Principales usos de insulina análoga basal e intensificación con basal-bolo

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Conflictos de interés

- He recibido honorarios por conferencias, advisory board y/o investigación clínica de:
  - Astra Zeneca
  - Novartis Pharma Logistics Inc
  - Novartis Oncology
  - Novo Nordisk
  - Merck Sharp & Dohme
  - Roche
  - Glaxo SmithKline
  - Sanofi Aventis
  - Boehringer
  - Organon
  - Abbott Nutrición

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Agenda

- Preservación de células beta con insulina
- Por qué insulinas basales después de falla a agentes orales?
- Hay diferencias entre análogos de insulina basales?
- Cuál es el mejor esquema para intensificar en el uso de insulinas?

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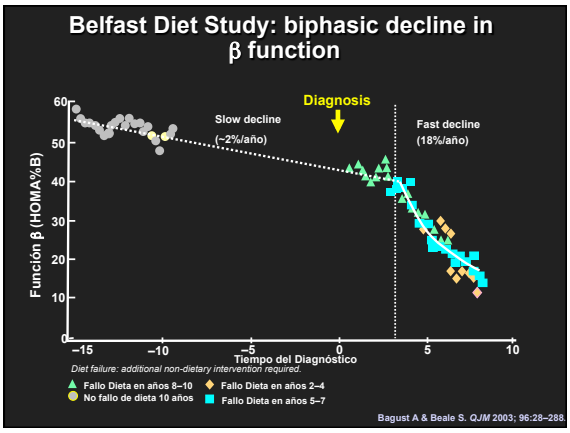

PODEMOS PRESERVAR LA CÉLULA BETA CON INSULINA TEMPRANAMENTE?

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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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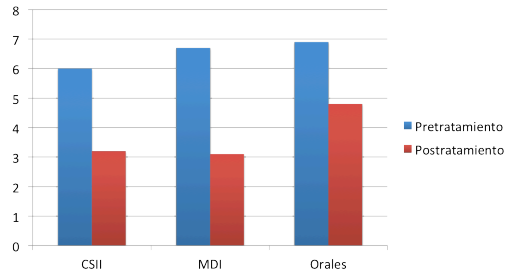
Weng J. Lancet. 2008;371:1753

HOMA-IR



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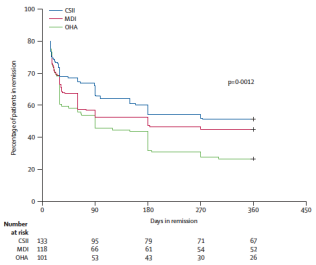
Weng J. Lancet. 2008;371:1753

Pacientes en remisión



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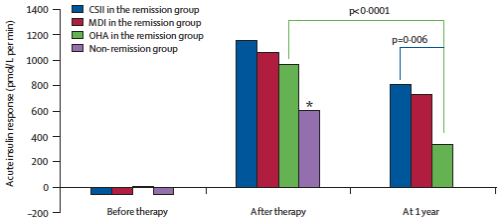
Weng J. Lancet. 2008;371:1753

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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QUÉ HACER CUANDO FALLAS 2 AGENTES ORALES?

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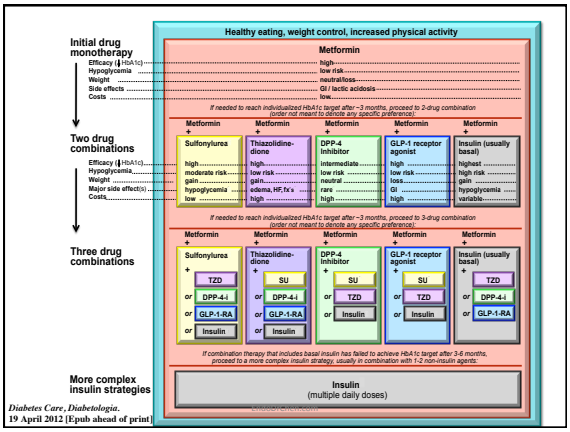

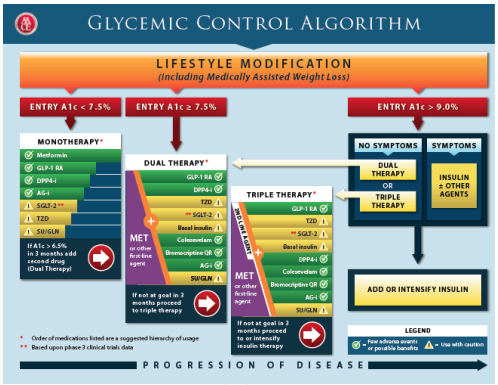

QUIÉN ES LA RESPONSABLE?

