Análogos de insulina en la práctica clínica

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PODEMOS PRESERVAR LA CÉLULA BETA CON INSULINA TEMPRANAMENTE?

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CSII VS MDI VS ORALES EN CHINA

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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

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Weng J. Lancet. 2008;371:1753

Características

	CSII	MDI	Oral hypoglycaemic agents
Number	133	118	101
Men (n)	88	81	58
Age (years)	50 (11)	51 (10)	52 (9)
Body-mass index (kg/m²)	25·1 (3·0)	24·4 (2·7)	25·1 (3·3)
Fasting plasma glucose (mmol/L)			
Before therapy	11·3 (3·3)	11·5 (3·2)	10·8 (2·9)
After therapy*	6·6 (1·5)	6·8 (1·6)	6·5 (1·6)
2-h postprandial plasma glucose (mmol/L)			
Before therapy	16·1 (5·5)	17·5 (5·5)	16·6 (5·0)
After therapy*	7·5 (2·2) (n=113)	8·1 (2·9) (n=111)	8·2 (2·7) (n=90)
HbA_{1c} (%)			
Before therapy	9·8 (2·3)	9·7 (2·3)	9·5 (2·5)
After therapy*	8·0 (1·5)	8·0 (1·6)	7·9 (1·7)

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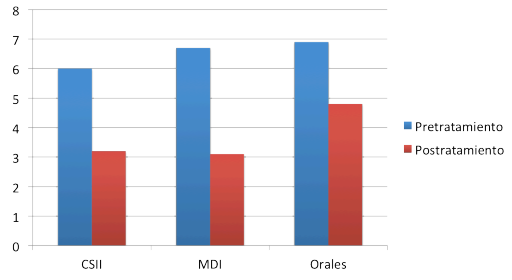
Weng J. Lancet. 2008;371:1753

HOMA-IR



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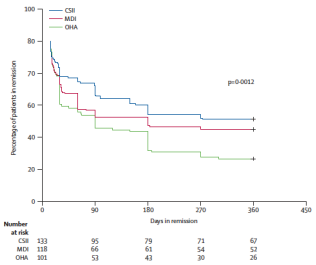
Weng J. Lancet. 2008;371:1753

Pacientes en remisión



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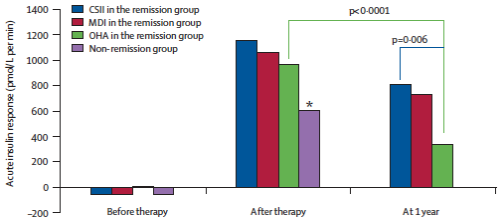
Weng J. Lancet. 2008;371:1753

Secreción aguda de insulina



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Weng J. Lancet. 2008;371:1753

Reflexiones…

- Qué impacto tendrá esto a largo plazo?
- En DM-1, se ha demostrado que pequeñas cantidades de péptido C que secreten predicen mejor control y menor riesgo de hipoglicemias
- Por lo tanto, si un paciente debuta hiperglicémico… valdrá la pena iniciar orales o será mejor insulina por un tiempo?

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HAY DIFERENCIAS ENTRE ANÁLOGOS BASALES?

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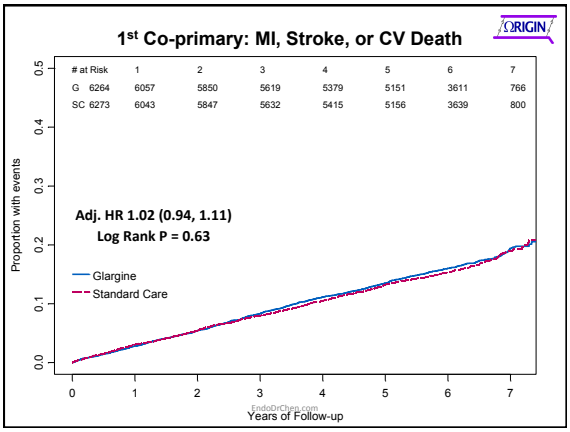

