CONGRESSO REGIONALE
SID-AMD MARCHE 2025

SID Società Italiana di Diabetologia
fondata nel 1964

AMD ASSOCIAZIONE MEDICI DIABETOLOGI
MARCHE

LA CURA DELLA PERSONA CON DIABETE NELL' ERA DELL' INTELLIGENZA ARTIFICIALE

TRAGUARDI, SFIDE E NUOVI ORIZZONTI

RESPONSABILE SCIENTIFICO Paola Canibus

JESI (AN) | 11 ottobre 2025
Hotel Federico II

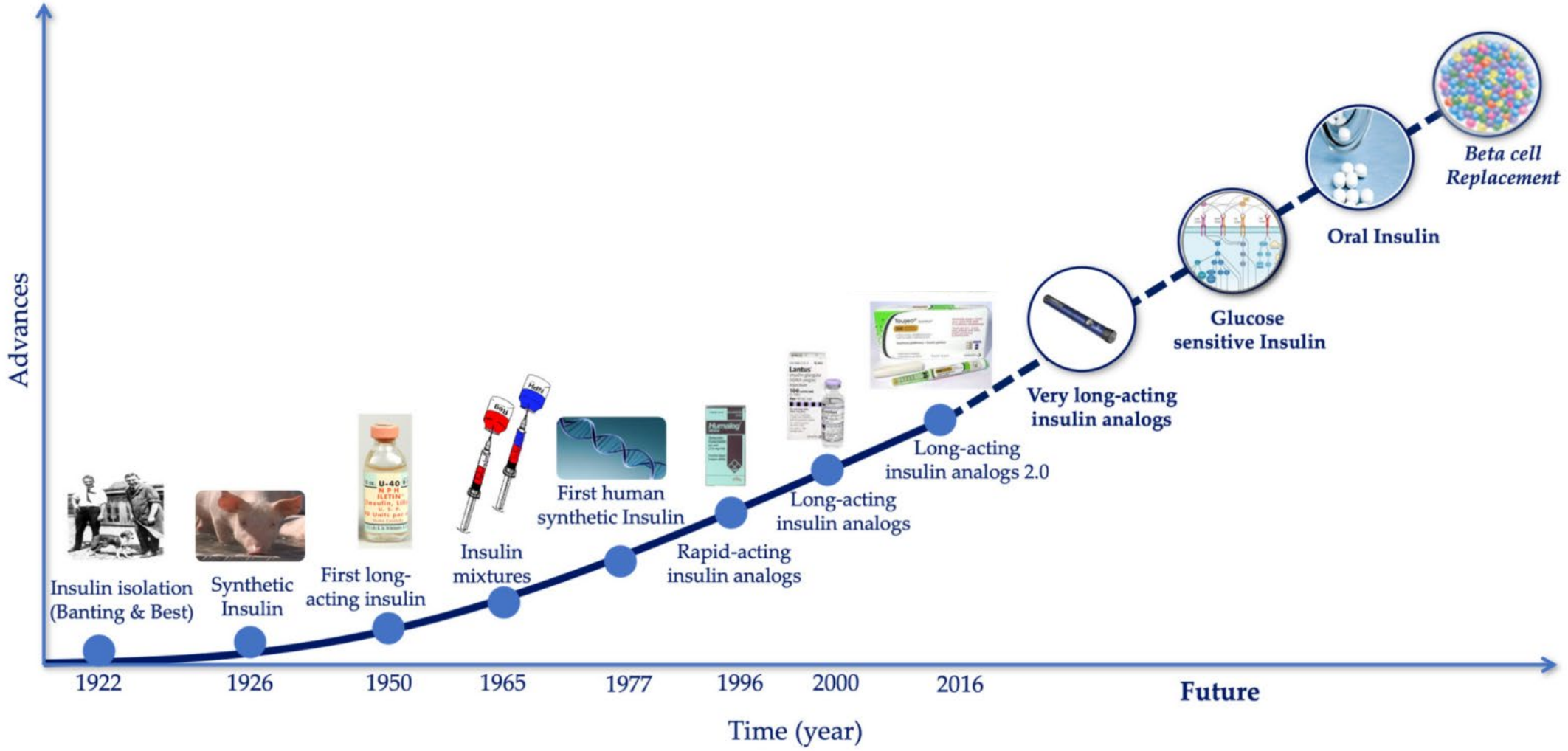
Nuove terapie in diabetologia:
le insuline
Gabriella Garrapa

DISCLOSURES

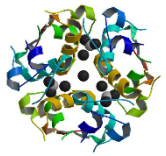
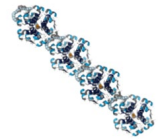
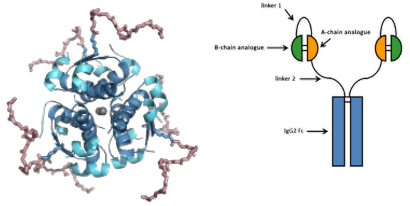
- La dr./ssa GARRAPA GABRIELLA dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:
- LILLY
- SANOFI
- ABBOTT

- *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.).*

Past and future advances in insulin development



L’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 di nuova generazione: l'elogio della... lentezza!

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

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

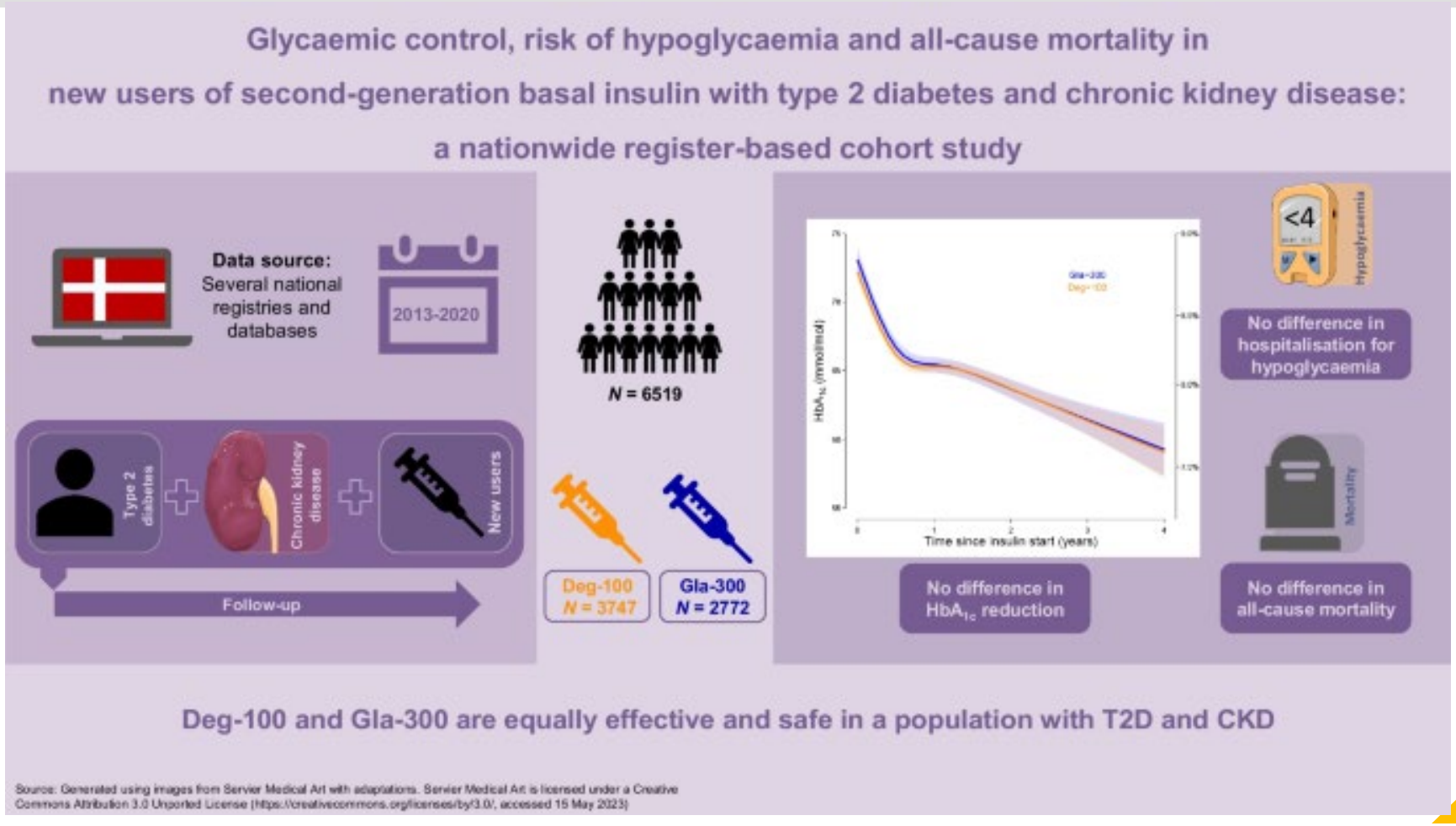
Diabetes Ther (2023) 14:1299–1317

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?

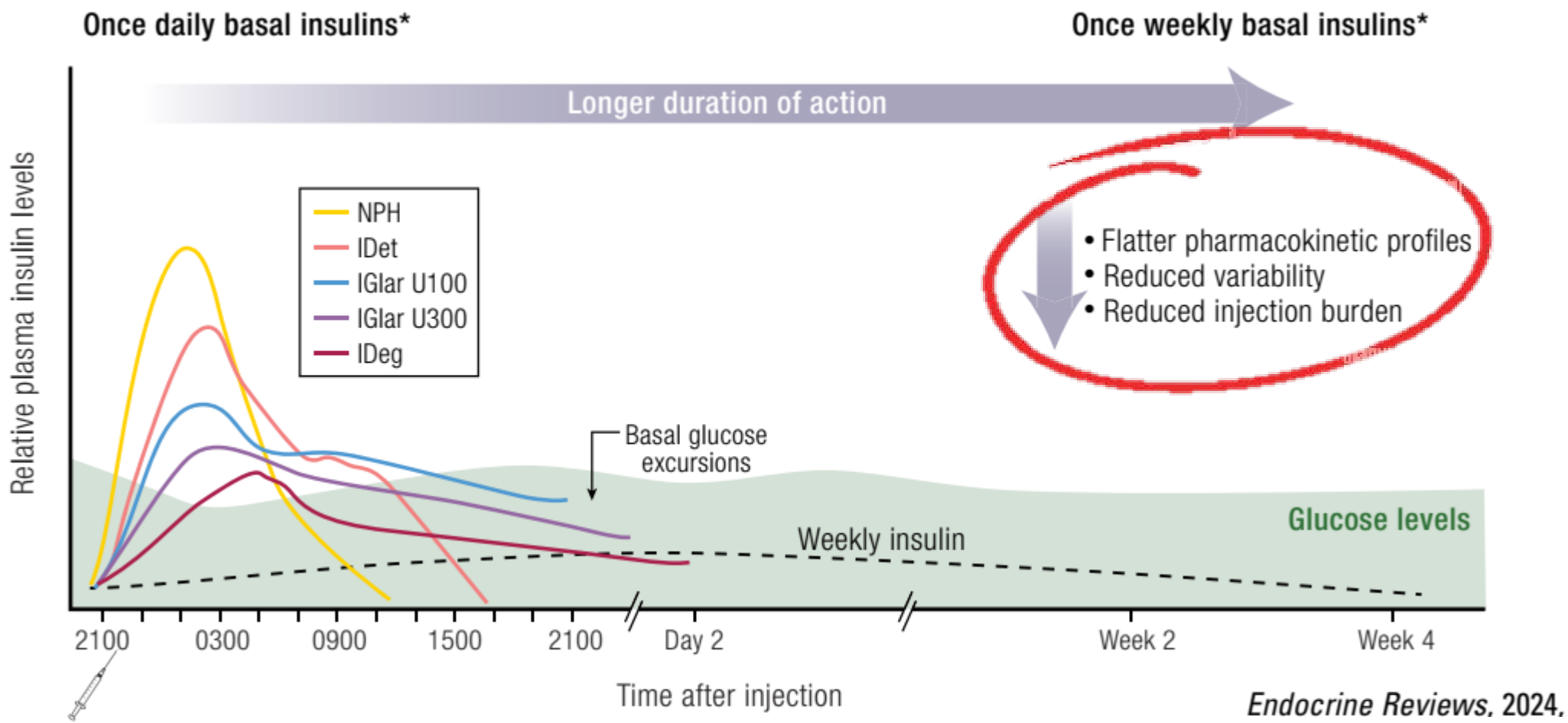
The most salient effects were observed for nocturnal hypoglycemia. Overall, second-generation insulin versus earlier intermediate/basal insulin users reported a 43% reduction in non-severe nocturnal hypoglycemia ($p < 0.001$) and a 44% reduction in severe nocturnal hypoglycemia ($p = 0.02$). These trends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

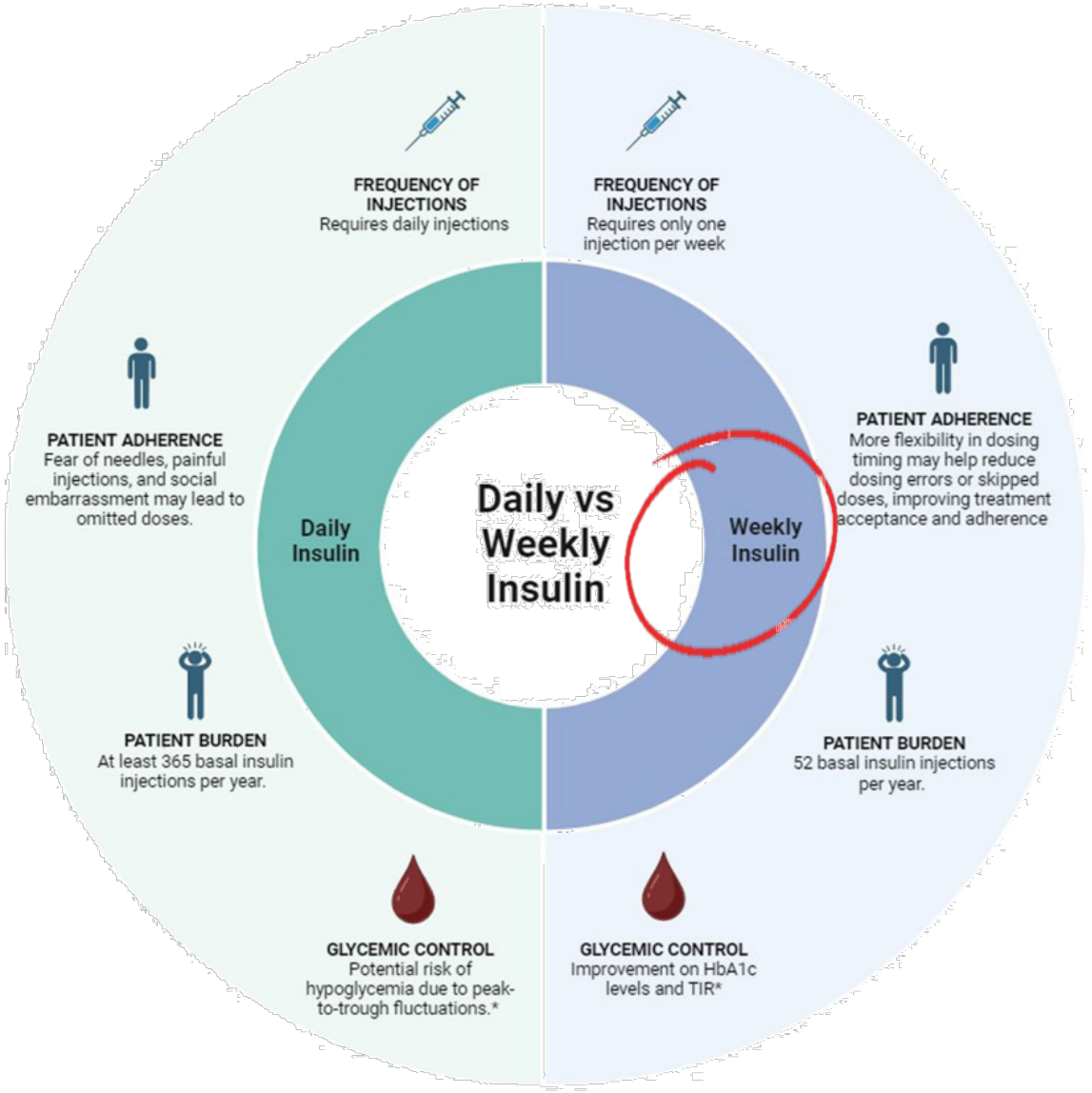


Conclusions/interpretation We found no difference in HbA_{1c} reduction, hospitalisation for hypoglycaemia or all-cause mortality between Gla-300 and Deg-100 in a real-world population of new users with type 2 diabetes and moderate to end-stage chronic kidney disease. Therefore, we conclude that these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

Diabetologia Published online: 28 July 2023



Endocrine Reviews, 2024.



Comparison of daily and weekly insulin regimens

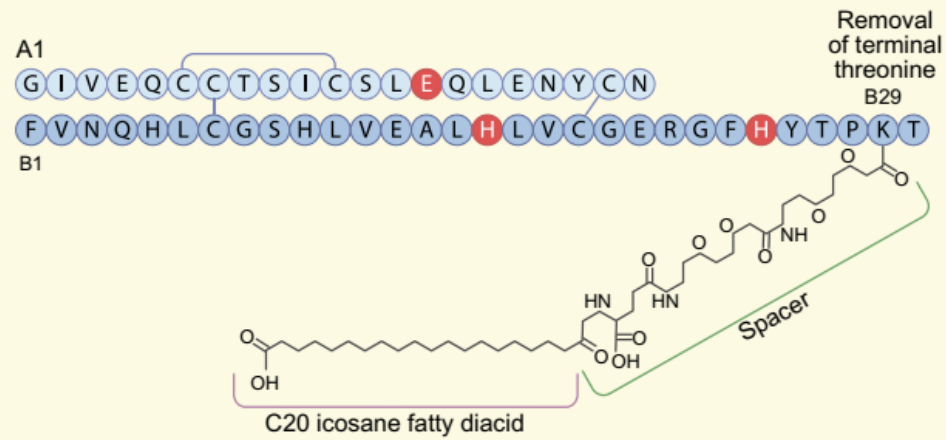
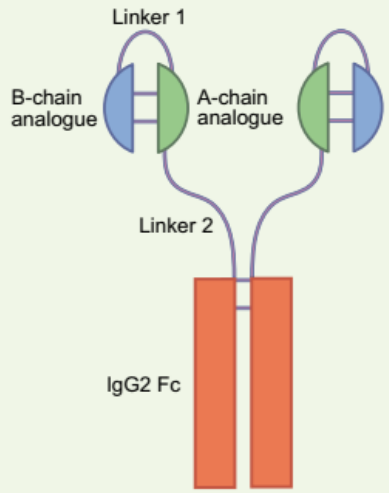
Diabetology & Metabolic Syndrome (2025)

- **Once-weekly insulins** provide a unique opportunity to **simplify** basal insulin therapy and to **allow good glycaemic** control with a **low risk** of **hypoglycaemia**

- As most peptides have a relatively short half-life, **substantial structural changes** to the **insulin molecule** are required to achieve the **pharmacokinetic properties** necessary to ensure **a flat profile** for at least **1 week**.

- The ways in which this has been **achieved** for **icodec** and **BIF** are **very different**

Molecular and pharmacokinetic features of icodec and BIF.

