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¿QUÉ TENEMOS EN LISTA DE ESPERA PARA EL TRATAMIENTO DE LA DIABETES?

Fármacos en desarrollo

- Mezclas insulina-aGLP1
  - iGlarLixi
  - iDegLira
- iSGLT2
  - Ertugliflozina: En revisión por FDA (similar a los actuales)
  - Sotagliflozina: En fase 3 (iSGLT1 + iSGLT2)
- aGLP1
  - Semaglutida: Semanal y oral diario (fase 3)
  - Unicorn Intarcia: Parche exenatida (en revisión por FDA)
- Insulinas:
  - FiAsp
  - GRI ("*smart insulin*")
  - Insulina inhalada
- Activadores de glucokinasa

Mezclas Insulina + aGLP1

LixiLan vs Glargina

	LixiLan (N = 161)	Glargine (N = 162)
Mean HbA_{1c}, %	8.1	8.0
Mean HbA_{1c} at week 24, %	6.3	6.5
Change in HbA_{1c} at week 24, %	-1.8	-1.5
Proportion achieving HbA_{1c} < 7.0%, %	84.4	78.3
Body weight at baseline, kg	90.3	91.7
Body weight at week 24, kg	89.1	92.1
Change in body weight at week 24, kg	-1.2	+0.4
Proportion with documented hypoglycemia (≤ 70 mg/dL), %	22	23

Rosenstock J, et al. ADA 2014. Abstract 332-OR.[14]
Venkat MV, et al. *J Diabetes.* 2014;6:491-495.[15]

IDegLira vs Glargina

	IDegLira* (N = 278)	Glargine (N = 279)	*P* Value
Mean HbA_{1c} at randomization, %	8.4	8.2	-
Mean HbA_{1c} at wk 26, %	6.6	7.1	< .001
HbA_{1c} change at wk 26, %	-1.8	-1.1	< .001
HbA_{1c} < 7% at wk 26, %	71.6	47.0	< .001
Body weight at baseline, kg	88.3	87.3	-
Body weight at wk 26, kg	86.9	89.1	< .001
Body weight change at wk 26, kg	-1.4	+1.8	< .001
Hypoglycemia rate, events/patient year of exposure			
Confirmed	2.23	5.05	< .001
Nocturnal	0.22	1.23	< .001

Buse JB, et al. ADA 2015. Abstract 166-OR.[11]

iSGLT2

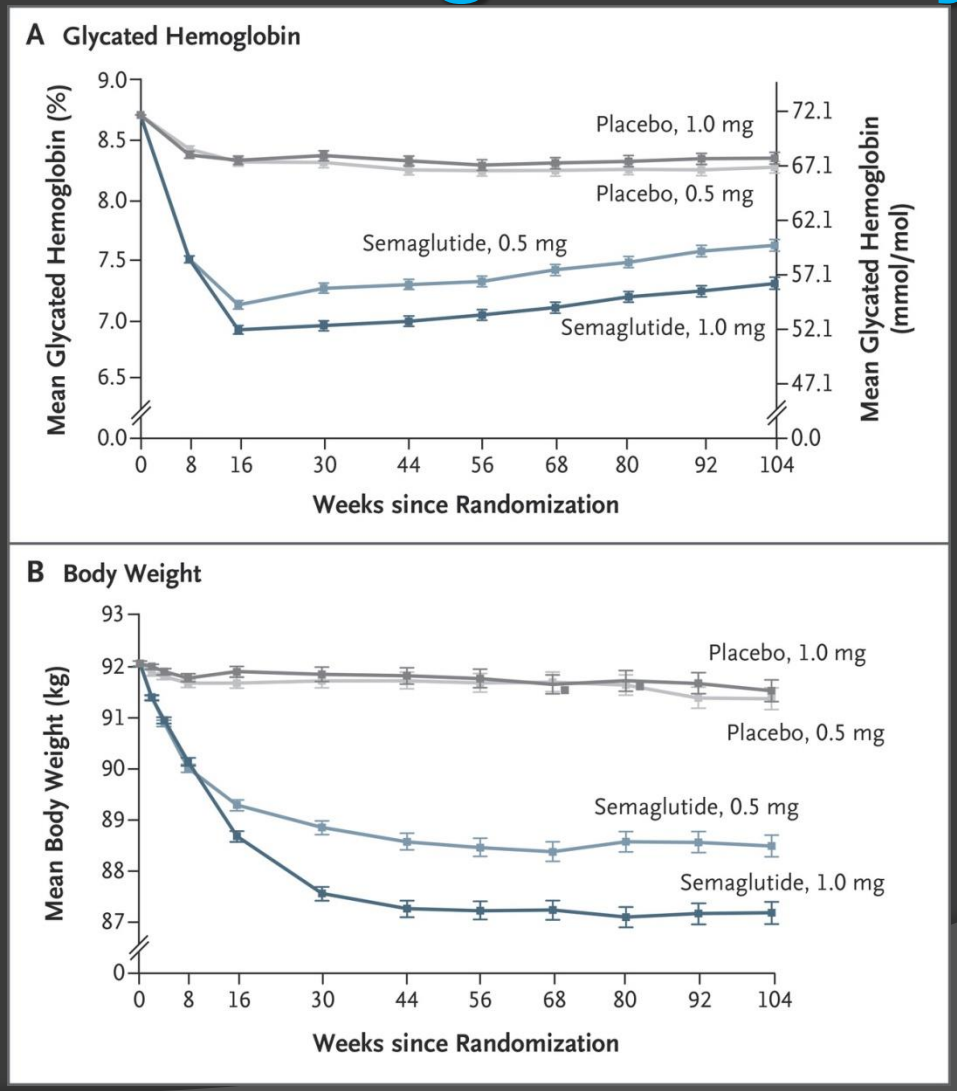
Sotagliflozina en DM1

	Placebo (N = 17)	Sotagliflozin (N = 16)	P
Efficacy			
HbA_{1c} change from baseline (%)	−0.06	−0.55*	**0.002**
FPG change from baseline assessed at day 29 (mg/dL)	39.0	−18.6	0.15
Daily bolus insulin change from baseline assessed at days 3–27 (%)	−6.4	−32.0*	**0.007**
Daily basal insulin change from baseline assessed at days 3–27 (%)	0.2	−2.4	0.53
Total daily insulin change from baseline assessed at days 3–27 (%)	−0.7	−15.3*	**0.029**
Mean body weight change from baseline assessed at day 29 (kg)	0.5	−1.7*	**0.005**
Postmeal urinary glucose (g/3 h) at day 29†	9.2	29.1	**0.025**
Postmeal plasma glucose AUC (mg · h/dL over 3 h) at day 29†	761	595	**0.005**
PYY postmeal AUC change from baseline assessed at day 29 (pmol/L · h over 3 h)	−0.7	6.0*	**0.018**
Seated systolic blood pressure change from baseline assessed at day 29 (mmHg)	−3.9	−4.9	0.45
Safety			
Patients with any TEAE (%)	12 (71)	14 (88)	N/A
Patients with SAE (both with DKA‡)	0	2	N/A
Hypoglycemic events (SMBG ≤70 mg/dL, baseline–day 36)	354	304	N/A
Documented symptomatic hypoglycemia (SMBG ≤70 mg/dL, baseline–day 36)	185	162	N/A
Asymptomatic hypoglycemia (SMBG ≤70 mg/dL, baseline–day 36)	117	80	N/A
SH	0	0	N/A
Hypoglycemia (SMBG ≤70 mg/dL, PPD) change from baseline at days 3–27	−0.4*	−0.7*	0.77
Hypoglycemia (CGM ≥10 continuous min <70 mg/dL, PPD) change from baseline assessed at days 3–27	−0.15	−0.09	0.75
Laboratory values associated with volume status			
Serum sodium (mmol/L), change from baseline at day 29 (day 36)	−1.00 (−0.53)	−0.50 (1.50)	N/A
Serum creatinine (μmol/L), change from baseline at day 29 (day 36)	−0.53 (1.53)	2.63 (0.63)	N/A
Serum BUN (mmol/L), change from baseline at day 29 (day 36)	0.41 (0.11)	1.02 (−0.41)	N/A
Hematocrit, change from baseline at day 29 (day 36)	−1.4 (0)	2.1 (1.5)	N/A