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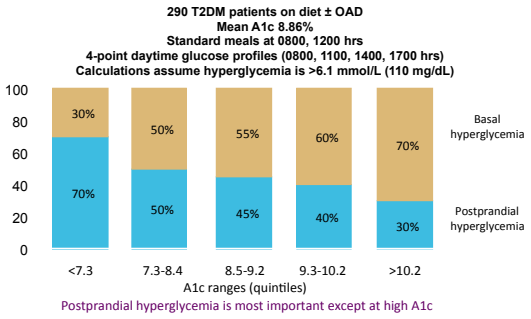
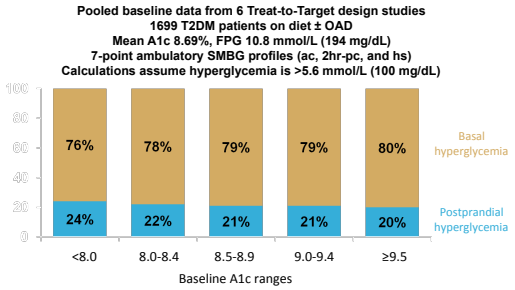
Basal and postprandial contributions to hyperglycemia by A1c range



Postprandial hyperglycemia is most important except at high A1c

Monnier L et al. Diabetes Care 2003;26:881-885

Basal and postprandial contributions to hyperglycemia by A1c range



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

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

Quién debe ser el 3er agente?

Hemoglobin A_{1c} Outcomes in Type 2 Diabetic Patients Taking Sitagliptin or a Thiazolidinedione

Hemoglobin A_{1c}	Sitagliptin (n = 102)	Thiazolidinedione (n = 104)	*P* value[a]
Hemoglobin A_{1c}, mean (SD), %			
Baseline	9.4 (1.8)	9.4 (1.9)	.952
4 Months	8.0 (1.8)	7.4 (1.3)	.007
Change	−1.3 (1.8)[b]	−2.0 (1.7)[b]	.006
Patients with hemoglobin A_{1c} <7.5%, No. (%)			
Baseline	9 (8.8)	11 (10.6)	.671
4 Months	47 (46.1)[c]	64 (61.5)[c]	.026
Patients sustaining hemoglobin A_{1c} <7.5% by 12 months, No. (%)	26/44 (59.1)	37/64 (57.8)	.895

[a] *P* value is for between-group differences by analysis of variance for hemoglobin A_{1c} or chi-square test for proportions.
[b] *P*<.001 for the change from baseline (determined by the paired Student *t* test).
[c] *P*<.001 for the change from baseline (determined by the chi-square test).

