L’insulina del futuro

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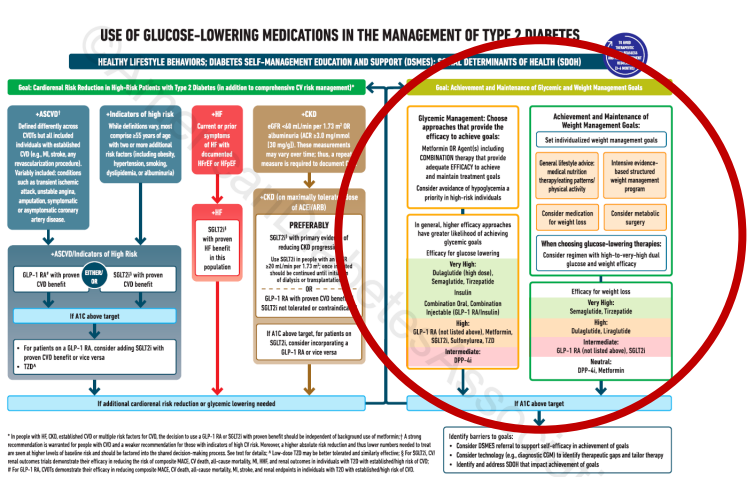
Napoli, 05.10.2024



Goal: Achievement and Maintenance of Glycemic and Weight Management Goals

Glycemic Management: Choose approaches that provide the efficacy to achieve goals:

Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals

Consider avoidance of hypoglycemia a priority in high-risk individuals

In general, higher efficacy approaches have greater likelihood of achieving glycemic goals

Efficacy for glucose lowering

Very High:
Dulaglutide (high dose), Semaglutide, Tirzepatide

Insulin

Combination Oral, Combination Injectable (GLP-1 RA/Insulin)

High:
GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonylurea, TZD

Intermediate:
DPP-4i

Achievement and Maintenance of Weight Management Goals:

Set individualized weight management goals

General lifestyle advice: medical nutrition therapy/eating patterns/ physical activity

Intensive evidence-based structured weight management program

Consider medication for weight loss

Consider metabolic surgery

When choosing glucose-lowering therapies:
Consider regimen with high-to-very-high dual glucose and weight efficacy

Efficacy for weight loss

Very High:
Semaglutide, Tirzepatide

High:
Dulaglutide, Liraglutide

Intermediate:
GLP-1 RA (not listed above), SGLT2i

Neutral:
DPP-4i, Metformin

Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB *Diabetes Care* 2022; https://doi.org/10.2337/dci22-0034.

Diabetologia 2022; https://doi.org/10.1007/s00125-022-05787-2.

PLACE OF INSULIN[1]

Consider immediate start of insulin

- Severe hyperglycemia
- Acute glycemic dysregulation
- When T1D is suspected

- Maintain cardiorenal protective agents
- Maintain metformin, SGLT2i, and GLP-1 RA to avoid weight gain and limit insulin dose and hypoglycemia risk
- Consider using combination products of basal insulin/GLP-1 RA

If not already on GLP-1 RA, consider use of GLP-1 RA

Consider adding insulin when personalized HbA_{1c} targets are not met with strategies described in Fig. 4

↓

Start using basal insulin*
(10 units or 0.1–0.2 units/kg per day) at bedtime or more flexibility with timing for longer-acting analogs

↓

Titrate to FPG target but avoid overbasalization of insulin
(consider introduction of CGM)

↓

When FPG is on target but HbA_{1c} or TIR is not

↓

If not already on GLP-1 RA, consider use of GLP-1 RA

↓

ADD MEALTIME INSULIN UNDER FORM OF:

- **Basal plus** (progressive addition of boluses)
- **Premixed insulins**
- **MDI (multiple daily injections)**

When not familiar with insulin use or when targets not reached, consider shared care with specialist team

Intensify along the way and preferentially at each step

- Healthy behavior
- Nutritional therapy
- DSMES: with additional focus on injection technique, hypoglycemia, weight

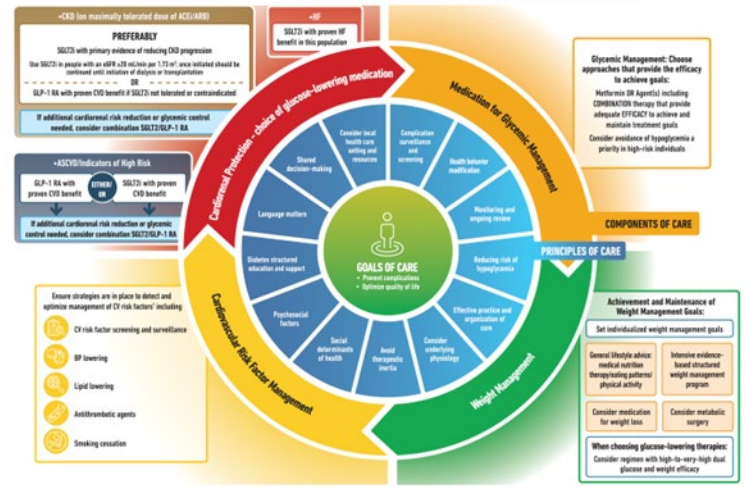
Diabetes Care
American Diabetes Association

Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Melanie J. Davies, Vanita R. Aroda, Billy S. Collins, Robert A. Gabbay, Jennifer Green, Nisa M. Maruthur, Sylvia E. Rosas, Stefano Del Prato, Chantal Mathieu, Geltrude Mingrone, Peter Rossing, Tsvetalina Tankova, Apostolos Tsapas, and John B. Buse

Diabetes Care 2022;45(11):2753–2786 | https://doi.org/10.2337/dci22-0034

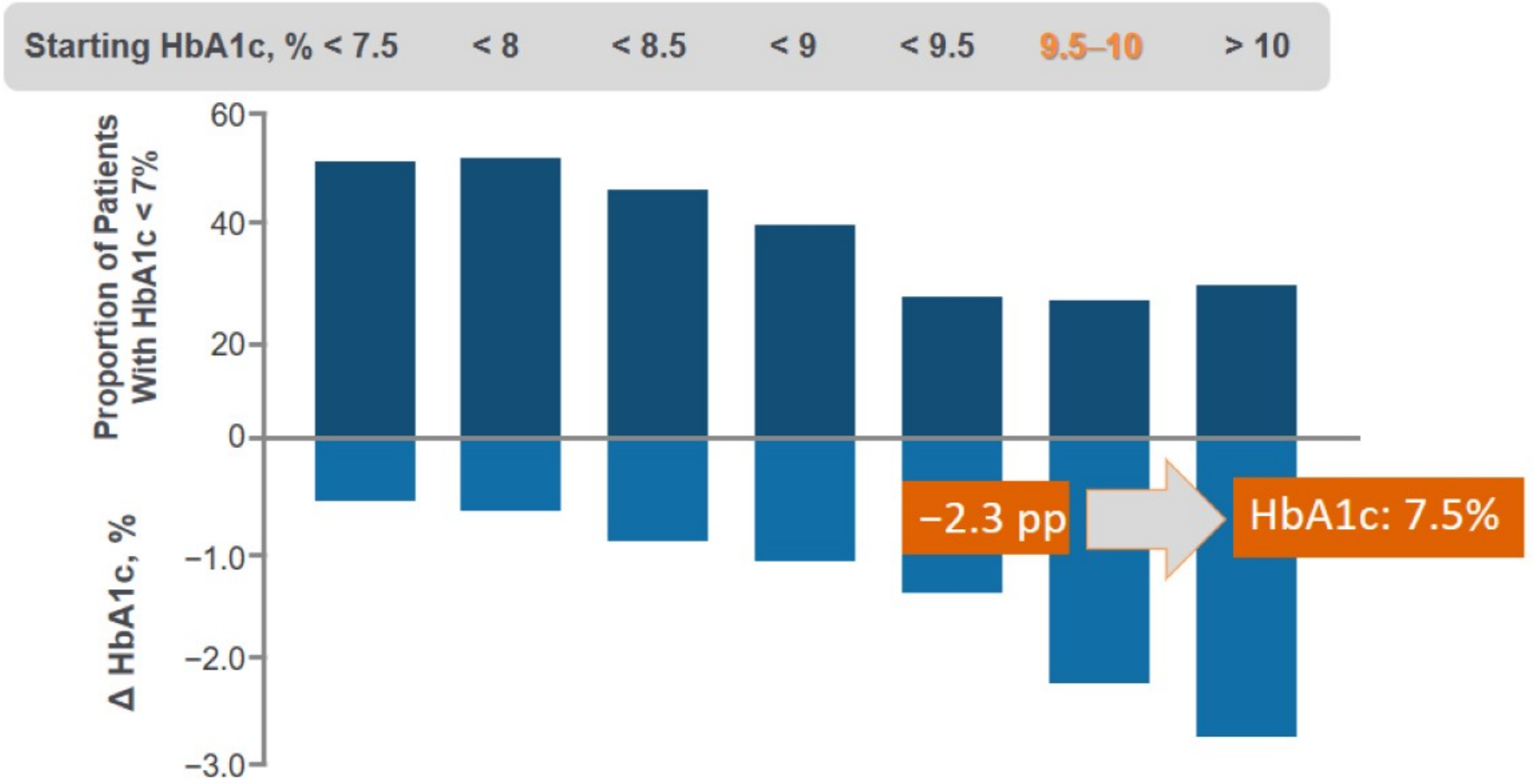
HOLISTIC PERSON-CENTERED APPROACH TO T2DM MANAGEMENT



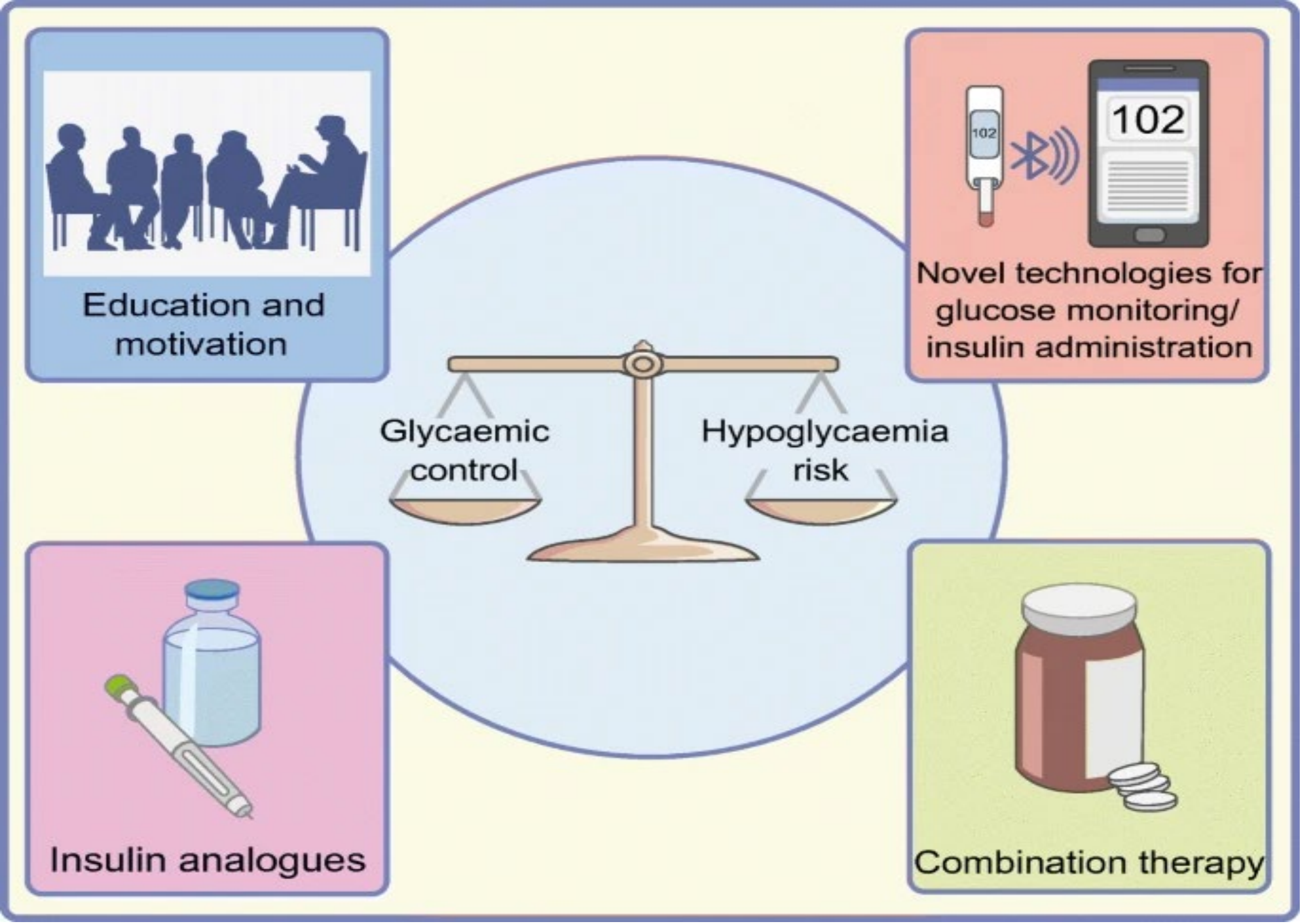
Relazione fra l'HbA1c di partenza, percentuale di pazienti a target e riduzione dell'HbA1c con la terapia insulinica

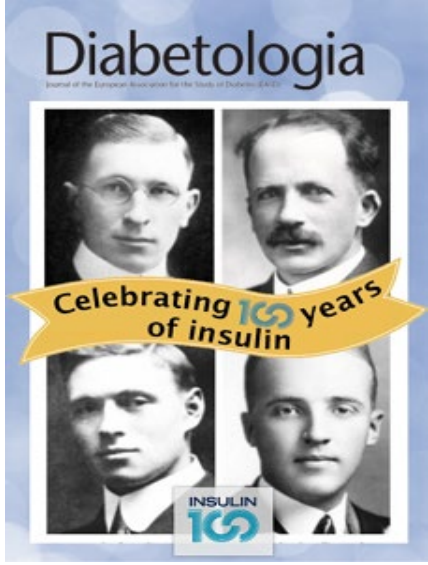
What happens to the HbA1c of patients who are on ≥ 2 oral GLAs when adding basal insulin therapy?