For laboratory values, change from baseline was assessed at day 29, the last day of therapy, and day 36, 1 week off therapy, unless otherwise specified. N/A, not applicable; SAE, serious adverse event. *$P < 0.05$, change from baseline. †Day 1 is not a true "baseline"; therefore, P values are calculated from two-sample t tests using the observed means. ‡Both were assessed as due to insulin pump and deemed not drug related. Bold values are statistically significant.

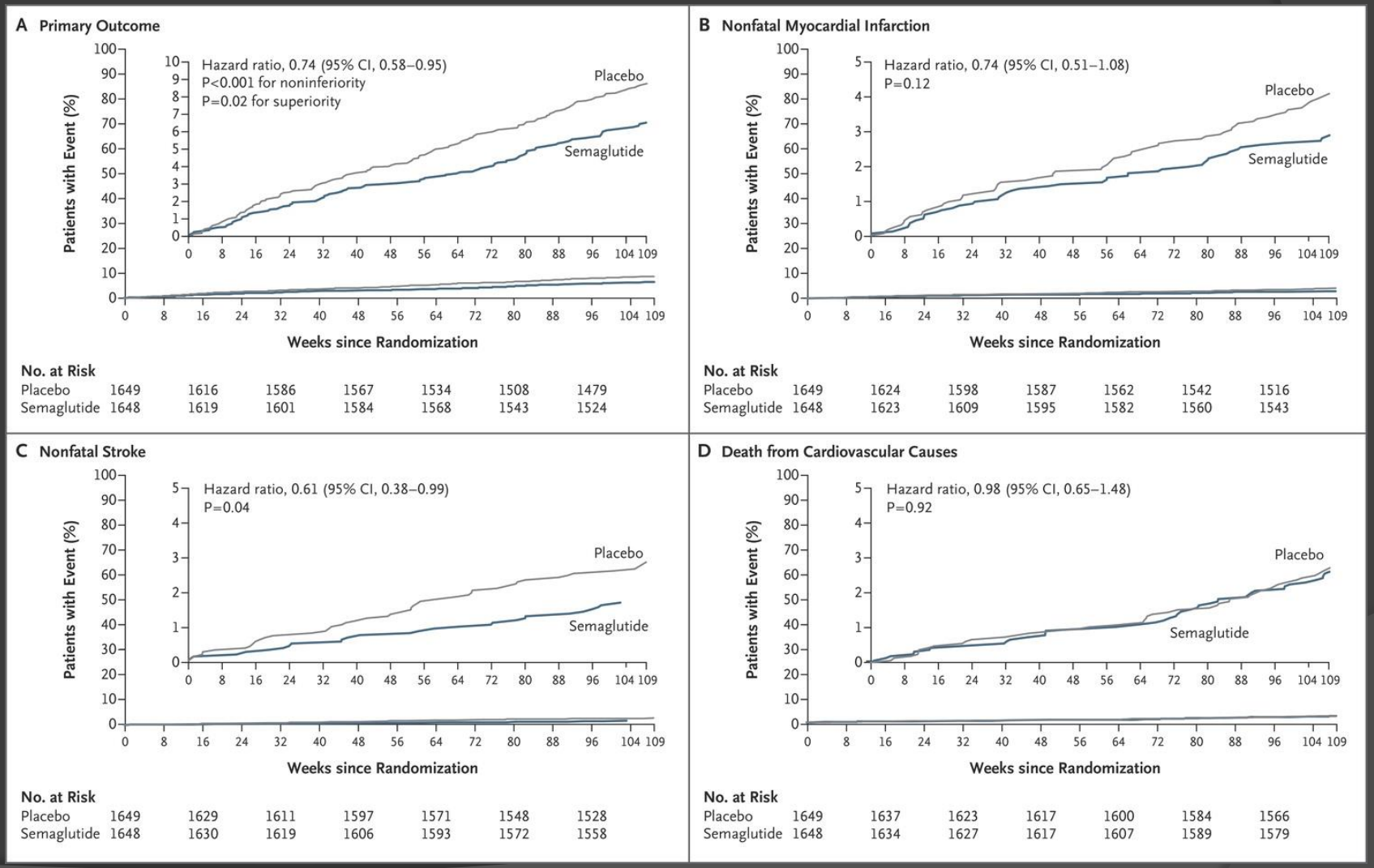
Diabetes Care 2015: 38.

SUSTAIN-6: Semaglutida Resultados en glucemia y peso



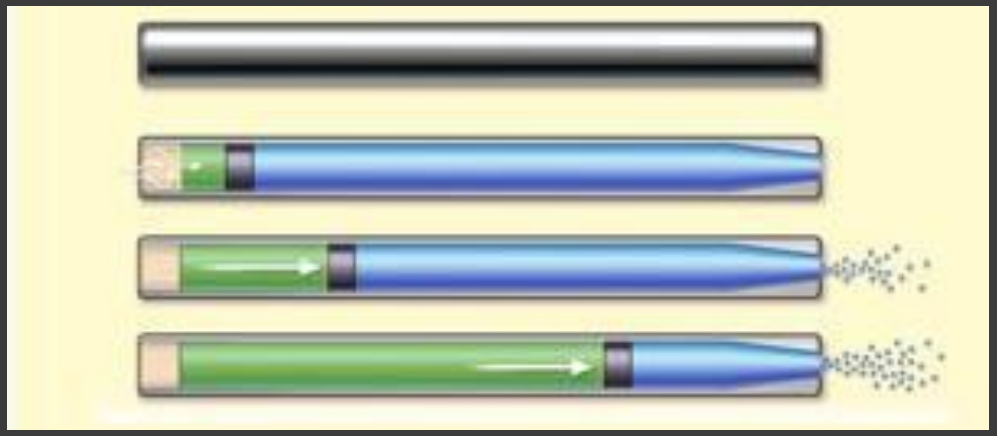
N Engl J Med 375;19 November 10, 2016

SUSTAIN-6: Semaglutida Resultados CV



N Engl J Med 375;19 November 10, 2016

Exenatida anual: DUROS (ITCA 650)



Exenatida anual: DUROS (ITCA 650)

FREEDOM-2 Trial: ITCA 650*

Drug	ITCA 650 60 µg (n=263)	Sitagliptin 100 mg (n=257)	*P* value
LS mean change from baseline in HbA_{1c}, %	-1.5	-0.8	$P < .001$
Change from baseline in weight, kg	-4	-1.3	$P < .001$

- Patients (N=535) with type 2 diabetes and taking metformin
- Baseline HbA_{1c} levels between 7.5% and 10.5%

ITCA 650 = matchstick-like device placed under the skin to continuously deliver exenatide

Rosenstock J, et al. ADA 2016. Abstract 183-OR.

