Quarto Meta Open Forum

"Al CUORE del DIABETE"

Roma | 14-15 marzo 2025

Aula Brasca, Policlinico Gemelli

Diabete tipo 2: terapia insulinica 3.0

AGOSTINO CONSOLI

DMSI & CAST Università d'Annunzio – CHIETI

ITALY

SID Società Italiana di Diabetologia

DISCLOSURES

Bristol Mayer Squibb , Astra Zeneca, Boheringer Ingelhaim , Eli Lilly, Merck Sharp & Dhome , Novartis, Novo-Nordisk, Sanofi-Aventis, Sigma-Tau, Takeda.
(Speaker)

Astra Zeneca, Bristol Mayer Squibb, Boheringer Ingelhaim, Eli Lilly, Janssen Farmaceutici, Merck Sharp & Dhome, Novo-Nordisk.
(Advisory Board)

Astra Zeneca, Novo-Nordisk
(Consultant)

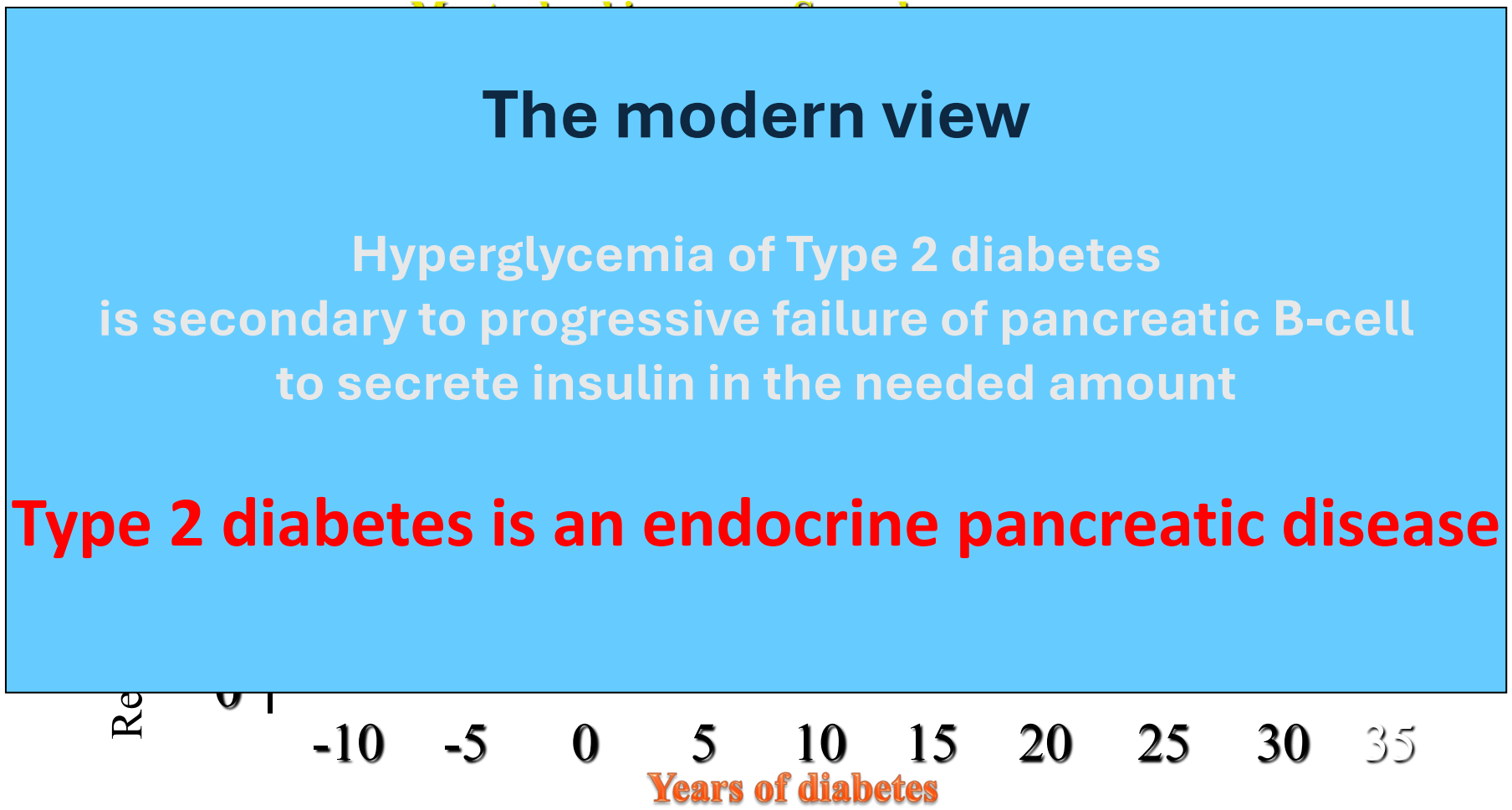
Eli Lilly, Novo-Nordisk
(Research Grant)


Li Santantonijri

I SANTANTONIANI

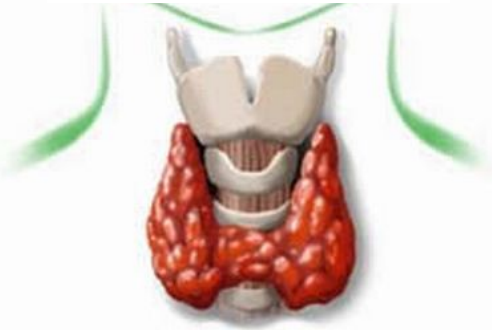
11.30	Ha ancora senso iniziare con la metformina? *Andrea Giaccari*
11.50	Discussione
12.00	Diabete tipo 2: terapia insulinica 3.0 *Agostino Consoli*
12.20	Discussione
12.30	Come personalizzare (senza molte evidenze) *Enzo Bonora*
12.50	Discussione
13.00	Uno sguardo al futuro (inclusa AI) *Stefano Del Prato*

Natural history of type 2 diabetes

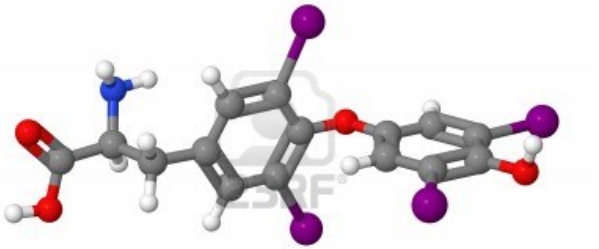


Endocrine Substitute Therapy

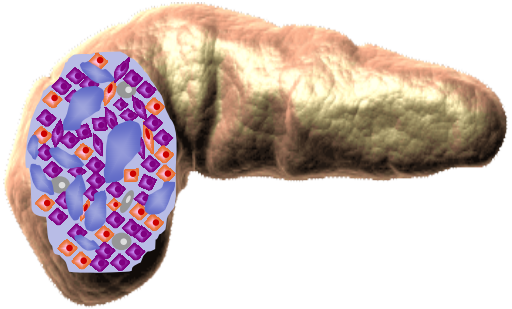
Tyroid Failure



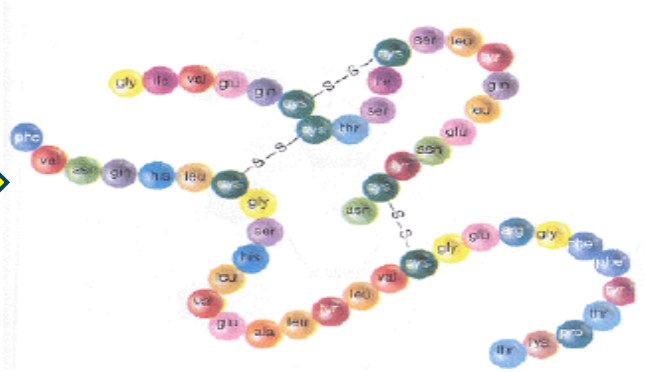
GIVE TYROXINE



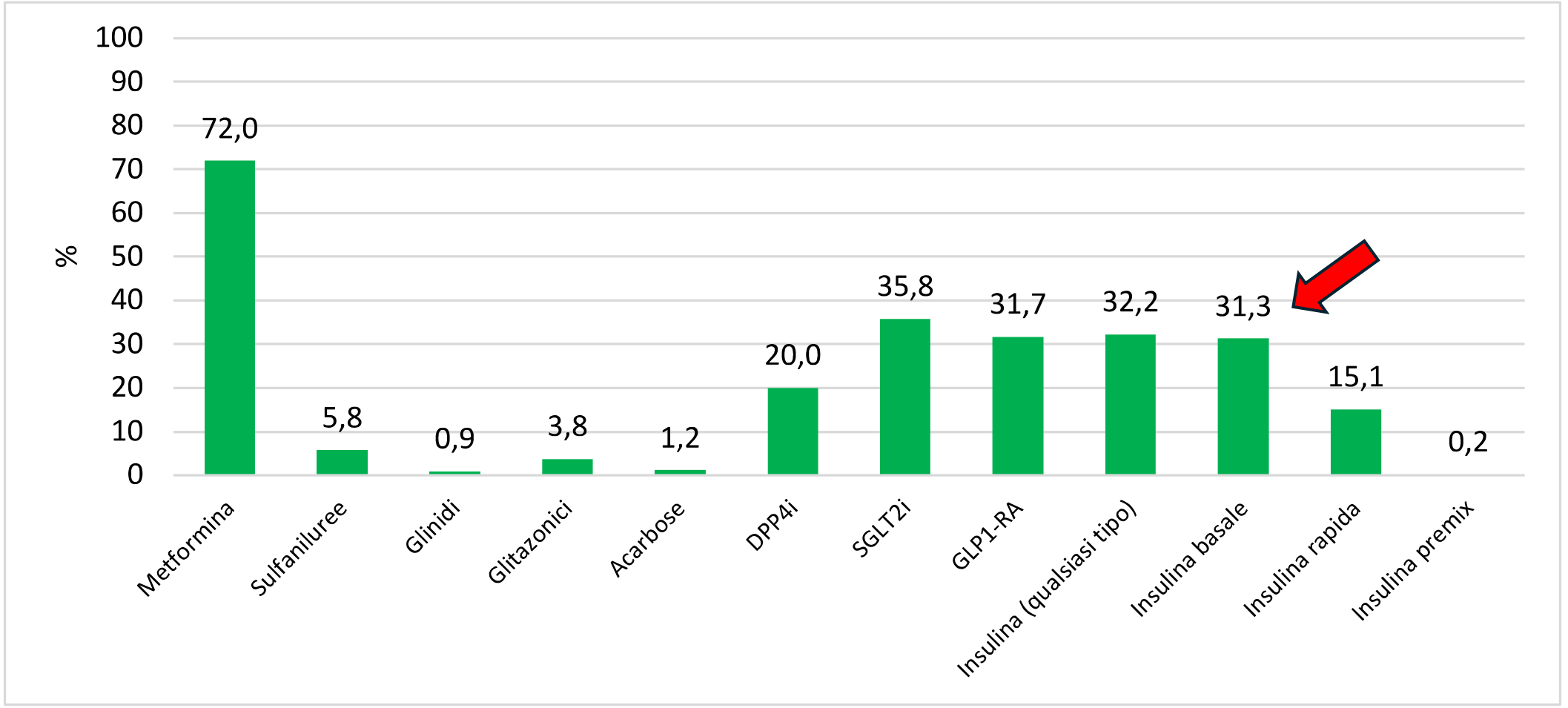
B-Cell Failure



GIVE INSULIN



Distribuzione per classe di farmaco ipoglicemizzante (%) – Annali AMD 2023

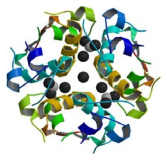
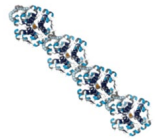
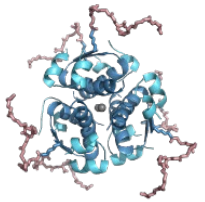


Barriers to initiating insulin therapy.

