Le Insuline Settimanali

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Programma Assistenza Diabetologica
AUSL della Romagna

Paolo Di Bartolo Disclosures

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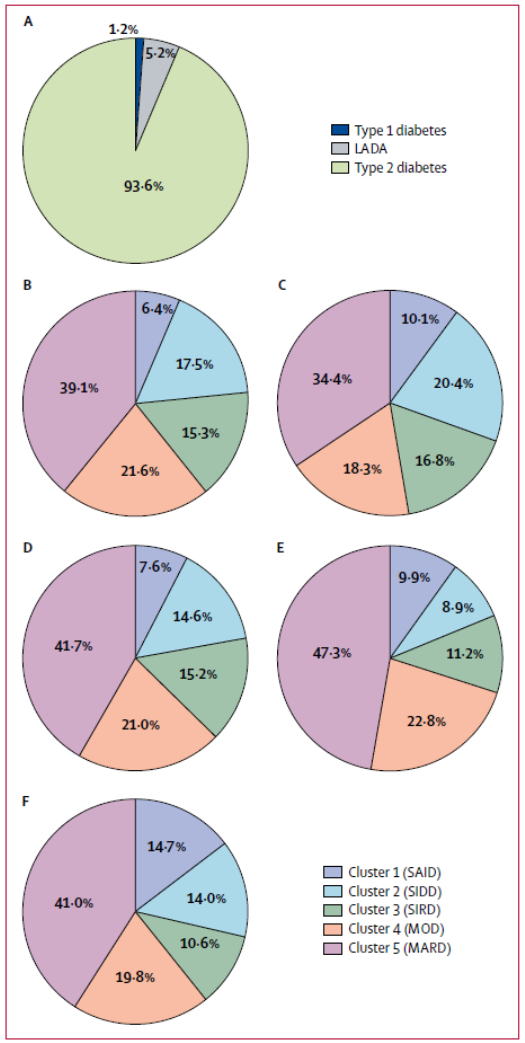
Ai sensi dell'art. 3.3 del Regolamento applicativo dell'Accordo Stato-Regioni 05.11.2009, dichiaro che negli ultimi due anni ho avuto i seguenti rapporti anche di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables

Emma Ahlqvist, Petter Storm, Annemari Käräjämäki, Mats Martinell*, Mozhgan Dorkhan, Annelie Carlsson, Petter Vikman, Rashmi B Prasad, Dina Mansour Aly, Peter Almgren, Ylva Wessman, Nael Shaat, Peter Spégel, Hindrik Mulder, Eero Lindholm, Olle Melander, Ola Hansson, Ulf Malmqvist, Åke Lernmark, Kaj Lahti, Tom Forsén, Tiinamaija Tuomi, Anders H Rosengren, Leif Groop*

Lancet Diabetes Endocrinol 2018; 6: 361–69



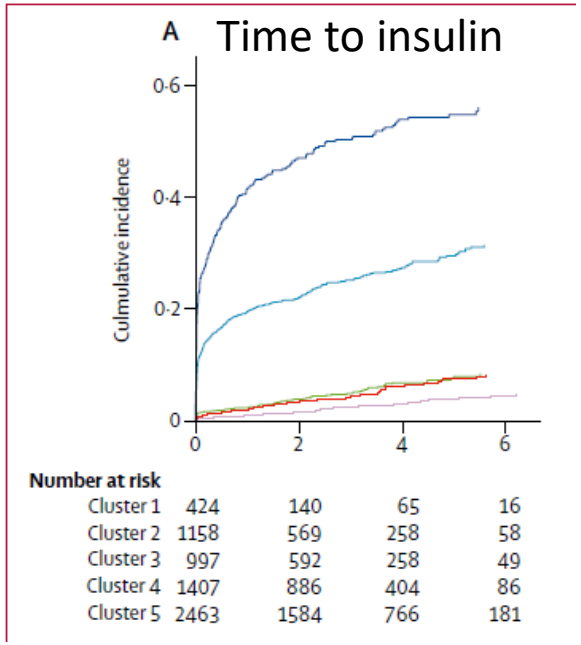


Figure 1: **Patient distribution according to method of classification**
(A) Distribution of ANDIS patients (n=8980) according to traditional classification. (B) Distribution of ANDIS patients (n=8980) according to k-means clustering. (C) Distribution of patients in the Scania Diabetes Registry (n=1466) according to k-means clustering. (D) Distribution of patients in the All New Diabetics in Uppsala cohort (n=844) according to k-means clustering. (E) Distribution of DIREVA patients with newly diagnosed diabetes (n=878) according to k-means clustering. (F) Distribution of DIREVA patients with longer-term diabetes (n=2607) according to k-means clustering. LADA=latent autoimmune diabetes in adults. SAID=severe autoimmune diabetes. SIDD=severe insulin-deficient diabetes. SIRD=severe insulin-resistant diabetes. MOD=mild obesity-related diabetes. MARD=mild age-related diabetes. ANDIS=All New Diabetics in Scania. DIREVA=Diabetes Registry Vaasa.

Heterogeneity of Diabetes: β-Cells, Phenotypes, and Precision Medicine: Proceedings of an International Symposium of the Canadian Institutes of Health Research's Institute of Nutrition, Metabolism and Diabetes and the U.S. National Institutes of Health's National Institute of Diabetes and Digestive and Kidney Diseases

William T. Cefalu,[1] Dana K. Andersen,[2] Guillermo Arreaza-Rubín,[1] Christopher L. Pin,[3] Sheryl Sato,[1] C. Bruce Verchere,[4–6] Minna Woo,[7–9] and Norman D. Rosenblum,[10–12] on behalf of the symposium planning committee, moderators, and speakers*

Diabetes Volume 71, January 2022

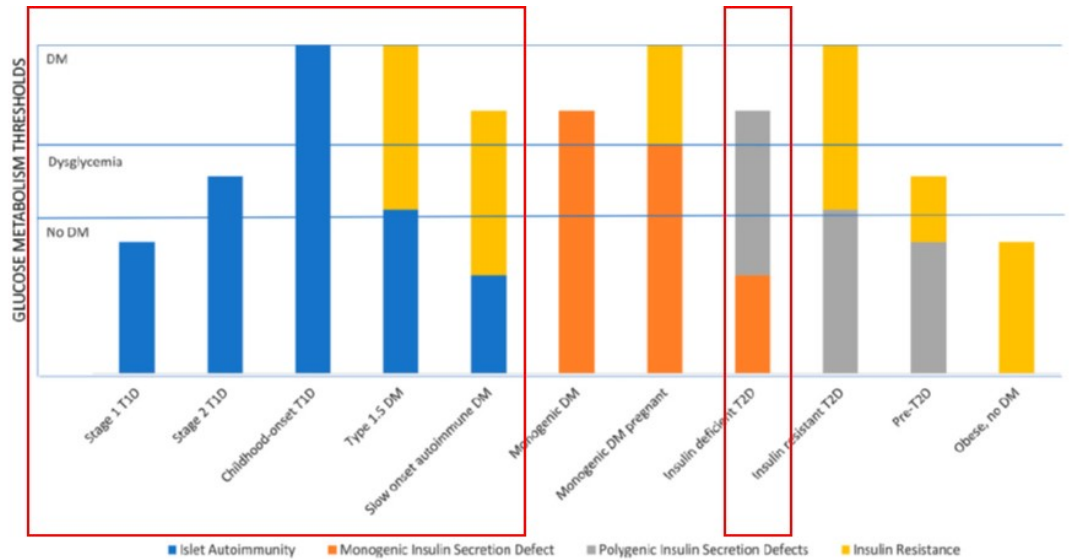


Figure 7—Model of diabetes etiopathogenesis based on the Palette Disease Model (78) and Threshold Hypothesis (79) that explain heterogeneity within diabetes types and overlap between diabetes types. Individuals (represented by bars) may have several diabetogenic mechanisms (represented by different colors) that, in combination, may cause glucose to reach a threshold. DM, diabetes mellitus; T1D, type 1 diabetes; T2D, type 2 diabetes.

Current barriers to initiating insulin therapy in individuals with type 2 diabetes

frontiers | Frontiers in Endocrinology

TYPE Review
PUBLISHED 14 March 2024
DOI 10.3389/fendo.2024.1366368

Alba Galdón Sanz-Pastor[1,2]*, Alicia Justel Enríquez[3], Ana Sánchez Bao[4] and Francisco Javier Ampudia-Blasco[5,6,7,8]*

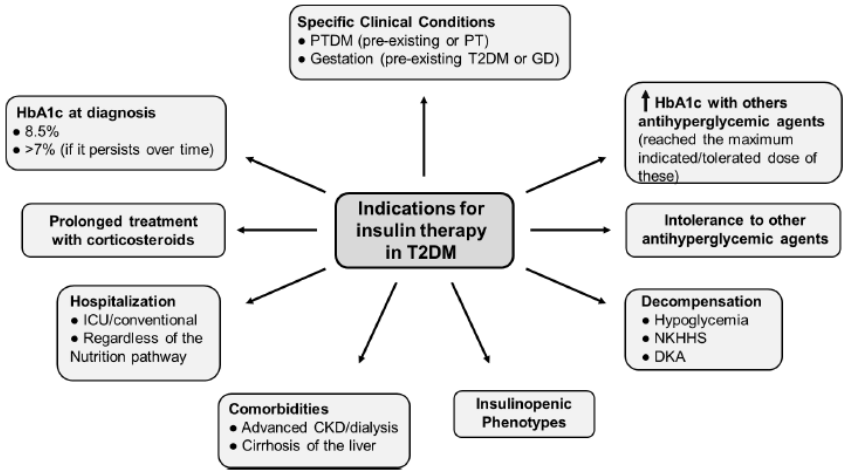


FIGURE 2
People with type 2 diabetes who are candidates for insulin therapy Modified from (9). Situations in which the patient's characteristics or clinical condition, make them candidates for the use of basal insulin are described. CKD, chronic kidney disease; DKA, diabetic ketoacidosis; GD, gestational diabetes; HbA1c, glycosylated hemoglobin; ICU, Intensive Care Unit; NKHHS, nonketotic hyperosmolar hyperglycemic state; PT, post-transplant; PTDM, post-transplant diabetes mellitus; T2DM, type 2 diabetes mellitus.

