



## Inhibidores de DPP-4, 10 años después... qué hemos aprendido?

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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, Stendhal
- Investigación clínica: Astra Zeneca, Novartis Pharma Logistics Inc., Merck Sharp & Dohme, Glaxo SmithKline, Organon, Boehringer Ingelheim, Roche, Novo Nordisk

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### Agenda

- Efecto de los inhibidores de DPP-4
  - Control glicémico: predictores de respuesta
  - hipoglicemia
  - Parámetros metabólicos
  - Seguridad cardiovascular
  - Insuficiencia cardíaca
- Papel en algoritmos de tratamiento

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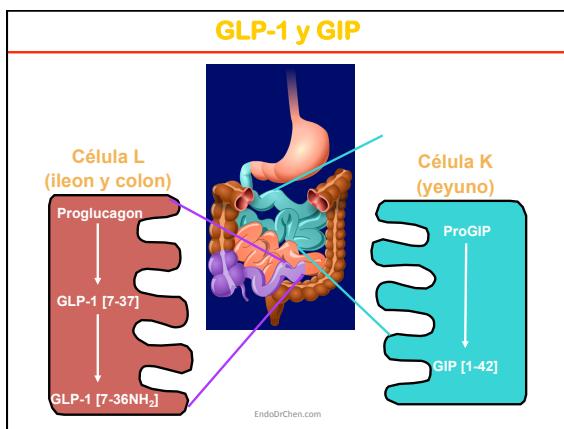
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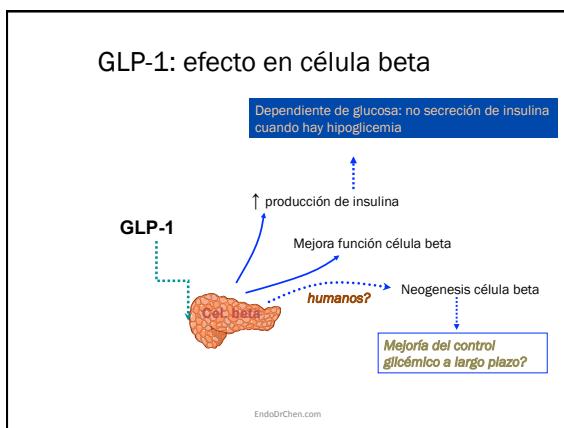

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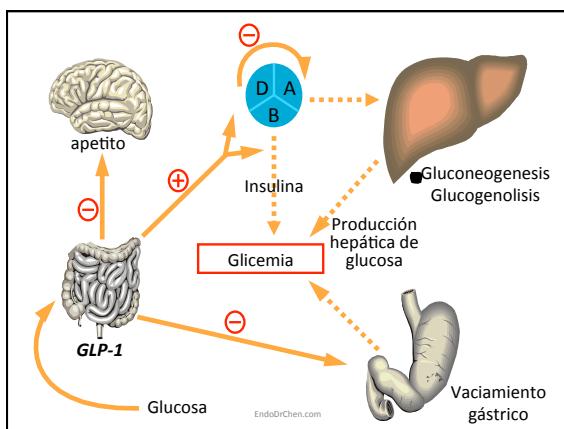

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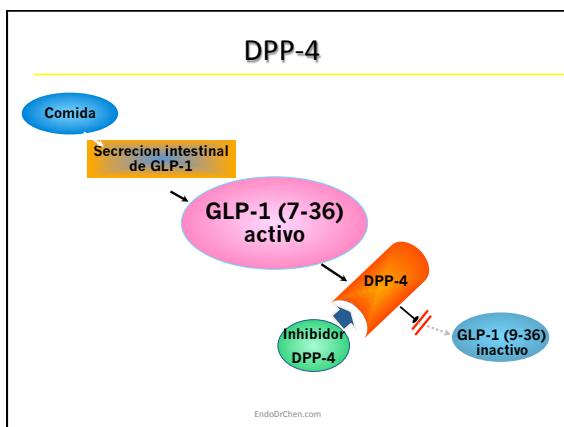

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### Caso #1

- Masculino de 55 años, DM-2 de 5 años de evolución, tratado con metformin 850 mg bid. Cursa asintomático. No tiene complicaciones ni comorbilidades.
- Tiene IMC 29.5 kg/m<sup>2</sup>.
- Hba1c 7.5%
- Cursa asintomático

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### Caso clínico #1

- Cuál es la alternativa?
  - Sulfonilureas
  - Inhibidores de DPP-4
  - Inhibidores de SGLT-2
  - Insulina basal
  - Análogo GLP-1

