Conceptos actuales de insulinización orientado a cardiología

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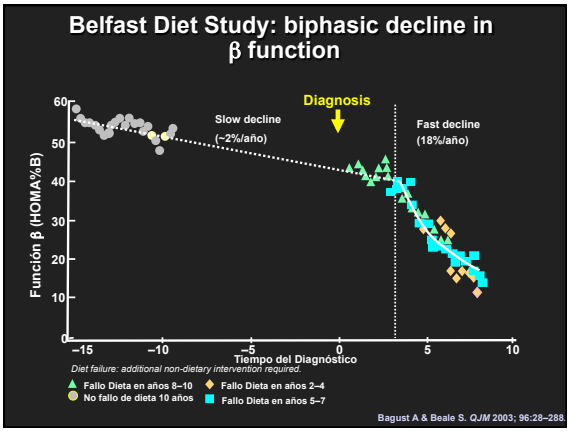
Conflictos de interés

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

Agenda

- Por qué insulinizar?
- Cuándo insulinizar?
- Beneficios más allá del control glicémico
- Diferencias entre insulinas basales
- Qué hacer cuando fallan las insulinas basales
- Manejo de hiperglicemia en el paciente agudo (emergencias, unidad coronaria)



Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials

Study	Microvasc		CVD		Mortality	
UKPDS	↓	↓	↔	↓	↔	↓
DCCT / EDIC*	↓	↓	↔	↓	↔	↔
ACCORD	↓		↔		↑	
ADVANCE	↓		↔		↔	
VADT	↓		↔		↔	

Kendall DM, Bergenstal RM. © International Diabetes Center 2009

UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:854.
Holman RR et al. *N Engl J Med*. 2008;359:1577. DCCT Research Group. N Engl J Med 1993;329:977.
Nathan DM et al. *N Engl J Med*. 2005;353:2643. Gerstein HC et al. *N Engl J Med*. 2008;358:2545.
Patel A et al. N Engl J Med 2008;358:2560. Duckworth W et al. N Engl J Med 2009;360:129. (erratum: Moritz T. *N Engl J Med* 2009;361:1024)

Initial Trial
Long Term Follow-up
* in T1DM

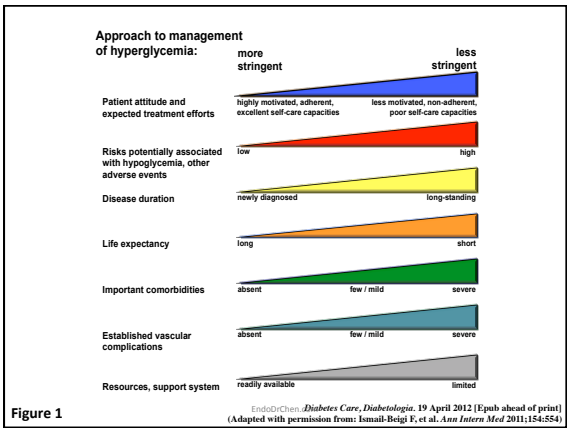
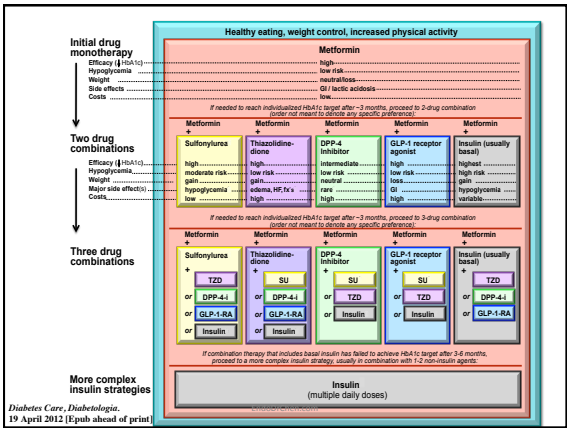


Figure 1

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)



Diabetes Care, Diabetologia.
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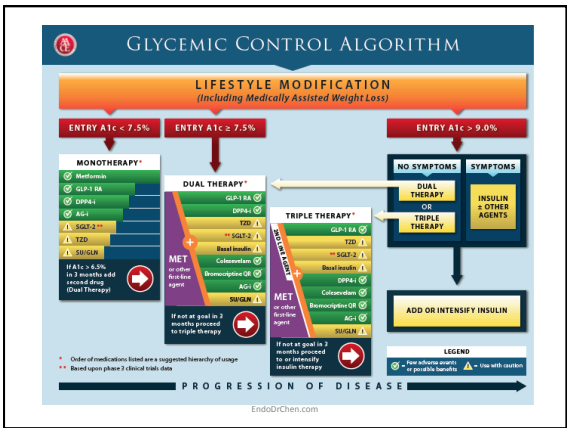
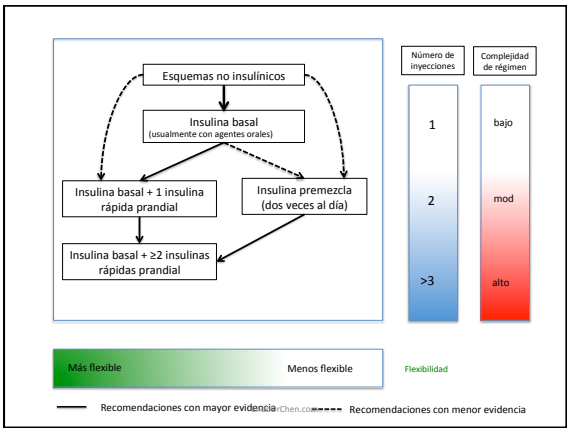
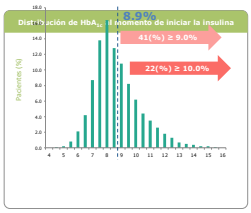




Existe la necesidad de un inicio más temprano de la insulina - HbA_{1c} basal



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

Cuándo empezar con una insulina basal?

- Debut?
- Terapia de segunda línea?
- Terapia de tercera línea luego de 2 agentes orales?

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INSULINA COMO TERAPIA PRIMERA LÍNEA

Diseño

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

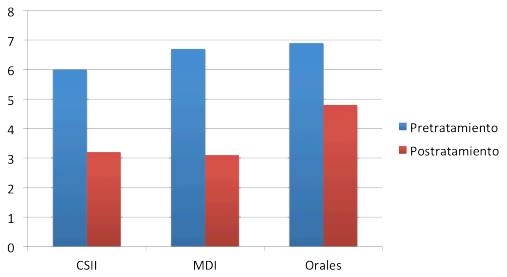
Weng J. Lancet. 2008;371:1753

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)

Weng J. Lancet. 2008;371:1753

HOMA-IR



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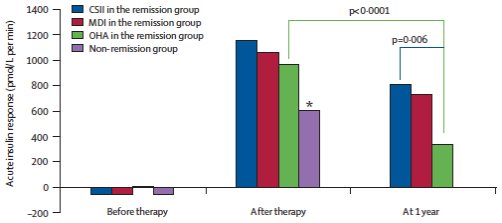
Weng J. Lancet. 2008;371:1753

Secreción aguda de insulina



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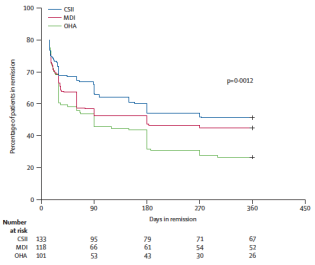
Weng J. Lancet. 2008;371:1753

Pacientes en remisión



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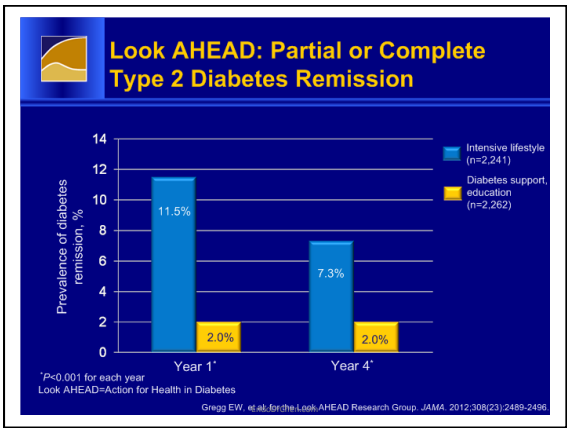
Weng J. Lancet. 2008;371:1753



Participants (Key Inclusion Criteria)

- **Age ≥ 50 yrs** *AND*
- **Dysglycemia** *AND*
  - *EITHER* IFG or IGT or new type 2 DM by OGTT
    [i.e. FPG ≥ 110 (6.1); or 2 Hr PG ≥ 140 (7.8)]
  - *OR* prior type 2 DM @ stable dose ≥ 10 wks & …
    - on no OADs … + HbA1c < 9.0%
    - < half-max 1 OAD + HbA1c < 8.5%
    - ≥ half-max 1 OAD + HbA1c < 8.0%
- **High CV Risk**
  - *EITHER* Prior MI, stroke, revasc, angina + doc. ischemia
  - *OR* MA, proteinuria, LVH, 50% art. stenosis, ABI < 0.9

