



Cuál es el papel de la terapia basada en incretinas en el manejo de DM-2?

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Departamento de Farmacología y Toxicología Clínica,
Universidad de Costa Rica

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Conflictos de interés

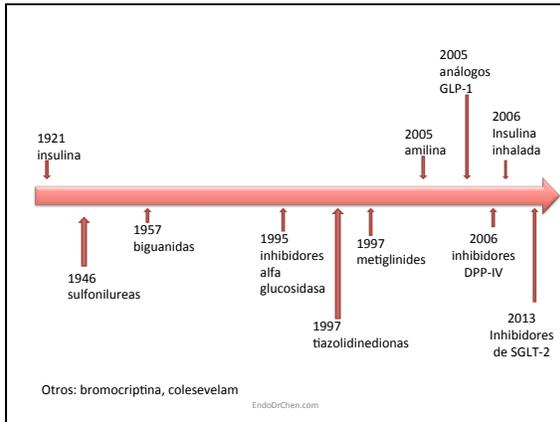
- He recibido honorarios por conferencias, advisory board y/o investigación clínica de:
 - Astra Zeneca
 - Novartis Pharma Logistics Inc
 - Novartis Oncology
 - Novo Nordisk
 - Merck Sharp & Dohme
 - Roche
 - Glaxo SmithKline
 - Sanofi Aventis
 - Boehringer
 - Organon
 - Abbott Nutrición

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Agenda

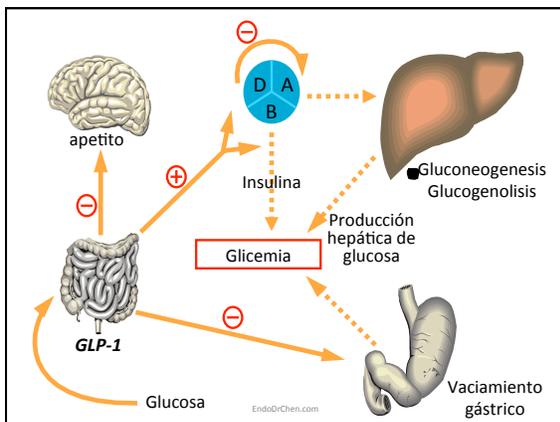
- Terapia basada en incretinas y sus diferencias
- Papel en terapia:
 - Primera línea
 - Segunda línea
 - Tercera línea
- Seguridad cardiovascular de la terapia basada en incretinas

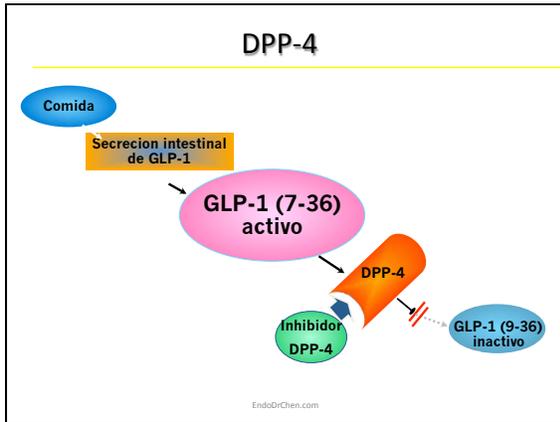
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TERAPIAS BASADAS EN INCRETINAS

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Terapia basada en incretinas

Inhibidores de DPP-4

- Sitagliptina
- Vildagliptina
- Linagliptina
- Saxagliptina
- alogliptina

Análogos GLP-1

- Exenatide bid
- Liraglutide
- Exenatide semanal
- lixisenatide

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Healthy eating, weight control, increased physical activity

Metformin

Efficacy (HbA1c)	high
Hypoglycemia	low risk
Weight	neutral/loss
Side effects	GI (nausea, diarrhea)
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).

Metformin + Sulfonurea	Metformin + Thiazolidinedione	Metformin + DPP-4 inhibitor	Metformin + GLP-1 receptor agonist	Metformin + Insulin (usually basal)
Efficacy (HbA1c)	high	intermediate	high	highest
Hypoglycemia	moderate risk	low risk	low risk	high risk
Weight	gain	neutral	loss	gain
Major side effect(s)	hypoglycemia	edema, HF, Tx	rare	GI
Costs	low	high	high	variable

