Ritorno al futuro: le insuline basali di nuova generazione e le mono-settimanali

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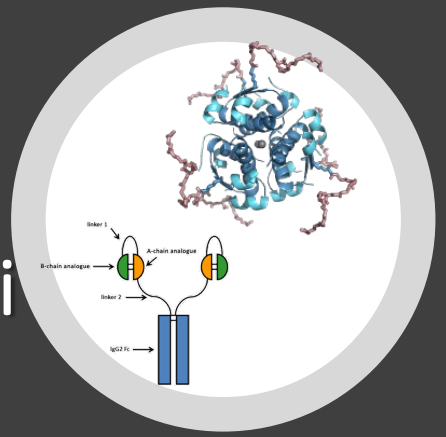
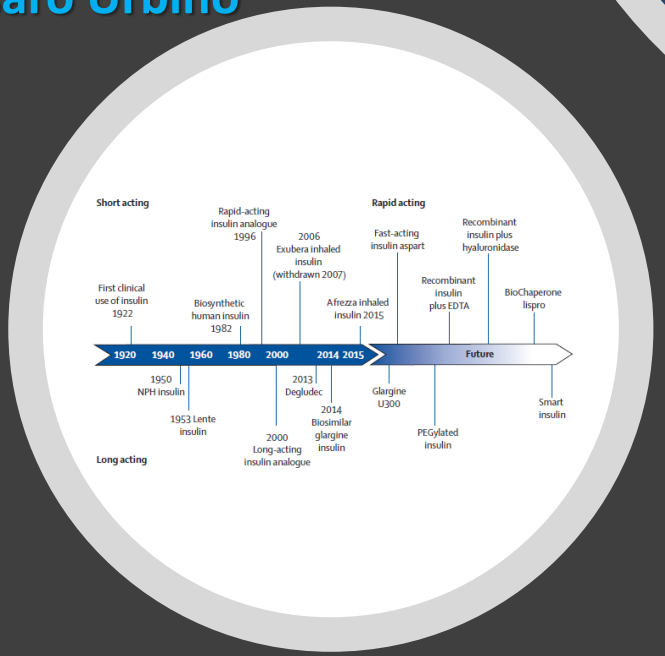
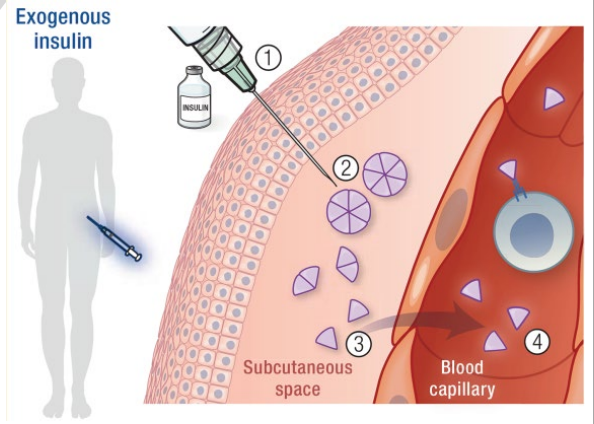
28 ottobre 2023







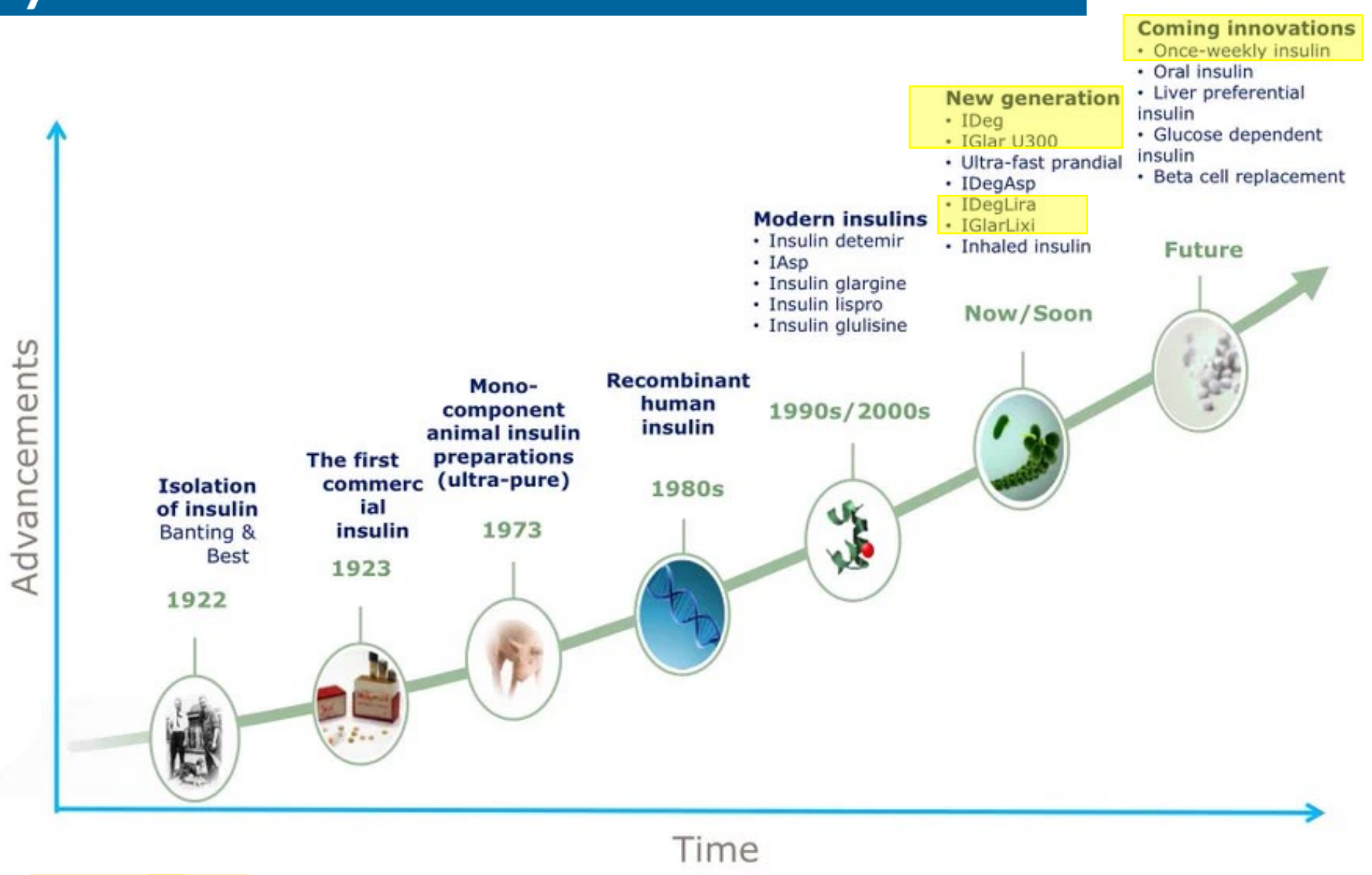
DISCLOSURES

- La dr./ssa GARRAPA GABRIELLA dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:
- - …LILLY
- - …SANOFI

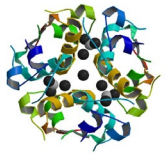
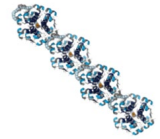
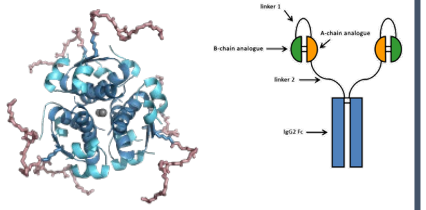
- *Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi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


BACK
TO THE FUTURE
TM

History of Insulin Timeline



Il passato, il presente ed il futuro dell'innovazione nella terapia insulinica basale

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

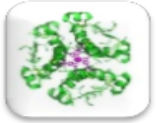
- **BID, twice-daily; NPH, neutral protamine Hagedorn; OD, once-daily; OW, once-weekly**

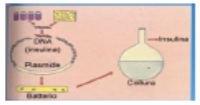
Insuline basali: l'elogio della... lentezza!

L’insulina ideale

Evoluzione della terapia insulinica

1921	1946	1979	Anni ‘90 e 2000
Isolamento dell’insulina	Insulina NPH	Insulina umana ricombinante	Analoghi rapidi e basali

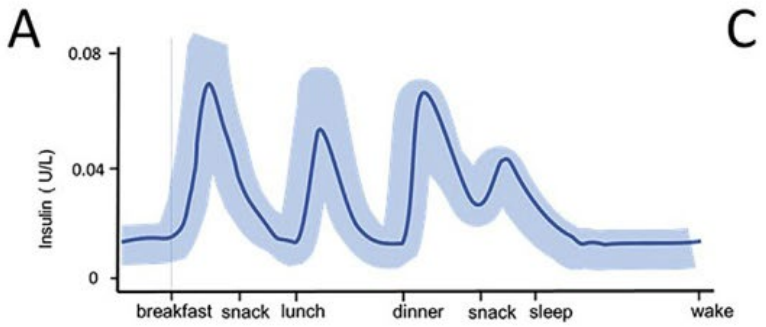


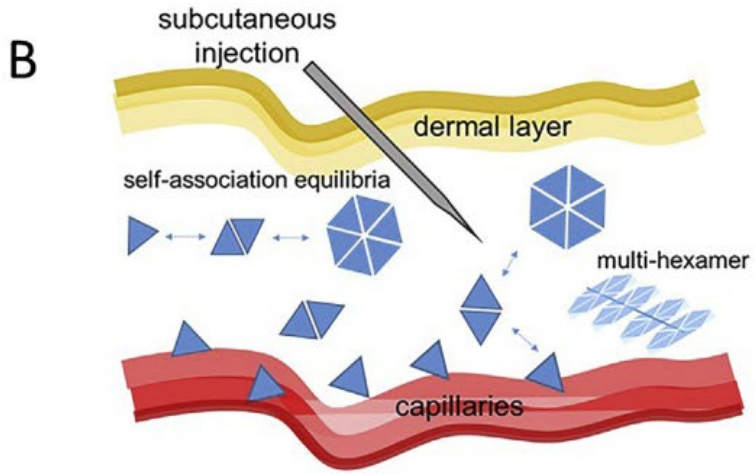


“Nuova terapia insulinica”: le caratteristiche da soddisfare

- ✓ Efficacia
- ✓ Adeguata durata d’azione
- ✓ Ridotta variabilità d’azione
- ✓ Flessibilità
- ✓ Sicurezza
- ✓ Basso rischio ipoglicemico
- ✓ Buon rapporto costo-efficacia

Tempo





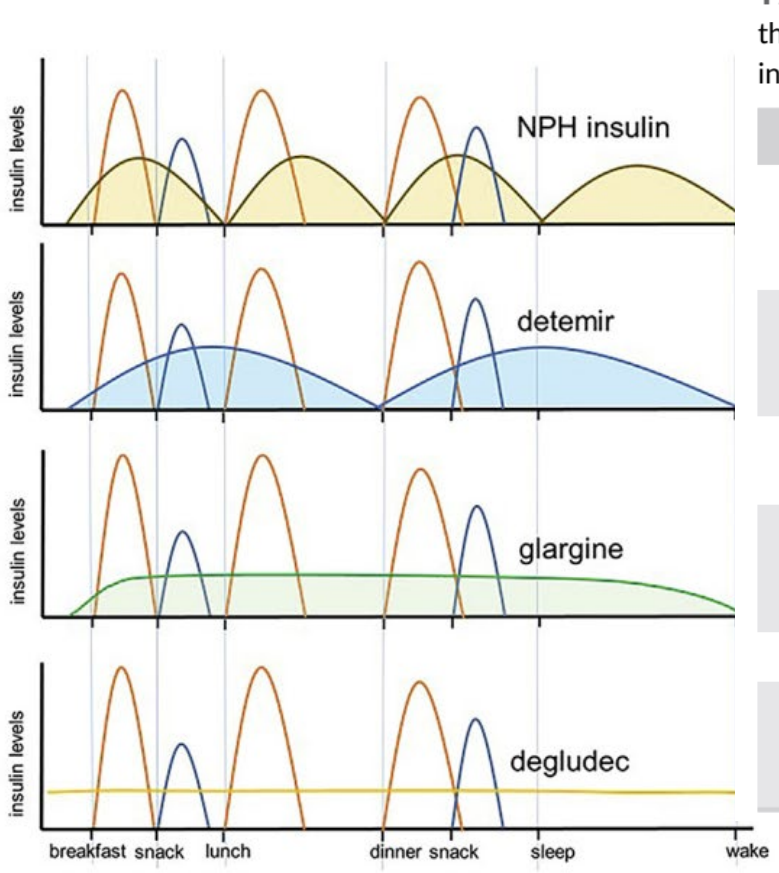


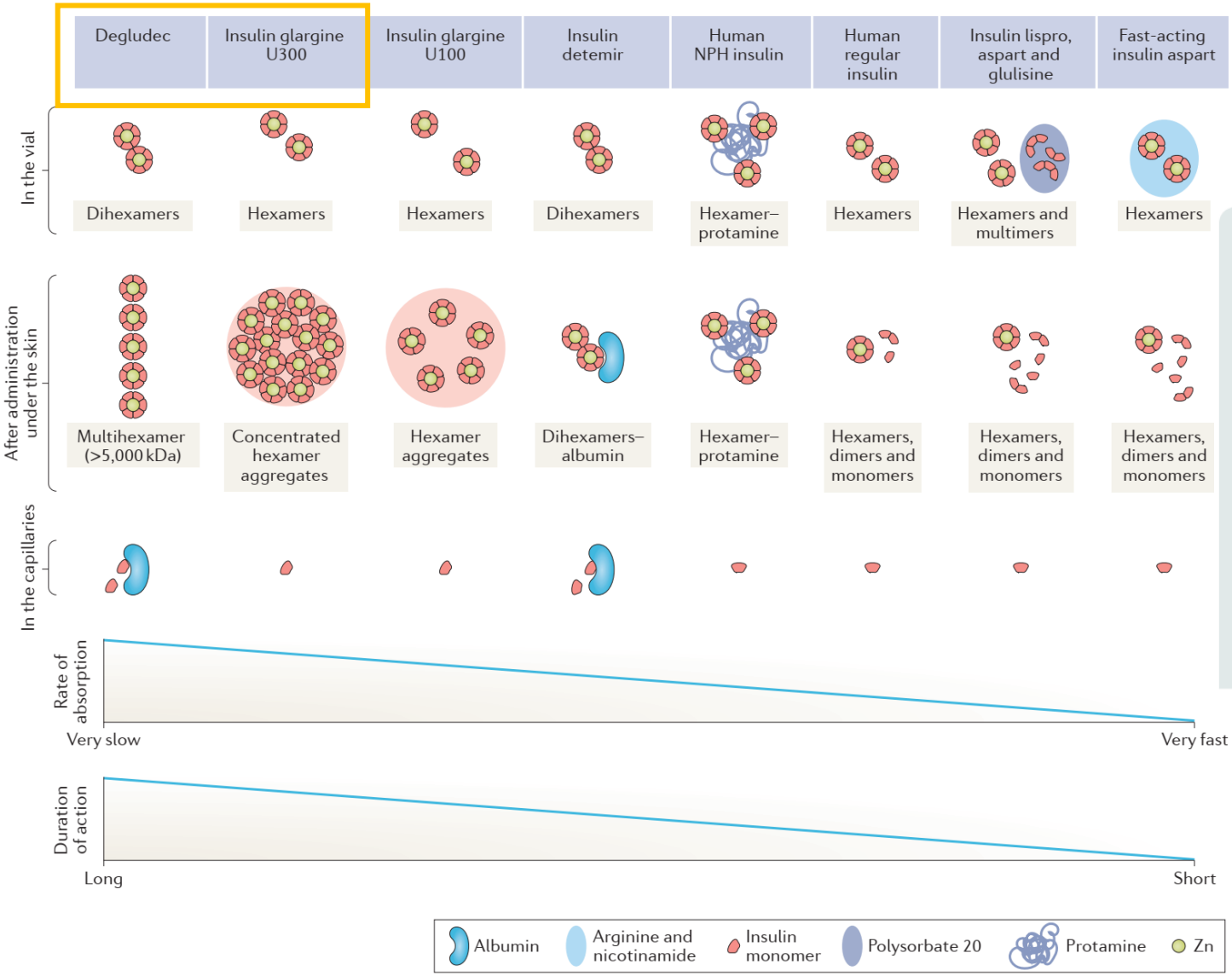
TABLE 1 Mechanisms by which bioengineered modifications of the structure of insulin have prolonged the duration of action of basal insulin analogues

Mechanism of protraction	Analogues
Micro-precipitation after injection followed by gradual dissociation and absorption of active monomers	Glargine U-100 Glargine U-300
Reduced surface area of micro-precipitates at injection depot, causing slower dissociation and absorption of active monomers	Glargine U-300
Self-association into higher-order structures	Detemir Degludec
Reversible binding to serum albumin	Detemir Degludec Icodec
Reduced enzymatic degradation	Icodec
Reduced affinity for insulin receptor and slower receptor-mediated clearance, while retaining agonism and bioactivity	Icodec

Diabetes Obes Metab. 2022;

Figure 1: Physiological insulin secretion and pharmacologic principles. (A) Pattern of insulin concentrations in the blood of healthy people following meals (adapted from [260]). (B) Insulin self-association equilibrium within SQ space. Depending on analog formulation, insulin may form zinc hexamers (blue hexagons) or multi-hexamer assemblies: these dissociate to liberate zinc-free dimers, as well as monomers amenable to capillary absorption (red). (C) Schematic PK profiles (24 h cycle). **MOLECULAR METABOLISM 52 (2021)**

Differente assorbimento e durata d'azione delle insuline umane vs gli analoghi



Key points

- Established rapid-acting and long-acting insulin analogues have enabled more patients with type 1 diabetes mellitus to reach better glucose targets, with lower hypoglycaemia rates and a better quality of life than was possible with short-acting and long-acting human insulin
- In patients who are prone to severe hypoglycaemia, using a full analogue regimen is rapidly cost saving and should therefore be the standard of care in all patients with type 1 diabetes mellitus
- The new long-acting insulin analogues insulin glargine U300 and insulin degludec have shown increased stability, which translates to a reduced risk of nocturnal hypoglycaemia and increased flexibility in timing of administration
- Faster and shorter acting insulin analogues are needed for use in insulin pumps and future 'artificial pancreas' systems; fast-acting insulin aspart, a new formulation of aspart, is well advanced in clinical development

NATURE REVIEWS | ENDOCRINOLOGY 2017

Motivazione della raccomandazione

Vi sono numerose evidenze provenienti da trial clinici che mostrano come l'uso degli analoghi lenti dell'insulina a maggiore durata di azione si associ ad un rischio minore di ipoglicemie totali e notturne e ad una tendenziale riduzione degli eventi ipoglicemici severi a parità di controllo metabolico e senza aumenti di peso corporeo.

La qualità delle evidenze è moderata, in particolare per il disegno in aperto della maggior parte degli studi inclusi e per la presenza di elevata eterogeneità per alcuni degli *outcome* critici.

Gli studi di farmacoeconomia mostrano che le nuove formulazioni hanno costi diretti maggiori; tuttavia, il rapporto costo-efficacia è generalmente favorevole per QALY guadagnati e per gli effetti positivi su rischio ipoglicemico. La disponibilità di biosimilari con costi diretti ridotti può ulteriormente migliorare il rapporto costo-efficacia.

Considerazioni sull'implementazione

Gli analoghi lenti sono già considerati in Italia lo *standard of care*[7,8]. La prescrizione di analoghi lenti a maggiore durata di azione dovrebbe essere incoraggiata e gradualmente sostituita a quelli a minore durata di azione indipendentemente dal controllo glicemico. I medici di medicina generale e gli specialisti dovrebbero essere informati sui contenuti di questa raccomandazione attraverso specifici corsi di educazione continua in medicina.