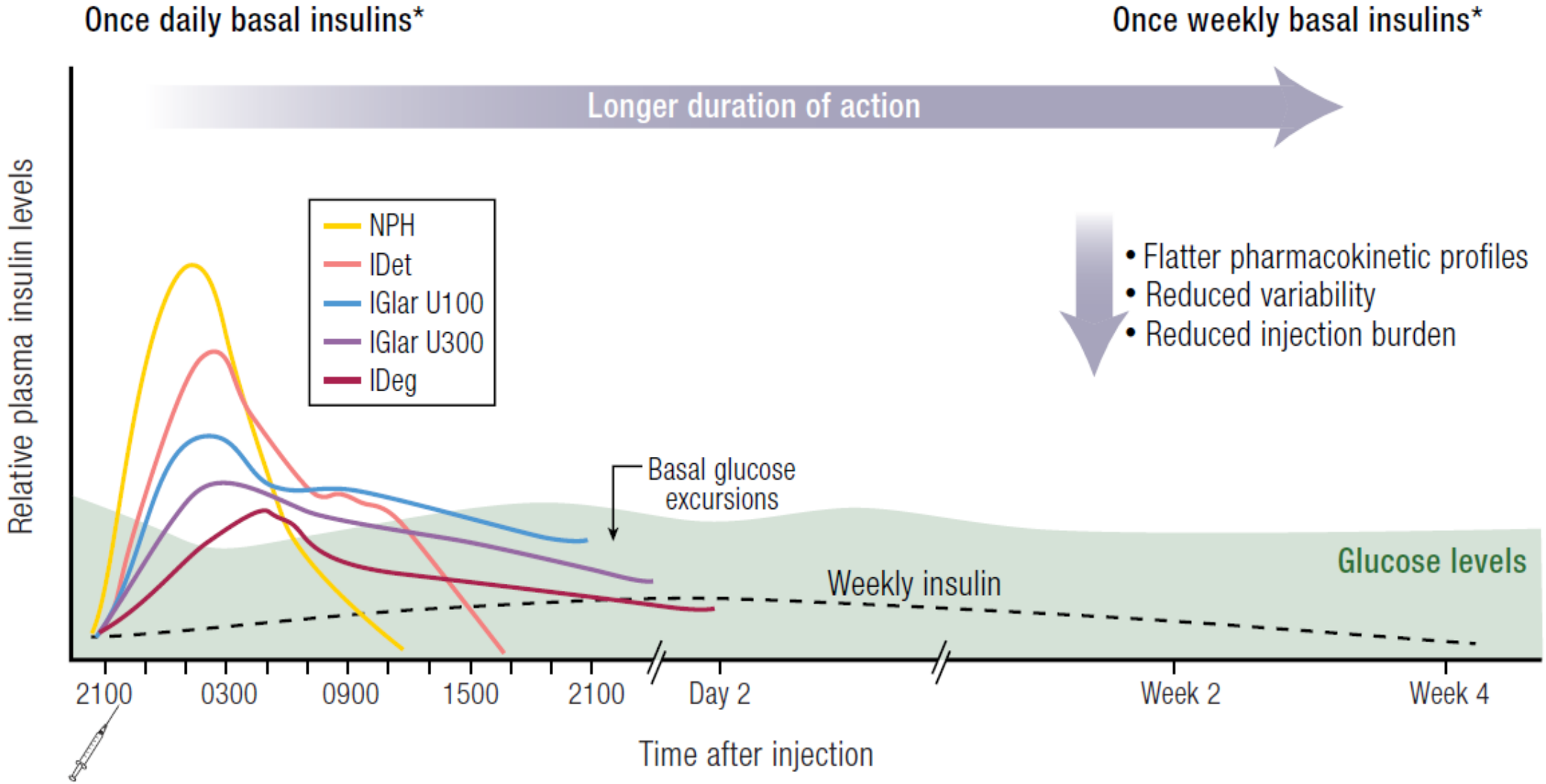
Conditioning factor	Barrier	Strategy
Patient	- Adherence - Perception of failure	- Use of long-acting insulin - Dose recall systems - Diabetes education program
Social environment	- Social rejection	- Community education
Treatment	- Dosage	- Use of simple adjustment guidelines - Implementation of FGM/CGM systems
	- Hypoglycemia	- Documentation of episodes by the patient - Determination of a greater number of self-monitoring blood glucose. - Implementation of FGM/CGM systems - Education on signs and symptoms - Adjustments in physical exercise - Instruction in the guidelines for dealing with hypoglycemia.
	- Method of administration	- Simple, intuitive devices adapted to different physical limitations. - Instruction in management technique. - Design of specific devices for patients with needle phobia.
	- Weight Gain	- Healthy eating education. - Prescription of physical exercise - Choice of type of insulin based on the reported weight evolution.

Galdon Sanz-Pastor A. et al., Front Endocrin 2024

The past and present of basal insulin innovation

	NPH insulin	1st generation basal insulin analogues	Ultra long-acting basal insulin analogues	Once-weekly Icodec Efsitora
				
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.



*Schematic representation of single doses

Strategies to Prolong Insulin action

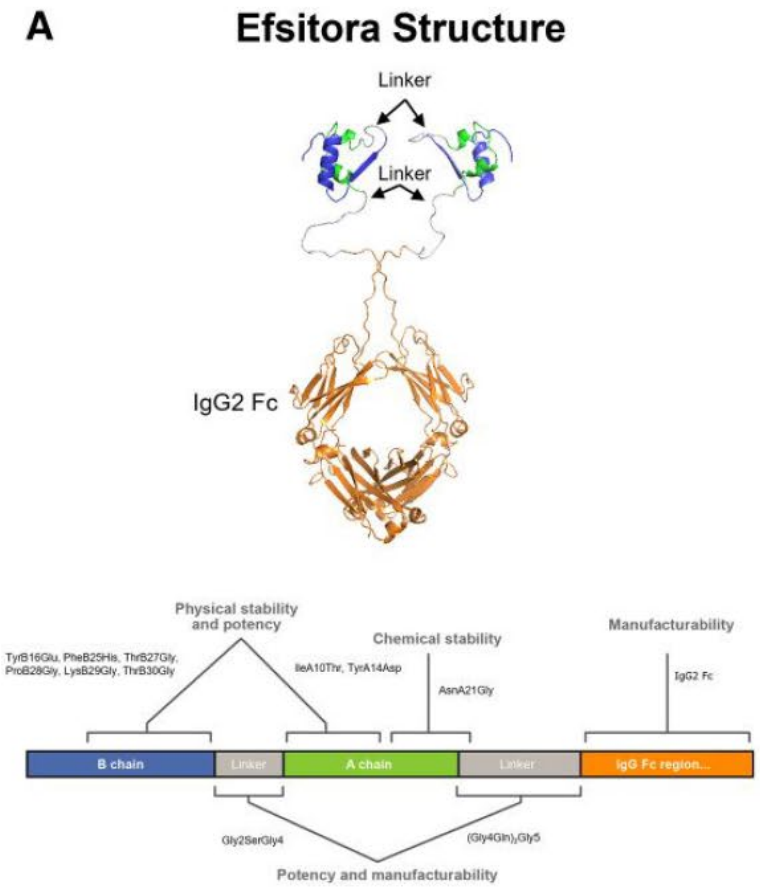
- **CREATE A "RESERVOIR" OF INSULIN THAT ENGAGES THE INSULIN RECEPTOR**
  - Icodec circulates in an albumin-bound pool (reservoir) of insulin that engages with the insulin receptor[1,2]
  - Insulin efsitora is an Fc fusion molecule that can bind to Fc receptors (FcRn) as a recycling mechanism to prevent degradation and extend time in circulation (creates a "pool"/reservoir)

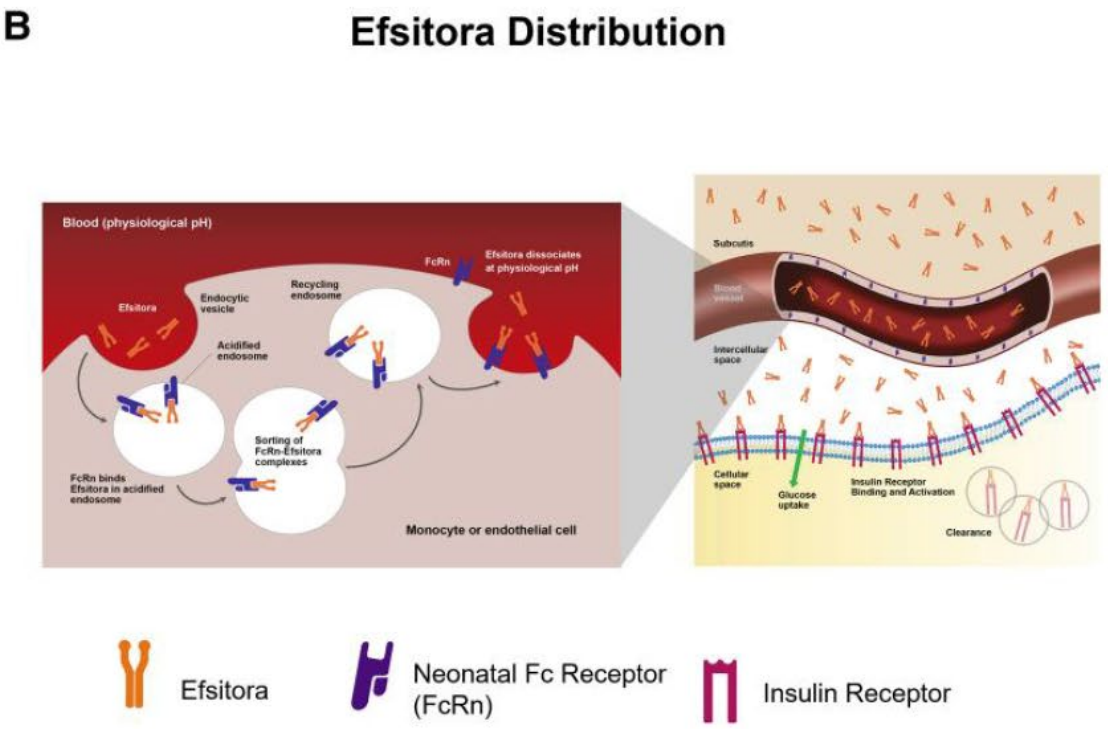
- ***REDUCE IR AFFINITY WHILE SIMULTANEOUSLY MAINTAINING FULL AGONISM***
  - The reduced affinity results in decreased receptor-mediated clearance, one of the primary means of insulin degradation, thus prolonging the half-life of the insulin[4,5]
  - Once bound to the IR, full receptor agonism and glucose uptake activity are observed[1-3]

