



# Intensificación: basal bolo vs premezcla

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## Agenda

- Qué sigue después de una insulina basal?
  - Premezcla
  - Basal plus
  - Bolos secuenciales
  - Basal bolo
- Pros y contras de cada uno
- Medicina basado en la evidencia
- Nuevas recomendaciones

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## Inercia luego de insulina basal

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### Inercia a intensificación

- 11696 pacientes de una base de datos del Reino Unido
- Hba1c 9.7% cuando iniciaron insulina basal
- 36% de pacientes intensificaron
  - Mediana 4.3 años
- Factores que retrasan intensificación: edad y duración de DM
- Factores que aceleran intensificación: IMC

EndoDrChen.com Khunti K. Diab Obes Metab. 2016;18:401

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### Inercia a intensificación

- Para pacientes que tenían indicación de intensificación (Hba1c >7.5%)
  - Sólo 30.9% intensificaron
    - 96.1% Hba1c >7.5%
    - 88.9% Hba1c >8%
    - 60.5% Hba1c >9%
    - Promedio 9.3%
  - 30.2% bajaron hba1c y quedaron con <7.5%
  - Mediana para intensificación 3.7 años

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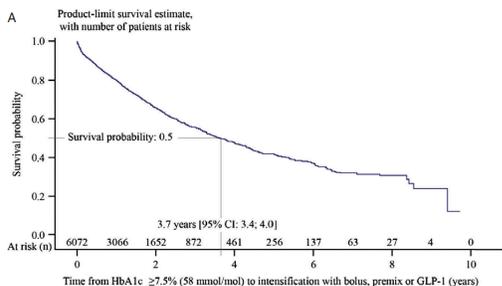
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### Tiempo para intensificación



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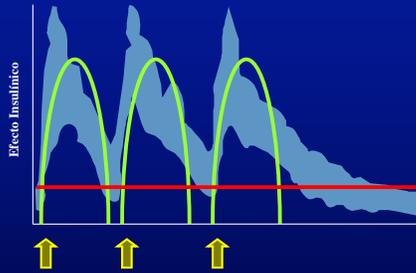
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### Basal bolo: 3 dosis ultrarrápida + 1 basal



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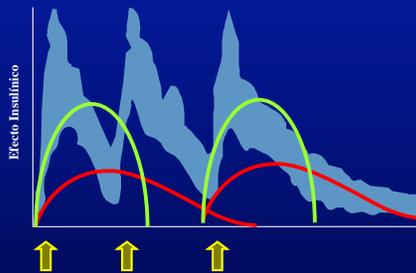
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### Premezcla: Dos dosis ultrarrápida combinado con 2 dosis de intermedias



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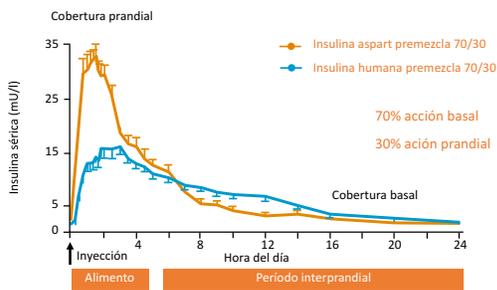
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### Premezclas: aspart bifásica vs insulina humana 70/30



EndoDrChen.com Weyer et al. Diabetes Care 1997;20:1612-4.