- **HbA1c alla diagnosi > 10 %**
- **Scompenso glicemico acuto**
- **Crisi Iperglicemiche: DKA, Iperglicemia Iperosmolare**
- **Fallimento o intolleranza altre terapie orali o iniettive non insuliniche**
- **Ospedalizzazioni**
- **Trattamenti prolungati con steroidi**
- **Comorbosità (CKD/dialisi, Cirrosi)**
- **Gravidanze o Diabete in persone sottoposte a trapianto di organo**
- **Fenotipi associati con carente riserva funzionale beta cellulare**

diabetesresearchandclinicalpractice 213 (2024) 111743

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Diabetes Research and Clinical Practice

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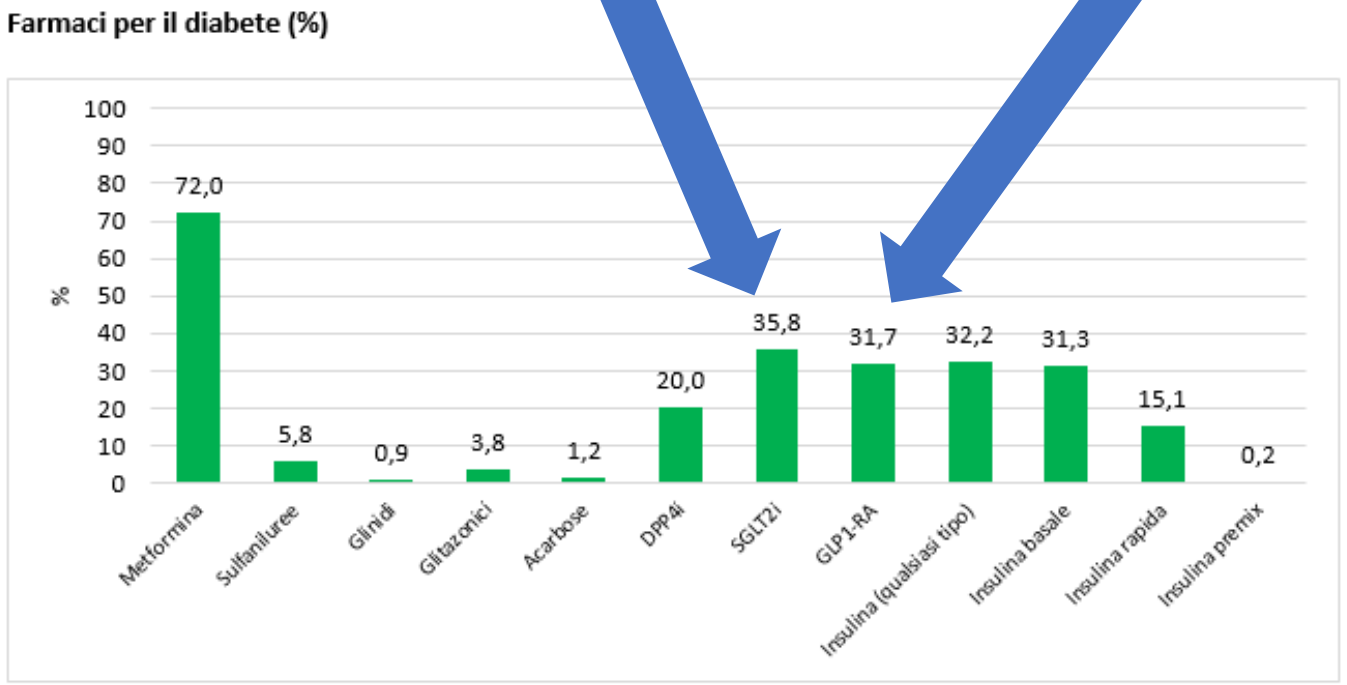
573.164 pazienti
296 Centri

2023 Vs 2022
+ 219 %

2023 Vs 2022
+ 201 %



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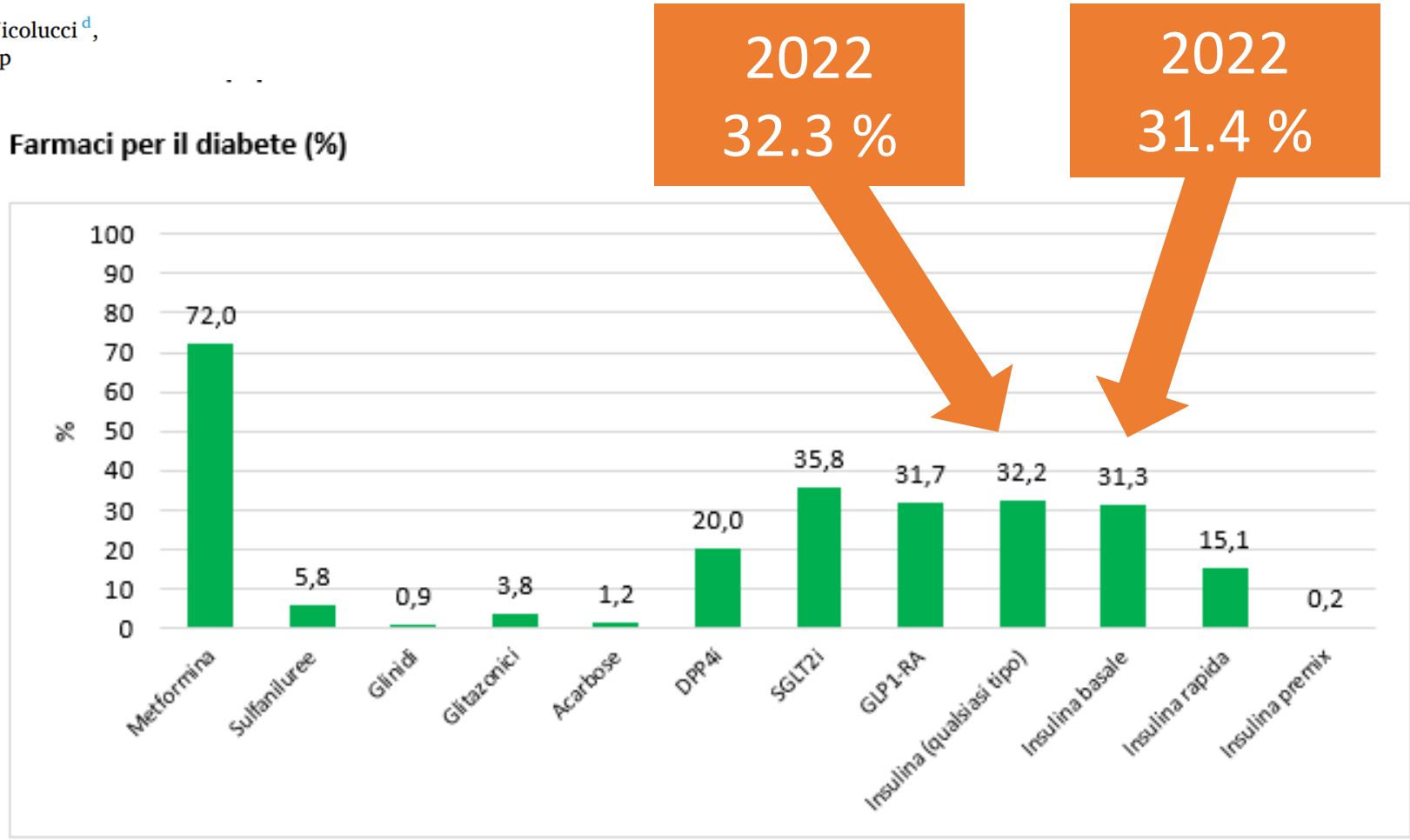
573.164 pazienti
296 Centri

- Insulina 32.2 %
- Insulina Basale 31.3 % (97 %)
- Insulina prandiale 15.1 %



Current barriers to initiating insulin therapy in individuals with type 2 diabetes

Alba Galdón Sanz-Pastor[1,2*], Alicia Justel Enríquez[3], Ana Sánchez Bao[4] and Francisco Javier Ampudia-Blasco[5,6,7,8*]

Barriere correlate ai Pazienti	**Percezione di fallimento Difficoltà nella aderenza**
Barriere correlate a determinanti sociali	Stigma sociale
Barriere correlate al trattamento	Ipoglicemia Incremento del peso Iniezione Necessità di titolare la dose
Barriere correlate ai Clinici/Professionisti della Salute	Scarsa esperienza del team di cura Mancanza di esplicite linee guida

frontiers | Frontiers in Endocrinology

TYPE Review
PUBLISHED 14 March 2024
DOI 10.3389/fendo.2024.1366368

Conditioning factor	Barrier	Strategy
Patient	- Adherence - Perception of failure	- Use of long-acting insulin - Dose recall systems - Diabetes education program
Social environment	- Social rejection	- Community education
Treatment	- Dosage - Hypoglycemia - Method of administration - Weight Gain	- Use of simple adjustment guidelines - Implementation of FGM/CGM systems - Documentation of episodes by the patient - Determination of a greater number of self-monitoring blood glucose. - Implementation of FGM/CGM systems - Education on signs and symptoms - Adjustments in physical exercise - Instruction in the guidelines for dealing with hypoglycemia. - Simple, intuitive devices adapted to different physical limitations. - Instruction in management technique. - Design of specific devices for patients with needle phobia. - Healthy eating education. - Prescription of physical exercise - Choice of type of insulin based on the reported weight evolution.
Professional	- Healthcare team experience - Clinical Guidelines of Scientific Societies	- Instruction and education of entire healthcare team. - Constant review of glycemic control goals - Proper device handling and management technique - Efficacy of insulin as an initial control tool in severe hyperglycemia. - Efficacy in certain diabetes profiles, such as diabetes secondary to the use of corticosteroids.

