



Terapia basada en incretinas

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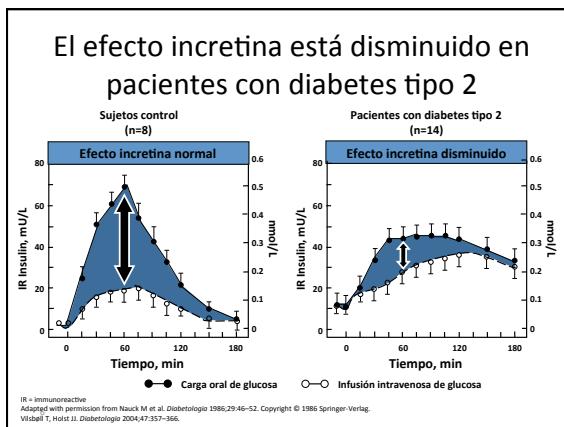
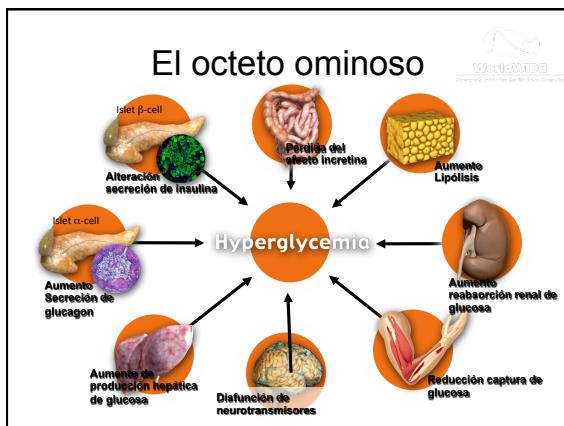
Conflictos de interés

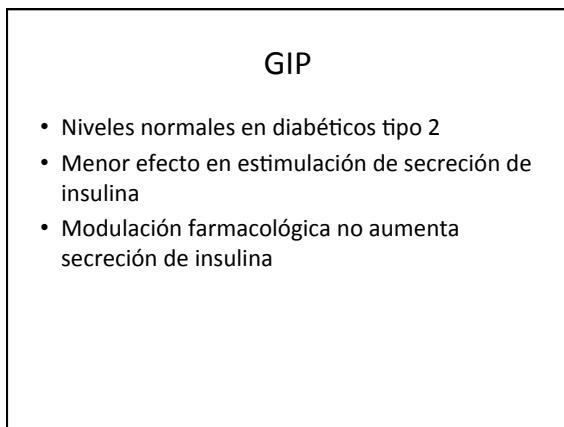
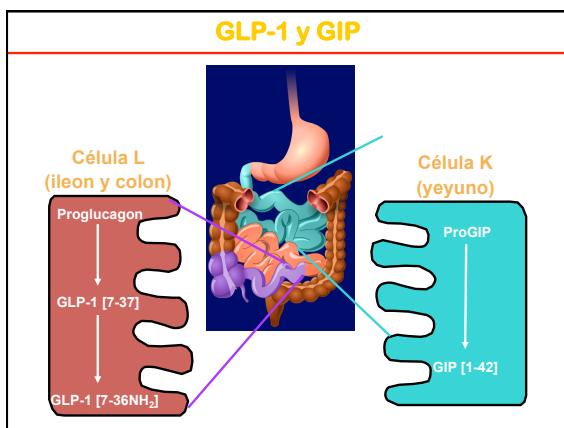
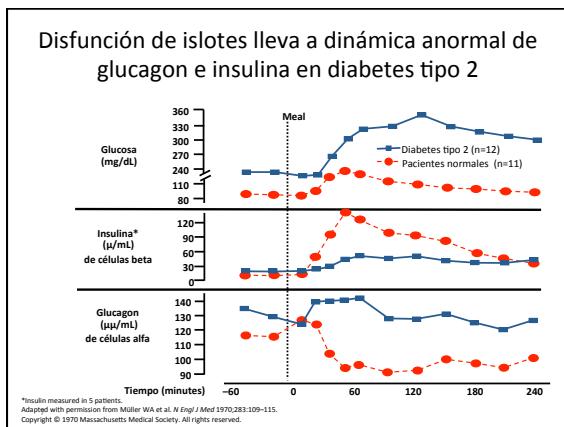
- Conferencista: Astra Zeneca, Abbott Nutrición, Novartis Oncology, Novo Nordisk, Merck Sharp & Dohme, Roche, Glaxo SmithKline, Sanofi Aventis
- Advisory Board: Novartis Oncology, Sanofi Aventis, Astra Zeneca, Novo Nordisk
- Investigación clínica: Astra Zeneca, Novartis Pharma Logistics Inc., Merck Sharp & Dohme, Glaxo SmithKline, Organon, Boehringer Ingelheim, Roche

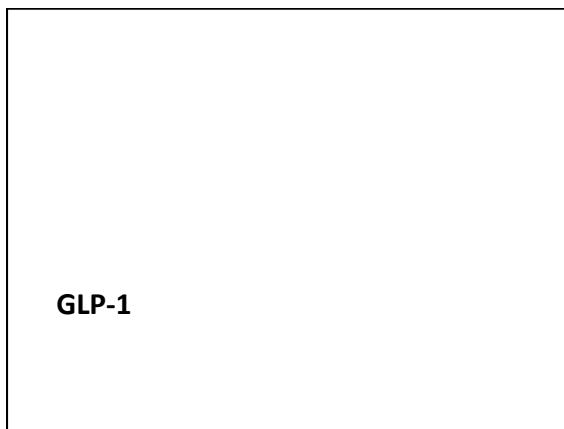
Agenda

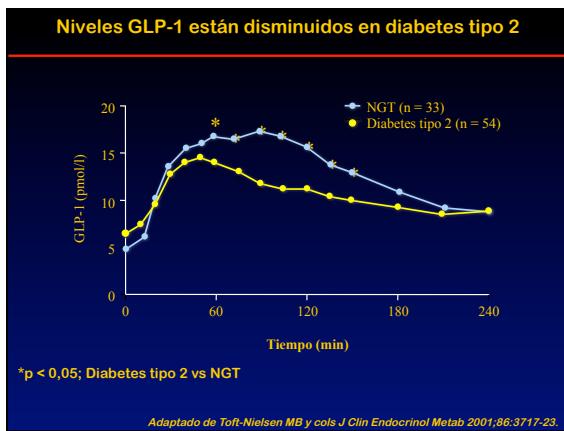
- Efecto incretínico
- Inhibidores de DPP-4
- Análogos de GLP-1