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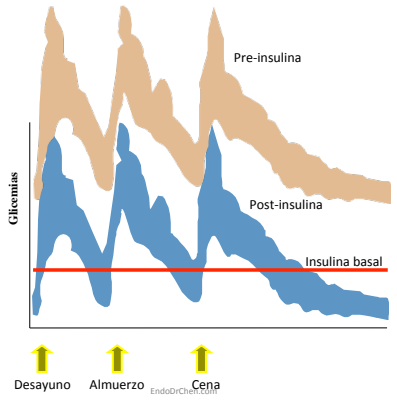
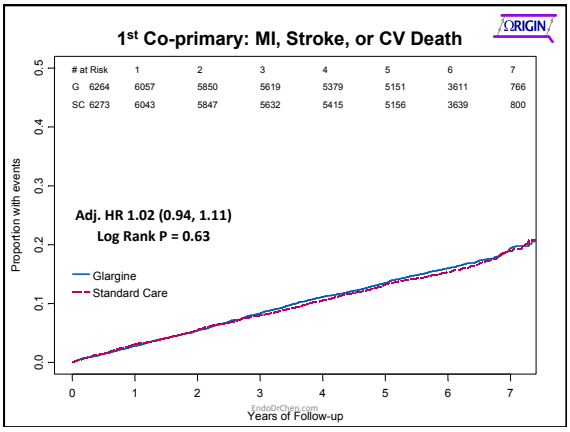
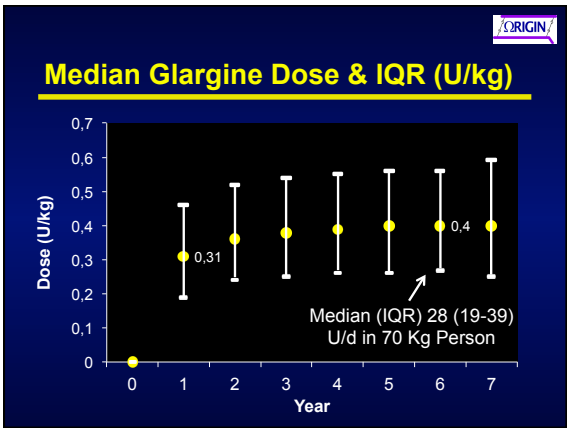
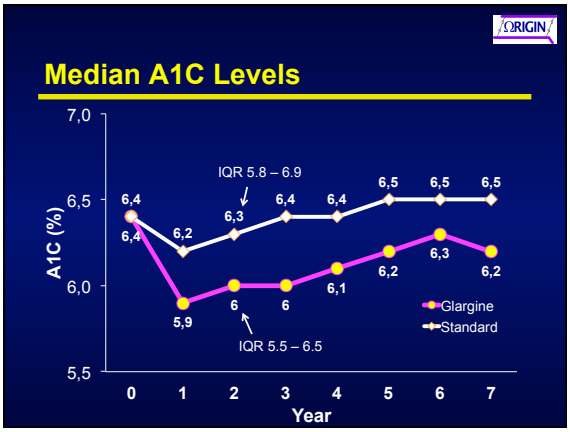
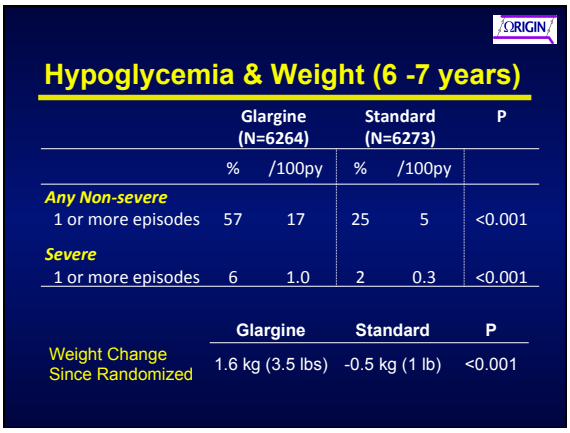
Hsia SH. Endocrine Pract. 2011;17(5);691











ORIGIN

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

HAY DIFERENCIAS ENTRE ANÁLOGOS BASALES?

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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

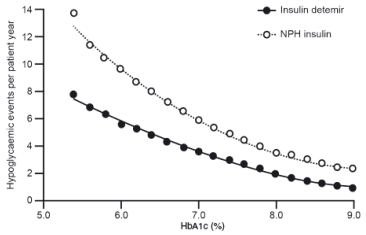
EndoDrChen.com Frier BM. Diab Obes Metab. 2013: online april 3.

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

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

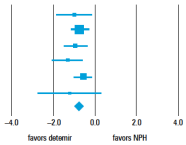
NPH vs detemir en DM-2: hipoglicemias



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

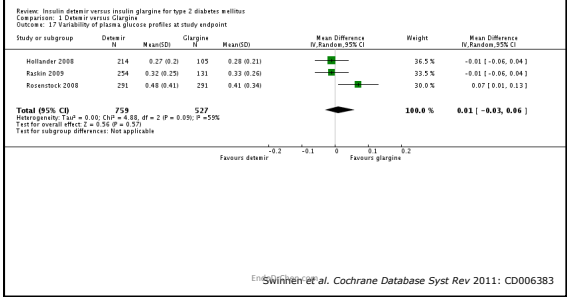
Diferencias en peso

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[23]	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.[24]	491	256	−0.540	−0.978	−0.102	0.116
Vague et al.[79]	282	138	−1.200	−2.763	0.363	0.132
total	1694	905	−0.779	−0.992	−0.567	0.000