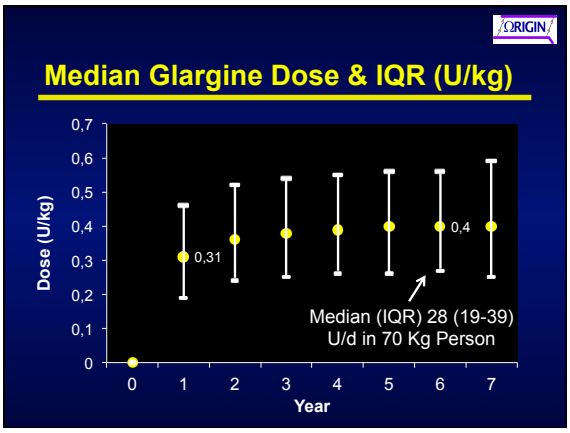

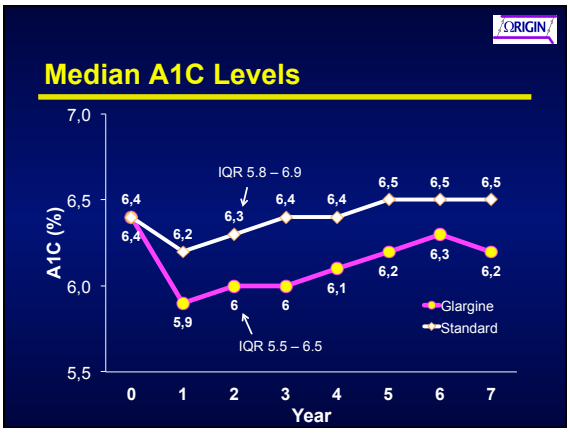

Hypoglycemia & Weight (6 -7 years)

	Glargine (N=6264)		Standard (N=6273)		P
	%	/100py	%	/100py	
Any Non-severe					
1 or more episodes	57	17	25	5	<0.001
Severe					
1 or more episodes	6	1.0	2	0.3	<0.001

	Glargine	Standard	P
Weight Change Since Randomized	1.6 kg (3.5 lbs)	-0.5 kg (1 lb)	<0.001

DURACIÓN DE ACCIÓN: NUEVOS DATOS Y RELEVANCIA CLÍNICA

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	Single-dose (Duration of action)		Steady-state (Duration of action)	
	Insulin detemir	Insulin glargine	Insulin detemir	Insulin glargine
N	18	18	18	18
h, mean (s.d.)	25.9 (4.6)	19.8 (14.4)	23.3 (4.9)	27.1 (7.7)
Range, h	15.0–30.0	0.0–30.0	10.5–29.0	4.0–30.0

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Koehler G. Diab Obes Metab. 2013;

Tiene sentido esta controversia?

- NPH duración de acción mucho más corta… a pesar de lo cual cuando comparamos NPH y glargina, la efectividad es la misma (no así la seguridad)
- Esto en DM-2 porque no están totalmente insulinopénicos
- Por lo tanto, para DM-2 parece que no tiene tanta relevancia

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DIFERENCIAS CLÍNICAS ENTRE INSULINAS BASALES

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Variabilidad glicémica: DM-1

Estudio	NPH	Detemir	P
Bartley	0	2	<0.001
Home	0	2	<0.001
Rusell-Jones	0	2	<0.001
Pieber	0	2	<0.001
Vague	0	2	0.001
De Leeuw	-	-	-
Standl	-	-	-
Kolendorf	0	2	<0.001
Hermansen	0	2	<0.001

EndoDrChen.com Frier BM. Diab Obes Metab. 2013: online april 3.

Variabilidad glicémica: DM-2

Estudio	NPH	Detemir	P
Raslova	0	2	<0.001
Hermansen	0	2	0.008
Haak	0	2	0.021
Fajardo Montaña 2008	0	2	<0.001
Philis-Tsimikas	1	1	NS

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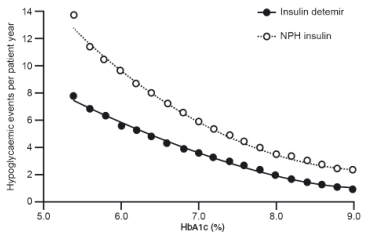
NPH vs detemir en DM-2: hipoglicemias



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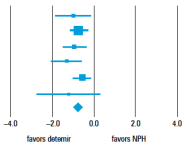
Diferencias en peso

Study	Sample size: detemir	Sample size: NPH	difference in means	Statistics for each study: lower limit	Statistics for each study: upper limit	P
Bartley et al.[24]	320	159	−0.990	−1.847	−0.133	0.024
Home et al.[30]	267	125	−0.730	−1.039	−0.421	0.000
NN304-1476[22]	195	98	−0.920	−1.497	−0.343	0.002
Pieber et al.[26]	139	129	−1.300	−2.066	−0.534	0.001
Russel-Jones et al.[28]	491	256	−0.540	−0.978	−0.102	0.116
Vague et al.[29]	282	138	−1.200	−2.763	0.363	0.132
total	1694	905	−0.779	−0.992	−0.567	0.000



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Szypowska A. Por Arch Med Wewn. 2011;121:737

Cochrane: variabilidad en perfil glicémico

Review: Insulin detemir versus insulin glargine for type 2 diabetes mellitus
Comparison: 1 Detemir versus Glargine
Outcome: 17 Variability of plasma glucose profiles at study endpoint

