SID Società Italiana di Diabetologia
fondata nel 1964

AMD ASSOCIAZIONE MEDICI DIABETOLOGI
1974 ANNO DI FONDAZIONE

RIUNIONE ANNUALE CONGIUNTA SID - AMD CAMPANIA 2022

IL *DIABETE* AL CENTRO DI *PERCORSI INNOVATIVI* DI *CURA*

NAPOLI
Via Ponte di Tappia, 25
HOTEL MEDITERRANEO RENAISSANCE
08 OTTOBRE 2022

I SESSIONE: L'UNIONE FA LA FORZA: TERAPIE DI COMBINAZIONE PER IL DIABETE TIPO 2 NELLA PRATICA CLINICA

Insulina + GLP-1RA

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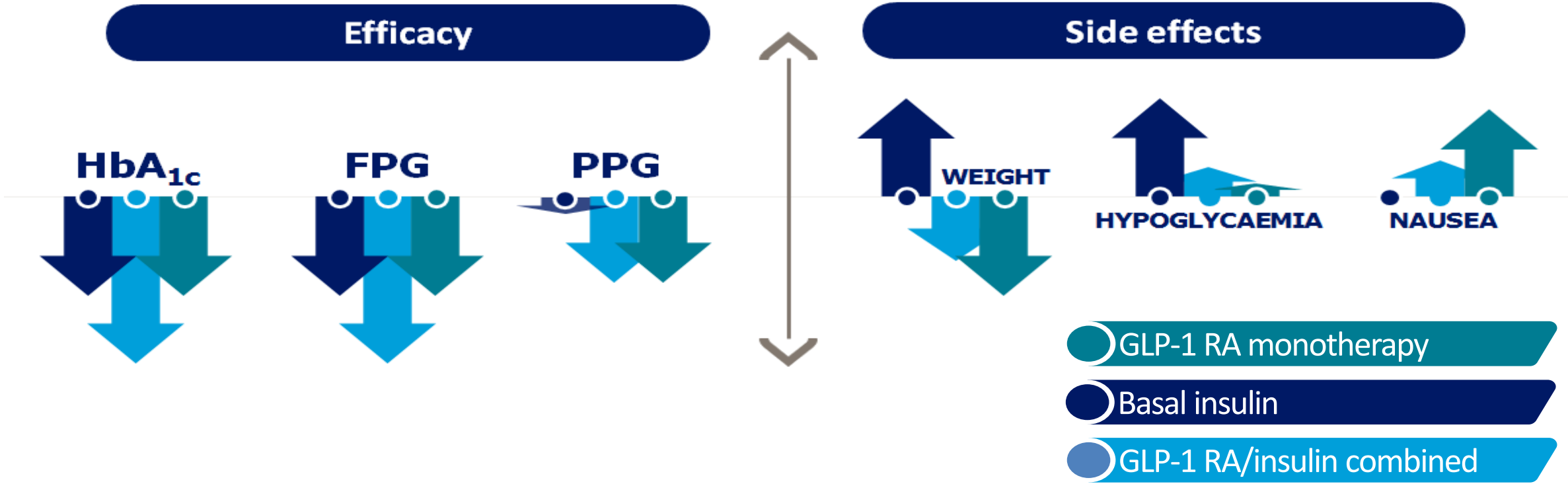
Cosa aspettarsi dalla terapia combinata INSULINA + GLP-1RA?



FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide-1 receptor agonist; PPG, postprandial glucose

Progressiva disfunzione beta-cellulare

Iperglicemia Residua

Complessità

Scarsa Aderenza

INTENSIFICARE

SEMPLIFICARE

Quando intensificare?

Mancato compenso con terapia orale

Mancato compenso con GLP-1RA

Mancato compenso con basal-oral

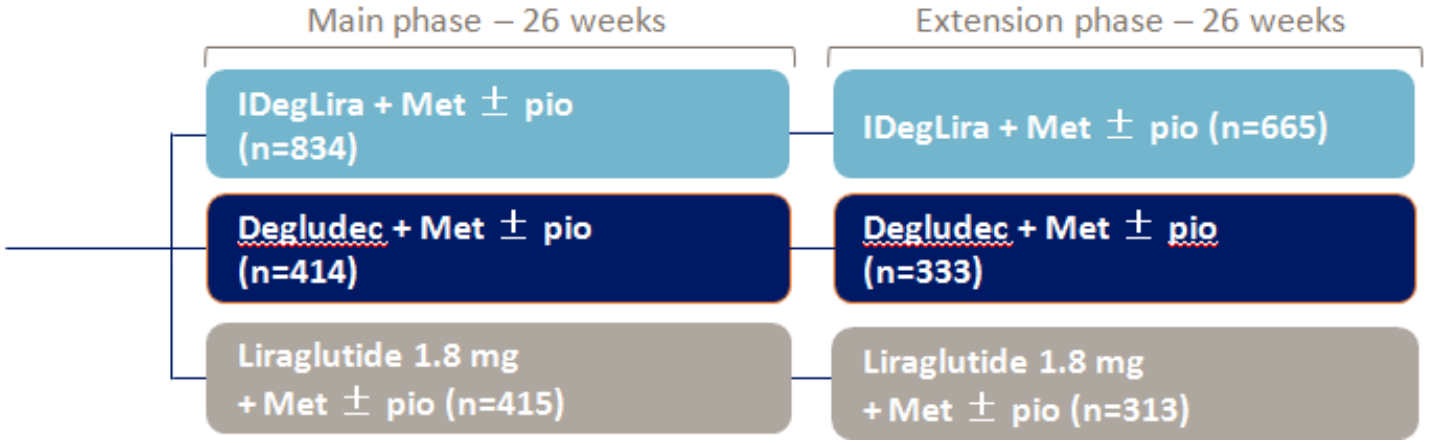
DUAL I and extension

Mancato compenso con terapia orale

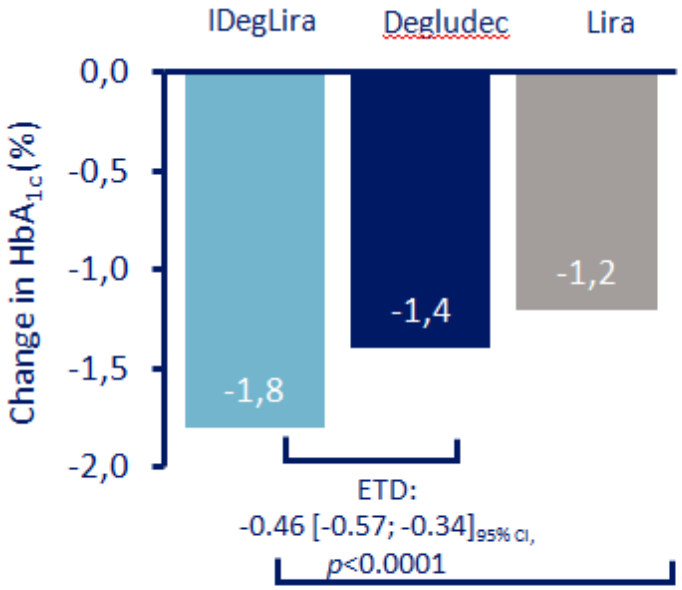
Inclusion criteria

- Type 2 diabetes
- Metformin ± pioglitazone
- HbA_{1c} 7.0–10.0%
- Age ≥18 years
- BMI ≤40 kg/m^2

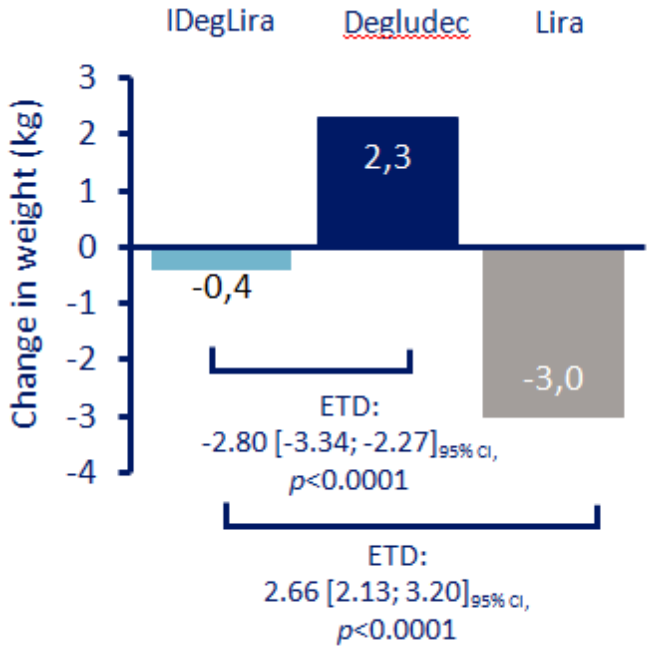
Subjects with T2D uncontrolled on OAD(s)
(N=1663)



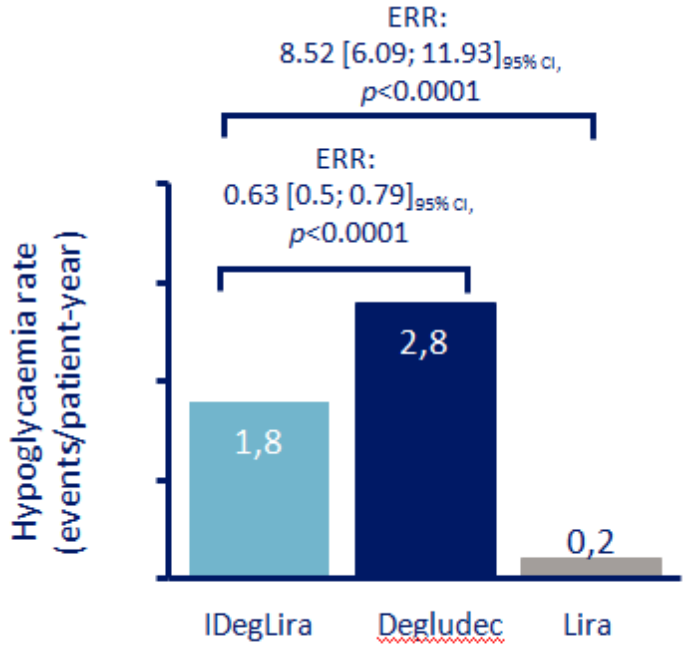
HbA_{1c}



Weight



Hypoglycaemia



EOT, end of trial;
ERR, estimated rate ratio;
ETD, estimated treatment difference

Gough et al. *Lancet Diabetes Endocrinol* 2014;2:885–93; Gough et al. *Diabetes Obes Metab* 2015;17:965–73