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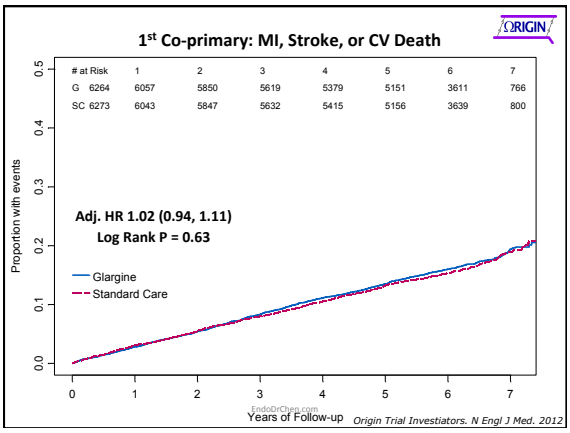
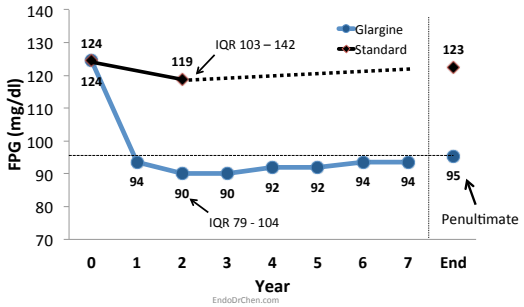
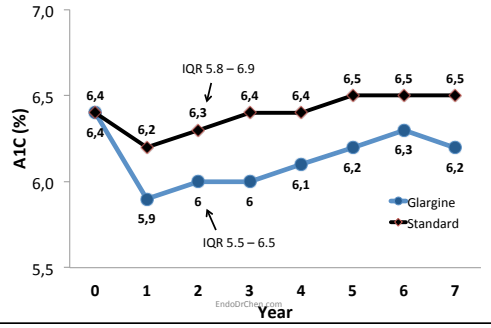


Median FPG (Conventional Units)



Median A1C Levels



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

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Numerically larger HbA1c difference with insulin glargine vs standard care in those with baseline HbA1c ≥6.4%

- In participants with baseline HbA1c ≥6.4%, the median HbA1c difference was 0.33% with insulin glargine vs standard care (P<0.00001)
- In participants with baseline HbA1c <6.4%, the median HbA1c difference was 0.22% with insulin glargine vs standard care (P<0.00001)

	HR for microvascular outcome (95% CI)	Median (IQR) HbA1c difference post-randomisation, %		Median HbA1c difference between groups, %
		Insulin glargine	Standard care	
HbA1c <6.4%	1.07 (0.95 to 1.20)	+0.06 (-0.21; +0.40)	+0.27 (-0.02; +0.64)	-0.22; P<0.0001
HbA1c ≥6.4%	**0.90 (0.81 to 0.99)**	-0.65 (-0.16; -0.91)	-0.33 (-0.83; +0.13)	**-0.33; P<0.0001**

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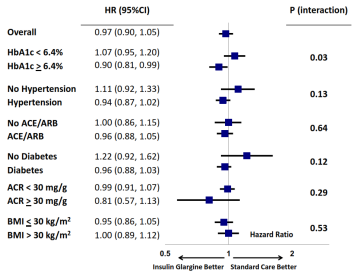
No difference in microvascular outcome in other subgroups



- Allocation to insulin glargine had no effect on the microvascular outcome in other subgroups

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INSULINAS BASALES COMO TERAPIA SEGUNDA LÍNEA

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Continuous coverage of the American Diabetes Association 72nd Scientific Sessions

EASIE Trial: Design

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

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

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

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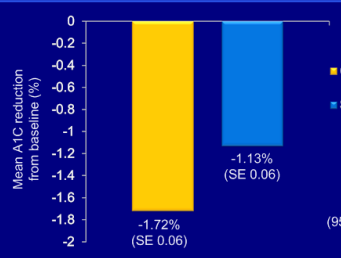
EASIE Trial: *Efficacy Population* Primary Outcome at Week 24— Change in A1C from Baseline

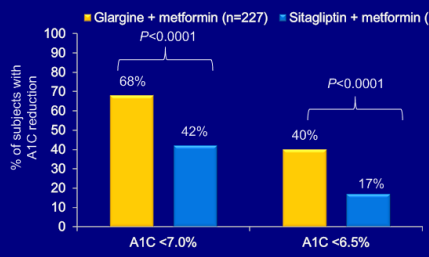


SE=standard error
EASIE=Evaluation of insulin glargine versus Sitagliptin in Insulin-naïve patients

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

Continuous coverage of the American Diabetes Association 72nd Scientific Sessions

EASIE Trial: *Efficacy Population* A1C <7.0% and <6.5% Week 24



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

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

EL ESCENARIO USUAL, COMO TERAPIA DE 3RA LÍNEA LUEGO DE 2 AGENTES ORALES

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QUIÉN ES LA RESPONSABLE DE LA HIPERGLICEMIA?

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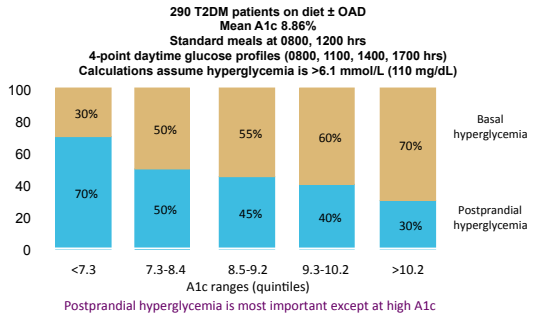
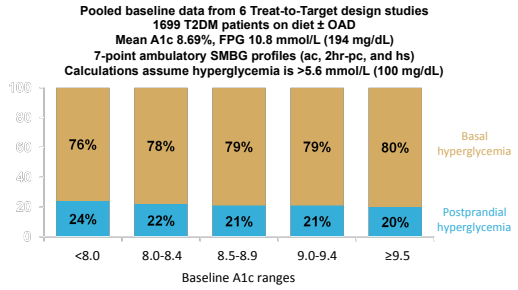
Basal and postprandial contributions to hyperglycemia by A1c range



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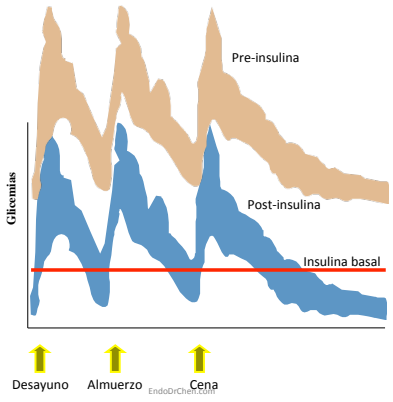
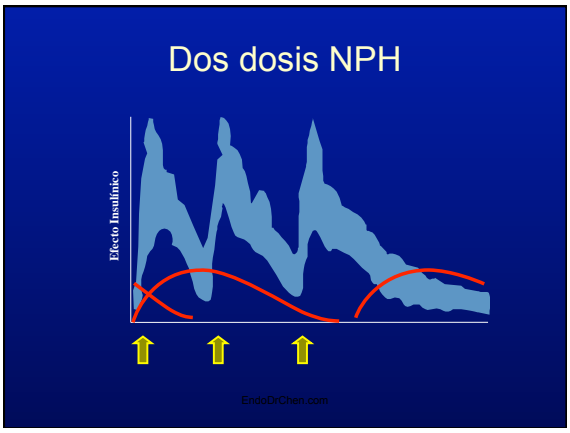
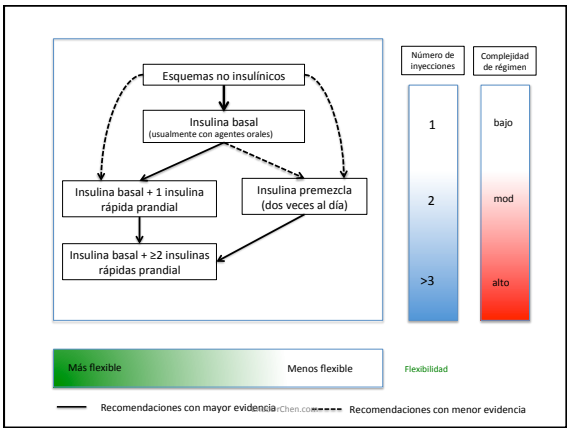
Riddle et al, Diabetes Care 34:2508–2514, 2011