- ~79,000 patients with T2D
- If started in a patient with basal HbA1c of 9.5%, adding basal insulin would reduce HbA1c by 2.3 percentage points (HbA1c: 7.5%)



GLA, glucose-lowering agents; pp, percentage points; T2D, type 2 diabetes.
Esposito K, et al. Diabetes Obes Metab. 2012;14:228–233.





Diabetologia volume 64, pages978–984 (2021)

Accepted 14 July 2021
Available online 16 July 2021

DIABETES RESEARCH AND CLINICAL PRACTICE 178 (2021) 108958

Contents available at ScienceDirect

Diabetes Research and Clinical Practice

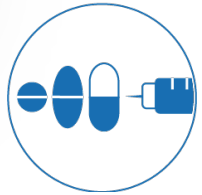
journal homepage: www.elsevier.com/locate/diabres

Review

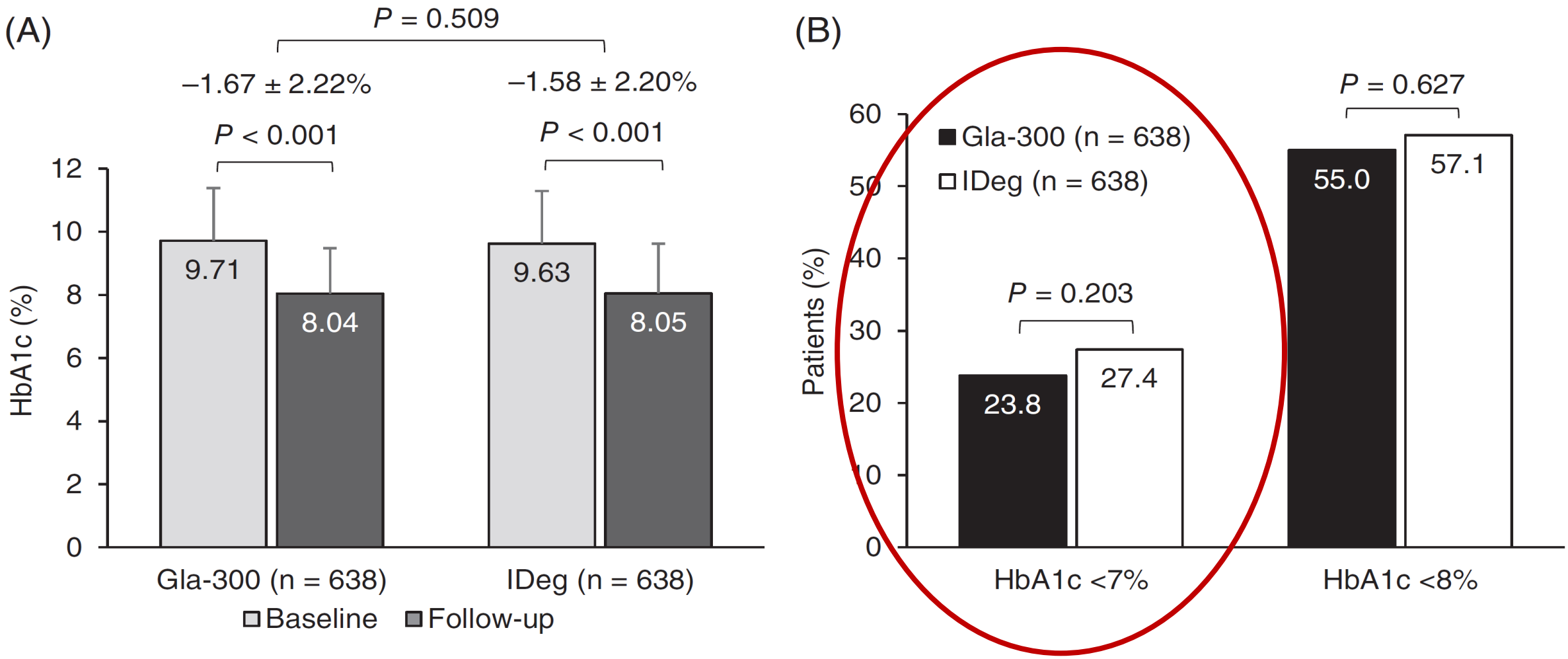
Simplification of complex insulin therapy: a story of dogma and therapeutic resignation

Dario Giugliano [a,b,*,1], *Lorenzo Scappaticcio* [a,b,1], *Miriam Longo* [a,b], *Paola Caruso* [a,b], *Maria Ida Maiorino* [c], *Giuseppe Bellastella* [a], *Katherine Esposito* [b,c]

Semplificare con intensità

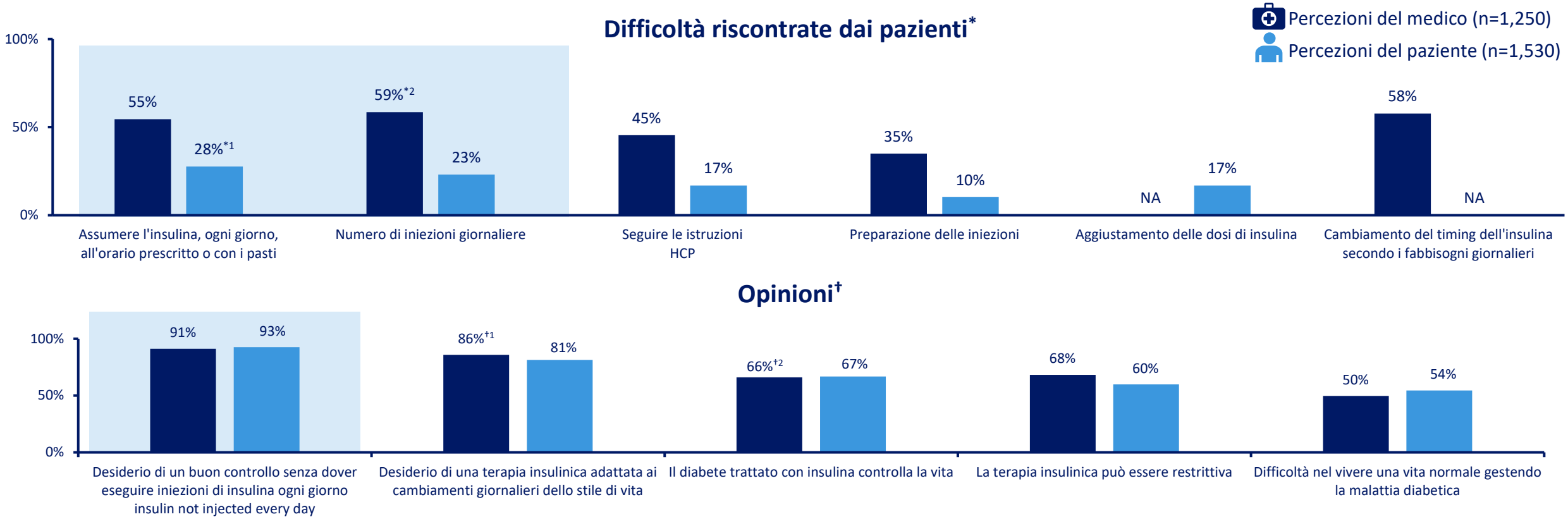
Barriere	Potenziali soluzioni
Barriere alla semplificazione della terapia insulinica complessa	
 Ipoglicemia	Semplificare con molecole associate a basso rischio di ipoglicemia
 Aumento peso	Semplificare con molecole associate ad un basso rischio di aumento del peso
 Complessità del trattamento	Semplificare il regime terapeutico
 Aderenza	Una singola iniezione è comoda per il paziente e aumenta l'aderenza alla terapia

- Retrospective observational study that used electronic medical record data from the IBM Watson Health Explorys database.
- Insulin-naïve adults with T2D who started Gla-300 or IDeg between March 2015 and September 2017 were identified.
- Patients were active in the system for ≥12 months before and ≥6 months after starting Gla-300 or IDeg and had HbA1c measurements during 6-month baseline and 3- to 6-month follow-up. Outcomes were compared among 1:1 propensity score-matched cohorts (N=638).



Diabetes Obes Metab. 2019;21:2123–2132.

I pazienti ed i medici identificano l'alta frequenza delle iniezioni di insulina come fonte di stress



*Very difficult or somewhat difficult (vs. very easy, somewhat easy, not applicable, 'don't know'). Absolute percentages reported for physicians cannot be compared with percentage of patients for whom this is difficult because physicians report whether this is difficult for their 'typical patient' rather than the percentage of their patients for whom this is difficult; rank order of reasons by patients and physicians can be compared. *1Average of response for two items (insulin at prescribed times, insulin with each meal). *2Physician item is 'taking insulin frequently'. †Strongly agree or somewhat agree (vs. strongly disagree, somewhat disagree, neither, 'don't know'). †Physician item is 'which insulin treatments could be more flexible'. †2Physician item is if his/her patients feel diabetes controls their lives. HCP, healthcare professional; n, number of subjects; NA, not asked. 1. Peyrot M et al. *Diabet Med*. 2012;29(5):682–689.

An online survey has shown that people with type 2 diabetes generally have a positive attitude towards once-weekly glucose-lowering medications, particularly among injection users.

A total of 1516 adults with type 2 diabetes drawn from a national Chronic Illness Panel completed an anonymous online survey that assessed perceived attributes of QW therapy, willingness to take an injectable QW medication and patient characteristics that might influence their willingness, such as current perceived glycemic control and diabetes quality of life (DQOL)

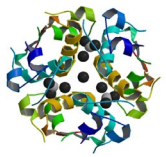
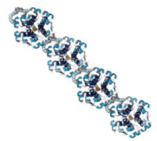
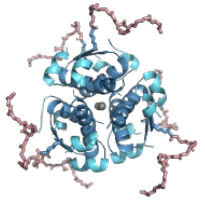
Table 2. Patient perception of attributes of once-weekly therapy blood glucose-lowering medication(s).

	Total sample (%)	Oral medication (%)	Injection medication (%)	χ^2 p value
Once-a-week medication could make taking that specific blood glucose-lowering medication more convenient.	813 (61.3)	454 (54.2)	359 (73.6)	<0.001
Once-a-week medication could help me stick to my blood glucose-lowering medications better.	483 (36.5)	260 (31.2)	222 (45.3)	<0.001
Once-a-week medication could make my blood glucose-lowering treatment seem less overwhelming.	584 (44.3)	300 (36.0)	284 (58.7)	<0.001
Once-a-week medication could improve my quality of life.	501 (38.1)	252 (30.2)	249 (51.7)	<0.001
Once-a-week medication could make it harder for me to remember to take my medication.	544 (41.1)	351 (42.3)	193 (39.2)	0.274
Once-a-week medication could make me feel healthier than taking a daily medication.	338 (25.8)	186 (22.4)	153 (31.5)	<0.001
I would not be sure whether a once-a-week medication is providing a consistent level of medication over the week.	752 (56.6)	439 (52.5)	314 (63.6)	<0.001

Number and % of patients agreeing (reporting 'agree' or 'strongly agree') to each of the listed statements.

