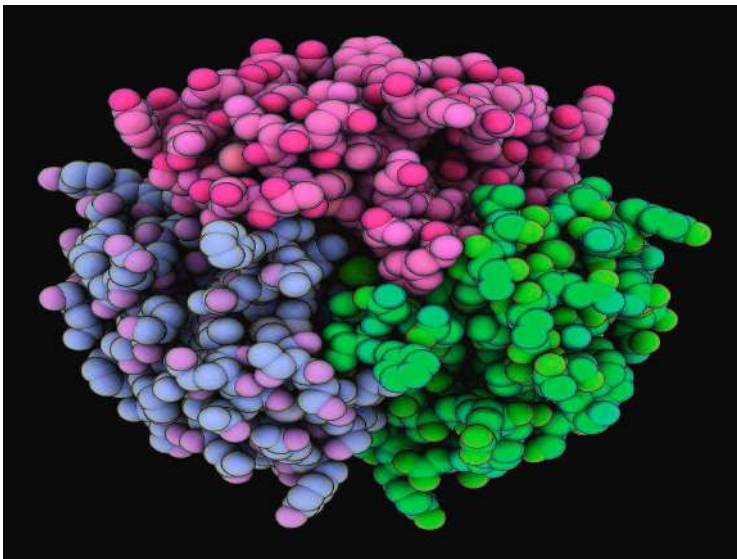


XVI CONGRESSO
REGIONALE
AMD MOLISE

La terapia insulinica: la best practice e gli
sviluppi futuri

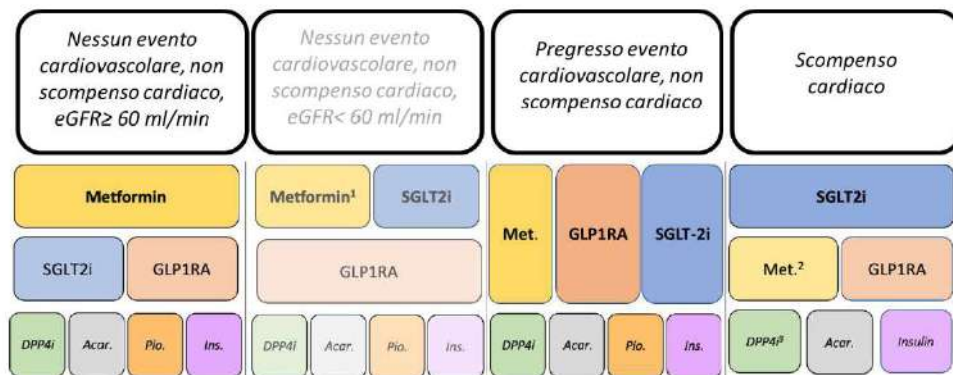


Elisa Forte

Presidente Associazione Medici
Diabetologi Regione Lazio

C'è ancora spazio per la terapia insulinica nella cura della Persona con DM2?

Linea Guida SID e AMD



¹Se la metformina non è controindicata per ridotta eGFR.



²Se la metformina non è controindicata per ridotta funzione cardiaca.

³Eccetto saxagliptin che non è indicata in caso di scompenso cardiaco.

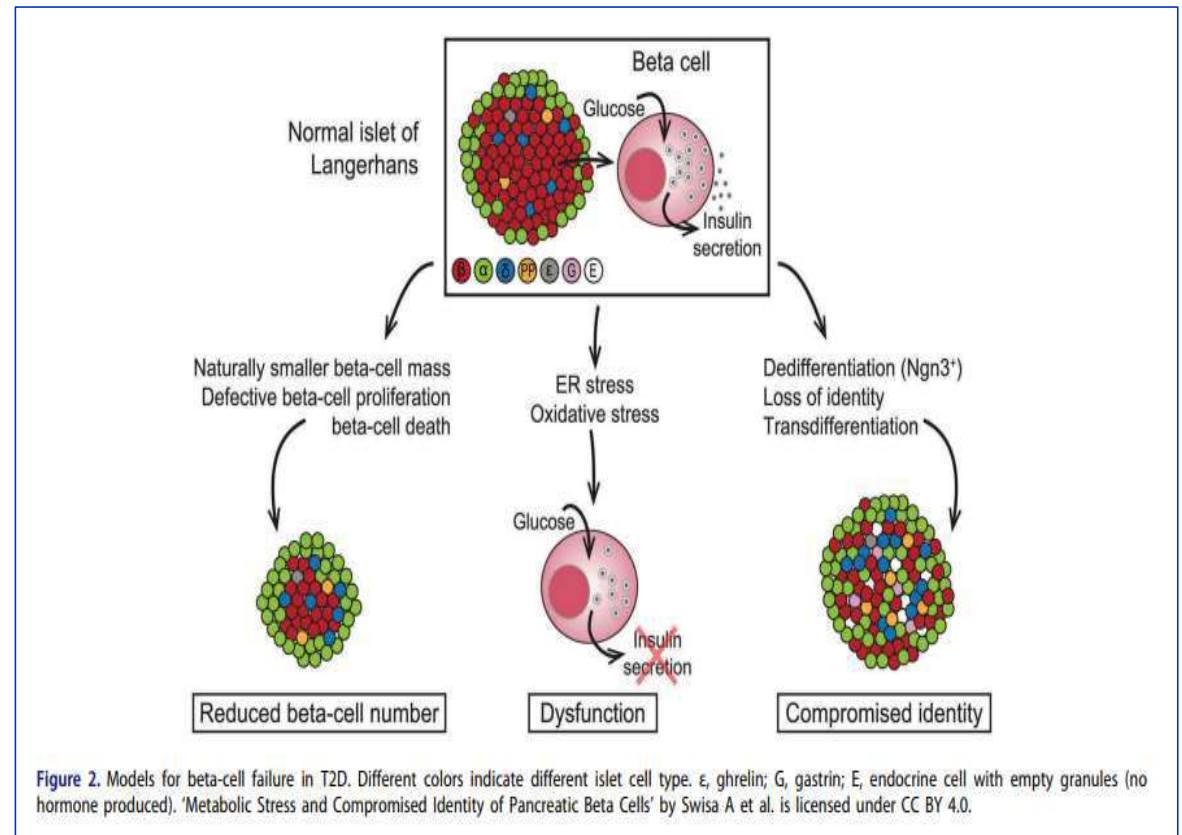
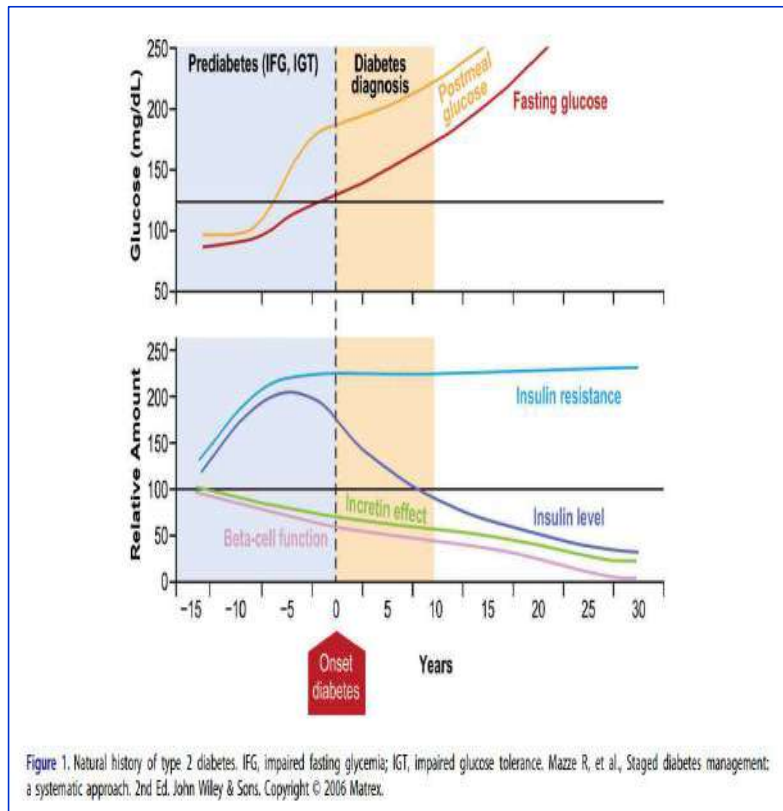
La raccomandazione sui pazienti con eGFR < 60ml/min è debole per carenza di studi clinici effettuati su questa popolazione. Si raccomanda la deprescrizione di sulfoniluree e glicinidi.

Le linee guida nazionali e internazionali raccomandano l'impiego dell'insulina basale in pazienti affetti da DM2 che non raggiungono gli obiettivi di trattamento nonostante duplice/triplice terapia orale e/o con gli agonisti del recettore del GLP-1 o in presenza di grave scompenso glicometabolico con sintomi/segni di deficit insulinico (Khunti 2020).

Beta-cell failure in type 2 diabetes: mechanisms, markers, and clinical implications

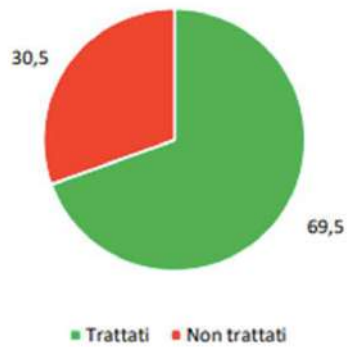
Carol Wysham ^a and Jay Shubrook ^b

^aDepartment of Diabetes and Endocrinology, Rockwood Diabetes & Endocrinology Clinic, Spokane, WA, USA; ^bCollege of Osteopathic Medicine, Touro University California, Vallejo, CA, USA

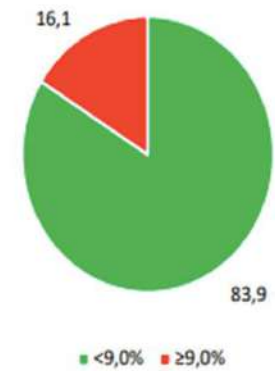




Soggetti con valori di HbA1c $\geq 9,0$ (%) non trattati con insulina



Soggetti con HbA1c $\geq 9,0\%$ nonostante il trattamento con insulina (%)





> J Med Internet Res. 2020 Jun 22;22(6):e16922. doi: 10.2196/16922.