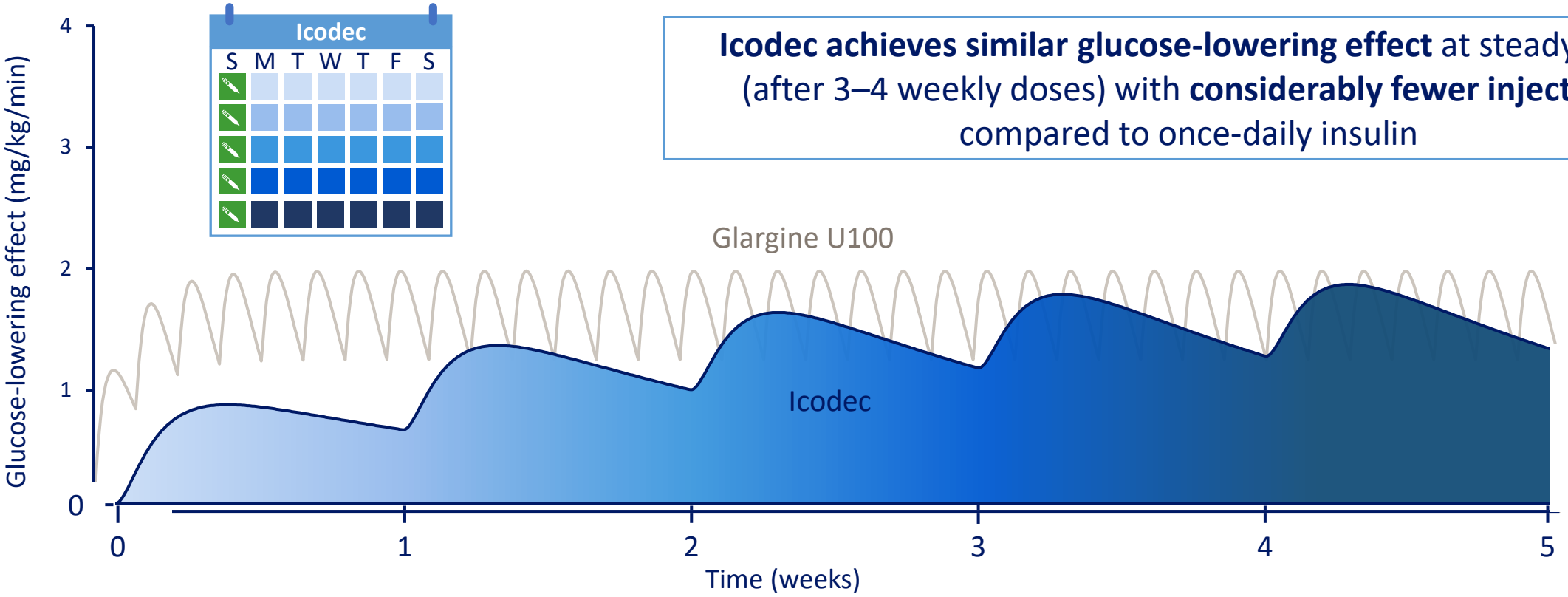
Icodec	BIF(basal insulin FC)
	
Covalently bound to C20 icosane fatty diacid	Single-chain insulin molecule bound to IgG2 Fc domain
Strong, reversible binding to albumin	Homodimer, molecular mass 64.1 kDa
Half-life: 8.2 days	Half-life: 17 days

[efsi-tor-a = Fc-receptor-agonist]

Diabetologia (2024)

Pharmacodynamic modelling showed an increase in glucose-lowering effect over time in T2D

Based on phase 1 clinical data



Icodec achieves similar glucose-lowering effect at steady state (after 3–4 weekly doses) with **considerably fewer injections** compared to once-daily insulin

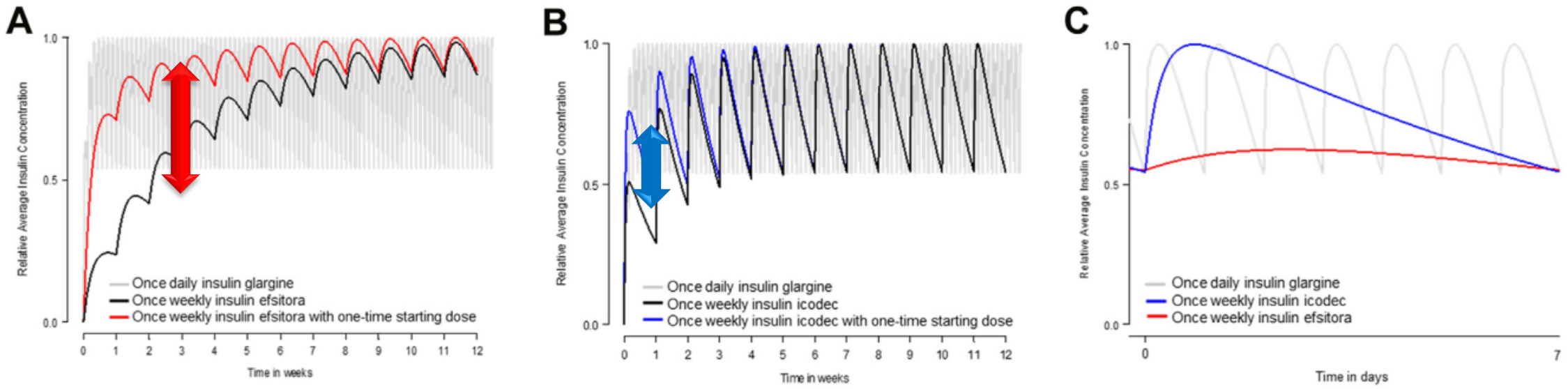


Fig. 5. Concentration of daily basal insulin glargine profiles and weekly basal insulin profiles simulated over 12 weeks with and without a one-time starting dose for (*A*) efsitora or (*B*) icodec and (*C*) glargine, icodec, and efsitora over 1 week at steady state.

Beyond reaching efficacious levels more quickly, the time to reach pharmacokinetic steady state or a stable dose can also be shorter with the use of a one-time starting dose than without one.

Between Day Variability and Impact on Glycemic Control

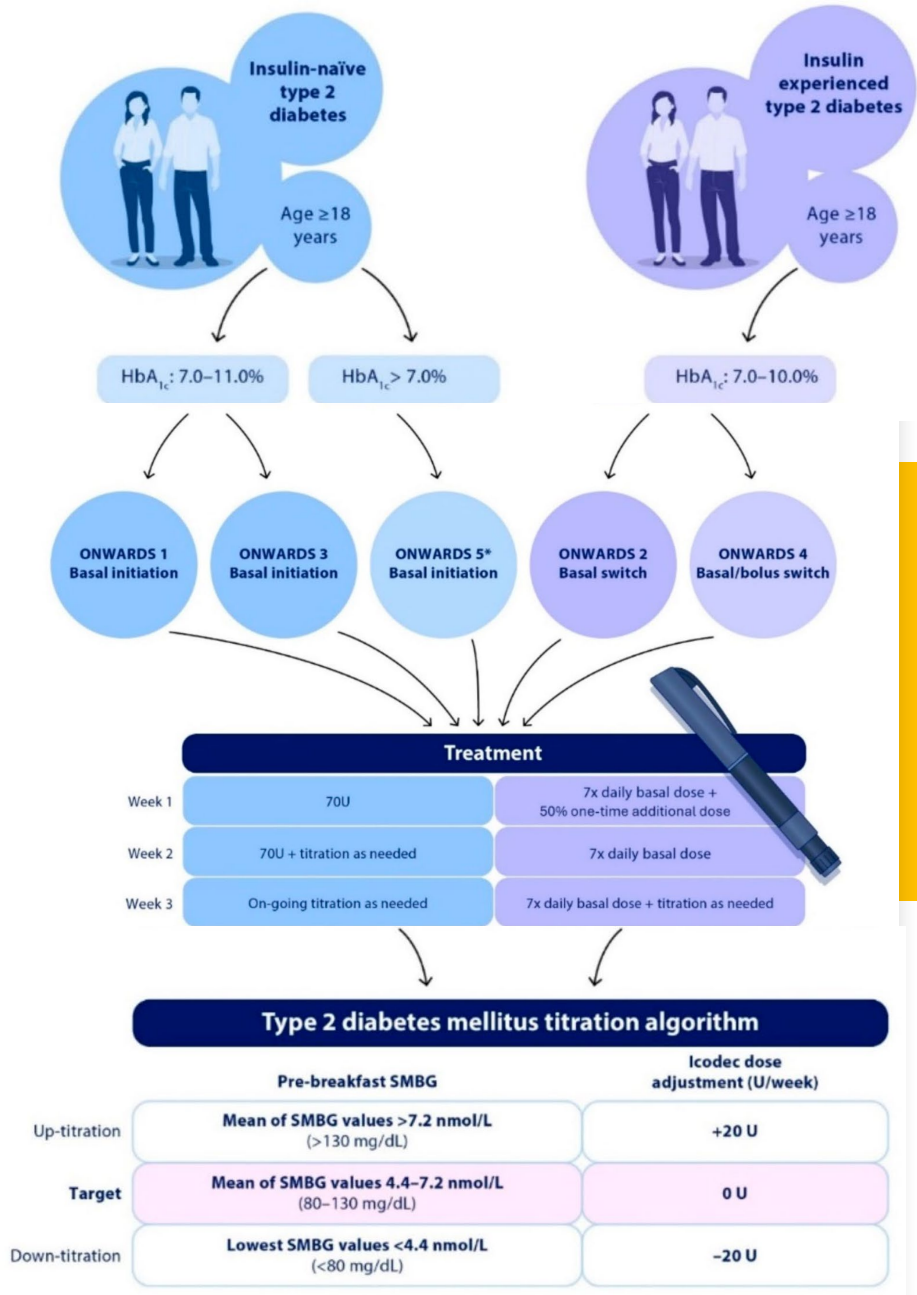
The flat and prolonged exposure profile of a weekly basal insulin can provide a consistent level of insulin from day-to-day over the course of a weekly dosing regimen compared to daily basal insulin (Fig. 5 *C*). This reduces within-day and between-day glycemic variability observed when using daily basal insulins. This is expected to manifest as a more consistent glycemic profile and has the potential to lower the risk of hypoglycemia compared to daily basal insulins.

Endocrine Practice 30 (2024)

Treatment of T2D patients with icodec weekly insulin

Diabetology & Metabolic Syndrome (2025)

	Pre-breakfast SMBG	Glargine U100 dose adjustment (U/day)	Icodec dose adjustment (U/week)
Up-titration	Mean of SMBG values >7.2 mmol/L (>130 mg/dL)	+3 U	+20 U
Target	Mean of SMBG values 4.4–7.2 mmol/L (80–130 mg/dL)	0 U	0 U
Down-titration	Lowest SMBG value <4.4 mmol/L (<80 mg/dL)	–3 U	–20 U



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 24, 2025 VOL. 393 NO. 4

Weekly Fixed-Dose Insulin Efsitora in Type 2 Diabetes without Previous Insulin Therapy

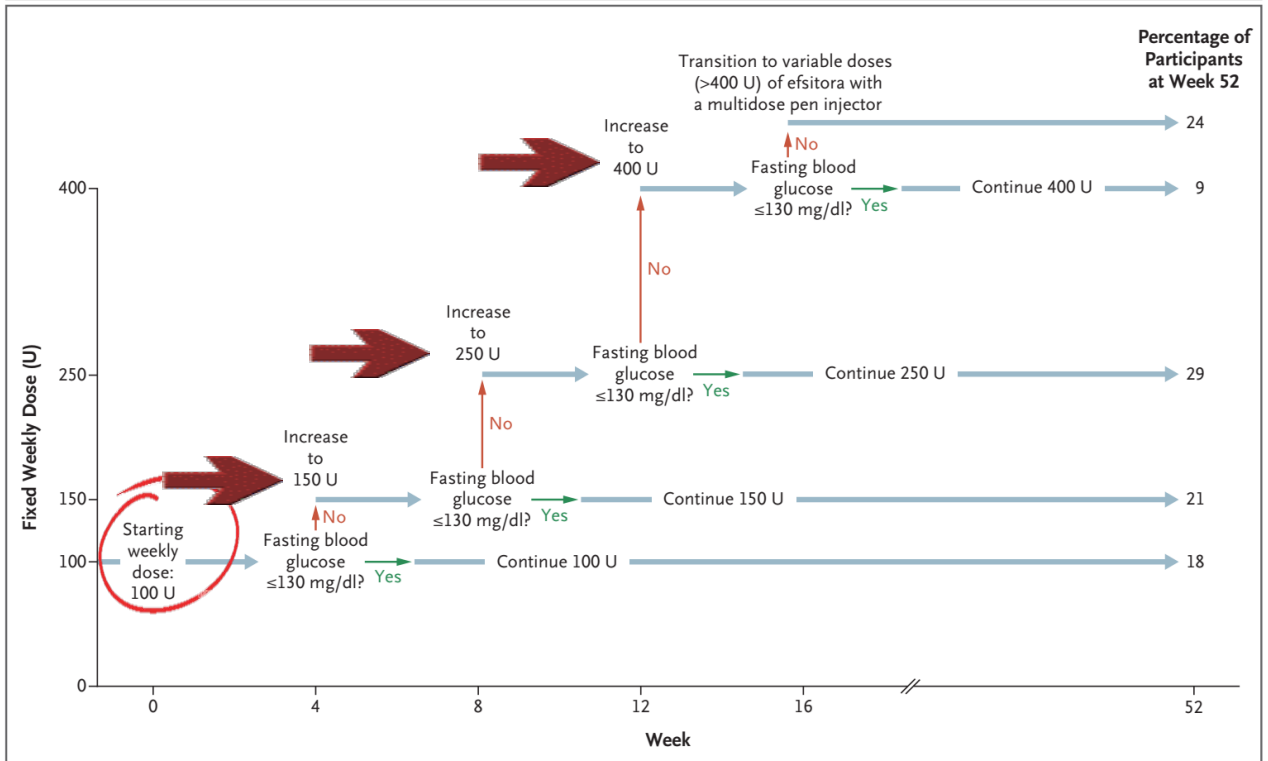
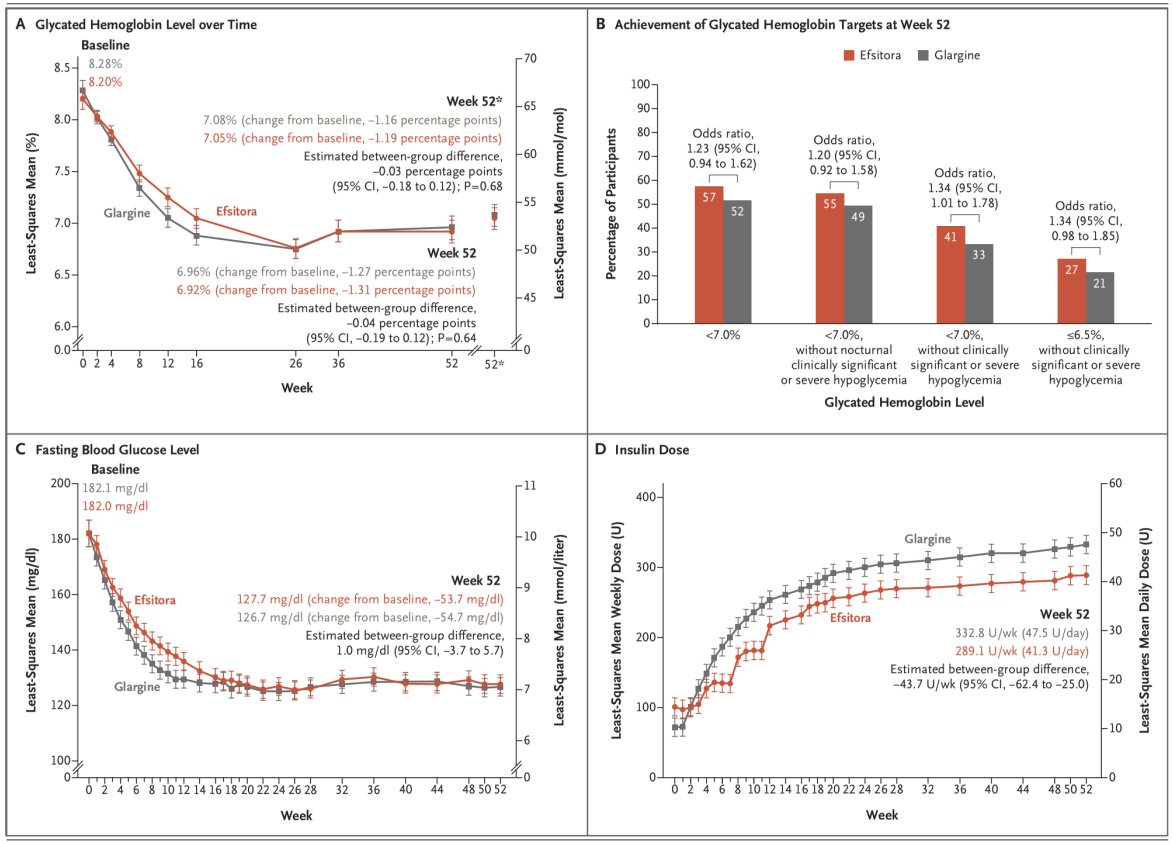


Figure 1. Fixed-Dose Regimen for Efsitora.



In this trial involving participants with type 2 diabetes who had not previously received insulin, once-weekly efsitora administered in a fixed-dose regimen was noninferior to once-daily glargine in reducing glycated hemoglobin levels at 52 weeks.

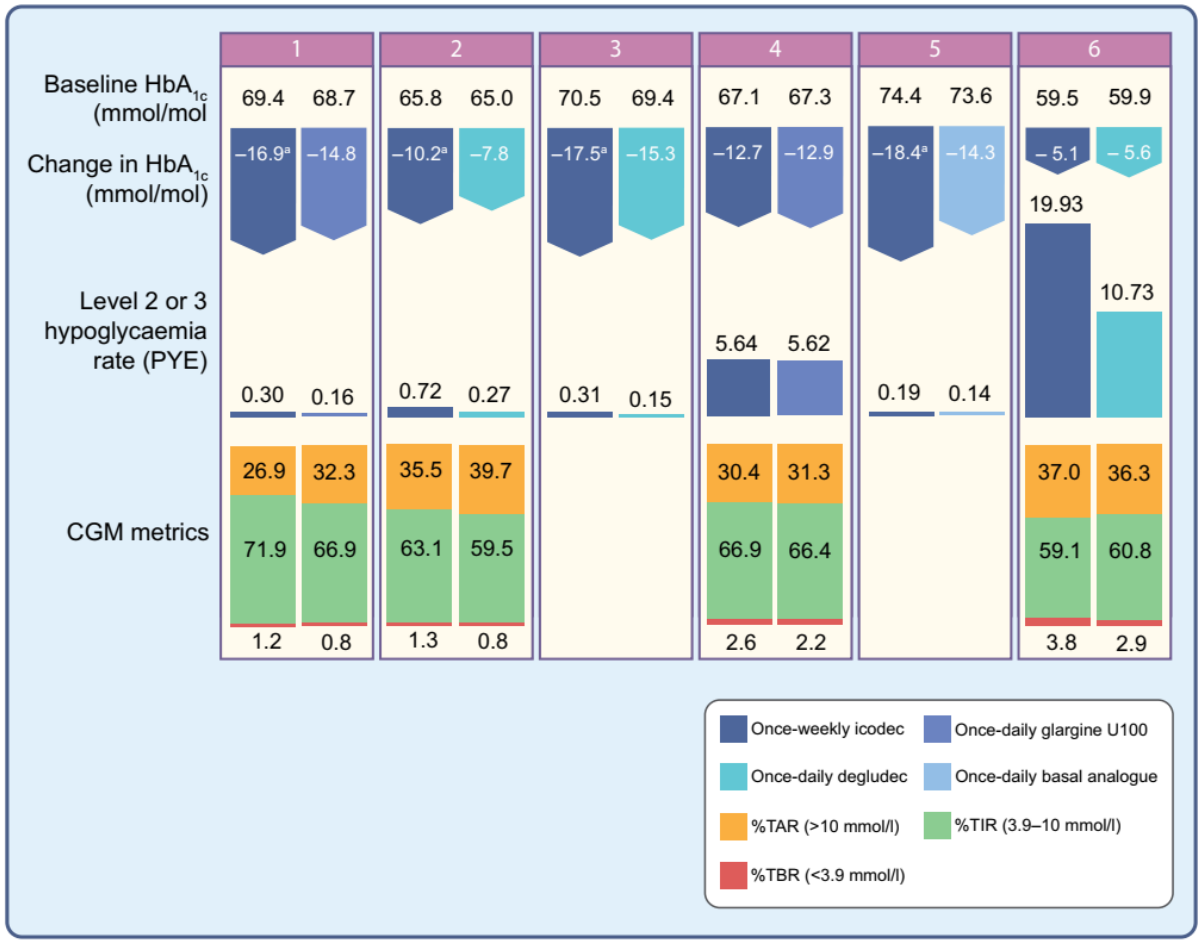
Once-weekly insulins: a promising approach to reduce the treatment burden in people with diabetes

Diabetologia (2024)

Table 2 Summary of Phase III clinical programmes icodec (ONWARDS) and BIF (QWINT)