Diabetes, Obesity and Metabolism 13: 144–149, 2011.

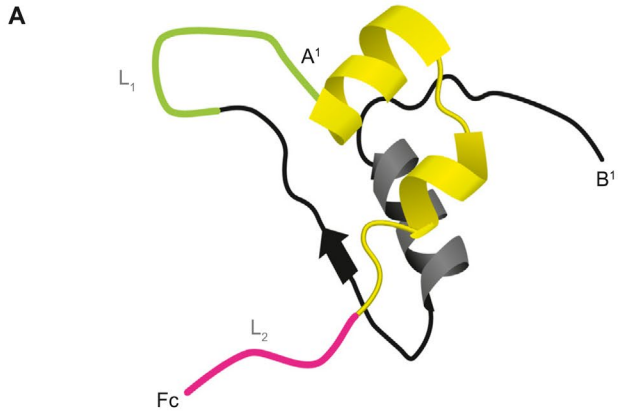
Il passato ed il presente dell'innovazione dell'insulina basale

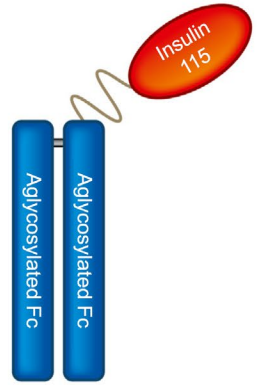
	Insulina NPH	1st generazione di analoghi dell'insulina basale	Analoghi dell'insulina basale ad azione ultra-lunga	icodec una volta a settimana
				
Emivita	**5–10 ore**	**~0.5 giorno**	**~1 giorno**	**~1 settimana**
Somministrazione	**OD/BID**	**OD/BID**	**OD**	**OW**

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

Once weekly insulin

single-chain insulin Fc-fusion variants





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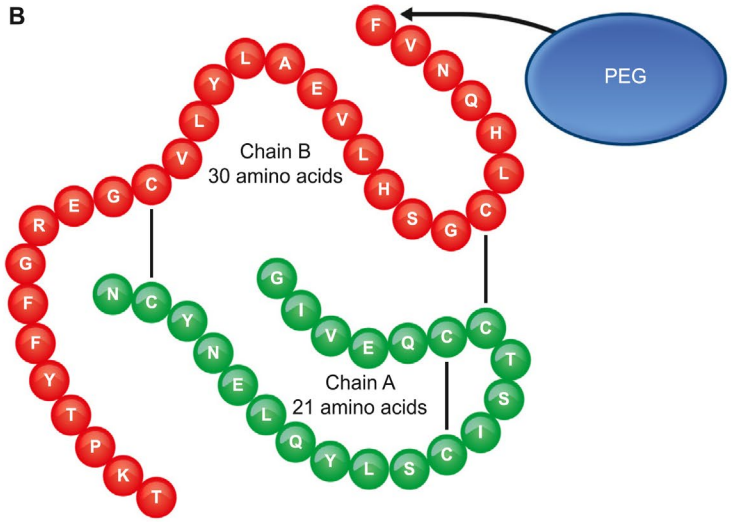
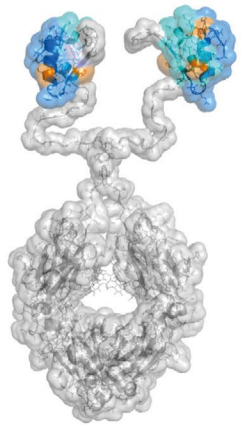
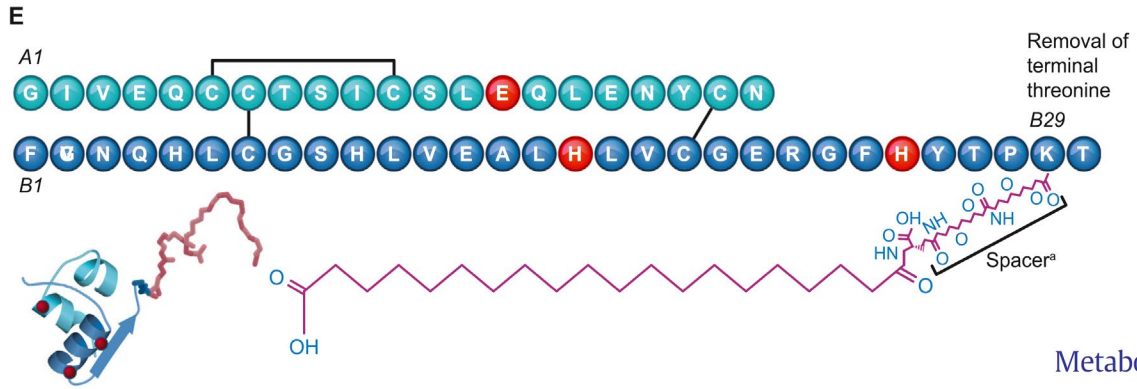




BIF (LY3209590)

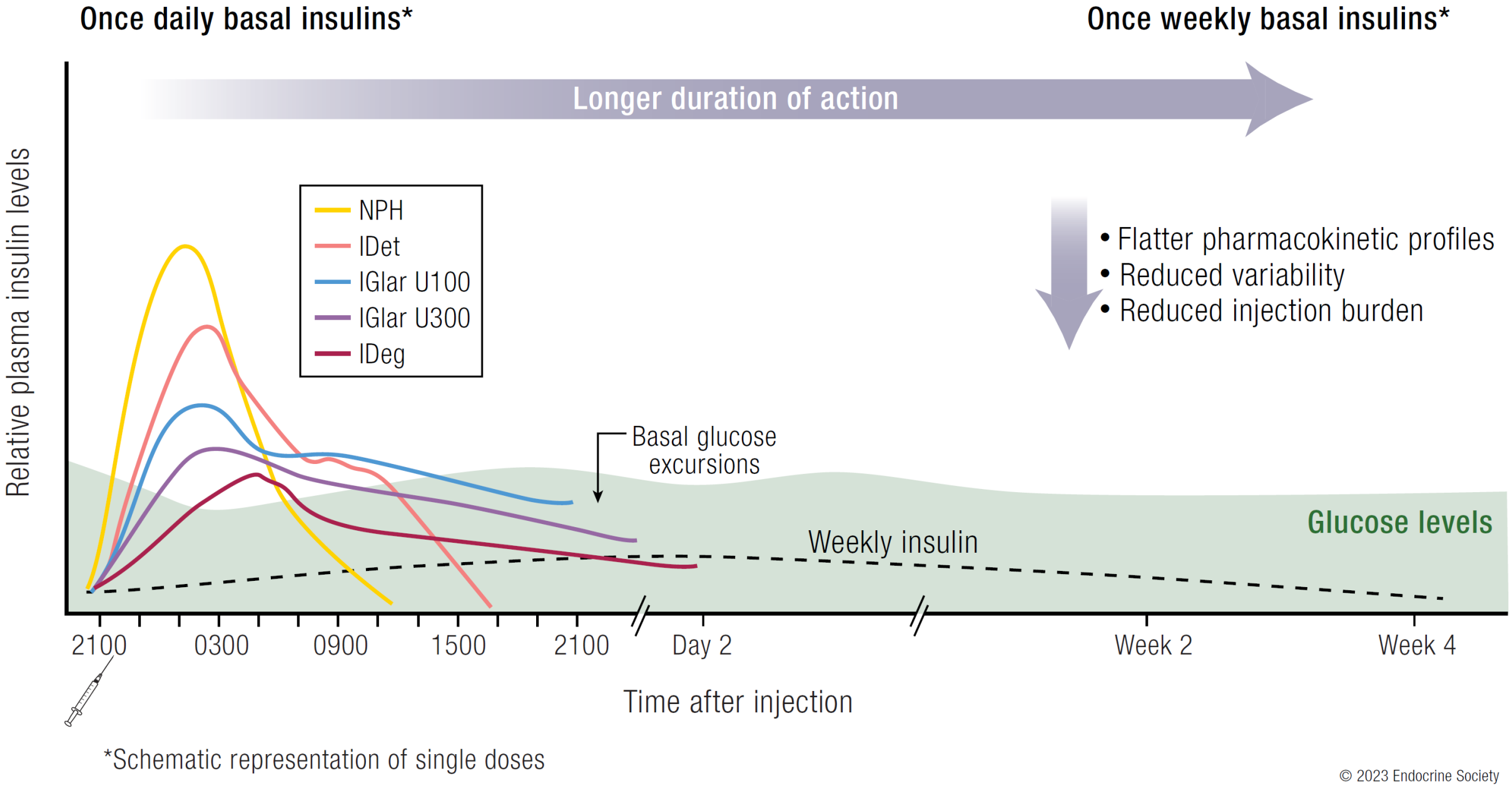
Single chain insulin, i.e., an insulin B chain analog, a short peptide linker, and an insulin A chain analog
• Fused to a second peptide linker that is fused to a human IgG2 Fc region to increase the half-life
• The IgG2 Fc was modified by removing a) six amino acid sequence, ERKCCV, to reduce hinge region disulfide bonds and b) C-terminal Lys

insulin icodec



Insulin analog (three amino acid substitutions) acylated with a C20 fatty diacid side chain, which allows strong reversible binding to albumin and leads to reduced affinity for the insulin receptor and reduced insulin receptor-mediated clearance
– Amino acid substitutions in the insulin analog lead to reduced affinity for insulin receptor and reduced insulin receptor-mediated clearance and enzymatic degradation

Metabolism Clinical and Experimental 126 (2022) 154924



*Schematic representation of single doses

Terapia con insulina basale una volta a settimana vs. una volta al giorno

Clinica

- Miglior (o simile) controllo glicemico con basso rischio di ipoglicemia
- Riduzione dei costi del trattamento
- Strumento per superare l'inerzia terapeutica

Molecolare

- Maggiore emivita
- Più stabile farmacocinetica/farmacodinamica
- Minor tasso di clearance

Migliore accettazione ed aderenza al trattamento

PD, pharmacodynamics; PK, pharmacokinetics.

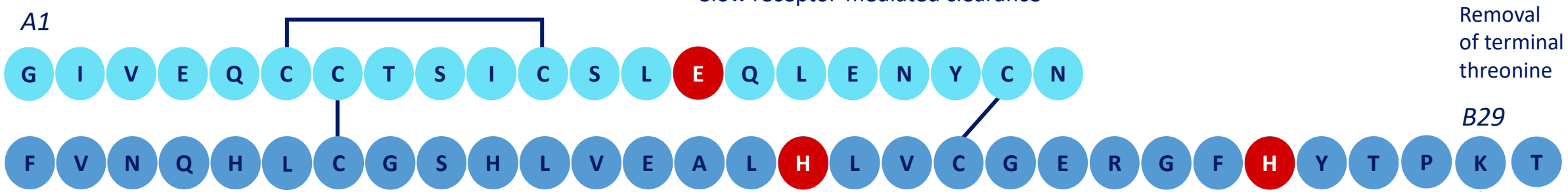
1. Nishimura E et al. *BMJ Open Diab Res Care*. 2021;9(1).