AMD ASSOCIAZIONE MEDICI DIABETOLOGI 1974 ANNO DI FONDAZIONE

SID Società Italiana di Diabetologia fondata nel 1964

Linea Guida della Società Italiana di Diabetologia (SID) e dell'Associazione dei Medici Diabetologi (AMD)

Raccomandazione forte a favore dell'intervento, con qualità delle prove moderata

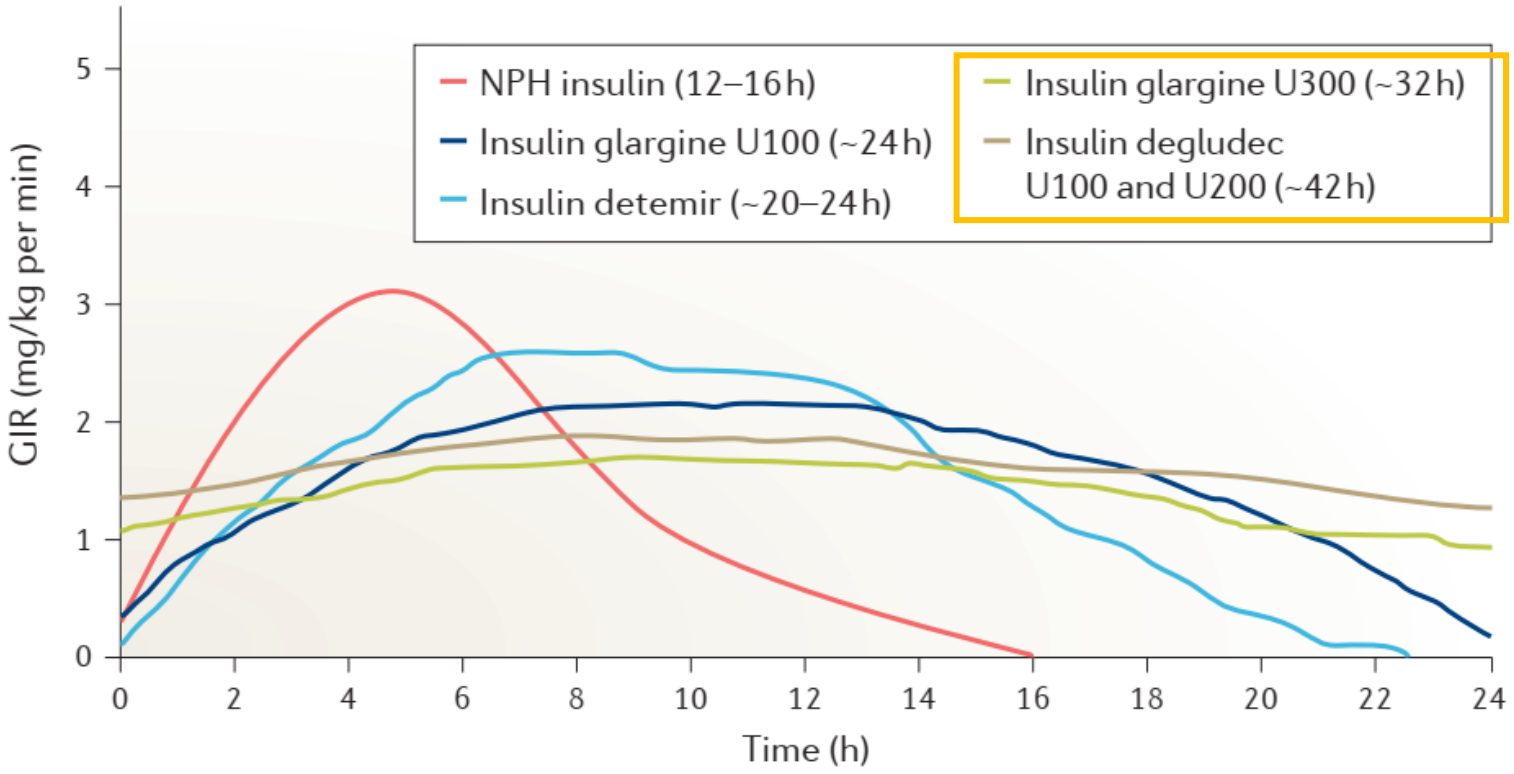
Si raccomanda l'uso degli analoghi lenti dell'insulina a maggiore durata di azione, rispetto a quelli a minore dura di azione, per tutti i pazienti con diabete di tipo 2 che necessitano di insulina basale.

Analoghi insulinici basali di Seconda Generazione

Insulina	Descrizione
Degludec	Analogo insulinico basale a lunga durata d'azione
Glargine U-300	Formulazione 3 volte concentrata di glargine U-100

- Le nuove insuline Degludec e Glargine U300 sono caratterizzate da una maggiore durata d'azione e una minore variabilità glicemica rispetto a Glargine U100

Profili di azione delle insuline long-acting



Long-acting insulins

- Duration of action — favours insulin analogues
- Flat profile — favours insulin analogues
- Variability — favours insulin analogues
- Risk of hypoglycaemia — favours insulin analogues
- Need for evening snacks — favours insulin analogues
- Risk of nocturnal hypoglycaemia — favours insulin analogues
- Flexibility — favours insulin analogues
- Cost — favours human insulin
- Experience — favours human insulin
- Availability — favours human insulin
- Availability of concentrated forms — favours insulin analogues

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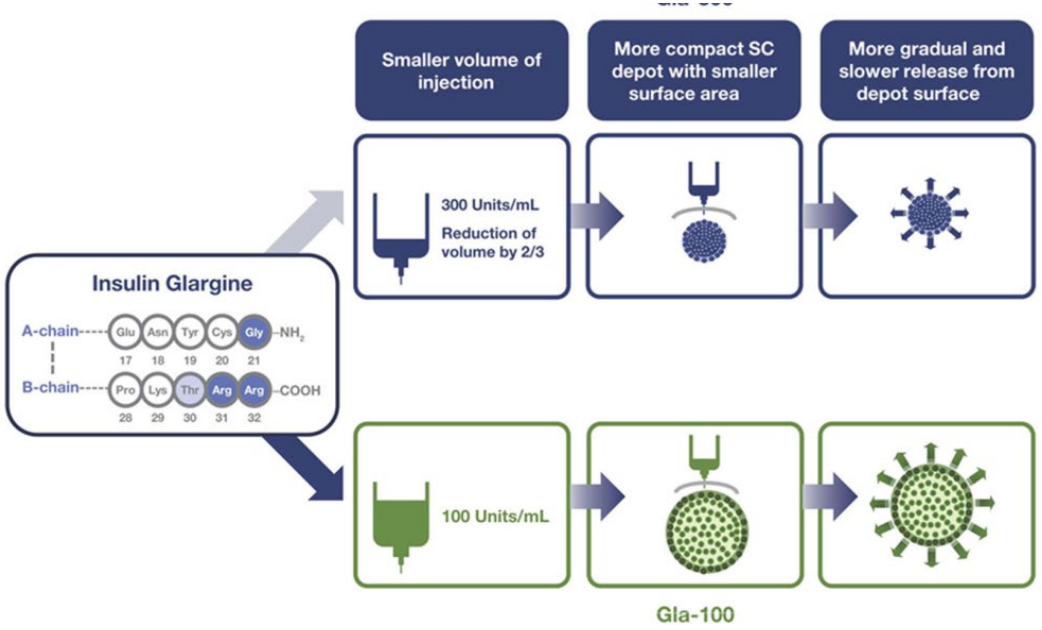
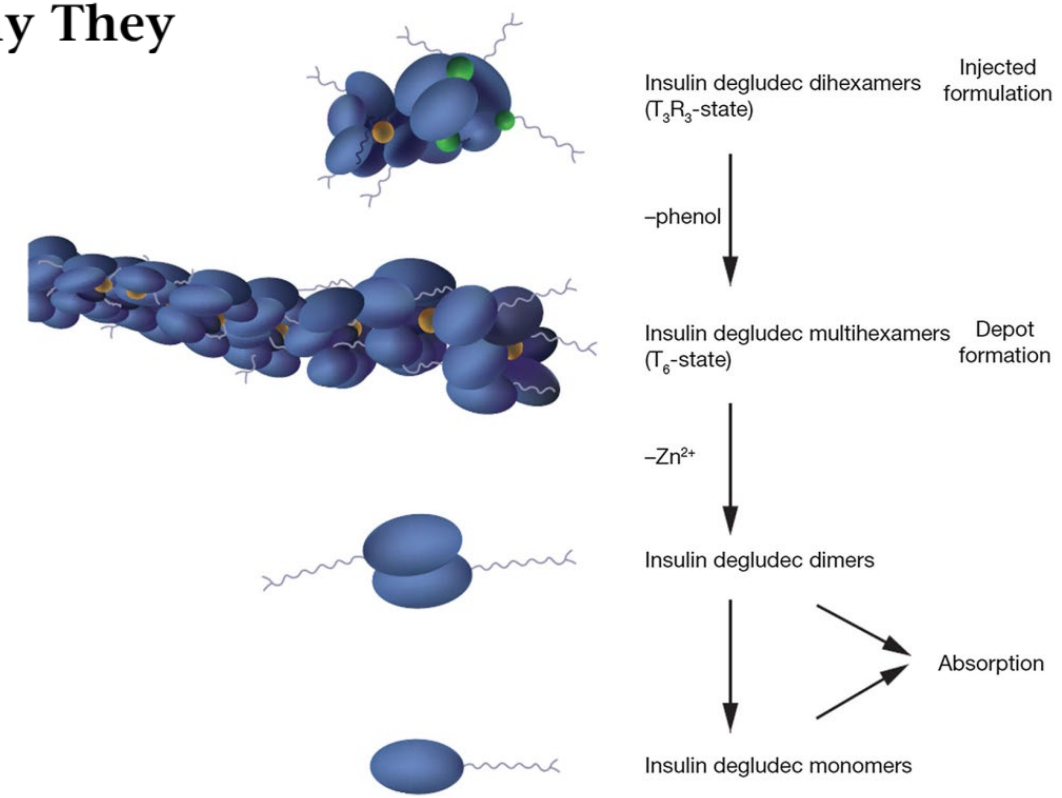
Differentiating Basal Insulin Preparations: Understanding How They Work Explains Why They Are Different



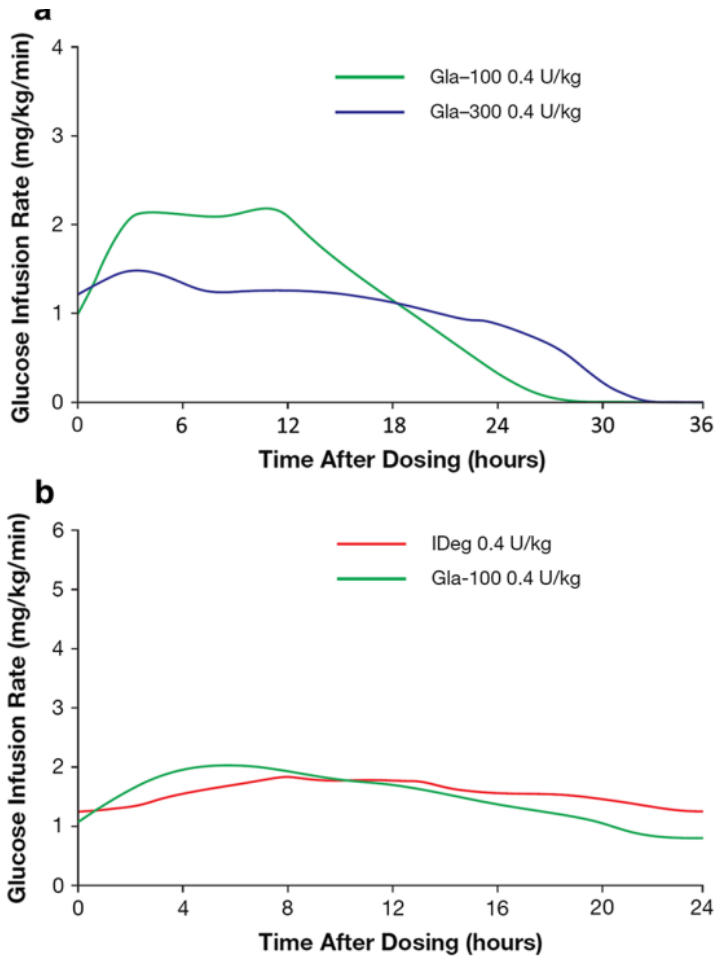
- **Gla-300** delivers the same dosage of insulin as Gla-100, but **in one-third of the volume**. This results in **reduced surface area** of injection depot, ultimately resulting in a **slower and more gradual release** of monomers of Gla-300 as compared with Gla-100.



- **IDeg** utilizes a **different method** of protraction

Adv Ther (2019) 36:1018–1030

Differentiating Basal Insulin Preparations: Understanding How They Work Explains Why They Are Different

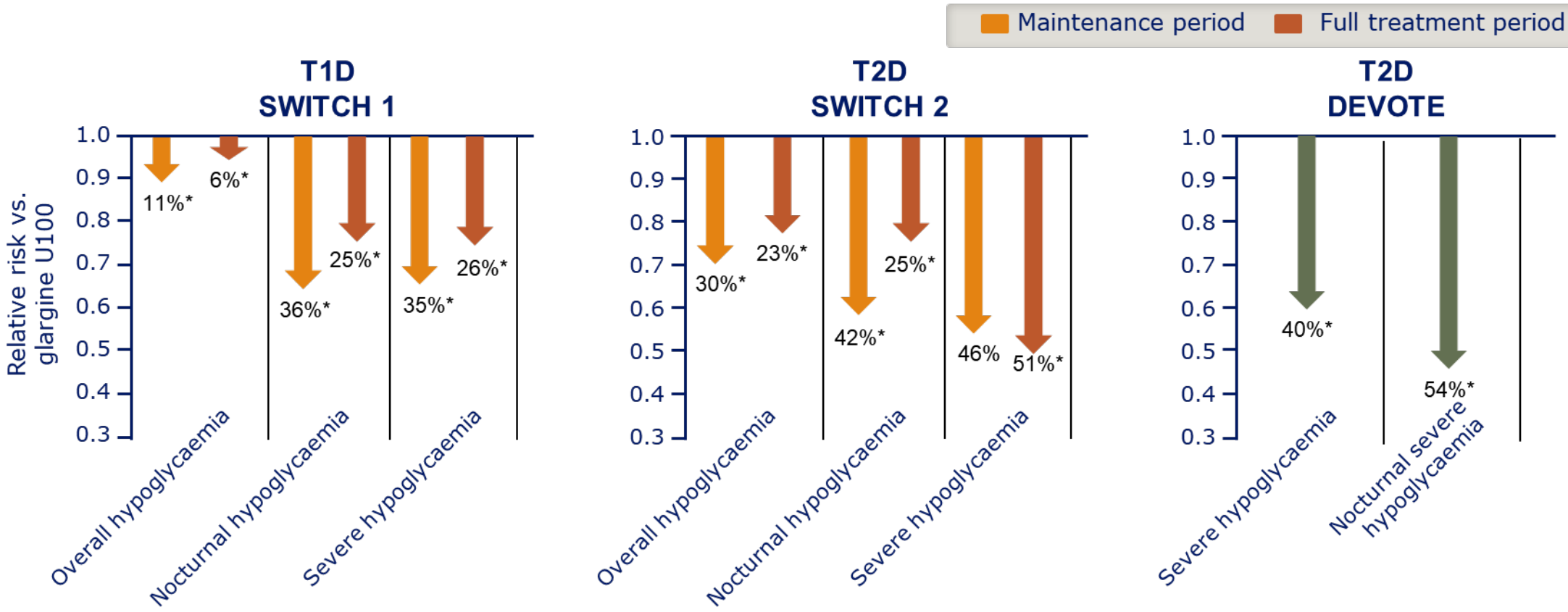


CONCLUSIONS

The time–action profile of an insulin preparation is determined by its time course and pattern of absorption and distribution from the subcutaneous injection site. Basal insulins have distinct mechanisms of protraction that give rise to equally distinct PK/PD profiles and accompanying clinical properties in people with T1D and T2D. Understanding these differential mechanisms is important to explain the clinical benefits and differences of the second-generation basal insulin analogs Gla-300 and IDeg over the earlier generation of basal insulins, Gla-100 and IDet. Gla-300 and IDeg show longer duration of action and smoother PK/PD profiles than these earlier-generation basal insulin analogs, leading to smaller glycemic excursions and a lowered risk of hypoglycemia, while retaining similar levels of glycemic control. Understanding the differences among first- and second-generation basal insulin analogs aids healthcare providers in making the most appropriate treatment decisions to address individual patient needs.

Adv Ther (2019) 36:1018–1030

Insulina Degludec vs Insulina Glargine 100: riduzione delle ipoglicemie

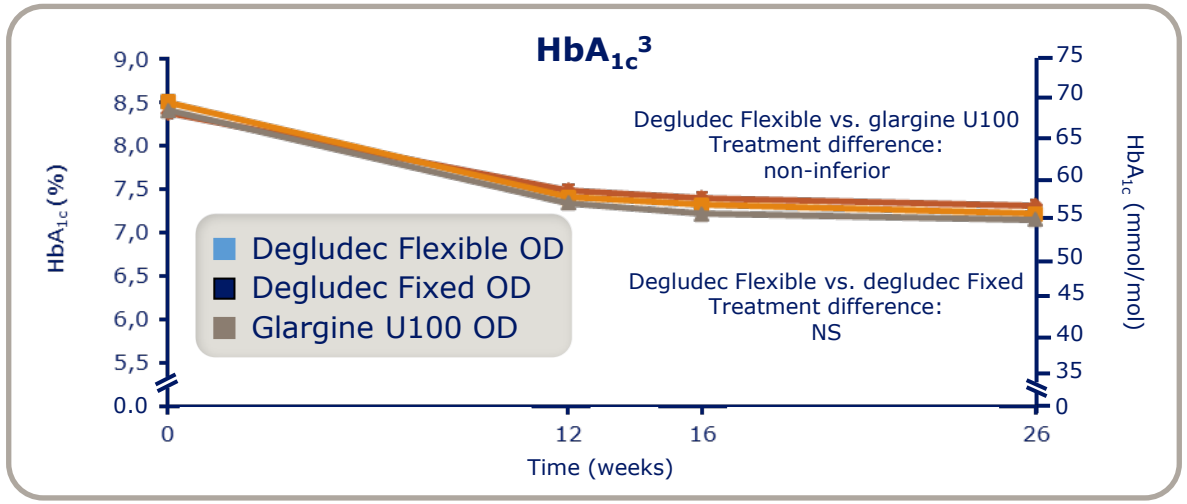


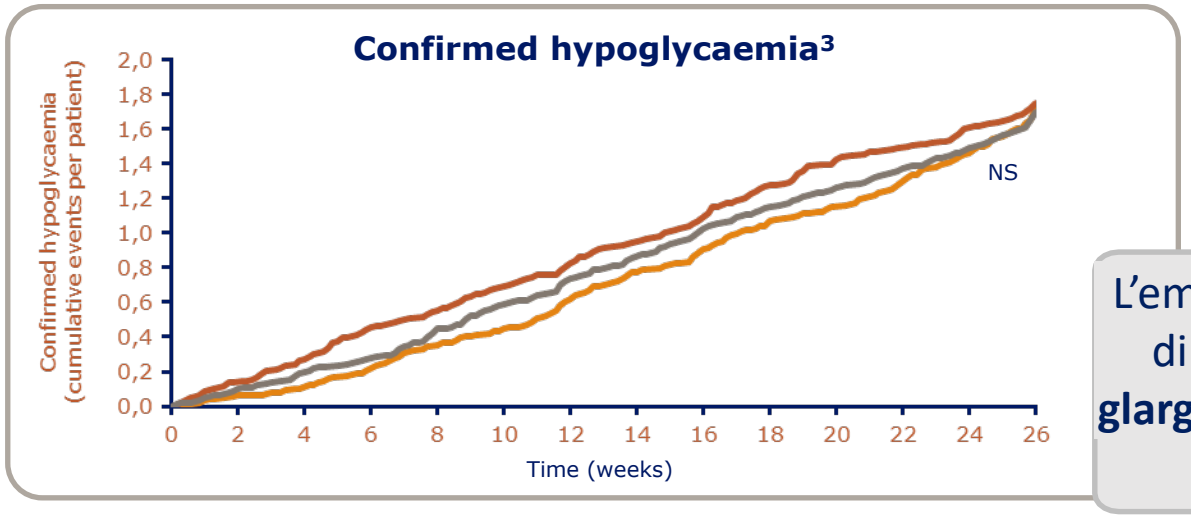
*Significant difference. Overall hypoglycaemia: severe or BG-confirmed hypoglycaemia; nocturnal hypoglycaemia, severe or BG-confirmed hypoglycaemia occurring between 00:01 am and 05:59 am, both inclusive; severe hypoglycaemia, an episode requiring third-party assistance and external adjudication

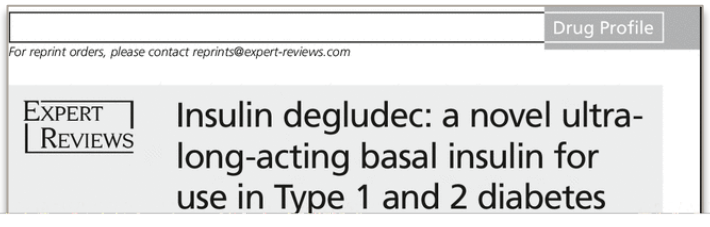
BG, blood glucose; glargine U100, insulin glargine 100 units/mL; T1D, type 1 diabetes; T2D, type 2 diabetes

Lane *et al. JAMA* 2017;318:33–44; Wysham *et al. JAMA* 2017;318:45–56; Marso *et al. N Engl J Med* 2017;377:723–32

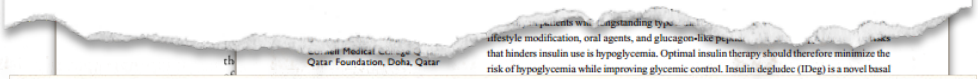
Degludec: la flessibilità



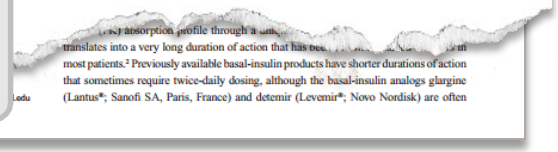




"Flexibility in the timing of insulin administration can benefit **patients who find it challenging to always inject insulin at the same time each day**."[2]