CGM, Continuous Glucose Monitoring; FGM, Flash Glucose Monitoring.

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Indicatori di appropriatezza

Indicatore	Denominatore	%	Gold standard (25° *percentile*)
Soggetti in sola dieta con HbA1c ≤7,0%	Soggetti in sola dieta (n=15.197)	94,7	100,0
Soggetti in sola dieta nonostante valori di HbA1c >8,0%	Soggetti con valori di HbA1c >8,0% (n=92.376)	0,1	0,0
Soggetti non trattati con insulina nonostante valori di HbA1c ≥9,0%	Soggetti con valori di HbA1c ≥9,0% (n=38.014)	28,5	21,4
Soggetti non trattati con GLP1-RA e/o SGLT2i e/o insulina nonostante valori di HbA1c ≥9,0%	Soggetti con valori di HbA1c ≥9,0% (n=38.014)	8,9	4,5
Soggetti con HbA1c ≥9,0% nonostante il trattamento con insulina	Soggetti trattati con insulina (n=178.632)	15,2	12,6
Soggetti con HbA1c ≥9,0% nonostante il trattamento con GLP1-RA e/o SGLT2i e/o insulina	Soggetti trattati con GLP1-RA e/o SGLT2i e/o insulina (n=308.695)	7,3	5,6
Soggetti con età ≥75 anni e HbA1c <7,0% trattati con secretagoghi e/o insulina	Soggetti con età ≥75 anni e HbA1c <7,0% (n=95.491)	29,0	22,5

Basal weekly insulins: the way of the future!

Julio Rosenstock [a,*], Stefano Del Prato [b]

Why a basal weekly insulin?

- **Poor adherence to daily administration**
- **Inefficient titration methods**
- **Poor treatment persistence, injection frequency is one important contributing factor.**

If a basal insulin could be injected just once weekly, it is reasonable to predict that this would

- **Reduce clinical inertia**
- **Increase treatment adherence, by reducing the total number of annual injections by more than 85%.**
- **Improve patients' quality of life, provided that the risk of hypoglycemia remains low.**

Metabolism Clinical and Experimental 126 (2022) 154924

The ongoing evolution of basal insulin therapy over 100 years and its promise for the future

Ravi Retnakaran[1,2,3] | Bernard Zinman[1,2,3]

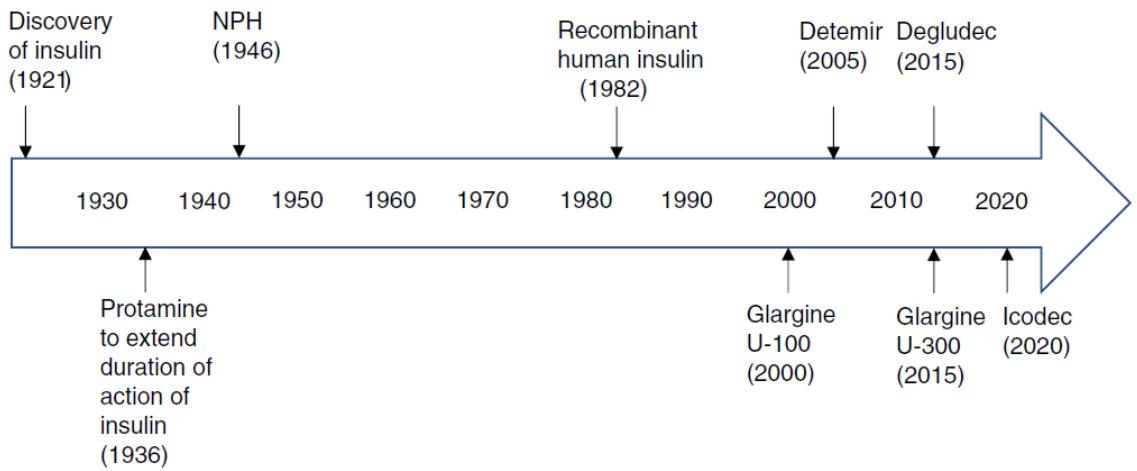


FIGURE 1 Milestones in the evolution of basal insulin formulations

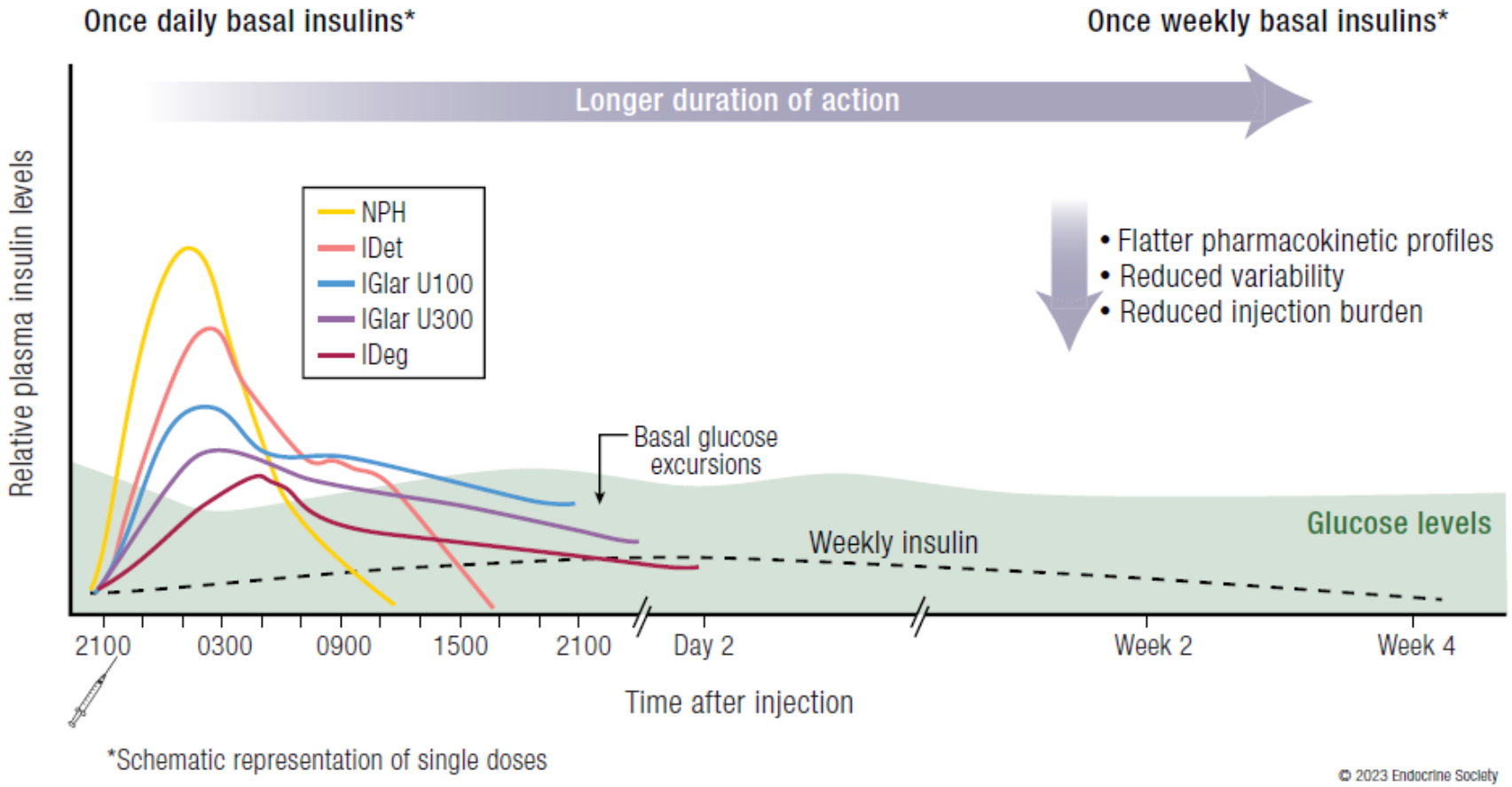
TABLE 1 Mechanisms by which bioengineered modifications of the structure of insulin have prolonged the duration of action of basal insulin analogues

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

Endocrine Reviews, 2024, **00**, 1–35
https://doi.org/10.1210/endrev/bnad037
Advance access publication 16 January 2024
Review

The Basis for Weekly Insulin Therapy: Evolving Evidence With Insulin Icodec and Insulin Efsitora Alfa

Julio Rosenstock,[1,*] Rattan Juneja,[2] John M. Beals,[2] Julie S. Moyers,[2] Liza Ilag,[2] and Rory J. McCrimmon[3]



