Congresso SID-AMD Regione Emilia-Romagna:

TERAPIE INNOVATIVE E MEDICINA DI PRECISIONE:

VERSO LA "DECRONICIZZAZIONE" DEL DIABETE

Efficacia delle insuline basali di seconda e terza generazione

Massimo Michelini
Diabetologia Montecchio AUSL Reggio Emilia

PARMA • 7 OTTOBRE 2022 • CDH Hotel Villa Ducale

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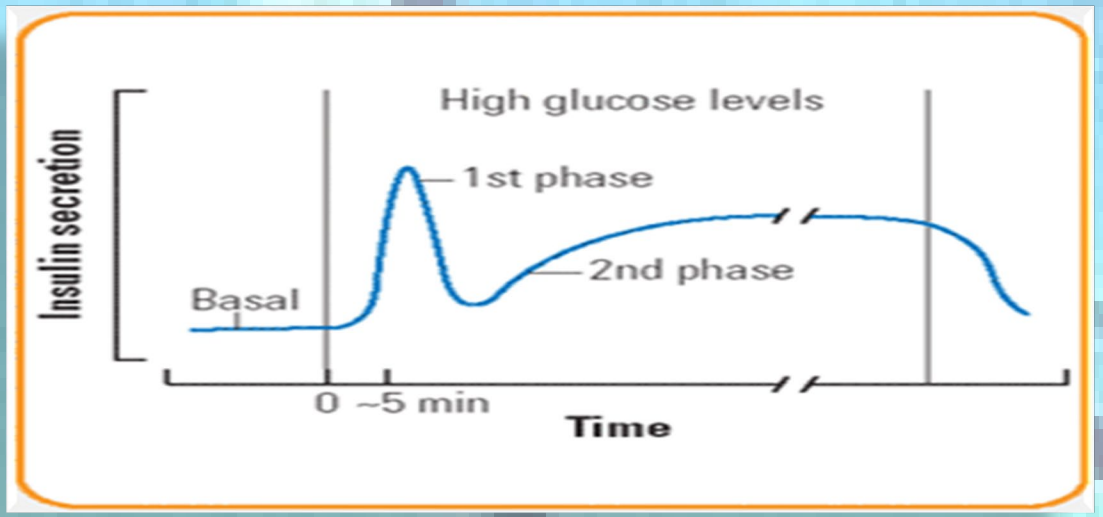
BANSHEE
BROWNIES
CATOBLEBA
GOLEM
ODRADEK
REMORA
A BA O A QU
...
...
...

LA BANSHEE

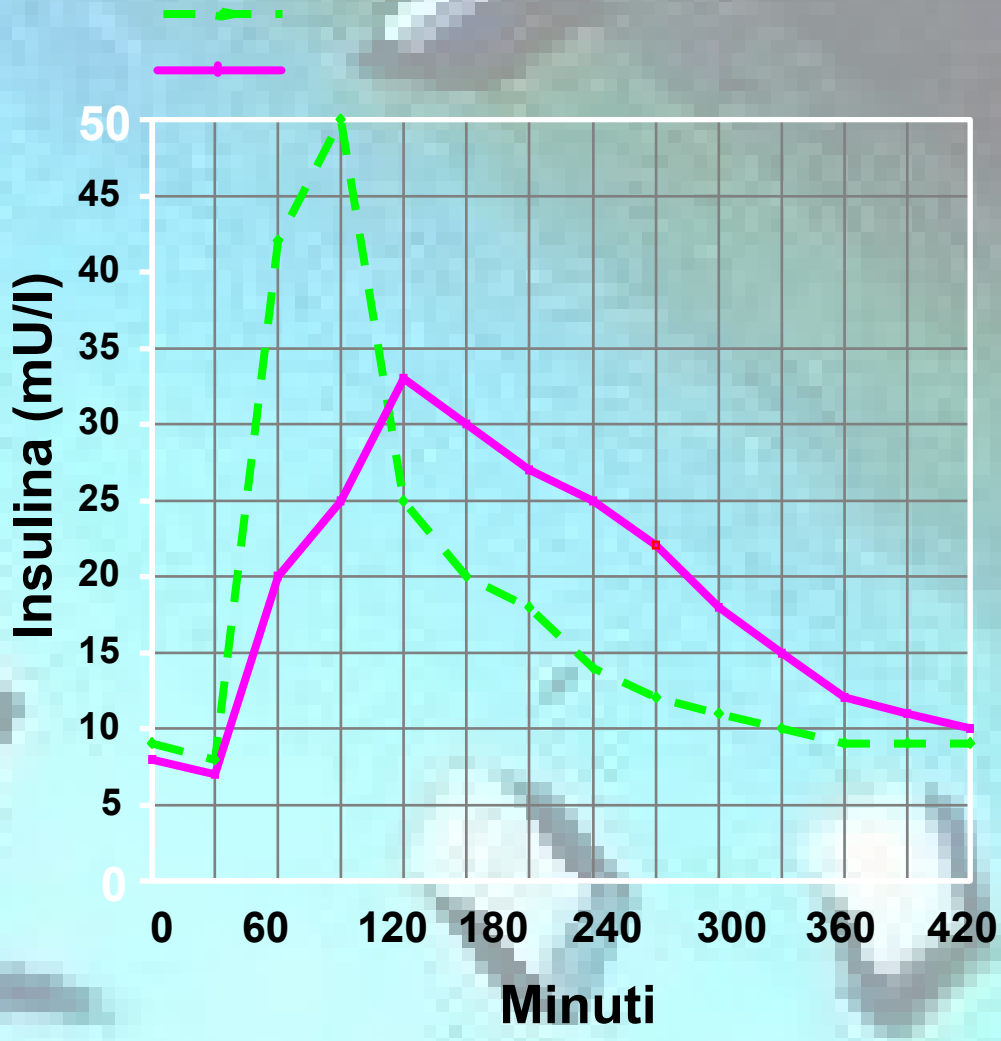
Nessuno sembra averla mai vista; è non tanto una forma quanto un gemito che colma di orrore le notti d'Irlanda e (secondo Demonologia e stregoneria di Sir Walter Scott) delle regioni montuose di Scozia.
Annuncia, sotto le finestre, la morte di qualche membro della famiglia. È un privilegio peculiare di certi lignaggi di puro sangue celtico, senza commistioni latine, sassoni o scandinave, La Banshee è stata udita anche nel Galles e in Bretagna. Appartiene alla stirpe delle fate.
Il suo gemito porta il nome di keening

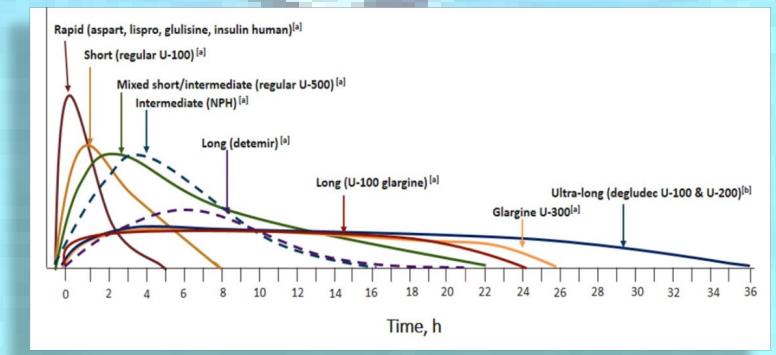
COME DOVRE
IL FARMACO IDEALE


ANCHE LE INSULINE
HANNO AVUTO LE LORO RIVOLUZIONI



gli analoghi rapidi riduzione dell'iperglicemia postprandiale precoce con minor rischio di ipoglicemia post-prandiale tardiva





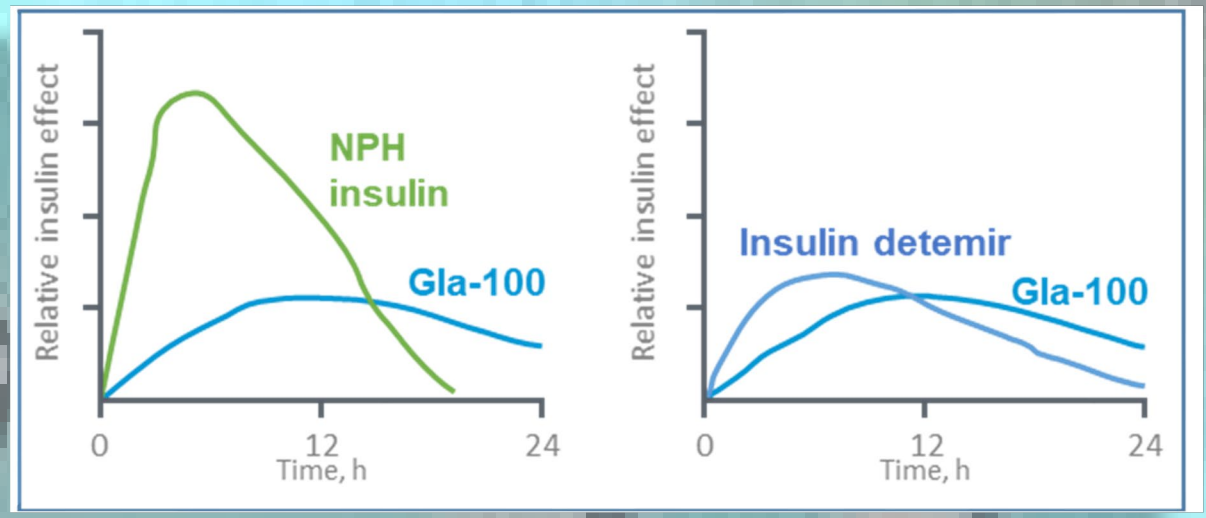
2000
glargine

2015
Empareg

The **first generation** of long-acting basal insulin analogs, **insulin glargine U100 and insulin detemir**, have half-lives of approximately 12 h and 5–7 h, respectively, and a duration of action of up to 24 h The PD profiles for insulin glargine U100 and insulin detemir have no pronounced peaks

These analogs can achieve **similar glycemic control to** each other, and both have **a lower risk of hypoglycemia than NPH insulin**

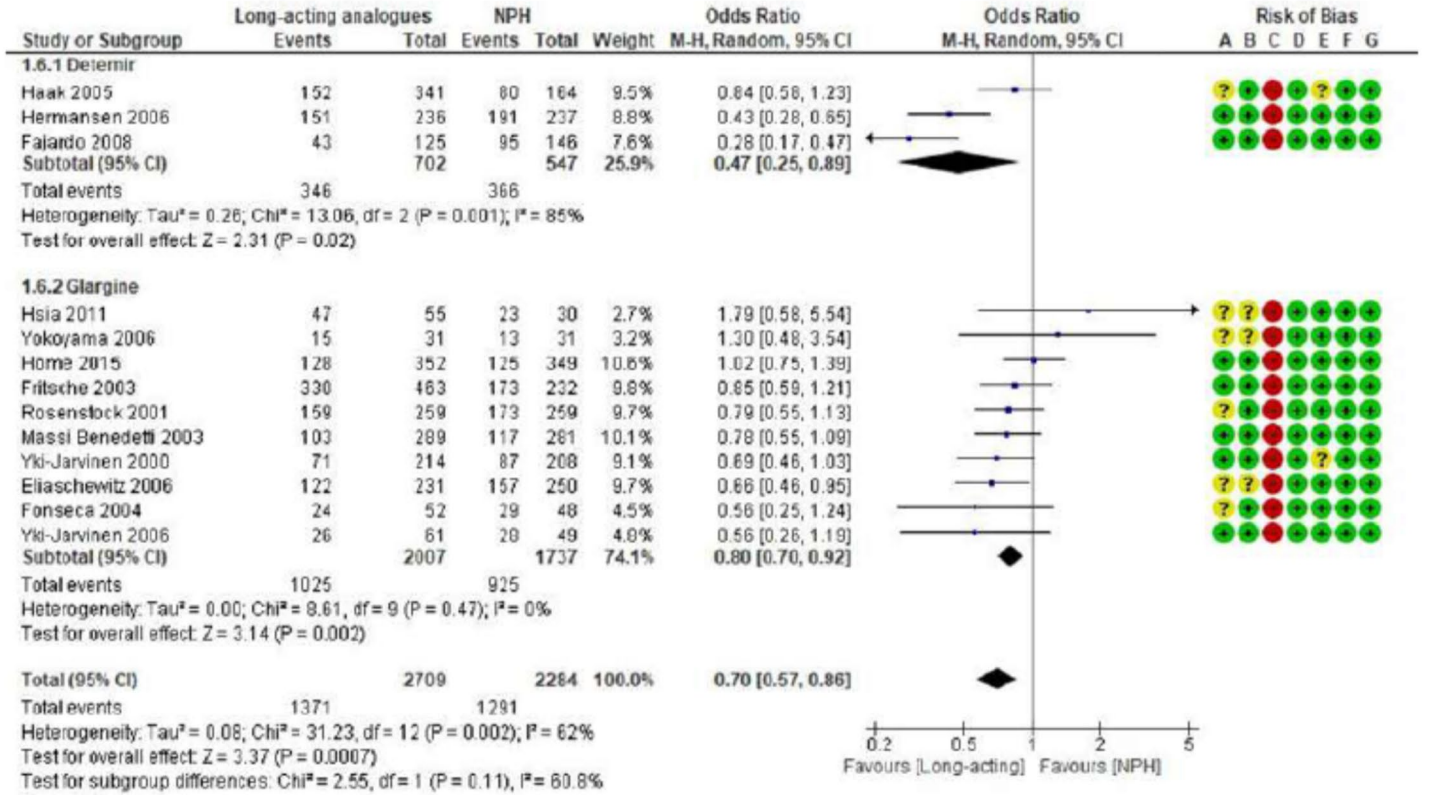
However, their half-lives – especially that of insulin detemir – are not long enough to consistently permit once-daily dosing in all patients



Linea Guida della Società Italiana di Diabetologia (SID) e dell'Associazione dei Medici Diabetologi (AMD)

La terapia del diabete mellito di tipo 2

Figura 1 – Effetti del trattamento con analoghi lenti dell'insulina rispetto ad insulina NPH sul rischio di ipogliemia totale.



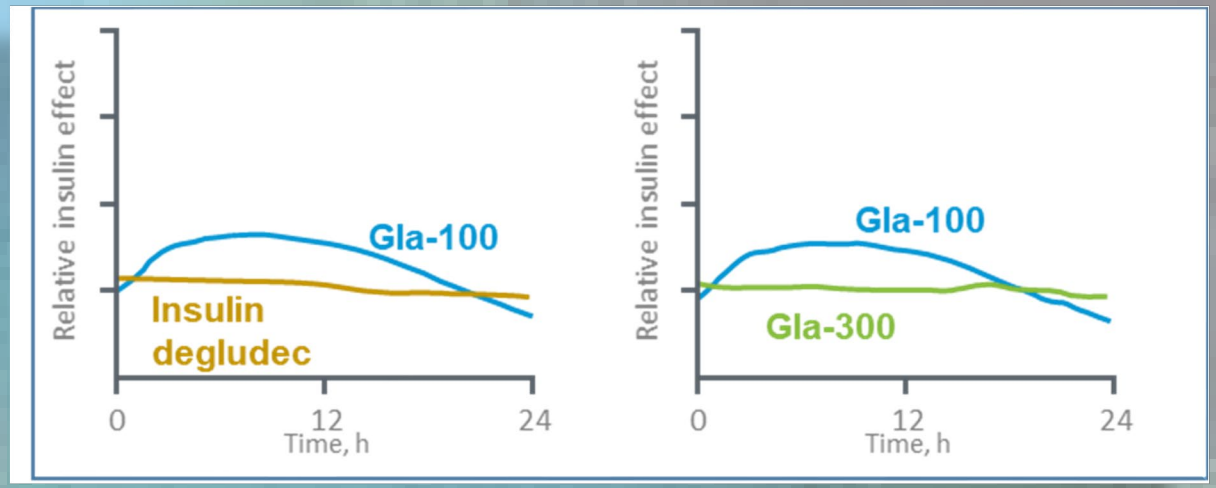
I «BROWNIES»

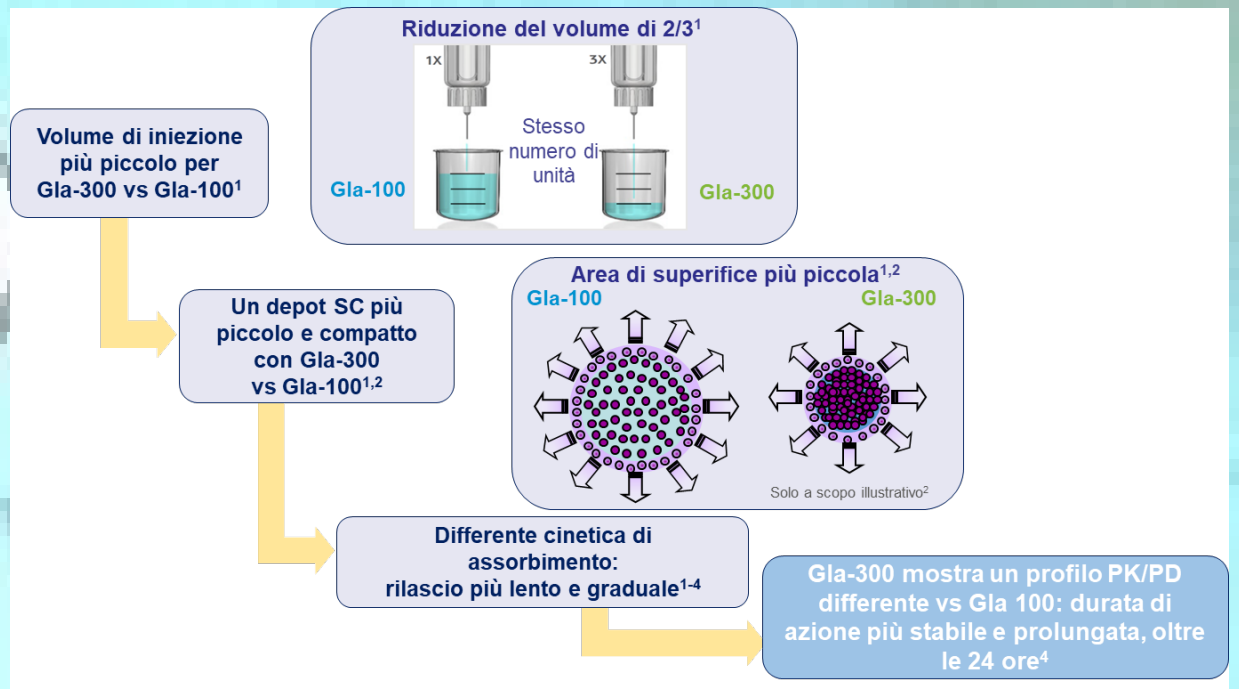
Sono ometti servizievoli di colore marroncino, dal quale hanno preso il nome. Hanno l'abitudine di far visita alle fattorie scozzesi e, quando la famiglia è immersa nel sonno, aiutano nelle faccende domestiche. Una fiaba dei fratelli Grimm riferisce un fatto analogo.
L'illustre scrittore Robert Louis Stevenson affermò di aver addestrato i suoi brownies al lavoro letterario. Quando sognava, questi gli suggerivano temi fantastici; per esempio, 1a strana trasformazione del Dottor Jekyll nel diabolico Mister Hyde…

The **second generation** of basal insulin analogs, **insulin degludec and insulin glargine U300**, have sufficiently prolonged (>24 h) and evenly distributed activity profiles to make reliable once-daily basal insulin doses a reality for many patients.

Insulin **degludec** has a half-life of 42 h and lower PD variability from day to day than insulin glargine U100. A meta-analysis of phase 3 trials confirmed that insulin degludec can achieve **similar improvements in glycemic control** to insulin glargine U100, **with significantly fewer hypoglycemic episodes**, including severe hypoglycemia, especially at night

Insulin glargine U300 is a concentrated formulation of insulin glargine U100, which slows dissolution from the injection site, producing a lower peak and longer duration of action….to a more sustained glycemic control and a significantly lower risk of nighttime as well as daytime hypoglycemia than insulin glargine U100





Linea Guida della Società Italiana di Diabetologia (SID) e dell'Associazione dei Medici Diabetologi (AMD)
Metodologia e sintesi delle raccomandazioni

5.3. Si raccomanda l'uso degli analoghi lenti dell'insulina, rispetto all'insulina NPH, per tutti i pazienti con diabete di tipo 2 che necessitano di insulina basale.

Forza della raccomandazione: forte. Qualità delle prove: molto bassa.

