

# Tractament combinat insulina i agonistes del R de GLP-1: teràpia combinada inicial o teràpia seqüencial?

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1-Ús combinat d'insulina i aRGLP1. Sentit fisiopatològic? Realitat clínica? Què diuen les guies de les societats científiques? Què diuen les fitxes tècniques?

2-Tractament amb insulina i afegir aRGLP1

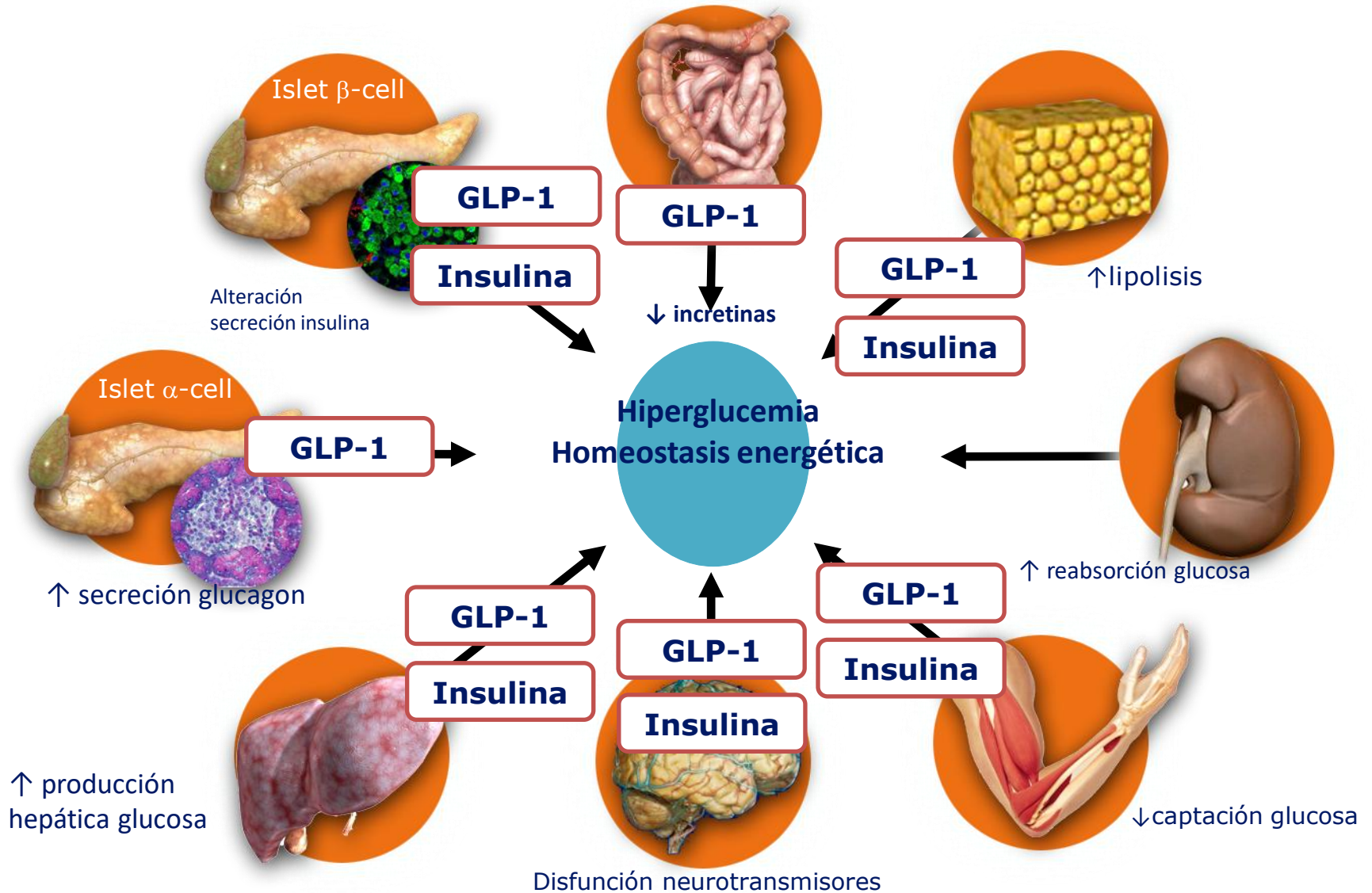
3-Tractament amb aRGLP1 i afegir insulina

4-Tractament combinat inicial

5-Tractament amb aRGLP1 en un escenari on la insulina és mandatòria: DM tipus 1

6-Conclusions

# Fisiopatología de la DM 2 i punts de millora farmacològica



**Mono-therapy**

- Efficacy\*
- Hypo risk
- Weight
- Side effects
- Costs\*

Healthy eating, weight control, increased physical activity, and diabetes education

**Metformin**

- high
- low risk
- neutral / loss
- GI / lactic acidosis
- low

*If HbA<sub>1c</sub> target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):*

**Dual therapy<sup>†</sup>**

- Efficacy\*
- Hypo risk
- Weight
- Side effects
- Costs\*

Metformin +	Metformin +	Metformin +	Metformin +	Metformin +	Metformin +
Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
high	high	intermediate	intermediate	high	highest
moderate risk	low risk	low risk	low risk	low risk	high risk
gain	gain	neutral	loss	loss	gain
hypoglycemia	edema, HF, fxs	rare	GU, dehydration	GI	hypoglycemia
low	low	high	high	high	variable

*If HbA<sub>1c</sub> target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):*

**Triple therapy**

Metformin +	Metformin +	Metformin +	Metformin +	Metformin +	Metformin +
Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
+ TZD	+ SU	+ SU	+ SU	+ SU	+ TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or Insulin <sup>5</sup>	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin <sup>5</sup>	or Insulin <sup>5</sup>		or GLP-1-RA
or Insulin <sup>5</sup>	or Insulin <sup>5</sup>				

*If HbA<sub>1c</sub> target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:*

**Combination injectable therapy**

Metformin +	Basal insulin + Mealtime insulin	or	GLP-1-RA
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## Indicacions autoritzades per fitxa tècnica al nostre medi (2017)

<b>Exenatide</b>	Byetta está indicado para el tratamiento de diabetes mellitus tipo 2 en combinación con: metformina, sulfonilureas, tiazolidindionas, metformina y una sulfonilurea, metformina y una tiazolidindiona en adultos que no hayan alcanzado un control glucémico adecuado con las dosis máximas toleradas de estos tratamientos orales. Byetta está también indicado como tratamiento coadyuvante a insulina basal con o sin metformina y/o pioglitazona en adultos que no hayan alcanzado un adecuado control glucémico con estos medicamentos.
<b>Liraglutide</b>	Terapia combinada: En combinación con medicamentos hipoglucemiantes orales y/o insulina basal cuando estos, junto con dieta y ejercicio, no logran un control glucémico
<b>Exenatide LAR</b>	Bydureon está indicado para el tratamiento de la diabetes mellitus tipo 2 en combinación con Metformina, Sulfonilurea, Tiazolidindiona, Metformina y una sulfonilurea Metformina y una tiazolidindiona, en adultos que no hayan alcanzado un control glucémico adecuado con las dosis máximas toleradas de estos tratamientos orales.
<b>Lixisenatide</b>	Lyxumia está indicado en el tratamiento de la diabetes mellitus tipo 2 en adultos para alcanzar el control glucémico, en combinación con medicamentos hipoglucemiantes y/o insulina basal cuando estos, junto con la dieta y el ejercicio, no proporcionan un control glucémico adecuado (ver secciones 4.4 y 5.1 sobre los datos disponibles para las diferentes combinaciones).
<b>Albiglutide</b>	En combinación con otros medicamentos antihiperoglucemiantes incluyendo insulina basal, cuando éstos, junto con la dieta y el ejercicio, no proporcionan un control glucémico adecuado (ver secciones 4.4 y 5.1 para datos disponibles acerca de las diferentes combinaciones).
<b>Dulaglutide</b>	En combinación con otros medicamentos Hipoglucemiantes incluyendo insulina, cuando éstos, junto con la dieta y el ejercicio, no proporcionan un control glucémico adecuado (ver sección 5.1 para datos disponibles acerca de las diferentes combinaciones)

Properament es comercialitzaran combinacions fixes d' insulina basal + aRGLP1:

-Xultophy (Insulina degludec 100 U/ml + Liraglutide 3,6 mg/ml) 1U/0,036 mg

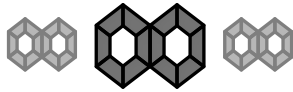
-Suliqua (Insulina glargina 100 U/ml + Lixisenatide 50 ug/ml) i (Insulina glargina 100 U/ml + Lixisenatide 33 ug/ml)

