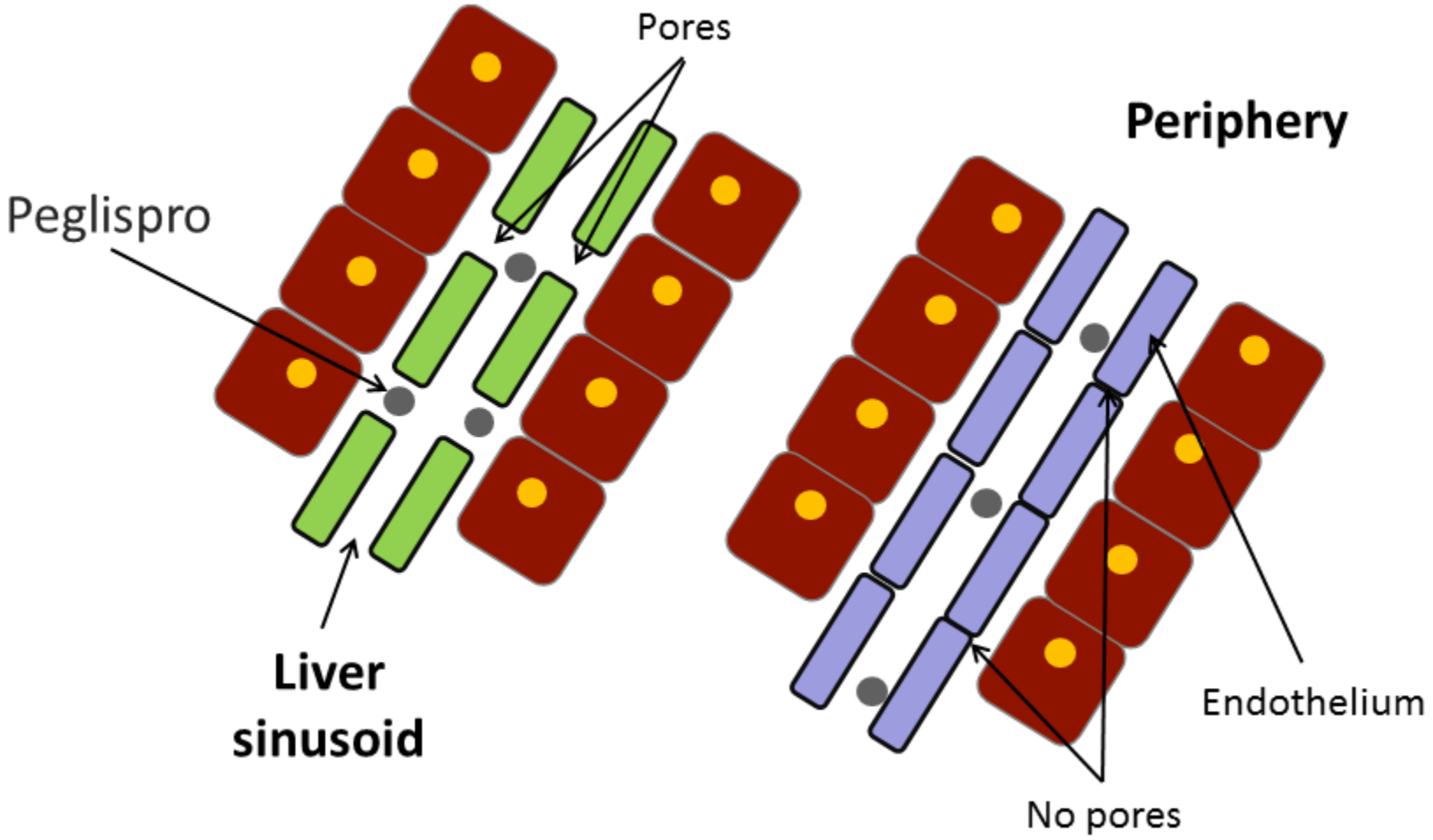
Hansen RJ et al. Diabetes. 2012; 61 (suppl 1): A228

Peglispro Characteristics

- Half-life 2-3 days
- Steady state in 7-10 days
- Duration of action >36 hours

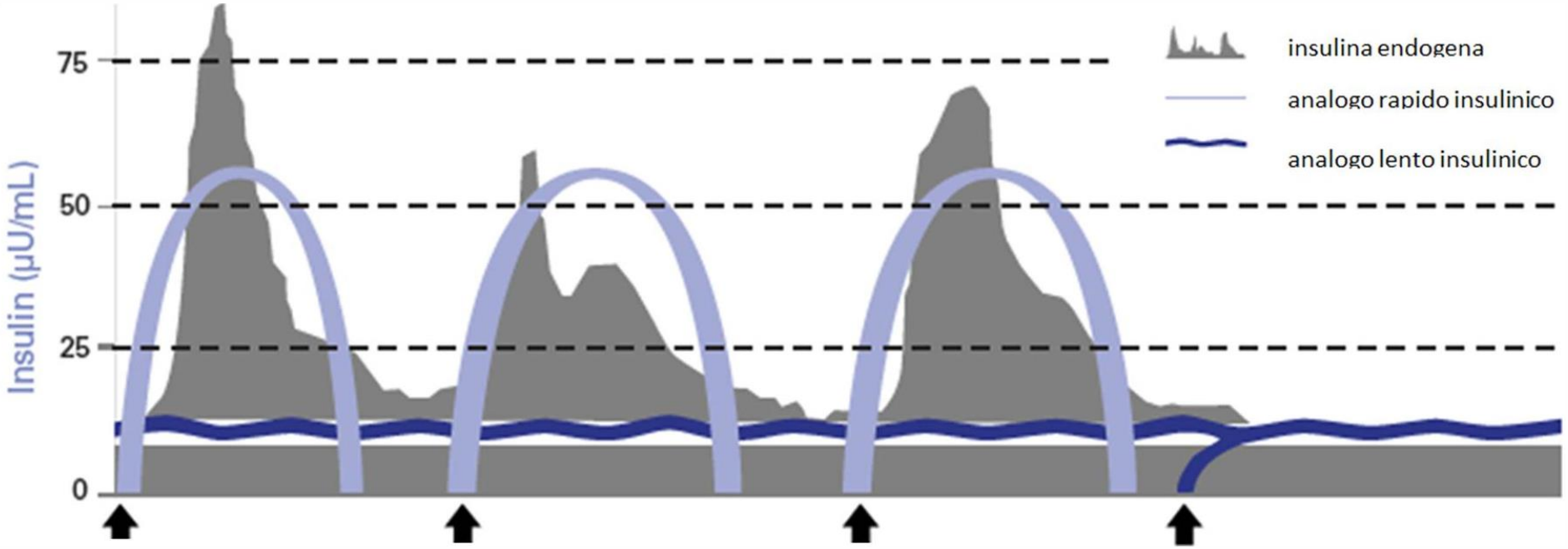
Sinha VP, et al. Diabetes. 2012; 61 (suppl 1): A273

The Endothelial Sieve and Peglispro



Herring R et al. Diabetes Obes Metab. 2014; 16: 1-8

Come mimare al meglio il profilo insulinico fisiologico?