Giustificazione

Vi sono numerose evidenze provenienti da trial clinici che mostrano come l'uso degli analoghi lenti dell'insulina, rispetto a NPH, si associ ad un rischio minore di ipoglicemie totali e notturne e ad una tendenziale riduzione degli eventi ipoglicemici severi. Inoltre, nonostante il disegno dei trial clinici inclusi nella valutazione sia nella maggior parte dei casi "*treat-to-target*", si è osservato un modesto, ma significativo, effetto positivo anche su HbA1c e glicemie a digiuno a favore degli analoghi lenti dell'insulina (detemir e glargine U100).

Non vi sono trial di confronto tra le nuove formulazioni di analoghi lenti dell'insulina con NPH; tuttavia, confronti diretti tra degludec e glargine U300 con glargine U100 mostrano simili effetti su ipoglicemia e HbA1c ed effetti migliori su glicemia a digiuno per degludec.

Per tali motivi, la raccomandazione ad usare gli analoghi lenti dell'insulina, rispetto a NPH, **può essere estesa a** tutte le formulazioni esistenti in commercio.

Linea Guida della Società Italiana di Diabetologia (SID) e dell'Associazione dei Medici Diabetologi (AMD)
Terapia farmacologica

Evidenze farmacoeconomiche per la terapia insulinica

La ricerca degli studi di farmacoeconomia è stata effettuata includendo come keyword il controllo glicemico; la selezione degli studi è stata effettuata considerando l'orizzonte temporale dell'analisi, la popolazione target ed escludendo report di valutazione del profilo (anche economico) di specifiche alternative realizzati dalle aziende produttrici degli stessi.

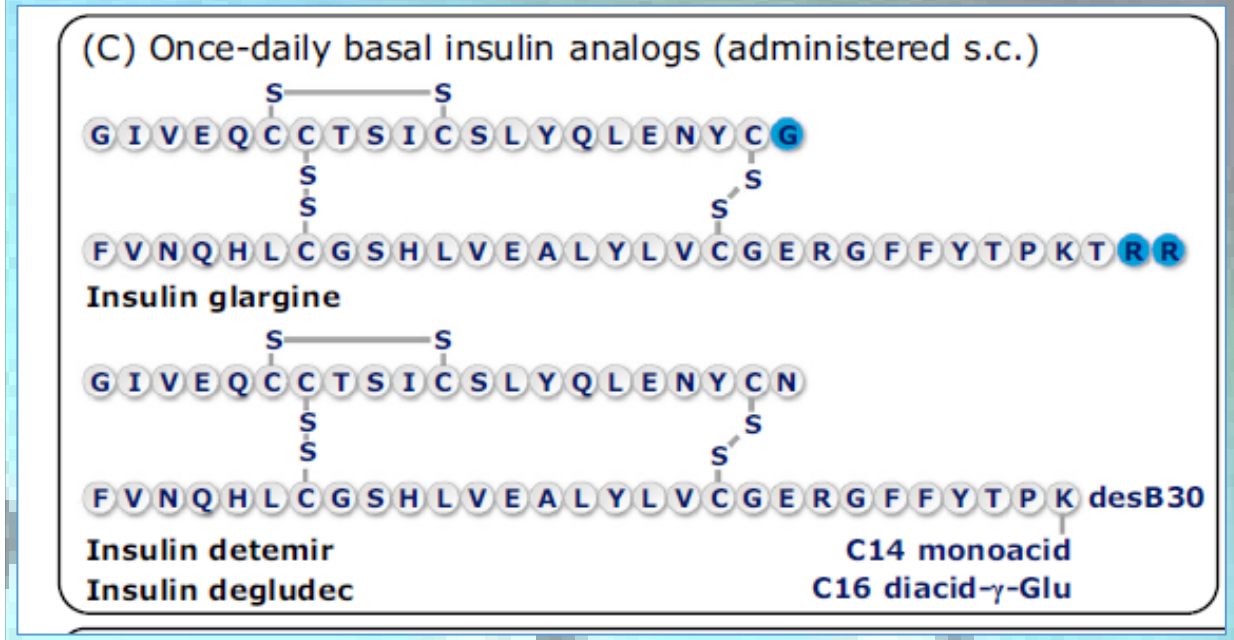
Gli studi di f**armacoeconomia** mostrano che le nuove formulazioni hanno **costi diretti maggiori; tuttavia**, il **rapporto costo-efficacia è generalmente favorevole per QALY guadagnati e per gli effetti positivi su rischio ipoglicemico e controllo glicemico**. La disponibilità di biosimilari con costi diretti ridotti può ulteriormente migliorare il rapporto costo-efficacia

L'insulina **glargine** è stata progettata con un **punto isoelettrico** aumentato che si traduce in una precipitazione degli esameri di insulina a pH fisiologico in vivo, producendo un deposito sottocutaneo con un assorbimento più lento

.

L'insulina **detemir** è **acilata** con una catena laterale degli acidi grassi la dimerizzazione degli esameri dell'insulina e il legame reversibile con l' albumina , sia nel sottocutaneo che nella circolazione, rallentando così l'assorbimento

L'insulina **degludec** è un analogo dell'insulina **acetilata** con 16 atomi di carbonio in catena laterale diacida. I diesameri di degludec nella formulazione possono assemblarsi in multiesameri nel deposito sottocutaneo, con le catene laterali degli acidi grassi che collegano gli esameri come "perle su un filo", prolungando così il tempo di permanenza nel deposito di iniezione. La catena laterale degli acidi grassi promuove anche il legame reversibile dei monomeri degludec nella circolazione all'albumina, che contribuisce a prolungarne l'emivita



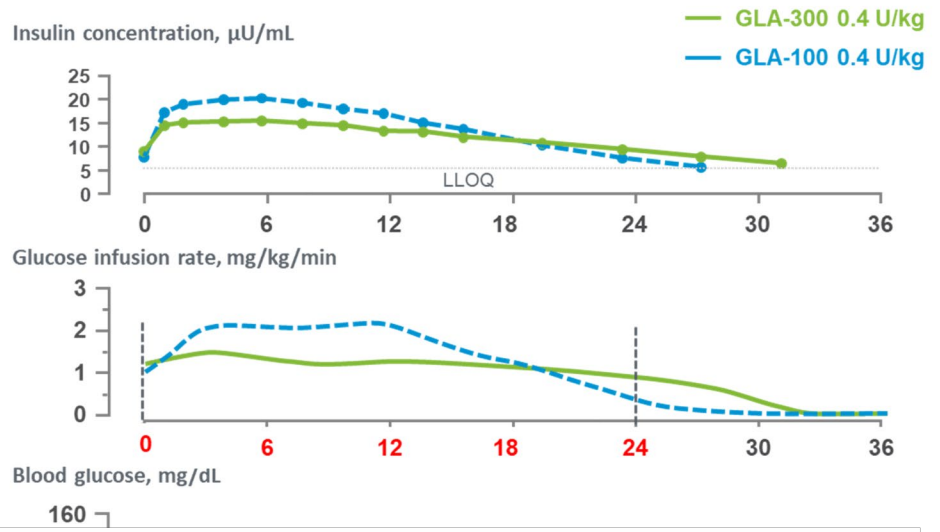
deposito sottocutaneo
legame reversibile nella circolazione all'albumina

Diabetes Care Volume 38, April 2015 637

New Insulin Glargine 300 Units·mL^{-1} Provides a More Even Activity Profile and Prolonged Glycemic Control at Steady State Compared With Insulin Glargine 100 Units·mL^{-1}

Reinhard H.A. Becker,[1] Raphael Dahmen,[1] Karin Bergmann,[1] Anne Lehmann,[1] Thomas Jax,[2] and Tim Heise[2]

Diabetes Care 2015;38:637–643 | DOI: 10.2337/dc14-0006



Received: 20 July 2017 | Revised: 18 August 2017 | Accepted: 26 August 2017
DOI: 10.1111/dom.13105

ORIGINAL ARTICLE

WILEY

Better glycaemic control and less hypoglycaemia with insulin glargine 300 U/mL vs glargine 100 U/mL: 1-year patient-level meta-analysis of the EDITION clinical studies in people with type 2 diabetes

Robert Ritzel MD[1] | Ronan Roussel MD, PhD[2,3,4] | Andrea Giaccari MD, PhD[5] | Jiten Vora MA, MD, FRCP[6] | Claire Brulle-Wohlhueter MD[7] | Hannele Yki-Järvinen MD, PhD[8]

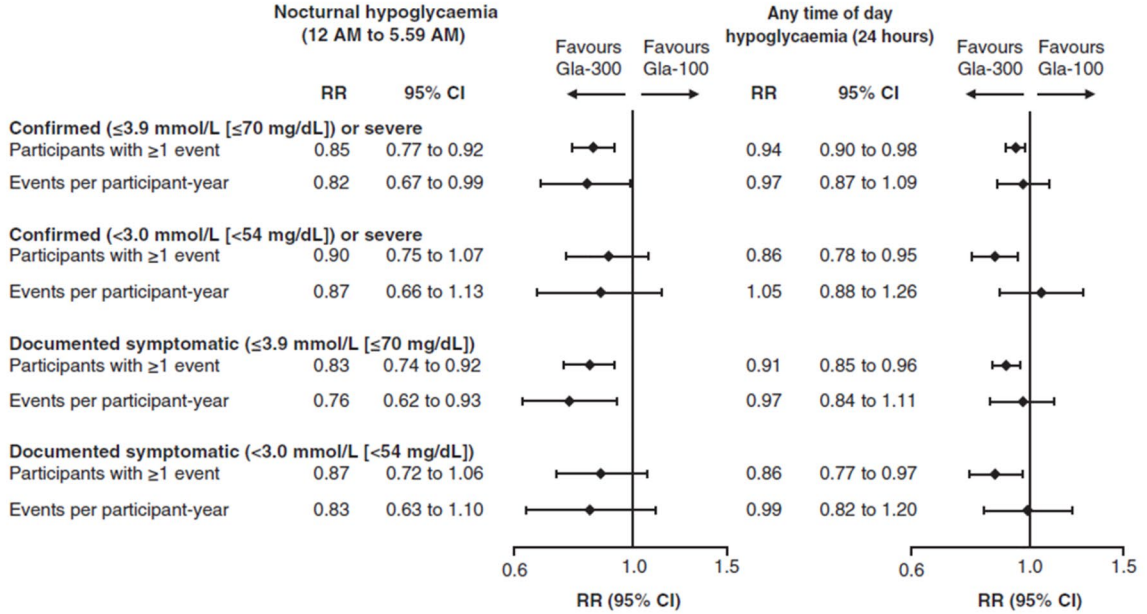


FIGURE 2 Percentage of participants with ≥1 hypoglycaemic event and annualized event rate (events per participant-year) over the 12-month treatment period (safety population). RR, relative risk for percentage of participants with ≥1 event, rate ratio for annualized event rates

Diabetes Ther (2020) 11:2539–2553
https://doi.org/10.1007/s13300-020-00915-w

REVIEW

Understanding the Clinical Profile of Insulin Degludec, the Latest Basal Insulin Approved for Use in Canada: a Narrative Review

Vincent Woo · Lori Berard · Robert Roscoe

Received: May 11, 2020 / Published online: September 17, 2020
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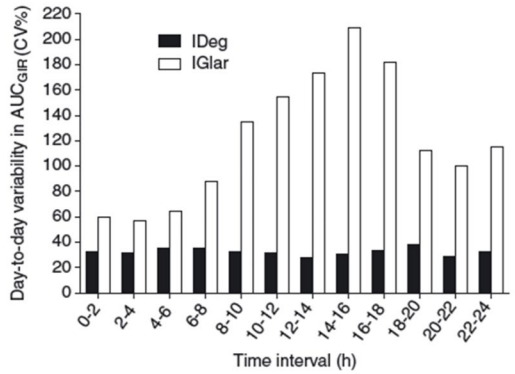

Figure 2. Day-to-day variability in glucose-lowering effect over 24 h at steady state.

original article

Diabetes, Obesity and Metabolism 15: 175–184, 2013.
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ORIGINAL ARTICLE

Hypoglycaemia risk with insulin degludec compared with insulin glargine in type 2 and type 1 diabetes: a pre-planned meta-analysis of phase 3 trials

R. E. Ratner[1], S. C. L. Gough[2], C. Mathieu[3], S. Del Prato[4], B. Bode[5], H. Mersebach[6], L. Endahl[6] & B. Zinman[7]

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[2]*Oxford Centre for Diabetes, Endocrinology and Metabolism and NIHR Oxford Biomedical Research Centre, Oxford, UK*
[3]*University Hospitals (UZ) Leuven, KU Leuven, Leuven, Belgium*
[4]*University of Pisa, Pisa, Italy*
[5]*Atlanta Diabetes Associates, Atlanta, GA, USA*
[6]*Novo Nordisk, Søborg, Denmark*
[7]*University of Toronto, Mount Sinai Hospital, Toronto, ON, Canada*

Aim: Hypoglycaemia and the fear of hypoglycaemia are barriers to achieving normoglycaemia with insulin. Insulin degludec (IDeg) has an ultra-long and stable glucose-lowering effect, with low day-to-day variability. This pre-planned meta-analysis aimed to demonstrate the superiority of IDeg over insulin glargine (IGlar) in terms of fewer hypoglycaemic episodes at equivalent HbA1c in type 2 and type 1 diabetes mellitus (T2DM/T1DM).

Methods: Pooled patient-level data for self-reported hypoglycaemia from all seven (five in T2DM and two in T1DM) randomized, controlled, phase 3a, treat-to-target trials in the IDeg clinical development programme comparing IDeg once-daily (OD) vs. IGlar OD were analysed.

Results: Four thousand three hundred and thirty subjects (2899 IDeg OD vs. 1431 IGlar OD) were analysed. Among insulin-naive T2DM subjects, significantly lower rates of overall confirmed, nocturnal confirmed and severe hypoglycaemic episodes were reported with IDeg vs. IGlar: estimated rate ratio (RR):0.83[0.70;0.98]$_{95\%CI}$, RR:0.64[0.48;0.86]$_{95\%CI}$ and RR:0.14[0.03;0.70]$_{95\%CI}$. In the overall T2DM population, significantly lower rates of overall confirmed and nocturnal confirmed episodes were reported with IDeg vs. IGlar [RR:0.83[0.74;0.94]$_{95\%CI}$ and RR:0.68[0.57;0.82]$_{95\%CI}$). In the T1DM population, the rate of nocturnal confirmed episodes was significantly lower with IDeg vs. IGlar during maintenance treatment (RR:0.75[0.60;0.94]$_{95\%CI}$). Reduction in hypoglycaemia with IDeg vs. IGlar was more pronounced during maintenance treatment in all populations.

Conclusions: The limitations of this study include the open-label design and exclusion of subjects with recurrent severe hypoglycaemia. This meta-analysis confirms that similar improvements in HbA1c can be achieved with fewer hypoglycaemic episodes, particularly nocturnal episodes, with IDeg vs. IGlar across a broad spectrum of patients with diabetes.

Keywords: confirmed hypoglycaemia, insulin degludec, insulin glargine, nocturnal hypoglycaemia, severe hypoglycaemia

Date submitted 14 August 2012; date of first decision 23 August 2012; date of final acceptance 1 November 2012

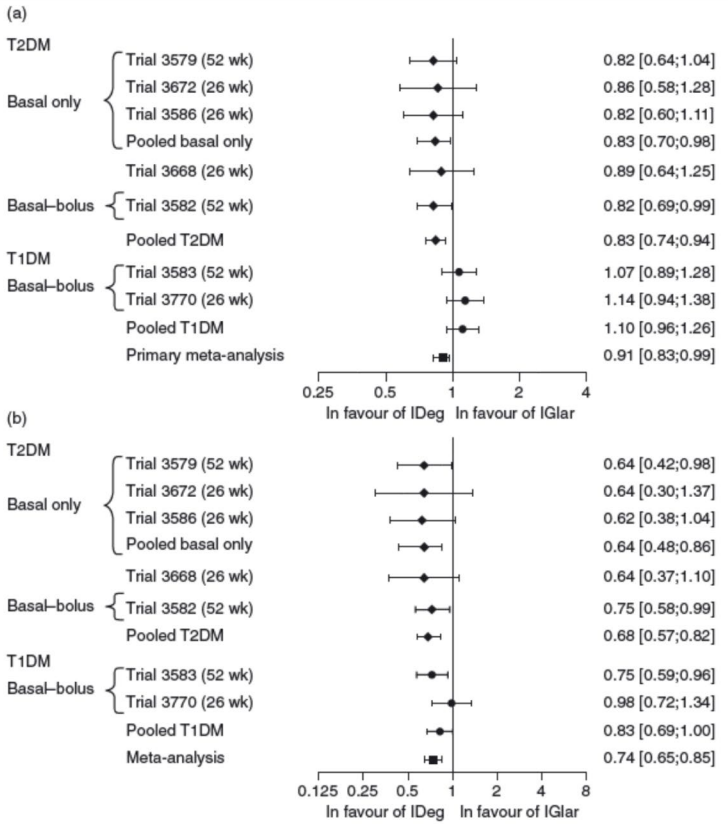


Figure 1. Estimated rate ratios (IDeg/IGlar) and 95% confidence intervals of (a) overall confirmed hypoglycaemic episodes and (b) nocturnal confirmed hypoglycaemic episodes for individual trials.

IL CATOBLEPA

Plinio (VIII, 32) racconta che ai confini dell'Etiopia, non lontano dalle sorgenti del Nilo, abita il catoblepa, «fiera di medie dimensioni e andatura pigra. La testa è notevolmente pesante e l'animale fa molta fatica a sostenerla: la tiene sempre chinata verso terra. Se così non fosse, il catoblepa metterebbe fine al genere umano, perché chiunque lo fissi negli occhi, cade morto.
Catoblepa, in greco, vuol dire «che guarda in basso»…

Verso la fine della Tentazione di Sant'Antonio si legge:

«Tozzo, malinconico, cupo, non faccio altro che stare a sentire il tepore del fango sotto il ventre. Ho un cranio così pesante che mi è impossibile tenerlo alzato. Lo giro lentamente e, a mascelle socchiuse strappo con la lingua le erbe velenose inumidite dal mio fiato. Una volta, senza accorgermene, mi divorai le zampe.
«Nessuno, Antonio, mi ha mai visto gli occhi, o chi li ha visti è morto. Se alzassi queste mie palpebre rosate e gonfie, moriresti all'istante»

Diabetes & Metabolism 45 (2019) 330–340

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com

Review

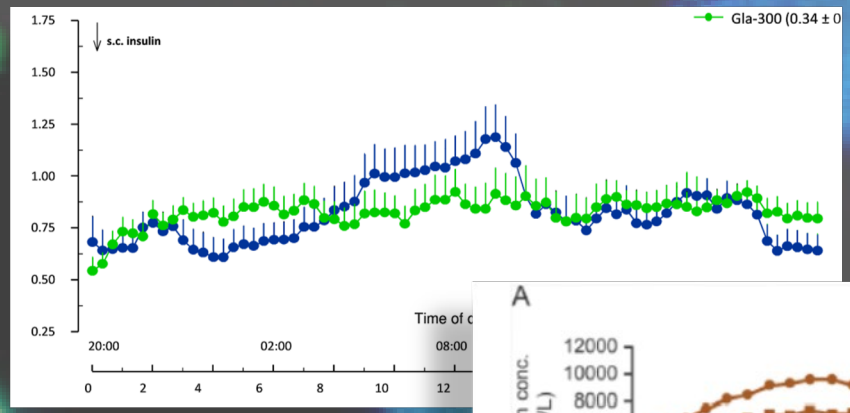
Clinical relevance of pharmacokinetic and pharmacodynamic profiles of insulin degludec (100, 200 U/mL) and insulin glargine (100, 300 U/mL) – a review of evidence and clinical interpretation

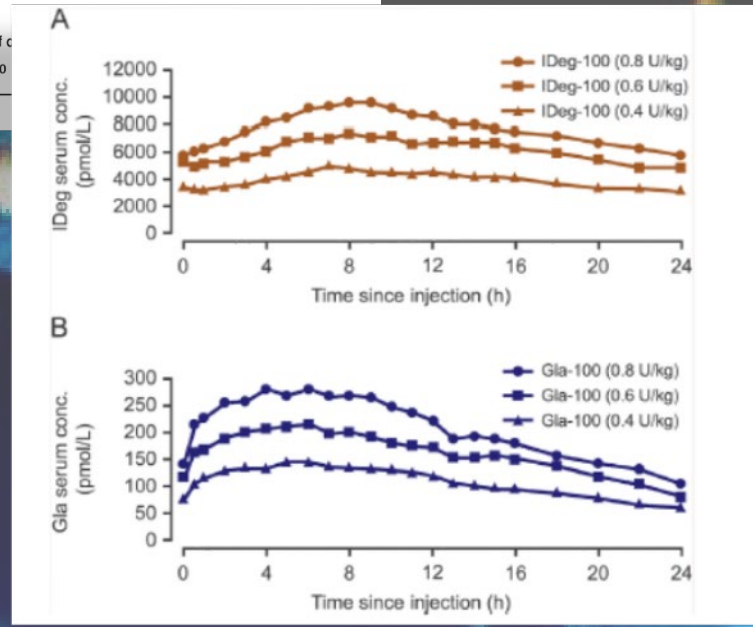
Diabetes Care Volume 44, January 2021 125