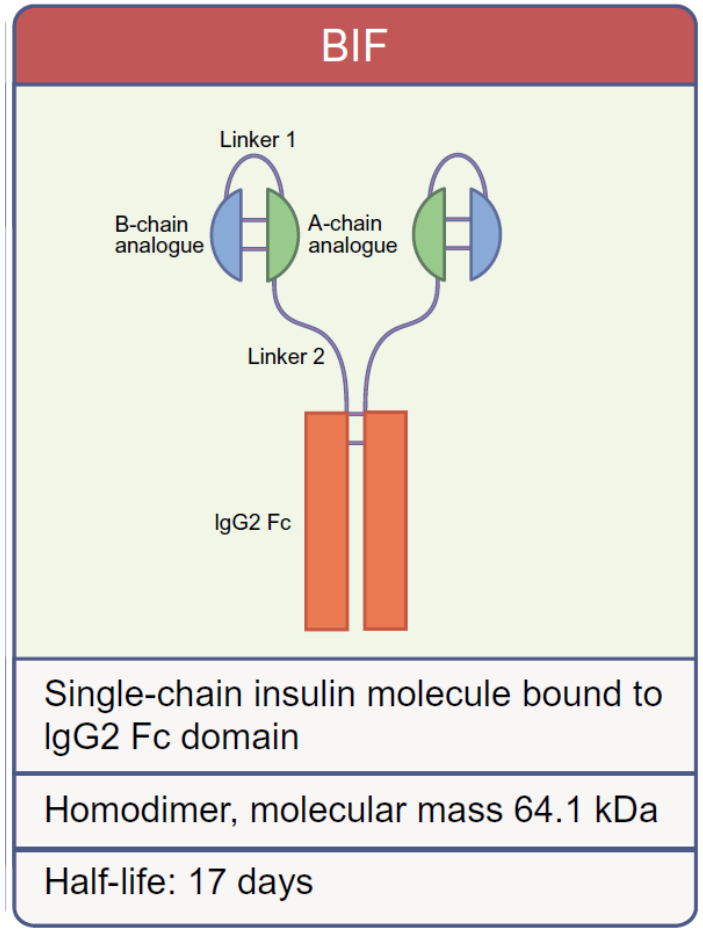
Diabetologia (2024) 67:1480–1492
https://doi.org/10.1007/s00125-024-06158-9

REVIEW

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

Roberto Trevisan[1,2] · Matteo Conti[1,3] · Stefano Ciardullo[1,3]

Received: 13 December 2023 / Accepted: 12 March 2024 / Published online: 29 April 2024



Efsitora o BIF (basal Insulin Fc) è una **proteina di fusione composta da un peptide biologicamente attivo, l'agonista del recettore dell'insulina umana e da un dominio del frammento cristallizzabile (Fc) dell'immunoglobulina G2 umana** (IgG2).
Questa si presenta in forma omodimerica; ogni monomero dell'omodimero è costituito da un analogo a catena singola di insulina, con la catena B collegata alla catena A da un breve linker di sette amminoacidi (Linker 1) ed un linker più lungo (Linker 2) che collega la catena A dell'insulina al dominio Fc dell'IgG2. Questa struttura conferisce a BIF un peso molecolare di 4.1 kDa.
A livello della catena di insulina sono state effettuate 9 sostituzioni amminoacidiche rispetto all'insulina umana per conferire stabilità chimica e fisica all'omodimero e per caratterizzarla dal punto di vista di affinità al recettore

La presenza del frammento Fc dell'immunoglobulina IgG2 e la ridotta affinità con il recettore insulinico (l'internalizzazione della molecola dopo il legame è la via principale di clearance) conferiscono alla molecola una emivita prolungata, **17 giorni**, ed una ridotta risposta immunitaria

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REVIEW

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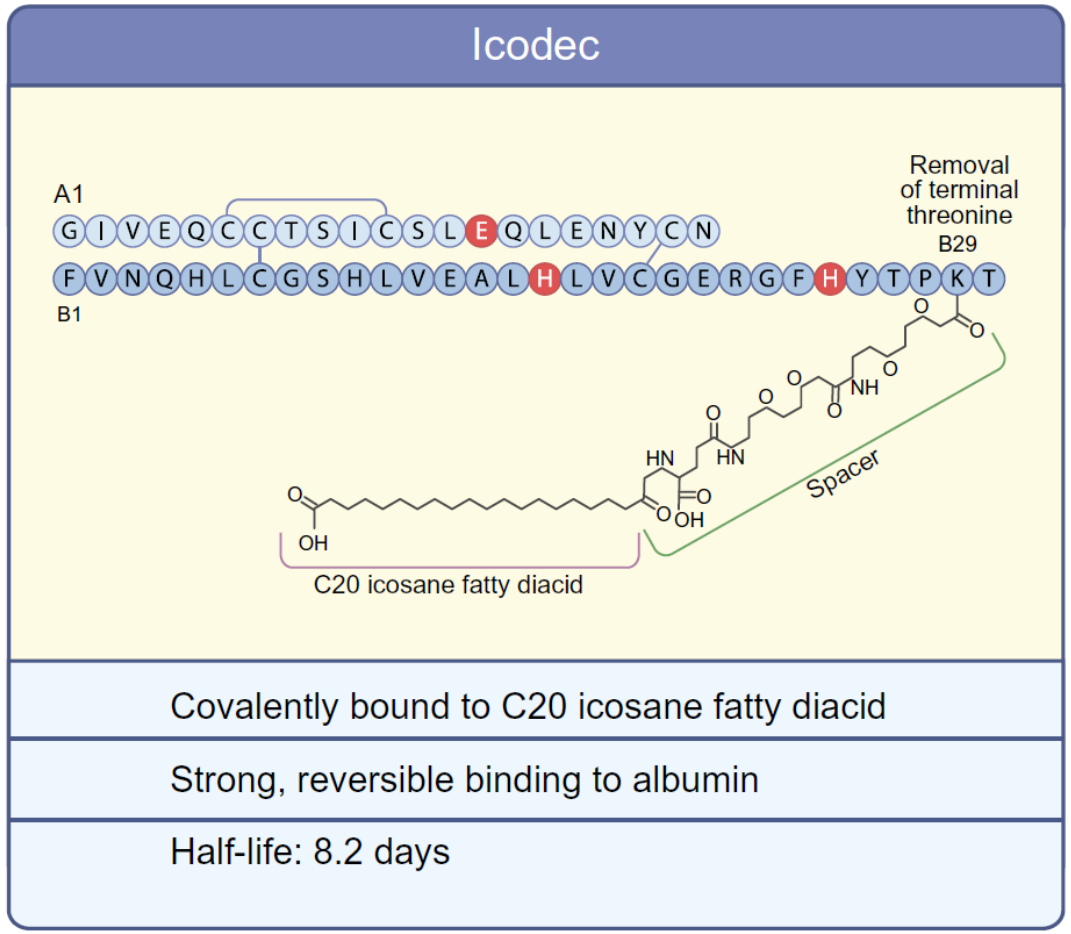
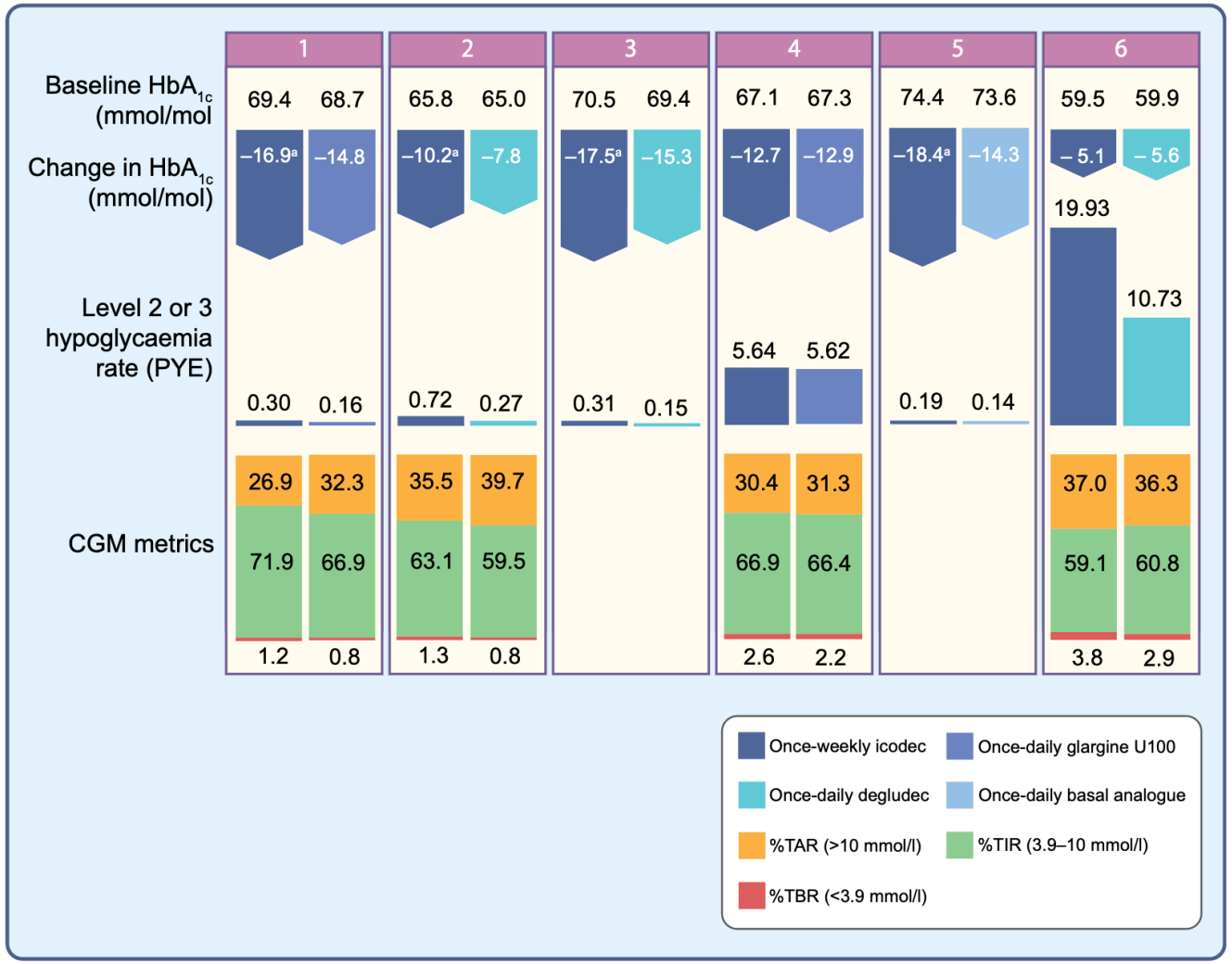