analogo rapido prima di colazione

analogo rapido prima di pranzo

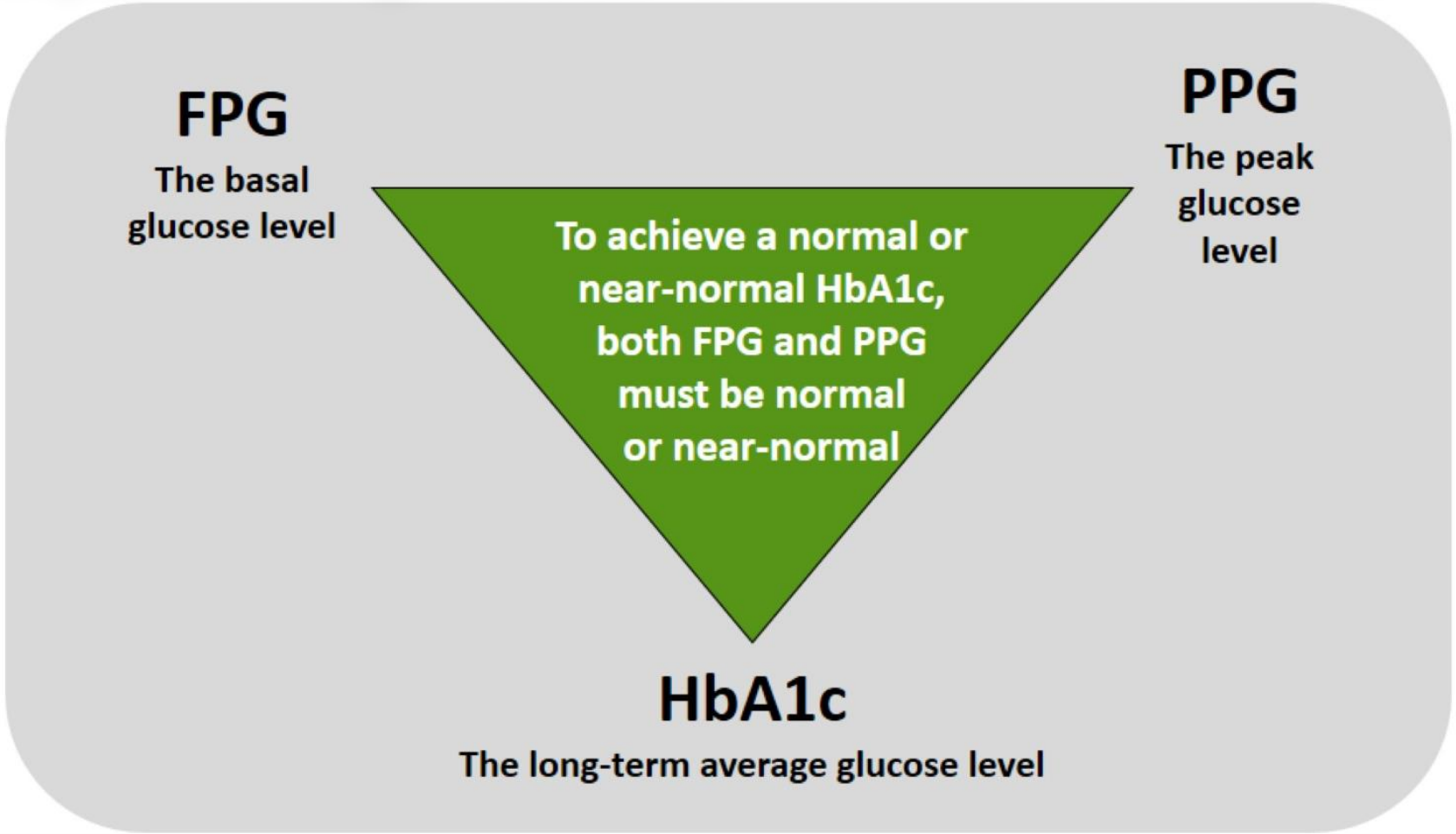
analogo rapido prima di cena

analogo lento prima di dormire

Accelerare l'assorbimento

Rallentare l'assorbimento

Glycemic Target Goals for Patients With T2DM



ADA. Diabetes care. 2016; 39 Suppl 1: S1-S104.
Inzucchi SE, et al. Diabetes Care. 2012; 35: 1364-1379. IDF, 2012

Major Mechanisms Linking Elevated PPG To Diabetes Complications

- Oxidative stress
- Inflammation
- Endothelial dysfunction

Ceriello A, et al. *Rev Endocr Metab Disord*. 2016;17:111-116.
de Vries MA, et al. *Adv Exp Med Biol*. 2014;824:161-170.

Elevated PPG Is Associaced With Diabetes Complications

- Elevated PPG has been shown to be associated with
  - Increased all-cause death
  - Increased CV death
  - Increased incidence of major CV events, including MI and stroke
  - Progression of diabetic retinopathy

Monami M, et al. *Nutr Metab Cardiovasc Dis*. 2013;23:591-598.
Mannucci E, et al. *Acta Diabetol*. 2012;49:307-314.

Limitations of Current Rapid-Acting Insulins

- Current rapid-acting insulin analogues were developed to more closely approach the physiological insulin response vs regular human insulin
- However, despite improvements in PK/PD profiles, current rapid-acting insulin analogues are still absorbed too slowly and do not replicate the physiological insulin secretion profile in healthy individuals

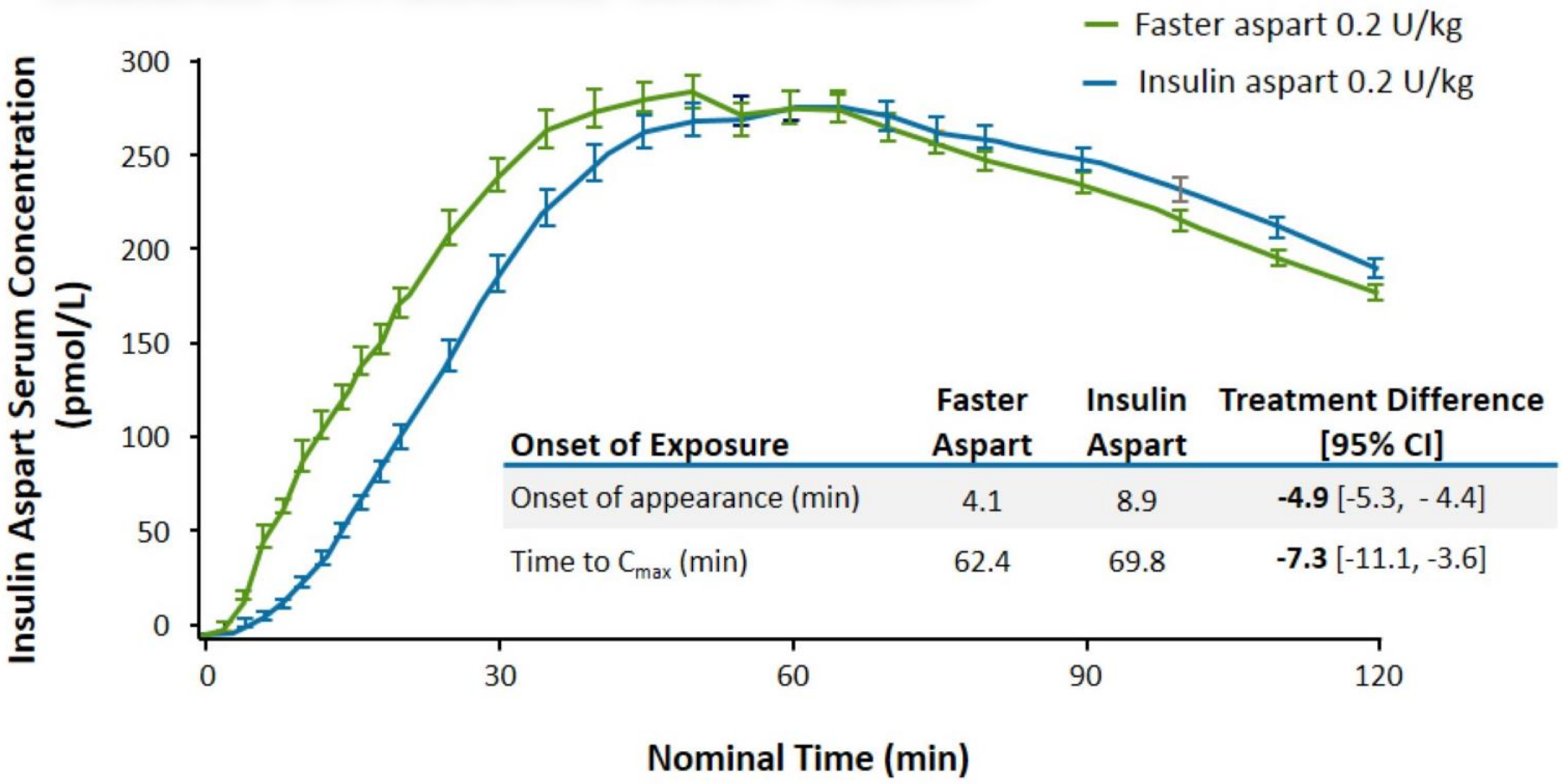
Heise T, et al. *Diabetes Obes Metab*. 2015;17:682-688.

