Insulinización: a quién, cuándo y cómo la realizamos?

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Conflictos de interés

- Conferencista: Astra Zeneca, Abbott Nutrición, Novartis Oncology, Novo Nordisk, Merck Sharp & Dohme, Roche, Glaxo SmithKline, Sanofi Aventis, Bayer, Pfizer, Novartis
- Advisory Board: Novartis Oncology, Sanofi Aventis, Astra Zeneca, Novo Nordisk, Stendhal, Pfizer
- Investigación clínica: Astra Zeneca, Novartis Pharma Logistics Inc., Merck Sharp & Dohme, Glaxo SmithKline, Organon, Boehringer Ingelheim, Roche, Novo Nordisk

Agenda

- Analizar el uso de insulina en diferentes escenarios clínicos (primera, segunda, tercera línea de tratamiento)
- Comparalo con otras terapias
- Titulación de dosis
- Qué indican las guías?

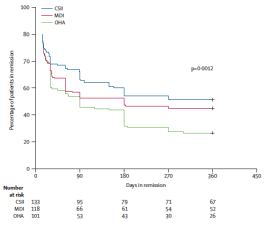
Insulina como terapia primera línea

Diseño

- Pacientes naives de tratamiento
- CSII vs MDI vs orales (glicazida, metformin o ambas)
- Titulación de insulina cada día y orales cada 3 días
- Se excluyen los que no alcanzan metas de tratamiento
- 2 semanas de tratamiento estable y suspende

Weng J. Lancet. 2008;371:1753

Pacientes en remisión



Weng J. Lancet. 2008;371:1753

Insulinas basales como terapia segunda línea

Continuous coverage of the American Diabetes Association 72nd Scientific Sessions

EASIE Trial: Design

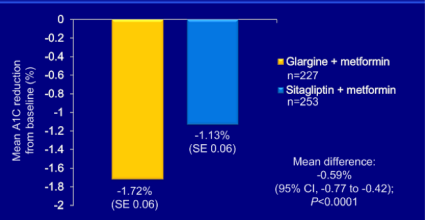
- Multicenter, randomized, parallel, open-label trial
- Examined efficacy, safety, and tolerability of insulin glargine vs sitagliptin among insulin-naïve patients with type 2 diabetes uncontrolled on metformin
- Subject profile:
  - Aged 35-70 yrs
  - Type 2 diabetes ≥6 months
  - A1C >7% and <11%
  - BMI 25-45 kg/m^2
  - Insulin naïve
- Randomized over 24 weeks to:
  - Insulin glargine (titrated from initial subcutaneous dose of 0.2 units/kg body weight to attain FPG 4.0-5.5 mmol/L) + metformin; n=250
  - Sitagliptin (100 mg qd oral dose) + metformin; n=265
- Primary outcome: change in A1C from baseline to Week 24

EASIE=Evaluation of insulin glargine versus Sitagliptin in Insulin-naïve patients

Aschner P, et al; on behalf of the EASIE investigators. *Lancet.* 2012;379(9833):2262-2269.

Continuous coverage of the American Diabetes Association 72nd Scientific Sessions

EASIE Trial: *Efficacy Population* Primary Outcome at Week 24—Change in A1C from Baseline

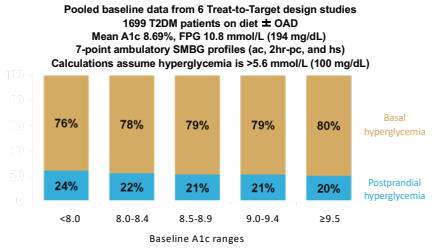


SE=standard error
EASIE=Evaluation of insulin glargine versus Sitagliptin in Insulin-naïve patients

Aschner P, et al; on behalf of the EASIE investigators. *Lancet.* 2012;379(9833):2262-2269.

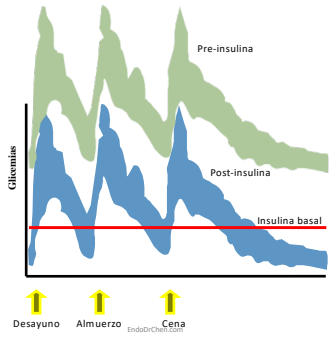
El escenario usual, después de fallo a antidiabéticos orales

Basal and postprandial contributions to hyperglycemia by A1c range



On oral therapy, fasting hyperglycemia dominates over a wide range of A1c

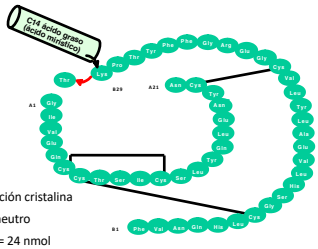
Riddle et al. Diabetes Care 34:2508–2514, 2011



Tipos de insulinas basales

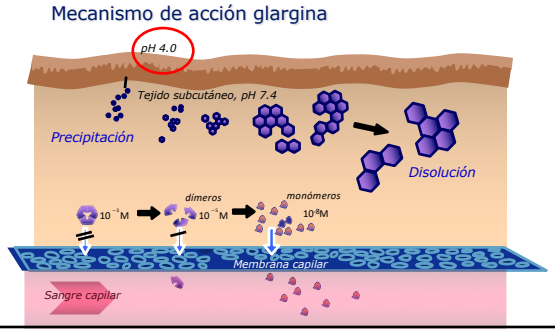
Insulina detemir

LysB29(N-tetradecanoyl)des(B30)

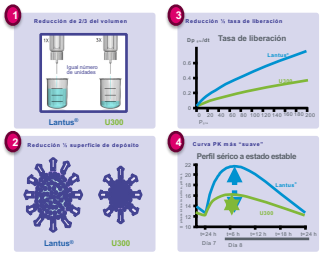


- Solución cristalina
- pH neutro
- 1 IU= 24 nmol

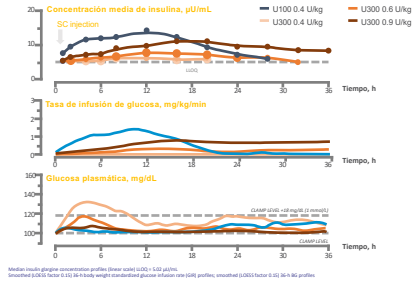
Mecanismo de acción glargina



U300 es una nueva insulina basal de acción prolongada que ofrece un perfil PK/PD más prolongado y plano que Lantus®



