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2022

SID Società Italiana di Diabetologia

AMD ASSOCIAZIONE MEDICI DIABETOLOGI 1974

T-HOTEL LAMEZIA TERME
25-26 NOVEMBRE 2022

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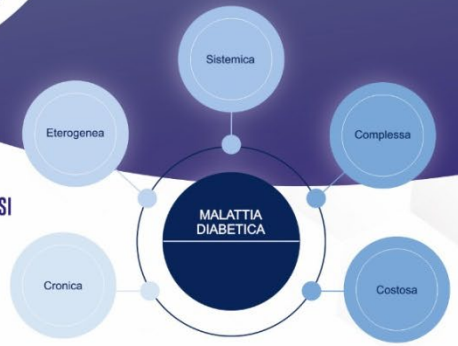

PRESIDENTE
DOTT. GIUSEPPE CERSOSIMO

RESPONSABILI SCIENTIFICI:
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PROVIDER
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SEGRETERIA ORGANIZZATIVA
XENIA

Il dr. Francesco Andreozzi dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Novo-Nordisk
- Lilly
- Boehringer-ingelheim

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.).

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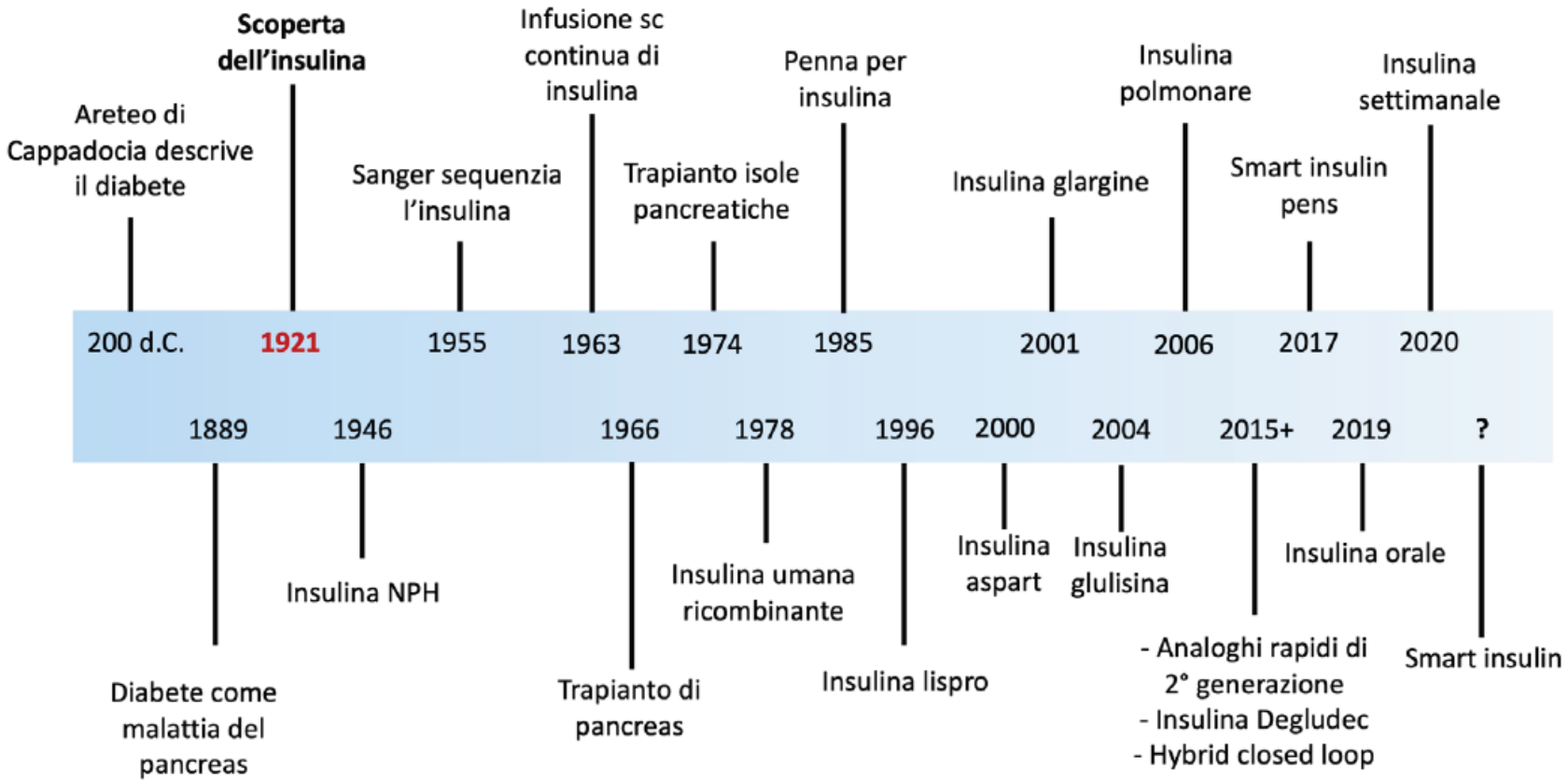
Nuove opportunità terapeutiche: Le nuove insuline

Francesco Andreozzi

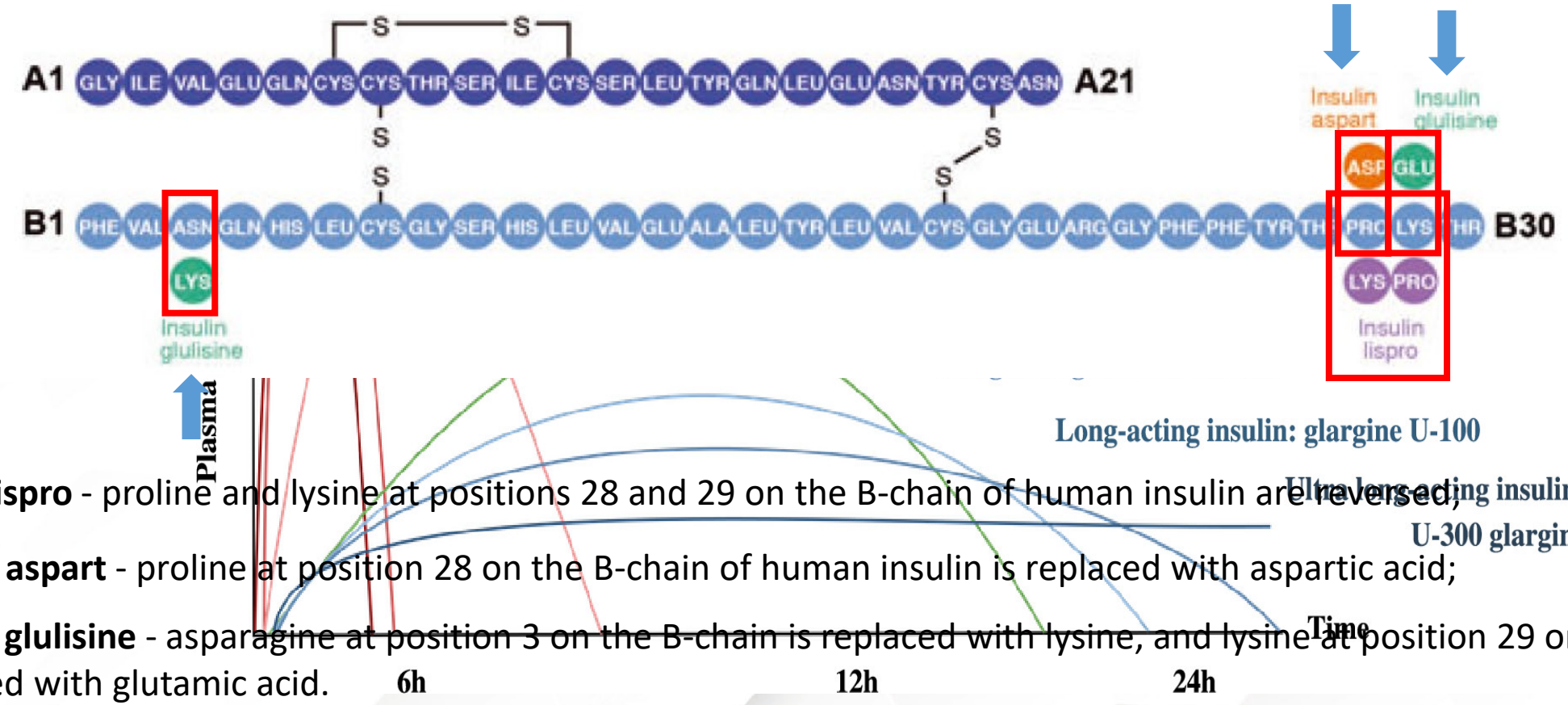
BPETTIΩN
UMG
Dubium sapientiae initium

Old and New Insulin Developments



Insulins beyond insulin Pierpaolo Falcetta, Monia Garofolo, Stefano Del Prato (2022)

In the 1990s and early 2000s, three insulin analogs (aspart, lispro, and glulisine) were developed through amino acid sequence modifications.

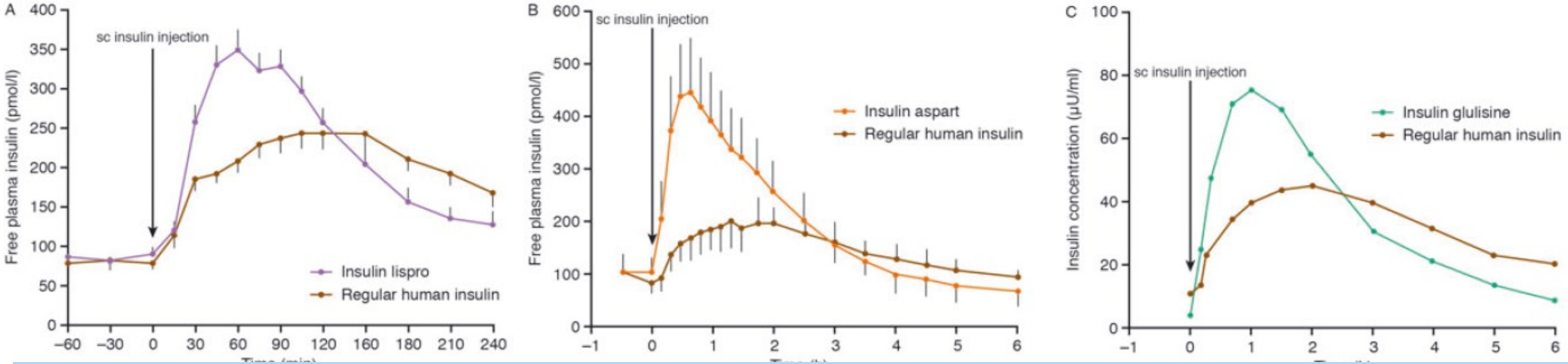


Isulin lispro - proline and lysine at positions 28 and 29 on the B-chain of human insulin are reversed;

Insulin aspart - proline at position 28 on the B-chain of human insulin is replaced with aspartic acid;

Insulin glulisine - asparagine at position 3 on the B-chain is replaced with lysine, and lysine at position 29 on the B-chain is replaced with glutamic acid.

PK of (A) insulin lispro, (B) insulin aspart and (C) insulin glulisine vs RHI



L'analogo rapido dell'insulina, nonostante abbia migliorato considerevolmente il controllo della glicemia post-prandiale rispetto all'insulina RHI, ha una cinetica ancora lenta rispetto all'insulina endogena (ridotta diffusione e assorbimento sottocutaneo)

P. D. Home Diabetes, Obesity and Metabolism 2012, The pharmacokinetics and pharmacodynamics of rapid-acting insulin analogues and their clinical consequences

Un profilo farmacocinetico sempre più simile, in termini di durata, al profilo medio dell'insulina endogena secreta durante il pasto

La rapidità di assorbimento dell'insulina rende possibile il ripristino dell'effetto del picco precoce di insulina, bloccando l'output epatico di glucosio

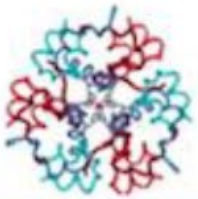
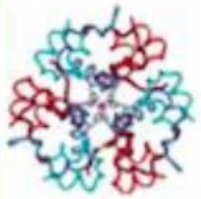
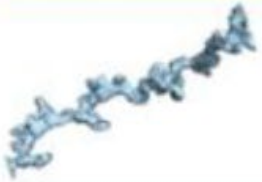
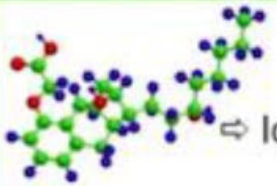
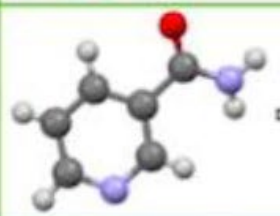
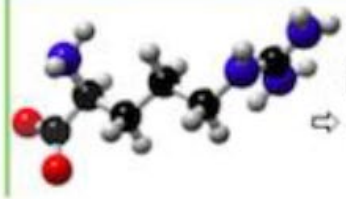
Il controllo della glicemia post-prandiale principalmente a carico dell'escursione glicemica precoce nella prima ora dopo un pasto

Tempo di somministrazione più flessibile. I pazienti con tendenza a tempi del pasto irregolari possono trarre vantaggio dalla possibilità di somministrare l'insulina dopo i pasti

Maggior profilo di sicurezza. Comparsa di eventi avversi come le ipoglicemie

To reduce postprandial glucose excursions, decrease hypoglycemic events, and increase injection time flexibility, **additives that facilitate insulin absorption were incorporated with rapid insulin analogs, resulting in the production of ultrarapid prandial insulins**

Ultra-Fast-Acting Prandial Insulins

Biochaperone Lispro	Ultra-Rapid Lispro	Faster acting Aspart
 Insulin lispro	 Insulin lispro	 Insulin aspart
 Biochaperone 222 ⇨ faster hexamer dissociation	 Treprostinil ⇨ local vasodilation	 Niacinamid ⇨ faster hexamer dissociation
 Citrate ⇨ higher vascular permeability	 Citrate ⇨ higher vascular permeability	 L-arginine ⇨ stabilization

* BioChaperone BC222 forms a physical complex with insulin protecting it from enzymatic degradation while enhancing both its stability and solubility