Faster Aspart: a New Formulation of Insulin Aspart

- Insulin aspart: reduced strength of the insulin dimer leading to fast absorption[a]
- Faster aspart is a new formulation of insulin aspart, which contains 2 excipients, nicotinamide and arginine[b]
  - Nicotinamide acts as an absorption modifier
  - Arginine acts as a stabilizing agent
  - The excipients result in a stable formulation and faster initial absorption after SC injection

a. Brange J, *et al. Diabetes Care.* 1990;13:923-954.
b. Heise T, et al. *Diabetes Obes Metab*. 2015;17:682-688.

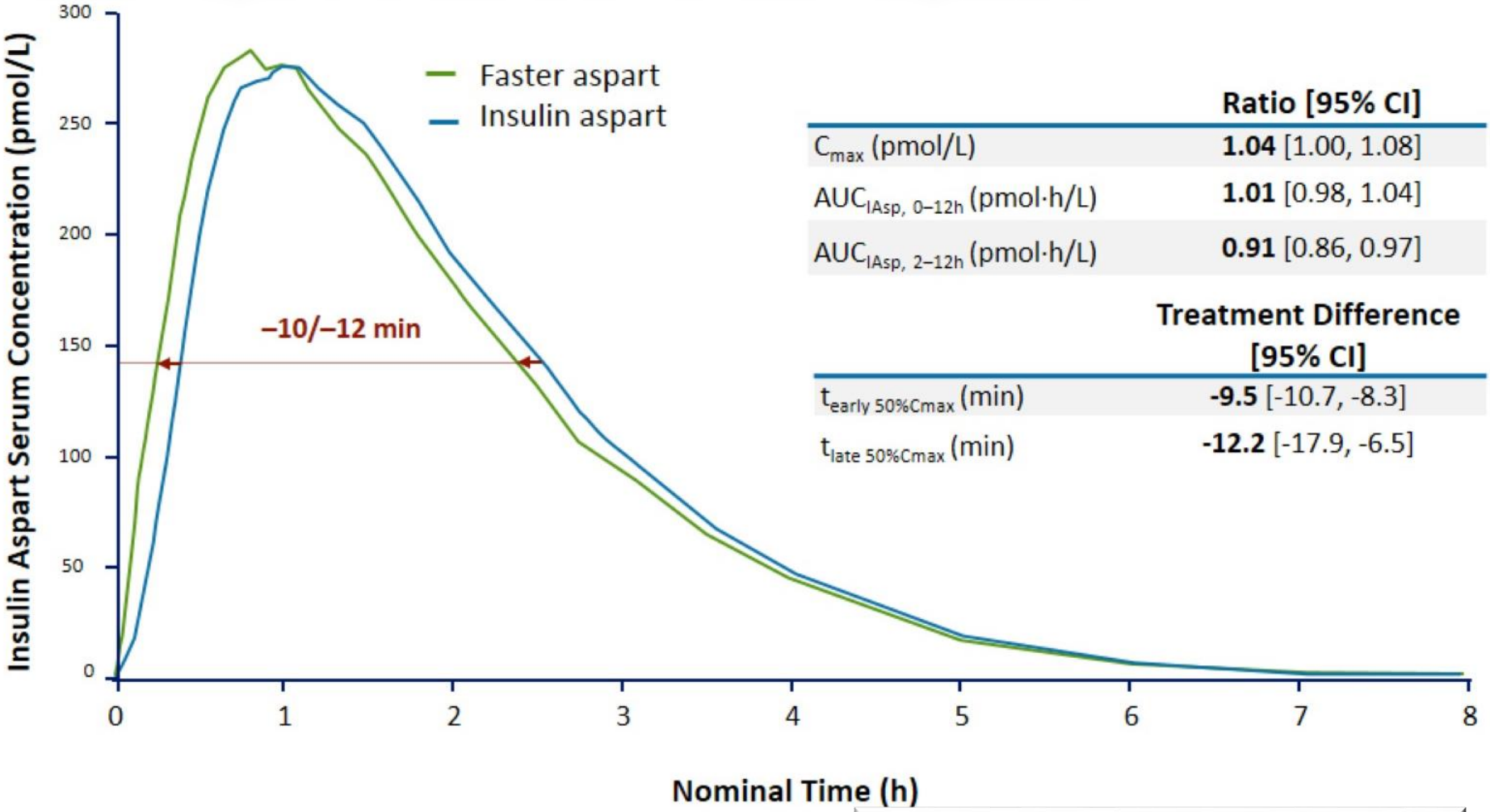
Early PK of Faster Aspart: Pooled Analysis of 6 Studies in Patients With T1DM



Onset of Exposure	Faster Aspart	Insulin Aspart	Treatment Difference [95% CI]
Onset of appearance (min)	4.1	8.9	**-4.9** [-5.3, - 4.4]
Time to C_{max} (min)	62.4	69.8	**-7.3** [-11.1, -3.6]

Heise T, *et al. Diabetes.* 2016;65 Suppl 1:929-P.

Faster Aspart: Onset and «Offset» Exposure*



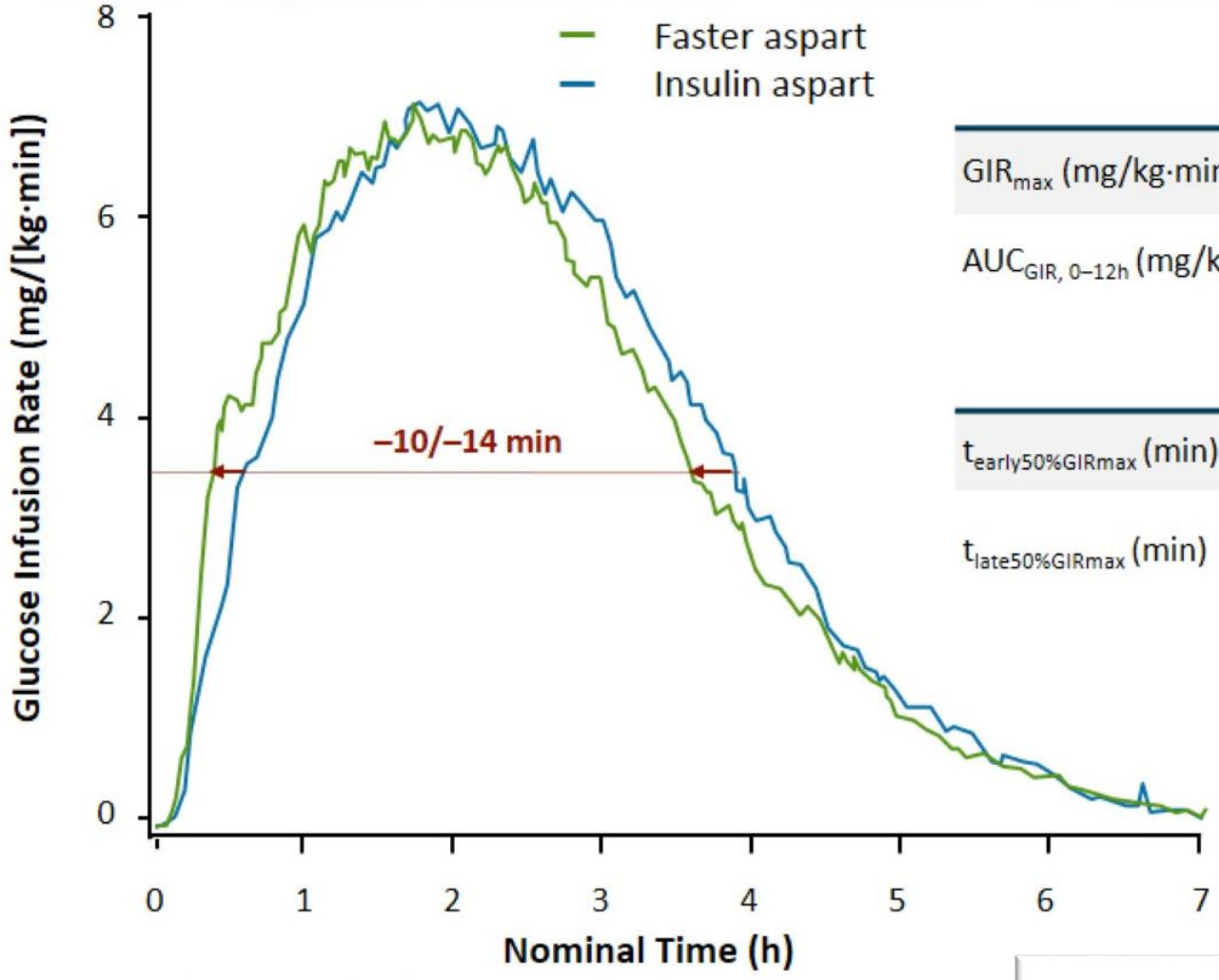
	Ratio [95% CI]
C_{max} (pmol/L)	**1.04** [1.00, 1.08]
$AUC_{IAsp,\ 0–12h}$ (pmol·h/L)	**1.01** [0.98, 1.04]
$AUC_{IAsp,\ 2–12h}$ (pmol·h/L)	**0.91** [0.86, 0.97]