Trial	Design	No. of participants	Population	Comparator	Baseline treatment	Dur (we
Icodec						
ONWARDS 1 [31]	Open label	984	Insulin-naive participants with T2D	Glargine U100	Any non-insulin drugs	78
ONWARDS 2 [32]	Open label	526	Insulin-treated participants with T2D	Degludec	Basal insulins ± non-insulin glucose-lowering agents	26
ONWARDS 3 [29]	Double-blind	588	Insulin-naive participants with T2D	Degludec	Any non-insulin drugs	26
ONWARDS 4 [33]	Open label	582	Insulin-treated participants with T2D	Glargine U100	Multiple daily insulin injections ± non-insulin drugs	26
ONWARDS 5 [30]	Open label	1085	Insulin-naive participants with T2D	Glargine U100/300 and degludec	Any non-insulin drugs	52
ONWARDS 6 [34]	Open label	583	Participants with T1D	Degludec	Multiple daily insulin injections	52
BIF						
QWINT-1 [38]	Open label	670	Insulin-naive participants with T2D	Glargine U100	At least one glucose-lowering medication	52
QWINT-2 [41]	Open label	912	Insulin-naive participants with T2D	Degludec	At least one glucose-lowering medication	52
QWINT-3 [42]	Open label	986	Insulin-treated participants with T2D	Degludec	Basal insulins ± up to three non-insulin drugs (except SUs)	78
QWINT-4 [40]	Open label	670	Insulin-treated participants with T2D	Glargine U100	Multiple daily insulin injections	26
QWINT-5 [39]	Open label	670	Participants with T1D	Degludec	Multiple daily insulin injections	52

Fig. 3 Main results of the Phase III ONWARDS programme evaluating the safety and efficacy of once-weekly icodec compared with once-daily glargine, degludec or a basal analogue in individuals with type 1 and type 2 diabetes. The numbers at the top of the figure correspond to the different ONWARDS trials (1–6 [29–34]). Features of



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Insulin Efsitora versus Degludec in Type 2 Diabetes without Previous Insulin Treatment

NEJM.ORG DECEMBER 12, 2024

Table 2. Hypoglycemic Episodes.*

Variable	Efsitora (N=466)		Degludec (N=462)		Estimated Rate Ratio (95% CI)†
	No. of Participants (%)	No. of Episodes (Events/PYE)	No. of Participants (%)	No. of Episodes (Events/PYE)	
Overall hypoglycemic episodes					
Hypoglycemia alert‡	297 (63.7)	1811 (4.15)	249 (53.9)	1485 (3.36)	1.24 (0.99–1.55)
Clinically significant hypoglycemia‡	130 (27.9)	253 (0.58)	97 (21.0)	190 (0.43)	1.34 (0.97–1.85)
Severe hypoglycemia§	0	0	6 (1.3)	6 (0.01)	—
Combined clinically significant or severe hypoglycemia‡	130 (27.9)	253 (0.58)	102 (22.1)	196 (0.45)	1.30 (0.94–1.78)
Noctural hypoglycemic episodes¶					
Combined clinically significant or severe hypoglycemia‡	23 (4.9)	32 (0.08)	23 (5.0)	35 (0.08)	1.01 (0.53–1.89)

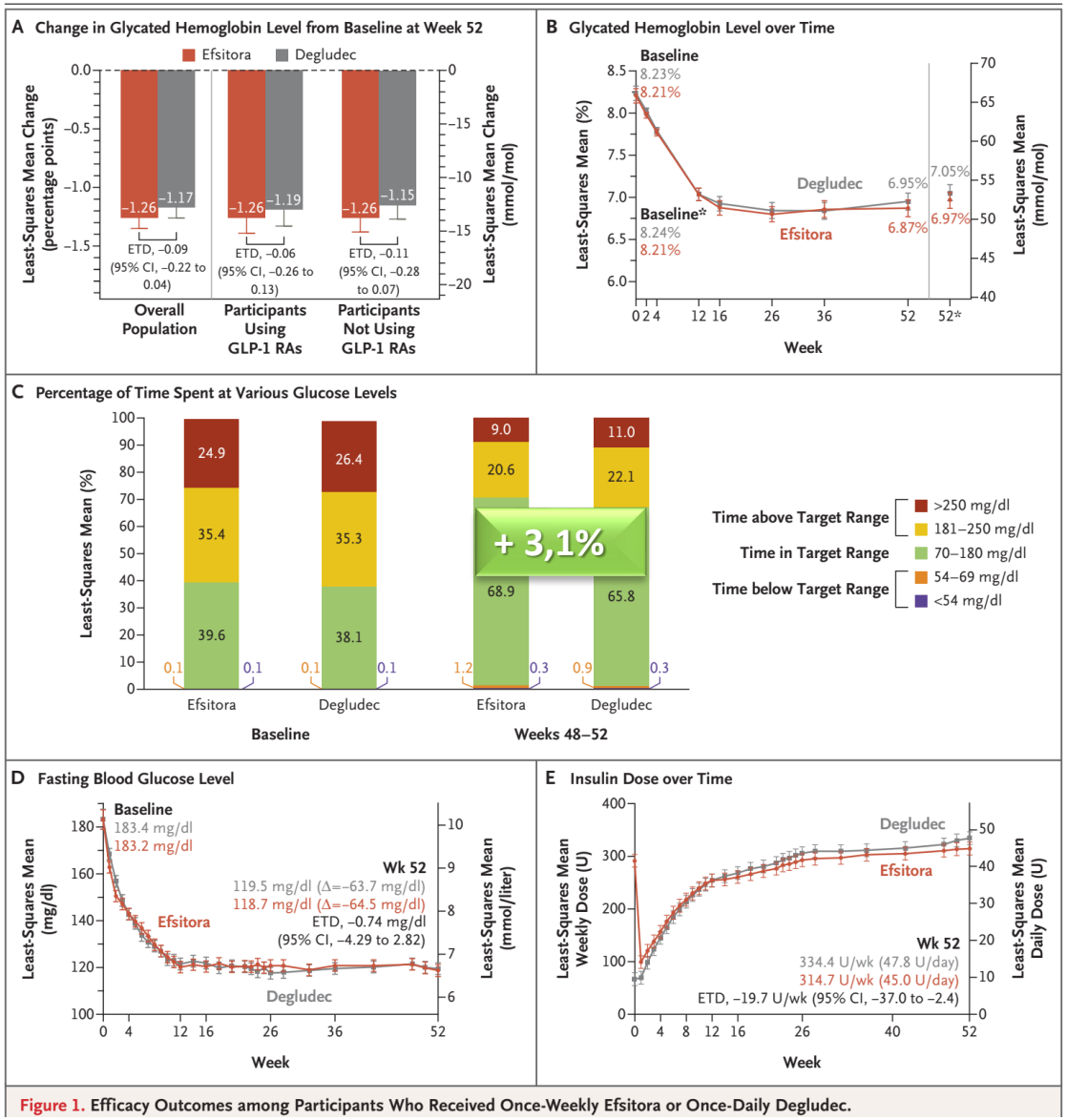


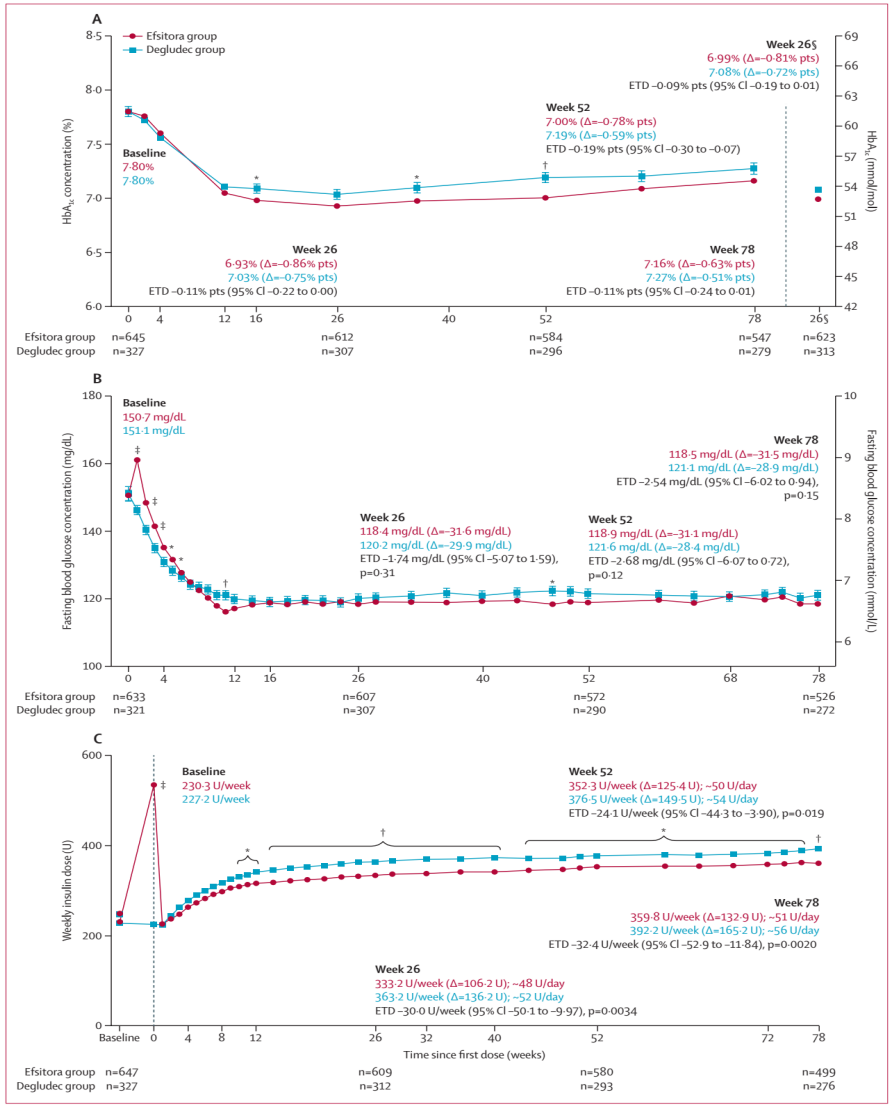
Figure 1. Efficacy Outcomes among Participants Who Received Once-Weekly Efsitora or Once-Daily Degludec.

CONCLUSIONS

In adults with type 2 diabetes who had not previously received insulin, once-weekly efsitora was noninferior to once-daily degludec in reducing glycated hemoglobin levels. (Funded by Eli Lilly; QWINT-2 ClinicalTrials.gov number, NCT05362058.)

Once-weekly insulin efsitora alfa versus once-daily insulin degludec in adults with type 2 diabetes currently treated with basal insulin (QWINT-3): a phase 3, randomised, non-inferiority trial

thelancet.com Published online June 22, 2025



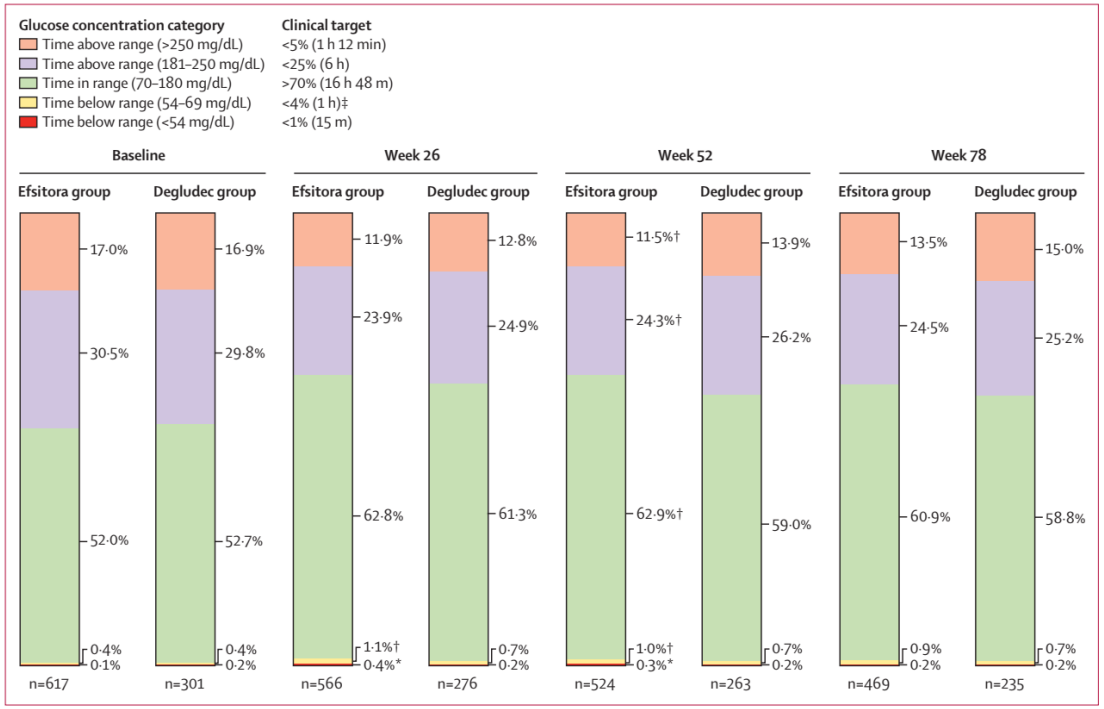


Figure 3: Continuous glucose monitoring metrics at baseline and weeks 26, 52, and 78 for efsitora and degludec (efficacy estimand)

Implications of all the available evidence

This randomised controlled trial in adults with type 2 diabetes already treated with daily basal insulin showed non-inferior glycaemic control of efsitora compared with degludec. The results highlight that the risk of transient hyperglycaemia is not increased with a once-weekly basal insulin. Together with the phase 2 and other phase 3 studies, the results underscore the efficacy and safety of efsitora as a treatment for type 2 diabetes and the possibility of a once-weekly basal insulin to reduce the burden on patients.

Once-weekly insulin efsitora alfa versus once-daily insulin glargine U100 in adults with type 2 diabetes treated with basal and prandial insulin (QWINT-4): a phase 3, randomised, non-inferiority trial

thelancet.com **Published online June 22, 2025**

Implications of all the available evidence

This randomised trial in adults with type 2 diabetes showed non-inferior glycaemic control of efsitora compared with glargine U100. In combination with other phase 2 and 3 studies, our results highlight the efficacy and safety of efsitora as a treatment for type 2 diabetes and the possibility of once-weekly basal insulin to reduce the burden on people with diabetes.

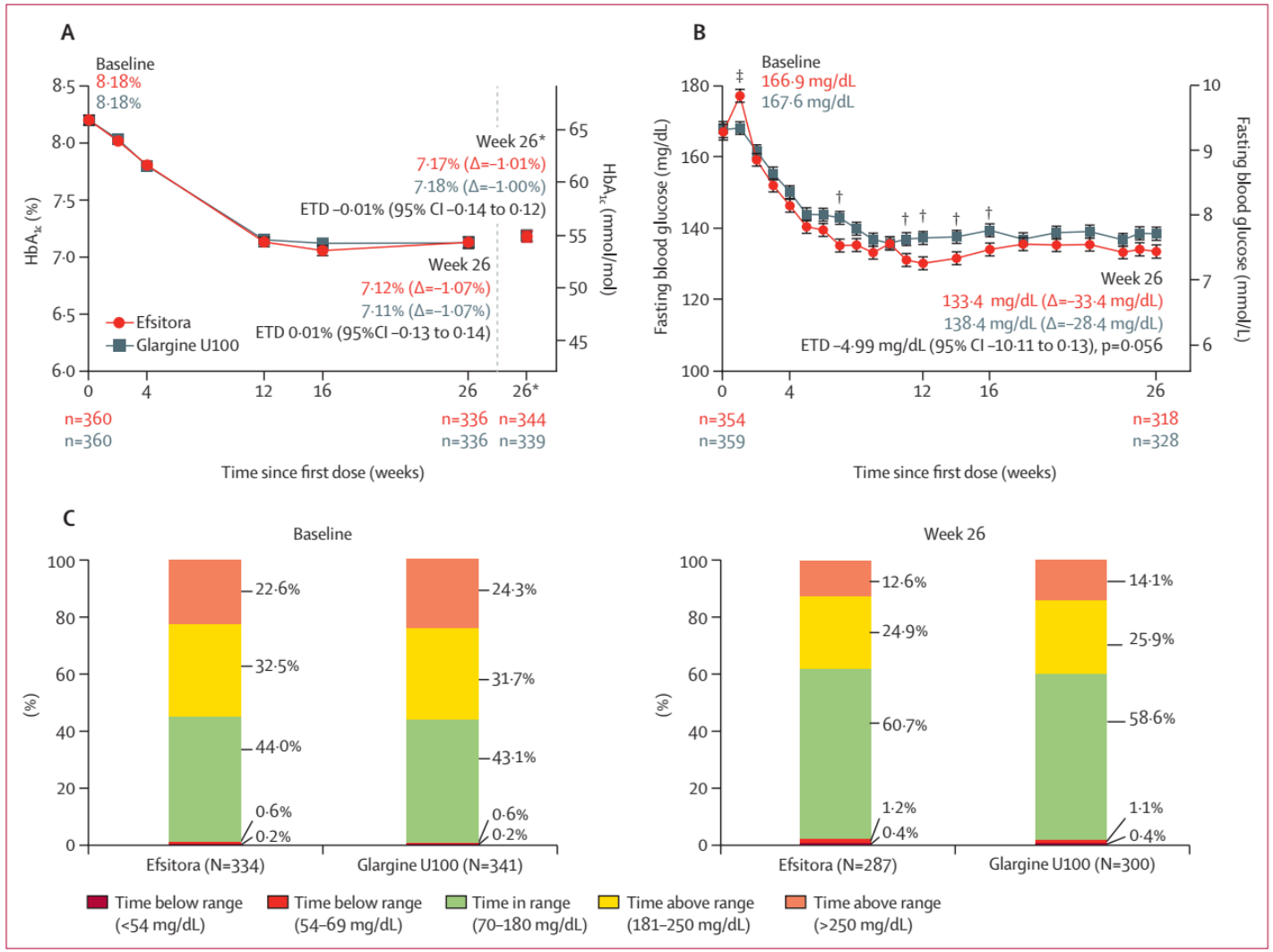
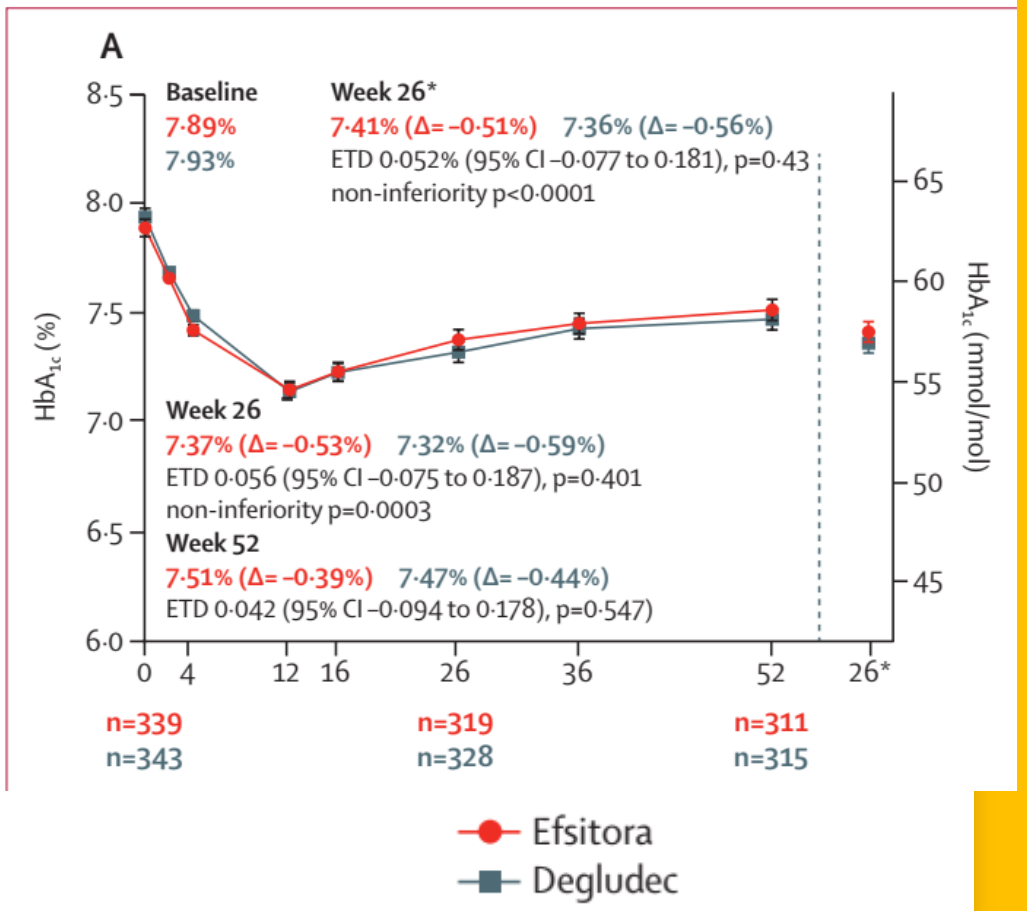


Figure 2: **Key efficacy outcomes among participants who received at least one dose of efsitora and glargine U100**