Artificial Intelligence and Big Data in Diabetes Care: A Position Statement of the Italian Association of Medical Diabetologists

Nicoletta Musacchio ¹, Annalisa Giancaterini ², Giacomo Guaita ³, Alessandro Dzzello ⁴, Maria A. Pellegrini ^{1, 5}, Paola Ponzani ⁶, Giuseppina T Russo ⁷, Rita Zillich ⁸, Alberto de Micheli ⁹

Machine Learning

Genera conoscenza

- Prendere decisioni basate sui dati
- Orientare i comportamenti

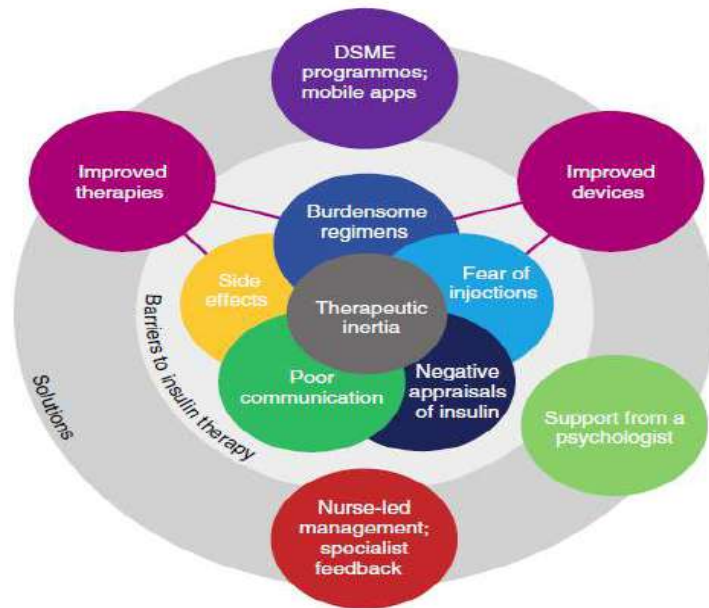


Andamento dell'HA1c al momento dell'intensificazione con insulina basale e nei 3 anni precedenti e successivi all'avvio di insulina basale

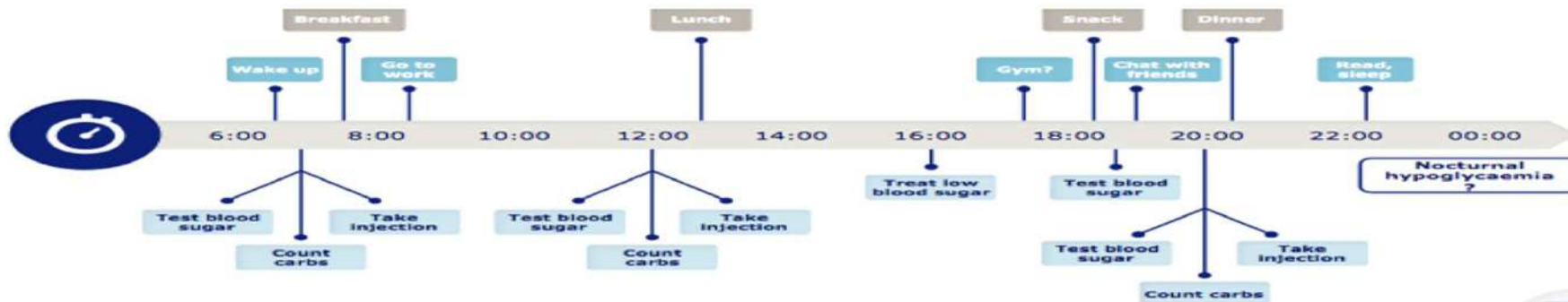


La terapia insulinica viene intrapresa in presenza di glicate attorno a 9%



Identification of barriers to insulin therapy and approaches to overcoming them



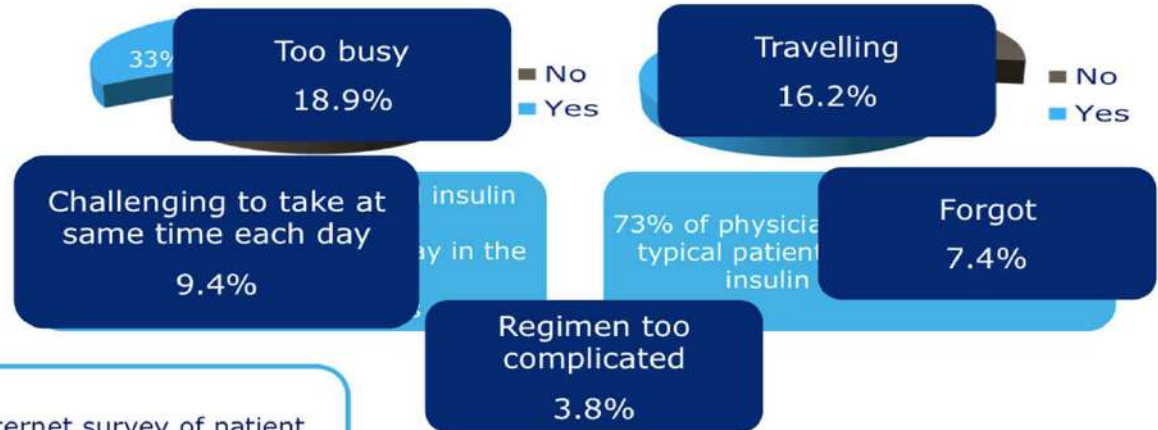
- Fear of hypoglycaemia and weight gain
- Fear of injections
- Impact on daily life
- Negative appraisal of insulin
- Lack of HCP resources, assistance and education for patients



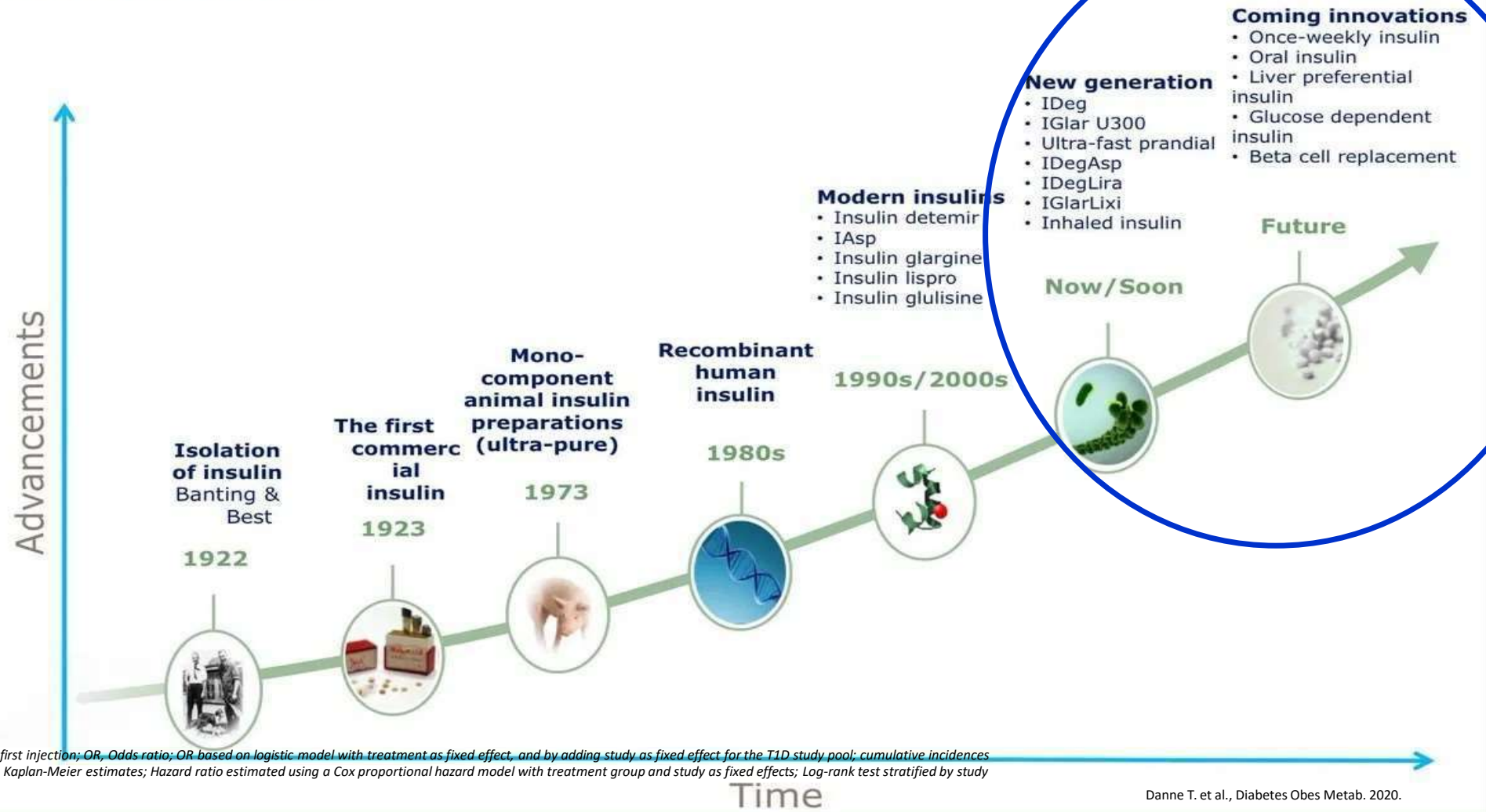
Insulin doses are being missed or not taken as prescribed

2 pens 
2-4* Injections³ 
Breakfast Lunch Evening Dinner
2-4* SMPG test²

GAPP™
 • A global internet survey of patient and physician beliefs regarding insulin therapy
 • n=1250 physicians