# IDegLira

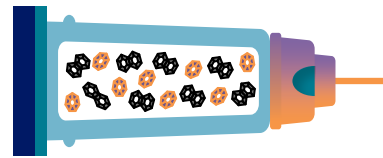
Combination in a single daily injection

## FORMULATION

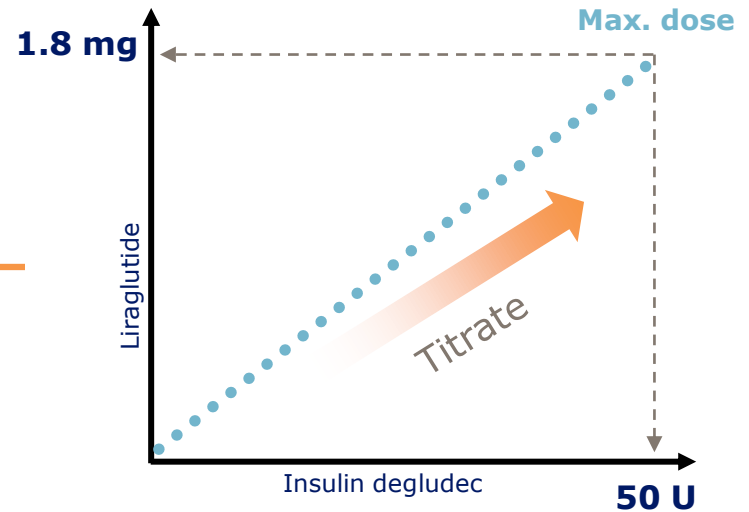
**IDeg dihexamers**  
(100 U/mL)



**Liraglutide heptamers**  
(3.6 mg/mL)



3 mL pre-filled pen



### ONE DOSE STEP

1 dose step

1 U insulin degludec  
+  
0.036 mg liraglutide

### STARTING DOSE

*Uncontrolled on:  
OADs*

10 dose steps

10 U insulin degludec  
+  
0.36 mg liraglutide

### STARTING DOSE

*Uncontrolled on:  
basal insulin or GLP-1 RA*

16 dose steps

16 U insulin degludec  
+  
0.58 mg liraglutide

### MAXIMUM DOSE

50 dose steps

50 U insulin degludec  
+  
1.8 mg liraglutide



# iGlarLixi

- iGlarLixi is administered via a once-daily injection
- iGlarLixi is administered using a modified SoloStar® pen
  - This pen is already widely used with iGlar and patients, PCPs and nurses are familiar with this device
- iGlarLixi is titrated like basal insulin
- iGlarLixi is available in two fixed-ratios for individual patient needs

**Dose range: 10 to 40 U**  
(2 U iGlar:1 µg lixisenatide ratio)



**Dose range: 30 to 60 U**  
(3 U iGlar:1 µg lixisenatide ratio)





Tractament amb insulina i  
afegir un aRGLP1

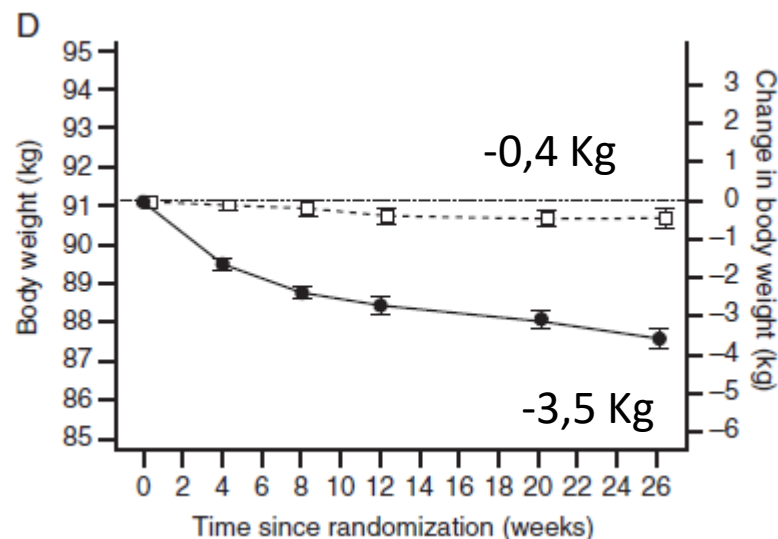
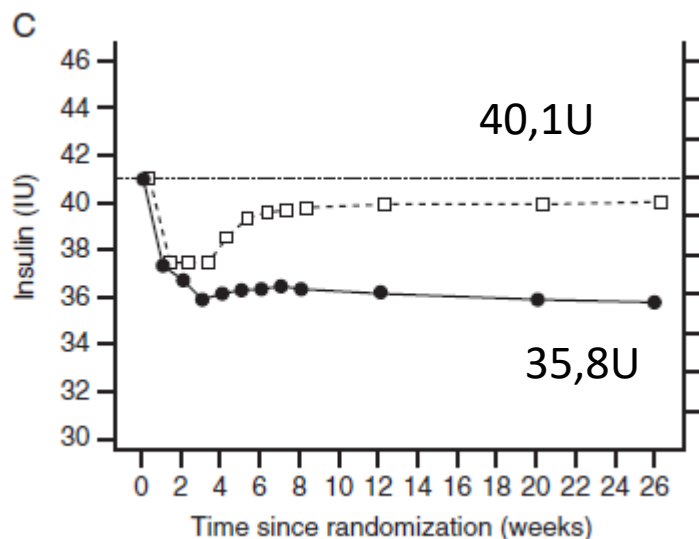
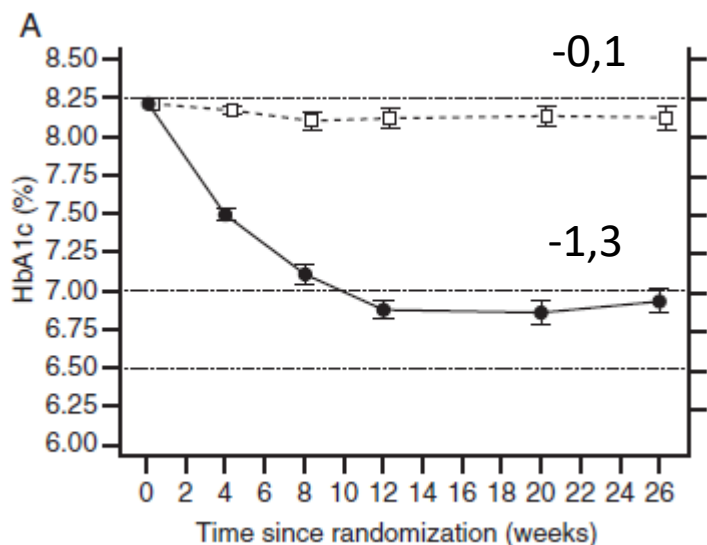
# Efficacy and safety of liraglutide versus placebo added to basal insulin analogues (with or without metformin) in patients with type 2 diabetes: a randomized, placebo-controlled trial

A. Ahmann<sup>1</sup>, H. W. Rodbard<sup>2</sup>, J. Rosenstock<sup>3</sup>, J. T. Lahtela<sup>4</sup>, L. de Loredó<sup>5</sup>, K. Tornøe<sup>6</sup>, A. Boopalan<sup>7</sup>, M. A. Nauck<sup>8</sup> & on behalf of the NN2211-3917 Study Group<sup>†</sup>

*Diabetes, Obesity and Metabolism* 17: 1056–1064, 2015.

## LIRA-ADD2BASAL

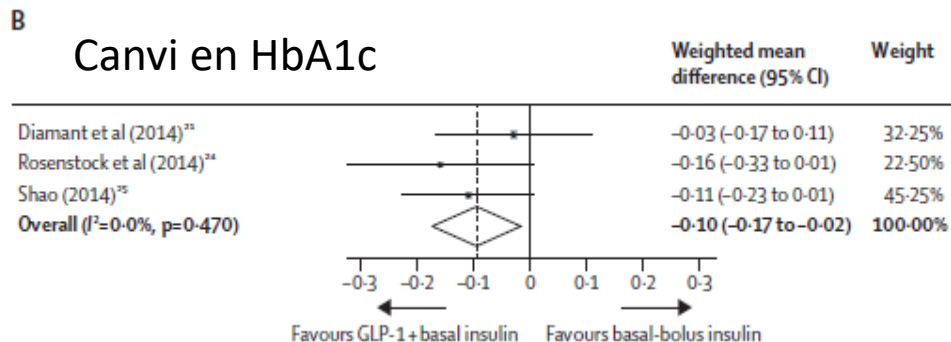
n=451. HbA1c mitja de 8,2 %, IMC 32, tractats amb metformina (93%) +insulina glargina o detemir (67-33 %) Aleatoritzats a lira fins 1,8 vs placebo. Possibilitat de titular insulina sense passar dosi inicial.