	Treatment Difference [95% CI]
$t_{early\ 50\%Cmax}$ (min)	**-9.5** [-10.7, -8.3]
$t_{late\ 50\%Cmax}$ (min)	**-12.2** [-17.9, -6.5]

*Pooled analysis of 6 studies in patients with T1DM

Heise T, *et al. Diabetes.* 2016;65 Suppl 1:929-P.

Faster Aspart: Onset and «Offset» of Metabolic Activity*



	Ratio [95% CI]
GIR_{max} (mg/kg·min)	**1.01** [0.96, 1.05]
$AUC_{GIR,\ 0–12h}$ (mg/kg)	**0.98** [0.94, 1.03]

	Treatment difference [95% CI]
$t_{early50\%GIRmax}$ (min)	**-9.5** [-12.5, -6.4]
$t_{late50\%GIRmax}$ (min)	**-14.3** [-22.1, -6.5]

*Pooled analysis of 6 studies in patients with T1DM

Heise T, *et al. Diabetes.* 2016;65 Suppl 1:929-P.

Onset® 1 Study

Onset® 2: Study

- The new faster aspart, which is still in clinical development, has earlier PK/PD effects than insulin aspart, and it has achieved better control of PPG in clinical trials in patients with T1DM and T2DM
- Faster aspart and insulin aspart have similar safety profiles in clinical trials
- These effects of faster aspart may translate into clinical benefits for patients

Russell-Jones D, et al. *Diabetologia*. 2016;59 Suppl 1:S6.

Bowering K, et al. *Diabetologia*. 2016;59 Suppl 1:S399.

Use of BioChaperone Lispro, the company's reformulated version of the standard lispro insulin, resulted in faster absorption and reduced postprandial glucose excursions compared with standard premeal lispro in type 1 patients

BIOCHAPERONE® LISPRO

BIOCHAPERONE® LISPRO: A MORE PHYSIOLOGIC ULTRA RAPID INSULIN

In December 2014, ADOCIA and Lilly entered into a license agreement for the BioChaperone® Lispro programs.
BioChaperone Lispro is an ultra-rapid acting formulation of insulin lispro (Humalog®, Eli Lilly), using ADOCIA's proprietary BioChaperone® technology. ADOCIA has developed this product in two concentrations: BioChaperone Lispro U100 and BioChaperone Lispro U200.
Under the terms of the agreement, Lilly is responsible for future development, manufacturing, and commercialization of BioChaperone Lispro. The total up-front and milestone payments could reach up to $570 million. Adocia also stands to receive tiered sales royalties.
The first clinical study under the partnership, consisting of a meal tolerance test, was successfully completed in June 2015. Since then, four other studies have been launched. To date, ADOCIA has received $60 million.

Ultra-Rapid Formulation of Lispro U 100: T2DM

- Phase 1b clinical trial of patients with T2DM (n=51)
- Significantly faster absorption in ultra-rapid insulin lispro vs insulin lispro, with a statistically significant 83% increase in exposure to insulin lispro over the first 30 min after injection vs insulin lispro
- Significant reduction in 2-h PPG excursion vs insulin lispro
- Similar safety results
  - AEs, injection site reactions, or rates of hypoglycemia

Adocia Press Release. 27 Apr 2016.

Ultra-Rapid Formulation of Lispro U 100: T1DM

- Phase 1b clinical trial of patients with T1DM (n=36)
- At the beginning of the 14-day treatment period, ultra-rapid insulin lispro U100 demonstrated a statistically significant 31% reduction in glycemic excursion during the first 2 hours vs insulin lispro, when injected an the time of the meal
  - At the end of the 14-day treatment period, that difference reached 42%
- Ultra-rapid insulin lispro U100 and insulin lispro were similarly well tolerated throughout the 14 day study

Adocia Press Release. 27 Apr 2016.

Potential Role of Ultra-Acting Insulins in Clinical Development

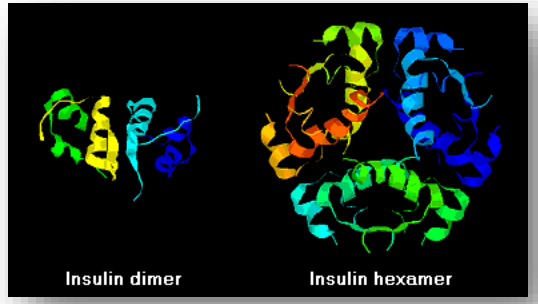
- The development of ultrafast-acting insulins are a meaningful step forward for many patients with diabetes
- The effects are clinically meaningful
  - In patients with T2DM
  - In patients with T1DM

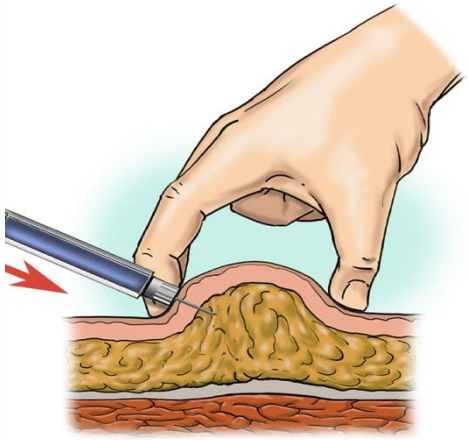
Gli analoghi lenti ed ultralenti non differiscono nella struttura molecolare dell'insulina

Quello che li differenzia è la formulazione che ne varia la farmacocinetica

Le differenze farmacocinetiche sono quelle responsabili delle diversità farmacodinamiche

Strategie di ritardo dell'assorbimento dell'insulina dal deposito sottocutaneo

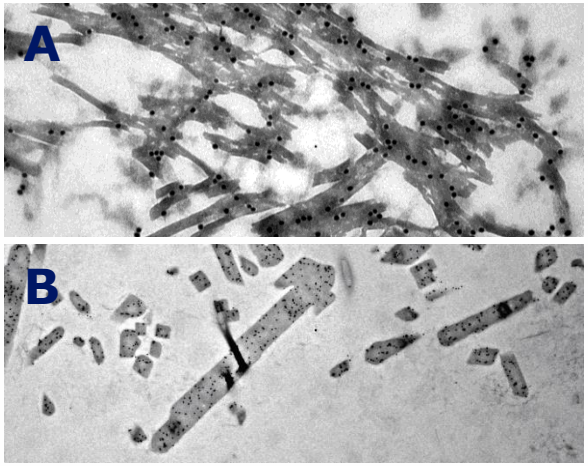




Modifiche della formulazione dell'insulina
- Protamina
- Zinco
- Cobalto

Modifiche della sequenza aminoacidica dell'insulina
- Shift pH isoelettrico
- aciliazione