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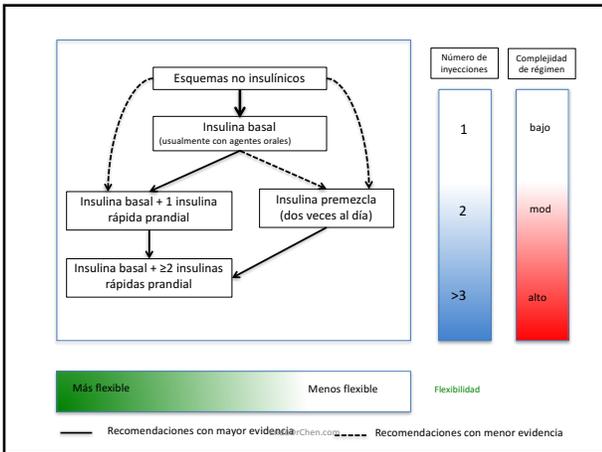
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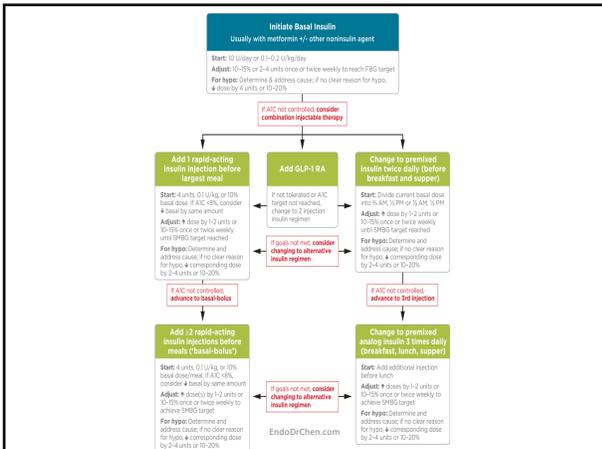
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### Cuál estrategia de intensificación?

- Basal plus/basal bolo
  - Mayor reducción de Hba1c?
  - Más fisiológico
  - Mejor titulación de dosificación
  - Uso de 2 lapiceros (tipos) 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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**EVIDENCIA CLÍNICA: CUANDO INICIA TRATAMIENTO**

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**PACIENTES CON DESAYUNOS LIGEROS**

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**Diseño**

- Es un hábito muy común desayunar muy poco o no desayunar del todo
  - Asociado a mayores descontrol metabólico
  - Asociado a mayor peso
  - Hábitos de la infancia persisten en la edad adulta
- Pacientes que consumen <15% del total de calorías diarias en el desayuno
- Premezcla tid (mix 25 ó 50) vs basal bolo (glargina + 1, 2 ó 3 dosis de lispro)

EndoDrChen.com Giugliano D. Diabetes Care. 2014;37:372

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## Diseño

- Esquemas de tratamiento:
  - 1 dosis de premezcla al almuerzo ó cena y luego se agrega la segunda dosis
  - 1 dosis de basal, luego se van agregando bolos secuenciales según las glicemias

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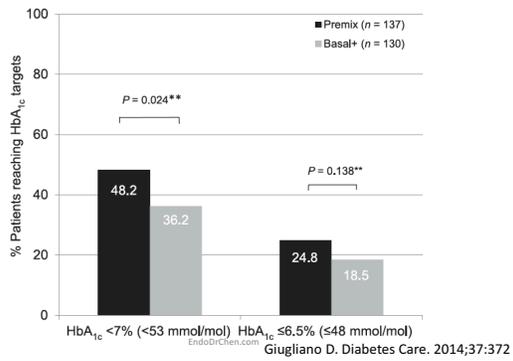
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## Metas de Hba1c




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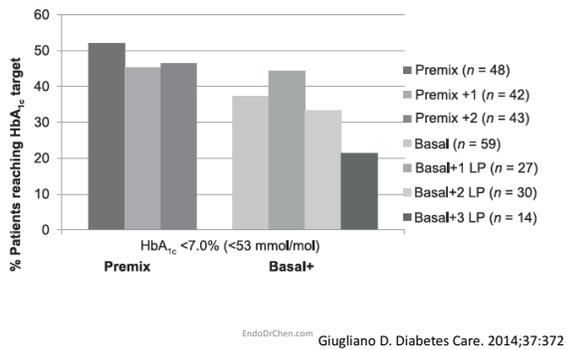
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## Metas de Hba1c




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## Hipoglicemias

Types	Premix (n = 169)		Basal+ (n = 173)		P value, incidence/rate
	Incidence, n (%)	Rate, mean (SD)	Incidence, n (%)	Rate, mean (SD)	
All hypoglycemia	109 (64.5)	9.63 (19.31)	104 (60.1)	8.13 (13.45)	0.379/0.435
Nocturnal episodes	58 (34.3)	1.91 (5.20)	41 (23.7)	1.09 (3.25)	0.018/0.068
Non-nocturnal episodes	102 (60.4)	7.72 (16.36)	98 (56.6)	7.04 (12.12)	0.472/0.733
Severe episodes	4 (2.4)	0.09 (0.74)	6 (3.5)	0.12 (0.80)	—/0.852

All treated patients with at least one dose of study medication. Incidence is the number/percentage of patients with a least one event between baseline and study end. Rate is per episode/patient/1 year.