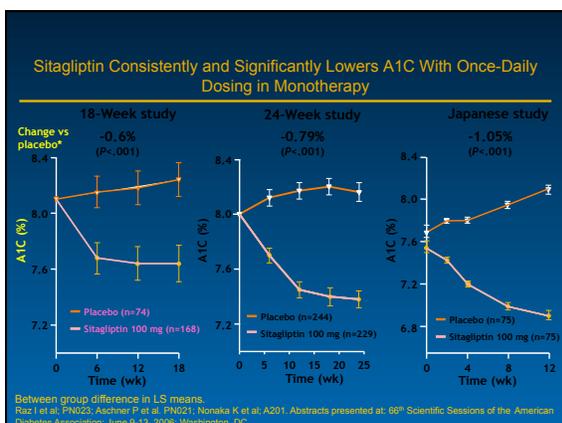
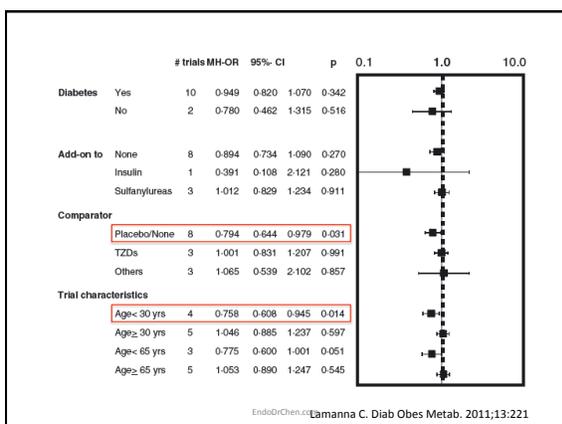
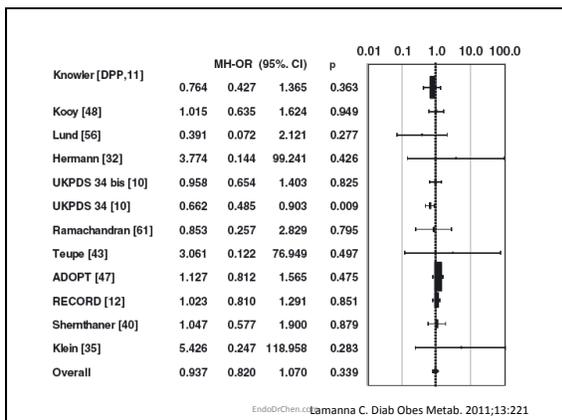
If needed to reach individualized HbA1c target after ~3 months, proceed to 3-drug combination (order not meant to denote any specific preference).

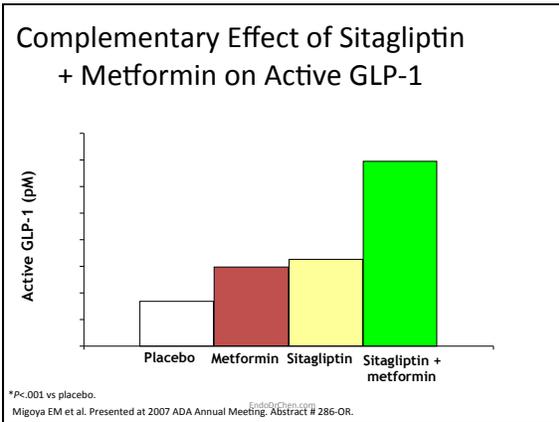
Metformin + Sulfonurea + TZD	Metformin + Sulfonurea + SU	Metformin + DPP-4 inhibitor + SU	Metformin + GLP-1 receptor agonist + SU	Metformin + Insulin (usually basal) + TZD
or	or	or	or	or
DPP-4i	DPP-4i	TZD	TZD	DPP-4i
or	or	or	or	or
GLP-1 RA	GLP-1 RA	Insulin	Insulin	GLP-1 RA
or	or	or	or	or
Insulin	Insulin	Insulin	Insulin	Insulin

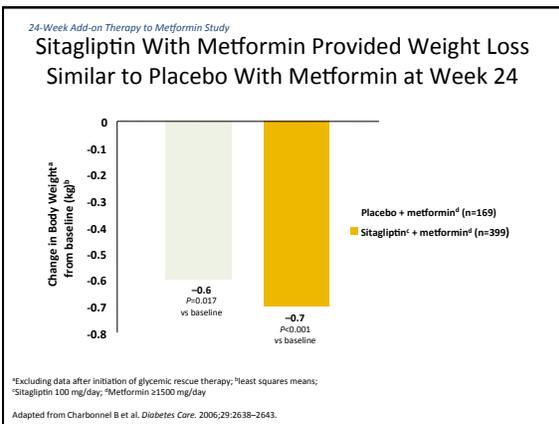
If combination therapy that includes basal insulin has failed to achieve HbA1c target after ~3-6 months, proceed to a more complex insulin strategy, usually in combination with 1-2 non-insulin agents.

