Uso de insulinas humanas vs análogos de insulina en la práctica clínica

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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

- Cuándo insulinizar?
- Por qué empezar con una insulina basal?
- Diferencias entre las insulinas basales
- Hay algún beneficio en pasar de insulinas humanas a análogas de insulina?
- Cuándo intensificar y cómo hacerlo?

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Caso #1

- Masculino de 53 años, diabético tipo 2 de 7 años de evolución, en tratamiento con metformin 500 mg tid y glibenclamida 10 mg AM y 5 mg PM. Su Hba1c está en 8.0%. Se encuentra asintomático. No tiene morbilidades asociadas, sólo hipertensión arterial.

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Caso #1

- Se encuentra el paciente bien controlado?
- Cuál es su meta de Hba1c?
- Cuál es el siguiente paso?

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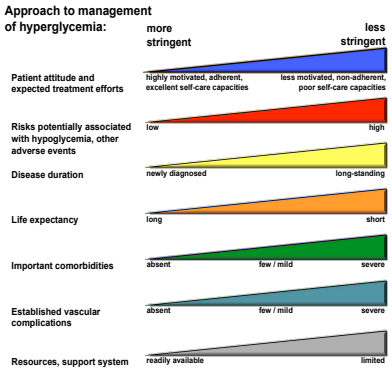
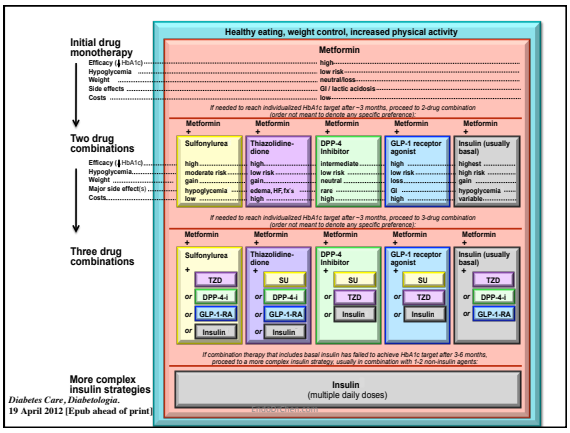
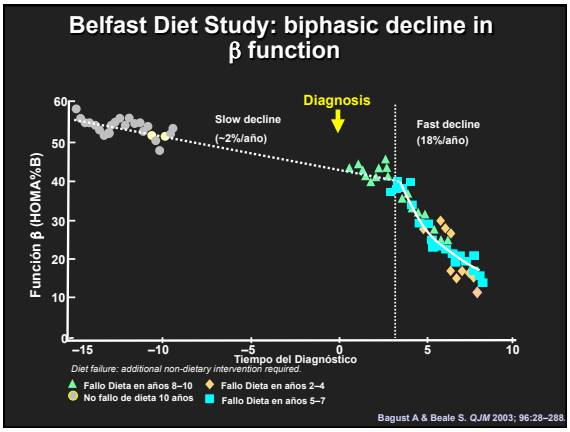


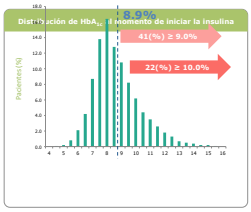
Figure 1

EndoDrChen ;*Diabetes Care*, *Diabetologia*. 19 April 2012 [Epub ahead of print]
(Adapted with permission from: Ismail-Beigi F, et al. *Ann Intern Med* 2011;154:554)





Existe la necesidad de un inicio más temprano de la insulina - HbA_{1c} basal



Existe inercia clínica a pesar de:

- Los beneficios del control glucémico oportuno
- Guías de tratamiento que alientan el uso más temprano de la insulina

Al iniciar la insulina en SOLVE™:

El promedio de la HbA1c era 8.9%

41% presentaba HbA1c ≥ 9.0%

22% presentaba HbA1c ≥ 10.0%

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Khunti et al Diabetologia 2011; 54 (Suppl.1): S160 and Poster

POR QUÉ EMPEZAR CON INSULINA BASAL?

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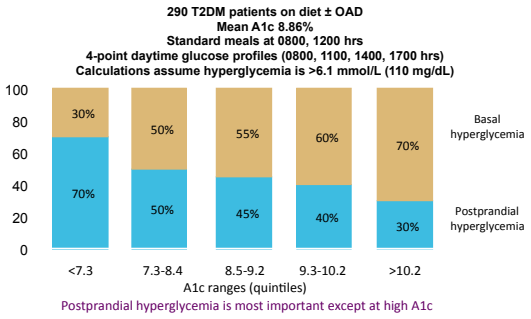
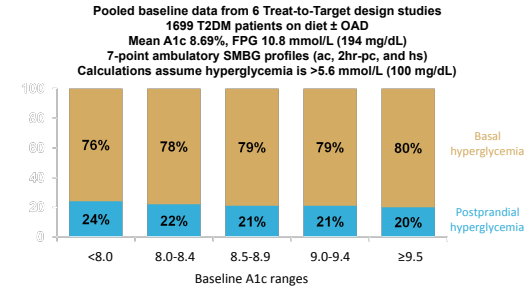
Basal and postprandial contributions to hyperglycemia by A1c range