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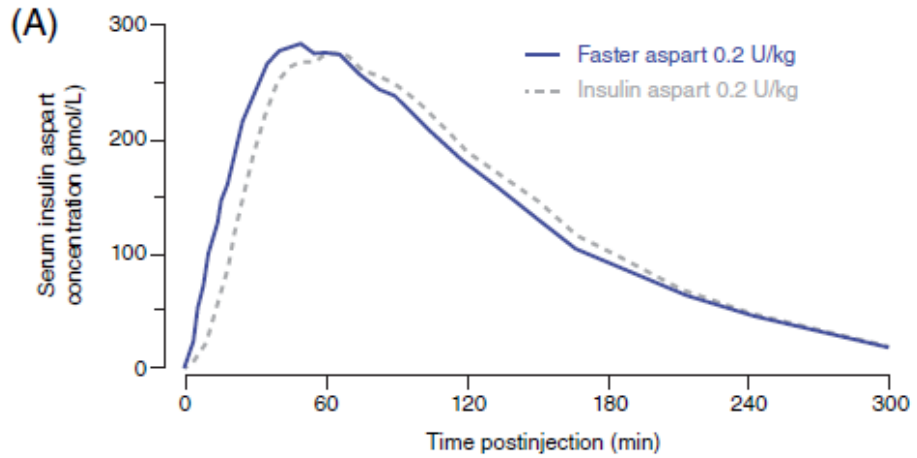
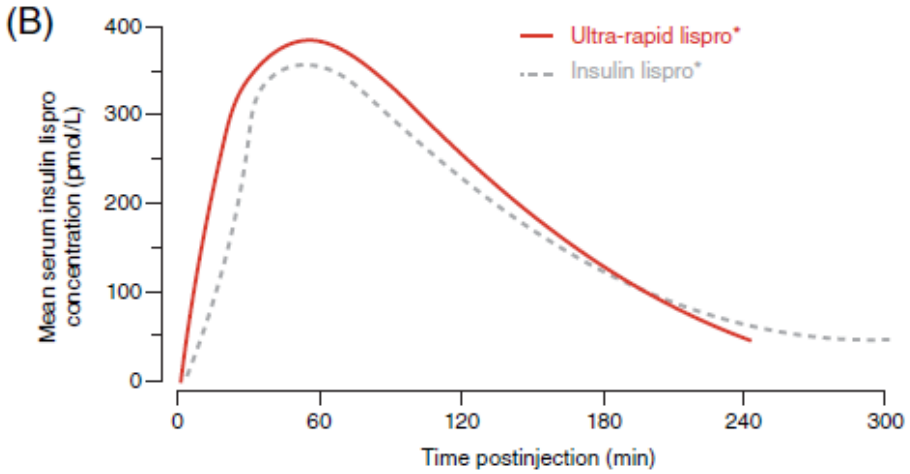
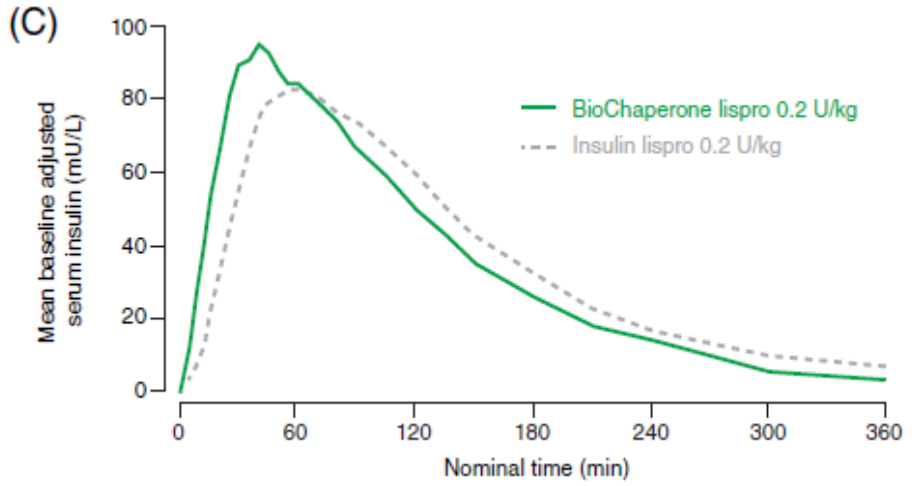
Pharmacokinetic action profiles (serum insulin levels) after subcutaneous injection in people with type 1 diabetes

Despite differences in the structure and mechanism of action, the pharmacokinetic profiles of the three candidates are quite similar







Pharmacokinetic action profiles (serum insulin levels) after subcutaneous injection of (A) faster aspart [adapted from Heise et al, (B) ultra-rapid lispro (adapted from Kazda et al) and (C) BioChaperone Lispro (adapted from Andersen et al), all versus insulin aspart or lispro in people with type 1 diabetes

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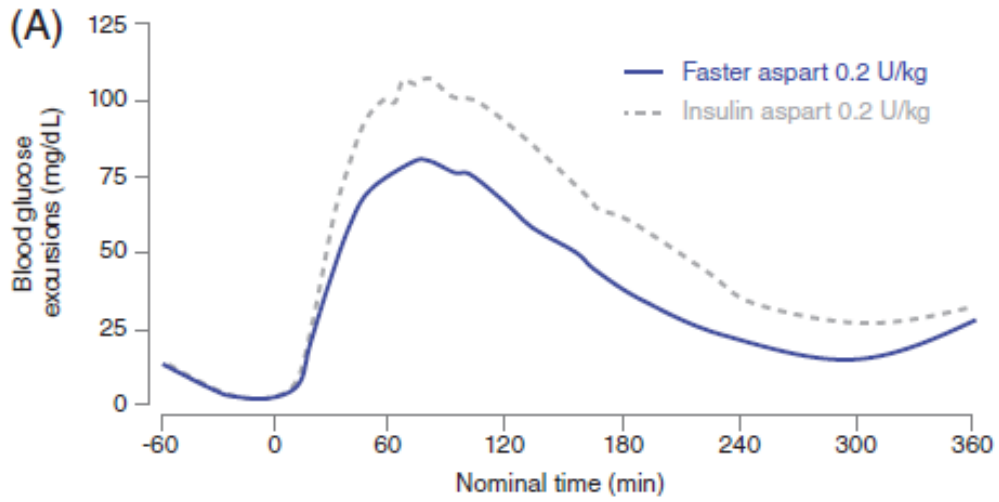
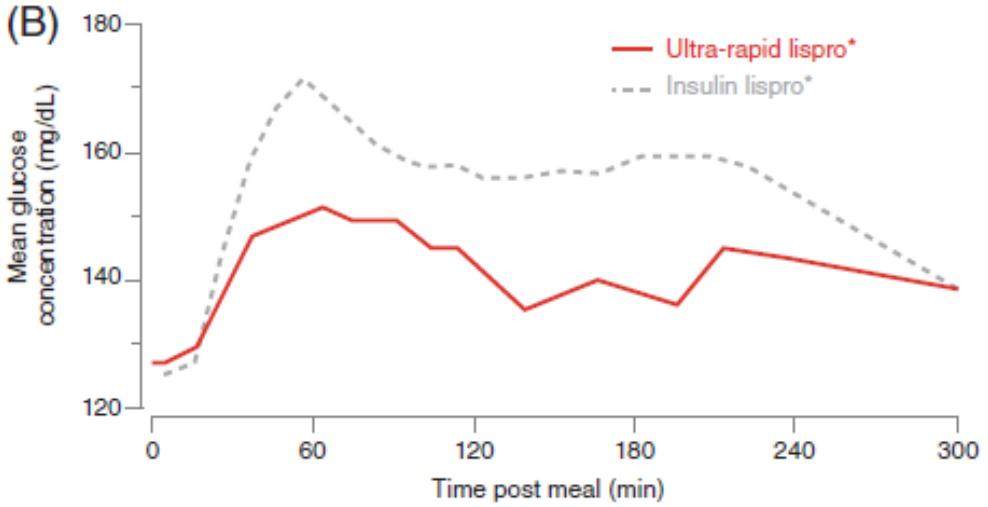
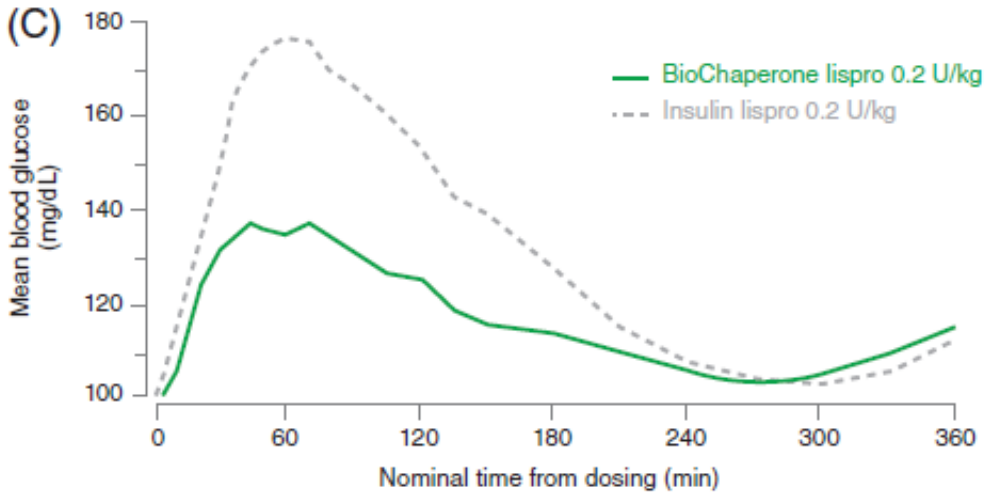
Postprandial blood glucose profiles after subcutaneous injection in people with type 1 diabetes

Their use resulted in significant reductions in 1- and 2-h PPG glucose levels by increasing inhibition of hepatic glucose production







Postprandial blood glucose profiles after subcutaneous injection of (A) faster aspart following a standardized liquid meal (67% carbohydrate, 600 kcal) (adapted from Heise et al53), (B) ultra-rapid lispro following a mixed meal (adapted from Kazda et al) and (C) BioChaperone Lispro following a standardized liquid meal (adapted from Andersen et al), all versus insulin aspart or lispro in people with type 1 diabetes.

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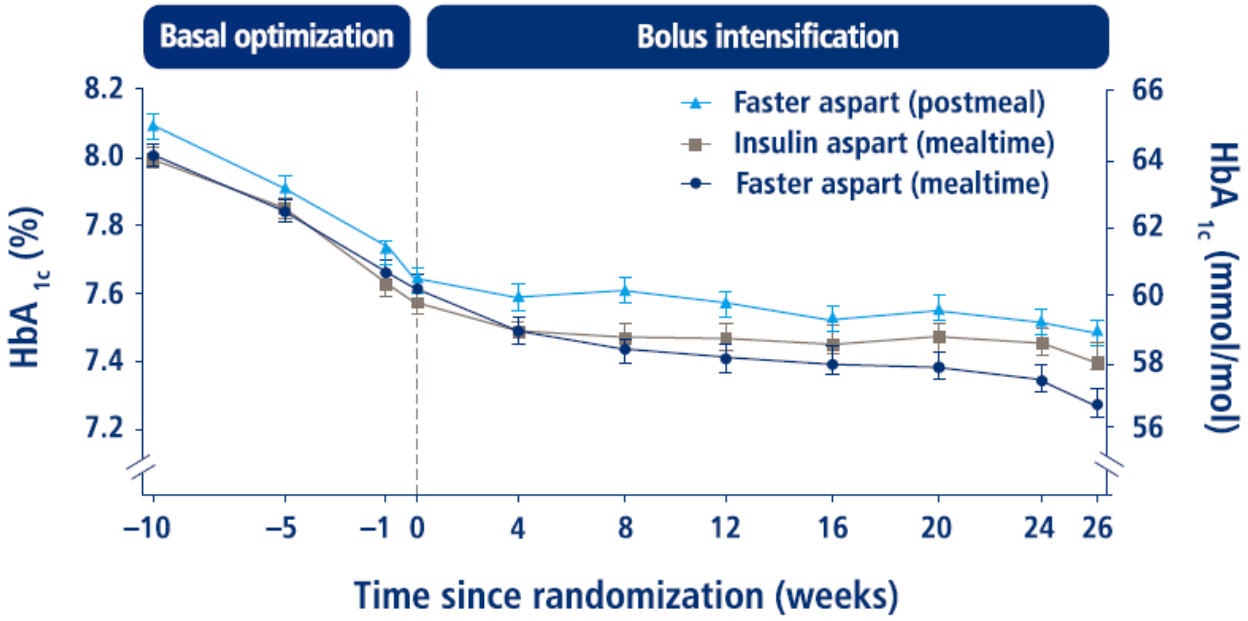
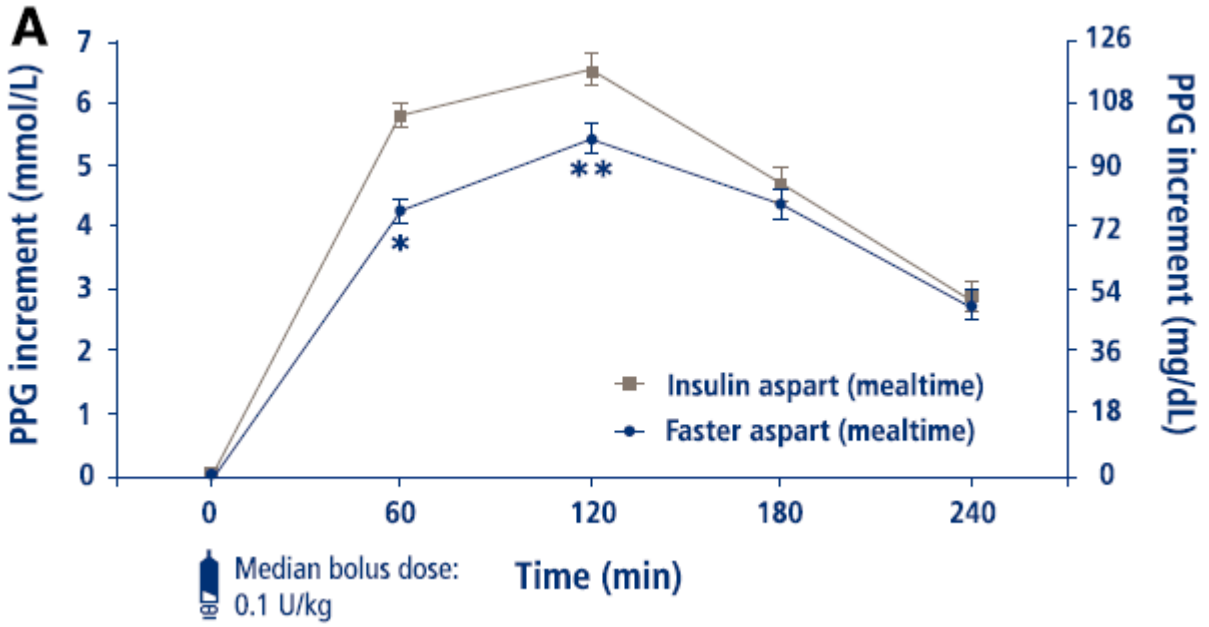
Fast-Acting Insulin Aspart Improves Glycemic Control in Basal-Bolus Treatment for Type 1 Diabetes: The Onset 1 Trial