Once-weekly insulin efsitora alfa versus once-daily insulin degludec in adults with type 1 diabetes (QWINT-5): a phase 3 randomised non-inferiority trial

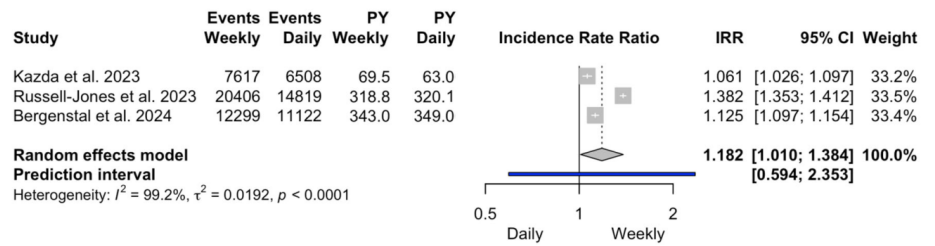
thelancet.com Vol 404 September 21, 2024

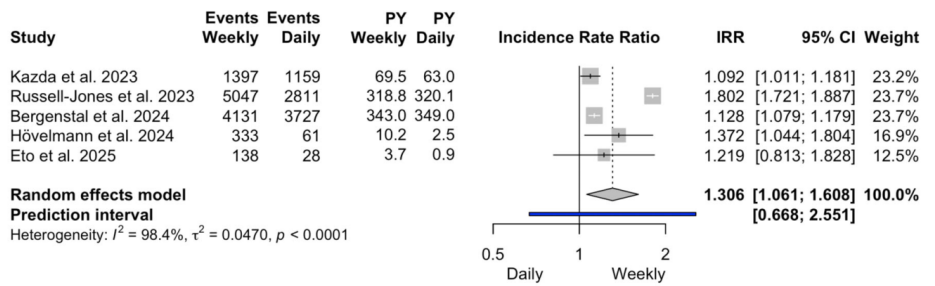
	Efsitora (n=343)		Degludec (n=349)		Efsitora *vs* Degludec
	Participants, n (%)	Episodes (rate per patient-year exposure)	Participants, n (%)	Episodes (rate per patient-year exposure)	Estimated relative rate (95% CI); p value
Hypoglycaemic episodes (overall)					
Level 1 hypoglycaemia					
Week 0–26	339 (99%)	7474 (46·04)	333 (95%)	6586 (39·13)	1·18 (1·05–1·32); p=0·0055
Week 0–52	340 (99%)	12 299 (39·19)	337 (97%)	11 122 (33·99)	1·15 (1·03–1·29); p=0·016
Combined level 2 or level 3 severe hypoglycaemia					
Week 0–26	293 (85%)	2662 (17·19)	289 (83%)	2319 (14·06)	1·22 (1·04–1·43); p=0·013
Week 0–52	305 (89%)	4175 (14·03)	306 (88%)	3740 (11·59)	1·21 (1·04–1·41); p=0·016
Level 3 severe hypoglycaemia					
Week 0–26	28 (8%)	35 (0·21)	9 (3%)	11 (0·06)	3·23 (1·42–7·38); p=0·0052
Week 0–52	35 (10%)	44 (0·14)	11 (3%)	13 (0·04)	3·44 (1·64–7·19); p=0·0011

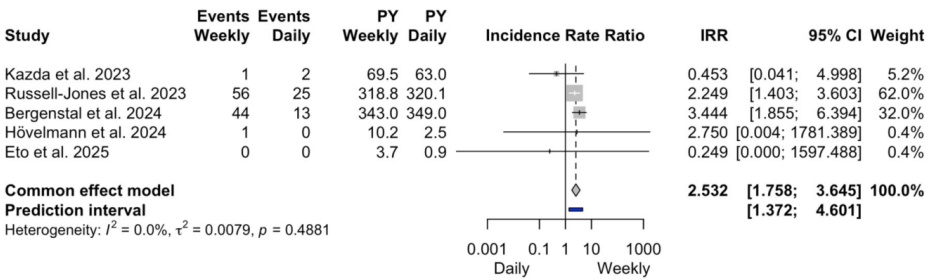


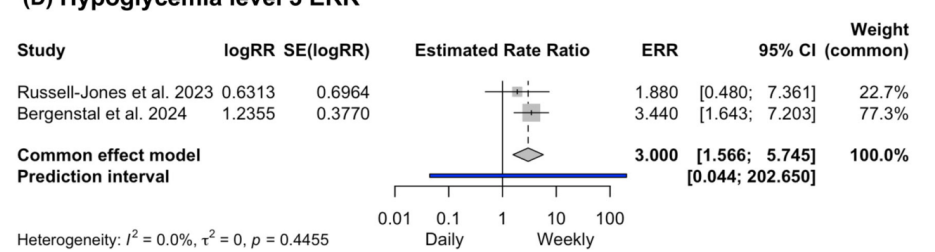
Interpretation In adults with type 1 diabetes, once-weekly efsitora showed non-inferior HbA_{1c} reduction compared with daily insulin degludec. Higher rates of combined level 2 or level 3 hypoglycaemia and greater incidence of severe hypoglycaemia in participants treated with efsitora compared with participants treated with degludec might suggest the need for additional evaluation of efsitora dose initiation and optimisation in people with type 1 diabetes.

Efficacy and safety of once-weekly basal insulin therapy in people with type 1 diabetes: A systematic review and meta-analysis







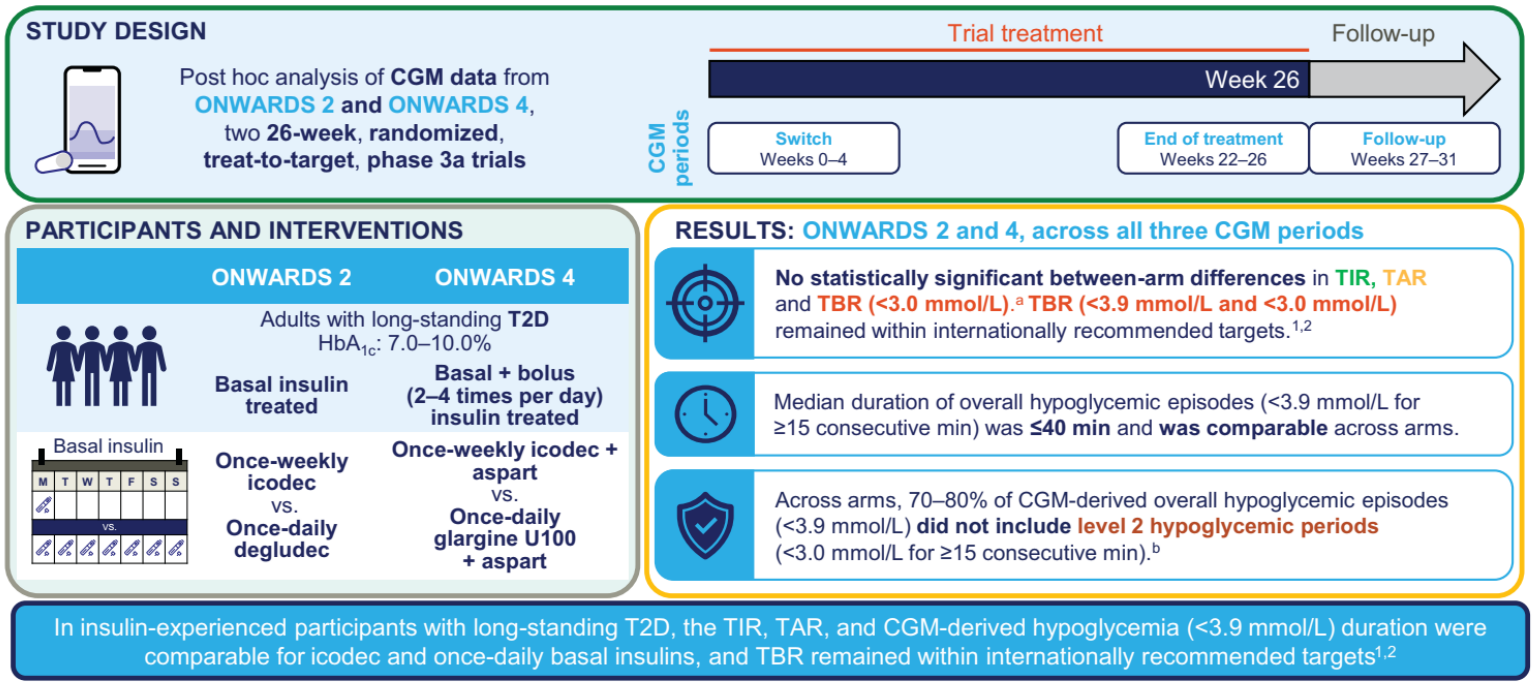


Results: Five RCTs were included, enrolling 1629 adults living with type 1 diabetes. Once-weekly and once-daily basal insulins had similar effects on HbA1c (high certainty), body weight (moderate certainty), time in range (moderate certainty) and time above range. However, safety concerns emerged due to increased rates of level 3 hypoglycaemia (incidence rate ratio 2.532, 95% confidence interval [CI] 1.758–3.645; moderate certainty). A significantly lower weekly bolus insulin dose was observed with once-weekly basal insulin therapy (estimated treatment ratio 0.837, 95% CI 0.794–0.882, $I^2 = 0\%$; high certainty).

Conclusions: This meta-analysis is the first to evaluate the efficacy and safety of once-weekly basal insulin therapy exclusively in adults with type 1 diabetes and including all published RCTs. The analysis demonstrated a similar glucose-lowering effect compared to once-daily basal insulin but revealed an increased occurrence of severe hypoglycaemia.

Diabetes Obes Metab. 2025;

Continuous Glucose Monitoring-Based Metrics and Hypoglycemia Duration in Insulin-Experienced Individuals With Long-Standing Type 2 Diabetes Switched From a Daily Basal Insulin to Once-Weekly Insulin Icodec: Post Hoc Analysis of ONWARDS 2 and ONWARDS 4



In insulin-experienced participants with long-standing T2D, the TIR, TAR, and CGM-derived hypoglycemia (<3.9 mmol/L) duration were comparable for icodec and once-daily basal insulins, and TBR remained within internationally recommended targets[1,2]

1. Battelino T et al. Lancet Diabetes Endocrinol 2023;11:42–57. 2. Battelino T et al. Diabetes Care 2019;42:1593–1603.[a]In the end of treatment period of ONWARDS 2, mean TBR (<3.9 mmol/L) was statistically significantly higher with icodec (1.3%) versus degludec (0.8%); no statistically significant between-arm differences were found during other periods of ONWARDS 2 or in ONWARDS 4.[b]Level 1 hypoglycemic episodes were defined as glucose <3.9 mmol/L for ≥15 consecutive min (without any periods of ≥15 consecutive min spent with sensor glucose <3.0 mmol/L), ending at the start of the first 15-min period when sensor glucose levels had been ≥3.9 mmol/L. Aspart, insulin aspart; CGM, continuous glucose monitoring; degludec, insulin degludec; glargine U100, insulin glargine U100; HbA_{1c}, glycated hemoglobin; icodec, insulin icodec; T2D, type 2 diabetes; TAR, time above range (>10 mmol/L); TBR, time below range (<3.9 mmol/L); TIR, time in range (3.9–10 mmol/L)

Diabetes Care 2024

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Continuous glucose monitoring data provide a detailed understanding of the efficacy and safety of once-weekly insulin icodec (icodec).
- **What is the specific question we wanted to answer?**
  This post hoc analysis investigated continuous glucose monitoring–based time in range, time above range, time below range, and hypoglycemia duration during three periods of two phase 3a trials in insulin-experienced individuals with long-standing type 2 diabetes.
- **What did we find?**
  In both trials, time in range, time above range, and median hypoglycemia duration were comparable for icodec versus once-daily insulin comparators (insulin degludec and insulin glargine U100); time below range remained within consensus targets.
- **What are the implications of our findings?**
  The findings support the efficacy and safety of switching to icodec in insulin-experienced individuals with type 2 diabetes.

Continuous Glucose Monitoring-Based Titration of Once-Weekly Insulin Icodec in Insulin-Naive Individuals with Type 2 Diabetes (ONWARDS 9): A Phase 3b, Multicenter, Single-Arm, Treat-to-Target Clinical Trial

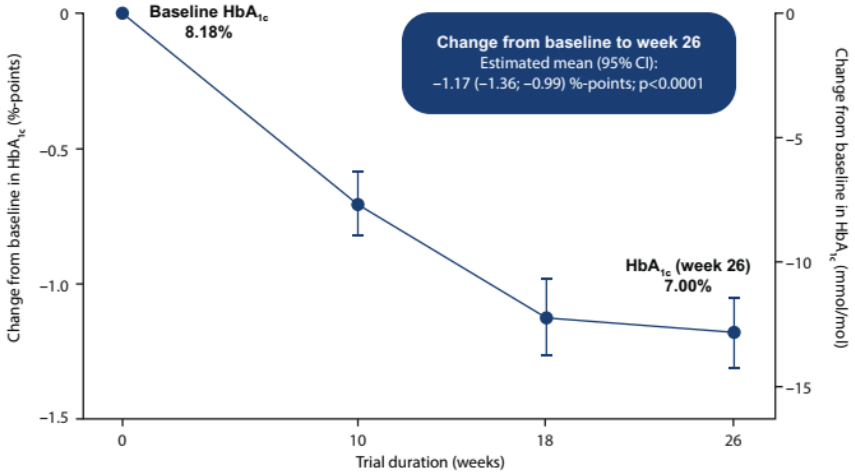


FIG. 1. Mean change in HbA1c from baseline to week 26. Full analysis set. Graph shows mean observed data (symbols) ± standard error of the mean (error bars). CI, confidence interval; HbA1c, glycated hemoglobin.

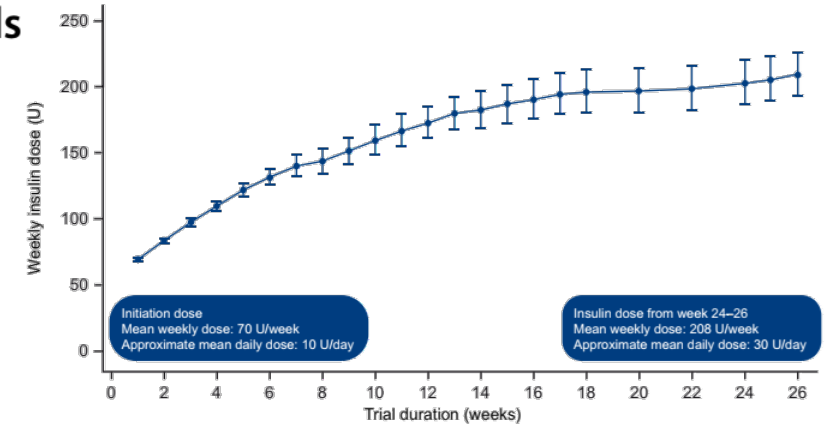


FIG. 3. Observed weekly insulin dose from week 0 to week 26. Observed data from the safety analysis set. Graph shows geometric mean (symbols) ± standard error of the mean on a back-transformed log scale (error bars). U, units.

Conclusions

In this 26-week, single-arm, phase 3b trial of insulin-naive individuals with T2D, CGM-based titration of once-weekly icodec resulted in a statistically significant reduction in HbA1c from baseline to week 26. Moreover, the internationally recommended CGM targets for TIR, TAR >180 mg/dL, and TBR <54 mg/dL were all achieved, without severe hypoglycemia. Taken together, these findings suggest that CGM-based titration of icodec is feasible in adults with T2D. Additional data, analyses, or studies exploring other

CGM-BASED TITRATION OF INSULIN ICODEC

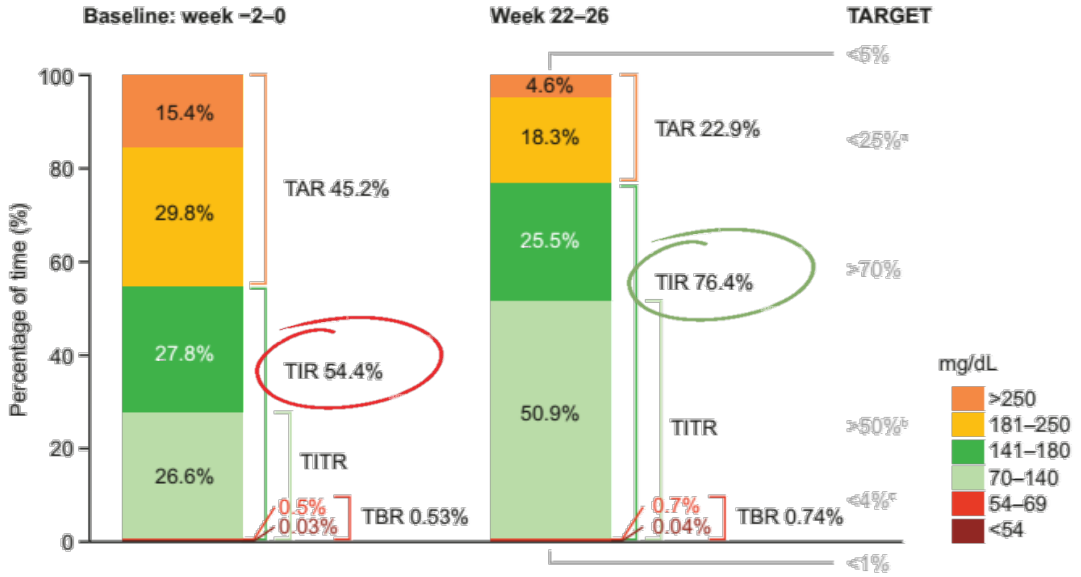
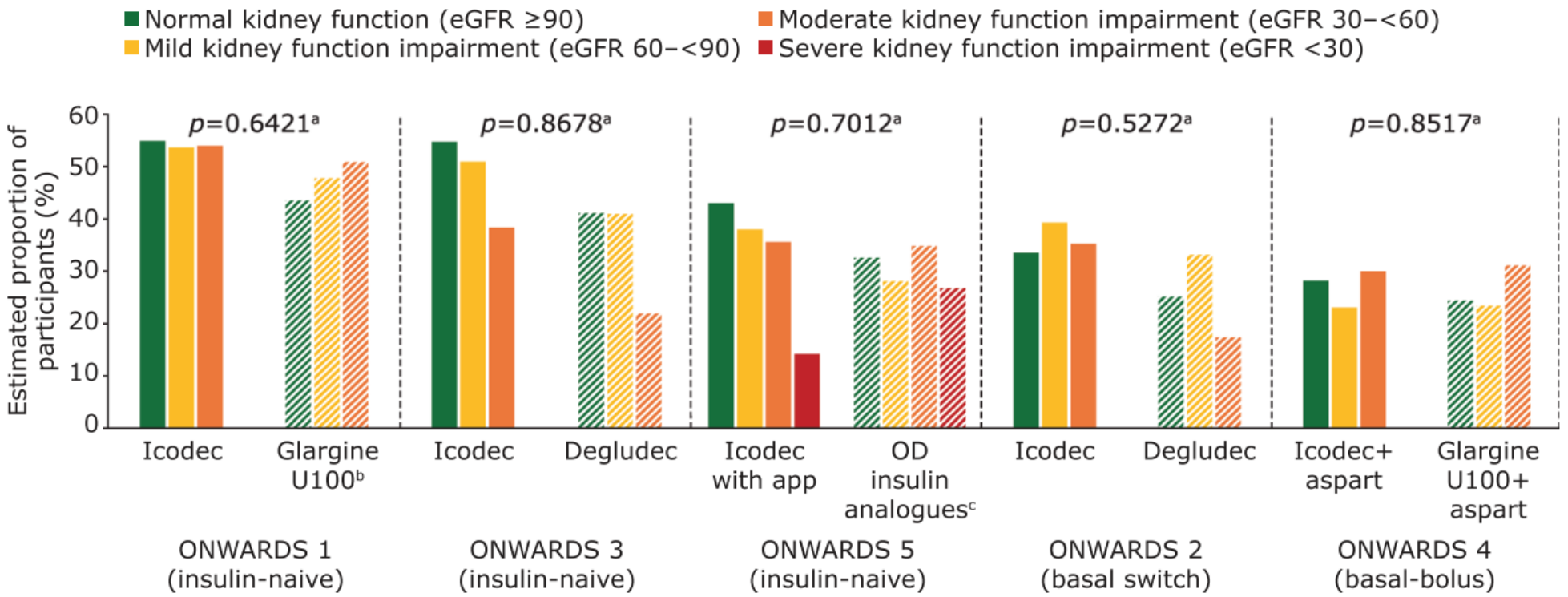


FIG. 2. Observed CGM metrics at baseline (week −2 to 0) and during the last 4 weeks of treatment (week 22–26)

Efficacy and hypoglycaemia outcomes with once-weekly insulin icodec versus once-daily basal insulin in individuals with type 2 diabetes by kidney function: A post hoc participant-level analysis of the ONWARDS 1–5 trials

Diabetes Obes Metab. 2025

In conclusion, the efficacy and hypoglycaemia outcomes with once-weekly icodec versus OD comparators were generally consistent among insulin-naive and insulin-experienced adults with T2D, regardless of kidney function. These findings suggest that no adjustments to the initiation dose or titration of icodec would be necessary based on kidney function.