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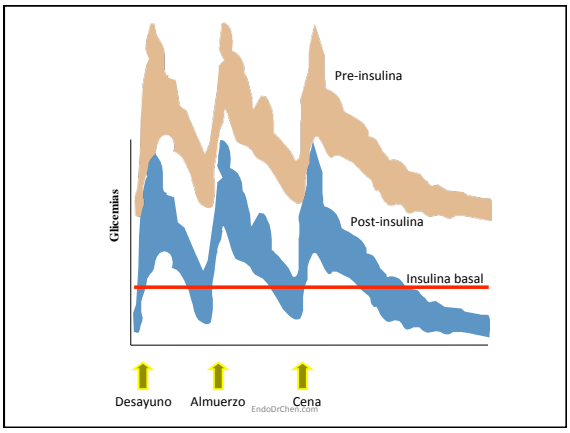
Riddle et al, Diabetes Care 34:2508–2514, 2011



DIFERENCIAS ENTRE INSULINAS BASALES

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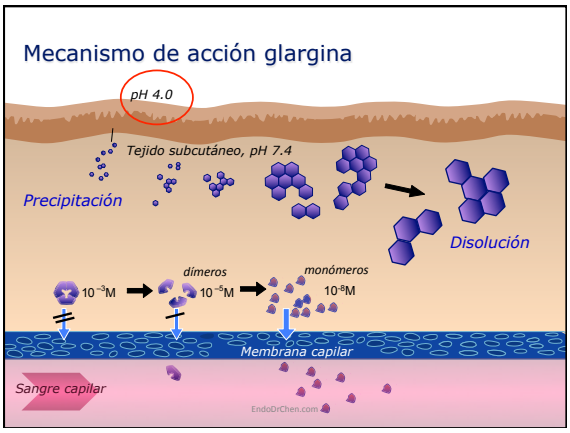
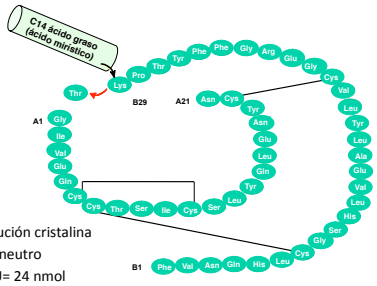


Insulina detemir

LysB29(N-tetradecanoyl)des(B30)



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

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DIFERENCIAS ENTRE INSULINAS: VARIABILIDAD, PESO E HIPOGLICEMIAS

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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

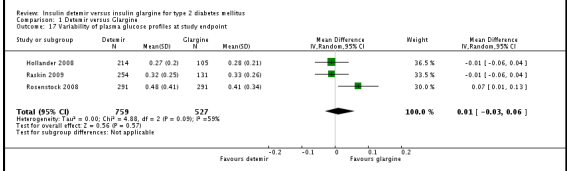
EndoDrChen.com Frier BM. Diab Obes Metab. 2013: online april 3.

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

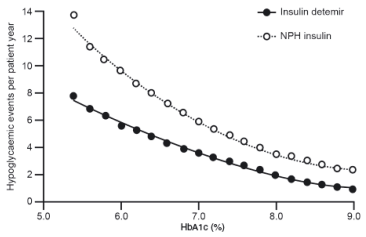
EndoDrChen.com Frier BM. Diab Obes Metab. 2013: online april 3.

Cochrane: variabilidad en perfil glicémico



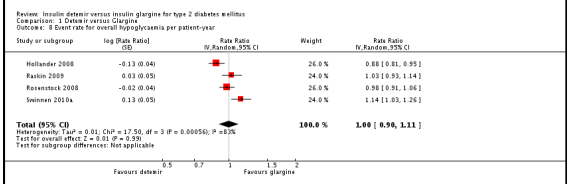
EndoDrChen.com Swinnen et al. *Cochrane Database Syst Rev* 2011: CD006383

NPH vs detemir en DM-2: hipoglicemias



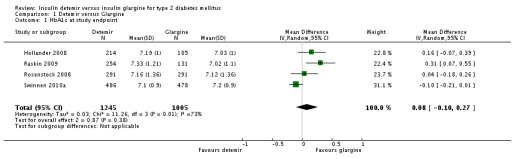
EndoDrChen.com Frier BM. Diab Obes Metab. 2013: online april 3.