Faster aspart effectively improved HbA1c, and noninferiority to IAsp was confirmed, with superior PPG control for mealtime faster aspart versus lasp

Diabetes Care 2017;40:943–950

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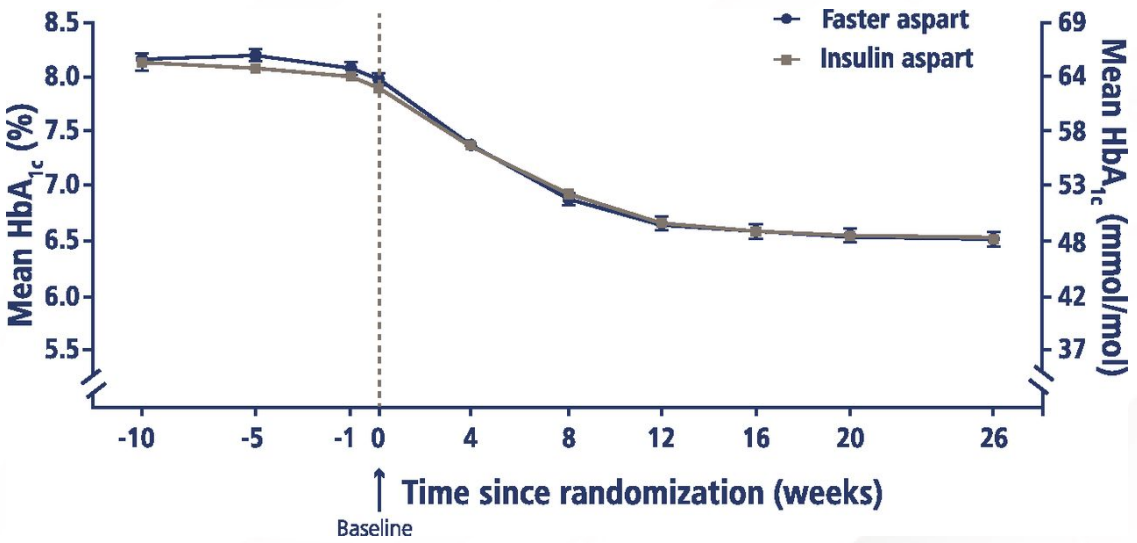
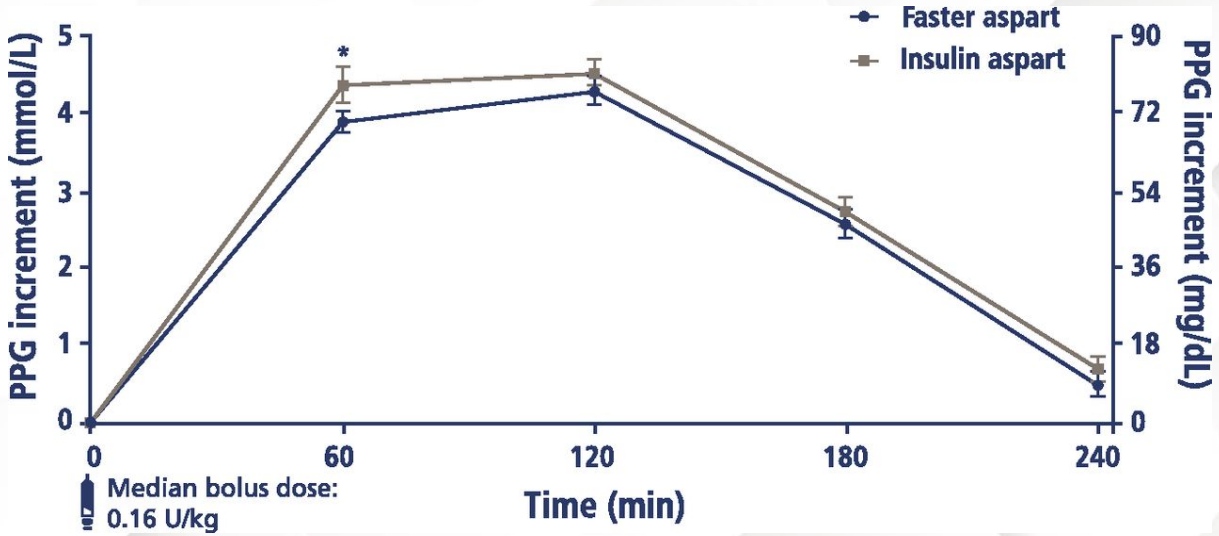
Faster Aspart Versus Insulin Aspart as Part of a Basal-Bolus Regimen in Inadequately Controlled Type 2 Diabetes: The Onset 2 Trial





*both in combination with insulin glargine U100

Faster aspart and IAsp were confirmed noninferior in a basal-bolus regimen regarding change from baseline in HbA1c.

Faster aspart improved 1-h PPG with no differences in 2–4-h PPG versus IAsp.

Overall hypoglycemia rates were similar except for an increase in 0–2-h postmeal hypoglycemia with faster aspart.

Diabetes Care 2017;40(7):951–957

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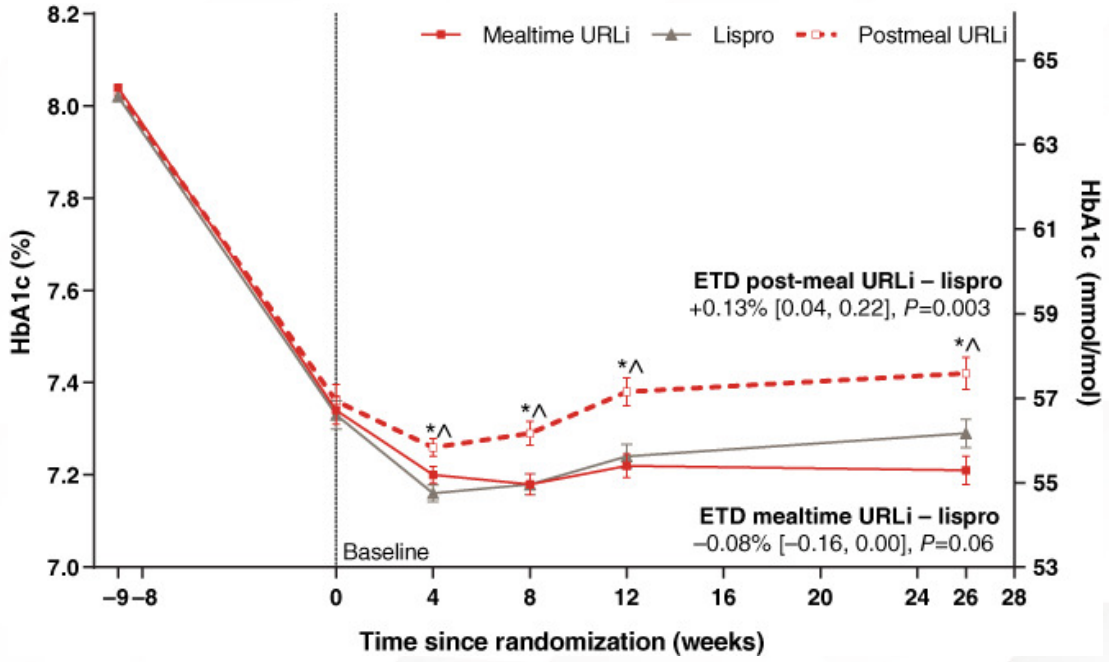
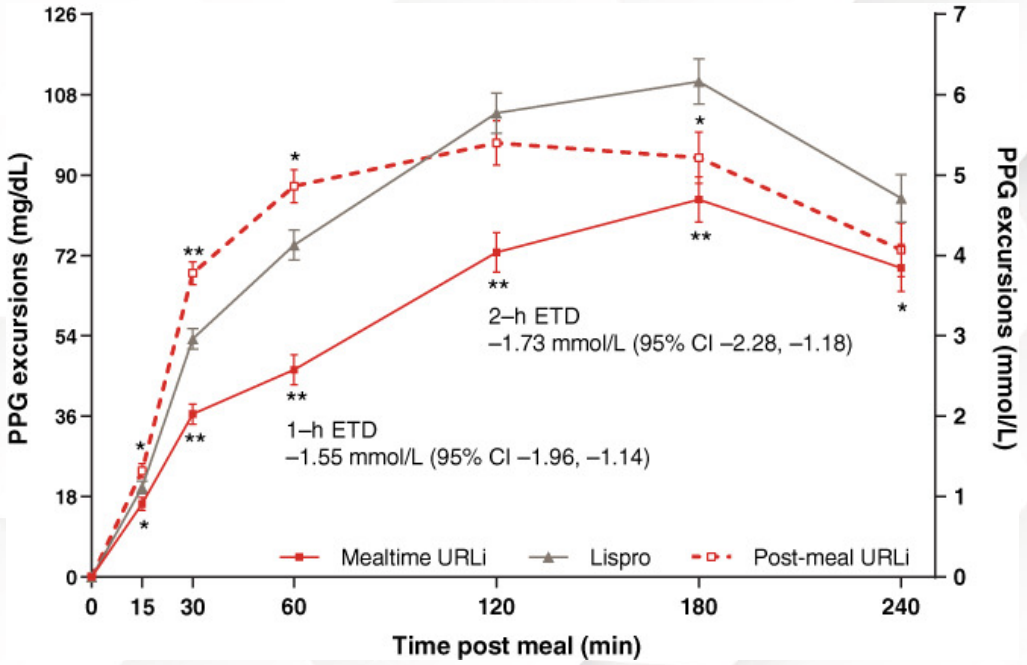
Ultra Rapid Lispro improves postprandial glucose control compared with lispro in patients with type 1 diabetes: PRONTO-T1D study





Post-meal dosing of URLi compared to pre-meal lispro resulted in non-inferiority of HbA1c.

Only pre-meal dosing of URLi improved postprandial glucose control

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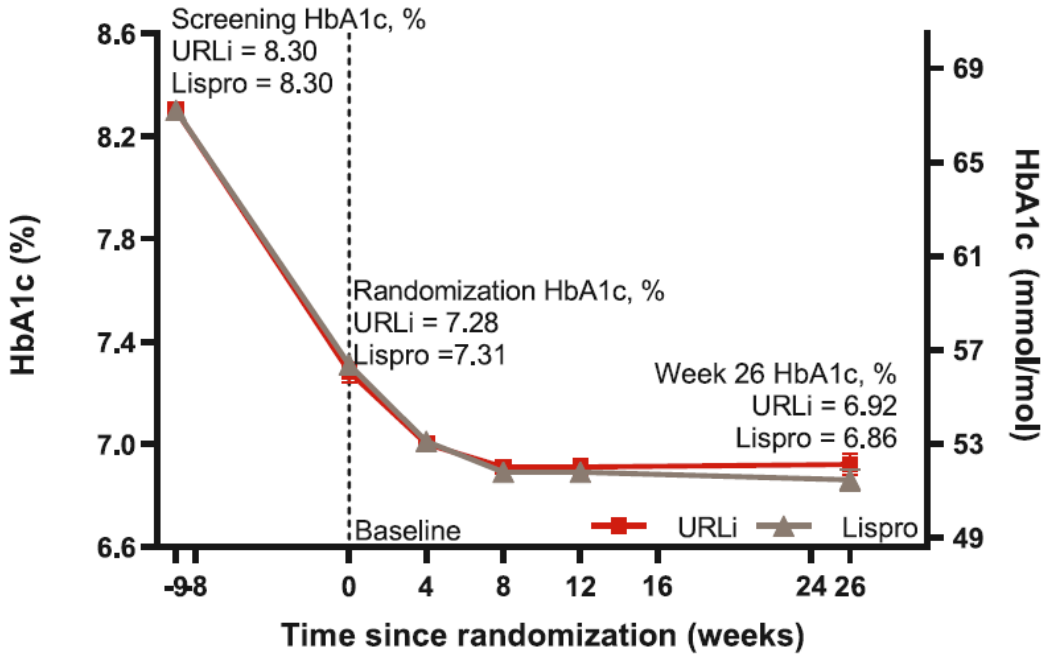
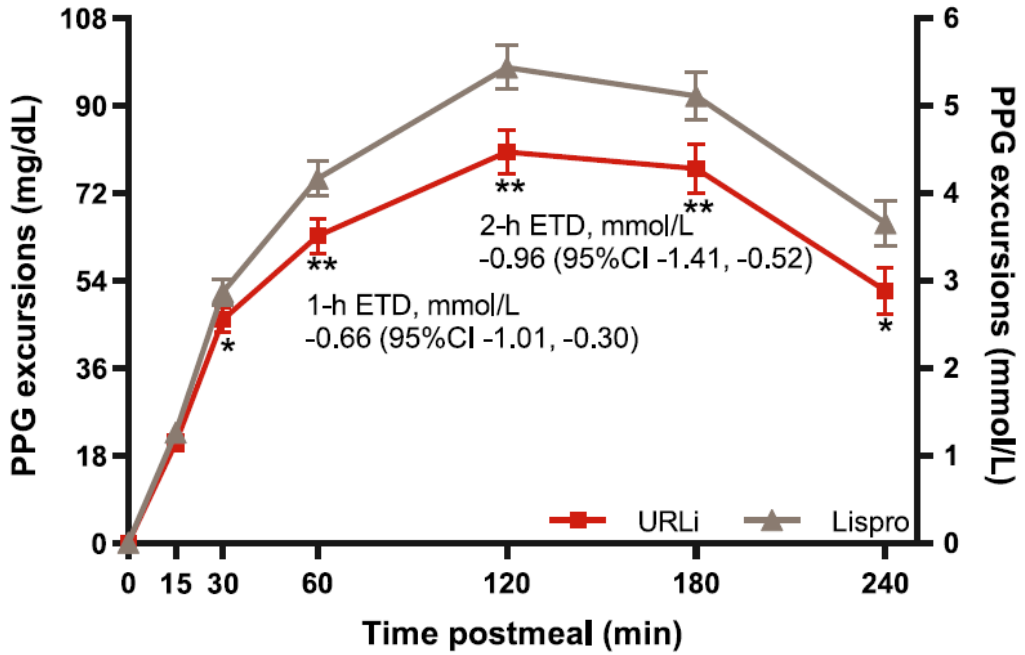
Randomized Double-Blind Clinical Trial Comparing Ultra Rapid Lispro With Lispro in a Basal-Bolus Regimen in Patients With T2D: PRONTO-T2D

Phase 3, treat-to-target, double-blind 26-week study. Basal insulin glargine or degludec in combination with prandial URLi or lispro injected 0–2 min prior to meals.