Insights on Hospitalisations from the Phase 3a ONWARDS 1–6 Trials of Once-Weekly Insulin Icodec

Table 3 Participant-reported hypoglycaemia before, during, and after the hospitalisation period in ONWARDS 1–5 (T2D) and ONWARDS 6 (T1D)

	ONWARDS 1–5 (T2D)				ONWARDS 6 (T1D)			
	Once-weekly icodec ($n = 165$)		Once-daily comparators[a] ($n = 159$)		Once-weekly icodec ($n = 15$)		Once-daily comparator[a] ($n = 15$)	
	N (%)	Episodes, *n* (rate per PYE)[b]	*N* (%)	Episodes, *n* (rate per PYE)[b]	*N* (%)	Episodes, *n* (rate per PYE)[b]	*N* (%)	Episodes, *n* (rate per PYE)[b]
4 weeks before hospitalisation								
Hypoglycaemia alert value[c]	32 (19.4)	88 (7.18)	15 (9.4)	29 (2.52)	12 (80.0)	68 (61.48)	11 (73.3)	37 (32.72)
Clinically significant hypoglycaemia[d]	4 (2.4)	10 (0.82)	3 (1.9)	7 (0.61)	4 (26.7)	23 (20.79)	4 (26.7)	6 (5.31)
Severe[e]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Clinically significant or severe[d,e]	4 (2.4)	10 (0.82)	3 (1.9)	7 (0.61)	4 (26.7)	23 (20.79)	4 (26.7)	6 (5.31)
During hospitalisation								
Hypoglycaemia alert value[c]	17 (10.3)	29 (7.72)	8 (5.0)	14 (3.80)	4 (26.7)	7 (13.60)	7 (46.7)	14 (34.79)
Clinically significant hypoglycaemia[d]	1 (0.6)	5 (1.33)	0 (0)	0 (0)	2 (13.3)	2 (3.89)	1 (6.7)	1 (2.48)
Severe[e,f]	0 (0)	0 (0)	1 (0.6)	1 (0.27)	3 (20.0)	4 (7.77)	1 (6.7)	1 (2.48)
Clinically significant or severe[d,e]	1 (0.6)	5 (1.33)[g]	1 (0.6)	1 (0.27)	5 (33.3)	6 (11.66)	2 (13.3)	2 (4.97)
4 weeks after discharge								
Hypoglycaemia alert value[c]	31 (18.8)	89 (7.32)	24 (15.2)	34 (2.90)	11 (73.3)	61 (56.69)	10 (66.7)	35 (30.44)
Clinically significant hypoglycaemia[d]	7 (4.2)	21 (1.73)	3 (1.9)	4 (0.34)	5 (33.3)	12 (11.15)	3 (20.0)	3 (2.61)
Severe[e]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Clinically significant or severe[d,e]	7 (4.2)	21 (1.73)	3 (1.9)	4 (0.34)	5 (33.3)	12 (11.15)	3 (20.0)	3 (2.61)

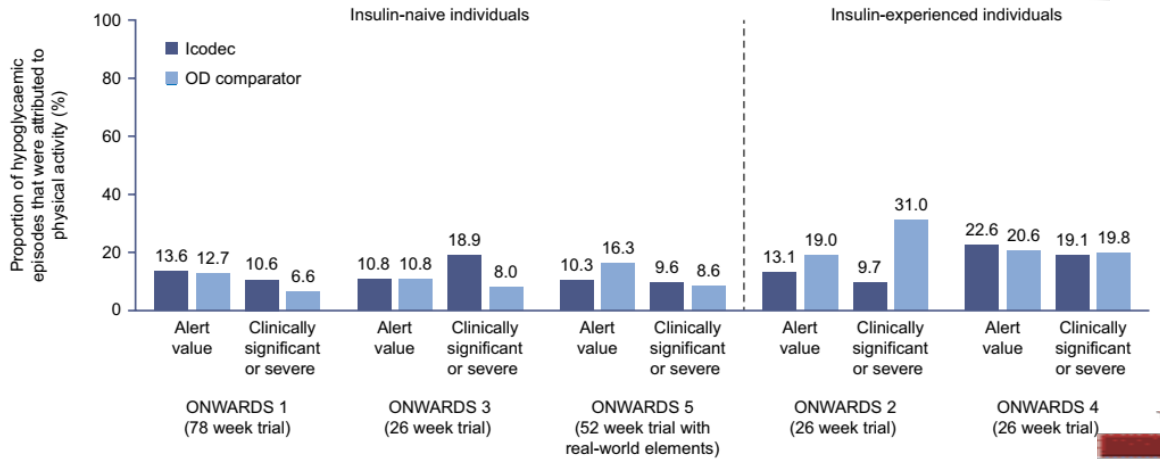
CONCLUSIONS

In conclusion, the number and duration of hospitalisations were similar for once-weekly icodec and once-daily comparators, with most participants continuing their assigned treatment to the end of the trials despite hospitalisation. Hospitalisation did not appear to have a substantial impact on glycaemic control or hypoglycaemia profiles in hospitalised participants from either treatment group. These findings suggest that once-weekly icodec treatment is not associated with a prolonged duration of stay for hospitalised individuals with T2D or T1D, and its use does not elicit worse efficacy or safety outcomes than those elicited with once-daily comparators during and around hospitalisation in a clinical trial setting. This post hoc analysis suggests that once-weekly icodec could be managed in a similar way to once-daily insulin analogues during hospitalisation.

Diabetes Ther (2025)

The effect of once-weekly insulin icodec vs once-daily basal insulin on physical activity-attributed hypoglycaemia in type 2 diabetes: a post hoc analysis of ONWARDS 1–5

Diabetologia 2025



Number of physical activity-attributed episodes/total number of episodes	Icodec	Glargine U100	Icodec	Degludec	Icodec with a dosing guide app	OD analogues[a]	Icodec	Degludec	Icodec + aspart	Glargine U100 + aspart
Hypoglycaemia alert value	314/2308 (13.6%)	136/1067 (12.7%)	43/400 (10.8%)	20/185 (10.8%)	106/1028 (10.3%)	139/851 (16.3%)	158/1209 (13.1%)	112/589 (19.0%)	1191/5264 (22.6%)	853/4145 (20.6%)
Clinically significant hypoglycaemia	23/226 (10.2%)	8/114 (7.0%)	10/53 (18.9%)	2/23 (8.7%)	10/104 (9.6%)	7/76 (9.2%)	11/113 (9.7%)	13/41 (31.7%)	180/937 (19.2%)	186/935 (19.9%)
Severe hypoglycaemia	1/1 (100.0%)	0/7 (0.0%)	0/0 (0.0%)	0/2 (0.0%)	0/0 (0.0%)	0/5 (0.0%)	0/0 (0.0%)	0/1 (0.0%)	0/7 (0.0%)	0/3 (0.0%)

Research in context

What is already known about this subject?

- During physical activity, increased glucose utilisation and enhanced insulin sensitivity can lead to hypoglycaemia in people with diabetes treated with insulin
- Once-weekly basal insulin usage could increase the physical activity-attributed hypoglycaemia risk in type 2 diabetes because the administered levels cannot be reduced in anticipation of increased physical activity

What is the key question?

- Does once-weekly basal insulin icodec (herein referred to as 'icodec') increase physical activity-attributed hypoglycaemia in adults with type 2 diabetes vs once-daily basal insulin?

What are the new findings?

- In a post hoc analysis of the ONWARDS 1–5 Phase 3a randomised controlled trials, which compared the efficacy and safety of icodec vs once-daily basal insulin comparators in insulin-naive (ONWARDS 1, 3 and 5) and insulin-experienced (ONWARDS 2 and 4) adults with type 2 diabetes, there were no consistent differences in the proportions of hypoglycaemic episodes attributed to physical activity between treatment groups across all five trials
- Across all trials, there were no consistent differences in the proportions of physical activity-attributed hypoglycaemic episodes with icodec vs the once-daily insulin comparators, and these episodes were mainly driven by alert value (blood glucose <3.9 mmol/l but ≥3.0 mmol/l) or clinically significant (blood glucose <3.0 mmol/l) hypoglycaemia
- There were no statistically significant differences in the odds of experiencing a physical activity-attributed clinically significant or severe hypoglycaemic episode with icodec vs once-daily insulin comparators

How might this impact on clinical practice in the foreseeable future?

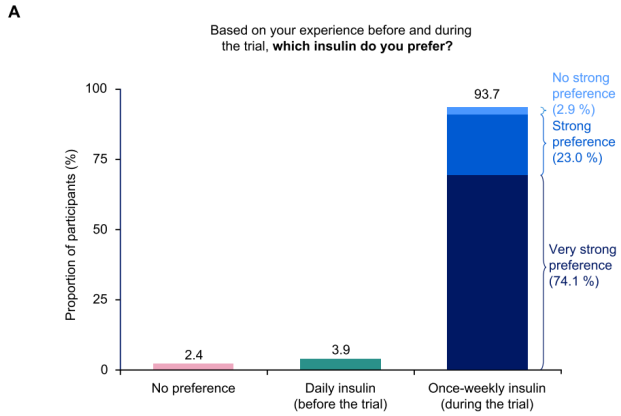
- These findings do not suggest an additional increase in the risk of physical activity-attributed hypoglycaemia with icodec vs once-daily basal insulins in adults with type 2 diabetes

4.1. Conclusion

These unique insights from insulin-naive and insulin-experienced participants with T2D from ONWARDS 5 and ONWARDS 2, as well as from physicians participating in ONWARDS 1, demonstrate clinically meaningful improvements in treatment satisfaction, strong preferences for once-weekly basal insulin and enhanced treatment compliance with once-weekly basal insulin. These results suggest the potential for tailored approaches to diabetes care, offering a suitable treatment option for individuals with T2D.

Improved treatment satisfaction with once-weekly insulin icodec compared with once-daily basal insulin in individuals with type 2 diabetes: An analysis of patient-reported outcomes and participant interviews from ONWARDS 2 and 5 and a physician survey from ONWARDS 1

Diabetes Research and Clinical Practice 217 (2024)



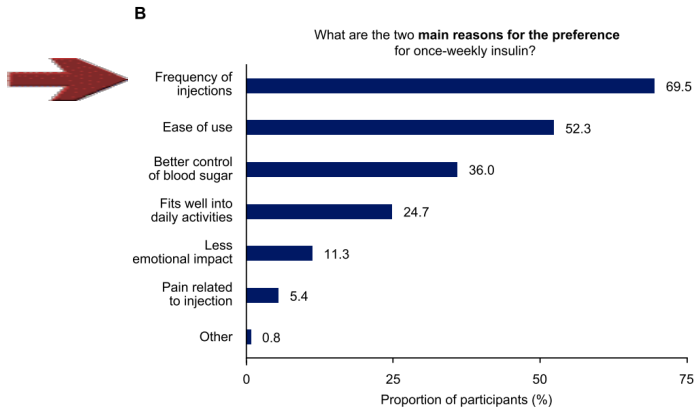


Fig. 2. Insulin Preference Questionnaire results from ONWARDS 2 (insulin-experienced participants) indicating (**A**) overall insulin preference and (**B**) reasons for the preference for once-weekly basal insulin given by participants who had received once-weekly icodec. All 239 participants who preferred once-weekly insulin provided two main reasons for their preference selection. Icodec, insulin icodec.

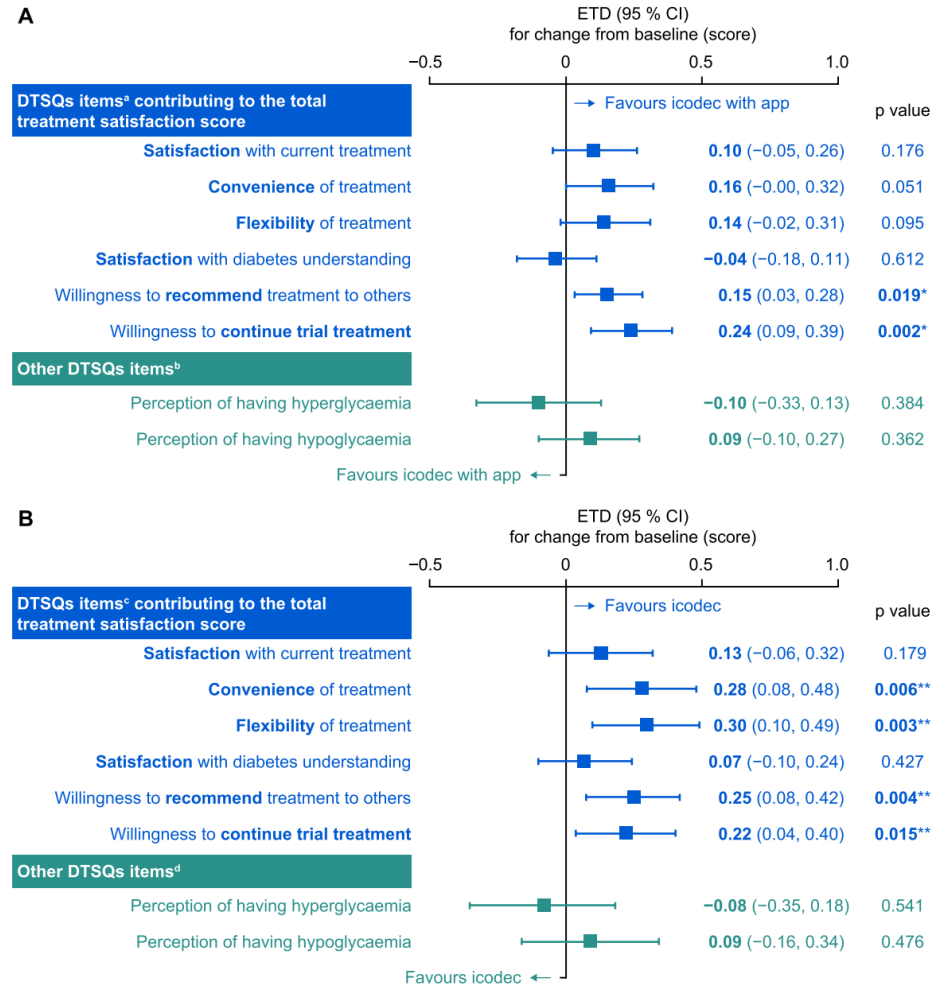
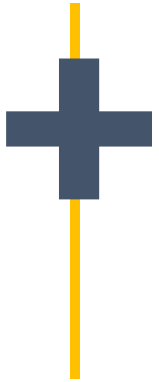


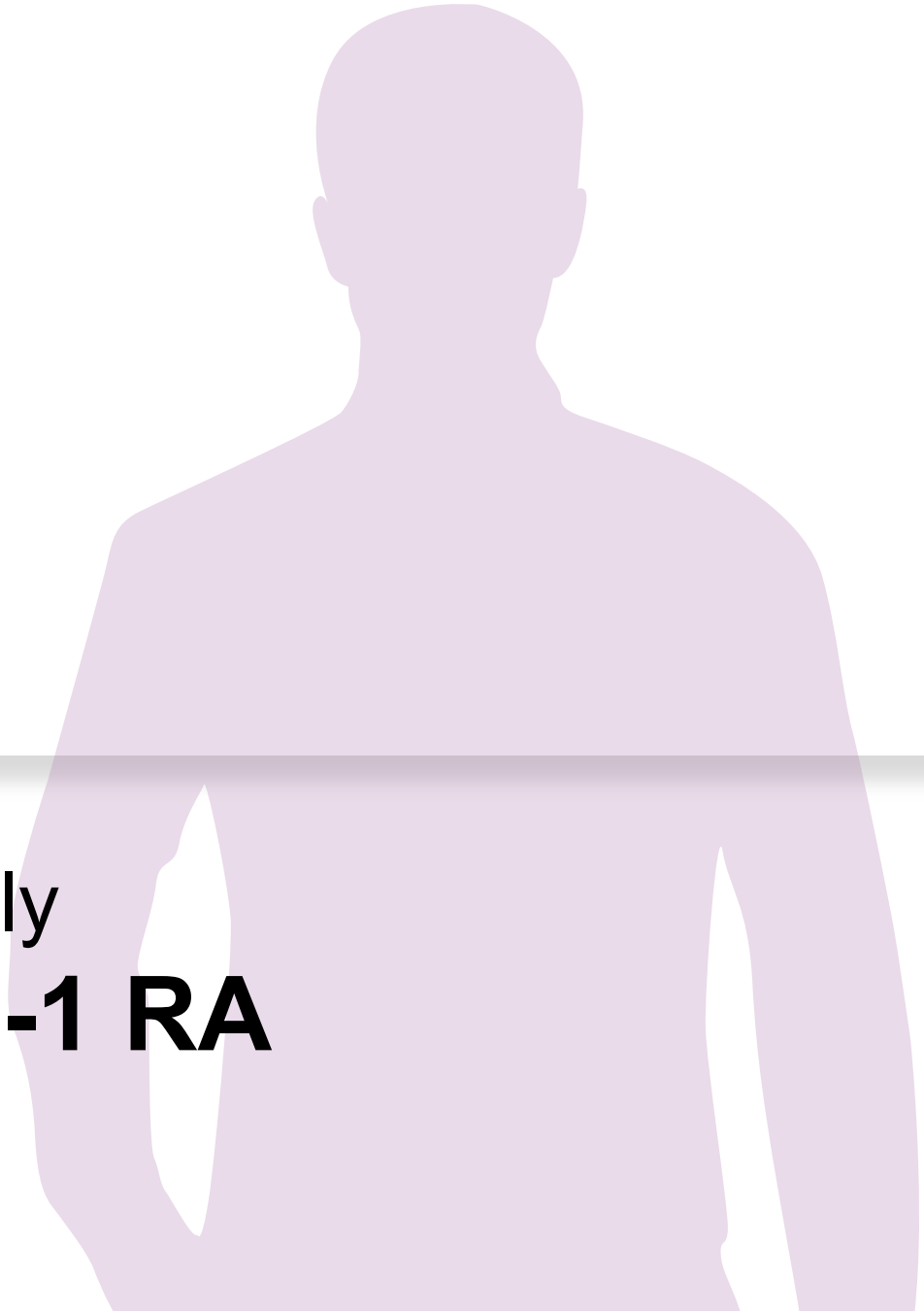
Fig. 1. Estimated treatment differences for change from baseline to end of treatment for items contributing to the change in DTSQs total treatment satisfaction scores in (**A**) ONWARDS 5 (insulin-naive participants) at 52 weeks and (**B**) ONWARDS 2 (insulin-experienced participants) at 26 weeks. *Statistically significant difference

The option of **weekly therapies**

Weekly
insulin



Weekly
GLP-1 RA

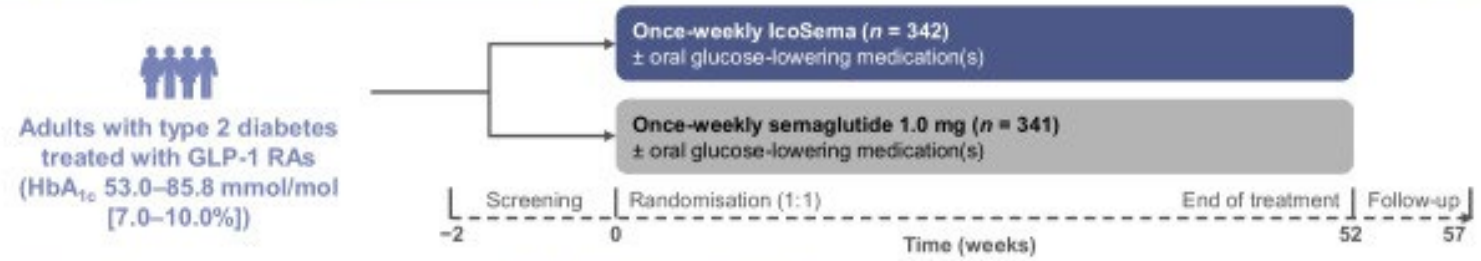


Conclusions In people living with type 2 diabetes inadequately managed with GLP-1 RA therapy, with or without additional oral glucose-lowering medications, switching to once-weekly IcoSema, compared with once-weekly semaglutide 1.0 mg, demonstrated statistical superiority in HbA_{1c} reduction, similar rates of clinically significant or severe hypoglycaemic episodes and comparable gastrointestinal tolerability. However, weight change was statistically significant in favour of semaglutide 1.0 mg.

