Insulinas: un nuevo abordaje, rompiendo paradigmas

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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
  - Organon

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Agenda

- Evolución de tipos de insulina
- Evolución de dispositivos de insulinas
- Mitos de insulinas
- Nuevos esquemas de insulinización

INSULINAS: PERSPECTIVA HISTÓRICA

黄帝内经
(Huang Di Nei Jing)

消渴
(emaciación-sed)

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Diabetes

- El término fue empleado por primera vez por Apollonio de Memphis
- Raro en la antigua Grecia
- Galeno describió que había visto sólo 2 casos en su vida
- Areteaus mencionó que “vida (con diabetes) era corta, desagradable y dolorosa”

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Medicina tradicional china

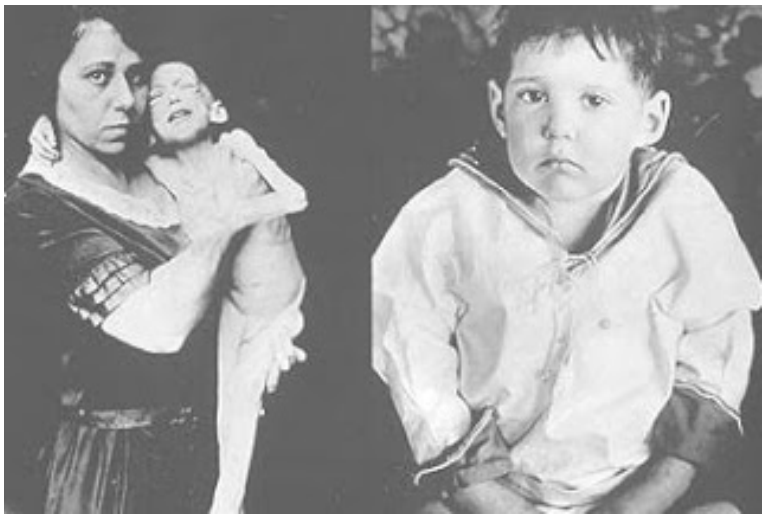
- Descripción hace 2000 años
- Causa: consumir demasiada comida rica en:
  - Grasa
  - Azúcares
  - Ricas
- Ocurre comúnmente en personas adineradas
- Tratamiento: resistir una dieta rica

Hindúes

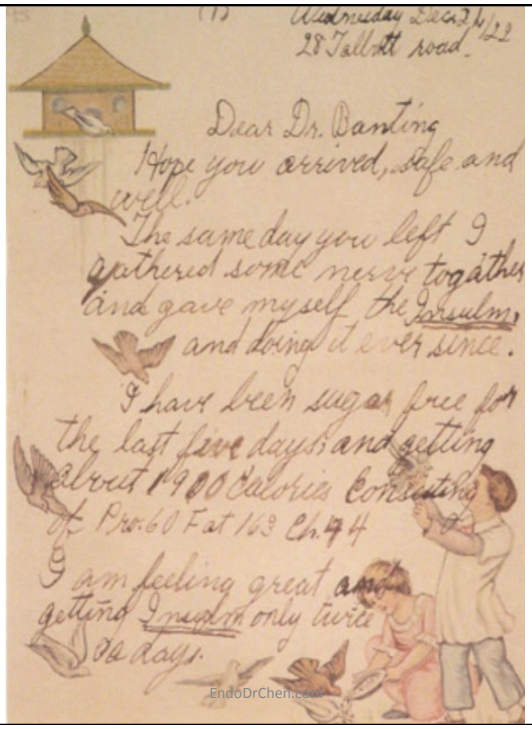
- Madhumeha
- Orina mielosa
- Orina que atrae hormigas
- Sushruta y Charaka en 400-500 AD por primera vez separaron tipo 1 y 2:
  - Tipo 1 en jóvenes
  - Tipo 2 en sobrepeso

Tratamiento en la era pre-insulina

- Dieta muy baja en carbohidratos y azúcares
- Alta en proteínas y grasas
- Esto permitía sobrevidas de alrededor de 1 año



Leonard Thompson: 11 de enero 1922
Insulina simple de administración IM 2 veces al día con volúmenes de entre 5 y 18 cc



Wednesday Dec 24/22
28 Talbott road.

Dear Dr. Banting
I hope you arrived, safe and well.
The same day you left I gathered some nerve together and gave myself the Insulin, and doing it ever since.
I have been sugar free for the last five days, and getting about 1900 Calories Consisting of Pro. 60 Fat 163 Ch. 44
I am feeling great and getting Insulin only twice a days.

Insulinas y premio Nobel

- Banting y MacLeod por descubrimiento de insulina
- Sir Frederick Sanger por determinar la secuencia de amino ácidos de la insulina
- Rosaly Yalow y Solomon Berson, premio Nobel de Medicina y Fisiología por el radioinmunoensayo para medir insulina

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1955: secuencia de amino ácidos

24/8/1978: ADN recombinante por Genentech

1921: Se descubre insulina

1936: descripción de NPH, se introdujo en 1946 por Nordisk

1953: lente ultralente y semilente

1996: lispro

2000: glargina

2004: detemir

2013: degludec

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EVOLUCIÓN EN FORMAS DE ADMINISTRACIÓN DE INSULINA

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1926

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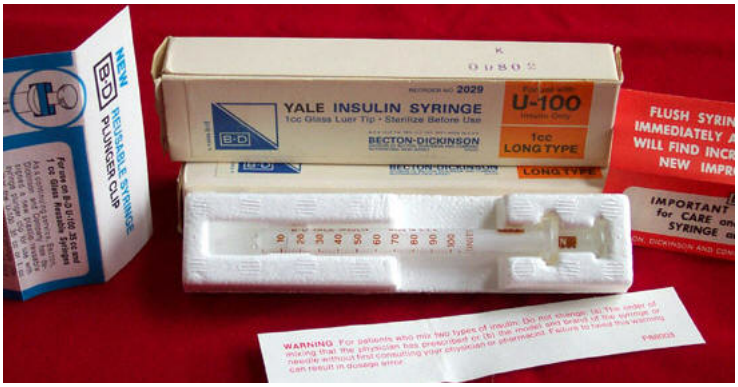
1954

1960s



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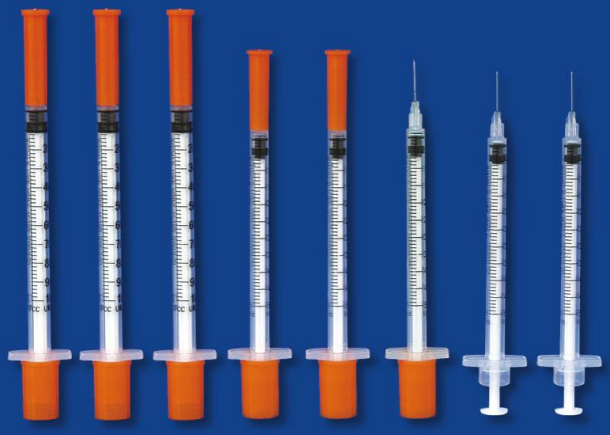
Insulin Syringes



All sizes of 1cc,1/2cc,3/10cc are avaliable

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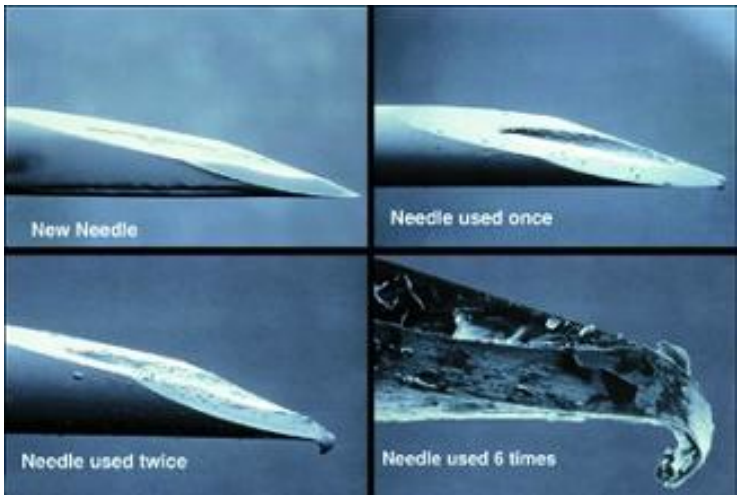
Jeringas luego de múltiples usos



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Evolución de agujas

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Ventajas de lapiceros

- Discreción
- Exactitud
- Facilidad de uso

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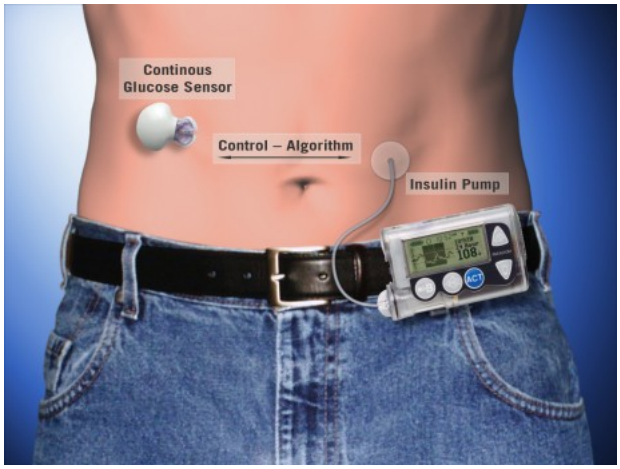
Vial vs lapiceros

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.

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



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EVOLUCIÓN DE LAS GUÍAS: PAPEL DE LAS INSULINAS

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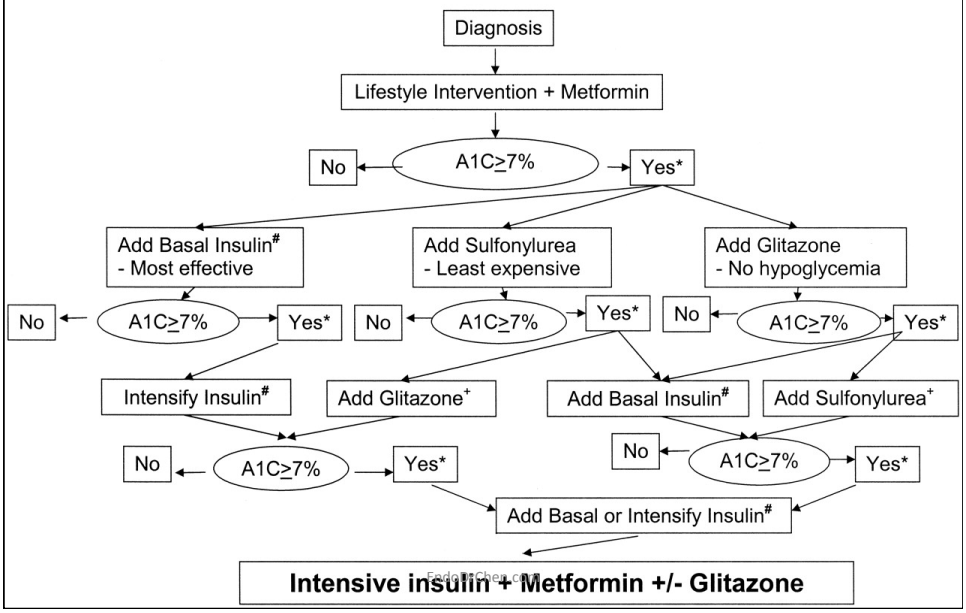
Guías AACE 2002