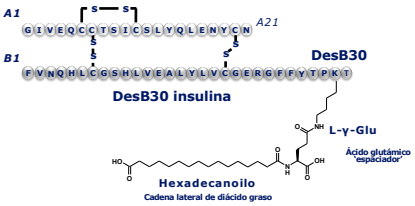
U300 presenta un perfil PK/PD más plano y prolongado vs U100



Median insulin glargine concentration profiles (linear scale) (LLOQ = 5.02 µU/mL
Smoothed (LOESS factor 0.15) 36-h body weight standardised glucose infusion rate (GIR) profiles; smoothed (LOESS factor 0.15) 36-h BG profiles

Insulina degludec: diseñado racionalmente, más allá de la modificación de la secuencia

Des(B30) LysB29(γ-Glu Nε-hexadecandioyl) insulina humana



Insulina degludec: inmediatamente después de la inyección

Jonassen et al. Pharm Res 2012;29:2104–14

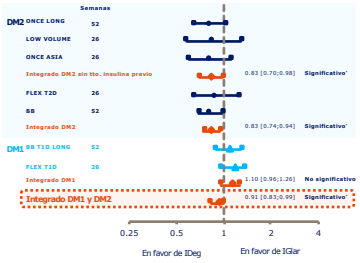
Insulinas basales

Tipo insulina	Inicio acción	Pico acción	Duración acción
NPH	1-2 horas	5-7 horas	13-18 horas
Glargina U100	6-8 horas	---	20 horas
Glargina U300		Más plano	24 horas
Detemir		6-7 horas	12-20 horas
Degludec			40 horas

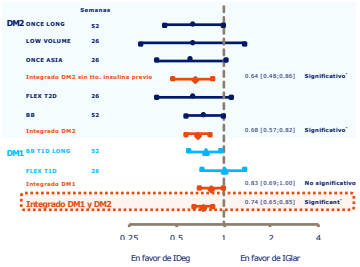
EndoDrChen.com

Cuál es la ventaja de las nuevas insulinas basales?

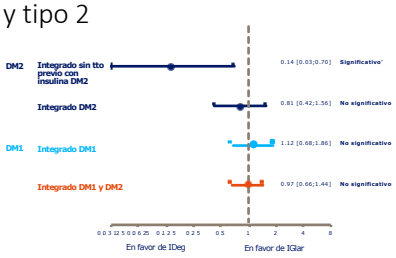
Metaanálisis preestablecido: hipoglucemia general confirmada



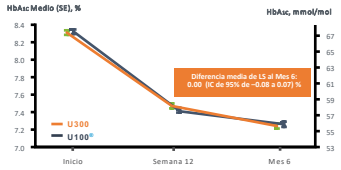
Metaanálisis preestablecido: hipoglucemia nocturna confirmada



Metaanálisis: hipoglucemia grave en diabetes tipo 1 y tipo 2



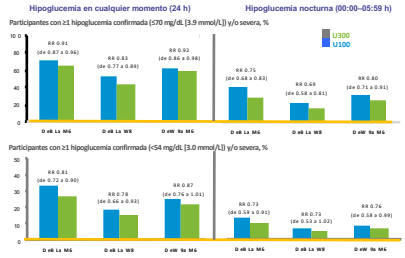
Reducciones similares en HbA1c y GPA



- En el Mes 6, GPA disminuyó de manera similar en ambo grupos
  - El cambio medio de LS (SE) fue de −36.8 (1.2) mg/dL con U300 y −40.6 (1.2) mg/dL con Lantus*
  - Diferencia media de LS de 3.9 (1.7) mg/dL

Análisis Combinado de DMT2 de EDITION I- II-III

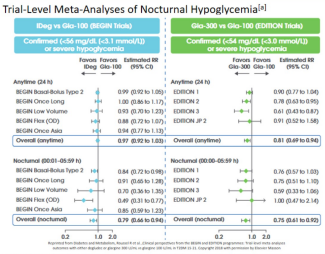
Hipoglucemia confirmada y/o severa generalmente inferior con U300 contra U100 en cualquier momento (24 h) y durante la noche



Rizzel R et al. Presentación de cartel en ADA 2014; Abstracto 90-LB Disponible en: http://ada.appinsor.org/app/AbstractADA.cfm?id=4 Accedido en junio de 2014

BEGIN and EDITION Trials for Deg-100 and Gla-300

Trial-Level Meta-Analyses of Nocturnal Hypoglycemia[a]



Reprinted from Diabetes Obes Metab, Russell-Jones D et al., Clinical perspectives from the BEGIN and EDITION programmes: insulin analogues versus with other regimens in groups with T2DM, 17:386-394, 2015. Copyright 2014 with permission by John Wiley & Sons, Inc.

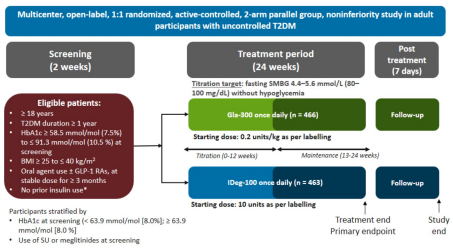
RCTs showed that Deg-100 and Gla-300 are:[b-j]

- As effective in lowering HbA1c as first-generation insulin analogues
- Associated with a lower risk of hypoglycemia, especially nocturnal hypoglycemia

a. Roussel R, et al. ATTD 2017. *ePoster* 273; b. Garber AJ, et al. *Lancet.* 2012;379:1498-1507; c. Zinman B, et al. *Diabetes Care,* 2012;35:2464-2471; d. Gough SC, et al. *Diabetes Care.* 2013;36:2536-2542; e. Meneghini L, et al. *Diabetes Care.* 2013;36:858-864; f. Onishi Y, et al. *J Diabetes Invest.* 2013;4:605-612; g. Riddle MC, et al. *Diabetes Care.* 2014;37:2755-2762; h. Yki-Järvinen H, et al. *Diabetes Care.* 2014;37:3235-3243; i. Bolli GB, et al. *Diabetes Obes Metab.* 2015;17:386-394; j. Terauchi Y, et al. *Diabetes Obes Metab.* 2016;18:366-374.