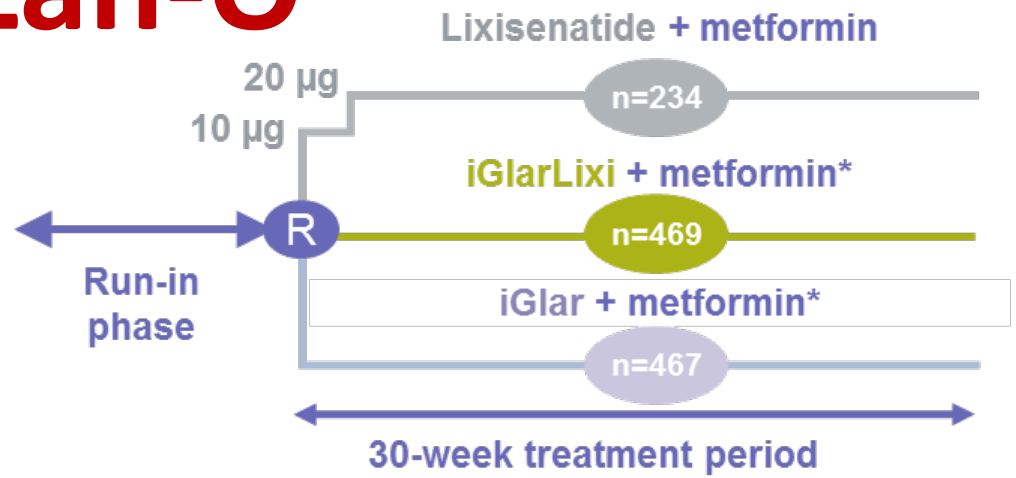
LixiLan-O

Mancato compenso con terapia orale

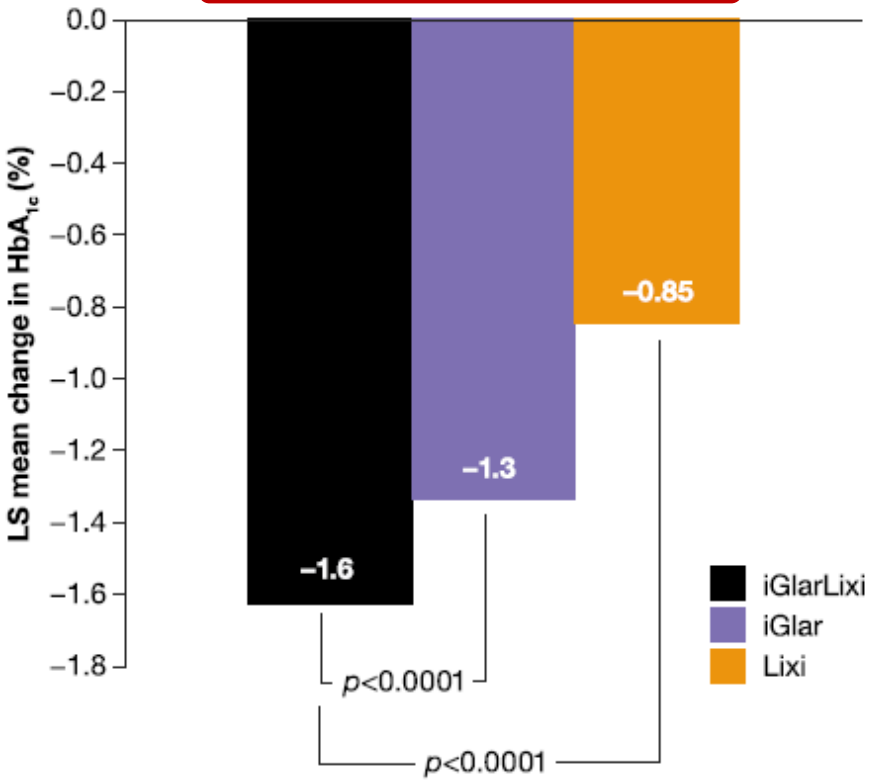
Primary objective: superiority of iGlarLixi over lixisenatide and non-inferiority of iGlarLixi over iGlar (if non-inferiority shown, superiority tested) in HbA1c change at Week 30

Inclusion criteria

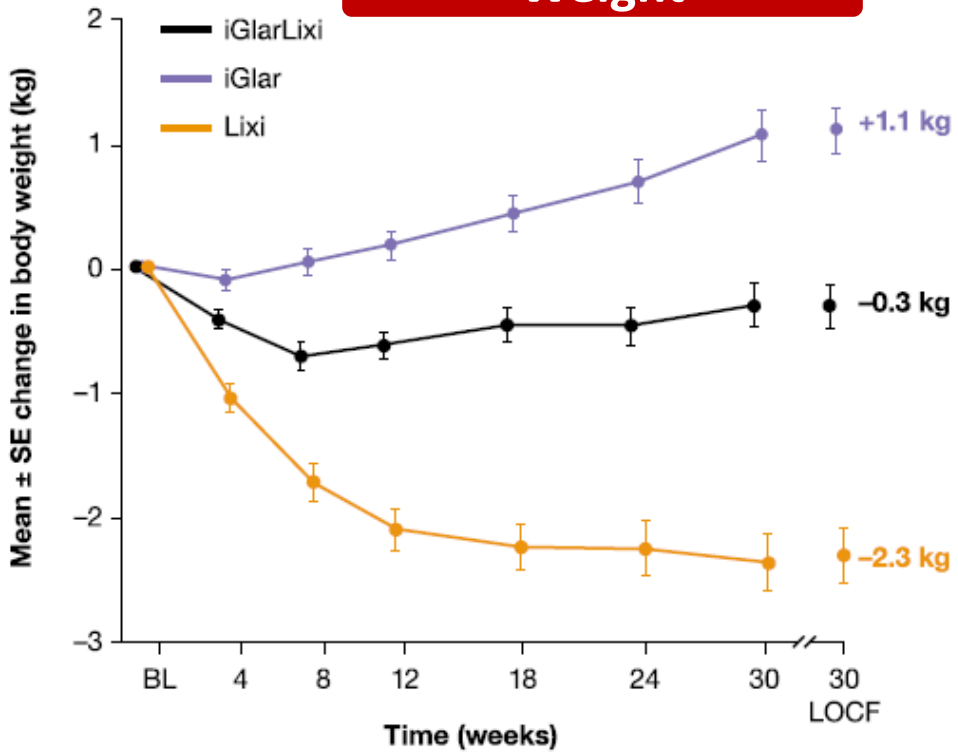
- Type 2 diabetes
- HbA_{1c} 7.5–10.0% while on an established treatment with MET alone, or HbA1c 7 - 9% while on MET combined with one of the follows: GLI, SUL, DPP-IVi, SGLT2i



HbA_{1c}



Weight

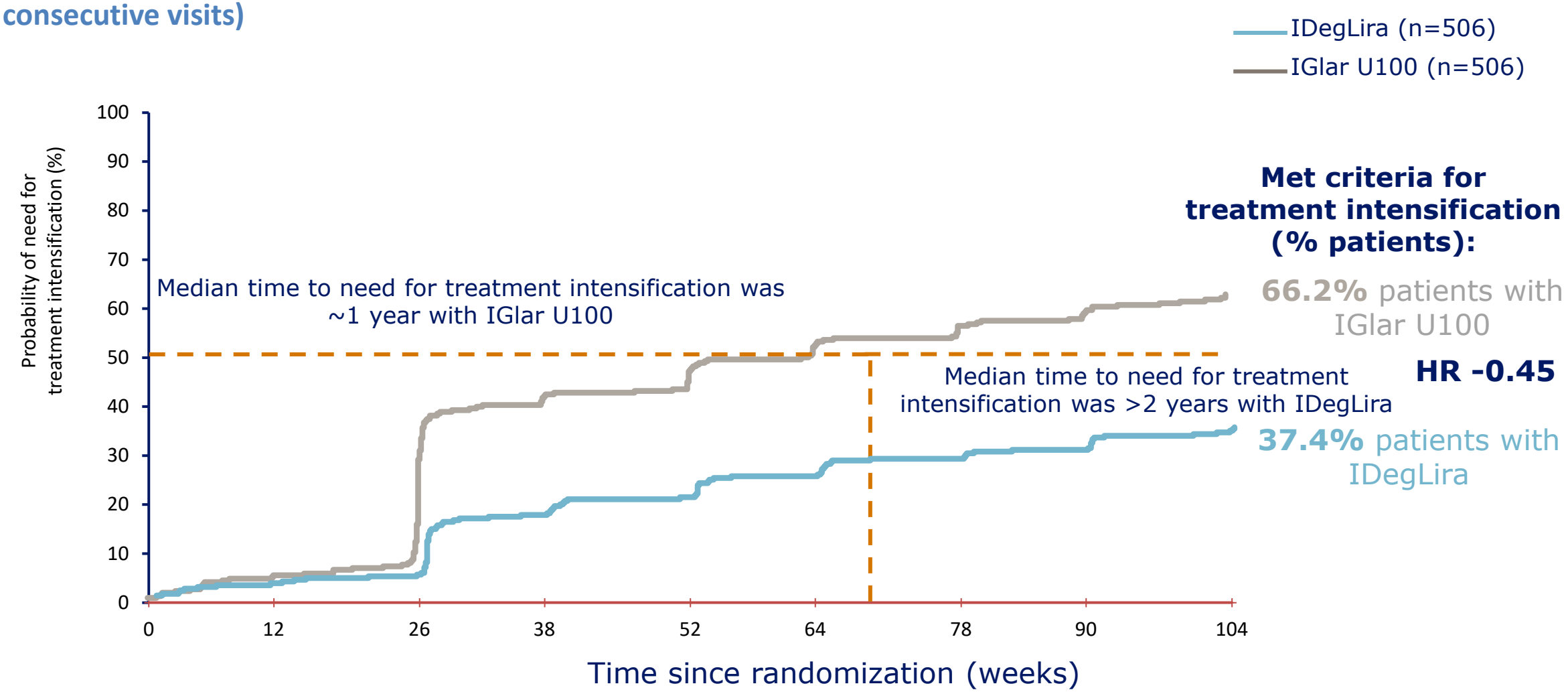


Rosenstock J, et al. Diabetes Care 2016;39:2026–35

Mancato compenso con terapia orale

DUAL VIII

Primary outcome: time to meeting criteria for need for treatment intensification (HbA1c ≥7% at two consecutive visits)



Aroda VR, et al. Lancet Diabetes Endocrinol. 2019;7(8):596-605

Quando intensificare?