- Fc=Fragment Crystallizable; FcRn=Neonatal Fc Receptor; IR= Insulin Receptor; GLP-1 RA=Glucagon-Like Peptide-1 Receptor Agonist.

- 1. Kjeldsen TB, et al. *J Med Chem*. 2021;64(13):8942-8950. 2. Nishimura E, et al. *BMJ Open Diabetes Res Care*. 2021;9(1):e002301. 3. Moyers JS, et al. *J Pharmacol Exp Ther*. 2022;382(3):346-355.
- 4 Tokarz VL, et al. *J Cell Biol*. 2018;217(7):2273-2289. 5. Heise T, et al. *Diabetes Obes Metab*. 2023;25(4):1080-1090.

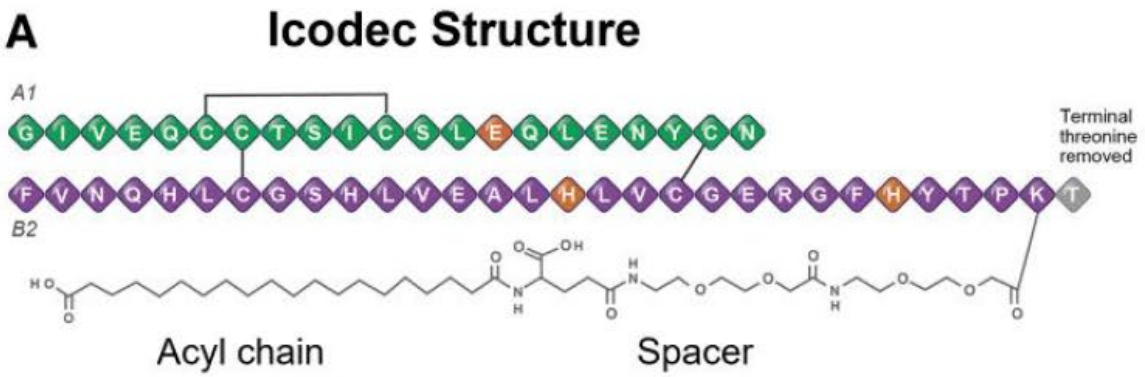
Efsitora Mode of Action

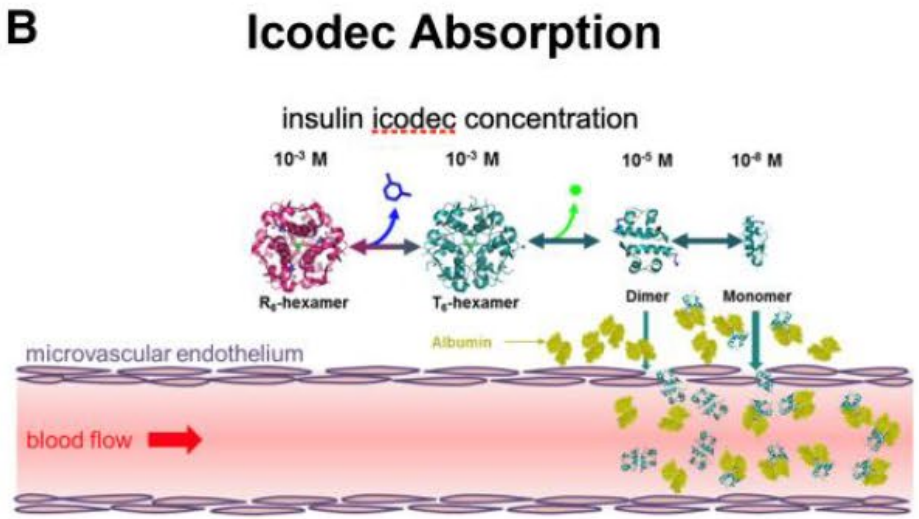


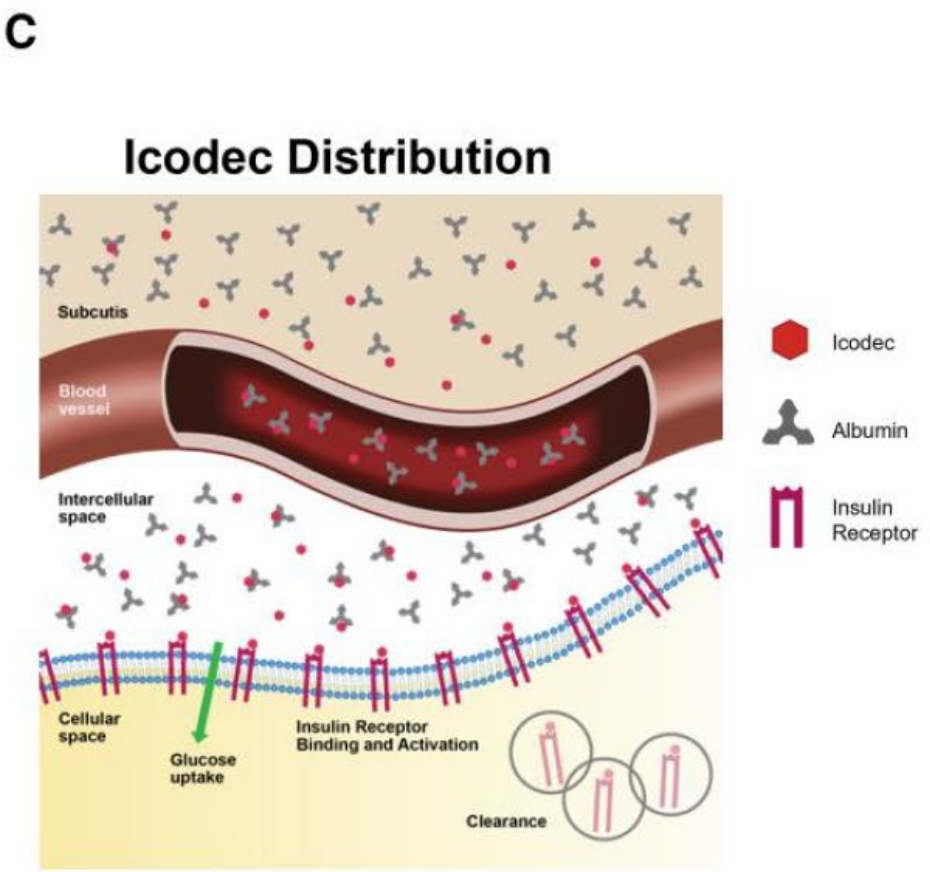


Endocrine Reviews, 2024, **45**, 379–413

Icodec Mode of Action

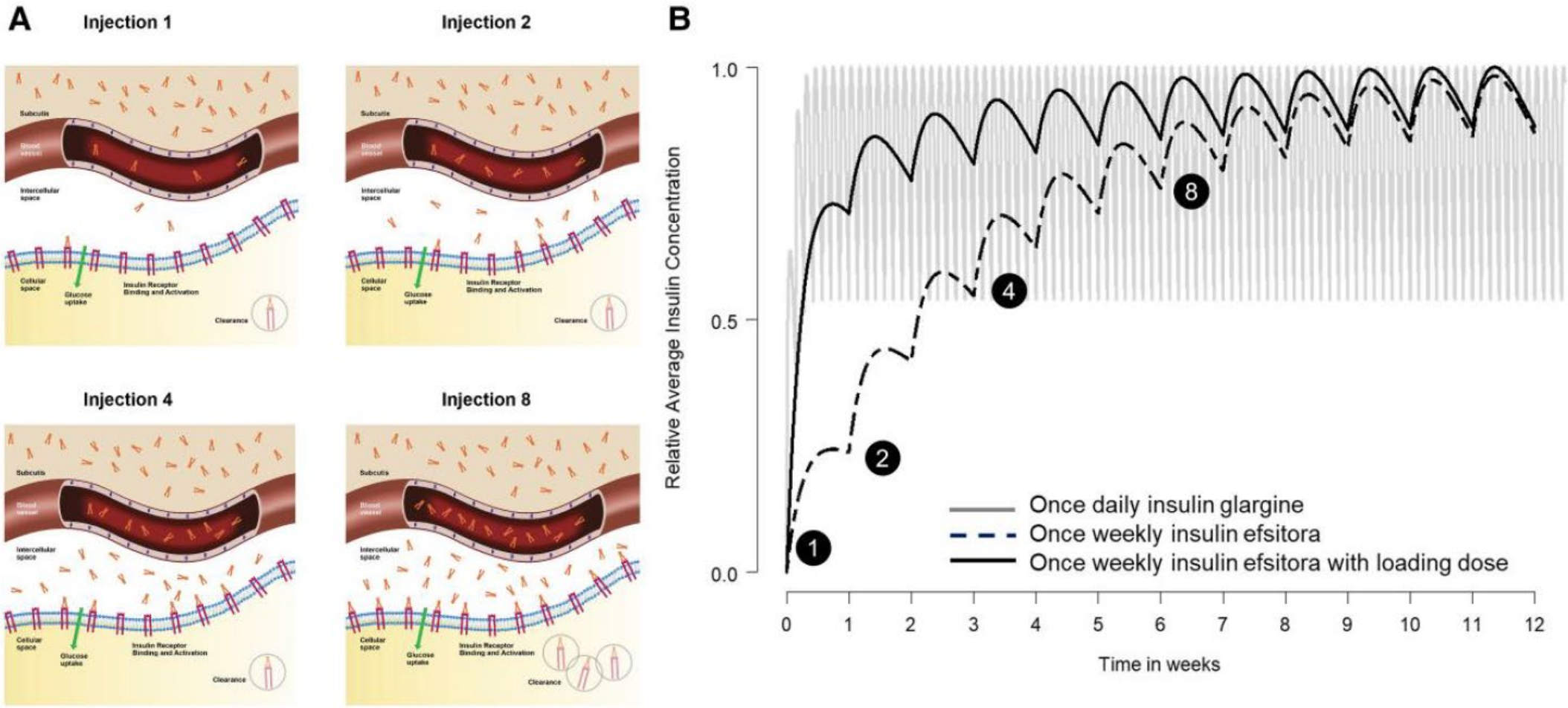






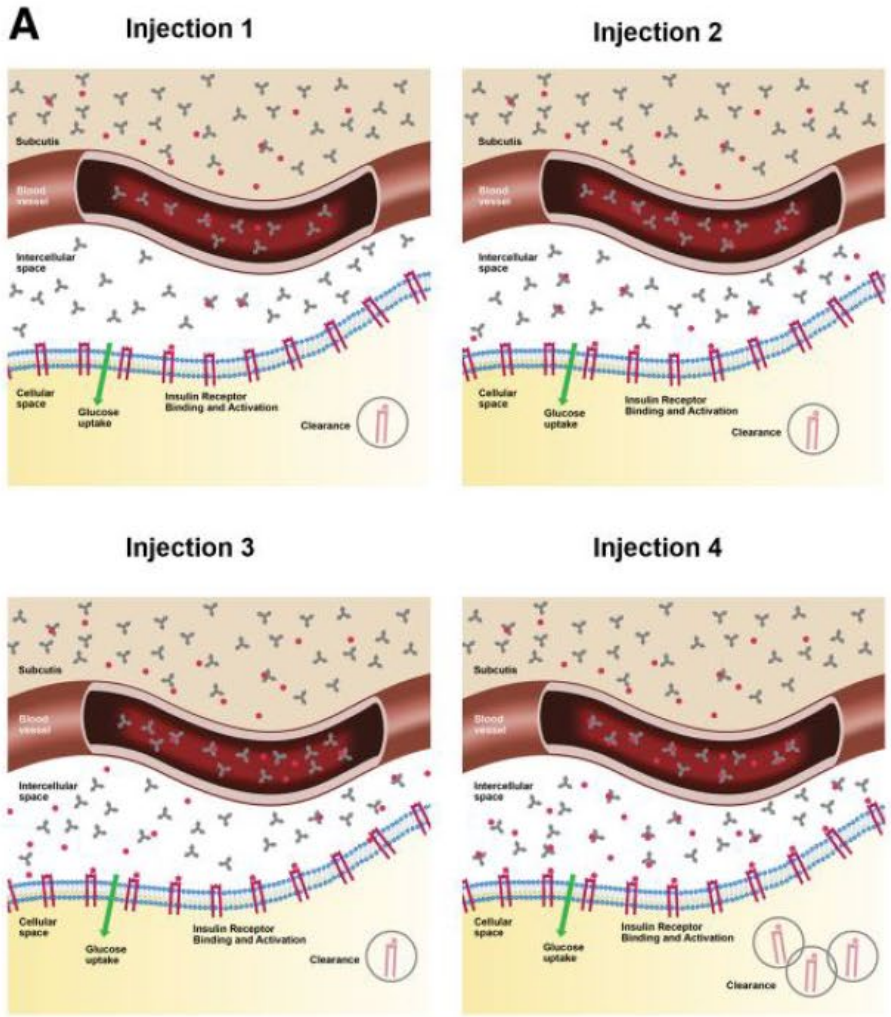
Endocrine Reviews, 2024, **45**, 379–413

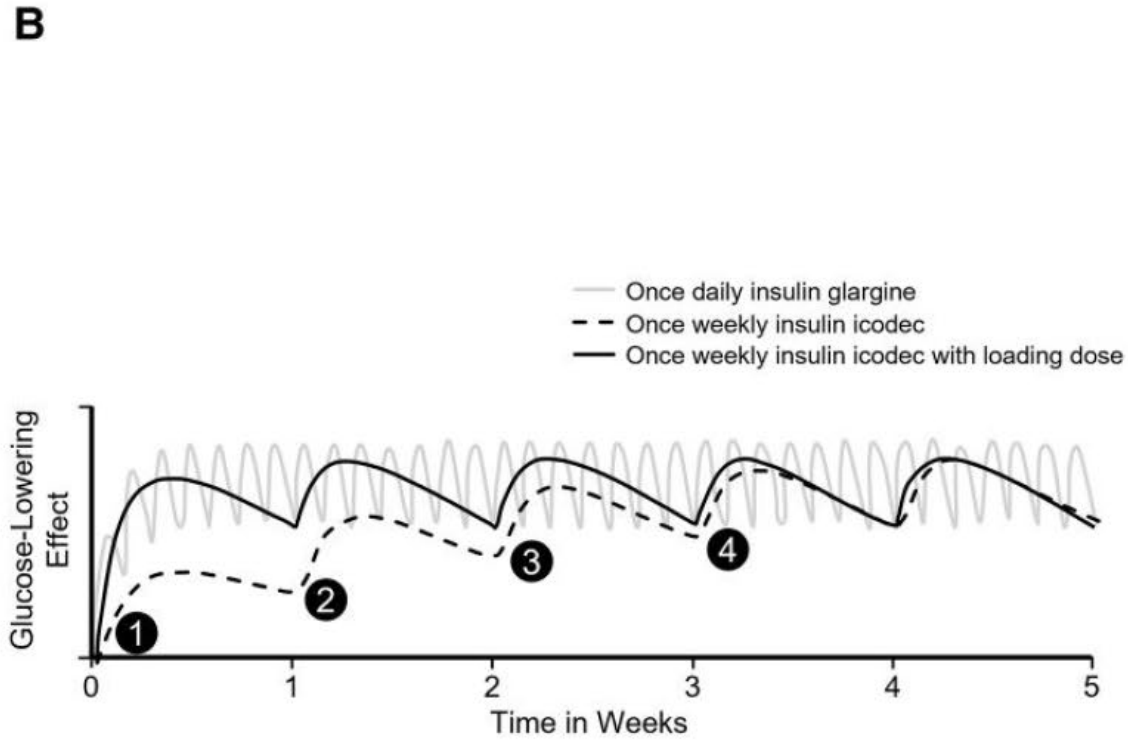
Efsitora build-up to efficacious exposure