Entonces... Cómo se comparan las nuevas insulinas basales?

BRIGHT: Head-to-Head Comparison of Gla-300 and Deg-100



*With the exception of a maximum of 8 consecutive days or 15 days total prior insulin use.

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BRIGHT: Study Endpoints and Glycemic Targets

Primary efficacy endpoint:
- Change in HbA1c from baseline to week 24
  - Analyzed using a MMRM approach, adjusted for covariates including baseline HbA1c
  - Non-inferiority margin was 0.3% (HbA1c units)

Secondary efficacy endpoints included:
- Change in FPG, fasting SMBG, and 8-point SMBG profiles from baseline to week 24
- Variability of 8-point SMBG profiles

Safety endpoints included:
- Incidence and annualized rates of hypoglycemia (≤ 3.9 mmol/L [70 mg/dL] and ≤3.0 mg/dL [54 mg/dL]) over the full 24-week period, and during weeks 0-12 (the active titration period) and weeks 13-24 (the maintenance period)
- TEAEs

Gla-300 and Deg-100 titrated weekly* to SMBG target of 4.4-5.6 mmol/L (80-100 mg/dL)

Median[1] fasting SMPG, mmol/L (mg/dL)	Dose change
> 7.8 (> 140)	+ 6 units
> 6.7 to ≤ 7.8 (> 120 to ≤ 140)	+ 4 units
> 5.6 to ≤ 6.7 (> 100 to ≤ 120)	+ 2 units
≥ 4.4 to ≤ 5.6 (≥ 80 to ≤ 100)	0
< 4.4 (80)[4]	- 2 units[5]

*But no more than every 3 days; [1]From last 3 measurements [4]or 1 symptomatic confirmed hypoglycemia episode in preceding week [5]or at investigator's discretion.
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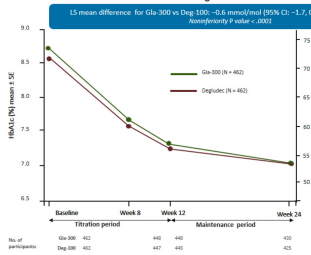
BRIGHT: Primary Endpoint: Glycemic Control

Gla-300 Noninferior to Deg-100 in HbA1c Reduction at Week 24

LS mean difference for Gla-300 vs Deg-100: −0.6 mmol/mol (95% CI: −1.7, 0.6) (-0.05% [-0.15, 0.05])
Noninferiority P value < .0001



Change in HbA1c from Baseline to Week 24

- Gla-300: -17 mmol/mol (-1.6%)
- Deg-100: -17 mmol/mol (-1.6%)

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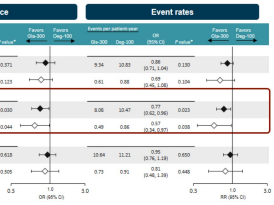
BRIGHT: Anytime (24 h) Hypoglycemia

	Incidence, %				Events per patient-year			
	Gla-300	Deg-100	OR (95% CI)	*P* value*	Gla-300	Deg-100	OR (95% CI)	*P* value*
Full study period (0–24 weeks)								
Confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL])	66.5	69.0	0.88 (0.66, 1.17)	0.371	9.34	10.83	0.86 (0.71, 1.04)	0.130
Confirmed (< 3.0 mmol/L [< 54 mg/dL])	14.7	18.4	0.76 (0.55, 1.08)	0.123	0.61	0.88	0.69 (0.45, 1.08)	0.104
Titration period (0–12 weeks)								
Confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL])	47.4	54.3	0.74 (0.57, 0.97)	0.030	8.08	10.47	0.77 (0.62, 0.96)	0.023
Confirmed (< 3.0 mmol/L [< 54 mg/dL])	7.8	11.7	0.63 (0.40 to 0.99)	0.044	0.49	0.86	0.57 (0.34, 0.97)	0.038
Maintenance period (13–24 weeks)								
Confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL])	54.1	55.8	0.93 (0.72, 1.22)	0.618	10.94	11.21	0.95 (0.76, 1.18)	0.650
Confirmed (< 3.0 mmol/L [< 54 mg/dL])	9.8	11.2	0.86 (0.56, 1.33)	0.505	0.73	0.91	0.81 (0.46, 1.39)	0.448



Confirmed hypoglycemia included documented symptomatic or asymptomatic hypoglycemia (≤ 3.9 mmol/L or < 3.0 mmol/L [≤ 70 mg/dL or < 54 mg/dL]), and severe events if any; only 1 participant experienced severe hypoglycemia (1 event), in the Gla-300 group, due to a skipped evening meal and not reducing her insulin dose after a non-severe event 2 days earlier.
All *P* values presented are nominal, not adjusted for multiplicity. Safety population (Gla-300, n = 463; Deg-100, n = 462).