***In vivo* (pig s.c.)**



A. Insulin glargine precipitates
B. NPH crystals

Brange et al. Diabetes Care 1990;13:923–54

Ideal characteristics of basal insulin

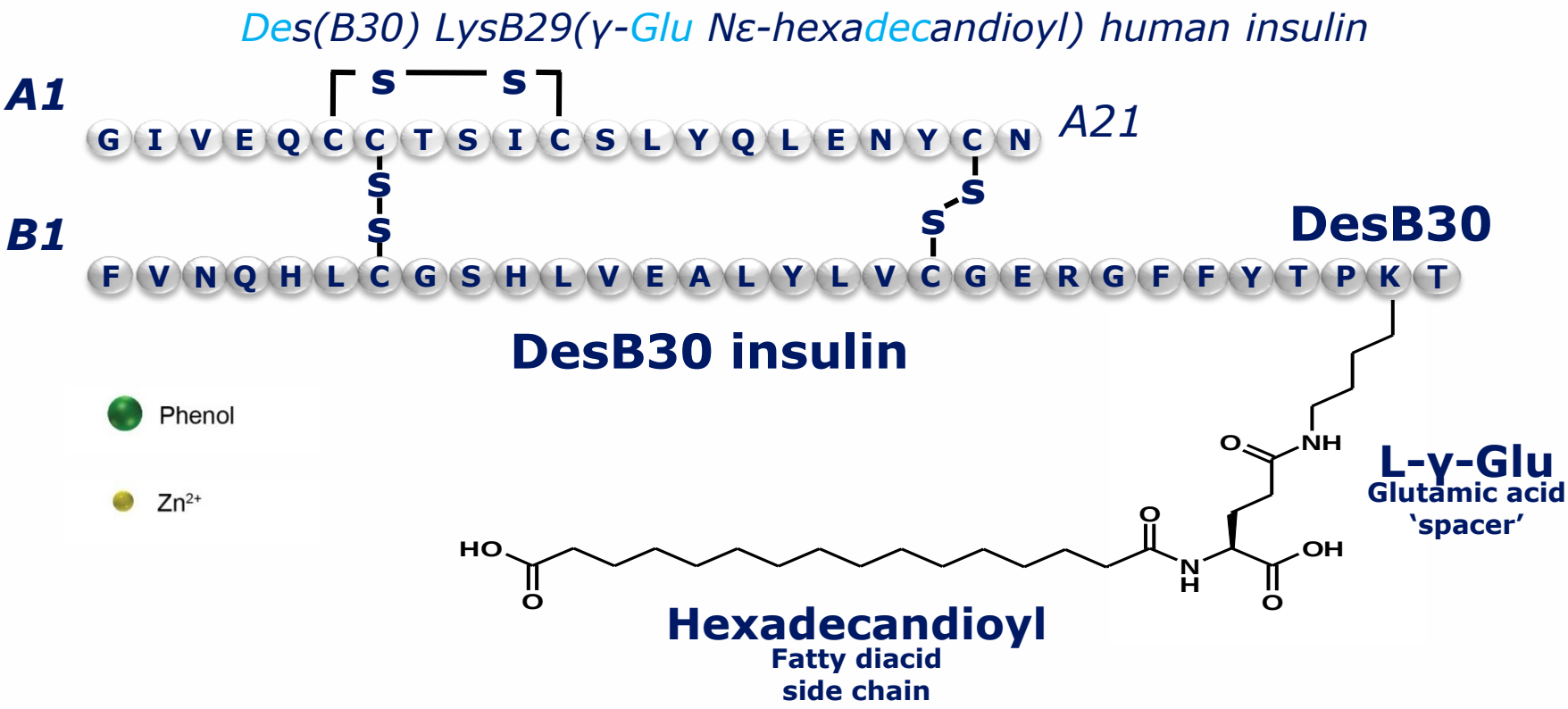
Longer duration of action	Control fasting blood glucose with one injection per day **ALLOW FLEXIBILITY**
Flat time-action profile	**Lower risk of hypoglycaemia**
Less day-to-day variability	Lower risk of hypoglycaemia Potential for titration to lower FPG target

Novel Basal Insulin Analogues

- Improved PK/PD profiles – duration of action 24 to ≥ 36 hours[c]
- Flatter glucose-lowering effect and flatter insulin concentration[c]
- Lower risk for hypoglycemia[a,b]
- **Degludec**[d], **Gla-300**[e], and **PEGLispro**[f] at the furthest stage of clinical development

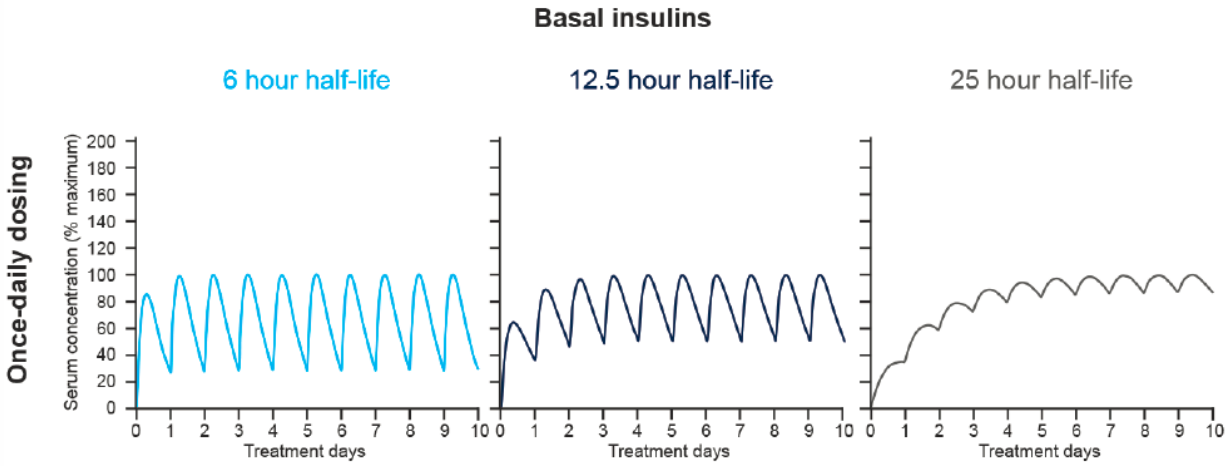
a. Riddle MC, et al. *Diabetes Care.* 2014;37:2755-2762; b. Yki-Järvinen H, et al. *Diabetes Care.* 2014;37:3235-3243; c. Owens DR, et al. *Diabetes Metab Res Rev.* 2014;30:104-119; d. Wang F, et al. *Diabetes Metab Syndr Obes.* 2012;5:191-204; e. Maiorino MI, et al. *Expert Opin Biol Ther.* 2014;14:799-808; f. Sinha VP, et al. ADA 2012. Poster 1063-P.