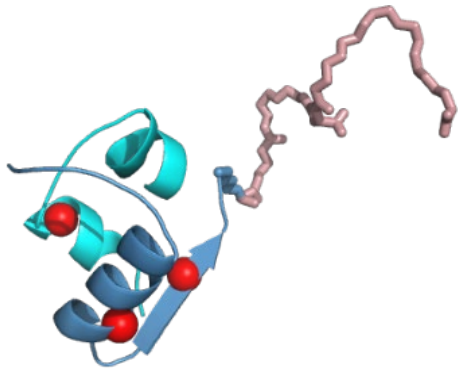
Icodec

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

Three amino acid substitutions

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



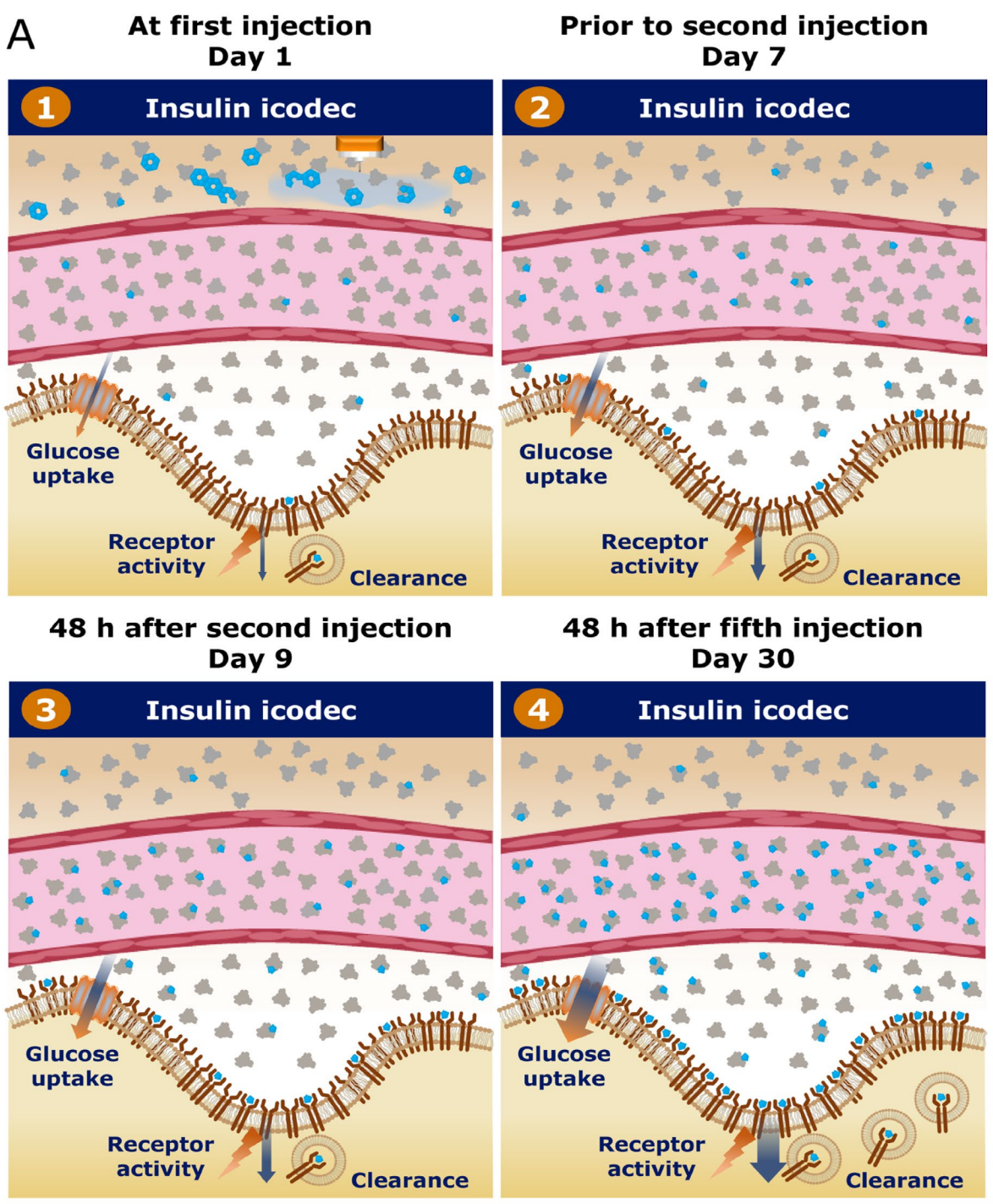


C20 icosane fatty diacid

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

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

1. Kjeldsen TB et al. *J Med Chem*. 2021;64(13):8942-8950.



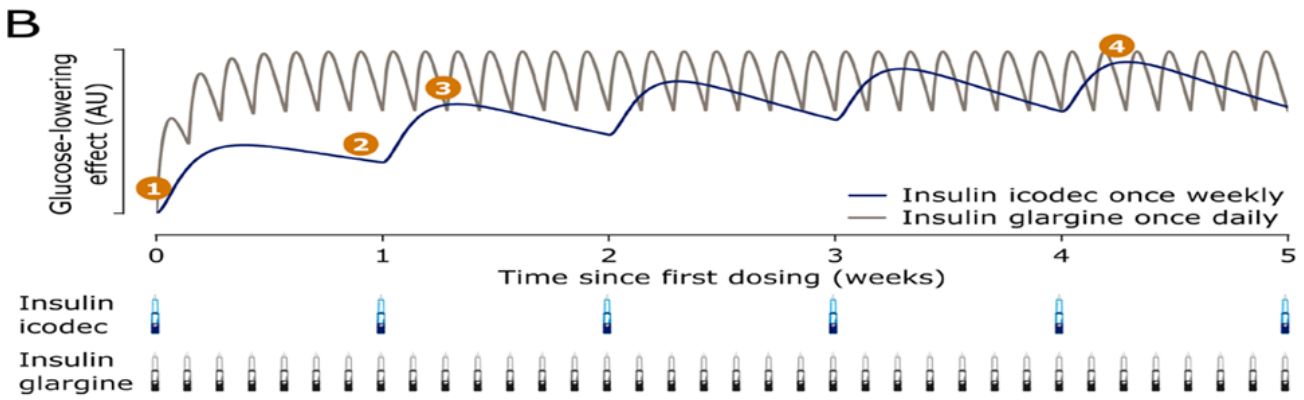


Grafico 1: distribuzione dell'insulina icodec dopo la prima iniezione, con la maggior parte dell'insulina icodec nel sottocute e una piccola percentuale assorbita nel sangue.

Grafico 2: giorno 7, prima della seconda iniezione, che mostra ancora la presenza di insulina icodec distribuita nel sottocute e nei vasi e i legame ai recettori prima dell'iniezione successiva.

Grafici 3–4: mostrano il graduale aumento dell'esposizione all'insulina icodec verso lo stato stazionario.

(B) Modello concettuale che mostra l'effetto ipoglicemizzante nel tempo dall'inizio della somministrazione settimanale di insulina icodec e della somministrazione giornaliera di insulina glargine U100 (a livelli di dose comparabili).

BMJ Open Diab Res Care 2021;**9**:e002301. doi:10.1136/bmjdrc-2021-002301

Potenziali vantaggi associati alle insuline settimanali

Less glycemic variability

Increased patient adherence

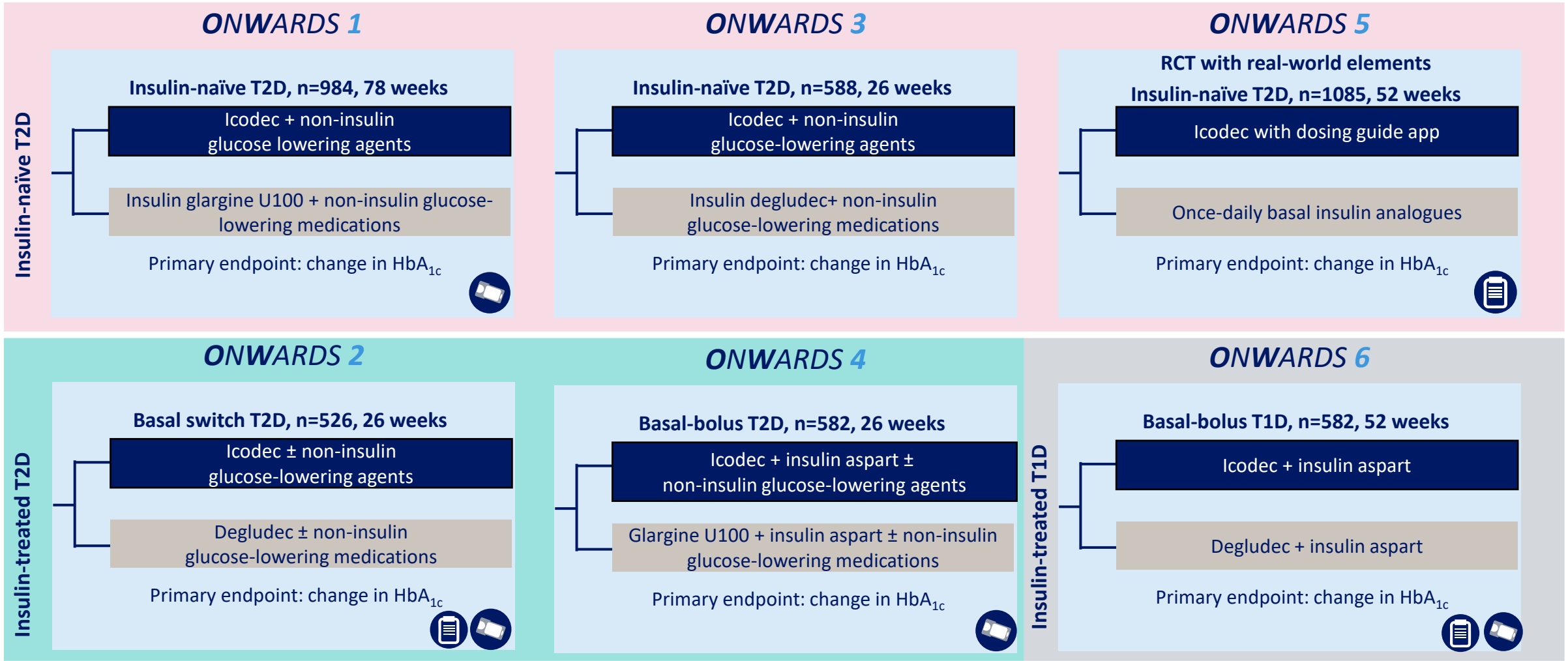
Less risk of hypoglycemia

Decreased clinical inertia

Smoother and simpler for patients

Rosenstock J, et al. Metabolism. 2022;126:154924.

Summary of the *ONWARDS* programme

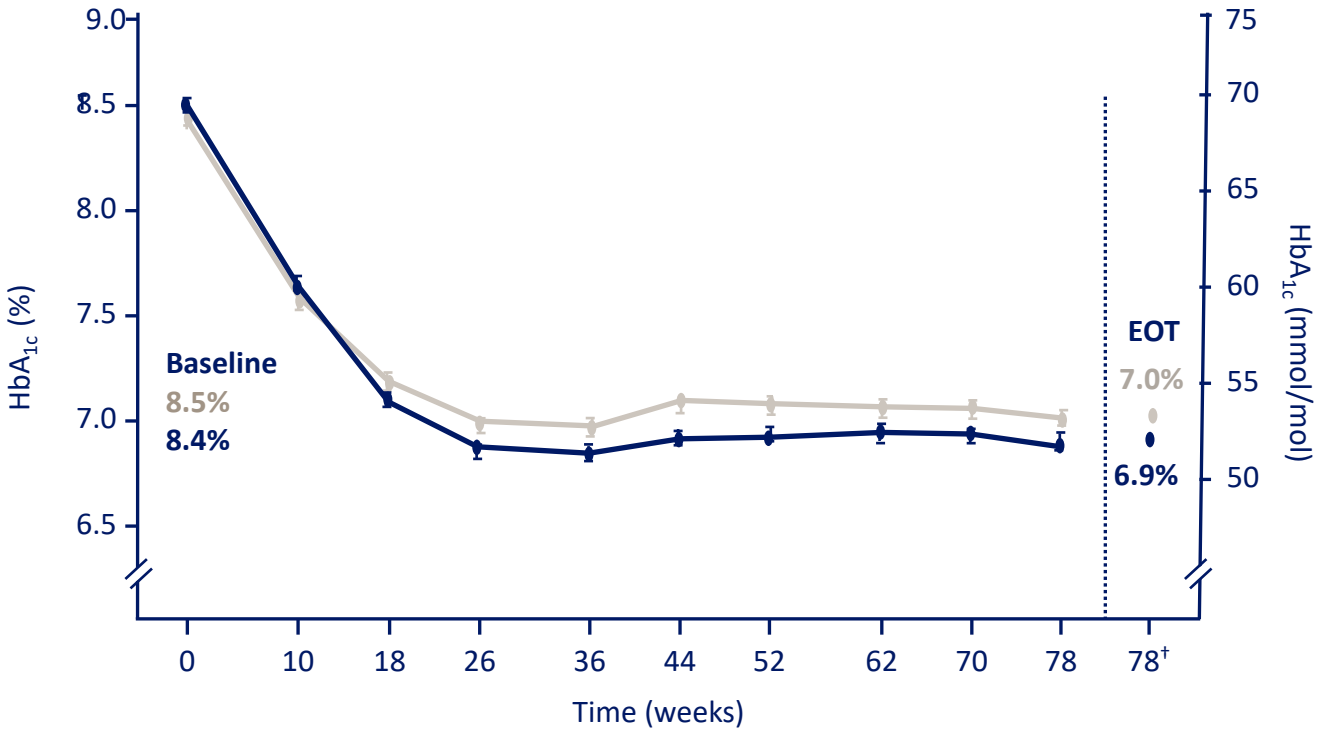


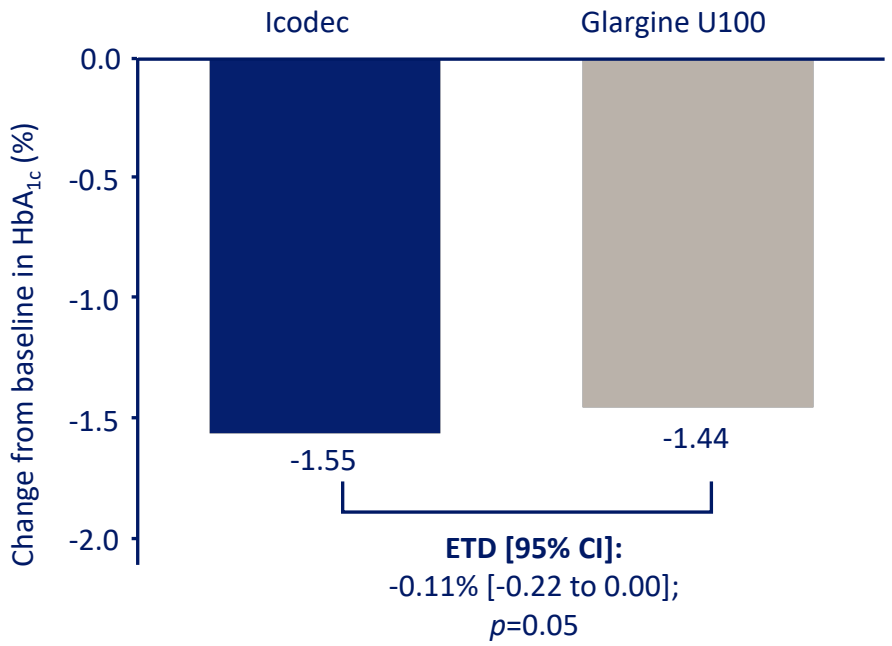
CGM, continuous glucose monitoring; n, number of subjects; PROs, patient reported outcomes; RCT, randomised controlled trial.