EndoDrChen.com Giugliano D. Diabetes Care. 2014;37:372

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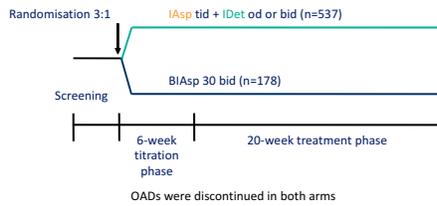
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## PREFER: study design

**Inclusion criteria:**  
 One or two OADs without insulin  
 One or two OADs with od NPH/glargine  
 7% ≤ HbA<sub>1c</sub> ≤ 12%



OAD, oral antidiabetic drug; od, once daily; NPH, neutral protamine Hagedorn; glargine, insulin glargine; HbA<sub>1c</sub>, glycated haemoglobin A<sub>1c</sub>; tid, three times daily  
 Liebl et al. Diabetes Obes Metab 2009;11:45-52  
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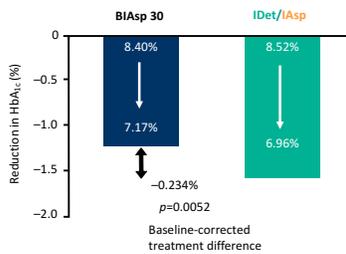
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## PREFER: HbA<sub>1c</sub> reduction



Liabl et al. Diabetes Obes Metab 2009;11:45-52  
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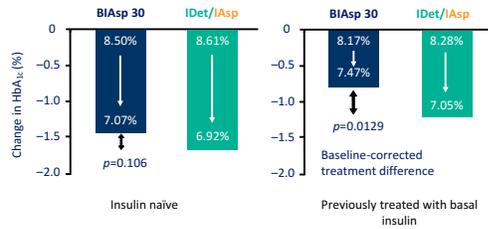
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**PREFER: HbA<sub>1c</sub> reduction in insulin-naïve vs. insulin-treated patients**



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

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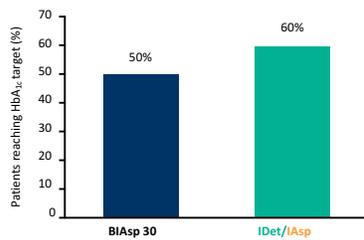
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**PREFER: percentage of patients achieving HbA<sub>1c</sub><7.0%**



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 <sup>#</sup> 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  
<sup>#</sup>Calculated for the final 20 weeks of the study

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

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### CUANDO FALLA UNA BASAL... BASAL BOLO VS PREMEZCLA

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### HABRÁ UNA FORMA MÁS SENCILLA DE HACERLO? BOLOS SECUENCIALES VS PREMEZCLA Y BASAL BOLO

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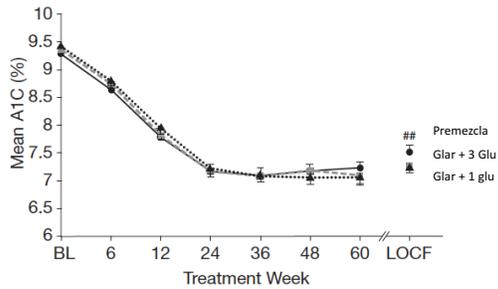
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### Reducción en Hba1c