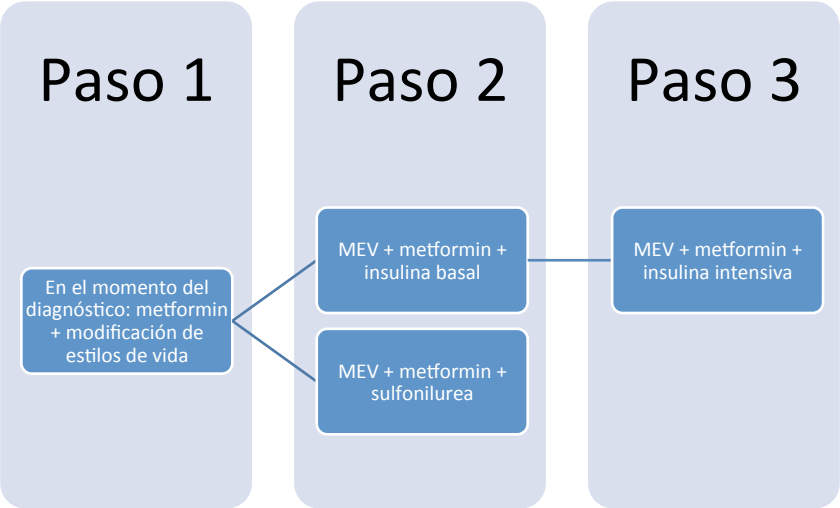
The choices of oral drug therapy for type 2 diabetes have become extremely complex. The physician must be positioned to use clinical judgment about the best combinations of drugs for the patient with diabetes. This discretion is particularly important in the long-term treatment of a chronic disease that is unrelenting and progressive and in which the response to therapy changes over time.

Endocrine Practice. 2002;8(Supl 1):40

Guías ADA 2006



Terapias bien validadas



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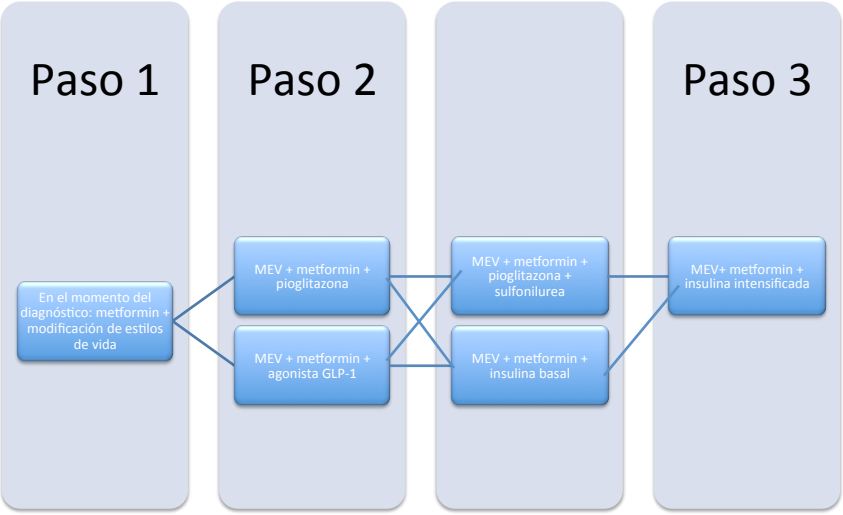
Nathan DM. Diabetes Care. 2009;32:1-11

Terapias menos validadas



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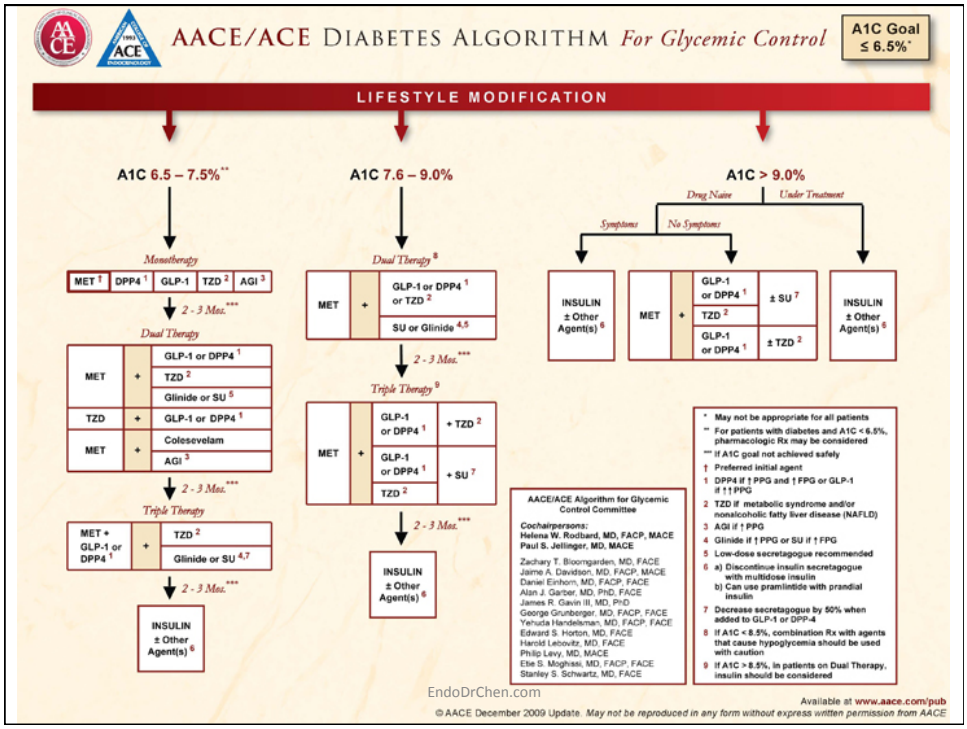
Nathan DM. Diabetes Care. 2009;32:1-11