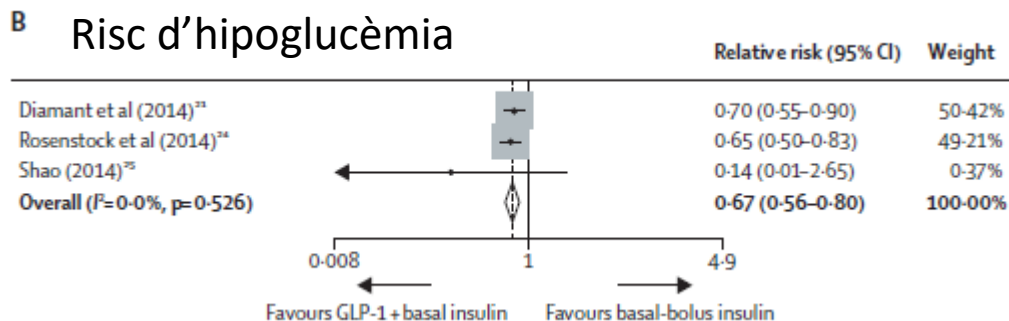
En el grup de liraglutide major incidència de nàusees (22,2 vs 3,1%) i hipoglucèmia que al grup de placebo (18,2 vs 12,4 %)

# Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis

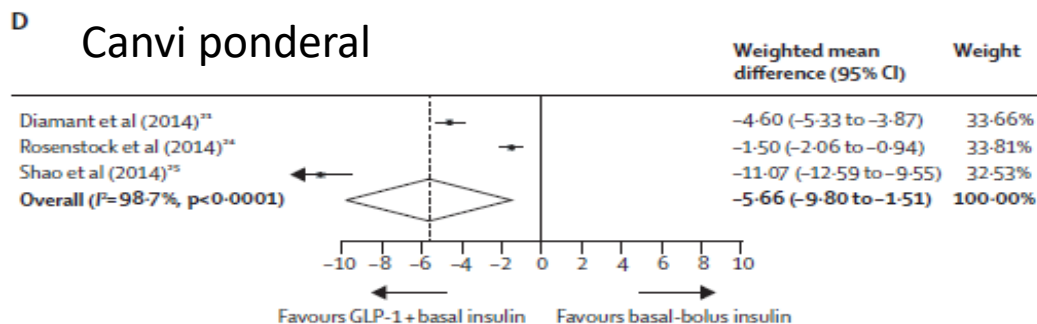
Conrad Eng\*, Caroline K Kramer\*, Bernard Zinman, Ravi Retnakaran



Selecció d'assaigs clínics en els que pacients amb control insuficient amb insulina basal s'aleatoritzen a tractament insulínic basal-bolus versus insulina basal + aRGLP



- Exenatide vs Lispro
- Albiglutide vs Lispro
- Exenatide vs Aspart

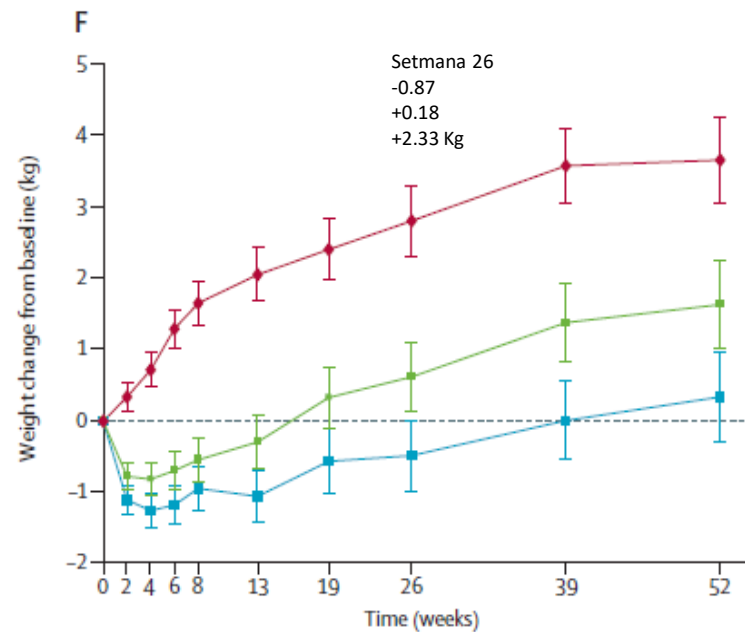
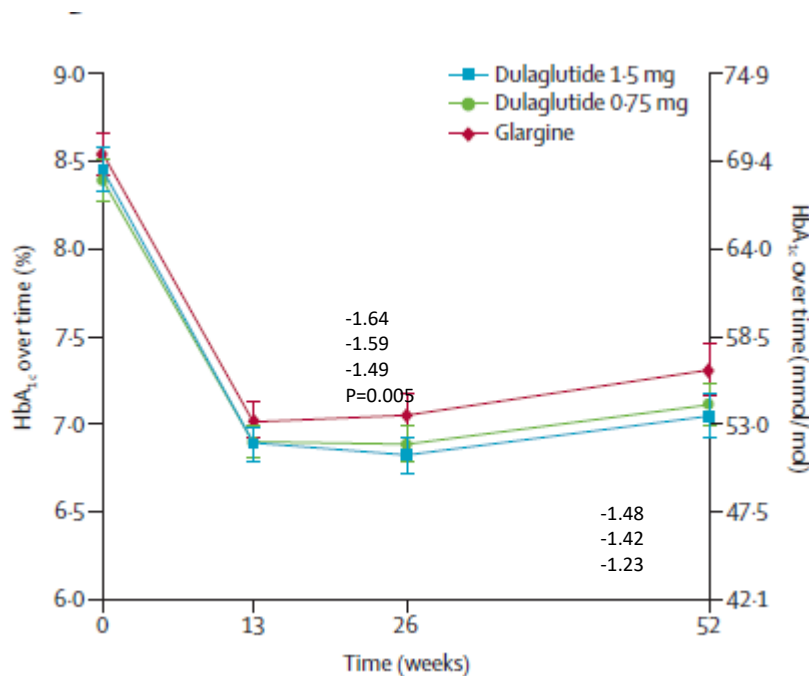


# Once-weekly dulaglutide versus bedtime insulin glargine, both in combination with prandial insulin lispro, in patients with type 2 diabetes (AWARD-4): a randomised, open-label, phase 3, non-inferiority study

Lawrence Blonde, Johan Jendle, Jorge Gross, Vincent Woo, Honghua Jiang, Jessie L Fahrbach, Zvonko Milicevic

www.thelancet.com Vol 385 May 23, 2015

n=884 patients with DM2 mal controlada (A1c 8.5%) amb insulina basal/premesclada amb metformina, aleatoritzats a basal-bolus amb glargina+lispro vs Dulaglutide setmanal + lispro prandial



	Dulaglutide 1.5 mg group (n=295)	p value	Dulaglutide 0.75 mg group (n=293)	p value	Glargine group (n=296)
Hypoglycaemia†	10 (3%)	0.31	8 (3%)	0.14	15 (5.1%)
Nausea	76 (26%)	<0.0001	52 (18%)	<0.0001	10 (3%)

# Liraglutide in people treated for type 2 diabetes with multiple daily insulin injections: randomised clinical trial (MDI Liraglutide trial)

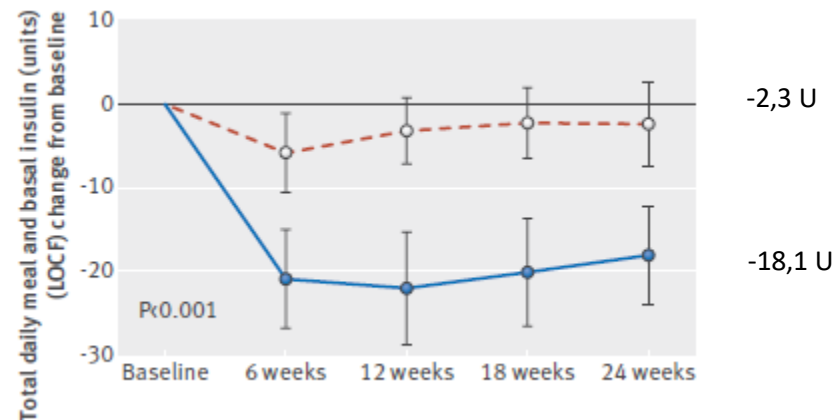
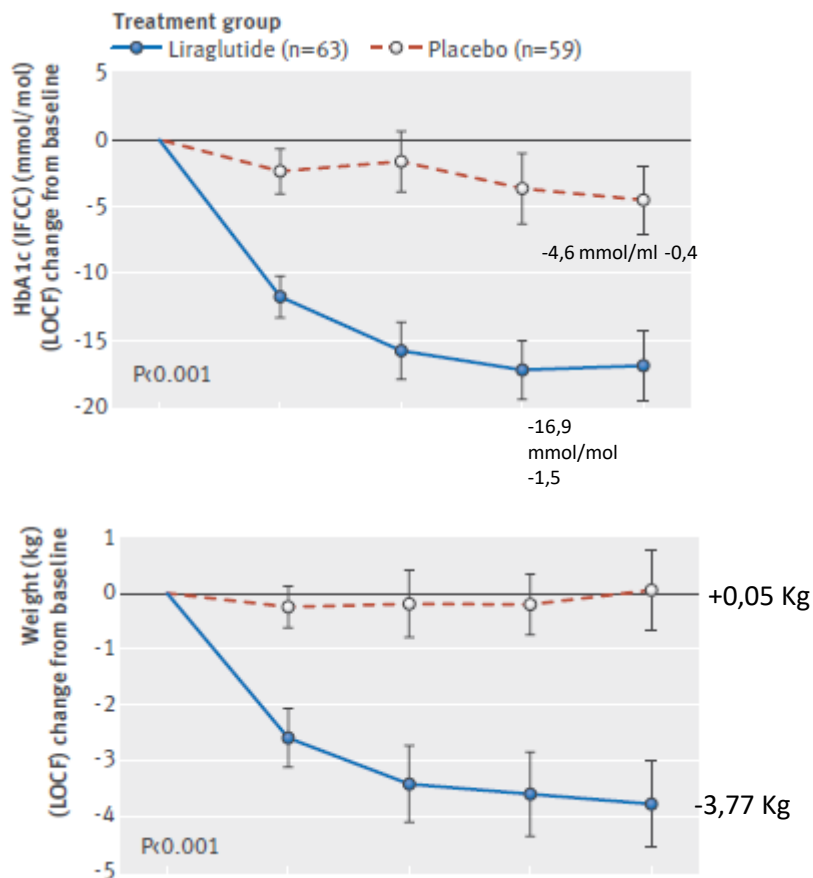
Cite this as: *BMJ* 2015;351:h5364