Pharmacokinetic and Pharmacodynamic Head-to-Head Comparison of Clinical, Equivalent Doses of Insulin Glargine 300 units · mL^{-1} and Insulin Degludec 100 units · mL^{-1} in Type 1 Diabetes

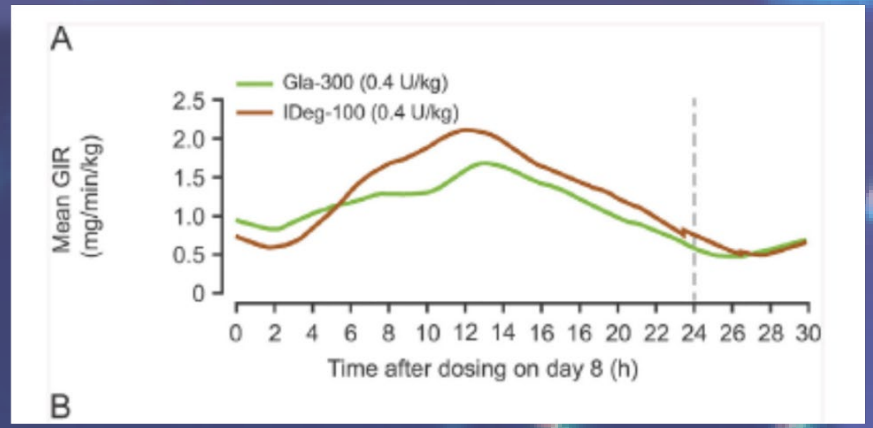
Paola Lucidi,[1] Paola Candeloro,[1] Patrizia Cioli,[1] Anna Marinelli Andreoli,[1] Chiara Pascucci,[1] Angela Gambelunghe,[2] Geremia B. Bolli,[1] Carmine G. Fanelli,[1] and Francesca Porcellati[1]

Diabetes Care 2021;44:125–132 | https://doi.org/10.2337/dc20-1033





In T1D, individualized, clinically titrated doses of Gla-300 and Deg-100 at steady state result in **similar glycemic control** and PD equivalence during euglycemic clamps. Clinical doses of Gla-300 compared with Deg-100 are higher and associated with quite similar even 24-h distribution of PD



Diabetes Ther
https://doi.org/10.1007/s13300-020-00982-z

ORIGINAL RESEARCH

Comparative Effectiveness of Switching From First-Generation Basal Insulin to Glargine 300 U/ml or Degludec 100 U/ml in Type 1 Diabetes: The RESTORE-1 Study

Luigi Laviola · Francesca Porcellati · Daniela Bruttomesso · Monica Larosa · Maria Chiara Rossi · Antonio Nicolucci on behalf of the RESTORE-1 Study Group

Received: October 2, 2020 / Accepted: December 2, 2020
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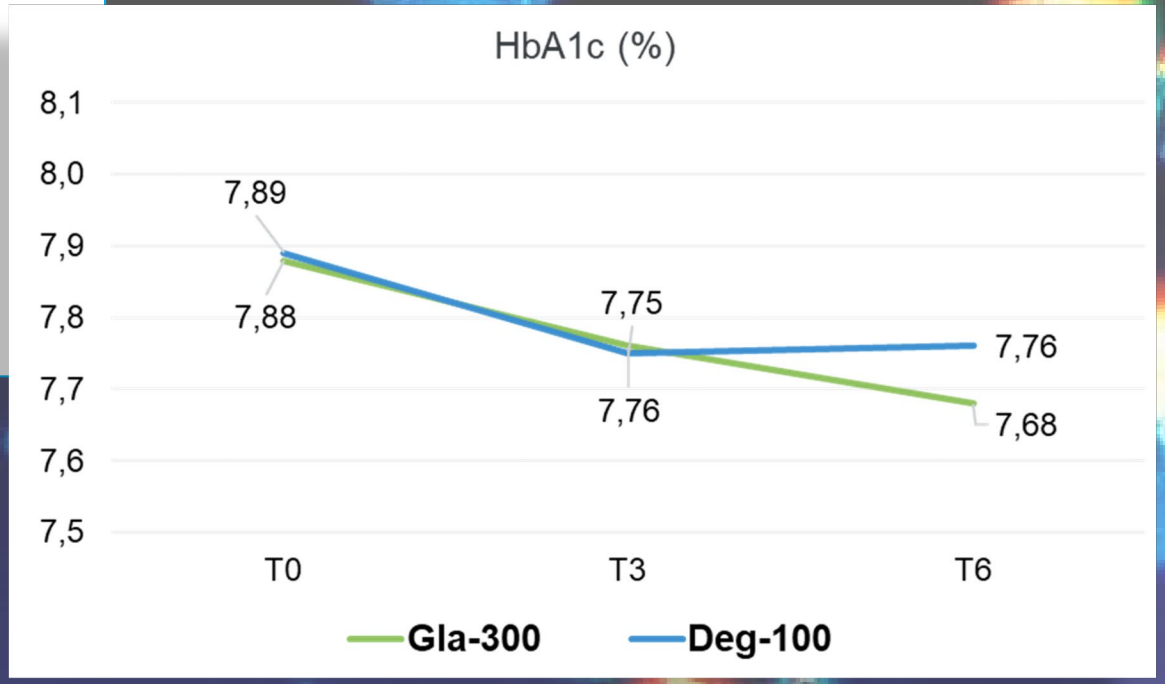
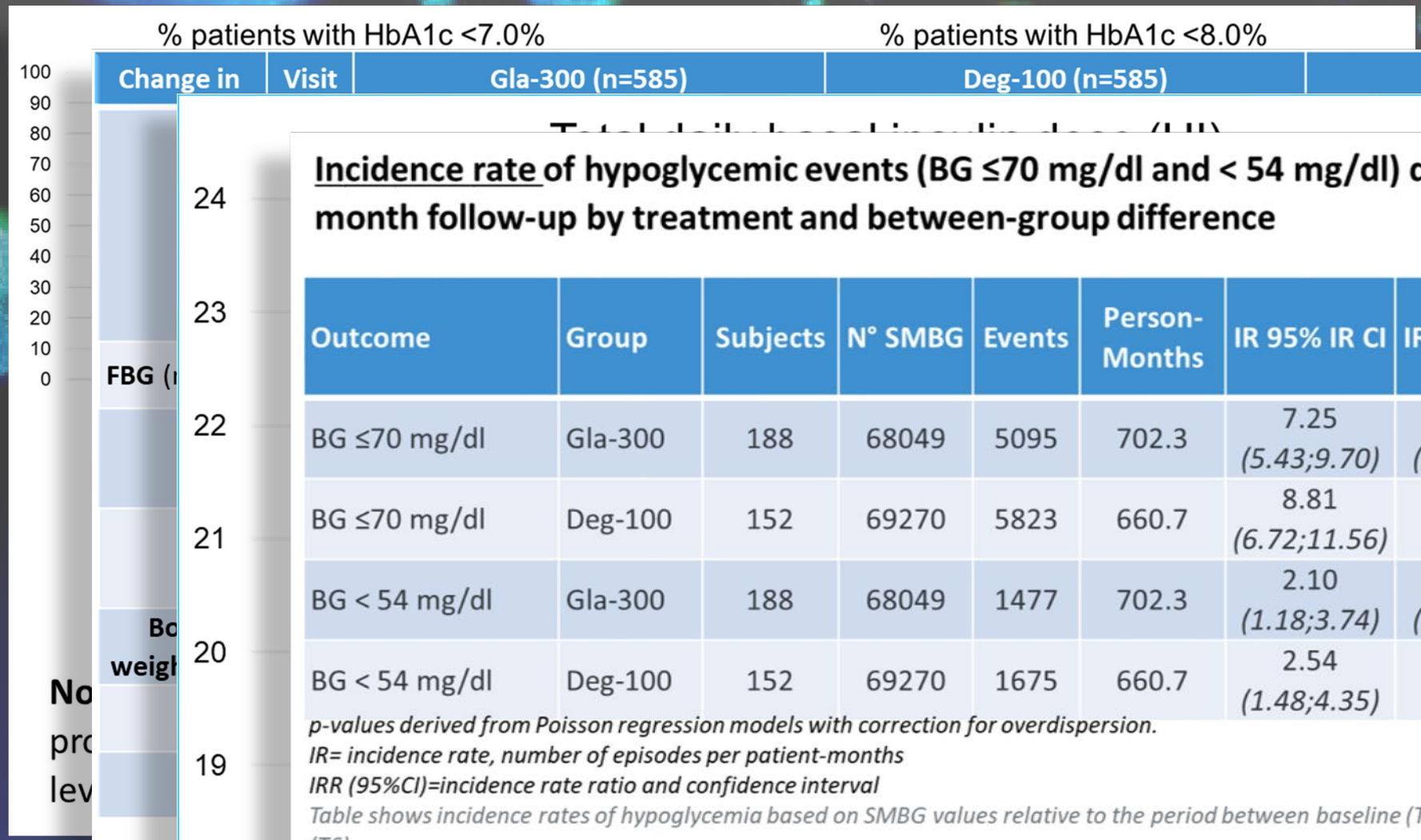


Conclusions: **Switching from 1BI to 2BI in adults with T1D was associated with similar improvements in glycemic control and overall significant decrease in hypoglycemia,** with no severe events with Gla-300.



Change in	Visit	Gla-300 (n=585)	Deg-100 (n=585)		

24
23
22
21
20
19

FBG (

Bo
weigh

No
pro
lev

At T6,
group vs. 151.38

Incidence rate of hypoglycemic events (BG ≤70 mg/dl and < 54 mg/dl) during the 6-month follow-up by treatment and between-group difference

Outcome	Group	Subjects	N° SMBG	Events	Person-Months	IR 95% IR CI	IRR (95% CI)	Between-group *p*-value
BG ≤70 mg/dl	Gla-300	188	68049	5095	702.3	7.25 *(5.43;9.70)*	0.82 *(0.55;1.22)*	0.34
BG ≤70 mg/dl	Deg-100	152	69270	5823	660.7	8.81 *(6.72;11.56)*	-	-
BG < 54 mg/dl	Gla-300	188	68049	1477	702.3	2.10 *(1.18;3.74)*	0.83 *(0.38;1.83)*	0.64
BG < 54 mg/dl	Deg-100	152	69270	1675	660.7	2.54 *(1.48;4.35)*	-	-

p-values derived from Poisson regression models with correction for overdispersion.
IR= incidence rate, number of episodes per patient-months
IRR (95%CI)=incidence rate ratio and confidence interval
Table shows incidence rates of hypoglycemia based on SMBG values relative to the period between baseline (T0) and 6 months visit (T6).

A similar number of SMBG tests was available in EMRs for both groups. **The incidence of BG measurements ≤70 mg/dl and <54 mg/dl was slightly lower in Gla-300 group than in Deg-100 group, but the statistical significance was not reached.**

ATTD 2022

27–30 April

Abstract LB009/ #1015

Time in Range Using Insulin Glargine 300 U/mL Versus Insulin Degludec 100 U/mL in Type 1 Diabetes: Head-to-Head Randomised Controlled InRange Trial

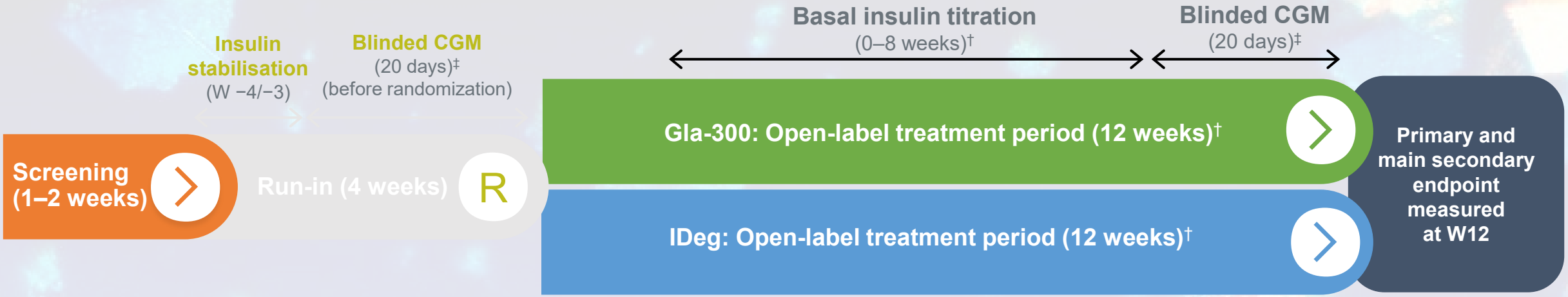
Tadej Battelino, MD, PhD[1], Thomas Danne, MD[2], Steve V. Edelman, MD[3], Pratik Choudhary, MD[4], Eric Renard, MD[5], Jukka Westerbacka, MD, PhD[6], Bhaswati Mukherjee, MD[6], Valerie Pilorget, MD[6], Pascaline Picard, MSc[7], Richard M. Bergenstal, MD[8]

[1]UMC–University Children's Hospital, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia; [2]Diabetes Centre for Children and Adolescents, Children's and Youth Hospital "Auf Der Bult", Hannover, Germany; [3]University of California, San Diego, CA, USA; [4]Diabetes Research Centre, University of Leicester, Leicester, UK; [5]Department of Endocrinology, Diabetes and Nutrition, Montpellier University Hospital, University of Montpellier, Montpellier, France ;[6]Sanofi, Paris, France; [7]IVIDATA Life Sciences, Levallois-Perret, France; [8]International Diabetes Center at Park Nicollet, Minneapolis, USA

Study design
12-week, multicentre, randomized, active-controlled, parallel-group, open-label study

Study population (N=343)
- Adults aged 18–70 years with T1D
- HbA_{1c} ≥7 % to ≤10 %
- MDI regimen with any
  - Basal insulin analogue
  - Rapid-acting insulin analogue
- No Gla-300 or IDeg-100 in last 30 days

- During the titration period, doses of Gla-300 or IDeg-100 were titrated to achieve the target fasting self-measured plasma glucose (SMPG) of ≥70 to <100 mg/dL
- Mealtime insulin analogue was titrated to achieve 2-hour post-prandial SMPG target of ≥130 to ≤180 mg/dL while avoiding hypoglycaemia
- CGM data was blinded to both investigators and participants
- Post-treatment safety information was collected 2–4 days after the last insulin dose



Primary endpoint

% TIR ≥70 to ≤180 mg/dL at Week 12

Main secondary endpoint

Glucose total CV at Week 12 (as a measure of glycaemic variability)

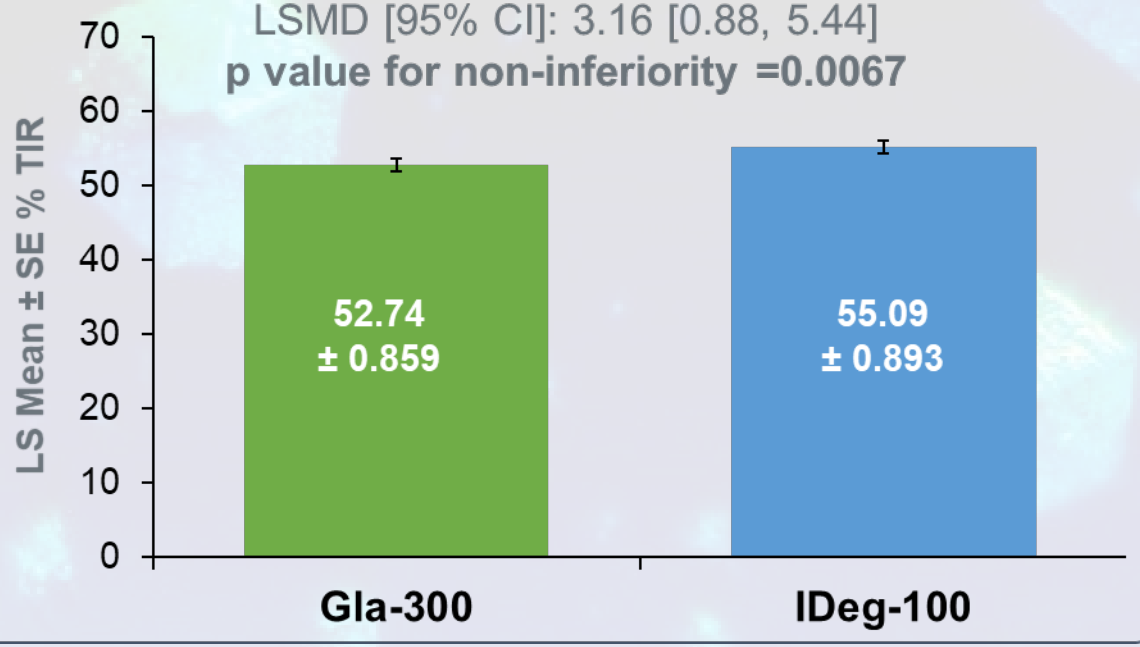
Hierarchical testing procedure

Step 1 Demonstrate **non-inferiority** of Gla-300 vs IDeg-100 on **primary endpoint**

Step 2 Demonstrate **non-inferiority** of Gla-300 vs IDeg-100 on **main secondary endpoint**

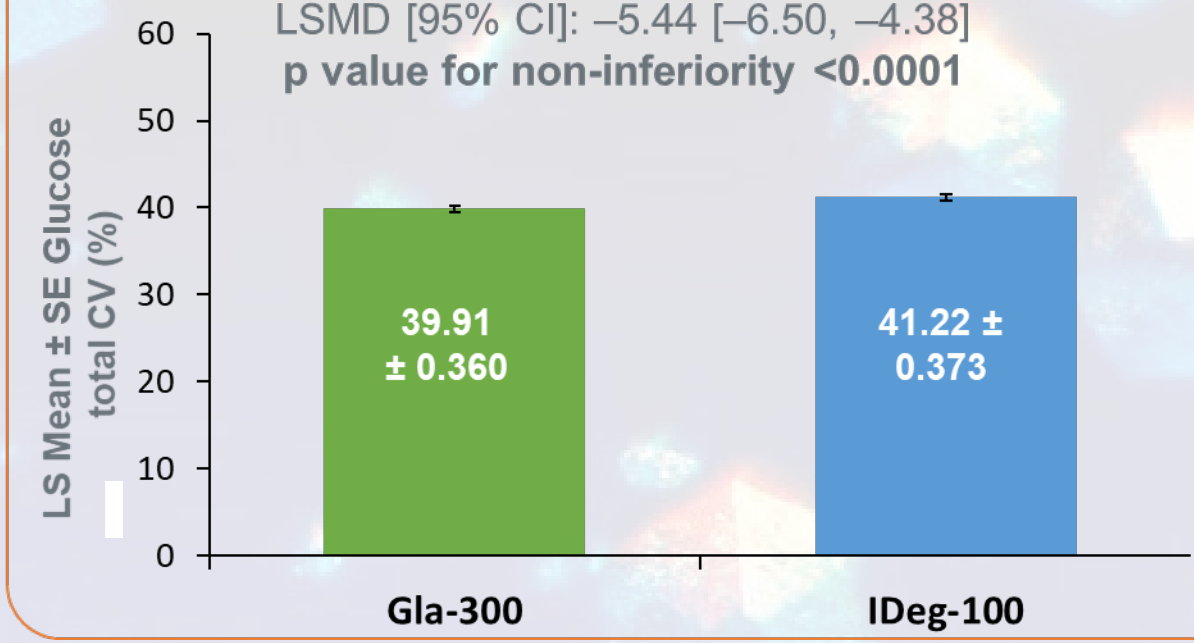
Primary endpoint

% TIR ≥70 to ≤180 mg/dL at Week 12



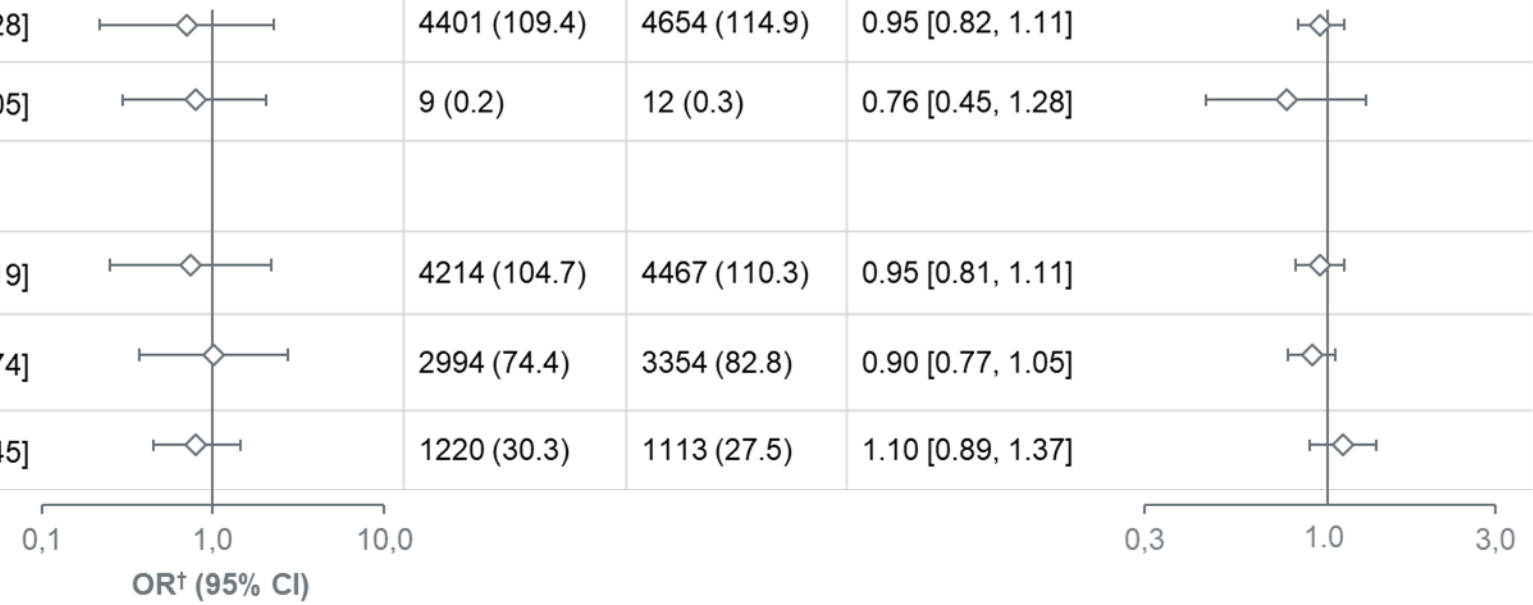
Main secondary endpoint

Glucose total CV at Week 12



Incidences and rates of hypoglycaemia (based on SMBG) of various categories were similar between treatment groups