Insulinas basales

- Cuáles agentes disponibles hay?
  - NPH
  - Glargina
  - Detemir

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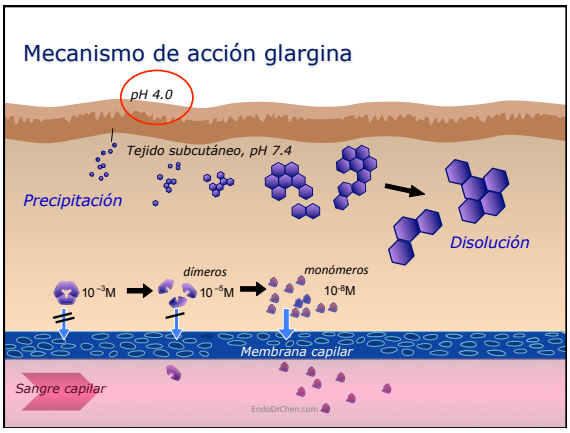
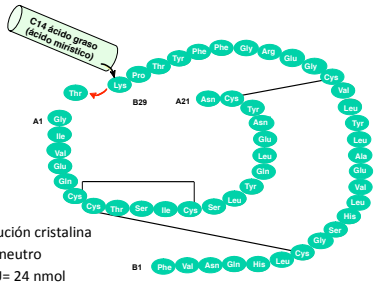


Insulina detemir

LysB29(N-tetradecanoyl)des(B30)



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

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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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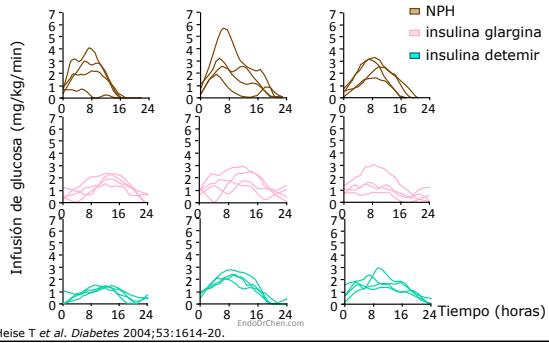
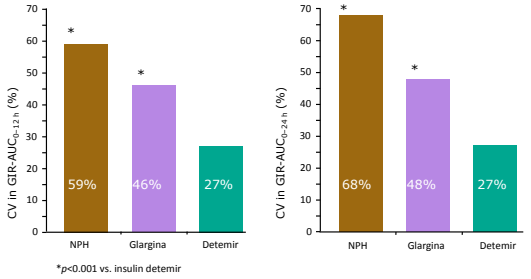
Menor variabilidad de efecto intra-individual: análogos vs NPH



Heise T *et al*. *Diabetes* 2004;53:1614-20.

Variabilidad con análogos y NPH



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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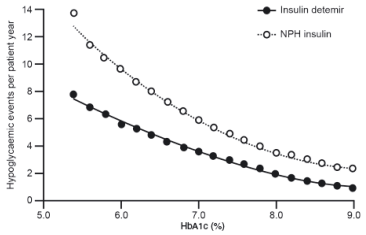
NPH vs detemir en DM-2: hipoglicemias



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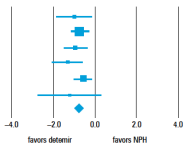
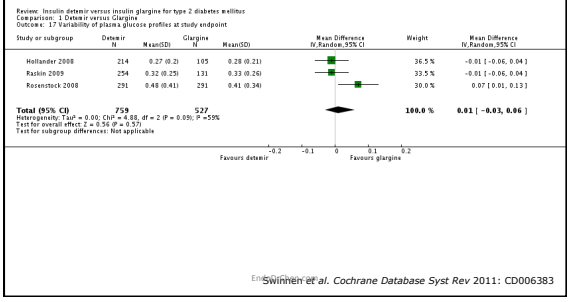
Diferencias en peso

Study	Sample size: detemir	Sample size: NPH	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
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



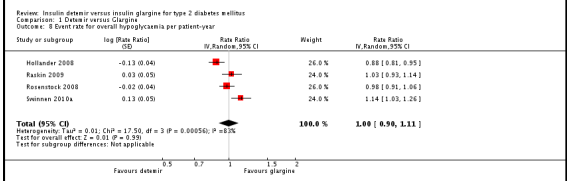
EndoDrChen.com Szypowska A. Por Arch Med Wewn. 2011;121:737

Cochrane: variabilidad en perfil glicémico



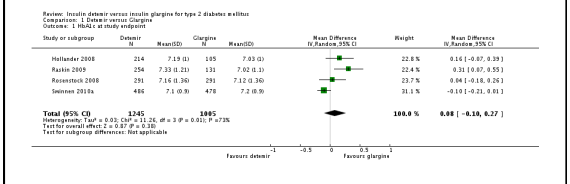
Swinnen et al. *Cochrane Database Syst Rev* 2011: CD006383

Cochrane: tasa de hipoglicemias



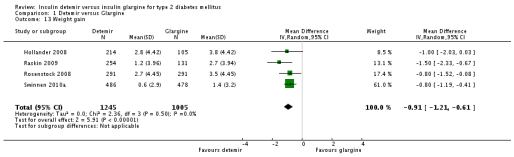
Swinnen et al. *Cochrane Database Syst Rev* 2011: CD006383

Cochrane: cambios en Hba1c



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

Cochrane: aumento de peso



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MECANISMOS DIFERENCIALES EN PESO

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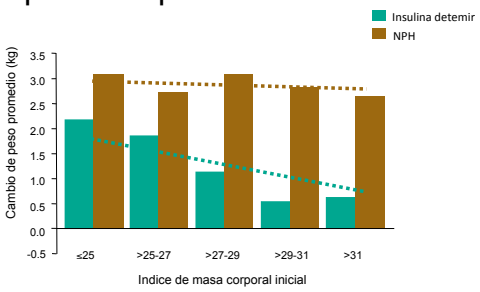
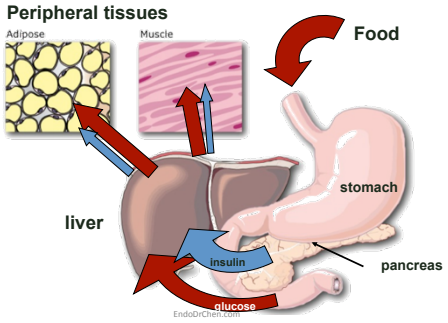
Detemir: menor ganancia de peso en pacientes obesos



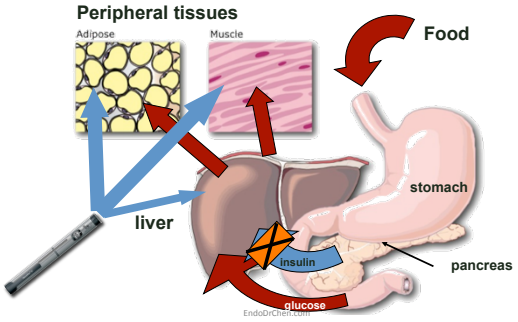
Hermansen *et al. Diabetes* 2005;54(Suppl 2):OR271

EndoDrChen.com

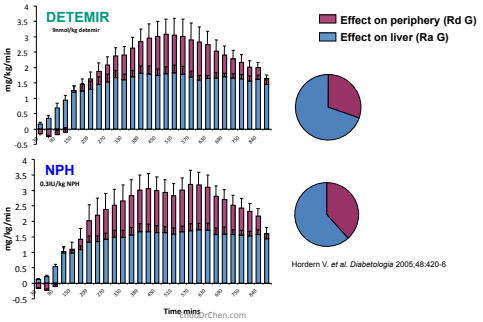
The 'Liver hypothesis': Systemic insulin in normal physiology



The 'Liver hypothesis':
Distribution of exogenous insulin

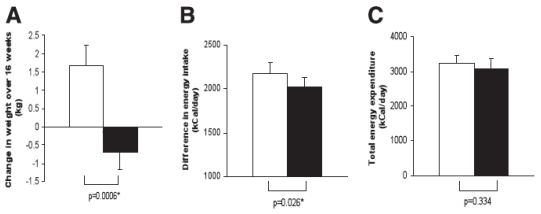


Relative peripheral and hepatic effects of detemir and NPH



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

Por qué las diferencias en peso?