Icodec è un analogo dell'insulina basale settimanale, sviluppata attraverso la tecnologia di acilazione delle molecole proteiche di grosse dimensioni.
Le modifiche strutturali chiave rispetto alla struttura originaria dell'insulina umana riguardano:
1-tre sostituzioni di amminoacidi che impediscono la degradazione enzimatica e assicurano stabilità e solubilità;
2-l'aggiunta di una catena laterale, contenente un di acido grasso a 20 atomi di carbonio (C20), che conferisce alla molecola un forte legame reversibile all'albumina plasmatica e una ridotta clearance mediata dal recettore a livello dei tessuti bersaglio.
Grazie a tali modifiche, gli esameri dell'insulina icodec si dissociano a livello del sito di iniezione lentamente in monomeri e si legano all'albumina dopo l'assorbimento nel circolo ematico, formando un deposito essenzialmente inattivo di icodec

Il rilascio, lento e continuo dei monomeri di icodec da questo deposito circolatorio legato all'albumina, porta a una durata d'azione prolungata del farmaco la cui emivita risulta essere **8 giorni**

ONWARDS

(A O



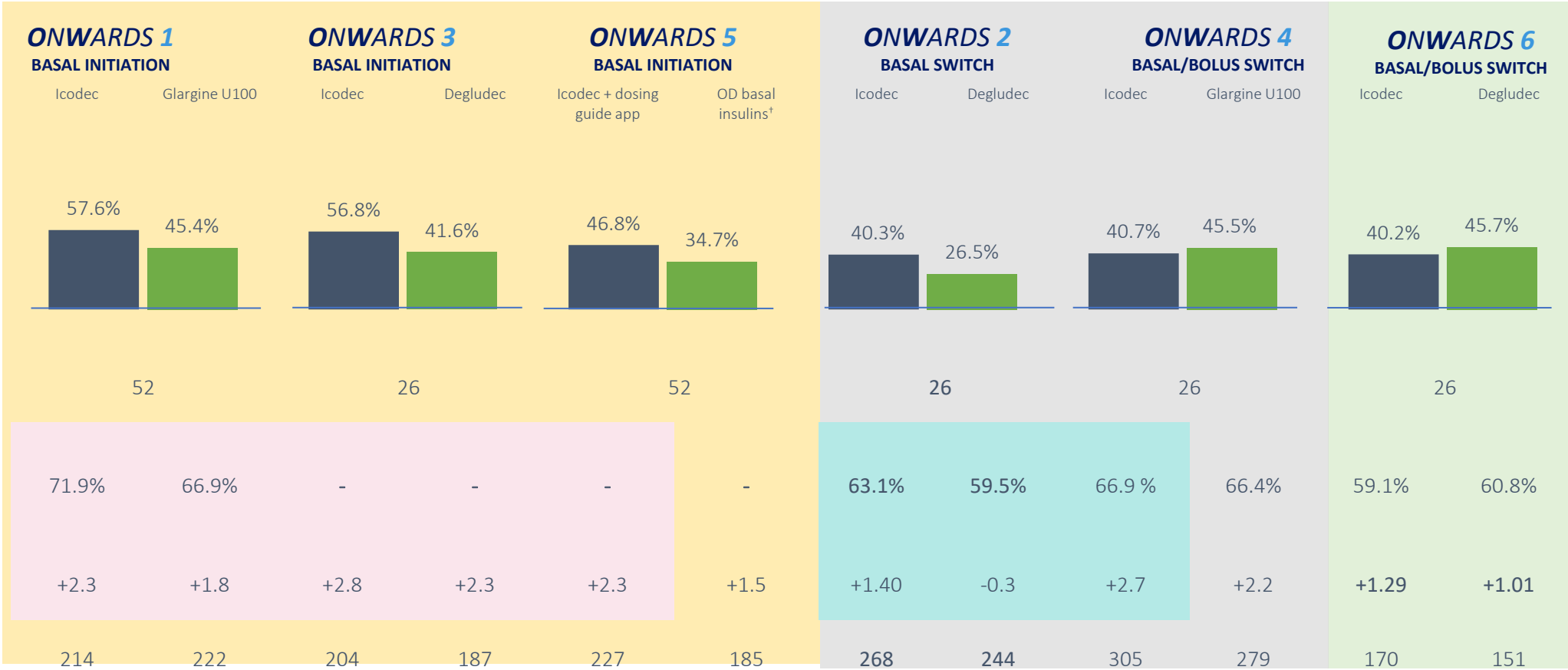
Diabetologia (2024) 67:1480–1492

*insulin degl… …recovery. OD, once-daily; RCT, randomis…

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. Lingvay I et al. 2023 ADA Scientific Sessions. 178-OR; 4. Bajaj H. 2023 ADA Scientific Sessions. 803-P. 5. Philis-Tsimikas A et al. *Lancet Diabetes Endocrinol*. 2023;11(6):414-425. 6. Mathieu C et al. *Lancet*. 2023;401(10392):1929-40; 7. Russell-Jones D et al. EASD 2023 Annual Meeting. OP-09; 8. Russell-Jones D et al. *Lancet*. 2023: DOI: 10.1016/S0140-6736(23)02179-7.

ONWARDS programme: secondary endpoints

(A ONce-Weekly insulin Analogue exploRing new options for DiabeteS treatment)



†insulin degludec or insulin glargine U100/U300; *assessed during the last 4 weeks of treatment, main phase. **assessed during the last 2 weeks of treatment. OD, once-daily.

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. Philis-Tsimikas A et al. 2022. EASD Annual Meeting. S42.; 6. Mathieu C et al. *Lancet*. 2023;401(10392):1929-40; 7. Mathieu C et al. 2022. DTS 22nd Annual Meeting. Virtual. 2 Nov 2022; 7. Russell-Jones D et al. *Lancet*. 2023: DOI: 10.1016/S0140-6736(23)02179-7.

ONWARDS T2D trials: composite endpoint

(A ONce-Weekly insulin Analogue exploRing new options for DiabeteS treatment)

Once-weekly icodec has shown superior glycemic efficacy compared to once-daily glargine (both HbA1c lowering and % of TIR in ONWARDS 1) and once-daily degludec (HbA1c lowering in ONWARDS-2 and 3) without any undue increase in level 2 and or level 3/severe hypoglycemia.

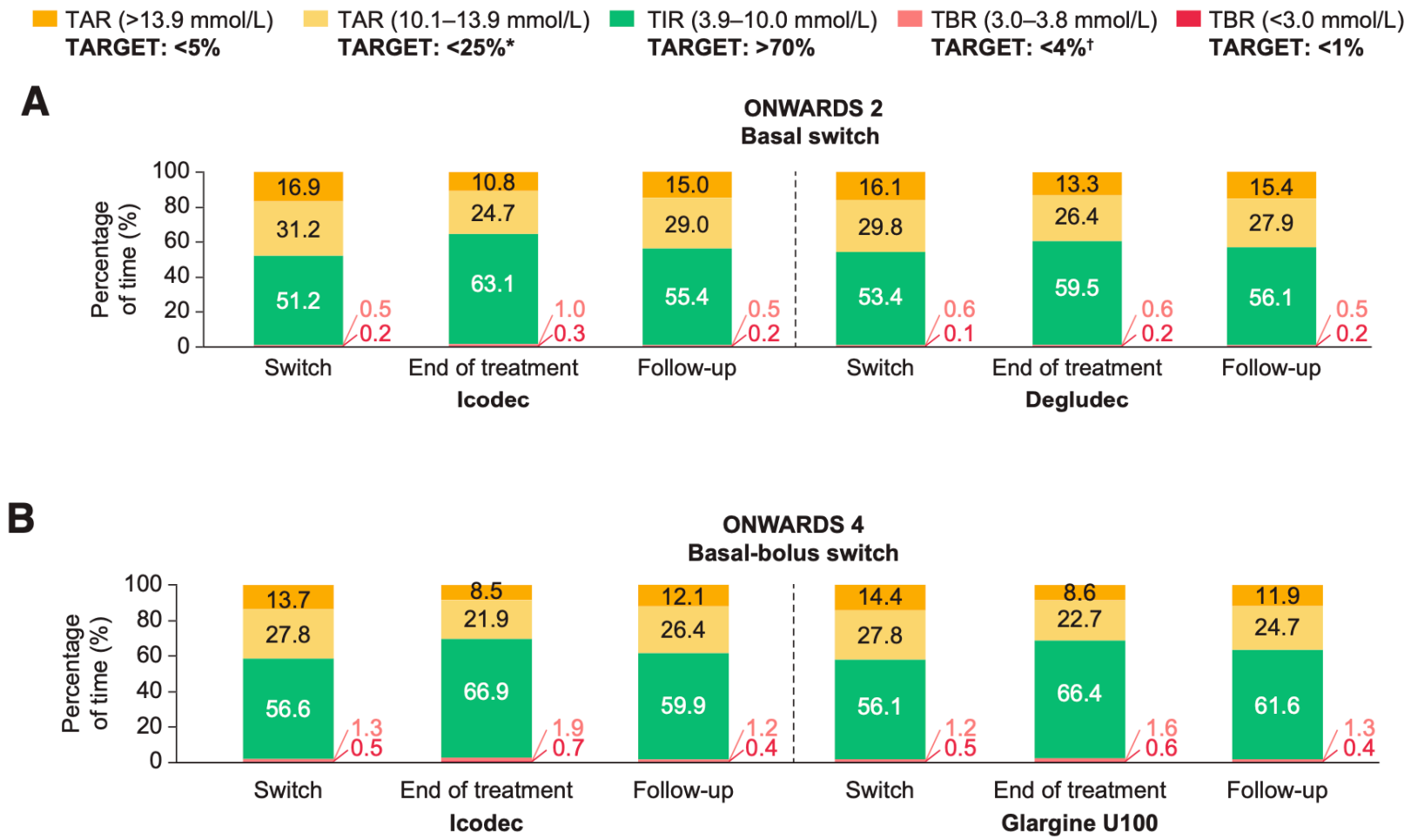
Clinically significant hypoglycaemia (level 2): blood glucose <3.0 mmol/L (<54 mg/dL) confirmed by blood glucose meter. Severe hypoglycaemia (level 3): hypoglycaemia with severe cognitive impairment requiring external assistance for recovery. † insulin degludec or insulin glargine U100/U300; CI, confidence 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.