"…In particular, this could include **individuals who travel** regularly … **Shift workers** may also greatly benefit from the freedom to change their dosing schedule…"[1]



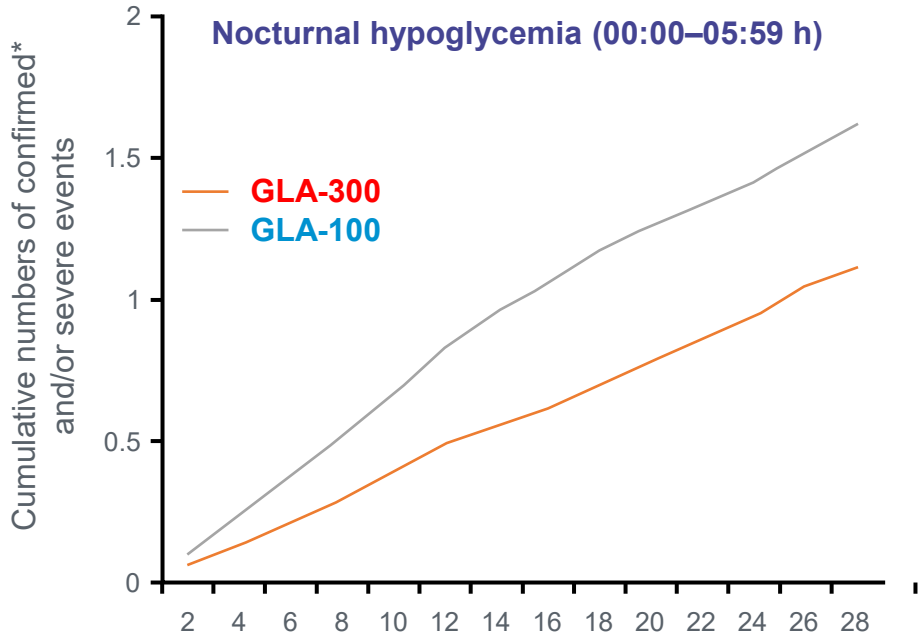
L'emivita dell'insulina **degludec** è di **25,4 ore** mentre l'insulina **glargine U100** ha emivita di **12,1 h**

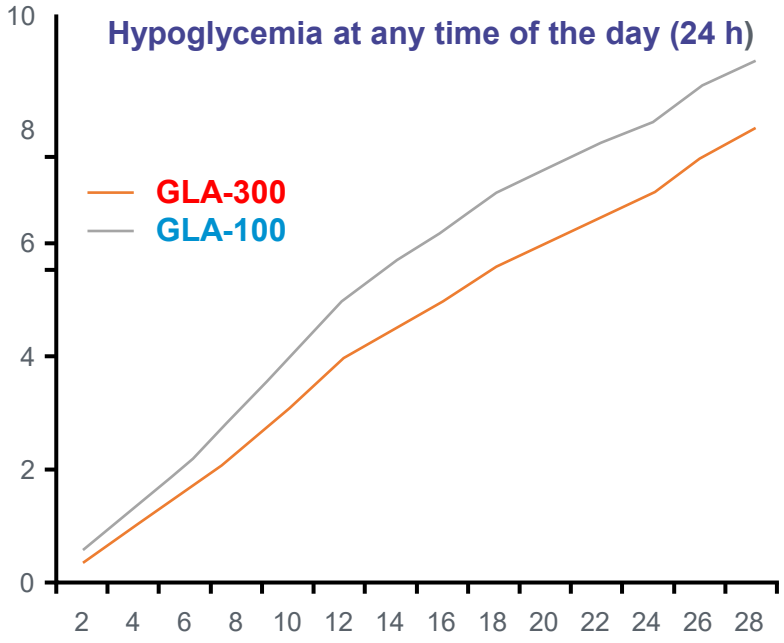
Glargine U100, insulin glargine 100 units/mL; NS, not significant; OD, once daily

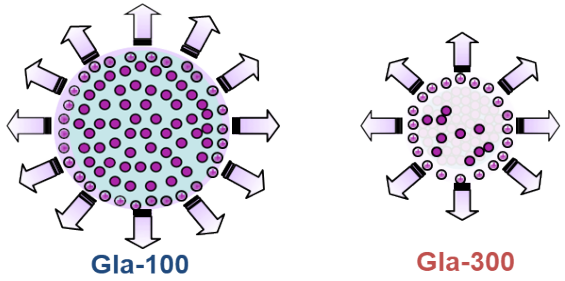
1. Aye & Atkin. *Drug Healthc Patient Saf* 2014;6:55–67; 2. Meneghini *et al. Expert Rev Endocrinol Metab* 2012;7:9–14; 3. Meneghini *et al. Diabetes Care* 2013;36:858–64

Minori ipoglicemie diurne e notturne con Glargine 300

EDITION 1-2-3 T2DM Pooled Analysis







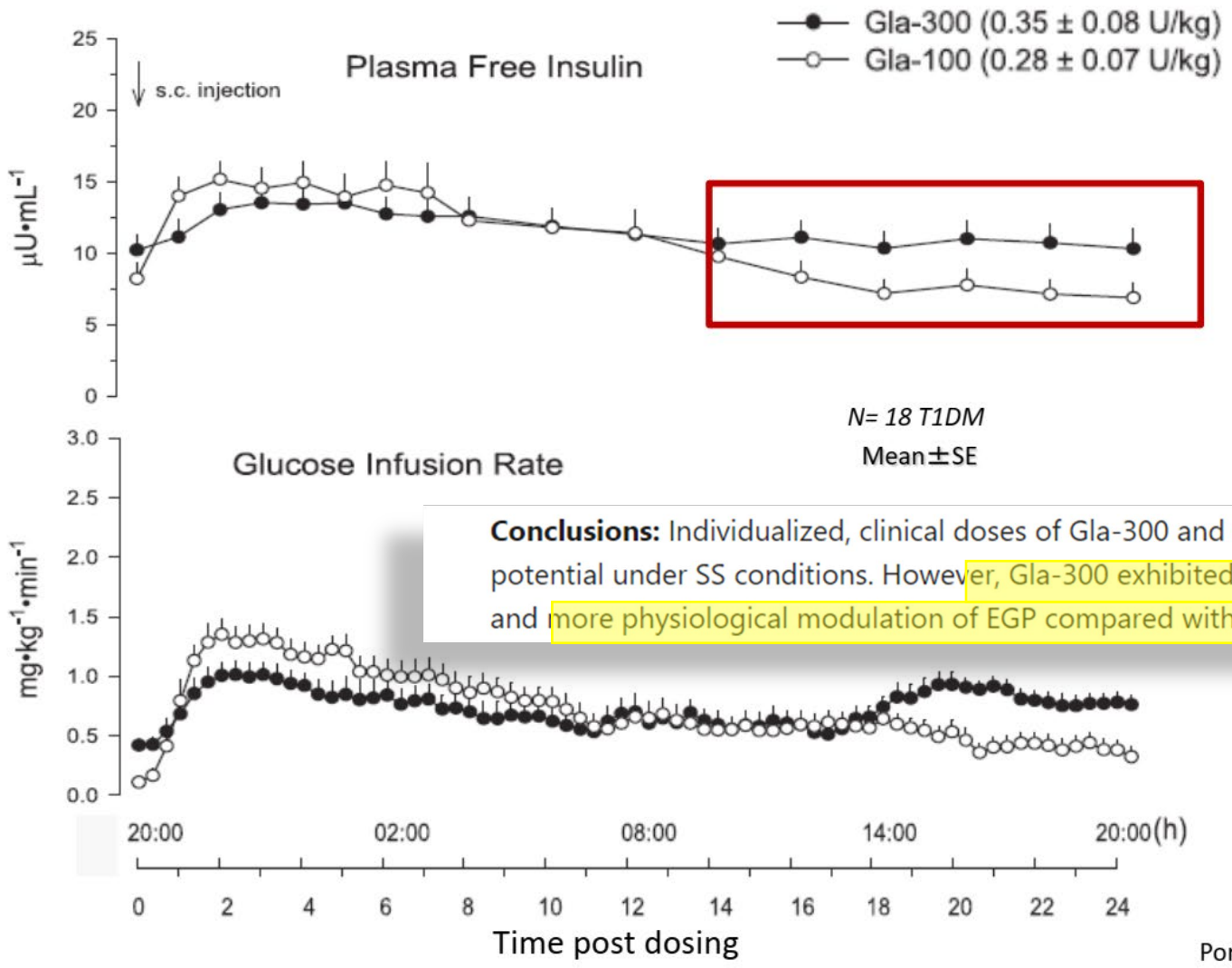
La riduzione del volume diminuisce la superficie depot, con un rallentato tasso di cessione di glargine

	GLA-300	GLA-100	
Rate per patient-year	2.10	3.06	-31%
RR (95% CI) vs U100	**0.69** (0.57 to 0.84)		
P value	0.0002		

	GLA-300	GLA-100	
Rate per patient-year	**15.22**	17.73	-14%
RR (95% CI) vs U100	**0.86** (0.77 to 0.97)		
P value	0.0116		

*Confirmed events based on plasma glucose ≤3.9 mmol/L (≤70 mg/dL)

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



Conclusions: Individualized, clinical doses of Gla-300 and Gla-100 resulted in a similar euglycemic potential under SS conditions. However, Gla-300 exhibited a more stable profile, with lower variability and more physiological modulation of EGP compared with Gla-100.

Porcellati F. et al., Diabetes Care 2019

Real-World Effects of Second-Generation Versus Earlier Intermediate/Basal Insulin Analogues on Rates of Hypoglycemia in Adults with Type 1 and 2 Diabetes (iNPHORM, US)

Table 4 Population-average adjusted hypoglycemia rate ratios comparing second-generation to earlier intermediate/basal insulin analogue use, by type of diabetes, event severity, and timing

Type of hypoglycemia	Estimated population-average adjusted rate ratios (95% CI)					
	All (n = 413)		T1DM (n = 81)		T2DM (n = 332)	
Non-severe		p-value		p-value		p-value
Overall	0.81 (0.68–0.97)	0.02*	0.85 (0.62–1.17)	0.33	0.81 (0.66–1.00)	0.05
Daytime	0.91 (0.76–1.10)	0.32	0.94 (0.67–1.31)	0.72	0.92 (0.73–1.15)	0.45
Nocturnal	0.57 (0.44–0.74)	< 0.001*	0.52 (0.34–0.81)	0.003*	0.63 (0.46–0.86)	0.004*
Severe		p-value		p-value		p-value
Overall	0.87 (0.65–1.16)	0.35	0.52 (0.26–1.07)	0.07	0.97 (0.70–1.36)	0.88
Daytime	0.98 (0.71–1.36)	0.91	0.60 (0.27–1.33)	0.21	1.10 (0.76–1.59)	0.60
Nocturnal	0.56 (0.35–0.90)	0.02*	0.23 (0.06–0.93)	0.04*	0.63 (0.38–1.06)	0.08

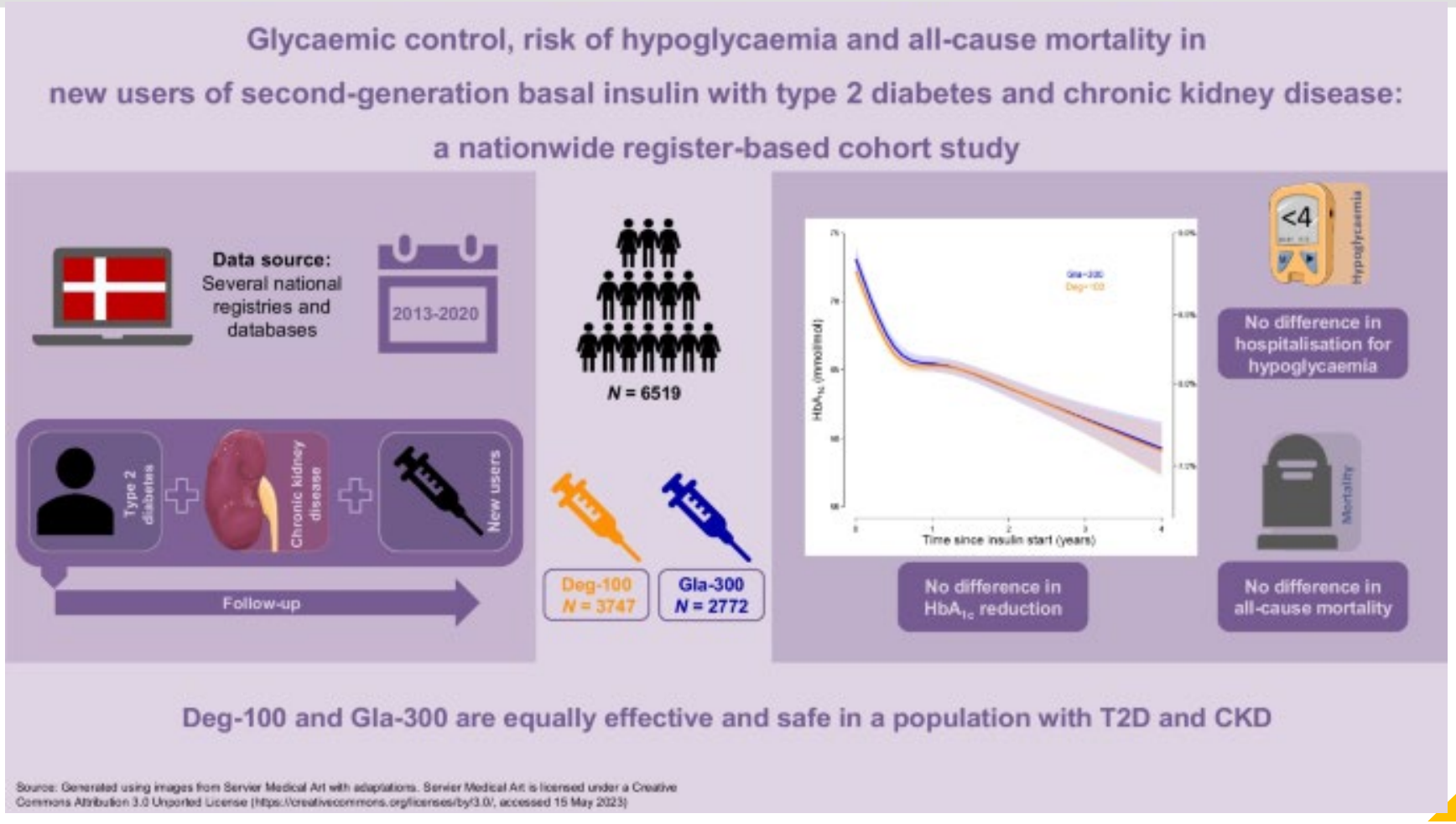
Diabetes Ther (2023) 14:1299–1317

This study evaluates the impact of second-generation insulins (insulin degludec and glargine U-300) versus earlier intermediate and basal insulins (NPH, insulin glargine U-100 and detemir, premixed and fixed-ratio [FRC] insulins) on rates of overall, daytime, and nocturnal non-severe and severe hypoglycemia

What was learned from the study?

The most salient effects were observed for nocturnal hypoglycemia. Overall, second-generation insulin versus earlier intermediate/basal insulin users reported a 43% reduction in non-severe nocturnal hypoglycemia ($p < 0.001$) and a 44% reduction in severe nocturnal hypoglycemia ($p = 0.02$). These trends persisted across diabetes types

Among patients with either type 1 or 2 diabetes mellitus on basal insulin (with or without bolus), the use of second-generation basal insulins over earlier formulations should be prioritized whenever possible



Conclusions/interpretation We found no difference in HbA_{1c} reduction, hospitalisation for hypoglycaemia or all-cause mortality between Gla-300 and Deg-100 in a real-world population of new users with type 2 diabetes and moderate to end-stage chronic kidney disease. Therefore, we conclude that these two treatment options are equally effective and safe in this vulnerable population.

Diabetologia Published online: 28 July 2023

Medical need for alternative options to intensify basal insulin in type 2 diabetes

Unmet needs

Glycaemic control

Most subjects on basal insulin are not at target HbA_{1c} [1,2]

Hypoglycaemia

Hypoglycaemic events are costly[3] and a barrier to achieving target HbA_{1c} [4]

Weight gain

Weight gain is a barrier to achieving target HbA_{1c} [5]

Complexity

Complex insulin regimens are a barrier to achieving target HbA_{1c} [4]

1. Dale et al. Prim Care Diabetes 2010;4:85–9; 2. Giugliano et al. Diabetes Care 2011;34:510–17; 3. Hex et al. Diabet Med 2012;29:855–62; 4. Peyrot et al. Diabet Med 2012;29:682–9; 5. Carver. Diabetes Educ 2006;32:910–17

Fixed-ratio combination of basal insulin and GLP-1 receptor agonist: is two better than one?

Stefano Del Prato


Insuline ed incretine:
partnership vincente!
GLP-1 RA
Liraglutide
Insulina
Degludec
IDegLira
GLP-1 RA
Lixisenatide
Insulina
Glargine
100
IGlarLixi

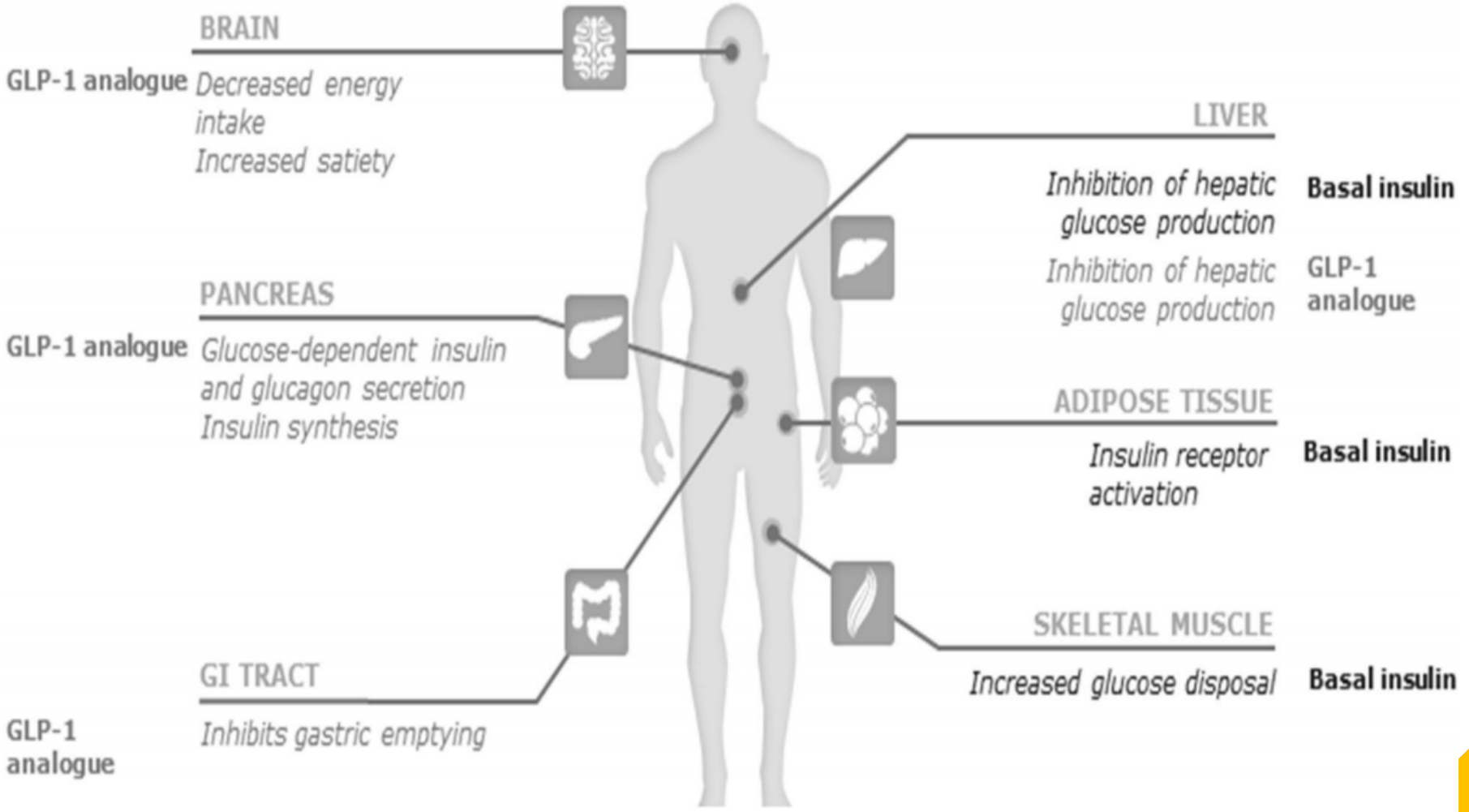
Combinazioni a rapporto fisso di insulina basale + GLP-1 RA: quali opportunità per medici e pazienti ?