URLi compared with lispro in a basal-bolus regimen was confirmed to be noninferior for HbA1c and superior to lispro for PPG control in patients with type 2 diabetes.

Diabetes Care 2020;43:2991–2998

La loro ridotta durata d'azione non garantisce un perfetto controllo glicemico ottimale nei periodi di digiuno inter-prandiali e notturni

INSULINA	ONSET	PICCO	DURATA DELL'EFFETTO IPOGLICEMIZZANTE	EMIVITA
Ultra rapide				
Faster Aspart	4 min	60 min	3-5 h	60-70 min
URLi	2 min	40-60 min	3-5 h	44 min

Owens DR, Bolli GB. The continuing quest for better subcutaneously administered prandial insulins: a review of recent developments and potential clinical implications. DOM 22: 743-54, 2020.

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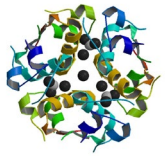
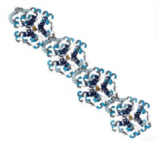
The past and present of basal insulin innovation

	NPH insulin	1st generation basal insulin analogues	Ultra long-acting basal insulin analogues
			
Half-life	**5–10 hours**	**~0.5 day**	**~1 day**
Administration	**OD/BID**	**OD/BID**	**OD**

BID, twice-daily; NPH, neutral protamine Hagedorn; OD, once-daily; OW, once-weekly.

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Insuline basali a confronto

Lower risk of hypos vs NPH
Their half-lives are not long enough to permit once-daily dosing in all patients

	Insulina NPH	Insulina glargine U-100	Insulina detemir
Onset	2-4 ore	1.3 ore	1.3 ore
Picco	4-10 ore	Picco non pronunciato	Picco non pronunciato
Durata effettiva	10-16 ore	Sino a 24 ore	Inferiore a 24 ore
Emivita	Non nota	14 ore	5-7 ore
Tempo per lo steady-state	Non noto	2 giorni	2 giorni

PorcellatiF.etal.DiabetesCare2007;30(10):247-252.
LucidiP.etal.DiabetesCare2011;34(6):1312-1314.
NiswenderK.ClinDiab2009;27:60-68.B
eckerRHetal.DiabetesCare2015;38:637-643.

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Insuline basali a confronto

	Insulina NPH	Insulina glargine U-100	Insulina detemir	Insulina glargine U-300	Insulina degludec
Onset	2-4 ore	1.3 ore	1.3 ore	6 ore	1 ora
Picco	4-10 ore	Picco non pronunciato	Picco non pronunciato	Piatto	Piatto
Durata effettiva	10-16 ore	Sino a 24 ore	Inferiore a 24 ore	≤ 36 ore	≤ 42 ore
Emivita	Non nota	14 ore	5-7 ore	~ 23 ore	~ 25 ore
Tempo per lo steady-state	Non noto	2 giorni	2 giorni	4 giorni	2-3 giorni

PorcellatiF.etal.DiabetesCare2007;30(10):247-252.

LucidiP.etal.DiabetesCare2011;34(6):1312-1314.

NiswenderK.ClinDiab2009;27:60-68.B

eckerRHetal.DiabetesCare2015;38:637-643.

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The second generation of basal insulin analogs

IDeg vs IGlar RCT: programma BEGIN

Gli studi BEGIN hanno dimostrato la non inferiorità di Degludec rispetto a Glargine U100 nella riduzione di HbA1c e una riduzione delle ipoglicemie notturne in differenti popolazioni diabetiche

Trial	Popolazione	Durata (Sett.)	Efficacia		Ipoglicemie	
			Non-inf HbA1c	FPG (mg/dl)	Totali	Notturne
ONCE LONG	Insulin naïve, **DM2**	104	SI	- 6.84	- 16%	-43%
BB	Prec. trattamento con insulina, **DM2**	52	SI	- 5.22	-18%	-25%
FLES	Insulin naïve e insulino-trattati, **DM2**	26	SI	- 7.56	+3%	-23%
LOW VOLUME	Insulin naïve, **DM2**	26	SI	- 7.56	-14%	-36%
ONCE ASIA	Insulin naïve, **DM2**	26	SI	- 1.62	-18%	-38%
T1 BB LONG	**DM1**	104	SI	- 5.22	+2%	-25%
T1 FLEX	**DM1**	52	SI	- 19.26	+9%	-25%

Gla-300 vs Gla-100: programma EDITION

T2DM

EDITION 1
N=807

BB
Insulina basale più insulina prandiale in bolo (analogo ad azione rapida)

EDITION 2
N=811

BOT
Insulina basale più OAD (escl. SU)

EDITION 3
N=878

BOT
Insulina basale più OAD (escl. SU) e/o agonisti del recettore GLP-1

EDITION JP 2
N=241

BOT
Insulina basale più OAD

T1DM

EDITION 4
N=549

BB
Insulina basale più insulina prandiale in bolo (analogo ad azione rapida)

EDITION JP 1
N=243

BB
Insulina basale più insulina prandiale in bolo (analogo ad azione rapida)

Tutti fase 3, ≥18 anni

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Gla-300 vs Gla-100: programma EDITION

Non inferiorità di Gla-300 rispetto a Glargine U100 nella riduzione di HbA1c e una riduzione delle ipoglicemie notturne in differenti popolazioni diabetiche

Trial	Popolazione	Durata	Variazioni rispetto al baseline (Gla-300 vs Gla-100)		Incidenza di eventi di ipoglicemia confermata (≤ 70 mg/dL) e/o grave	
			HbA1c (%)	FPG (mg/dl)	Nelle 24 ore	Notturne
EDITION 1	**DM2**, 807 pz. in insulina basal-bolus +/- met.	6 mesi	- 0.83 vs - 0.83 **(non inferiorità)**	- 26.7 vs - 30.4	74.8 % vs 77.6% (RR 0.96)	**36.1 % vs 45.8%** (RR 0.79, p = 0.0045)
EDITION 2	**DM2**, 811 pz. in insulina basale + IGO	6 mesi + 6 mesi di osservazione	- 0.57 vs - 0.56 **(non inferiorità)**	- 20.5 vs - 19.2	59.3 % vs 65.0% (RR 0.91)	**21.6 % vs 27.9%** (RR 0.77, p=0.038)
EDITION 3	**DM2**, 878 pz. insulina naïve in IGO	6 mesi + 6 mesi di osservazione	- 1.42 vs - 1.46 **(non inferiorità)**	- 61.4 vs - 68.4	39.8 % vs 46.3% (RR 0.86)	15.4 % vs 17.1% (RR 0.90, p=0.45)
EDITION 4	**DM1**, 549 pz. in insulina basal-bolus	6 mesi + 6 mesi di osservazione	- 0.42 vs - 0.44 **(non inferiorità)**	- 7.6 vs - 26.1	59.1 % vs 55.6% (RR 1.06)	82.1 % vs 84.0% (RR 0.98)

Glycemic control matters

GLYCAEMIC CONTROL MATTERS

BASAL INTENSIFICATION IS OFTEN DELAYED

BARRIERS TO BASAL INTENSIFICATION

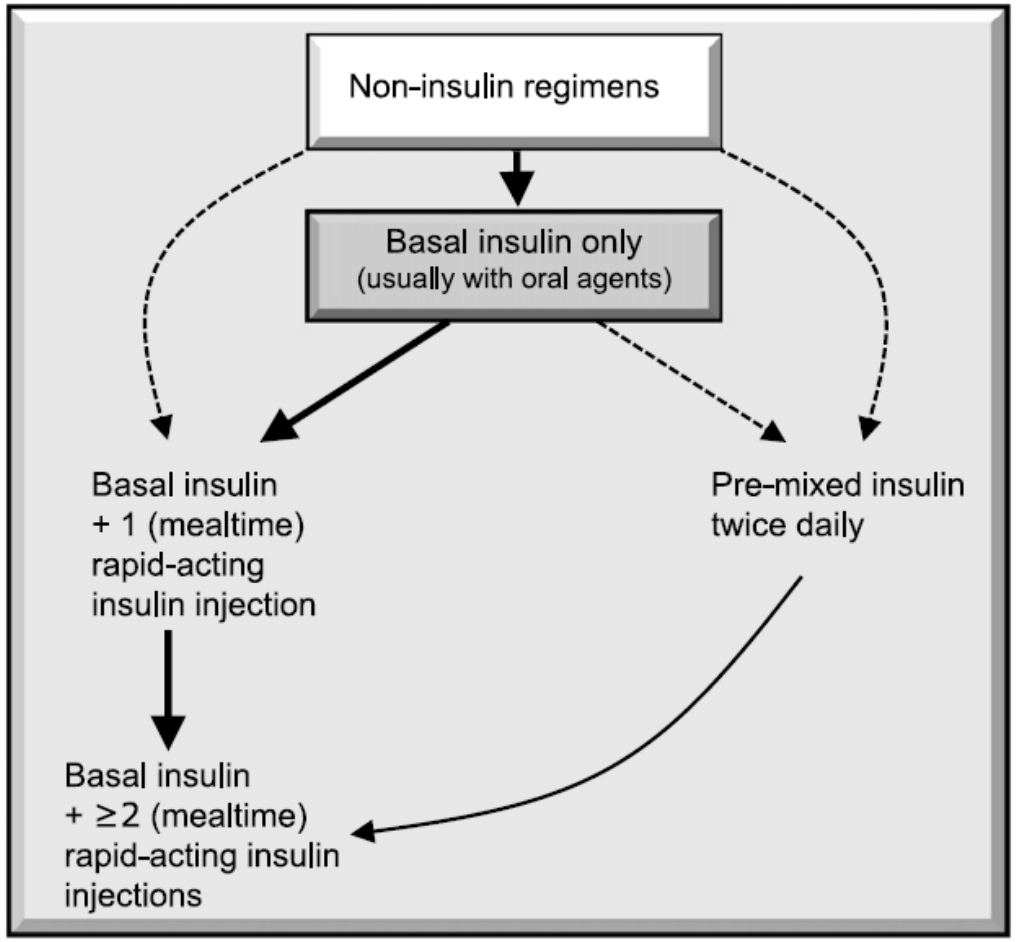
There are understandable concerns when considering basal insulin treatment/intensification

- Lack of patient adherence[6]
- Weight gain[5]
- Hypoglycaemia[5]
- Complex regimens[5]

HCP, healthcare professional

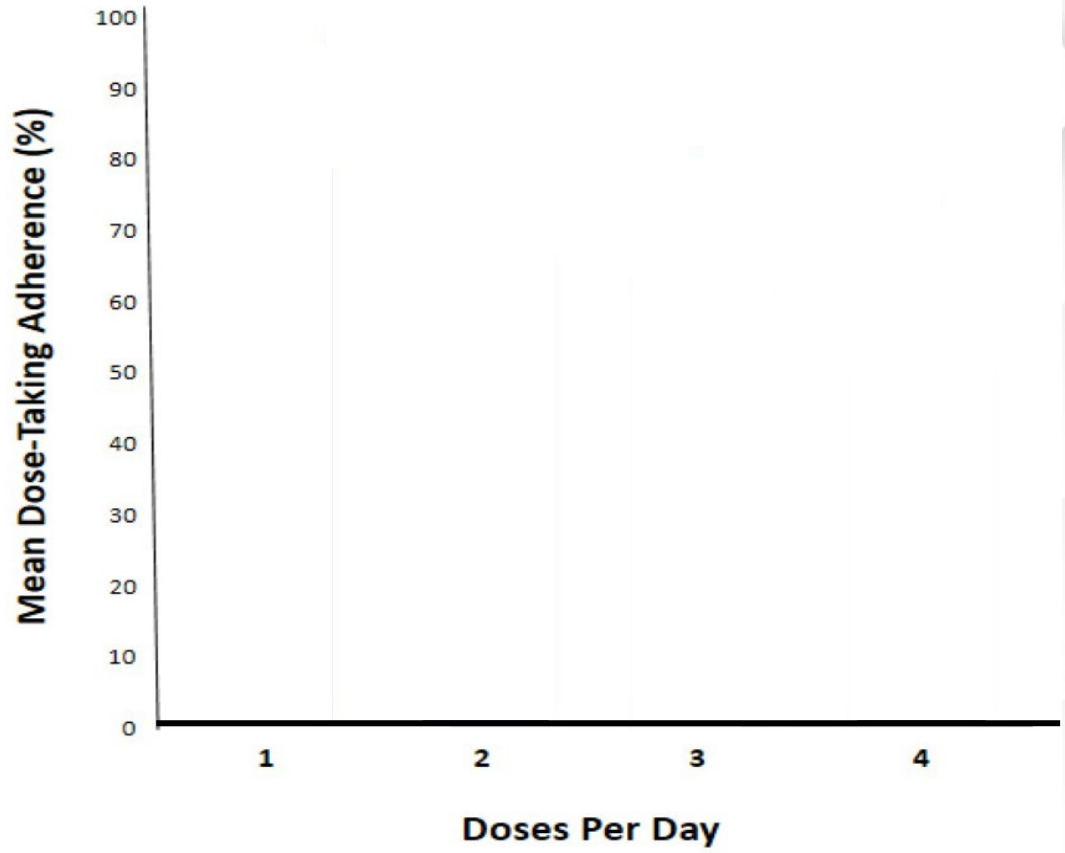
1. Stratton *et al. BMJ* 2000;321:405–12. 2. Shetty *et al. J Manag Care Pharm* 2005;11:559–64; 3. Curtis & Lage. *J Med Econ* 2014;17:21–31;
4. Blak *et al. Diabet Med* 2012;29:e13–20; 5. Kunt & Snoek. *Int J Clin Pract* 2009;63(Suppl. 164):6–10; 6. Vijan *et al. J Gen Intern Med* 2005;20:479–82;
7. Cuddihy *et al. Diabetes Educ* 2011;37:111–23

Regimen Complexity



Number of injections

Regimen complexity



Reduced dosing frequency may improve adherence to insulin treatment and enhance convenience

New strategies are required to overcome these barriers

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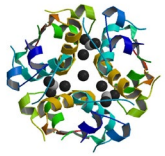
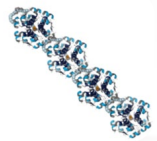
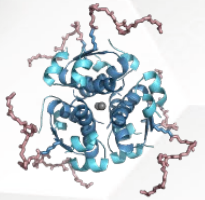
The past and present of basal insulin innovation

	NPH insulin	1st generation basal insulin analogues	Ultra long-acting basal insulin analogues	Once-weekly
				
Half-life	**5–10 hours**	**~0.5 day**	**~1 day**	**~1 week**
Administration	**OD/BID**	**OD/BID**	**OD**	**OW**

BID, twice-daily; NPH, neutral protamine Hagedorn; OD, once-daily; OW, once-weekly.