Cochrane: tasa de hipoglicemias



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

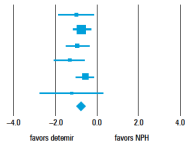
Cochrane: cambios en Hba1c



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

Diferencias en peso

Study	Sample size: detemir	Sample size: NPH	Statistics for each study: difference in means	lower limit	upper limit	*P*
Bartley et al.[24]	320	159	−0.990	−1.847	−0.133	0.024
Horne 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.[29]	282	138	−1.200	−2.763	0.363	0.132
total	1694	905	−0.779	−0.992	−0.567	0.000



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

Cochrane: aumento de peso

Review: Insulin detemir versus insulin glargine for type 2 diabetes mellitus
Comparison: 1 Detemir versus Glargine
Outcome: 13 Weight gain

Study or subgroup	Detemir N	Mean(SD)	Glargine N	Mean(SD)	Weight	Mean Difference IV,Random,95% CI
Hollander 2008	214	2.8 (4.42)	105	3.8 (4.42)	8.5 %	-1.00 [-2.03, 0.03]
Raskin 2009	254	1.2 (3.96)	131	2.7 (3.94)	13.1 %	-1.50 [-2.33, -0.67]
Rosenstock 2008	291	2.7 (4.45)	291	3.5 (4.45)	17.4 %	-0.80 [-1.52, -0.08]
Swinnen 2010a	486	0.6 (2.5)	478	1.4 (3.2)	61.0 %	-0.80 [-1.19, -0.41]
Total (95% CI)	**1245**		**1005**		**100.0 %**	**-0.91 [-1.21, -0.61]**

Heterogeneity: Tau² = 0.0; Chi² = 2.56, df = 3 (P = 0.58); I² =0.0%
Test for overall effect: Z = 5.91 (P < 0.00001)
Test for subgroup differences: Not applicable

Favours detemir -4 -2 0 2 4 Favours glargine

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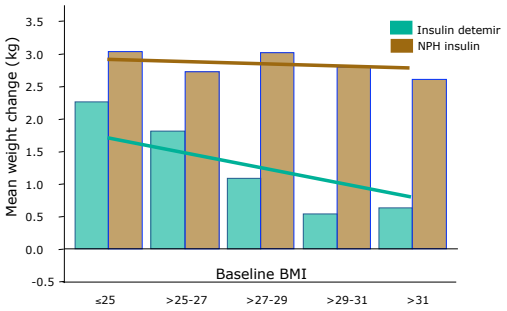
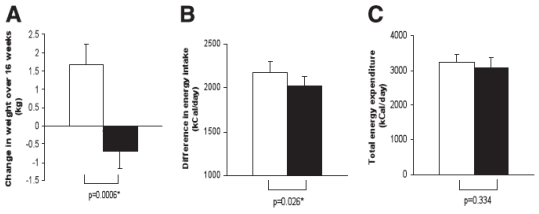
Weight change by BMI in treat-to-target study in type 2 diabetes



Hermansen K *et al. Diabetes Care* 2006

Por qué las diferencias en peso?



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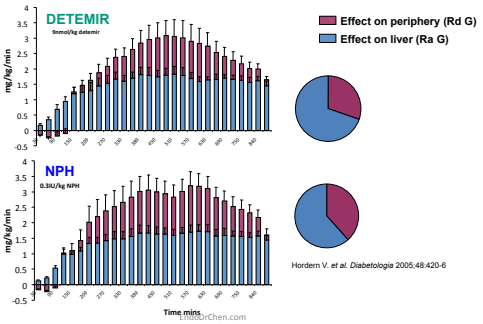
Zachariah S. Diabetes Care. 2011;34:1487

Relative peripheral and hepatic effects of detemir and NPH



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

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INICIO Y TITULACIÓN DE DOSIS

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Caso #1

- Masculino de 53 años, diabético tipo 2 de 7 años de evolución, en tratamiento con metformin 500 mg tid y glibenclamida 10 mg AM y 5 mg PM. Su Hba1c está en 8.0%. Se encuentra asintomático. No tiene morbilidades asociadas, sólo hipertensión arterial.

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Preguntas caso #1

- Ya optamos por iniciar con una insulina basal
- Con qué dosis empezamos?
- Cómo subimos la dosis?
- Con cuál glicemia titulamos?

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Metas de tratamiento

Meta	Glicemia ayunas	Glicemias postprandiales
<6.5%	70-110 mg/dl	<140 mg/dl
<7%	80-140 mg/dl	<180 mg/dl

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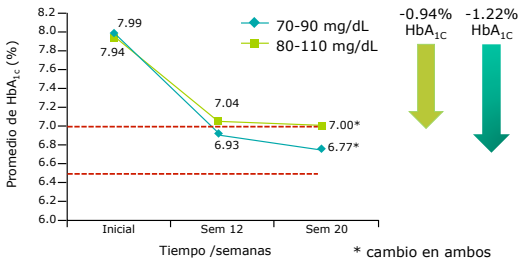
Ajuste de dosis por el paciente mejoría en $HbA_{1c:}$ estudio Titrate



-0.94% HbA_{1C} -1.22% HbA_{1C}

* cambio en ambos grupos
p = 0.019 at 20 weeks

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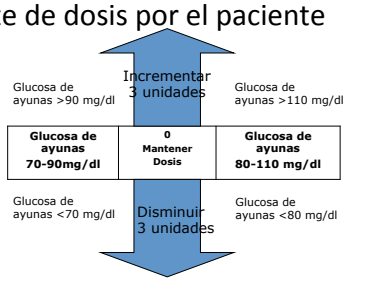
Blonde L. Diabetes Obes Metab. 2009;11:623