	Incidence (%)				Event rate, number of events (events per patient-year)		
	Gla-300 N=172	IDeg-100 N=171	OR [95% CI]	Favours Gla-300 / Favours IDeg-100	Gla-300 PY=40.23	IDeg-100 PY=40.51	RR [95% CI]
Any hypoglycaemia	165 (95.9)	166 (97.1)	0.71 [0.22, 2.28]		4401 (109.4)	4654 (114.9)	0.95 [0.82, 1.11]
Severe hypoglycaemia*	8 (4.7)	10 (5.8)	0.79 [0.30, 2.05]		9 (0.2)	12 (0.3)	0.76 [0.45, 1.28]
Documented hypoglycaemia							
<70 mg/dL	164 (95.3)	165 (96.5)	0.74 [0.25, 2.19]		4214 (104.7)	4467 (110.3)	0.95 [0.81, 1.11]
<70 mg/dL and ≥54 mg/dL	164 (95.3)	163 (95.3)	1.01 [0.37, 2.74]		2994 (74.4)	3354 (82.8)	0.90 [0.77, 1.05]
<54 mg/dL	143 (83.1)	147 (86.0)	0.80 [0.45, 1.45]		1220 (30.3)	1113 (27.5)	1.10 [0.89, 1.37]



IL GOLEM

… i cabalisti e si dedicarono a contare, combinare e permutare le lettere delle Sacre Scritture, spinti dall'ansia di penetrare gli arcani di Dio. .. uno dei segreti che cercarono nel testo divino fu la creazione di esseri organici… Golem venne chiamato l'uomo creato attraverso combinazioni di lettere; il termine, alla lettera, significa «materia amorfa o senza vita ».

Nel Talmud (Sanhedrin, 65, b) si legge:
« Se i giusti volessero creare un mondo, potrebbero farlo. Combinando le lettere degli ineffabili nomi ogni venerdì, due maestri erano soliti studiare le leggi della Creazione e creare un vitello di tre anni, che poi usavano per la cena».

In Occidente, la fama del Golem si deve allo scrittore austriaco Gustav Meyrink, che nel quinto capitolo del suo romanzo onirico Der Golan (1915) scrive:

« L'origine della storia risale al XVII secolo. Ricorrendo a formule perdute della Cabbala, un rabbino costruì un uomo artificiale il cosiddetto Golem perchè suonasse le campane della sinagoga e facesse i lavori pesanti. *Non era, tuttavia, un uomo come gli altri e lo animava a stento una vita sorda e vegetativa. Questa durava fino a sera e doveva la sua virtù all'influsso di un'iscrizione magica, posta dietro ai denti della creatura per attrarre le libere forze siderali dell'universo.* Una sera, prima delle preghiere, il rabbino si dimenticò di togliere il sigillo dalla bocca del Golem e questi, preso da un delirio, corse per le strade buie investendo quanti gli si paravano innanzi. Il rabbino finalmente lo fermò e ruppe il sigillo che lo animava. La creatura crollò a terra. Rimase solo la sua rachitica figura di creta, visibile ancora oggi nella sinagoga

Eleazar di Worms ha conservato la formula necessaria per costruire un Golem… Sulla fronte si dovrà tatuare la parola emet, che significa verità. Per distruggere la creatura, si cancellerà la lettera iniziale, poichè in tal modo vi resterà la parola met, che significa morto


SE NON E’ UNA RIVOLUZIONE QUESTA....

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Articles from the An insulin centennial: Past, present, and future Special Issue, Edited by Alexander Kokkinos and Eleuterio Ferrannini

Basal weekly insulins: the way of the future!

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ABSTRACT

Basal insulin treatment is indispensable for patients with type 1 diabetes and often required by many with type 2 diabetes. Incremental advances lengthening the duration of action of insulin analogs and reducing pharmacodynamic variability have resulted in truly once-daily, long-acting basal insulin analogs. In the quest for better basal insulins to facilitate improvements in glycemic control and long-term outcomes, the driving need is to remove barriers delaying timely initiation of basal insulin, to maximize treatment adherence and persistence and reduce treatment burden without increasing risk of hypoglycemia. We review the range of investigational once-weekly insulins and their molecular strategies and profiles. Currently, the two most advanced clinical development programs are: (1) basal insulin icodec, an insulin analog acylated with a C20 fatty diacid (icosanedioic acid) side chain (Novo Nordisk) and (2) basal insulin Fc, a fusion protein that combines a single-chain insulin variant with a human immunoglobulin G fragment crystallizable domain (Eli Lilly). Available phase 2 data for these two once-weekly agents show comparable glycemic control to existing once-daily insulin analogs, with no greater risk of hypoglycemia. While phase 3 data are awaited to confirm efficacy and safety, we provide future clinical perspectives on practical considerations for the potential use of once-weekly insulins.

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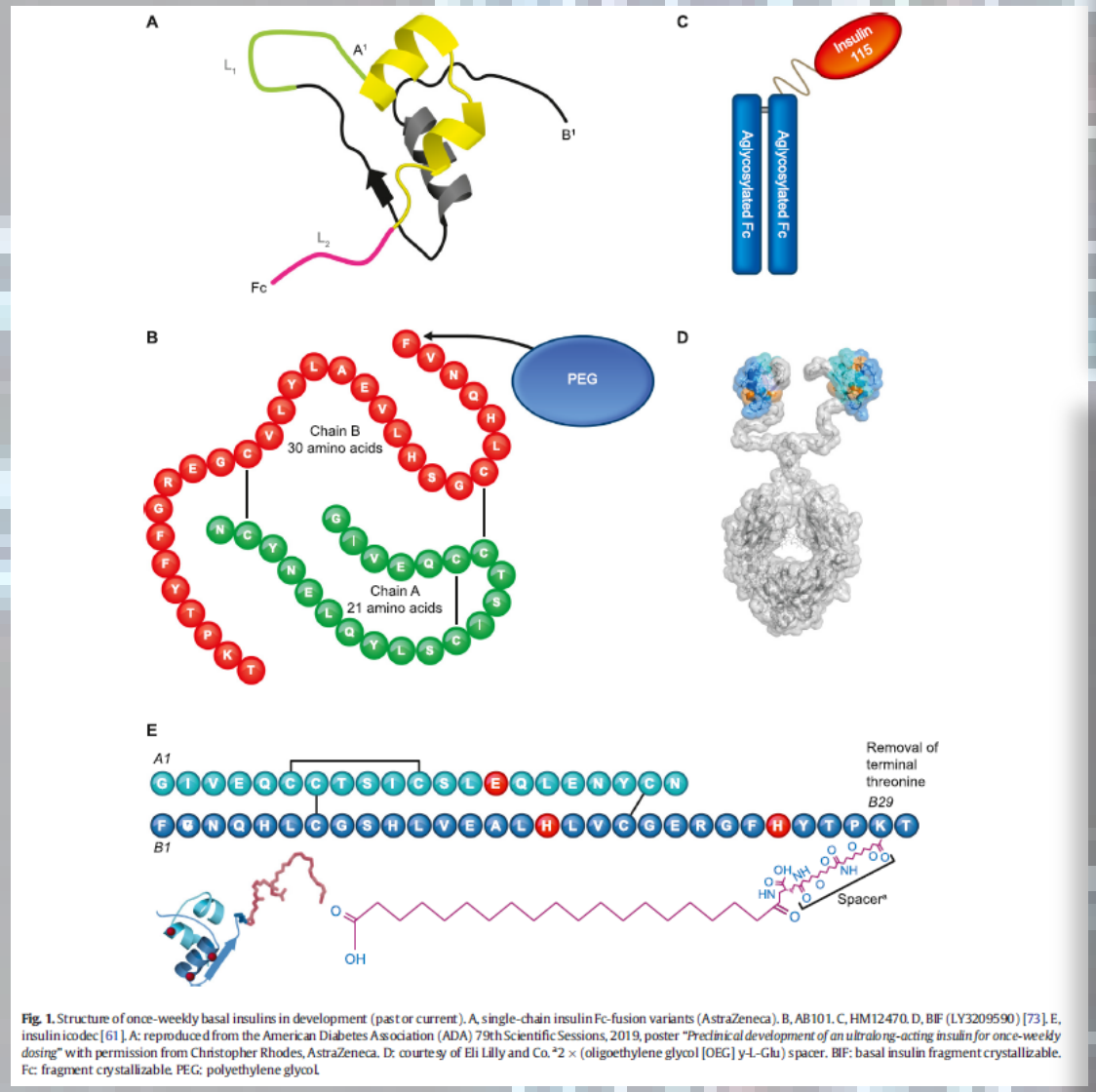


Fig. 1. Structure of once-weekly basal insulins in development (past or current). A, single-chain insulin Fc-fusion variants (AstraZeneca). B, AB101. C, HM12470. D, BIF (LY3209590) [73]. E, insulin icodec [61]. A: reproduced from the American Diabetes Association (ADA) 79th Scientific Sessions, 2019, poster *"Preclinical development of an ultralong-acting insulin for once-weekly dosing"* with permission from Christopher Rhodes, AstraZeneca. D: courtesy of Eli Lilly and Co. *2 × (oligoethylene glycol [OEG] γ-L-Glu) spacer. BIF: basal insulin fragment crystallizable. Fc: fragment crystallizable. PEG: polyethylene glycol.

- Proteine di fusione Fc dell'insullina nativa a catena singola
- AB 101
- HM12460A e HM12470
- Insumera (PE0139)
- Insulina basale Fc (BIF LY3209590)
- **Icodec**

Insulin icodec [1]

Acylated insulin: 20-carbon fatty diacid sidechain

High albumin binding

Reduced enzymatic degradation

Reduced insulin receptor-mediated clearance

Time-action profile (t½ = approx. 8 days) supports once-weekly dosing in humans

Currently in Phase 3 Trials

Basal Insulin Fc [2]

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

Homo-dimer

Reduced insulin receptor potency with full agonism

Time-action profile (t½ = approx. 17 days) supports once-weekly dosing in humans[3]

Currently in Phase 2 Trials

BIF

Il collegamento dell'insulina alla regione cristallizzabile del **frammento (Fc) dell'immunoglobulina G (IgG)** estende l'emivita dell'insulina perché la proteina di fusione beneficia della stessa via di riciclo che conferisce un'emivita relativamente lunga alle IgG endogene

Diabetes Mellitus and Glucose Metabolism
DYSREGULATED METABOLIC RESPONSE
Preclinical Characterization of Once Weekly Basal Insulin Fc (BIF)

Julie S. Moyers, PhD, Ryan J. Hansen, PhD, Jonathan W. Day, PhD, Craig D. Dickinson, PhD, Chen Zhang, MS, Steven D. Kahl, BS, Xiaoping Ruan, MD, Liyun Ding, BS, Robin M. Brown, BS, Hana E. Baker, PhD, John M. Beals, PhD.
Eli Lilly and Company, Indianapolis, IN, USA.

Diabetes Mellitus and Glucose Metabolism
CLINICAL TRIALS IN DIABETES AND METABOLIC DISEASE
Basal Insulin Fc (BIF), A Novel Insulin Suited For Once Weekly Dosing For The Treatment of Patients With Diabetes Mellitus

Tim Heise, MD1, Jenny Chien, PhD2, John Beals, PhD2, Charles Benson, MD, PhD2, Oliver Klein, MD1, Julie S. Moyers, PhD2, Axel Haupt, MD2, Edward J. Pratt, MD2.
1Profil, Neuss, Germany, 2Eli Lilly and Company, Indianapolis, IN, USA.

L'insulina settimanale BIF, è un **agonista selettivo per il recettore dell'insulina** e fornisce un agonismo completo, sebbene abbia **un'affinità inferiore** (2 ordini di grandezza) per questo rispetto all'insulina umana.
È interiorizzato dal recettore dell'insulina in misura simile all'insulina umana, ma ha una **potenza alquanto ridotta.**

- **la concentrazione plasmatica massima dopo singola dose sottocutanea è stata raggiunta il giorno 4;**
- **un'emivita media di circa 17 giorni;**
- **l'attività ipoglicemizzante è stata mantenuta per ≥5 giorni**

il **rapporto picco : minimo settimanale allo stato stazionario del BIF una volta alla settimana era di circa 1,1** rispetto a un rapporto picco : minimo giornaliero di 1,8 per l'insulina glargine giornaliera: **profilo insulinico molto più piatto.**

Diabetes Mellitus and Glucose Metabolism
IMPROVING DIABETES CARE: HOSPITAL DISCHARGE, COMPLICATIONS, AND NOVEL INSULIN THERAPY

Once Weekly Basal Insulin Fc (BIF) is Safe and Efficacious in Patients with Type 2 Diabetes Mellitus (T2DM) Previously Treated With Basal Insulin

Juan Pablo Frias, MD1, Jenny Chien, PhD2, Qianyi Zhang, PhD2, Emmanuel Chigutsa, PhD2, William Landschulz, MD, PhD2, Paula Wullenweber, BS2, Axel Haupt, MD2, Christof Kazda, MD, PhD, MscPM2.
1National Research Institute, San Diego, CA, USA, 2Eli Lilly and Company, Indianapolis, IN, USA.

The study design included **2 different dosing algorithms** for BIF (BIF-A1 and BIF-A2) with two different fasting glucose **(FG) targets of ≤140 mg/dL (BIF-A1) and ≤120 mg/dL (BIF-A2). Insulin degludec was titrated to a FG target of ≤100mg/ dL**

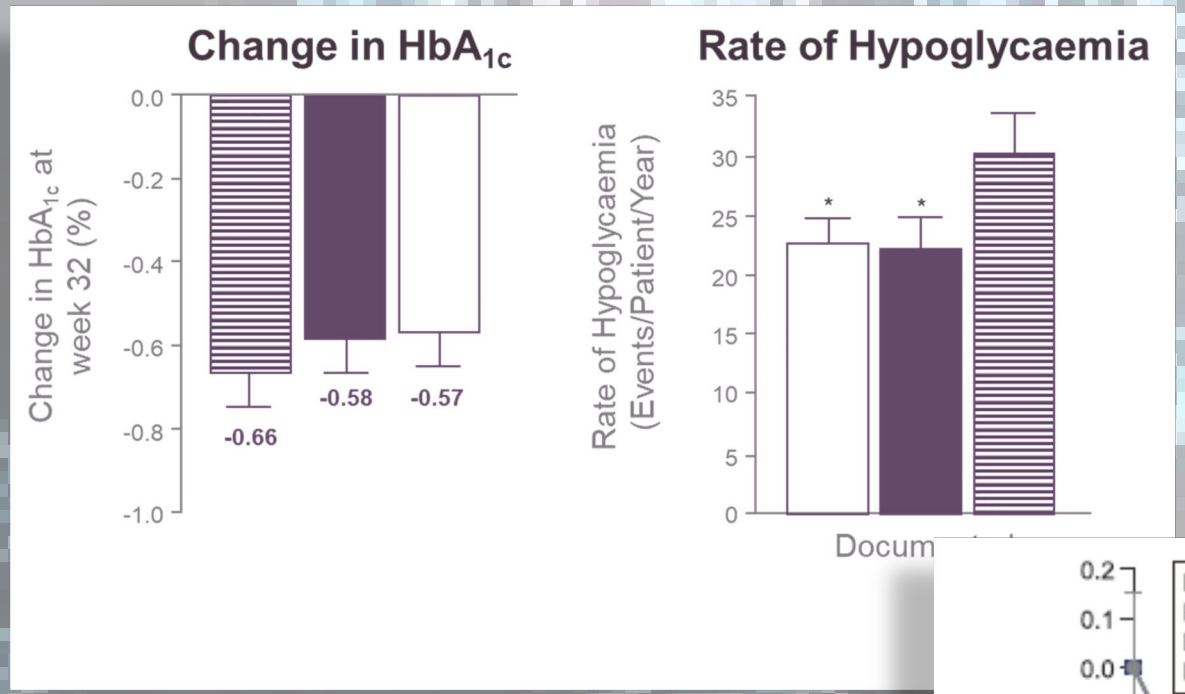
Table 2
Summary of phase 2 clinical data for BIF in patients with T2D who were previously treated with basal insulin and up to three oral antidiabetic medications for 32 weeks (NCT03736785) [73,74].