AACE/ACE DIABETES ALGORITHM For Glycemic Control
A1C Goal ≤ 6.5%*
LIFESTYLE MODIFICATION
A1C 6.5 – 7.5%**
A1C 7.6 – 9.0%
A1C > 9.0%
Drug Naive
Under Treatment
Symptoms
No Symptoms
Monotherapy
MET 1 | DPP4 1 | GLP-1 | TZD 2 | AGI 3
2 - 3 Mos.***
Dual Therapy
MET + GLP-1 or DPP4 1
MET + TZD 2
MET + Glinide or SU 5
TZD + GLP-1 or DPP4 1
MET + Colesevelam
MET + AGI 3
2 - 3 Mos.***
Triple Therapy
MET + GLP-1 or DPP4 1 + TZD 2
MET + Glinide or SU 4,7
2 - 3 Mos.***
INSULIN ± Other Agent(s) 6
Dual Therapy 8
MET + GLP-1 or DPP4 1 or TZD 2
MET + SU or Glinide 4,5
2 - 3 Mos.***
Triple Therapy 9
MET + GLP-1 or DPP4 1 + TZD 2
MET + GLP-1 or DPP4 1 + TZD 2
MET + GLP-1 or DPP4 1 + SU 7
2 - 3 Mos.***
INSULIN ± Other Agent(s) 6
INSULIN ± Other Agent(s) 6
MET + GLP-1 or DPP4 1 ± SU 7
MET + TZD 2 ± TZD 2
MET + GLP-1 or DPP4 1 ± TZD 2
INSULIN ± Other Agent(s) 6
AACE/ACE Algorithm for Glycemic Control Committee
Cochairpersons:
Helena W. Rodbard, MD, FACP, MACE
Paul S. Jellinger, MD, MACE
Zachary T. Bloomgarden, MD, FACE
Jaime A. Davidson, MD, FACP, MACE
Daniel Einhorn, MD, FACP, FACE
Alan J. Garber, MD, PhD, FACE
James R. Gavin III, MD, PhD
George Grunberger, MD, FACP, FACE
Yehuda Handelsman, MD, FACP, FACE
Edward S. Horton, MD, FACE
Harold Lebovitz, MD, FACE
Philip Levy, MD, MACE
Etie S. Moghissi, MD, FACP, FACE
Stanley S. Schwartz, MD, FACE
* May not be appropriate for all patients
** For patients with diabetes and A1C < 6.5%, pharmacologic Rx may be considered
*** If A1C goal not achieved safely
† Preferred initial agent
1 DPP4 if ↑ PPG and ↑ FPG or GLP-1 if ↑↑ PPG
2 TZD if metabolic syndrome and/or nonalcoholic fatty liver disease (NAFLD)
3 AGI if ↑ PPG
4 Glinide if ↑ PPG or SU if ↑ FPG
5 Low-dose secretagogue recommended
6 a) Discontinue insulin secretagogue with multidose insulin
b) Can use pramlintide with prandial insulin
7 Decrease secretagogue by 50% when added to GLP-1 or DPP-4
8 If A1C < 8.5%, combination Rx with agents that cause hypoglycemia should be used with caution
9 If A1C > 8.5%, in patients on Dual Therapy, insulin should be considered
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Available at www.aace.com/pub
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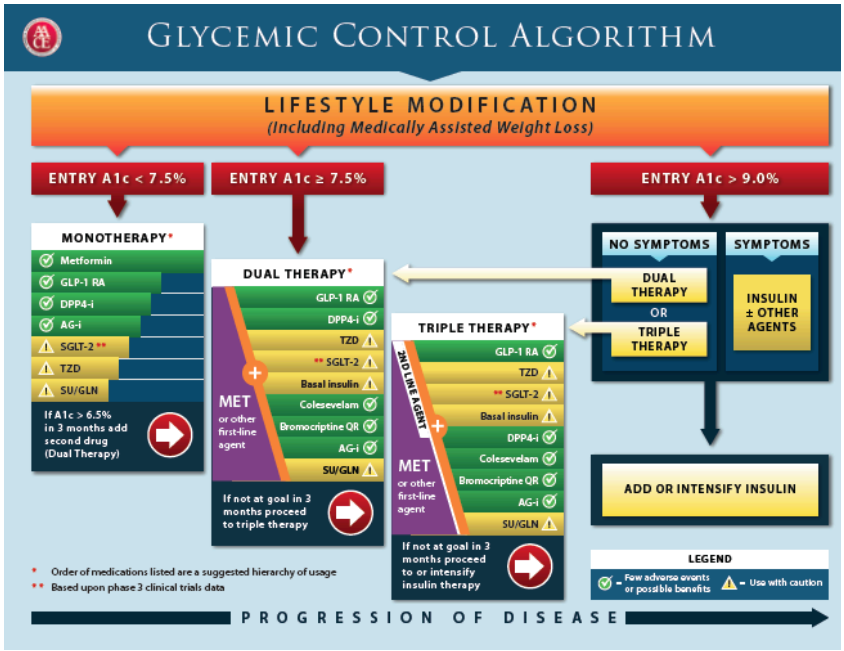
GLYCEMIC CONTROL ALGORITHM
LIFESTYLE MODIFICATION
(Including Medically Assisted Weight Loss)
ENTRY A1c < 7.5%
ENTRY A1c ≥ 7.5%
ENTRY A1c > 9.0%
MONOTHERAPY*
Metformin
GLP-1 RA
DPP4-i
AG-i
SGLT-2 **
TZD
SU/GLN
If A1c > 6.5% in 3 months add second drug (Dual Therapy)
DUAL THERAPY*
GLP-1 RA
DPP4-i
TZD
** SGLT-2
Basal insulin
Colesevelam
Bromocriptine QR
AG-i
SU/GLN
MET or other first-line agent
If not at goal in 3 months proceed to triple therapy
TRIPLE THERAPY*
2ND LINE AGENT
GLP-1 RA
TZD
** SGLT-2
Basal insulin
DPP4-i
Colesevelam
Bromocriptine QR
AG-i
SU/GLN
MET or other first-line agent
If not at goal in 3 months proceed to or intensify insulin therapy
NO SYMPTOMS
SYMPTOMS
DUAL THERAPY
OR
TRIPLE THERAPY
INSULIN ± OTHER AGENTS
ADD OR INTENSIFY INSULIN
LEGEND
= Few adverse events or possible benefits
= Use with caution
* Order of medications listed are a suggested hierarchy of usage
** Based upon phase 3 clinical trials data
PROGRESSION OF DISEASE
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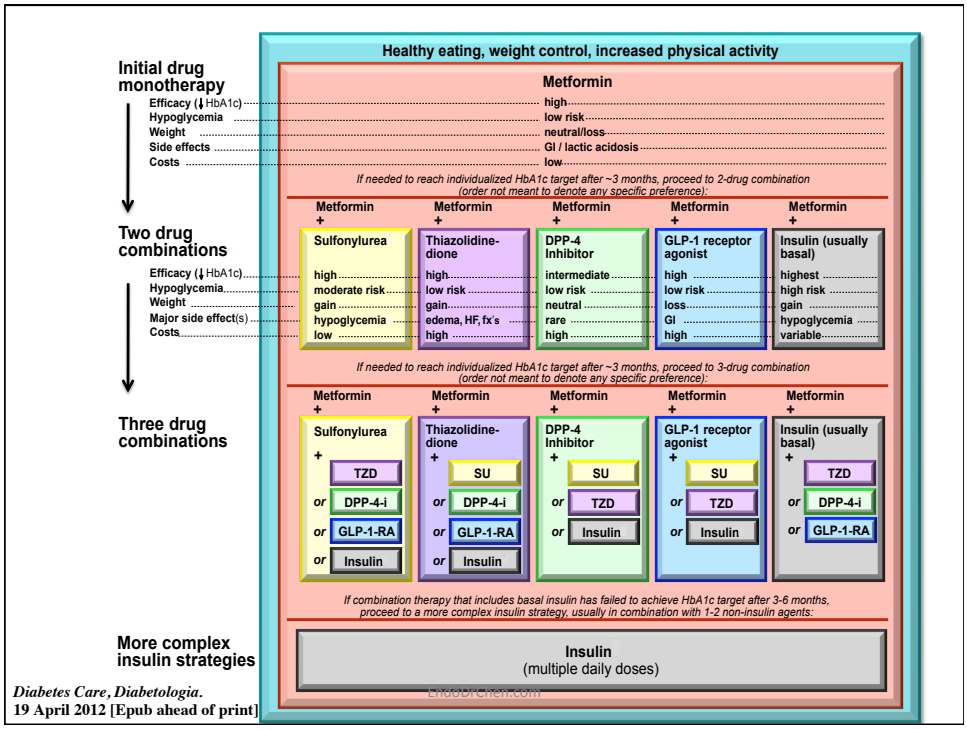
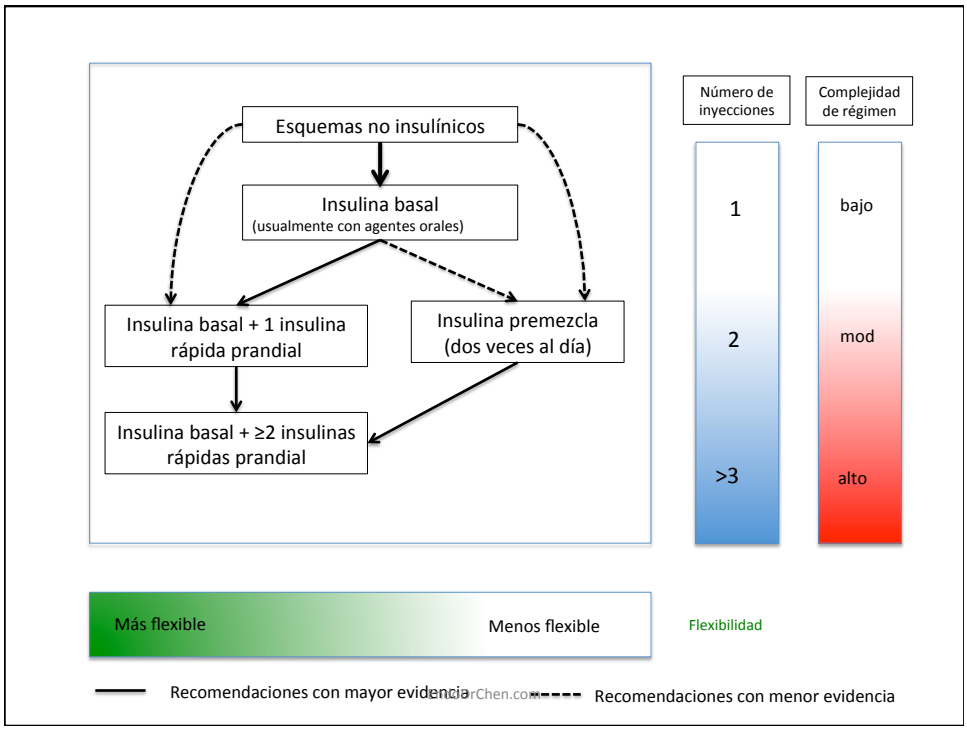

Healthy eating, weight control, increased physical activity
Initial drug monotherapy
Metformin
Efficacy (↓HbA1c) high
Hypoglycemia low risk
Weight neutral/loss
Side effects GI / lactic acidosis
Costs low
If needed to reach individualized HbA1c target after ~3 months, proceed to 2-drug combination (order not meant to denote any specific preference):
Two drug combinations
Metformin + Sulfonylurea: Efficacy (↓HbA1c) high; Hypoglycemia moderate risk; Weight gain; Major side effect(s) hypoglycemia; Costs low
Metformin + Thiazolidine-dione: Efficacy high; Hypoglycemia low risk; Weight gain; Major side effect(s) edema, HF, fx's; Costs high
Metformin + DPP-4 Inhibitor: Efficacy intermediate; Hypoglycemia low risk; Weight neutral; Major side effect(s) rare; Costs high
Metformin + GLP-1 receptor agonist: Efficacy high; Hypoglycemia low risk; Weight loss; Major side effect(s) GI; Costs high
Metformin + Insulin (usually basal): Efficacy highest; Hypoglycemia high risk; Weight gain; Major side effect(s) hypoglycemia; Costs variable
If needed to reach individualized HbA1c target after ~3 months, proceed to 3-drug combination (order not meant to denote any specific preference):
Three drug combinations
Metformin + Sulfonylurea + TZD or DPP-4-i or GLP-1-RA or Insulin
Metformin + Thiazolidine-dione + SU or DPP-4-i or GLP-1-RA or Insulin
Metformin + DPP-4 Inhibitor + SU or TZD or Insulin
Metformin + GLP-1 receptor agonist + SU or TZD or Insulin
Metformin + Insulin (usually basal) + TZD or DPP-4-i or GLP-1-RA
If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3-6 months, proceed to a more complex insulin strategy, usually in combination with 1-2 non-insulin agents:
More complex insulin strategies
Insulin (multiple daily doses)
Diabetes Care, Diabetologia.
19 April 2012 [Epub ahead of print]


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

Por qué evolucionar con las insulinas?

- Hemos dado por sentado que las insulinas:
  - Producen hipoglicemia
  - Aumentan de peso
- … y que además esto es inevitable

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Mitos de los pacientes

- Precipitación de complicaciones como ceguera
- La diabetes es “terminal”
- Es difícil
- Voy a aumentar de peso
- Voy a tener hipoglicemias

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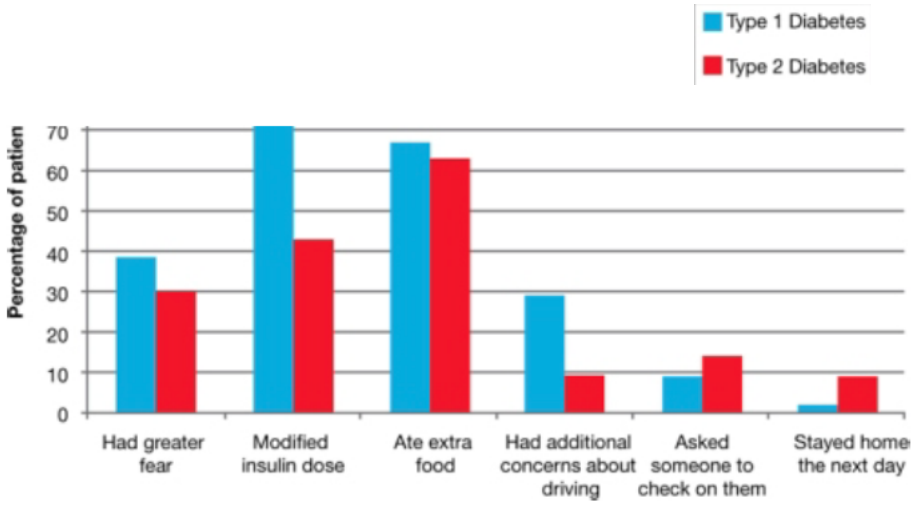

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Tenzer-Iglesias. J Fam Prac. 2012;61(10):S1

POR QUÉ INICIAR CON INSULINAS BASALES?