Barriere	Potenziali soluzioni
Ipoglicemia	Intensificare con molecole associate ad **un basso rischio di ipoglicemia** [2]
Aumento peso	Intensificare con molecole associate ad un **basso rischio di aumento del peso** [2]
Complessità del trattamento	Intensificare **semplificando il regime terapeutico** [2]
Aderenza	Una singola iniezione giornaliera potrebbe garantire la comodità per il paziente e di conseguenza **l'aderenza alla terapia** [2]

Barriere all'intensificazione della terapia insulinica [1]

1- Russel-Jones D et al., Diabetes Obes Metab 2018;20:488-496
2 - Liakopoulou P, et al. Endocrine 2017;56:485–94.

Complementary actions of basal insulin and GLP-1 analogue target the underlying pathophysiology of T2DM



Diabetol Metab Syndr (2018)

Rationale for a titratable fixed-ratio co-formulation of a basal insulin analog and a glucagon-like peptide 1 receptor agonist in patients with type 2 diabetes

CURRENT MEDICAL RESEARCH AND OPINION
2019, VOL. 35, NO. 5, 793–804

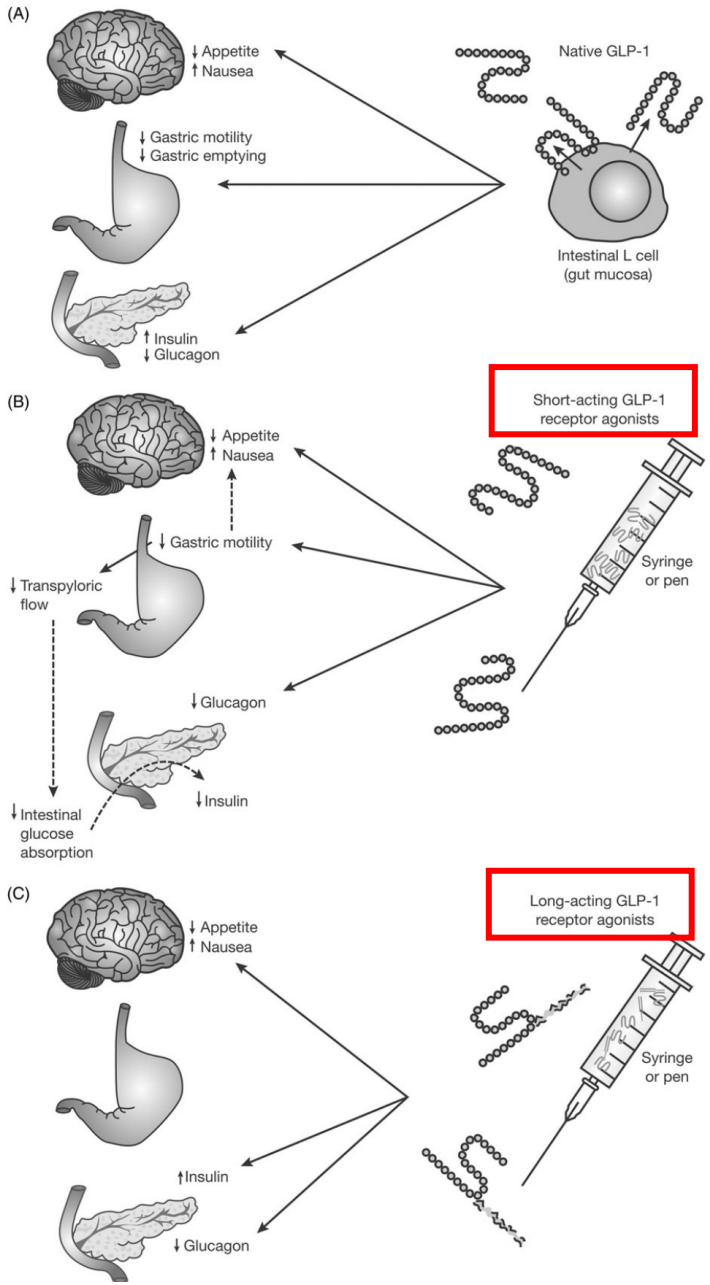
- **Reducing** regimen **complexity** has the potential to **curtail clinical inertia** and, along **with fewer adverse events**, improve **adherence and persistence to therapy**, which may improve clinical outcomes

Table 2. The complementary mechanisms of action of basal insulin and a GLP-1 receptor agonist.

	Basal insulin	GLP-1 receptor agonist
Primary effects	• ↓ Mainly FPG • ↓ Interprandial glucose	• ↓ PPG[a] • ↓ FPG[b]
Mechanism	• ↓ Hepatic glucose production • ↑ Non-glucose-dependent endogenous insulin • ↓ Glucagon secretion • ↑ Insulin concentration	• ↑ Glucose-dependent insulin secretion[b] • ↓ Glucose-dependent glucagon secretion • ↓ Gastric emptying rate[a] • ↑ Satiety • ↓ Food intake
Effect on weight	• ↑ Body weight	• ↓ Body weight

[a]short-acting formulations.
[b]long-acting formulations.

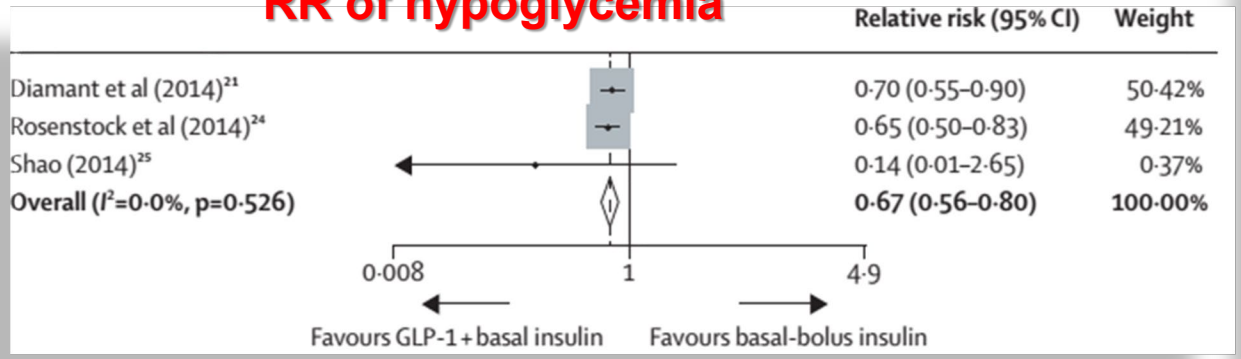
Mechanisms of GLP-1 and GLP-1 receptor agonist action.



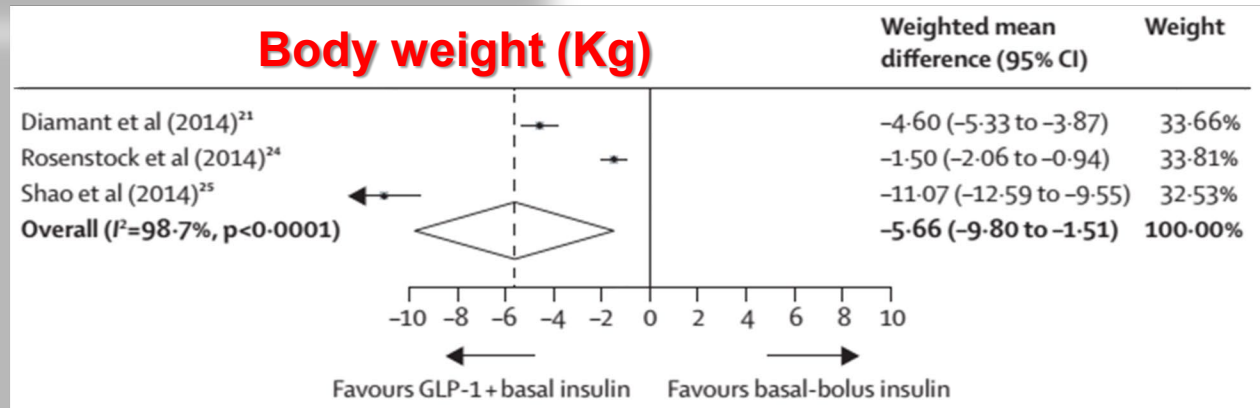
Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis

Conrad Eng, Caroline K Kramer*, Bernard Zinman, Ravi Retnakaran*

RR of hypoglycemia

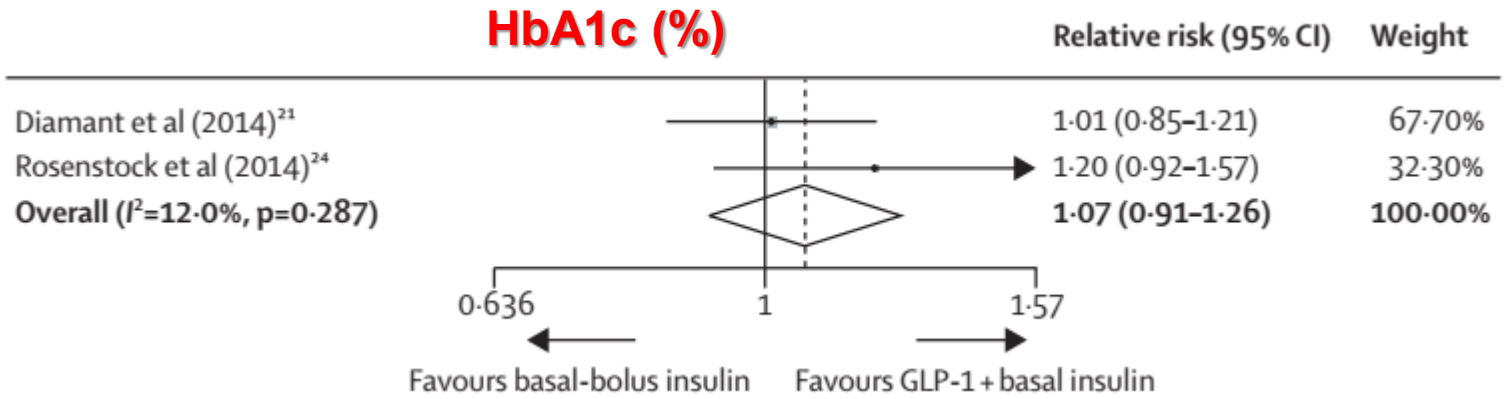


Body weight (Kg)



Interpretation GLP-1 agonist and basal insulin combination treatment can enable achievement of the ideal trifecta in diabetic treatment: robust glycaemic control with no increased hypoglycaemia or weight gain. This combination is thus a potential therapeutic strategy that could improve the management of patients with type 2 diabetes.

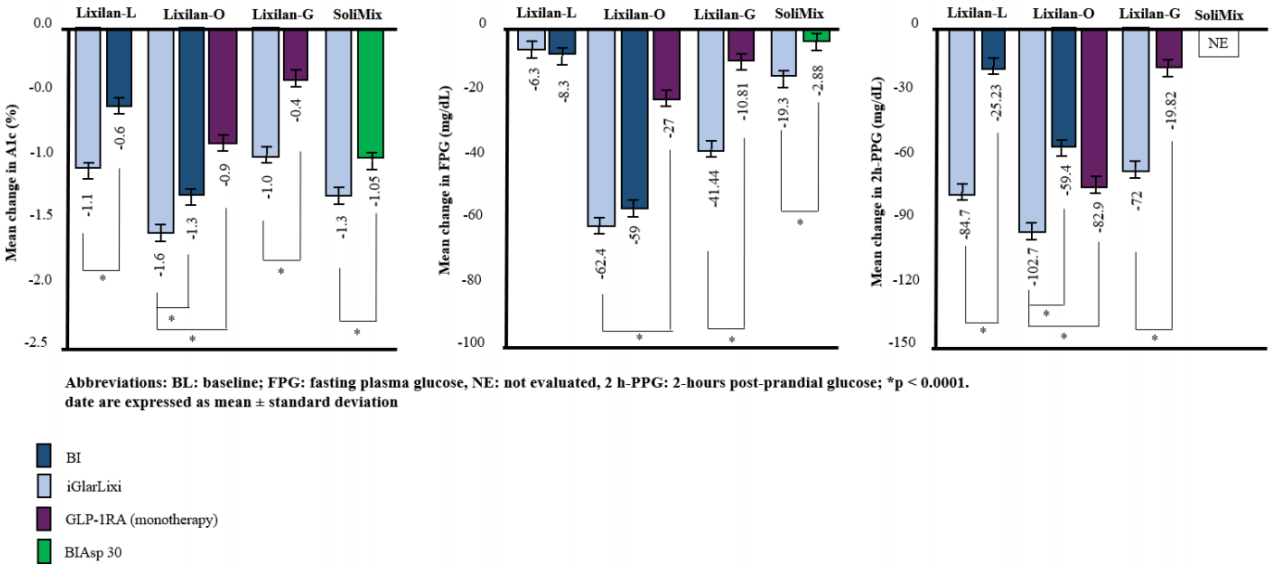
HbA1c (%)



Lancet 2014; 384: 2228–34

Fixed-Ratio combinations (Basal Insulin Plus GLP-1RA) in Type 2 diabetes. An analytical review of pivotal clinical trials

The Review of Diabetic Studies
Vol. 19 · No. 1 · 2023



Abbreviations: BL: baseline; FPG: fasting plasma glucose, NE: not evaluated, 2 h-PPG: 2-hours post-prandial glucose; *p < 0.0001. date are expressed as mean ± standard deviation

Figure 1. Results of the LixiLan program on: mean changes from BL in (a), A1c (%); (b), fasting plasma glucose (FPG); (c), 2-hours post-prandial glucose (2 h-PPG)

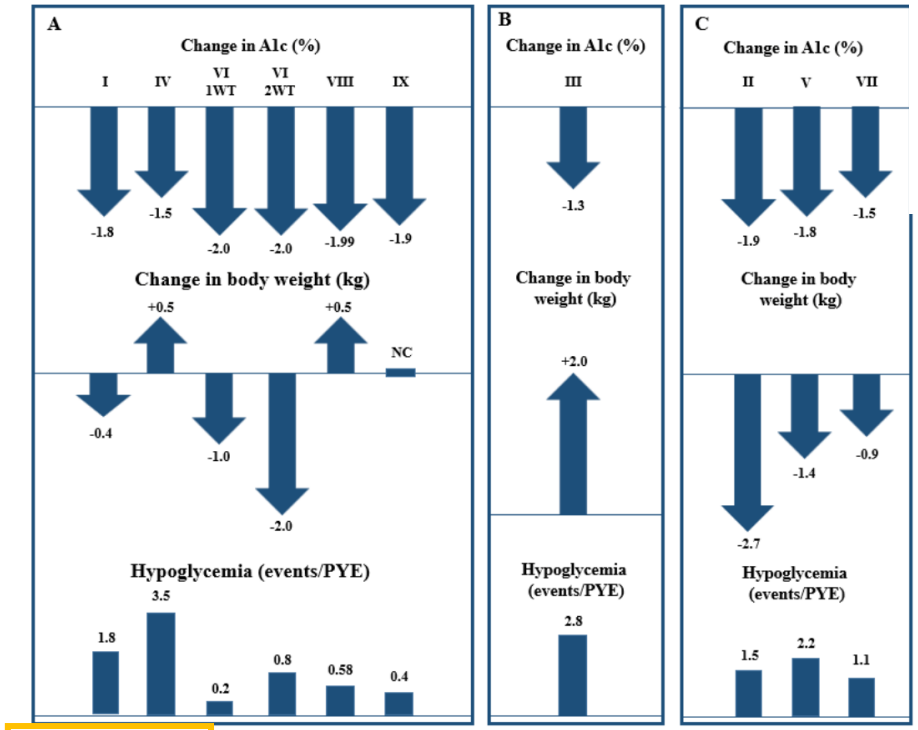


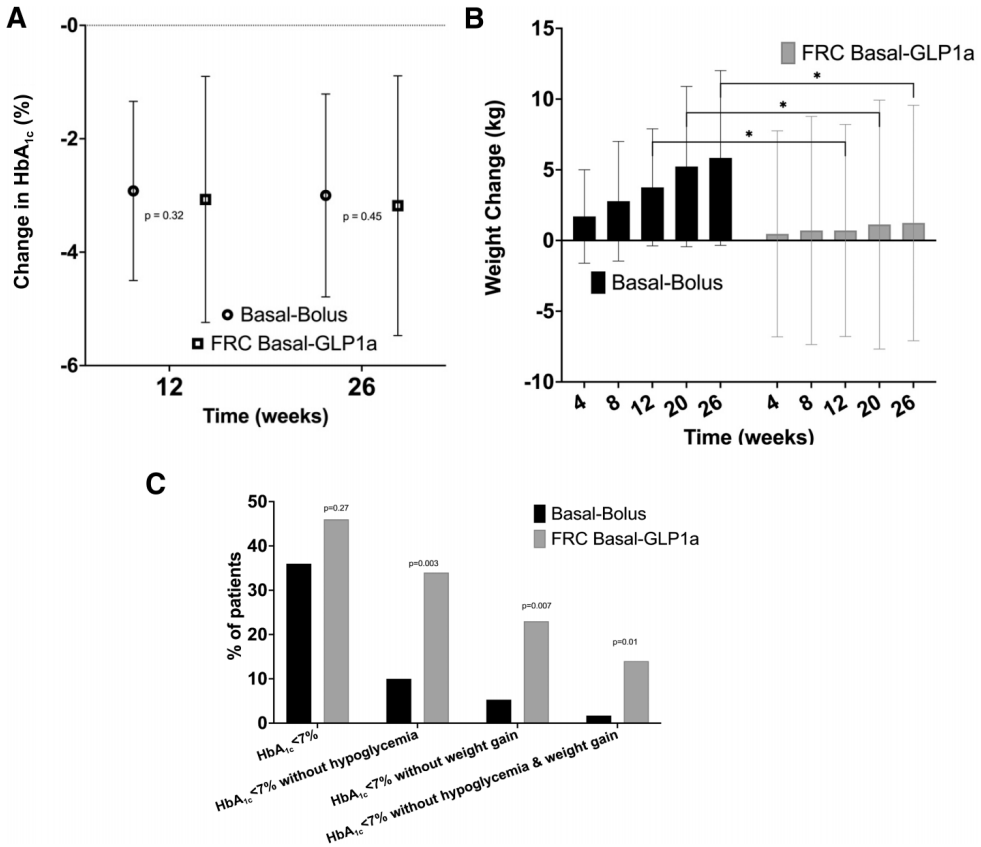
Figure 2. Results of the DUAL program on: changes in A1c value; effects on body weight; and hypoglycemic events in participants with OADs -DUAL IV, VI, VIII, and IX- (a); uncontrolled participants with GLP-1RA -DUAL III- (b); and uncontrolled participants with BI -DUAL II, V, and VII- (c)
Abbreviations: A1c: glycosylated hemoglobin; PYE: events per patient-year of exposure; 1WT: once-weekly titration; 2WT: twice-weekly titration

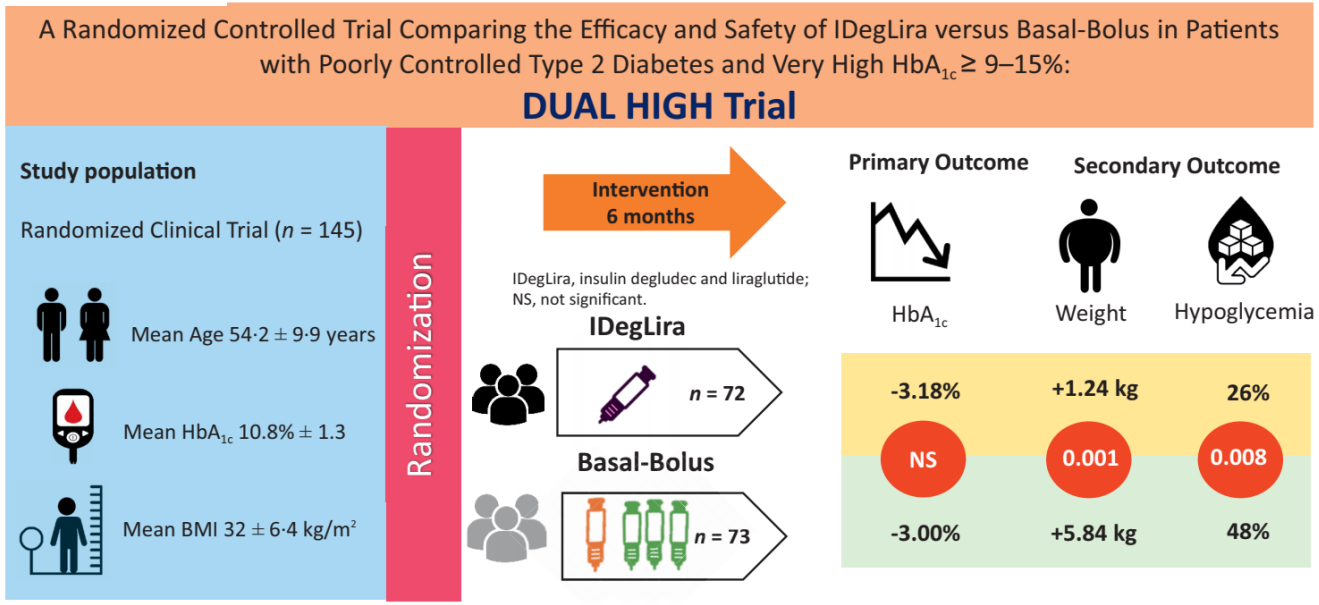
The purpose of this review was to evaluate and analyze the results of pivotal studies with both fixed-ratio combinations in individuals with type 2 diabetes, finding that, they are capable of achieving better glycemic control when compared with each of its components separately (with a lower risk of hypoglycemia vs basal insulin and lower risk of gastrointestinal adverse effects vs GLP-1 receptor agonists) in various clinical scenarios, especially in individuals who do not achieve control with oral antidiabetics or who do not achieve control with basal insulin (associated with oral antidiabetics) or in those under management with GLP-1RA plus oral antidiabetics.