Study or subgroup	Detemir N	Detemir Mean(SD)	Glargine N	Glargine Mean(SD)	Weight	Mean Difference IV,Random,95% CI
Hollander 2008	214	0.27 (0.2)	105	0.28 (0.21)	36.5 %	-0.01 [-0.06, 0.04]
Raskin 2009	254	0.32 (0.25)	131	0.33 (0.26)	33.5 %	-0.01 [-0.06, 0.04]
Rosenstock 2008	291	0.48 (0.41)	291	0.41 (0.34)	30.0 %	0.07 [0.01, 0.13]
Total (95% CI)	**759**		**527**		**100.0 %**	**0.01 [-0.03, 0.06]**

Heterogeneity: Tau² = 0.00; Chi² = 4.88, df = 2 (P = 0.09); I² =59%
Test for overall effect: Z = 0.56 (P = 0.57)
Test for subgroup differences: Not applicable

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Swinnen et al. *Cochrane Database Syst Rev* 2011: CD006383

Cochrane: tasa de hipoglicemias

Review: Insulin detemir versus insulin glargine for type 2 diabetes mellitus
Comparison: 1 Detemir versus Glargine
Outcome: 8 Event rate for overall hypoglycaemia per patient-year

Study or subgroup	log [Rate Ratio] (SE)	Weight	Rate Ratio IV,Random,95% CI
Hollander 2008	-0.13 (0.04)	26.0 %	0.88 [0.81, 0.95]
Raskin 2009	0.03 (0.05)	24.0 %	1.03 [0.93, 1.14]
Rosenstock 2008	-0.02 (0.04)	26.0 %	0.98 [0.91, 1.06]
Swinnen 2010a	0.13 (0.05)	24.0 %	1.14 [1.03, 1.26]
Total (95% CI)		**100.0 %**	**1.00 [0.90, 1.11]**

Heterogeneity: Tau² = 0.01; Chi² = 17.50, df = 3 (P = 0.00056); I² =83%
Test for overall effect: Z = 0.01 (P = 0.99)
Test for subgroup differences: Not applicable

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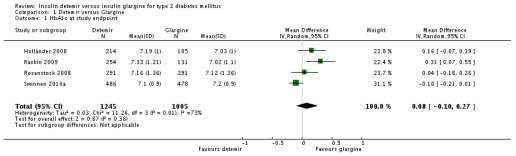
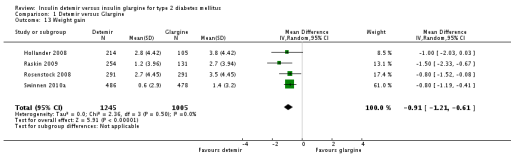
Swinnen et al. *Cochrane Database Syst Rev* 2011: CD006383

Cochrane: cambios en Hba1c



Swinnen et al. *Cochrane Database Syst Rev* 2011: CD006383

Cochrane: aumento de peso



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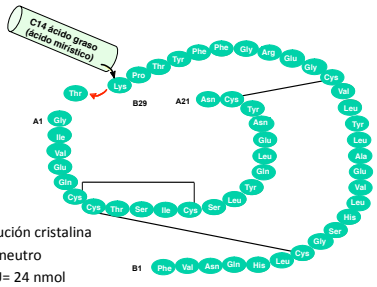
Insulina detemir

LysB29(N-tetradecanoyl)des(B30)



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

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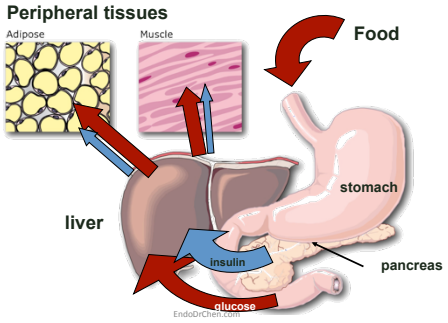
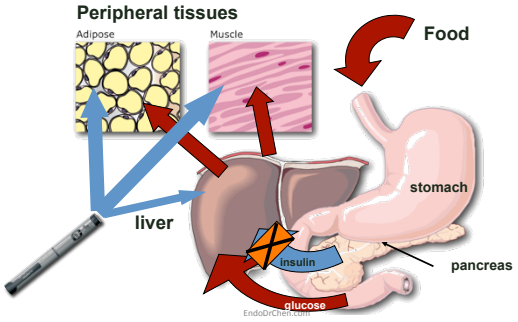
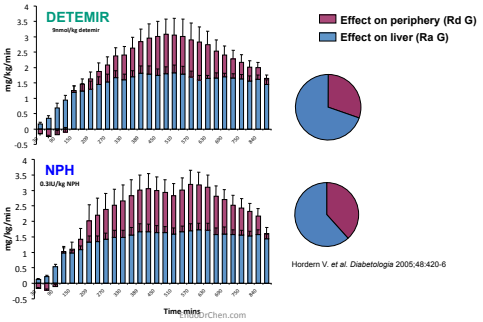
The 'Liver hypothesis': Systemic insulin in normal physiology



The 'Liver hypothesis': Distribution of exogenous insulin

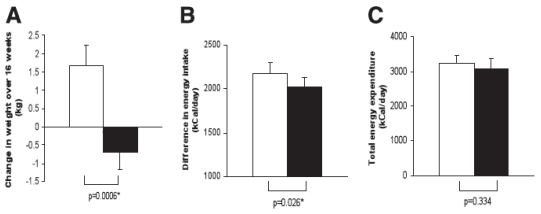


Relative peripheral and hepatic effects of detemir and NPH



Hordern V. *et al. Diabetologia* 2005;48:420-6

Por qué las diferencias en peso?