doi: 10.1136/bmj.h5364

Accepted: 20 September 2015

Marcus Lind,<sup>1,2</sup> Irl B Hirsch,<sup>3</sup> Jaakko Tuomilehto,<sup>4</sup> Sofia Dahlqvist,<sup>2</sup> Bo Ahrén,<sup>5</sup> Ole Torffvit,<sup>5</sup> Stig Attvall,<sup>1</sup> Magnus Ekelund,<sup>5</sup> Karin Filipsson,<sup>5</sup> Bengt-Olov Tengmark,<sup>6</sup> Stefan Sjöberg,<sup>7</sup> Nils-Gunnar Pehrsson<sup>8</sup>

n= 124, IM 33, A1c 9,0 utilitzat metformina (aprox 70 %) + múltiples dosis d'insulina- Titulació protocolitzada d'insulina sense limitació a l'alça



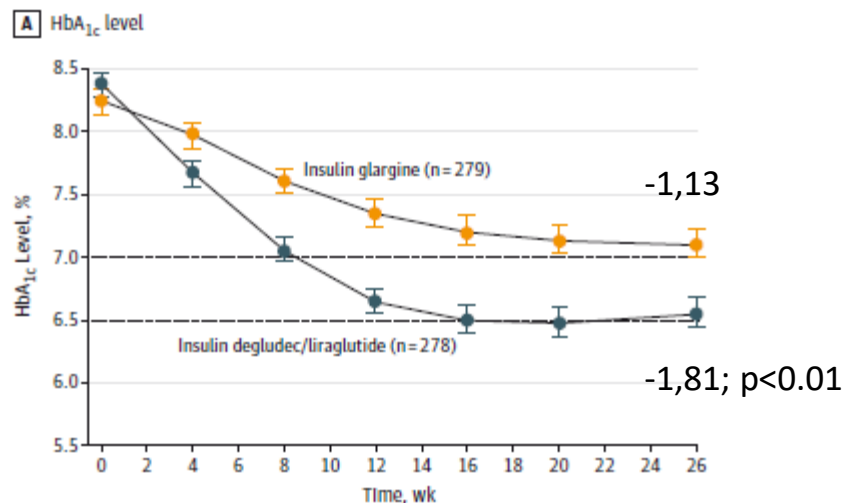
-No diferències en hipos  
-Nàusea més freqüent en el grup de liraglutide (32%)

# Effect of Insulin Glargine Up-titration vs Insulin Degludec/Liraglutide on Glycated Hemoglobin Levels in Patients With Uncontrolled Type 2 Diabetes

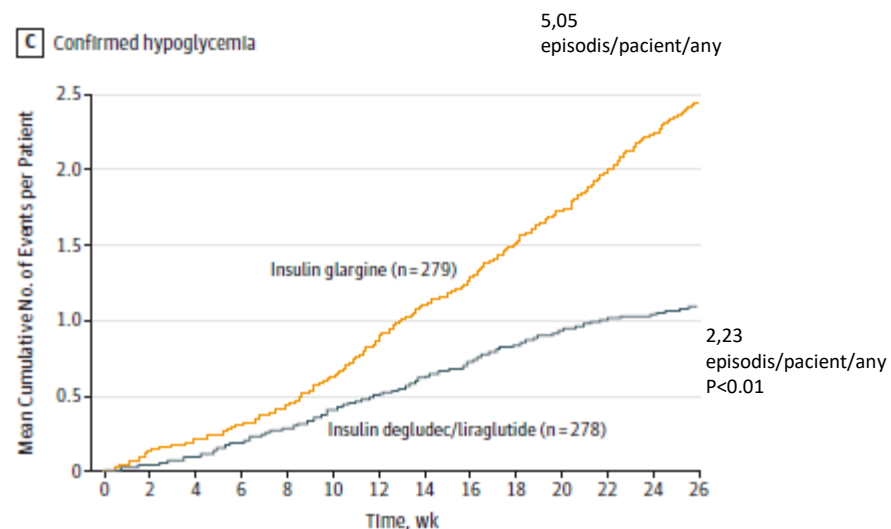
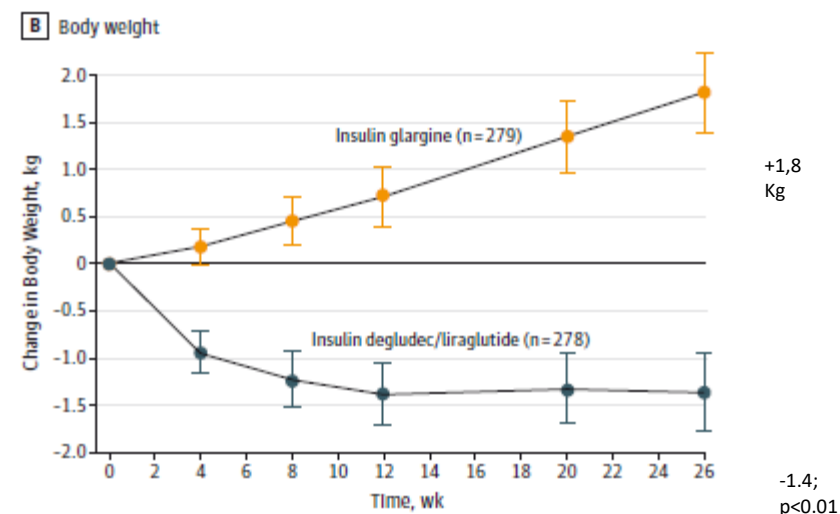
## The DUAL V Randomized Clinical Trial

Ildiko Lingvay, MD, MPH, MSCS; Federico Pérez Manghi, MD; Pedro García-Hernández, MD; Paul Norwood, MD; Lucine Lehmann, MD; Mads Jeppe Tarp-Johansen, PhD; John B. Buse, MD, PhD; for the DUAL V Investigators

JAMA. 2016;315(9):898-907.