Insulinas

Glucose Responsive Insulin

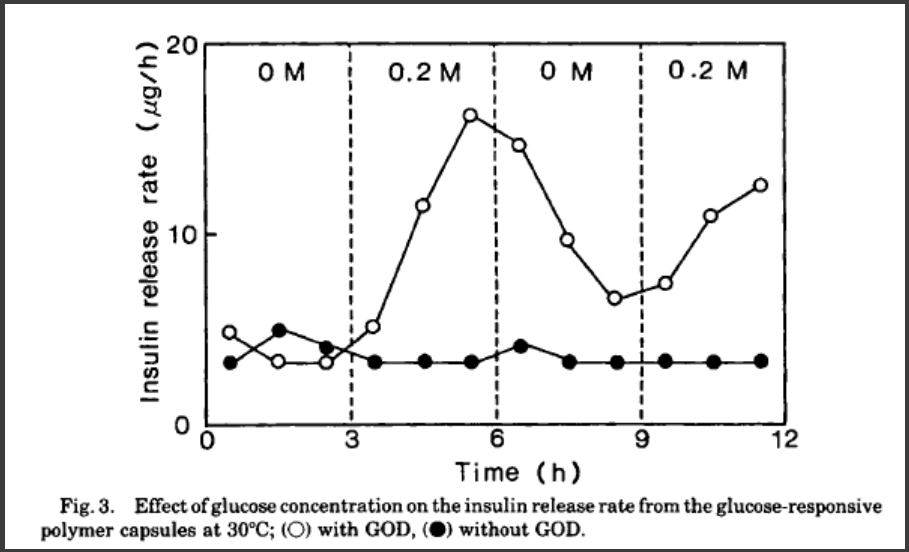
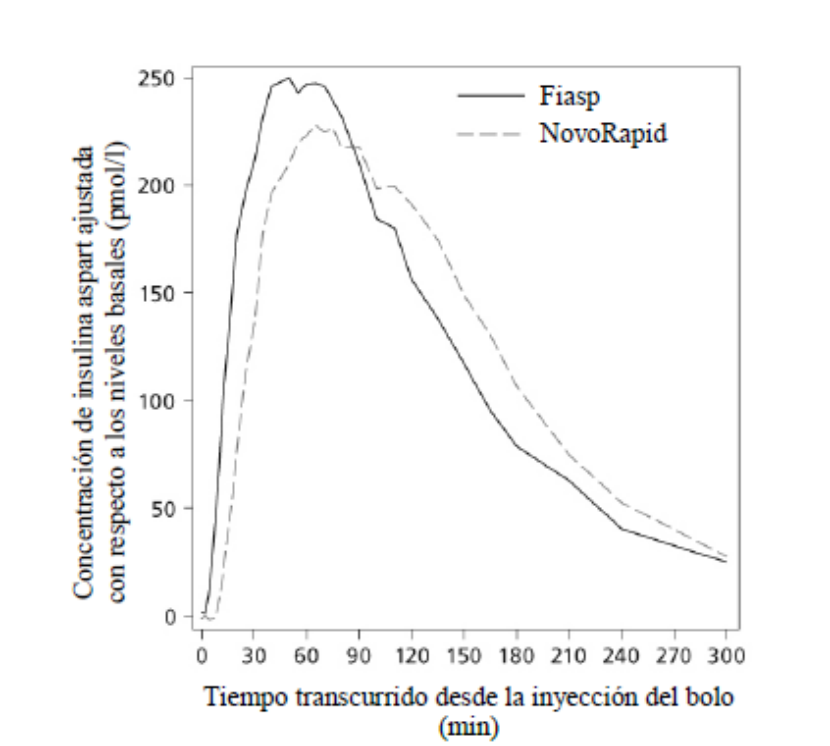


Fig. 3. Effect of glucose concentration on the insulin release rate from the glucose-responsive polymer capsules at 30°C; (○) with GOD, (●) without GOD.

- Sistemas basados en un polímero unido a Glucosa Oxidasa
- Todavía en fase experimental en animales.

Journal of Polymer Science: Polymer Letters Edition, Vol. 24, 413–417 (1986)

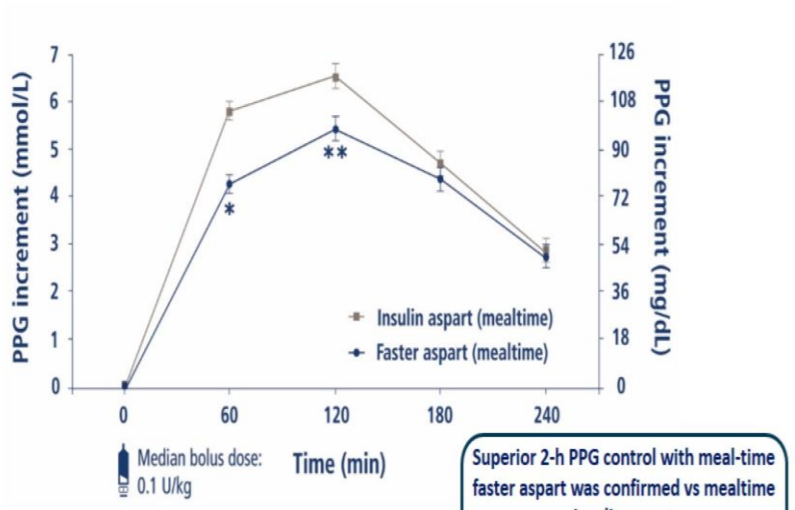
FiAsp



- IAsp + Niacinamida (vit B3) + L-arginina
- Administración desde 2 min antes a 20 min tras comenzar la comida
- No inferioridad a Iasp
- Se puede usar en bombas de insulina

FiASP: Farmacodinamia

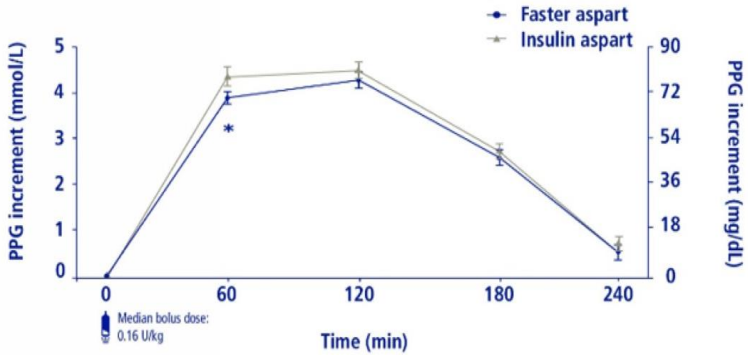
ONSET-1



Superior 2-h PPG control with meal-time faster aspart was confirmed vs mealtime insulin aspart

*P <.0001; **P =.0375. *P* values are 2-sided. ETD represents PPG changes from baseline estimate.
Changes from baseline in PPG increments were analyzed based on an ANOVA model.
Error bars: ±SE (mean).
†This agent is not yet approved by the FDA.
Russell-Jones D, et al. *Diabetes Care*. 2017. dc161771.