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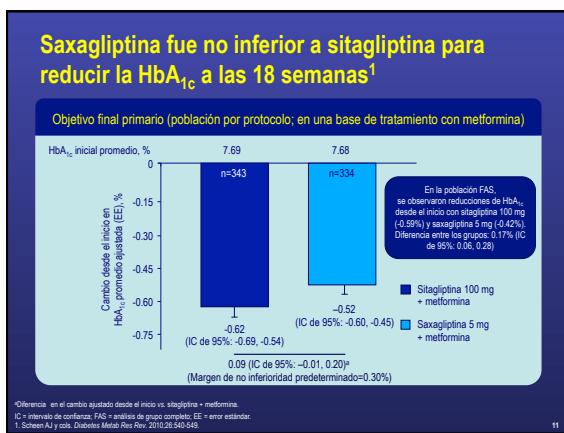
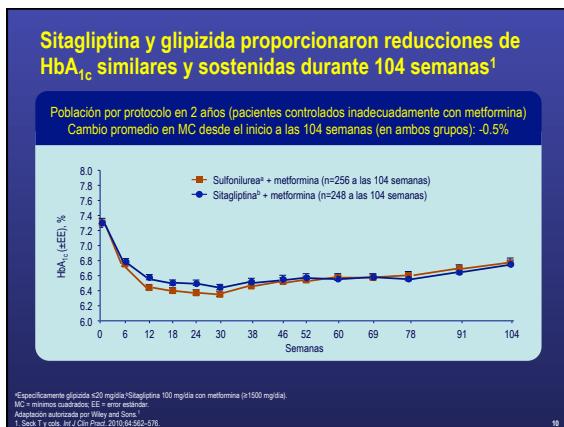
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### Caso clínico #1

- Si optan por iniciar un inhibidor de DPP-4, cuál sería la escogencia?
  - Sitagliptina/metformin 50/1000 mg 1 tab bid
  - Vildagliptina/metformin 50/850 mg 1 tab bid
  - Linagliptina/metformin 2.5/850 mg 1 tab bid
  - Saxagliptina/metformin XR 2.5/1000 mg 2 tab HS
  - Gemigliptina 50 mg 1 tab diaria más metformin 850 mg bid

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## Inhibidores de DPP-4

- Sitagliptina
- Vildagliptina
- Linagliptina
- Saxagliptina
- Alogliptin
- Gemigliptina
- Hay alguna diferencia entre ellas?

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## Los inhibidores de DDP-4 difieren en estructuras moleculares y propiedades farmacológicas<sup>a</sup>

Clase química	β-Fenetilaminas <sup>1</sup>	Cianopirrolidinas <sup>3,7</sup>	Aminopiperidinas <sup>8</sup>	Xantina <sup>9</sup>
Denominación genérica	Sitagliptina <sup>2</sup>	Vildagliptina <sup>6</sup>	Saxagliptina <sup>3</sup>	Alogliptina <sup>10</sup>
Estructura molecular <sup>3</sup>				
Actividad inhibitoria de DPP-4 (IC <sub>50</sub> )	~18 nM <sup>1</sup>	5.3 nM <sup>4</sup>	3.4 nM <sup>4</sup>	6.9 nM <sup>11</sup>
Vida media	12.4 horas <sup>2</sup>	~2-3 horas <sup>6</sup>	2.5 horas (fármaco original) 3.1 horas (metabolito) <sup>8</sup>	21 horas <sup>10</sup> $T_{1/2}$ eficaz ~12 h <sup>12</sup> $T_{1/2}$ terminal ~100 h <sup>12</sup>

<sup>a</sup>Los estudios farmacodinámicos se realizaron en diferentes sistemas de ensayo y no deben compararse.DPP-4 = dipeptidil peptidasa 4.  
1. Vildagliptina: 2. Sitagliptina: 3. Saxagliptina: 4. Alogliptina: 5. Linagliptina: 6. Vildagliptina: 7. Sitagliptina: 8. Alogliptina: 9. Linagliptina: 10. Alogliptina: 11. Lee B y cols. *J Med Chem*. 2002;45:2714-2719. 12. EU/PC for Galvus. 7. Auger DJ y cols. *J Med Chem*. 2002;45:2026-2037. & EU/PC for Onglyza. 8. Feng J y cols. *J Med Chem*. 2007;50:2297-2300. 10. EU/PC for Vida. 11. Lee B y cols. *Eur J Pharmacol*. 2008;589:306-314. 12. EU/PC for Trajetta. 14