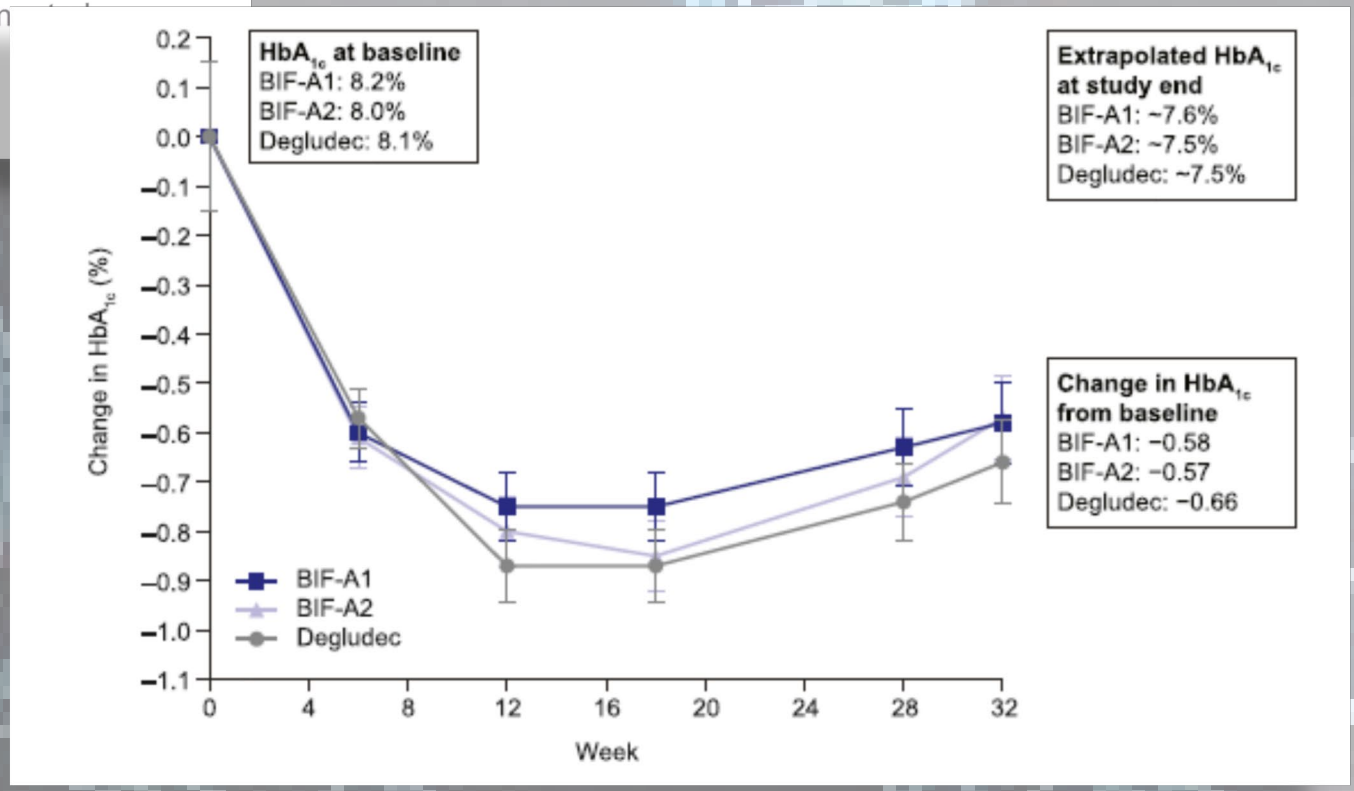
Outcome	BIF-A1 ($n = 135$) FPG target of 140 mg/dL	BIF-A2 ($n = 132$) FPG target of 120 mg/dL	Insulin degludec (n = 132) FPG target of 100 mg/dL
Mean baseline $HbA_{1c} \pm SD$, %	8.20 ± 0.87	8.03 ± 0.89	8.13 ± 0.88
Change in HbA_{1c}, LS mean ± SE, %	−0.58 ± 0.083 (noninferior to insulin degludec)	−0.57 ± 0.085 (noninferior to insulin degludec)	−0.66 ± 0.084
Change in FPG, LS mean ± SE, mg/dL	−13.1 ± 4.01	−18.6 ± 4.14	−31.5 ± 4.03
Hypoglycemic events (<54 mg/dL [<3.0 mmol/L]),[a] mean ± SE, *n* events/patient/year	0.73 ± 0.12 (not significant vs. degludec)	1.22 ± 0.38 (not significant vs. degludec)	1.56 ± 0.38
Change in body weight, LS mean ± SE, kg	1.0 ± 0.33 (significant vs. degludec)	1.0 ± 0.33 (significant vs. degludec)	2.0 ± 0.33
Nonserious AEs, n patients (%)[b]	17 (12.6)	29 (22.0)	13 (9.9)
Serious AEs, n patients (%)[b]	7 (5.2)	8 (6.1)	10 (7.6)
Serious hypoglycemic AEs, *n* events[c]	0	2	0

AE: adverse event. BIF: basal insulin fragment crystallizable. CI: confidence interval. FPG: fasting plasma glucose. HbA_{1c}: glycated hemoglobin. LS: least-squares. SD: standard deviation. SE: standard error. T2D: type 2 diabetes.
An inclusion criterion was the use of up to three oral antidiabetic medications, including dipeptidyl peptidase-4 inhibitors, sodium–glucose cotransporter-2 inhibitors, biguanides, alpha-glucosidase inhibitors, or sulfonylureas.
[a] Patients in the BIF-A1 and BIF-A2 treatment arms had significantly fewer hypoglycemic events than those in the insulin degludec treatment arm for all documented events of plasma glucose ≤70 mg/dL (≤3.9 mmol/L).
[b] Time frame up to 37 weeks.
[c] Patient-reported events of blood glucose of <54 mg/dL (<3.0 mmol/L).

In summary, BIF, when administered weekly according to either dosing algorithm, **was noninferior** to insulin degludec for glycemic control as measured by change in HbA1c after 32 weeks **with a lower rate** of documented and nocturnal hypoglycemia ≤70 mg/dL and less weight gain.

Sono in corso due studi per confrontare BIF con insulina degludec in pazienti **mai trattati con insulina con T2D** (NCT04450394)
e in pazienti con T1D (NCT04450407).


Change in HbA1c
Change in HbA1c at week 32 (%)
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-0.66
-0.58
-0.57
Rate of Hypoglycaemia
Rate of Hypoglycaemia (Events/Patient/Year)
35
30
25
20
15
10
5
0
*
*


HbA1c at baseline
BIF-A1: 8.2%
BIF-A2: 8.0%
Degludec: 8.1%
Extrapolated HbA1c at study end
BIF-A1: ~7.6%
BIF-A2: ~7.5%
Degludec: ~7.5%
Change in HbA1c from baseline
BIF-A1: −0.58
BIF-A2: −0.57
Degludec: −0.66
Change in HbA1c (%)
0.2
0.1
0.0
−0.1
−0.2
−0.3
−0.4
−0.5
−0.6
−0.7
−0.8
−0.9
−1.0
−1.1
BIF-A1
BIF-A2
Degludec
0
4
8
12
16
20
24
28
32
Week

L'ODRADEK

…Ha l'aspetto di un rocchetto di filo, piatto e a forma di stella, e in effetti sembra fatto di filo, ma di pezzi di filo tagliati, vecchi, annodati e confusi, di diverso tipo e colore. Non è solo un rocchetto; dal centro della stella parte un bastoncino trasversale, e da questo bastoncino se ne stacca un altro ad angolo retto. Con l'aiuto di quest'ultimo bastoncino da un lato, e di un raggio della stella dall'altro, l'insieme può sollevarsi, come se avesse due gambe… Odradek è straordinariamente mobile e non si lascia catturare.

Può stare in soffitta, nel vano delle scale, nei corridoi; nell'androne. A volte passa mesi senza farsi vedere. Si è spostato nelle case vicine, ma torna sempre nella nostra. Spesso, quando uno esce dalla porta e lo trova sul pianerottolo delle scale, viene voglia di parlargli: Naturalmente non gli osi fanno domande difficili, ma lo si tratta — per via delle dimensioni minuscole — come un bambino. « Come ti chiami?» gli chiedono, «Odradek» risponde. «E dove vivi?». «Senza fissa dimora» dice e ride, *ma è una risata senza polmoni. Suona come un fruscio di foglie secche*. In genere il dialogo finisce lì….

Mi chiedo invano cosa gli accadrà. Può morire? Tutto ciò che muore ha avuto prima uno scopo, una specie di attività, e per questo si è logorato; non è così per Odradek. Scenderà la scala trascinando filacce davanti ai piedi dei miei figli e dei figli dei miei figli? Non fa male a nessuno, ma l'idea che possa sopravvivermi è quasi dolorosa per me.

Franz Kafka


ICODEC

ICODEC

Sia l'insulina degludec che l'insulina icodec sono **analoghi dell'insulina acilata**
L'adesione di un **diacido grasso a 20 atomi di carbonio** (acido icosandioico) alla catena B della molecola di insulina consente un forte legame reversibile con l'albumina. Inoltre, tre sostituzioni di amminoacidi , in A14, B16 e B25, migliorano la stabilità e riducono al minimo la degradazione enzimatica . Queste modifiche riducono anche l' affinità di legame del recettore dell'insulina di icodec e la successiva clearance mediata dal recettore dell'insulina, per conferire un'emivita più lunga

L'insulina icodec è progettata per avere un profilo farmacocinetico prolungato e un effetto ipoglicemizzante lento e costante **principalmente attraverso il ridotto legame del recettore dell'insulina e il tasso di clearance mediata dal recettore dell'insulina, piuttosto che attraverso il rilascio prolungato dal sito di iniezione**

- *tempo alla concentrazione plasmatica massima di 16 h (mediana)*
- *un'emivita media di 196 h l'effetto ipoglicemizzante era distribuito uniformemente nel periodo di somministrazione di 7 giorni*

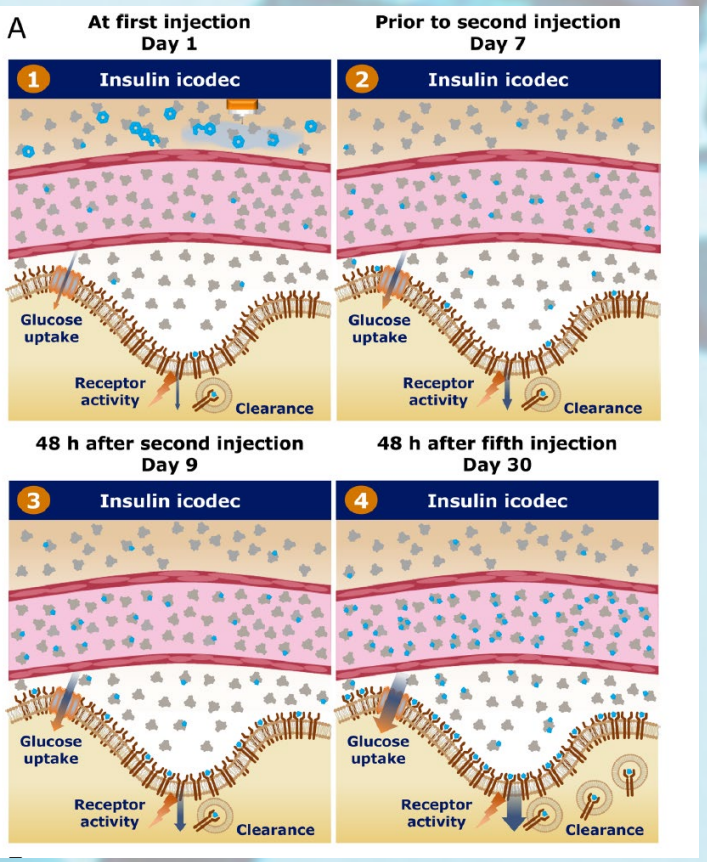
L'effetto ipoglicemizzante completo dell'insulina icodec una volta alla settimana non si osserva per circa 3-4 settimane fino a quando icodec non raggiunge lo stato stazionario, quindi potrebbe **essere necessaria insulina aggiuntiva** nel periodo di transizione quando si passa da un'insulina basale giornaliera a insulina icodec

Open access Original research

BMJ Open Diabetes Research & Care

Molecular and pharmacological characterization of insulin icodec: a new basal insulin analog designed for once-weekly dosing

Erica Nishimura ,[1] Lone Pridal,[1] Tine Glendorf,[1] Bo Falk Hansen,[1] František Hubálek,[1] Thomas Kjeldsen,[1] Niels Rode Kristensen,[2] Anne Lützen,[1] Karsten Lyby,[2] Peter Madsen,[1] Thomas Åskov Pedersen,[1] Rasmus Ribel-Madsen,[2] Carsten Enggaard Stidsen,[1] Hanne Haahr[2]



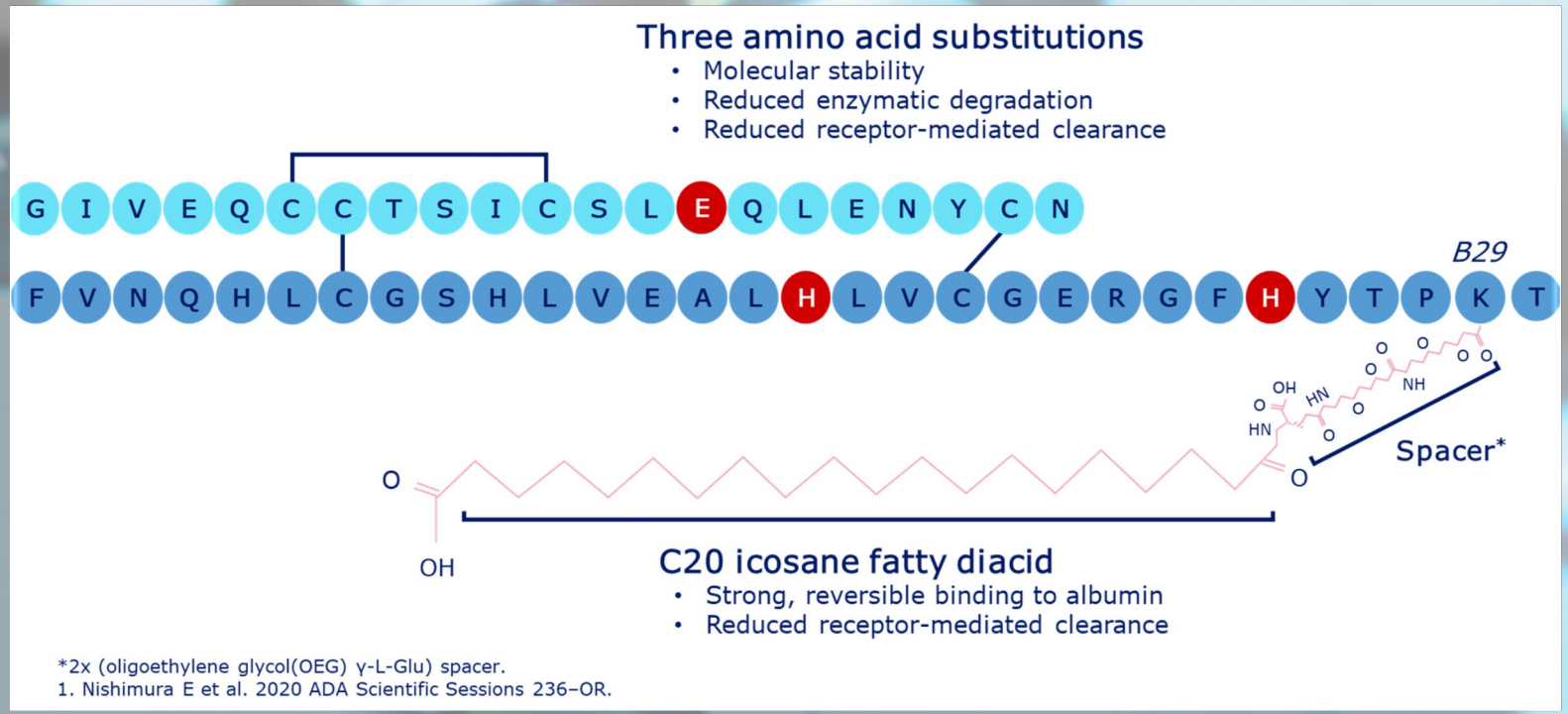
Journal of Medicinal Chemistry

pubs.acs.org/jmc Article

Molecular Engineering of Insulin Icodec, the First Acylated Insulin Analog for Once-Weekly Administration in Humans

Thomas B. Kjeldsen,* František Hubálek, Claudia U. Hjørringgaard, Tina M. Tagmose, Erica Nishimura, Carsten E. Stidsen, Trine Porsgaard, Christian Fledelius, Hanne H. F. Refsgaard, Sanne Gram-Nielsen, Helle Naver, Lone Pridal, Thomas Hoeg-Jensen, Claus Bekker Jeppesen, Valentina Manfè, Svend Ludvigsen, Inger Lautrup-Larsen, and Peter Madsen

Cite This: https://doi.org/10.1021/acs.jmedchem.1c00257 Read Online



ONWARDS

Insulin-naïve T2D

ONWARDS 1
Insulin naïve T2D

- Insulin icodec + non-insulin anti-diabetic drugs
- IGlar U100 + non-insulin anti-diabetic drugs

ONWARDS 3
Insulin naïve T2D

- Insulin icodec + non-insulin anti-diabetic drugs
- IDeg + non-insulin anti-diabetic drugs

ONWARDS 5
RCT with real world elements
Insulin naïve T2D

- Insulin icodec with DoseGuide
- Once Daily basal insulin analogues

Insulin-experienced T2D

ONWARDS 2
Basal switch T2D

- Insulin icodec + non-insulin anti-diabetic drugs
- IDeg + non-insulin anti-diabetic drugs

ONWARDS 4
Basal switch T2D

- Insulin icodec + IAsp ± non-insulin anti-diabetic drugs
- IGlar U100 + IAsp ± non-insulin anti-diabetic drugs

T1D

ONWARDS 6
Basal-bolus T1D

- Insulin icodec + IAsp
- IDeg + IAsp

Weekly Insulin Becoming a Reality

Jay S. Skyler

Diabetes Care 2021;44:1459–1461 | https://doi.org/10.2337/dci21-0011

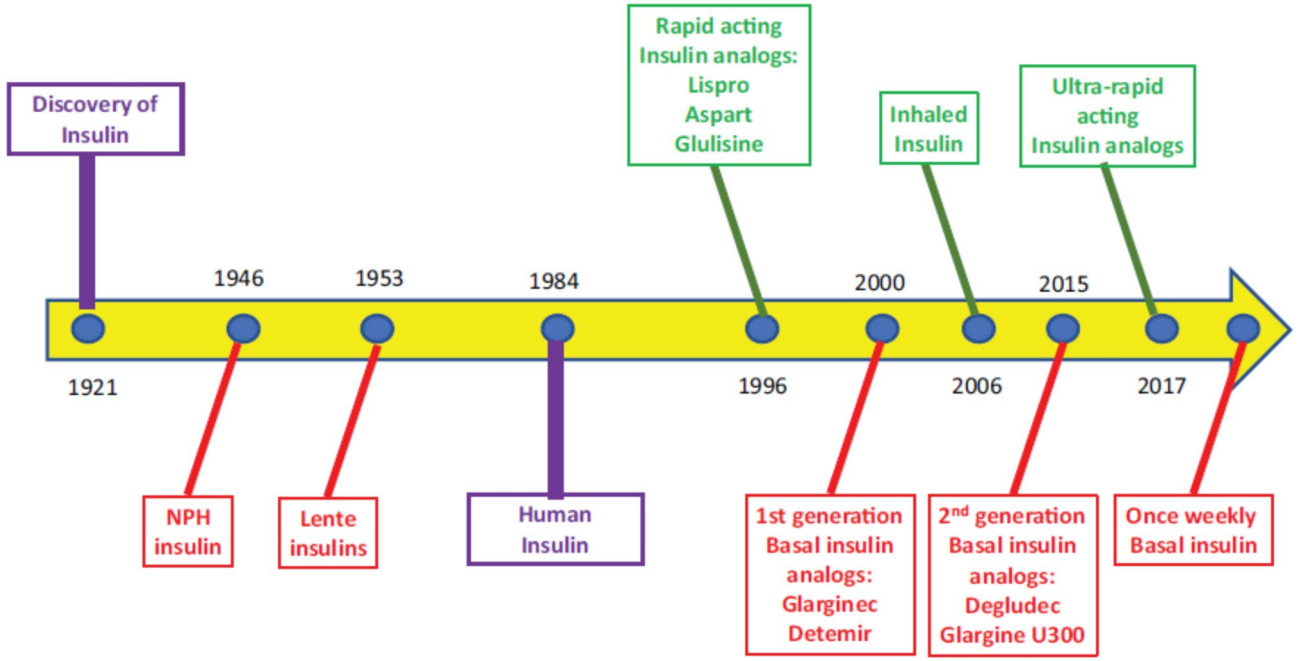


Figure 1—Timeline of major clinical developments in insulin's evolution. Green highlights meal-related insulin developments; red highlights basal insulin developments; and purple highlights discovery of insulin and development of human insulins.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 26, 2020 VOL. 383 NO. 22

Once-Weekly Insulin for Type 2 Diabetes without Previous Insulin Treatment

Julio Rosenstock, M.D., Harpreet S. Bajaj, M.D., M.P.H., Andrej Janež, M.D., Ph.D., Robert Silver, M.D., Kamilla Begtrup, M.Sc., Melissa V. Hansen, M.D., Ph.D., Ting Jia, M.D., Ph.D., and Ronald Goldenberg, M.D., for the NN1436-4383 Investigators*

>>> Once-weekly treatment with insulin icodec had **glucose-lowering efficacy and a safety profile similar** to those of once-daily insulin glargine U100 in patients with type 2 diabetes.

We conducted a **26-week**, randomized, double-blind, double-dummy, phase 2 trial to investigate the efficacy and safety of once-weekly insulin icodec

- as compared with once-daily insulin **glargine U100**
- in patients **who had not previously received long-term insulin treatment**
- and whose **type 2 diabetes** was
- inadequately controlled (glycated hemoglobin level, 7.0 to 9.5%)
- while taking metformin with or without a dipeptidyl peptidase 4 inhibitor.