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 2009;11(6):623-631

SOSTENIBILIDAD CON INSULINA BASAL

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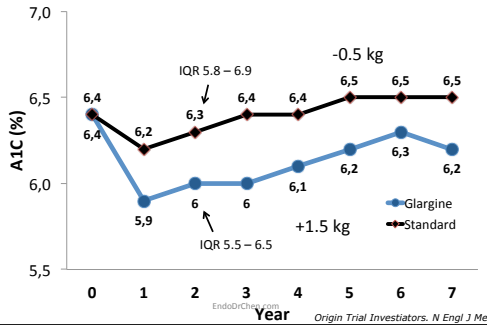
ORIGIN: Median A1C Levels



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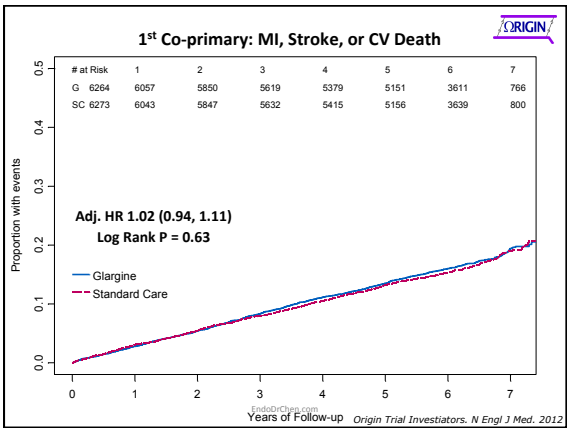
Origin Trial Investiators. N Engl J Med. 2012



Origin Trial Investigators. N Engl J Med. 2012

Factores predictores para alcanzar hba1c <6.5%

Factor	OR para alcanzar Hba1c <6.5%
Mayor edad	1.014 (1.008-1.019)
Uso de alcohol (>2 veces por semana)	1.727 (1.561-1.911)
A1c (por %)	0.191 (0.179-0.205)
Depresión	1.457 (1.256-1.691)
Relación cintura cadera (por unidad)	0.371 (0.244-0.565)
Diabetes	0.102 (0.081-0.128)

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Origin Trial Investigators. Diabetes Care. 2013. Online May 8.

Basal Insulin: Percent of patients with HbA1c < 7%

29 trials, with 17,588 patients

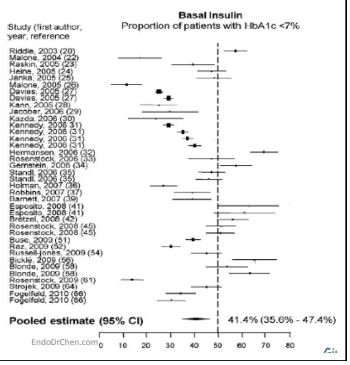
HbA1c < 7% was achieved in 41.4% (95% CI, 35.6–47.4%).

Predictors of response:
- **first insulin treatment,**
- **lower insulin dose**
- **use of 2 oral drugs**

Hypoglycemic events: 0 to 4.71 events/patient/30 days

Weight gain ~1.75 kg (1.2-2.1)

Final Insulin dose: 0.48 (0.4-0.57)



Giugliano et al. Diabetes Research & Clinical Practice 92 (2011) 1–10

Insulinas basales

- Análogos producen menos hipoglicemia y variabilidad comparado con NPH
- Detemir y glargina con tasas similares de reducción de Hba1c e hipoglicemias
- Menor aumento de peso observado con insulina detemir

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SWITCH DE INSULINAS HUMANAS A ANÁLOGOS DE INSULINA

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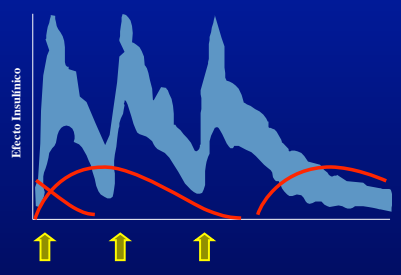
Dos dosis NPH



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Chen-Ku CH. AMPMD. Nov 2012

Aspectos prácticos

- Cuando se convierte de insulinas humanas basales, reducir 20% la dosis e ir titulando a partir de ahí
- Regla 3-0-3
- Por lo general, cuando se empieza una insulina basal se dejan los dos agentes orales con los que venía el paciente para manejar las hiperglicemias postprandiales

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QUÉ HACER CUANDO LA INSULINA BASAL NO ES SUFICIENTE?

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Caso #1

- Masculino de 53 años, diabético tipo 2 de 7 años de evolución, en tratamiento con metformin 500 mg tid y glibenclamida 10 mg AM y 5 mg PM. Su Hba1c está en 8.0%. Se encuentra asintomático. No tiene morbilidades asociadas, sólo hipertensión arterial.