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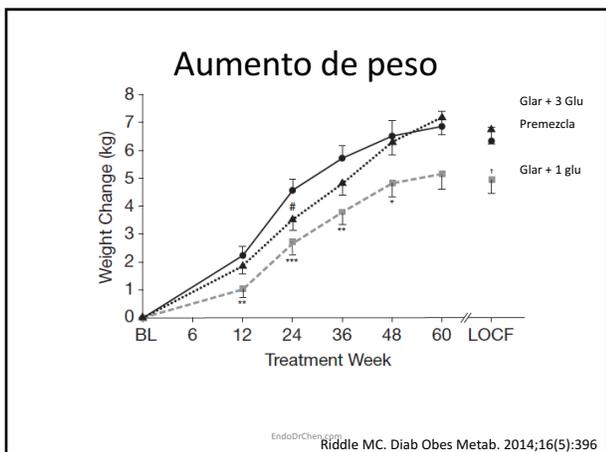
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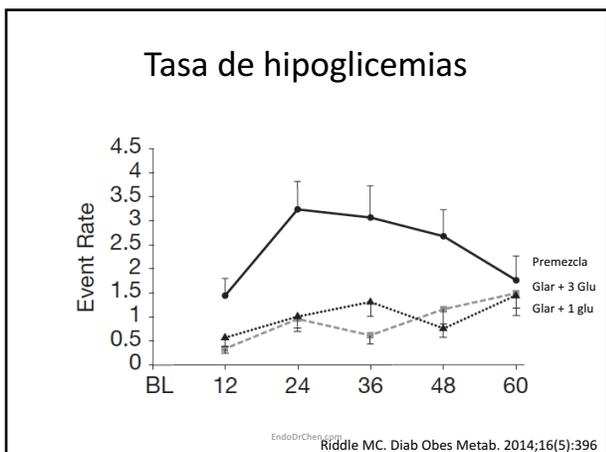
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- ### Otros parámetros
- Dosis de insulina (diferencias no significativas)
    - Glargina + 1 glulisina:  $0.92 \pm 0.47$  u/kg/día
    - Premezcla:  $1.05 \pm 0.66$  u/kg/día
    - Glargina + 3 glulisina:  $1.05 \pm 0.73$  u/kg/día
  - Necesidad de bolos
    - Glargina + 1 glulisina: 75%
    - Glargina + 3 bolos:
      - 23% 1 bolo
      - 21% 2 bolos
      - 18% 3 bolos
- EndoDrChen.com Riddle MC. Diab Obes Metab. 2014;16(5):396

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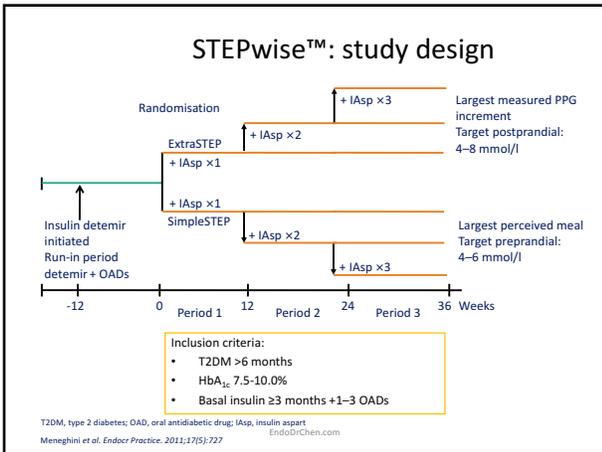
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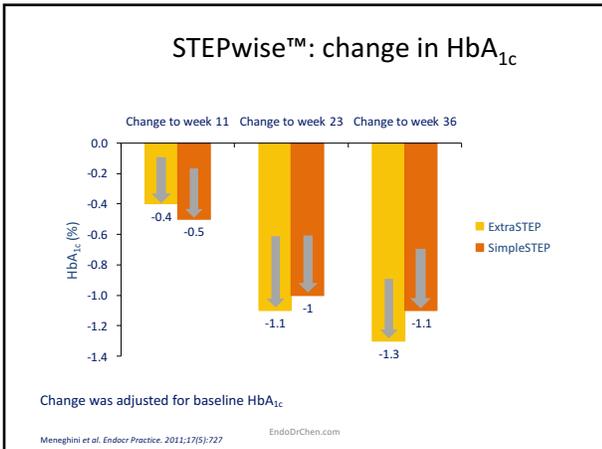
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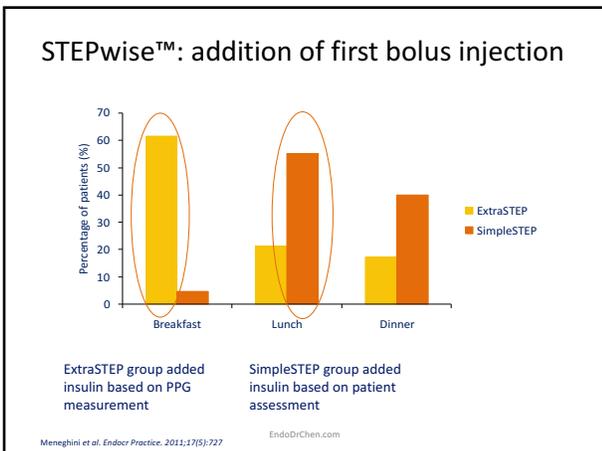
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### Comparación

- Ya que los bolos secuenciales son efectivos, cómo son comparados con el esquema de un basal bolo completo
- El inicio secuencial de bolos hará alguna diferencia en Hba1c a largo plazo?