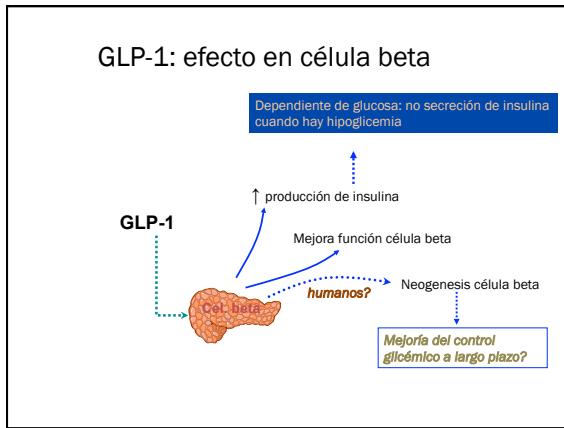
PAPEL DE LAS INCRETINAS EN FISIOPATOLOGÍA DE DM

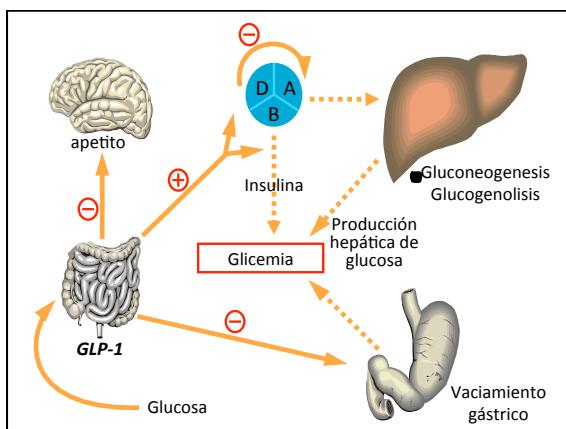


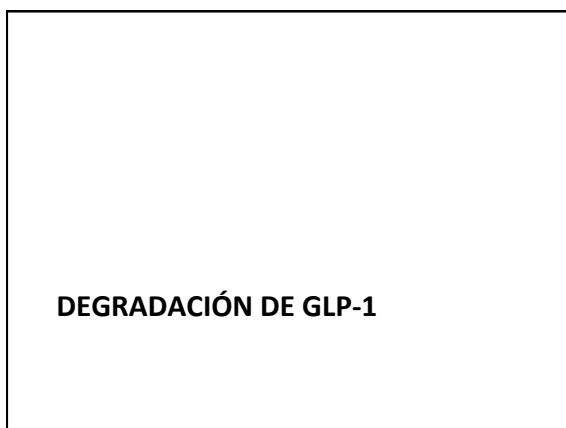


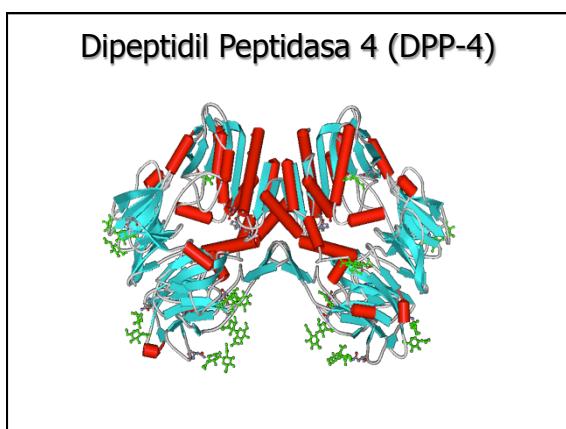


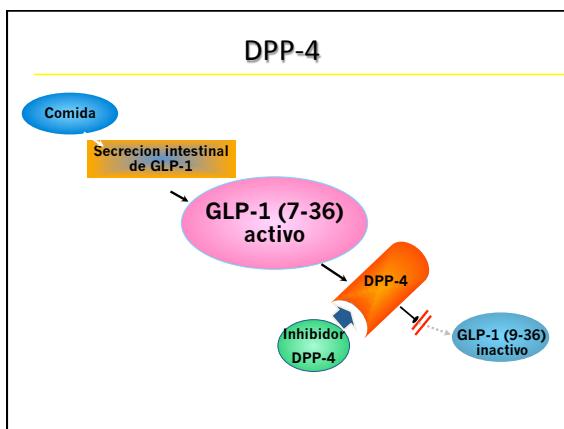


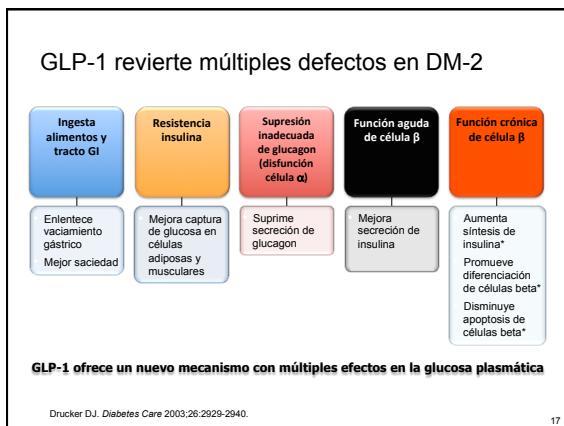


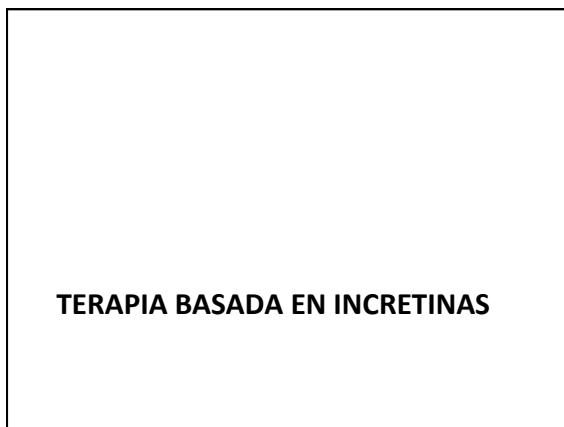












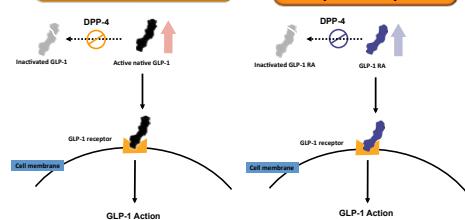
Beneficios vs otras terapias

- No hipoglicemias
- Pérdida o neutralidad sobre peso
- Efectos cardiovasculares
- Preservación de células beta

Two Pharmacologic Approaches to Increasing GLP-1 Action in Patients

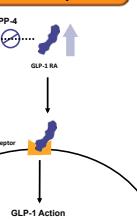
DPP-4 Inhibitors

Increase circulating native GLP-1 levels by inhibiting the DPP-4 enzyme



GLP-1 Receptor Agonists

Bind & activate the GLP-1 receptor
and are resistant to degradation
by the DPP-4 enzyme



Images based upon: Fineman MS et al. Diabetes Obes Metab. 2012;14(5):546-554; Diambra I et al. Exp Diabetes Res. 2012;2011:89913; Amori RÉ et al. JAMA. 2007;298(2):154-206; Davidson JA. Mayo Clin Proc. 2010;85 (suppl 12):S37-S37; Shyanglan S et al. AMC Festschr Diabet. 2010;10:20.