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

Harpreet S. Bajaj,[1] Björg Ásbjörnsdóttir,[2] Lisbeth Carstensen,[2] Christian Laugesen,[2] Chantal Mathieu,[3] Athena Philis-Tsimikas,[4] and Tadej Battelino[5,6]

Diabetes Care 2024;47:729–738 | https://doi.org/10.2337/dc23-2136



Continuous Glucose Monitoring–

A

ONWARDS 2

In insulin-experienced participants with long-standing type 2 diabetes, CGM- based TIR, TAR, and CGM-derived hypoglycemia duration (<3.9 mmol/L) were comparable for icodec and once-daily basal insulin analogs during all time periods. TBR remained within recommended targets

treatment with daily basal insulin; therefore, hypoglycemia duration is shown according to the treatment arm assigned during the trial.

Switching to once-weekly insulin icodec versus once-daily insulin degludec in individuals with basal insulin-treated type 2 diabetes (ONWARDS 2): a phase 3a, randomised, open label, multicentre, treat-to-target trial

Athena Philis-Tsimikas, Marisse Asong, Edward Franek, Ting Jia, Julio Rosenstock, Karolina Stachlewska, Hirotaka Watada, Monika Kellerer

Lancet Diabetes Endocrinol 2023

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May 3, 2023
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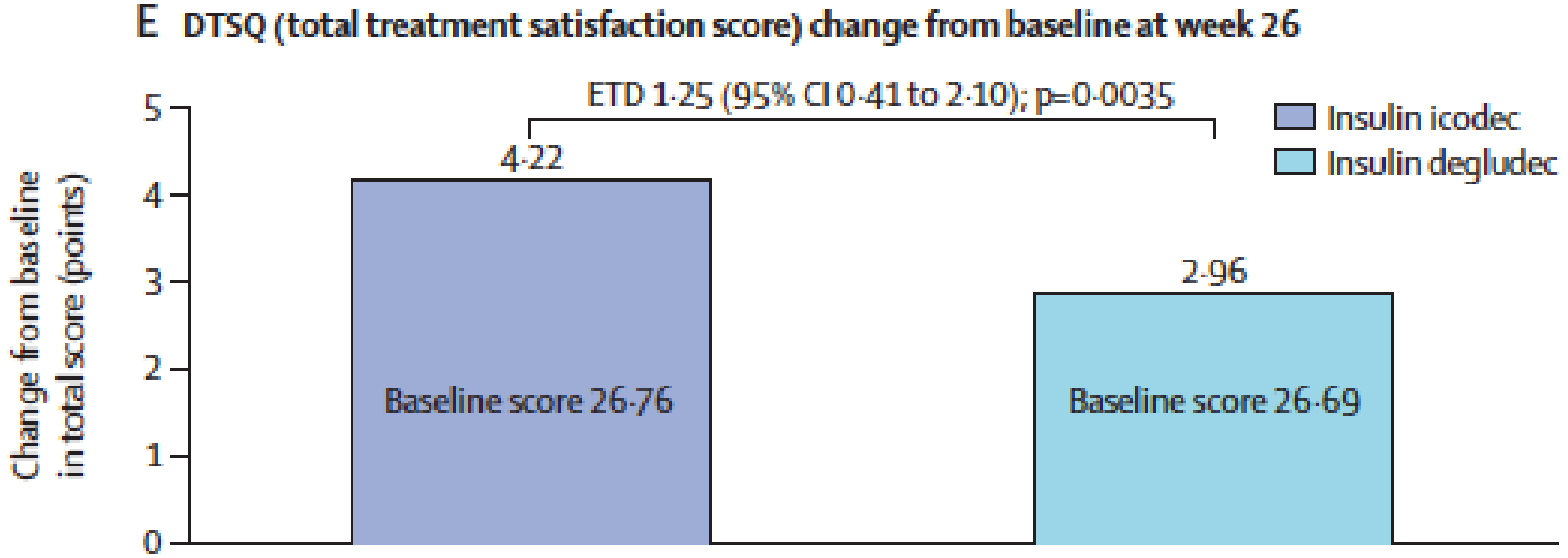

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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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

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Lancet 2024; 404: 1132–42
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In adults with type 1 diabetes, once-weekly efsitora showed non-inferior HbA1c 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

Fasting blood glucose (mmol/L)

Efisitora: Istruzione per l'uso

Pazienti Insuline Naive	Pazienti già in terapia insulinica
Formulazione: 100/150/250/400 UI in 0.5 ml, oppure 500 UI/ml	Formulazione 500 UI/ml
DMT2 Schema 1 (dosi fisse) Avvio Prima dose 100 UI Titolazione Successivi aumenti, ogni 4 settimane, a dose fisse, 150 UI, 250 UI, 400 UI, sulla base FBG o eventuali ipoglicemia, target 80-130 mg/dl Schema 2 Avvio Prima dose 300 UI (loading dose) Titolazione Alla seconda settimana una dose di 100 UI. Dalla terza settimana + 20/40 UI, - 20/40 UI sulla base FBG o eventuali ipoglicemia, target 80-120 mg/dl	DMT2 Avvio L'ultima dose di insulina basale giornaliera, es 20 UI, X 7 = 140 UI, alla quale sommare, solo per la prima somministrazione, una "loading dose" corrispondente al 300 % della dose totale di icodec (ES: 20 X 7 X 3 = 420 UI). Titolazione Alla seconda settimana una dose pari alla dose abituale di insulina basale giornaliera x 7. Dalla terza settimana aggiustamenti + 20/40 UI, - 20/40 UI sulla base FBG o eventuali ipoglicemia, target 80-120 mg/dl DMT1 Avvio Nei soggetti con DMT1 se FBG > 140 mg/dl, incremento della starting dose del 10-20/20-30 % Titolazione + 20/40 UI, - 20/40 UI sulla base FBG o eventuali ipoglicemia, target 80-120 mg/dl