Zachariah S. Diabetes Care. 2011;34:1487

Efectos centrales de la insulina

- Insulina actúa como señal de saciedad
- La administración intranasal de insulina en mujeres produce saciedad
- El ácido graso del detemir puede facilitar su paso al cerebro a través de la BHE

Van Golen LW. Diabetes Care. 2013;36:4050

Estudios de flujo cerebral: NPH vs detemir

	CMR_{glu}			CBF		
	NPH	Detemir	*P*	NPH	Detemir	*P*
Total gray matter	0.15 ± 0.02	0.16 ± 0.02	0.2	0.31 ± 0.05	0.34 ± 0.05	0.06
Regions of interest						
OFC L				0.38 ± 0.06	0.40 ± 0.08	0.2
OFC R				0.39 ± 0.07	0.41 ± 0.08	0.3
Insula L				0.40 ± 0.07	0.44 ± 0.09	0.04
Insula R				0.39 ± 0.08	0.43 ± 0.08	0.05
Putamen L				0.40 ± 0.07	0.44 ± 0.09	0.04
Putamen R				0.40 ± 0.06	0.45 ± 0.09	0.02
Caudate L				0.34 ± 0.06	0.37 ± 0.08	0.08
Caudate R	0.19 ± 0.04	0.20 ± 0.03	0.2	0.31 ± 0.06	0.36 ± 0.09	0.02
Striatum				0.37 ± 0.06	0.42 ± 0.09	0.02
Thalamus L				0.39 ± 0.06	0.43 ± 0.07	0.07
Thalamus R				0.38 ± 0.06	0.43 ± 0.08	0.04
Cingulate ant L				0.36 ± 0.07	0.39 ± 0.09	0.03
Cingulate ant R				0.38 ± 0.07	0.41 ± 0.09	0.04
Cingulate post L				0.38 ± 0.06	0.41 ± 0.08	0.1
Cingulate post R				0.39 ± 0.06	0.43 ± 0.08	0.02

Todas estas zonas son aquellas relacionadas a regulación de apetito y recompensa

Al final del estudio, hubo mayor sensación de saciedad y pérdida de peso de 0.7 kg a favor de detemir

Data are mean ± SD un… min^{-1}. CMR_{glu} in $\mu mol \cdot cm^{-3} \cdot min^{-1}$.
Paired data, n = 24 for CMR_{glu} and n = 18 for CBF. ant, anterior; L, left; OFC, orbitofrontal cortex; post, posterior; R, right.

Van Golen LW. Diabetes Care. 2013;36:4050

INICIO Y TITULACIÓN DE DOSIS

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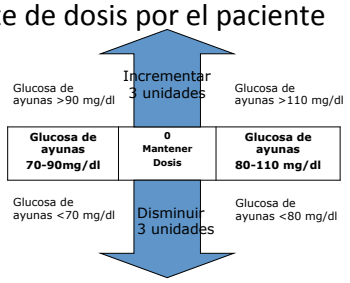
Insulina basal: Ajuste de dosis por el paciente



•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

EndoDrChen.com

Diabetes Obes Metab. Jun 2009;11(6):623-631

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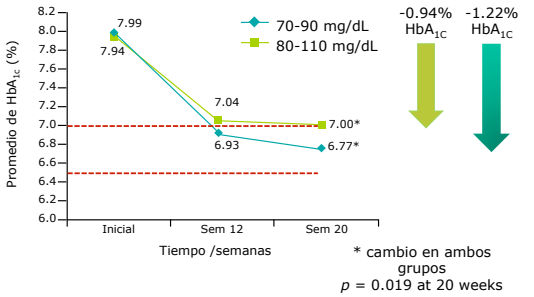
Ajuste de dosis por el paciente mejoría en HbA_{1c}: estudio Titrate



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

Basal Insulin: Percent of patients with HbA1c < 7%

29 trials, with 17,588 patients

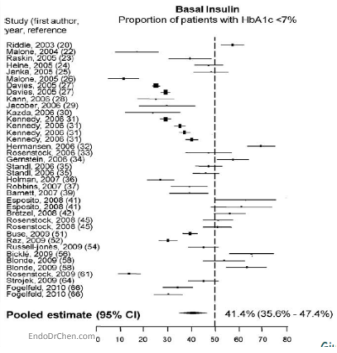
HbA1c < 7% was achieved in 41.4% (95% CI, 35.6–47.4%).

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

QUÉ PASA SI PERSISTE CON HBA1C ALTO A PESAR DE TENER GLICEMIA EN AYUNAS ÓPTIMO?

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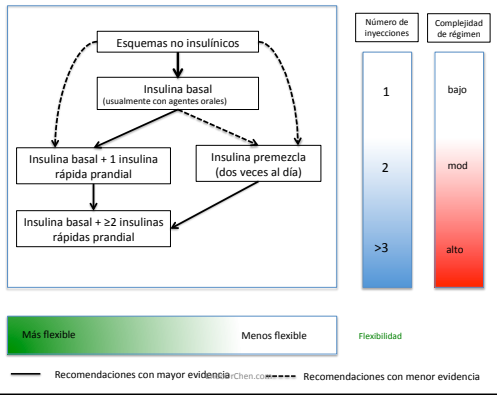

Consideraciones

- Realmente no hay diferencias clínicamente significativas entre las 3 disponibles:
  - Lispro
  - Aspart
  - Glulisina
- La modificación de las 3 insulinas le permite evitar formar hexámeros y por lo tanto la velocidad de absorción es mayor

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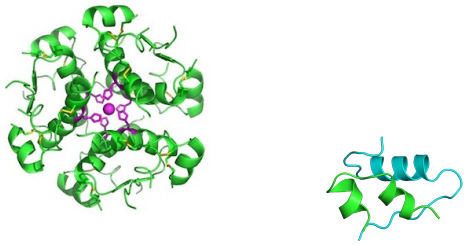

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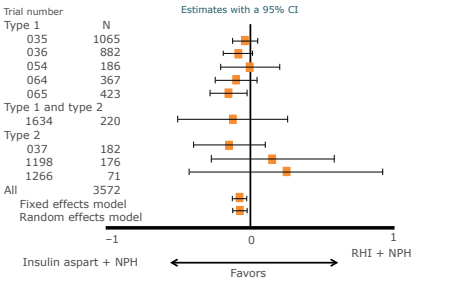
Overall change in A1C with insulin aspart



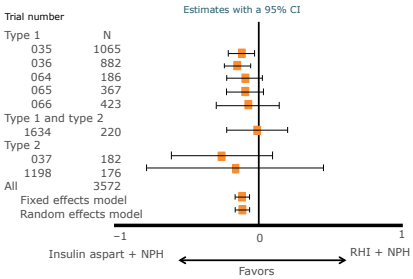
Data from one trial (066) are missing as no measurements were done in the first 16 weeks

RHI, regular human insulin

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

EndoDrChen.com

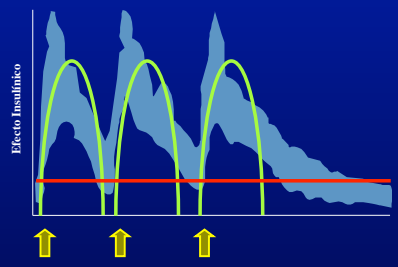
Nocturnal hypoglycemic episodes with insulin aspart



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

EndoDrChen.com

3 dosis ultrarápida + 1 basal



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Optimizando e intensificando

Optimice la dosis de insulina basal

Dosis prandial única	Dosis prandial secuencial	Cobertura prandial completa	Terapia con premezclas de insulinas
OPAL	STEPwise	4T	PREFER
		Fix *vs* Flex	
	Basal bolo secuencial vs completa		

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

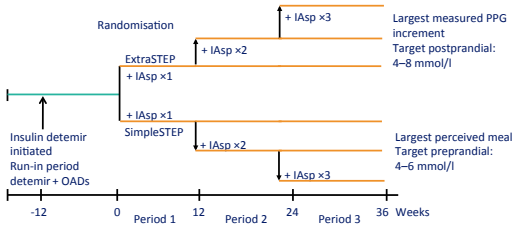
Meneghini *et al. Diabetes* 2010;59(Suppl. 1):A199

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

EndoDrChen.com

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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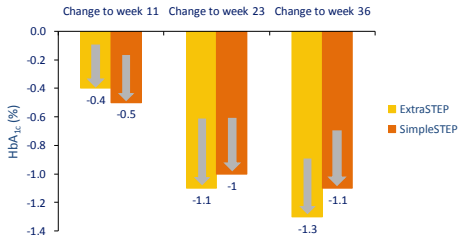
STEPwise™: change in HbA_{1c}



Change was adjusted for baseline HbA_{1c}

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

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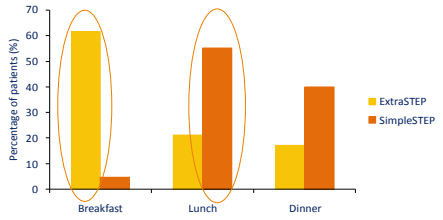
STEPwise™: addition of first bolus injection



ExtraSTEP group added insulin based on PPG measurement

SimpleSTEP group added insulin based on patient assessment

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

Treatment intensification with stepwise addition of prandial insulin aspart boluses compared with full basal-bolus therapy (FullSTEP Study): a randomised, treat-to-target clinical trial

Helena W Rodbard, Virginia E Visco, Henning Andersen, Line C Hiort, David H W Shu

Lancet Diabetes Endocrinol
2014; 2: 30–37

EndoDrChen.com

Procedimientos

- Basal bolo:
  - 2 u de insulina aspart con cada comida
- Stepwise:
  - 4 u insulina aspart con la mayor comida agregando un segundo bolo a la semana 11 o tercer bolo a la semana 22 si hba1c >7%
  - Mayor comida: definido como la comida con mayor contenido de carbohidrato determinado por el paciente