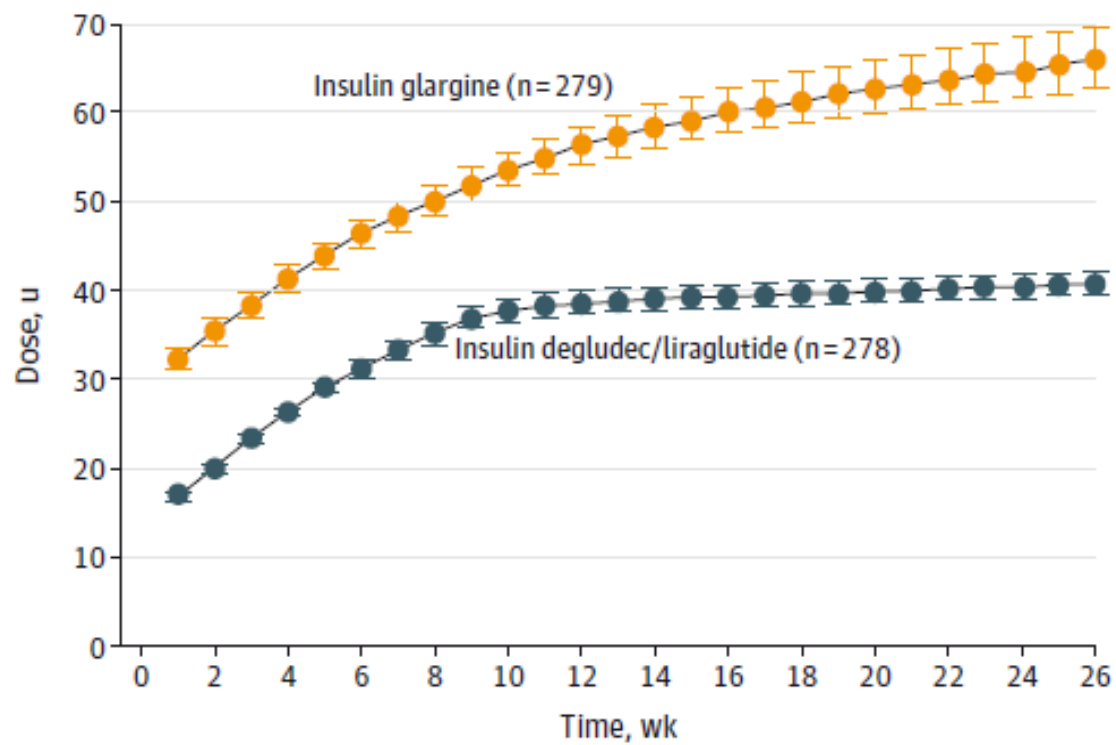


n=557. Tractats amb metformina+glargina (dosi mitjana 30 U) i A1c mitja de 8,3. Aleatoritzats a Xultophy ( reducció inicial d'insulina a 16 U=0,6 mg i titulació fins objectiu amb màxim de 50 U) vs titulació de glargina fins objectiu (glucèmia basal 72-90 mg/dl).



Major incidència de nàusea al grup de Xultophy (9.8%) que al de glargina (1.1%).

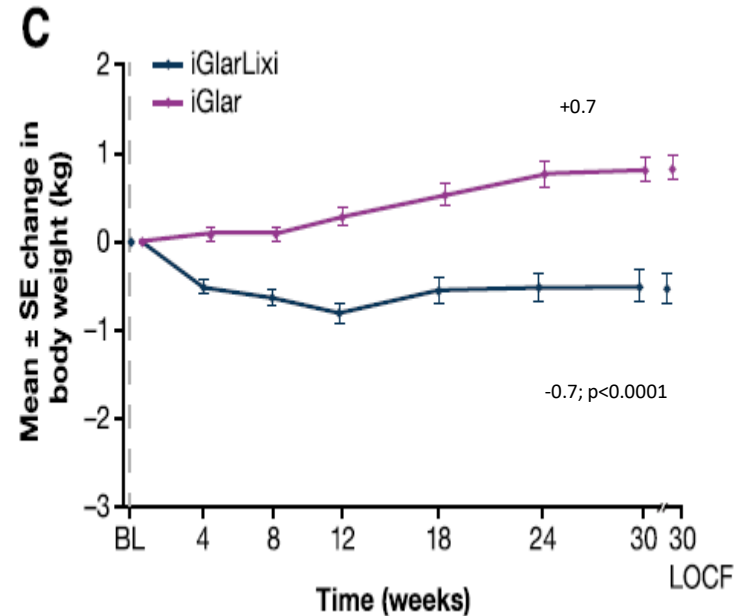
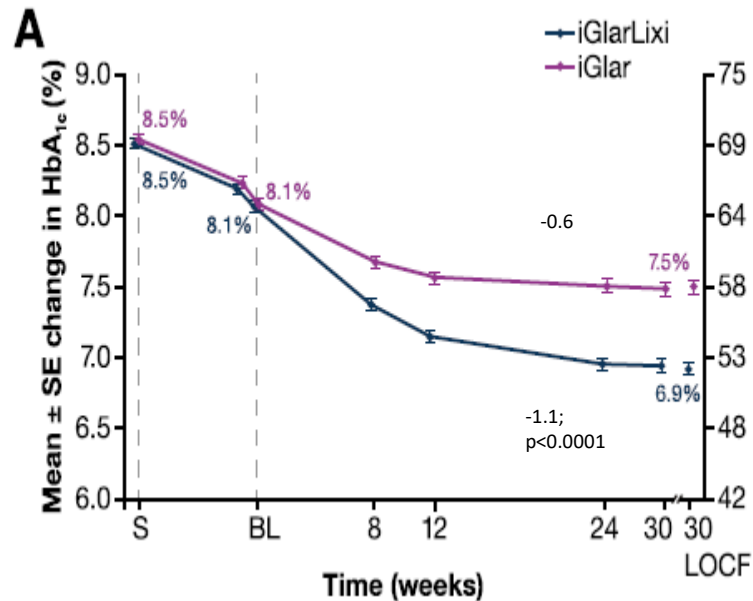
**D** Mean daily insulin dose



# Efficacy and Safety of LixiLan, a Titratable Fixed-Ratio Combination of Insulin Glargine Plus Lixisenatide in Type 2 Diabetes Inadequately Controlled on Basal Insulin and Metformin: The LixiLan-L Randomized Trial

Diabetes Care 2016;39:1972–1980

n= 736, IMC 31, Tractats amb insulina basal i ADOs i amb HbA1c mitjana de 8.5 (després del run-in period 8,1). Aleatoritzats a Suliqua reduint inicialment insulina fins dosi equivalent a 10 mcg de lixi (20 o 30 U de glargina) versus titulació de glargina amb objectiu de basal <100 mg/dl (màxim 60 U/dia)



Documented hypoglycemia	iGlarLixi	iGlar
Symptomatic*		
Patients with events, n (%)	146 (40.0)	155 (42.5)
Events per patient-year†, n	3.03	4.22
Severe‡		
Patients with events, n (%)	4 (1.1)	1 (0.3)
Events per patient-year†, n	0.02	<0.01
Event rate ratio (95% CI) vs. iGlar	0.77 (0.55–1.07)	–

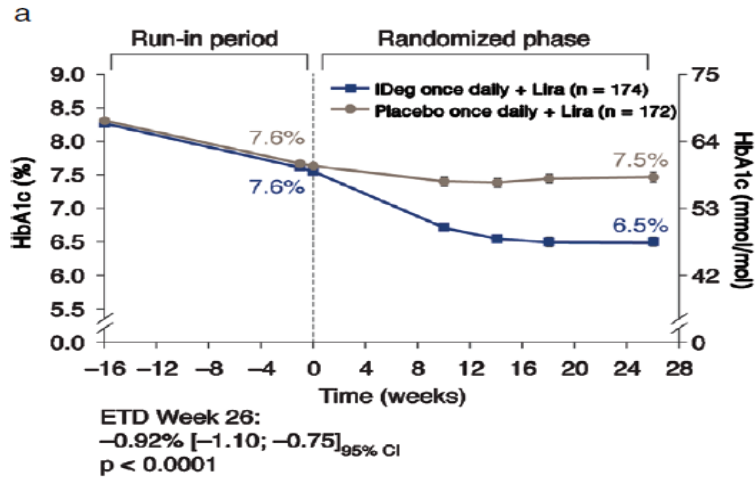
	iGlarLixi	iGlar
Gastrointestinal disorders (overall)	62 (17.0)	29 (7.9)
Nausea	38 (10.4)	2 (0.5)
Discontinuation due to nausea	4 (1.1)	0
Vomiting	13 (3.6)	2 (0.5)
Discontinuation due to vomiting	0	0



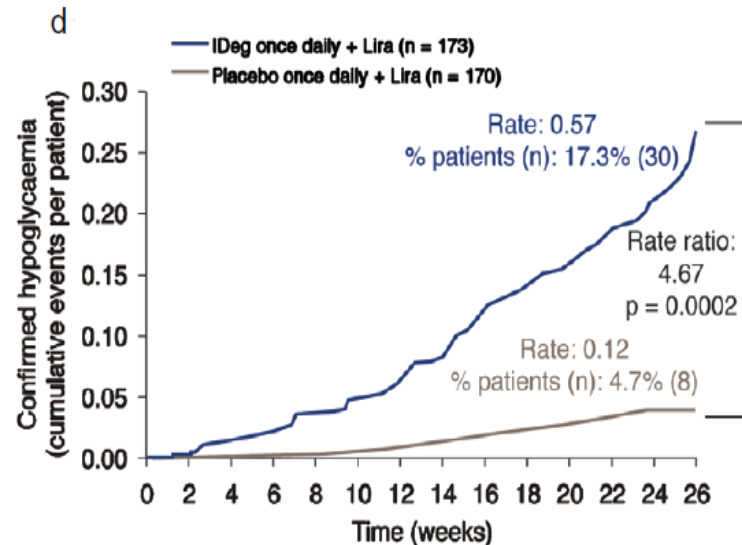
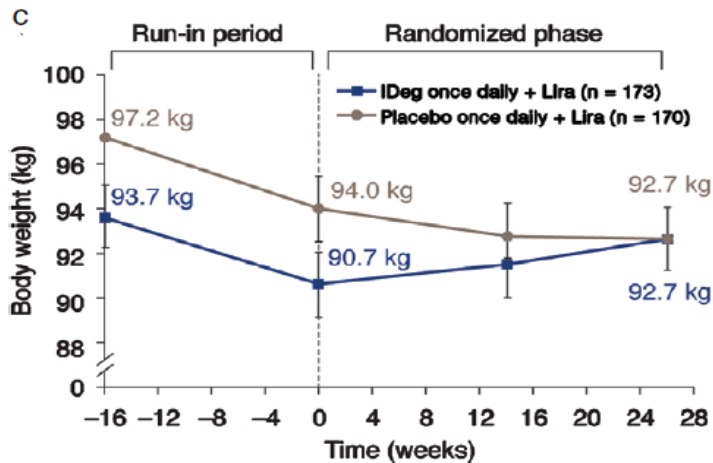
Tractament amb aRGLP1 i afegir insulina

# Effect of adding insulin degludec to treatment in patients with type 2 diabetes inadequately controlled with metformin and liraglutide: a double-blind randomized controlled trial (BEGIN: ADD TO GLP-1 Study)

*Diabetes, Obesity and Metabolism* 18: 663–670, 2016.