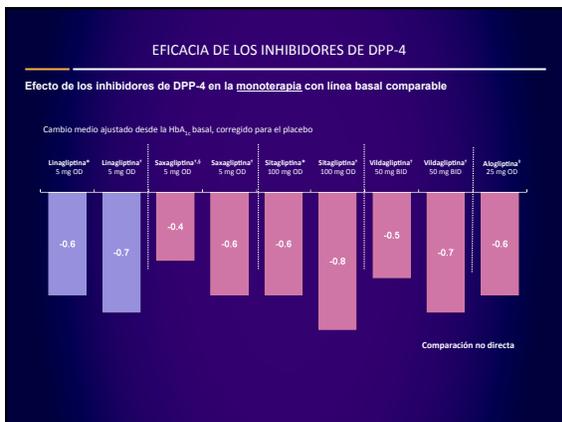
Insulin (multiple daily doses)

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

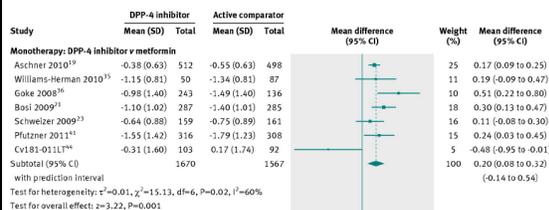








Metanálisis inhibidores DPP-4: terapia primera línea



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Karagiannis T. *BMI*. 2012;344:e1369

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%

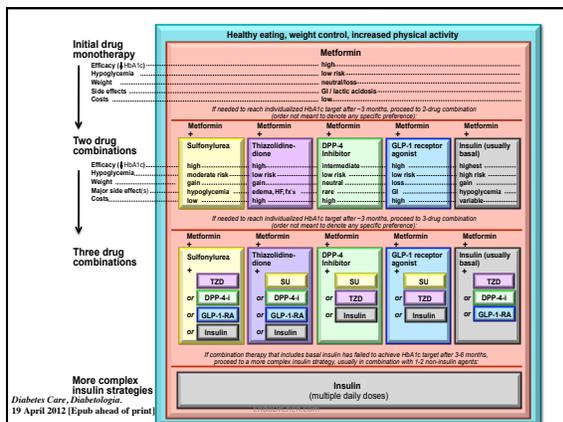
1. Moretto TJ. *Clin Ther*. 2008;30:1448

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

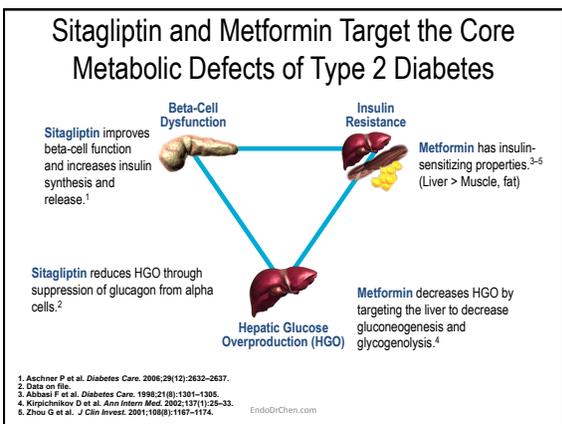
2. McConnell L. *Diab Metab Syndr Obes*. 2013;6:31

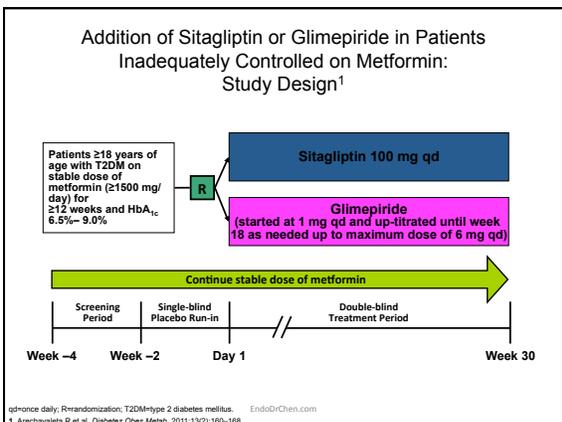
4. Fonseca VA. *Diabetes Care*. 2012;35:1225