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

HbA_{1c} change over time and at week 78

Icodec in insulin-naïve T2D





At week 78 the estimated mean HbA_{1c} change from baseline was sustained with icodec (–1.55%) vs glargine U100 (–1.44%); there was no statistically significant difference between the groups

ETD: icodec – glargine U100
Estimated mean HbA_{1c} at week 78 derived based on multiple imputation . Full analysis set. Observed data are shown as mean (symbol) ± standard error of the mean (error bars).
CI, confidence interval; EOT, end of trial; ETD, estimated treatment difference.
1. Rosenstock J, et al. *N Engl J Med* 2023;10.1056/NEJMoa2303208.

Titration algorithm

Icodec in insulin-naïve T2D

Pre-breakfast SMBG		Starting 10 U/day Glargine U100 dose adjustment (U/day)	Starting 70 U/week 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**

Dose adjustment was based on three pre-breakfast SMBG values, measured two days prior to and on the day of titration. If any of the three pre-breakfast SMBG values were below the lower limit of the target range, titration was based on the lowest recorded value. If all three SMBG values were above the lower limit of the target range, titration was based on the mean of the three measurements. Both insulins were titrated once-weekly.

SMBG, self-measured blood glucose; U, unit(s).

1. Appendix to: Rosenstock J, et al. *N Engl J Med* 2023;10.1056/NEJMoa2303208.

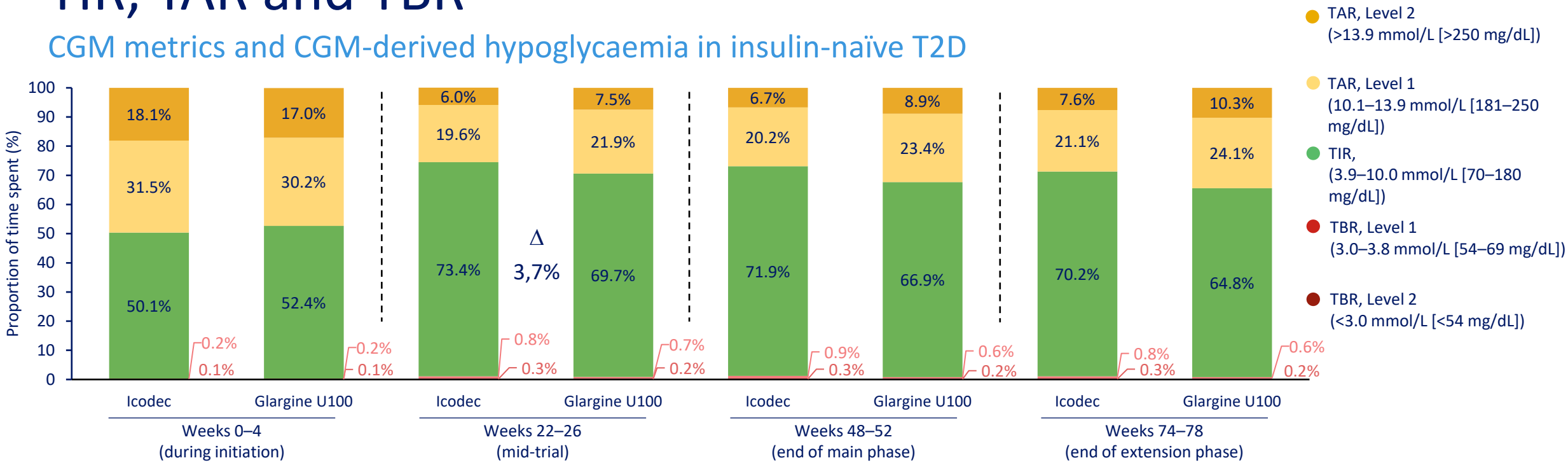
Inizio del trattamento con icodec

Pazienti con diabete mellito di tipo 2 (naïve all'insulina)

La dose iniziale settimanale totale raccomandata è di 70 unità, seguita da aggiustamenti posologici individuali una volta alla settimana.

TIR, TAR and TBR

CGM metrics and CGM-derived hypoglycaemia in insulin-naïve T2D



		Weeks 0–4 (during initiation)	Weeks 22–26 (mid-trial)	Weeks 48–52 (end of main phase)	Weeks 74–78 (end of extension phase)
Estimated treatment difference (95% confidence interval)	$TAR_{>10.0\ mmol/L}$	2.34 (−1.09, 5.77)[d]	**−3.69 (−6.03, −1.34)**[d]	**−4.58 (−6.99, −2.17)**[d]	**−4.65 (−7.20, −2.10)**[d]
	$TIR_{3.9–10.0\ mmol/L}$	−2.39 (−5.79, 1.02)[d]	**3.57 (1.27, 5.87)**[d]	**4.27 (1.92, 6.62)**[d,e]	**4.41 (1.92, 6.90)**[d]
Estimated treatment ratio (95% confidence interval)	$TBR_{<3.9\ mmol/L}$	1.20 (0.85, 1.70)[f]	1.10 (0.89, 1.38)[f]	**1.48 (1.19, 1.84)**[f]	**1.34 (1.07, 1.68)**[f]
	$TBR_{<3.0\ mmol/L}$	1.27 (0.81, 1.97)[f]	1.16 (0.86, 1.55)[f]	1.27 (0.94, 1.71)[f]	1.20 (0.89, 1.61)[f]

Data based on the full analysis set. Bold text indicates a statistically significant difference in favour of icodec (TIR and TAR) or glargine U100 (TBR <3.9 mmol/L [70 mg/dL]). Estimated treatment difference = icodec – glargine U100; estimated treatment ratio = icodec/glargine U100.
[d]Analysis of variance model, with region and randomised treatment as fixed factors. [e]Confirmatory endpoint. [f]Negative binomial model using the number of recorded measurements below range, with a log-link function and the logarithm of the total number of recorded measurements as an offset. Region and randomized treatment were included as fixed factors. CGM, continuous glucose monitoring; TAR, time-above-range; TBR, time-below-range; TIR, time-in-range. 1. Battelino T et al. *Lancet Diabetes Endocrinol* 2023;11:42–57; 2. Battelino T et al. *Diabetes Care* 2019; 42:1593–603; 3. Bergenstal R. et al. 2023 ADA scientific sessions. ePoster 85-LB

Change in HbA_{1c} and safety summary

Icodec basal switch in T2D

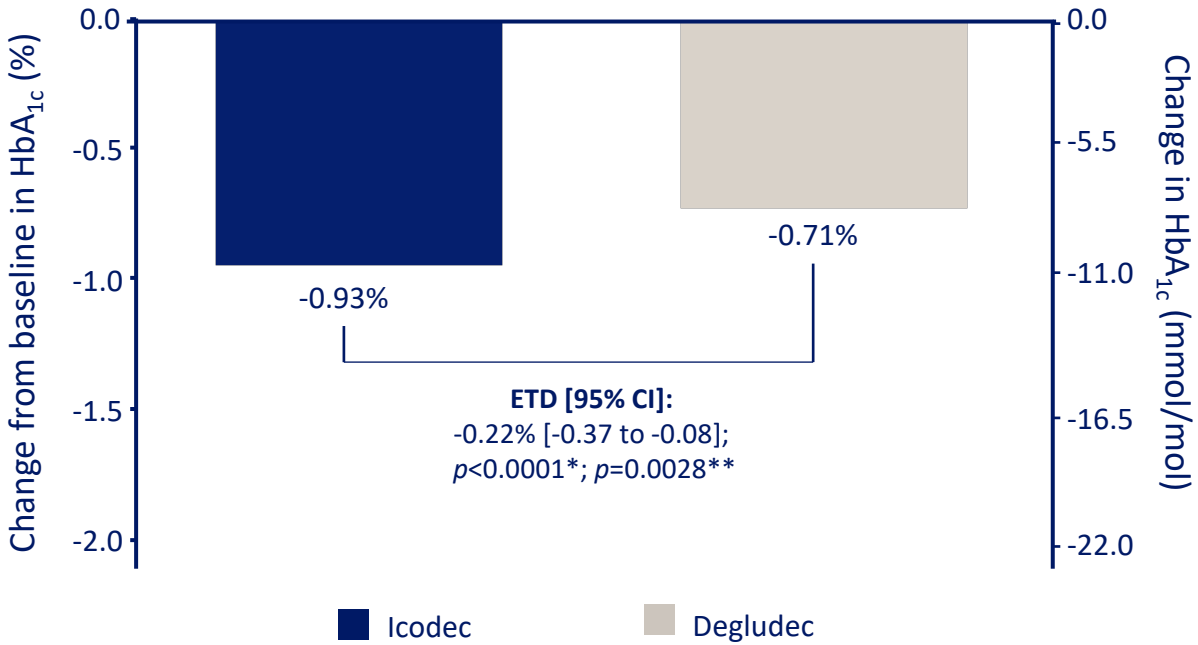
ONWARDS 2

Basal switch T2D, n=526, 26 weeks

- Icodec ± non-insulin glucose-lowering agents
- Degludec ± non-insulin glucose-lowering medications

Primary endpoint: change in HbA_{1c}

Baseline HbA_{1c}: 8.13%



Rate of severe or clinically significant hypoglycaemia† (events per patient-year exposed to treatment)

Icodec	0.73
Degludec	0.27

No statistically significant difference in estimated rate of clinically significant or severe hypoglycaemia

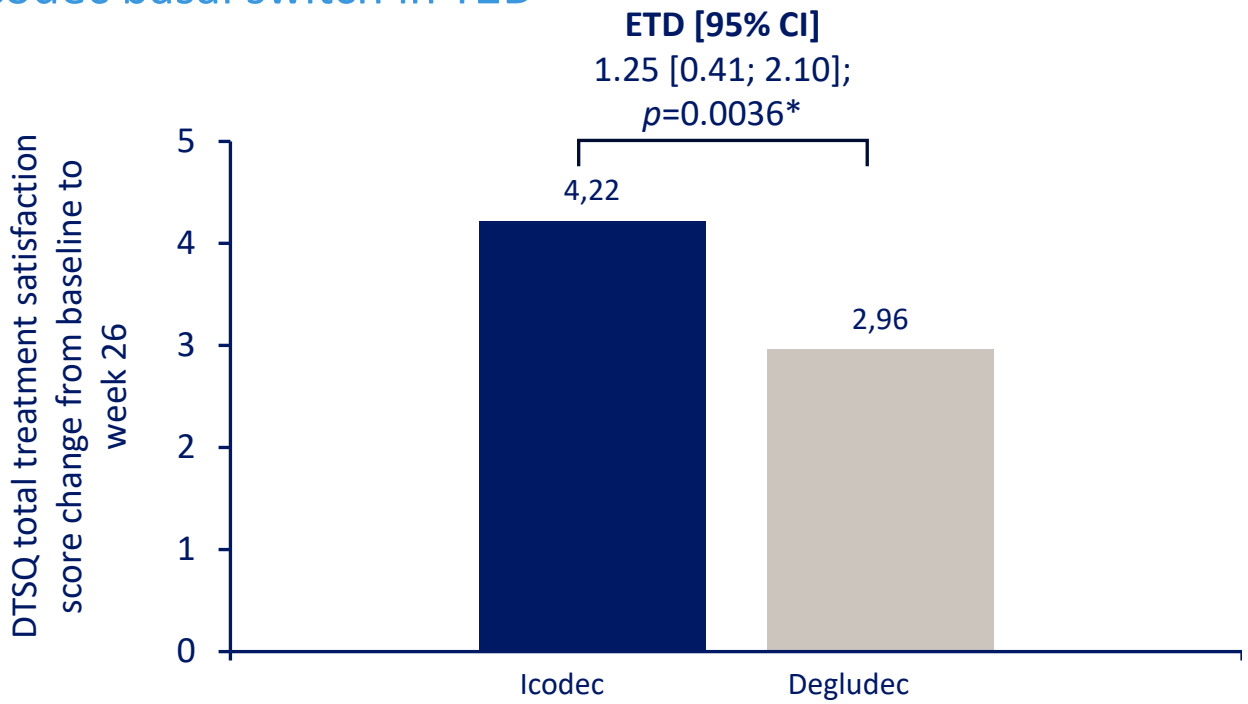
The trial demonstrated non-inferiority and superiority in HbA_{1c} change from baseline to week 26 with insulin icodec compared to insulin degludec

*Significant reduction in HbA_{1c} was observed with icodec versus degludec showing non-inferiority; **Significant reduction in HbA_{1c} was observed with icodec versus degludec establishing superiority of icodec versus degludec; †Clinically significant hypoglycaemia (level 2): blood glucose <3.0 mmol/L (<54 mg/dL) confirmed by blood glucose meter. Severe hypoglycaemia (level 3): hypoglycaemia with severe cognitive impairment requiring external assistance for recovery.
ETD, estimated treatment difference.