## Propiedades farmacocinéticas de los inhibidores de DPP-4<sup>a</sup>

	T <sub>max</sub> de absorción (media)	Biodisponibilidad	Vida media (T <sub>1/2</sub> ) a la dosis clínicamente relevante	Distribución	Metabolismo	Eliminación
Sitagliptina (Merck) <sup>1</sup>	1-4 horas	~87%	12.4 horas	38% unido a proteínas	~16% metabolizado	Renal 87% (79% intacto)
Vildagliptina (Novartis) <sup>2</sup>	1.7 horas	85%	~2-3 horas	9.3% unido a proteínas	69% metabolizado principalmente renal (metabolito inactivo)	Renal 85% (23% intacto)
Saxagliptina (BMS/AZ) <sup>3</sup>	2 horas (4 horas para el metabolito activo)	≥75% <sup>4</sup>	2.5 horas (fármaco original) 3.1 horas (metabolito)	Baja unión a proteínas	Hepático (metabolito activo CYP3A4/5)	Renal 75% (24% como compuesto original; 36% como metabolito activo)
Alogliptina (Takeda) <sup>5</sup>	1-2 horas	100%	~21 horas	Unión a proteínas 20-30%	~7% metabolizado	Renal 76% (60-70% intacto)
Linagliptina (BI) <sup>6</sup>	1.5 horas	~30%	T <sub>1/2</sub> eficaz ~12 horas T <sub>1/2</sub> terminal >100 horas	Unión a proteínas dependiente de la concentración: 1 nM: 99% (DPP-4) >30 nM: 75%-89%	~1% metabolizado	Hígado 80% Renal 5%

<sup>a</sup>Las estimaciones se basan en datos de ensayos en diferentes sistemas de ensayo y no deben compararse.

DPP-4 = dipeptidil peptidasa 4.

1. JANUVIA WPC. 2. EU/PC for Galvus. 3. EPAR for Onglyza. 4. EPAR for Onglyza. [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_Public\\_assessment\\_report/human/001039/WC5004415.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Public_assessment_report/human/001039/WC5004415.pdf). Accessed November 11, 2010. 5. EU/PC for Vida. 6. EU/PC for Trajetta.

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## 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

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## 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

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## Combinación con metformin

- Nuevos lineamientos para uso de metformin por FDA:
  - AEC >45 cc/min: uso seguro
  - AEC 30-45 cc/min: uso con precaución y la mitad de las dosis máximas
- Por lo tanto,
  - AEC mayores a 45 cc/min usar la dosis completa de metformin/iDPP4
  - AEC 30-45 cc/min: usar la mitad de la dosis