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Caso #1

- Se le inició con insulina detemir 10 u al día y se fue titulando hasta 32 u al día, se dejó la metformin y glibenclamida
- Glicemia en ayunas 104 mg/dl y Hba1c en 6.4%
- 2 años después presenta glicemia en ayunas en 113 mg/dl y Hba1c 7.2%
- Quién es el responsable de la elevación de Hba1c?
- Cuál es el siguiente paso?

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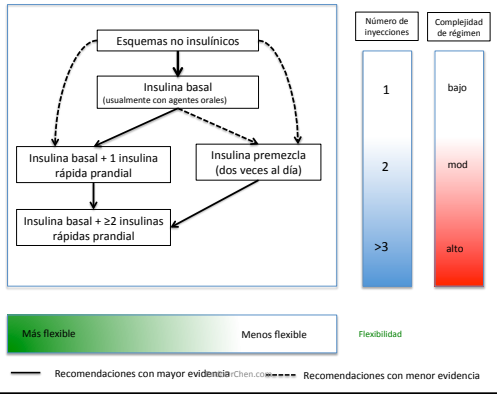

Introducción

- Todos los diabéticos tipo 1 requieren intensificación de su insulinización
- Mayoría de diabéticos tipo 2 luego de una insulina basal requieren intensificar en algún momento
  - No estamos alterando el deterioro progresivo de la célula beta

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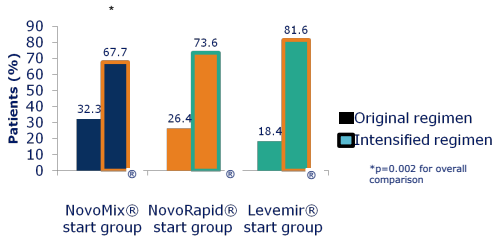
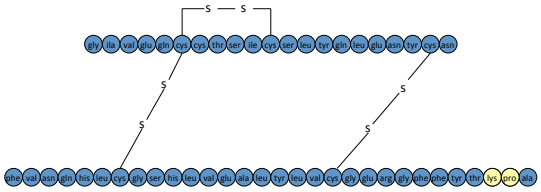
The majority of patients were intensified with a second insulin

74.3% of patients had an intensified regimen



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

Lispro



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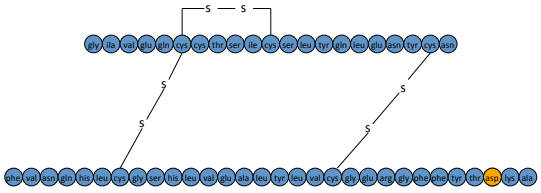
Aspart



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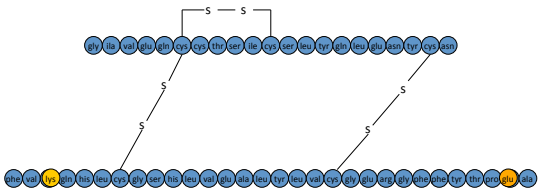
Glulisina



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POR QUÉ ANÁLOGOS DE INSULINA EN LUGAR DE INSULINA REGULAR?

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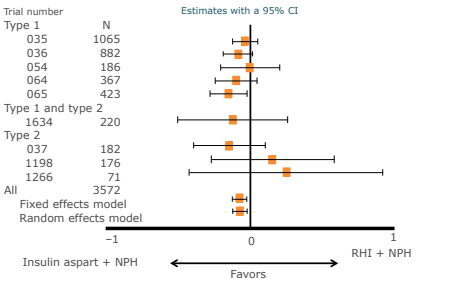
Overall change in A1C with insulin aspart



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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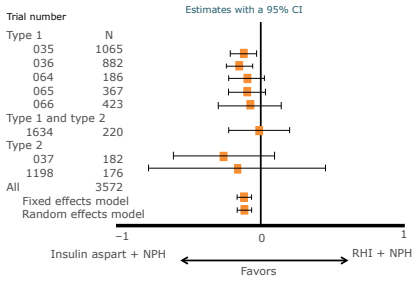
Nocturnal hypoglycemic episodes with insulin aspart



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

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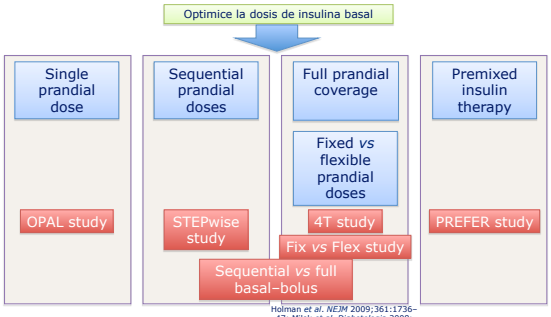
Optimizando e intensificando



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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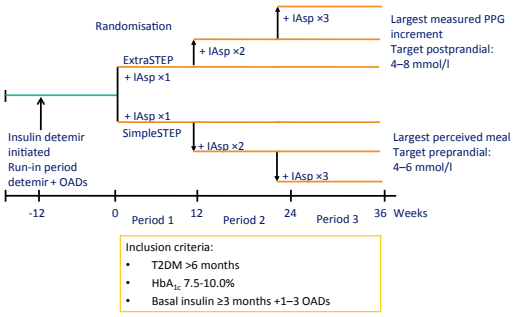
STEPwise™: study design