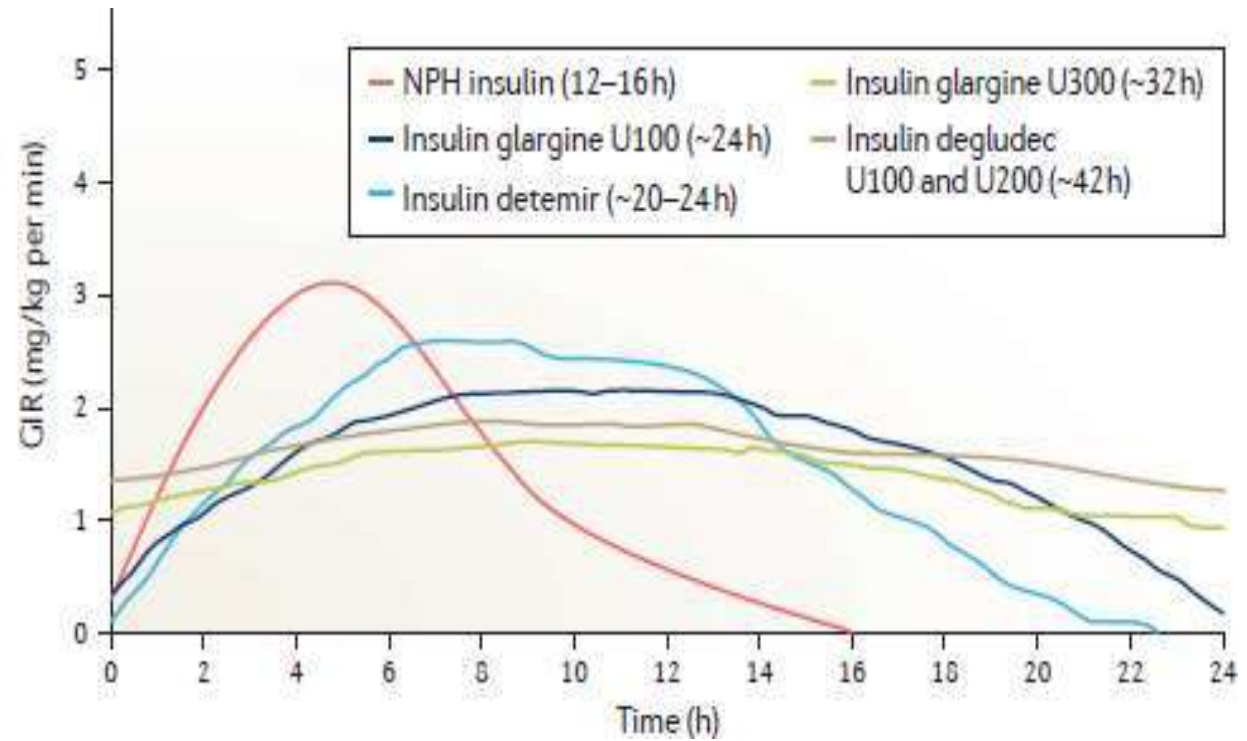
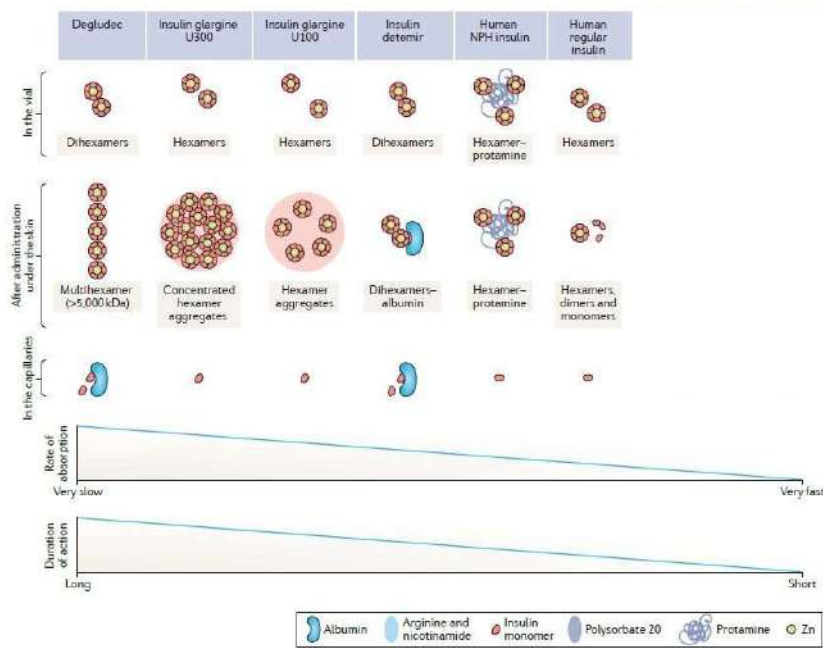


Insulin therapy development: A rich history, a good present, a bright future



BL, baseline; W, weeks since first injection; OR, Odds ratio; OR based on logistic model with treatment as fixed effect, and by adding study as fixed effect for the T1D study pool; cumulative incidences curves were calculated using Kaplan-Meier estimates; Hazard ratio estimated using a Cox proportional hazard model with treatment group and study as fixed effects; Log-rank test stratified by study

Different determinants and duration of action of human and analogue insulins



Pharmacodynamic action profiles of long acting insulins in steady state

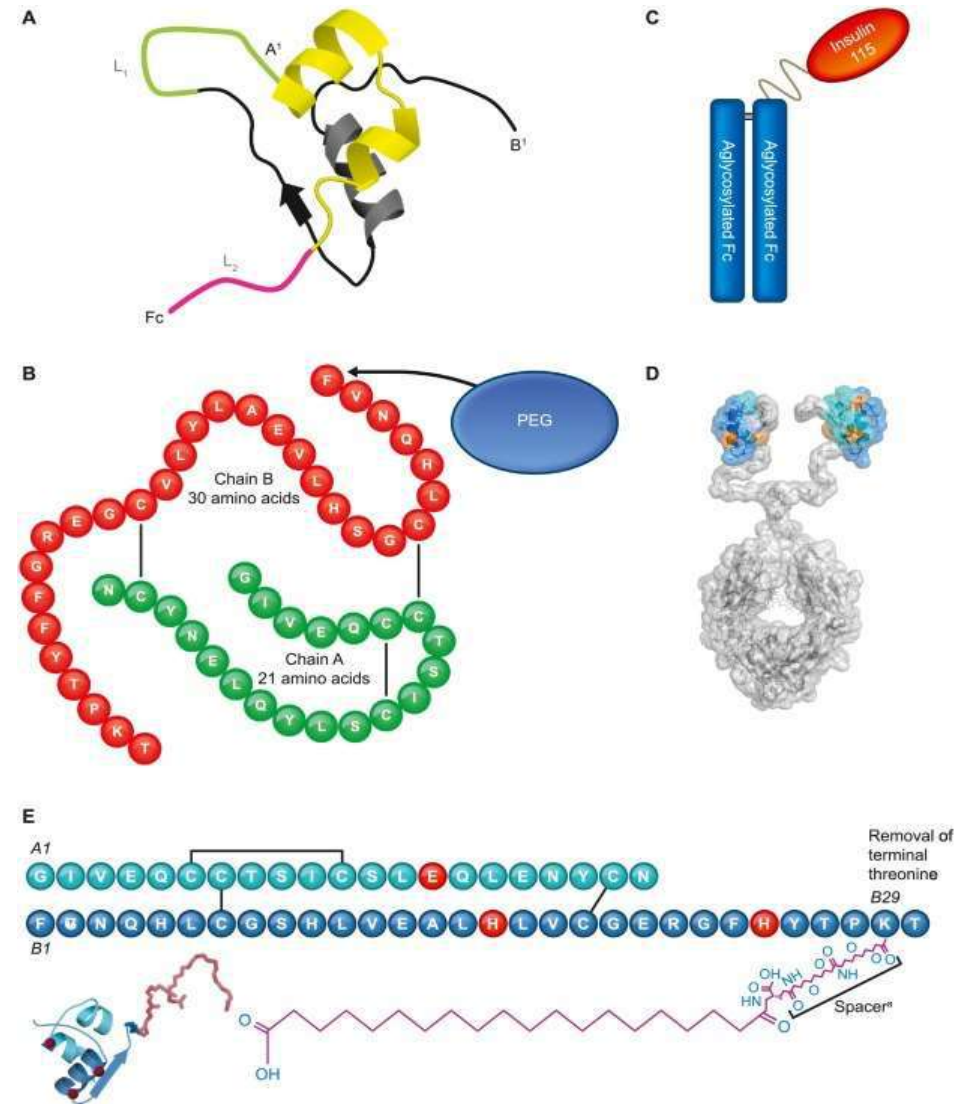
Second-generation basal insulin analogues (degludec - glargine U300) have a longer duration of action, with lower glucose variability and lower risk of hypoglycaemia than other basal insulins

Once weekly basal insulin

is anticipated to be the next important advancement in insulin therapy

- The convenience of a once weekly insulin could result in earlier adoption of insulin therapy
- A once weekly regimen may improve adherence and persistence to insulin therapy and could lead to better real-world patient outcomes
- Daily basal insulins' peak-to-trough ratios are associated with increased within-day glucose variability. It is believed that weekly basal insulins could result in more stable glycemic control and lower risk of hypoglycemia

Kazda C. European Association for the Study of Diabetes, 58th Annual Meeting; 20 September – 23 September, 2022



Once-weekly vs. once-daily insulin therapy

Improved treatment acceptance and adherence

- Improved (or similar) glycaemic control with low hypoglycaemia risk
- Reduced treatment burden
- Easier to overcome clinical inertia

Insulin icodec

Acylated insulin: 20-carbon fatty diacid sidechain

High albumin binding

Reduced enzymatic degradation

Reduced insulin receptor-mediated clearance

Time-action profile ($t_{1/2}$ = approx. 8 days) supports once-weekly dosing in humans

Currently in Phase 3 Trials

Basal Insulin Fc Efsitora

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

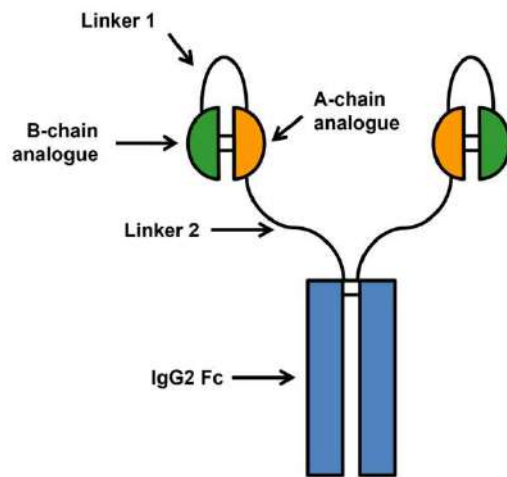
Homo-dimer

Reduced insulin receptor potency with full agonism

Time-action profile ($t_{1/2}$ = approx. 17 days) supports once-weekly dosing in humans

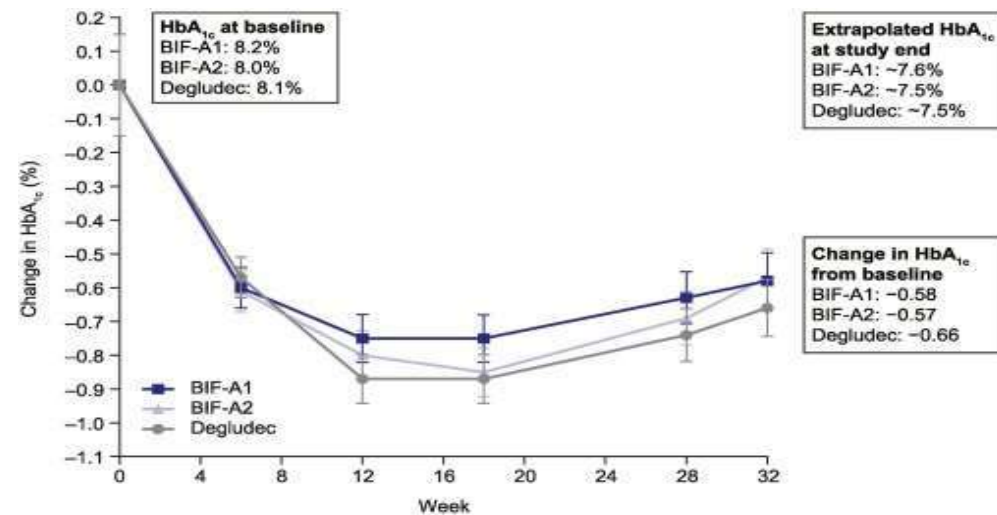
Currently in Phase 2 Trials

Weekly basal insulin Fc (insulin efsitora alfa BIF) is an insulin receptor agonist that combines a novel single-chain variant of insulin with a human immunoglobulin G2 (IgG2) Fc domain