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## Diferencias cinéticas

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

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## Otras diferencias

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

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## EFICACIA

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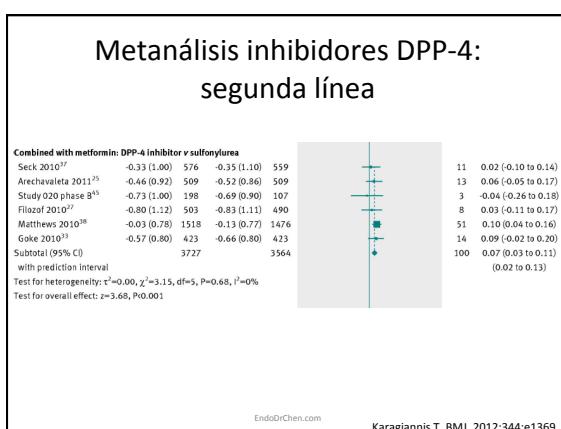
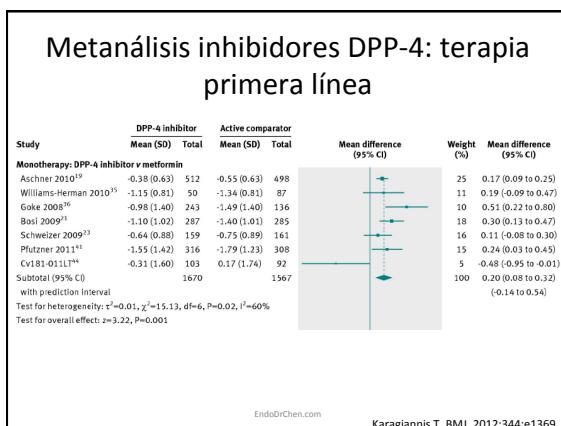
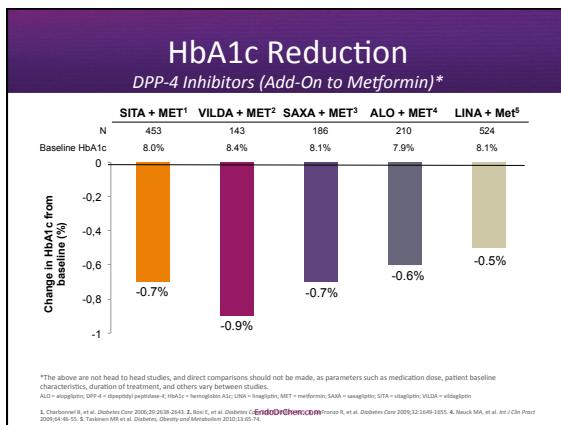
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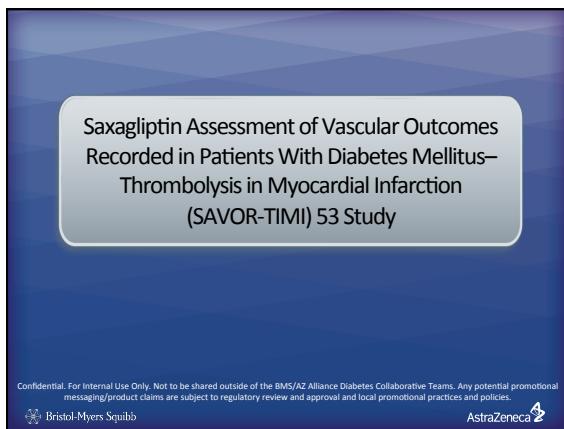
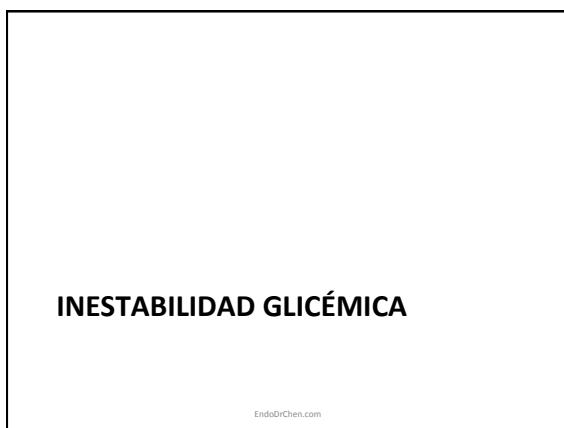
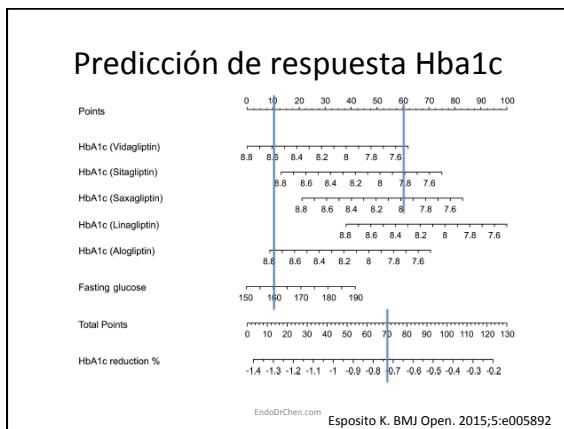
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### Inestabilidad glicémica

- Necesidad de agregar otro antidiabético por más de 3 meses
- Aumento de dosis de insulina >25% por más de 3 meses
- Necesidad de inicio de insulina por más de 3 meses
- Aumento de Hba1c >0.5% después de la aleatorización

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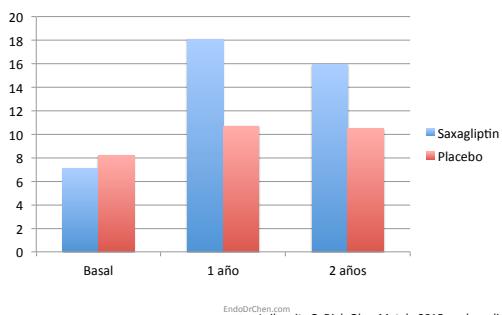


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### SAVOR: pacientes con hba1c <6.5%




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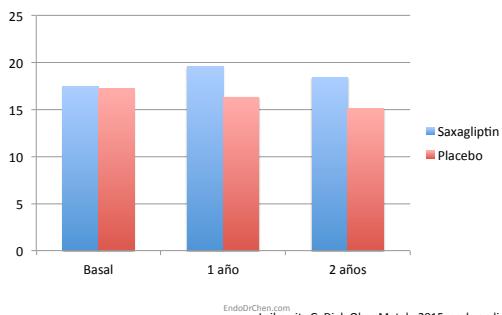