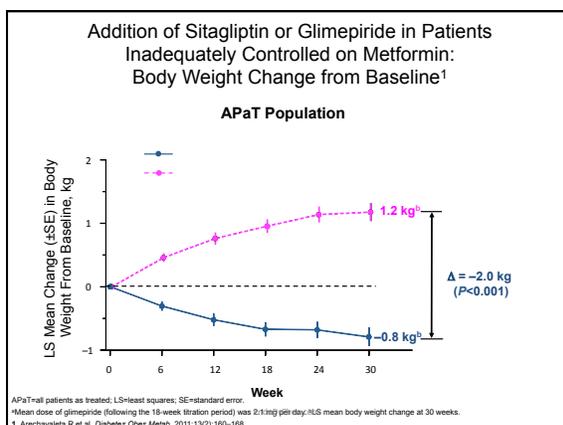
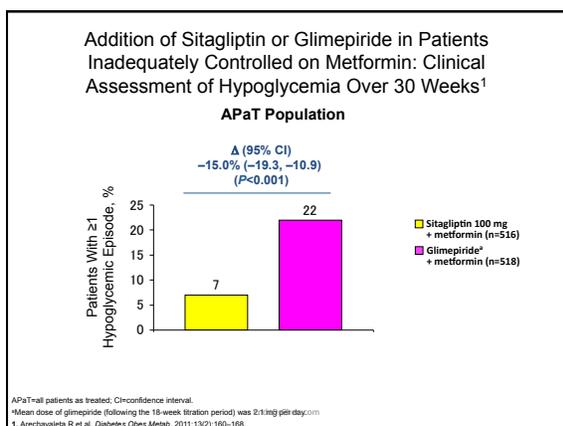
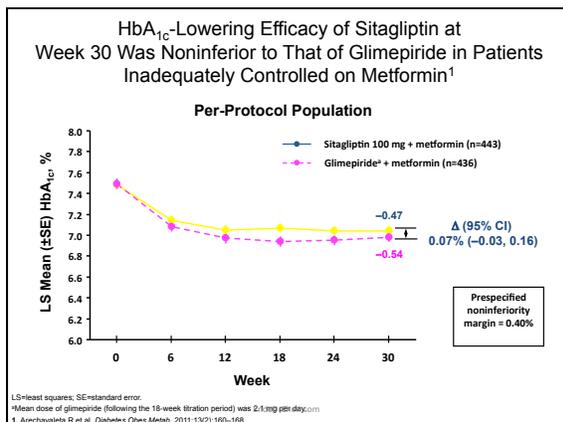


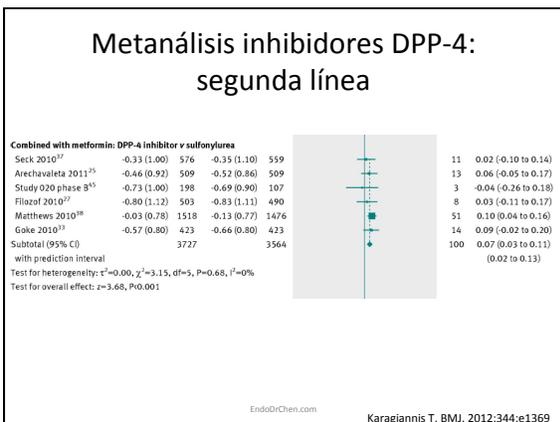
TERAPIA AGREGADO A METFORMIN: INCRETINAS VS SU

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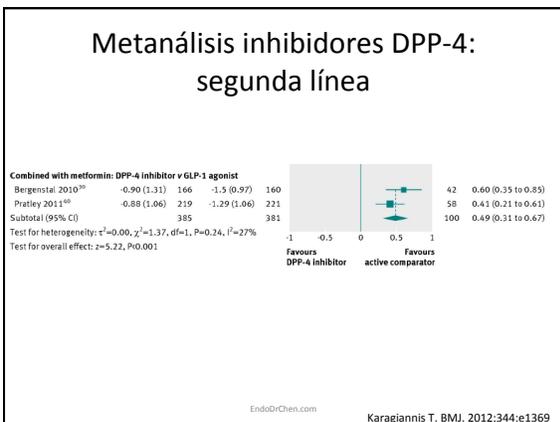




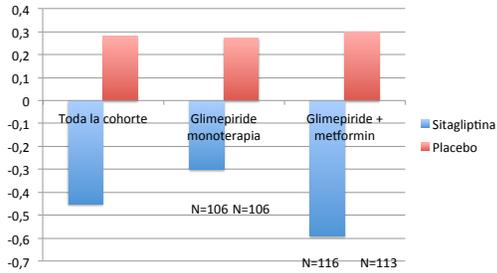
Análogos GLP-1: agregado a metformin

	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
 2. Diamant M. *Diabetes Care*. 2012;35:683
 3. Garber A. *Lancet*. 2009;373:473

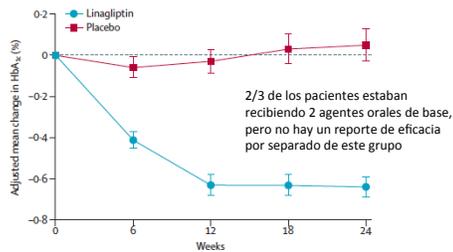


Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin



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

Linagliptin for patients aged 70 years or older with type 2 diabetes inadequately controlled with common antidiabetes treatments: a randomised, double-blind, placebo-controlled trial