Insulin degludec: rationally designed, beyond sequence modification



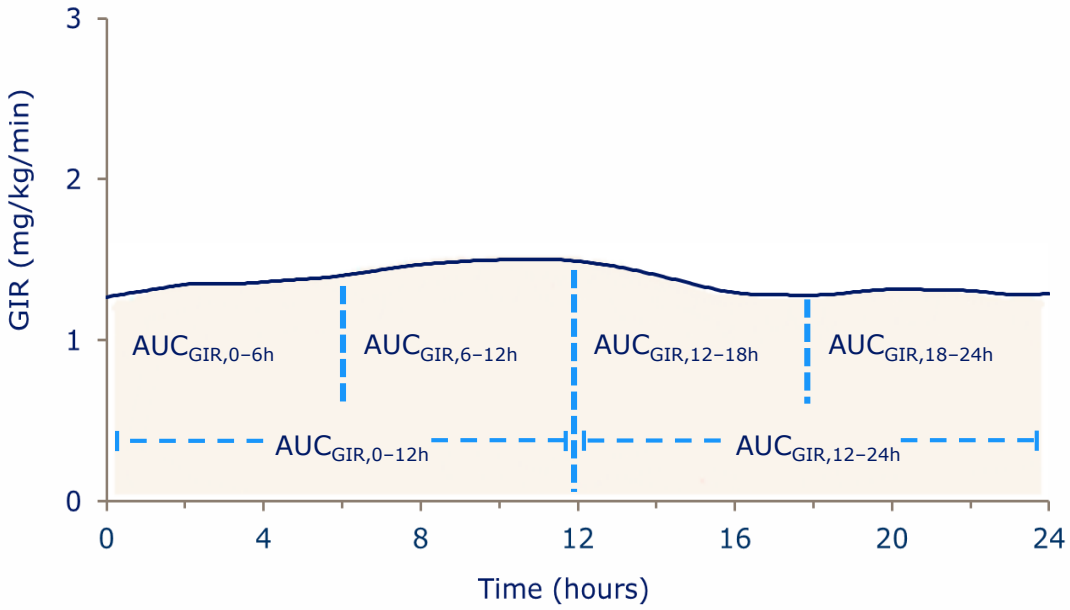
Insulin degludec: PK & PD

	Insulin degludec			Insulin glargine		
	0.4 U/kg	0.6 U/kg	0.8 U/kg	0.4 U/kg	0.6 U/kg	0.8 U/kg
Half-life (hours)	25.9	27.0	23.6	11.5	12.9	11.9
Mean half-life	**25.4**			**12.1**		



Emivita lunga = migliore qualità del profilo farmacocinetico allo steady state

Insulin degludec: PK & PD



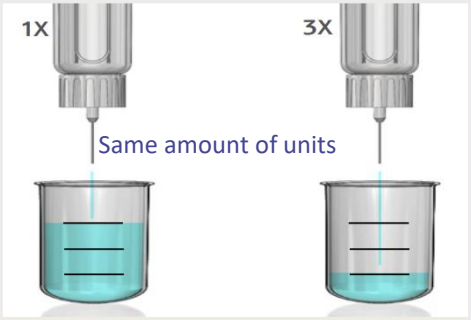
AUC = area under the curve
GIR = glucose infusion rate

RIASSUNTO DELLE CARATTERISTICHE DEL PRODOTTO

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

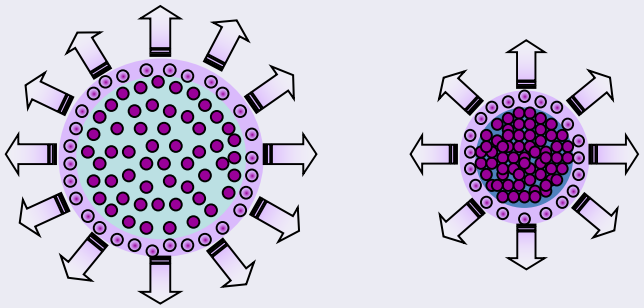
GLA-300 is a new long-acting basal insulin with a more even and prolonged PK/PD profile vs GLA-100

Reduction of volume by 2/3



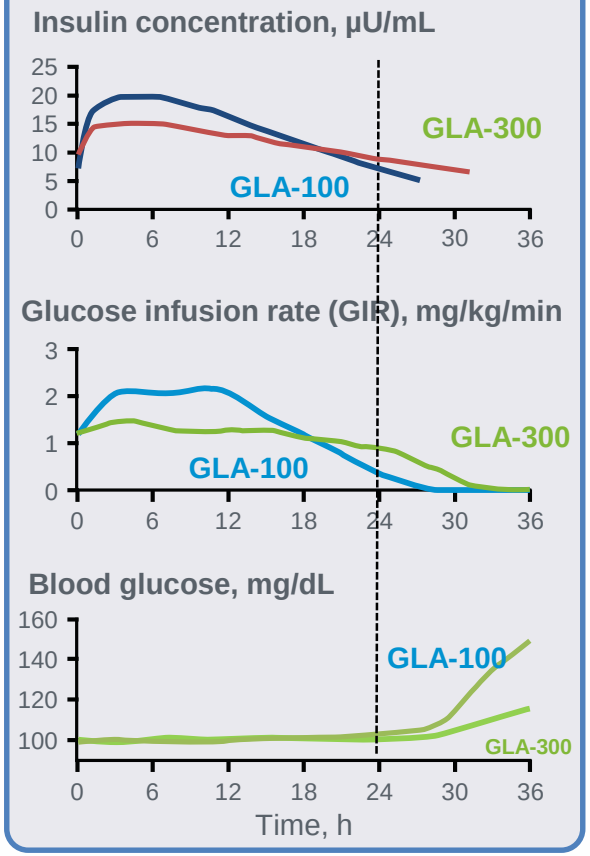
GLA-100 GLA-300

Reduction of depot surface by 1/2



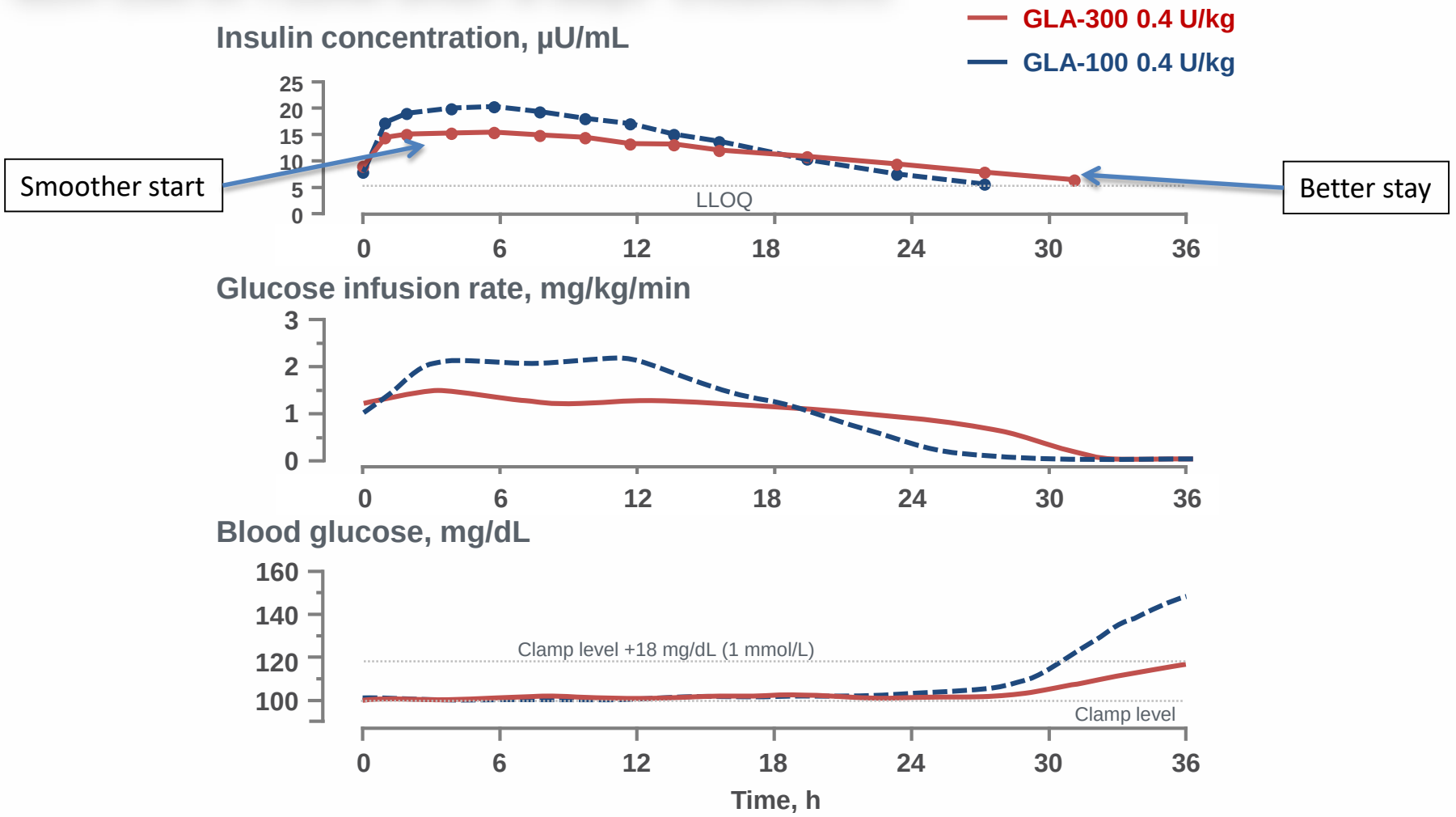
GLA-100 GLA-300

More even and prolonged PK/PD profile



Steinstraesser A et al. Diabetes Obes Metab. 2014;16:873-6; Becker RHA et al. Diabetes Care. 2014 Aug 22. pii: DC_140006. [Epub ahead of print]