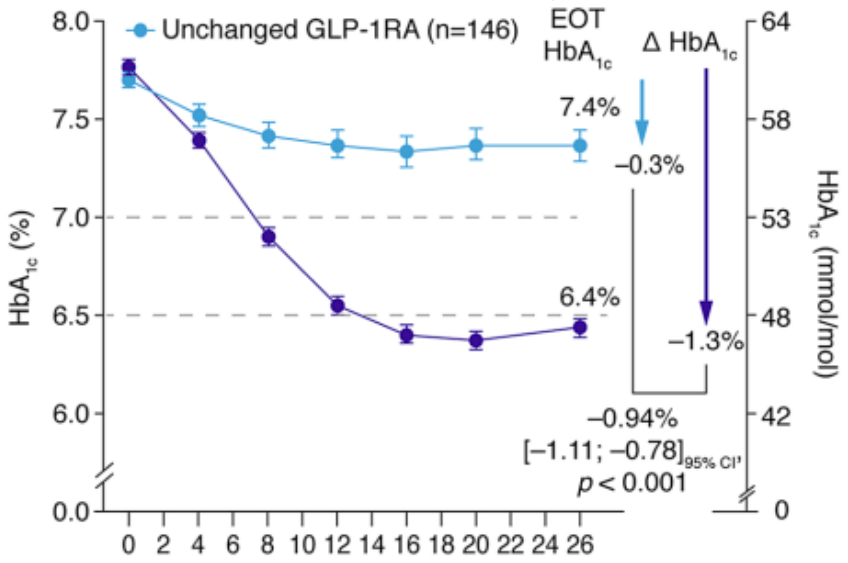
Mancato compenso con terapia orale

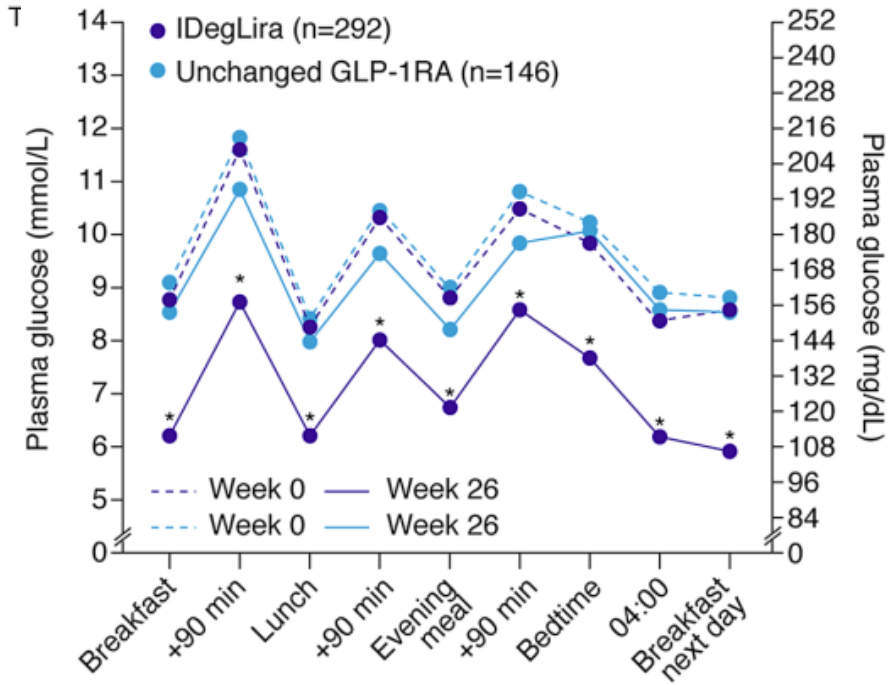
Mancato compenso con GLP-1RA

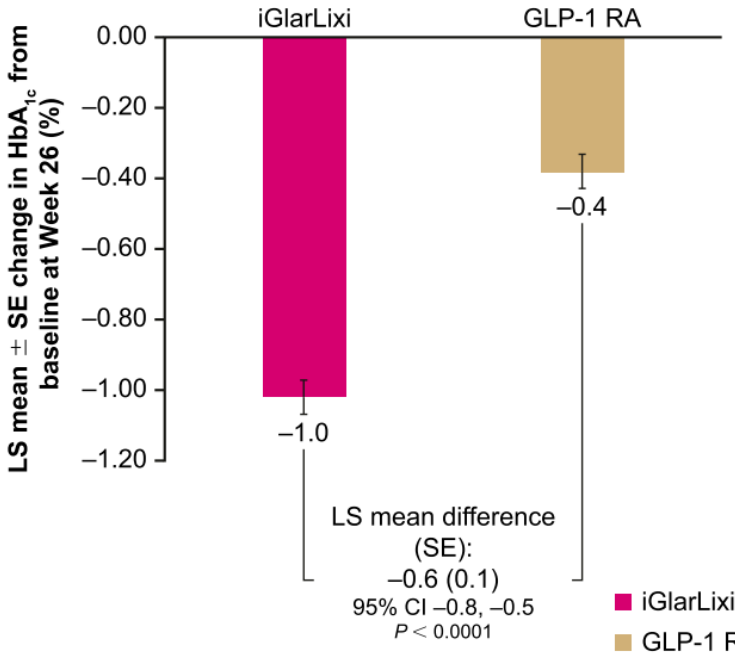
Mancato compenso con basal-oral

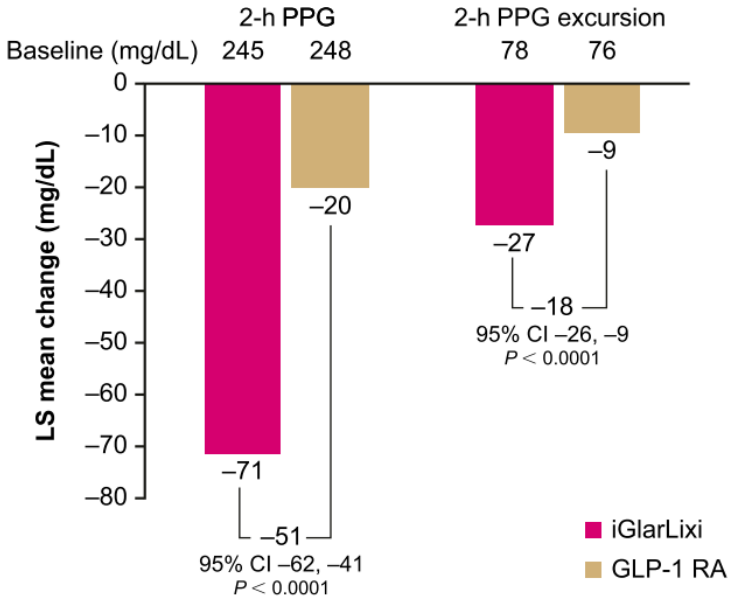
DUAL III e LixiLan-G

Mancato compenso con GLP-1RA



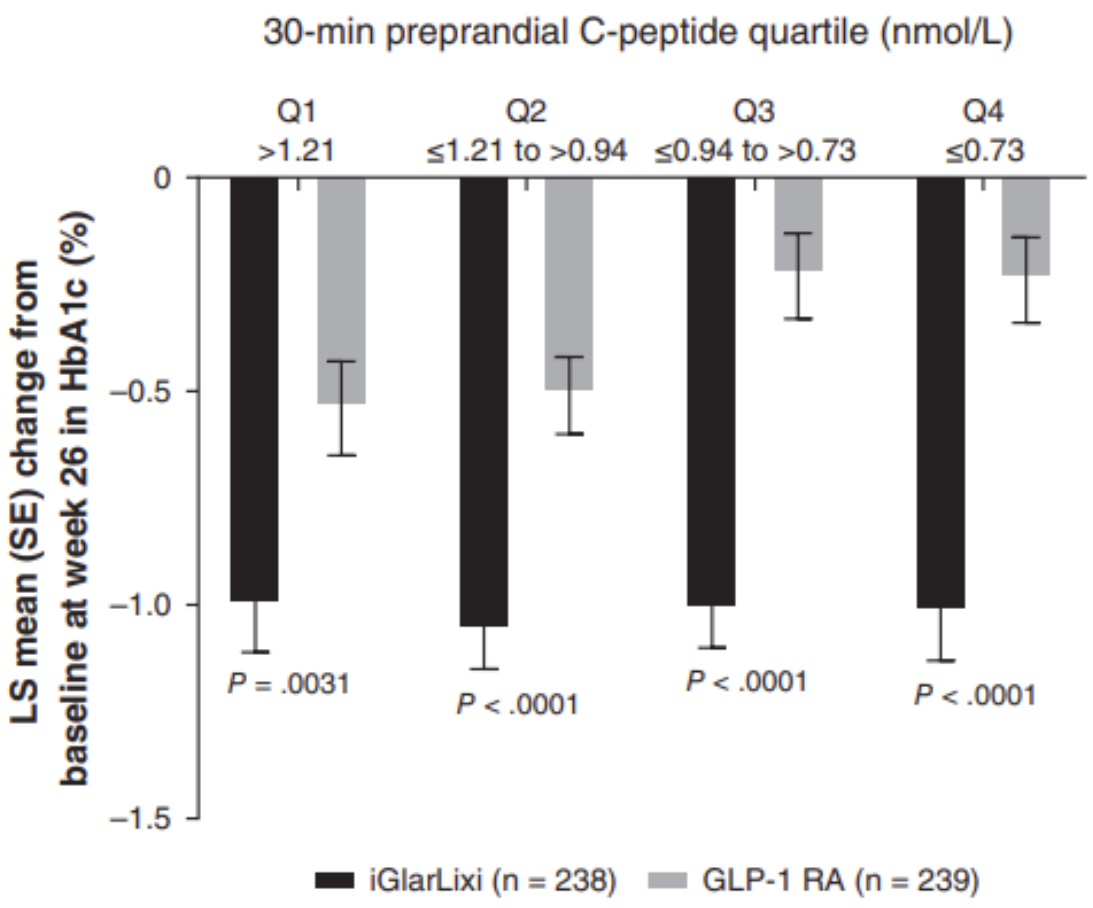


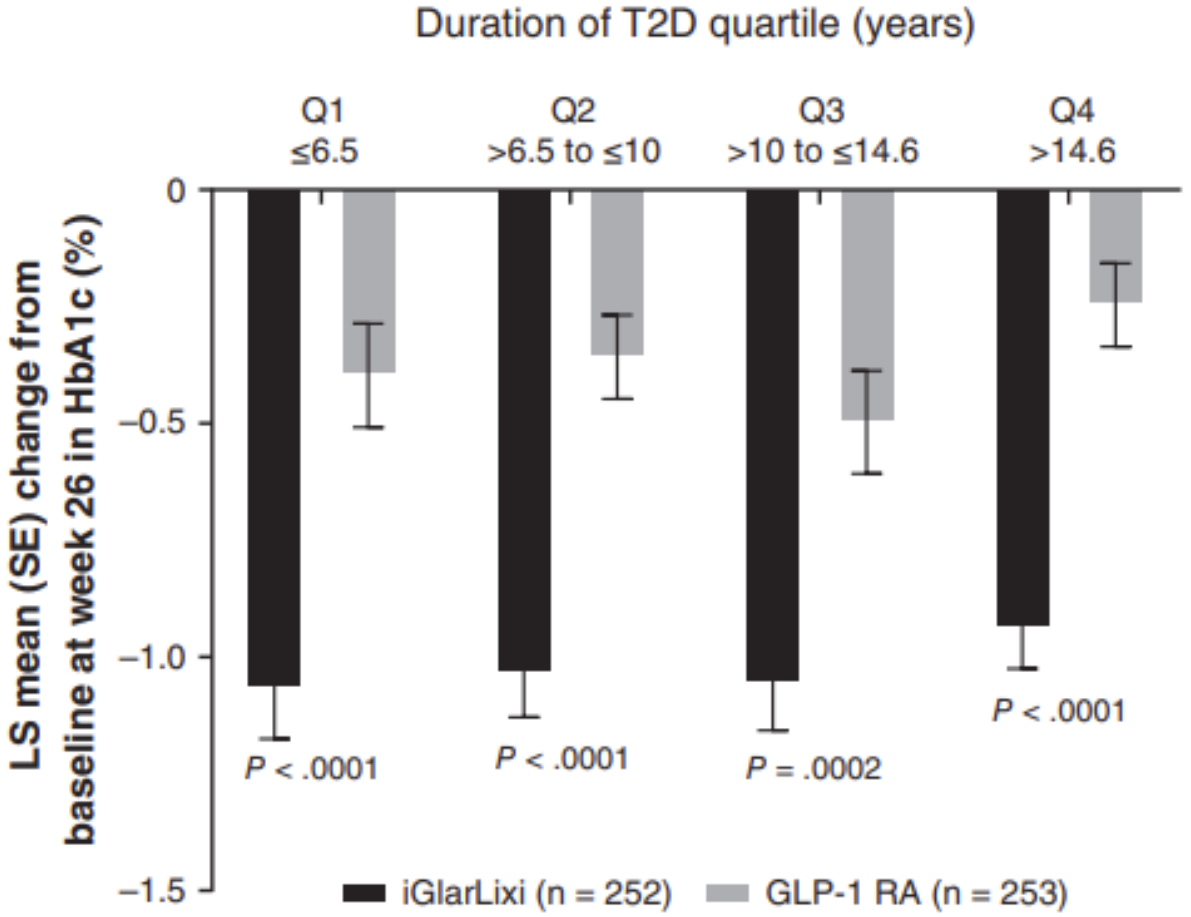




Mancato compenso con GLP-1RA

Impact of disease duration and β-cell reserve on the efficacy of switching to iGlarLixi in adults with type 2 diabetes on glucagon-like peptide-1 receptor agonist therapy: Exploratory analyses from the LixiLan-G trial





Del Prato S et al. Diabetes Obes Metab. 2020;22:1567–1576

Quando intensificare?