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**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  
Rodbard HW. Lancet Diabetes Endocrinol. 2014;2:30-37

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### 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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Rodbard HW. Lancet Diabetes Endocrinol. 2014;2:30-37

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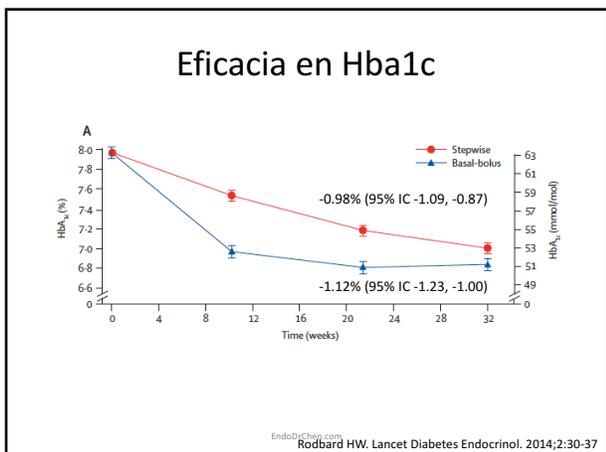
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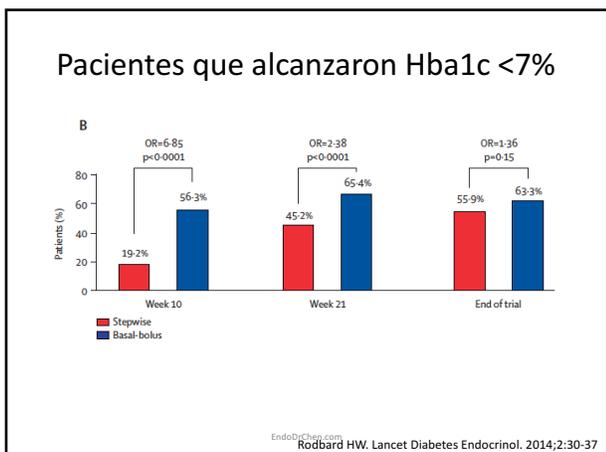
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### Requerimientos de insulina

- 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

EndoDjCheg.com  
Rodbard HW. Lancet Diabetes Endocrinol. 2014;2:30-37

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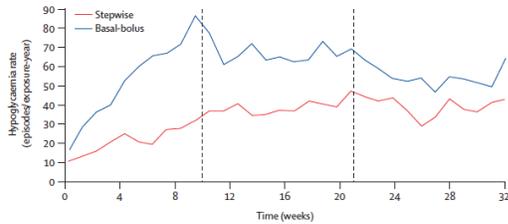
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### Hipoglicemia



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 Rodbard HW. Lancet Diabetes Endocrinol. 2014;2:30-37

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### FULLSTEP

- Los bolos secuenciales fueron no inferiores a basal bolo al final de las 32 semanas
- En el grupo STEPWISE 17% de los pacientes se controlaron con 1 sólo bolo de insulina rápida y 27% con 2 bolos
- Menores tasas de hipoglicemias en el grupo FULLSTEP

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 Rodbard HW. Lancet Diabetes Endocrinol. 2014;2:30-37

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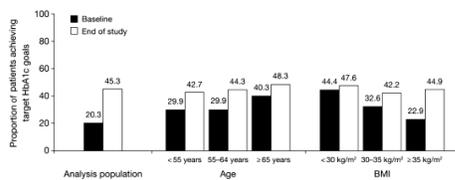
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### Metanálisis eficacia de bolos secuenciales por edad y peso



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 Lankisch MR. Prim Care Diab. 2016;10(1):51