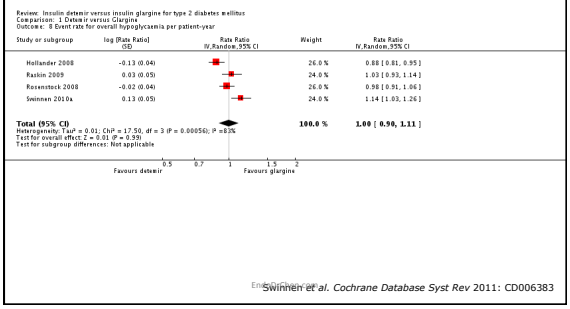
EndoDrChen.com Szypowska A. Por Arch Med Wewn. 2011;121:737

Cochrane: variabilidad en perfil glicémico



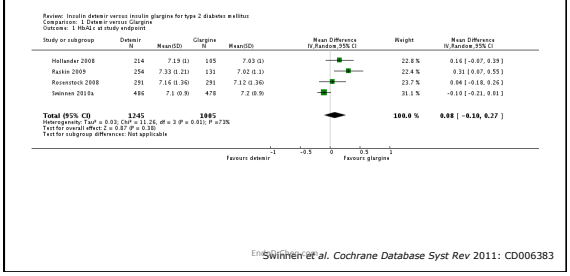
Swinnen et al. *Cochrane Database Syst Rev* 2011: CD006383

Cochrane: tasa de hipoglicemias



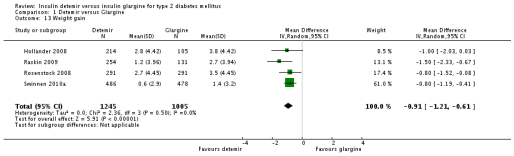
Swinnen et al. *Cochrane Database Syst Rev* 2011: CD006383

Cochrane: cambios en Hba1c



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

Cochrane: aumento de peso



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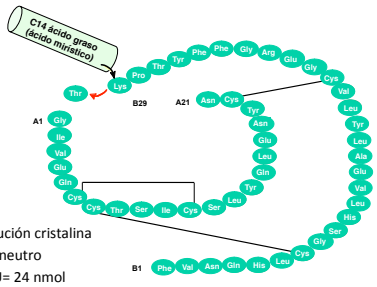
Insulina detemir

LysB29(N-tetradecanoyl)des(B30)



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

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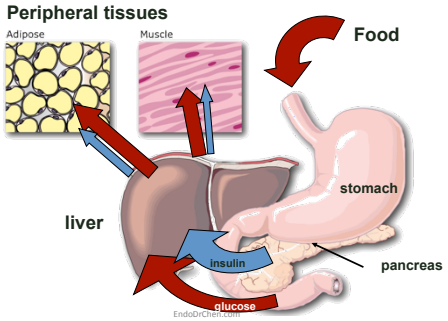
The 'Liver hypothesis': Systemic insulin in normal physiology



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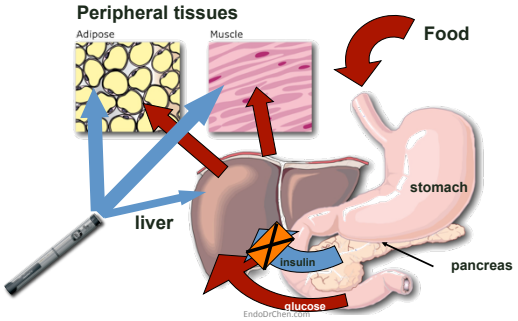
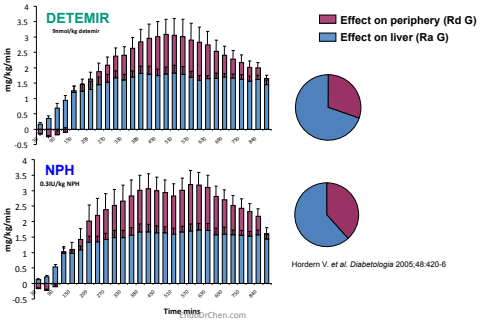
The 'Liver hypothesis':
Distribution of exogenous insulin

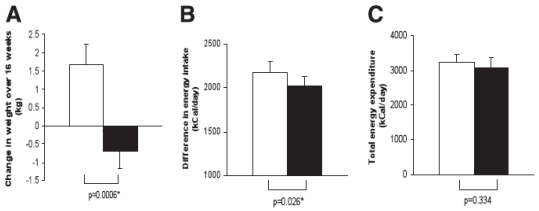


Relative peripheral and hepatic effects of detemir and NPH



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

Por qué las diferencias en peso?