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Titulación

- Dosis de insulina se ajustaban según automonitoreo antes de las comidas y hora sueño
- Algoritmo para autotitulación para alcanzar una glicemia entre 4.0-7.2 mmol/L (72-130 mg/dl) antes de la siguiente comida
- En el grupo Stepwise se titulaba únicamente según la glicemia antes de la siguiente comida con la que se aplicaba la insulina

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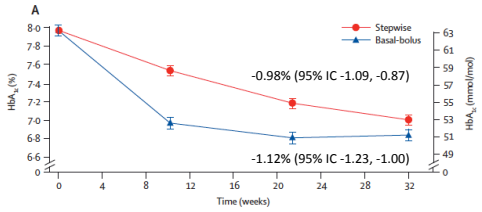
Eficacia en Hba1c



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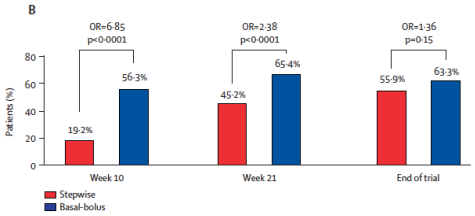
Pacientes que alcanzaron Hba1c <7%



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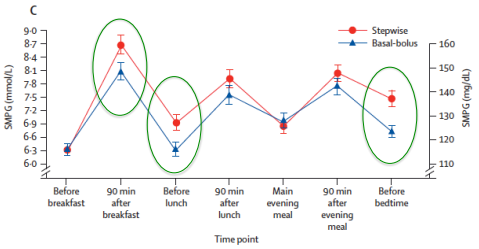
Perfil de glicemias al final del estudio



EndoDrChen.com

Requerimientos de insulina

- Basal bolus: 0.6 u/kg de bolo
- Stepwise: 0.5 u/kg de bolo
  - 17% requirieron un sólo bolo
  - 27% requirieron 2 bolos
  - 40% requirieron 3 bolos
- En ambos grupos, la insulina basal fue 0.6 u/kg

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Satisfacción

- En general mayor satisfacción con el stepwise comparado con el basal bolo, menos carga del tratamiento y mayor percepción de eficacia

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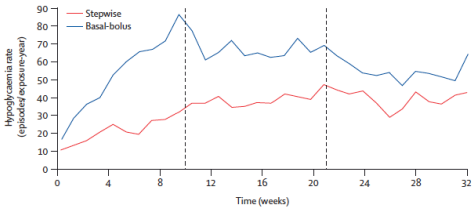
Hipoglicemia



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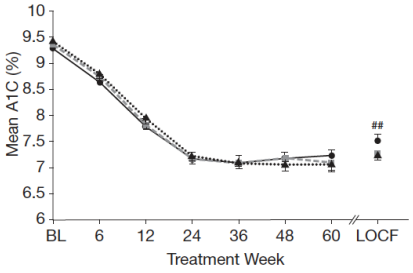
Reducción en Hba1c



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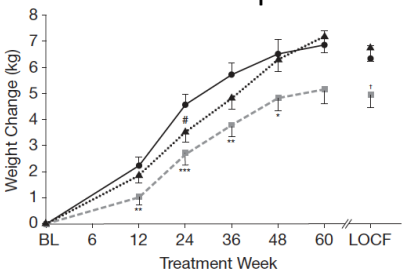
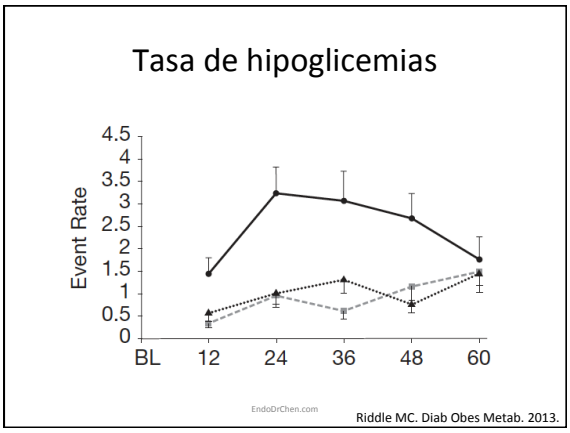
Riddle MC. Diab Obes Metab. 2013.

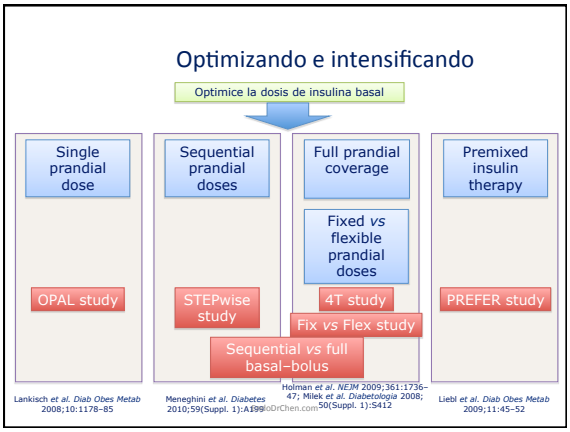
Aumento de peso

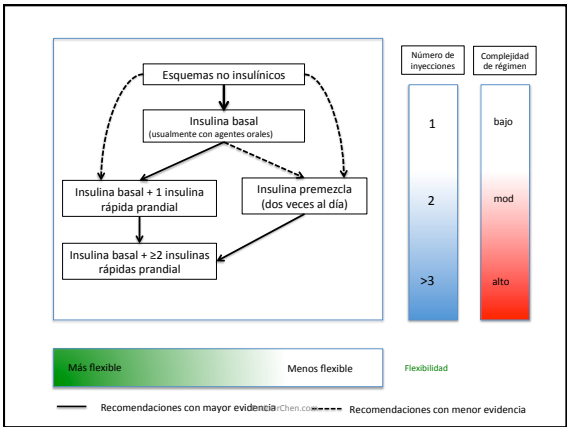


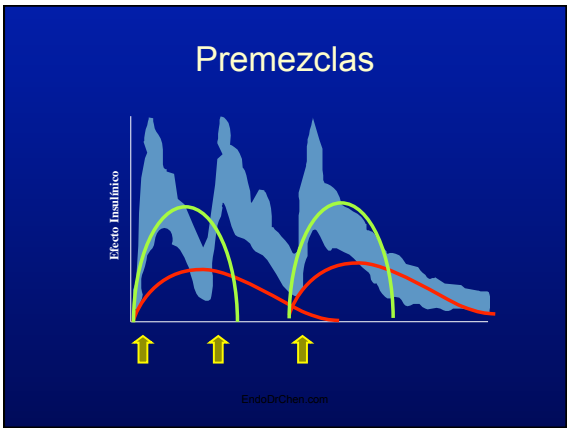
EndoDrChen.com

Riddle MC. Diab Obes Metab. 2013.


Tasa de hipoglicemias
Event Rate
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
BL
12
24
36
48
60
EndoDrChen.com
Riddle MC. Diab Obes Metab. 2013.

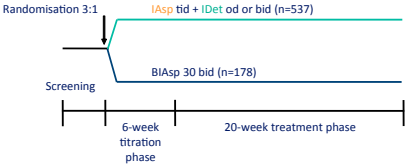

Optimizando e intensificando
Optimice la dosis de insulina basal
Single prandial dose
OPAL study
Sequential prandial doses
STEPwise study
Full prandial coverage
Fixed vs flexible prandial doses
4T study
Fix vs Flex study
Sequential vs full basal–bolus
Premixed insulin therapy
PREFER study
Lankisch et 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
EndoDrChen.com


Esquemas no insulínicos
Insulina basal
(usualmente con agentes orales)
Insulina basal + 1 insulina rápida prandial
Insulina premezcla (dos veces al día)
Insulina basal + ≥2 insulinas rápidas prandial
Número de inyecciones
1
2
>3
Complejidad de régimen
bajo
mod
alto
Más flexible
Menos flexible
Flexibilidad
Recomendaciones con mayor evidencia
Recomendaciones con menor evidencia
EndoDrChen.com



PREFER: study design

Inclusion criteria:
One or two OADs without insulin
One or two OADs with od NPH/glargine
7%≤HbA_{1c}≤12%



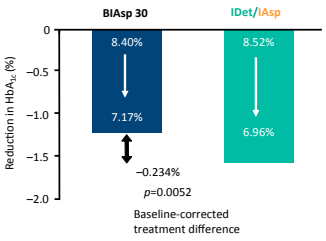
OADs were discontinued in both arms

OAD, oral antidiabetic drug; od, once daily; NPH, neutral protamine Hagedorn; glargine, insulin glargine; HbA_{1c}, glycated haemoglobin A_{1c}; tid, three times daily

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

EndoDrChen.com

PREFER: HbA_{1c} reduction



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

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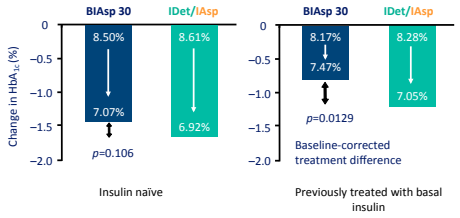
PREFER: HbA_{1c} reduction in insulin-naïve vs. insulin-treated patients