EndoDrChen.com Barnett AH. Lancet. 2013;382:1413

TERCERA LÍNEA: AGREGADO A INSULINA + METFORMIN

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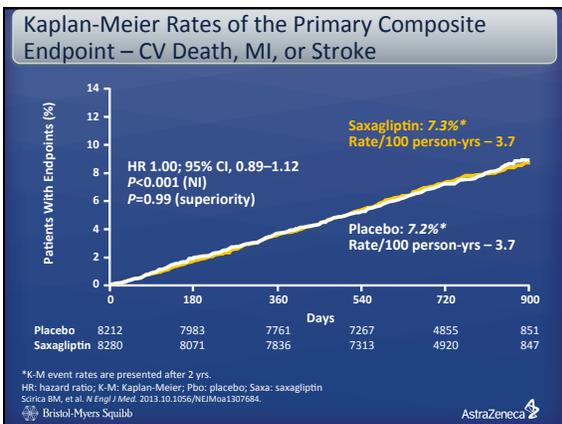
DATOS NUEVOS EN SEGURIDAD

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Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus—Thrombolysis in Myocardial Infarction (SAVOR-TIMI) 53 Study

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Bristol-Myers Squibb AstraZeneca



ORIGINAL ARTICLE

Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes

William B. White, M.D., Christopher P. Cannon, M.D., Simon R. Heller, M.D., Steven E. Nissen, M.D., Richard M. Bergenstal, M.D., George L. Bakris, M.D., Alfonso T. Perez, M.D., Penny R. Fleck, M.B.A., Cyrus R. Mehta, Ph.D., Stuart Kupfer, M.D., Craig Wilson, Ph.D., William C.ushman, M.D., and Faiez Zannad, M.D., Ph.D., for the EXAMINE Investigators*

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End Point	Placebo (N=2679)	Alogliptin (N=2701)	Hazard Ratio for Alogliptin Group (95% CI)	P Value ^o
	<i>no. (%)</i>			
Primary end point [†]	316 (11.8)	305 (11.3)	0.96 (≤1.16) [‡]	0.32
Components of primary end point				
Death from cardiovascular causes	111 (4.1)	89 (3.3)	0.79 (0.60–1.04)	0.10
Nonfatal myocardial infarction	173 (6.5)	187 (6.9)	1.08 (0.88–1.33)	0.47
Nonfatal stroke	32 (1.2)	29 (1.1)	0.91 (0.55–1.50)	0.71
Principal secondary end point [‡]	359 (13.4)	344 (12.7)	0.95 (≤1.14) [‡]	0.26
Other end points				
Death from any cause	173 (6.5)	153 (5.7)	0.88 (0.71–1.09)	0.23
Death from cardiovascular causes [¶]	130 (4.9)	112 (4.1)	0.85 (0.66–1.10)	0.21

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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)

EndoDrChen.com EASD Barcelona 2013

VIVID

- 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

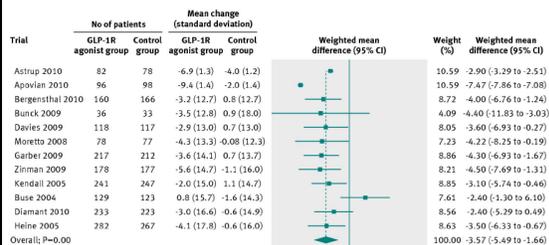
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Análogos GLP-1

- No hay estudios aleatorizados controlados publicados con análogos de GLP-1
- Están en marcha