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Zachariah S. Diabetes Care. 2011;34:1487

EL HACER UNA MODIFICACIÓN DE ESTILO DE VIDA ADICIONAL AYUDA CON EL PESO EN PACIENTES CON INSULINA DETEMIR?

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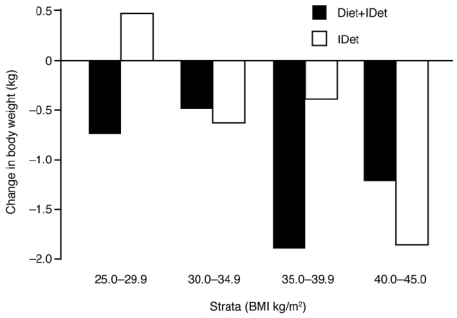
Estudio DIET



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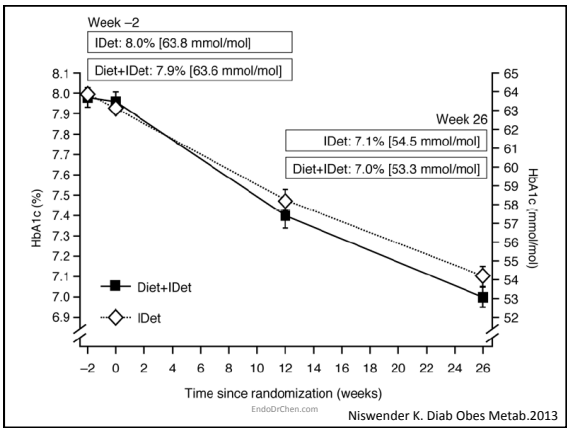
Niswender K. Diab Obes Metab.2013



Niswender K. Diab Obes Metab.2013

QUÉ HACER CUANDO FALLA UNA BASAL?

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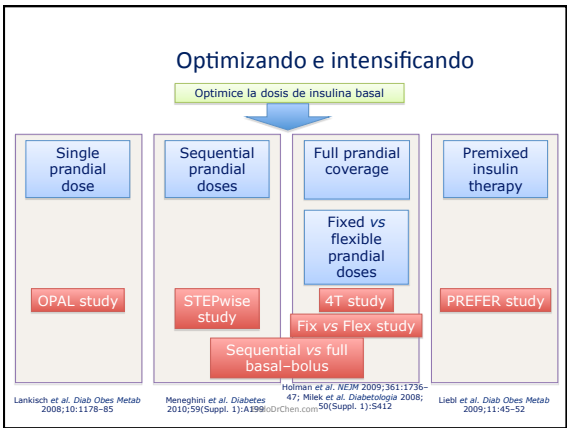
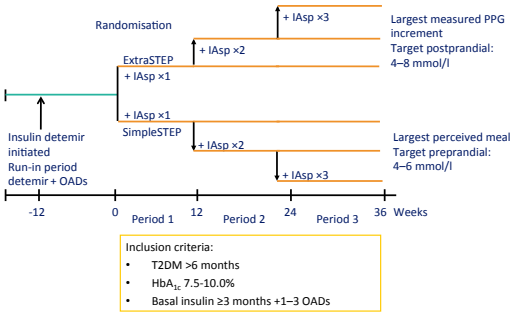


STEPwise™: study design



Inclusion criteria:
- T2DM >6 months
- HbA_{1c} 7.5-10.0%
- Basal insulin ≥3 months +1–3 OADs

T2DM, type 2 diabetes; OAD, oral antidiabetic drug; IAsp, insulin aspart

Meneghini *et al. Diabetes* 2010;59(Suppl. 1):A199

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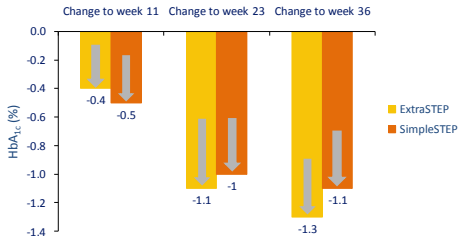
STEPwise™: change in HbA_{1c}



Change was adjusted for baseline HbA_{1c}

Meneghini *et al. Diabetes* 2010;59(Suppl. 1):A199

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POR QUÉ ANÁLOGOS DE INSULINA EN LUGAR DE INSULINA REGULAR?