The starting dose of **icodec was 70 U** once per week, and the starting dose of glargine was 10 U once per day.
After randomization, insulin doses were adjusted weekly to achieve a pre-breakfast patient-measured blood glucose target **of 70 to 108 mg** per deciliter (3.9 to 6.0 mmol per liter).

The primary end point was the change in the glycated hemoglobin level from baseline to week 26,

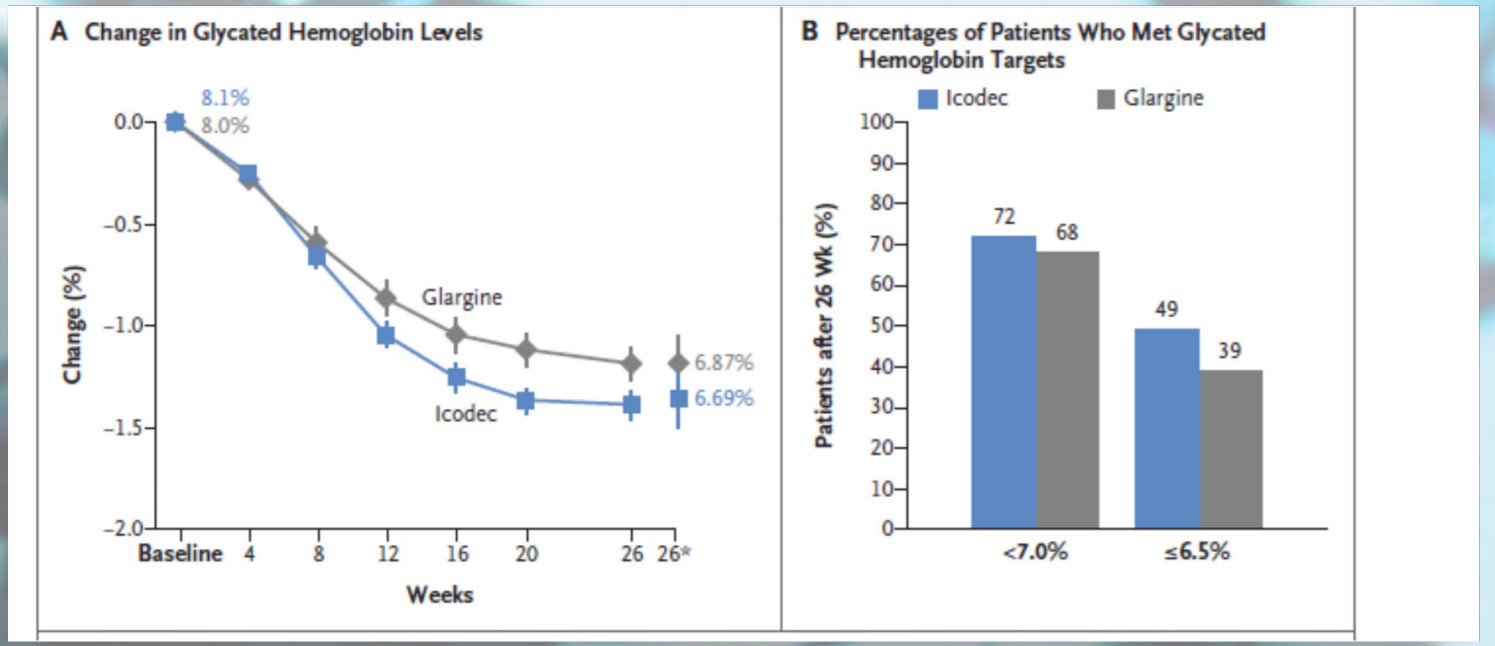
Key secondary end points included

- the changes in fasting plasma glucose level,
- body weight,
- and the mean of the 9-point patient measured blood glucose profile from baseline to
- week 26 and the mean weekly insulin dose during the last 2 weeks of treatment. In addition,
- the time spent with the blood glucose level in the tight glycemic range of 70 to 140 mg per deciliter (3.9 to 7.8 mmol per liter), monitored by flash glucose monitoring (FreeStyle Libre Pro) during the last 2 weeks of treatment,

- *During the trial, a similarly robust reduction in the glycated hemoglobin level was observed with both drugs, with more than two thirds of patients reaching a glycated hemoglobin level of less than 7%;*

- *the reduction in the fasting plasma glucose level was also similar in the two groups,*

- *and greater improvements in the 9-point patient-measured blood glucose profile were observed with once-weekly insulin icodec than with once-daily glargine,*



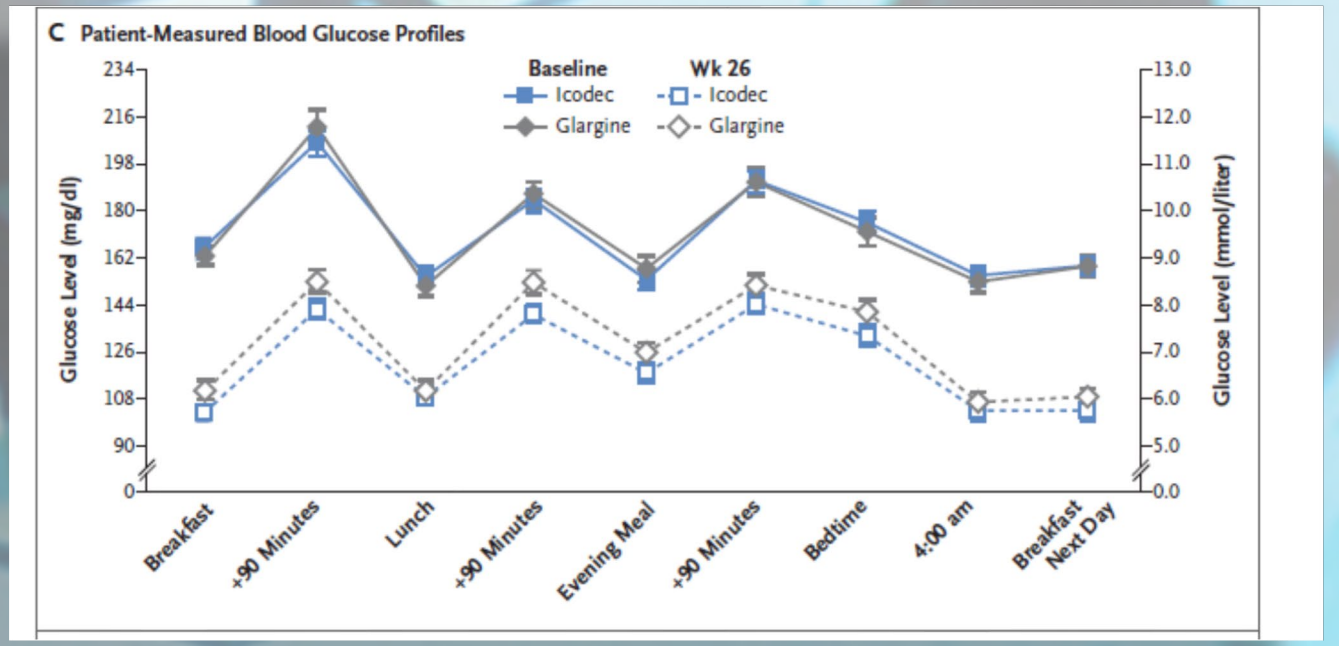
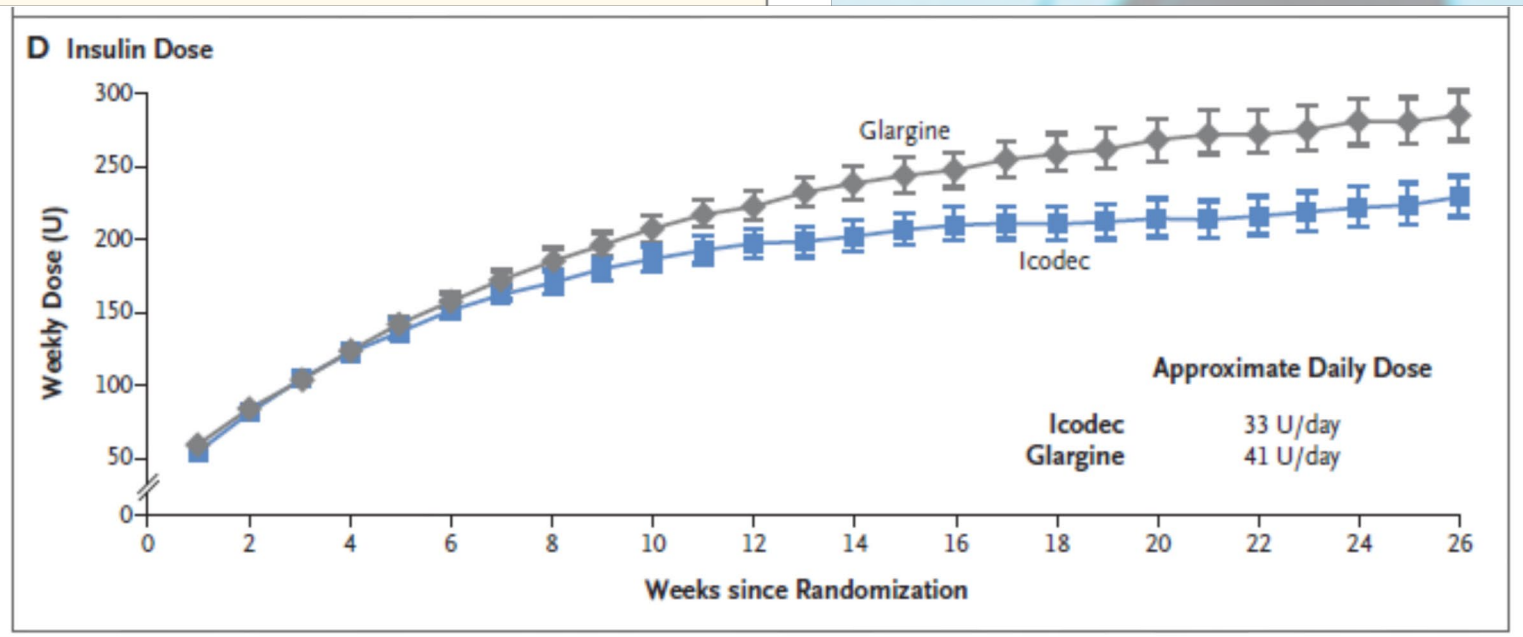


Table 2. Key Secondary End Points.

End Point	Icodec (N=125)		Glargine (N=122)		Difference or Ratio (95% CI)
	No. of Patients	Change from Baseline	No. of Patients	Change from Baseline	
End points assessed as estimated mean change from baseline to week 26*					
Fasting plasma glucose level — mg/dl	121	−57.74	116	−53.86	−3.9 (−11.9 to 4.2)†
Mean 9-point patient-measured blood glucose level — mg/dl	112	−48.63	111	−40.77	−7.86 (−14.10 to −1.62)†
Body weight — kg	122	1.49	119	1.56	−0.08 (−1.08 to 0.93)†
End points assessed as estimated mean during the last 2 weeks of treatment‡					
Time with glucose level in range of 70–140 mg/dl — %	85	66.11	83	60.71	5.39 (0.69 to 10.09)†
Insulin dose — U/wk	120	229.06§	117	284.05¶	0.81 (0.69 to 0.94)‖

* Fasting plasma glucose level, mean 9-point patient-measured blood g
for repeated measures with an unstructured covariance matrix. The m
graphic region, treatment, and visit as fixed factors and the relevant b
and covariates were also included in the model.
† Value is the estimated difference between the groups (icodec minus g
‡ Time in range and weekly insulin dose were analyzed in an analysis of
graphic region, and treatment as fixed factors and with no imputation
analysis.
§ Value represents approximately 33 U per day.
¶ Value represents approximately 41 U per day.
‖ Value is the estimated ratio (icodec:glargine).



- The **higher number of level 1 hypoglycemic events in the icodec group** than in the glargine group may reflect the trial design and **suggests** that the **fasting glucose target may need to be slightly higher** and **the insulin dose increments smaller**

- rates of **level 2 hypoglycemic events are similar**

- **with only one case of questionable severe hypoglycemia** reported in a patient receiving icodec, which was resolved with oral carbohydrate administration.

The mean weekly insulin dose was higher in the glargine group than in the icodec group

no difference in changes in body weight was noted between the two treatment groups

Facilitate insulin management, **reducing the number of injections per year from 365 to 52.**

with once-weekly icodec **spent a greater amount of time in the tight glycemic range (70 to 140 mg per deciliter)** than did those treated with once daily glargine. **to an extra 78 minutes** spent in the target glycemic .

an injectable once-weekly glucagon-like peptide 1 (GLP-1….**extrapolating these data** to our trial results could suggest that once-weekly insulin icodec has the potential to **improve treatment satisfaction, adherence, and persistence …., by reducing clinical inertia and promoting better acceptance of insulin therapy**

Switching to Once-Weekly Insulin Icodec Versus Once-Daily Insulin Glargine U100 in Type 2 Diabetes Inadequately Controlled on Daily Basal Insulin: A Phase 2 Randomized Controlled Trial

Harpreet S. Bajaj,[1,2] Richard M. Bergenstal,[3] Andreas Christoffersen,[4] Melanie J. Davies,[5,6] Amoolya Gowda,[4] Joakim Isendahl,[4] Ildiko Lingvay,[7] Peter A. Senior,[8] Robert J. Silver,[9] Roberto Trevisan,[10] and Julio Rosenstock[11]

Diabetes Care 2021;44:1586–1594 | https://doi.org/10.2337/dc20-2877

This multicenter, open-label, treat-to-target phase 2 trial randomized (1:1:1) eligible

- **basal insulin–treated** (total daily dose 10–50 units) people
- with **type 2 diabetes** (HbA_{1c} 7.0–10.0% [53.0–85.8 mmol/mol])
- to icodec with an initial 100% **loading dose** (in which only the first dose was doubled [icodec LD]),
- icodec with **no loading dose** (icodec NLD),
- or IGlar U100
- for **16 weeks.**

Primary end point was percent time in range (**TIR; 3.9–10.0 mmol/L [70–180 mg/dL])** during weeks 15 and 16, measured using **continuous glucose monitoring**

Key secondary end points included HbA_{1c}, adverse events (AEs), and hypoglycemia.

A treat-to-target approach was used to ensure optimal titration of insulin; doses of icodec and IGlar U100 were titrated weekly to achieve a **prebreakfast self-measured blood glucose (SMBG) target of 4.4–7.2 mmol/L (80–130 mg/dL).** Participants measured SMBG levels each day before breakfast.

Doses were uptitrated weekly by 4 units/day (IGlarU100) or 28 units/week (icodec LD and icodec NLD) if the mean of the three most recent prebreakfast SMBG values in a week was >7.2 mmol/L (>130 mg/dL).

However, if any one of the three prebreakfast SMBG values was <4.4 mmol/L (<80 mg/dL), the insulin doses were downtitrated 4 units/day (IGlar U100) or 28 units/week (icodec LD and icodec NLD)

RESULTS

Estimated **mean TIR** during weeks 15 and 16 was **72.9%** (icodec LD; n 5 54), 66.0% (icodec NLD; n 5 50), and 65.0% (IGlar U100; n 5 50), with a statistically significant difference favoring icodec LD versus IGlar U100 (7.9%-points [95% CI 1.8–13.9]).

Mean HbA_{1c} reduced from 7.9% (62.8 mmol/mol) at baseline to **7.1%** (54.4 mmol/ mol icodec LD) and 7.4% (57.6 mmol/mol icodec NLD and IGlar U100);

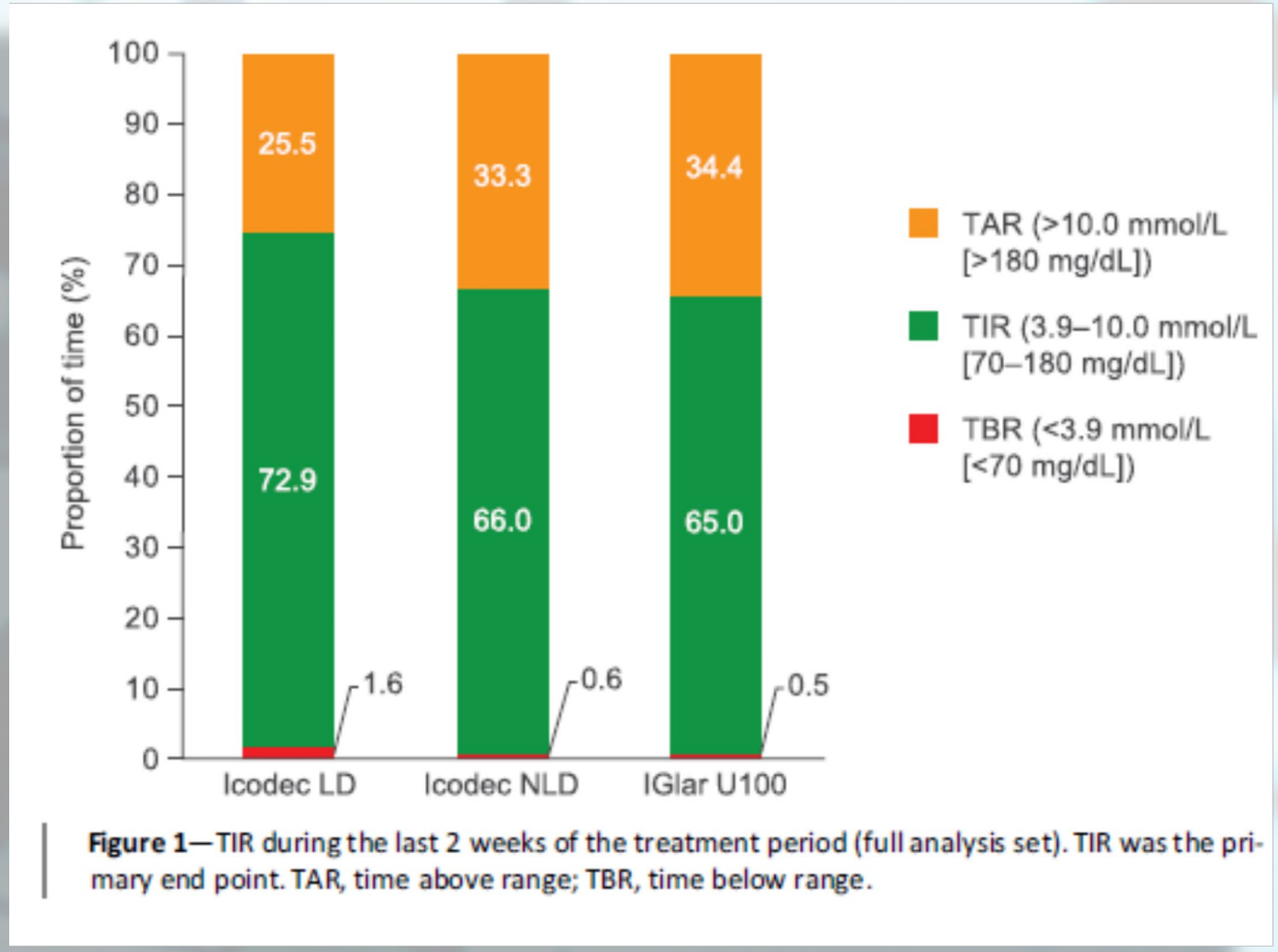
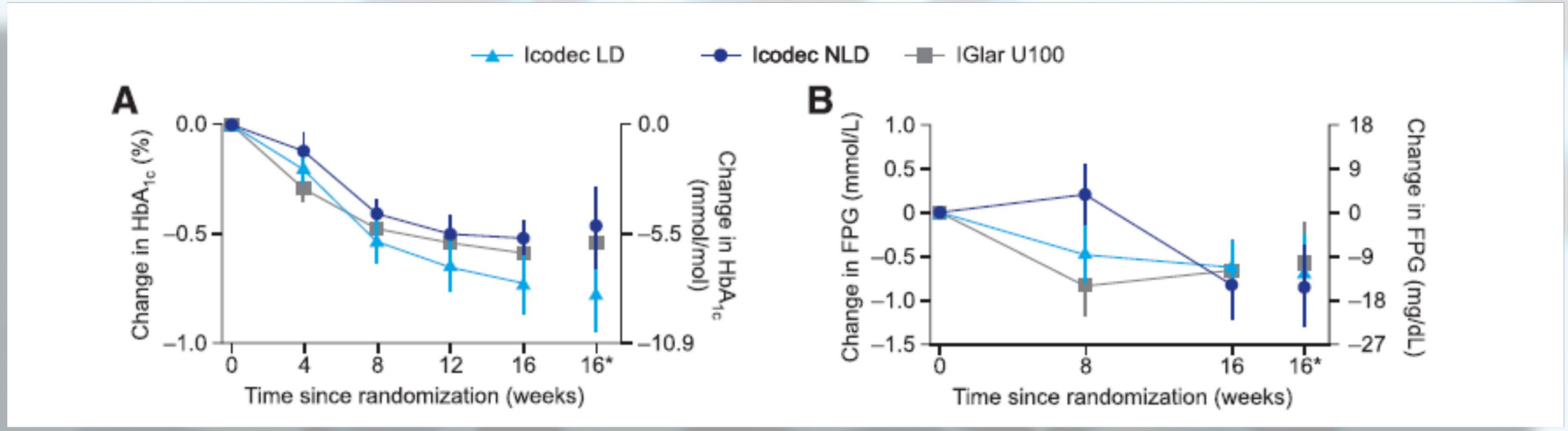
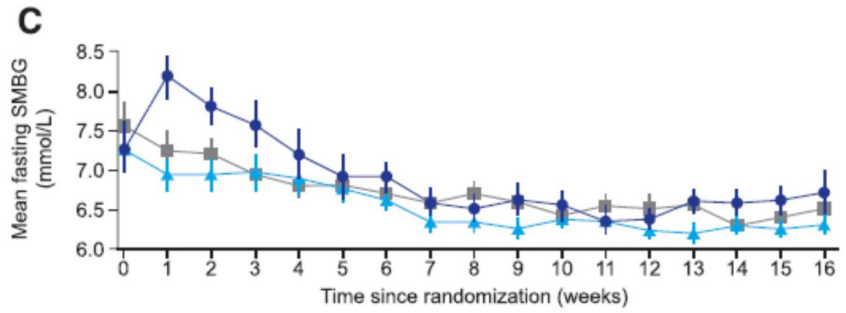
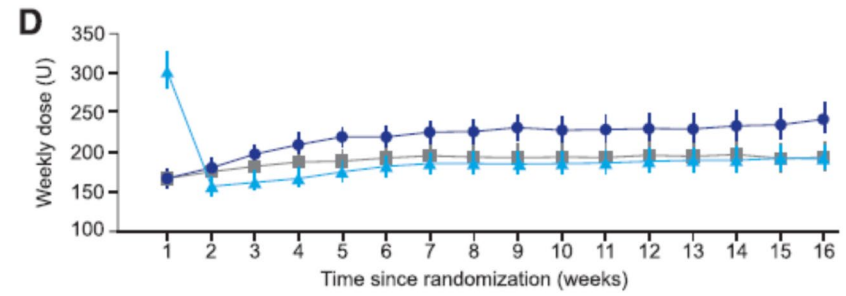


Figure 1—TIR during the last 2 weeks of the treatment period (full analysis set). TIR was the primary end point. TAR, time above range; TBR, time below range.