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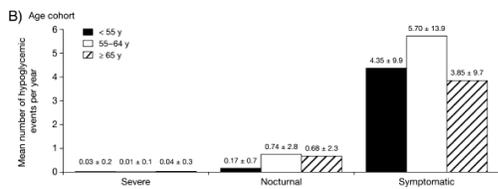
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### Metanálisis de seguridad de bolos secuenciales por edad



EndoDrChen.com Lankisch MR. Prim Care Diab. 2016;10(1):51

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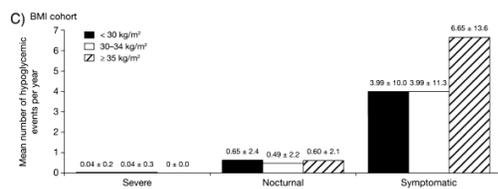
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### Metanálisis de seguridad de bolos secuenciales por peso



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### Diseño

- Población caucásica 55%, fallo a glargina con o sin orales
- Antidiabéticos orales se continúan durante el estudio
- Lispro mix 50 tid, la dosis de la noche podía cambiarse a mix 25 en caso de que glicemia en ayunas mayor a 110 mg/dl

EndoDrChen.com Rosenstock J. Diabetes Care. 2008;31:20

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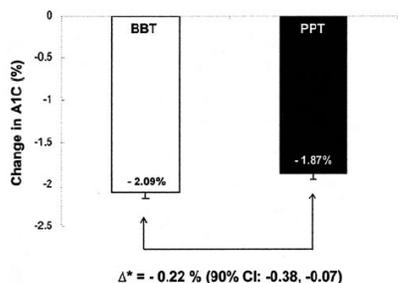
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### Reducción media de Hba1c



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### Hipoglicemias

Type of symptomatic hypoglycemia	PPT	BBT	P
Overall hypoglycemia			
Incidence	169 (90.37)	166 (88.77)	0.736
Rate (number of episodes · patient <sup>-1</sup> · year <sup>-1</sup> )	51.20 ± 50.08	48.70 ± 48.41	0.610
Nocturnal hypoglycemia			
Incidence	100 (58.29)	110 (58.82)	1.000
Rate (number of episodes · patient <sup>-1</sup> · year <sup>-1</sup> )	4.78 ± 7.15	6.17 ± 10.68	0.139
Severe hypoglycemia			
Incidence	6 (3.21)	4 (2.14)	0.751
Rate (number of episodes · patient <sup>-1</sup> · year <sup>-1</sup> )	0.10 ± 0.65	0.04 ± 0.31	0.266
Hypoglycemia confirmed by PG values			
PG <72 mg/dl (<4.0 mmol/l)			
Incidence	165 (88.24)	165 (88.24)	1.000
Rate (number of episodes · patient <sup>-1</sup> · year <sup>-1</sup> )	46.50 ± 48.00	44.95 ± 46.80	0.747
PG <60 mg/dl (<3.3 mmol/l)			
Incidence	148 (79.14)	150 (80.21)	0.898
Rate (number of episodes · patient <sup>-1</sup> · year <sup>-1</sup> )	20.75 ± 26.86	19.26 ± 24.51	0.574
PG <50 mg/day (<2.8 mmol/l)			
Incidence	104 (55.61)	115 (61.50)	0.294
Rate (number of episodes · patient <sup>-1</sup> · year <sup>-1</sup> )	7.34 ± 12.88	5.93 ± 9.92	0.230

Data are means ± SD or n (%) unless otherwise indicated. PG, plasma glucose.

EndoDrChen.com Rosenstock J. Diabetes Care. 2008;31:20

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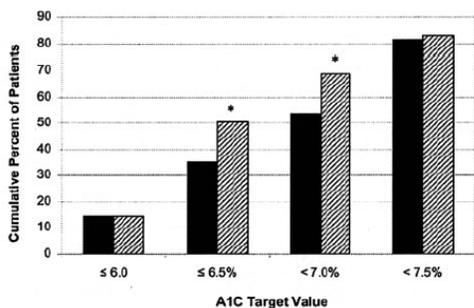
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### % que alcanzan metas