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### SAVOR: pacientes con hba1c 6.5-7%




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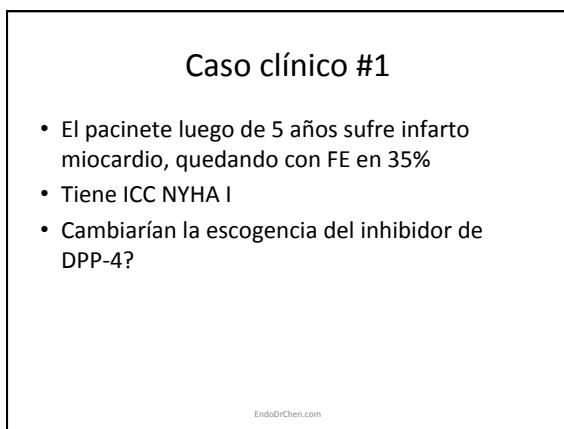
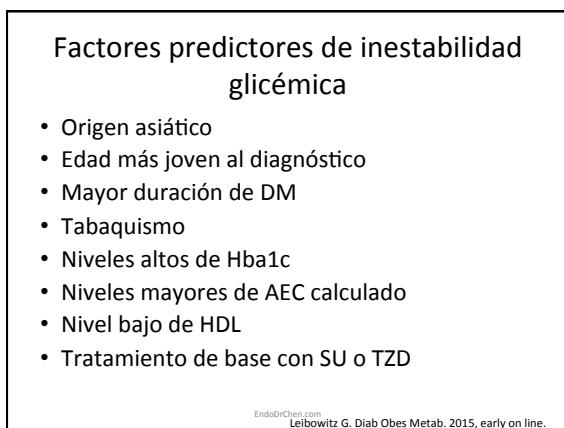
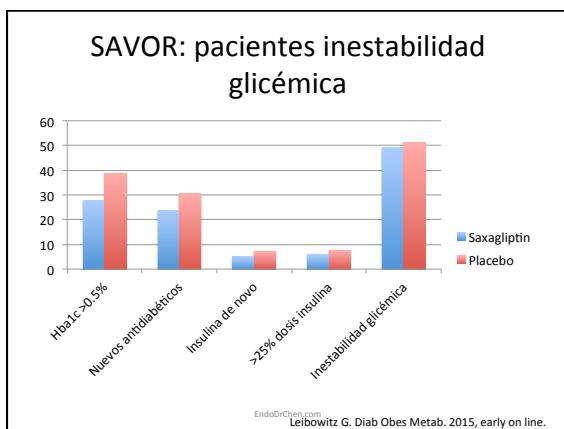
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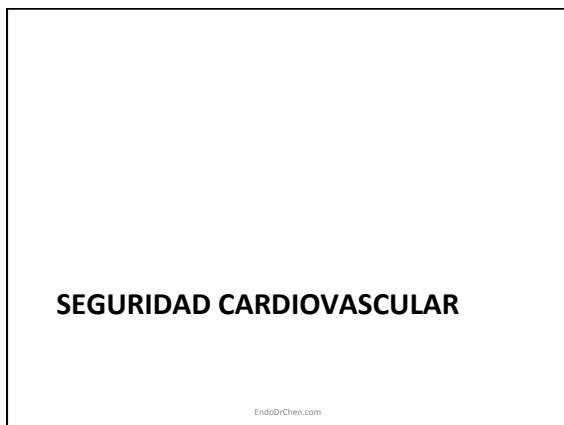


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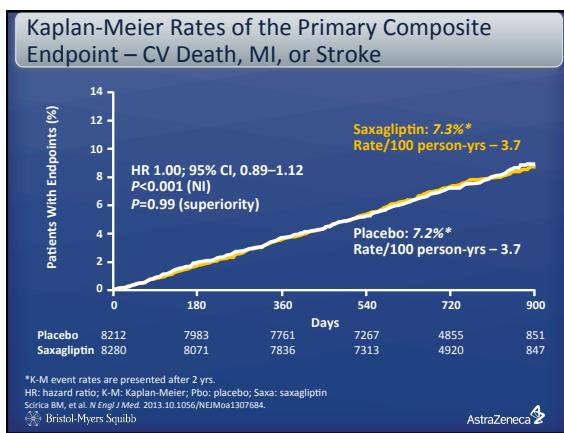
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**Individual Components of the Composite Endpoints**

Efficacy endpoint	Saxagliptin n (%) <sup>*</sup> (N = 8,280)	Placebo n (%) <sup>*</sup> (N = 8,212)	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.  
Soricic BM, et al. *N Engl J Med.* 2013;10.1056/NEJMoa1307684.  
© Bristol-Myers Squibb AstraZeneca