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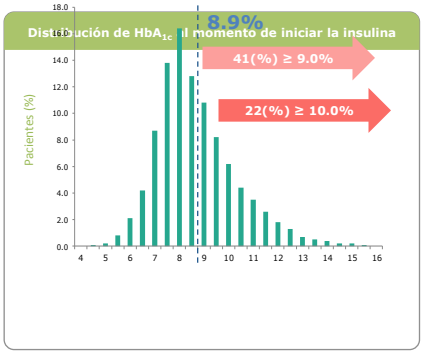
Existe la necesidad de un inicio más temprano de la insulina - HbA_{1c} basal



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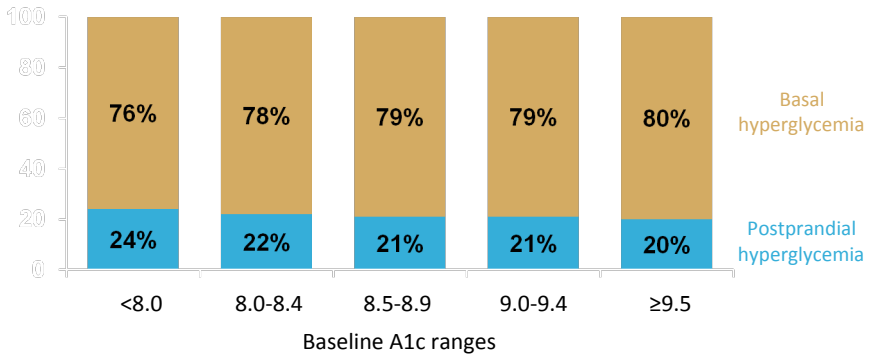
Khunti et al Diabetologia 2011; 54 (Suppl.1): S160 and Poster

Basal and postprandial contributions to hyperglycemia by A1c range

Pooled baseline data from 6 Treat-to-Target design studies
1699 T2DM patients on diet ± OAD
Mean A1c 8.69%, FPG 10.8 mmol/L (194 mg/dL)
7-point ambulatory SMBG profiles (ac, 2hr-pc, and hs)
Calculations assume hyperglycemia is >5.6 mmol/L (100 mg/dL)



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

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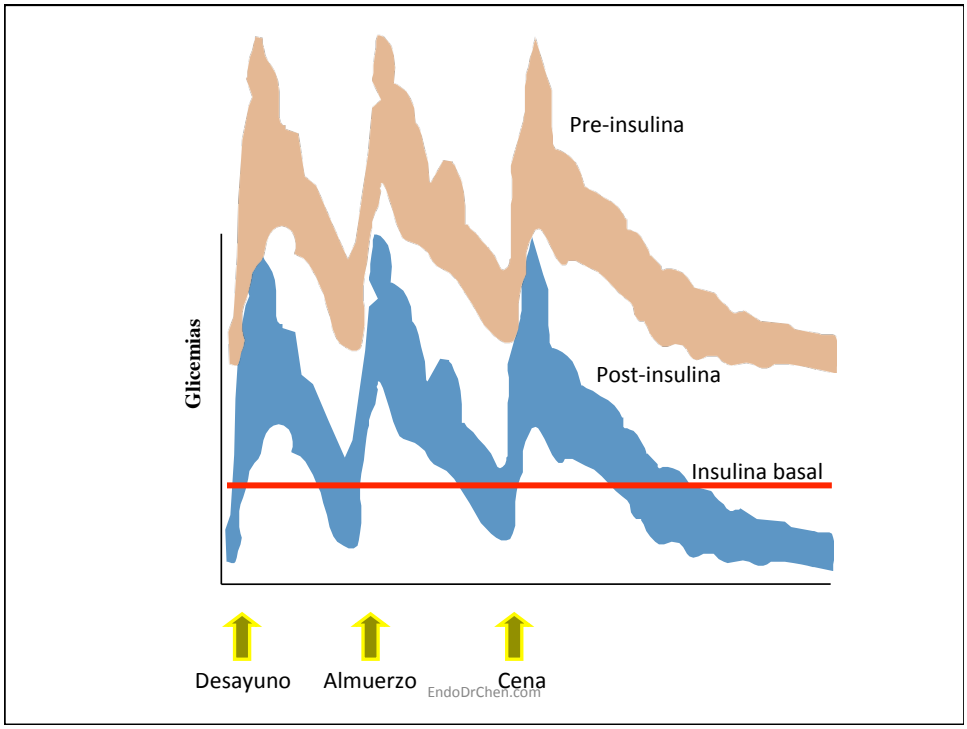
Riddle et al, Diabetes Care 34:2508–2514, 2011


Pre-insulina
Glicemias
Post-insulina
Insulina basal
Desayuno
Almuerzo
Cena
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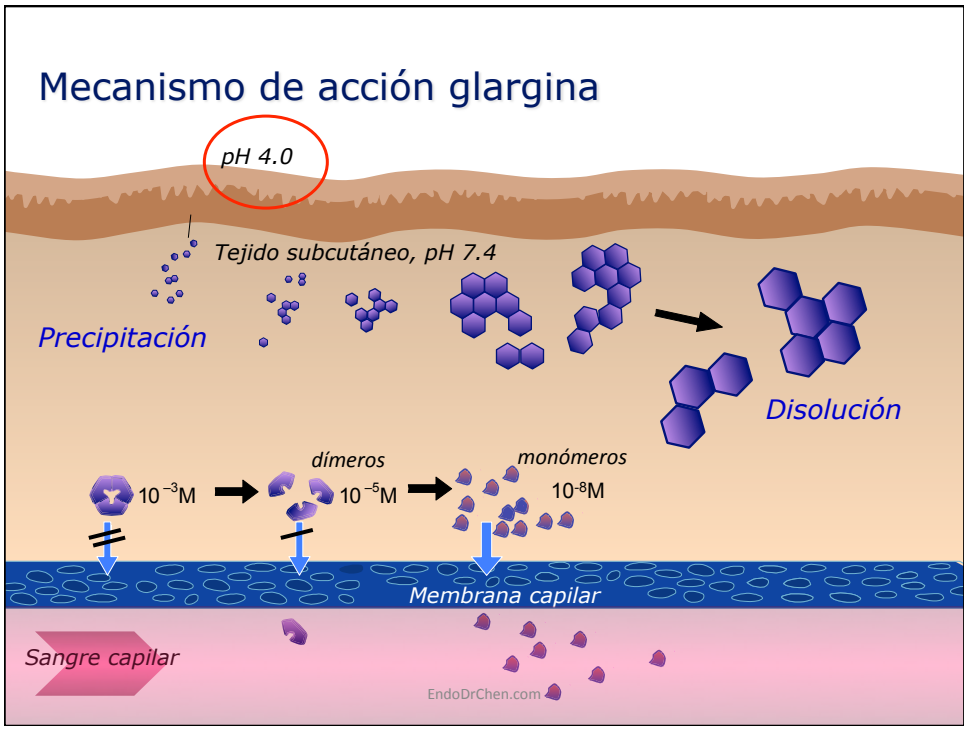
Mecanismo de acción glargina
pH 4.0
Tejido subcutáneo, pH 7.4
Precipitación
Disolución
dímeros
monómeros
10 -3M
10 -5M
10-8M
Membrana capilar
Sangre capilar
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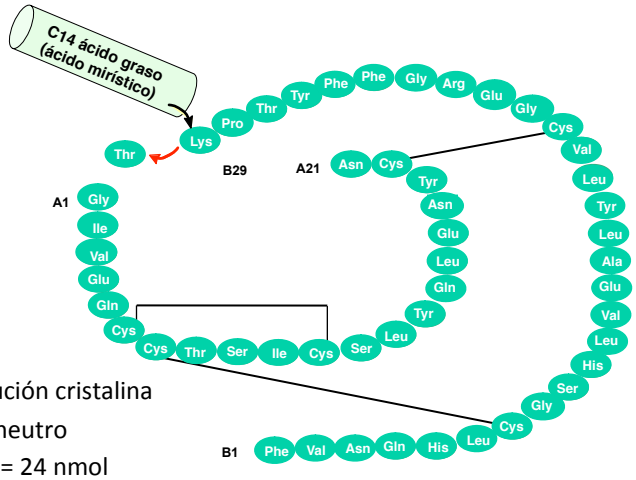
Insulina detemir

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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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

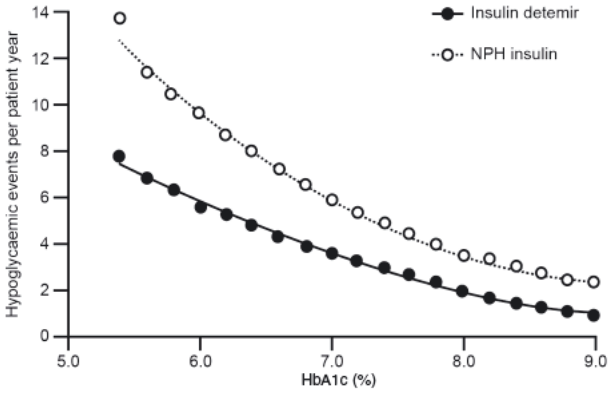
EndoDrChen.com Frier BM. Diab Obes Metab. 2013: online april 3.

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.

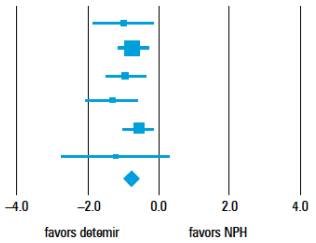
NPH vs detemir en DM-2: hipoglicemias



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

Diferencias en peso

Study	Sample size		Statistics for each study			
	detemir	NPH	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[33]	195	98	–0.920	–1.497	–0.343	0.002
Pieber et al.[26]	139	129	–1.300	–2.066	–0.534	0.001
Russel-Jones et al.[28]	491	256	–0.540	–0.978	–0.102	0.116
Vague et al.[29]	282	138	–1.200	–2.763	0.363	0.132
total	1694	905	–0.779	–0.992	–0.567	0.000



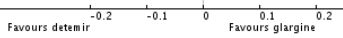
Szypowska A. Por Arch Med Wewn. 2011;121:737

Cochrane: variabilidad en perfil glicémico

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

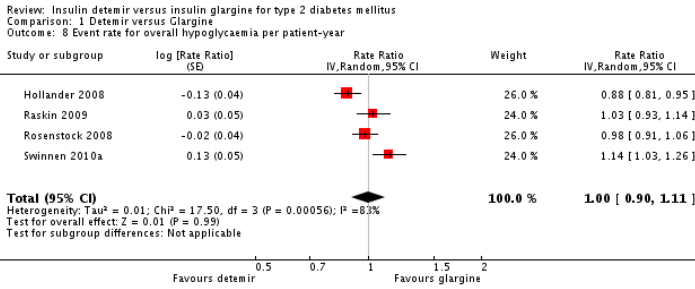
Study or subgroup	Detemir N	Mean(SD)	Glargine N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Hollander 2008	214	0.27 (0.2)	105	0.28 (0.21)		36.5 %	-0.01 [-0.06, 0.04]
Raskin 2009	254	0.32 (0.25)	131	0.33 (0.26)		33.5 %	-0.01 [-0.06, 0.04]
Rosenstock 2008	291	0.48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

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



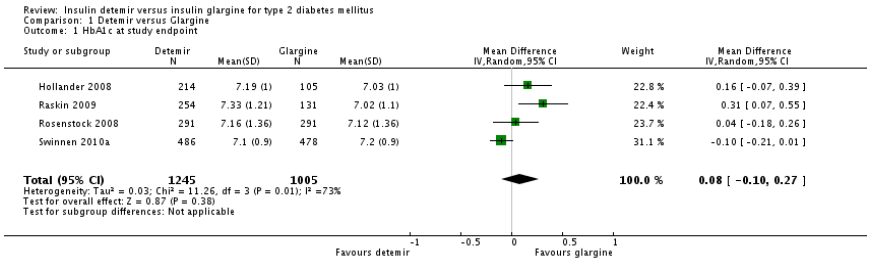
Swinnen *et al. Cochrane Database Syst Rev* 2011: CD006383