Terapia basada en incretinas

Inhibidores de DPP-4

- Sitagliptina
- Vildagliptina
- Linagliptina
- Saxagliptina
- alogliptina

Análogos GLP-1

- Exenatide bid
- Liraglutide
- Exenatide semanal
- Lixisenatide
- Albiglutide
- dulaglutide

INHIBIDORES DE DPP-4

Inhibidores de DPP-4

- Sitagliptina
- Vildagliptina
- Linagliptina
- Saxagliptina
- Alogliptin

- Hay alguna diferencia entre ellas?

Inhibidores de DPP-4

- Eficacia clínica:
 - No hay estudios comparativos directos
 - Comparaciones indirectas muestran eficacia similar
- Posología:
 - OD: sitagliptina, linagliptina, saxagliptina, alogliptina
 - Bid: vildagliptina
 - Por seguridad hepática en fase II
 - Semanal: omarigliptina

Diferencias cinéticas

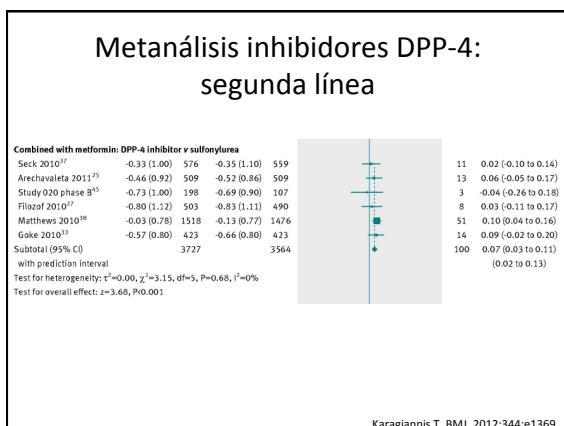
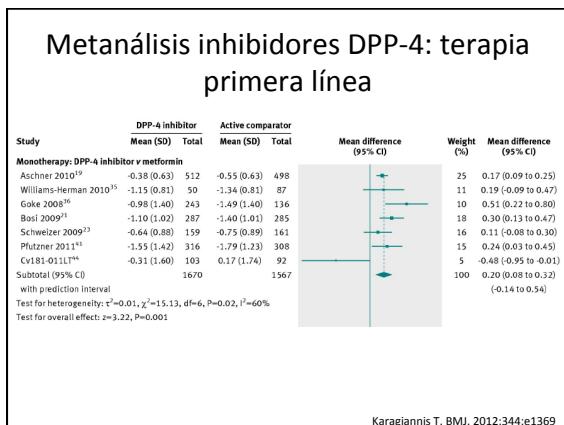
- Inhibición del DPP-4
 - No relevante por tener vidas medias largas de inhibición
- Vía de eliminación
 - Renal: sitagliptina, saxagliptina, vildagliptina
 - Reducir dosis 50% si AEC <50 cc/min
 - Hepático: linagliptina
 - No ajuste de dosis en insuficiencia renal
 - La ventaja se pierde en combinación con metformin

Diferencias cinéticas

- Sustrato de citocromos:
 - CYP3A4: saxagliptina
 - Interacciones con inhibidores o inductores potentes como ketoconazole

Otras diferencias

- Seguridad cardiovascular:
 - Estudios publicados: SAVOR y EXAMINE
 - Todos los demás en curso
- Terapia combinada:
 - Metformin liberación rápida: sitagliptina, vildagliptina, linagliptina
 - Metformin XR: saxagliptina

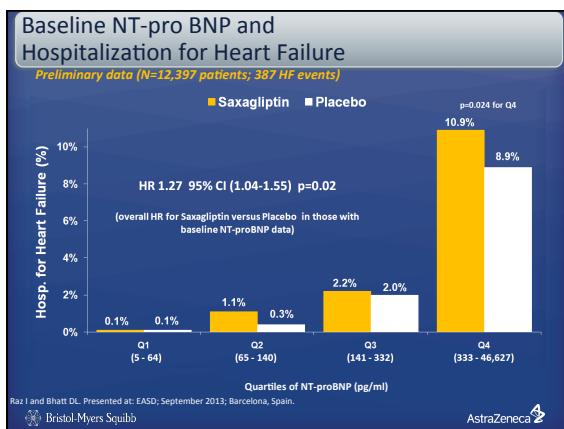


Individual Components of the Composite Endpoints

| Efficacy endpoint | Saxagliptin n (%)* | Placebo n (%)* | HR (95% CI) | P value |
|---------------------------|-----------------------|-------------------|------------------|---------|
| CV death | 269 (3.2) | 260 (2.9) | 1.03 (0.87–1.22) | 0.72 |
| MI | 265 (3.2) | 278 (3.4) | 0.95 (0.80–1.12) | 0.52 |
| Ischemic stroke | 157 (1.9) | 141 (1.7) | 1.11 (0.88–1.39) | 0.38 |
| Hosp for UA | 97 (1.2) | 81 (1.0) | 1.19 (0.89–1.60) | 0.24 |
| Hosp for HF | 289 (3.5) | 228 (2.8) | 1.27 (1.07–1.51) | 0.007 |
| Hosp for coronary revasc. | 423 (5.2) | 459 (5.6) | 0.91 (0.80–1.04) | 0.18 |

*K-M event rates are presented after 2 yrs.
Source BM, et al. N Engl J Med. 2013;305(13):1307-1308.