Once-weekly IcoSema versus once-weekly semaglutide in adults with type 2 diabetes: the COMBINE 2 randomised clinical trial

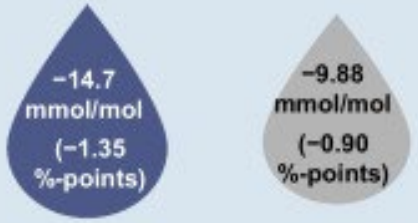
Diabetologia (2025)

Aim: to assess the efficacy and safety of IcoSema, a once-weekly combination therapy of basal insulin icodec and semaglutide, versus semaglutide 1.0 mg in type 2 diabetes inadequately controlled with GLP-1 RA therapy



Primary endpoint

Superior HbA_{1c} reduction with IcoSema (baseline to week 52)



ETD (95% CI): −4.85 (95% CI −6.13, −3.57) mmol/mol (−0.44 [−0.56, −0.33] %-points); *p*<0.0001

Additional endpoints

Change in body weight favoured semaglutide 1.0 mg (baseline to week 52)

ETD (95% CI): 4.54 (3.84, 5.23) kg; *p*<0.0001

Similar rates of hypoglycaemic episodes* (baseline to week 57)

ERR (95% CI): 1.20 (0.53, 2.69); *p*=0.6646

*Combined clinically significant (level 2) hypoglycaemia (blood glucose value of <3.0 mmol/l [<54 mg/dl] confirmed by blood glucose meter) or severe (level 3) hypoglycaemia (hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery). ERR, estimated rate ratio; ETD, estimated treatment difference; GLP-1 RA, glucagon-like peptide 1 receptor agonist; PYE, patient-year of exposure

Once-weekly IcoSema versus once-weekly insulin icodec in type 2 diabetes management (COMBINE 1): an open-label, multicentre, treat-to-target, randomised, phase 3a trial

Lancet Diabetes Endocrinol 2025

Implications of all the available evidence

To our knowledge, this is the first phase 3a trial in adults with inadequately controlled type 2 diabetes on daily basal insulin to show superiority of once-weekly IcoSema to icodec in changes in HbA_{1c} and bodyweight from baseline to week 52, and statistical superiority in terms of lower rates of hypoglycaemia. Overall, IcoSema might provide an option for insulin therapy intensification in adults with type 2 diabetes, reducing concerns around hypoglycaemia and weight gain while minimising the injection burden compared with a loose combination of basal insulin and an injectable GLP-1 receptor agonist.

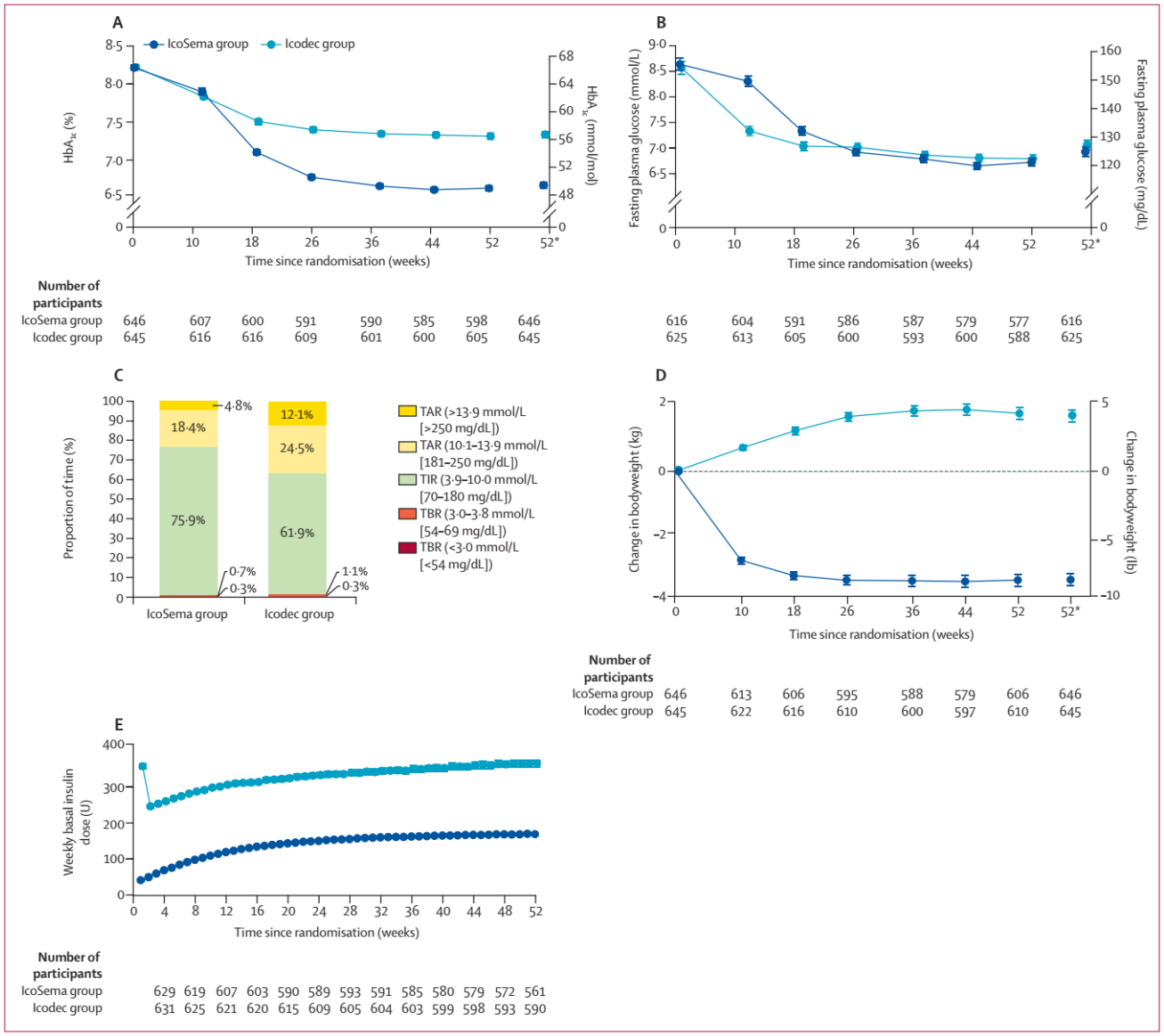


Figure 2: Key outcomes

Once-weekly IcoSema versus multiple daily insulin injections in type 2 diabetes management (COMBINE 3): an open-label, multicentre, treat-to-target, non-inferiority, randomised, phase 3a trial

Lancet Diabetes Endocrinol 2025

Implications of all the available evidence

For individuals with type 2 diabetes inadequately controlled on basal insulin, IcoSema offers a promising alternative to BBT, with fewer injections (52 injections per year versus up to 1460 injections per year with BBT [assuming up to three bolus injections per day]), non-inferior HbA_{1c} reductions, superior weight benefits, a superior hypoglycaemia profile with lower rates of clinically significant or severe hypoglycaemia, and an acceptable safety profile. Overall, when compared with BBT, IcoSema might substantially reduce the injection burden for insulin therapy in type 2 diabetes, while addressing the concerns about hypoglycaemia and weight gain.

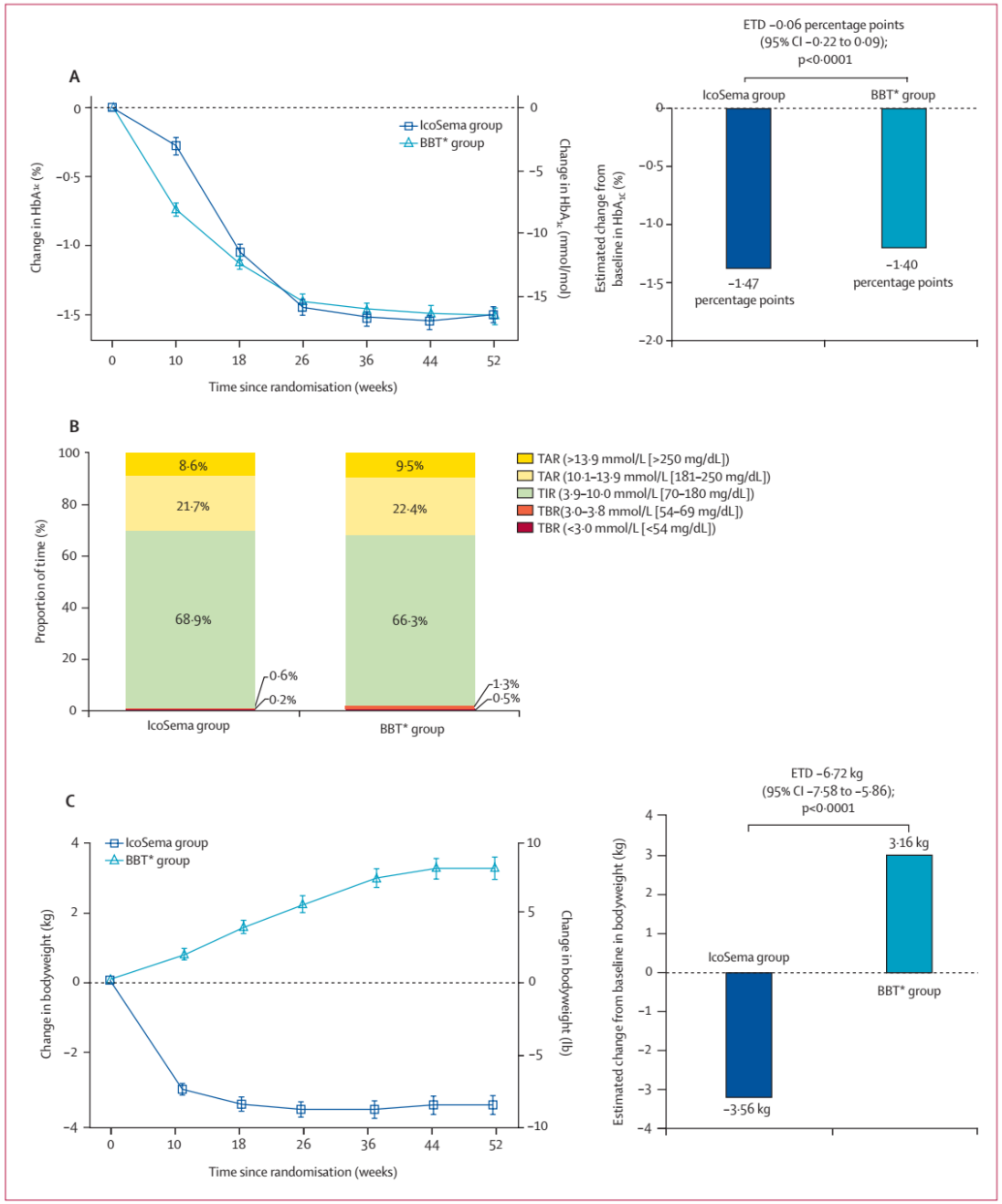
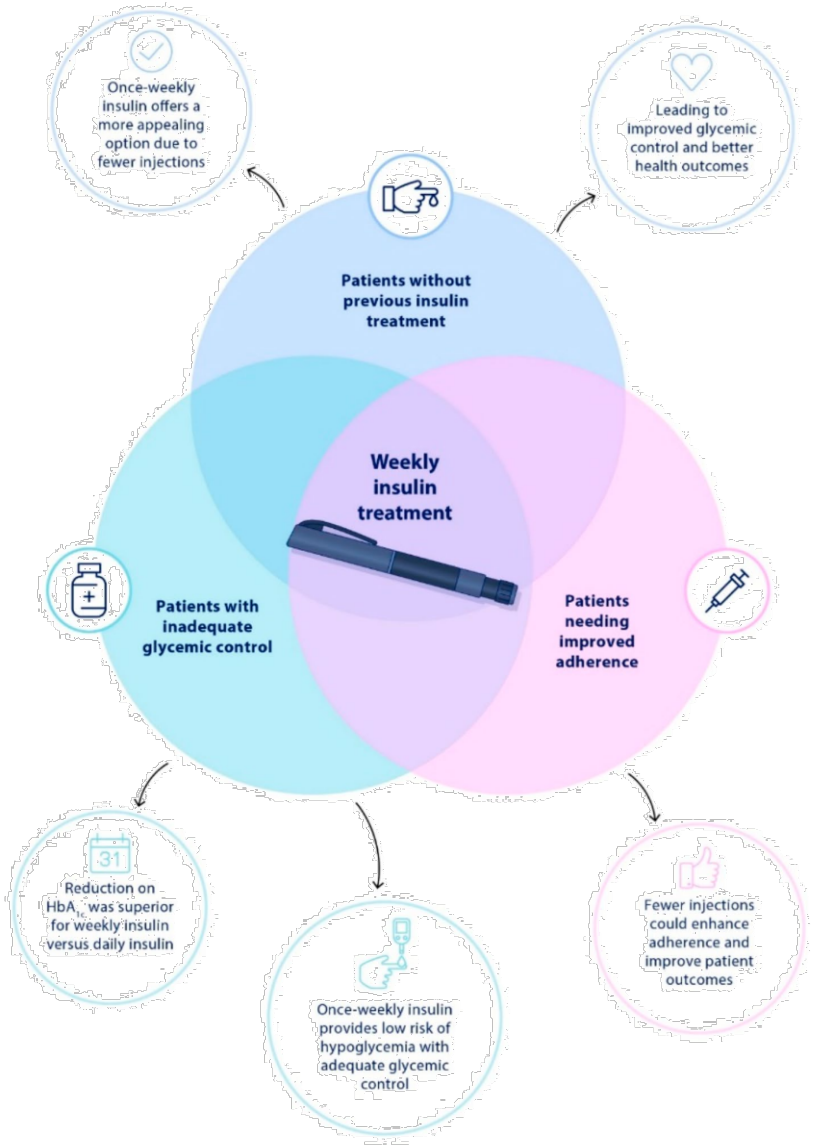


Figure 2: **Key efficacy outcomes**



Groups of T2D patients that could benefit from weekly insulin treatment

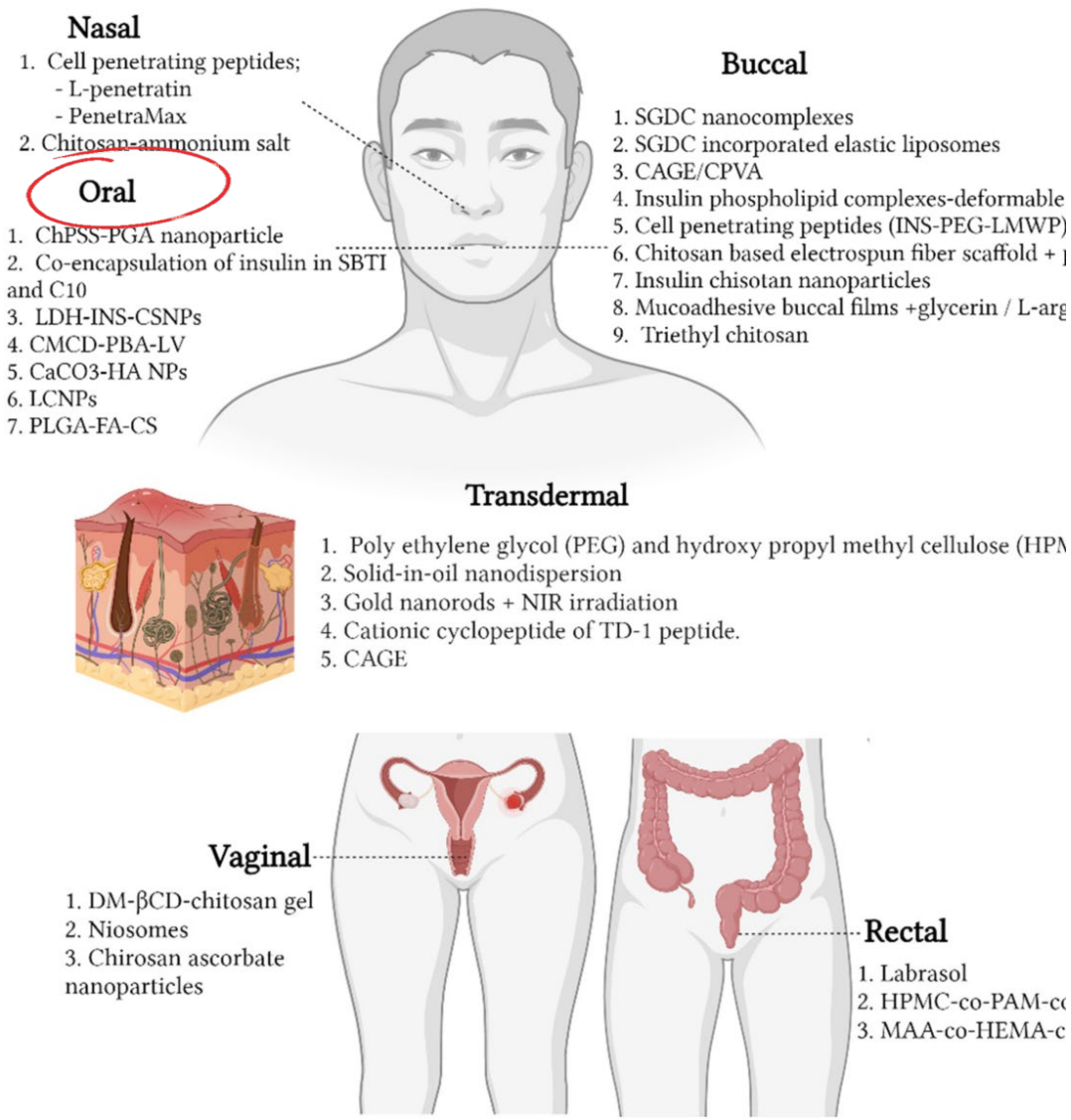
Diabetology & Metabolic Syndrome (2025)

- **Once-weekly insulins** provide a **unique opportunity** to **simplify** basal insulin therapy and to allow **good glycaemic** control with a **low risk** of **hypoglycaemia**

Diabetologia (2024)

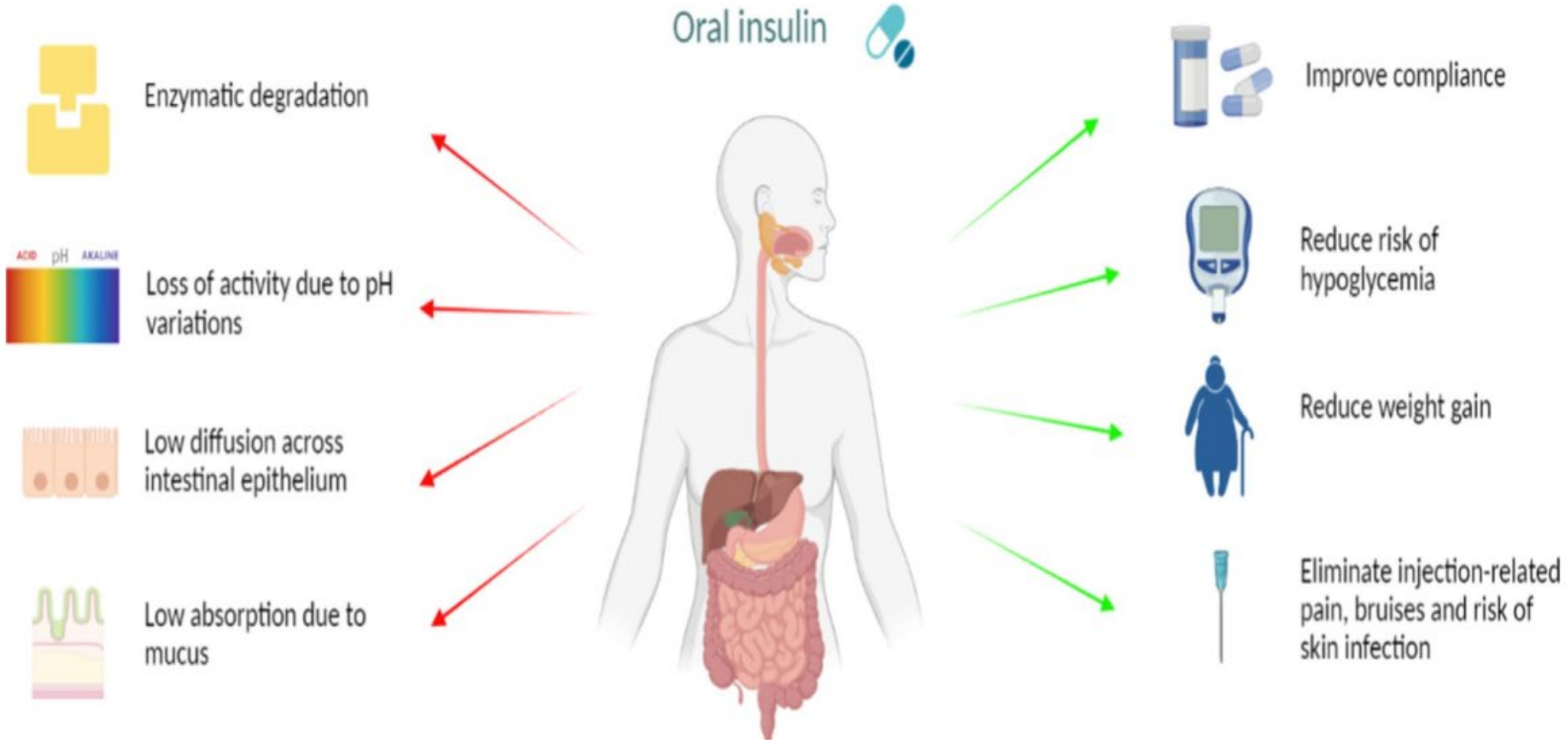
- Potential **alternative routes** for the **delivery of insulin**, such as oral, nasal, buccal, transdermal, vaginal, and rectal routes