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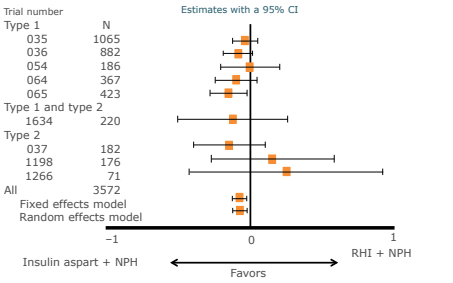
Overall change in A1C with insulin aspart



Data from one trial (066) are missing as no measurements were done in the first 16 weeks

RHI, regular human insulin

Heller *et al. Diabetologia* 2009;52(Suppl. 1):S359 (Poster 916)

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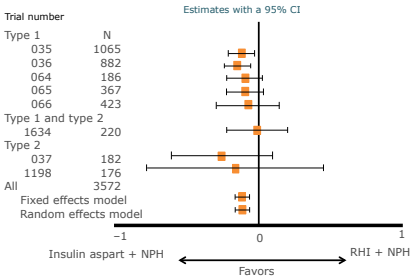
Nocturnal hypoglycemic episodes with insulin aspart



Heller *et al. Diabetologia* 2009;52(Suppl. 1):S359 (Poster 916)

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CUÁL ES LA MEJOR ALTERNATIVA? PREMEZCLAS, BASAL PLUS O INTENSIFICAR?

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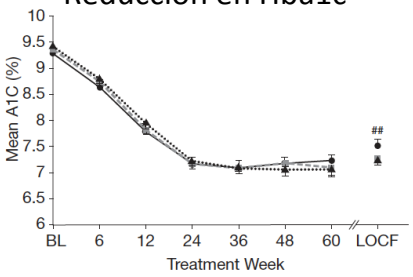
Reducción en Hba1c



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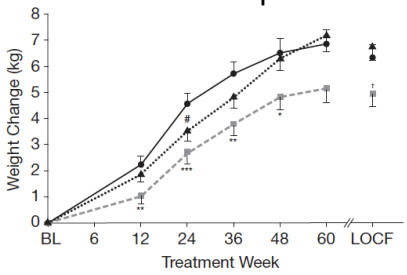
Riddle MC. Diab Obes Metab. 2013.

Aumento de peso



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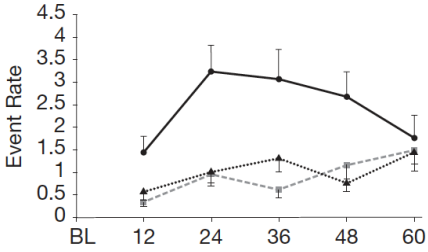
Riddle MC. Diab Obes Metab. 2013.

Tasa de hipoglicemias



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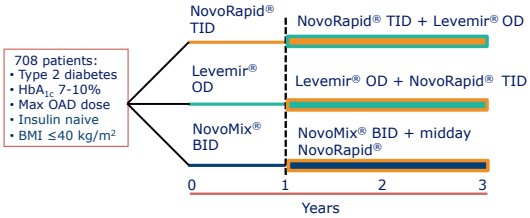
Riddle MC. Diab Obes Metab. 2013.

3 year study design to investigate insulin initiation and intensification



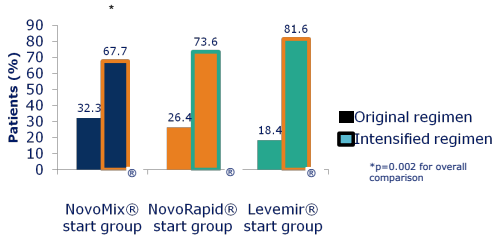
SU therapy replaced by second insulin in the first year if:
- HbA_{1c} ≥10% or
- HbA_{1c} ≥8% on two consecutive occasions

Or if:
- HbA_{1c} >6.5% at end of year one

Adapted from Holman *et al.* *NEJM* 2009; 361:1736-47

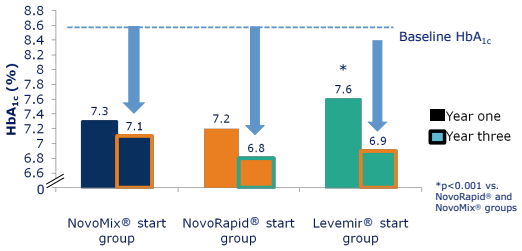
The majority of patients were intensified with a second insulin

74.3% of patients had an intensified regimen



Holman *et al.* *NEJM* 2007; 357:1716-30

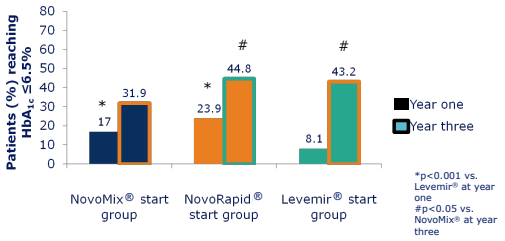
Sustainable HbA_{1c} control in all three arms