Bristol-Myers Squibb AstraZeneca



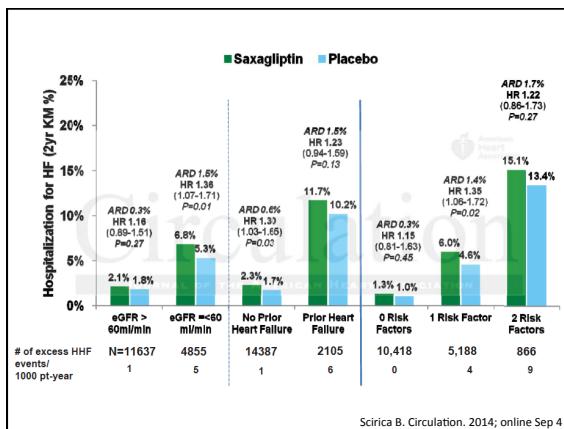
EXAMINE e ICC

- Análisis post hoc eliminando el punto final de muerte del punto primario
- HR de falla cardíaca 1.19 (p 0.22)
- Consideraciones:
 - Cambiaron la definición de falla cardíaca
 - Análisis post hoc
- Cuando se combinan los datos de SAVOR y EXAMINE HR 1.24 (IC 1.07-1.45)

EASD Barcelona 2013

VIVIDD

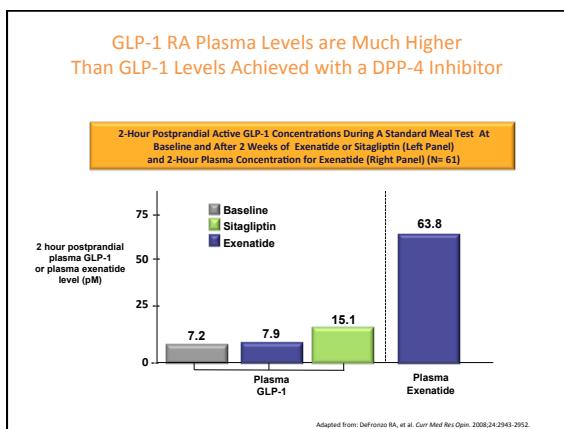
- Vildagliptin in ventricular dysfunction diabetes trial
- Estudio de no inferioridad en 254 pacientes con ICC, NYHA I-III
- Aumento en volumen ventricular izquierdo telediastólico y volumen telesistólico



| Sitagliptina e ICC | | | | | | |
|--|--------------|-----------------------------|---------------------------------|-----------------------|------------------------------|----------|
| Outcome | Agent | Exposed Cases/Total Exposed | Unexposed Cases/Total Unexposed | Unadjusted Odds Ratio | Adjusted Odds Ratio (95% CI) | p Value* |
| All-cause death or hospital admission | Sitagliptin | 110/1,163 | 4,361/4,700 | 0.26 (0.19-0.32) | 0.79 (0.63-0.93) | <0.01 |
| | Metformin | 750/0.724 | 3,361/4,700 | 0.64 (0.55-0.72) | 0.78 (0.71-0.85) | <0.001 |
| All-cause death | Insulin | 800/1,149 | 3,337/9,205 | 1.37 (1.25-1.50) | 1.16 (0.95-1.38) | 0.004 |
| | Sulfonylurea | 670/3,710 | 3,464/37,724 | 0.94 (0.86-1.03) | 1.10 (1.00-1.29) | 0.043 |
| | Other | 109/1,429 | 4,028/44,005 | 0.81 (0.67-1.00) | 0.95 (0.77-1.17) | 0.64 |
| All-cause hospital admission | Sitagliptin | 19/224 | 389/4,193 | 0.73 (0.45-1.18) | 1.16 (0.68-1.97) | 0.59 |
| | Metformin | 66/1,530 | 342/2,937 | 0.33 (0.25-0.44) | 0.52 (0.37-0.70) | <0.001 |
| | Insulin | 142/1,411 | 266/3,056 | 1.18 (0.95-1.41) | 1.11 (0.84-1.47) | 0.46 |
| | Sulfonylurea | 73/1,247 | 335/3,220 | 0.53 (0.41-0.69) | 0.83 (0.61-1.14) | 0.25 |
| | Other | 13/214 | 395/4,553 | 0.63 (0.36-1.12) | 0.87 (0.46-1.63) | 0.66 |
| All-cause hospital admission | Sitagliptin | 112/1,489 | 3,964/43,274 | 0.80 (0.6-0.98) | 0.93 (0.76-1.14) | 0.46 |
| | Metformin | 250/30,556 | 3,326/34,207 | 0.65 (0.59-0.71) | 0.79 (0.71-0.87) | <0.001 |
| | Insulin | 795/7,215 | 3,281/37,548 | 1.34 (1.23-1.47) | 1.13 (1.03-1.25) | 0.01 |
| | Sulfonylurea | 669/7,683 | 3,407/37,080 | 0.93 (0.85-1.09) | 1.08 (0.97-1.19) | 0.15 |
| | Other | 109/1,277 | 3,967/43,486 | 0.93 (0.76-1.19) | 1.06 (0.86-1.31) | 0.56 |
| HF-related hospital admission or death | Sitagliptin | 31/200 | 1,040/34,207 | 0.30 (0.21-0.41) | 0.44 (0.31-0.57) | 0.17 |
| | Metformin | 154/2,556 | 932/70,025 | 0.53 (0.44-0.64) | 0.70 (0.57-0.86) | 0.001 |
| | Insulin | 217/2,126 | 929/70,455 | 1.20 (1.01-1.42) | 1.03 (0.84-1.24) | 0.81 |
| | Sulfonylurea | 156/2,063 | 990/70,518 | 0.76 (0.63-0.92) | 0.92 (0.75-1.13) | 0.41 |
| | Other | 21/200 | 1,125/2,279 | 0.74 (0.47-1.16) | 0.85 (0.53-1.36) | 0.50 |
| HF-related hospital admission | Sitagliptin | 25/200 | 799/8,862 | 1.47 (0.95-2.27) | 1.84 (1.16-2.92) | 0.01 |
| | Metformin | 106/1,278 | 718/7,684 | 0.76 (0.60-0.96) | 0.87 (0.66-1.12) | 0.28 |
| | Insulin | 113/1,114 | 717/9,948 | 1.19 (0.94-1.50) | 0.97 (0.75-1.27) | 0.83 |
| | Sulfonylurea | 103/1,067 | 721/7,995 | 1.09 (0.86-1.39) | 1.11 (0.84-1.45) | 0.47 |
| | Other | 14/147 | 810/8,905 | 0.98 (0.56-1.72) | 1.08 (0.59-1.96) | 0.81 |

Weir D. JACC: Heart Failure. 2014

ANÁLOGOS DE GLP-1



Cómo podemos diferenciar los análogos de GLP-1?