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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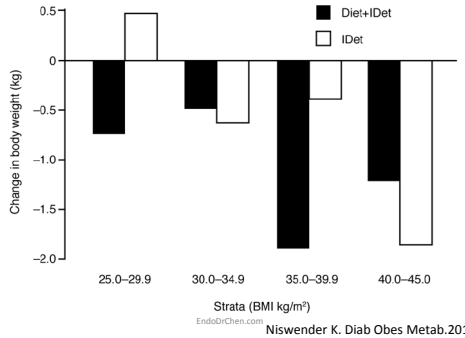
Estudio DIET



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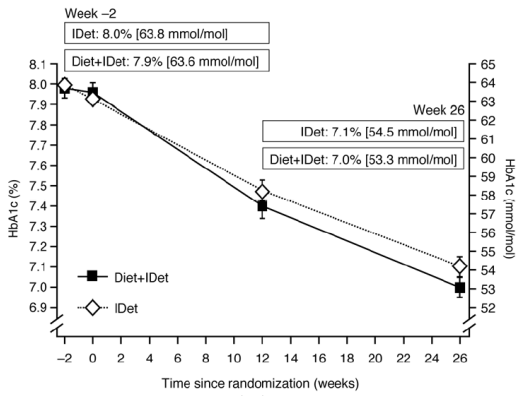
Niswender K. Diab Obes Metab.2013



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Niswender K. Diab Obes Metab.2013

República Dominicana

- Indicaciones aprobadas de detemir para República Dominicana:
  - Monoterapia o terapia combinada
  - Una vez al día
  - Mayores de 6 años

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QUÉ HACER CUANDO FALLA UNA BASAL?

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POR QUÉ ANÁLOGOS DE INSULINA EN LUGAR DE INSULINA REGULAR?

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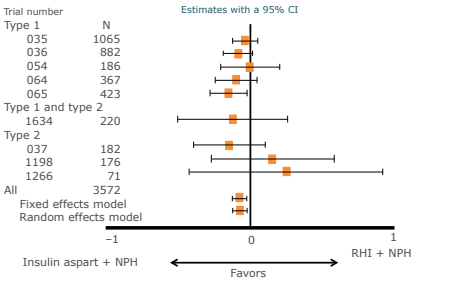
Overall change in A1C with insulin aspart



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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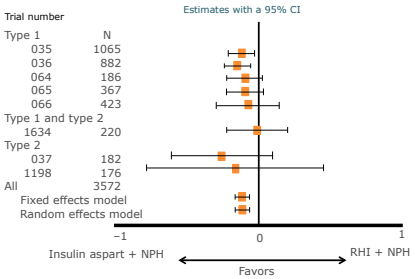
Nocturnal hypoglycemic episodes with insulin aspart



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

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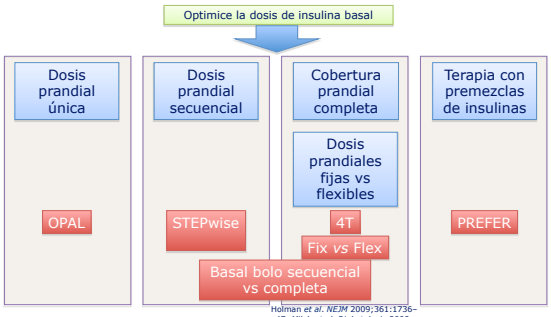
Optimizando e intensificando



Lankisch *et al. Diab Obes Metab* 2008;10:1178–85

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

Holman *et al. NEJM* 2009;361:1736–47; Milek *et al. Diabetologia* 2008;50(Suppl. 1):S412

Liebl *et al. Diab Obes Metab* 2009;11:45–52

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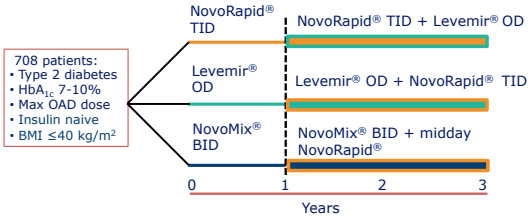
3 year study design to investigate insulin initiation and intensification