NB. Mean HbA_{1c} at 1 year; median HbA_{1c} at 3 years

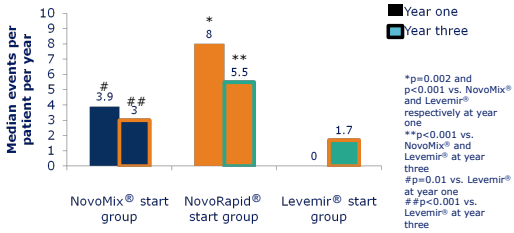
Adapted from Holman *et al.* *NEJM* 2007; 357:1716-30

Sustainable glycaemic control: patients with HbA_{1c} ≤6.5% at 3 years



Holman *et al. NEJM* 2007; 357:1716-30

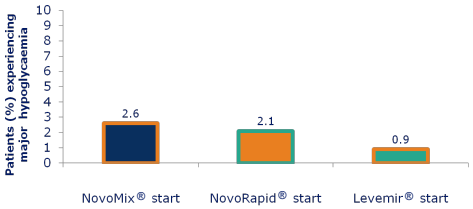
Low median rates of minor hypoglycaemia



Minor hypoglycaemia did occur in the first year with Levemir®, however the median rate was 0

Holman *et al. NEJM* 2007; 357:1716-30

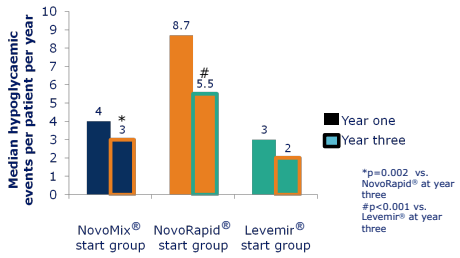
Low proportion of patients experiencing major hypoglycaemia over 3 years



No. of patients in the NovoMix® 30 start group	No. of patients in the NovoRapid® start group	No. of patients in the Levemir® start group
6	5	2

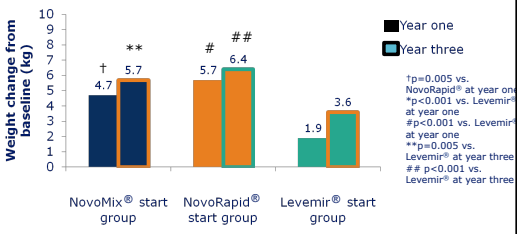
Holman *et al. NEJM* 2007; 357:1716-30

Achievement of HbA_{1c} ≤6.5% did not compromise hypoglycaemia rates

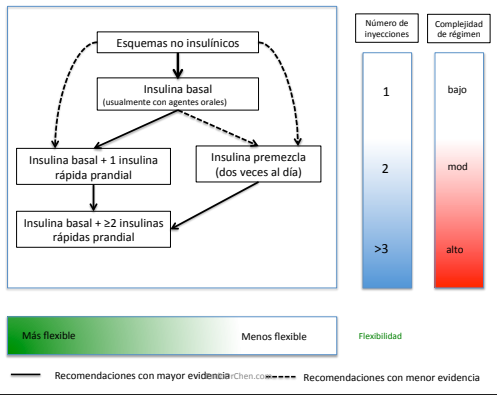


Holman *et al. NEJM* 2007; 357:1716-30

Detemir weight advantage was sustained throughout intensification



Holman *et al. NEJM* 2007; 357:1716-30



LA FORMA DE ADMINISTRAR INSULINA… HACE ALGUNA DIFERENCIA?

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Vial vs lapiceros

Database Outcome Measure, Mean (SD)	Vial/Syringe	Pen	*P* Value[a]
MarketScan	*N* = 5523	*N* = 6065	
Number of insulin aspart prescription claims	5.48 (3.50)	4.82 (2.99)	<0.001
Number of post-index period visits (any type of visit/medical claim) for hypoglycemia	1.27 (8.12)	0.87 (4.70)	<0.001
Post-index period health care costs for any type of hypoglycemia diagnosis ($)	466 (4689)	213 (2191)	<0.001
Post-index period diabetes-related health care costs ($)	6469 (14,770)	5753 (9387)	<0.001
Post-index period all-cause health care costs ($)	21,551 (37,495)	19,070 (29,913)	0.503
LifeLink	*N* = 3782	*N* = 4512	
Number of insulin aspart prescription claims	6.21 (4.16)	5.58 (3.45)	<0.001
Number of post-index period visits (any type of visit/medical claim) for hypoglycemia	0.58 (3.66)	0.31 (2.10)	<0.001
Post-index period health care costs for any type of hypoglycemia diagnosis ($)	390.75 (3792.84)	221.35 (2157.48)	<0.001
Post-index period diabetes-related health care costs ($)	6887.99 (12,162.62)	6458.37 (9798.04)	0.700
Post-index period all-cause health care costs ($)	19,255.68 (37,912.35)	17,911.02 (30,307.66)	0.890

[a]*P*-values were from chi square tests, Student's *t*-tests, or nonparametric median tests for variables that were not distributed normally.