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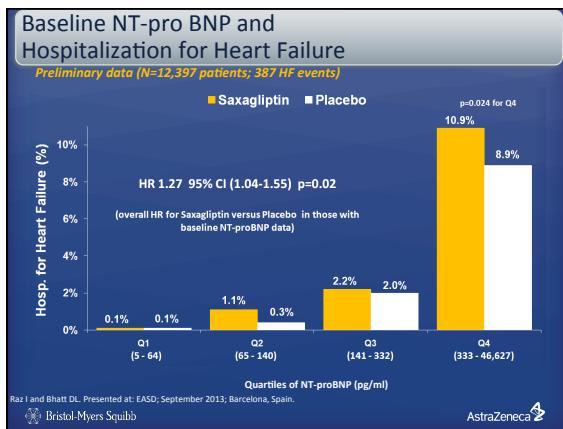
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### EXAMINE e ICC

- 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)

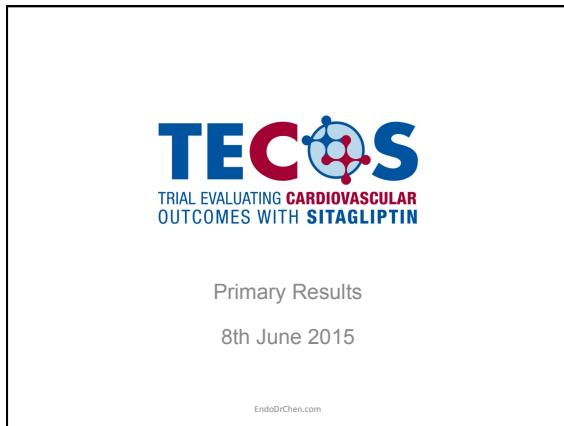
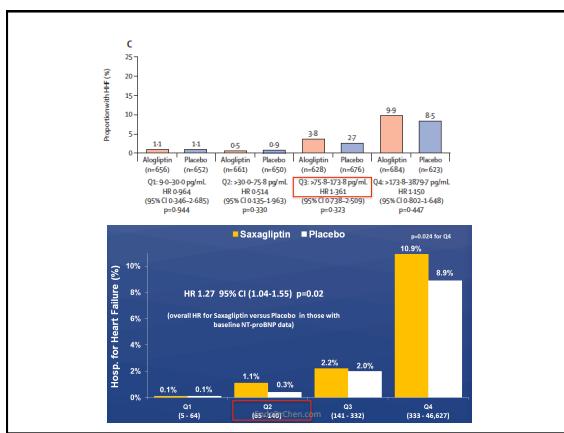
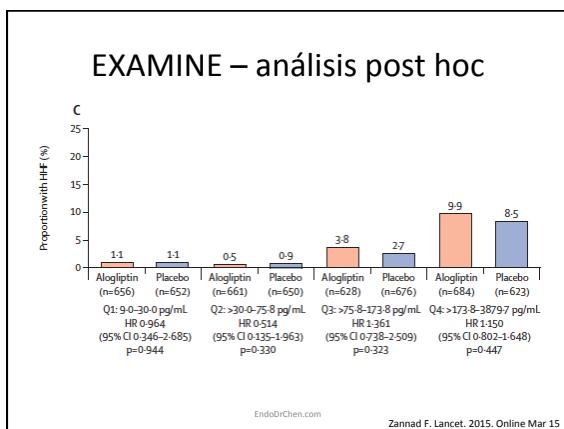
EndoDrChen.com EASD Barcelona 2013

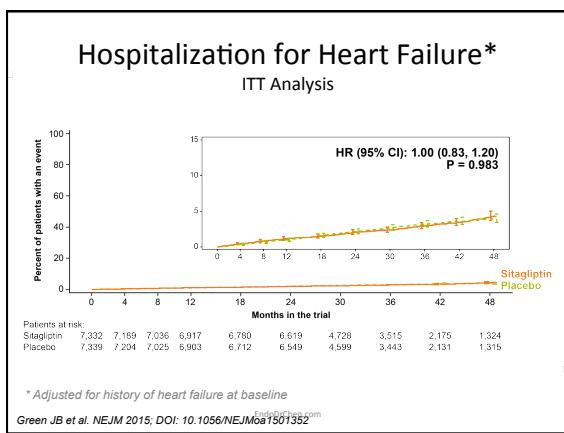
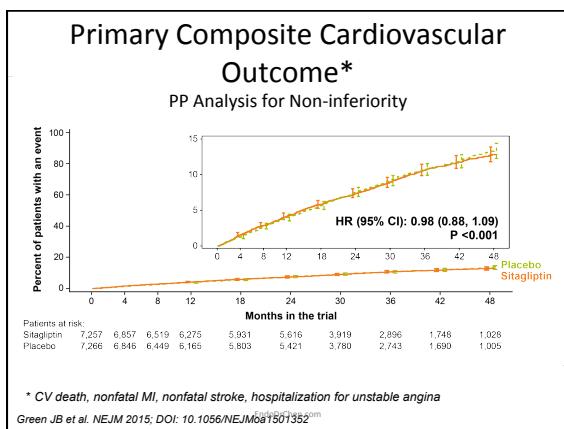
### EXAMINE-análisis post hoc