- Estructura química
- Duración de acción
- Sitio de acción

Estructura química

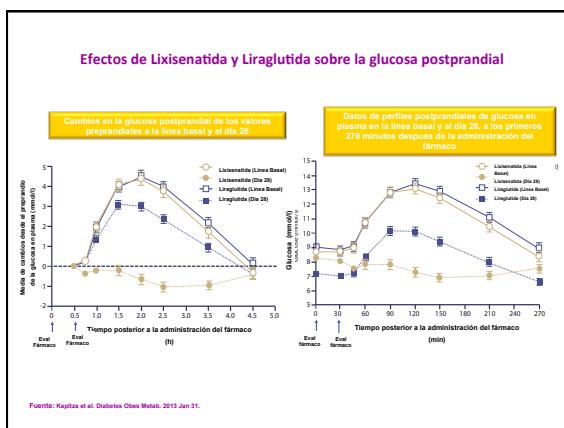
Basado en GLP-1 nativo

- Liraglutide
- Albiglutide
- dulaglutide

Basado en exendin-4

- Exenatide bid
- Exenatide LAR
- lixisenatide

| Sítio de acción | |
|---|---|
| Glicemias postprandiales | Glicemias ayunas |
| <ul style="list-style-type: none"> • Exenatide bid • Lixisenatide | <ul style="list-style-type: none"> • Exenatide LAR • Liraglutide • Albiglutide |



| Análogos GLP-1: monoterapia | | | | |
|-----------------------------|--------------------------------|--------------------------|---------------------------|------------------------|
| Exenatide bid ¹ | Exenatide semanal ² | Liraglutide ³ | Lixisenatide ⁴ | |
| HbA1c basal (%) | 7.8 ± 1.0 | 8.2 ± 1.0 | 8.3 ± 1.1 | 7.98 ± 0.9 |
| Duración de DM (años) | 2 ± 3 | 7 ± 5 | 5.3 ± 5.1 | 1.4 (0.2-21.5) |
| Duración del estudio | 24 semanas | 3 años | 52 semanas | 12 semanas |
| Reducción de HbA1c | 0.9 ± 0.1 | 1.4 ± 0.08 | 1.6 ± 0.15% | 0.54 ± 0.05 |
| % HbA1c <7% | 46% | 50% | 62% | 52% |
| Reducción en peso (kg) | 3.1 ± 0.3 | 2.3 ± 0.6 | 2.26 kg | 2 (no dif con placebo) |
| Síntomas GI | 10% (náuseas) | 18.6% (náusea) | 51% | 32.5% |

1. Moretto T1. Clin Ther. 2008;30:1448

2. McConnell L. Diab Metab Synd Obes. 2013;6:31

3. Garber A. Lancet. 2009;373:473

4. Fonseca VA. Diabetes Care. 2012;35:1225

Análogos GLP-1: agregado a metformin

| | Exenatide bid ¹ | Exenatide semanal ² | Liraglutide ³ | Lixisenatide ¹ |
|------------------------|----------------------------|--------------------------------|--------------------------|---------------------------|
| HbA1c basal (%) | 8.02 ± 0.8 | 8.3 ± 1.1 | 8.3 ± 1.1 | 8.03 ± 0.8 |
| Duración de DM (años) | 6.8 ± 4.9 | 8.0 ± 6.0 | 5.3 ± 5.1 | 6.8 ± 5.5 |
| Duración del estudio | 24 semanas | 84 semanas (extensión) | 52 semanas | 24 semanas |
| Reducción de HbA1c | 0.96 ± 0.05 | 1.2 ± 0.1 | 0.71 ± 0.09 | 0.79 ± 0.05 |
| % HbA1c <7% | 49.8% | 44.6% | 51% | 48.5% |
| Reducción en peso (kg) | 3.98 ± 0.23 | 2.1 kg | 2.26 kg | 2.96 ± 0.23 |
| Síntomas GI | 50.6% | 44.6% | 51% | 43.1% |

1. Rosenstock J. Diabetes Care. 2013;36:2945

3. Garber A. Lancet. 2009;373:473

2. Diamant M. Diabetes Care. 2012;35:683

Análogos GLP-1: agregado a insulina

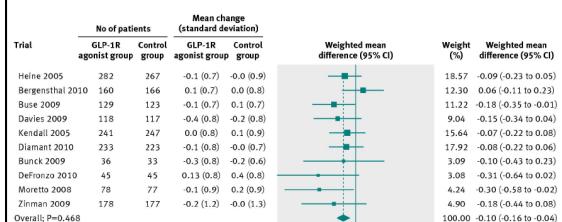
| | Exenatide bid ¹ | Exenatide semanal | Liraglutide* ² | Lixisenatide ³ |
|------------------------|----------------------------|-------------------|---------------------------|---------------------------|
| HbA1c basal (%) | 8.32 ± 0.35 | NA | 8.2 ± 0.7 | 8.4% |
| Duración de DM (años) | 12 ± 7 | NA | 8.6 ± 5.8 | 12.5 ± 7 |
| Duración del estudio | 30 semanas | NA | 24 semanas | 24 semanas |
| Reducción de HbA1c | 0.69% (IC 0.46-0.93) | NA | 0.52% (IC 0.36-0.68) | 0.4% (IC 0.6-0.2%) |
| % HbA1c <7% | 60% | NA | 43% | 28.3% |
| Reducción en peso (kg) | 1.8 (1.1-2.5) | NA | 0.79 (0.08-1.49) | 1.3 (1.8-0.7) |
| Síntomas GI | 41% (Náusea) | NA | 14.1% | 40.2% |