ONSET-2

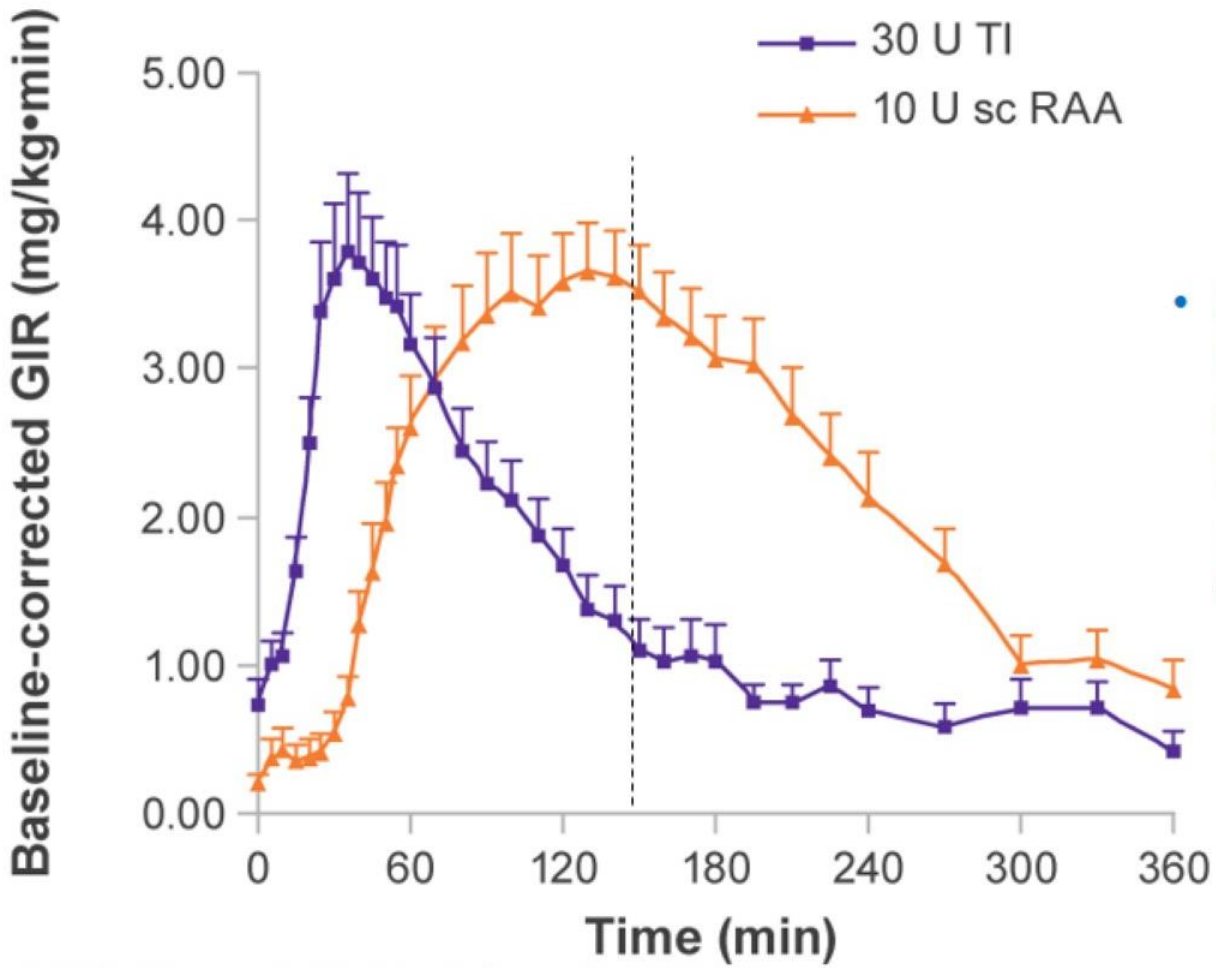


1-h ETD:*
−0.59 mmol/L [95% CI: −1.09; −0.09]
−10.6 mg/dL [95% CI: −19.6; −1.7]

2-h ETD:
−0.36 mmol/L [95% CI: −0.81; 0.08]
−6.6 mg/dL [95% CI: −14.5; 1.4]

*P =.0198.
ETD represents PPG change from baseline estimates. The analysis was based on an ANOVA model.
Error bars: ±SE (mean).
†This agent is not yet approved by the FDA.
Bowering K. et al. *Diabetes*. 2016;65(suppl 1):A63.

Insulina inhalada: Farmacodinamia



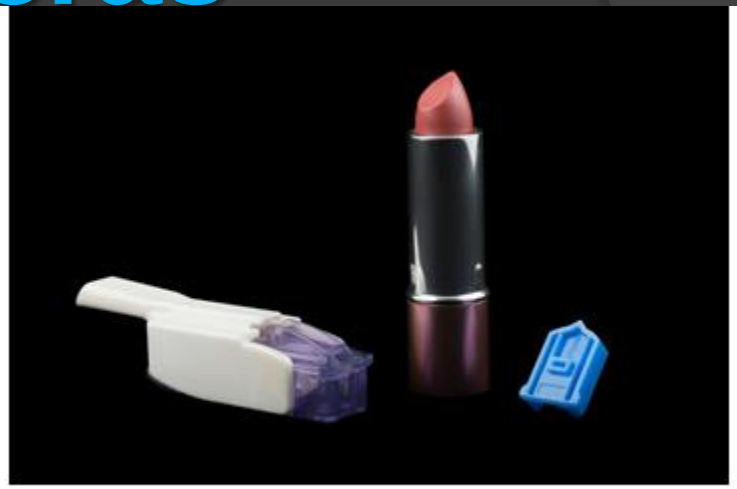
- At 150 min, both insulins have delivered the same amount of glucose-lowering effect, with 10% remaining for TI and 40% for RAA

RAA = rapid-acting analogue; TI = Technosphere® Insulin

Hijazi Y, et al. ADA. 2016. Poster 931-P.

Insulina inhalada: Tecnosferas

- Dispositivo de plástico pequeño.
- Cartuchos de 4 y 8 UI fijas de un solo uso.
- Compuesta por insulina recombinante adsorbida en partículas de Fumaril Diketopiperacina y Polisorbato 80.



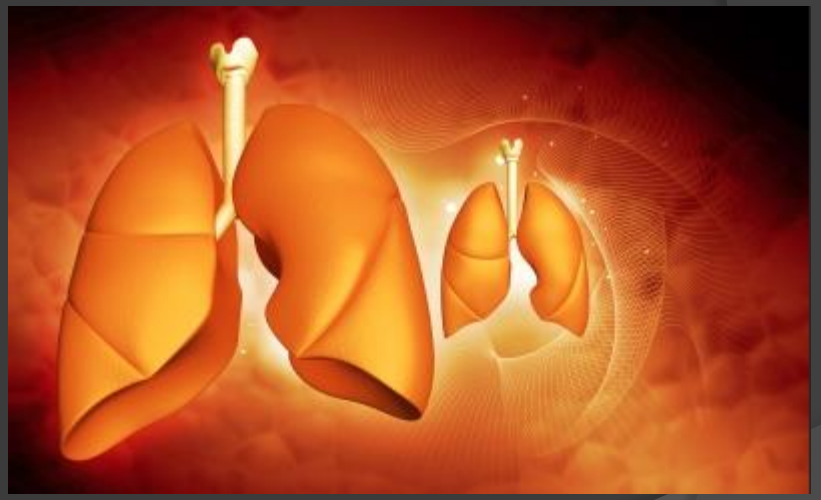
Insulina inhalada: Precauciones

- La absorción depende de la función pulmonar: **CONTRAINDICADO** en asma, COPD o cualquier enfermedad pulmonar crónica