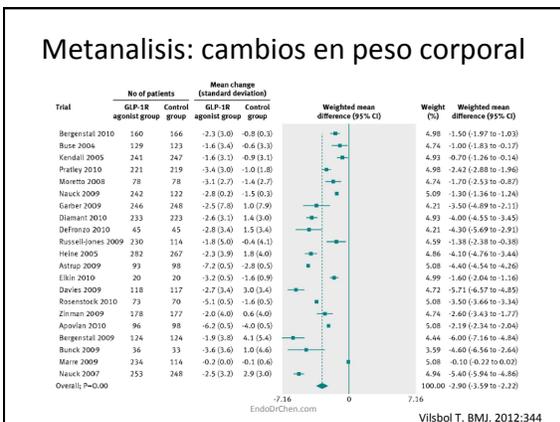
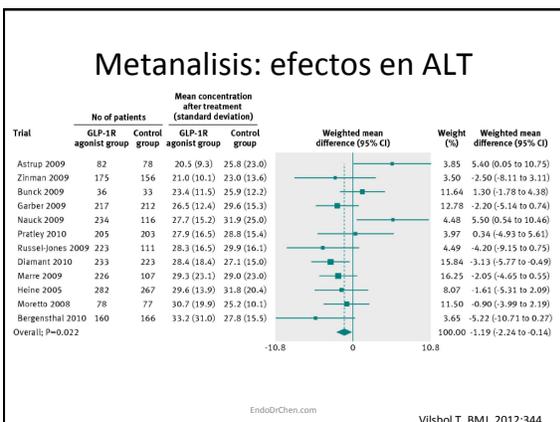
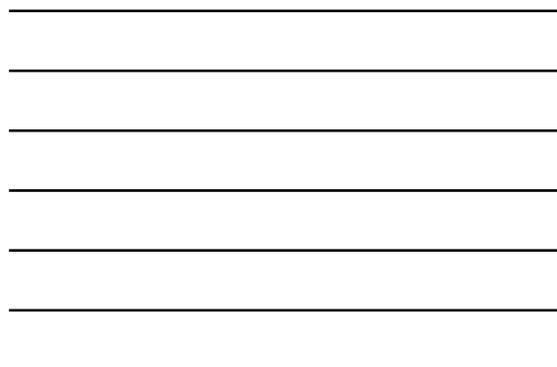
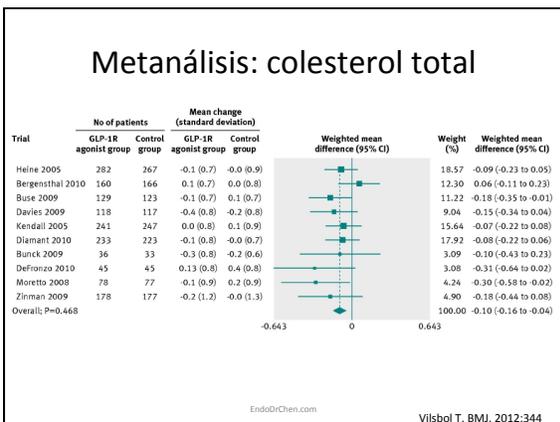
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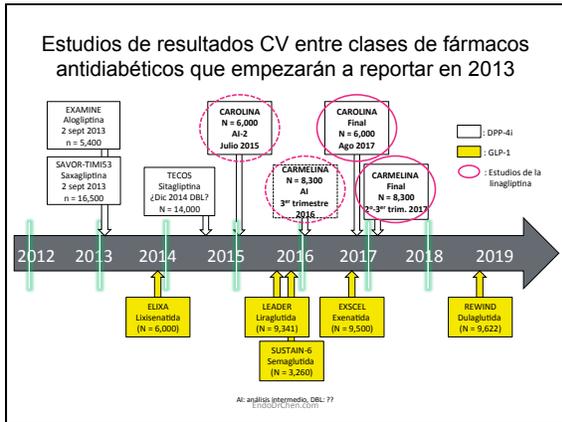
Metanálisis: presión arterial sistólica



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Vislbo T. BMJ. 2012;344





POR QUÉ ES TAN IMPORTANTE EVITAR LA HIPOGLICEMIA?

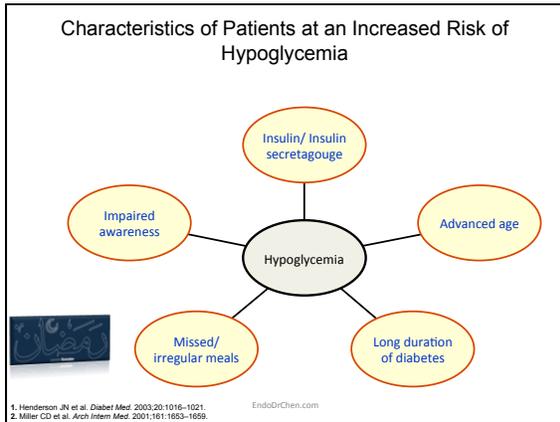
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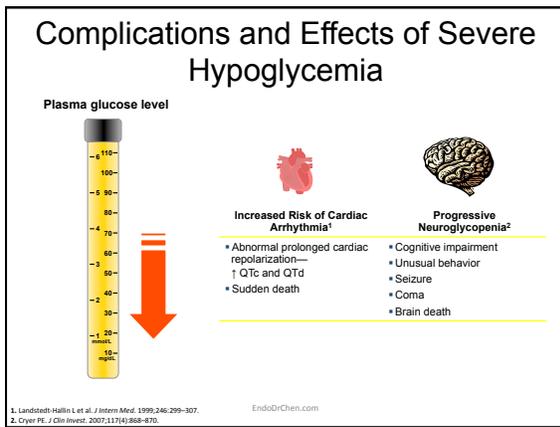
380,000 Emergency Department visits per year in the U.S (1993 -2005) were attributed to Hypoglycemia