1. Philis-Tsimikas A et al. *Lancet Diabetes Endocrinol*. 2023;11(6):414-425.

DTSQ total treatment satisfaction score change from baseline to week 26

Icodec basal switch in T2D



The treatment satisfaction score is calculated from six questions covering:

- Convenience
- Flexibility
- Satisfaction
- Willingness to recommend treatment

Statistically significantly higher change from baseline to week 26 in total treatment satisfaction score with once-weekly icodec versus once-daily degludec

*Statistically significant difference in favour of icodec. In-trial. Full analysis set. No correction for multiplicity. The DTSQ domain score in total treatment satisfaction is calculated by adding the scores of items 1, 4, 5, 6, 7 and 8. The score can range from 0 to 36, with 0 being the lowest and 36 being the highest score. The response and change from baseline in response after 26 weeks are analysed using an ANCOVA model with treatment, region and personal CGM device use as fixed factors, and baseline response as covariate. Missing values at week 26 are imputed by the baseline value and a random term, using multiple imputation. The random term is normally distributed with mean 0 and standard deviation equal to the estimated residual standard deviation from the ANCOVA model fitted to the LAOT-WOB values. The model includes the same factors and covariates as the model used for analysis. Each imputed dataset is analysed separately, and estimates are combined using Rubin's rules. ANCOVA, analysis of covariance; CI, confidence interval; DTSQ, Diabetes Treatment Satisfaction Questionnaire; ETD, estimated treatment difference; LAOT-WOB, last available on-treatment without initiation of bolus insulin for more than 2 weeks.

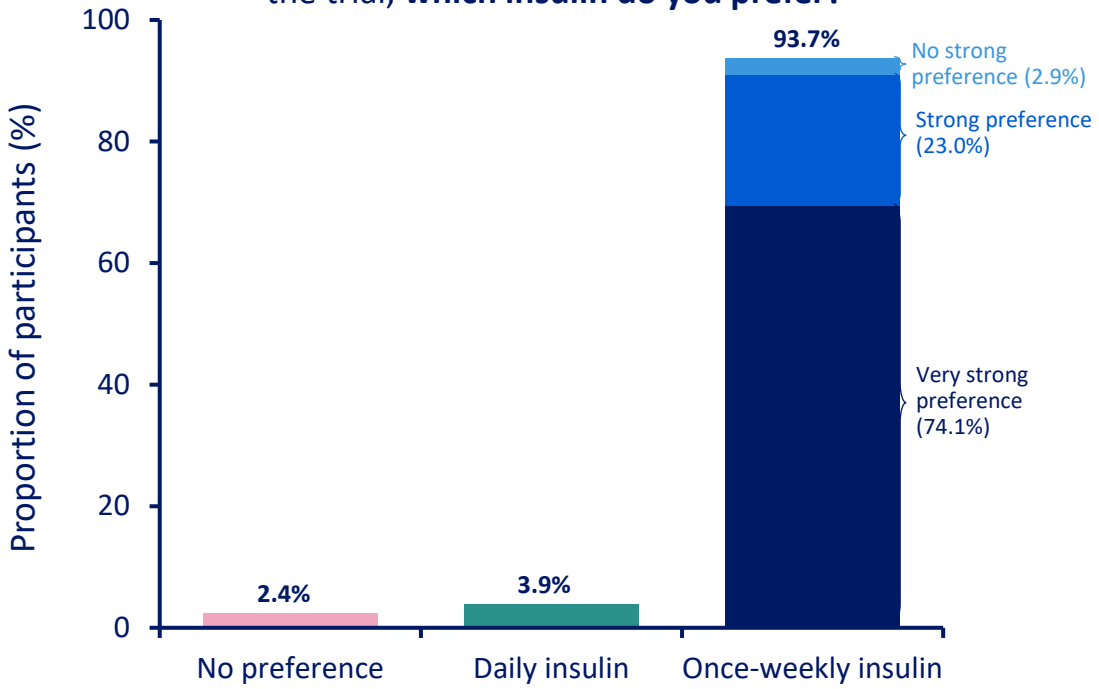
1. Philis-Tsimikas A et al. Lancet Diabetes Endocrinol. 2023;11(6):414-425.

Insulin Preference Questionnaire (icodec participants)

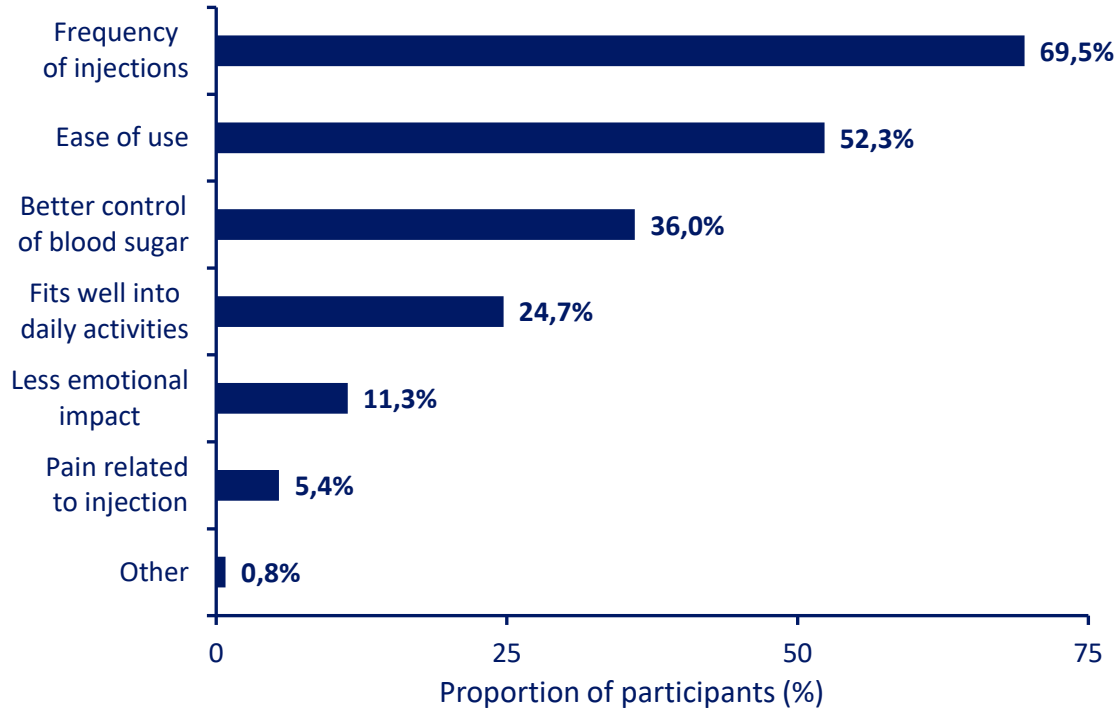
Icodec basal switch in T2D

Post-hoc analysis

Based on your experience before and during the trial, **which insulin do you prefer?**



What are the two **main reasons for the preference** for once-weekly insulin?

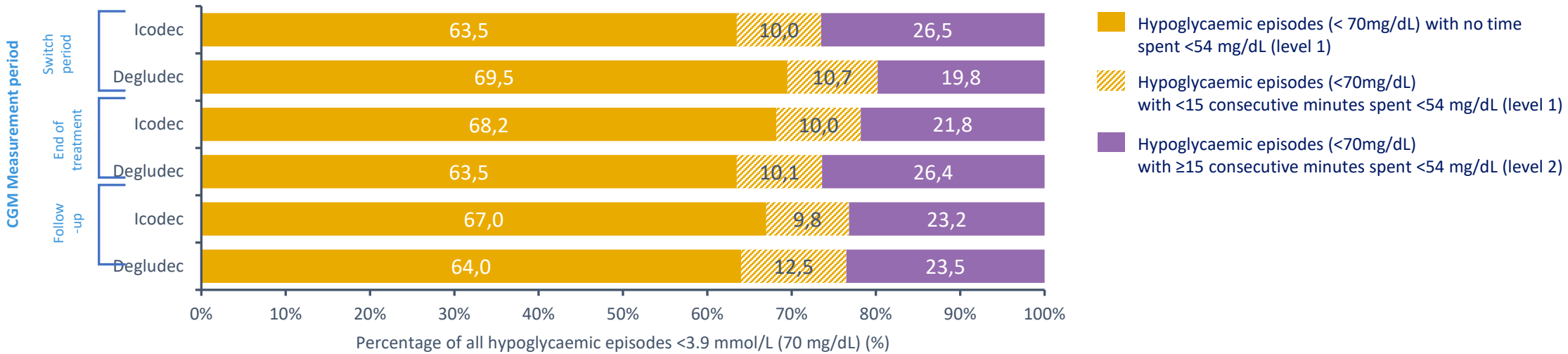


Majority of the icodec participants had a **very strong preference towards once-weekly insulin icodec** (during the trial) versus their previous daily basal insulin (before the trial)

Pre-trial daily basal insulins were administered once-daily or twice-daily.
Of 263 participants who received insulin icodec, 255 completed the Insulin Preference Questionnaire (239 expressed a preference for once-weekly insulin and provided two reasons each for their preference).
1. Polonsky W et al. 2023 ESD Annual Meeting. SO-780.

Classification of CGM-derived overall hypoglycaemic episodes (<70 mg/dL) by time spent <54 mg/dL

CGM metrics in insulin-experienced T2D



- Durante tutti i periodi dello studio, la maggior parte degli episodi ipoglicemici derivati da CGM <70 mg/dL non includeva tempo in ipo <54 mg/dL, o almeno 15 minuti con glicemie <54 mg/dL (livello 1)
- Non vi erano differenze sostanziali tra icodec e i comparatori OD nella percentuale di episodi ipoglicemici derivati da CGM con tempo trascorso <54 mg/dL per ≥15 minuti (livello 2)

CGM, continuous glucose monitoring; OD, once-daily

1. Bajaj H et al. 2023 ADA scientific sessions. ePoster 804-P.

Titration algorithm

Icodec in insulin-naïve T2D

Pre-breakfast SMBG		Starting: pre trial dose/day Glargine U100 dose adjustment (U/day)	Starting: pre trial dose x7 + loading dose 50% only for week 1/week 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**

Dose adjustment was based on three pre-breakfast SMBG values, measured two days prior to and on the day of titration. If any of the three pre-breakfast SMBG values were below the lower limit of the target range, titration was based on the lowest recorded value. If all three SMBG values were above the lower limit of the target range, titration was based on the mean of the three measurements. Both insulins were titrated once-weekly.

SMBG, self-measured blood glucose; U, unit(s).

1. Appendix to: Rosenstock J, et al. *N Engl J Med* 2023;10.1056/NEJMoa2303208.

Passaggio da medicinali insulinici basali una o due volte al giorno a icodec *nel diabete di tipo 2 e di tipo 1*

La prima dose settimanale di icodec deve essere somministrata il giorno successivo all'ultima dose dell'insulina basale somministrata una o due volte al giorno.