Mancato compenso con terapia orale

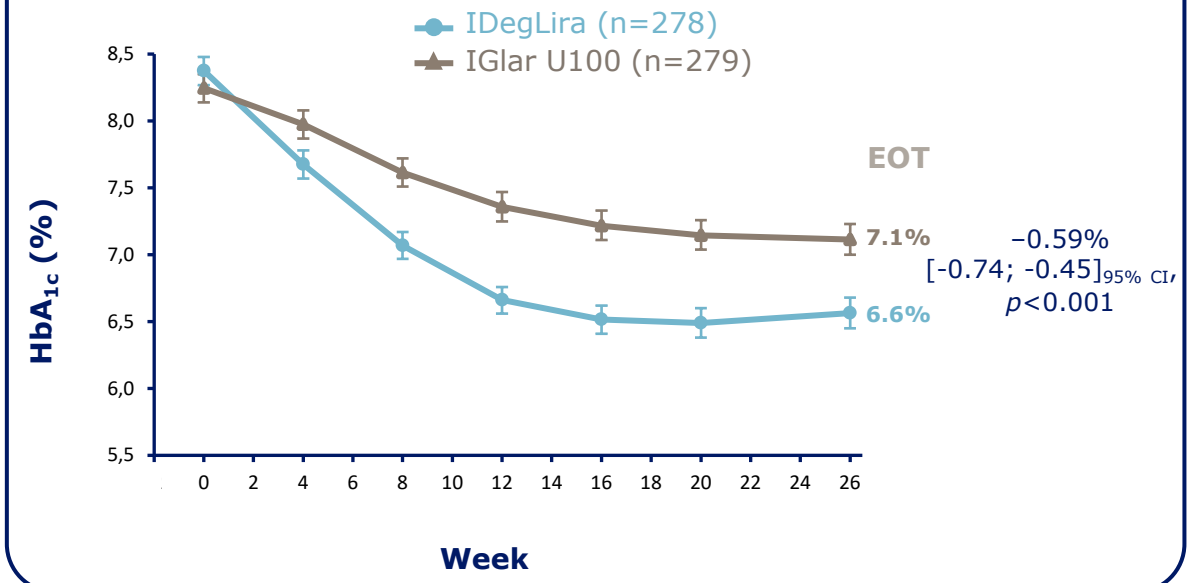
Mancato compenso con GLP-1RA

Mancato compenso con basal-oral

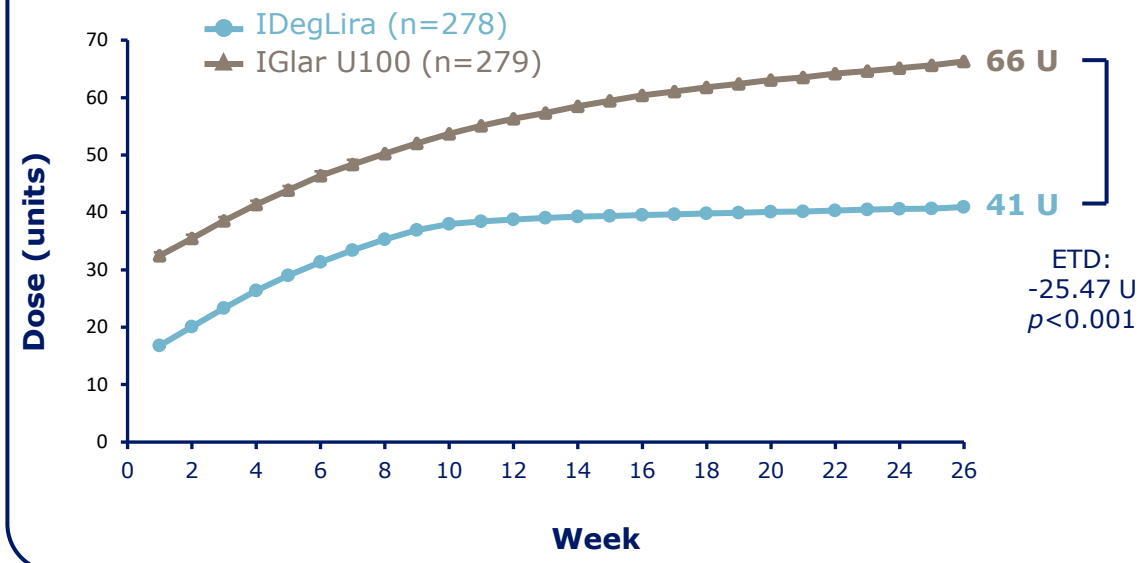
Mancato compenso con basal-oral

DUAL V

HbA_{1c}



Daily insulin dose



Hypoglycaemia

IDegLira	IGlar U100
2.23 events/ PYE	5.05 events/ PYE

57% lower rate with IDegLira (p<0.001)

Body Weight

IDegLira	IGlar U100
-1.4 kg	+1.8 kg

ETD -3.20 kg, p<0.001 vs IGlar U100

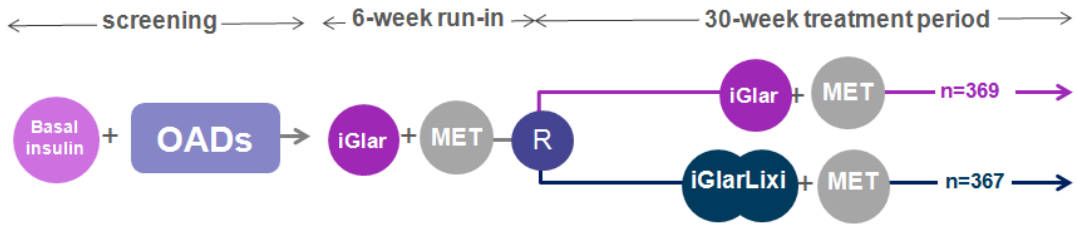
EOT, end of treatment; ETD, estimated treatment difference; IDegLira, insulin degludec/liraglutide; IGlar U100, insulin glargine U100; PYE, patient years of exposure

Lingvay *et al. JAMA* 2016;315:898–907

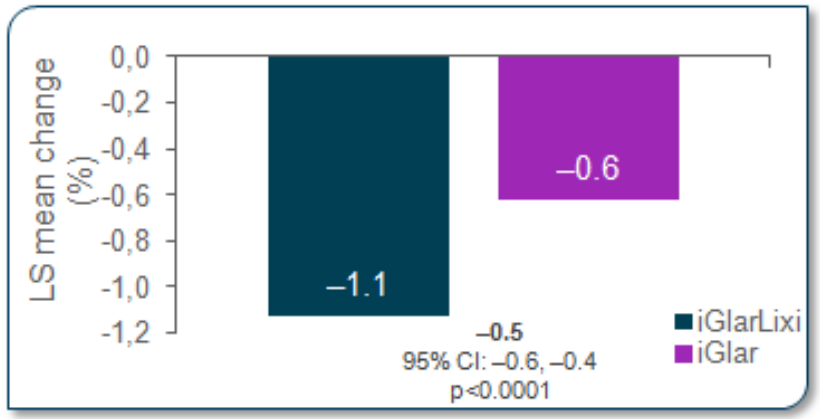
Mancato compenso con basal-oral

LixiLan-L

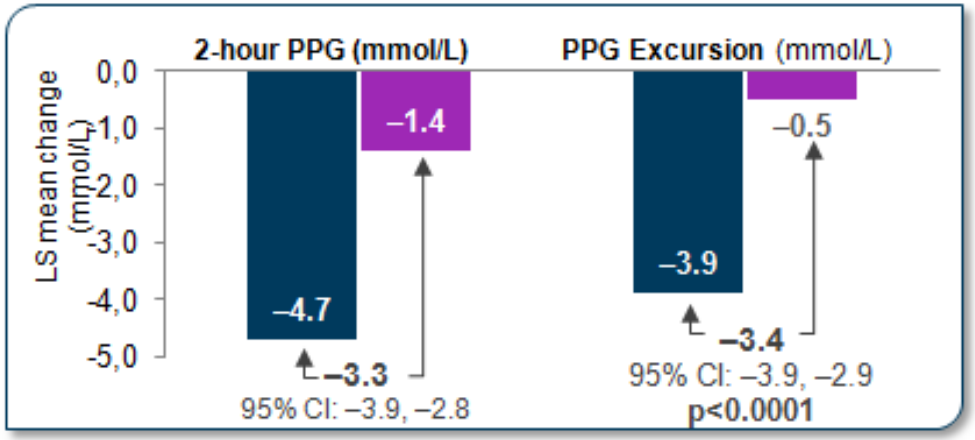
Primary objective: Superiority of iGlarLixi over iGlar in HbA1c change at Week 30



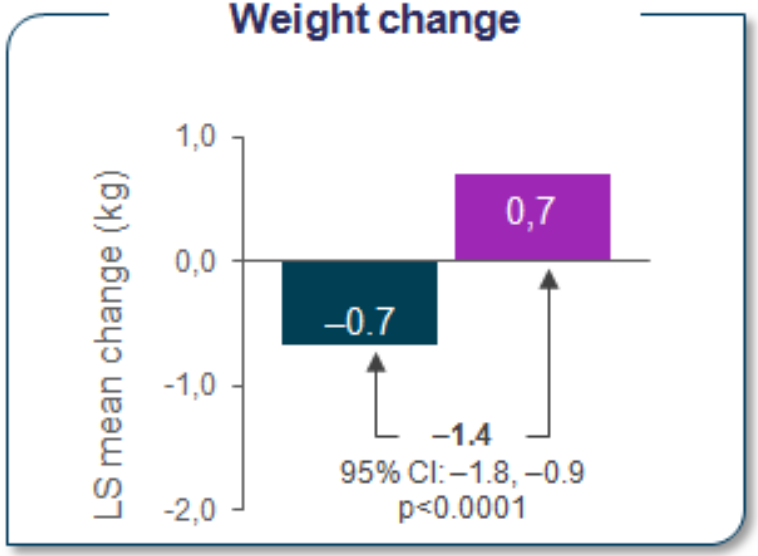
HbA1c reduction



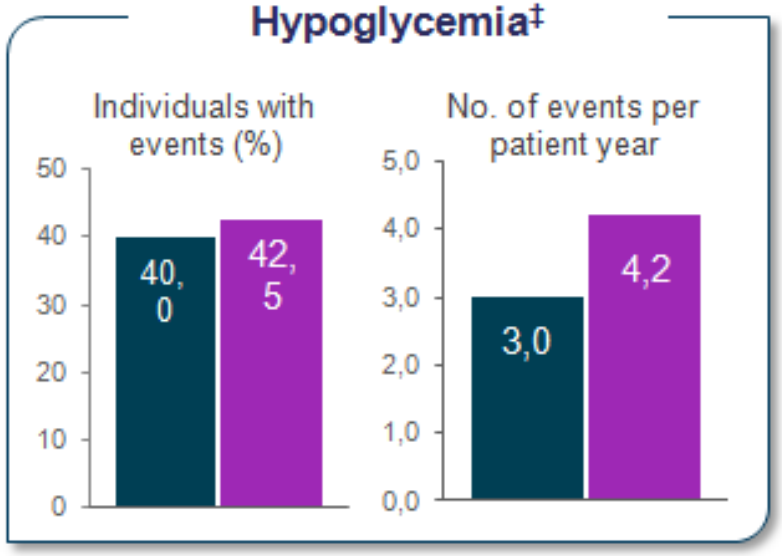
PPG Reduction



Weight change



Hypoglycemia‡



†Mean body weight (kg) at baseline

‡Documented symptomatic hypoglycemia, defined as plasma glucose ≤70 mg/dL

Aroda VR, et al. Diabetes Care 2016;39:1972–80

Mancato compenso con basal-oral

Bedtime-to-Morning Glucose Difference and iGlarLixi in Type 2 Diabetes: Post Hoc Analysis of LixiLan-L

Table 1 BeAM values for iGlar and iGlarLixi groups

	iGlarLixi (n = 259)	iGlar (n = 258)	P value[a]
BeAM values (mg/dL), mean (SD)			
Baseline	58.98 (51.18)	54.21 (48.23)	
Week 30	43.93 (46.45)	55.40 (47.21)	
LS mean change (SE)	−13.52 (2.68)	−0.25 (2.68)	< 0.001
BeAM < 50 mg/dL at week 30, n (%)	172 (66)	133 (52)	< 0.001

To convert mg/dL to mmol/L use the following formula: mmol/L = (mg/dL)/18

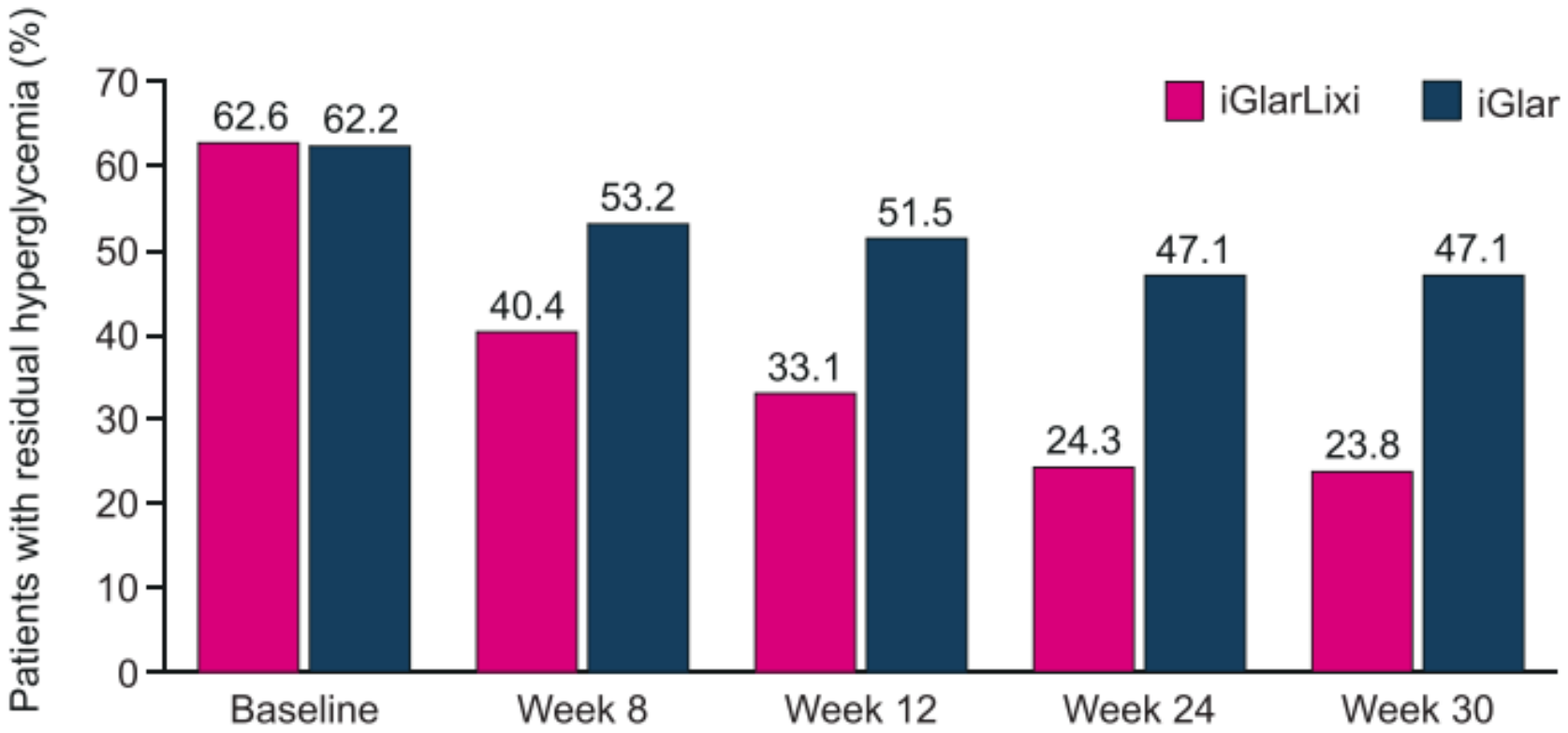
[a] P values determined from analysis of covariance with treatment arms (iGlarLixi, iGlar) as fixed effects and baseline analysis value as a covariate