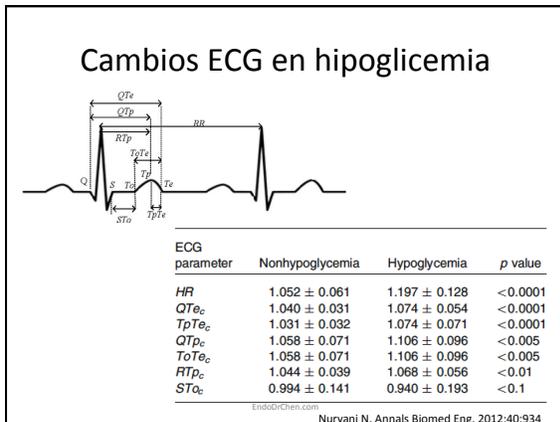
- 5 million emergency department visits^a between 1993 and 2005 for hypoglycemia¹
 - 25% resulted in hospital admission
 - 72% of patients had hypoglycemia as the primary (first-listed) diagnosis
 - ~44% of reported cases occurred in adults ≥65 years of age

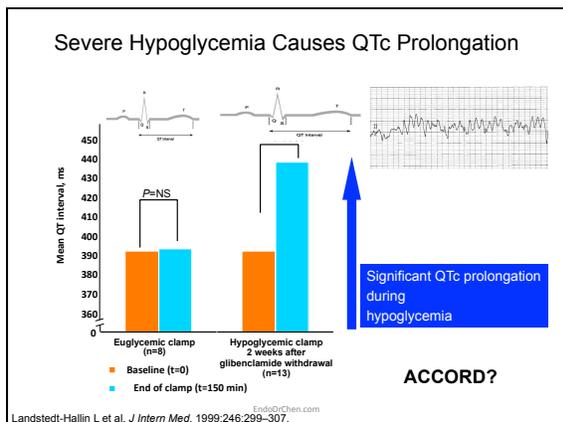
¹ Girle AA et al. Diabetes Care. 2008;31:511-513.
² Mahyka K et al. Diabetes Care. 1997;20(2):135-141.

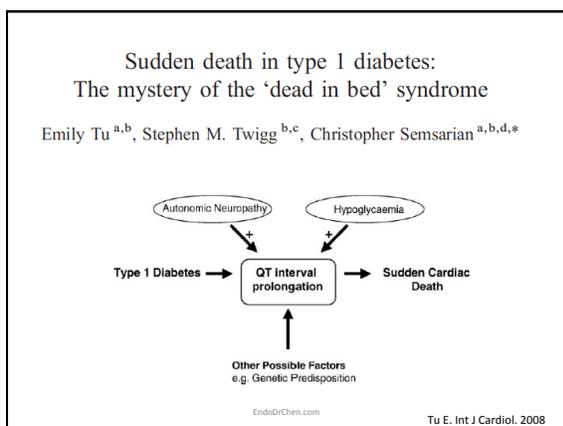
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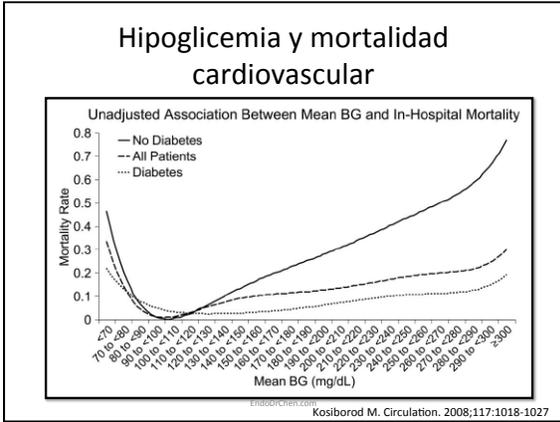


Hipoglicemia e isquemia miocárdica

	Total episodes	Episodes with chest pain/angina	Episodes with ECG abnormalities
Hypoglycemia	54	10*	6*
Symptomatic	26	10*	4*
Asymptomatic	28	—	2
Normoglycemia without rapid changes	N/A	0	0
Hyperglycemia	59	1	0
Rapid changes in glucose (>100 mg · dl ⁻¹ · h ⁻¹)	50	9*	2

*P < 0.01 vs. episodes during hyperglycemia and normoglycemia.

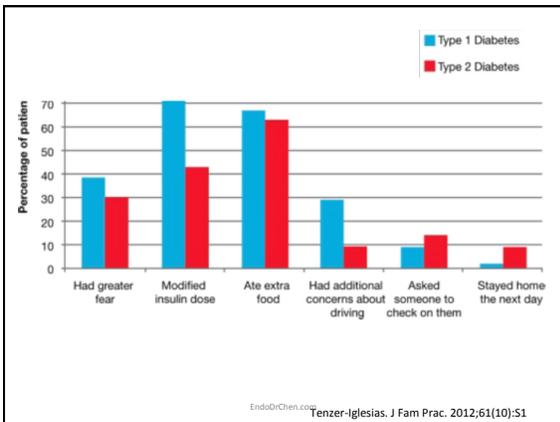
Desouza C. *Diabetes Care.* 2003;26:1485



Hypoglycemia May Be a Barrier to Glycemic Control in Patients With Type 2 Diabetes

- Hypoglycemia is an important limiting factor in glycemic management and may be a significant barrier to treatment adherence.
- Fear of hypoglycemia is an additional barrier to control.
 - A study in patients with type 2 diabetes showed increased fear of hypoglycemia as the number of mild/moderate and severe hypoglycemic events increased.