Diabetes Care
American Diabetes Association

A Randomized Controlled Trial Comparing the Efficacy and Safety of IDegLira Versus Basal-Bolus in Patients With Poorly Controlled Type 2 Diabetes and Very High HbA_{1c} ≥9–15%: DUAL HIGH Trial

Diabetes Care 2023;46(9):1–6

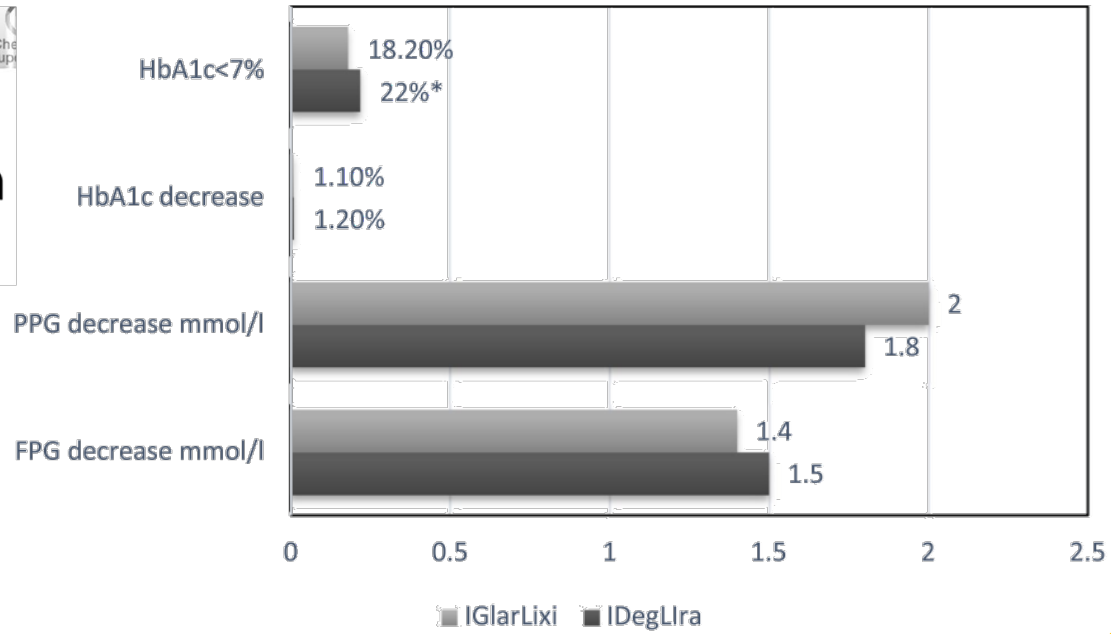




ARTICLE HIGHLIGHTS

- In this randomized controlled trial of patients with type 2 diabetes and very high HbA_{1c} ≥9–15% (75–140.4 mmol/mol), the fixed-ratio combination of basal insulin degludec and liraglutide resulted in similar improvement of glycemic control but less hypoglycemia, less weight gain, and lower insulin requirements compared with basal-bolus insulin regimen.
- This study calls for a paradigm shift to change from the widely used basal-bolus insulin approach to a simpler and more physiologic combination regimen of basal insulin and glucagon-like peptide-1 receptor agonist as the preferred option for patients with severe hyperglycemia and very high HbA_{1c} ≥9–15% (75–140.4 mmol/mol).

Direct comparison two fixed-ratio combination glucagon-like peptide receptor agonist and basal insulin on glycemic and non glycemic parameters in type 2 diabetes



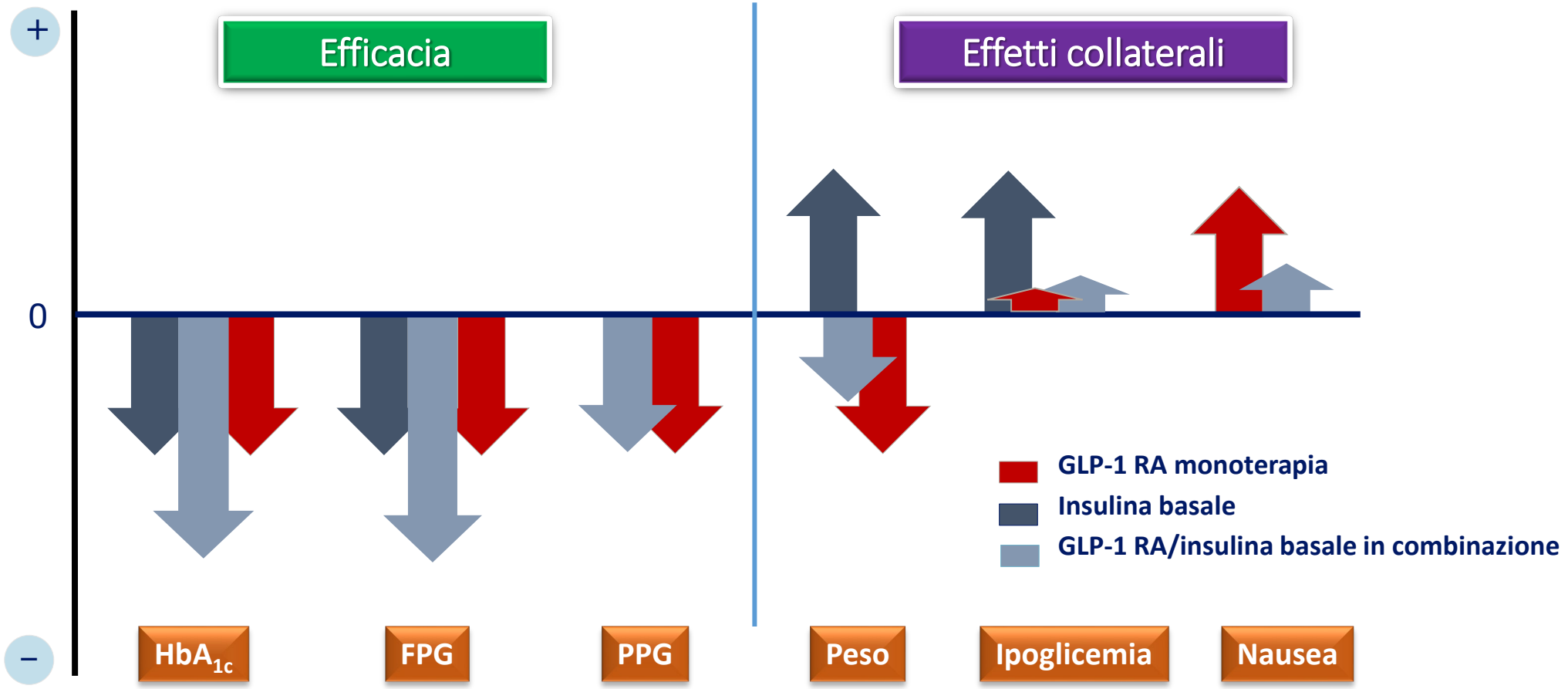
Conclusion

Our results had showed that more patients with iDegLira had HbA1c less than 7% and these combination had better effect on weight loss. Both preparations had similar effect on FPG and PPG, benefit on lipid profile and similar rate of hypoglycemia.

Table 1 Baseline, demographics and disease characteristics, baseline and the end of study

	IDegLira			IGlarLixi		
	Baseline	**At the end**	***p* value**	**Baseline**	**At the end**	***p* value**
Gender,male, %	53.5	53.5	ns	48.5	48.5	ns
Age, years	58.6 ± 9.7	59.2 ± 3.5	ns	60.2 ± 8.3	60.8 ± 7.4	ns
Duration of DM, years	9.6 ± 3.6	10.2 ± 3.2	ns	10.5 ± 3.9	11.1 ± 4.1	ns
HbA1c, %	8.9 ± 1.1	7.7 ± 1	< 0.001	9 ± 1.4	7.9 ± 1.1	< 0.001
FPG, mmol/l	7.5 ± 1.5	6.0 ± 1.1	< 0.001	7.8 ± 1.7	6.4 ± 0.37	< 0.001
PPG, mmol/l	10.1 ± 2.5	8.3 ± 0.9	< 0.001	10.3 ± 1.8	8.3 ± 1.2	< 0.001
Weight, kg	87.1 ± 15.4	85.3 ± 14.5	< 0.001	89.4 ± 14.9	88.7 ± 14.5	< 0.001
BMI, kg/m^2	30.2 ± 7.3	28.8 ± 3.2	< 0.001	30.8 ± 4.3	30.2 ± 4.1	< 0.001
Insulin dose, units	27 ± 5.5	26 ± 4	< 0.05	28 ± 5	26 ± 3.5	< 0.001

Effetti complementari di insulina basale e analoghi GLP-1



Treatment intensification following glucagon-like peptide-1 receptor agonist treatment in type 2 diabetes: The RESTORE-G real-world study

The study provides a comprehensive overview of the intensification strategies adopted in the real-world following GLP-1 RA treatment, the switch to BI being the most common approach. Further education on the role of combination therapy of BI and GLP-1RA is needed to optimize T2D therapy at the right time. The effectiveness and the safety of adding-on or switching to BI or FRC in everyday clinical activity was documented, although under-titration has been observed. As per the guidance, to overcome clinical inertia, given the proven effectiveness and safety of intensification with BI, the timely addition and titration of the new BI analogs to GLP-1 RA and appropriate FRC use could be considered as one of the valuable therapeutic options.

Table 2 Effectiveness analyses. Changes in estimated mean levels of continuous endpoints during the follow-up and within-group comparisons (overall population, T0 ≥2011).

Endpoints	Visit	ADD-ON (N = 718)			SWITCH-BI (N = 2138)			SWITCH-FRC (N = 308)		
		Estimated mean levels (95%CI)	Estimated mean difference from T0 and 95% CI	p-value	Estimated mean levels (95%CI)	Estimated mean difference from T0 and 95% CI	p-value	Estimated mean levels (95%CI)	Estimated mean difference from T0 and 95% CI	p-value
HbA1c (%)	T0	9.03 (8.89; 9.17)			9.41 (9.33; 9.49)			8.98 (8.81; 9.15)		
	T6	7.97 (7.84; 8.10)	−1.06 (−1.22;-0.90)	**<0.0001**	8.25 (8.18; 8.32)	−1.16 (−1.25;-1.07)	**<0.0001**	8.00 (7.82; 8.18)	−0.98 (−1.20;-0.76)	**<0.0001**
	T12	8.03 (7.89; 8.17)	−0.99 (−1.16;-0.82)	**<0.0001**	8.26 (8.18; 8.34)	−1.15 (−1.25;-1.05)	**<0.0001**	7.92 (7.69; 8.15)	−1.06 (−1.31;-0.81)	**<0.0001**
FBG (mg/dl)	T0	206.72 (200.19; 213.25)			213.36 (209.84; 216.88)			197.47 (188.79; 206.15)		
	T6	158.80 (153.26; 164.34)	−47.92 (−55.88;-39.96)	**<0.0001**	163.64 (160.59; 166.69)	−49.73 (−54.05;-45.41)	**<0.0001**	155.25 (146.76; 163.74)	−42.22 (−53.26;-31.18)	**<0.0001**
	T12	161.23 (155.07; 167.39)	−45.49 (−53.66;-37.32)	**<0.0001**	165.57 (162.23; 168.91)	−47.79 (−52.18;-43.40)	**<0.0001**	148.97 (138.10; 159.84)	−48.49 (−61.96;-35.02)	**<0.0001**
Body weight (kg)	T0	95.16 (93.60; 96.72)			91.35 (90.43; 92.27)			93.63 (91.16; 96.10)		
	T6	94.91 (93.36; 96.46)	−0.25 (−0.74; 0.24)	0.31	92.25 (91.34; 93.16)	0.90 (0.61; 1.19)	**<0.0001**	93.93 (91.45; 96.41)	0.30 (−0.42; 1.02)	0.42
	T12	95.19 (93.59; 96.79)	0.02 (−0.65; 0.69)	0.94	92.97 (92.04; 93.90)	1.62 (1.23; 2.01)	**<0.0001**	94.97 (92.40; 97.54)	1.34 (0.14; 2.54)	**0.03**
Basal insulin dose (U)	T0	12.12 (11.71; 12.53)			12.39 (12.15; 12.63)			16.61 (15.96; 17.26)		
	T6	18.72 (17.87; 19.57)	6.61 (5.84; 7.38)	**<0.0001**	18.17 (17.69; 18.65)	5.79 (5.36; 6.22)	**<0.0001**	20.89 (19.53; 22.25)	4.28 (3.02; 5.54)	**<0.0001**
	T12	21.52 (20.49; 22.55)	9.40 (8.41; 10.39)	**<0.0001**	20.08 (19.51; 20.65)	7.69 (7.14; 8.24)	**<0.0001**	22.87 (21.00; 24.74)	6.26 (4.45; 8.07)	**<0.0001**
Basal insulin dose (U/kg)	T0	0.13 (0.12; 0.14)			0.14 (0.14; 0.14)			0.18 (0.17; 0.19)		
	T6	0.20 (0.19; 0.21)	0.07 (0.06; 0.08)	**<0.0001**	0.20 (0.19; 0.21)	0.06 (0.05; 0.07)	**<0.0001**	0.23 (0.21; 0.25)	0.04 (0.02; 0.06)	**<0.0001**
	T12	0.23 (0.22; 0.24)	0.10 (0.09; 0.11)	**<0.0001**	0.21 (0.20; 0.22)	0.07 (0.06; 0.08)	**<0.0001**	0.25 (0.23; 0.27)	0.06 (0.04; 0.08)	**<0.0001**

p-values = paired *t*-test derived from linear mixed models for repeated measurements. Statistically significant p-values ($p < 0.05$) are in bold.

R. Candido et al. Nutrition, Metabolism & Cardiovascular Diseases https://doi.org/10.1016/j.numecd.2023.

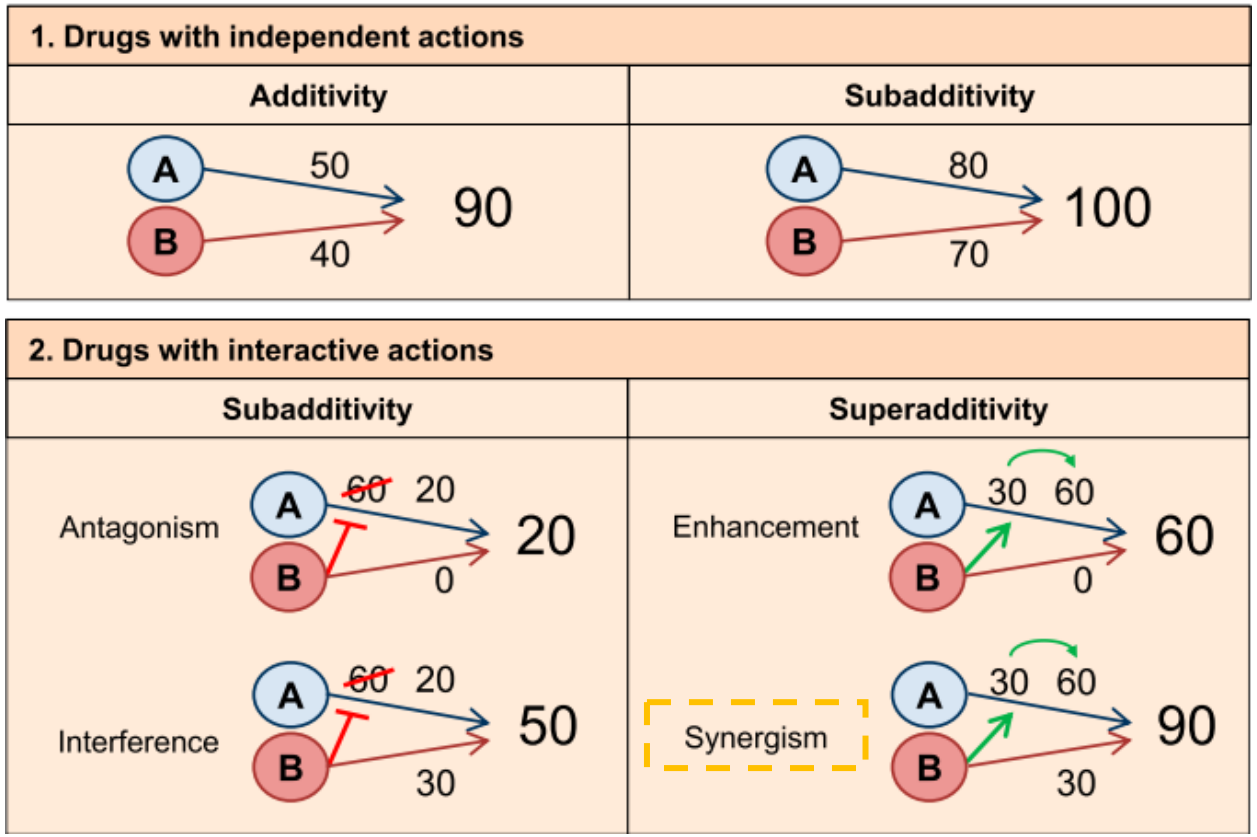


Figure 2—Mechanistic principles for net effects of drugs in combination therapy. The quantitative or net effect of two or more drugs depends on whether the individual drug effects are independent or interactive. When drug effects are independent, the quantitative effect is either additive or subadditive. When drug effects interact, the quantitative effect can be subadditive by antagonism or interference, or superadditive by enhancement or synergism. The effect of the individual drugs is indicated next to the arrows, and the net effect of the combination is indicated by the number at the right of each pair. The maximum effect is 100. A represents drug

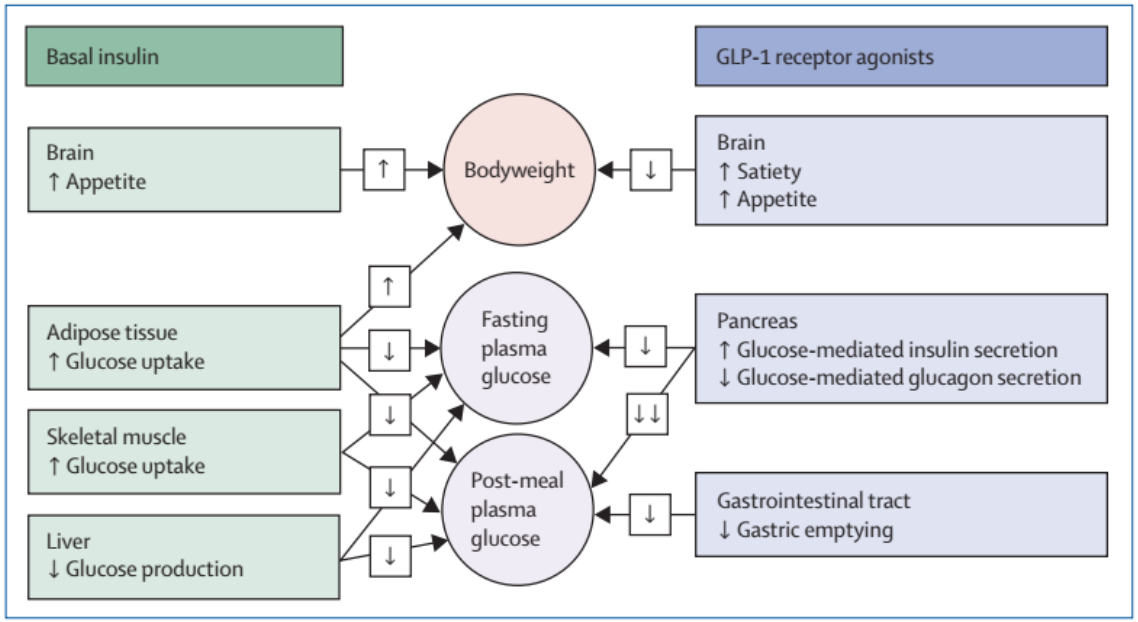


Figure: Schematic representation of the potential synergistic effects of treatment with basal insulin and a longacting GLP-1 agonist

Fixed-ratio combination of basal insulin and GLP-1 receptor agonist: is two better than one?