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### Otros resultados

- No se alcanzó no inferioridad de premezcla
- Mayores dosis de insulina en grupo premezcla (146 u vs 123 u por día)
- 55% hicieron switch a mix 25 en la noche, alcanzando Hba1c menor (6.9% switch vs 7.1% en no switch)

EndoDrChen.com Rosenstock J. Diabetes Care. 2008;31:20

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### CUANDO FALLA PREMEZCLA: BASAL BOLO VS PREMEZCLA TID

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### Introducción

- Realizado en población asiática
- Lispro mix 50 antes del desayuno y almuerzo y mix 25 antes de cena vs glargina + 3 dosis de lispro
- Es una alternativa que se incluye en las guías chinas de manejo de DM
- 24 semanas de tratamiento
- Todos usando premezcla bid de base

EndoDrChen.com Jia W. Lancet Diab Endocrinol. 2015;3:254

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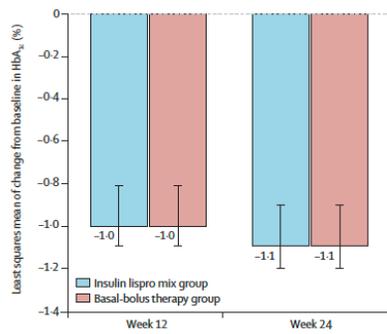
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### Reducción de Hba1c



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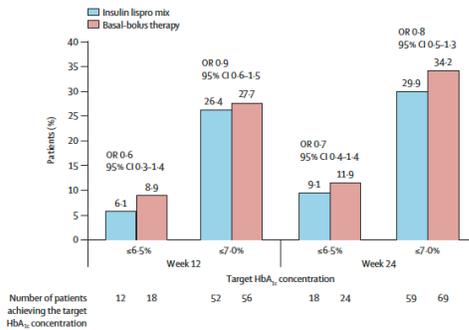
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### % con Hba1c <7%



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### Hipoglicemias

	Premix group (n=197)	Basal-bolus group (n=202)	p value
<b>Overall hypoglycaemia</b>			
Incidence	108 (55%)	111 (55%)	--
Number of episodes	519	446	--
Rate (number of episodes per patient per 30 days)	0.47 (1.04)	0.41 (0.67)	0.148
<b>Nocturnal hypoglycaemia</b>			
Incidence	27 (14%)	22 (11%)	--
Number of episodes	37	44	--
Rate (number of episodes per patient per 30 days)	0.03 (0.09)	0.05 (0.21)	0.235
<b>Severe hypoglycaemia</b>			
Incidence	0	0	--
Number of episodes	0	0	--
Rate (number of episodes per patient per 30 days)	0	0	--
<b>Documented symptomatic hypoglycaemia</b>			
Incidence	76 (39%)	68 (34%)	--
Number of episodes			
<b>Asymptomatic hypoglycaemia</b>			
Incidence	60 (31%)	70 (35%)	--
Number of episodes	145	209	--

EndoDrChen.com Jia W. Lancet Diab Endocrinol. 2015;3:254

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## Consideraciones

- Dos premezclas diferentes
  - Pierde la ventaja de usar un solo lapicero y más bien crea un poco más de confusión
- 3 inyecciones diarias vs 4 inyecciones diarias
- Titulación más rígida
- Población asiática

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## BASAL PLUS VS PREMEZCLA

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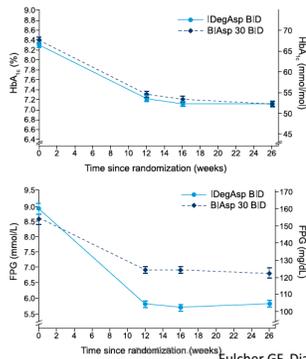
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## Eficacia



Fulcher GF. Diabetes Care. 2014;37:2084

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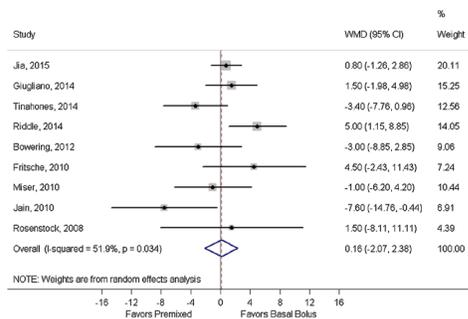
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### Metanálisis basal bolo vs premezcla