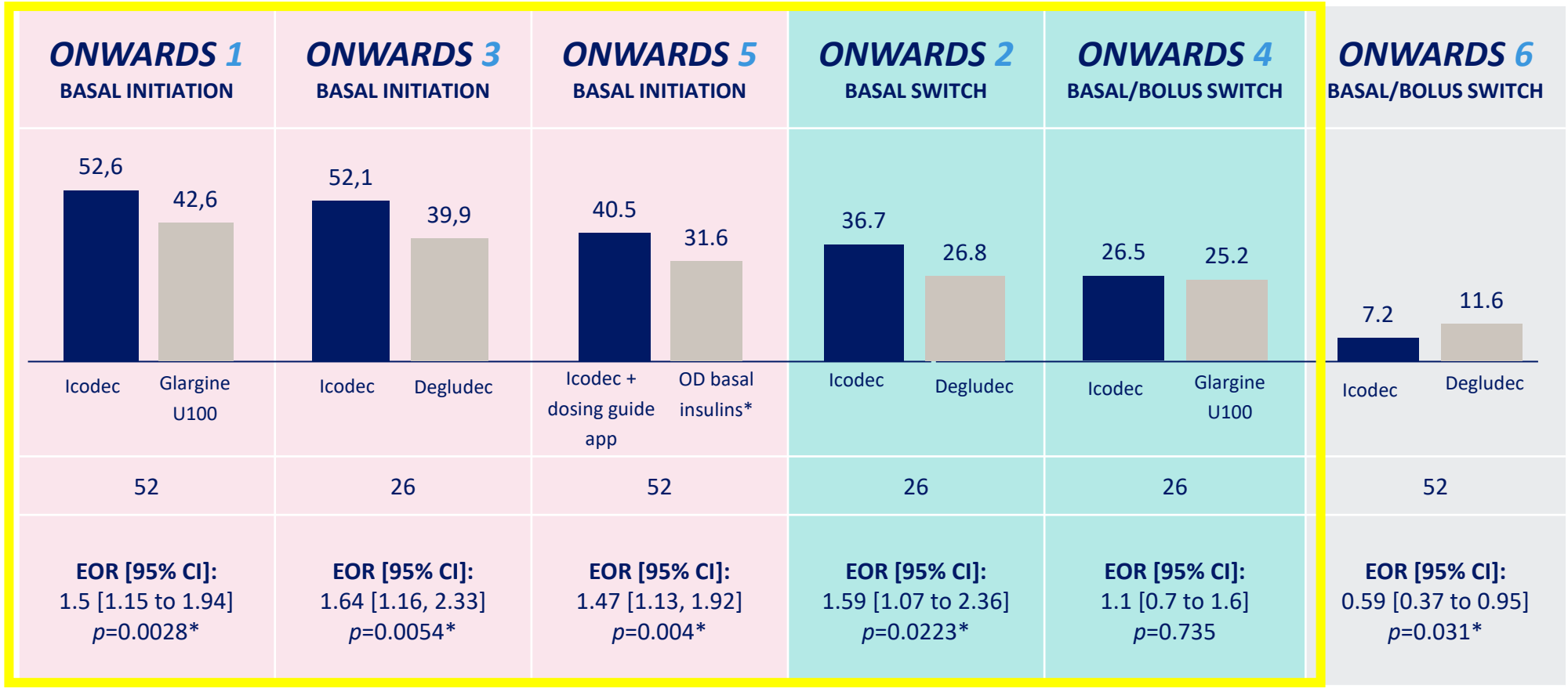
Nel passaggio dei pazienti dall'insulina basale una o due volte al giorno, la dose raccomandata di icodec una volta alla settimana è la dose basale giornaliera totale moltiplicata per 7. Solo per la prima iniezione (dose della settimana 1), si raccomanda un'ulteriore dose aggiuntiva del 50% di icodec se si ricerca un raggiungimento più rapido del controllo glicemico nei pazienti con diabete di tipo 2. Per i pazienti affetti da diabete di tipo 1, questa dose aggiuntiva è sempre raccomandata (solo per la prima iniezione). Se viene somministrata la dose aggiuntiva una tantum di icodec del 50%, la dose della settimana 1 dovrebbe essere la dose di insulina basale giornaliera totale moltiplicata per 7 e poi moltiplicata per 1,5, arrotondata alle 10 unità più vicine (vedere Tabella 1).

La dose aggiuntiva una tantum non deve essere aggiunta a partire dalla seconda iniezione (vedere paragrafo 4.4). La seconda dose settimanale di icodec è la dose basale giornaliera totale moltiplicata per 7.

La terza dose settimanale e quelle successive devono basarsi sulle esigenze metaboliche del paziente, sui risultati del monitoraggio della glicemia e sull'obiettivo del controllo glicemico fino al raggiungimento della glicemia plasmatica a digiuno desiderata. L'aggiustamento della dose deve essere effettuato sulla base dei valori di glucosio a digiuno automonitorati il giorno della titolazione e nei due giorni precedenti.

Si raccomanda un monitoraggio costante della glicemia durante il passaggio e nelle settimane seguenti. Dosi e tempi di somministrazione di medicinali insulinici in bolo o di altri trattamenti antidiabetici concomitanti possono necessitare di un aggiustamento.

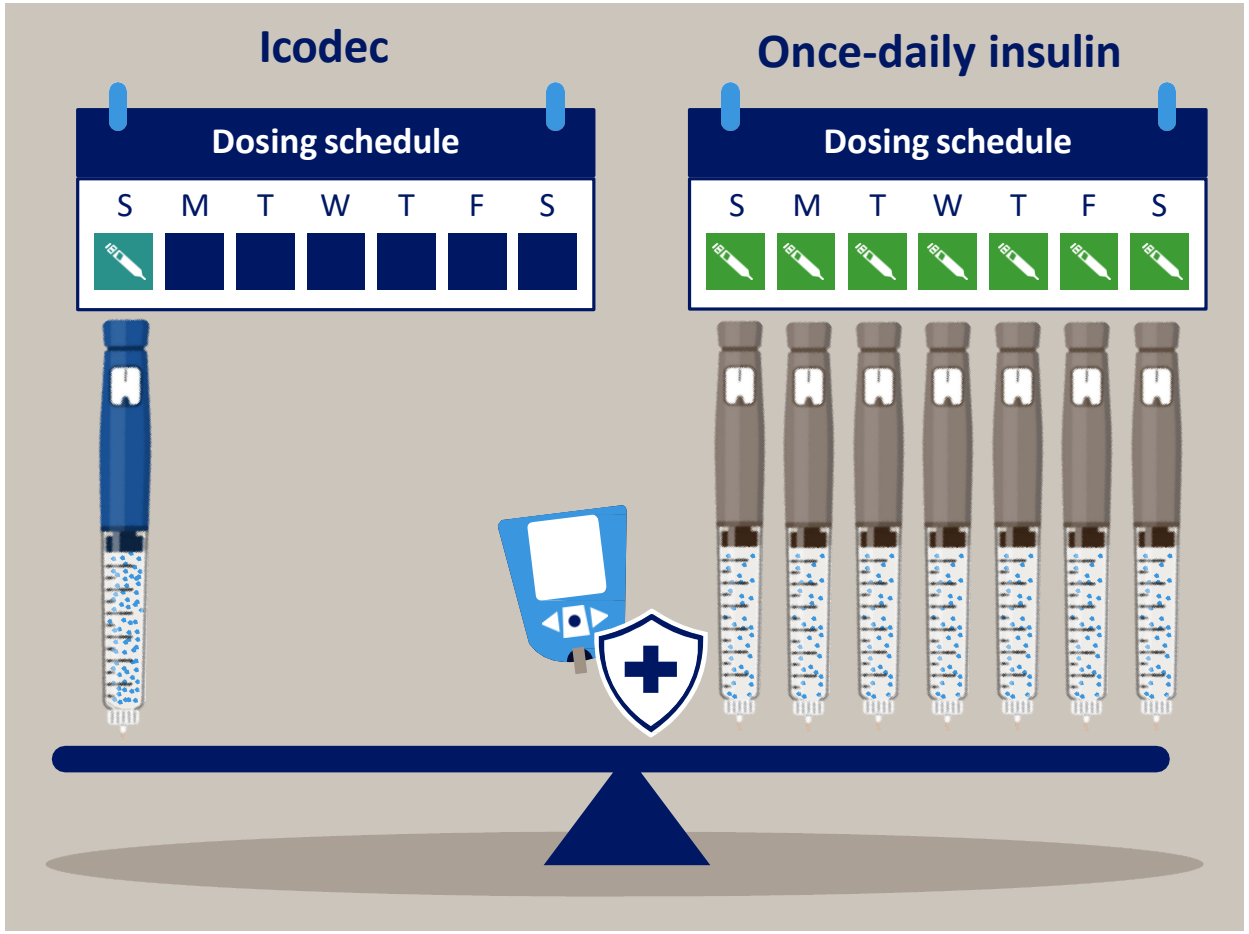
ONWARDS programme: composite endpoint



Clinically significant hypoglycaemia (level 2): blood glucose <3.0 mmol/L (<54 mg/dL) confirmed by blood glucose meter. Severe hypoglycaemia (level 3): hypoglycaemia with severe cognitive impairment requiring external assistance for recovery. † insulin degludec or insulin glargine U100/U300; CI, confidence interval; EOR, estimated odds ratio; OD, once-daily; PYE, patient years of exposure; *p-value indicating statistical significance.

1. Rosenstock J et al. *N Engl J Med*. 2020;383:2107–2116; 2. Lingvay I et al. *JAMA*. 2023:10.1001/jama.2023.11313; 3. Bajaj H. 2023 ADA Scientific Sessions. 803-P. 4. Philis-Tsimikas A et al. *Lancet Diabetes Endocrinol*. 2023;11(6):414-425. 5. Mathieu C et al. *Lancet.* 2023;401(10392):1929-40; 6. Rosenstock J et al. 2023 ADA Scientific Sessions. 179-OR; 7. Lingvay I et al. 2023 ADA Scientific Sessions. 178-OR; 8. Mathieu C et al. 2022. DTS 22nd Annual Meeting. Virtual. 2 Nov 2022; 9. Philis-Tsimikas A et al. 2022. EASD Annual Meeting. S42; 10. Russell-Jones D et al. *Lancet*. 2023: DOI: 10.1016/S0140-6736(23)02179-7.

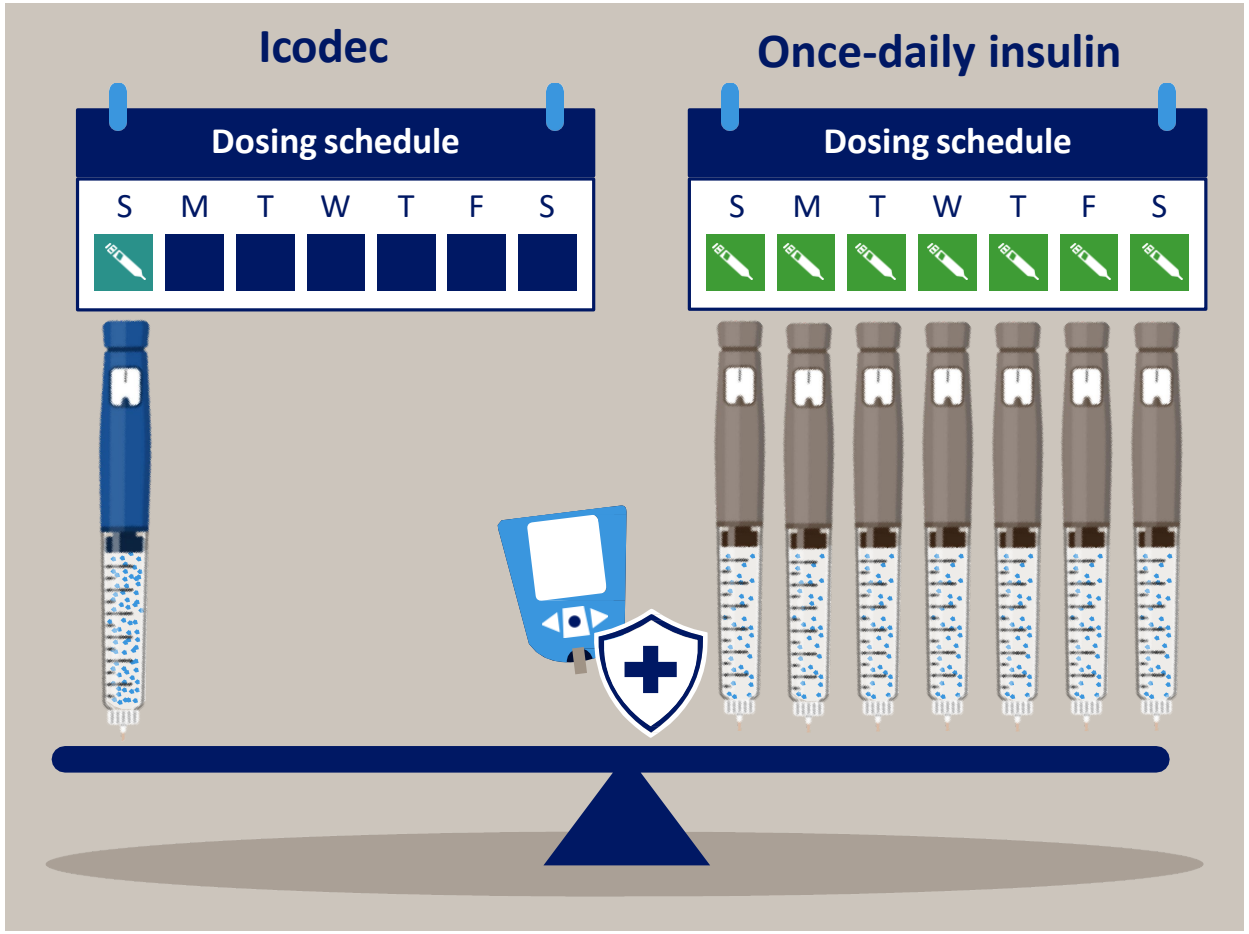
Clinical application of icodec



- Un'iniezione settimanale rispetto a sette iniezioni con insulina giornaliera
- La formulazione (700 U/mL) garantisce che il volume di iniezione sia simile all'insulina basale somministrata una volta al giorno
- La copertura settimanale è ottenuta mediante il rilascio graduale di icodec dalla quota legata all'albumina
- Dati recenti dimostrano che il controllo glicemico, la sicurezza e la dose sono paragonabili all’insulina giornaliera

U, unit(s).