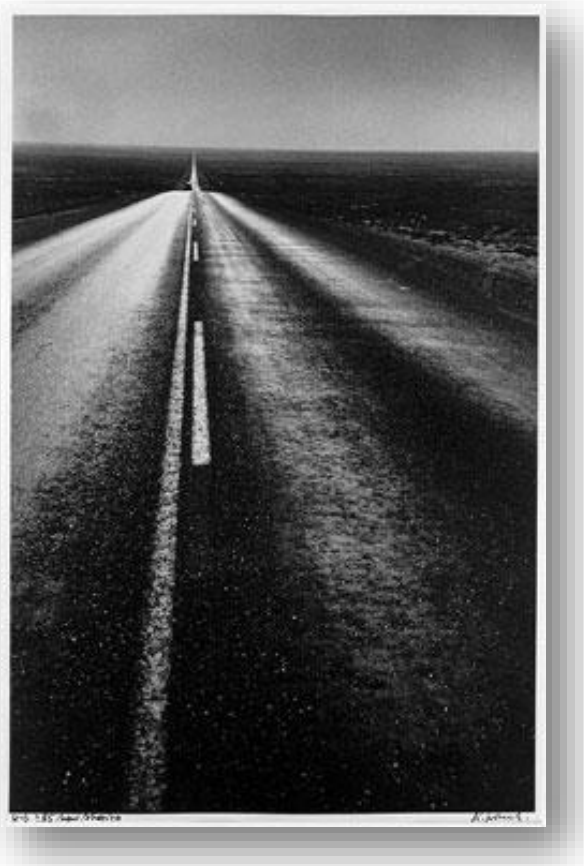
More even and prolonged profile with GLA-300 vs GLA-100 in T1DM after 8 days' treatment



Becker RHA et al. Diabetes Care. 2014 Aug 22. pii: DC_140006. [Epub ahead of print]

… vi è un'altra frontiera per la basalizzazione

… oltre l'insulina?



Annals of Internal Medicine
CLINICAL GUIDELINE

Pharmacologic Therapy for Type 2 Diabetes: Synopsis of the 2017 American Diabetes Association Standards of Medical Care in Diabetes

James J. Chamberlain, MD; William H. Herman, MD, MPH; Sandra Leal, PharmD; Andrew S. Rhinehart, MD; Jay H. Shubrook, DO; Neil Skolnik, MD; and Rita Rastogi Kalyani, MD, MHS

Figure 1. Antihyperglycemic therapy for type 2 diabetes: general recommendations.

Start With Monotherapy Unless:

- HbA_{1c} level is ≥9%, consider dual therapy.
- HbA_{1c} level is ≥10%, blood glucose level is ≥300 mg/dL, or patient is markedly symptomatic, consider combination injectable therapy.

Monotherapy — Metformin — Lifestyle Management

EFFICACY*	High
HYPOGLYCEMIA RISK	Low risk
WEIGHT	Neutral/loss
SIDE EFFECTS	GI/lactic acidosis
COSTS*	Low

If HbA_{1c} target not achieved after approximately 3 mo of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference; choice dependent on a variety of patient- and disease-specific factors):

Dual Therapy — Metformin + — Lifestyle Management

	Sulfonylurea	Thiazolidinedione	DPP-4-i	SGLT-2-i	GLP-1-RA	Insulin (basal)
EFFICACY*	High	High	Intermediate	Intermediate	High	Highest
HYPOGLYCEMIA RISK	Moderate risk	Low risk	Low risk	Low risk	Low risk	High risk
WEIGHT	Gain	Gain	Neutral	Loss	Loss	Gain
SIDE EFFECTS	Hypoglycemia	Edema, HF, and fractures	Rare	GU, dehydration, and fractures	GI	Hypoglycemia
COSTS*	Low	Low	High	High	High	High

If HbA_{1c} target not achieved after approximately 3 mo of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference; choice dependent on a variety of patient- and disease-specific factors):

Triple Therapy — Metformin + — Lifestyle Management

Sulfonylurea +	Thiazolidinedione +	DPP-4-i +	SGLT-2-i +	GLP-1-RA +	Insulin (basal) +
Thiazolidinedione	Sulfonylurea	Sulfonylurea	Sulfonylurea	Sulfonylurea	Thiazolidinedione
or DPP-4-i	or DPP-4-i	or Thiazolidinedione	or Thiazolidinedione	or Thiazolidinedione	or DPP-4-i
or SGLT-2-i	or SGLT-2-i	or SGLT-2-i	or DPP-4-i	or SGLT-2-i	or SGLT-2-i
or GLP-1-RA	or GLP-1-RA	or Insulin†	or GLP-1-RA	or Insulin†	or GLP-1-RA
or Insulin†	or Insulin†		or Insulin†		

If HbA_{1c} target not achieved after approximately 3 mo of triple therapy and patient on oral combination, move to basal insulin or GLP-1-RA; if the patient is on GLP-1-RA, add basal insulin; or if the patient is on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. Metformin therapy should be maintained, whereas other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

Combination Injectable Therapy

James J. Chamberlain, et al. *Ann Intern Med.* 14 March 2017.

Complexity of diabetes pathophysiology may benefit from a multi-targeted approach

GLP-1 analogue

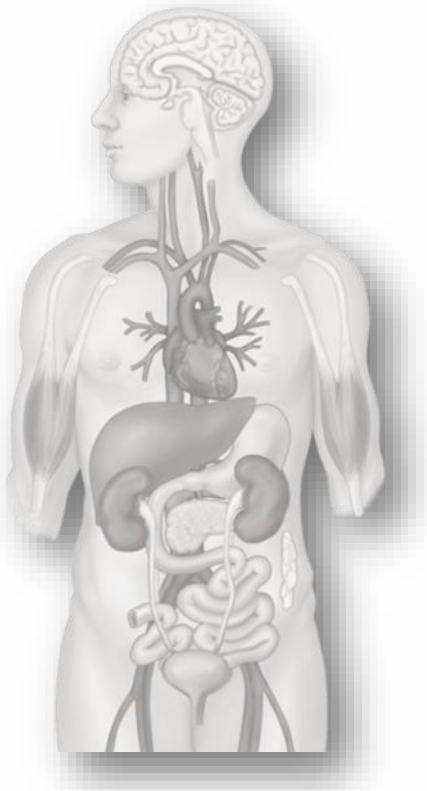
Brain
Energy intake
Satiety
Learning and memory*
Neuroprotection

Heart
Cardioprotection
Cardiac function

Pancreas
Glucose-dependent insulin and glucagon secretion
Insulin synthesis
Beta-cell mass*

Liver
Hepatic glucose output

GI tract
Gastric emptying



Basal insulin

Skeletal muscle
Glucose disposal

Liver
Hepatic glucose production

Adipose tissue
Insulin receptor activation

GLP-1, glucagon-like peptide-1; *in animal studies
Baggio, Drucker. *Gastroenterol* 2007;132:2131–57