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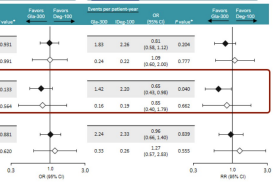
BRIGHT: Nocturnal (00:00–06:00 h) Hypoglycemia

	Incidence, %				Events per patient-year			
	Gla-300	Deg-100	OR (95% CI)	*P* value*	Gla-300	Deg-100	OR (95% CI)	*P* value*
Full study period (0–24 weeks)								
Confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL])	28.6	28.8	0.99 (0.74, 1.32)	0.931	1.83	2.26	0.81 (0.58, 1.12)	0.204
Confirmed (< 3.0 mmol/L [< 54 mg/dL])	6.1	6.1	1.00 (0.58, 1.72)	0.991	0.24	0.22	1.09 (0.60, 2.00)	0.777
Titration period (0–12 weeks)								
Confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL])	15.2	18.8	0.77 (0.54, 1.08)	0.133	1.42	2.20	0.65 (0.43, 0.98)	0.040
Confirmed (< 3.0 mmol/L [< 54 mg/dL])	2.8	3.5	0.80 (0.38, 1.69)	0.564	0.16	0.19	0.88 (0.40, 1.79)	0.662
Maintenance period (13–24 weeks)								
Confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL])	21.4	21.0	1.03 (0.74, 1.42)	0.881	2.24	2.33	0.96 (0.66, 1.40)	0.839
Confirmed (< 3.0 mmol/L [< 54 mg/dL])	4.5	3.8	1.18 (0.61, 2.29)	0.620	0.33	0.26	1.27 (0.37, 2.63)	0.555



Confirmed hypoglycemia included documented symptomatic or asymptomatic hypoglycemia (≤ 3.9 mmol/L or < 3.0 mmol/L [≤ 70 mg/dL or < 54 mg/dL]), and severe events if any; only 1 participant experienced severe hypoglycemia (1 event), in the Gla-300 group, due to a skipped evening meal and not reducing her insulin dose after a non-severe event 2 days earlier.
All *P* values presented are nominal, not adjusted for multiplicity. Safety population (Gla-300, n = 463; Deg-100, n = 462).

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BRIGHT: Insulin Dosage and Body Weight Over 24 Weeks

Mean Daily Insulin Dose

	Gla-300 (n = 462)		Deg-100 (n = 462)	
	Units	Units /kg	Units	Units /kg
Initial	16.9 ± 4.4	0.19 ± 0.04	10.2 ± 1.9	0.12 ± 0.04
Between-treatment difference at baseline	0.07 units/kg			
Week 24	50.5 ± 25.6	0.54 ± 0.26	39.2 ± 23.3	0.43 ± 0.24
Between-treatment difference at week 24	0.11 units/kg			
Change from baseline to week 24	33.6 ± 24.4	0.36 ± 0.25	29.1 ± 23.3	0.31 ± 0.24

Data are mean ± SD, except for between-treatment differences (only mean presented)

Mean Body Weight

	Gla-300 (n = 462)	Deg-100 (n = 462)
	Kg	Kg
Initial	90.6 ± 16.1	88.7 ± 15.9
Week 24	92.5 ± 16.6	91.4 ± 16.7
Change from baseline to week 24	2.0 ± 3.8	2.3 ± 3.6

Data are mean ± SD

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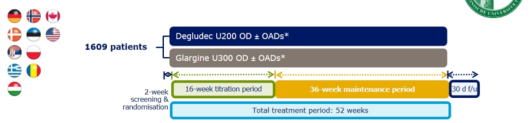
CONCLUDE: degludec vs glargina U300

Trial design



Key inclusion criteria
- Age ≥18 years
- T2D
- Basal insulin ± OADs*
- HbA_{1c} ≤9.5%
- BMI ≤45 kg/m²
- At increased risk of hypoglycaemia

Key exclusion criteria
- Planned or current CSII users
- Bolus insulin
- GLP-1RA treatment
- Impaired liver function
- Renal impairment (eGFR <30 mL/min/1.73 m²)

Trial design elements
- Open-labelled, randomised, treat-to-target, multicentre
- Randomised to insulin administered in morning or evening
- Insulin titrated once weekly (target 4–5 mmol/L)
- Initial dose: degludec U200 reduced 20%/glargine U300 as per label

*Metformin, DPP-4 inhibitors, alpha-glucosidase inhibitor, thiazolidinediones and SGLT-2 inhibitors
BMI, body mass index; CSII, continuous subcutaneous insulin infusion; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; glargine U300, insulin glargine 300 units/mL; GLP-1RA, glucagon-like peptide-1 receptor agonist; OAD, oral antidiabetic drug; OD, once daily; SGLT-2, sodium-glucose co-transporter-2; T2D, type 2 diabetes; https://clinicaltrials.gov/ct2/show/NCT03078478; Philis-Tsimikas *et al. J Diabetes Sci Technol* 2019;13:498–506

JOANNEUM RESEARCH HEALTH

Titration algorithm

Pre-breakfast (fasting) SMBG*		Total daily dose adjustment of degludec U200 and glargine U300
mmol/L	mg/dL	Units
<3.1	<56	−4
3.1–3.9	56–70	−2
4.0–5.0	**71–90**	**0**
5.1–7.0	91–126	+2
7.1–8.0	127–144	+4
8.1–9.0	145–162	+6
>9.0	>162	+8

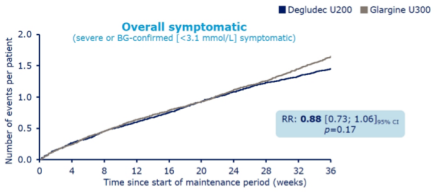
*For dose increases the mean of 3 pre-breakfast SMBG measurements were used. For dose reductions the lowest SMBG measurement was used
Glargine U300, insulin glargine 300 units/mL; SMBG, self measured blood glucose

JOANNEUM RESEARCH HEALTH

Hypoglycaemia endpoints

MAINTENANCE period – primary endpoint

Prespecified analysis



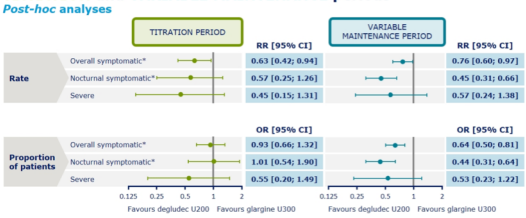
BG, blood glucose; CI, confidence interval; glargine U300, insulin glargine 300 units/mL; RR, rate ratio