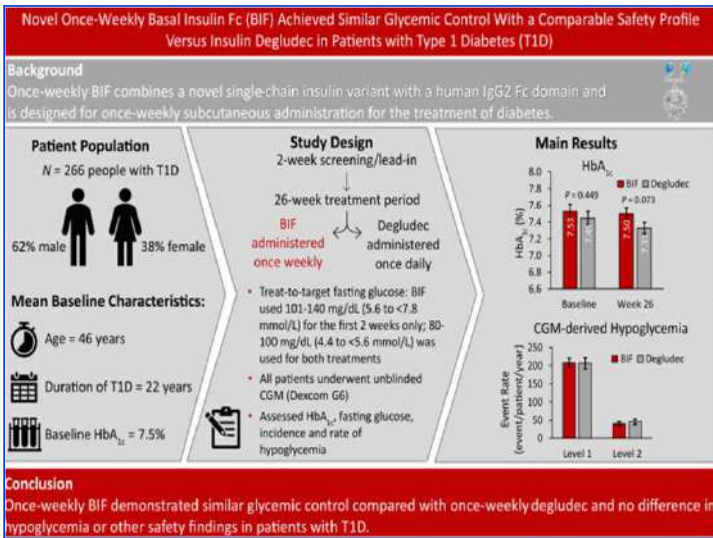


Attributes

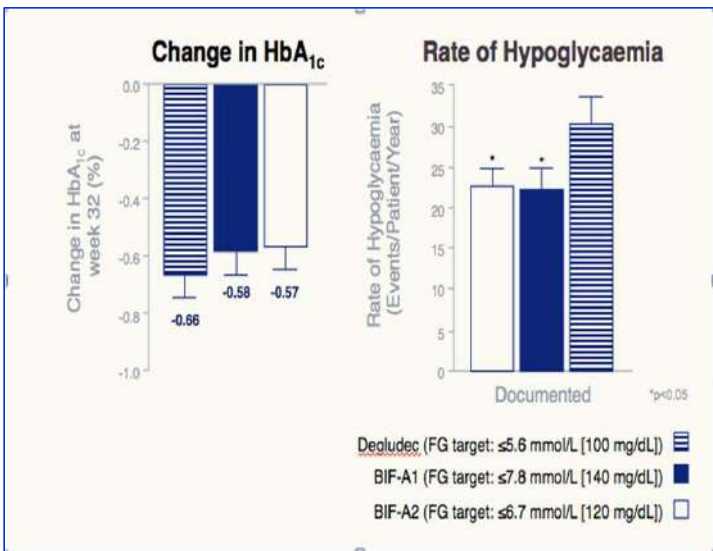
- Selective insulin receptor agonist
 - Mean half life: 17 days
 - Weekly peak-to-trough ratio: 1.14
 - Reduced affinity for the insulin receptor, resulting in low receptor-mediated clearance
 - Large molecule likely with reduced renal clearance
 - Neonatal Fc receptor (FcRn) binding prolongs efsitora activity



Bue-Valleskey J et al. American Diabetes Association - 82nd Annual Scientific Sessions; New Orleans, LA, USA; 3 – 7 June 2022



Novel Once-Weekly Basal Insulin Fc Achieved Similar Glycemic Control With a Safety Profile Comparable to Insulin Degludec in Patients With Type 1 Diabetes
Christof M Kazda et al.
Diabetes Care. 2023.

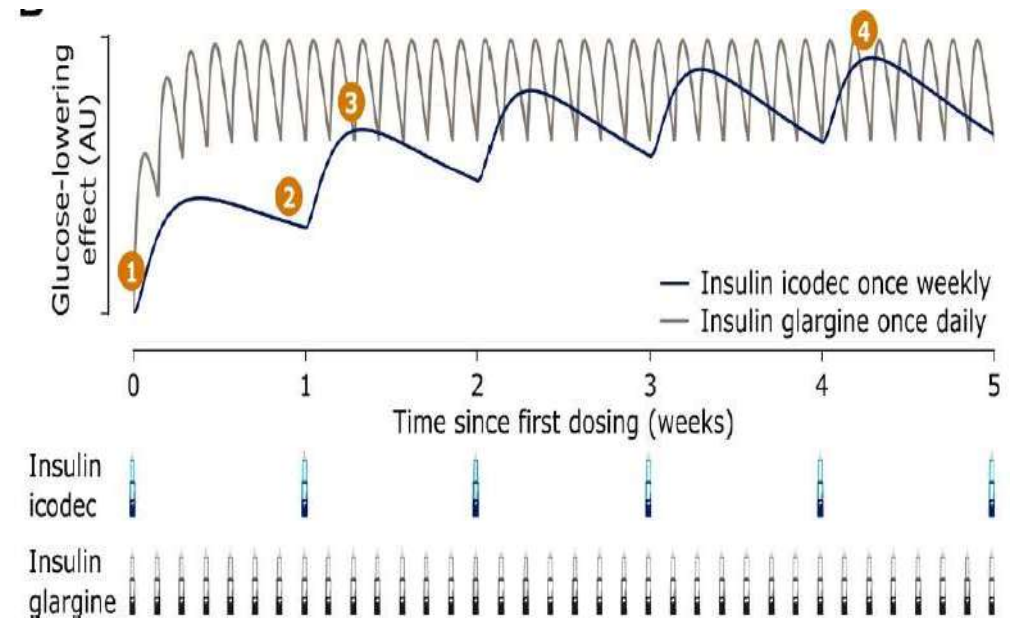
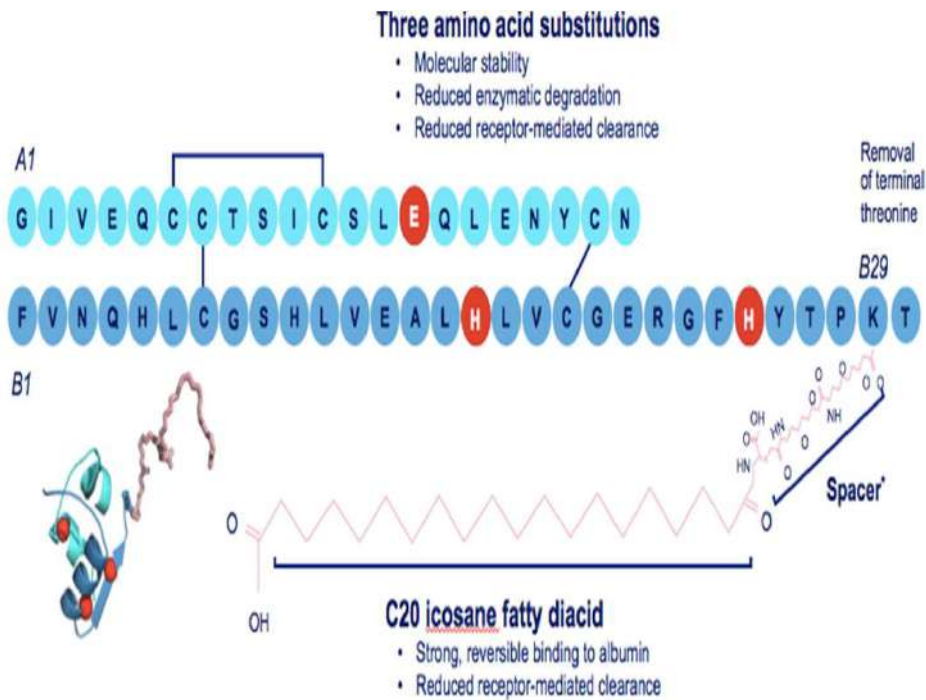


Safety and efficacy of once-weekly basal insulin Fc in people with type 2 diabetes previously treated with basal insulin: a multicentre, open-label, randomised, phase 2 study

Juan Frias

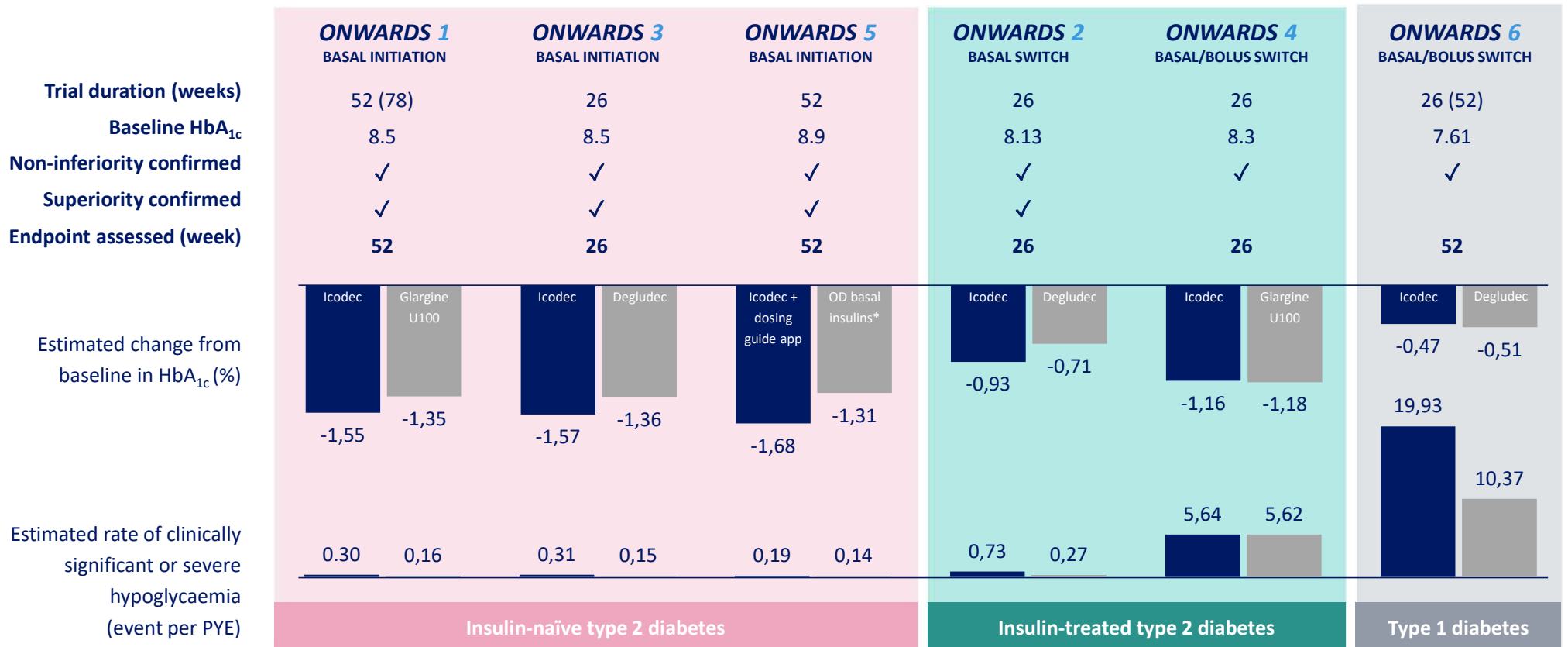
Journal of the Endocrine Society, Volume 5, Issue Supplement_1, April-May 2021

Insulin icodec



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

ONWARDS programme: topline results



- *insulin degludec or insulin glargine U100/U300. Clinically significant hypoglycaemia (level 2): blood glucose <3.0 mmol/l (<54 mg/dl) confirmed by blood glucose meter. Severe hypoglycaemia (level 3): blood glucose <2.8 mmol/l (<50 mg/dl) confirmed by blood glucose meter.