Complexity of diabetes pathophysiology may benefit from a multi-targeted approach

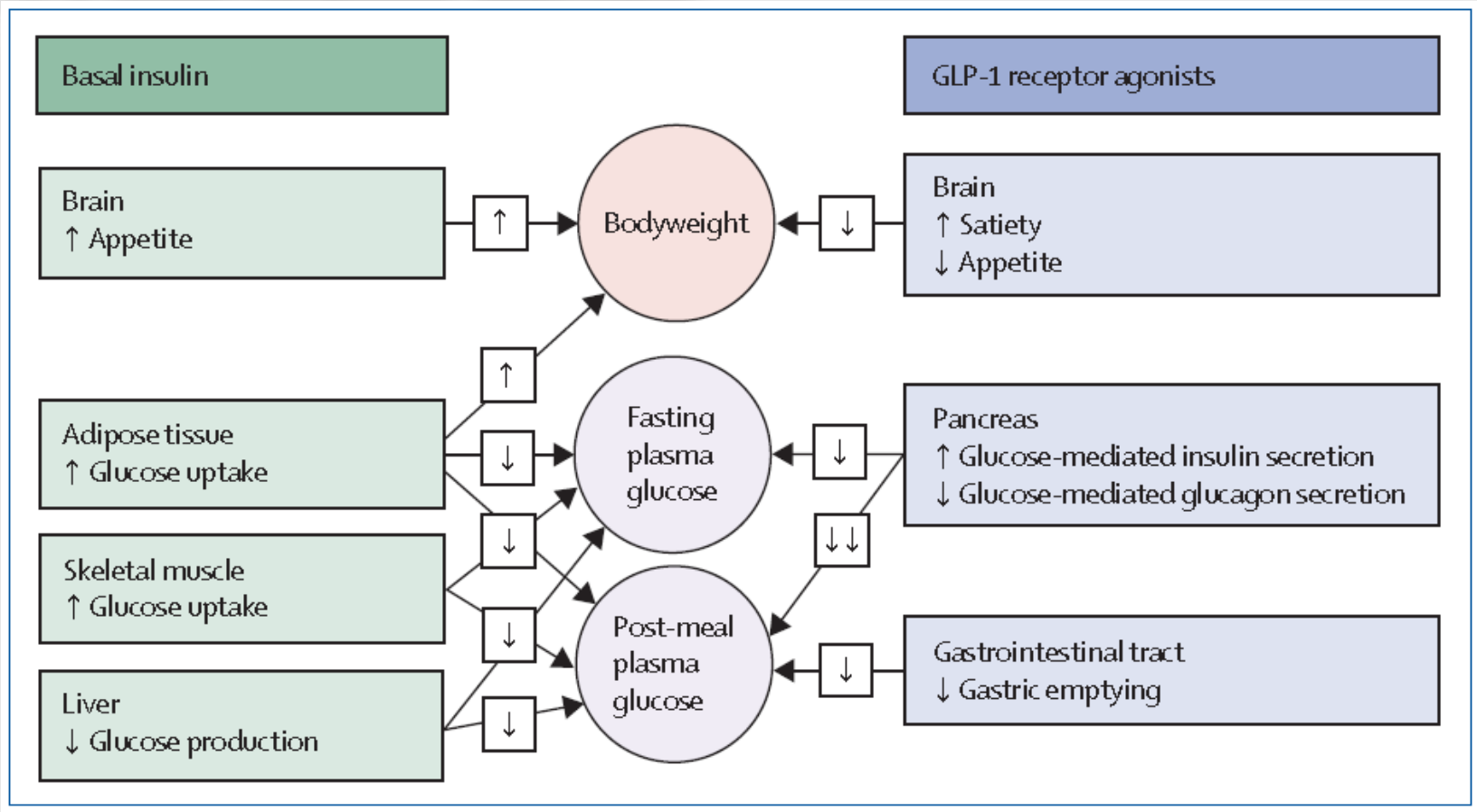
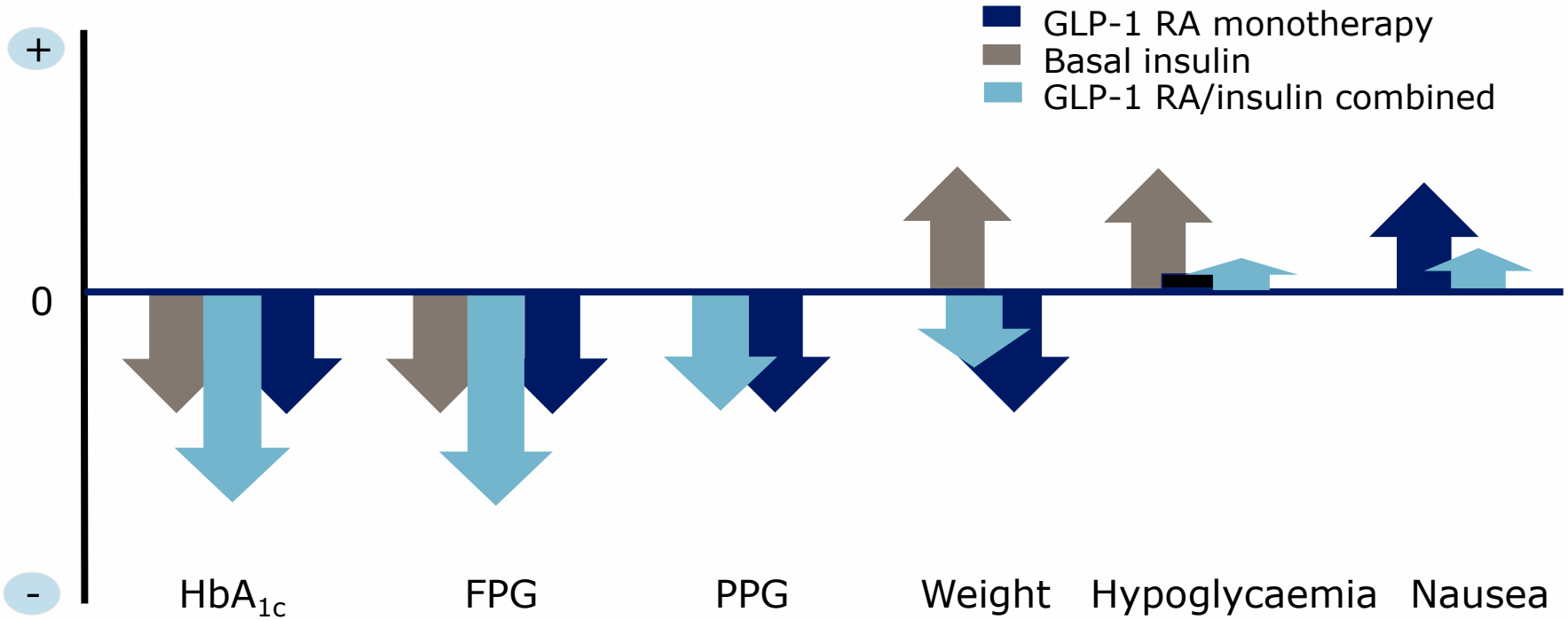


Figure: **Schematic representation of the potential synergistic effects of treatment with basal insulin and a longacting GLP-1 agonist**

Del Prato www.thelancet.com/diabetes-endocrinology Vol 2 November 2014

Combining therapies offers opportunities to enhance efficacy and diminish side effects



For illustrative purposes only, not meant to quantify or imply magnitude of change in either direction

Basal Insulin/GLP-1 Analog Combination Products (In Development)

- Degludec/liraglutide
- Glargine/lixisenatide

NOVONORDISK IS ALSO DEVELOPING IDegLira, A MIX OF BASAL INSULIN Degludec WITH GLP-1 Liraglutide TARGETED AT TYPE 2.

SANOFI IS ALSO DEVELOPING LIXILAN, A MIX OF BASAL INSULIN Glargine WITH GLP-1 Lixisenatide TARGETED AT TYPE 2.

GRAZIE DELL'ATTENZIONE