Cochrane: tasa de hipoglicemias



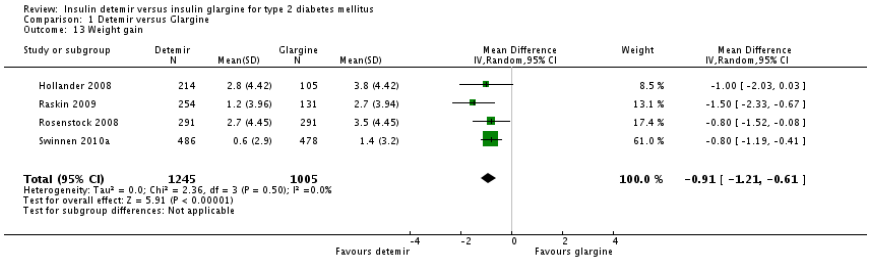
Swinnen *et al. Cochrane Database Syst Rev* 2011: CD006383

Cochrane: cambios en Hba1c



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

Cochrane: aumento de peso



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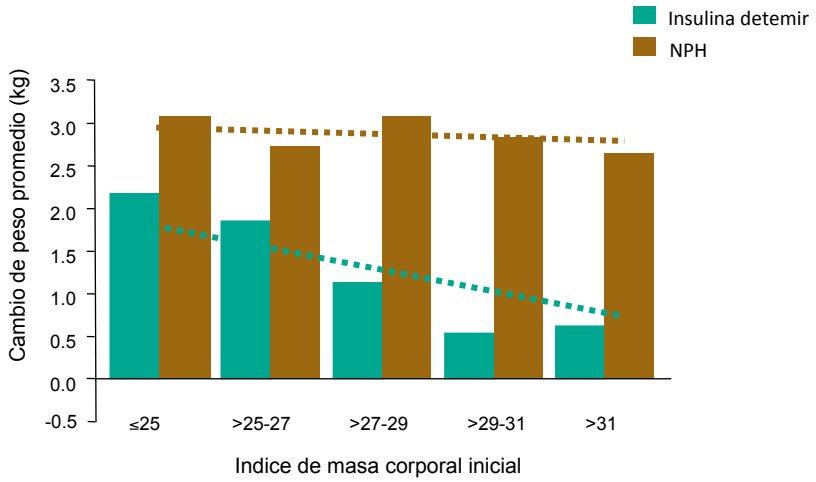
Detemir: menor ganancia de peso en pacientes obesos



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

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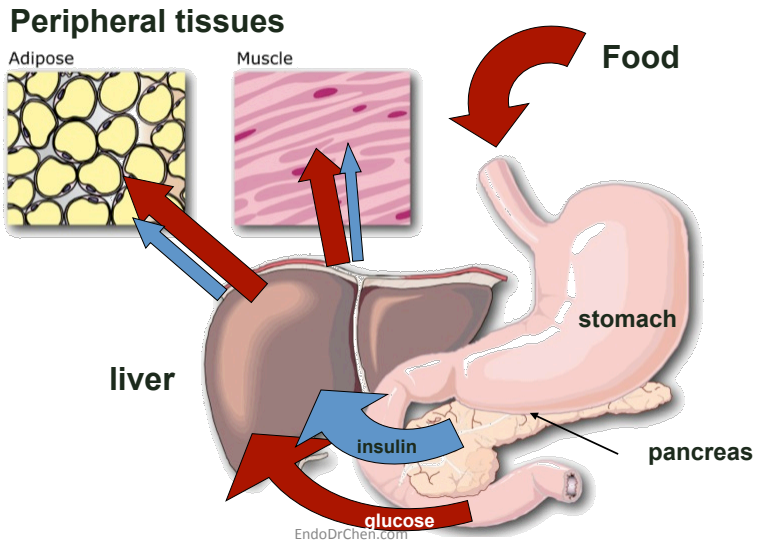
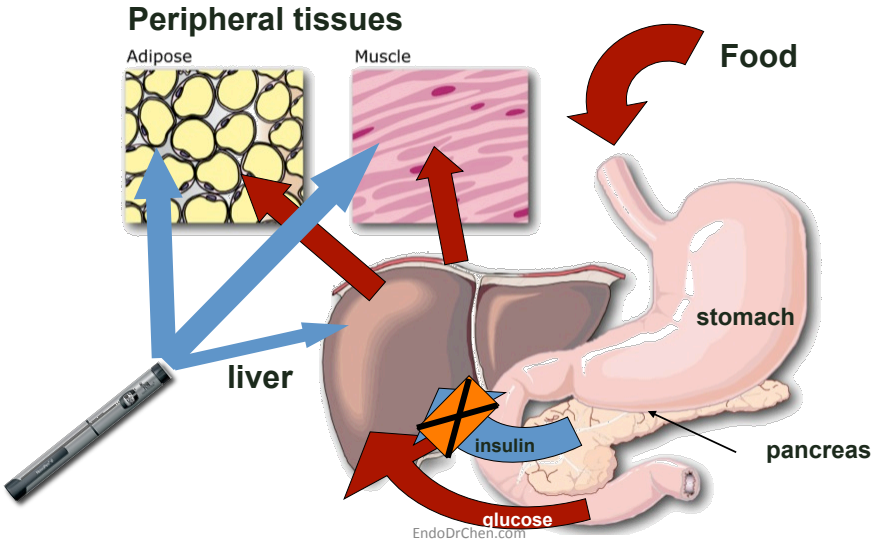
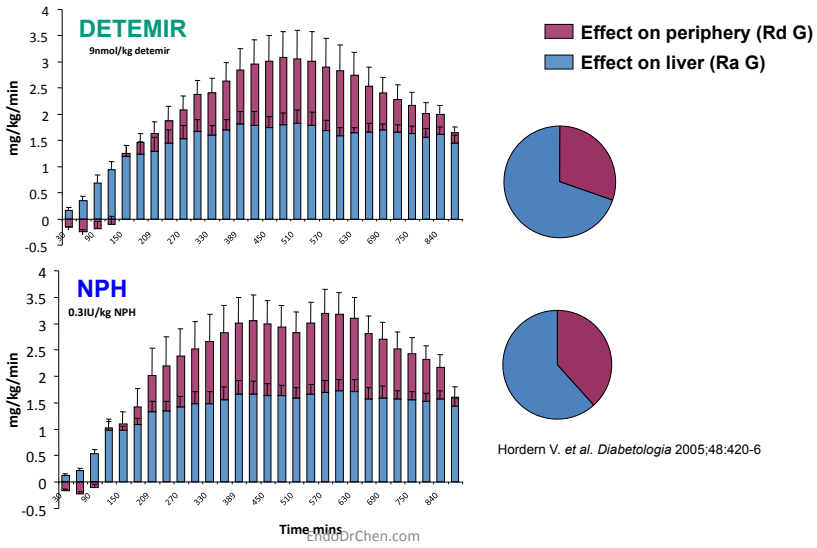
The 'Liver hypothesis': Systemic insulin in normal physiology



The 'Liver hypothesis': Distribution of exogenous insulin

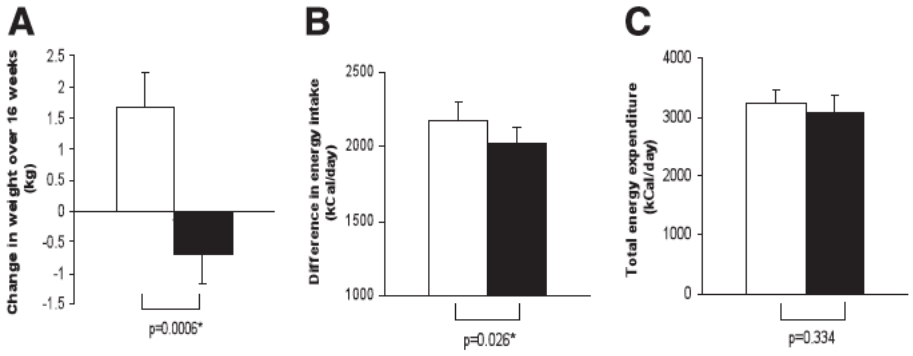


Relative peripheral and hepatic effects of detemir and NPH



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

Por qué las diferencias en peso?



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Zachariah S. Diabetes Care. 2011;34:1487

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	[illegible]	[illegible]	[illegible]	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[illegible] 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

EVIDENCIA CLÍNICA PARA EMPEZAR CON UNA INSULINA BASAL

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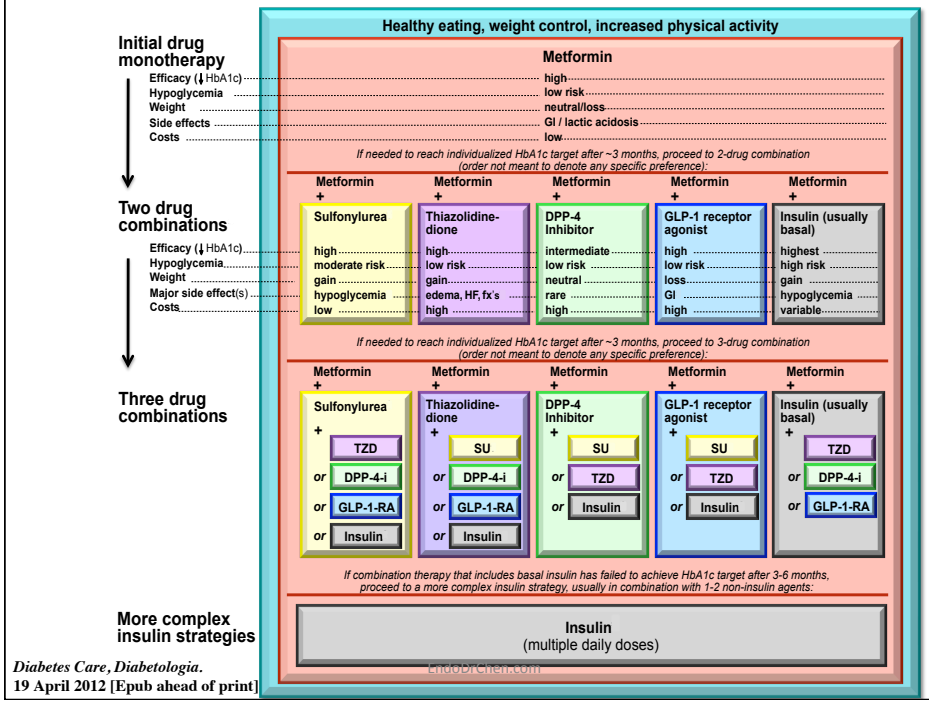


Diabetes Care, Diabetologia.
19 April 2012 [Epub ahead of print]

Continuous coverage of the American Diabetes Association 72nd Scientific Sessions

EASIE Trial: Design

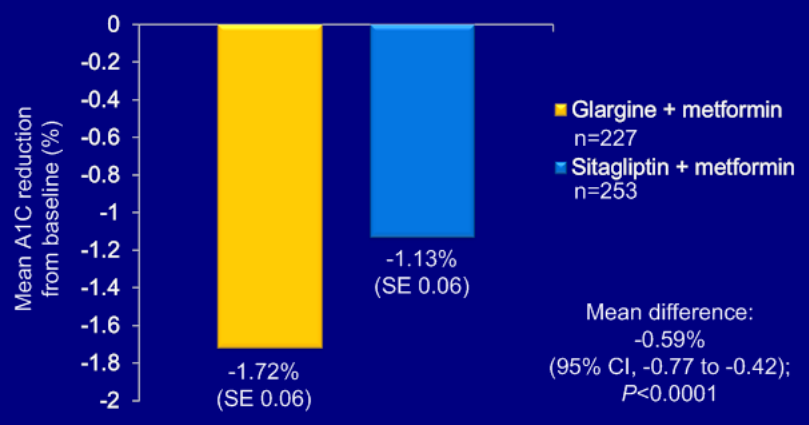
- Multicenter, randomized, parallel, open-label trial
- Examined efficacy, safety, and tolerability of insulin glargine vs sitagliptin among insulin-naïve patients with type 2 diabetes uncontrolled on metformin
- Subject profile:
  - Aged 35-70 yrs
  - Type 2 diabetes ≥6 months
  - A1C >7% and <11%
  - 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.