Endocrine Reviews, 2024, **45**, 379–413

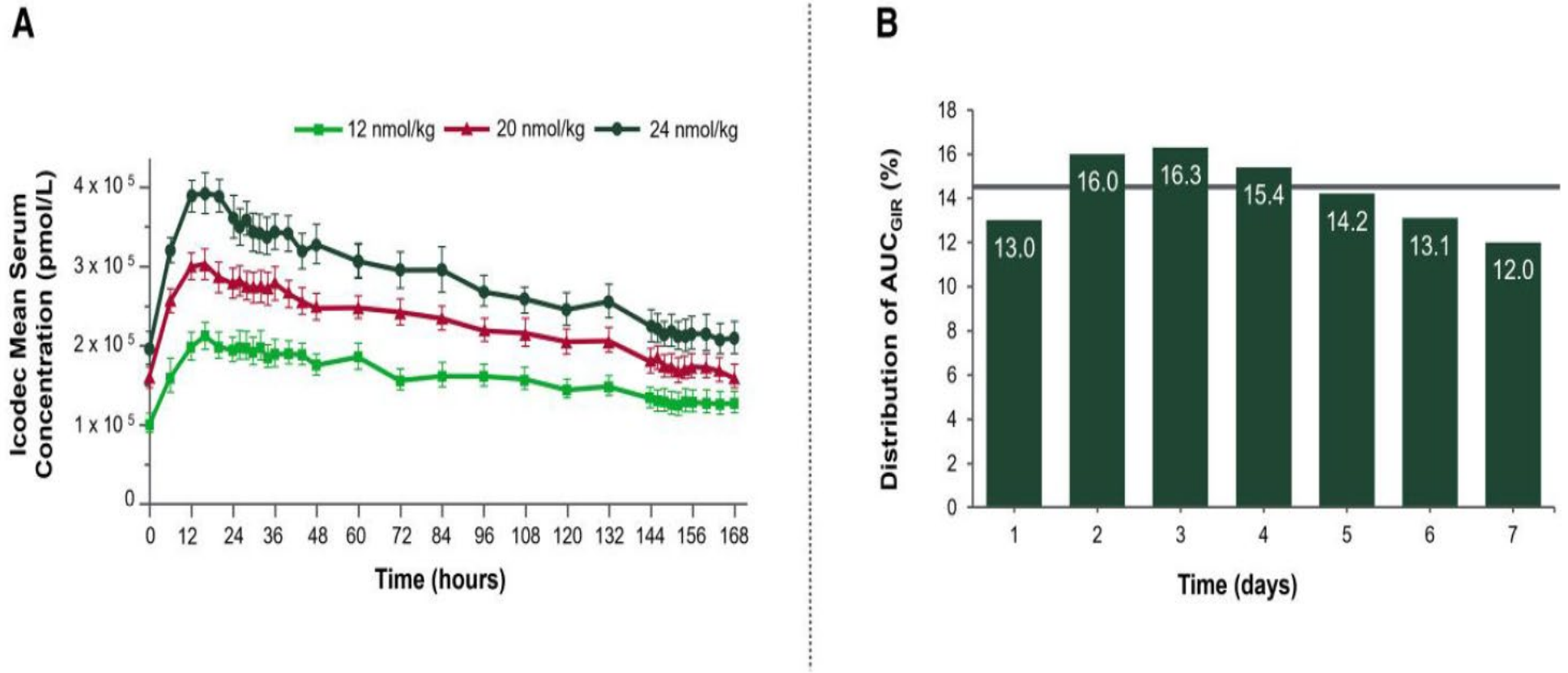
Icodec build-up to efficacious exposure





Endocrine Reviews, 2024, **45**, 379–413

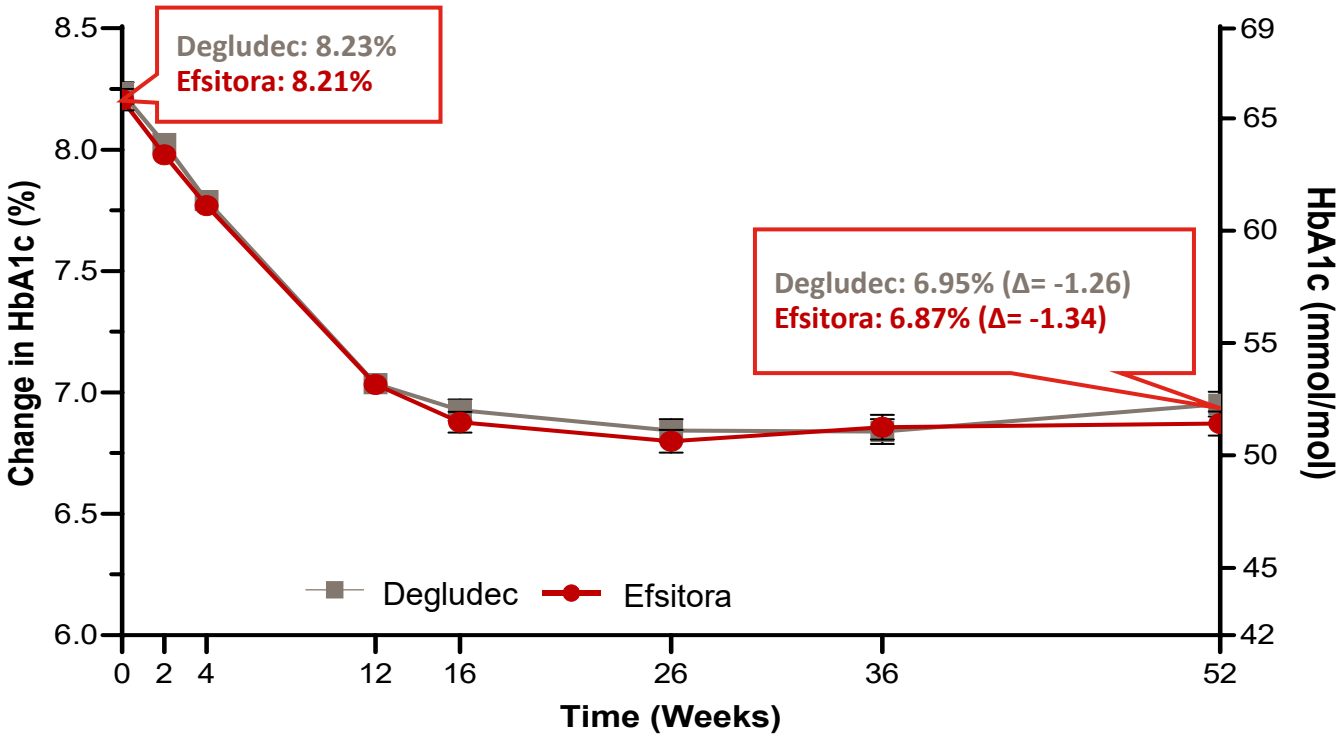
Pharmacokinetic and pharmacodynamic profiles of icodec in people with type 2 diabetes.



Endocrine Reviews, 2024, **45**, 379–413

Change in HbA1c From Baseline to Week 52 with Efsitora Compared to Degludec-Primary Endpoint

	Efsitora vs. degludec	*P* Value
ETD % (95% CI)	-0.08 (-0.22 to 0.06)	0.262



Insulin Naïve T2DM: Efsitora vs Degludec

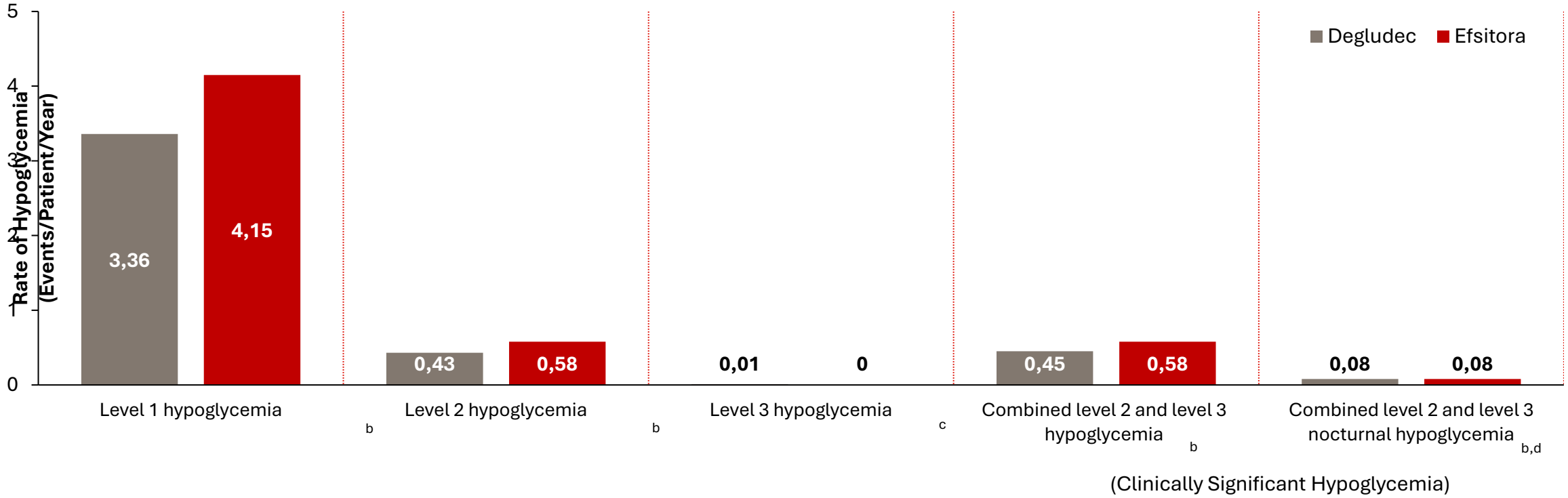
- CI=Confidence Interval; ETD=Estimated Treatment Difference; HbA1c=Glycated Hemoglobin.
- Wysham C, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2403953 (Ahead of print).

Incidence and Event Rates of Hypoglycemia

	Degludec (n=462)		Efsitora (n=466)		Efsitora vs. Degludec
	Participants (%)	Episodes (Rate/PYE)	Participants (%)	Episodes (Rate/PYE)	ERR (95% CI)
Hypoglycemic episodes (overall)					
Hypoglycemia alert value (level 1)[b]	249 (53.9)	1485 (3.36)	297 (63.7)	1811 (4.15)	1.24 (0.99 to 1.55)
Clinically significant (level 2) hypoglycemia[b]	97 (21.0)	190 (0.43)	130 (27.9)	253 (0.58)	1.34 (0.97 to 1.85)
Severe (level 3) hypoglycemia[c]	6 (1.3)	6 (0.01)	0	0	—
Combined clinically significant (level 2) and severe (level 3) hypoglycemia[b]	102 (22.1)	196 (0.45)	130 (27.9)	253 (0.58)	1.30 (0.94 to 1.78)
Hypoglycemic episodes (nocturnal)[d]					