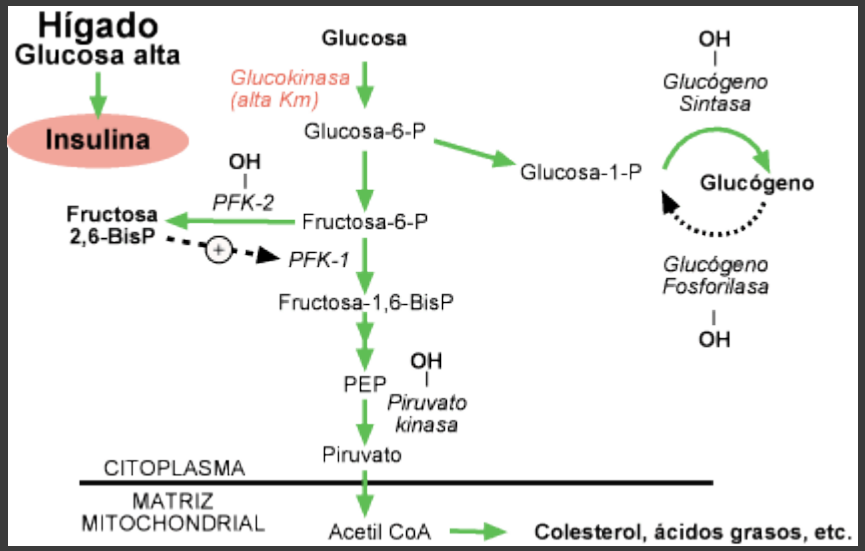
- **CONTRAINDICADO** durante periodos de hipoglucemia

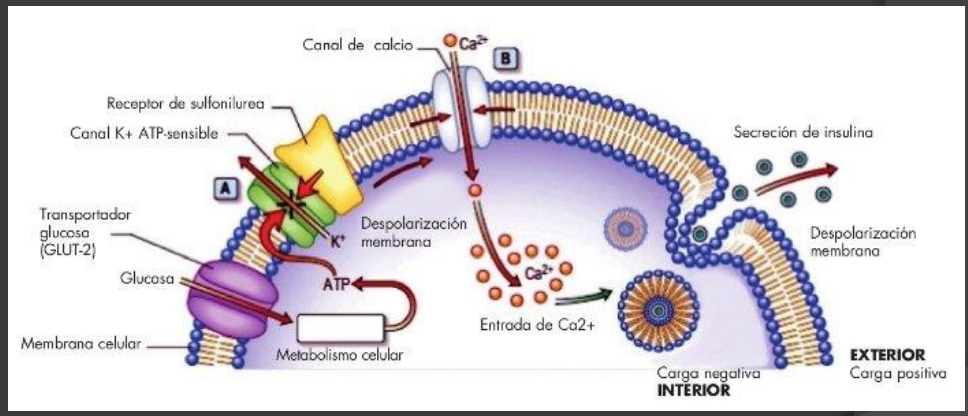
- En DM1 siempre usar con **insulina basal**.

- No se recomienda su uso en **fumadores**.



Activadores de glucokinasas





Activadores de glucokinasas: Estudios Fase 2b

PROPIEDADES DE GK

❖Se expresa en las células del islote, el hígado, células intestinales y en las neurona del SNC

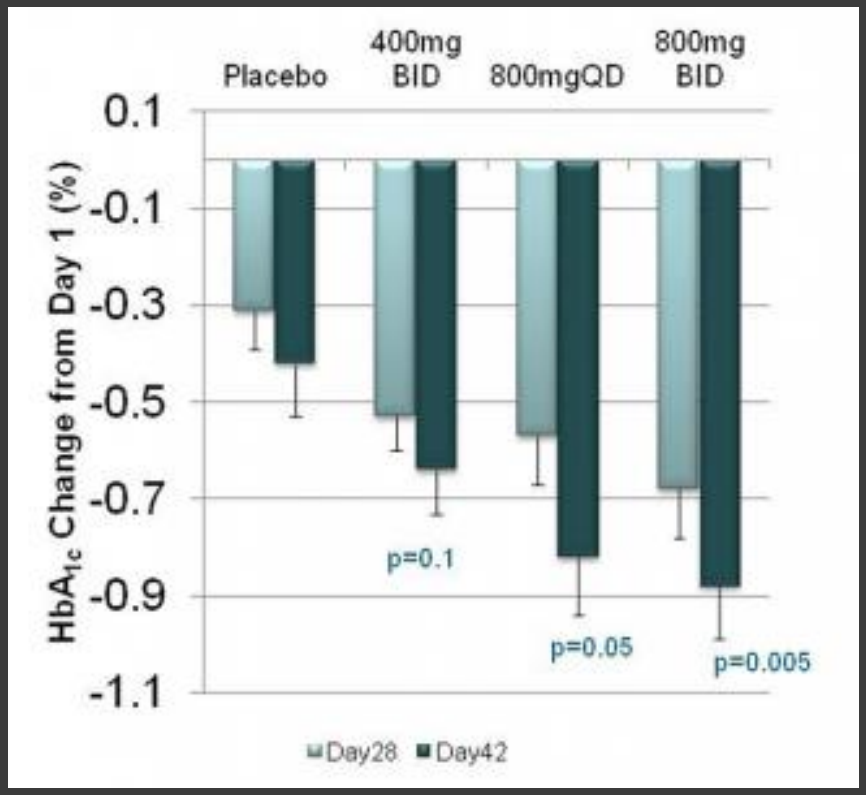
❖Es el sensor fisiológico de la glucemia en estas células

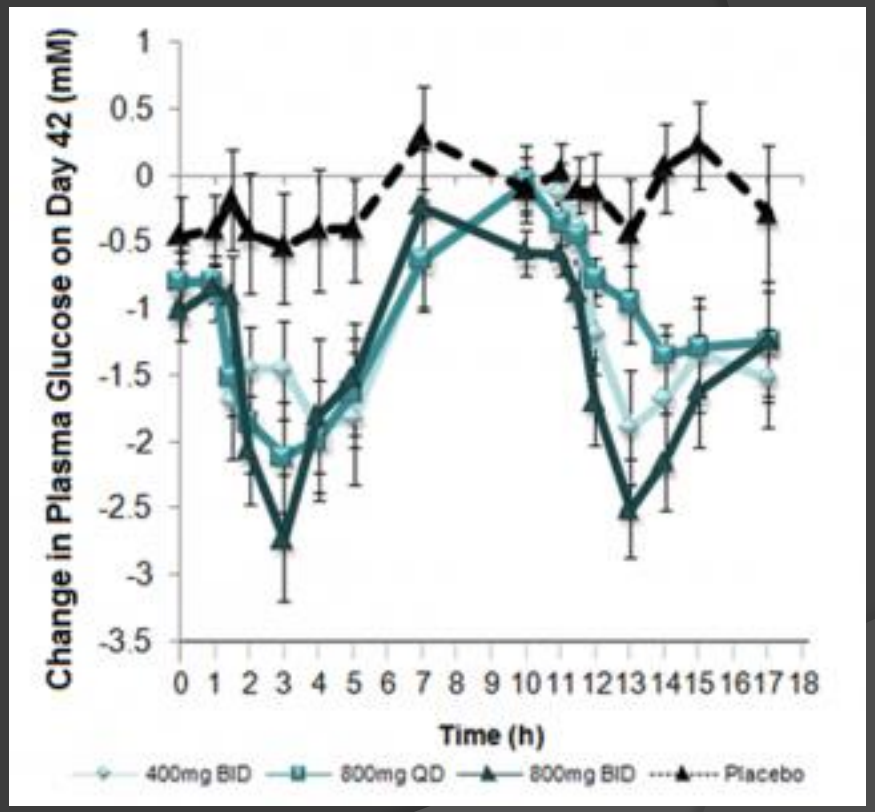
❖Modula la producción hepática de glucosa y la secreción de insulina en las células beta.