After 16 weeks of treatment, **the proportions of participants achieving a target HbA1c of <7.0%** (53 mmol/mol) were **44.2%**, 25.0%, and 30.6% for the icodec LD, icodec NLD, and IGlar U100 groups, respectively (no statistical analyses were performed).

SMBG levels decreased in all treatment groups over the course of the trial; however, **in the icodec NLD group, mean SMBG levels were seen to increase slightly** versus baseline during the first 3 weeks before reverting to levels similar to those for the icodec LD and Iglar U100 groups at about week 5.

Although the mean change in **body weight** from baseline was not statistically significantly different between the icodec LD and Iglar U100 groups (ETD, 0.51 kg [95% CI –0.44 to 1.47]; P 5 NS), **a statistically significantly greater increase in body weight was seen with icodec NLD compared with IGlar U100** (ETD, 1.22 kg [95% CI 0.24–2.2]; P 5 0.01).

- The rate and pattern of **level 1 hypoglycemia** over the on-treatment period **were similar** across all groups.
- **The rate and pattern of combined level 2 and level 3 hypoglycemic** episodes **were similar** between the icodec LD and IGlar U100 groups and **appeared to be lower for the icodec NLD** group than for the IGlar U100 group.
- **No initial increase** in level 1 or combined level 2 and level 3 hypoglycemia was **observed in the icodec LD group.**

doubling of the first dose

- resulted in statistically significantly **longer TIR** than switching to IGlar U100.
- furthermore, doubling the initial dose **did not increase the risk of hypoglycemia** at any point during the trial period
- and **prevented the mild, transient prebreakfast** SMBG elevation observed in those randomized to icodec without a loading dose during the immediate postswitch period

This may be explained by the molecular characteristics and pharmacokinetic and pharmacodynamic properties of icodec.
While the long half-life of icodec makes it suitable for once-weekly dosing, it also extends the time to steady state (by 3–4 weeks).This could consequently produce an initial mild deterioration in fasting glucose levels in those switching from a prior basal insulin therapy who will have an initial treatment …indicated that using a loading dose of icodec could offset this by ensuring the availability of an adequate albumin- bound inactive reservoir; slow release of icodec molecules would provide effective glucose lowering without an increased risk of hypoglycemia versus once daily basal insulin.

- ✓ **mean TIR of >70%, a target recommended by the** International Consensus
- ✓ the HbA1c reductions and **proportion of participants who achieved HbA1c <7.0%** (<53.0 mmol/mol) with icodec are consistent with the observed increase in percent TIR.

A Randomized, Open-Label Comparison of Once-Weekly Insulin Icodec Titration Strategies Versus Once-Daily Insulin Glargine U100

Ildiko Lingvay,[1,2] John B. Buse,[3] Edward Franek,[4] Melissa V. Hansen,[5] Mette M. Koefoed,[5] Chantal Mathieu,[6] Jeremy Pettus,[7] Karolina Stachlewska,[5] and Julio Rosenstock[8]

Diabetes Care 2021;44:1595–1603 | https://doi.org/10.2337/dc20-2878

This was a phase 2, randomized, open-label, **16-week**, treat-to-target study. **Insulin-naive** adults (n 5 205) **with type 2 diabetes** and HbA_{1c} 7–10% while treated with oral glucose-lowering medications initiated once-weekly icodec titrations

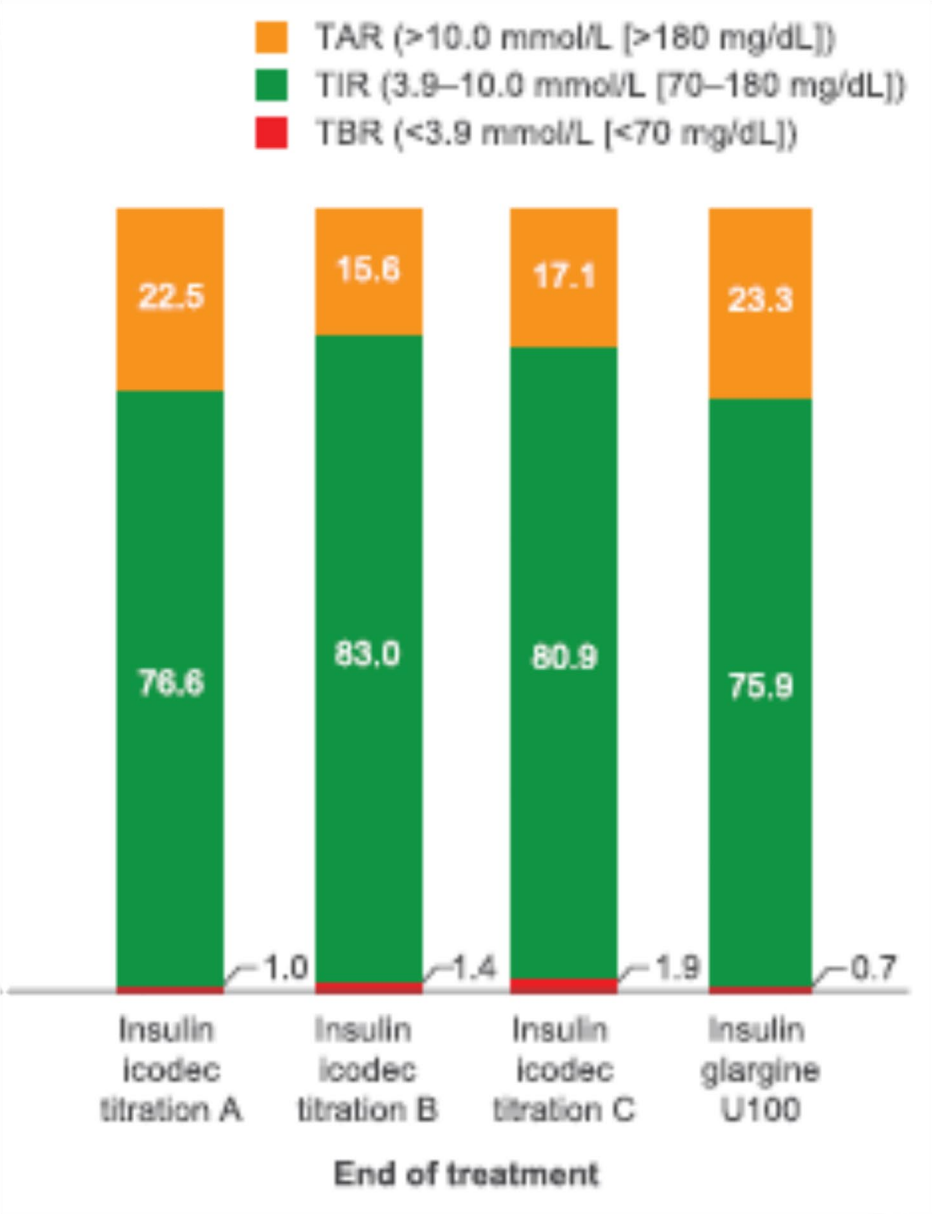
A (prebreakfast self-measured blood glucose **target 80–130 mg/dL**; adjustment **±21 units/week**; n 5 51),

B (80–130 mg/dL; ±28 units/week; n 5 51),

C (70–108 mg/dL; ±28 units/week; n 5 52),

or once-daily insulin glargine 100 units/mL (IGlar U100) (80–130 mg/dL; ±4 units/day; n 5 51), all titrated weekly.
Percentage of time in range **(TIR)** (70–180 mg/dL) during weeks 15 and 16 was measured using continuous glucose monitoring.

- icodec **titration A** was included for investigation of the effect of smaller dose increments.
- Icodec **titration B** was intended to provide a direct comparator to Iglar U100, with the same plasma glucose target and corresponding dose increments,
- The more stringent target used in icodec **titration C** was included not only to explore the effect of such a stringent target but also to serve as a reference for comparison of the present data with those from the 26-week phase 2 trial



A (prebreakfast self-measured blood glucose **target 80–130 mg/dL**; adjustment **±21 units/week**)

B (80–130 mg/dL; ±28 units/week)

C (70–108 mg/dL; ±28 units/week)

RESULTS

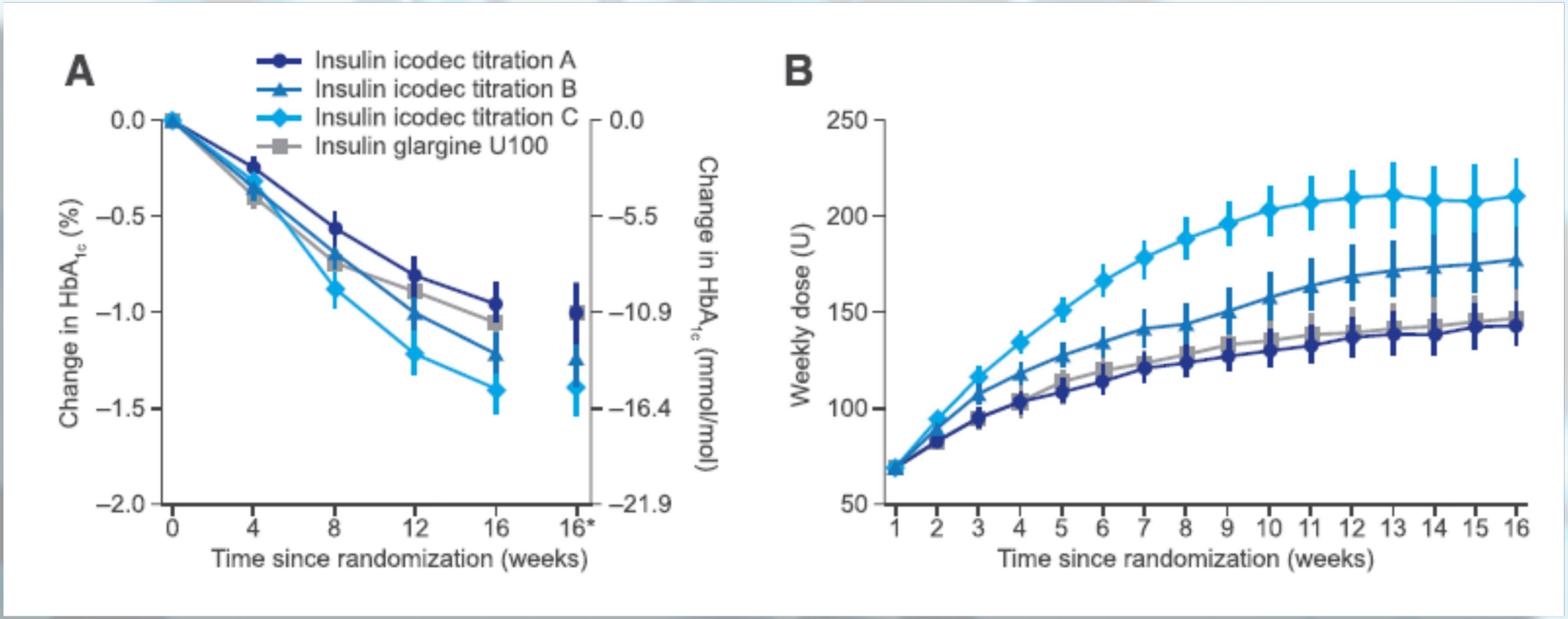
TIR improved from baseline to weeks 15 and 16 (estimated mean: **A, 76.6%; B, 83.0%; C, 80.9%;** IGlar U100,75.9%); **TIR was greater for titration B** than for IGlar U100 (estimated treatment difference 7.08%-points; 95% CI 2.12 to 12.04; P5 0.005).

Level 2 hypoglycemia (<54 mg/dL) **was low in all groups** (0.05, 0.15, 0.38, 0.00 events), with no episodes of severe hypoglycemia.

A (prebreakfast self-measured blood glucose **target 80–130 mg/dL**; adjustment **±21 units/week**)

B (80–130 mg/dL; ±28 units/week)

C (70–108 mg/dL; ±28 units/week)



titration B,

- **a greater TIR** was achieved with insulin icodec, corresponding approximately to an extra 102 min spent in the target glycemic range daily.
- HbA1c was lower with insulin icodec,
- and there was a slightly higher rate of level 2 and level 1 hypoglycemia; the hypoglycemia event rate was very low overall.

Titration to attain a more stringent glucose target of 3.9–6.0 mmol/L (70–108 mg/dL), as used in titration **algorithm C**, was also associated

- with a **higher rate of hypoglycemia** in comparison with IGlar U100 titrated to a target of 4.4–7.2 mmol/L (80–130 mg/ dL),
- while TIR was numerically greater
- and HbA1c lower with insulin icodec

Lastly, **titration algorithm A**, which used the same glucose target of 4.4–7.2 mmol/L (80–130 mg/dL) and a smaller titration increment of ±21 units in comparison with IGlar U100, which was titrated in ±4 unit increments (weekly equivalent ±28 units), led to

- **comparable** glucose control, as assessed by both TIR and HbA1c,and comparable hypoglycemia rates.

CONCLUSIONS

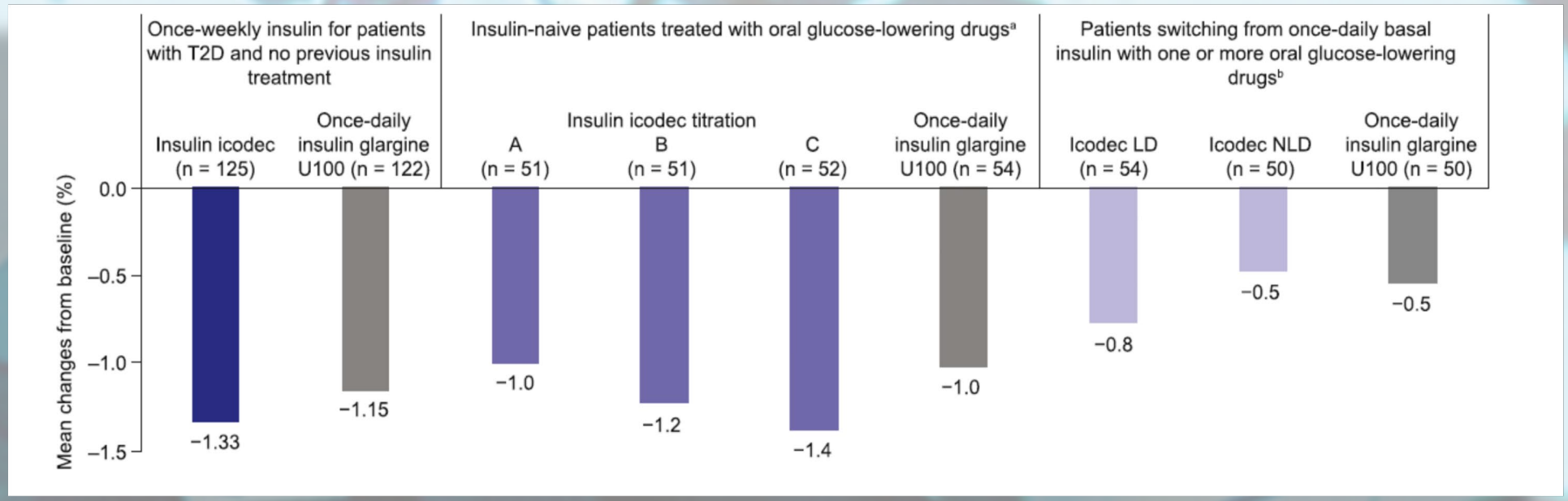
Once-weekly icodec was efficacious and well tolerated across all three titration algorithms investigated.

The results for **icodec titration A (80–130 mg/dL; ±21 units/week) displayed the best balance between glycemic control and risk of hypoglycemia.**

A (prebreakfast self-measured blood glucose **target 80–130 mg/dL**; adjustment **±21 units/week**)

B (80–130 mg/dL; ±28 units/week)

C (70–108 mg/dL; ±28 units/week)



Icodec **head-to-head** vs. glargine U100 in insulin-naïve T2D[1]

- Icodec + OADs
- Glargine U100 + OADs

Icodec **titration trial** in insulin-naïve T2D[2]

- Icodec titration A
- Icodec titration B
- Icodec titration C
- Glargine U100

Switching from daily basal insulin to icodec in T2D

- Icodec with loading dose
- Icodec without loading dose
- Glargine U100

REMORA

Remora, in latino, significa «ritardo». …Plinio enuncia i suoi poteri;

« C'è un pesce, chiamato remora; avvezzo ad aggirarsi fra gli scogli, il quale si attacca alle carene e fa muovere le navi più lentamente; per questo l'hanno chiamato così, …ma compensa questi mali con una qualità, quella di trattenere le creature nel ventre delle donne fino al momento del parto.
Remora, in senso proprio, è il pesce e, in senso figurato, l'ostacolo
Da mangiare non è buono e non si usa….conservato nel sale, ha la virtù di ripescare l'oro caduto nei pozzi più profondi poi ché questo gli si attacca
E strano vedere come dall'idea di rallentare le barche si è giunti a quella di rallentare i processi e i bambini.
In un altro punto, Plinio riferisce che una remora decise le sorti dell' Impero romano, trattenendo nella battaglia di Azio la galera da cui Marco Antonio passava in rivista la flotta…
« Non sempre vince la forza più grande. La corsa di una nave è fermata da una piccola remora»

BIF e insulina icodec hanno dimostrato **durate d'azione sufficientemente lunghe, profili PD piatti e bassa variabilità PD per supportare la somministrazione una volta alla settimana**; i **dati di fase 3 sono necessari per stabilirne i profili di efficacia e sicurezza**

- **impatto psicologico** della somministrazione di grandi dosi di insulina una volta alla settimana (dose giornaliera per sette).

- **nuove strategie pratiche di inizio e titolazione dell'insulina (che dose iniziale, che incremento settimanale, che target FPG usare)**

- Non è previsto un rapido abbassamento della glicemia con le dosi iniziali poiché è probabile che lo **stato stazionario richieda circa 3-4 settimane** di somministrazione e possono essere **necessarie dosi di carico** evitare **riduzione transitoria del controllo glicemico** prima del raggiungimento di un nuovo stato stazionario

- **il potenziale sovratrattamento con insulina basale**, evidenziato dalle ultime linee guida dell'American Diabetes Association.