The future basal insulins under development

Table 1
Once-weekly insulins in development (past or current).

Molecule	Company	Phase of development	Diabetes type	Structural features to enhance activity and prolong half-life
AKS-433	Akston Biosciences	Preclinical	T1D and T2D	**Fc-fusion protein** (https://www.akstonbio.com/) • Modified human Fc region paired with an insulin analog
Single-chain insulin Fc-fusion variants	AstraZeneca	Preclinical	Not reported	**Fc-fusion proteins** [63] • Panel of recombinant, native, single-chain insulin molecules, with linker variants fused to an Fc region
AB101	Antria/Rezolute	Phase 1 Not in active development [64]	T1D and T2D	**PEGylation and microsphere delivery** [89,90] • 5 kDa PEGylated human recombinant insulin encapsulated in PLGA microspheres extending the time-of-action by depot release
HM12460A (LAPS insulin) and HM12470 (LAPS-insulin-115)	Hanmi Pharmaceutical Co., Ltd.	Phase 1	T1D and T2D	**Fc-fusion proteins** [58–60,91] • HM12470: insulin-115 analog conjugated with a nonglycosylated human IgG4 Fc via a flexible 3.4 kDa nonpeptidyl linker • HM12460A: insulin conjugated with human Fc via a nonpeptidyl linker to minimize loss of intrinsic activity and extends the time-of-action profile by depot release [90] – Analog insulin-115 has a lower affinity for the human insulin receptor than the insulin in HM12460A and is more stable in serum. These properties likely underpin the longer PK and PD profiles of HM12470 than of HM12460A [59]
Insumera, PE0139	PhaseBio	Phase 2a [92] Completed in November 2016	T2D	**ELPylation** [52–54,92] • Monomeric human insulin fused with an ELP – a recombinant PEG mimetic strategy

The future insulins under development

- Ingestible injecting device
- Glucose–responsive insulins

- Ultralong–acting insulin
  Basal insulin Fc
- Hepatopreferential insulin
  Hepatic directed vesicle insulin lispro

- Ultrarapid analog
  Faster aspart
  Ultrarapid lispro

Preclinical | Phase 1 | Phase 2 | Phase 3 | Marketed

- Ultralong–acting insulin
  LAPS Insulin (HM12470)

- Ultrarapid–acting insulin
  BioChaperone insulin lispro
- Ultralong–acting insulin
  Insulin icodec
- Oral insulin
  Insulin tregopil
  ORMD–0801

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Characteristics of once-weekly vs. once-daily insulin therapy

Improved treatment acceptance and adherence

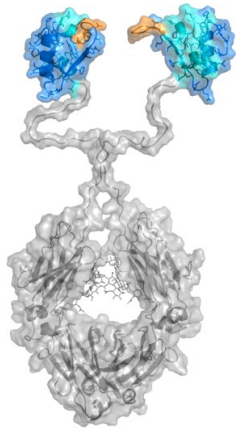
CLINICAL

Improved (or similar) glycaemic control with low hypoglycaemia risk

Reduced treatment burden

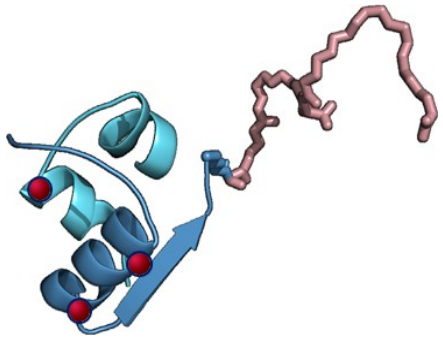
Easier to overcome clinical inertia

Various approaches have been investigated to slow the absorption of insulin analogs, to prolong their activity (half-life)



Basal Insulin Fc (BIF)

Linking insulin to the fragment Fc region of immunoglobulin G extends the insulin's half-life



Insulin Icodec

Attaching icosanedioic acid to the B chain enhances reversible binding to albumin

MOLECULAR

Longer half-life

More stable PK/PD

Slower clearance rate

PD, pharmacodynamics; PK, pharmacokinetics.
Nishimura E et al. 2020 ADA Scientific Sessions 236–OR.

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Insulin icodec and Basal Insulin Fc

Currently explored technologic approaches to increase half-life of basal insulin

Insulin icodec [1]

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

Basal Insulin Fc [2]

Novel single-chain variant of insulin fused to human IgG Fc domain

Homo-dimer

Reduced insulin receptor potency with full agonism

Time-action profile (t½ = approx. 17 days) supports once-weekly dosing in humans[3]

Currently in Phase 2 Trials

1. 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; 2. Heise T et al. Basal Insulin Fc (BIF), A Novel Insulin Suited For Once Weekly Dosing For The Treatment of Patients With Diabetes Mellitus, Journal of the Endocrine Society, Volume 5, Issue Supplement_1, April-May 2021, Page A329, https://doi.org/10.1210/jendso/bvab048.672.

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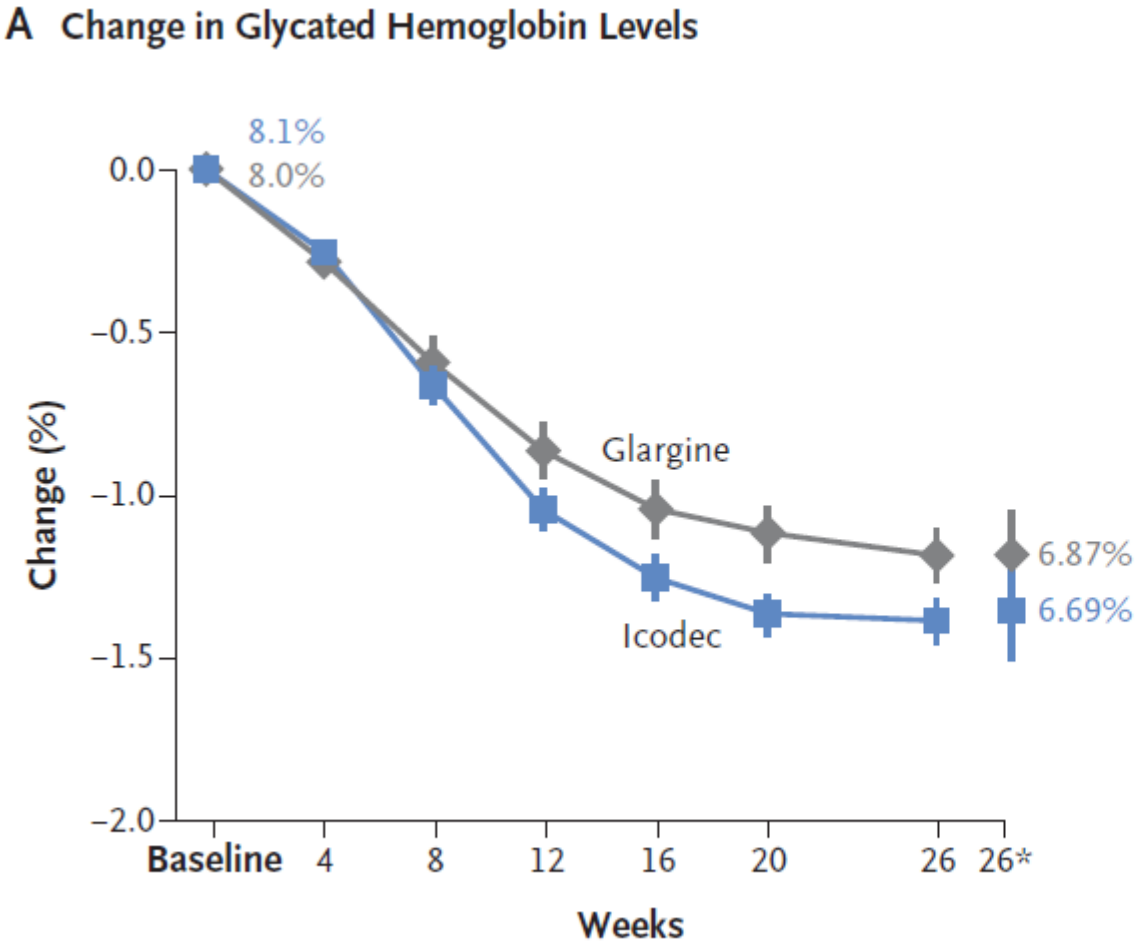
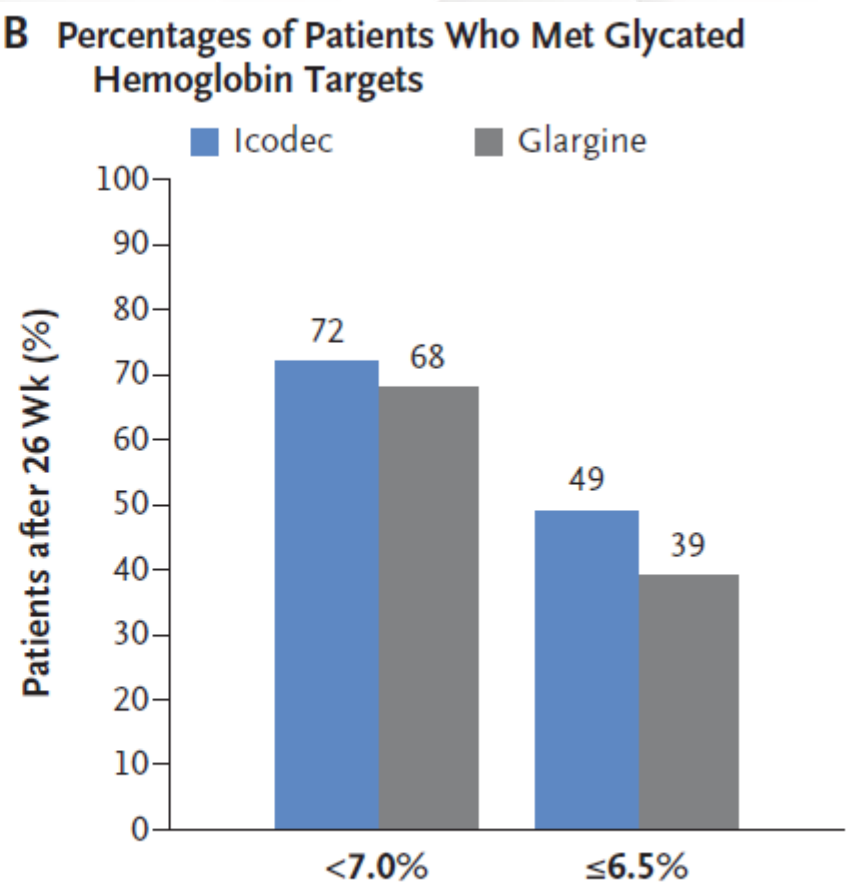
ORIGINAL ARTICLE

Once-Weekly Insulin for Type 2 Diabetes without Previous Insulin Treatment

Phase 2 clinical trial (Julio Rosenstock et al. Nejm. 2020)





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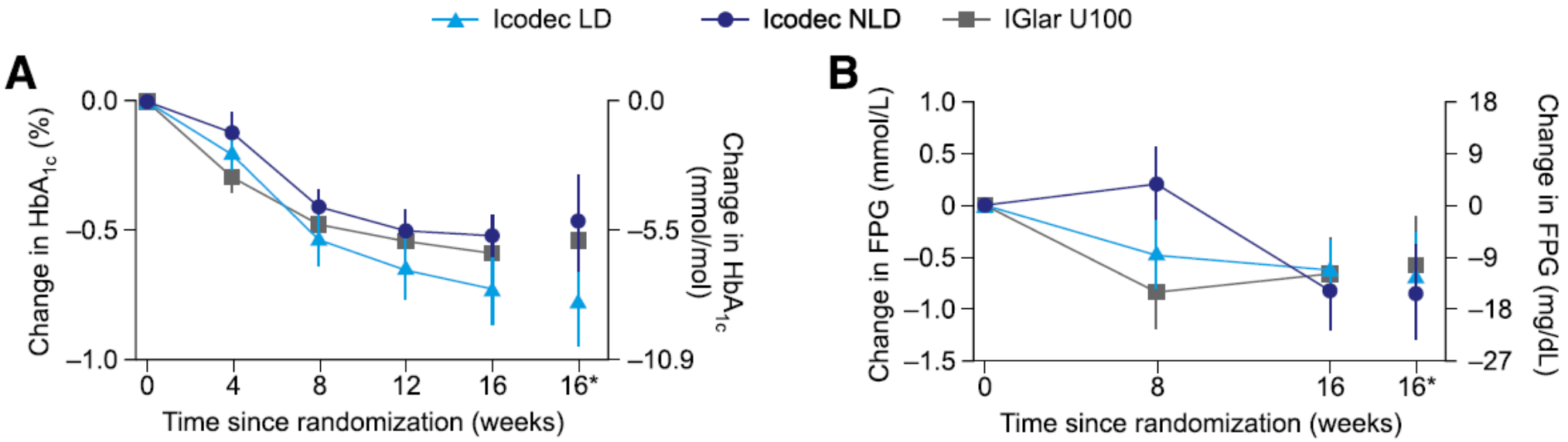
Switching to Once-Weekly Insulin Icodec Versus Once-Daily Insulin Glargine U100 in Type 2 Diabetes Inadequately Controlled on Daily Basal Insulin: A Phase 2 Randomized Controlled Trial



Icodec showed comparable glycaemic control,
with a low risk of clinically relevant hypoglycaemia that is comparable to once-daily basal insulin

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Insulin icodec and Basal Insulin Fc

Currently explored technologic approaches to increase half-life of basal insulin

Insulin icodec [1]

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Once Weekly Basal Insulin Fc (BIF) is Safe and Efficacious in Patients with Type 2 Diabetes Mellitus (T2DM) Previously Treated With Basal Insulin

Characteristic	Degludec (N=132)	BIF-A1 (N=135)	BIF-A2 (N=132)	Total (N=399)
Age, years	60.8 (10)	60.2 (9.9)	59.6 (11.3)	60.2 (10.4)
Women/Men, %	49.2/50.8	49.6/50.4	53/47	50.6/49.4
Race, n (%)				
American Indian or Alaska Native	19 (14.4)	16 (11.9)	18 (13.7)	53 (13.3)
Asian	6 (4.5)	4 (3)	5 (3.8)	15 (3.8)
Black or African American	10 (7.6)	16 (11.9)	10 (7.6)	36 (9)
White	94 (71.2)	97 (71.9)	97 (74)	288 (72.4)
Hispanic or Latino, n (%)	73 (55.3)	67 (49.6)	78 (59.1)	218 (54.6)
BMI, kg/m^2	31.8 (5.7)	32.5 (5.9)	32.4 (5.8)	32.2 (5.8)
Duration of T2D, years	15.1 (8)	15 (8.5)	14.1 (9.1)	14.7 (8.5)
Sulfonylureas, n (%)	36 (27.3)	43 (31.9)	37 (28)	116 (29.1)
HbA1c, (mmol/mol)	65.41 (9.62)	66.09 (9.51)	64.21 (9.78)	65.24 (9.64)