	400-mg BID (n=29)	800-mg QD (n=31)	800-mg BID (n=30)	Placebo (n=30)	All (n=120)
Age	57.8 ± 8.7	55.2 ± 7.5	57.1 ± 8.0	57.5 ± 7.2	56.9 ± 7.8
Gender	14 F, 15 M	14 F, 17 M	11 F, 19 M	7 F, 23 M	46 F, 74 M
Weight (kg)	85.5 ± 13.1	90.3 ± 12.9	84.4 ± 18.6	96.6 ± 16.6	89.2 ± 16.1
BMI	30.5 ± 4.6	31.7 ± 3.9	30.4 ± 4.8	32.6 ± 3.6	31.3 ± 4.3
HbA_{1c} (%)	8.22 ± 0.89	8.23 ± 1.01	8.36 ± 0.92	8.04 ± 0.77	8.21 ± 0.90
Diabetic Hx (years)	7.7 ± 4.2	7.5 ± 3.7	11.2±8.3	8.4 ± 5.7	8.7 ± 5.9
Metformin dose (mg/day)	1565.5 ± 431.2	1541.9 ± 538.2	1558.3 ± 501.4	1686.7 ± 418.3	1587.9 ± 473.3

mean ± SD

Activadores de glucokinasas: Estudios Fase 2b

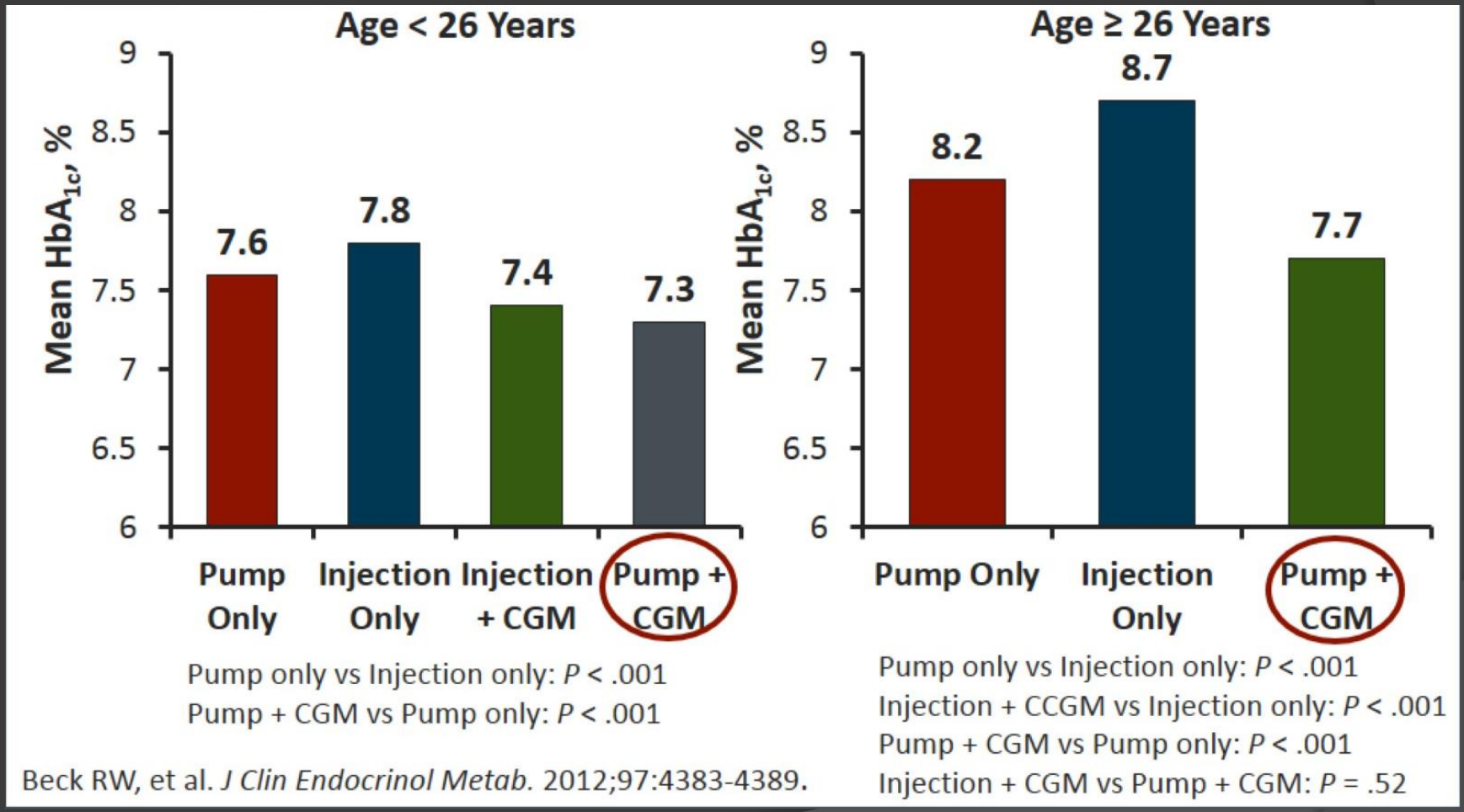




Avances tecnológicos

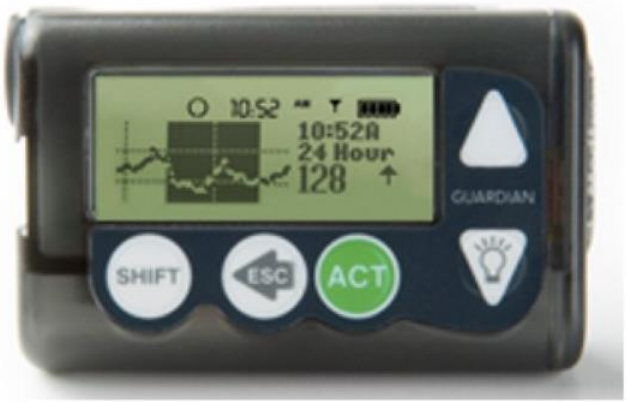
- Monitorización Continua de Glucosa
- Bombas de insulina *inteligentes*
  - *Sensor Augmented Insulin Pump*
- Páncreas artificial
  - Diseñado por pacientes
  - iLet: Glucagón solo.
  - Asa abierta y cerrada
- Trasplante de islotes
- Células madre

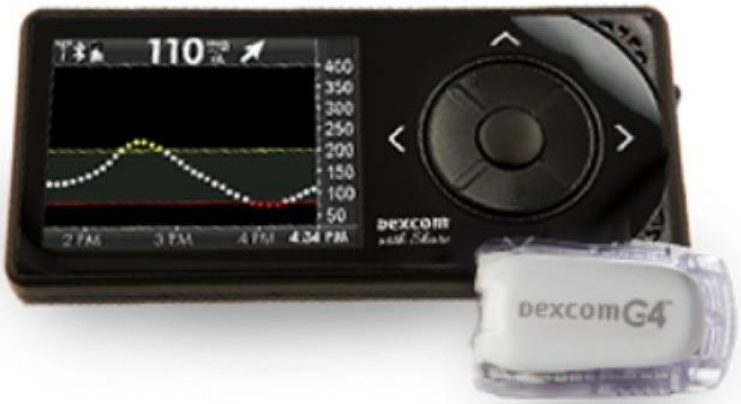
DM1: HbA1c según sistema de insulinización y MCG



Beck RW, et al. *J Clin Endocrinol Metab.* 2012;97:4383-4389.