Endocrine Reviews, 2024, **00**, 1–35
https://doi.org/10.1210/endrev/bnad037
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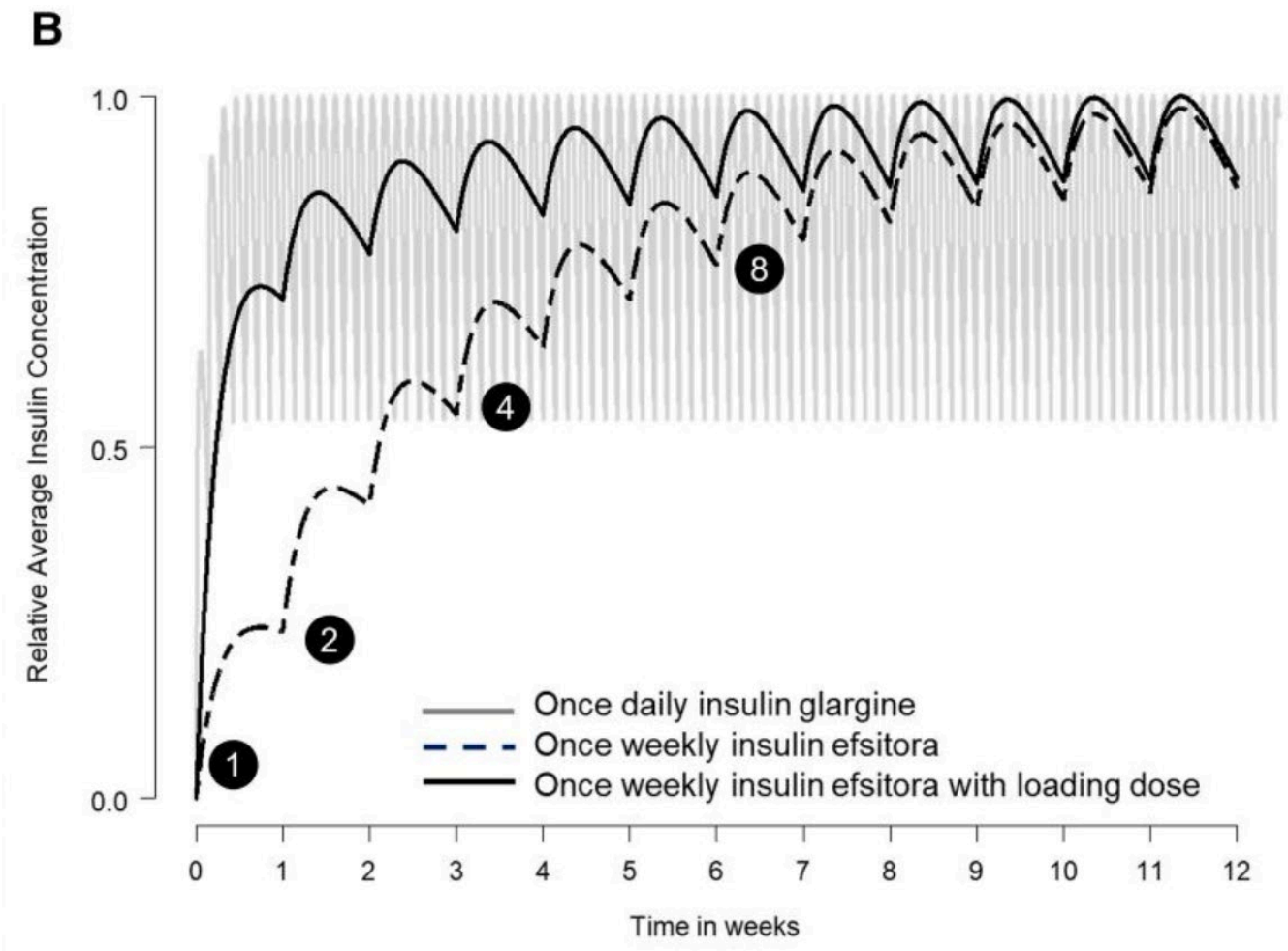
Review

The Basis for Weekly Insulin Therapy: Evolving Evidence With Insulin Icodec and Insulin Efsitora Alfa

Julio Rosenstock,[1,*] Rattan Juneja,[2] John M. Beals,[2] Julie S. Moyers,[2] Liza Ilag,[2] and Rory J. McCrimmon[3]



Model of insulin efsitora concentration when dosed without a loading dose (black dashed) and with a loading dose (black solid) compared to once-daily insulin glargine U100 (gray).

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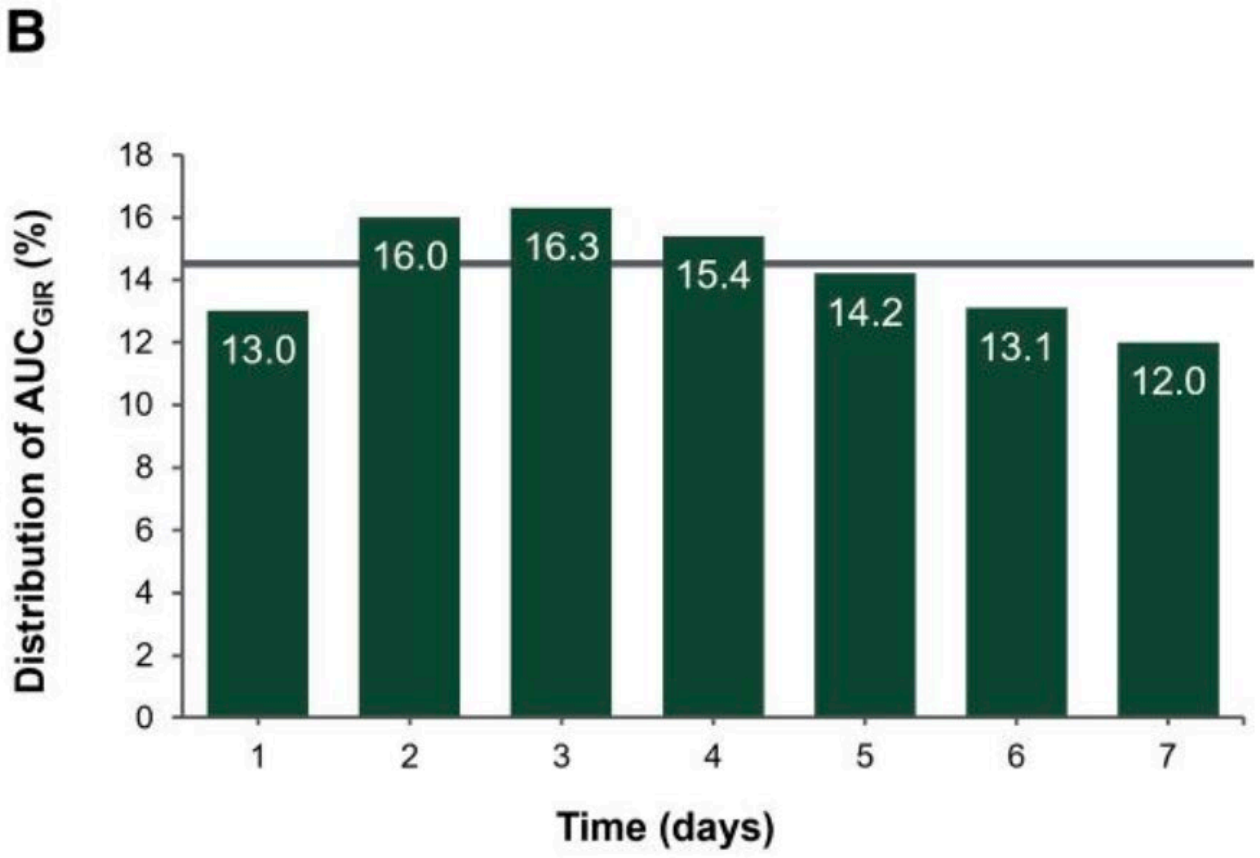

PD effect of insulin icodec over a weekly dosing interval

Icodec: Istruzione per l'uso

Pazienti Insuline Naive	**Pazienti già in terapia insulinica**
Formulazione 700 UI/ml, penne da 1, 1.5 o 3 ml	Formulazione 700 UI/ml, penne da 1, 1.5 o 3 ml
Avvio Prima dose 70 UI, corrispondenti a 10 UI di insulina basale giornaliera Titolazione Sulla base del FBG + 20 UI, - 20 UI rispetto al target 80-130 mg/dl	<u>DMT2</u> Avvio L'ultima dose di insulina basale giornaliera, es 20 UI, X 7 = 140 UI, alla quale sommare, solo per la prima somministrazione, una "loading dose" corrispondente al 50 % della dose totale di icodec (ES: 20 X 7 X 1.5 = 210 UI). Titolazione Sulla base del FBG + 20 UI, - 20 UI rispetto al target, 80-130 mg/dl <u>DMT1</u> Avvio Nei soggetti con DMT1 se HbA1c > 8 %, solo alla prima somministrazione aumentare del 100 % la dose stimata di icodec Titolazione Sulla base del FBG + 20 UI, - 20 UI rispetto al target 80-130 mg/dl

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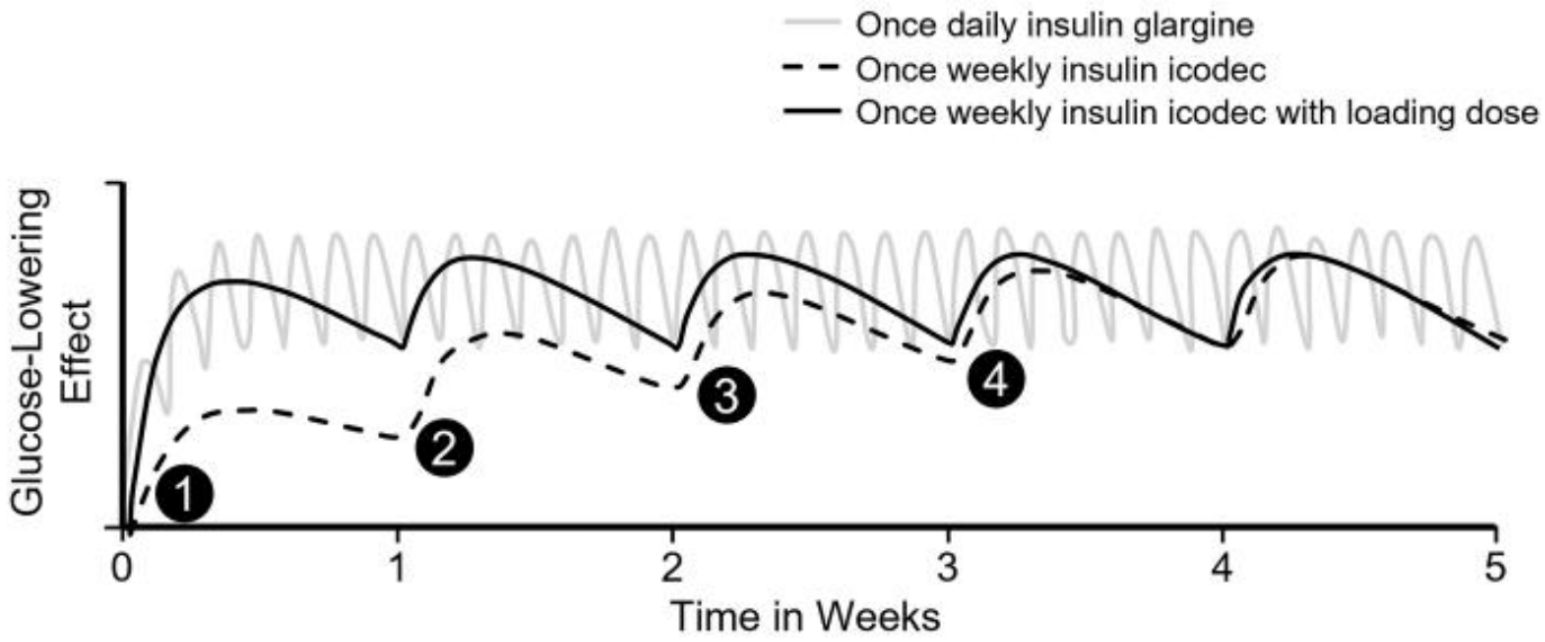

Basal weekly insulins: the way of the future!