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



Pharmaceutics **2022,**

Critical updates on oral insulin drug delivery systems for type 2 diabetes mellitus



Low *et al. Journal of Nanobiotechnology* (2025)

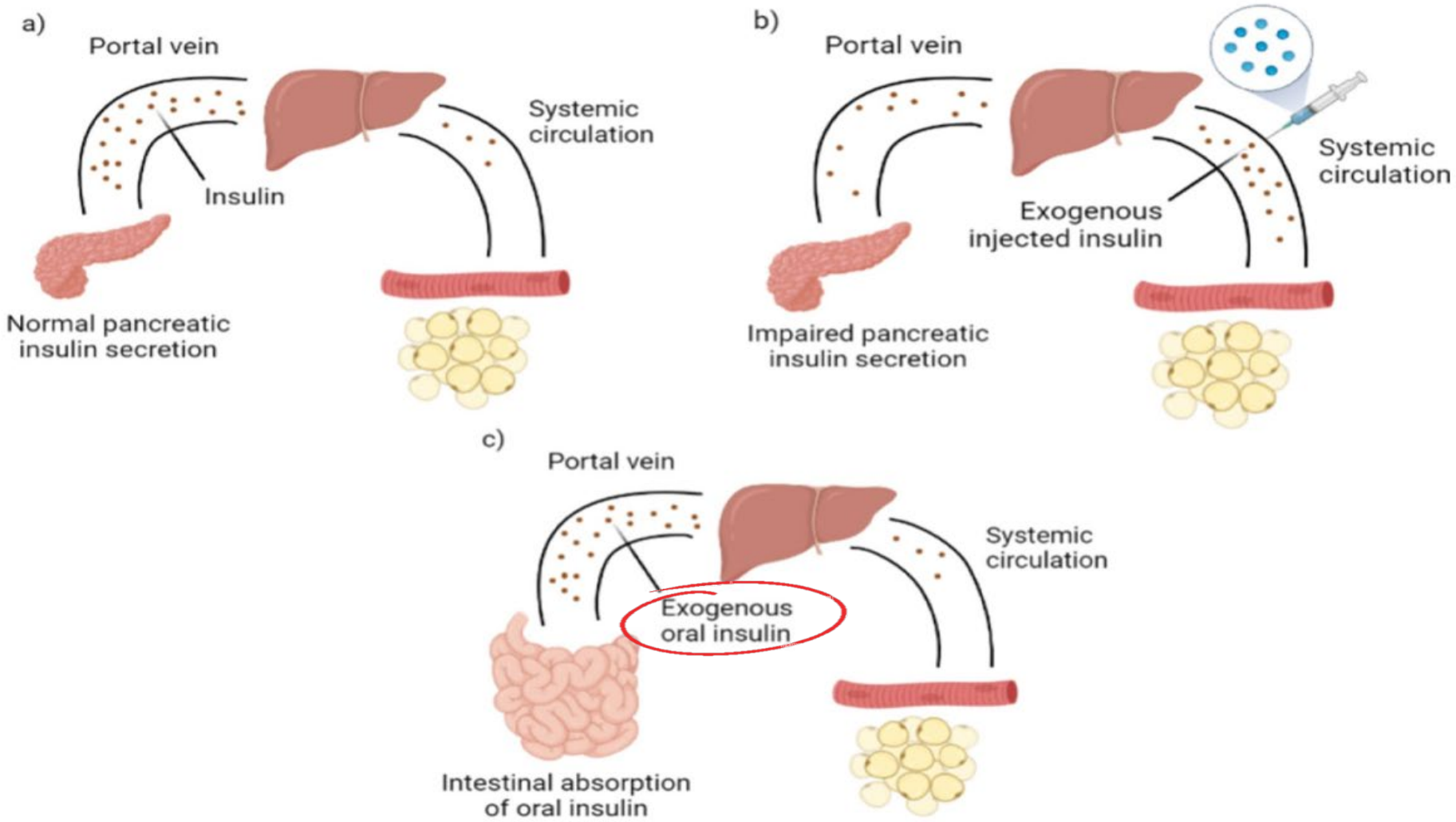
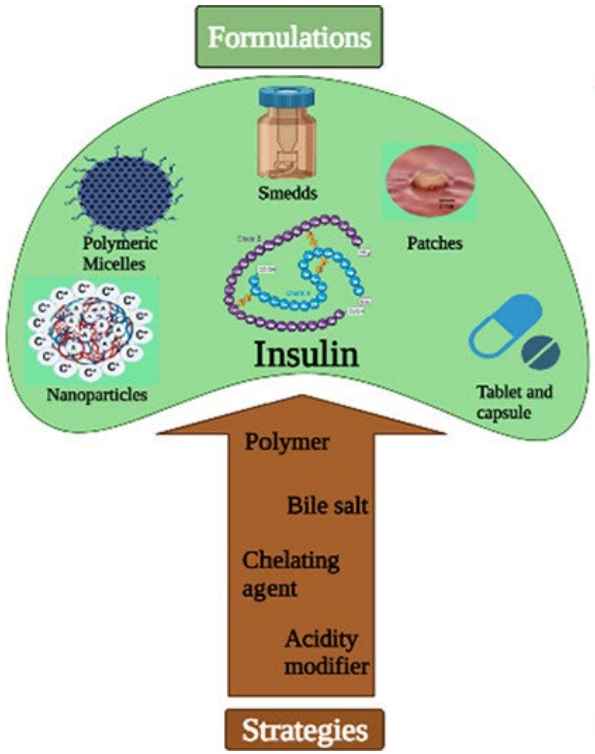


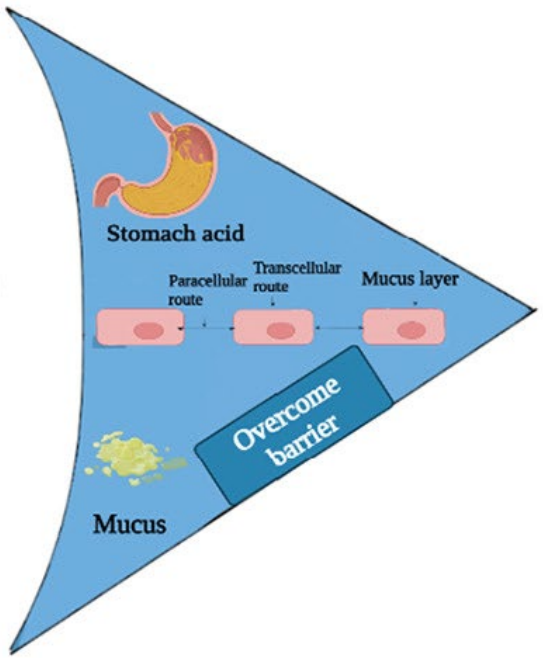
Fig. 1 Portal/systemic insulin gradient in normal physiology and after insulin administration. **a** Normal insulin secretion by the pancreatic beta cells results in the uptake of most endogenous insulin by the liver. **b** A low portal/systemic insulin gradient through injection results in lowered glucose suppression in the liver. **c** Oral insulin absorbed in the intestines passes the portal vein and enters the liver, establishing a portal/systemic insulin gradient similar to that observed under normal physiological conditions

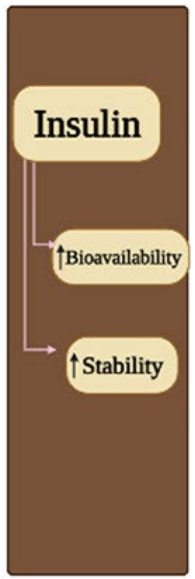
International Journal of Biological Macromolecules
Volume 242, Part 3, 1 July 2023, 125114

Review

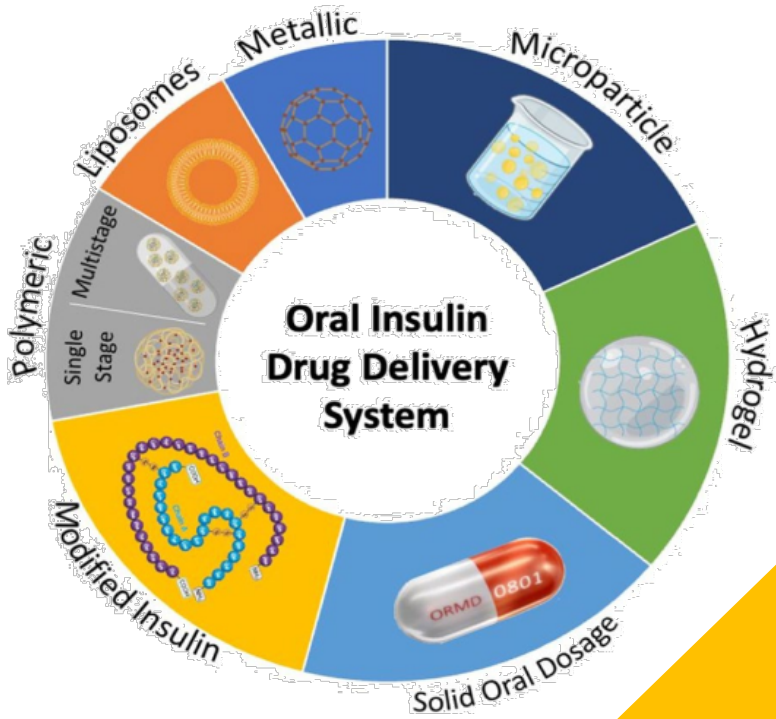
Oral insulin delivery: Barriers, strategies, and formulation approaches: A comprehensive review







Low *et al. Journal of Nanobiotechnology* (2025)



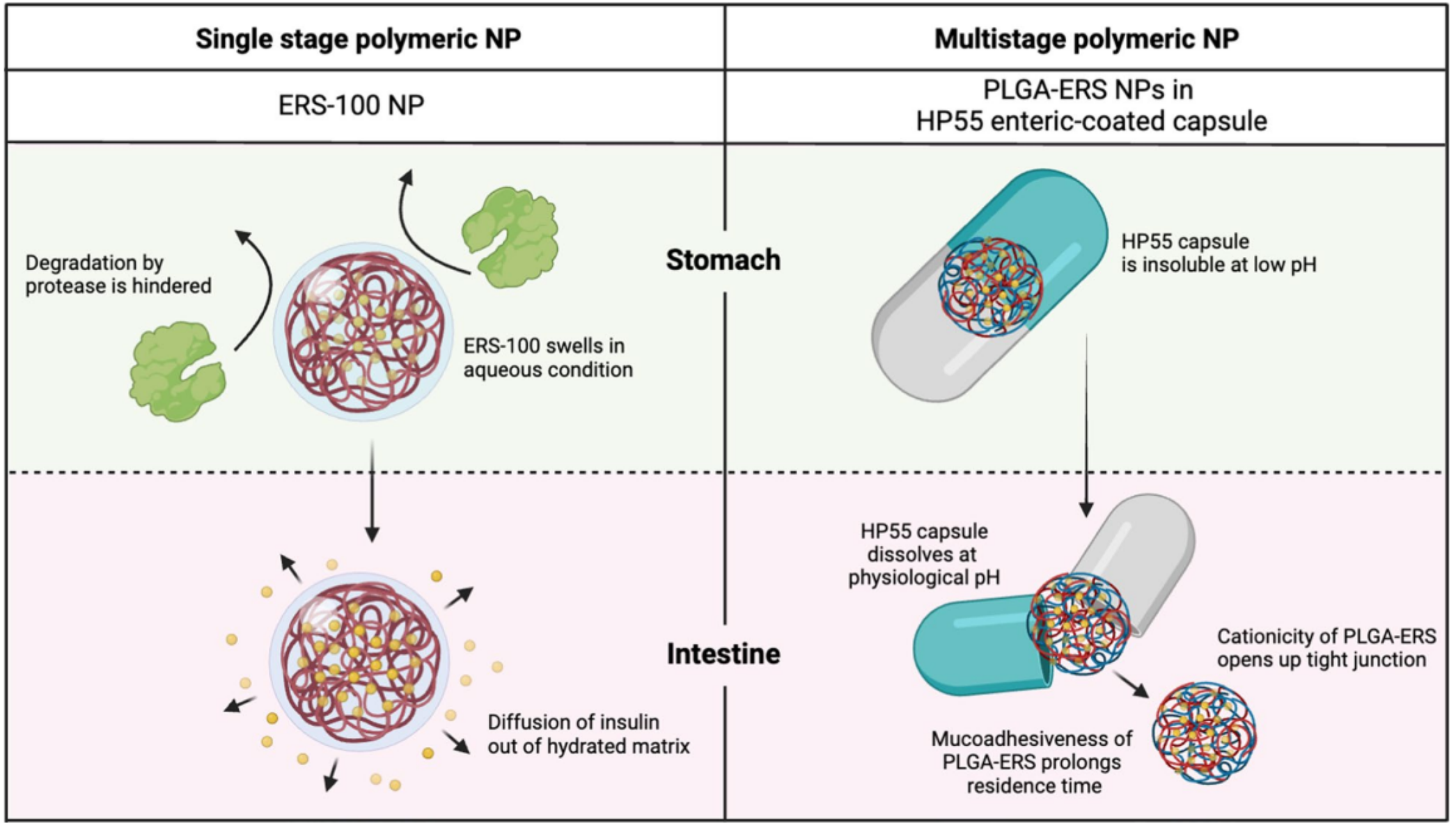


Fig. 3 Comparison between single-stage and multi-stage polymeric nanoparticles. Comparison between single-stage and multi-stage polymeric nanoparticles. ERS-100 NPs and PLGA-ERS NPs in HP55 enteric-coated capsules were compared on the basis of ERS-100 as the common excipient.

An open-label, multiple ascending dose trial of orally administered insulin Tregopil in patients with type 1 diabetes mellitus to evaluate its pharmacokinetics, pharmacodynamics, safety and tolerability

Results: The overall safety profile of insulin Tregopil indicated no safety concerns except a PD effect (hypoglycaemia). The incidence of hypoglycaemia did not increase with increasing doses of insulin Tregopil, and none of the episodes were severe. In general, the variability of the PK/PD parameters was high. Insulin Tregopil demonstrated a rapid onset of action, with peak blood concentrations reached within 15–20 min post-dosing. Subsequently, insulin Tregopil exerted a PD effect for up to 105 min.

5 | CONCLUSION

This trial demonstrated that insulin Tregopil was well tolerated. It reduced the blood glucose levels in patients with controlled FPG. In T1DM patients who lack endogenous insulin secretion, optimal glucose levels could not be maintained during the entire inter-meal duration because of the short duration of insulin Tregopil's action, resulting in the need for supplementary insulin aspart. Although treatment with fixed-dose insulin Tregopil reduced the required amount of supplementary insulin aspart, it did not support a viable stand-alone option for the daily management of T1DM. As with any insulin, insulin Tregopil could be explored with a flexible dosing approach and be titrated based on individual needs.

TABLE 3 Mean values of CGM endpoints over the treatment period.

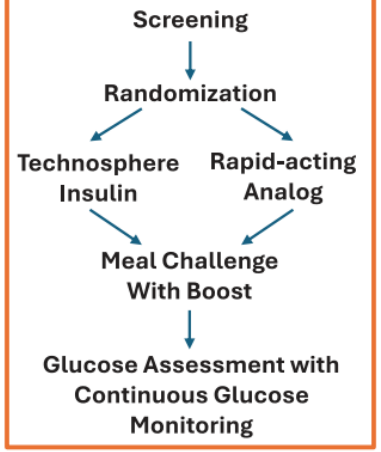
Parameter (unit)	Dose of insulin Tregopil				
	30 mg ($N = 10$)	45 mg ($N = 7$)	60 mg ($N = 10$)	60 + 30 mg rescue ($N = 9$[a])	All doses ($N = 36$[a])
A1c (%)	7.5	7.9	6.8	6.6	7.2
Daily CV glucose (%)	39.3	35.5	37.5	36.2	37.3
Daily mean glucose (mg/dL)	169.8	185.4	149.2	143.9	160.6
Daily SD glucose (mg/dL)	66.8	65.8	55.1	51.9	59.6
Time in hyperglycaemia (>180 mg/dL) (%)	39.6	47.0	28.6	25.4	34.4
Time in hypoglycaemia (<70 mg/dL) (%)	3.8	2.0	6.3	7.5	5.1
Time in level 1 hyperglycaemia (>180 mg/dL, ≤250 mg/dL/) (%)	23.6	26.9	19.8	20.5	22.4
Time in level 1 hypoglycaemia (<70 mg/dL, ≥54 mg/dL) (%)	2.5	1.4	5.0	5.3	3.7
Time in level 2 hyperglycaemia (>250 mg/dL) (%)	16.0	20.1	8.8	5.0	12.1
Time in level 2 hypoglycaemia (<54 mg/dL) (%)	1.4	0.6	1.3	2.2	1.4
Time in normal range (70–180 mg/dL) (%)	56.5	51.1	65.1	67.1	60.5

Randomized Comparison of Postprandial Glucose Excursion Using Inhaled Insulin Versus Rapid-Acting Analog Insulin in Adults with Type 1 Diabetes

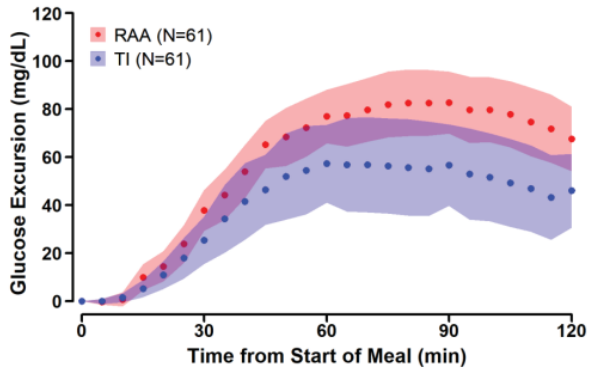
Background: Postmeal hyperglycemia is difficult to prevent with subcutaneous rapid-acting analog (RAA) insulin. Technosphere insulin (TI) has a more rapid onset of action, which may reduce the postmeal glucose rise compared with RAA.

Aim: In adults with type 1 diabetes, compare postmeal glucose excursion with RAA versus TI in people who use automated insulin delivery (AID) or multiple daily injection (MDI).

Study Design



Results



	P-value
Area Under the Curve >180 mg/dL	0.02
Peak Glucose	0.01
Time to Peak Glucose	0.007
Excursion	0.02

Participant Characteristics
- Age 18-77 years
- Type 1 diabetes for at least 6 months
- HbA_{1c} 5.4-10.5% (36-91 mmol/mol)

Insulin delivery
- AID 48%
- MDI 43%
- Non-automated pump 6%
- Predictive low-glucose suspend pump 2%

Conclusion: Postmeal glucose excursion was smaller with TI than with RAA insulin in a cohort of adults with type 1 diabetes that included both AID and MDI users.

A Randomized Comparison of Postprandial Glucose Excursion Using Inhaled Insulin Versus Rapid-Acting Analog Insulin in Adults With Type 1 Diabetes Using Multiple Daily Injections of Insulin or Automated Insulin Delivery

Diabetes Care 2024;47:1682–1687 | https://doi.org/10.2337/dc24-0838

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Postmeal hyperglycemia is difficult to prevent with subcutaneous rapid-acting analog insulins (RAA).
- **What is the specific question(s) we wanted to answer?**
  Does postmeal glycemia improve with technosphere insulin inhalation powder (TI) compared with subcutaneous RAA insulin?
- **What did we find?**
  Postmeal hyperglycemia was less with TI than with RAA insulin, with the glucose excursion being less, the peak glucose being lower, and the time to peak glucose being shorter with TI.
- **What are the implications of our findings?**
  Use of TI can improve postmeal glucose management.