Combined clinically significant (level 2) and severe (level 3) hypoglycemia[b]	23 (5.0)	35 (0.08)	23 (4.9)	32 (0.08)	1.01 (0.53 to 1.89)

- Note: Level 1 hypoglycemia= glucose <70 mg/dL and ≥54 mg/dL; Level 2 hypoglycemia=glucose <54 mg/dL; Level 3 hypoglycemia=severe hypoglycemia (confirmed by the investigator to be an event that required assistance for treatment).
- [a]ERR denotes estimated rate ratio, and PYE patient-years of exposure.
- [b]Rate and estimated rate ratio were estimated using a negative binomial model.
- [c]Rate was calculated by the number of episodes divided by total exposure.
- [d]Occurring between midnight and 6:00 am.
- CI=Confidence Interval; ERR=Estimated Rate Ratio; PYE=Patient-Years of Exposure.
- Wysham C, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2403953 (Ahead of print).

Hypoglycemic Episodes from Baseline to Week 52



- Note: Level 1 hypoglycemia= glucose <70 mg/dL and ≥54 mg/dL; Level 2 hypoglycemia=glucose <54 mg/dL; Level 3 hypoglycemia=severe hypoglycemia (confirmed by the investigator to be an event that required assistance for treatment).
- [a]ERR denotes estimated rate ratio, and PYE patient-years of exposure.
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- [c]Rate was calculated by the number of episodes divided by total exposure.
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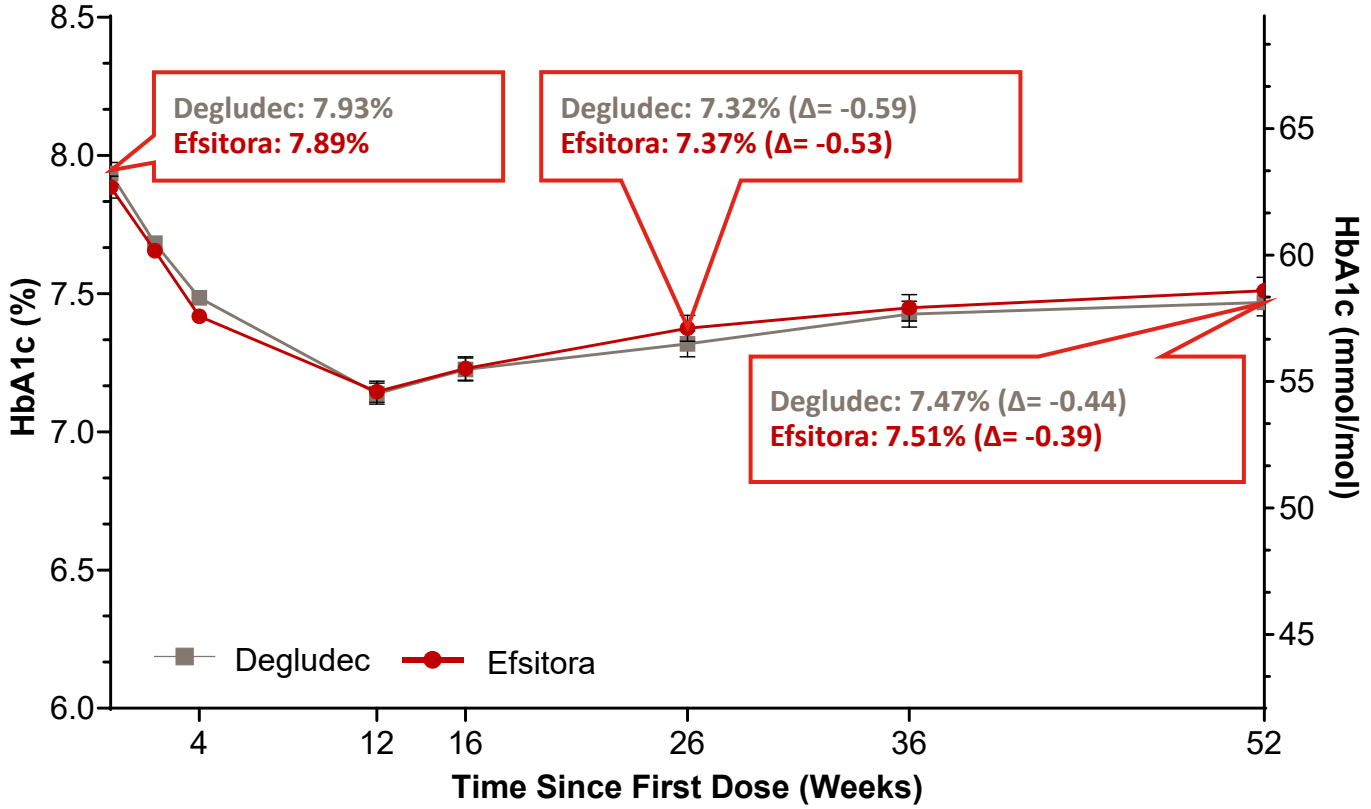
- CI=Confidence Interval; ERR=Estimated Rate Ratio; PYE=Patient-Years of Exposure.
- Wysham C, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2403953 (Ahead of print).