Stefano Del Prato

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

Insulina basale e analoghi GLP-1: Effetti positivi sulla qualità di vita

European Review for Medical and Pharmacological Sciences 2021; 25: 923-931

Real-world study on the effectiveness and safety of basal insulin IDegLira in type 2 diabetic patients previously treated with multi-injective insulin therapy

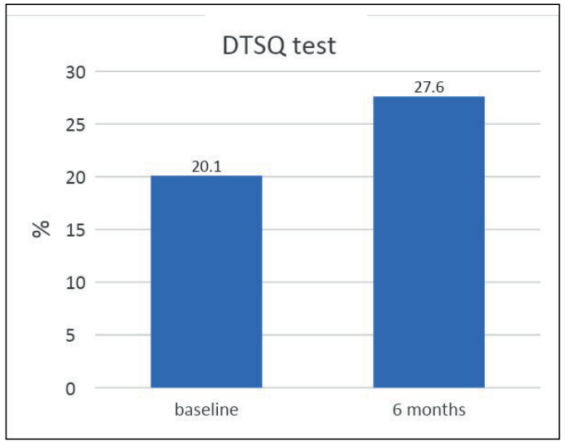


Figure 2. Variation of Diabetes Treatment Satisfaction Questionnaire score from baseline to 6 months (n=21). *p<0.0001. DTSQ: Diabetes Treatment Satisfaction Questionnaire.

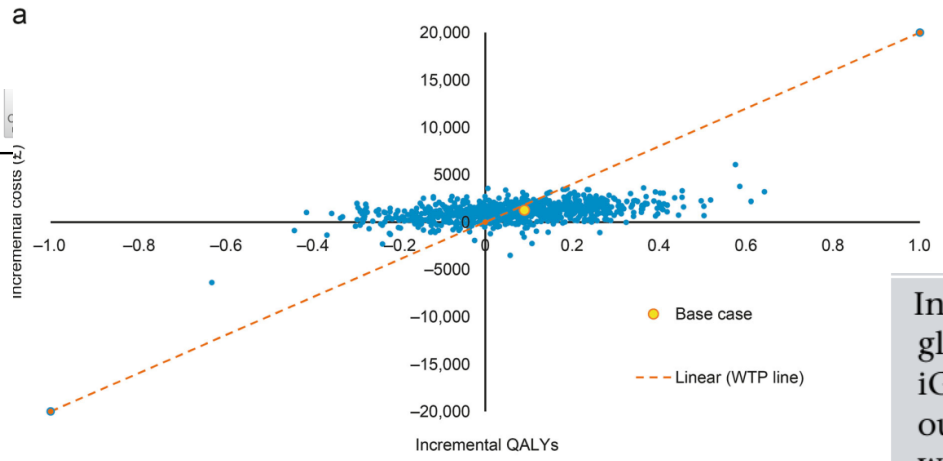
CONCLUSIONS: These real-world findings show that degludec/liraglutide seems to be more effective than basal-bolus insulin in achieving glycemic control, allowing cost sustainability and improving patient satisfaction.

Diabetes Ther
https://doi.org/10.1007/s13300-022-01267-3

ORIGINAL RESEARCH

Cost-Effectiveness of iGlarLixi Versus Premix BIAsp 30 in Patients with Type 2 Diabetes Suboptimally Controlled by Basal Insulin in the UK

Received: January 24, 2022 / Accepted: April 20, 2022



In people living with T2D with suboptimal glycemic control during BI therapy, iGlarLixi confers slightly improved QALY outcomes at an acceptable cost compared with premix BIAsp 30.

Once-weekly vs. once-daily insulin therapy

Clinical	Molecular
Improved (or similar) glycaemic control with low hypoglycaemia risk	Longer half-life
Reduced treatment burden	More stable PK/PD
Easier to overcome clinical inertia	Slower clearance rate

Better treatment acceptance and adherence

Diabetes Obes Metab. 2023;

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.

Pharmacology of once-weekly insulins

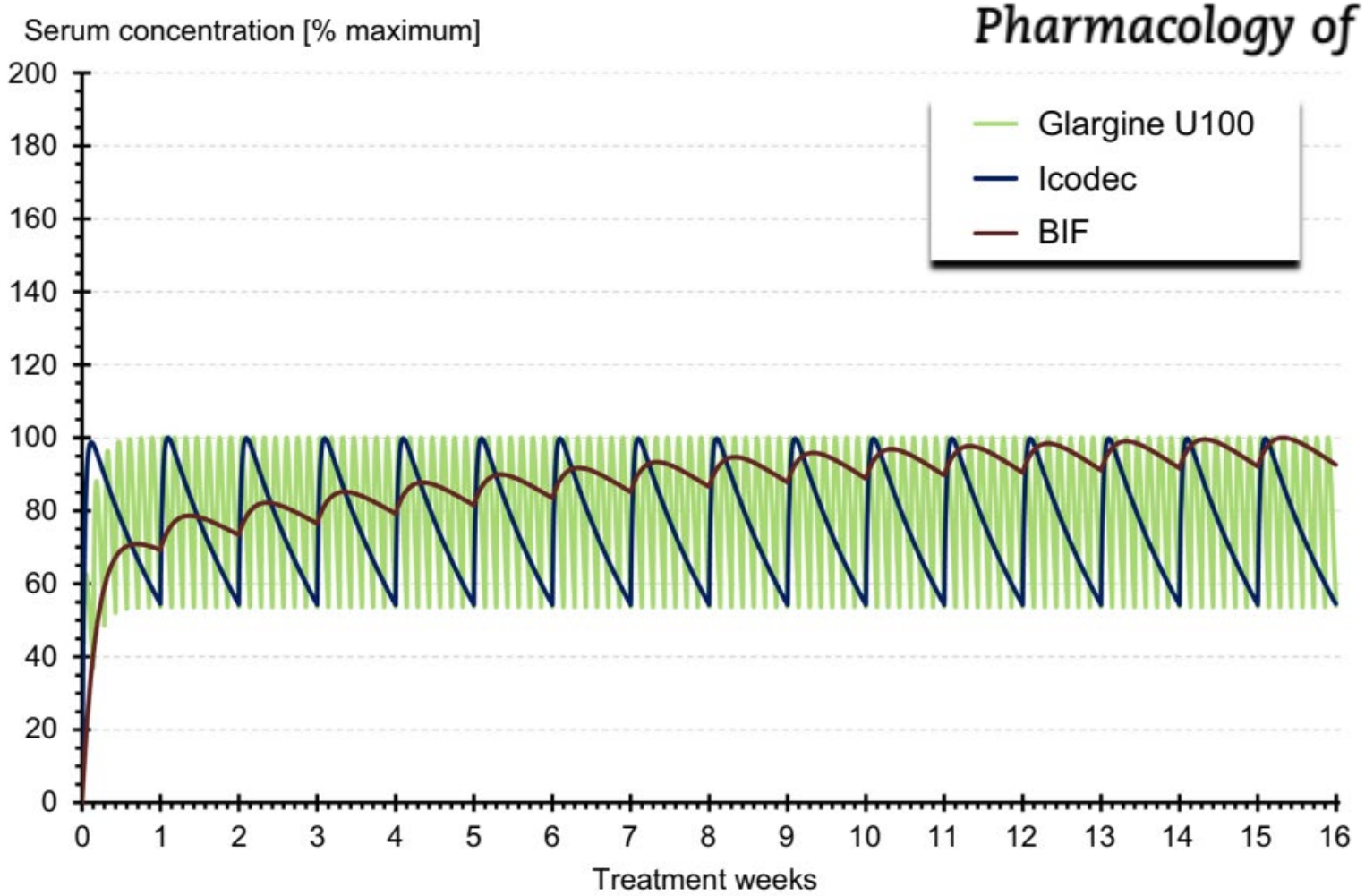


Fig. 1 – Simulated pharmacokinetic profiles of insulin glargine U100 (injected once daily), insulin icodec and basal insulin Fc BIF (both injected once weekly with a loading dose at first administration). Simulated serum concentrations are given as percentages of maximum concentrations at steady state. BIF as the insulin with the longest half-life needs more time to reach steady state, but shows the lowest peak-to-trough fluctuations at steady state. Insulin icodec shows similar peak-to-trough fluctuations over a one-week treatment interval as insulin glargine over 24 h.

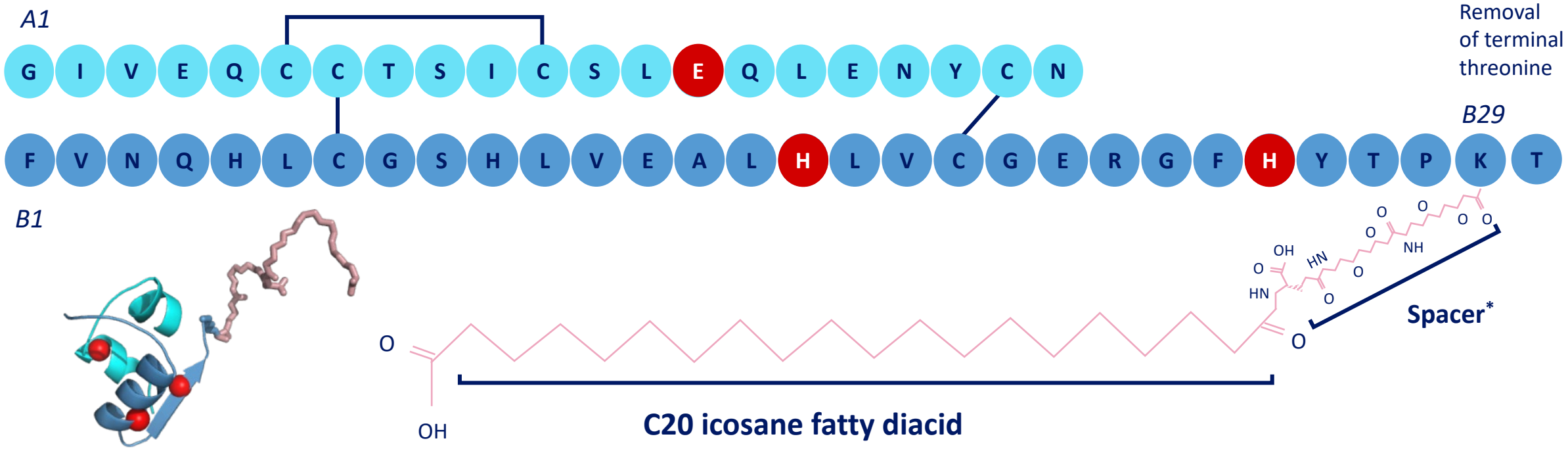
Insulin icodec

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

- Strong albumin binding combined with reduced insulin receptor affinity ensures slow clearance and the formation of an essentially inactive albumin-bound depot, providing slow and continuous insulin action.
- Insulin icodec retains the same biological properties as natural human insulin, with no increase in insulin-like growth factor-1 receptor binding or mitogenicity.

Three amino acid substitutions

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



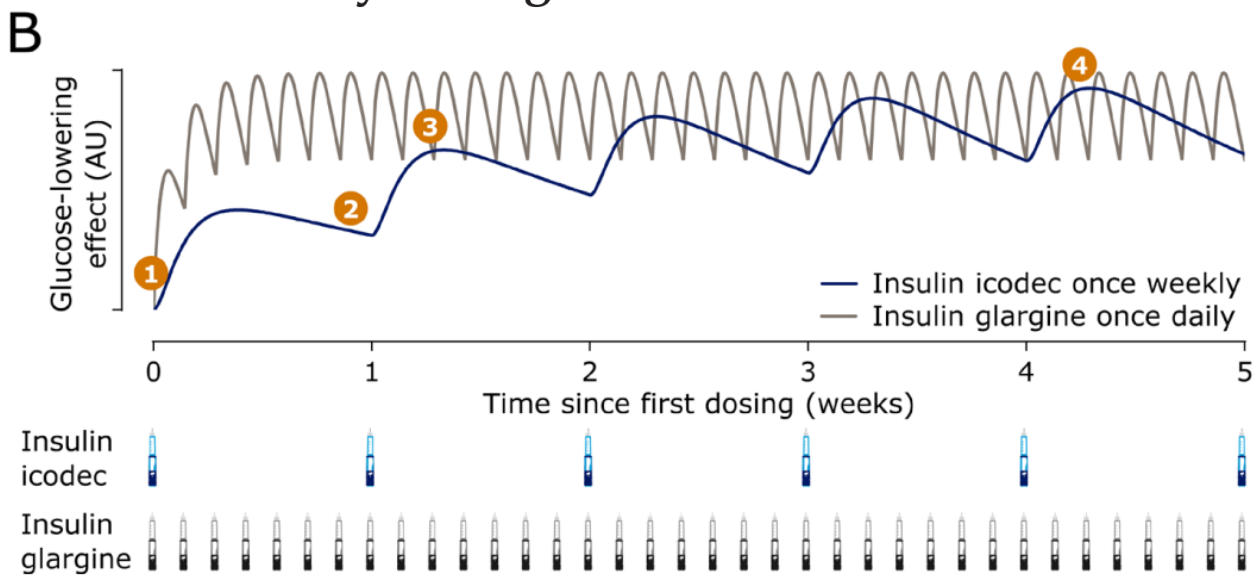
C20 icosane fatty diacid

- 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.

Molecular and pharmacological characterization of insulin icodec: a new basal insulin analog designed for once-weekly dosing



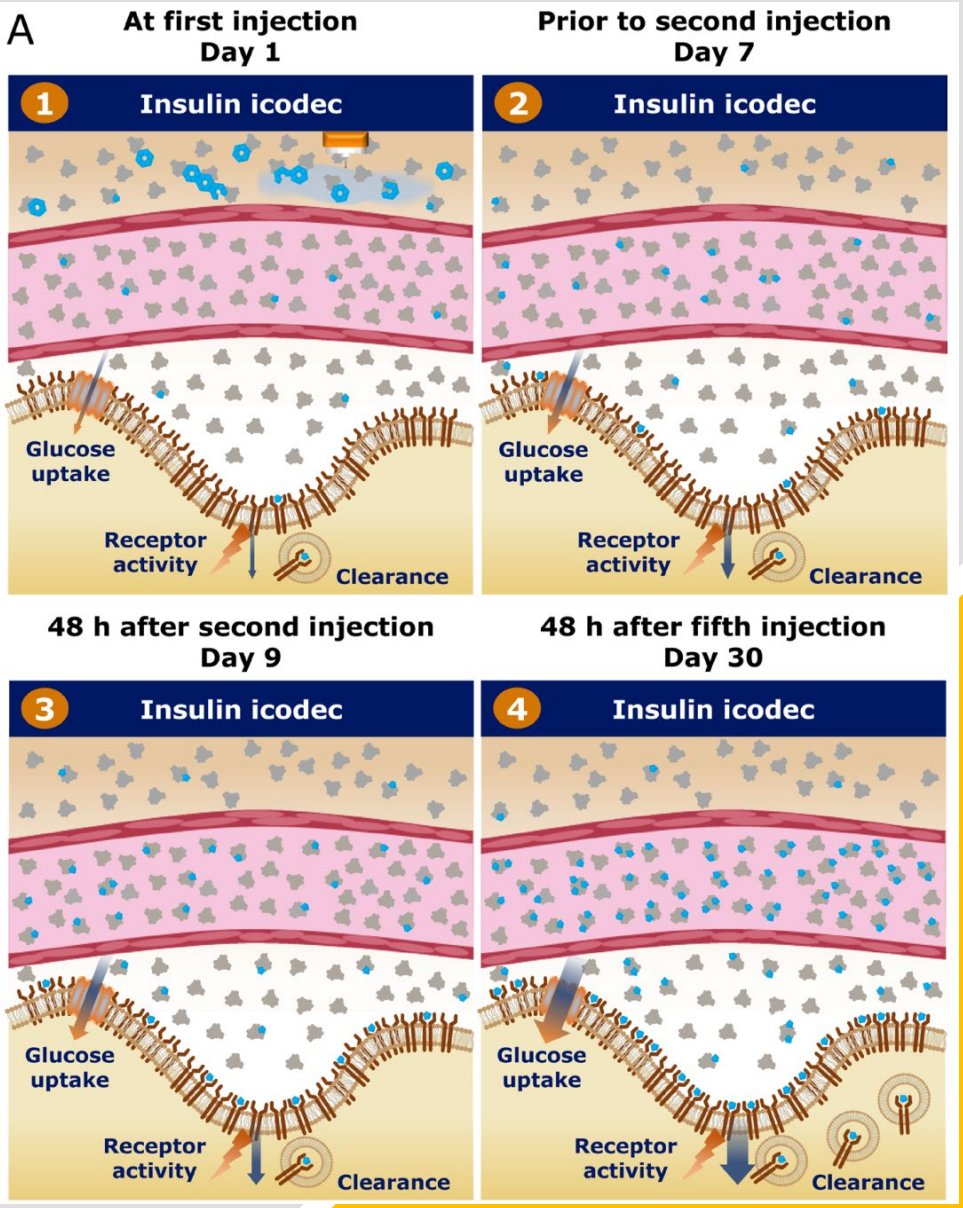
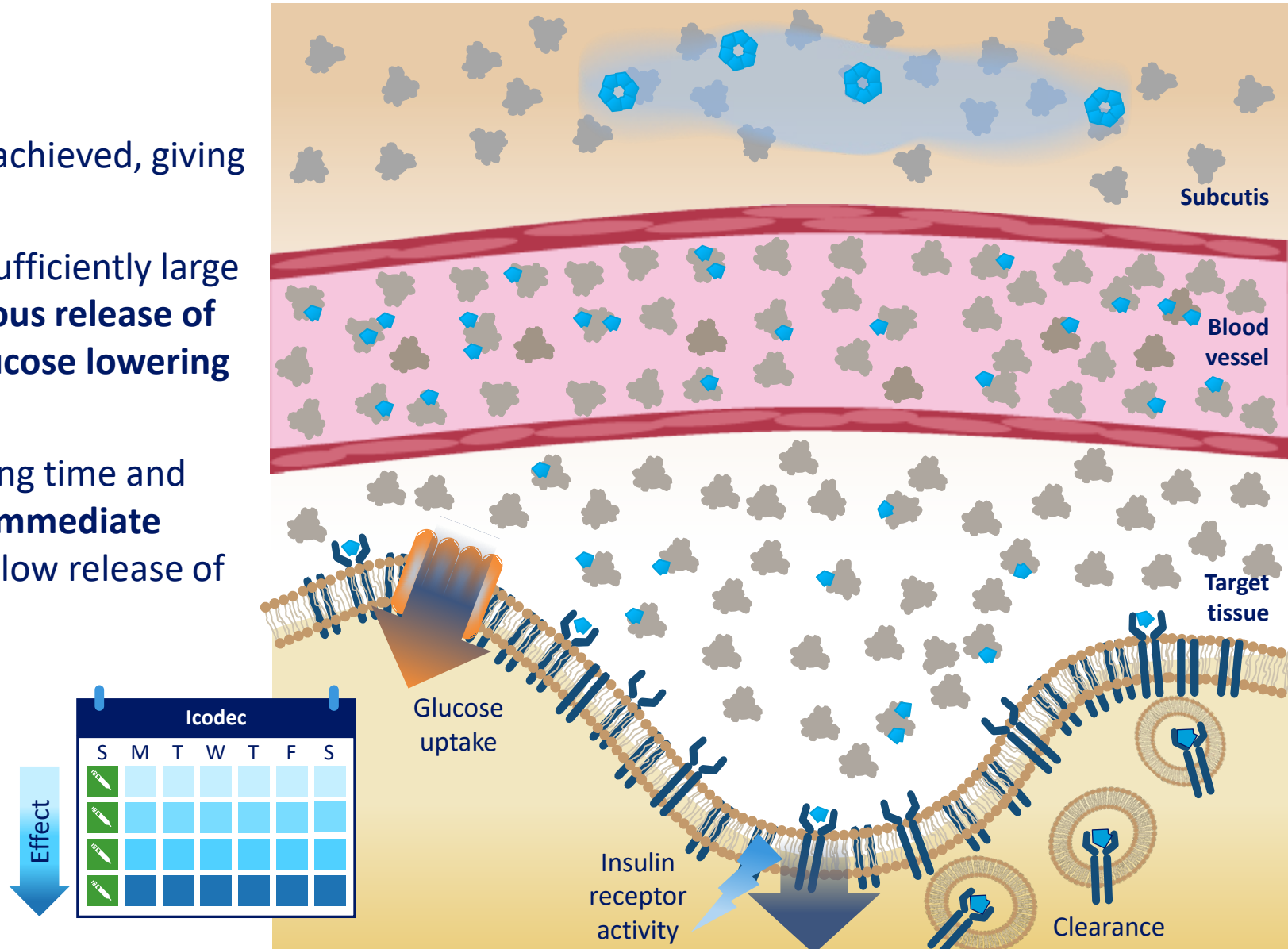


Figure 3 Schematic depiction of build-up to steady state and mechanism of action of insulin icodec. (A) Distribution of insulin icodec (light blue) bound to albumin (grey) in the different compartments over time from initiation of once-weekly dosing. Chart 1: distribution of insulin icodec after the first injection, with the majority of insulin icodec in the subcutis and a small proportion absorbed into the blood. Chart 2: day 7, prior to the second injection, showing that there is still insulin icodec distributed prior to the next injection. Charts 3–4: showing the gradual build-up of insulin icodec exposure towards steady state. (B) Conceptual model showing glucose-lowering effect over time from initiation of once-weekly dosing of insulin icodec and once-daily dosing of insulin glargine U100 (at comparable dose levels). Blue curve: insulin icodec; grey curve: insulin glargine U100. Orange labels refer to charts 1–4 in panel A. AU, arbitrary units.