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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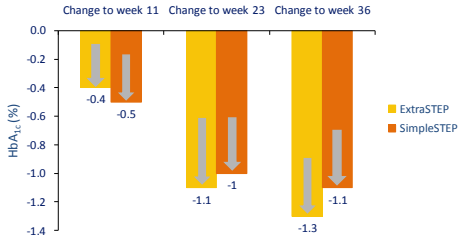
STEPwise™: change in HbA_{1c}



Change was adjusted for baseline HbA_{1c}

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

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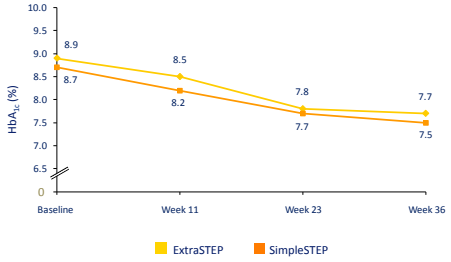
STEPwise™: HbA_{1c} reduction from baseline



Meneghini *et al. Diabetes* 2010;59(Suppl. 1):A199 and data on file

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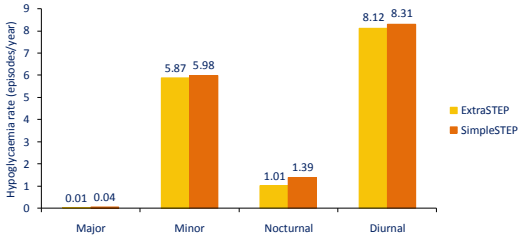
STEPwise™: overall hypoglycaemia rates



Both nocturnal and diurnal rates include all hypoglycaemia (including unclassified and symptoms only)

Meneghini *et al. Diabetes* 2010;59(Suppl. 1):A199 and data on file

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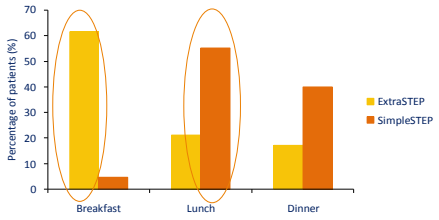
STEPwise™: addition of first bolus injection



ExtraSTEP group added insulin based on PPG measurement

SimpleSTEP group added insulin based on patient assessment

Meneghini *et al. Diabetes* 2010;59(Suppl. 1):A199 and data on file

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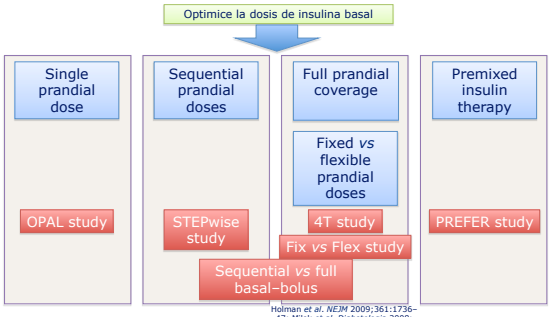
Optimizando e intensificando



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

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

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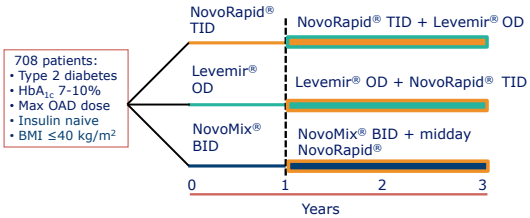
3 year study design to investigate insulin initiation and intensification



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

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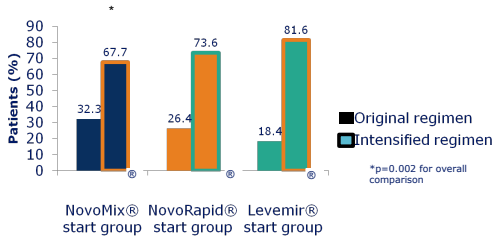
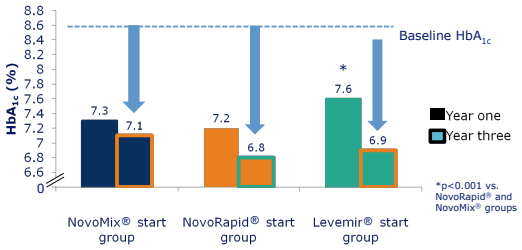
The majority of patients were intensified with a second insulin

74.3% of patients had an intensified regimen



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

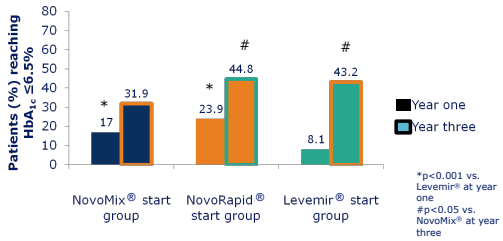
Sustainable HbA_{1c} control in all three arms