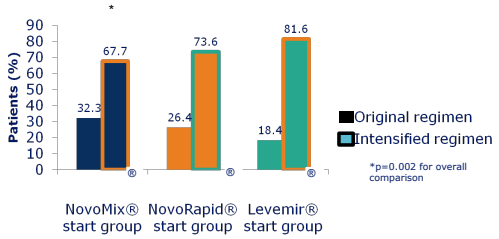
SU therapy replaced by second insulin in the first year if:
- HbA_{1c} ≥10% or
- HbA_{1c} ≥8% on two consecutive occasions

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

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

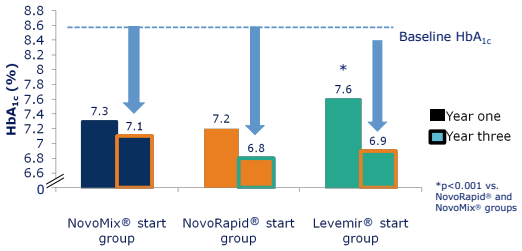
The majority of patients were intensified with a second insulin

74.3% of patients had an intensified regimen



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

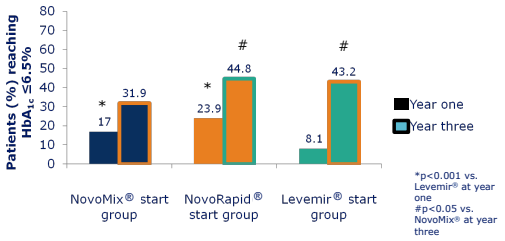
Sustainable HbA_{1c} control in all three arms



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

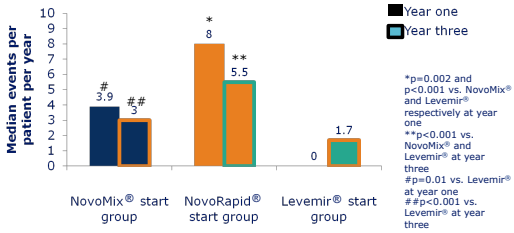
Adapted from Holman *et al.* *NEJM* 2007; 357:1716-30

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



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

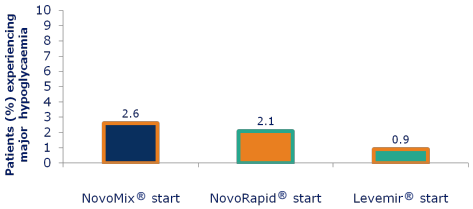
Low median rates of minor hypoglycaemia



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

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

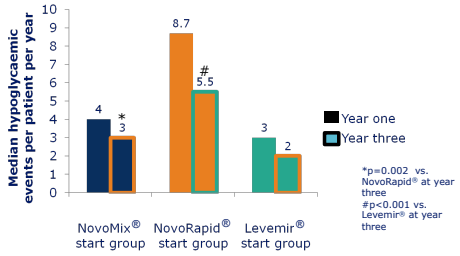
Low proportion of patients experiencing major hypoglycaemia over 3 years



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

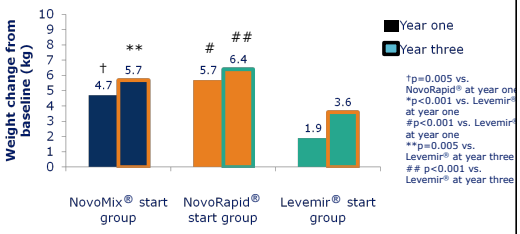
Holman *et al. NEJM* 2007; 357:1716-30

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

PERO… PASAR A UN ESQUEMA INTENSIFICADO COMPLETO A VECES CUESTA (TANTO PARA EL MÉDICO COMO PARA EL PACIENTE)
CÓMO PODEMOS SIMPLIFICARLO?

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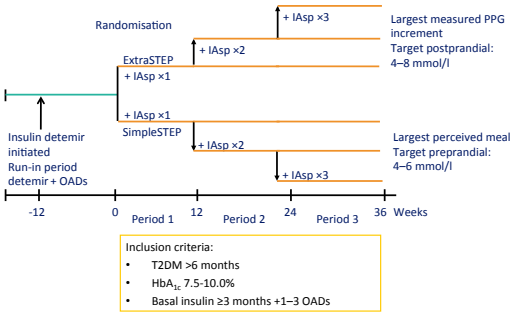
STEPwise™: study design