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Ache CV. Curr Res Med Opin. 2013;29:1287

Por qué las diferencias?

- El lapicero:
  - Permite hacer titulaciones más finas de las dosis
  - Menos error en la medición
    - Especialmente en adultos mayores o pacientes con trastornos visuales
  - Mayor facilidad de aplicación

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QUÉ OTROS BENEFICIOS PODEMOS OBTENER DE ANÁLOGOS ULTRARÁPIDOS COMPARADOS CON INSULINA REGULAR?

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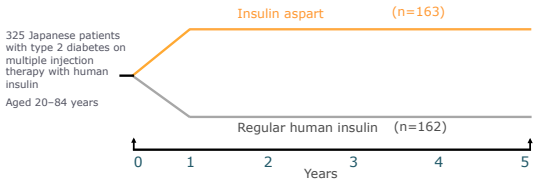
The effect of insulin aspart on cardiovascular disease

- Aim: to investigate the morbidity and mortality by cardiovascular disease in patients with type 2 diabetes treated either with insulin aspart or regular human insulin
- A prospective, randomized, open-label, blinded endpoint trial
- Intermediate/long-acting insulin was added when necessary. The primary endpoint was composite cardiovascular events (MI, angina, PCI/CABG, TIA/cerebral infarction)



CABG, coronary artery bypass graft; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischemic attack

Nishimura *et al. Diabetologia* 2008;51(Suppl. 1):S543 (Poster 1349)

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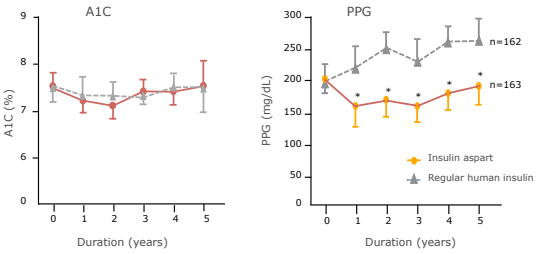
A1C and postprandial glucose control



Postprandial glucose levels 90 minutes after breakfast. Values are given as mean ± SD. *$p<0.02$

Nishimura *et al. Diabetologia* 2008;51(Suppl. 1):S543 (Poster 1349)

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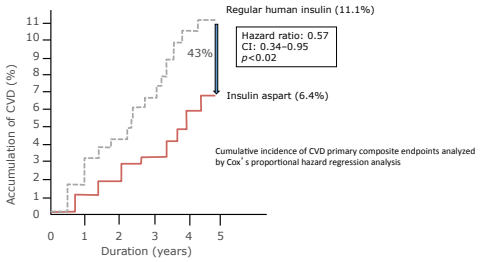
Long-term use of insulin aspart and effect on cardiovascular disease (CVD)



Nishimura *et al. Diabetologia* 2008;51(Suppl. 1):S543 (Poster 1349)

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Lower incidence of recorded cardiovascular outcomes in patients with type 2 diabetes using insulin aspart vs. those on human regular insulin: observational evidence from general practices

W. Rathmann[1] & K. Kostev[2]

[1] *German Diabetes Center, Institute of Biometrics and Epidemiology, Düsseldorf, Germany*
[2] *Department LifeLink Epidemiology, IMS HEALTH, Frankfurt, Germany*

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Rathman A. Diab Obes Metab. 2013;15:358

Metodología

- Análisis de bases de datos en atención primaria de Alemania
- Sólo pacientes que han usado insulina aspart o insulina simple, no permitía combinaciones
- Pacientes a quienes se les prescribió por primera vez la insulina

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Rathman A. Diab Obes Metab. 2013;15:358

Variables	Insulin aspart	Regular insulin
N	3154	3154
Age (years)	60.0 (10.2)	60.0 (10.2)
Diabetes treatment period (practice) (years)	2.2 (2.5)	2.2 (2.5)
Males (%)	57.4	57.4
Private health insurance (%)	5.8	5.8
Diabetologist treatment (%)	42.1*	32.6*
Region (West Germany) (%)	73.1*	78.6*
Urban residency†(%)	26.6	26.2
Antidiabetic treatment‡(%)		
Biguanides	26.2	26.1
Sulphonylureas	13.5*	19.7*
Acarbose	4.1*	6.0*
NPH insulin	47.6*	67.9*
Long-acting analogues	50.7*	27.6*
Co-medication‡(%)		
Antihypertensives	59.4	62.5
Lipid-lowering drugs	32.0	28.6
Antithrombotic agents	20.9	23.4

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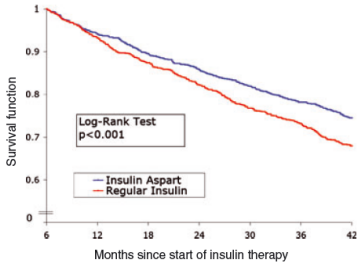
Rathman A. Diab Obes Metab. 2013;15:358

Eventos cardiovasculares



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Rathman A. Diab Obes Metab. 2013;15:358

HAY ALGÚN BENEFICIO EN PASAR A INSULINAS ANÁLOGAS?