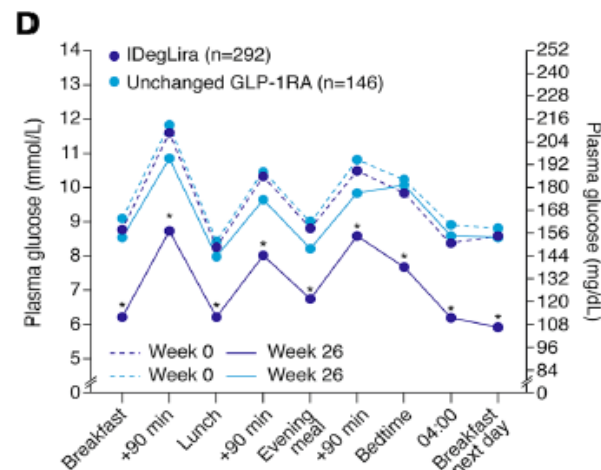
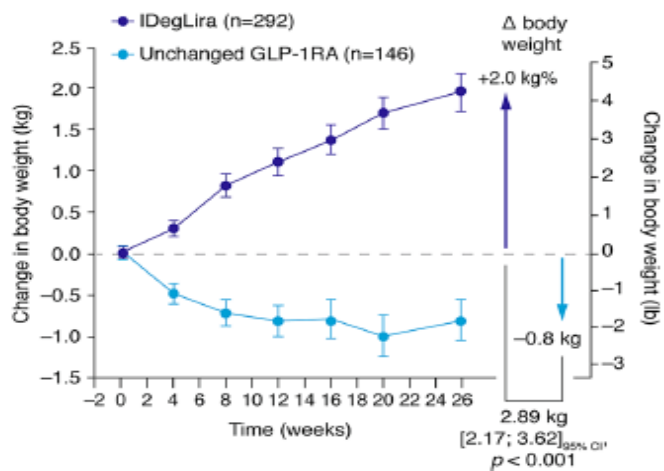
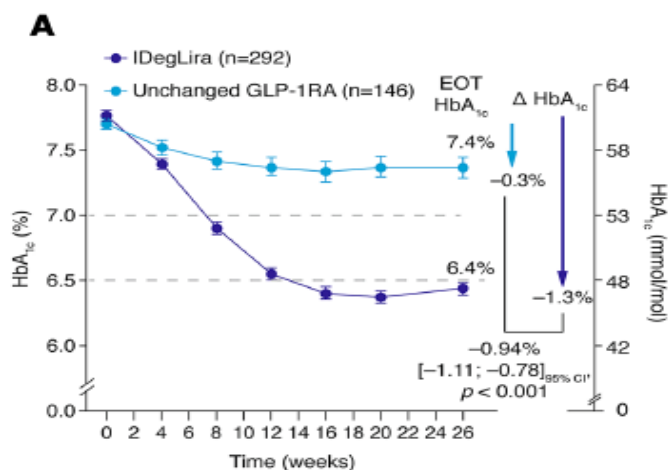


n=386 amb control insuficient (A1c 7,6) amb metformina + lira 1,8 mg, aleatoritzats a degludec o placebo treat-to target



# The Efficacy of IDegLira (Insulin Degludec/Liraglutide Combination) in Adults with Type 2 Diabetes Inadequately Controlled with a GLP-1 Receptor Agonist and Oral Therapy: DUAL III Randomized Clinical Trial

n=438 amb control insuficient amb liraglutide o exenatide a dosi màxima + agents orals (met, pio, SU) aleatoritzats a Xultophy (reduint dosi de lira inicialment a 0,6 mg/dia-16 U de degludec) i treat-to target vs continuar igual



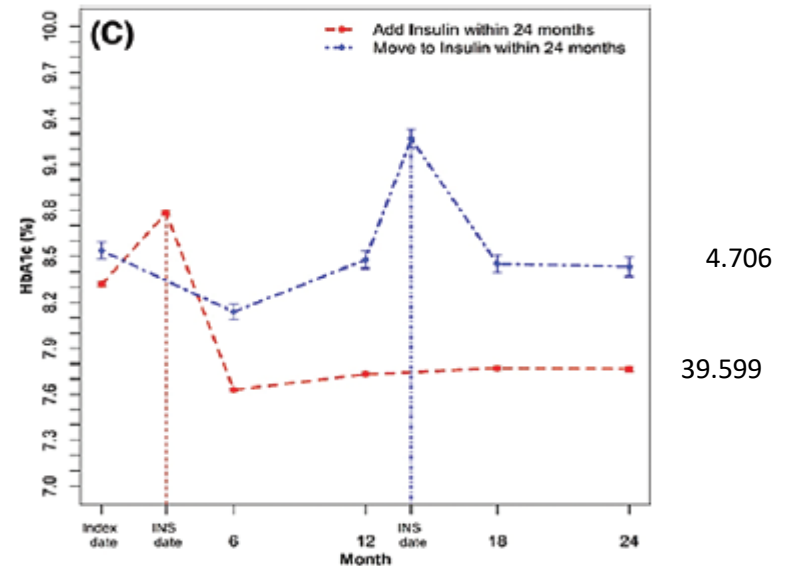
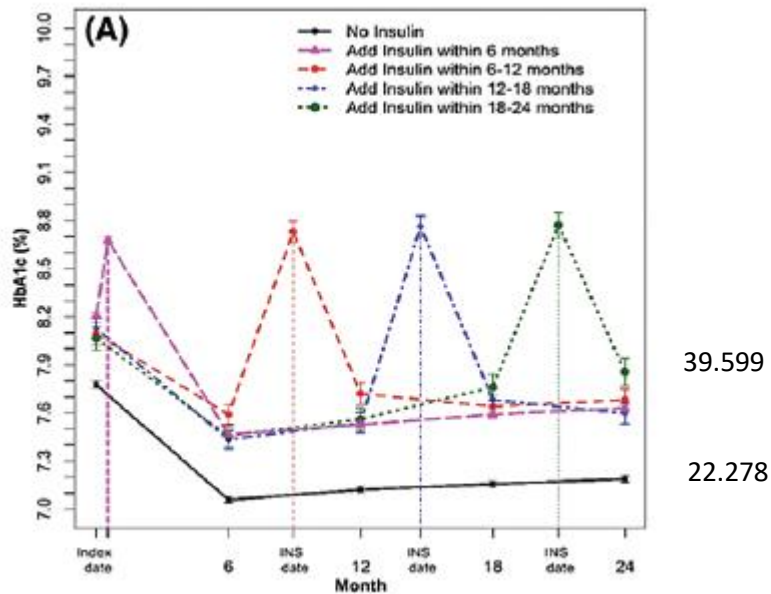
## Hipoglucèmies

	Degl+Lira	Control
Amb SU	6,34 epa	0,51 epa
Sense SU	1,75 epa	0 epa

# Addition of or switch to insulin therapy in people treated with glucagon-like peptide-1 receptor agonists: A real-world study in 66 583 patients

*Diabetes Obes Metab* 2017; 19(1):108-117

Estudi de cohorts de pràctica clínica habitual amb el registre americà CEMR que inclou dades de més de 35.000 metges (75% d'atenció primària)