Hypoglycemia (episodes per year) *Gugliano D. Endocrine. 2016;51:417*

### ADHERENCIA A INSULINOTERAPIA SEGÚN ESQUEMAS

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	Skipping doses		P-value
	Yes (n=88)	No (n=241)	
Age (years)	54.0±10.5	57.2±12.0	0.03*
Sex (F/M), n	42/46	139/102	0.5*
Diabetes duration (year)	7.6±5.5	9.6±6.7	0.07*
Daily insulin dose (IU/day)	46.9±24.0	40.2±24.0	0.03*
Insulin regimen, n (%)			
Basal bolus	54 (61.3)	111 (46.0)	0.04*
Premixed	20 (22.7)	58 (24.0)	
Basal insulin	14 (15.9)	72 (27.3)	
Fasting blood glucose (mg/dL)	153.7±53.0	146.5±57.0	0.30*
Postprandial blood glucose (mg/dL)	191.5±65.0	179.6±72.0	0.04**
Omitting dose for >1 day (2-5 days), n (%)	8 (9.4)	-	-

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Gogas Yavuz D. Pat Pref Adh. 2015;9:1225

Reasons for treatment discontinuation,* n (%)	
Patient-related	66 (75.9)
Negative beliefs (risk of dependency, weight gain) about insulin therapy	21 (24.1)
Preference of oral medication	18 (20.6)
Normalization of blood glucose levels	16 (18.3)
Fear of injection/bleeding	5 (5.7)
Influence of family members and friends	6 (6.8)
Physician-related	12 (13.7)
Adverse events	7 (8.0)
Major hypoglycemia	2 (2.3)
Allergic skin reaction	3 (3.5)
Leg edema	2 (2.3)
Challenges in drug procurement	2 (2.2)
Reasons for dose skipping (n=88), n (%)	
Forgetting	36 (40.9)
Hypoglycemia	8 (9.0)
Normalization of blood glucose	5 (5.6)
Drug unavailability	8 (9.0)
Feeling good/consideration of injection unnecessary	20 (22.7)
Workload	7 (7.9)
Inability to eat	4 (4.5)

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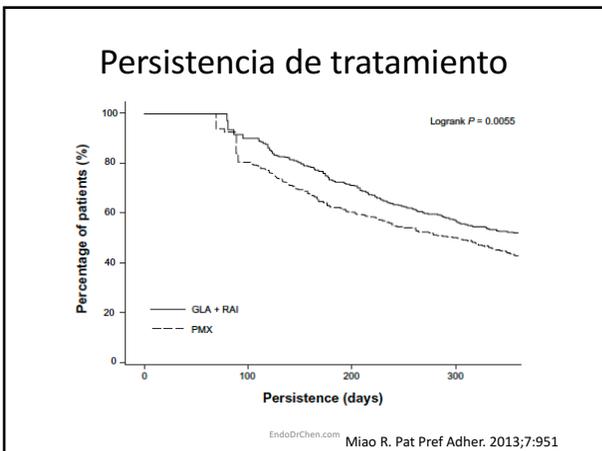
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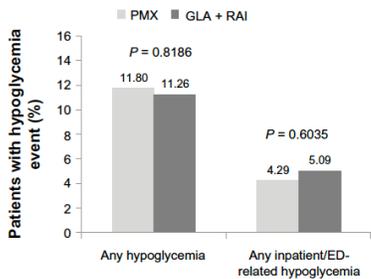
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### Tasa de hipoglicemias



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### CONCLUSIONES

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### Cuál paciente para qué esquema?

Premix insulin analogs	Basal plus/basal bolus
Patient preference	Type 1 diabetes (any age)
Older age	Younger age
Need assistance with injections	Highly motivated and compliant
Organized lifestyle	Active lifestyle
Two meals a day or evening main meal	High variability in eating habits

EndoDrChen.com Mosenson O. Diabetes Care. 2013;36:S212

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### Cuál estrategia de intensificación?

- Basal plus/basal bolo
  - Mayor reducción de Hba1c?
  - Más fisiológico
  - Mejor titulación de dosificación
  - Uso de 2 lapiceros (tipos) 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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Malmberg K. Eur Heart J. 2005;26:650

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