At steady state

Icodec mode of action

- After 3–4 injections, steady state* is achieved, giving **the full effect of the icodec dose**
- The icodec albumin-bound depot is sufficiently large enough to provide **slow and continuous release of active icodec to achieve effective glucose lowering throughout the week**
- At steady state, any variations in dosing time and amount lead to **minimal changes in immediate glucose-lowering effects** due to the slow release of icodec



*When the number of molecules dosed = number of molecules cleared. For illustrative purposes the albumin to icodec ratio have been considerably exaggerated (eg, in reality, at steady state, ~2000:1 albumin:icodec molecules).

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

Once-weekly basal insulin icodec: Looking ONWARDS from pharmacology to clinical trials

Diabetes & Metabolic Syndrome: Clinical Research & Reviews 16 (2022)

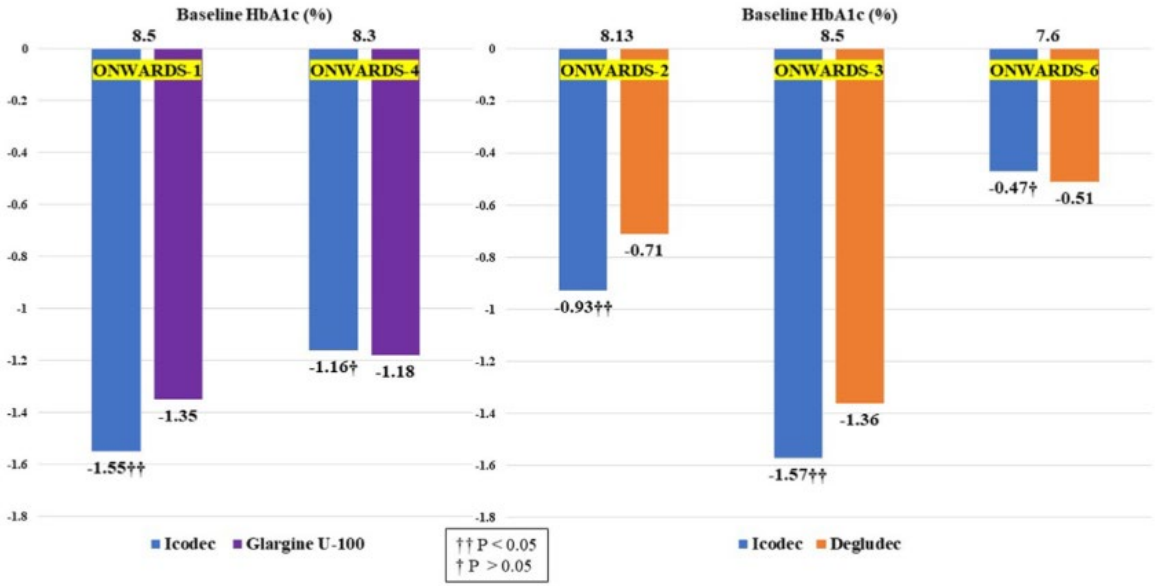


Fig. 2. HbA1c lowering with once-weekly insulin icodec vs. once-daily insulin glargine (U-100) or degludec.

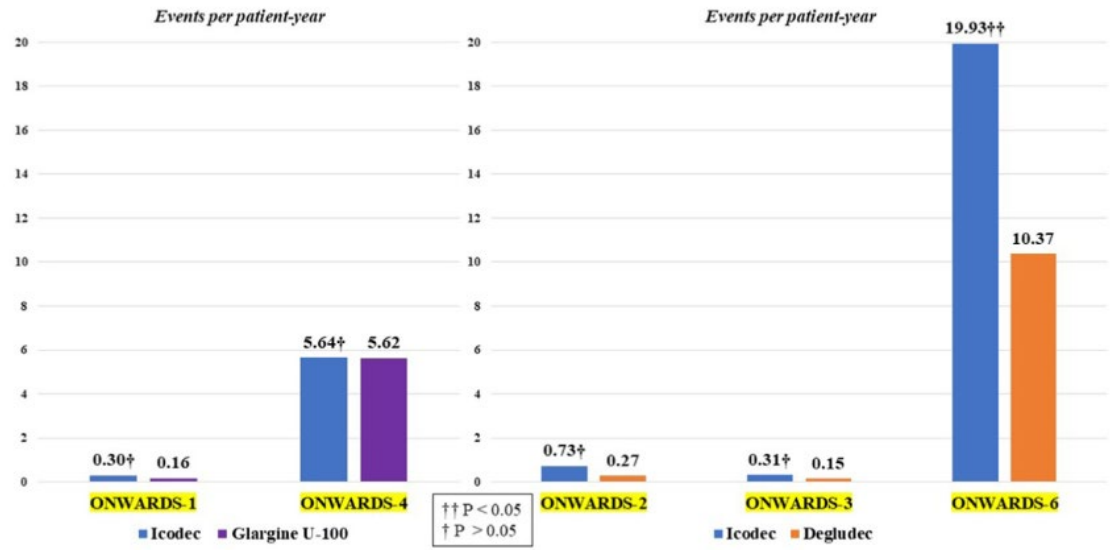


Fig. 3. Rate of level 2 or 3 hypoglycemia with once-weekly insulin icodec vs. once-daily insulin glargine (U-100) or degludec.

Results: Phase 1 study showed insulin icodec having a half-life of 196 h (>1 week) while a steady state is achieved after 3 to 4 weekly injections. Phase 2 studies compared once-weekly icodec to insulin glargine (U-100) and found a similar glucose control with no significantly greater hypoglycemia risks. Top-line results from the five phase 3 studies reported better glucose control with once-weekly icodec compared to both once-daily insulin glargine (ONWARDS 1) and once-daily degludec (in both ONWARDS 2 and 4) with similar rates of hypoglycemia in type 2 diabetes, although there was a higher hypoglycemic event with insulin icodec in type 1 diabetes (ONWARDS 6) compared to once-daily degludec despite a similar glycemic control.

Conclusion: A brighter prospect of once-weekly insulin icodec is on the card in particular in type 2 diabetes in terms of reducing injection pricks by >85% vs. once-daily basal insulin analogs, although few unknowns still exist.

Weekly Basal Insulin Fc (BIF)

- Weekly basal insulin Fc (BIF Weekly basal insulin Fc) s designed for once-weekly subcutaneous administration. BIF is comprised of a human insulin receptor (IR) agonist fused to a human immunoglobulin G2 (IgG2) fragment crystallizable (Fc) domain. Similar to other Fc-conjugated molecules, it is expected that the presence of the Fc domain, in combination with controlled IR-mediated clearance because of reduced IR affinity, will lead to prolonged half-life

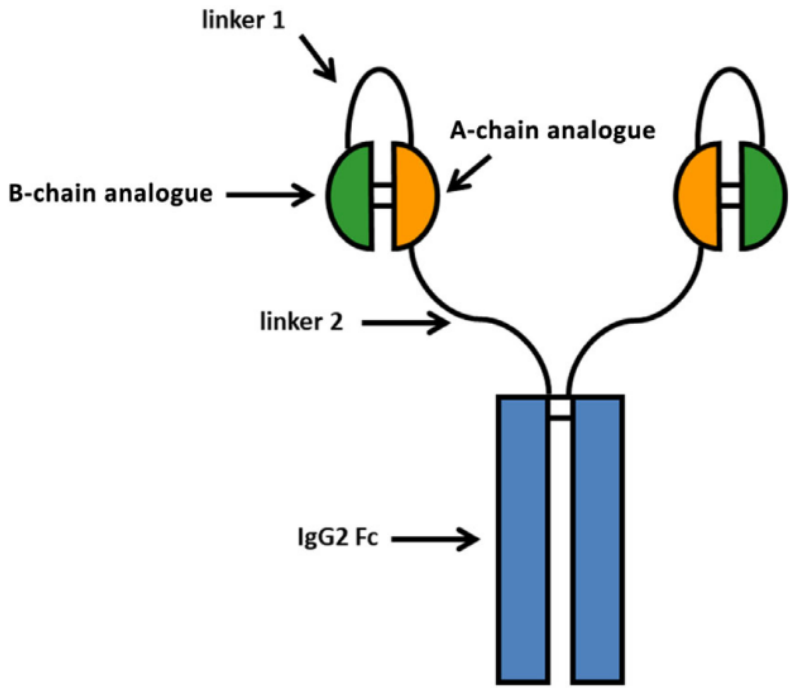


FIGURE 1 Schematic of weekly basal insulin Fc (BIF) structure.[22]
IgG2, immunoglobulin G2

Diabetes Obes Metab. 2023;

Attributes

- Selective insulin receptor agonist
  - Selectivity versus IGF-1 receptor
  - Low mitogenicity potential
- Pharmacokinetic profile consistent with once weekly subcutaneous dosing
- Formulation compatible with single-use or multi-use devices
  - Can be co-formulated with weekly incretins
- Low immunogenicity risk

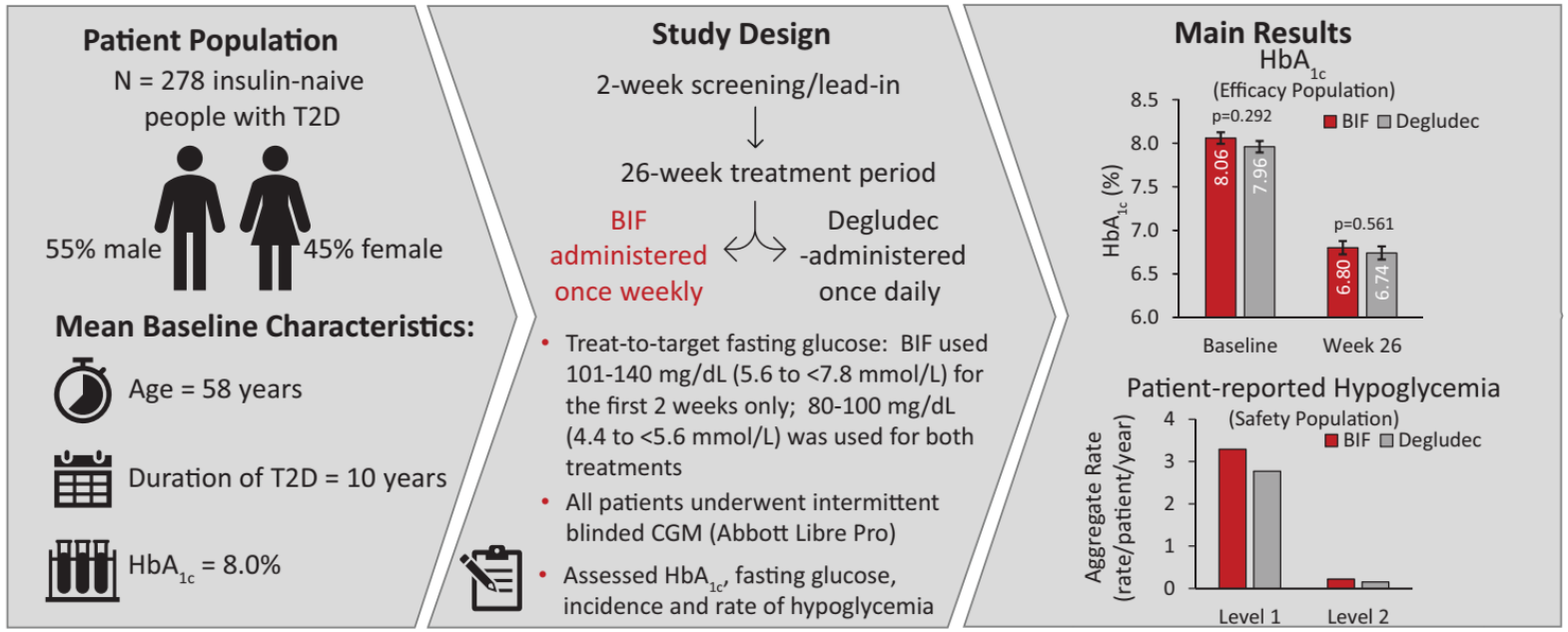
Once-Weekly Basal Insulin Fc Demonstrated Similar Glycemic Control to Once-Daily Insulin Degludec in Insulin-Naive Patients With Type 2 Diabetes: A Phase 2 Randomized Control Trial

Diabetes Care 2023;46:1060–1067 | https://doi.org/10.2337/dc22-2396

Once-weekly basal insulin Fc (BIF) demonstrated similar glycemic control to once-daily insulin degludec in insulin-naive patients with type 2 diabetes (T2D) in this phase 2 randomized controlled trial. CGM, continous glucose monitoring.

Background

Once-weekly BIF combines a novel single-chain insulin variant with a human IgG_2 Fc domain and is designed for once-weekly subcutaneous administration for the treatment of diabetes.



Conclusion

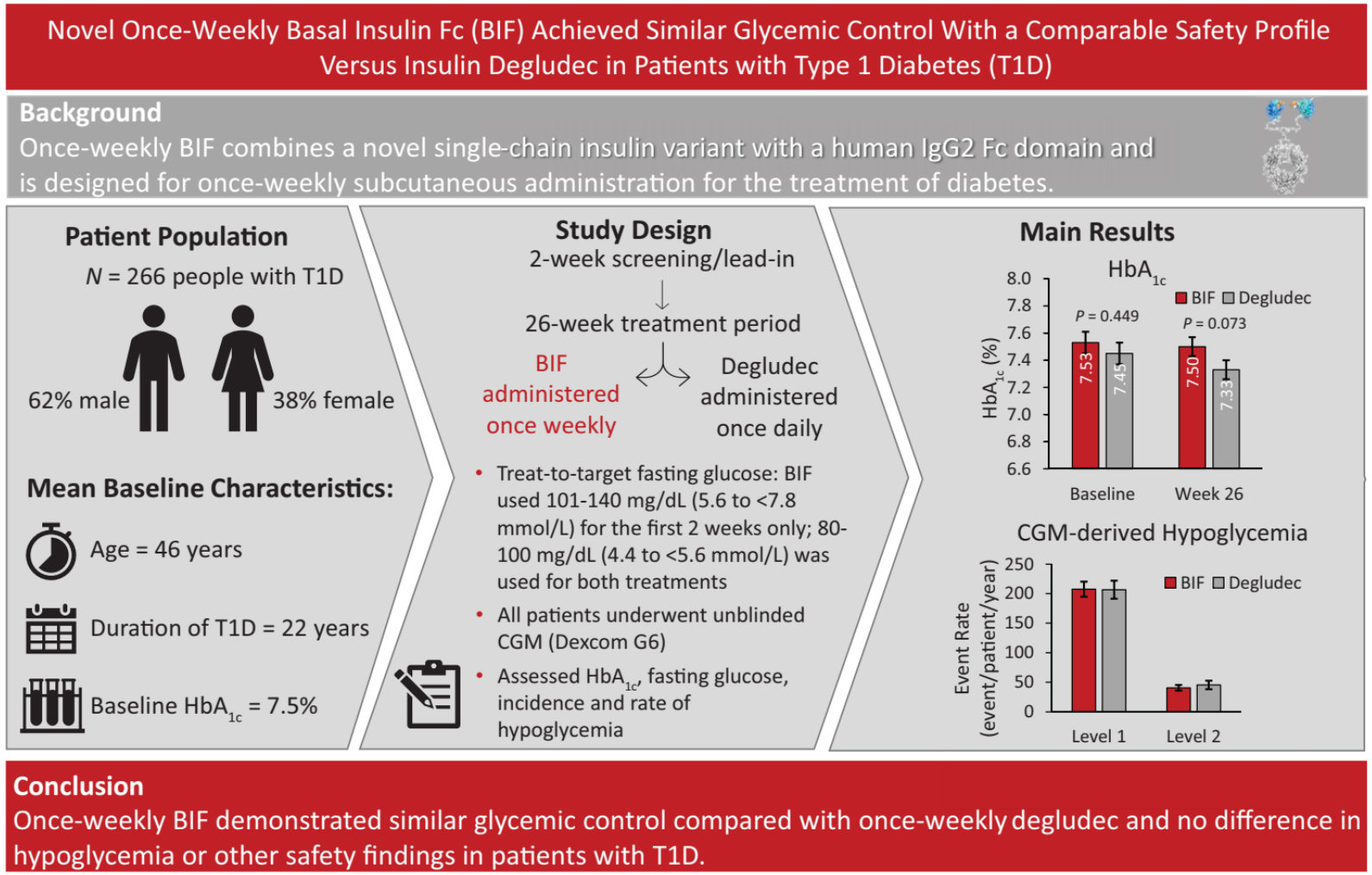
Once-weekly BIF demonstrated excellent glycemic control similar to Once-daily degludec and no difference in hypoglycemia or other safety findings in insulin-naive patients with T2D.

ARTICLE HIGHLIGHTS

- This study assessed once-weekly basal insulin Fc (BIF) as a treatment option for insulin-naive patients with type 2 diabetes (T2D).
- The research question was whether BIF is a safe and efficacious treatment for insulin-naive patients with T2D.
- BIF administered once weekly achieved similar glycemic control with similar hypoglycemia risk compared with once-daily degludec.
- BIF has the potential to safely and effectively manage glycemic control in insulin-naive patients with T2D while reducing injection burden.

Novel Once-Weekly Basal Insulin Fc Achieved Similar Glycemic Control With a Safety Profile Comparable to Insulin Degludec in Patients With Type 1 Diabetes

Diabetes Care 2023;46:1052–1059 | https://doi.org/10.2337/dc22-2395



ARTICLE HIGHLIGHTS

- Once-weekly basal insulin Fc (BIF) was administered as treatment for patients with type 1 diabetes (T1D).
- We wanted to determine if BIF is safe and efficacious for patients with T1D.
- BIF demonstrated similar glycemic control to daily insulin degludec, without increasing the risk of hypoglycemia in patients with T1D.
- BIF has the potential to safely and effectively provide glycemic control while reducing the injection burden in T1D.

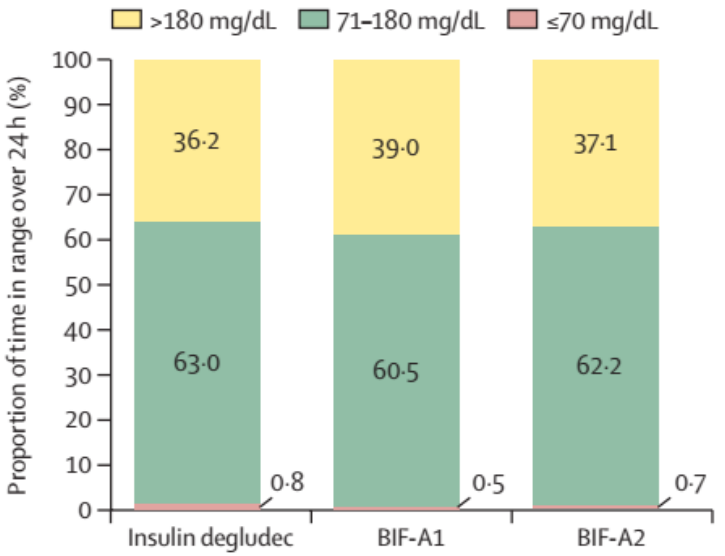
Diabetes Care 2023;46(5):1052–1059

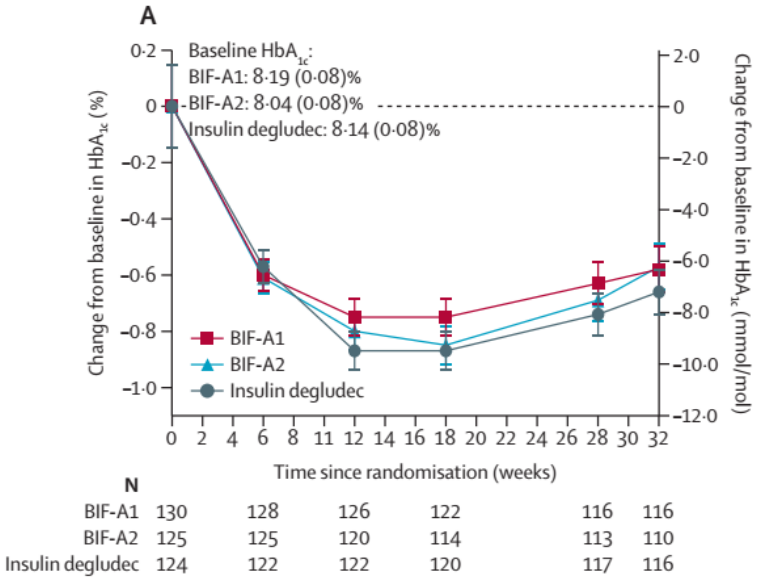
Safety and efficacy of once-weekly basal insulin Fc in people with type 2 diabetes previously treated with basal insulin: a multicentre, open-label, randomised, phase 2 study

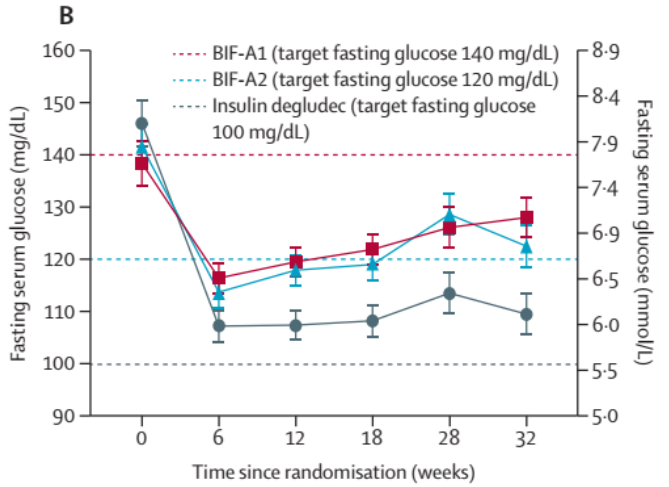
Lancet Diabetes Endocrinol
2023; 11: 158–68

Implications of all the available evidence
Weekly BIF treatment resulted in stable glycaemic control in people with type 2 diabetes previously treated with basal insulin. The reduced treatment burden of once-weekly insulin compared with daily insulin has the potential to improve treatment adherence and positively affect glycaemic outcomes. These BIF data show promise for patients who require insulin treatment intensification. These findings support continued development of BIF as a once-weekly insulin treatment of diabetes.