CONCLUDE

Hypoglycaemia endpoints

TITRATION and VARIABLE MAINTENANCE periods

***Post-hoc* analyses**



*Event defined as severe (requiring third-party assistance) or blood glucose <3.1 mmol/L confirmed with symptoms. All nocturnal hypoglycaemia reported between 00:01 and 05:59
CI, confidence interval; glargine U300, insulin glargine 300 units/mL; OR, odds ratio; RR, rate ratio

CONCLUDE

Hypoglycaemia endpoints
TITRATION and VARIABLE MAINTENANCE periods

		Degludec U200				Glargine U300			
		n	%	Events	Rate	n	%	Events	Rate
Titration period	Overall symptomatic*	69	8.6	95	39.3	74	9.3	132	55.2
	Nocturnal symptomatic*	20	2.5	26	10.8	20	2.5	40	16.7
	Severe	6	0.7	6	2.5	11	1.4	13	5.4
Variable maintenance period	Overall symptomatic*	160	20.6	331	91.4	224	29.2	440	121.7
	Nocturnal symptomatic*	46	5.9	67	18.5	97	12.6	148	40.9
	Severe	9	1.2	12	3.3	16	2.1	20	5.5

*Event defined as severe (requiring third-party assistance) or blood glucose <3.1 mmol/L confirmed with symptoms. All nocturnal hypoglycaemia reported between 00:01 and 05:59
%, proportion of patients with events; events, number of events; glargine U300, insulin glargine 300 units/mL; n, number of patients with events; rate, events per 100 patient-years of observation

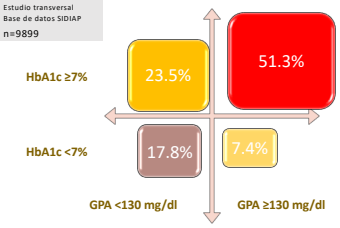
CONCLUDE

Inicio y titulación

Falla en la optimización del tratamiento con insulina basal

Distribución de la población total bajo tratamiento con insulina basal de acuerdo a sus niveles de HbA1c y GPA

Estudio transversal
Base de datos SIDIAP
n=9899



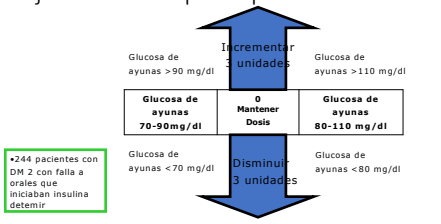
1. Adaporto de Mata-Cases M. et al. *Journal of Diabetes* 9 (2016), 34–44

Insulina Glargina (100 U/mL) + Lixisenatida

Cómo cambia la titulación con las nuevas insulinas basales?

- Iniciar con 10 u al día ó 0.1-0.2 u/kg
- Al tener una vida media más larga, se dura más tiempo en alcanzar el estado estacionario
- Con las insulinas basales usuales (NPH, detemir, glargina U100) se recomendaba titular cada 3 días
- Con las nuevas insulinas basales (glargina U300, degludec) la recomendación es titular una vez a la semana
  - BRIGHT: 80-100 mg/dl
  - CONCLUDE 70-90 mg/dl
- Lo usual es una meta entre 90 y 120 mg/dl

Insulina basal: Ajuste de dosis por el paciente



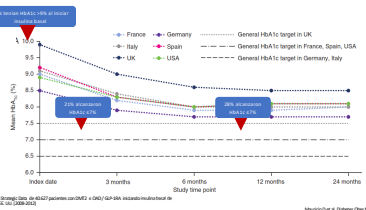
•244 pacientes con DM 2 con falla a orales que iniciaban insulina detemir

Ajuste cada 3er día según el promedio de la glucosa de ayunas

Diabetes Obes Metab. Jun

La respuesta glucémica durante los primeros 3 meses de terapia con IB es un predictor para el control glucémico a mediano y largo plazo

- Muchos pacientes inician insulina basal con HbA1c >9% = intensificación retardada
- La media de HbA1c muestra la mayor disminución en los primeros 3 meses, antes de permanecer estable durante el resto del período



Análisis observacional retrospectivo de Cegedim Strategic Data de 40,627 pacientes con DMT2 + OHG / GLP-1RA iniciando insulina basal de Francia, Alemania, Italia, España, Reino Unido y EE. UU. (2008-2012)

Mauricio D et al. Diabetes Obes Metab. 2017;19:1151–64

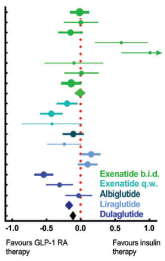
IB, insulina basal; OHG, fármaco antidiabético oral; GLP-1 RA, agonista del receptor del péptido 1 similar al glucagón