Amiel SA et al. Diabet Med. 2008;25(3):245-254. EndoOrChen.com

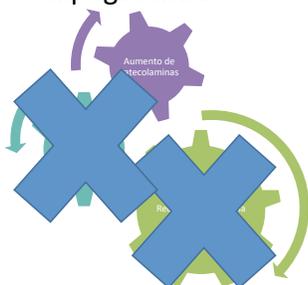


Otras consecuencias

- Ansiedad
- Depresión
- Uso de recursos de salud
- Costo
- Pobre adherencia a tratamiento
- Accidente automonitriz
- Fracturas

EndoDrChen.com Moghissi E. Endocr Pract. 2013;19(3):526

Mecanismos lesionales de hipoglicemia

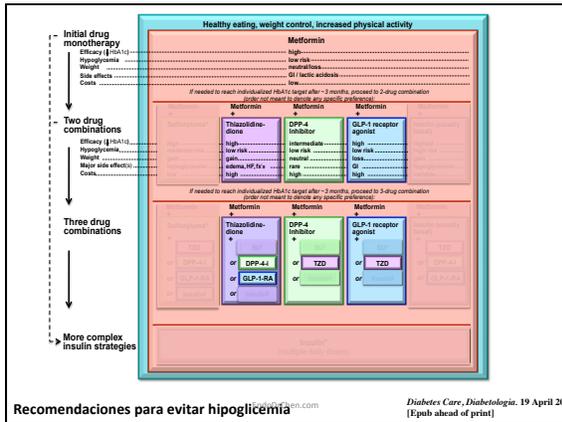


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Mecanismos lesionales de hipoglicemia



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SON TODAS LAS TERAPIAS BASADAS EN INCRETINAS IGUALES?

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Inhibidores de DPP-4

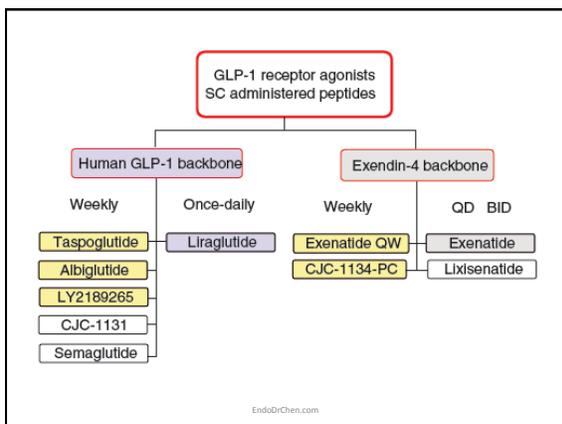
- Cómo se pueden diferenciar?
- Farmacocinética
 - Excreción renal con todos los agentes renales excepto linagliptina
 - Interacciones con citocromos: saxagliptina
- Farmacodinamia: no mucha diferencia
- Seguridad: no mucha diferencia. Pancreatitis sitagliptina? Elevación transaminasas vildagliptina?

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Diferencias entre inhibidores de DPP-4

- En la práctica clínica, realmente no hay mucha diferencia y no hay un claro factor diferenciador para escoger entre los diferentes agentes
- Únicamente tener cuidado con AEC y ajustar la dosis en caso necesario

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	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	✓	✓✓✓

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Conclusiones

- La terapia basada en incretinas puede usarse en primera, segunda o tercera línea de tratamiento
- Los inhibidores de DPP-4 son al menos igual de efectivo comparado con metformin y SU, con mejor tolerancia y muy bajo riesgo de hipoglicemias
- Datos nuevos de seguridad son tranquilizantes en la parte pancreática, se debe poner cuidado con los datos de ICC

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X CONGRESO ENDOCRINOLOGÍA
 Centroamérica y el Caribe
 28 al 30 de agosto, 2014

INCLUYE:
 Certificado de participación
 Acceso a las charlas expuestas
 Almuerzos y refrigerios los tres días
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 \$ 225 antes del 16 de julio, 2014
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Metamorfosis por la salud...

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 Tel. 2487 4318

ASOCIACIÓN PRO ESTUDIO DE LA DIABÉTIS, ENDOCRINOLOGÍA Y METABOLISMO

Preguntas...
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