Zisman A, et al. Diabetes Ther (2018) 9:2155–2162

Mancato compenso con basal-oral

iGlarLixi effectively reduces residual hyperglycaemia in patients with type 2 diabetes on basal insulin: A post hoc analysis from the LixiLan-L study

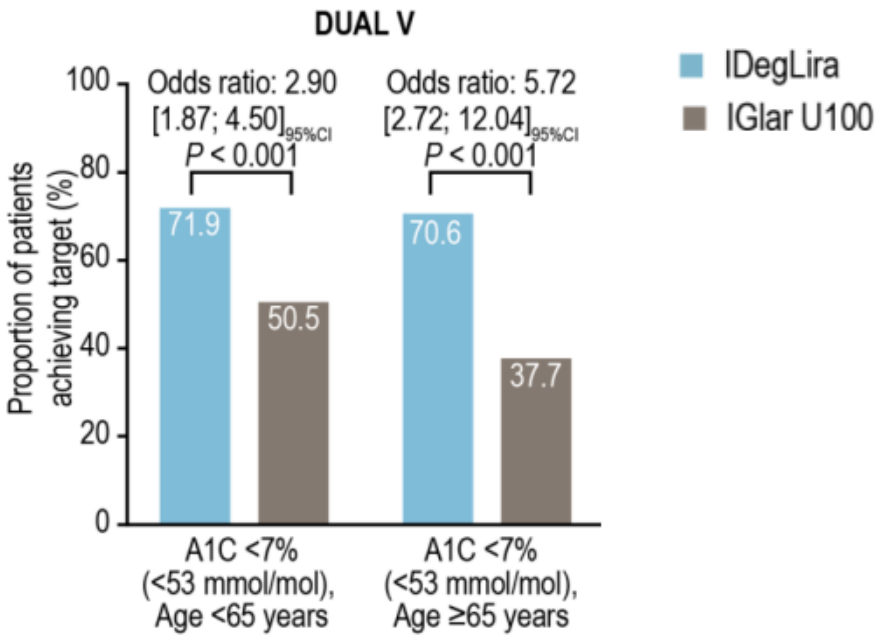
FIGURE 2 Proportion of patients with residual hyperglycaemia (HbA1c ≥ 7.0%/FPG < 140 mg/dL) throughout the study. *P* = .0004 for week 8; *P* < .0001 for weeks 12, 24 and 30. iGlar, insulin glargine Gla-100; iGlarLixi, fixed-ratio combination of insulin glargine and lixisenatide

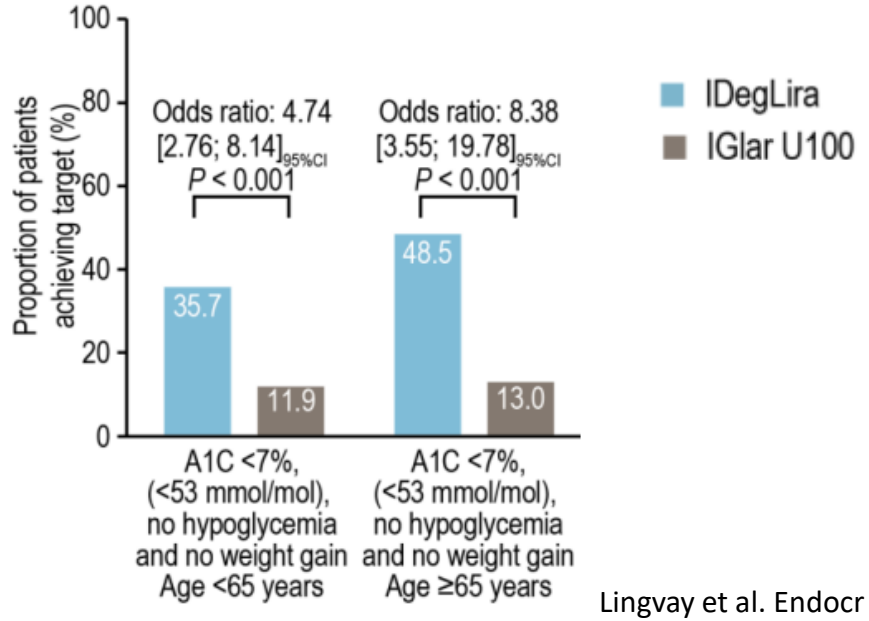


Morea N, et al. Diabetes Obes Metab. 2020;22:1683–1689

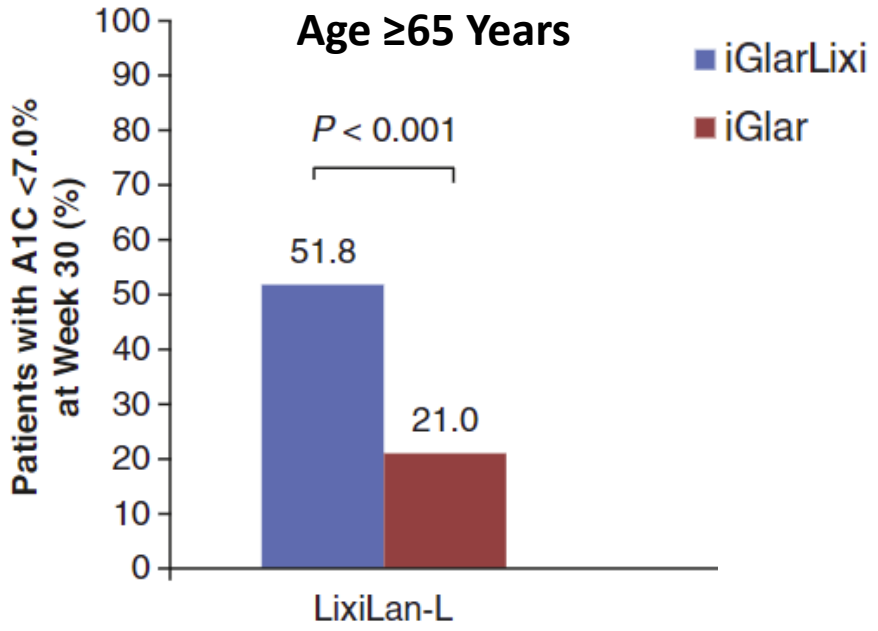
Mancato compenso con basal-oral

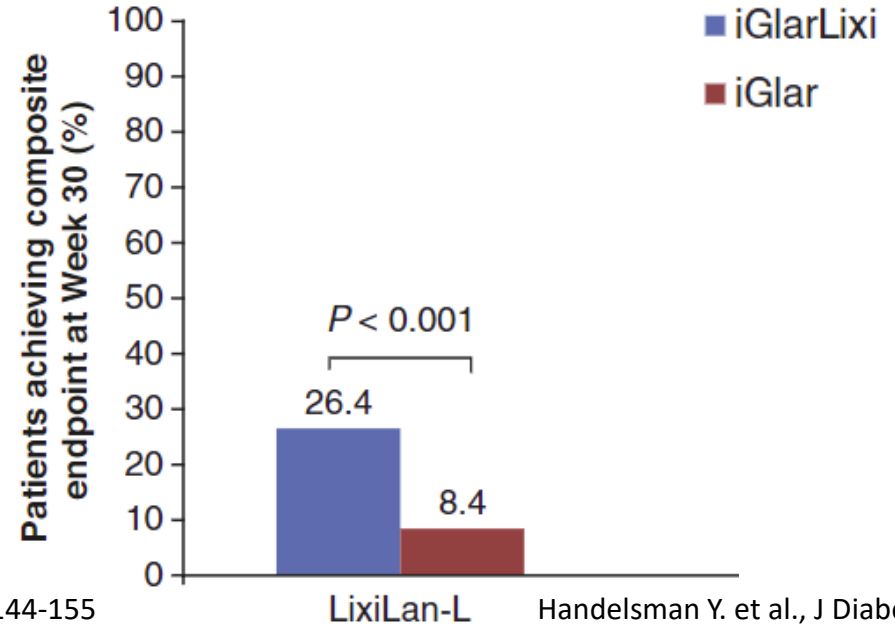
Achievement of Therapeutic Goals in Patients Aged ≥65 Years





Lingvay et al. Endocr Pract 2019, 25(2) 144-155





Handelsman Y. et al., J Diabetes Complications 2019

Quando semplificare?

INSULINA + GLP-1RA
in sostituzione di regimi insulinici più intensivi

- Complessità
- Scarsa Aderenza

SEMPLIFICARE

DUAL VII

In sostituzione di regimi insulinici più intensivi

Inclusion criteria

- Age ≥18 years
- HbA_{1c} 7.0–10.0%
- IGlar U100 20–50 U + metformin
- BMI ≤40 kg/m²

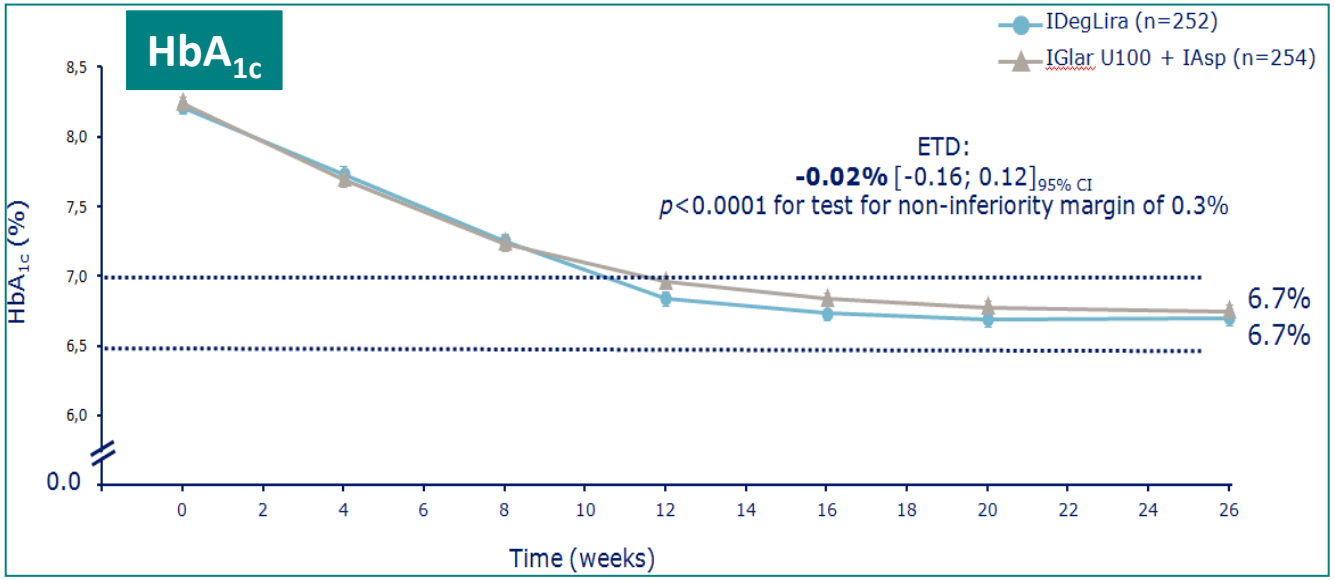
IDegLira + metformin (n=252)