arGLP-1 vs insulina basal después de agentes orales

Metanálisis: arGLP1 vs insulina basal: Hba1c

A **GLP-1 RA versus insulin treatment (OGLM background)**

Study	Duration of action	Difference in means	Lower Limit	Upper Limit	Z-value	p-value
Heine et al. 2005 [44]	short	-0.02	-0.16	0.12	-0.24	0.81
Barnett et al. 2007 [33]	short	0.00	-0.25	0.25	0.00	1.00
Nauck et al. 2007 [47]	short	-0.15	-0.33	0.03	-1.63	0.10
Bergenstal et al. 2009 a [34]	short	0.59	0.21	0.97	3.02	0.0026
Bergenstal et al. 2009 b [34]	short	1.01	0.59	1.43	4.72	< 0.0001
Bunck et al. 2009 [35]	short	-0.10	-0.53	0.33	-0.46	0.65
Davies et al. 2009 [38]	short	0.01	-0.24	0.26	0.08	0.94
Gallwitz et al. 2011 [41]	short	-0.14	-0.29	0.01	-1.87	0.061
All short-acting GLP-1 RAs		**-0.02**	**-0.09**	**0.06**	**-0.39**	**0.70**
Diamant et al. 2010 [40]	long	-0.20	-0.35	-0.05	-2.67	0.010
Inagaki et al. 2012 [45]	long	-0.43	-0.60	-0.26	-5.08	< 0.0001
Davies et al. 2013 [37]	long	-0.42	-0.86	0.02	-1.87	0.061
Weissman et al. 2014 [50]	long	-0.11	-0.27	0.05	-1.39	0.16
Russell-Jones et al. 2009 [49]	long	-0.24	-0.49	0.01	-1.89	0.059
D'Alessio et al. 2015 [36]	long	0.15	0.01	0.29	2.12	0.034
Gough et al. 2015 [43]	long	0.10	-0.04	0.24	1.37	0.17
Araki et al. 2015 [32]	long	-0.54	-0.68	-0.40	-7.66	< 0.0001
Giorgino et al. 2015 a [42]	long	-0.31	-0.50	-0.12	-3.13	0.0018
Giorgino et al. 2015 b [42]	long	-0.03	-0.22	0.16	-0.30	0.76
All long-acting GLP-1 RAs		**-0.17**	**-0.22**	**-0.12**	**-6.24**	**< 0.0001**
All GLP-1 RAs		**-0.12**	**-0.16**	**-0.07**	**-5.30**	**< 0.0001**

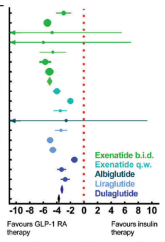


Abd El Aziz MS. Diab Obes Metab. 2017;19:216

Metanálisis: arGLP1 vs insulina basal: peso

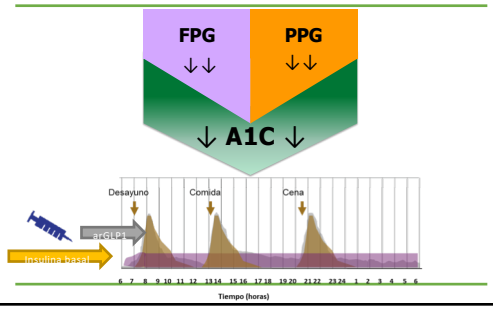
A **GLP-1 RA versus insulin treatment (OGLM background)**

Study	Duration of action	Difference in means	Lower Limit	Upper Limit	Z-value	p-value
Barnett et al. 2007 [33]	short	-3.00	-4.11	-1.89	-5.30	< 0.0001
Nauck et al. 2007 [47]	short	-5.40	-5.95	-4.85	-19.09	< 0.0001
Bergenstal et al. 2009 a [34]	short	-4.70	-14.96	5.56	-0.90	0.37
Bergenstal et al. 2009 b [34]	short	-6.00	-18.94	6.94	-0.91	0.36
Bunck et al. 2009 [35]	short	-4.80	-6.54	-2.86	-4.85	< 0.0001
Davies et al. 2009 [38]	short	-5.71	-6.57	-4.85	-13.03	< 0.0001
Gallwitz et al. 2011 [41]	short	-5.10	-5.71	-4.49	-16.39	< 0.0001
All short-acting GLP-1 RAs		**-5.10**	**-5.44**	**-4.75**	**-28.93**	**< 0.0001**
Diamant et al. 2010 [40]	long	-4.00	-4.56	-3.45	-14.13	< 0.0001
Inagaki et al. 2012 [45]	long	-2.01	-2.48	-1.54	-8.38	< 0.0001
Davies et al. 2013 [37]	long	-3.50	-4.50	-2.50	-6.85	< 0.0001
Weissman et al. 2014 [50]	long	-2.63	-14.58	9.32	-0.43	0.67
Russell-Jones et al. 2009 [49]	long	-3.40	-4.32	-2.49	-7.29	< 0.0001
D'Alessio et al. 2015 [36]	long	-5.00	-5.48	-4.52	-20.41	< 0.0001
Gough et al. 2015 [43]	long	-4.60	-5.11	-4.09	-17.60	< 0.0001
Araki et al. 2015 [32]	long	-1.42	-1.89	-0.95	-5.90	< 0.0001
Giorgino et al. 2015 a [42]	long	-3.31	-3.98	-2.64	-9.75	< 0.0001
Giorgino et al. 2015 b [42]	long	-2.77	-3.44	-2.11	-8.16	< 0.0001
All long-acting GLP-1 RAs		**-3.28**	**-3.47**	**-3.09**	**-33.48**	**< 0.0001**
All GLP-1 RAs		**-3.71**	**-3.88**	**-3.54**	**-43.32**	**< 0.0001**

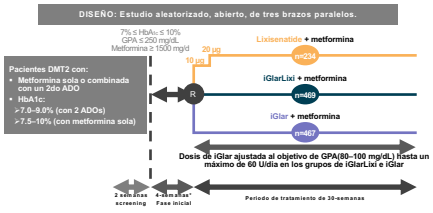


Abd El Aziz MS. Diab Obes Metab. 2017;19:216

Y si empezamos con terapia combinada (insulina basal + arGLP1)?



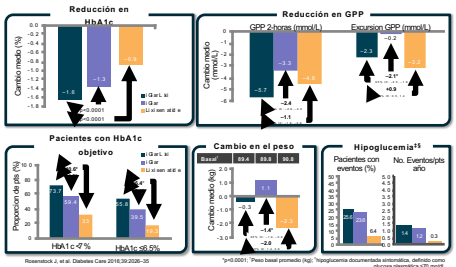
LixiLan-O: Pacientes con DMT2 no controlados con ADOs



Objetivo Primario: superioridad de iGlarLixi sobre lixisenatide y no-inferioridad de iGlarLixi sobre iGlar en el cambio de HbA1c a la semana 30

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

LixiLan-O: Resumen de resultados



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

*p<0.0001. †Peso basal promedio (kg). ‡Hipoglucemia documentada sintomática, definido como glucosa plasmática ≤70 mg/dL.
§Un evento de hipoglucemia severa fue reportado durante el estudio y ocurrió en el grupo de iGlar.