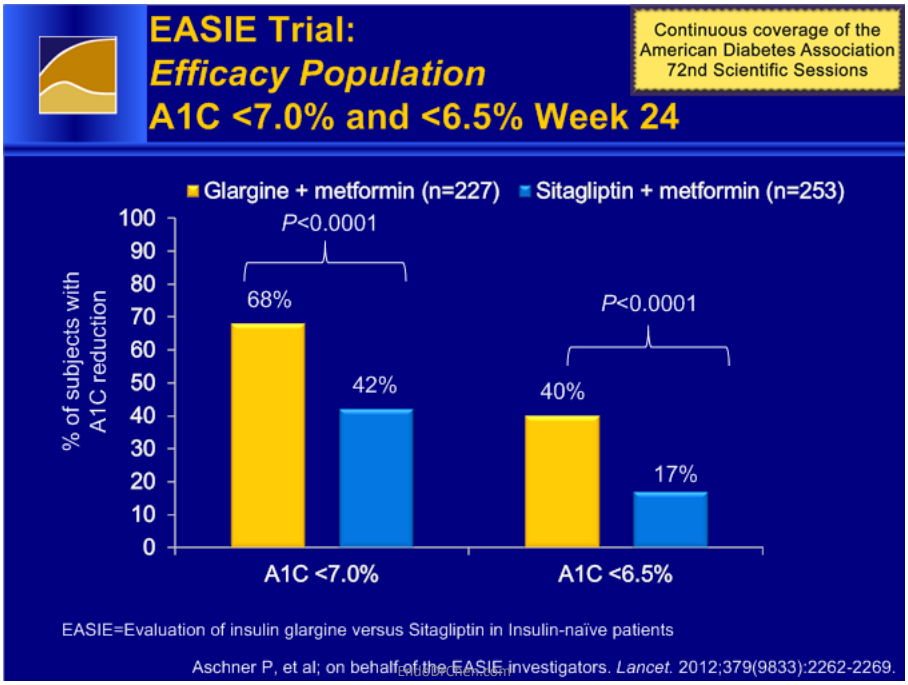
Continuous coverage of the American Diabetes Association 72nd Scientific Sessions

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.



TERCERA LÍNEA DE TRATAMIENTO:
LUEGO DE FALLA A 2 ORALES (MET+SU)

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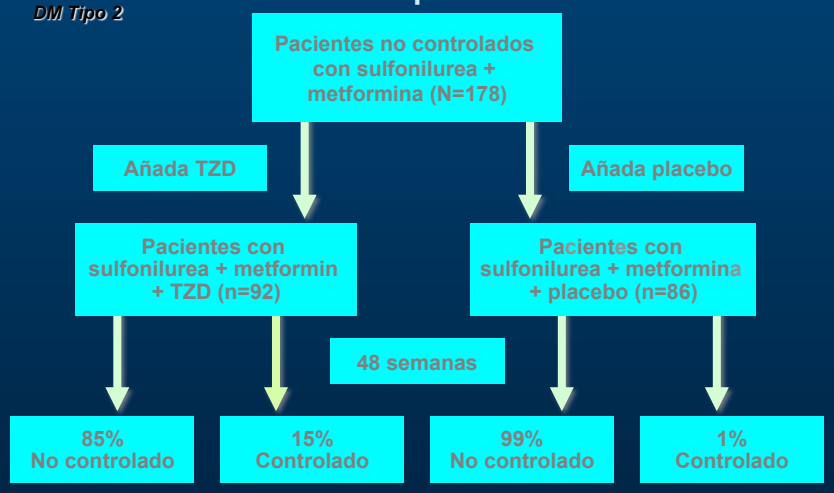
Mínimo control de la glucemia con máxima terapia con AHO

DM Tipo 2



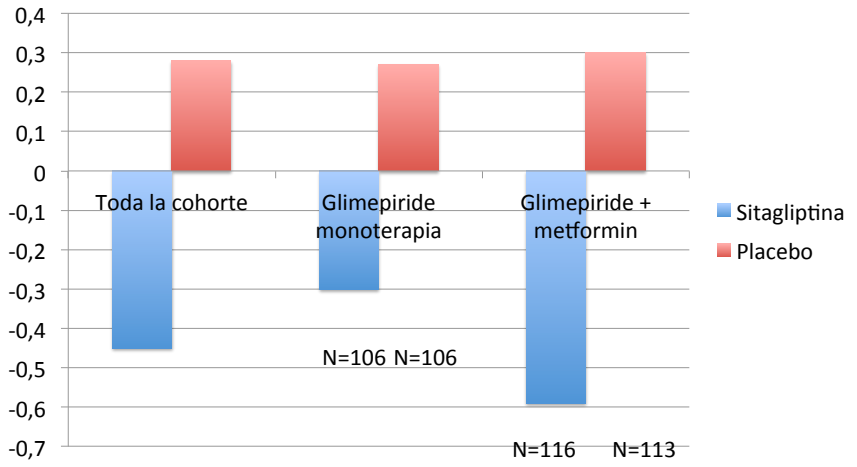
AHO, agente hipoglucemiante oral; TZD, tiazolidinediona. Yale JF et al. *Ann Intern Med.* 2001;134:737-745.

Metanálisis: eficacia luego de metformin más SU

Hemoglobin A_{1c}, change from baseline (%)			
Treatment (compared with placebo + Met + SU)	Studies	Direct estimate, WMD (95% CI)	MTC estimate MD (95% CrI)
Basal insulin + Met + SU	2[34,48]	−1.22 (−2.33 to −0.10)	−1.17 (−1.57 to −0.81)
Biphasic insulin + Met + SU	NA	NA	−1.10 (−1.59 to −0.67)
TZD + Met + SU	2[33,35]	−1.16 (−1.36 to −0.96)	−0.96 (−1.35 to −0.59)
DPP-4 + Met + SU	1[51]	−0.89 (−1.11 to −0.66)	−0.89 (−1.51 to −0.26)
AG inhibitor + Met + SU	3[32,34,50]	−0.43 (−0.72 to −0.14)	−0.46 (−0.96 to 0.03)
GLP-1 + Met + SU	2[28,48]	−0.96 (−1.14 to −0.89)	−1.06 (−1.45 to −0.69)
IAsp + Met + SU	NA	NA	−1.01 (−1.71 to −0.35)
Meglitinide + Met + SU	NA	NA	−0.18 (−2.08 to 1.71)
No. of RCTs included in MTC meta-analysis	21 RCTs[23,27,28,30,32–35,38,40–44,48,50,51,53–55,57]		

McIntosh B. Open Medicine. 2012;6(2):e62

Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin



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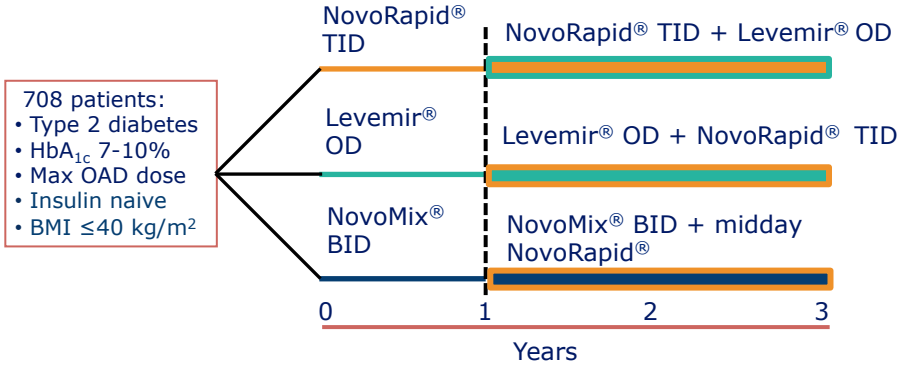
Hermansen K. Diab Obes Metab. 2007;9:733

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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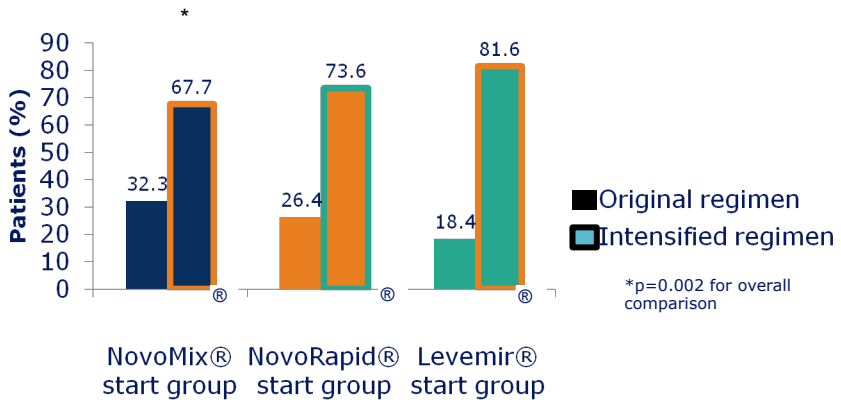
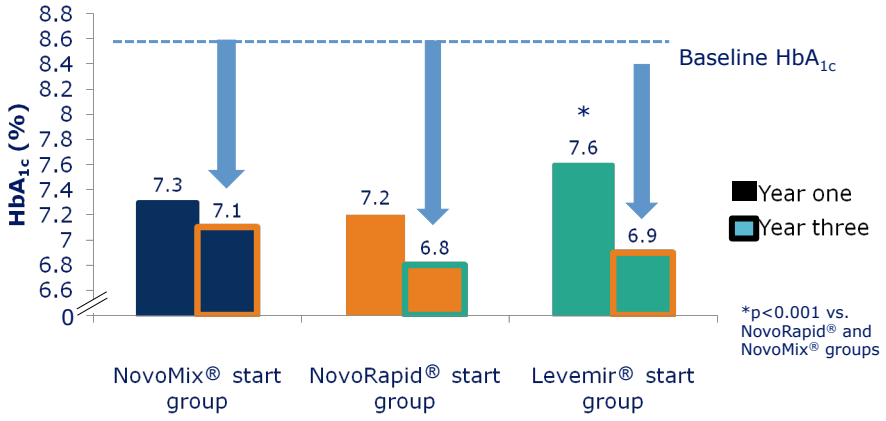
The majority of patients were intensified with a second insulin