IGlar U100 + IAsp (≤4 times) + metformin (n=254)

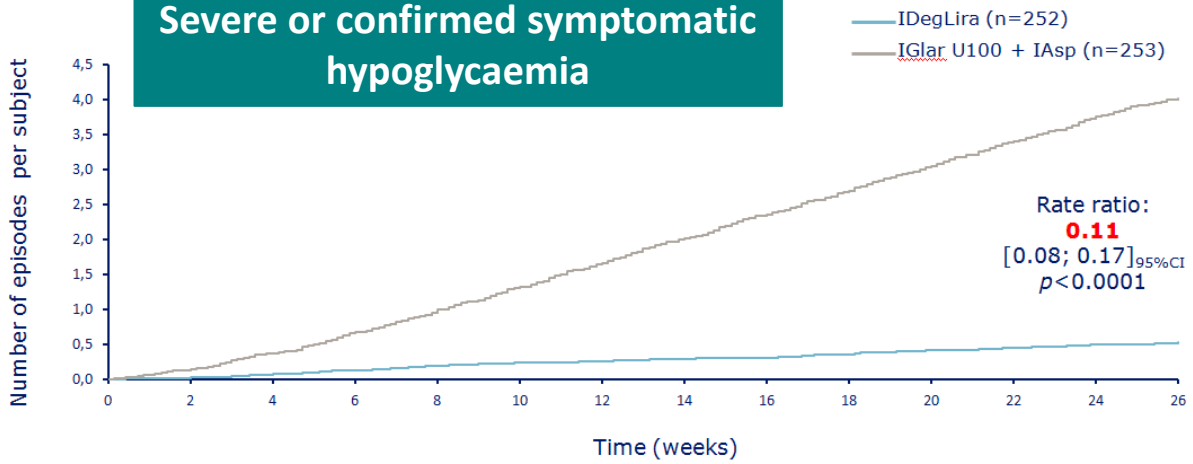
Trial information:

- Non-inferiority
- Treat-to-target

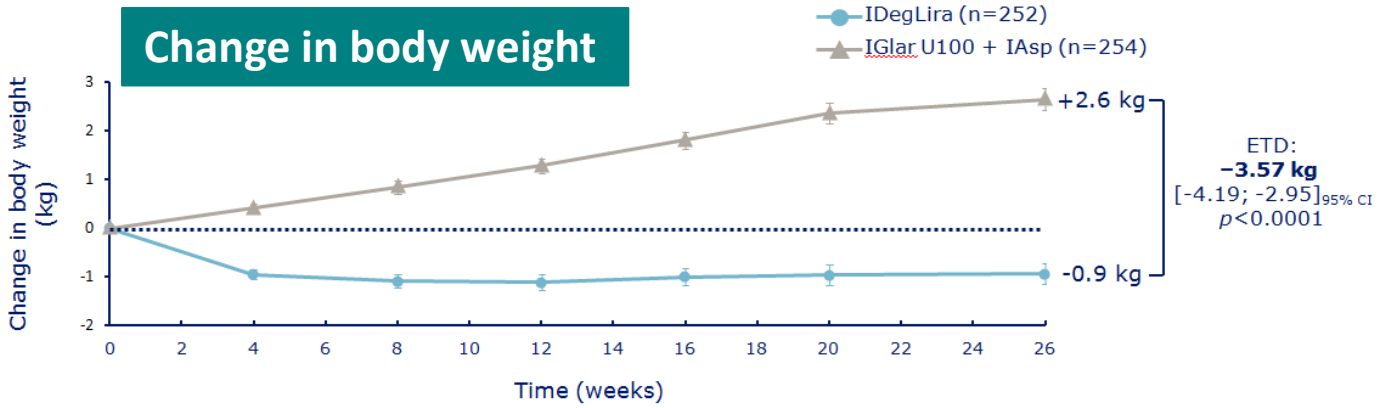
HbA_{1c}



Severe or confirmed symptomatic hypoglycaemia



Change in body weight



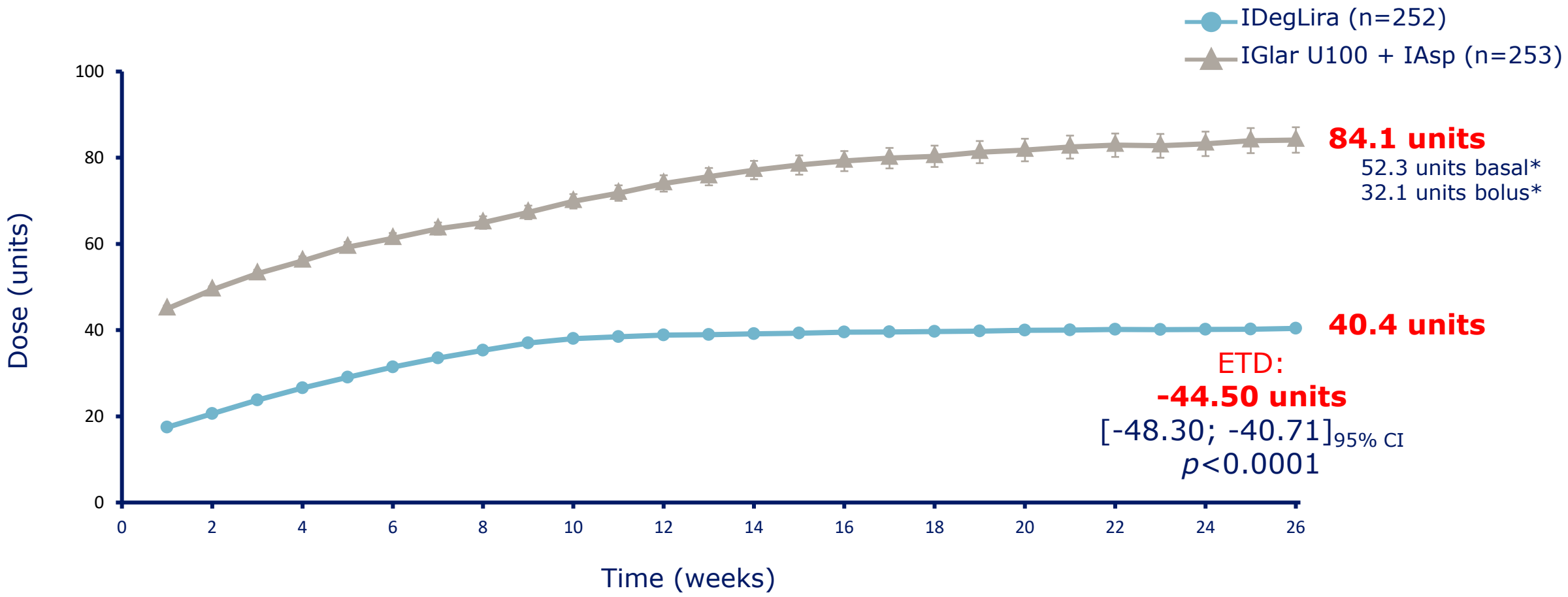
ETD, estimated treatment difference; IAsp, insulin aspart; IGlar U100, insulin glargine U100

Billings et al. *Diabetes Care* 2018;41(5):1009-1016

In sostituzione di regimi insulinici più intensivi

DUAL VII

Total daily insulin dose over time

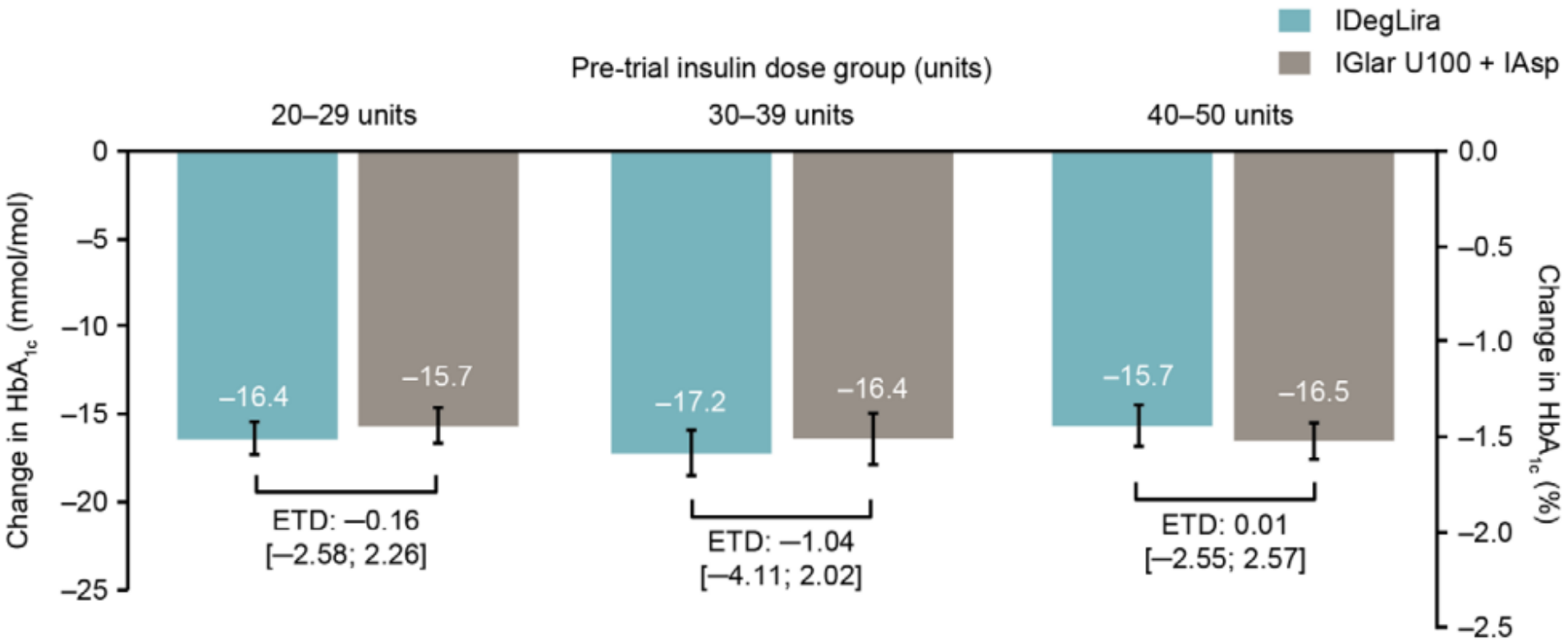


CI, confidence interval; ETD, estimated treatment difference; IAsp, insulin aspart; IGlar U100, insulin glargine U100

Billings et al. *Diabetes Care* 2018;41(5):1009-1016

In sostituzione di regimi insulinici più intensivi

Insulin degludec/liraglutide (IDegLira) maintains glycaemic control and improves clinical outcomes, regardless of pre-trial insulin dose, in people with type 2 diabetes that is uncontrolled on basal insulin