Change in HbA1c From Baseline to Week 26 -Primary Endpoint

Weeks	ETD % (95% CI) Efsitora vs. degludec	*P* Value
Week 26	**0.056 (-0.075 to 0.187)**	**0.401**
Week 52	**0.042 (-0.094 to 0.178)**	**0.547**



T1DM Efsitora vs Degludec

- CI=Confidence Interval; ETD=Estimated Treatment Difference; HbA1c=Glycated Hemoglobin.
- Bergenstal RM, et al. *Lancet*. 2024;doi:https://doi.org/10.1016/S0140-6736(24)01804-X (Ahead of print).

Hypoglycemic Rates

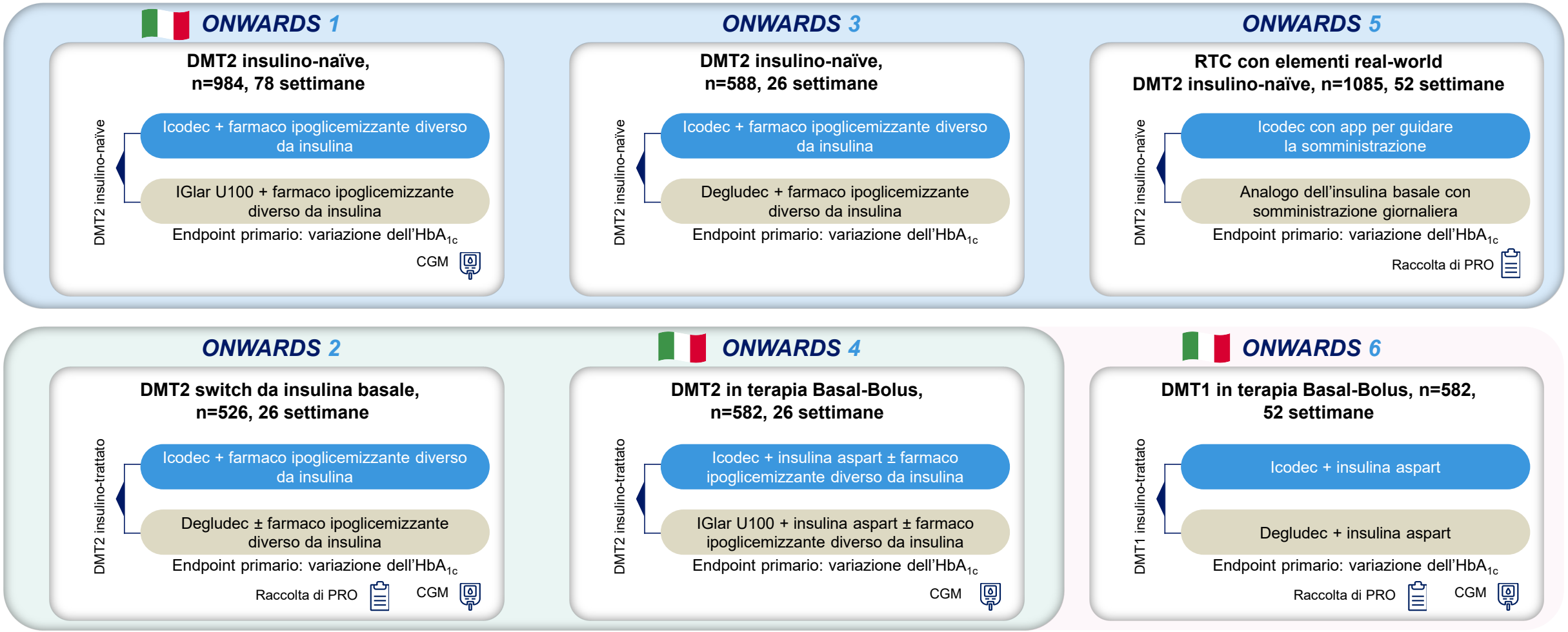
- Secondary Endpoint

		Degludec (N=349)		Efsitora (N=343)		Efsitora vs. Degludec	
		Participants (%)	Episodes (Rate/PYE)	Participants (%)	Episodes (Rate/PYE)	ERR[a] (95% CI)	*P* value
Level 1 hypoglycemia	Week 0-26	333 (95)	6586 (39.13)	339 (99)	7474 (46.04)	1.18 (1.05-1.32)	0.0055
	Week 0-52	337 (97)	11122 (33.99)	340 (99)	12299 (39.19)	1.15 (1.03-1.29)	0.016
Combined clinically significant (level 2) or severe (level 3) hypoglycemia	Week 0-26	289 (83)	2319 (14.06)	293 (85)	2662 (17.19)	1.22 (1.04-1.43)	0.013
	Week 0-52	306 (88)	3740 (11.59)	305 (89)	4175 (14.03)	1.21 (1.04-1.41)	0.016
Severe (level 3) hypoglycemia	Week 0-26	9 (3)	11 (0.06)	28 (8)	35 (0.21)	3.23 (1.42-7.38)	0.0052
	Week 0-52	11 (3)	13 (0.04)	35 (10)	44 (0.14)	3.44 (1.64-7.19)	0.0011

T1DM Efsitora vs Degludec

- Note: Level 1 hypoglycemia=glucose <70 mg/dL and ≥54 mg/dL; Level 2 hypoglycemia=glucose <54 mg/dL; Level 3 hypoglycemia=severe hypoglycemia characterized by altered mental or physical status requiring assistance from another person for the treatment of hypoglycemia.
- [a]ERR denotes estimated rate ratio, and PYE patient-years of exposure.
- CI=Confidence Interval; ERR=Estimated Rate Ratio; PYE=Patient-Years of Exposure.
- Bergenstal RM, et al. *Lancet.* 2024;doi:https://doi.org/10.1016/S0140-6736(24)01804-X (Ahead of print).

Insulin ICODEC: ONWARDS Studies Program

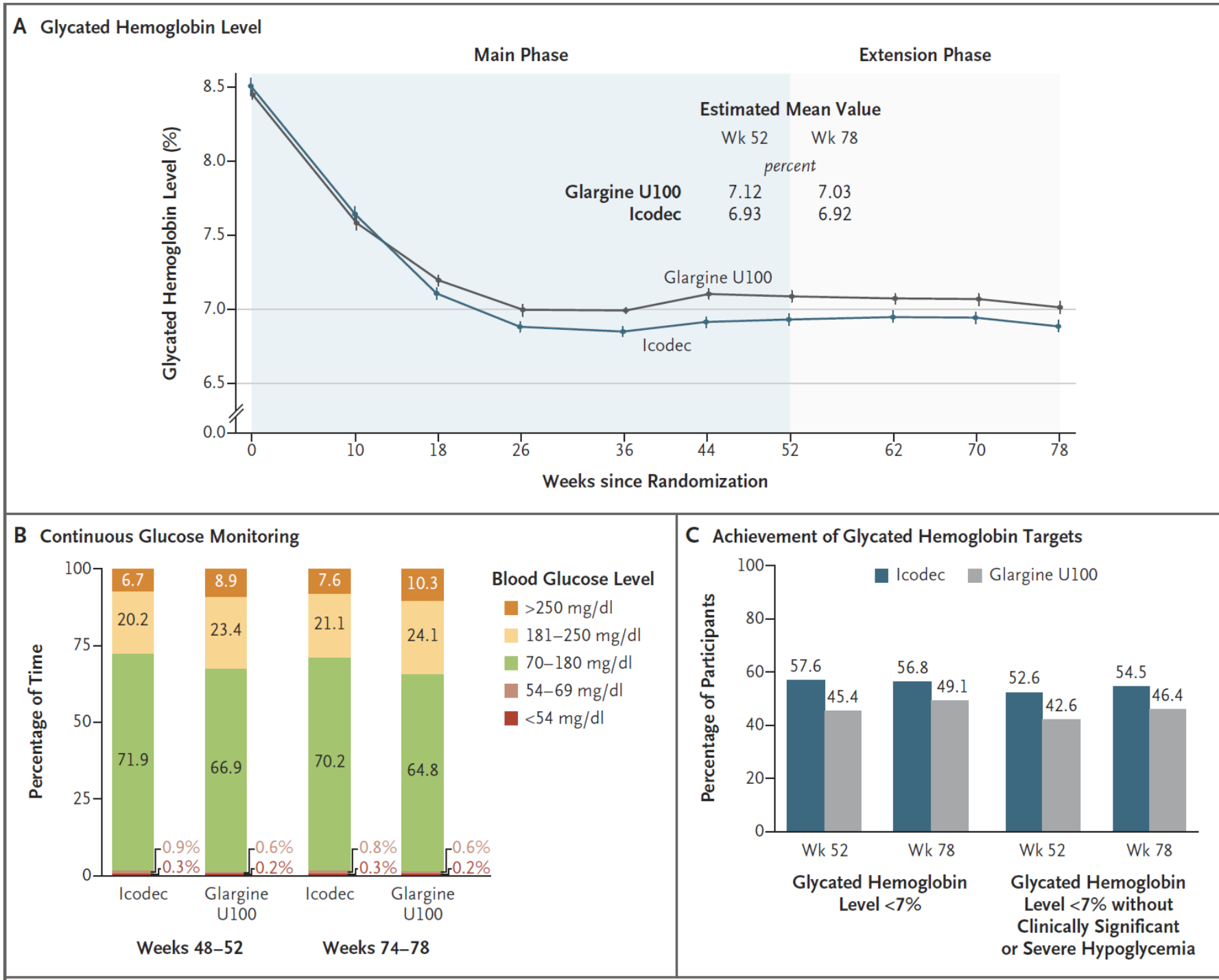


CGM, *continuous glucose monitoring*, monitoraggio glicemico continuo; **DMT1**, diabete di tipo 1; **DMT2**, diabete di tipo 2; **HbA_{1c}**, emoglobina glicata; **IGlar**, insulina glargine; **PRO**, *patient reported outcome*, outcome riportati dai pazienti; **RTC**, *randomised controlled trial*, studio ranomizzato e controllato.