1. Buse JB. Ann Intern Med. 2011;154:103

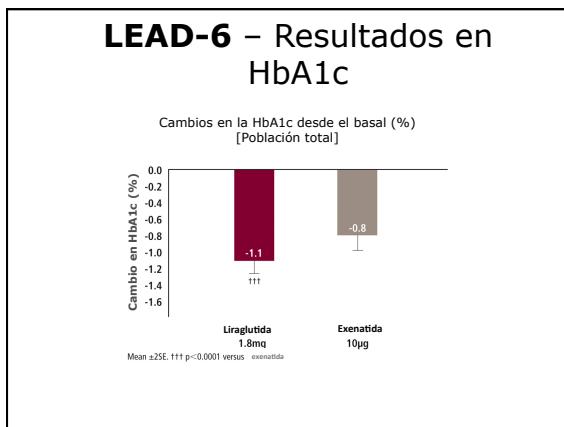
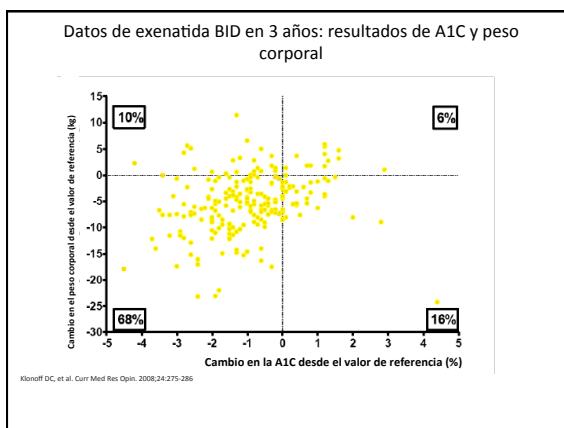
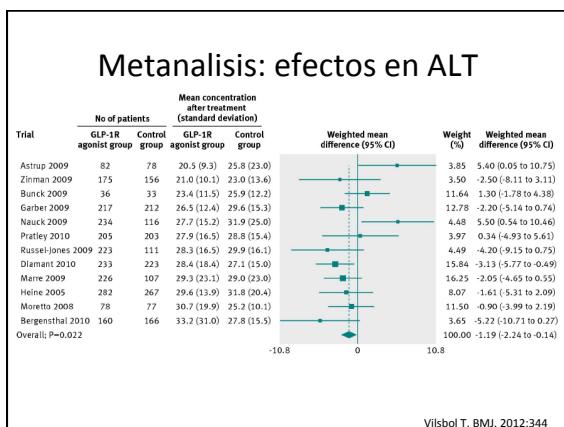
3. Riddle MC. Diabetes Care. 2013;36:2489

2. DeVries JH. Diabetes Care. 2012;35:1446

Metanálisis: colesterol total

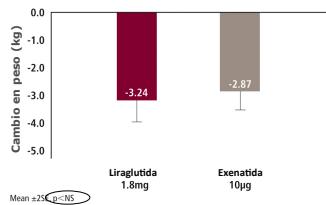


Vilsbol T. BMJ. 2012;344

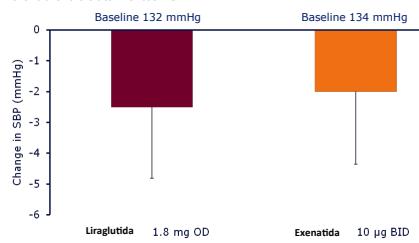


LEAD-6 cambios en el peso corporal

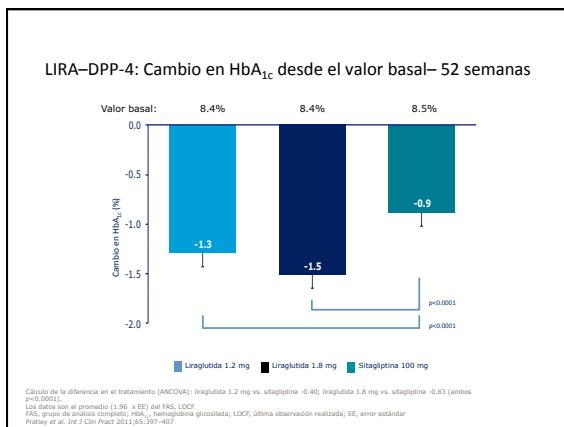
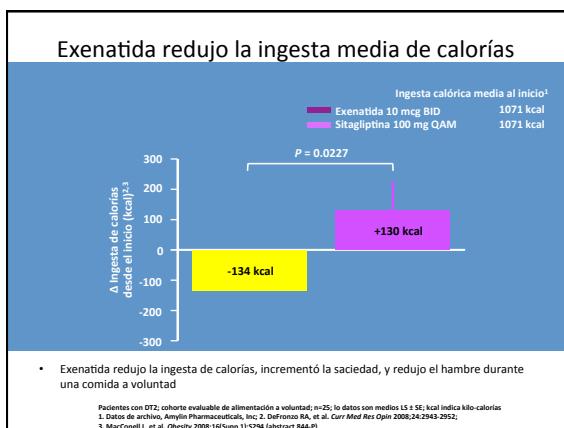
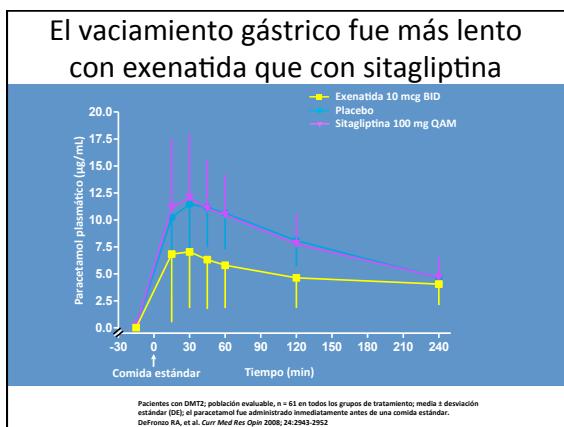
¹ Cambio en peso corporal desde el basal (Kg) [Población total]