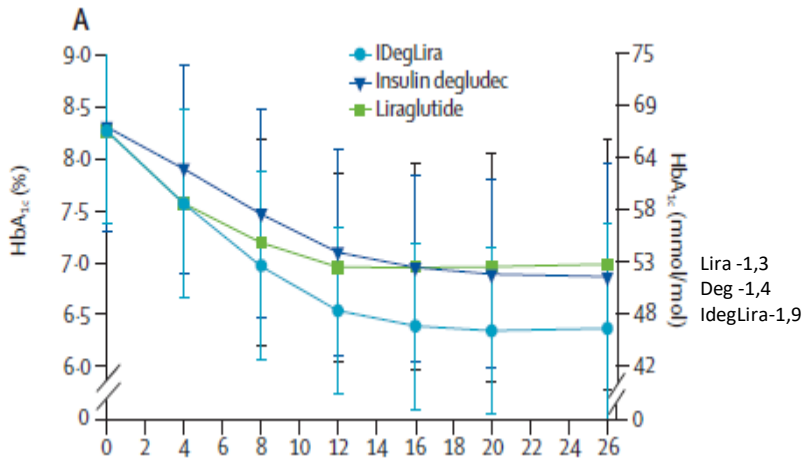


Tractament combinat inicial

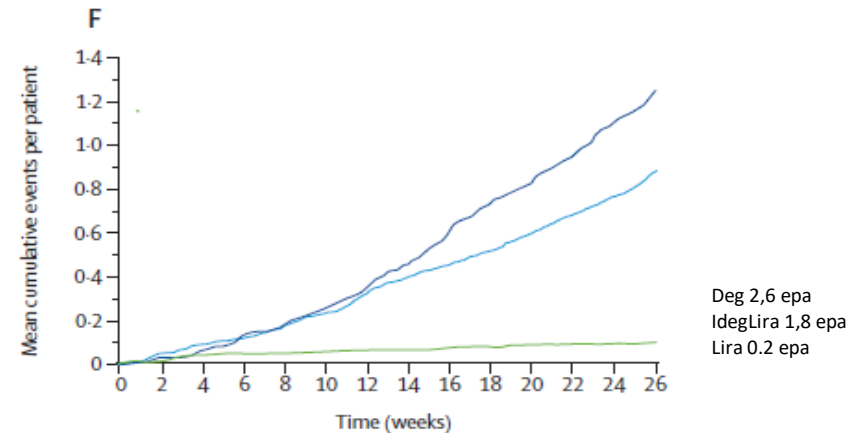
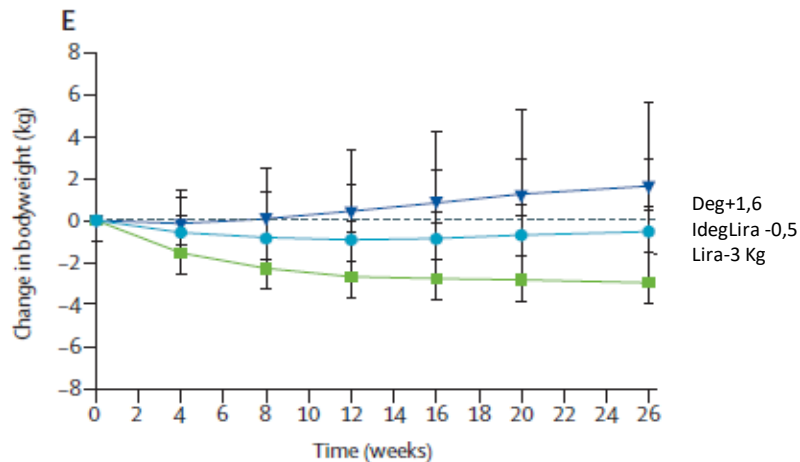
# Efficacy and safety of a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with its components given alone: results of a phase 3, open-label, randomised, 26-week, treat-to-target trial in insulin-naïve patients with type 2 diabetes

www.thelancet.com/diabetes-endocrinology Vol 2 November 2014

DUAL I



n=1663, Fase III, obert. DM2 amb HbA1c mitja de 8,3% amb metformina (+/- pio) i IMC de 31,5 Kg/m<sup>2</sup> aleatoritzats a IDegLira vs Degludec vs Liraglutide treat to target per glucemia basal (4-5 mmol/l).

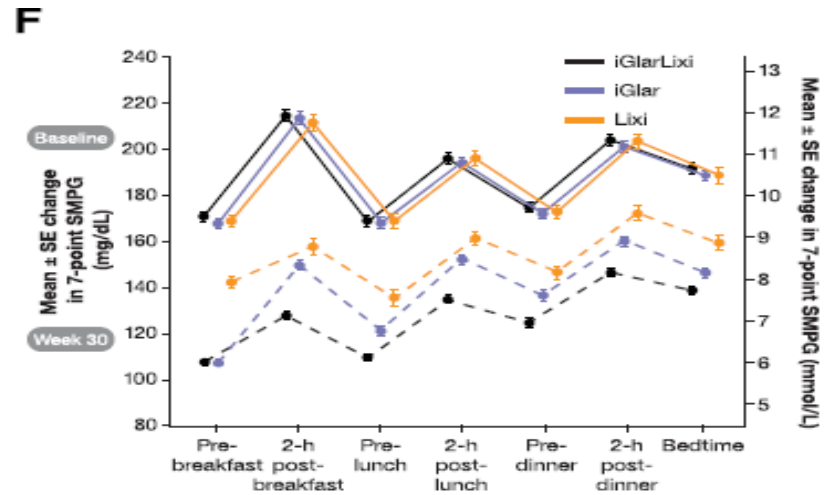
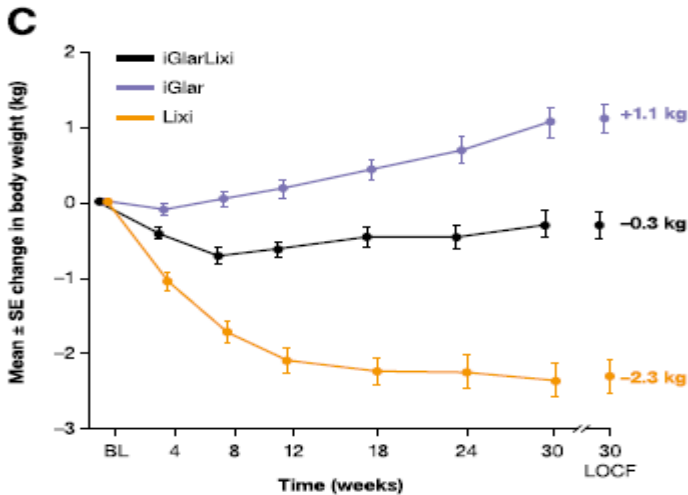
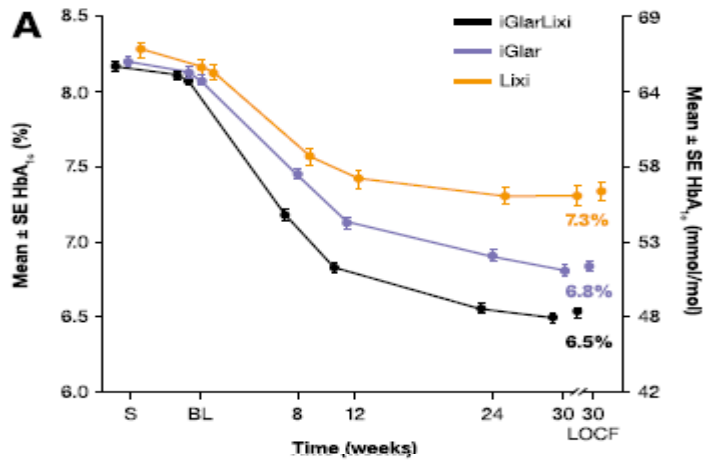


	IDegLira (n=825)		Insulin degludec (n=412)		Liraglutide (n=412)	
	n (%)	Rate	n (%)	Rate	n (%)	Rate
Nausea	73 (9%)	20.9	15 (4%)	8.8	81 (20%)	54.3
Diarrhoea	66 (8%)	23.5	19 (5%)	10.3	52 (13%)	39.8
Vomiting	32 (4%)	10.1	6 (1%)	3.1	35 (8%)	23.6

# Benefits of LixiLan, a Titratable Fixed-Ratio Combination of Insulin Glargine Plus Lixisenatide, Versus Insulin Glargine and Lixisenatide Monocomponents in Type 2 Diabetes Inadequately Controlled on Oral Agents: The LixiLan-O Randomized Trial

Diabetes Care 2016;39:2026–2035 | DOI: 10.2337/dc16-0917

n=1170 patients amb IMC mig de 31.7 Kg/m<sup>2</sup> i HbA<sub>1c</sub> de 8.1 % en tractament amb metformina, aleatoritzats a iGlarLixi o GlarLixi o GlarLixi + Lixi. El resultat principal és la reducció de l'HbA<sub>1c</sub> respecte a les monocomponents iGlar i Lixi.