74.3% of patients had an intensified regimen



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

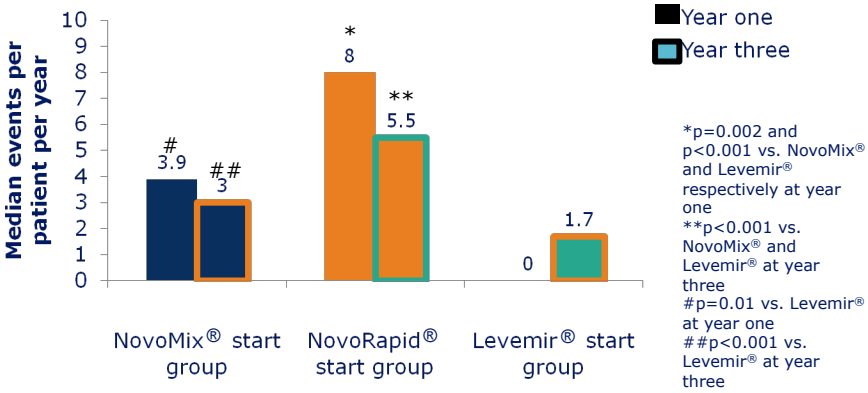
Sustainable HbA_{1c} control in all three arms



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

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

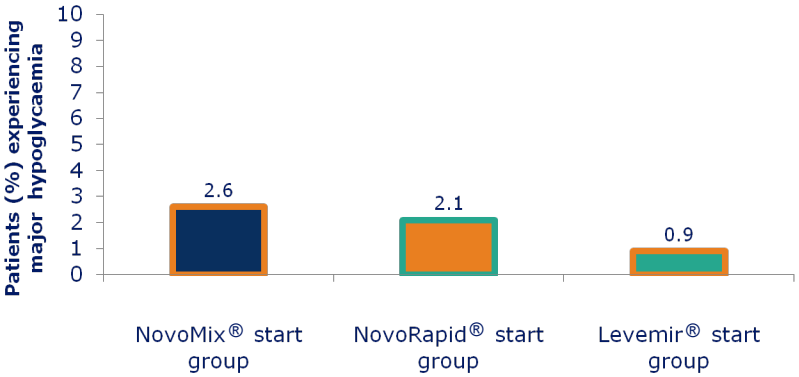
Low median rates of minor hypoglycaemia



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

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

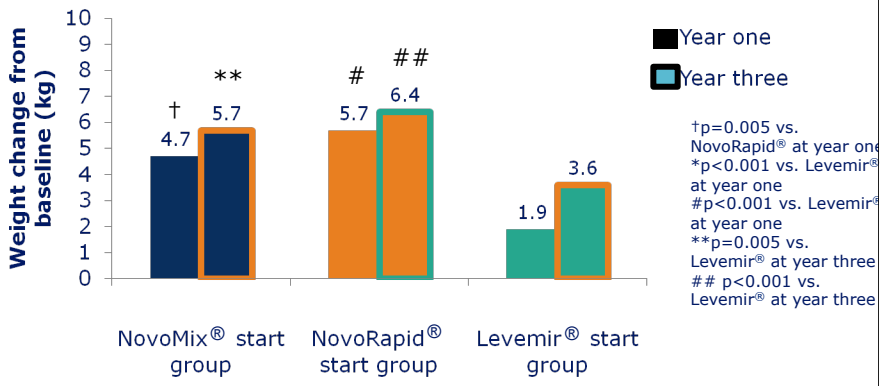
Low proportion of patients experiencing major hypoglycaemia over 3 years



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

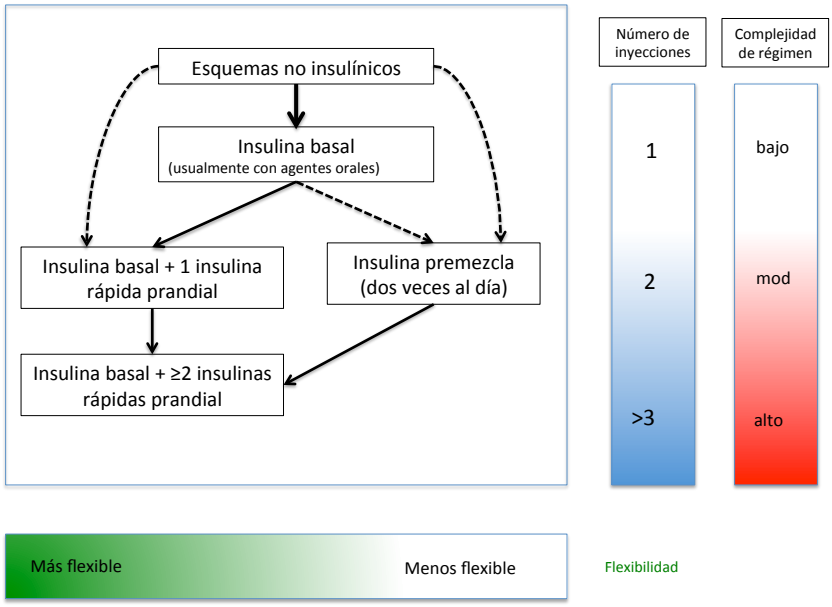
Holman *et al. NEJM* 2007; 357:1716-30

Detemir weight advantage was sustained throughout intensification

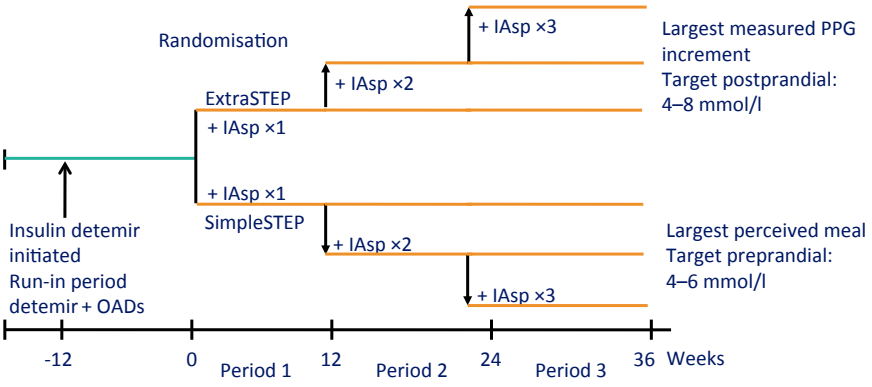


Holman *et al. NEJM* 2007; 357:1716-30

QUÉ PASA CUANDO FALLA LA INSULINA BASAL?



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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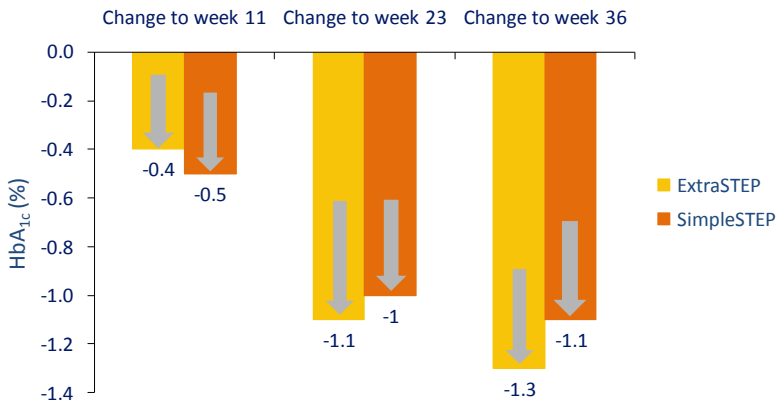
STEPwise™: change in HbA_{1c}



Change was adjusted for baseline HbA_{1c}

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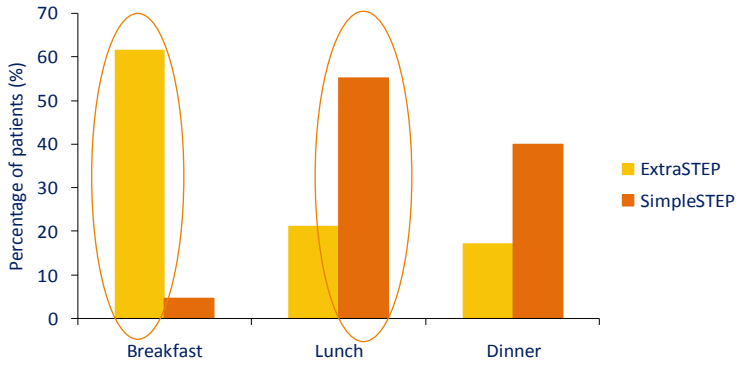
Meneghini *et al. Diabetes* 2010;59(Suppl. 1):A199

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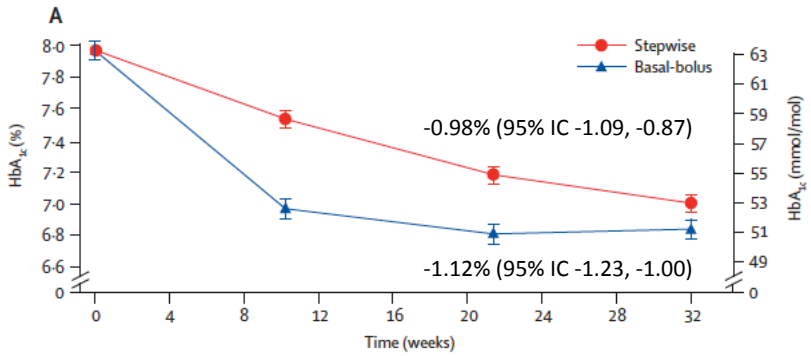
Meneghini *et al. Diabetes* 2010;59(Suppl. 1):A199 and data on file

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

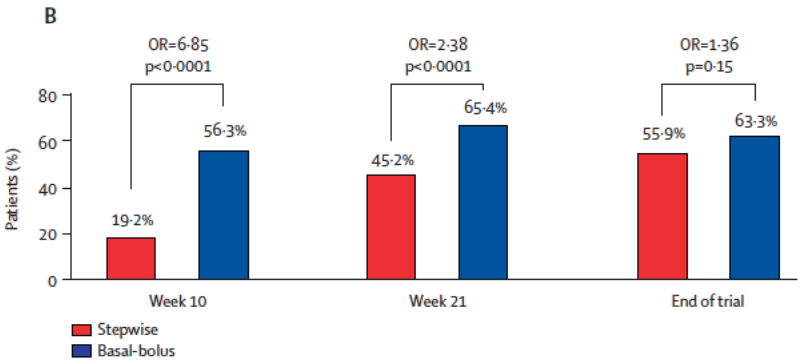
Helena W Rodbard, Virginia E Visco, Henning Andersen, Line C Hiort, David H W Shu

Lancet Diabetes Endocrinol
2014; 2: 30–37

Eficacia en Hba1c



Pacientes que alcanzaron Hba1c <7%



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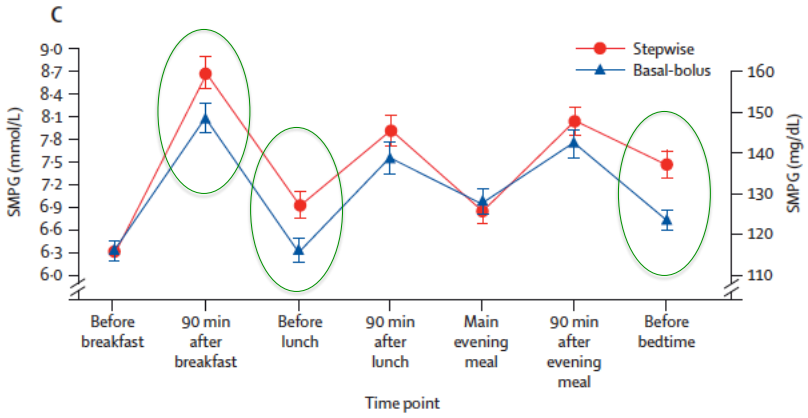
Perfil de glicemias al final del estudio



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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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QUÉ NOS DEPARA EL FUTURO INMEDIATO DE LAS INSULINAS?