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

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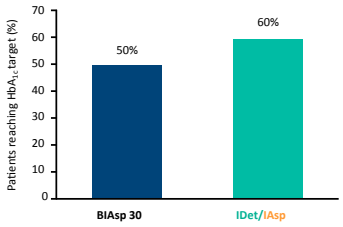
PREFER: percentage of patients achieving HbA_{1c}<7.0%



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

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PREFER: rate of hypoglycaemia

Hypoglycaemia	BIAsp 30	IDet/IAsp
Major (n)	0	5
Minor* (% patients)	28%	31%
Nocturnal minor (% patients)	7.3%	7.4%
Incidence# of minor (events/subject/year)	1.9	1.8
Incidence of nocturnal minor (events/subject/year)	0.5	0.7

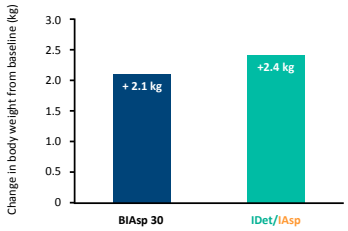
Between-treatment differences not significant

*Confirmed by blood glucose<3.1 mmol/l
#Calculated for the final 20 weeks of the study

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

EndoDrChen.com

PREFER: change in body weight



Baseline*: 88.4 kg 89.4 kg

*ITT population (all subjects who received at least one treatment dose)

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

EndoDrChen.com

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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Conclusiones

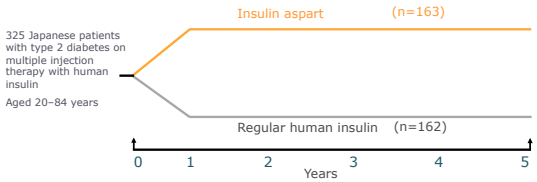
- La adición de bolos secuenciales es no inferior al regimen basal bolos en diabetes tipo 2:
  - Con menor riesgo de hipoglicemia
  - Mayor satisfacción por parte del paciente
- Dura un poco más en alcanzar la meta
- Alrededor del 60% de los pacientes se logran controlar con 1-2 bolos de insulina prandial sin tener que recurrir a un esquema completo basal-bolo

EndoDrChen.com

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

The effect of insulin aspart on cardiovascular disease

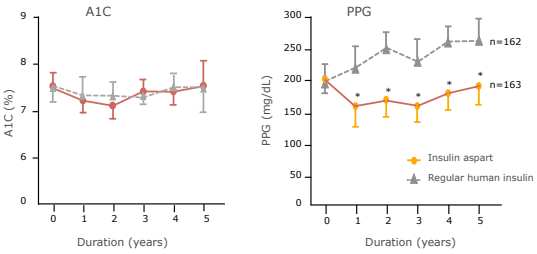
- Aim: to investigate the morbidity and mortality by cardiovascular disease in patients with type 2 diabetes treated either with insulin aspart or regular human insulin
- A prospective, randomized, open-label, blinded endpoint trial
- Intermediate/long-acting insulin was added when necessary. The primary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

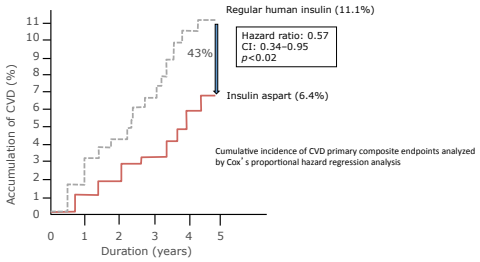
A1C and postprandial glucose control



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)

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



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

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*

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

Metodología

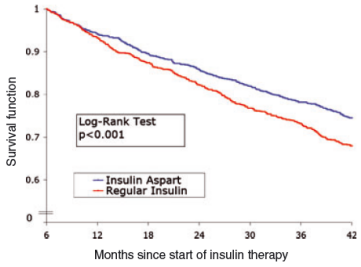
- Análisis de bases de datos en atención primaria de Alemania
- Sólo pacientes que han usado insulina aspart o insulina simple, no permitía combinaciones
- Pacientes a quienes se les prescribió por primera vez la insulina

Rathman W. 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

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

Eventos cardiovasculares

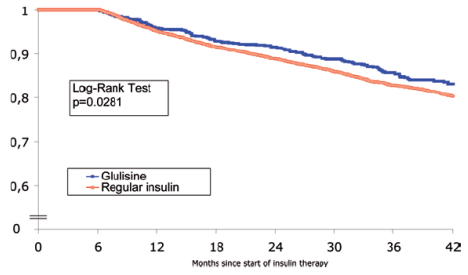


Rathman W. Diab Obes Metab. 2013;15:358

Variables	Insulin glulisine	Regular insulin
n	952	11,157
Age (y)	60.7 (11.2)*	64.7 (10.9)*
Observational period prior to the index date (y)	2.6 (3.7)*	1.6 (3.0)*
Males (%)	54.3	52.4
Diabetologist treatment (%)	43.0	44.5
Private health insurance (%)	9.8*	3.5*
Region (West Germany) (%)	71.5*	68.2*
Urban residency[a] (%)	26.5	25.6
Antidiabetic treatment[b] (%):		
Any oral antidiabetics	41.3*	33.1*
Sulfonylureas	18.3	16.4
Biguanides	34.0*	27.2*
Acarbose	7.4*	4.2*
NPH insulin	25.6*	64.6*
Long-acting insulin analogs	74.5*	30.7*
Co-Medication[c] (%)		
Antihypertensives	55.5	56.3
Lipid-lowering drugs	32.3	30.1
Antithrombotic agents	17.7*	21.7*

Kress S. Int J Clin Pharm Ther. 2012;50:821

Sobrevida libre de enfermedad cardiovascular



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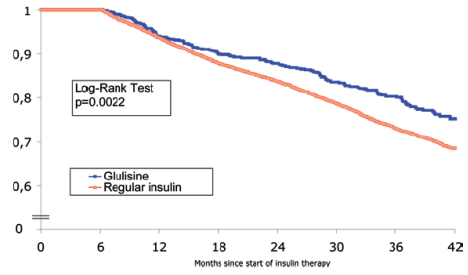
Kress S. Int J Clin Pharm Ther. 2012;50:821

Sobrevida libre de enfermedad microvascular



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Kress S. Int J Clin Pharm Ther. 2012;50:821

Caraterísticas basales

Variable	IA N = 2 764[b]	HI N = 4 193[b]	p-value[c]
duration of follow-up on IA or HI treatment from index date [days], mean (SD)	1 891 (698)	1 835 (608)	0.266
age [years], mean (SD)	61.0 (11.3)	64.7 (10.5)	< 0.001
males [%]	56.9	53.5	0.006
private health insurance [%]	8.0	3.3	< 0.001
treated by diabetologist [%]	23.5	22.7	0.424
treated in West Germany [%]	73.8	71.3	0.022
urban residency (> 100 000 inhabitants) [%]	23.6	22.8	0.411
type of insulin treatment [%]			
multiple daily injection therapy	88.2	86.0	0.008
use of long-acting insulin analogue	53.6	29.8	< 0.001
HI/IA treatment before the index date[d]	25.7	9.7	< 0.001
concomitant oral medications* [%]			
biguanides	50.5	53.2	0.028
sulfonylurea	26.1	36.5	< 0.001
diuretics	46.7	52.8	< 0.001
β-blockers	49.6	55.2	< 0.001
calcium channel blockers	35.2	38.1	0.016
ACE inhibitors	57.6	62.5	< 0.001
angiotensin II receptor antagonists	28.2	26.7	0.177
lipid-lowering agents	52.1	52.3	0.907
acetyl salicylic acid	35.1	38.8	0.002

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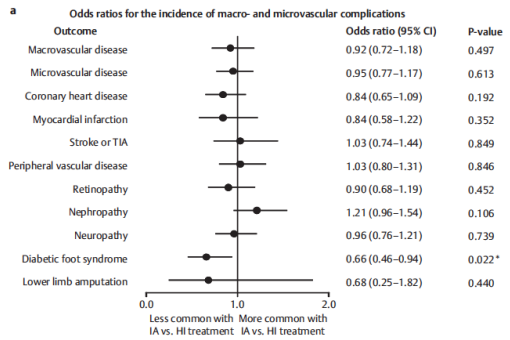
Rathman W. Exp Clin Endocrinol Diabetes. 2014;122:92



Rathman W. Exp Clin Endocrinol Diabetes. 2014;122:92

GLICEMIA EN AYUNAS O POSTPRANDIALES: QUIÉN DEBE SER EL PRIMER OBJETIVO?