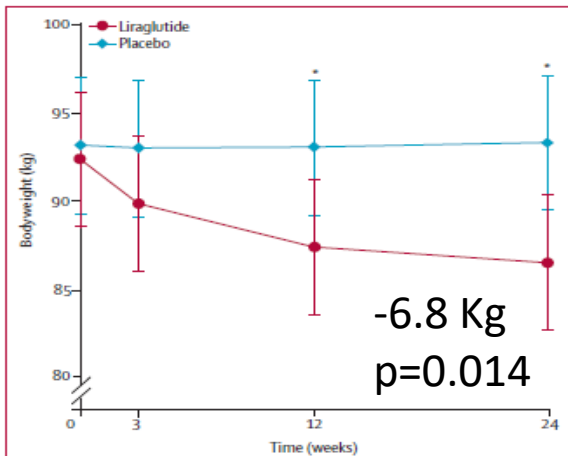
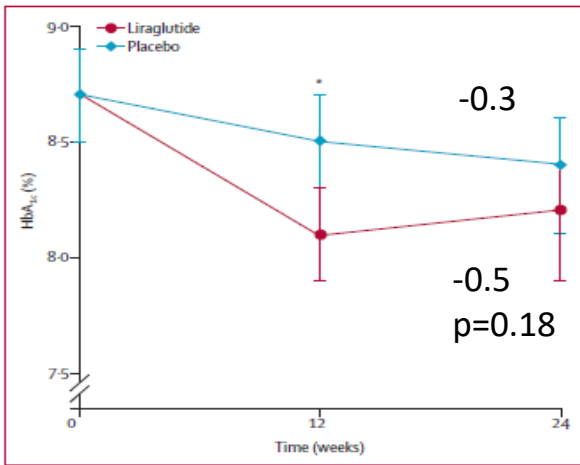
	iGlarLixi (n = 469)	iGlar (n = 467)	Lixi (n = 233)
<b>AE by organ class</b>			
Gastrointestinal disorders (overall)	102 (21.7)	59 (12.6)	86 (36.9)
Nausea	45 (9.6)	17 (3.6)	56 (24.0)
Discontinuation due to nausea	2 (0.4)	0	6 (2.6)
Vomiting	15 (3.2)	7 (1.5)	15 (6.4)
Discontinuation due to vomiting	2 (0.4)	0	4 (1.7)
Diarrhea	42 (9.0)	20 (4.3)	21 (9.0)
Discontinuation due to diarrhea	1 (0.2)	0	2 (0.9)
<b>Hypoglycemia</b>			
Documented symptomatic hypoglycemia (plasma glucose $\leq$ 70 mg/dL [3.9 mmol/L])			
Patients with events	120 (25.6)	110 (23.6)	15 (6.4)
Number of events per patient-year†	1.4	1.2	0.3
Documented symptomatic hypoglycemia (plasma glucose <60 mg/dL [3.3 mmol/L])			
Patients with events	66 (14.1)	50 (10.7)	6 (2.6)
Number of events per patient-year†	0.5	0.3	0.1
Severe symptomatic hypoglycemia			
Patients with events	0	1 (0.2)	0
Number of events per patient-year†	0	<0.01	0

Tractament amb aRGLP1 en un escenari on la  
insulina és mandatòria: DM tipus 1



# Efficacy and safety of liraglutide for overweight adult patients with type 1 diabetes and insufficient glycaemic control (Lira-1): a randomised, double-blind, placebo-controlled trial

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	Week 24		
	Liraglutide	Placebo	Liraglutide vs placebo
Bolus insulin (IU/day)	27.1 (23.6 to 30.6)	32.8 (29.3 to 36.3)	-5.8 (-10.7 to -0.8) [0.0227]
Basal insulin (IU/day)	35.9 (31.1 to 40.7)	41.2 (36.4 to 46.0)	-5.3 (-12.0 to 1.5) [0.1257]
MAGE	8.4 (7.9 to 8.9)	9.1 (8.3 to 10.0)	-0.7 (-1.7 to 0.3) [0.1549]
CONGA <sub>10min</sub>	9.9 (9.2 to 10.6)	9.7 (9.1 to 10.3)	0.2 (-0.7 to 1.1) [0.7171]
SD of mean glucose	4.3 (4.0 to 4.6)	4.3 (4.0 to 4.6)	-0.03 (-0.5 to 0.4) [0.8650]

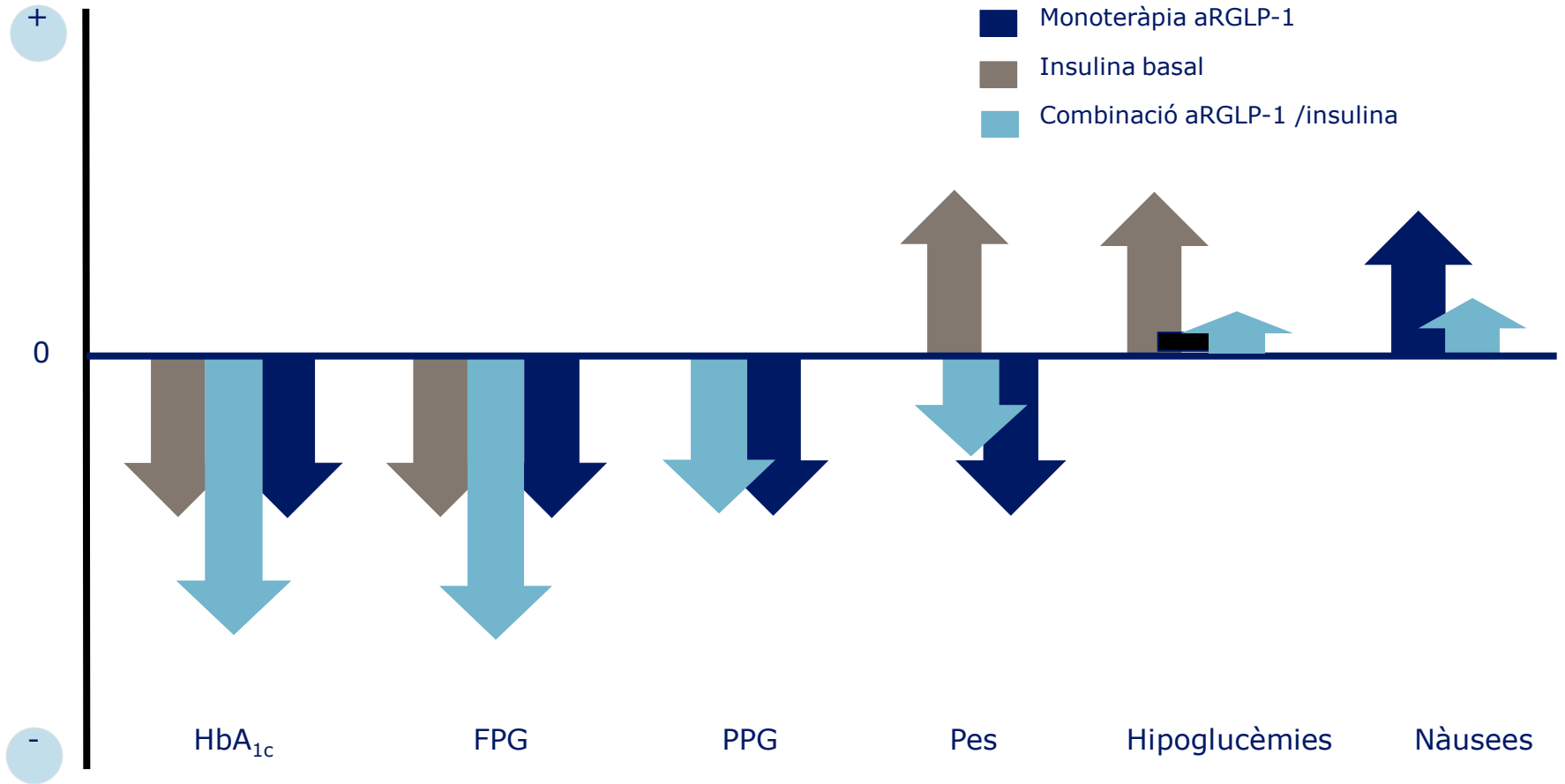
Continuous glucose monitoring			
Hypoglycaemia (h/day)	1.3 (1.0 to 1.8)	1.8 (0.8 to 2.8)	-0.5 (-1.5 to 0.6) [0.3970]
Near normoglycaemia (h/day)	10.3 (9.0 to 11.5)	10.8 (9.4 to 12.1)	-0.5 (-2.3 to 1.3) [0.5838]
Hyperglycaemia (h/day)	12.4 (10.9 to 13.9)	11.4 (9.8 to 13.0)	1.0 (-1.2 to 3.2) [0.3583]

n=100 DM1 amb IMC >25 Kg/m<sup>2</sup> amb HbA<sub>1c</sub> mitja de 8,7 %, aleatoritzats a placebo o liraglutide ascendent fins 1.8 mg/dia.

En glucèmies capil.lars discreta reducció d'hipoglucèmies confirmades en el grup de liraglutide. Incident Rate Ratio de 0,82 (95% IC 0.74-0.95)

# Conclusions

# Efectes esperables de la combinació d'un aRGLP1 i insulina basal en pacients amb DM2



Gràcies per la vostra atenció