	All patients	History of heart failure at baseline		No history of heart failure at baseline		
	Alogliptin (n=2701)	Placebo (n=2679)	Alogliptin (n=771)	Placebo (n=762)	Alogliptin (n=1930)	Placebo (n=1917)
Cardiovascular death and hospital admission for heart failure	201 (7.4)	201 (7.5)	107 (13.9)	120 (15.7)	94 (4.9)	81 (4.2)
Hazard ratio (95% CI)	1.00 (0.82-1.21)		0.90 (0.70-1.17)		1.14 (0.85-1.54)	
p value	0.976		0.446		0.337	
P <sub>treatment</sub> for treatment and history of heart failure	–	–	0.221	–	–	–
Cardiovascular death*	112 (4.1)	130 (4.9)	55 (7.1)	69 (9.1)	57 (3.0)	61 (3.2)
Hazard ratio (95% CI)	0.85 (0.66-1.10)		0.77 (0.54-1.09)		0.92 (0.64-1.32)	
p value	0.212		0.141		0.643	
P <sub>treatment</sub> for treatment and history of heart failure	–	–	0.508	–	–	–
Hospital admission for heart failure	106 (3.9)	89 (3.3)	63 (8.2)	65 (8.5)	43 (2.2)	24 (1.3)
Hazard ratio (95% CI)	1.19 (0.90-1.58)		1.0 (0.71-1.42)		1.76 (1.07-2.90)	
p value	0.220		0.996		0.026	
P <sub>treatment</sub> for treatment and history of heart failure	–	–	0.068	–	–	–

\*Analysis includes all cardiovascular deaths, including those that followed heart failure that were not counted in the analysis of the composite endpoint.

EndoDrChen.com Zannad F. Lancet. 2015. Online Mar 15





**Hospitalization for Heart Failure\***

ITT Population

Numbers of patients with events	Sitagliptin n=7332	Placebo n=7339
Hospitalization for heart failure†	228 (3.1%)	229 (3.1%)
	1.07 per 100 pyrs	1.09 per 100 pyrs
	ITT HR=1.00 (0.83, 1.20), p=0.98	
Hospitalization for heart failure or cardiovascular death†	538 (7.3%)	525 (7.2%)
	2.54 per 100 pyrs	2.50 per 100 pyrs
	ITT HR=1.02, (0.90, 1.15), p=0.74	

\* Adjusted for history of heart failure at baseline  
† Prespecified analyses  
Green JB et al. NEJM 2015; DOI: 10.1056/NEJMoa1501352

## Por qué las diferencias?

- Diseño del estudio?
  - Recolección de datos cada 6 meses
  - No protocolizado los laboratorios control
  - Subgrupos por BNP?

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## Comparación

	SAVOR <sup>1</sup>	EXAMINE <sup>2</sup>	TECOS <sup>3</sup>
N	16492	5380	14724
Edad	65.1	61	66
IMC	31.1	28.7	30.2
Duración DM	10.3	7.3	11
Hba1c	8.0%	8.0%	7.3%
Caucásicos	75.4%	72.5%	68%
Contexto	Alto riesgo CV	ACS	43% post IAM
ICC	12.8%	27.8%	18%
Aumento hosp ICC	0.7% (3.5-2.8%)	0.6% (3.9-3.3%)	0 (3.1-3.1%)
Uso IECA	53.6%	82.5%	54%
Uso ARAII	28.2%		28%

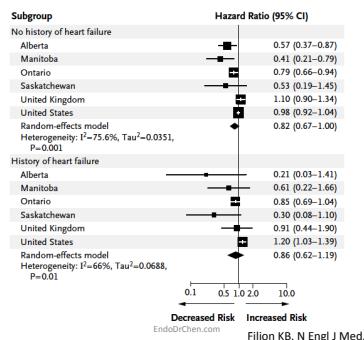
1. Scirica BM. N Engl J Med. 2013.