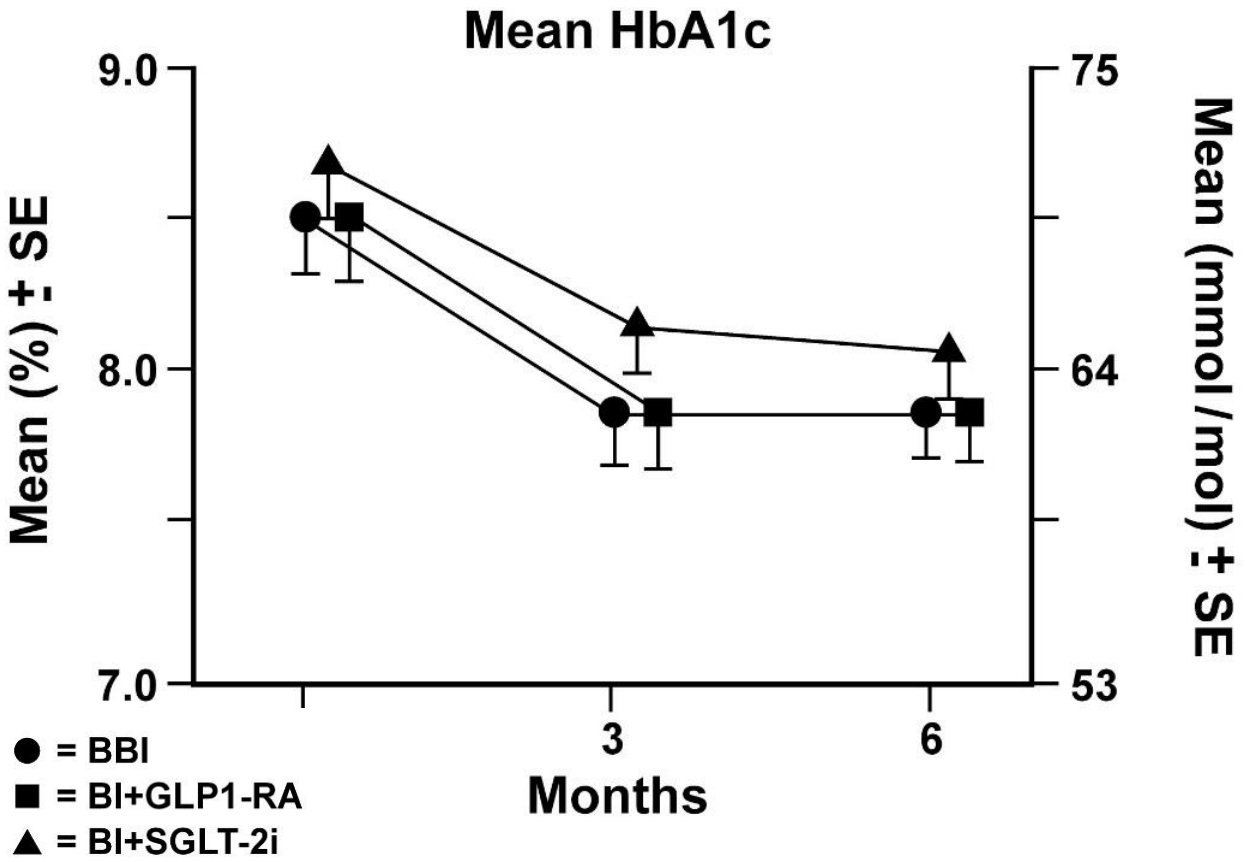
Meneghini L et al. Diabet. Med. 37, 267–276 (2020)

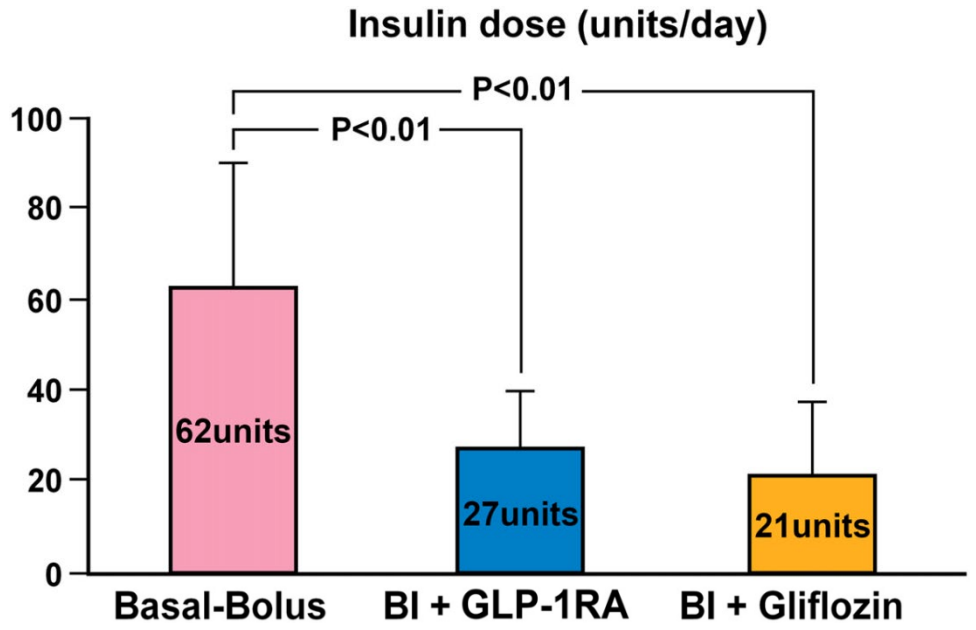
In sostituzione di regimi insulinici più intensivi

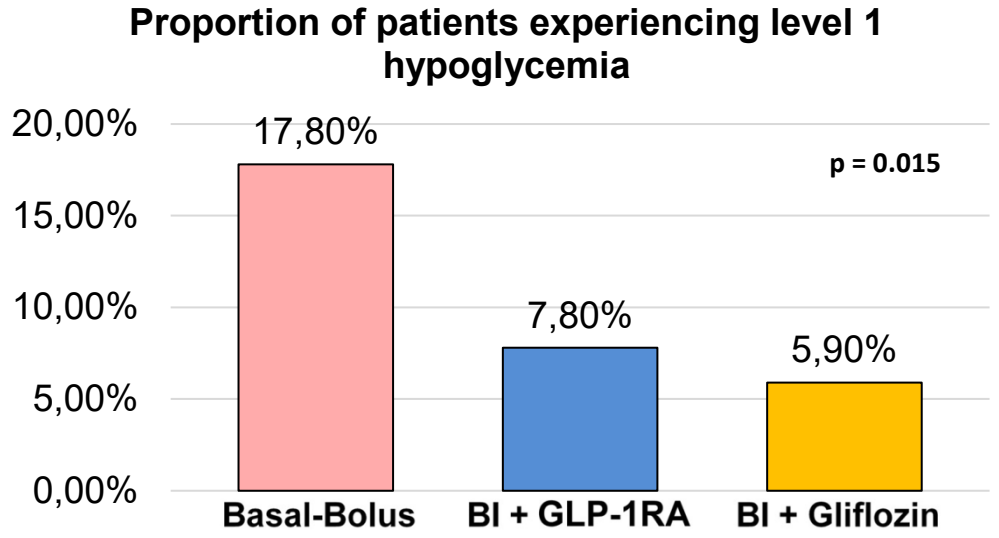
Feasibility of Simplification From a Basal-Bolus Insulin Regimen to a Fixed-Ratio Formulation of Basal Insulin Plus a GLP-1RA or to Basal Insulin Plus an SGLT2 Inhibitor: BEYOND, a Randomized, Pragmatic Trial

Dario Giugliano,[1] Miriam Longo,[1] Paola Caruso,[1] Rosa Di Fraia,[1] Lorenzo Scappaticcio,[1] Maurizio Gicchino,[2] Michela Petrizzo,[2] Giuseppe Bellastella,[1] Maria Ida Maiorino,[1] and Katherine Esposito[2]

Diabetes Care 2021;44:1–8 | https://doi.org/10.2337/DC20-2623







In sostituzione di regimi insulinici più intensivi

...dal punto di vista del paziente...

Expert Opinion on the Therapeutic Use of the Fixed-Ratio Combination of Insulin Glargine 100 U/mL and Lixisenatide: a Central/Eastern European Perspective

Haluzík M et al. Diabetes Ther. 2020;11:1029-1043

Potential clinical benefits

- Weight loss
- Reduced risk of hypoglycaemia
- Reduced therapy burden
- Better compliance
- Better health-related quality of life
- Lower treatment complexity (e.g. no need for precise carbohydrate counting), and
- Reduced health resource utilization:

–Reduced need for SMBG

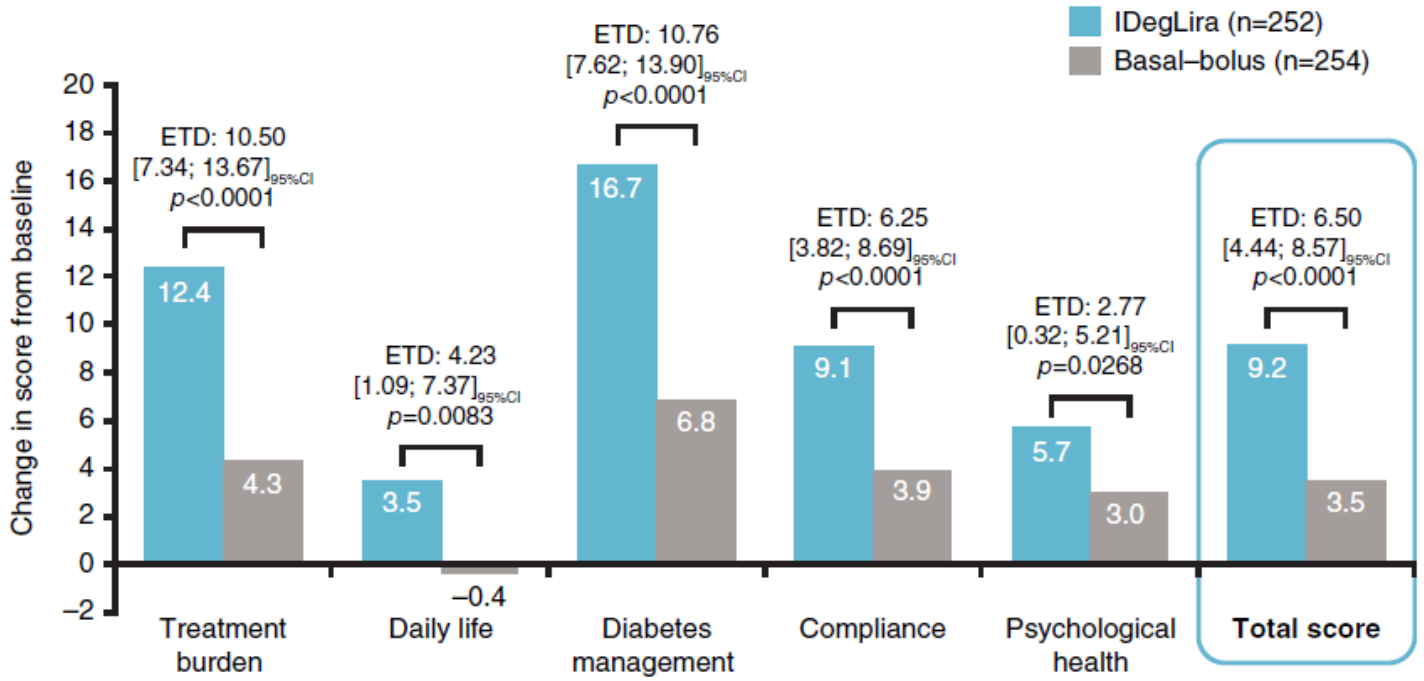
–Fewer emergency room visits due to hypoglycaemic events, and

–Less consultation with diabetes specialists.