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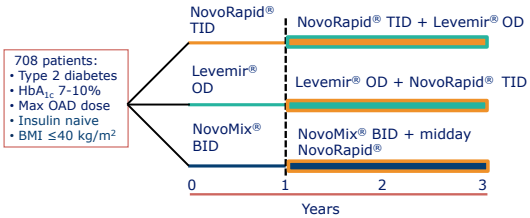
3 year study design to investigate insulin initiation and intensification



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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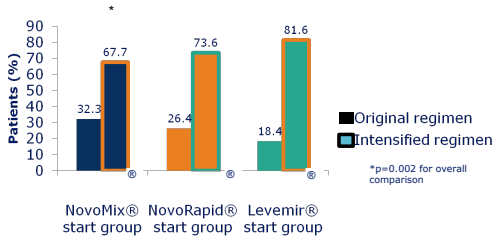
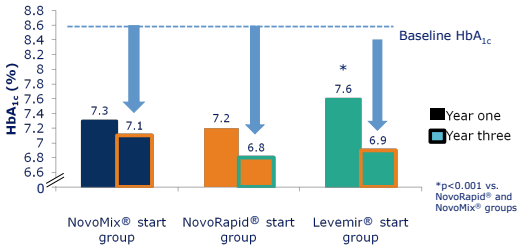
The majority of patients were intensified with a second insulin

74.3% of patients had an intensified regimen



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

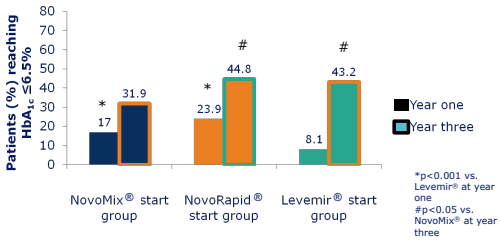
Sustainable HbA_{1c} control in all three arms



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

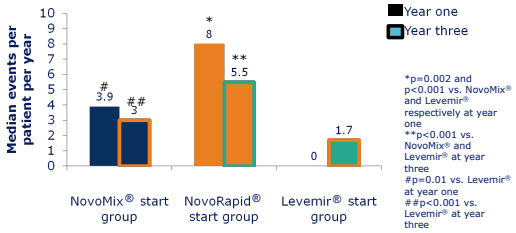
Adapted from Holman *et al. NEJM* 2007; 357:1716-30

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



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

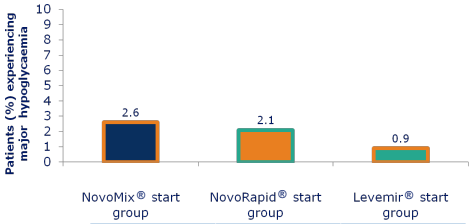
Low median rates of minor hypoglycaemia



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

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

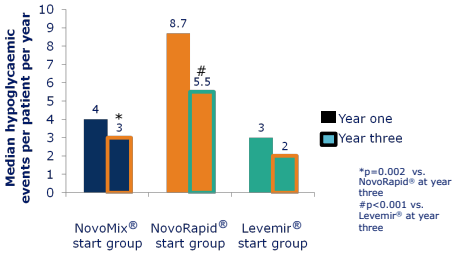
Low proportion of patients experiencing major hypoglycaemia over 3 years



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

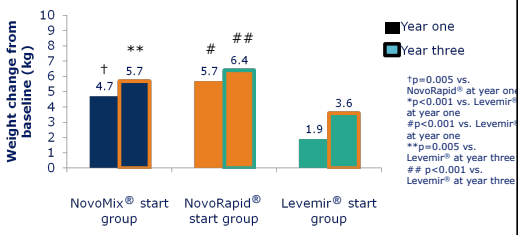
Holman *et al. NEJM* 2007; 357:1716-30

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

HEART 2D

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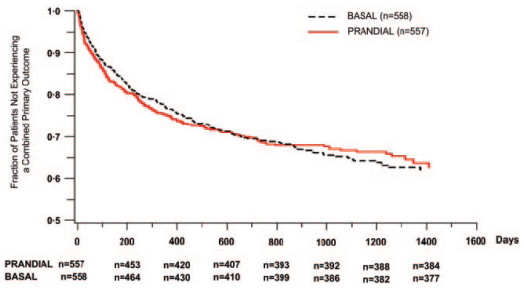

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Raz I. Diabetes Care. 2009;32:381

HAY ALGÚN BENEFICIO EN PASAR A INSULINAS ANÁLOGAS?

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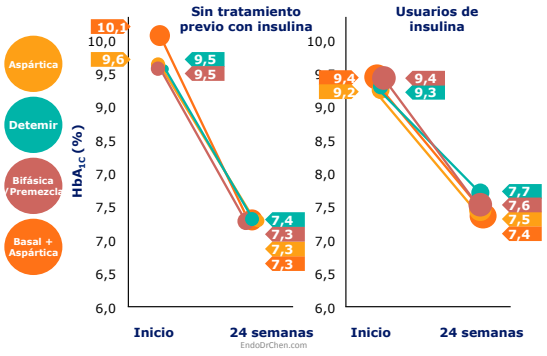
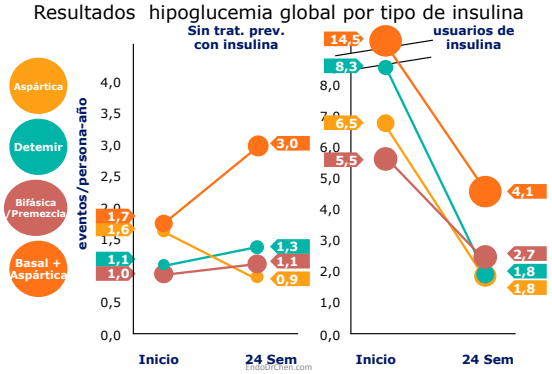
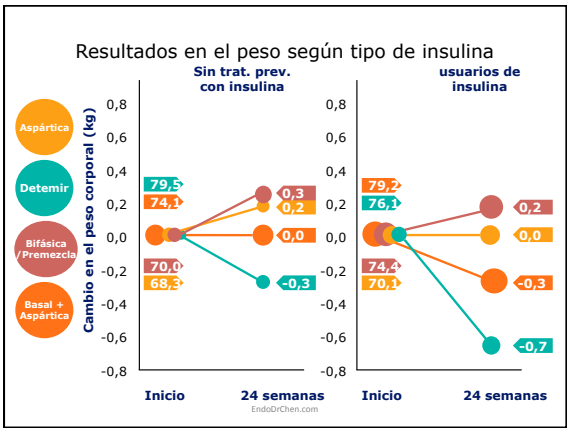
Resultados en HbA_{1c} por tipo de insulina



Resultados hipoglucemia global por tipo de insulina





QUÉ HACER EN EL PACIENTE AGUDO?

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Consideraciones

- Varios contextos:
  - Conocido DM que se presenta descompensado
  - Paciente no conocido DM que presenta hiperglicemia (“de stress”)
- Independientemente del dilema diagnóstico…. cuándo tratar?
  - Cuando la hiperglicemia es persistente

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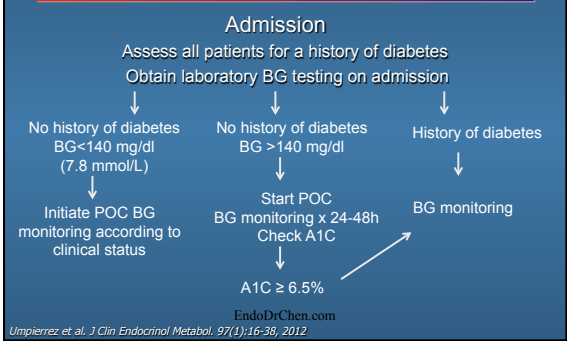
Diagnosis and recognition of hyperglycemia and diabetes in the hospital setting

1. Assess all patients for a history of diabetes. (1)
2. All patients, independent of a prior diagnosis of diabetes, should have laboratory blood glucose testing on admission.(2)
3. Patients without a history of diabetes with BG > 140 mg/dl (7.8 mmol/liter) should be monitored with POC testing for 24 to 48 h. Those with BG > 140 mg/dl require ongoing POC testing. (1)
4. Patients receiving therapies associated with hyperglycemia (i.e., corticosteroids) be monitored with POC testing for 24 to 48 h. Those with BG >140 mg/dl require ongoing POC testing. (1)
5. Patients with known diabetes or with hyperglycemia should have a HbA1C test if this has not been performed in the preceding 2–3 months.(1)

Umpierrez et al. J Clin Endocrinol Metabol. 97(1):16-38, 2012

Diagnosis & recognition of hyperglycemia and diabetes in the hospital setting



Umpierrez et al. J Clin Endocrinol Metabol. 97(1):16-38, 2012

A1C for Diagnosis of Diabetes in the Hospital

- Implementation of A1C testing can be useful:
  - assist with differentiation of newly diagnosed diabetes from stress hyperglycemia
  - assess glycemic control prior to admission
  - assist designing an optimal regimen at the time of discharge
- HbA1c > 6.5% can be identified as having diabetes.