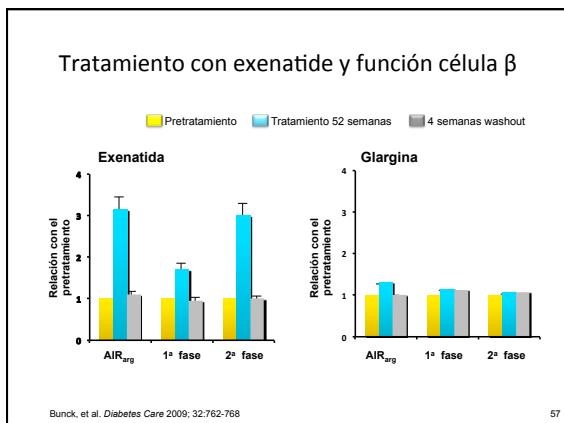
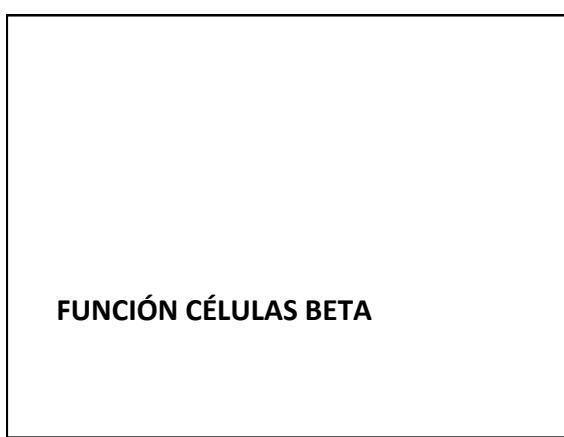
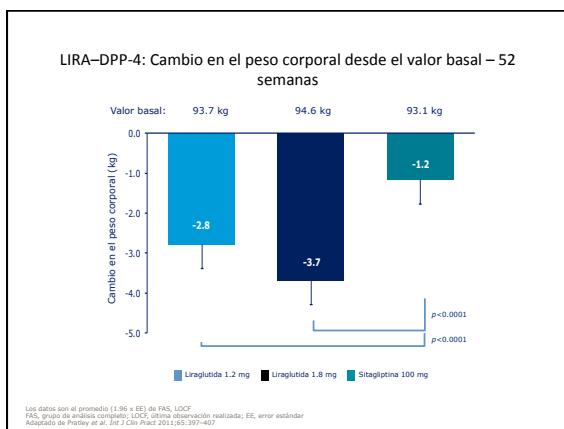


Diferencia entre tratamientos NS

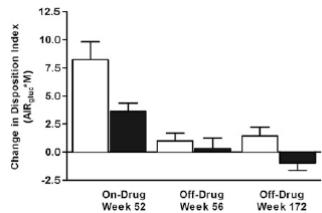


ANÁLOGOS GLP-1 VS IDPP-4 EN MONOTERAPIA





Exenatide 3 años y función células beta



Bunck, et al. Diabetes Care 2011; 34:2071

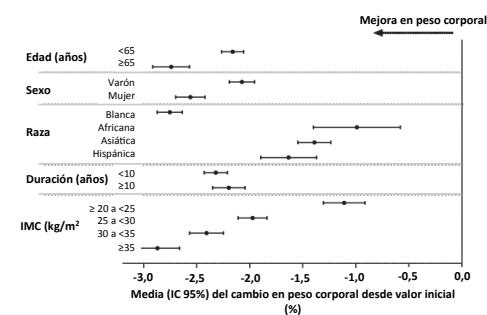
Agregar GLP1RA a insulina

| Citation | Treatment duration | Background treatment* | Randomly assigned treatment | HbA1c (%) | | Body Wt (kg) | | Δ Insulin dose (total daily) | |
|--|--------------------|-----------------------|---------------------------------|--------------|----------------|--------------|--------------|------------------------------|--------------------|
| | | | | BL | Δ | BL | Δ | BL | Δ |
| GLP-1 receptor agonist added to insulin | | | | | | | | | |
| Buse et al. [52] | 30 weeks | InsGlar ± MET ± PIO | EXEN (N = 138) PBO (N = 123) | 8.32 8.50 | ±1.7 ±1.0 | 95.4 93.4 | ±1.8 ±1.0 | 49.5 U 47.4 U | ±13 U ±20 U |
| Saito et al. [53] | 24 weeks | SU + BasalIns† | LIXI (N = 154) PBO (N = 157) | 8.54 8.52 | ±0.77 ±0.11 | 65.9 65.6 | ±0.4 ±0.1 | 24.9 U 24.1 U | ±1.39 U ±0.11 U |

Agregar insulina a GLP1RA

| Citation | Treatment duration | Background treatment* | Randomly assigned treatment | HbA1c (%) | | Body Wt (kg) | | Δ Insulin dose (total daily) | |
|--|--------------------|--|--|--------------|--------------|----------------|--------------|------------------------------|------------|
| | | | | BL | Δ | BL | Δ | BL | Δ |
| Insulin added to GLP-1 receptor agonist | | | | | | | | | |
| Riddle et al. [54] | 24 weeks | MET + EXEN | EXEN + InsGlar (N = 17) PBO+ InsGlar (N = 17) | 7.8 10.5 | ±1.35 NR | 10.4 14.1 | NR NR | 0.50 U/kg§ | 0.56 U/kg§ |
| Blevins et al. [55] | 24 weeks | EXEN + MET ± SU or EXEN + MET ± PIO | InsGlar (N = 168) ILPS (N = 171) | 8.2 8.2 | ±1.4 ±1.2 | 102.3 101.6 | ±0.7 ±0.3 | NR NR | 38 U§ |
| Arakaki et al. [56] | | MET + LIRA | InsDX (N = 162) <Control> (N = 161) | 7.6 10.02 | ±0.5 95.3 | 96.0 11.0 | ±0.2 NR | NA NA | 31 U§ |
| DeVries et al. [57]¶ | 26 weeks | MET + LIRA | InsDX (N = 130) <Control> (N = 92) | 7.6 10.01 | ±0.5 NR | 10.1 11.0 | ±0.1 NR | NA NA | NA |
| Bain et al. [58]¶ | 52 weeks | MET + LIRA | InsDX (N = 130) <Control> (N = 92) | 7.6 10.01 | ±0.5 NR | 10.1 11.0 | ±0.1 NR | NA NA | NA |

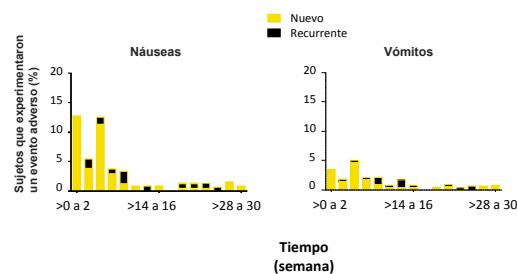
La exenatida BID estuvo asociada a una mejora significativa en el peso corporal en los subgrupos