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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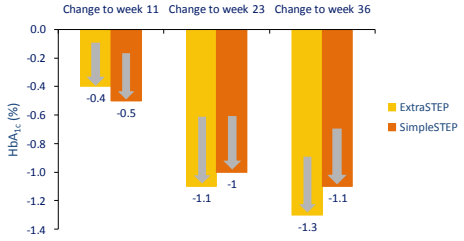
STEPwise™: change in HbA_{1c}



Change was adjusted for baseline HbA_{1c}

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

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

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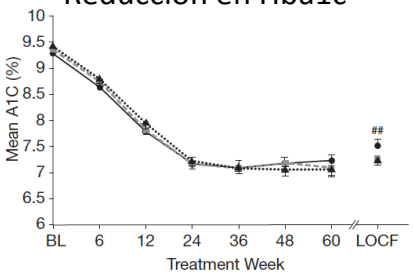
Reducción en Hba1c



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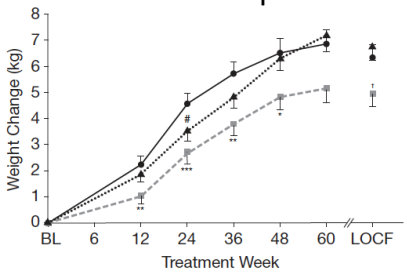
Riddle MC. Diab Obes Metab. 2013.

Aumento de peso



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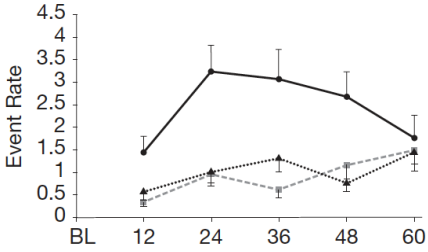
Riddle MC. Diab Obes Metab. 2013.

Tasa de hipoglicemias



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Riddle MC. Diab Obes Metab. 2013.

Cuál estrategia de intensificación?

- Basal plus/basal bolo
  - Mayor reducción de Hba1c
  - Más fisiológico
  - Mejor titulación de dosificación
  - Uso de 2 lapiceros de insulina que pueden producir confusión
  - Un poco más difícil
- Premezclas
  - Hba1c ligeramente mayor
  - Más rígido
  - Al titular, modifica dosis de ambos componentes
  - Un sólo lapicero
  - Más sencillo

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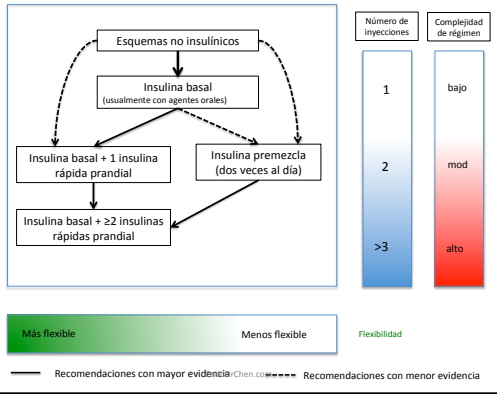

LA FORMA DE ADMINISTRAR INSULINA… HACE ALGUNA DIFERENCIA?

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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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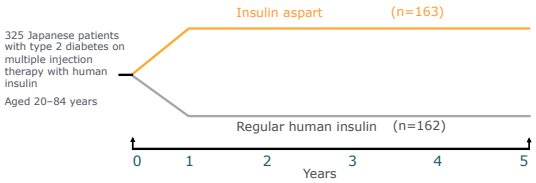
The effect of insulin aspart on cardiovascular disease

- 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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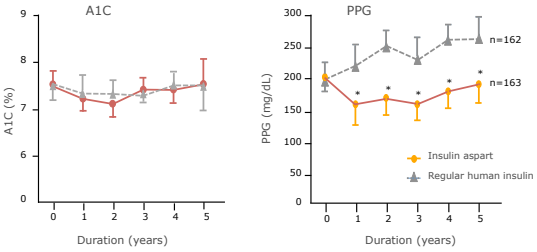
A1C and postprandial glucose control



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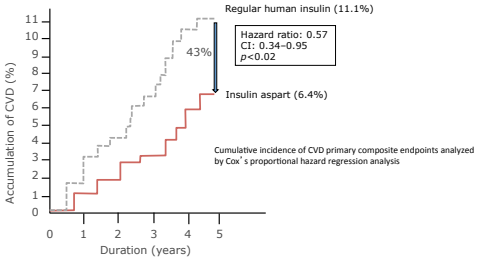
Long-term use of insulin aspart and effect on cardiovascular disease (CVD)