Moghissi ES, et al; AACE/ADA Inpatient Glycemic Control Consensus Panel. *Endocr Pract.* 2009;15(4).
Umpierrez et al, Endocrine Society Non-ICU Guideline. J Clin Endocrinol Metabol 97(1):16-38, 2012

Caveats – Using A1c

- Values altered with several conditions:
  - Hemoglobinopathies like sickle cell disease
  - High dose salicylates
  - Hemodialysis
  - Transfusions, iron deficiency anemia
- Analysis should be performed using a method certified by the National Glycohemoglobin Standardization program

JAMA 2006, 295:1688-1697.
Diabetes Care 2011 ADA Standards:34 (suppl 1): S11-61

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Glycemic Targets in Non-Critical Care Setting

1. Premeal BG target of <140 mg/dl and random BG <180 mg/dl for the majority of patients.(1)
2. Glycemic targets be modified according to clinical status. (2)
   - For patients who achieve and maintain glycemic control without hypoglycemia, a lower target range may be reasonable.
   - For patients with terminal illness and/or with limited life expectancy or at high risk for hypoglycemia, a higher target range (BG <200 mg/dl) may be reasonable.
3. To avoid hypoglycemia, reassess and modify diabetes therapy when BG values are ≤100 mg/dl. Modification of glucose-lowering treatment is usually necessary when BG values are <70 mg/dl.(2)

GE Umpierrez, R Hellman, MT Korytkowski, M Kosiborod, GA Maynard, VM Montori, JJ Seley, GV den Berghe. J Clin Endocrinol Metabol. 97(1):16-38, 2012

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Pharmacological Treatment of Hyperglycemia in Non-ICU Setting

Antihyperglycemic Therapy

SC Insulin
Recommended for most medical-surgical patients

OADs
Not Generally Recommended

Continuous IV Infusion
Selected medical-surgical patients

1. ACE/ADA Task Force on Inpatient Diabetes. Diabetes Care. 2006 & 2009
2. Umpierrez et al, Endocrine Society Non-ICU Guideline. J Clin Endocrinol Metabol 97: January 2012
3. Smiley et al. HospMed5:212–217, 2010

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Non-insulin therapies in the hospital

- Sulfonylureas are a major cause of hypoglycemia
- Metformin contraindicated in setting of decrease renal blood flow, surgery, and with use of iodinated contrast dye
- Thiazolidinediones associated with edema and CHF
- GLP1-directed therapies can cause nausea and have a greater effect on postprandial glucose

ACE/ADA Task Force on Inpatient Diabetes. Diabetes Care. 2006 & 2009
GE Umpierrez, R Hellman, MT Korytkowski, M Kosiborod, GA Maynard, VM Montori, JJ Seley, GV den Berghe. J Clin Endocrinol Metabol. 97(1):16-38, 2012

Pharmacologic Therapy in Non-ICU Setting

- Patients treated with insulin at home require scheduled SQ insulin therapy in the hospital (1)
- Avoid prolonged use of sliding scale insulin (SSI) as sole method for glycemic management in hyperglycemic patients with diabetes (2)
- Scheduled SQ insulin consists of basal or intermediate acting insulin in combination with RAI or Regular insulin administered before meals in patients who are eating(1)
- Include correction insulin as a component of scheduled SQ insulin for treatment of BG above desired range (2)

GE Umpierrez, R Hellman, MT Korytkowski, M Kosiborod, GA Maynard, VM Montori, JJ Seley, GV den Berghe. J Clin Endocrinol Metabol. 97(1):16-38, 2012

Insulin Therapy in patients with type 2 Diabetes

- D/C oral antidiabetic drugs on admission
- Insulin naïve: starting total daily dose (TDD):
  - 0.3 U/kg to 0.5 U/kg
  - Lower doses in the elderly and renal insufficiency
- Previous insulin therapy: reduce outpatient insulin dose by 20-25%
- Half of TDD as basal insulin given at the same time of day and half as rapid-acting insulin in three equally divided doses (AC)

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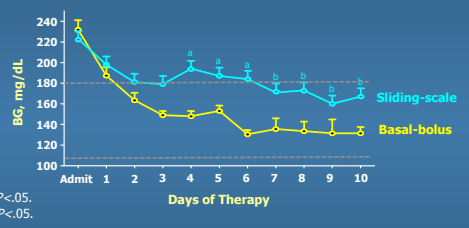
Umpierrez et al, Diabetes Care 30:2181–2186, 2007

Rabbit 2 Trial: Changes in Glucose Levels With Basal-Bolus vs. Sliding Scale Insulin



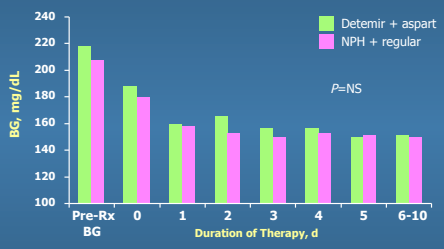
[a]$P<.05$.
[b]$P<.05$.

- Sliding scale regular insulin (SSRI) was given 4 times daily
- Basal-bolus regimen: glargine was given once daily; glulisine was given before meals.

0.4 U/kg/d x BG between 140-200 mg/dL
0.5 U/kg/d x BG between 201-400 mg/dL

Umpierrez GE, et al. *Diabetes Care.* 2007;30(9):2181-2186.

DEAN Trial: Changes in Mean Daily Blood Glucose Concentration



Data are means ±SEM.

Basal-bolus regimen: detemir was given once daily; aspart was given before meals.
NPH/regular regimen: NPH and regular insulin were given twice daily, two thirds in AM, one third in PM.

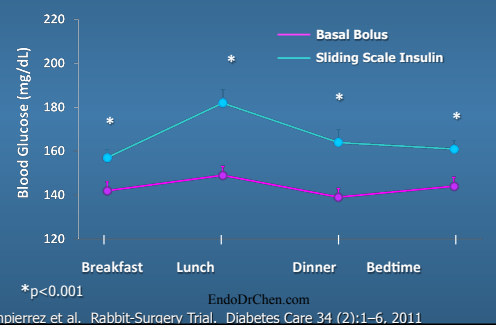
Umpierrez GE, et al. *J Clin Endocrinol Metab.* 2005;94(2):564-569.

AACE/ADA Metas de control glucémico fuera de UCI

- Metas en el contexto no UCI:
  - Preprandial <140 mg/dL
  - Glicemia al azar <180 mg/dL
  - Para evitar hipoglicemia, revalorar regimen insulínico si glicemia <100 mg/dL
  - Algunos pacientes pueden mantenerse por arriba o abajo de estas metas

Moghissi ES, et al; AACE/ADA Inpatient Glycemic Control Consensus Panel. *Endocr Pract.* 2009;15(4).
http://www.aace.com/pub/pdf/guidelines/InpatientGlycemicControlConsensusStatement.pdf

Mean BG before meals and at bedtime during basal bolus and SSI therapy in general surgery patients



*p<0.001

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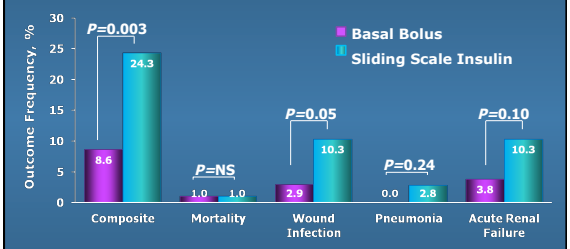
Umpierrez et al. Rabbit-Surgery Trial. Diabetes Care 34 (2):1–6, 2011

Postoperative Complications during basal bolus and SSI therapy in general surgery patients



* Composite of hospital complications: wound infection, pneumonia, respiratory failure, acute renal failure, and bacteremia.

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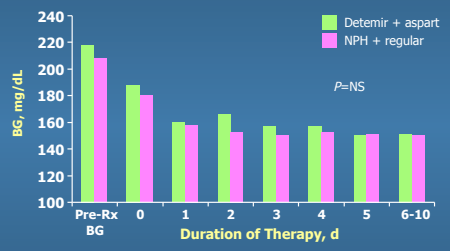
Umpierrez et al. Rabbit-Surgery Trial. Diabetes Care 34 (2):1–6, 2011

DEAN Trial: Changes in Mean Daily Blood Glucose Concentration



Data are means ±SEM.

Basal-bolus regimen: detemir was given once daily; aspart was given before meals. NPH/regular regimen: NPH and regular insulin were given twice daily, two thirds in AM, one third in PM.

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Umpierrez GE, et al. *J Clin Endocrinol Metab.* 2009;94(2):564-569.

FORMA DE ADMINISTRARLO… IMPORTA?

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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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Conclusiones

- La evolución natural de DM-2 lleva a insulinopenia por lo que se hace necesario insulinizar en la mayoría de pacientes
- Metas diferenciadas según paciente y si es intrahospitalario o ambulatorio
- El mejor esquema es iniciar con un basal e ir progresando en basal bolus

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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
- Se debe tratar de simplificar el esquema con insulina para pacientes y colegas

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ARTÍCULO DE REVISIÓN
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INSULINIZACIÓN:
CÓMO HACERLO MÁS SENCILLO PARA TODOS

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Preguntas…

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