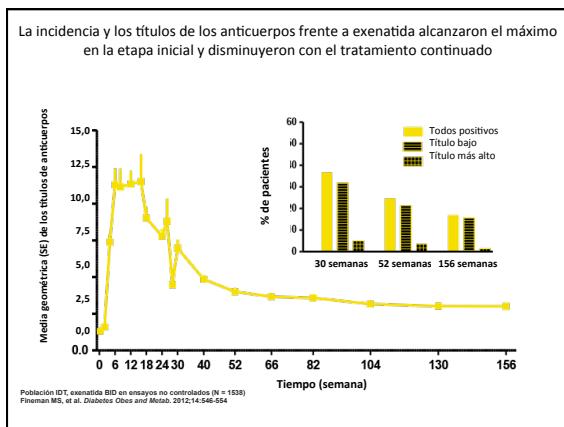
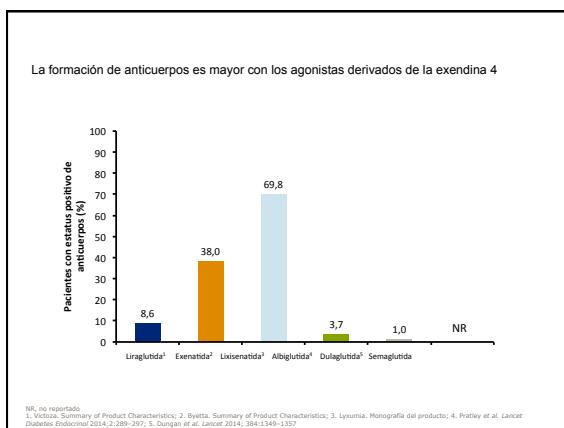
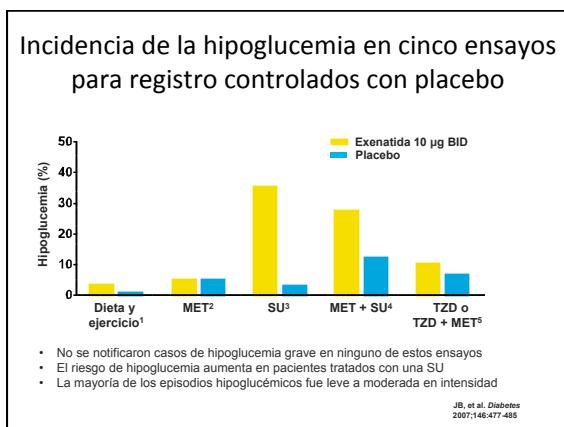
Pencik R, et al. Postgraduate Med. 2012;124(4): en prensa

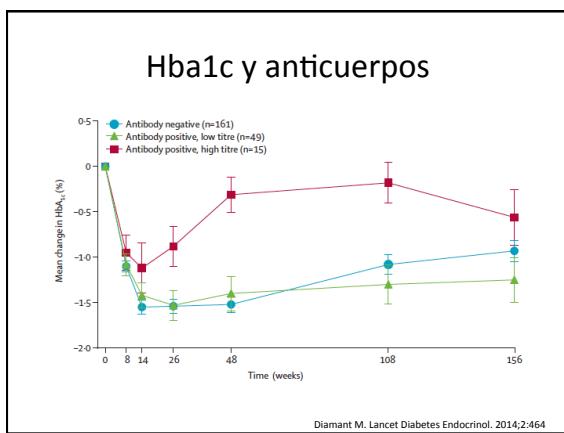
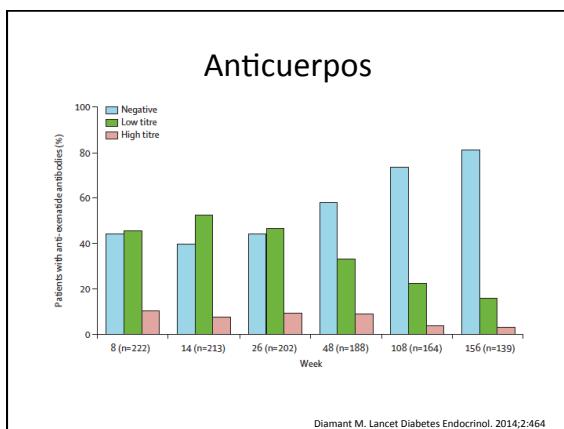
PERFIL DE SEGURIDAD

Las náuseas y los vómitos disminuyeron con el tiempo



Ridge T, et al. Diabetes Obes Metab. 2012; En prensa: doi: 10.1111/j.1463-1326.2012.01639.x





Medscape Medical News

FDA Sides With EMA on Incretin Diabetes Drugs

Megan Brooks
August 01, 2013

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EDITORS' RECOMMENDATIONS

- EU Agency Has No New Concerns on Incretin Diabetes Drugs
- Pancreatic Cancer and Incretins: No Signal as Yet at NIDDK
- BMJ Digs Deep Into Incretins and Pancreatic Cancer Debate

DRUG & REFERENCE INFORMATION

Diabetic Lumbosacral Plexopathy

The US Food and Drug Administration (FDA) agrees with the European Medicines Agency (EMA) that available data do not confirm recent concerns over an increased risk for pancreatic side effects with glucagonlike peptide-1 (GLP-1)-based diabetes therapies, a spokeswoman for the FDA told Medscape Medical News today.

The EMA announced their conclusions, based on the evidence to date, on July 26, as reported by Medscape Medical News.

"There is no change in evidence regarding the risks," concluded the EMA's Committee for Medicinal Products for Human Use (CHMP), which has finalized a review of GLP-1-based diabetes therapies, also known as incretins. These comprise 2 classes of medicines: GLP-1 agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors.

| | Inhibidores de DPP-4 | Análogos de GLP-1 |
|--|----------------------|-------------------|
| Eficacia en reducción de Hba1c | ✓✓✓ | ✓✓✓ |
| Reducción de eventos cardiovasculares | - | ? |
| Mejoría en parámetros intermedios cardiovasculares | - | ✓✓ |
| Falla cardíaca | X? | ✓? |
| Sostenibilidad del control glicémico | ✓ | ✓✓✓ |
| Tolerabilidad | ✓✓✓ | ✓ |
| Pérdida de peso | ✓ | ✓✓✓ |

Diferencias entre las terapias basadas en incretinas

Análogos de GLP-1

- Más potente en reducción de Hba1c
- Pérdida de peso
- Mejoría perfil de lípidos y presión arterial
- Náuseas y vómitos como efecto adverso
- Administración parenteral
- Sostenibilidad control a largo plazo

Inhibidores de DPP-4

- Menos potentes en reducción de Hba1c
- Neutro en peso
- Neutro en presión arterial y perfil de lípidos
- Muy bien tolerados
- Administración vía oral
- No sostienen control a largo plazo

Conclusiones

- Los inhibidores DPP-4 son un grupo homogéneo efectivo y muy bien tolerado
- Los análogos de GLP-1 son más potentes que los inhibidores de DPP-4 en reducción de Hba1c y además logran pérdida de peso y mejoría otros parámetros cardiovasculares
- Pueden ser utilizados en todo el espectro de la diabetes tipo 2
- Efecto adverso principal náuseas y vómitos

Preguntas...
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