Insulina glargina & lixisenatide

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LIXILAN-O

Perfil de eventos adversos (EA)

Pacientes n (%) con al menos un…	iGlarLixi (n=469)	insulina glargina 100 U/mL (n=467)	lixisenatida (n=233)
EA relacionado al tx			
Cualquiera	267 (56.9%)	227 (48.6%)	157 (67.4%)
Serio	18 (3.8%)	19 (4.1%)	9 (3.9%)
Relacionado a muerte	2 (0.4%)	3 (0.6%)	1 (0.4%)
Relacionado a descontinuación	12 (2.6%)	9 (1.9%)	21 (9%)
EA Gastrointestinal relacionado al tx			
Náusea	45 (9.6%)	17 (3.6%)	56 (24%)
Descontinuación	2 (0.4%)	0	6 (2.6%)
Vómito	15 (3.2%)	7 (1.5%)	15 (6.4%)
Descontinuación	2 (0.4%)	0	4 (1.7%)
Diarrea	42 (9%)	20 (4.3%)	21 (9%)
Descontinuación	1 (0.2%)	0	2 (0.9%)

Rosenstock J, et al. Diabetes Care Aug 2016; dc160917; DOI: 10.2337/dc16-0917

Insulina glargina & lixisenatide

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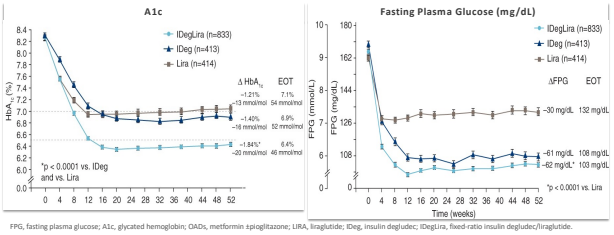
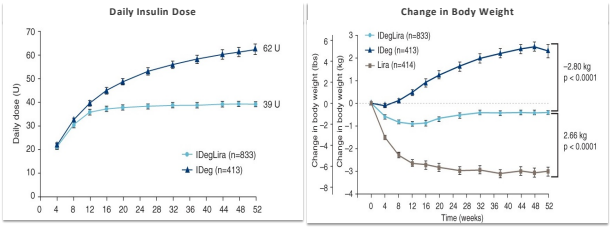
IDegLira in Insulin-Naïve Patients with T2DM not Controlled on OADs: DUAL I



FPG, fasting plasma glucose; A1c, glycated hemoglobin; OADs, metformin ±pioglitazone; LIRA, liraglutide; IDeg, insulin degludec; IDegLira, fixed-ratio insulin degludec/liraglutide.

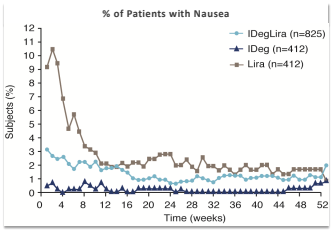
Gough SCL, et al. Diabetes Obes Metab. 2015;17:965-973.

IDegLira in Insulin-Naïve Patients with T2DM not Controlled on OADs: DUAL I *(cont)*



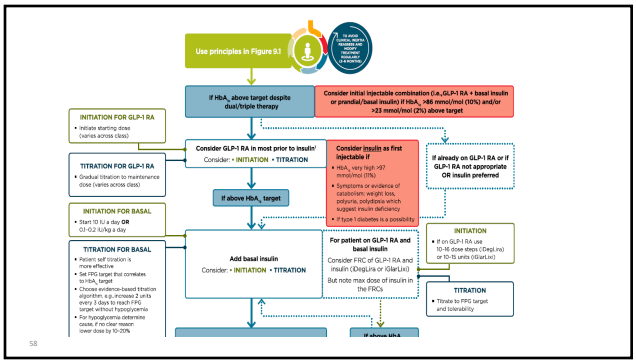
Gough SCL, et al. *Diabetes Obes Metab.* 2015;17:965-973.

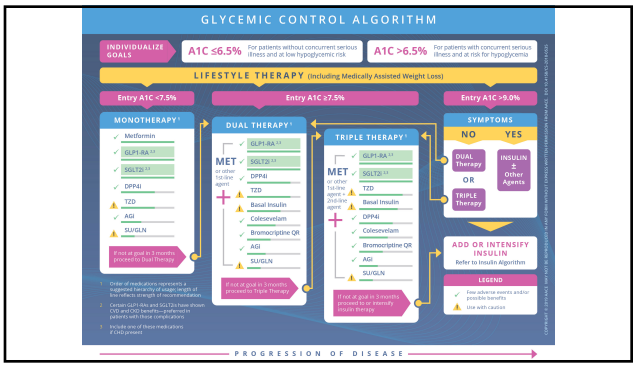
IDegLira in Insulin-Naïve Patients with T2DM not Controlled on OADs: DUAL I *(cont)*

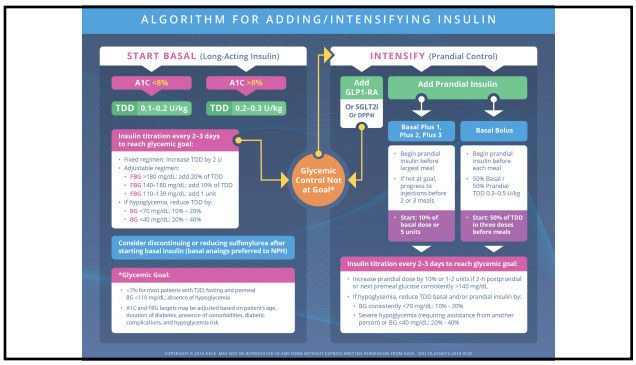


Gough SCL, et al. *Diabetes Obes Metab.* 2015;17:965-973.

Qué nos dicen las guías?