Titration algorithm

Icodec in insulin-naïve T2D

	Pre-breakfast SMBG	Glargine U100 dose adjustment	Icodec dose adjustment
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.

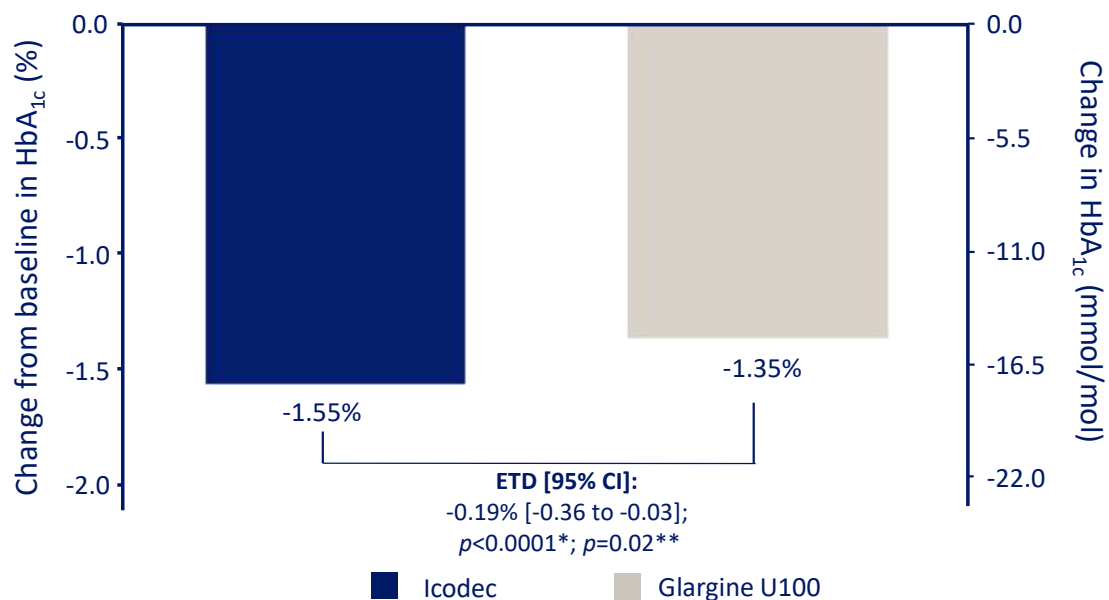


Onward 1

Change in HbA_{1c} and safety summary

Icodec in insulin-naïve T2D - main phase (Baseline to week 52)

Baseline HbA_{1c}: 8.5%



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

Icodec	0.30
Glargine U100	0.16

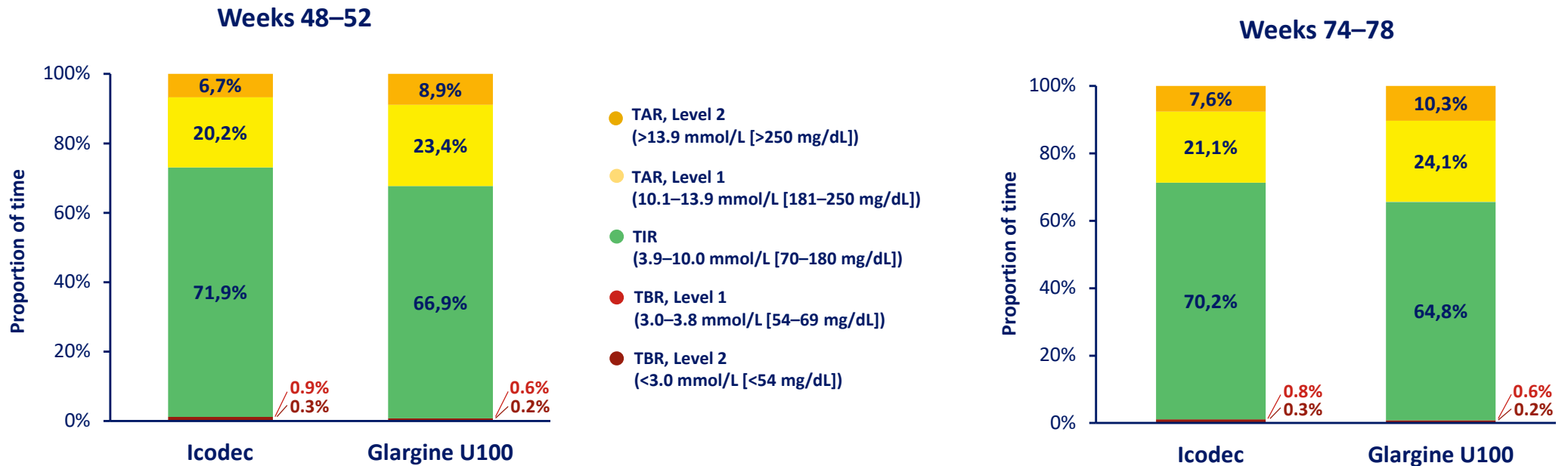
No statistical difference in estimated rates of clinically significant or severe hypoglycaemia

The trial demonstrated non-inferiority and superiority in HbA_{1c} change from baseline to week 52 with insulin icodec compared to insulin glargine U100



Onward 1 CGM parameters during weeks 48 to 52 and weeks 74 to 78

Icodec in insulin-naïve T2D



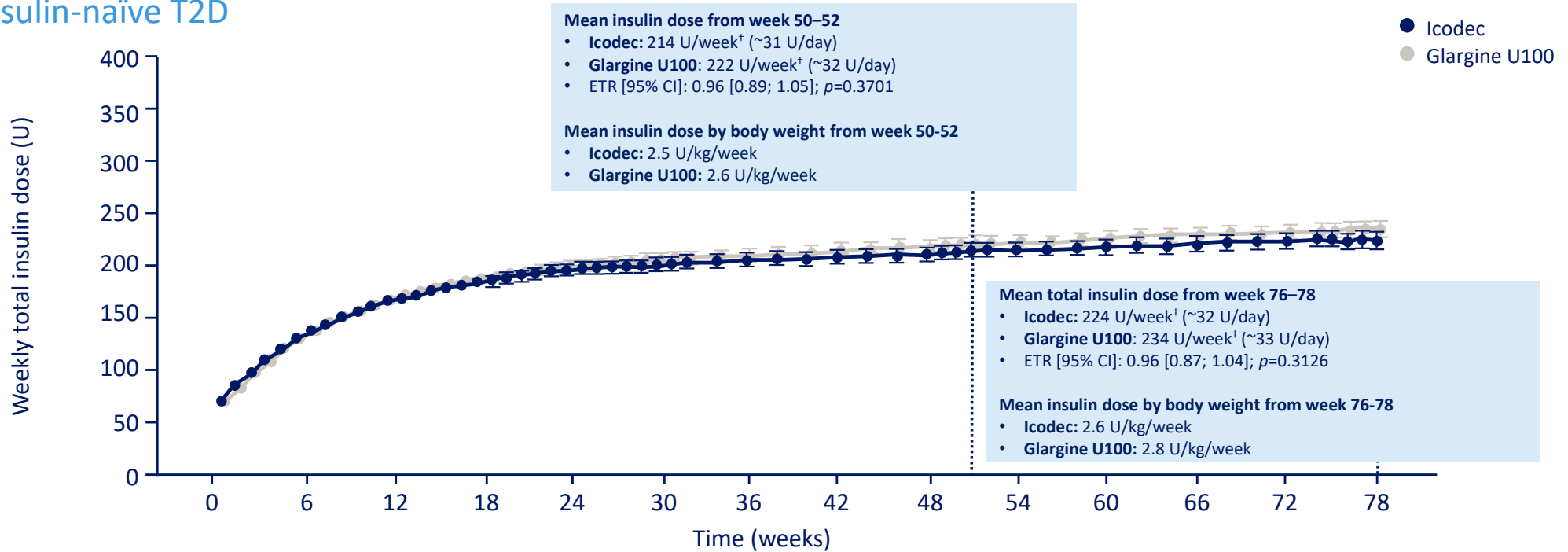
Statistically significant difference in favour of icodec vs glargine U100 in TIR 3.9–10.0 mmol/L (70–180 mg/dL) during weeks 48 to 52 and 74 to 78

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



Weekly insulin dose change over time

Icodec in insulin-naïve T2D



No statistically significant difference in mean weekly basal insulin dose



Onward 1

Icodec in insulin-naïve T2D versus Glargine 100

Significant reductions in HbA_{1c} from 8.5% to 6.9% after 52 weeks

Sustained reductions in HbA_{1c} throughout 78 weeks

Statistically significantly more TIR_{3.9-10.0 mmol/L} (70–180 mg/dL) with icodec compared to glargine U100 during weeks 48–52 and weeks 74–78

Statistically significantly more participants achieved HbA_{1c} <7.0% without clinically significant or severe hypoglycaemia after 52 and 78 weeks