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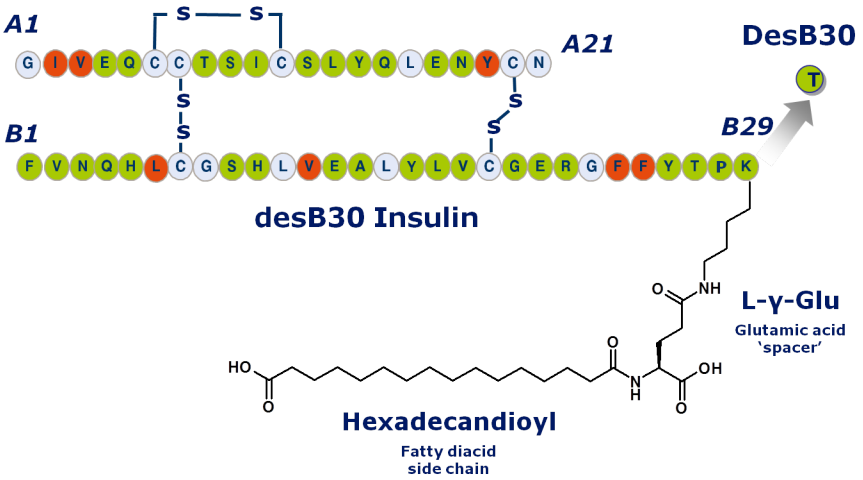
Diseño de Degludec: estructura

Des(B30) LysB29(γ-Glu Nε-hexadecandioyl) human insulin



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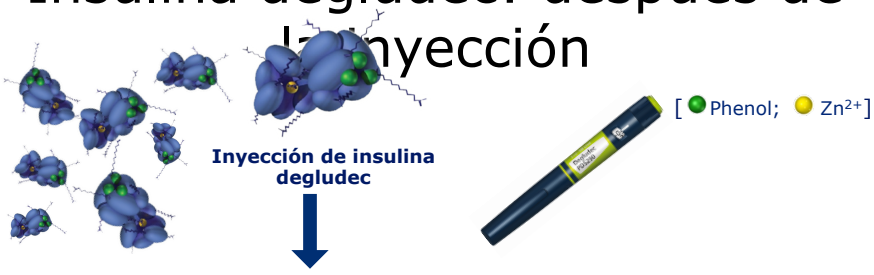
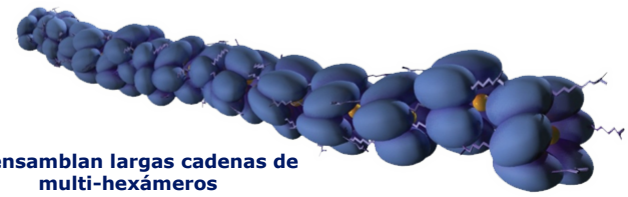
Jonassen I et al. *Diabetes*. 2010;59(suppl 1):A11

Insulina degludec: después de la inyección



El fenol del vehículo difunde rápidamente, y degludec se enlaza a través del contacto de cadenas laterales únicas



Se ensamblan largas cadenas de multi-hexámeros

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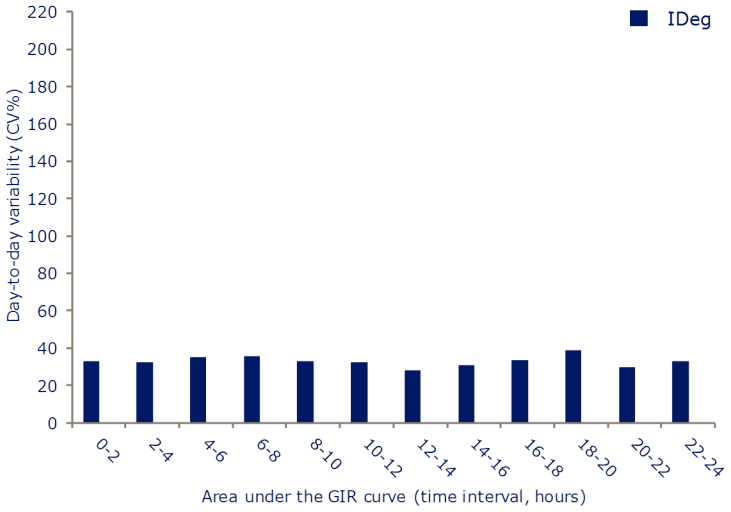
Baja variabilidad de degludec día-día y hora-hora



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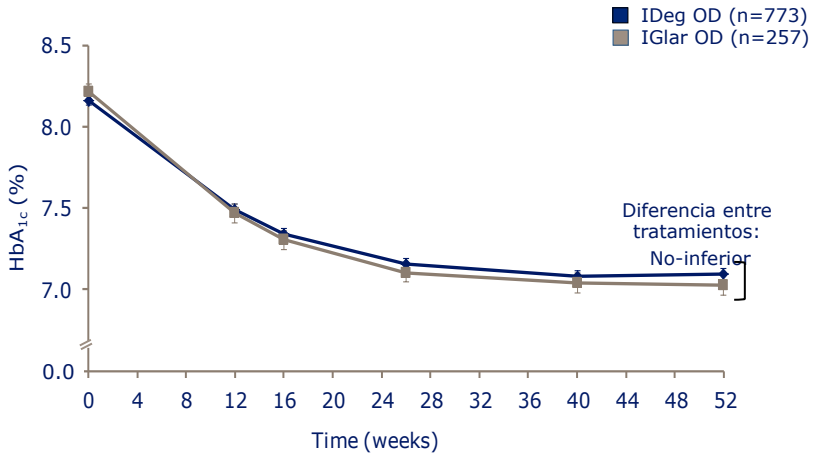
Heise *et al. Diabetes Obes Metab* 2012;14:859–64

ONCE LONG: HbA_{1c} a lo largo del tiempo



Mean±SEM; FAS; LOCF
Comparisons: Estimates adjusted for multiple covariates.
NN1250-3579; IDeg OD vs IGlar OD in T2DM.
Zinman *et al. Diabetes Care* 2012: Published online 05 October DOI: 10.2337/dc12-1205.

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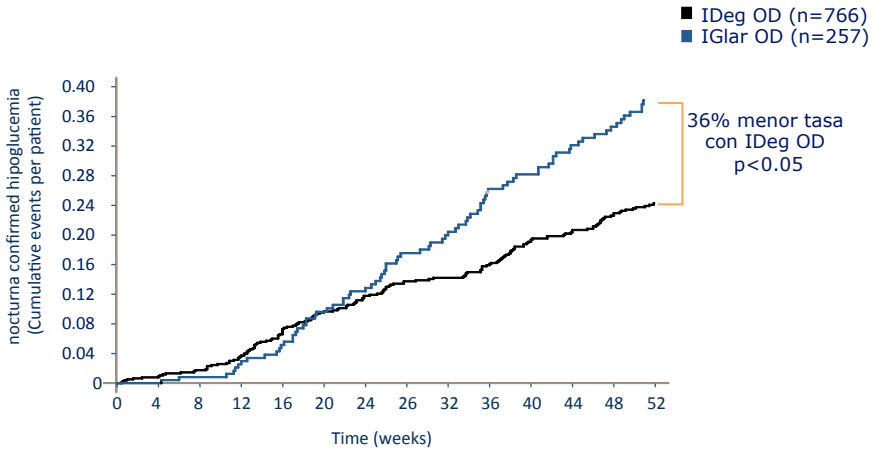
ONCE LONG: hipoglucemia nocturna confirmada



SAS; Comparisons: Estimates adjusted for multiple covariates
NN1250-3579; IDeg OD vs IGlar OD in T2DM.
Zinman *et al*. *Diabetes Care* 2012: Published online 05 October DOI: 10.2337/dc12-1205.

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Nuevas insulinas

- Lys-PEG
  - Insulina lispro más polietilenglicol
  - Prolonga vida media
  - Recientemente presentado estudios fase III vs glargina con menor riesgo de hipoglicemias
- Glargina U300
  - Mayor concentración que le permite prolongar su duración de acción
- Degludec + aspart (degludec plus)

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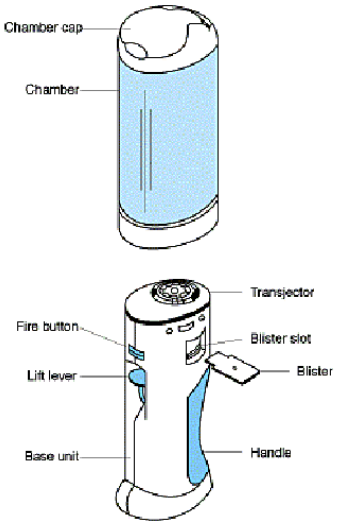

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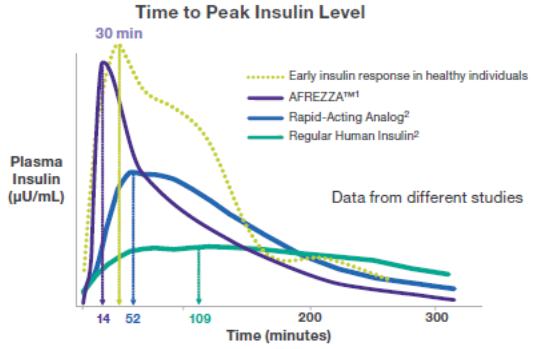
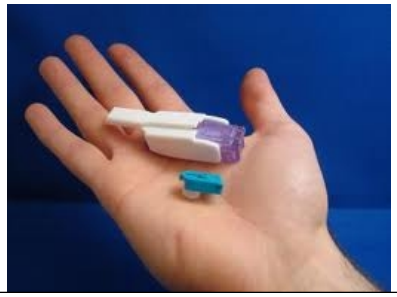


1. Non-diabetic obese subjects after 100 g oral glucose. Adapted from Kipnis D. *Ann Intern Med.* 1968;69:891-900.
2. Insulin Aspart, 0.2 U/kg. Regular Human Insulin, 0.2 U/kg units. Subcutaneous injection in abdomen. Adapted from Mudaliar SR et al. *Diabetes Care.* 1999;22:1501-1506.



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Conclusiones

- El descubrimiento de la insulina es uno de los hitos de la historia de la medicina
- Grandes avances en dispositivos para administrar insulina
- Los análogos de insulina basal proveen un avance para facilitar la insulinización con pocos efectos adversos
- No todos los análogos de insulina basal son iguales

Preguntas…
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