Julio Rosenstock [a,*], Stefano Del Prato [b]

PATIENTS SELECTION

- **People with T2D with inadequate glycemic control while receiving multiple glucose-lowering agents.**
- Treatment adherence and quality of life may be considered as well when selecting the best candidates.
  - All individuals with insufficient glycemic control with other injectable treatments such as GLP-1 RAs, or with contraindications or intolerance to other glucose-lowering treatments
  - For patients needing intensification of a once-weekly GLP-1 RA regimen, taking a basal insulin with the same injection frequency would simplify management.
  - The relative inflexibility introduced by once-weekly dosing suggests that it may be best suited to patients with stable glucose control, relatively low variation in basal insulin requirements (allowing for slow but consistent weekly titration), and predictable lifestyles.
  - Patients who need assistance with injections. Requiring one rather than seven injections per week will reduce the workload of visiting nurses or family members.

Metabolism Clinical and Experimental 126 (2022) 154924

Alla scoperta di un nuovo mondo

- Capire come gestire situazioni particolari:
  - Ipoglicemia
  - Digiuno
  - L’esercizio fisico
  - Le ospedalizzazioni
  - Ecc.

DIABETES RESEARCH AND CLINICAL PRACTICE 175 (2021) 108820

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International Diabetes Federation

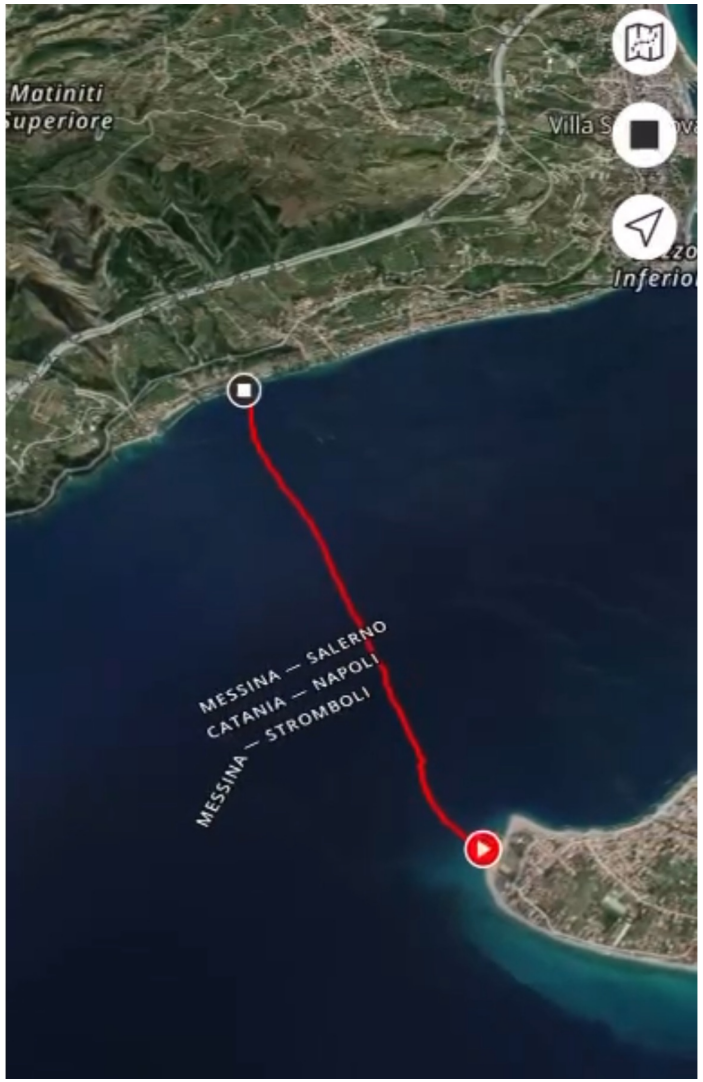
The future of insulin therapy

*Tim Heise**

Profil, Neuss, Germany

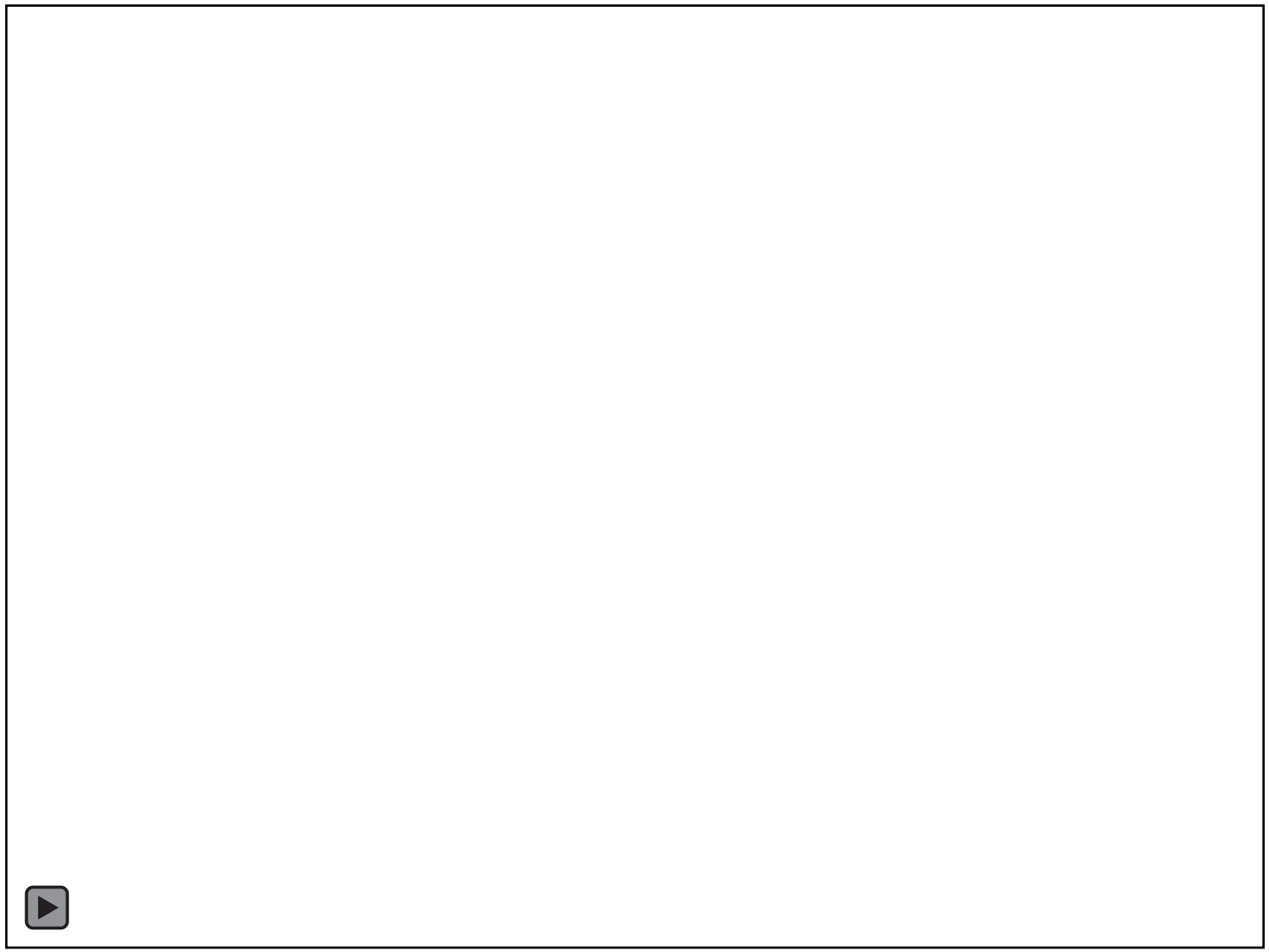
- Once weekly insulins
- Hepatopreferential insulins
- Oral insulins
  - Prandial
  - Basal
- Glucose-responsive “smart insulins»
- Single-chain insulins with high thermal stability (HCL/AHCL)
- Selective Insulin on Vascular Function and Liver Triglycerides
- ……

Torre Faro Messina 14 Luglio 2024



The Insulin History….
A Never Ending Story

Phantasia è il mondo
della fantasia umana, ogni suo elemento,
ogni sua creatura, scaturisce dai sogni e dalla speranza dell'umanità



Ci sono cose che non si possono capire con la riflessione bisogna viverle