Mean (SD) for continuous variables

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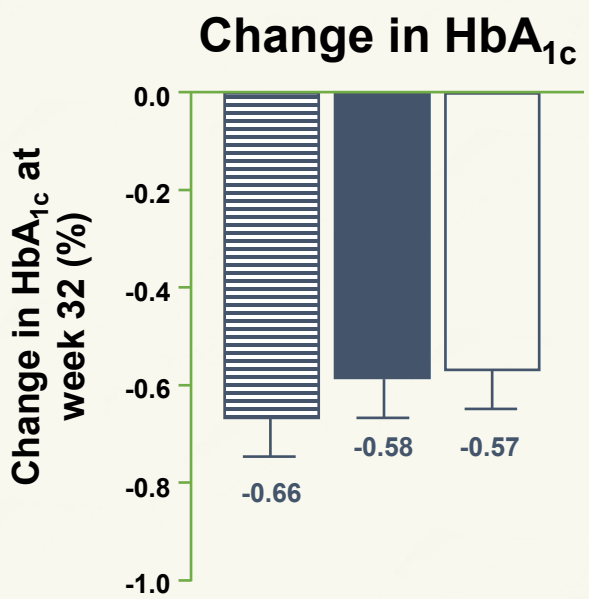
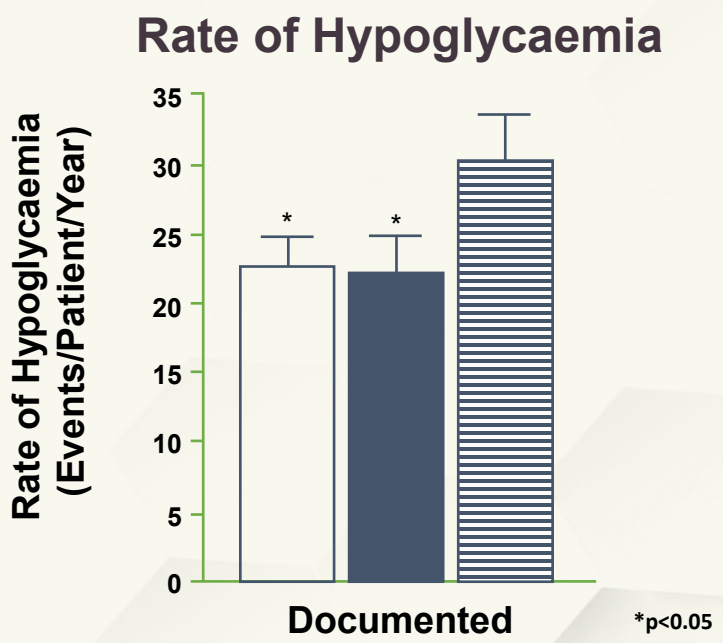
Once Weekly Basal Insulin Fc (BIF) is Safe and Efficacious in Patients with Type 2 Diabetes Mellitus (T2DM) Previously Treated With Basal Insulin





Degludec (FG target: ≤5.6 mmol/L [100 mg/dL])
BIF-A1 (FG target: ≤7.8 mmol/L [140 mg/dL])
BIF-A2 (FG target: ≤6.7 mmol/L [120 mg/dL])

- Similar glycaemic control to degludec in previously insulin-treated patients with T2D
- Lower rates of documented hypoglycaemia
- Similar overall safety profile

Further Phase 2 studies are currently exploring the efficacy and safety of BIF Independently of titration protocol

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Oral delivery of diabetes treatments: Rationale & challenges

Benefits

Improved patient compliance & treatment options[1]

Early commencement of treatment for better patient outcomes[2]

Physiological delivery of insulin: delivery of insulin to liver[3]

Basal, liver-preferentiality expected to provide a weight benefit vs. s.c. basal insulin[4]

s.c., subcutaneous

1. Peyrot et al. Insulin adherence behaviours and barriers in the multinational Global Attitudes of Patients and Physicians in Insulin Therapy study Diabet Med. 2012;29:682–9; 2. Herman et al. Early Detection and Treatment of Type 2 Diabetes Reduce Cardiovascular Morbidity and Mortality: A Simulation of the Results of the Anglo-Danish-Dutch Study of Intensive Treatment in People With Screen-Detected Diabetes in Primary Care (ADDITION-Europe) Diabetes Care 2015;38:1449–55; 3. Halberg et al. Efficacy and safety of oral basal insulin versus subcutaneous insulin glargine in type 2 diabetes: a randomised, double-blind, phase 2 trial Lancet Diabetes Endocrinol 2019;7;179–88; 4. Hubálek F et al. Molecular engineering of safe and efficacious oral basal insulin Nat. Commun. 2020, 11;3746

Oral insulins under clinical development

ORMD-0801[1]

Novel oral human insulin formulation with an absorption enhancer

Phase 2b dose ranging study, in patients with T2D:

- At week 12, 8 mg of ORMD-0801 was associated with **1.29% mean reduction** from baseline HbA_{1C}
- **0.81% mean reduction** when adjusted for placebo (p=0.028)

Buccal insulin spray[4,5]

Short acting insulin sprayed into the mouth; insulin does not enter lungs (**Ecuador, India, Canada**)

Glucose-lowering activity at **5 minutes**, peaks at **30 mins, and stops working at 2 hours**

Investigational New Drug approval in US (2009) for those with “serious or life threatening” T1D or T2D who have no alternative treatments or who cannot participate in the phase 3 trial

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Basal, liver-preferentiality expected to provide a weight benefit vs. s.c. basal insulin[4]

Challenges

Permeability

Enzymatic stability

Food effect

s.c., subcutaneous

1. Peyrot et al. Insulin adherence behaviours and barriers in the multinational Global Attitudes of Patients and Physicians in Insulin Therapy study Diabet Med. 2012;29:682–9; 2. Herman et al. Early Detection and Treatment of Type 2 Diabetes Reduce Cardiovascular Morbidity and Mortality: A Simulation of the Results of the Anglo-Danish-Dutch Study of Intensive Treatment in People With Screen-Detected Diabetes in Primary Care (ADDITION-Europe) Diabetes Care 2015;38:1449–55; 3. Halberg et al. Efficacy and safety of oral basal insulin versus subcutaneous insulin glargine in type 2 diabetes: a randomised, double-blind, phase 2 trial Lancet Diabetes Endocrinol 2019;7;179–88; 4. Hubálek F et al. Molecular engineering of safe and efficacious oral basal insulin Nat. Commun. 2020, 11;3746

(Nano)Tecnologia

Negli ultimi anni, la progettazione e lo sviluppo di nuovi farmaci, materiali impiantabili ed iniettabili, ma anche di dispositivi medici in scala nanometrica, hanno prodotto una rivoluzione nel settore del drug delivery

- **Migliorare le proprietà chimico-fisiche del farmaco da veicolare**
- **Migliorare il rilascio del farmaco nel sito bersaglio**
- **Ridurre gli effetti collaterali del farmaco veicolato**
- **Ridurre la frequenza di somministrazione**
- **Migliorare la compliance del paziente**

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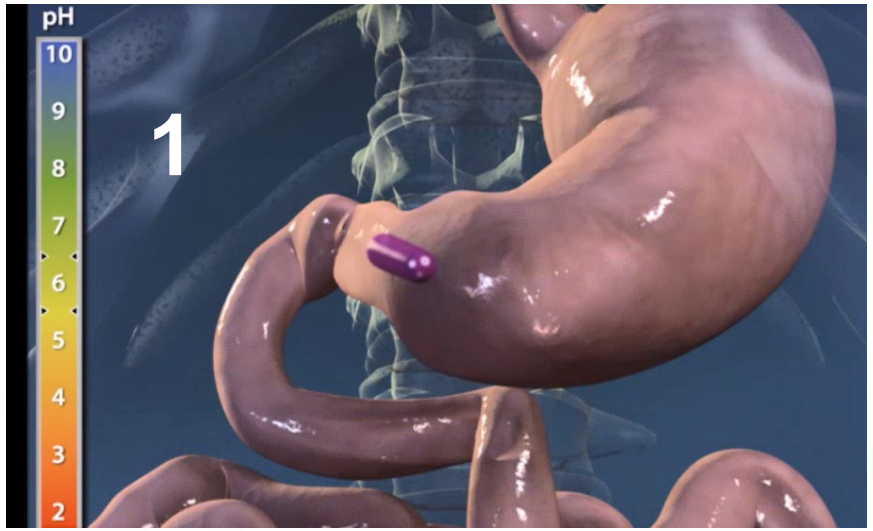
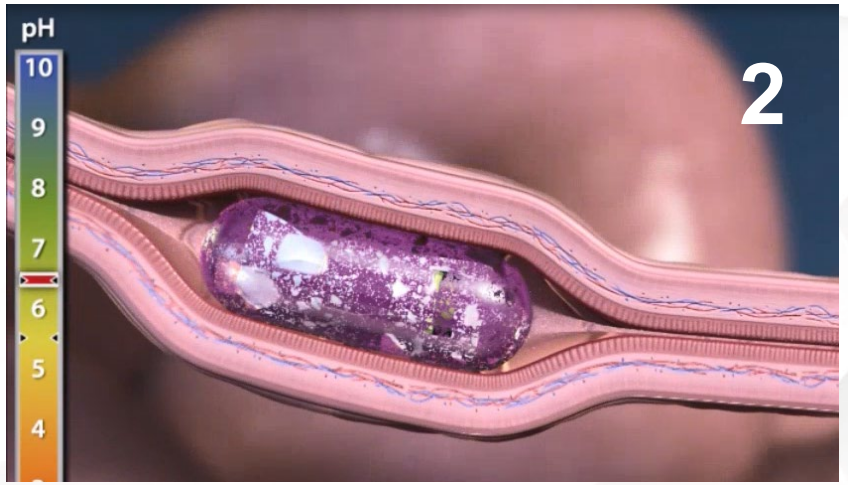
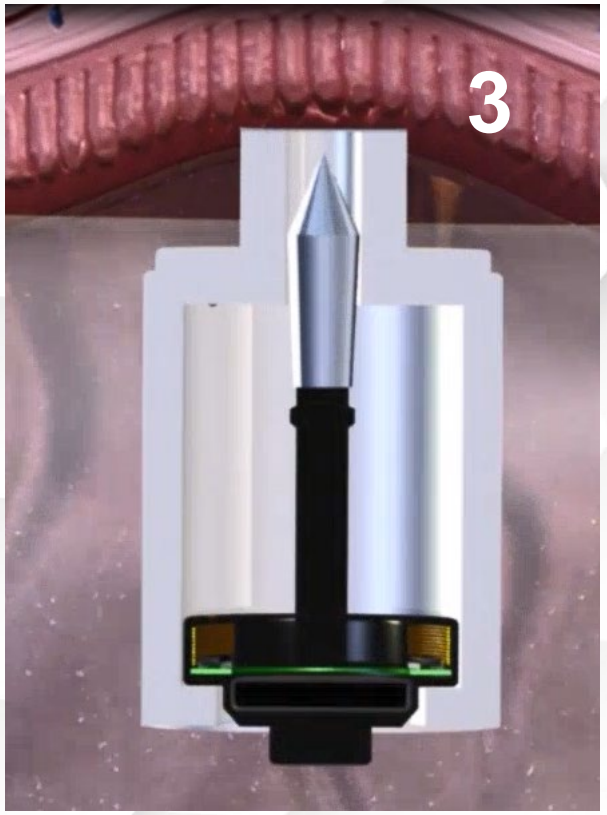
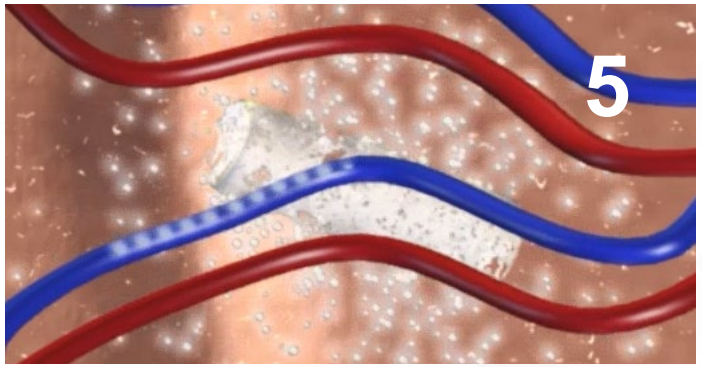
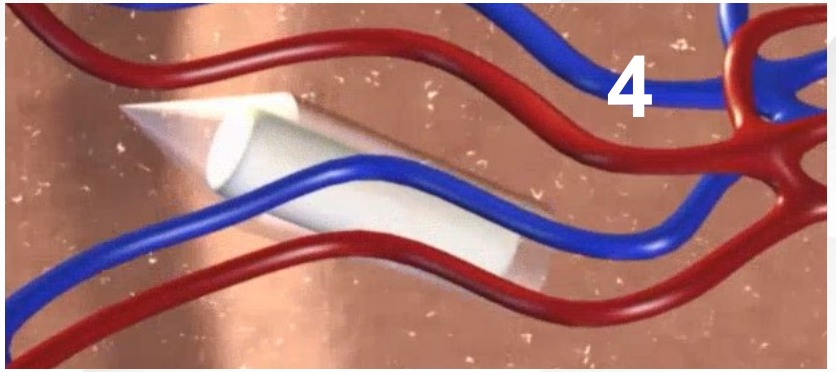
Engineered capsule devices for oral delivery into the gastrointestinal tract











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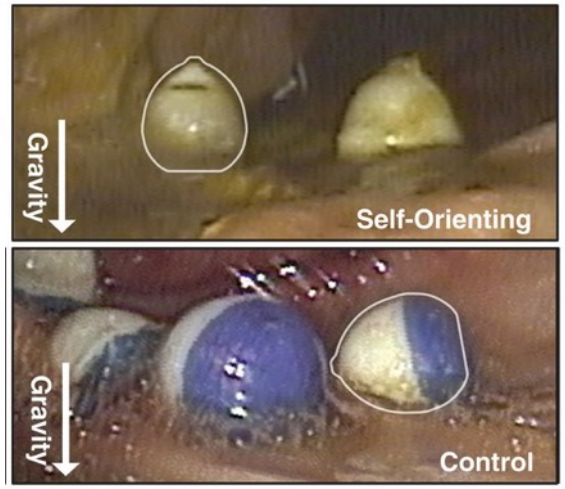
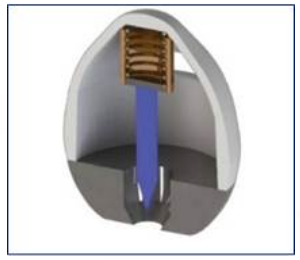
Oral injection devices for delivery of insulin and other biomacromolecules