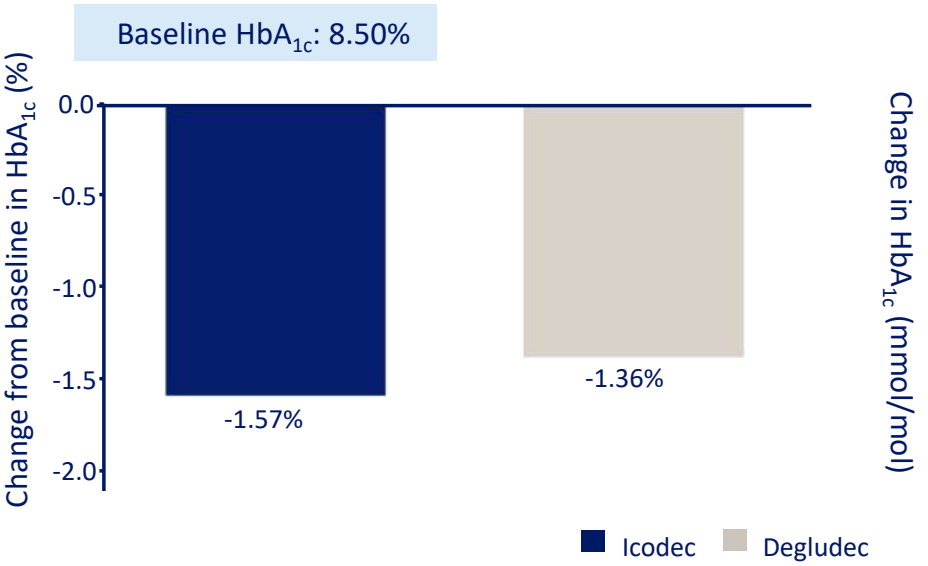
No statistically significant difference in overall observed rates of combined clinically significant or severe hypoglycaemia from week 0 to 52

When including the extension phase of up to 83 weeks, overall observed rates of combined clinically significant or severe hypoglycaemia remained less than 1 event per PYE for both groups, with a statistically significant difference in favour of glargine U100 vs icodec



Onward 3

Icodec in insulin-naïve T2D compared with once-daily degludec



Greater HbA_{1c} reduction from baseline to week 26

Higher rates of combined clinically significant hypoglycaemia in the context of overall low rates (<1 event per PYE in both groups)

No severe hypoglycaemic episodes were experienced by people treated with icodec

More participants achieving HbA_{1c} target < 7.0% without combined clinically significant or severe hypoglycaemia

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

Icodec	0.31
Degludec	0.15

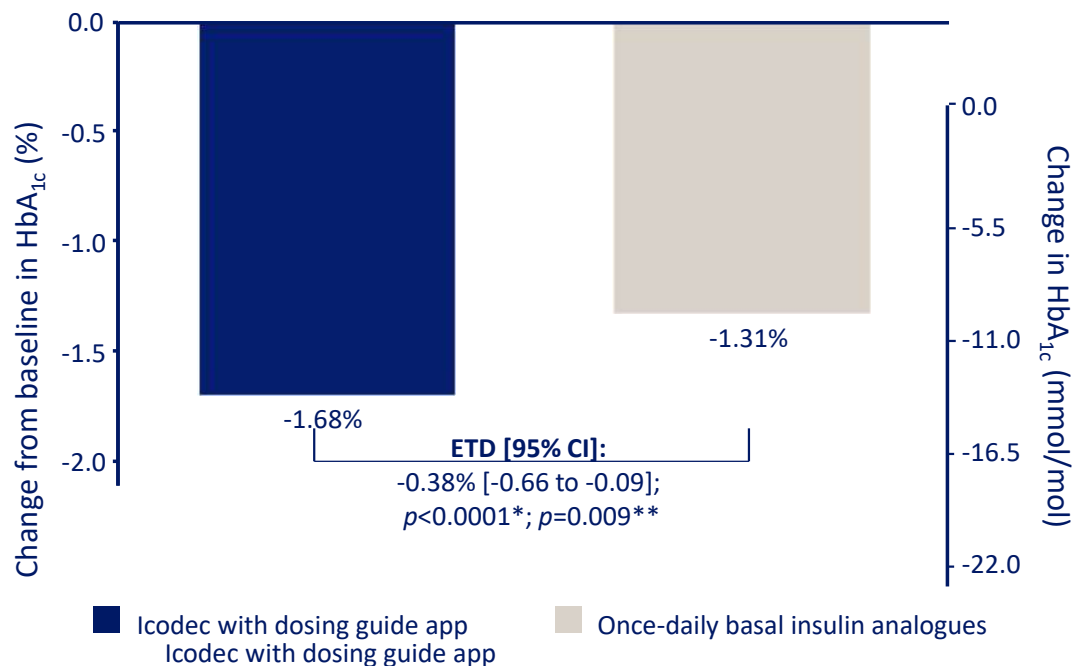
Clinically significant hypoglycaemia (level 2): blood glucose <3.0 mmol/L (<54 mg/dL) confirmed by blood glucose meter. Severe hypoglycaemia (level 3): hypoglycaemia with severe cognitive impairment requiring external assistance for recovery. PYE, patient-year of exposure.
 1. Lingvay I et al. *JAMA*. 2023;10.1001/jama.2023.11313.



Onward 5

Icodec in insulin-naïve T2D, in an RCT with real-world

Baseline HbA_{1c}: 8.9%



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

Icodec with dosing guide app	0.19
Once-daily basal insulin analogues*	0.14

Greater HbA_{1c} reduction from baseline to week 26 and 52

Significant improvement from baseline in DTSQ total treatment satisfaction score and significantly higher TRIM-D compliance domain score at week 52

Titration to a higher mean weekly insulin dose

Higher rates of combined clinically significant hypoglycaemia in the context of overall low rates
No severe hypoglycaemic episodes were experienced by people treated with icodec

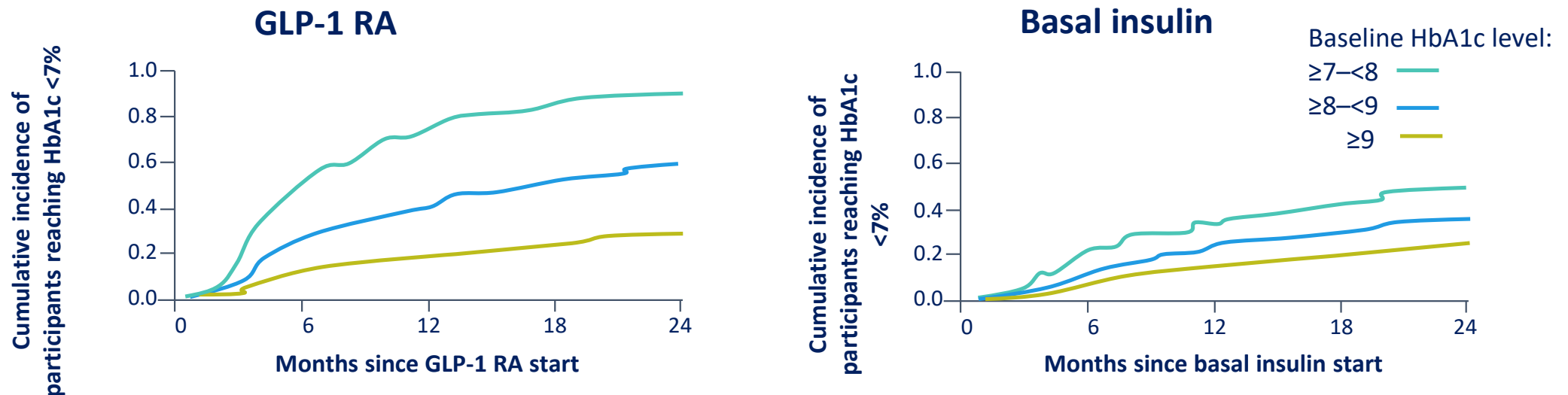
More participants achieving HbA_{1c} target < 7.0% without combined clinically significant or severe hypoglycaemia

Basal weekly insulins: the way of the future!

- Practical new insulin **titration strategies** will need to be developed.
- **Rapid glucose lowering is not expected** with the initial doses because steady state is likely to take approximately 3–4 weeks of dosing.
- **Frequent adjustments to basal insulin levels may not be possible**, and loading doses may be necessary when initiating once-weekly basal insulins, even in insulin-naive patients who have inadequate glycemic control with multiple glucose-lowering agents.
- **Longer-lasting hypoglycemia** may be a common theoretical concern among some clinicians. However, evidence to date has been reassuring, indicating that the risk of level 2 or 3 hypoglycemic events with once-weekly insulin is relatively low and not greater than that associated with once-daily basal insulin

This novel once-weekly formulation has the potential to be a true game changer and will represent one of the great strides in the development of insulin therapies

The Probability of Achieving Sufficient Glycemic Control with a Single Injectable is Low

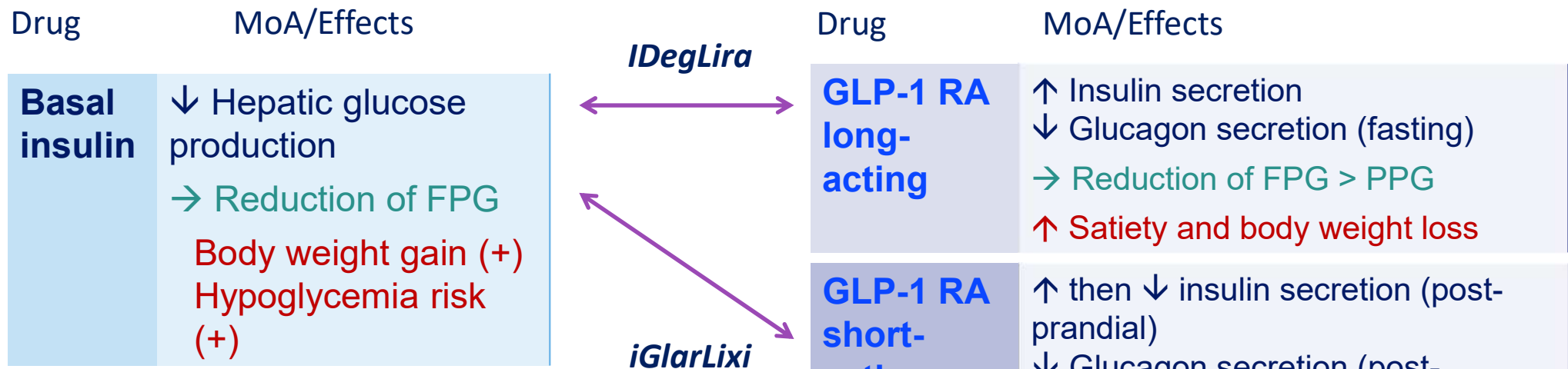


- For individuals with **HbA1c ≥9%**, the probability of achieving glycemic control with one injectable agent is low
- In this population, the probability of achieving glycemic control was **<20% within 1 year** and **<30% within 2 years** in people treated with GLP-1 RA or basal insulin

Real-world retrospective study using **UK CPRD data** to evaluate glycemic control with GLP-1 RA (n=5583) or basal insulin (n=5606) in T2D. Percentages presented represent the estimated cumulative probability of reaching HbA1c <7% within 1 and 2 years post-index date based on Kaplan–Meier curve. CPRD, Clinical Practice Research Datalink.