Persone che traggono vantaggi dall'uso di insulina settimanale



- L'uso di insulina settimanale può semplificare la terapia negli anziani, in cui la somministrazione dell'insulina è gestita da familiari o care-givers.
- Adulti in età lavorativa per i quali è necessaria maggiore flessibilità nella gestione della terapia insulinica.
- Persone con diabete di tipo 2 in follow-up ambulatoriale che non raggiungono un adeguato controllo glicemico con metformina, SGLT2i e/o GLP1-RA o per i quali esistono controindicazioni o intolleranza a questi agenti.
- Persone con diabete tipo 2, con ridotta riserva pancreatica e con prolungato scompenso glicemico.
- Pazienti in buon controllo glicemico e in trattamento con dosi stabili di insulina basale giornaliera.
- Persone naive all'insulina per le quali un regime di terapia insulinica basale a somministrazione settimanale può risultare maggiormente accettabile, con miglioramento della compliance.

U, unit(s).

Razionale d’uso per insuline settimanali

Le iniezioni frequenti possono essere un carico fisico e psicologico oneroso da sostenere per le persone con diabete, contribuendo all’inerzia clinica o a una scarsa aderenza terapeutica

Le insuline settimanali possono offrire la possibilità di una maggiore aderenza terapeutica e una migliore QoL
Riducono il numero di iniezioni settimanali da 7 a 1 o da 365 a 52

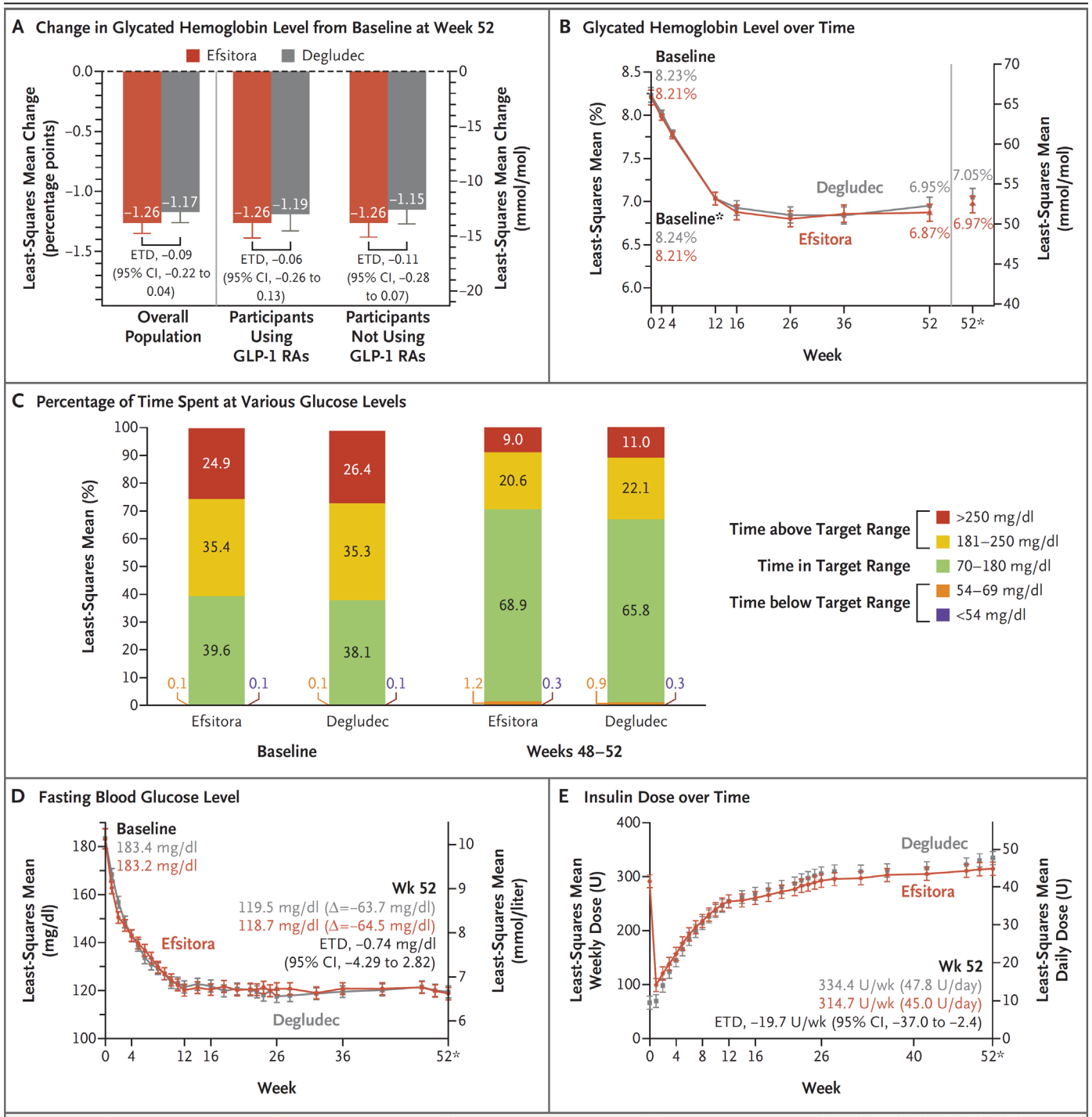
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

- A total of 928 participants underwent randomization (466 to the efsitora group and 462 to the degludec group).
- The mean glycated hemoglobin level decreased from 8.21% at baseline to 6.97% at week 52 with efsitora and from 8.24% to 7.05% with degludec (estimated treatment difference, −0.09 percentage points; 95% confidence interval [CI], −0.22 to 0.04), findings that showed noninferiority.
- Efsitora was noninferior to degludec with respect to the change in the glycated hemoglobin level in participants using and not using GLP-1 receptor agonists.
- The percentage of time that the glucose level was within the target range was 64.3% with efsitora and 61.2% with degludec (estimated treatment difference, 3.1 percentage points; 95% CI, 0.1 to 6.1).

published on September 10, 2024, at NEJM.org.
DOI: 10.1056/NEJMoa2403953



The NEW ENGLAND JOURNAL of MEDICINE

published on September 10, 2024, at NEJM.org.
DOI: 10.1056/NEJMoa2403953

ORIGINAL ARTICLE

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

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)

Icodec + Semaglutide Combo Shows Benefit in Type 2 Diabetes

Miriam E. Tucker
September 12, 2024

MADRID — Novo Nordisk's investigational once-weekly combination of insulin icodec plus semaglutide (IcoSema) could benefit people with type 2 diabetes who don't reach target glycemic goals with either single agent alone, new research suggests.

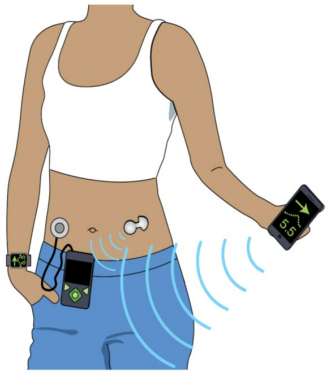
Data for three 52-week multicenter randomized open-label trials from the company's phase 3a COMBINE program were presented on September 11, 2024, in a 1-hour symposium at the European Association for the Study of Diabetes (EASD) 2024 Annual Meeting. Among people with type 2 diabetes not meeting target A1c goals with their current therapy, COMBINE 1 compared IcoSema with icodec alone, COMBINE 2 compared the combination with semaglutide alone, and COMBINE 3 examined IcoSema with once-daily basal glargine and premeal insulin aspart in people not achieving glycemic targets with basal insulin alone.

All three trials met their primary endpoints for A1c reduction — superiority in COMBINE 1 and 2, and non-inferiority in COMBINE 3. All other endpoints were either superior or non-inferior except for the expected greater weight gain compared with semaglutide alone and more gastrointestinal adverse effects compared with basal insulin alone.

Diabetologia (2021) 64:1016–1029
https://doi.org/10.1007/s00125-021-05422-6

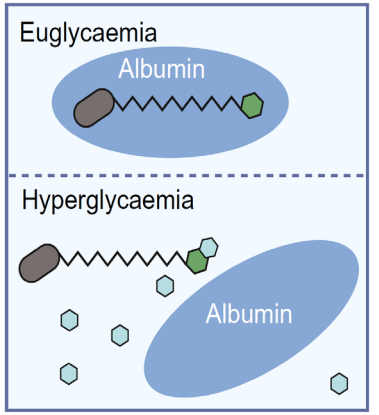
REVIEW

‘Smart’ insulin-delivery technologies and intrinsic glucose-responsive insulin analogues

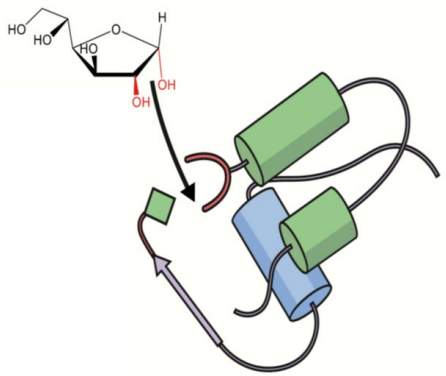


Coupling of continuous glucose monitoring (CGM) to delivery devices (algorithm-based ‘closed-loop’ systems)

Glucose-responsive polymer encapsulation of insulin



Mechanism-based hormone modifications



Journal of Endocrinological Investigation (2019) 42:495–503
https://doi.org/10.1007/s40618-018-0951-8

REVIEW

Clinical inertia, reverse clinical inertia, and medication non-adherence in type 2 diabetes

D. Giugliano[1] · M. I. Maiorino[2] · G. Bellastella[1] · K. Esposito[2]

- La non-aderenza alla terapia e l'inerzia clinica restano barriere importanti al raggiungimento degli obiettivi glicemici nel diabete tipo 2
- Una parte dell'inerzia terapeutica potrebbe essere una risposta del clinico alla incertezza tuttora presente in Medicina (linee guida, algoritmi)
- I clinici dovrebbero considerare la "reverse clinical inertia" come causa di terapia inappropriata e persistente, specialmente nel paziente più vulnerabile

Nel frattempo, i clinici potrebbero considerare l'uso di:

- Farmaci anti-iperglicemici più innovativi
- Regimi terapeutici meno complessi
- Device di più facile utilizzo e accettazione dal paziente diabetico
- Intensificazione più precoce del regime terapeutico

In ultima analisi, i clinici dovrebbero trovare l'equilibrio tra i pericoli dell'inerzia clinica e quelli dell'eccessiva cura medica, senza tralasciare la non-aderenza alla terapia.

Giugliano D. et al.; J Endocrinol Invest 2019; 42: 495-503

PreVen ENDO

Prof. Katherine Esposito

“PreVenENDO” è una iniziativa di natura educativa e culturale ideata dalla Prof. Katherine Esposito, incentrata sulla divulgazione di informazioni in tema di prevenzione delle patologie endocrino-metaboliche e andrologiche a tutta la popolazione per favorire il benessere e la salute.

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