- implicazioni a lungo termine, per quanto riguarda **l'aumento di peso corporeo**

- **comprensione del rischio di ipoglicemia rispetto a gravità, frequenza e durata** e come gestirli; **così** l'esercizio, i giorni di malattia e l'intervento chirurgico. **>>>>>>**

Complessivamente, il **profilo di sicurezza dell'insulina icodec era paragonabile a quello dell'insulina glargine U100 una volta al giorno in tutti e tre gli studi di fase 2**

in un'analisi post hoc dei due studi di fase 2 di 16 settimane la **durata degli episodi ipoglicemici era simile** con insulina icodec e insulina glargine U100 **sia nei pazienti naive che in quelli precedentemente trattati con insulina, indipendentemente dalla titolazione algoritmo o uso della dose di carico**

- Nei **pazienti naïve all'insulina** che hanno iniziato l'insulina icodec con un target di titolazione di **80–130 mg/dl e aggiustamenti della dose di ±21 U/settimana**, la durata mediana dell'ipoglicemia è stata di 35 minuti complessivi e di 30 minuti per gli eventi notturni; i valori corrispondenti per l'insulina glargine U100 erano **simili**, durando rispettivamente 35 min e 30 min

- Nei **pazienti che sono passati dall'insulina basale giornaliera**, anche la durata mediana complessiva dell'episodio ipoglicemico è stata **simile**, della durata di 40 min, 40 min e 35 min per insulina icodec **con una dose di carico, insulina icodec senza una dose di carico**, e insulina glargine U100, rispettivamente.

Le persone con **T2D** **con controllo glicemico inadeguato** indicazione non è diversa da quella attualmente adottata per l'insulina basale una volta al giorno.

- **ridurre l'inerzia clinica aumentando così l'aderenza del pz al trattamento e la qualità della vita**
- pazienti che **necessitano di assistenza con le iniezioni**. (una anziché sette iniezioni a settimana)
- **un'intensificazione di terapia** es con GLP-1 RA una volta alla settimana, l'assunzione di un'insulina basale con la stessa frequenza di iniezione semplificherebbe la gestione.

T1D

- **minor numero di iniezioni**
- migliorare l'aderenza e il controllo della glicemia nei pazienti che possono saltare le dosi, in particolare **gli adolescenti.**
- avere un livello di insulina relativamente costante potrebbe **ridurre la frequenza della chetoacidosi diabetica** ,

Le combinazioni **a rapporto fisso attualmente disponibili di un'insulina basale e un GLP-1 RA – IDegLira e iGlarLixi** – hanno una forte efficacia, profili di sicurezza rassicuranti e carichi di iniezione ridotti; gli eventi avversi gastrointestinali sono mitigati

associazioni precostituite di degludec e liraglutide (iDegLira) e **di glargine e lixisenatide** (LixiLan). Nei trial clinici di confronto diretto con la sola insulina basale, con adeguata titolazione, queste associazioni producono una riduzione dell'emoglobina glicata più ampia, con effetti più favorevoli sul peso corporeo e con minor rischio di ipoglicemia (Liskopoulou et al., 2017).
Le associazioni non possono essere considerate sostitutive delle associazioni estemporanee di insulina basale e agonisti del recettore del GLP-1, in **quanto, a causa della necessità di titolare l'insulina, in gran parte dei pazienti non consentono di raggiungere dosi piene di agonista del recettore del GLP-1.**
Esse possono però rappresentare un'alternativa all'insulina basale, oppure un'opzione per l'intensificazione della terapia con insulina basale

sono state studiate le **insuline basali una volta alla settimana** su un background di un massimo di tre farmaci antidiabetici orali

di particolare interesse sarà il loro **uso con un GLP-1 RA iniettabile**.

in fase di sviluppo clinico 1 un rapporto fisso di insulina icodec una volta alla settimana e **semaglutide** una volta alla settimana

Received: 27 January 2022 | Revised: 14 April 2022 | Accepted: 28 April 2022
DOI: 10.1111/dom.14739

ORIGINAL ARTICLE

WILEY

Real-world outcomes of addition of insulin glargine 300 U/mL (Gla-300) to glucagon-like peptide-1 receptor agonist (GLP-1 RA) therapy in people with type 2 diabetes: The DELIVER-G study

Timothy S. Bailey[1] | Jasvinder Gill[2] | Merwyn Jones S.[3] | Laxmi Shenoy[3] | Charlie Nicholls[4] | Jukka Westerbacka[5]

Conclusions: In US real-world clinical practice, **adding Gla-300 to GLP-1RA significantly improved glycaemic control without significantly increasing hypoglycaemia** in PWD2.

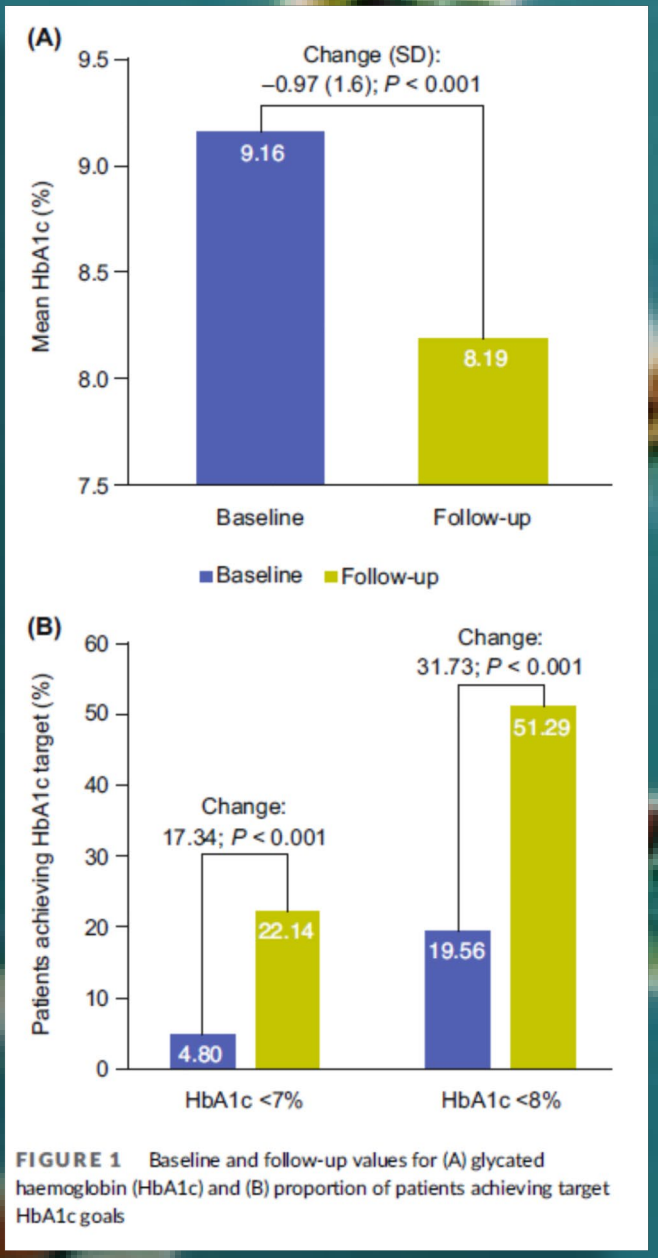


FIGURE 1 Baseline and follow-up values for (A) glycated haemoglobin (HbA1c) and (B) proportion of patients achieving target HbA1c goals

Clinical Care/Education/Nutrition/Psychosocial Research
ORIGINAL ARTICLE

Rationale and Design of the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE)

David M. Nathan, MD[1]
John B. Buse, MD[2]
Steven E. Kahn, MB[3]
Heidi Krause-Steinrauf, MS[4]
Mary E. Larkin, MS[1]
Myrlene Staten, MD[5]
Deborah Wexler, MD[1]
John M. Lachin, ScD[4]
the GRADE Study Research Group*

OBJECTIVE—The epidemic of type 2 diabetes (T2DM) threatens to become the major public health problem of this century. However, a comprehensive comparison of the long-term effects of medications to treat T2DM has not been conducted. GRADE, a pragmatic, unmasked clinical trial, aims to compare commonly used diabetes medications, when combined with metformin, on glycemia-lowering effectiveness and patient-centered outcomes.

estimate of T2DM prevalence in the U.S. is >24 million people, with an incidence of 1.9 million new cases per year (1). Major human and economic costs associated with the epidemic are related to the development of long-term complications, including retinopathy, nephropathy, and neuropathy, that cause more cases of blindness, renal failure, and amputations than any other disease (2). Cardiovascular disease (CVD) is increased by two- to five-

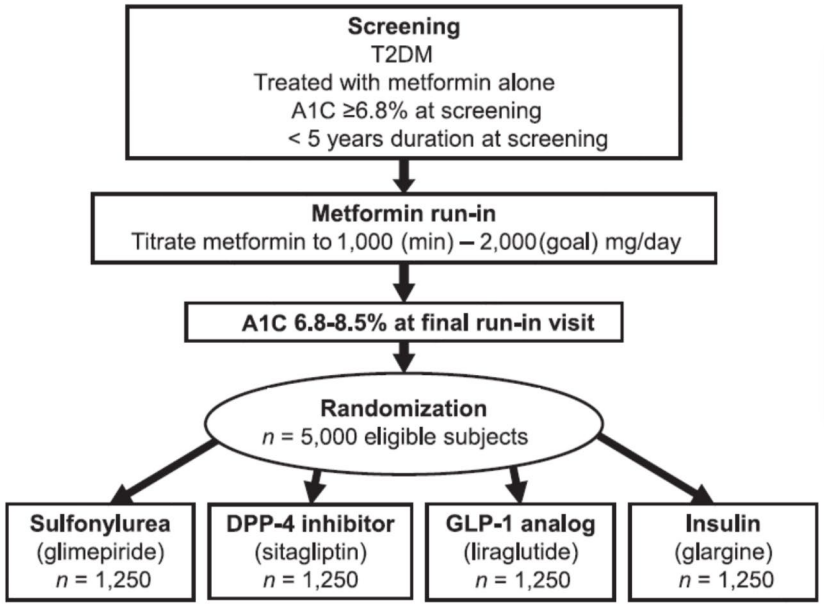


Figure 1—*Study design.*

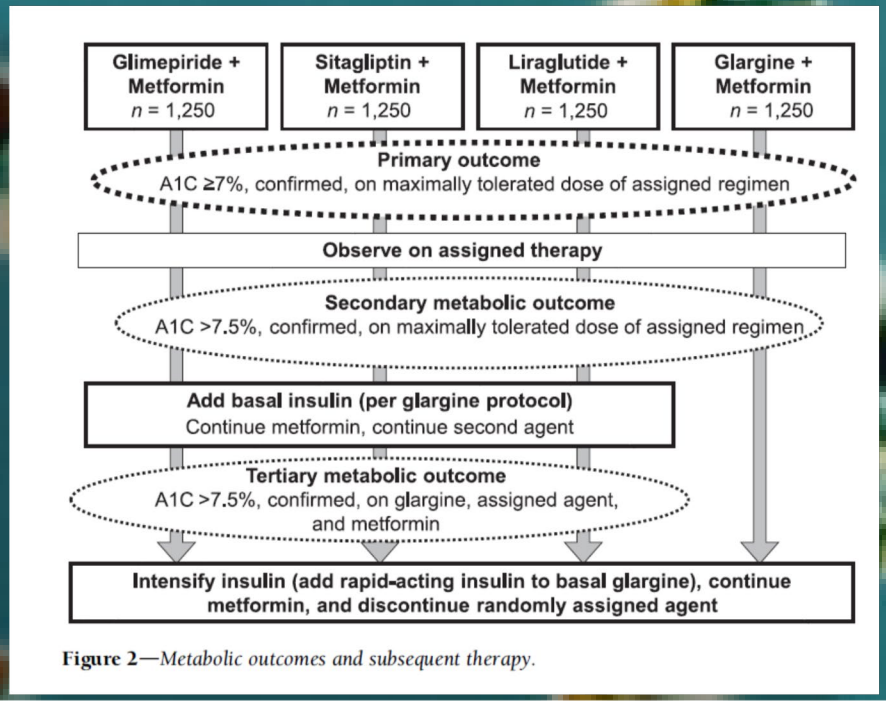


Figure 2—*Metabolic outcomes and subsequent therapy.*

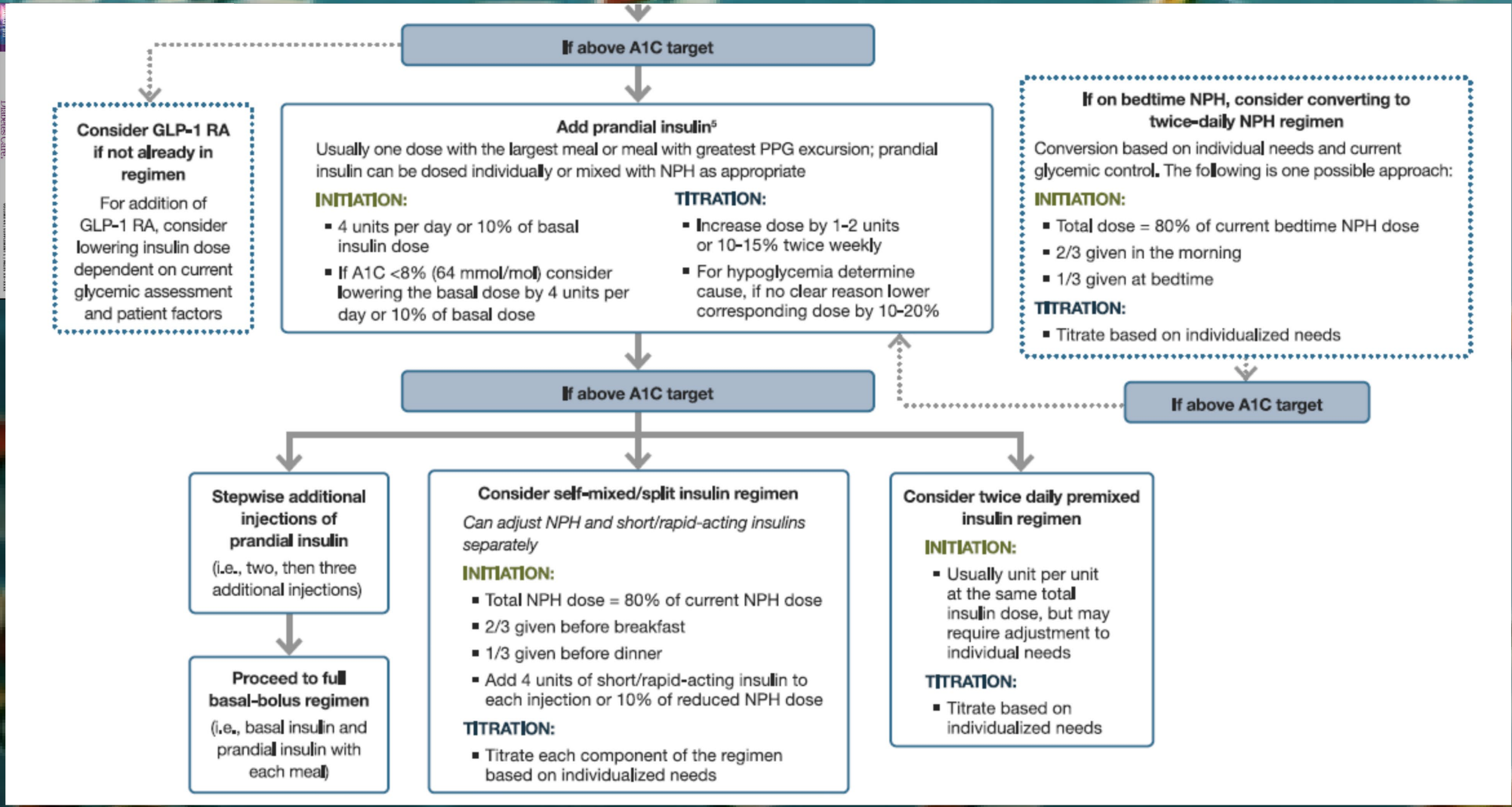
ADA 2021: Effectiveness of Liraglutide and Insulin Based on GRADE Study
Jul 10, 2021

Editor: Steve Freed, R.PH., CDE

Author: Alan Martinez, PharmD Candidate, University of South Florida Taneja College of Pharmacy

Practice Pearls

- Liraglutide and glargine were the most effective in managing HbA1c below 7%.


If above A1C target
Consider GLP-1 RA if not already in regimen
For addition of GLP-1 RA, consider lowering insulin dose dependent on current glycemic assessment and patient factors
Add prandial insulin[5]
Usually one dose with the largest meal or meal with greatest PPG excursion; prandial insulin can be dosed individually or mixed with NPH as appropriate
INITIATION:
4 units per day or 10% of basal insulin dose
If A1C <8% (64 mmol/mol) consider lowering the basal dose by 4 units per day or 10% of basal dose
TITRATION:
Increase dose by 1-2 units or 10-15% twice weekly
For hypoglycemia determine cause, if no clear reason lower corresponding dose by 10-20%
If on bedtime NPH, consider converting to twice-daily NPH regimen
Conversion based on individual needs and current glycemic control. The following is one possible approach:
INITIATION:
Total dose = 80% of current bedtime NPH dose
2/3 given in the morning
1/3 given at bedtime
TITRATION:
Titrate based on individualized needs
If above A1C target
If above A1C target
Stepwise additional injections of prandial insulin
(i.e., two, then three additional injections)
Proceed to full basal-bolus regimen
(i.e., basal insulin and prandial insulin with each meal)
Consider self-mixed/split insulin regimen
Can adjust NPH and short/rapid-acting insulins separately
INITIATION:
Total NPH dose = 80% of current NPH dose
2/3 given before breakfast
1/3 given before dinner
Add 4 units of short/rapid-acting insulin to each injection or 10% of reduced NPH dose
TITRATION:
Titrate each component of the regimen based on individualized needs
Consider twice daily premixed insulin regimen
INITIATION:
Usually unit per unit at the same total insulin dose, but may require adjustment to individual needs
TITRATION:
Titrate based on individualized needs

A BAO A QU

Per contemplare il paesaggio più meraviglioso del mondo, bisogna raggiungere l'ultimo piano della Torre della Vittoria, a Chitor. Là c'è una terrazza rotonda che permette di dominare tutto l'orizzonte. Una scala a chiocciola porta alla terrazza, ma si azzarda a salire solo chi non crede alla favola, che dice così:

Sulla scala della Torre della Vittoria abita fin dal principio dei tempi l'A Bao A Qu, sensibile ai valori delle anime umane. Vive in uno stato letargico, sul primo gradino, e gode di vita cosciente solo quando qualcuno sale la scala. Le vibrazioni della persona che si avvicina gli infondono Vita, e si insinua in lui una luce interiore. Allo stesso tempo, il suo corpo e la pelle quasi traslucida iniziano a muoversi. Quando qualcuno imbocca la scala, l'A Bao A Qu si mette quasi ai talloni del visitatore e sale aggrappandosi al bordo dei gradini curvi e consunti dai piedi di generazioni di pellegrini. A ogni scalino il suo colore si intensifica, la sua forma si perfeziona e la luce che emana diventa sempre più brillante.

E prova della sua sensibilità il fatto che raggiunge la forma perfetta solo all'ultimo gradino, e solo quando colui che sale è un essere spiritualmente evoluto. Altrimenti resta come paralizzato prima di arrivare, il corpo incompleto, il colore indefinito e la luce vacillante. L'A Bao A Qu soffre se non può formarsi del tutto e il suo lamento è un suono appena percettibile, simile al fruscio della seta. Ma quando l'uomo o la donna che lo rianimano sono colmi di purezza, l'A Bao A Qu può giungere all'ultimo scalino, completamente formato, irradiando una viva luce azzurra. Il suo ritorno alla vita è molto breve perché, quando il pellegrino scende, l'A Bao A Qu ruzzola e cade fino al gradino iniziale, dove, ormai spento e simile a un'incisione dai contorni vaghi, aspetta il prossimo visitatore. E possibile vederlo bene solo quando arriva a metà della scala, dove i prolungamenti del suo corpo, che lo aiutano a salire come piccole braccia, si definiscono con chiarezza. C'è chi dice che guarda con tutto il corpo e che al tatto ricorda la buccia della pesca. Nel corso dei secoli, l'A Bao A Qu è giunto solo una volta a perfezione.

Il capitano Burton riporta la leggenda dell'A Bao A Qu in una nota della sua traduzione delle Mille e una notte.


grazie per l’attenzione