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

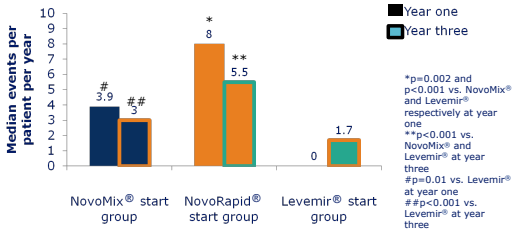
Adapted from Holman *et al. NEJM* 2007; 357:1716-30

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



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

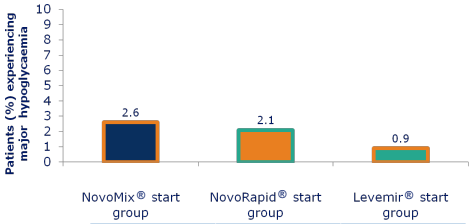
Low median rates of minor hypoglycaemia



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

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

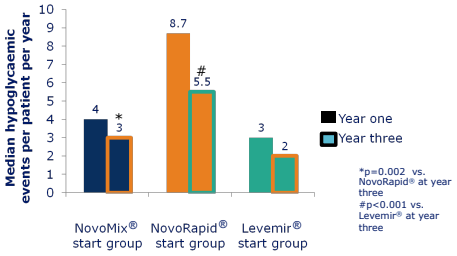
Low proportion of patients experiencing major hypoglycaemia over 3 years



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

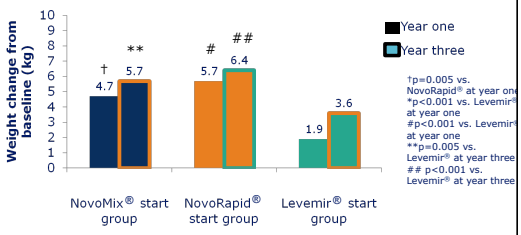
Holman *et al. NEJM* 2007; 357:1716-30

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

Insulina basal bolus: Porcentaje de pacientes con HbA1c < 7%

12 ensayos, with 2114 ptes

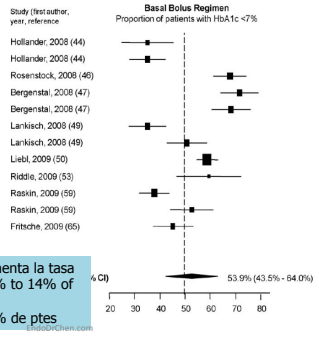
HbA1c < 7% se logró en 53.9% (95% CI, 43.5–64)

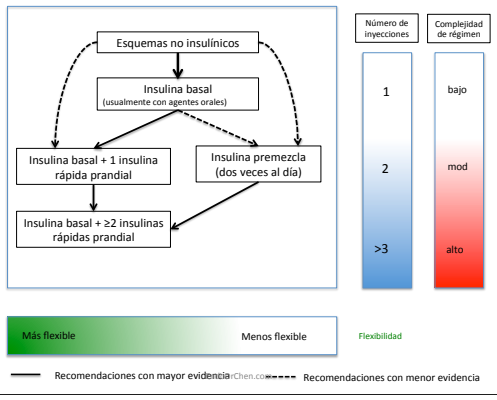
Eventos hipoglicémicos (promedio/paciente/30 días): 0.88 (0.35-1.3)

Aumento peso ~2.75 kg (1.8-3.7)

Dosis final insulina: 0.89 U/kg (0.78-1.3)

Pasar de basal a basal bolus aumenta la tasa de éxito adicionalmente en ~12% to 14% of pacientes
- HbA1c < 7% se logra en ~54% de ptes





Qué hacer con los agentes orales?

- La metformin usualmente se mantiene porque ayuda a evitar aumento de peso y disminuye requerimientos de insulina
- Usualmente se suspenden los secretagogos ya que indica agotamiento pancreático
- Análogos GLP-1?

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Cómo hacer el switch de insulinas humanas a análogos basales?

- NPH a basal
  - Reducir 20% la dosis (para evitar hipoglicemias)
  - Titular cada 3 días
- Esquemas intensificados con simple y NPH
  - De la dosis total, 50% corresponde a efecto basal
    - Reducir 10%
  - El otro 50% corresponde a bolos
    - Pasar a análogos ultrarápidos

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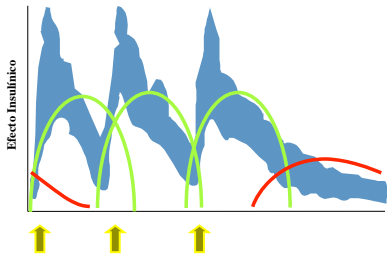
3 dosis simple + 1 dosis NPH



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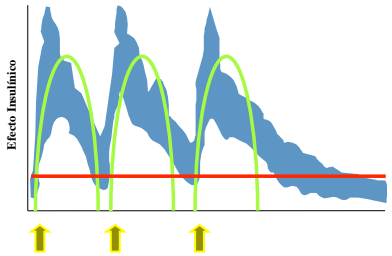
Chen-Ku CH. AMPMD. 2012;138

3 dosis aspart + 1 detemir



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Chen-Ku CH. AMPMD. 2012;138

HAY ALGÚN BENEFICIO EN PASAR A INSULINAS ANÁLOGAS?