Dispositivos de MCG





Images courtesy of Dexcom, Abbott Laboratories, and Medtronic, Inc.

Monitorización *Flash* de glucosa

Currently approved and in use in Europe

*The US FDA has not yet approved this device for use.

Images courtesy of Abbott Laboratories.

Minimed Connect

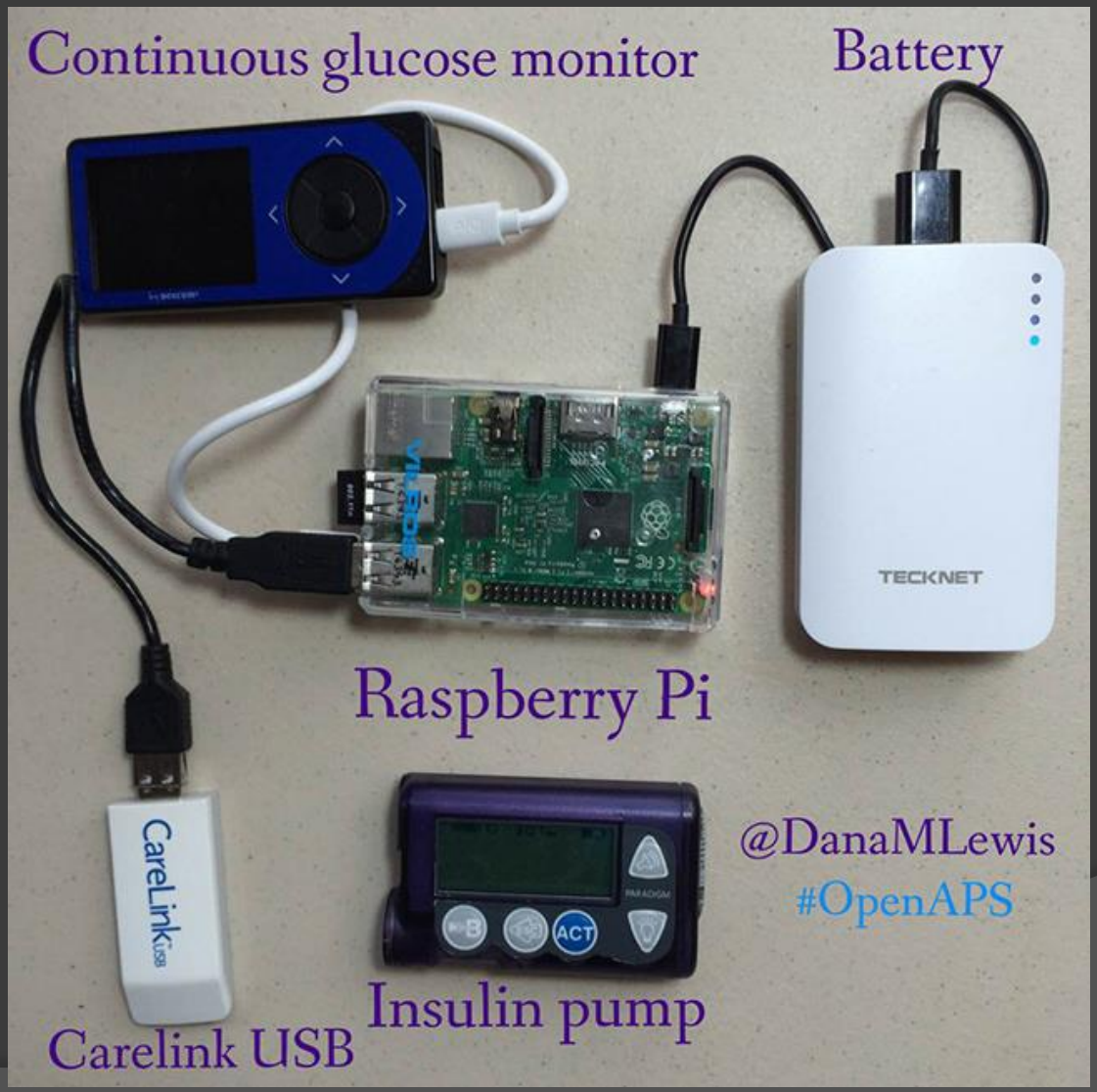
Images courtesy of Medtronic, Inc.

Bombas de insulina
"Sensor Augmented"