Inhaled Technosphere Insulin Plus Insulin Degludec for Adults with Type 1 Diabetes: The INHALE-3 Extension Study

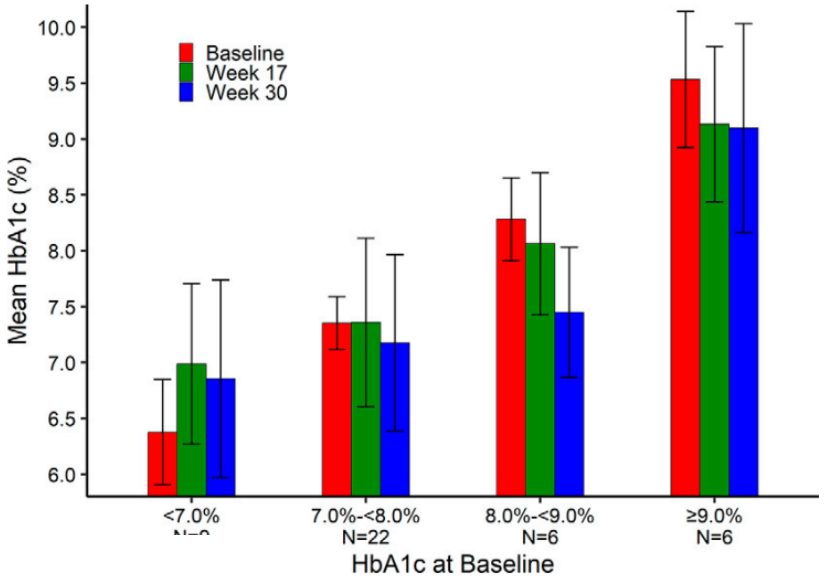


FIG. 1. Change in HbA1c over time within subgroups of baseline HbA1c. The bars represent the mean HbA1c within each subgroup and the error bars show the mean ± 1 standard deviation.

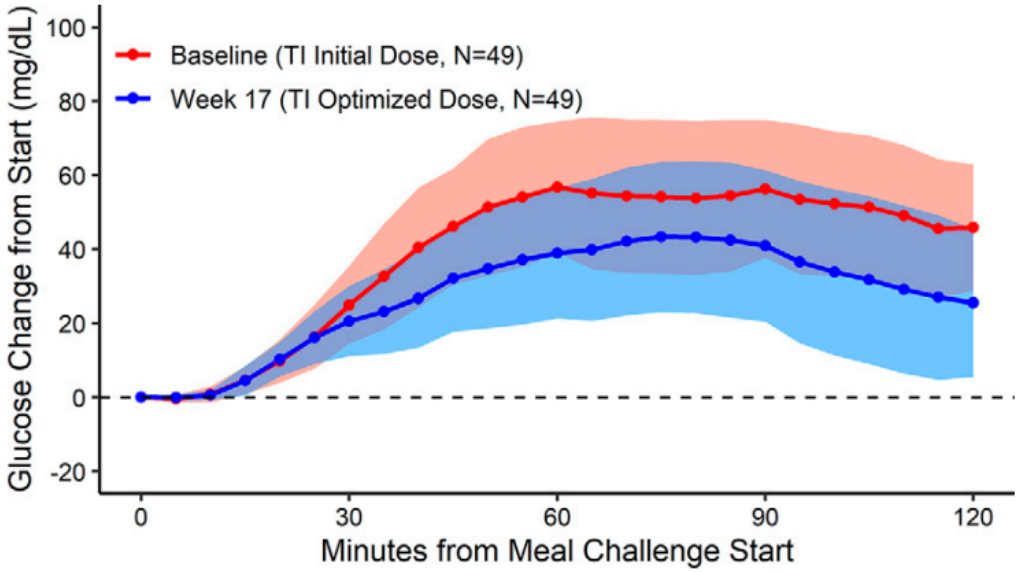


FIG. 3. Glucose change from meal challenge start at baseline and 17 weeks. The points represent the mean CGM glucose at 5-min intervals following the start of the meal challenge (minute 0). The shaded bands represent the 95% confidence interval around the mean. Means and confidence intervals are shown separately at baseline (red) and week 17 (blue). CGM, continuous glucose monitoring.

Conclusions: HbA1c levels were sustained over 30 weeks using a TI-degludec regimen after switching from AID or MDI. TI should be considered an option for people with T1D.

Recent Progress in Glucose-Responsive Insulin

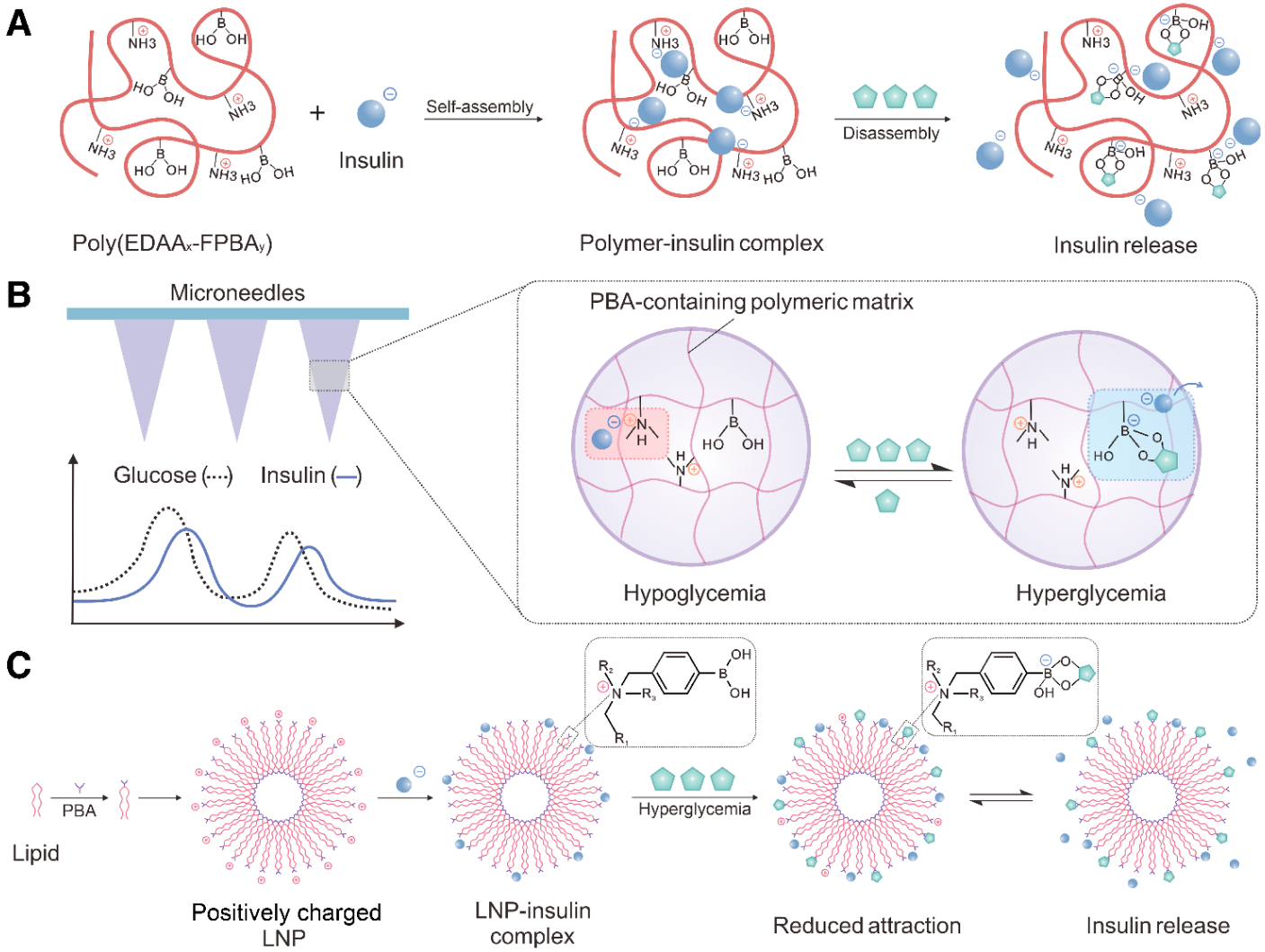


Figure 3—Glucose-responsive carriers for insulin delivery. *A*: Illustration of the assembly and disassembly of a glucose-responsive complex composed of polymers bearing positive charges and insulin molecules bearing negative charges (8). *B*: Schematic of a glucose-responsive microneedle patch integrated with PBA-containing polymeric matrix and the mechanism of glucose-triggered insulin release (13). *C*: Schematic of the formation of a PBA-decorated LNP-insulin complex and the mechanism of insulin release from LNP (24).

- **To mitigate acute and chronic** risks of **glucose excursions**, glucose-responsive insulin (GRI) has long been pursued for clinical application.

- By integrating GRI with glucose-sensitive elements, GRI is capable of **releasing or activating insulin** in **response to plasma or interstitial glucose levels without external monitoring**, thereby improving glycemic control and reducing hypoglycemic risk.

Diabetes 2024;

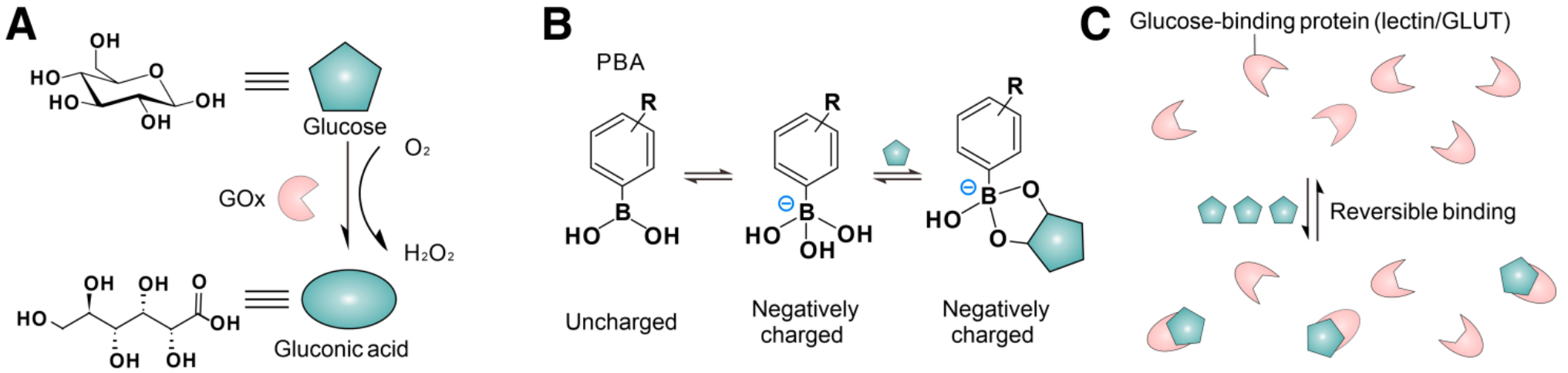


Figure 2—Glucose-responsive mechanisms of three major glucose-sensing components. *A*: Schematic of catalytic effect of GOx on glucose to achieve glucose responsiveness. *B*: Schematic of PBA binding to glucose molecules through reversible chemical covalent bonds. *C*: Schematic of glucose-binding proteins reversibly binding to glucose via noncovalent interactions.

Recent Progress in Glucose-Responsive Insulin

Diabetes 2024;

Table 3—Features and efficacy of distinct GRI delivery systems

Insulin delivery system	Administration route(s)	Unique property(ies)	Efficacy (reference)
Microneedles	Transdermal delivery	Avoidance of first-pass effect; minimal invasiveness; pain alleviation; convenience; rapid response	4 h in mice (19); >10 h in mice and 20 h in minipigs (13); 6 h with inflammation alleviation on microneedles-treated skin (21); 9 h with no hypoglycemia in mice and >24 h in minipigs (14)
Hydrogels	Subcutaneous injection	Degradability	12 h in mice with no fibrous encapsulation (10)
Polymer/insulin complexes	Subcutaneous injection	Long retention; rapid response; easy preparation	>8 h in mice and >8 h in minipigs (8); >28 h in mice (25); 3 weeks in mice and >5 days in minipigs with fibrous capsule resistance and minimal toxicity (37)
Liposomes	Oral; subcutaneous injection	High biocompatibility	Postprandial glucose regulation for 12 h in mice (39); 5 days in mice (41)
LNP	Subcutaneous injection	Low toxicity; rapid response	6 h in mice (24)
Insulin analogs	Subcutaneous injection; intravenous injection	Antihypoglycemia; no exogenous carriers; prolonged retention or circulation	Regulated PG to prechallenge levels during the glucose tolerance test performed 7 h after GRI treatment (45); 20 h normoglycemia in mice (15); >10 h in mice with negligible hypoglycemia (16)

Glucose-sensitive insulin with attenuation of hypoglycaemia

- We report the design and properties of **NNC2215, an insulin** conjugate with bioactivity that **is reversibly responsive to a glucose range** relevant for diabetes, as demonstrated in vitro and in vivo.
- The **insulin receptor affinity** for NNC2215 **increased 3.2-fold** when the **glucose** concentration was **increased** from 3 to 20 mM.
- In **animal studies**, the glucose-sensitive bioactivity of NNC2215 was demonstrated to **lead to protection against hypoglycaemia** while **partially covering glucose excursions**.
- **Future GRIs** might offer **both fast-acting and long-acting formulations** for improved postprandial and fasting glycaemic control. Research is ongoing regarding various GRI formulations, and **GRIs are not clinically available** for **treatment** of diabetes

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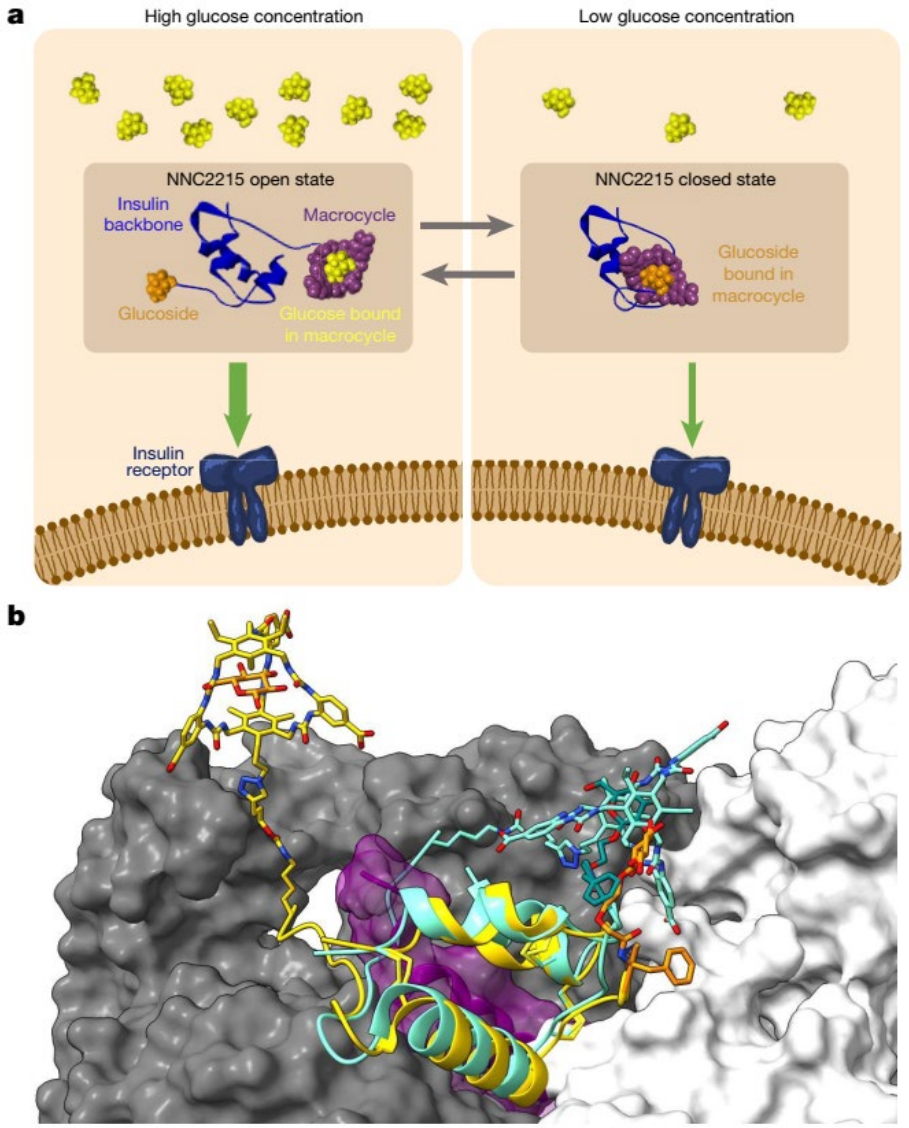
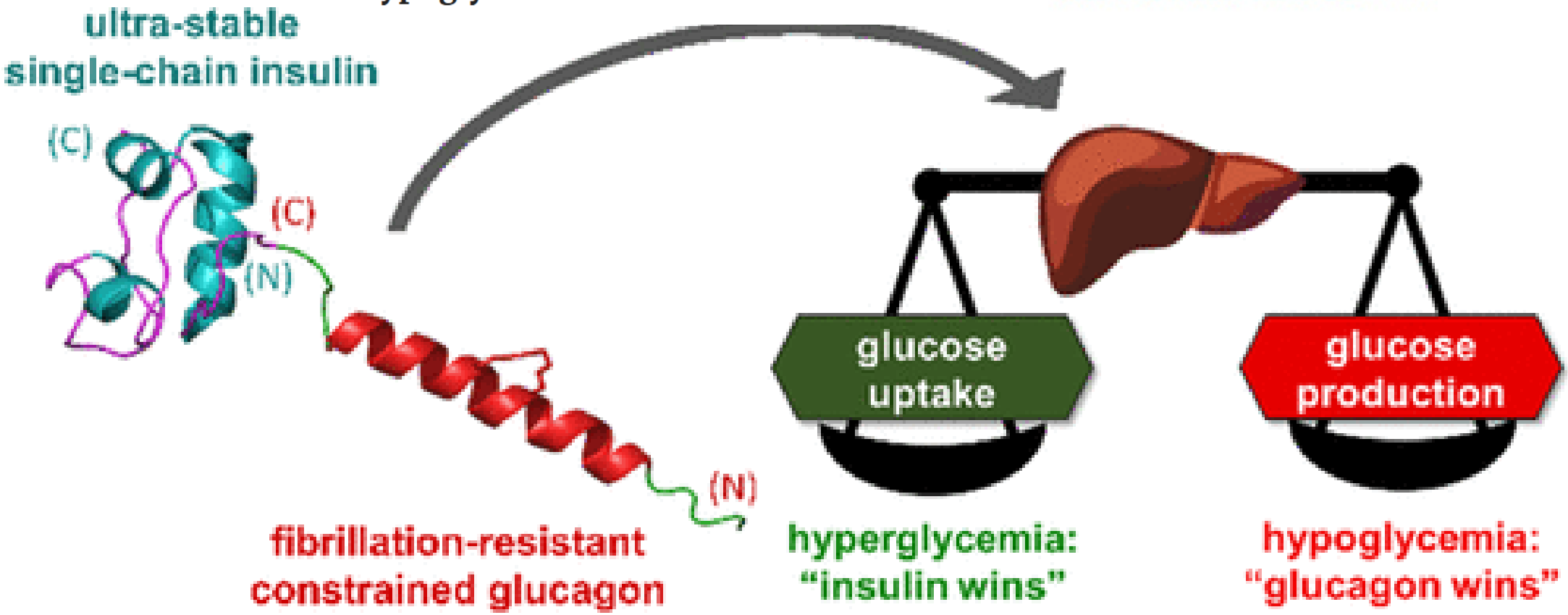


Fig. 1 | Functional principle and 3D model of NNC2215. a, NNC2215 is an insulin

Nature | Vol 634 | 24 October 2024

Ultrastable Insulin–Glucagon Fusion Protein Exploits an Endogenous Hepatic Switch to Mitigate Hypoglycemic Risk

ACS Pharmacol Transl Sci. 2025



- We describe an alternative approach that exploits an endogenous glucose-dependent switch in hepatic physiology: preferential insulin signaling (under hyperglycemic conditions) *versus* preferential counter-regulatory glucagon signaling (during hypoglycemia). Motivated by prior reports of **glucagon-insulin coinfusion**, we designed and tested an **ultrastable glucagon-insulin fusion protein**

"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