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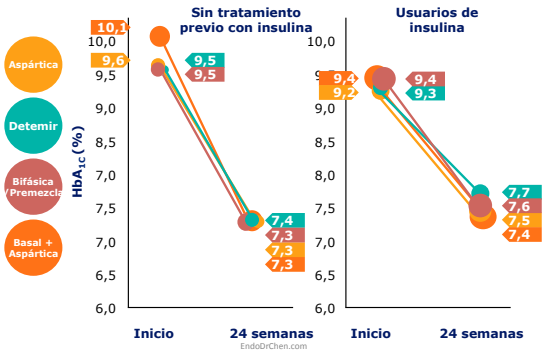
Resultados en HbA_{1c} por tipo de insulina



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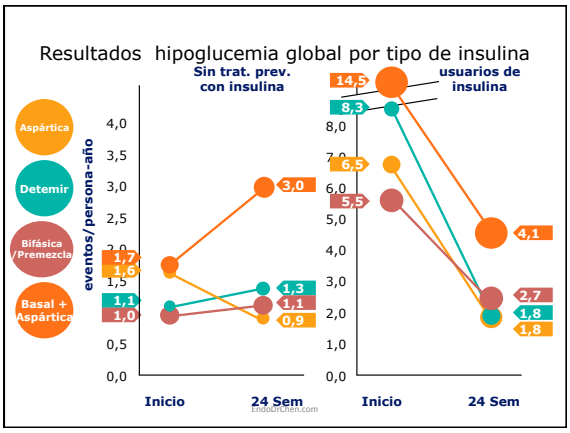

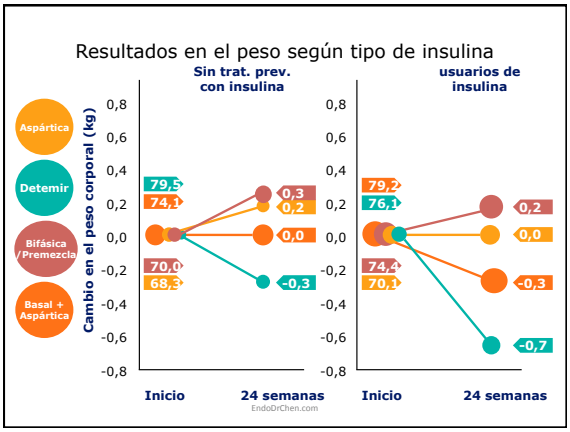

Conclusiones

- Hay diferentes formas de intensificar, pero la mayoría de los pacientes van a terminar en un esquema intensificado
- Los esquemas con un bolo inicial facilitan la transición de un esquema basal a uno intensificado
- Entre 50% y 60% de pacientes en esquemas intensificados van a lograr Hba1c <7%

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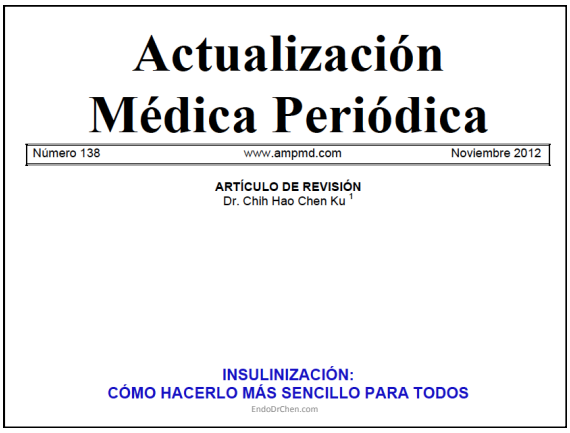
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Número 138
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Noviembre 2012
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Dr. Chih Hao Chen Ku [1]
INSULINIZACIÓN:
CÓMO HACERLO MÁS SENCILLO PARA TODOS
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info@menopausiacr.com iofla@iofbonehealth.org

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Centroamérica y el Caribe
28 al 30 de agosto, 2014
2014
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Almuerzos y refrigerios los tres días
Actividad social
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Dólares: 001-0293954-1
Cuenta Cliente: 15201001029395418
Asociación Pro Estudio de la Diabetes, Endocrinología y Metabolismo
Cédula jurídica: 3-002 53 30 62
PRECIO:
$ 225 antes del 16 de julio, 2014
$ 250 Inscripción
HORARIO:
De 7:30 a.m. - 4:00 p.m.
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Metamorfosis por la salud...
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INSCRÍBASE A: endocrinocr2014@medicos.cr
Tel. 2487 4318
ASOCIACIÓN PRO ESTUDIO DE LA DIABETES, ENDOCRINOLOGÍA Y METABOLISMO

Preguntas…

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