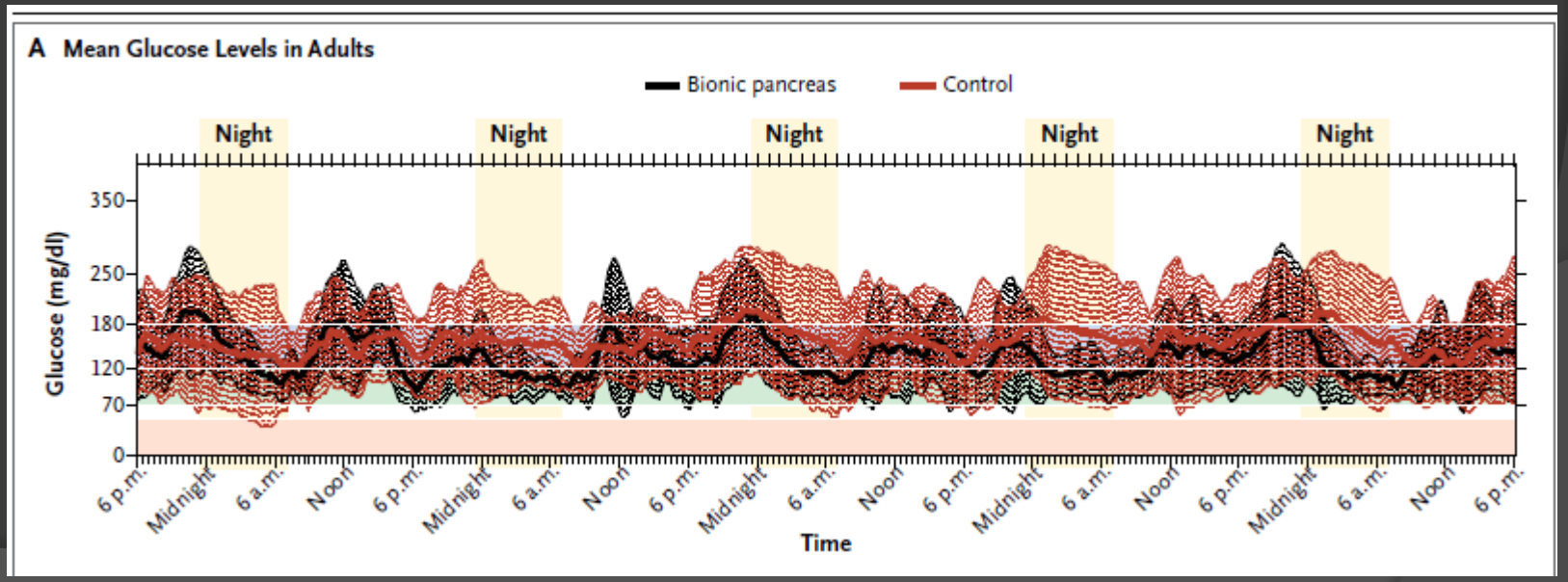
640G: Smart Guard

670G: Asa cerrada

Dana Lewis' OpenAPS



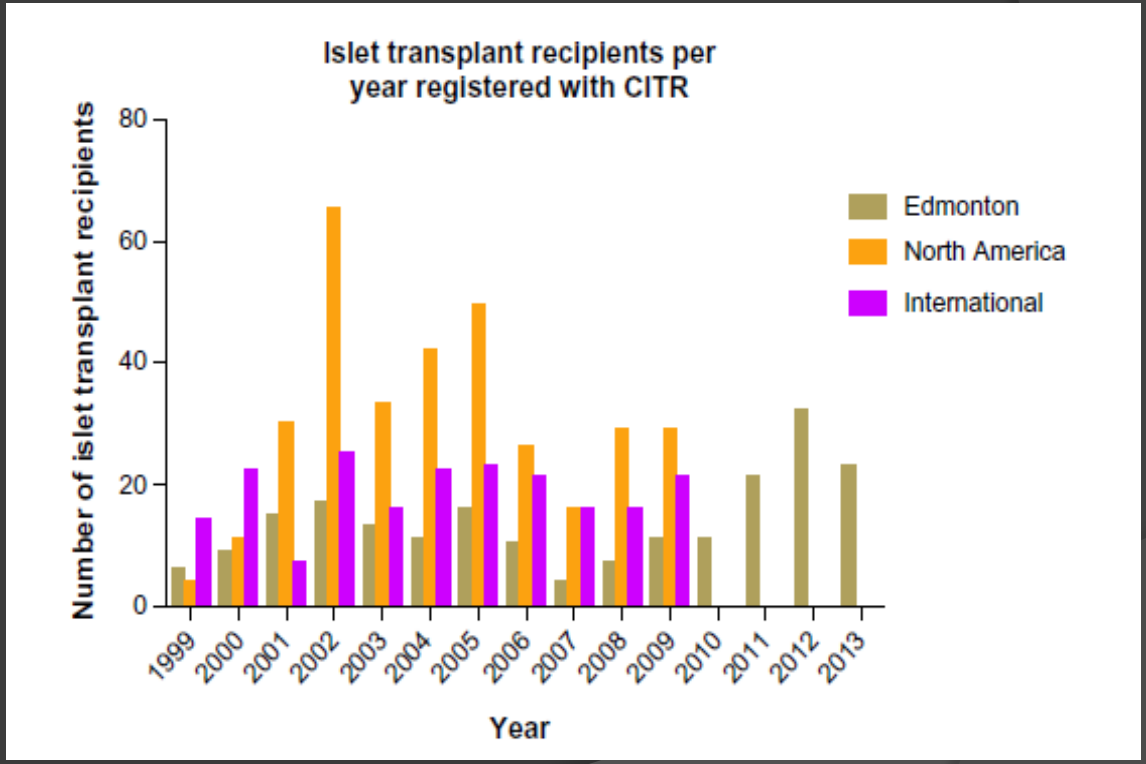
Páncreas biónico: iLet



Transplante de islotes

Obstáculos

- Disponibilidad y selección de donantes
- Digestión del páncreas y aislamiento de islotes
- Sitio del injerto de islotes
- Independencia de insulina ≈ 34 meses de mediana



Células madre

Secreción de insulina:

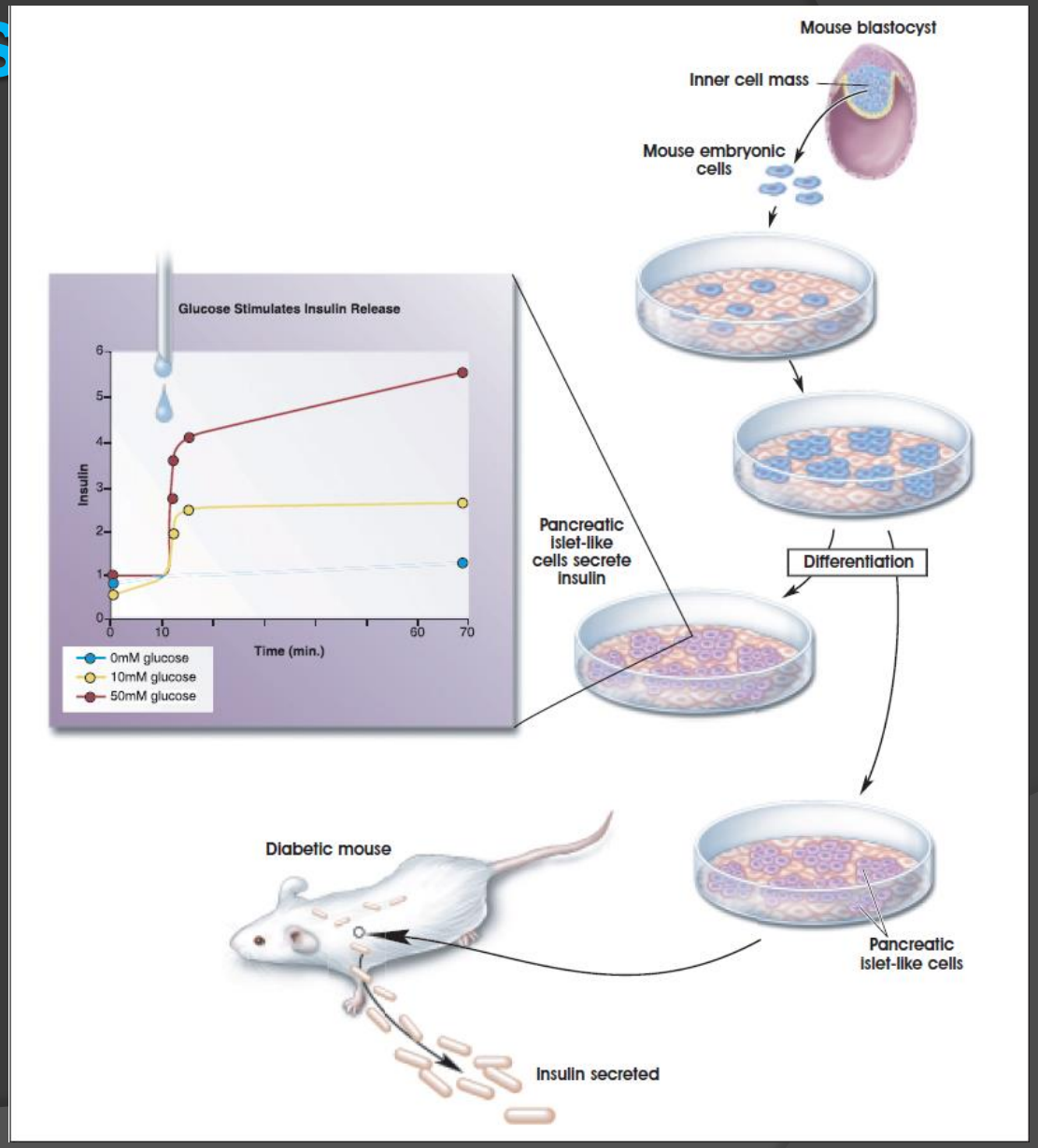
- Islotes pancreáticos: Secreción en dos fases.
- Células beta aisladas: Secreción en una fase (todo o nada).

Fuentes de células madre

- **Tejido fetal**: Proliferan mal cuando maduran
- **Tejidos adultos**:
  - Células beta de cadáveres: Cuando proliferan y maduran producen muy poca insulina
  - Células de los conductos pancreáticos: Pueden desdiferenciarse y luego diferenciarse de nuevo en islotes pancreáticos
- **Células embrionarias**

Formación de células madre embrionarias

Formación de ISLOTES pancreáticos a partir de células madre embrionarias



¡Muchas gracias!