Cumulative incidence of CVD primary composite endpoints analyzed by Cox's proportional hazard regression analysis

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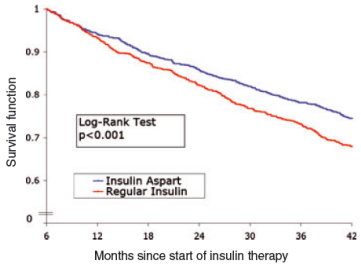
Rathman A. Diab Obes Metab. 2013;15:358

Eventos cardiovasculares



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

República Dominicana

- Indicaciones aprobadas de aspart para República Dominicana:
  - Niños mayores de 2 años
  - Embarazo
  - Pacientes geriátricos

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HAY ALGÚN BENEFICIO EN PASAR A INSULINAS ANÁLOGAS?

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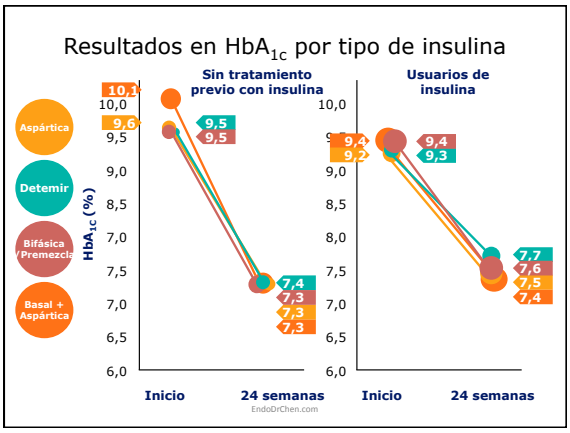
Resultados en HbA1c por tipo de insulina
Sin tratamiento previo con insulina
Usuarios de insulina
Aspártica
Detemir
Bifásica /Premezcla
Basal + Aspártica
HbA1c (%)
10,1
9,6
9,5
9,5
7,4
7,3
7,3
7,3
9,4
9,2
9,4
9,3
7,7
7,6
7,5
7,4
Inicio
24 semanas
Inicio
24 semanas
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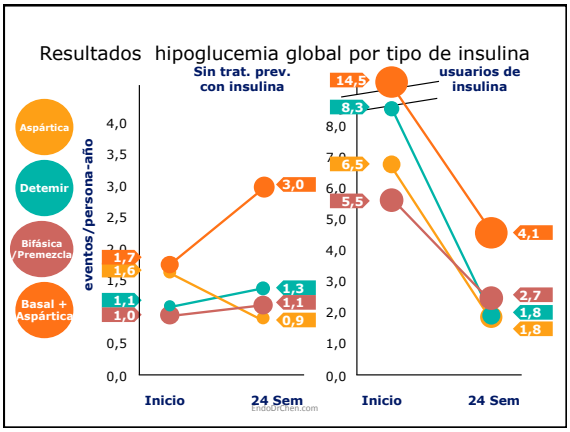
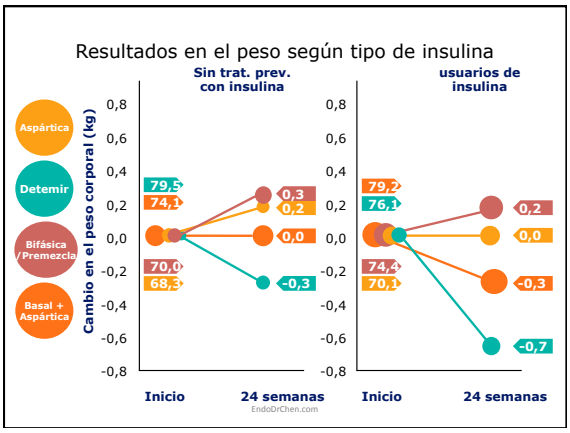

Resultados hipoglucemia global por tipo de insulina
Sin trat. prev. con insulina
usuarios de insulina
Aspártica
Detemir
Bifásica /Premezcla
Basal + Aspártica
eventos/persona-año
3,0
1,7
1,6
1,1
1,0
1,3
1,1
0,9
14,5
8,3
6,5
5,5
4,1
2,7
1,8
1,8
Inicio
24 Sem
Inicio
24 Sem
EndoDrChen.com


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
EndoDrChen.com

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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