Insulin and GLP-1 RA in T2D:

The Complementary Modes of Action Provide a Rationale for Fixed-ratio Combination



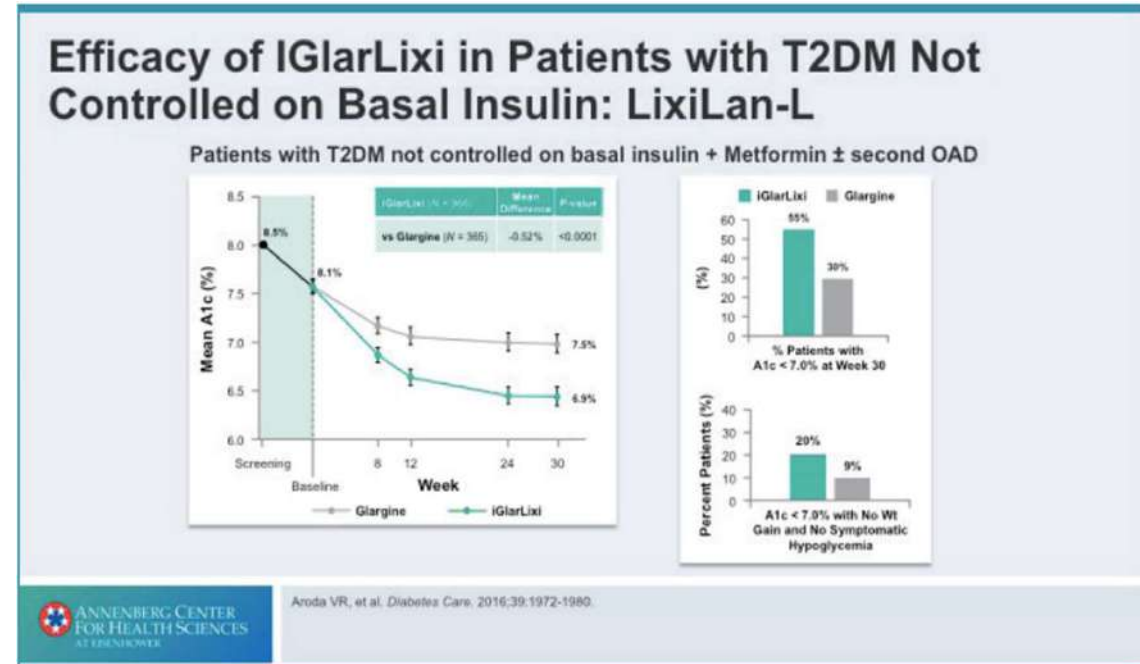
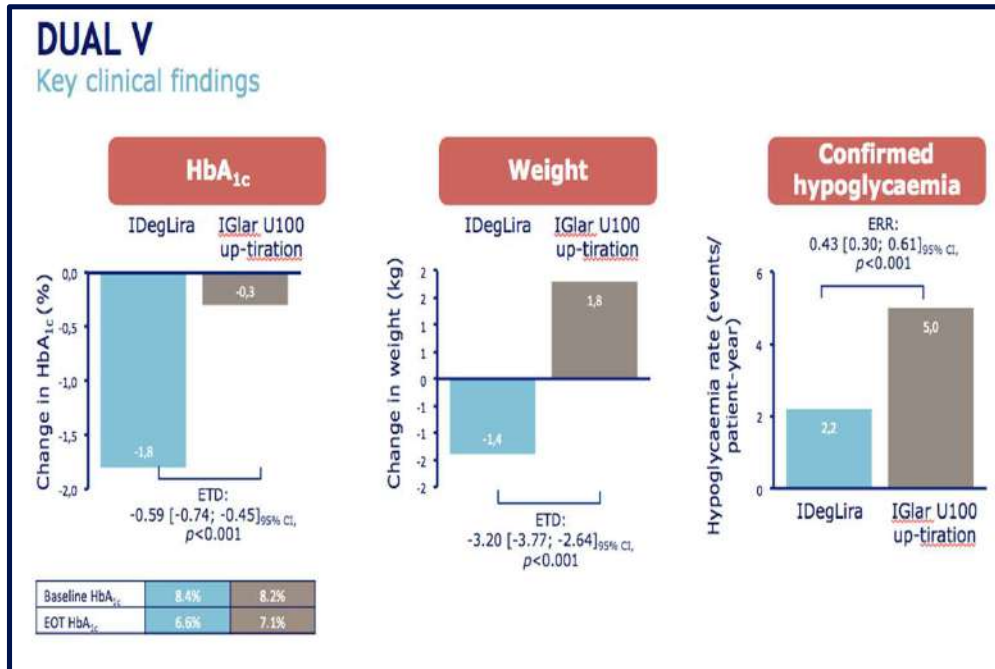
iGlarLixi

- Reduce excess body weight
- Reduce CV outcomes, mortality
- Prevent heart failure outcomes
- Prevent CKD progression
- Ameliorate NAFLD/NASH
- Ameliorate cognitive impairment

adapted from **Giorgino F, et al., Diabetes Res Clin Pract. 2020 Sep 28;170:108478.**

IdegLira

IGlarLixi





Management of hyperglycaemia 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^{1,2} · Vanita R. Aroda² · Billy S. Collins³ · Robert A. Gabbay⁴ · Jennifer Green⁵ ·
Nisa M. Maruthi⁷ · Sylvia E. Rosas⁸ · Stefano Del Prato⁹ · Chantal Mathieu¹⁰ · Gaius M. Ingrone^{11,12,13} ·
Peter Rossing^{14,15} · Tsvetelina Tankova¹⁶ · Apostolos Tsapas^{17,18} · John B. Buse¹⁹

Received: 2 August 2022 / Accepted: 18 August 2022 / Published online: 24 September 2022
© American Diabetes Association and the European Association for the Study of Diabetes 2022

Combination glucagon-like peptide-1/insulin therapy Two fixed-ratio combinations of GLP-1 RA with basal insulin analogues are available: insulin degludec plus liraglutide (IDegLira) and insulin glargine plus lixisenatide (iGlarLixi).

The combination of basal insulin with GLP-1 RA results in greater glycaemic lowering efficacy than the mono-components, with less weight gain and lower rates of hypoglycaemia than with intensified insulin regimens, and better gastrointestinal tolerability than with GLP-1 RA alone [214, 215]. In studies of people with type 2 diabetes inadequately controlled on basal insulin or GLP-1 RA, switching to a fixed-ratio combination of basal insulin and GLP-1 RA demonstrated significant improvements in blood glucose levels and achievement of glycaemic goals with fewer hypoglycaemic events than with basal insulin alone [216–220].

Place of insulin in type 2 diabetes

analogue-based combinations have the advantage of resulting in fewer hypoglycaemic events and weight gain than are typically observed with human premixed insulin [330].

Finally, it needs to be re-emphasised that, in all insulin-treated people with type 2 diabetes, agents associated with

cardiorenal protection or weight reduction should be kept in the treatment regimen whenever possible [331]. The combination of a basal insulin analogue and GLP-1 RA in one injection may be a simple way to reduce the burden and complexity of treatment [332].

The option of weekly therapies

Weekly
insulin



IcoSema

Weekly
GLP-1 RA

- Once weekly administration
- Independent of meals
- Single pen
- Simple titration compared to basal-bolus insulin therapy

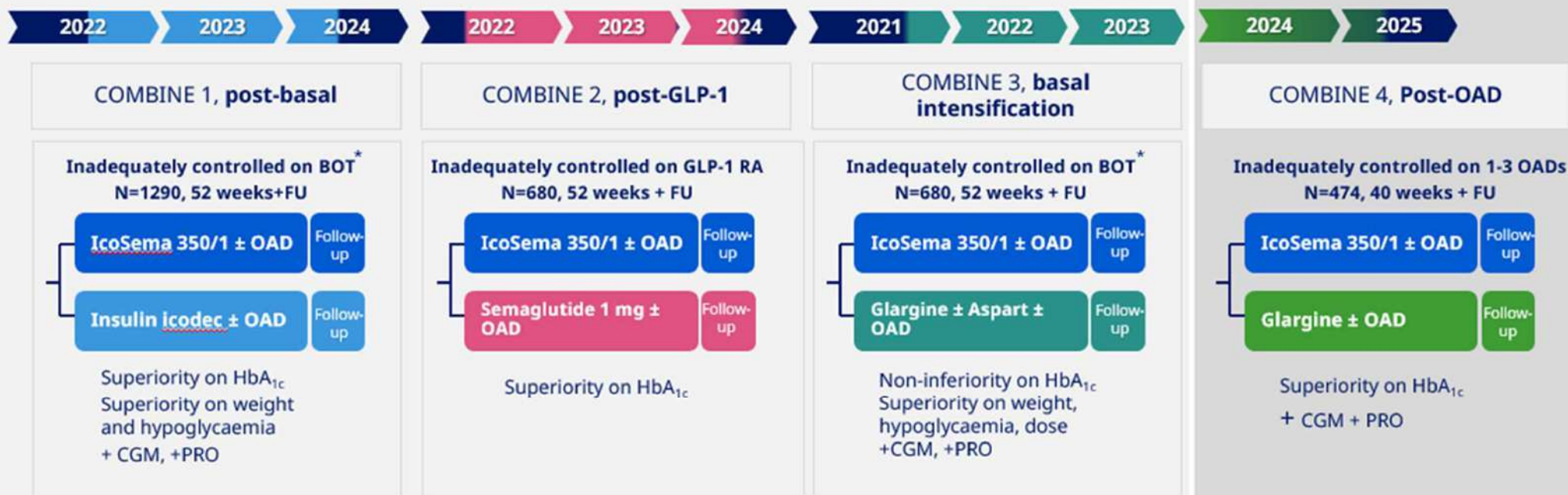
- Better adherence
- Superior HbA_{1c} reduction compared to the mono- components
- Non-inferior HbA_{1c} reduction compared to basal-bolus insulin therapy*
- Weight benefit compared to basal insulin and basal-bolus insulin therapy

- Less risk of level 2 and 3 hypoglycaemia compared to basal and basal-bolus insulin therapy