1. Philis-Tsimikas A et al. Diabetes Obes Metab. 2022; 25(2): 331-341.

ONWARDS 1

DMT2 insulino-naïve, n=984, 78 settimane



N Engl J Med 2023;389:297-308.

ONWARDS 1

DMT2 insulino-naïve,
n=984, 78 settimane

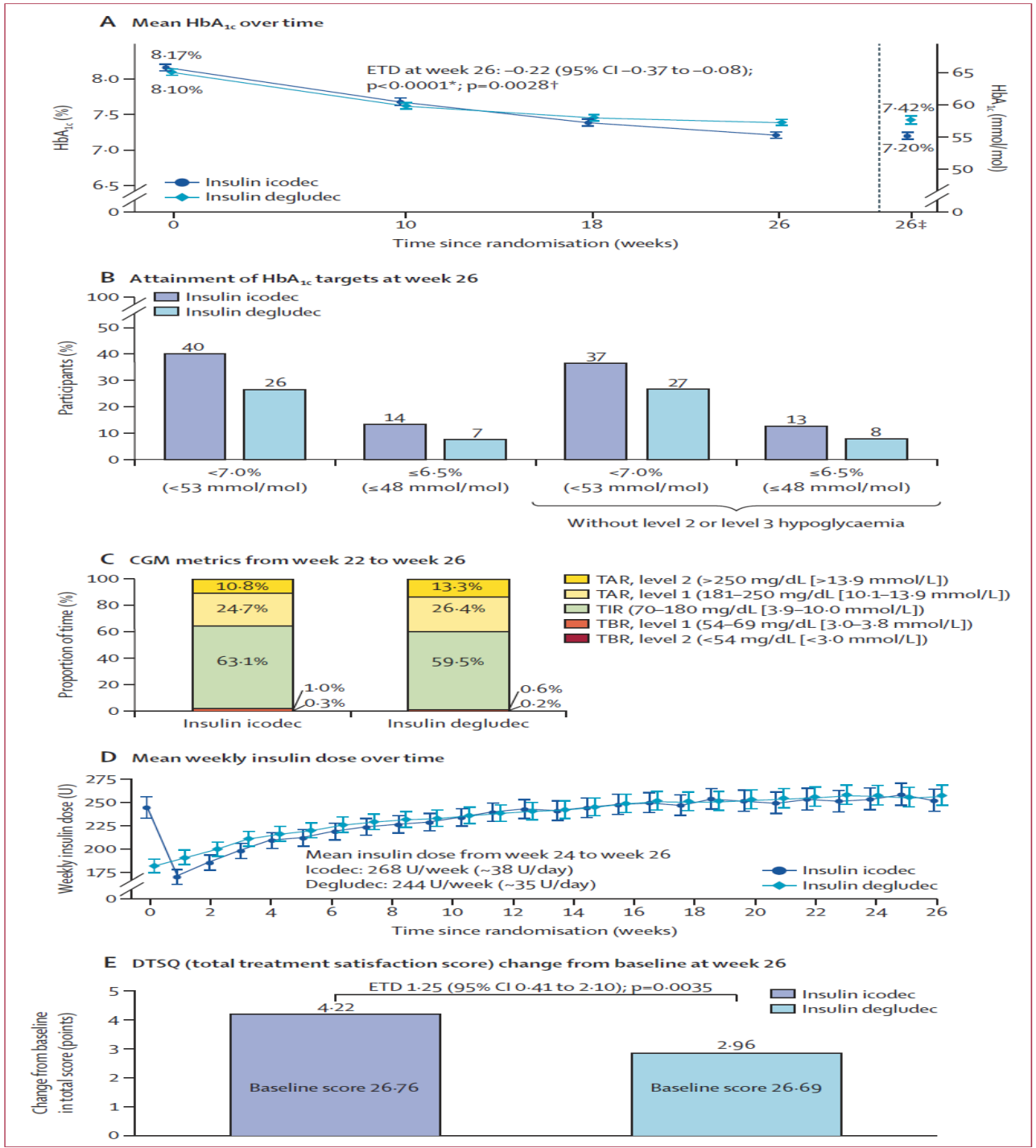
Variable	Icodec (N=492)	Glargine U100 (N=492)
Overall hypoglycemic episodes, safety analysis, baseline to wk 52 — no. of participants (%) [events data]		
Hypoglycemia alert value**	232 (47.2) [1447 events; 2.98/PYE]	191 (38.8) [632 events; 1.30/PYE]
Clinically significant hypoglycemia††	48 (9.8) [143 events; 0.29/PYE]	49 (10.0) [75 events; 0.15/PYE]
Severe hypoglycemia‡‡	1 (0.2) [1 event; <0.01/PYE]	3 (0.6) [3 events; 0.01/PYE]
Combined clinically significant or severe hypoglycemia	48 (9.8) [144 events; 0.30/PYE]	52 (10.6) [78 events; 0.16/PYE]

N Engl J Med 2023;389:297-308.

ONWARDS 2

DMT2 switch da insulina basale, n=526, 26 settimane

Lancet Diabetes Endocrinol
2023; 11: 414–25



ONWARDS 2

DMT2 switch da insulina basale, n=526, 26 settimane

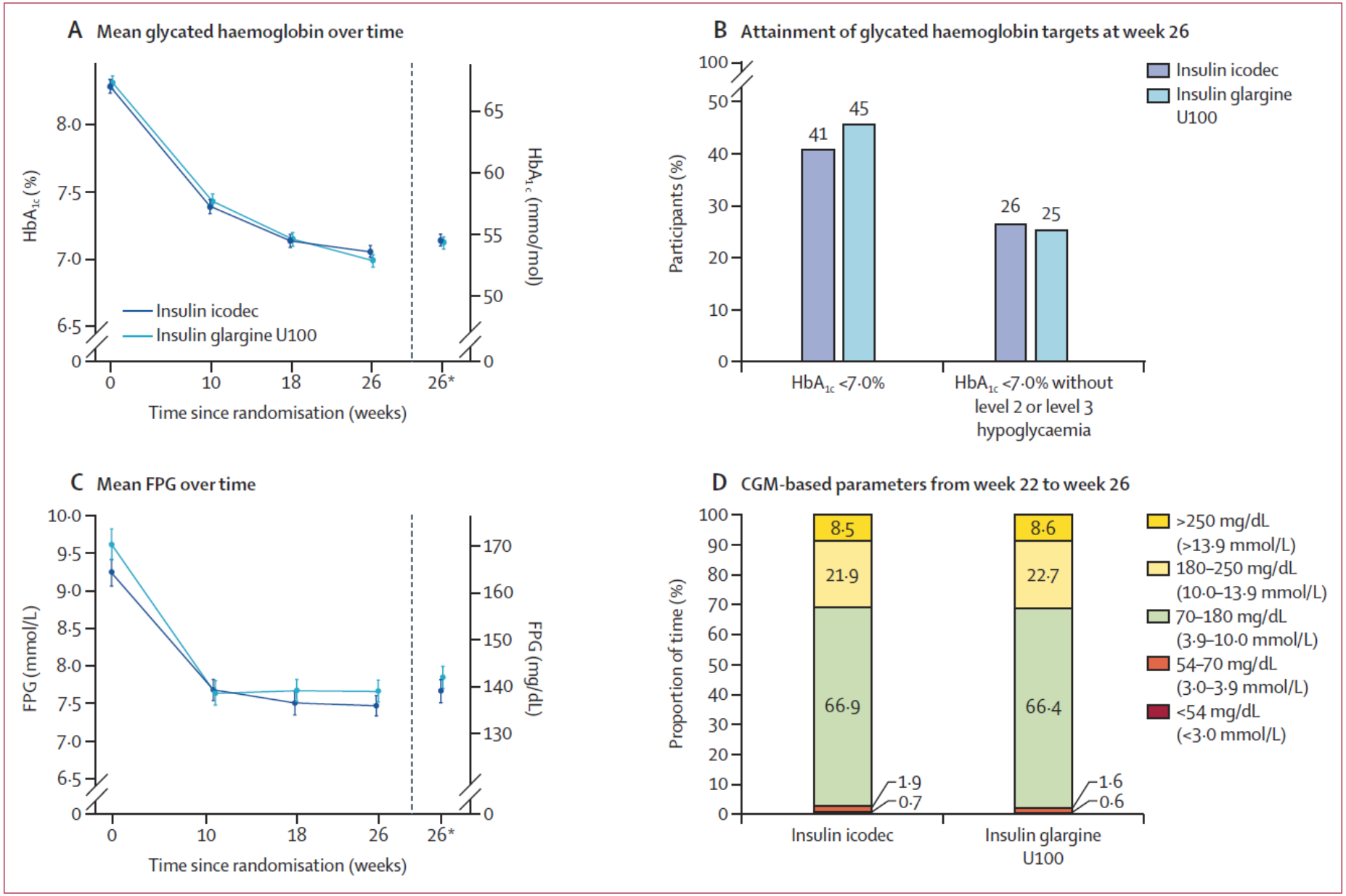
	Insulin icodec (n=262)		Insulin degludec (n=263)		Insulin icodec *vs* insulin degludec
	Participants (%)	Episodes (rate per PYE)	Participants (%)	Episodes (rate per PYE)	ERR (95% CI), p value
Hypoglycaemic episodes (overall)					
Hypoglycaemia alert value (level 1)*	145 (55%)	1209 (7·79)	118 (45%)	589 (3·86)	1·88 (1·34–2·63), p=0·0002
Clinically significant (level 2) hypoglycaemia†	37 (14%)	113 (0·73)	19 (7%)	41 (0·27)	1·98 (0·95–4·12), p=0·067
Severe (level 3) hypoglycaemia‡	0	..	1 (<1%)	1 (0·01)	..
Combined clinically significant (level 2)† or severe (level 3)‡ hypoglycaemia	37 (14%)	113 (0·73)	19 (7%)	42 (0·27)	1·93 (0·93–4·02), p=0·078
Hypoglycaemic episodes (nocturnal)					
Hypoglycaemia alert value (level 1)*	60 (23%)	144 (0·93)	35 (13%)	102 (0·67)	..
Clinically significant (level 2) hypoglycaemia†	16 (6%)	32 (0·21)	9 (3%)	13 (0·09)	..
Severe hypoglycaemia (level 3)‡	0	..	0	..	..
Combined clinically significant (level 2)† or severe (level 3)‡ hypoglycaemia	16 (6%)	32 (0·21)	9 (3%)	13 (0·09)	..