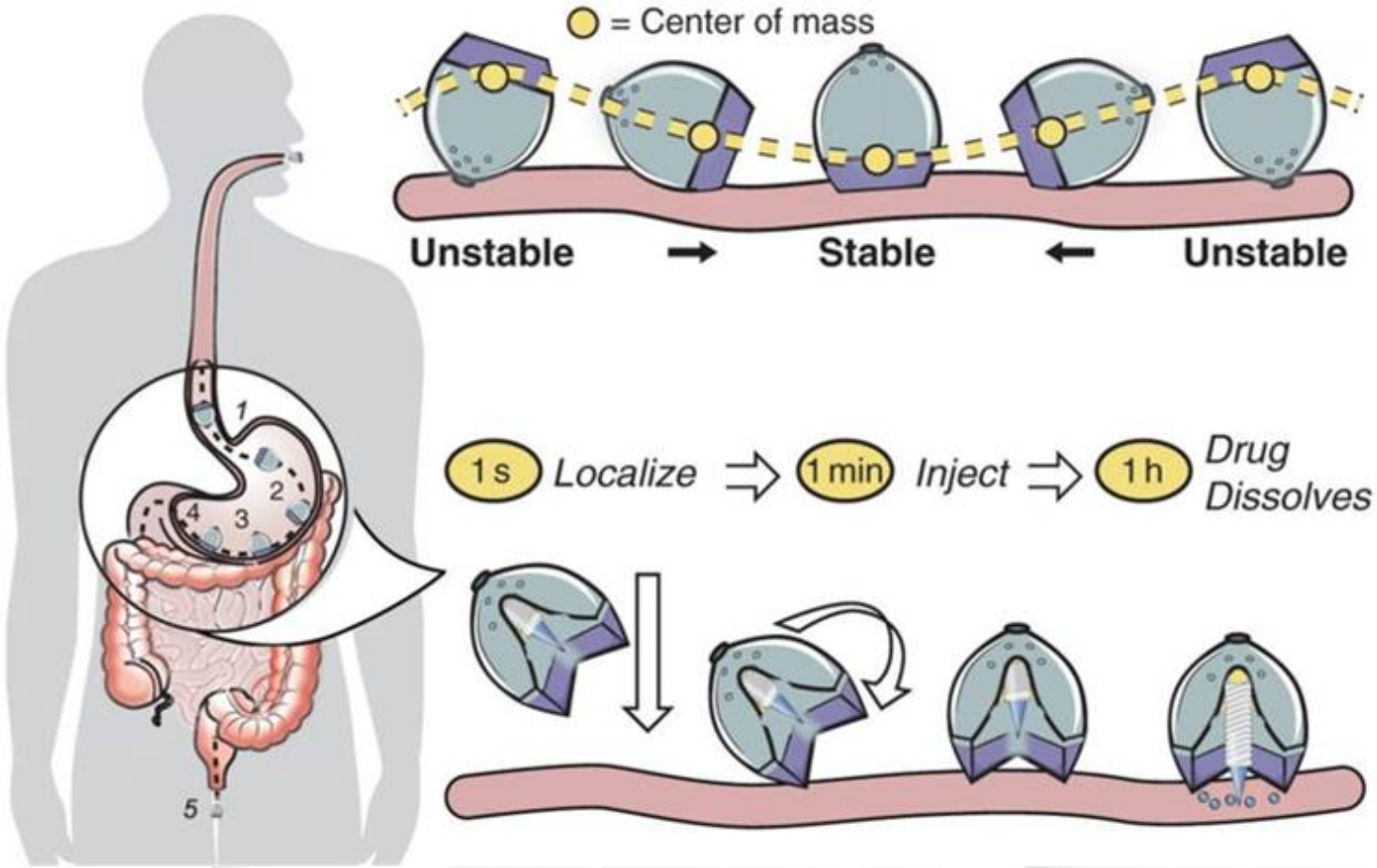


SOMA self-orients quickly from any position and remains stable once oriented[1]



Self-orienting millimetre-scale applicator

Leopard tortoise
(*S. pardalis*)



mAb, monoclonal antibody., GI, gastrointestinal; SOMA, self-orienting millimeter-scale applicator 1. Abramson et al. An ingestible self-orienting system for oral delivery of macromolecules Science. 2019;363(6427):611–5; 2. Hashim et al. Jejunal wall delivery of insulin via an ingestible capsule in anesthetized swine-A pharmacokinetic and pharmacodynamic study Pharmacol Res Perspect. 2019;7(5):e00522

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Glucose-sensitive insulin: A 'smart' insulin to normalise glucose and eliminate hypoglycaemia

Low glucose (< 5mM)
Insulin in inactive conformation
Cannot bind to/activate insulin receptor

High glucose (5–20 mM)
Insulin in active conformation
Binds to/activates insulin receptor

Jarosinski MA et al. 'Smart' insulin-delivery technologies and intrinsic glucose-responsive insulin analogues, Diabetologia. 2021;10.1007/s00125-021-05422-6.

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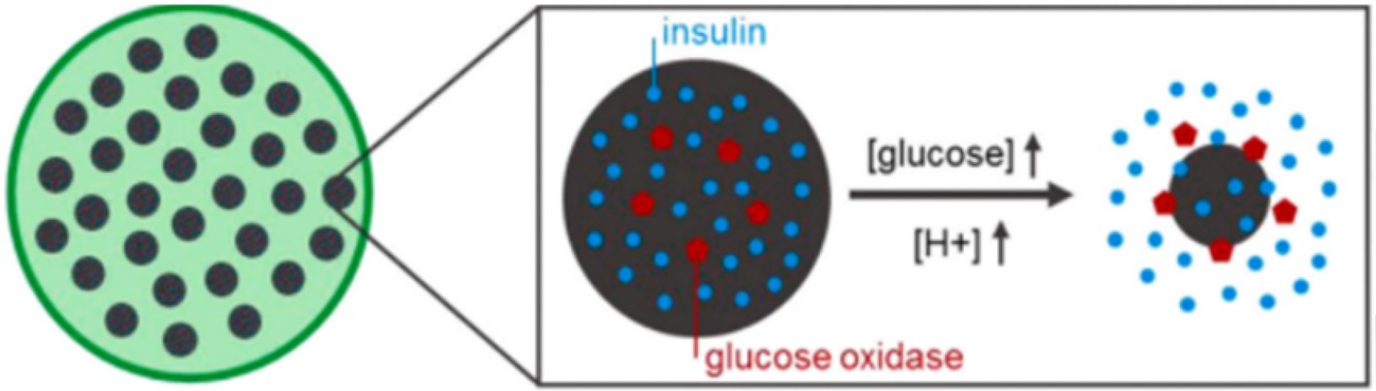
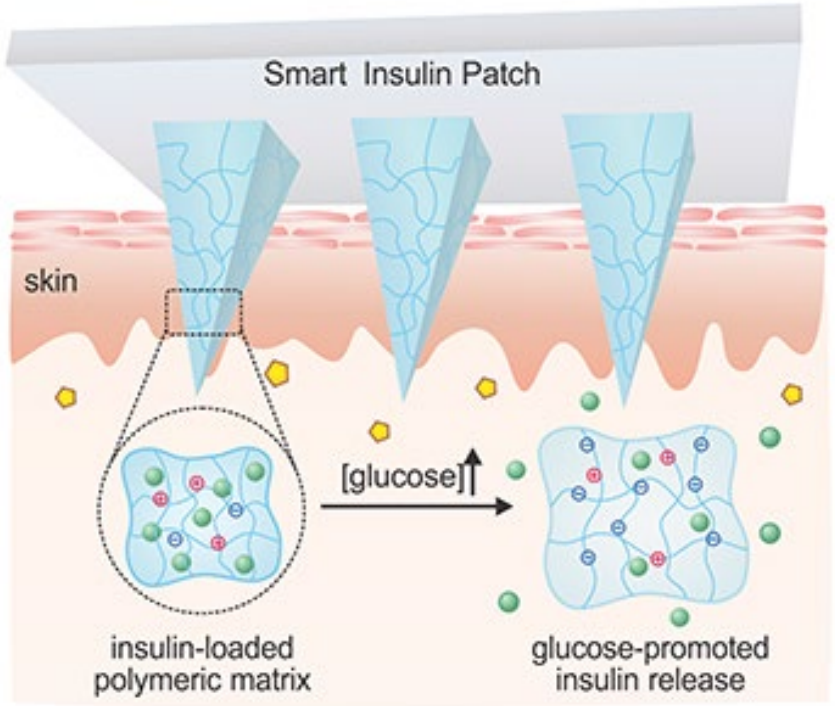
Devices for delivery of insulin and other biomacromolecules

Glucose-responsive insulin release from Ac-dextran nanoparticles encapsulated in alginate microgels



smart insulin-delivery patch



Rege NK, Phillips NFB, Weiss MA. Development of glucose-responsive "smart" insulin systems. Curr Opin Endocrinol Diabetes Obes 24: 267-78, 2017

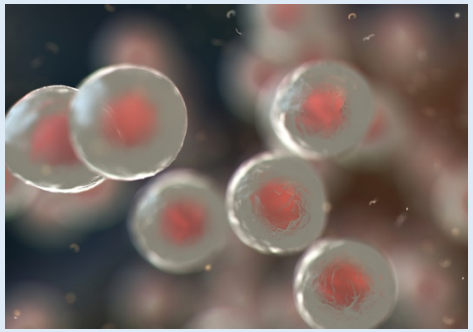
Stem cell therapy: Generating functional insulin-producing beta cells

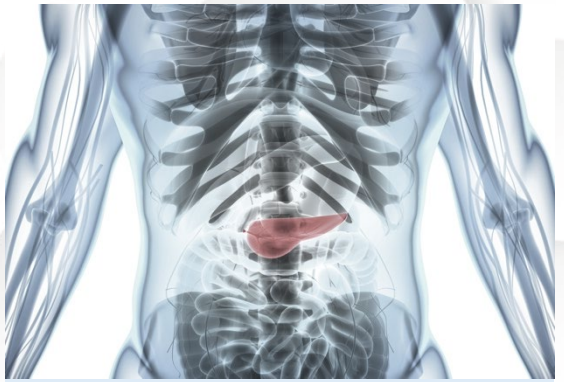
Differentiation and hESC-line[1]

QC & manufacturing

Device development

Stem cell-derived beta cells encapsulated in a hydrogel transplantation device[2]





Transplantation

DE, definitive endoderm; EP, endoderm of pancreas; hESC, human embryonic stem cell; PE, posterior foregut endoderm; QC, quality control. 1. Madsen and Serup, Towards cell therapy for diabetes, Nat Biotech 2006;24,1481–1483; 2. Duo An et al. Designing a retrievable and scalable cell encapsulation device for potential treatment of type 1 diabetes PNAS 2018;115:2:E263-E272

La terapia insulinica ha negli ultimi tempi visto degli incredibili progressi grazie allo sviluppo di molecole efficaci, sicure e semplici da maneggiare

La ricerca di base e le (nano)tecnologie rappresentano l'anima della "**(Nano)Medicina di Precisione**", sempre più di orientata a migliorare la qualità di vita e la compliance del paziente rendendo più semplice e agile il trattamento della patologia diabetica

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SID Società Italiana di Diabetologia

AMD 1974 Associazione Medici Diabetologi

T-HOTEL LAMEZIA TERME
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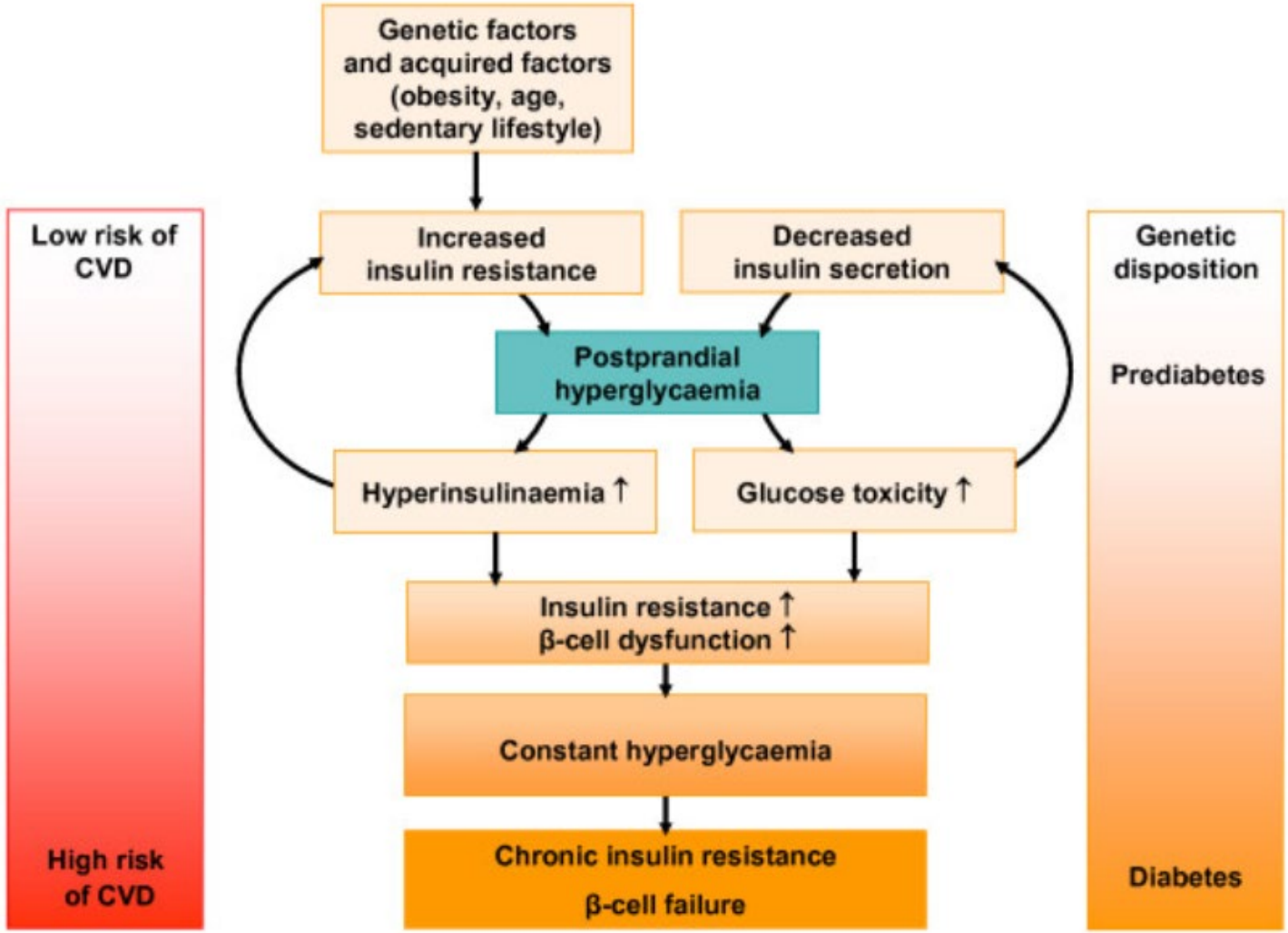
GRAZIE!!!!