The COMBINE programme

Phase 3a

Phase 3b

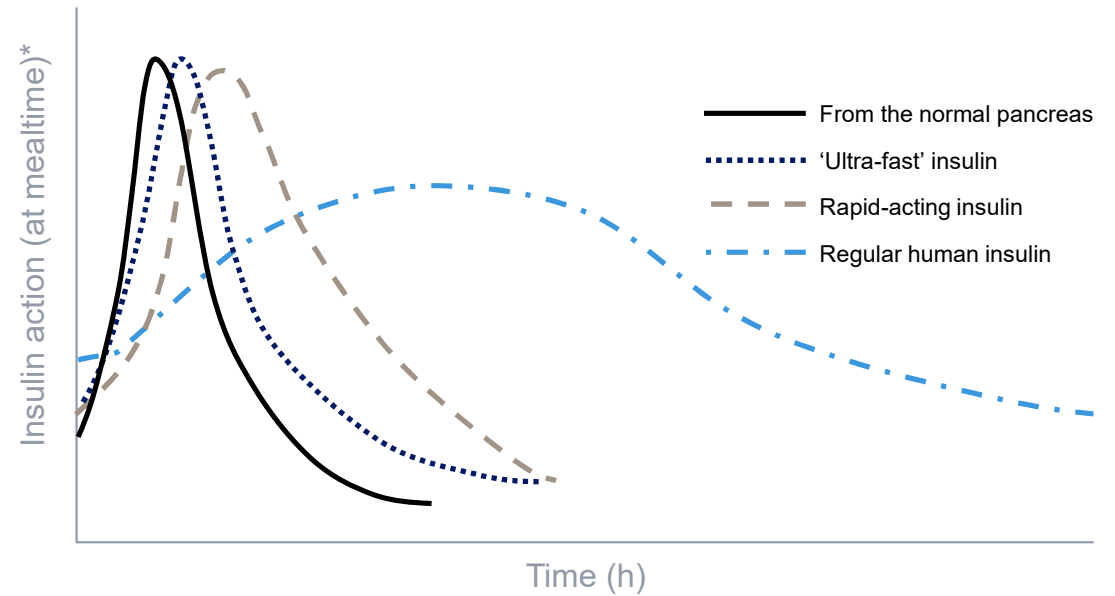


*Basal only therapy, 20-80 units/day of basal insulin at inclusion, expected baseline mean 30-40U/day
Total N randomized accounted for 1.7% not completing randomized treatment for all three trials
BOT, basal only therapy; FU, follow up; GLP-1 RA, glucagon like peptide -1 receptor agonist; N, number of subjects; OAD, oral anti-diabetic drugs

Insuline ultrarapide

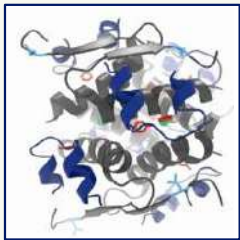
- più efficace riduzione del picco glicemico post-prandiale
- maggiore riduzione dei livelli di HbA1c
- migliore inibizione della produzione epatica di glucosio
- ridotta incidenza di ipoglicemie
- maggiore efficacia in gruppi selezionati di pazienti (bambini, anziani, donne in gravidanza)
- maggiore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

- Better approach physiological insulin secretion in T1D
- Replace early insulin secretion in T2D
- Have a better profile for pump therapy



Ultra fast-acting insulins

Fast-acting insulin aspart¹

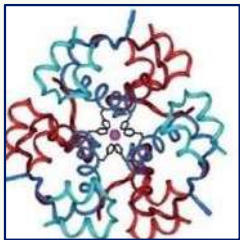


Insulin aspart

Niacinamide: absorption modifier

Arginine: increased stability

Ultra Rapid Lispro (URLi, insulin lispro-aabc)²



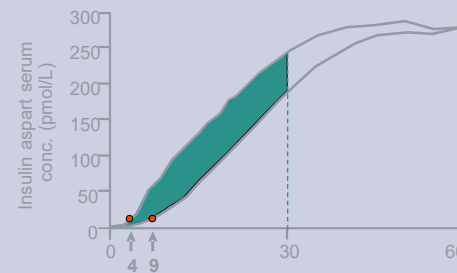
Insulin lispro

Treprostinil: local vasodilator

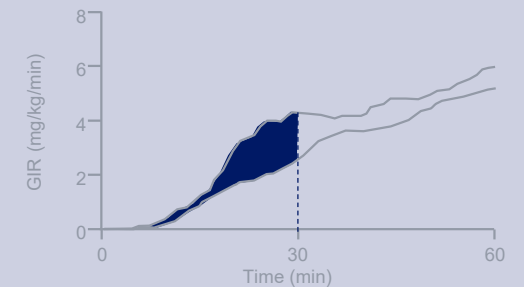
Citrate: increases vascular permeability

Compared to **insulin aspart**, faster aspart has:¹

2x faster onset

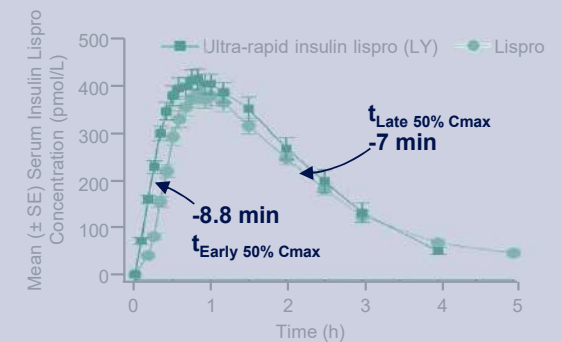


2x higher exposure in first 30 min



Compared to **insulin lispro**, ultra-rapid lispro has:²

- **2x higher exposure in first 30 min**



1. Heise et al. *Clin Pharmacokinet* 2017;56:551–9; 2. Kazda et al. *Diabetes* 2017;66 (Suppl. 1):A247–8.

Missed and Mistimed Insulin Doses in People with Diabetes: A Systematic Literature Review

Susan Robinson, PhD,¹ Rachel S. Newson, PhD,^{2,1} Birong Liao, PhD,³ Tessa Kennedy-Martin, MSc,¹ and Tadej Battelino, MD, PhD⁴

- From 19% to 43% of patients with Type 1 diabetes missed ≥ 1 bolus dose/week;
- From 16% to 23% of patients with Type 2 diabetes missed ≥ 1 basal or bolus dose/week;

ORIGINAL RESEARCH

Timing of Insulin Injections, Adherence, and Glycemic Control in a Multinational Sample of People with Type 2 Diabetes: A Cross-Sectional Analysis

Nicolaas C. Schaper · Annie Nikolajsen · Anna Sandberg · Sarah Buchs · Mette Bogelund

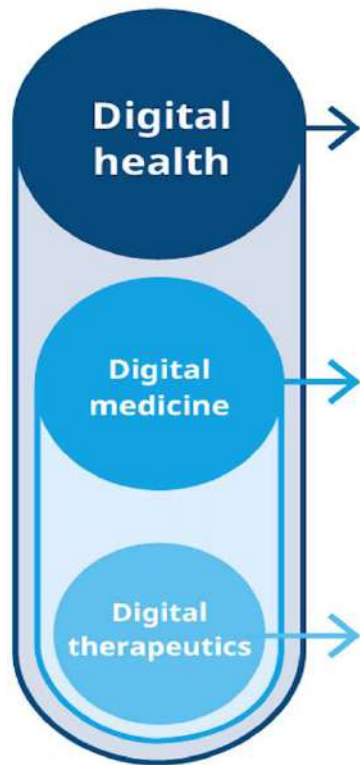
Conclusions: Approximately 24% of respondents never comply with guidelines for insulin dose timing, with higher risk of non-adherence and increased participation in diabetes care programs. Respondents dosing insulin post-meal are more likely to have poor glycemic control ($HbA_{1c} \geq 9\%$, 74.9 mmol/mol). Given that many respondents had high HbA_{1c} and were non-adherent, a treatment which satisfies patient preference for bolus insulin with flexible dose timing could be considered.

Livelli medi dell'HbA1c (ultimo valore)



	% Media \pm ds
Solo dieta	6,2 \pm 0,6
Secretagoghi	7,4 \pm 1,1
Iporali / GLP1-RA	6,8 \pm 1,0
Insulina + Iporali / GLP1-RA	7,7 \pm 1,5
Solo insulina	7,9 \pm 1,4

Sfide della terapia insulinica MDI tradizionale: l'aiuto della tecnologia



- Omissione e ritardo della dose
- Registrazione ed analisi dei dati
- Calcolo della dose
- Educazione del paziente
- Cinetica dell'insulina
- Traccia della dose e dell'ora di somministrazione
- Integrazione cinetica con cibo ed attività fisica
- Stabilità dell'insulina
- Paura dell'ipoglicemia
- Difficoltà a calcolare la IOB

La smart Pen



Benefits of smart insulin pens:

- Improved patient adherence to treatment^{2,3}
- Improved outcomes, e.g. time-in-range³
- Improved injection behaviour²
- Lower cost than an insulin pump¹
- No logs, forgotten doses or accidental insulin stacking^{1,2}
- Access to reports that help recognised patterns and optimise therapy^{1,2}



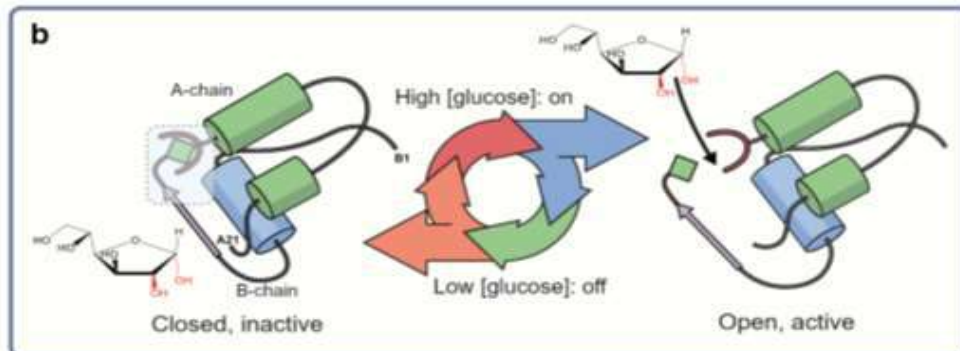
Nel futuro???

Uniche info disponibili.
Fase di sperimentazione
non ancora iniziata

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

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

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



- Disruptive approach
- Targets the core of diabetes care: normalization
- NO fear of hypoglycemia
- Replace basal-bolus and basal-only therapy as well as replace pump treatment
- Relieve type 1 and type 2 patients from multiple daily injections, intense self-monitoring, carb counting and frequent dose adjustments.

While the first century of insulin therapy focused on supply, purification, and improved pharmacokinetics, the future will likely focus on development of more user-friendly and physiologic formulations that will minimize the risk of hypoglycemia, weight gain and other insulin therapy-associated complications.