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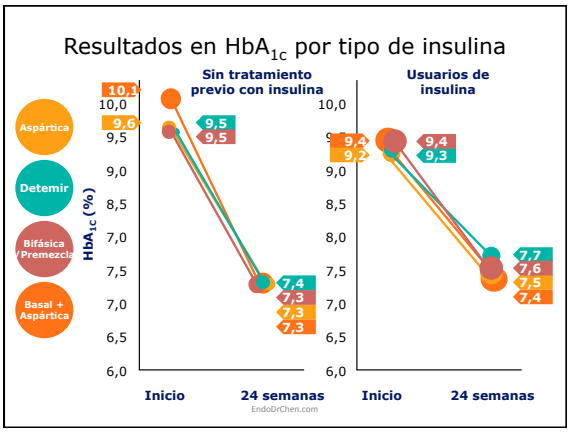
Resultados en HbA1c por tipo de insulina
Sin tratamiento previo con insulina
Usuarios de insulina
Aspártica
Detemir
Bifásica /Premezcla
Basal + Aspártica
HbA1c (%)
10,1
9,6
9,5
9,5
7,4
7,3
7,3
7,3
9,4
9,2
9,4
9,3
7,7
7,6
7,5
7,4
Inicio
24 semanas
Inicio
24 semanas
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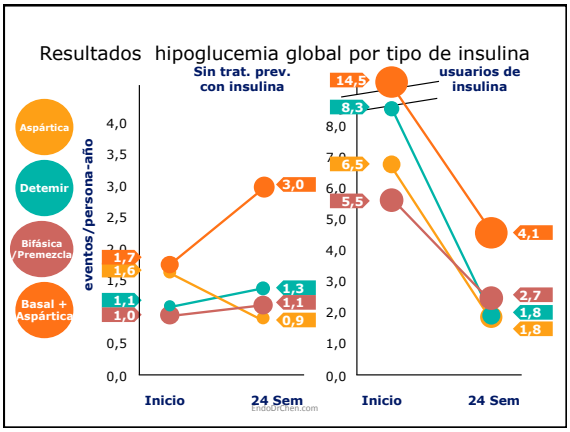
Resultados hipoglucemia global por tipo de insulina
Sin trat. prev. con insulina
usuarios de insulina
Aspártica
Detemir
Bifásica /Premezcla
Basal + Aspártica
eventos/persona-año
3,0
1,7
1,6
1,1
1,0
1,3
1,1
0,9
14,5
8,3
6,5
5,5
4,1
2,7
1,8
1,8
Inicio
24 Sem
Inicio
24 Sem
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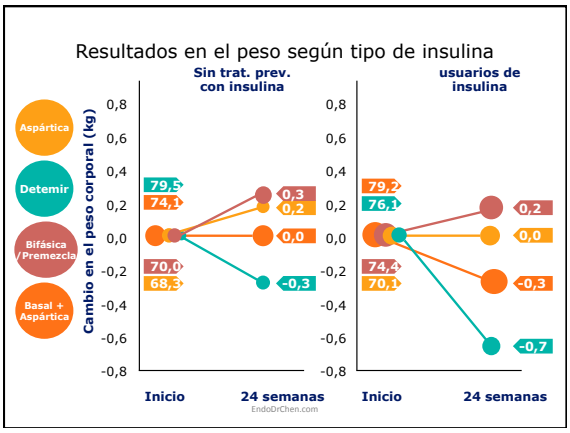
Resultados en el peso según tipo de insulina
Sin trat. prev. con insulina
usuarios de insulina
Aspártica
Detemir
Bifásica /Premezcla
Basal + Aspártica
Cambio en el peso corporal (kg)
79,5
74,1
70,0
68,3
0,3
0,2
0,0
-0,3
79,2
76,1
74,4
70,1
0,2
0,0
-0,3
-0,7
Inicio
24 semanas
Inicio
24 semanas
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Conclusiones

- Los análogos de insulina basal son una forma muy práctica y cómoda para empezar a insulinar
  - Insulina detemir produce menos aumento de peso
- La intesificación con basal plus produce menos hipoglicemia y aumento de peso
- Los dispositivos tipo lapicero producen menor riesgo de hipoglicemia

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Preguntas…

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