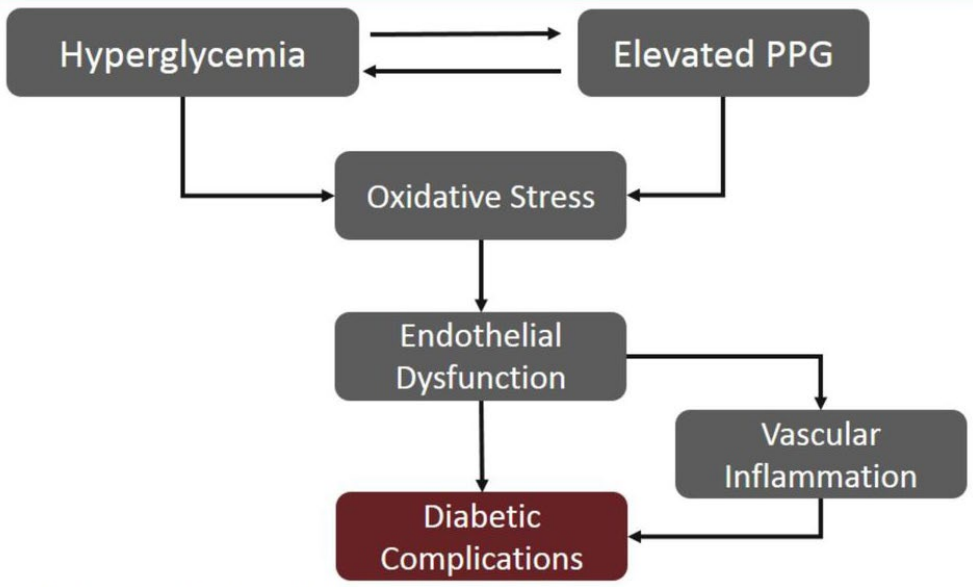
The role of postprandial hyperglycaemia in the development of type 2 diabetes

Uncontrolled PPG is linked to i thrombosis, endothelial dysfu oxidative stress generation, all contribute to the pathc cardiovascular disease



Adapted from Cavalot F et al. JCEM 2006; 91, 813-819

PPBG elevation independently predicts CV risk in T2DM



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

Model	Hazard ratio for 3rd tertile versus 1st and 2nd (95% CI)	
	Men	Women
Fasting plasma glucose	0.73 (0.35-1.54)	2.34 (0.66-8.20)
Postmeal glucose (2 hours after lunch)	2.12 (1.04-4.32)	5.54 (1.45-21.20)*
HbA_{1c}	1.11 (0.55-2.21)	1.35 (0.43-4.26)

CI = confidence interval
HbA1c = glycated haemoglobin

*P<0.01 for comparison between women and men (post lunch values)

The present study supports the conclusion that PPBG should be carefully considered in type 2 diabetic patients, because it plays a relevant predictive role for cardiovascular events.

Adapted from Cavalot F et al. JCEM 2006; 91, 813-819

The continuing quest for better subcutaneously administered prandial insulins: a review of recent developments and potential clinical implications

David R. Owens MD[1] | Geremia B. Bolli MD[2]

REVIEW ARTICLE

Abstract

The class of rapid-acting insulin analogues were introduced more than 20 years ago to control postprandial plasma glucose (PPG) excursions better than unmodified regular human insulin. Insulins, lispro, aspart and glulisine all achieved an earlier onset of action, greater peak effect and shorter duration of action resulting in lower PPG levels and a reduced risk of late postprandial hypoglycaemia. However, the subcutaneous absorption rate of these analogues still fails to match the physiological profile of insulin in the systemic circulation following a meal. Recent reformulations of aspart and lispro have generated a second generation of more rapid-acting insulin analogue candidates, including fast-acting aspart (faster aspart), ultra-rapid lispro and BioChaperone Lispro. These modifications have the potential to mimic physiological prandial insulin secretion better with an even earlier onset of action with improved PPG control, shorter duration of effect and reduced risk of hypoglycaemia.

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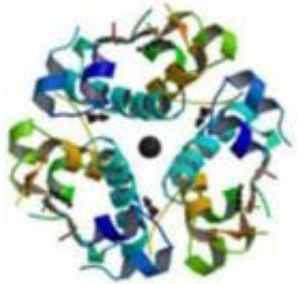
Ultra-Fast-Acting Prandial Insulins

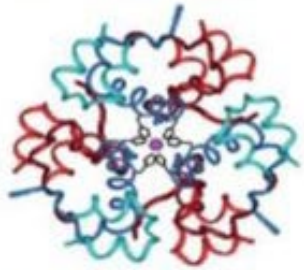
Faster-Acting Insulin Aspart[a,b]

Insulin Aspart*



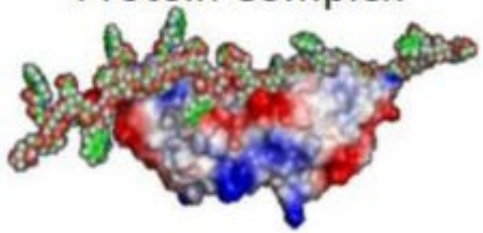
Faster-Acting Insulin Lispro (LY900014)[c]

Insulin Lispro



BioChaperone® Lispro[d]

BioChaperone Lispro Protein Complex

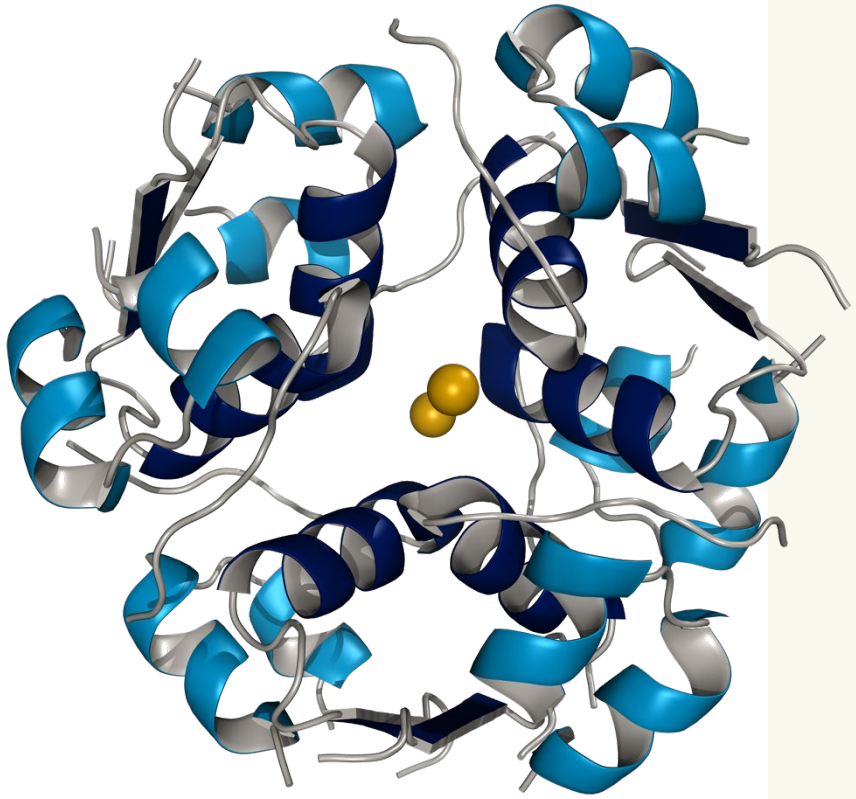


- Each ultra-fast-acting insulin with additives that are designed to stabilize the molecule and improve absorption
- Faster-acting insulin aspart has been approved by FDA and EMA. LY900014 and BioChaperone® are in clinical development

Vantaggi delle insuline ‘ultrarapide’

Vantaggi delle insuline ‘ultrarapide’ nel DM1: più efficace riduzione del picco glicemico post-prandiale maggiore riduzione dei livelli di HbA1c migliore inibizione della produzione epatica di glucosio ridotta incidenza di ipoglicemie maggiore efficacia in gruppi selezionati di pazienti (bambini, anziani, donne in gravidanza) maggiore efficacia quando utilizzate nella pompa di infusione sottocutanea di insulina

The next steps in insulin innovation



Once weekly insulin

Convenience, compliance and glycaemic control

Oral insulin

Convenience, compliance and mimicking physiology

Glucose-sensitive insulin

Very low/no hypoglycaemia, glucose normalisation

Stem cell therapies

Beta-cell replacement

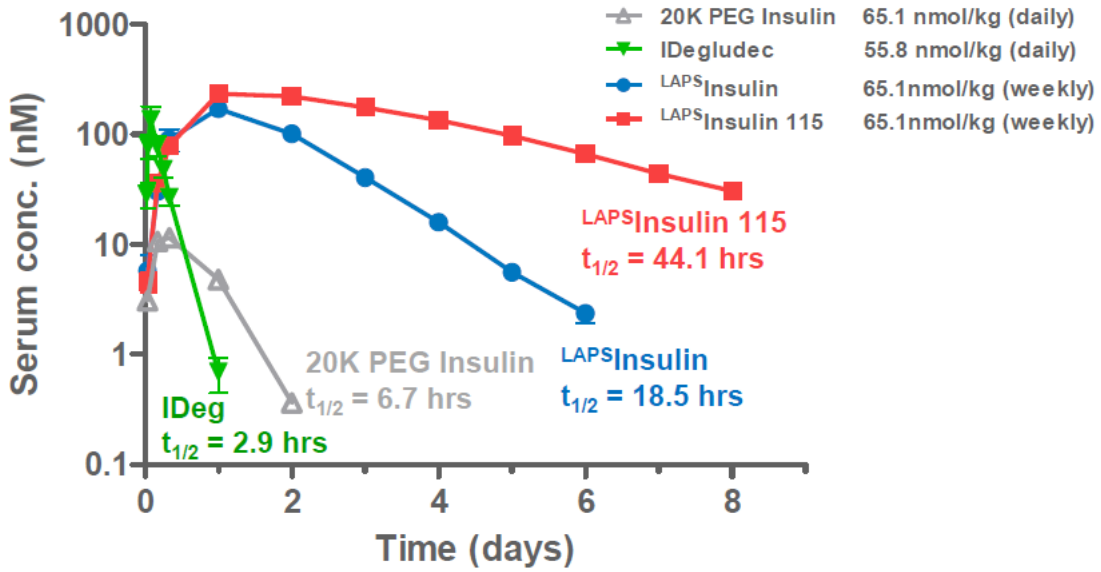
Devices & digital solutions

Use of technology to optimise insulin therapy

A Novel Very Long-Acting Insulin Analog (HM12470)

The long-acting basal insulin, HM12470, has been developed for once-weekly administration to provide for a better basal insulin treatment option.

Figure 2. PK in SD rats (n=3, s.c.)



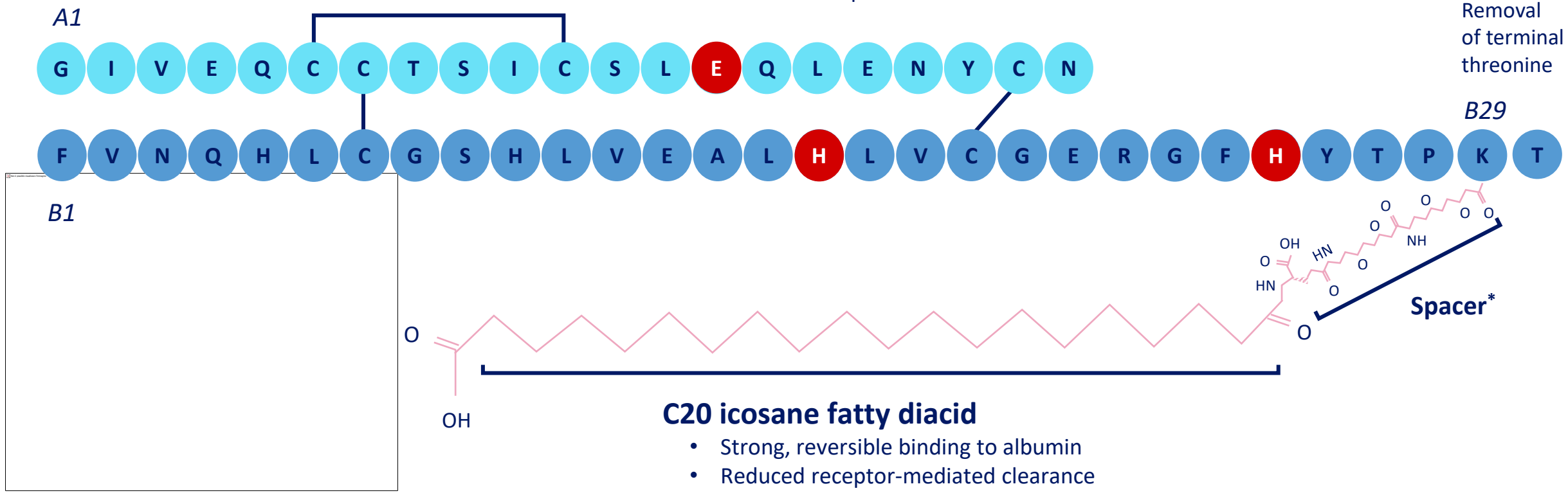
- LAPSInsulin 115 had extended half-life than LAPSInsulin and daily insulins.

Insulin icodec

Designed to achieve a long half-life by changes to the human insulin molecule

Three amino acid substitutions

- Molecular stability
- Reduced enzymatic degradation
- Reduced receptor-mediated clearance



C20 icosane fatty diacid

- Strong, reversible binding to albumin
- Reduced receptor-mediated clearance

*2x (oligoethylene glycol(OEG) γ-L-Glu) spacer.

1. Nishimura E et al. 2020 ADA Scientific Sessions 236–OR.