Interpretation Weekly BIF achieved a similar efficacy compared with degludec despite higher fasting glucose targets in the BIF groups. Higher fasting glucose targets and lower glucose variability might have contributed to lower hypoglycaemia rates for BIF compared with degludec. These findings support continued development of BIF as a once-weekly insulin treatment for people with diabetes.







Safety and efficacy of once-weekly basal insulin Fc in people with type 2 diabetes previously treated with basal insulin: a multicentre, open-label, randomised, phase 2 study

Lancet Diabetes Endocrinol
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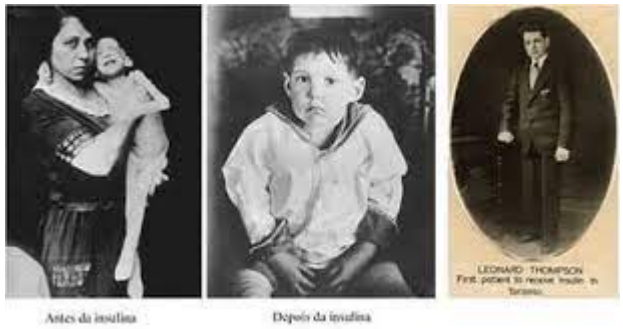
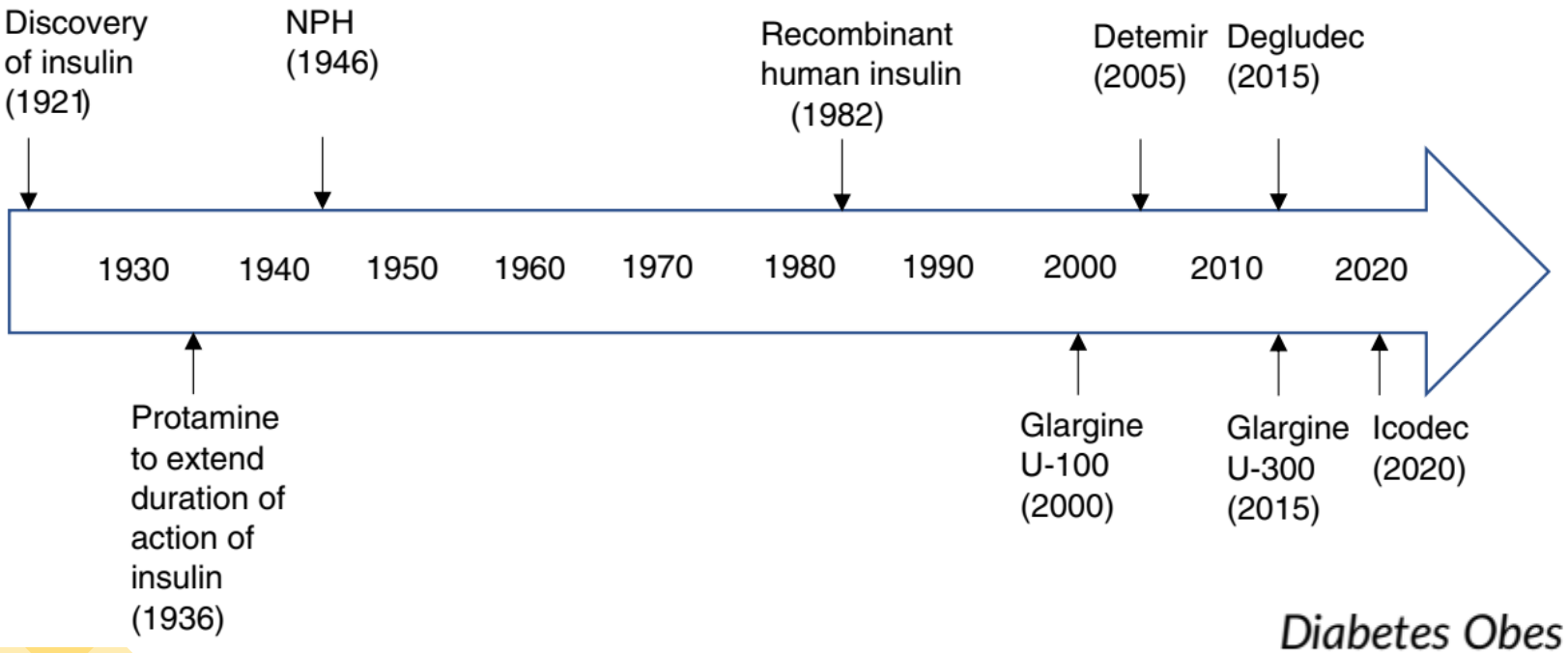
In conclusion, in people with type 2 diabetes previously treated with basal insulin, once-weekly BIF did not show meaningful differences from once-daily insulin degludec in terms of safety and efficacy. The findings suggest that weekly insulin dosing is a viable option for this patient population and might provide the benefit of more stable glycaemic control with reduced treatment burden. Further phase 2 studies were conducted to evaluate BIF in people with type 1 diabetes (NCT04450407) or type 2 diabetes (insulin-naive patients; NCT04450394) compared with insulin degludec with a strict glycaemic target of 100 mg/dL (5·6 mmol/L). Together, these studies informed a large, phase 3 programme, entitled Once Weekly Insulin Therapy (QWINT), that is currently underway.

	BIF-A1 (n=135)	BIF-A2 (n=131)	Insulin degludec (n=132)
Documented 24-h hypoglycaemia (≤70 mg/dL; ≤3·9 mmol/L)			
Incidence	124 (91·85%)	117 (89·31%)	117 (88·64%)
Event rate	23·0	22·5	30·5
Event rate ratio (90% CI)	0·75 (0·61–0·93)	0·74 (0·58–0·94)	..
Documented nocturnal hypoglycaemia (≤70 mg/dL; ≤3·9 mmol/L)			
Incidence	105 (77·78%)	88 (67·18%)	105 (79·55%)
Event rate	7·6	6·5	11·4
Event rate ratio (90% CI)	0·67 (0·52–0·85)	0·57 (0·43–0·74)	..
Documented non-nocturnal hypoglycaemia (≤70 mg/dL; ≤3·9 mmol/L)			
Incidence	119 (88·15%)	107 (81·68%)	113 (85·61%)
Event rate	15·0	16·2	19·0
Event rate ratio (90% CI)	0·79 (0·62–1·02)	0·86 (0·65–1·12)	..
Documented 24-hr hypoglycaemia (<54 mg/dL; <3·0 mmol/L)			
Incidence	66 (48·89%)	68 (51·91%)	76 (57·58%)
Event rate	2·2	2·4	3·0
Event rate ratio (90% CI)	0·72 (0·50–1·04)	0·78 (0·48–1·26)	..
Documented nocturnal hypoglycaemia (<54 mg/dL; <3·0 mmol/L)			
Incidence	39 (28·89%)	32 (24·43%)	46 (34·85%)
Event rate	1·0	0·8	1·2
Event rate ratio (90% CI)	0·83 (0·53–1·29)	0·67 (0·43–1·05)	..
Documented non-nocturnal hypoglycaemia (<54 mg/dL; <3·0 mmol/L)			
Incidence	45 (33·33%)	52 (39·69%)	56 (42·42%)
Event rate	1·2	1·5	1·8
Event rate ratio (90% CI)	0·66 (0·42–1·01)	0·79 (0·46–1·37)	..

100 anni dell'insulina: il percorso di Leonard





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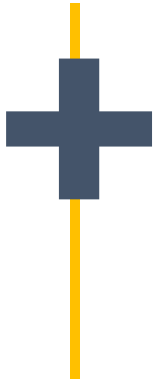
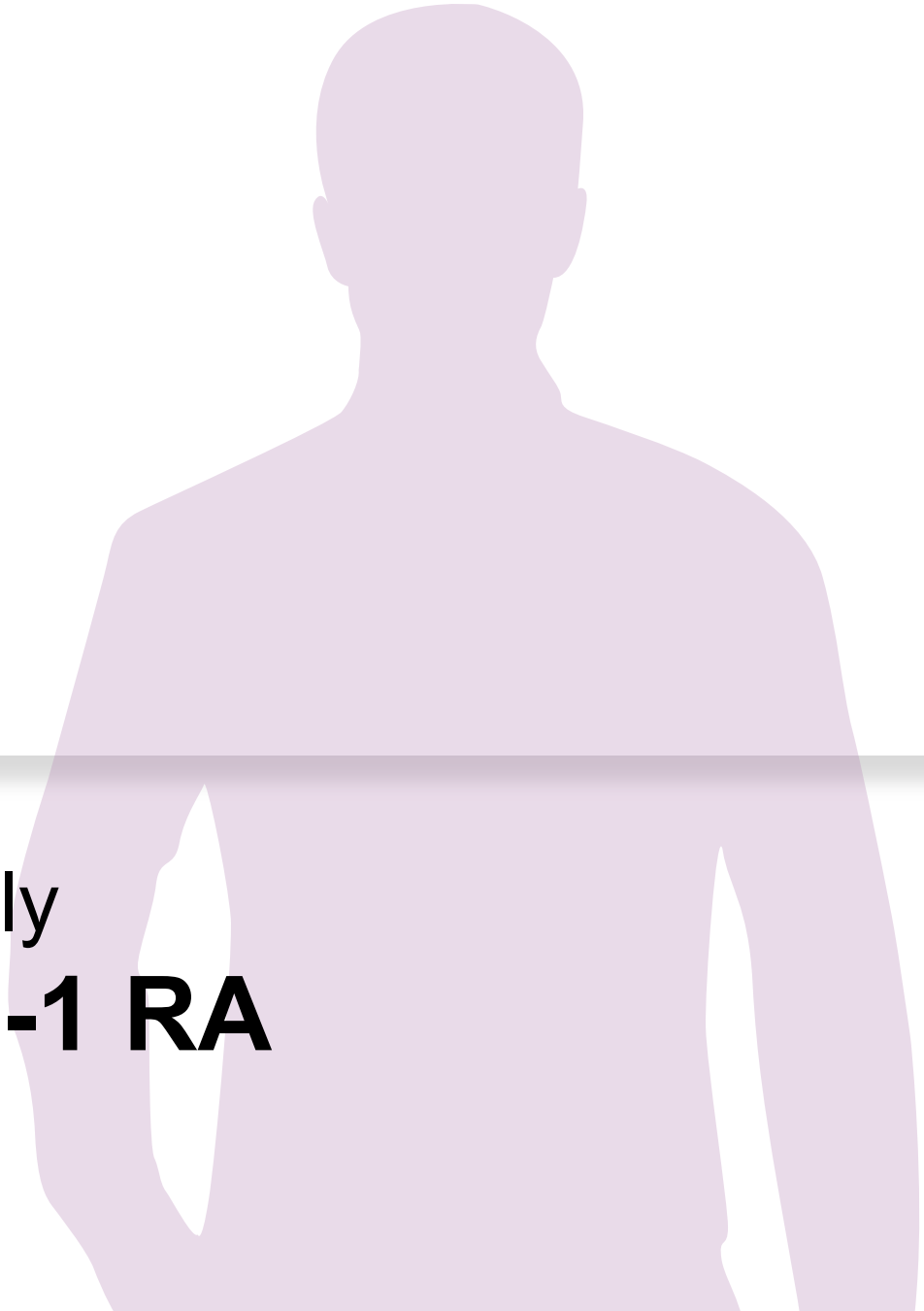
The option of **weekly therapies**

Weekly
insulin



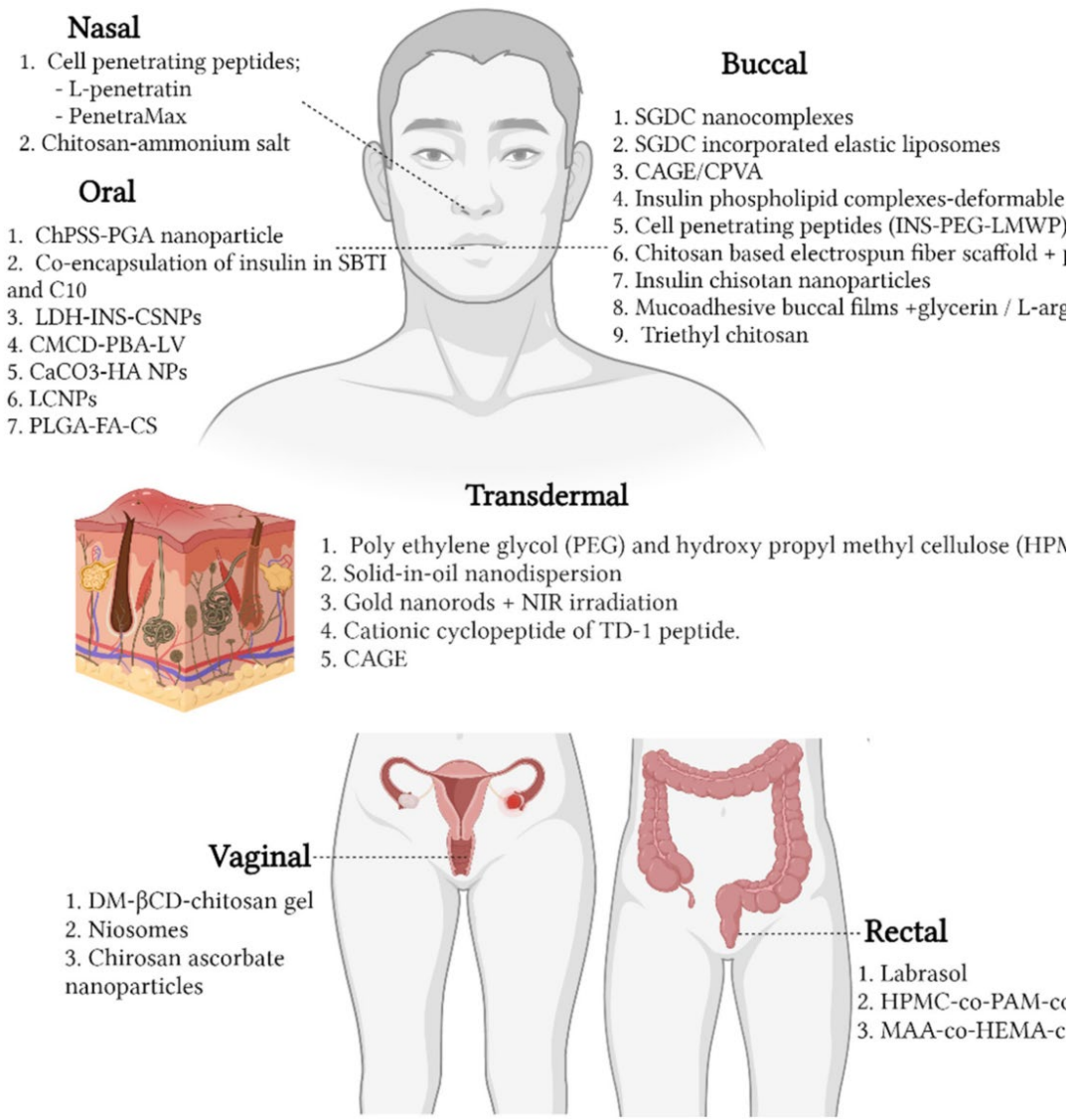
Weekly
GLP-1 RA



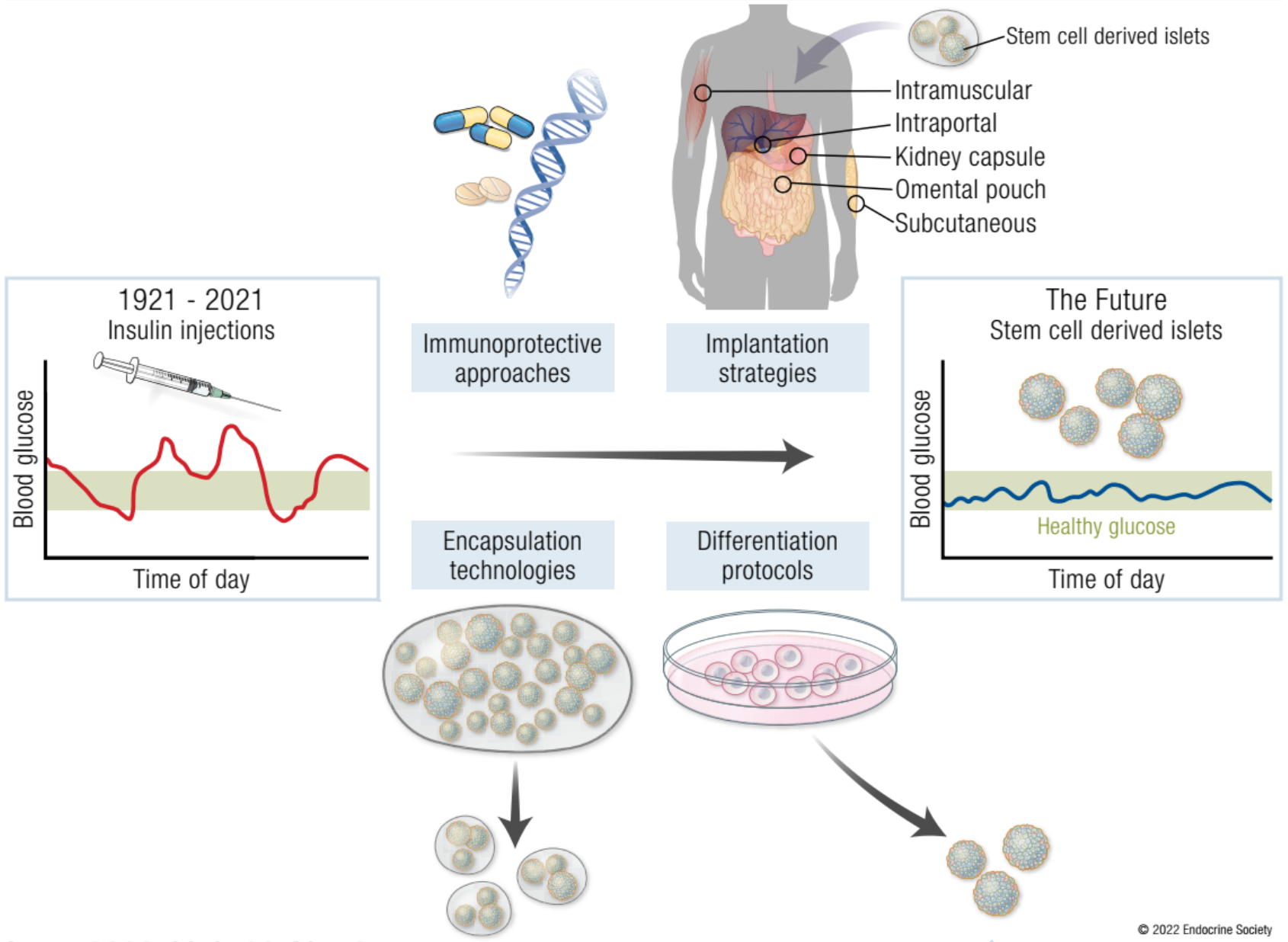
- Potential **alternative routes** for the **delivery of insulin**, such as oral, nasal, buccal, transdermal, vaginal, and rectal routes

- These **noninvasive** insulin treatments remain of interest and could represent **new paradigms** for the **future** treatment of diabetes

Pharmaceutics **2022,**



From insulin injections to stem cell derived islets



"Although insulin therapy has been introduced 100 years ago, the development of insulin has not come to an end.
It is reassuring that ongoing insulin developments have a high potential of further improving the safety and efficacy of insulin therapy in the future"

Tim Heise