Lancet Diabetes Endocrinol
2023; 11: 414–25

ONWARDS 4

DMT2 in terapia Basal-Bolus, n=582, 26 settimane

Lancet 2023; 401: 1929–40



ONWARDS 4

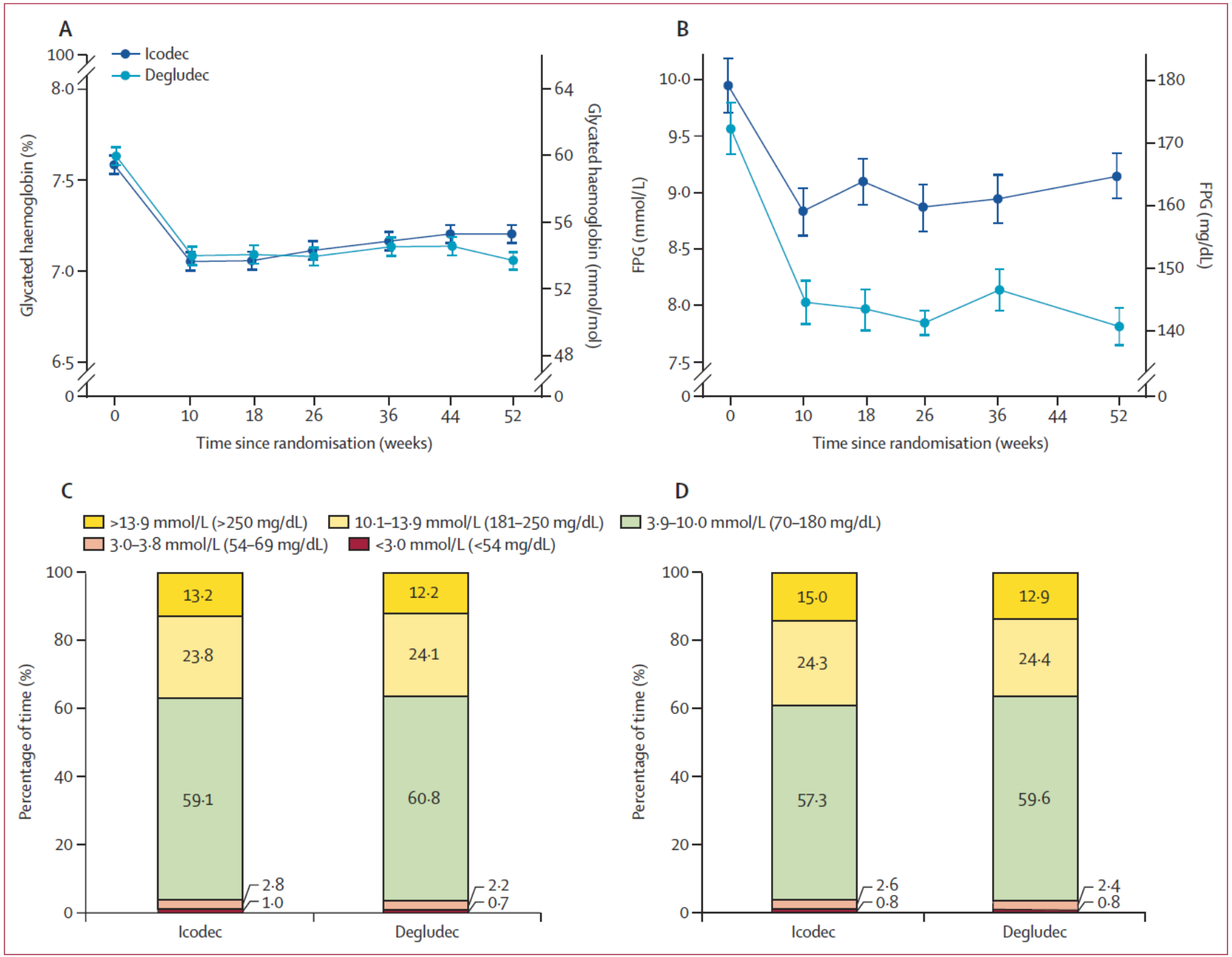
DMT2 in terapia Basal-Bolus, n=582, 26 settimane

	Insulin icodec (n=291)		Insulin glargine U100 (n=291)		Insulin icodec *vs* insulin glargine U100
	Participants (%)	Episodes (rate per PYE)	Participants (%)	Episodes (rate per PYE)	ERR (95% CI), p value
Hypoglycaemic episodes (overall)					
Hypoglycaemia alert value (level 1)*	244 (84%)	5264 (31·45)	251 (86%)	4145 (24·85)	1·25 (1·03–1·52), p=0·025
Clinically significant (level 2) hypoglycaemia†	148 (51%)	937 (5·60)	160 (55%)	935 (5·61)	0·99 (0·73–1·34), p=0·93
Severe (level 3) hypoglycaemia‡	4 (1%)	7 (0·04)	2 (1%)	3 (0·02)	2·19 (0·20–24·44), p=0·53
Combined clinically significant (level 2)† or severe (level 3)‡ hypoglycaemia	150 (51%)	944 (5·64)	162 (56%)	938 (5·62)	0·99 (0·73–1·33), p=0·93
Hypoglycaemic episodes (nocturnal)					
Hypoglycaemia alert value (level 1)*	108 (37%)	380 (2·27)	132 (45%)	440 (2.64)	..
Clinically significant (level 2) hypoglycaemia†	54 (19%)	131 (0·78)	71 (24%)	171 (1·02)	0·74 (0·47–1·15) p=0·18
Severe (level 3) hypoglycaemia‡	0	..	1 (<1%)	2 (0·01)	..
Combined clinically significant (level 2)† or severe (level 3)‡ hypoglycaemia	54 (19%)	131 (0·78)	72 (25%)	173 (1·04)	0·73 (0·47–1·14), p=0·17

Lancet 2023; 401: 1929–40

ONWARDS 6

DMT1 in terapia Basal-Bolus, n=582, 52 settimane



Lancet 2023, 402:1636-47

ONWARDS 6

DMT1 in terapia Basal-Bolus, n=582, 52 settimane

Lancet 2023, 402:1636-47

	Insulin icodec (n=290)		Insulin degludec (n=292)		Insulin icodec vs insulin degludec
	Participants	Events (rate)	Participants	Events (rate)	Estimated rate ratio (95% CI), p value
Overall hypoglycaemic episodes (baseline to week 26)					
Hypoglycaemia alert value*	288 (99%)	10799 (75·88)	287 (98%)	7402 (51·36)	..
Clinically significant hypoglycaemia†	246 (85%)	2789 (19·60)	223 (76%)	1478 (10·26)	1·88 (1·53 to 2·32), p<0·0001
Severe hypoglycaemia‡	9 (3%)	47 (0·33)	9 (3%)	17 (0·12)	2·08 (0·39 to 10·96), p=0·39
Combined clinically significant† or severe‡ hypoglycaemia	247 (85%)	2836 (19·93)	223 (76%)	1495 (10·37)	1·89 (1·54 to 2·33), p<0·0001
Overall hypoglycaemic episodes (baseline to week 57)					
Hypoglycaemia alert value*	288 (99%)	20406 (67·98)	289 (99%)	14819 (47·87)	..
Clinically significant hypoglycaemia†	262 (90%)	5047 (16·81)	250 (86%)	2811 (9·08)	1·79 (1·48 to 2·18), p<0·0001
Severe hypoglycaemia‡	13 (4%)	56 (0·19)	12 (4%)	25 (0·08)	1·88 (0·48 to 7·36), p=0·37
Combined clinically significant† or severe‡ hypoglycaemia	263 (91%)	5103 (17·00)	250 (86%)	2836 (9·16)	1·80 (1·48 to 2·18), p<0·0001
Nocturnal hypoglycaemic episodes (baseline to week 26)					
Hypoglycaemia alert value*	214 (74%)	980 (6·89)	171 (59%)	734 (5·09)	..
Clinically significant hypoglycaemia†	135 (47%)	476 (3·34)	98 (34%)	224 (1·55)	2·13 (1·56 to 2·91), p<0·0001
Severe hypoglycaemia‡	2 (1%)	5 (0·04)	3 (1%)	3 (0·02)	..
Combined clinically significant† or severe‡ hypoglycaemia	135 (47%)	481 (3·38)	98 (34%)	227 (1·58)	2·13 (1·56 to 2·91), p<0·0001
Nocturnal hypoglycaemic episodes (baseline to week 57)					
Hypoglycaemia alert value*	237 (82%)	1953 (6·51)	211 (72%)	1523 (4·92)	..
Clinically significant hypoglycaemia†	171 (59%)	861 (2·87)	140 (48%)	458 (1·48)	1·88 (1·43 to 2·47), p<0·0001
Severe hypoglycaemia‡	4 (1%)	9 (0·03)	4 (1%)	4 (0·01)	1·62 (0·22 to 11·86), p=0·63
Combined clinically significant† or severe‡ hypoglycaemia	171 (59%)	870 (2·90)	140 (48%)	462 (1·49)	1·89 (1·44 to 2·48), p<0·0001

Terapia insulinica 3.0

LA TERAPIA INSULINICA CON SOMMINISTRAZIONE SETTIMANALE:

- Riduce nei pazienti in sola terapia basale il numero di iniezioni annue da 365 a 52, facilitando enormemente l'aderenza
- Ha efficacia almeno pari alla terapia insulinica giornaliera praticata con gli analoghi lenti di ultima generazione
- Ha, almeno nei pazienti con DM2, un profilo di sicurezza comparabile a quello degli analoghi lenti di ultima generazione, e quindi eccellente
- Si associa ad una maggiore soddisfazione dei pazienti relativamente alla loro qualità di vita
- Vanno ponderati con maggiore attenzione vantaggi ed eventuali rischi per l'utilizzo nei soggetti con DM1