Use principles in Figure 9.1
If HbA1c above target despite dual/triple therapy
Consider initial injectable combination (i.e., GLP-1 RA + basal insulin or prandial/basal insulin) if HbA1c >86 mmol/mol (10%) and/or >33 mmol/mol (2%) above target
INITIATION FOR GLP-1 RA
Initiate starting dose (varies across class)
TITRATION FOR GLP-1 RA
Gradual titration to maintenance dose (varies across class)
INITIATION FOR BASAL
Start 10 IU a day OR 0.1-0.2 IU/kg a day
TITRATION FOR BASAL
Patient self titration is more effective
Set FPG target that correlates to HbA1c target
Choose evidence-based titration algorithm, e.g. increase 2 units every 3 days to reach FPG target without hypoglycemia
For hypoglycemia determine cause, if no clear reason lower dose by 10-20%
Consider GLP-1 RA in most prior to insulin!
Consider: • INITIATION • TITRATION
If above HbA1c target
Add basal insulin
Consider: • INITIATION • TITRATION
Consider insulin as first injectable if
HbA1c very high >97 mmol/mol (11%)
Symptoms or evidence of catabolism: weight loss, polyuria, polydipsia which suggest insulin deficiency
If type 1 diabetes is a possibility
If already on GLP-1 RA or if GLP-1 RA not appropriate OR insulin preferred
INITIATION
If on GLP-1 RA use 10-16 dose steps (Cdeg2.ins) or 10-15 units (IGlarLxx)
For patient on GLP-1 RA and basal insulin
Consider FRC of GLP-1 RA and insulin (DdegLira or IGlarLixi).
But note max dose of insulin in the FRCs
TITRATION
Titrate to FPG target and tolerability
58


GLYCEMIC CONTROL ALGORITHM
INDIVIDUALIZE GOALS
A1C ≤6.5%
For patients without concurrent serious illness and at low hypoglycemic risk
A1C >6.5%
For patients with concurrent serious illness and at risk for hypoglycemia
LIFESTYLE THERAPY (Including Medically Assisted Weight Loss)
Entry A1C <7.5%
Entry A1C ≥7.5%
Entry A1C >9.0%
MONOTHERAPY 1
Metformin
GLP1-RA 2,3
SGLT2i 2,3
DPP4i
TZD
AGI
SU/GLN
If not at goal in 3 months proceed to Dual Therapy
DUAL THERAPY 1
MET or other 1st-line agent
GLP1-RA 2,3
SGLT2i 2,3
DPP4i
TZD
Basal Insulin
Colesevelam
Bromocriptine QR
AGI
SU/GLN
If not at goal in 3 months proceed to Triple Therapy
TRIPLE THERAPY 1
MET or other 1st-line agent + 2nd-line agent
GLP1-RA 2,3
SGLT2i 2,3
TZD
Basal Insulin
DPP4i
Colesevelam
Bromocriptine QR
AGI
SU/GLN
If not at goal in 3 months proceed to or intensify insulin therapy
SYMPTOMS
NO
YES
DUAL Therapy
OR
TRIPLE Therapy
INSULIN ± Other Agents
ADD OR INTENSIFY INSULIN
Refer to Insulin Algorithm
LEGEND
Few adverse events and/or possible benefits
Use with caution
1 Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation.
2 Certain GLP1-RAs and SGLT2s have shown benefit for CVD risk reduction in patients with these complications.
3 Include one of these medications if CVD present
PROGRESSION OF DISEASE


ALGORITHM FOR ADDING/INTENSIFYING INSULIN
START BASAL (Long-Acting Insulin)
A1C <8%
A1C ≥8%
TDD 0.1–0.2 U/kg
TDD 0.2–0.3 U/kg
Insulin titration every 2–3 days to reach glycemic goal:
Fixed regimen: Increase TDD by 2 U
Adjustable regimen:
FBG >180 mg/dL: add 20% of TDD
FBG 140–180 mg/dL: add 10% of TDD
FBG 110–139 mg/dL: add 1 unit
If hypoglycemia, reduce TDD by:
BG <70 mg/dL: 10% – 20%
BG <40 mg/dL: 20% – 40%
Consider discontinuing or reducing sulfonylurea after starting basal insulin (basal analogs preferred to NPH)
*Glycemic Goal:
<7% for most patients with T2D; fasting and premeal BG <110 mg/dL; absence of hypoglycemia
A1C and FBG targets may be adjusted based on patient's age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk
Glycemic Control Not at Goal*
INTENSIFY (Prandial Control)
Add GLP1-RA
Or SGLT2i
Or DPP4i
Add Prandial Insulin
Basal Plus 1, Plus 2, Plus 3
Basal Bolus
Begin prandial insulin before largest meal
If not at goal, progress to injections before 2 or 3 meals
Start: 10% of basal dose or 5 units
Begin prandial insulin before each meal
50% Basal / 50% Prandial
TDD 0.3–0.5 U/kg
Start: 50% of TDD in three doses before meals
Insulin titration every 2–3 days to reach glycemic goal:
Increase prandial dose by 10% or 1-2 units if 2-h postprandial or next premeal glucose consistently >140 mg/dL
If hypoglycemia, reduce TDD basal and/or prandial insulin by:
BG consistently <70 mg/dL: 10% – 20%
Severe hypoglycemia (requiring assistance from another person) or BG <40 mg/dL: 20% – 40%

Reflexiones

- arGLP-1 debería ser el primer inyectable
- … limitante es el costo!
- Es una alternativa para intensificación
- Facilidad de usar un único dispositivo

Conclusiones

- En la progresión de la enfermedad, tarde o temprano la mayoría de los pacientes requieren insulinizar
- La forma más fácil de insulinizar es iniciar con una insulina basal
- Titulación de la dosis es fundamental
- Con insulinas basales el riesgo de hipoglicemias es bajo
- Una opción es la combinación fija de insulina basal más arGLP1

Preguntas…

chenku2409@gmail.com

Puede descargar la presentación en:

www.EndoDrChen.com