IDegLira improves patient-reported outcomes while using a simple regimen with fewer injections and dose adjustments compared with basal–bolus therapy

Miller E et al. Diabetes Obes Metab. 2019;21:2643-2650

Change from baseline in Treatment-Related Impact Measure for Diabetes (TRIM-D) domains and total score after 26 weeks of treatment



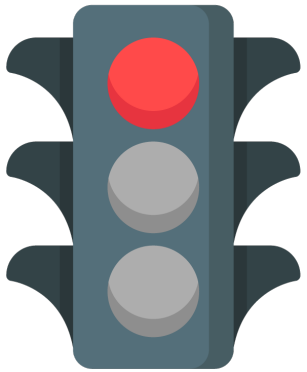
In sostituzione di regimi insulinici più intensivi

Transitioning from basal–bolus or premix insulin therapy to a combination of basal insulin and glucagon-like peptide-1 receptor agonist in people with type 2 diabetes

- Intensified to MDI after metabolic decompensation, acute illness or surgery and then kept on MDI
- Significant body weight gain or frequent hypoglycaemic events with BBI, with no improvement in glycaemic control
- Good glycaemic control with MDI but want to reduce treatment burden/improve HRQoL
- Struggle to comply with complex MDI and/or SMBG regimens
- Require a large dose of insulin, or currently use MDI
- Has obesity and is far from reaching their glycaemic targets
- History or risk of cardiovascular disease

→ TDD of insulin <50 U → FRC of basal insulin and GLP-1RA

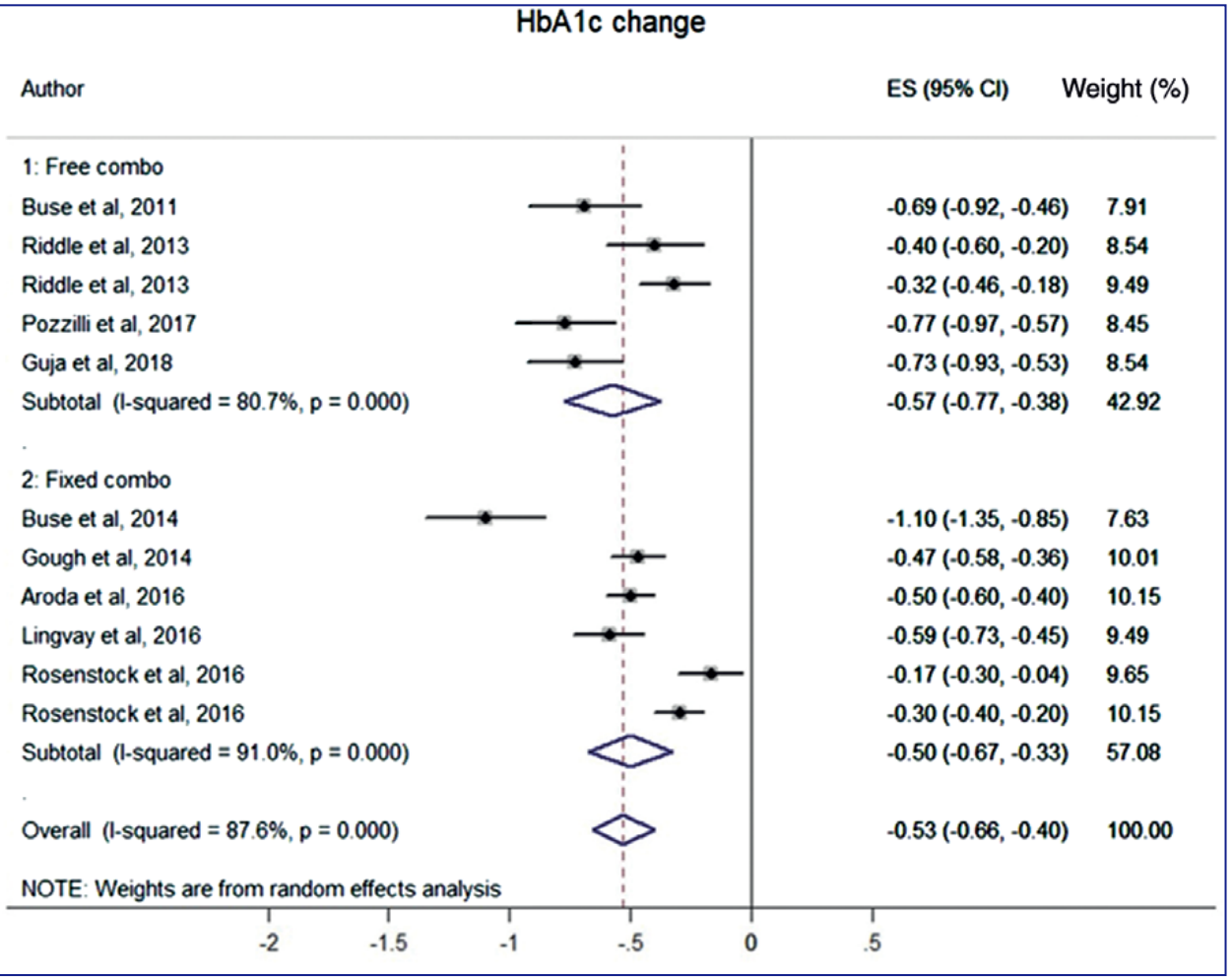
→ TDD of insulin ≥50 U → Loose combination of basal insulin and GLP-1RA

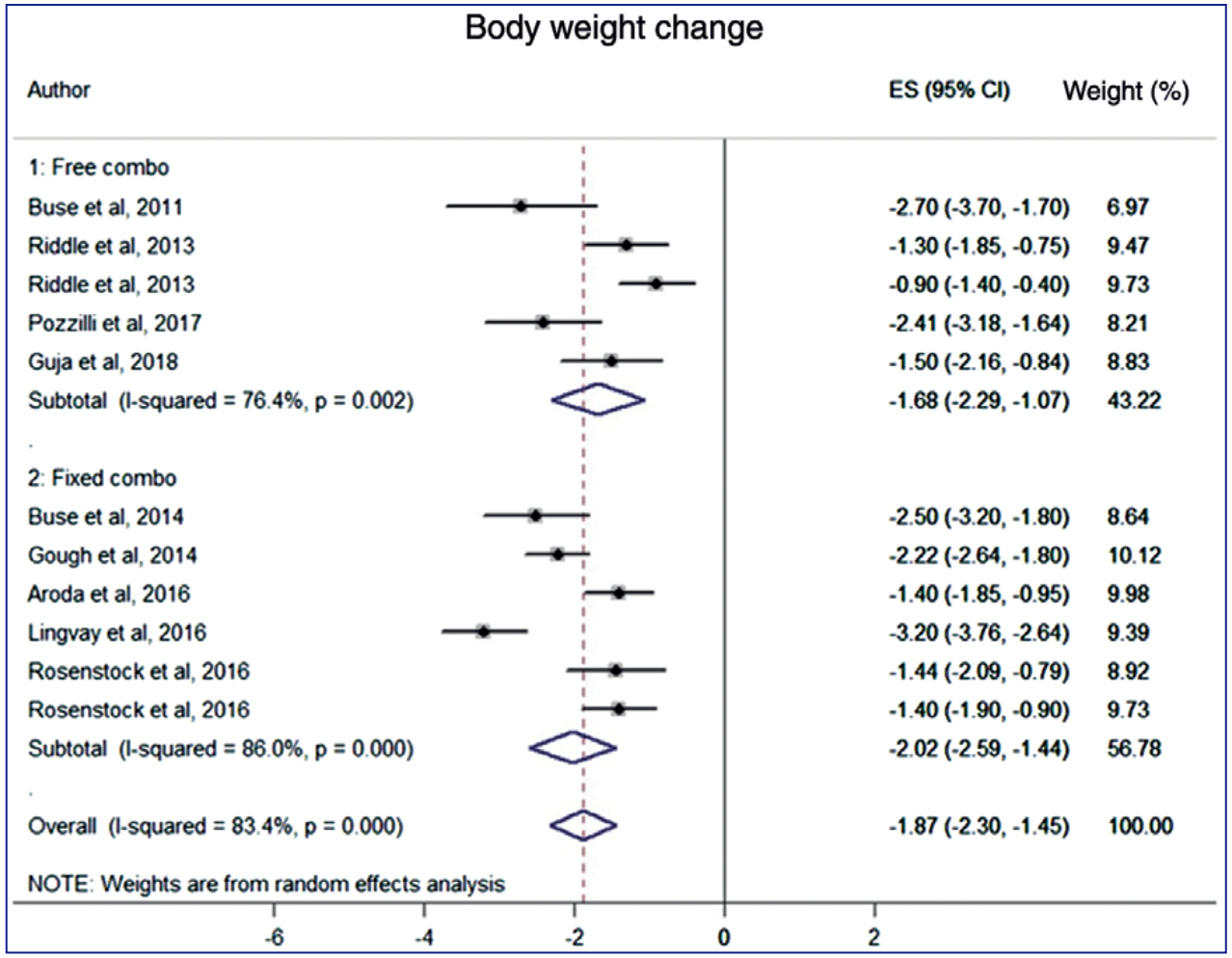


- Failed previous, or contraindications to, GLP-1RA therapy
- Transitioning off prandial insulin will not be appropriate
- Type 1 diabetes

Metha R et al. Diabetic Medicine. 2022;39:e14901

Fixed-ratio or loose combinations?





Parameter	Comparisons (n)	Intervention/control (n)	Estimate (95% CI)	*P* value	I^2	*P* value Q Test
Hypoglycaemia			RR			
All	11	3386/2790	0.97 (0.84, 1.12)	0.684	71.6	<0.001
Free combo	5	1070/893	1.13 (0.95, 1.36)	0.166	35.3	0.186
Fixed combo	6	2316/1897	0.87 (0.72, 1.04)	0.114	72.9	0.002

Maiorino MI et al. Diabetes Obes Metab. 2018;20:2309–2313

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Fixed versus flexible combination of GLP-1 receptor agonists with basal insulin in type 2 diabetes: A retrospective multicentre comparative effectiveness study

		Flexible group				Fixed group					
Comparison	Outcome	N	Baseline	Follow-up	Change	N	Baseline	Follow-up	Change	ETD (SE)	*P*
ITT matched	HbA1c	131	8.9 ± 1.5	8.4 ± 1.5	−0.6 ± 1.6[a]	131	8.9 ± 1.3	8.1 ± 1.4	−0.8 ± 1.4[a]	−0.26 (0.20)	.189
	Weight	117	94.3 ± 16.2	91.8 ± 15.7	−2.5 ± 3.9[a]	114	96.7 ± 17.3	95.5 ± 18.0	−1.2 ± 3.9[a]	1.20 (0.57)	.038
	SBP	111	143.7 ± 19.8	140.9 ± 19.8	−2.8 ± 22.7[a]	100	142.1 ± 23.1	141.3 ± 21.4	−0.9 ± 21.3	2.2 (3.2)	.482
	FPG	106	178.1 ± 64.8	161.6 ± 54.7	−16.5 ± 71[a]	117	181.4 ± 56.4	155.2 ± 61.4	−26.2 ± 68.4[a]	−9.0 (10.0)	.370
PP matched	HbA1c	109	8.8 ± 1.2	8.0 ± 1.1	−0.8 ± 1.3[a]	109	8.9 ± 1.3	8.1 ± 1.3	−0.8 ± 1.3[a]	−0.02 (0.20)	.934
	Weight	99	96.4 ± 17.2	93.6 ± 16.5	−2.8 ± 3.6[a]	96	97.8 ± 17.6	96.6 ± 18.2	−1.1 ± 4.0[a]	1.64 (0.62)	.009
	SBP	91	145.4 ± 20.3	137.5 ± 17.5	−7.9 ± 19.9[a]	84	141.1 ± 21.2	140.7 ± 20.0	−0.4 ± 21.1	5.3 (3.4)	.120
	FPG	95	176.9 ± 60.2	149.6 ± 43.7	−27.3 ± 58.2[a]	97	180.7 ± 56.9	151.4 ± 58.2	−29.3 ± 66.9[a]	−4.3 (9.9)	.666

Note. For each comparison and outcome, number of patients, values at baseline and follow-up, change from baseline and estimated treatment difference (ETD) with standard error (SE), along with respective *P* values are reported. For matched cohorts, the mean value of the first imputed dataset (out of 10) is reported. Pooled ETDs from the 10 imputed datasets are presented.

Abbreviations: FPG, fasting plasma glucose; ITT, intention to treat; PP, per protocol; SBP, systolic blood pressure.

[a]$P < .05$.

The estimated total cost of treatment was, on average, 878.8 ± 412.6 €/patient (n = 131) in the fixed group (36.9 ± 12.9 €/week/patient) and 1096.0 ± 374.1 €/patient (n = 127) in the flexible group (44.8 ± 9.2 €/week/patient). The difference was statistically significant, with cost in the fixed group being lower (ETD, −188.6 ± 56.3 €; $P = .001$), equivalent to a lower weekly cost of treatment of 7.9 ± 1.5 €/patient.

Morieri et al. Diabetes Obes Metab. 2019;21:2542–2552

Conclusioni

Le combinazioni precostituite INSULINA + GLP-1RA:

- Presentano un’efficacia e sicurezza superiore alla sola insulina basale sia in soggetti mai trattati con insulina che in soggetti non controllati con l’insulina basale
- Si sono dimostrate non inferiori alla terapia multiiniettiva nel ridurre l’HbA1c con risultati migliori in termini di rischio di ipoglicemia e di incremento ponderale
- Rappresentano, dunque, un utile strumento per ridurre inerzia terapeutica e problematiche connesse all’intensificazione terapeutica e all’aderenza

Grazie!