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2. Zannad F. Lancet. 2015. Online Mar 15

3. Bethel MA. Diab Obes Metab. 2015;17:395

## CNODES



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Filion KB. N Engl J Med. 2016;374:1145

### CNODES: análisis por tipo de terapia

Treatment†	Hospitalization for Heart Failure		Adjusted Hazard Ratio (95% CI)‡	$I^2$ §		
	Case Patients (N=23,205)					
	no. (%)	%				
Two or more oral antidiabetic drugs	3167 (13.6)	51,968 (11.9)	1.00 (reference)			
Incretin-based drugs	2457 (10.6)	42,706 (9.8)	0.82 (0.67–1.00)	75.6		
DPP-4 inhibitors	2228 (9.6)	38,586 (8.9)	0.84 (0.69–1.02)	74.3		
GLP-1 analogues	231 (1.0)	4,120 (0.9)	0.95 (0.83–1.10)	0.0		
Duration of treatment with incretin-based drugs						
<365 days	1748 (7.5)	28,982 (6.7)	0.83 (0.66–1.05)	76.6		
365–729 days	388 (1.7)	7,847 (1.8)	0.79 (0.71–0.89)	0.0		
≥730 days	320 (1.4)	5,876 (1.3)	0.96 (0.75–1.22)	39.3		

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Filion KB. N Engl J Med. 2016;374:1145

### FDA Safety Communication:

- Saxagliptin and alogliptin may increase the risk of heart failure, particularly in patients who already have heart or kidney disease
- Warning about heart failure risk added to the label for medications containing saxagliptin and alogliptin

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### Por qué los hallazgos en ICC?

- NPY y PYY son péptidos metabolizados por DPP4
- Estimulan receptores Y1 que aumentan la presión y el número de fibroblastos cardíacos
- En modelos animales aumentan la presión y el número de fibroblastos

Doggrell S. Exp Opin Pharmacother. 2016;17(6):757-60

	Sitagliptin	Vildagliptin	Saxagliptin	Alogliptin	Linagliptin
Daily recommended dose	100 mg	100 mg	5 mg	25 mg	5 mg
Pharmacokinetic properties					
Oral bioavailability	87%	85%	75%	70%	30%
Volume distribution	198 l	71 l	151 l	300 l	368 – 918 l
Fraction bound to proteins	38%	9.3%	< 10%	20%	70%
Half-life ( $t_{1/2}$ )	8 – 14 h	2 – 3 h	2.2 – 3.8 h	12.4 – 21.4 h	120 – 184 h
Kidney excretion	87%	85%	75%	76%	5%
Liver metabolism	13%	45%	23%	13%	85%
Proportion excreted unchanged	79%	23%	24%	95%	~ 90%
Substrate for CYP3A4/S	Low	No	Yes	No	No
Active metabolites	ND	No	Yes	ND	ND
Inactive metabolites	ND	Yes	No	ND	ND
Pharmacodynamic properties					
In vitro DPP-4 inhibition ( $IC_{50}$ )	19 nM	62 nM	50 nM	24 nM	1 nM
Selectivity for DPP-4 versus DPP-8/DPP-9	> 2,600	< 100	< 100	> 14,000	> 10,000

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## Propiedades farmacodinámicas exclusivas de los inhibidores de DPP-4<sup>a</sup>

	Inhibición max. de DPP-4	$IC_{50}$ para DPP-4, nM	$IC_{50}$ para DPP-8 (DPP-8/DPP-4), nM	$IC_{50}$ para DPP-9 (DPP-9/DPP-4), nM	$IC_{50}$ para FAP (FAP/DPP-4), nM
<b>Sitagliptina (Merck)<sup>1-3</sup></b>	97%	~18	48,000 (~2,700)	>100,000 (>5,000)	>100,000 (>5,000)
<b>Vildagliptina (Novartis)<sup>4-5</sup></b>	~95%	5.3	1,112 (210)	66.2 (13)	73,000 (>10,000)
<b>Saxagliptina (BMS/AZ)<sup>3,6,7</sup></b>	80%	3.4	244 (72)	104 (31)	>1,000 (300)
<b>Alogliptina (Takeda)<sup>8,9</sup></b>	≥95%	6.9	>100,000 (>10,000)	>100,000 (>10,000)	>100,000 (>10,000)
<b>Linagliptina (BI)<sup>7,9</sup></b>	92%	~1	40,000 (~40,000)	>10,000 (>10,000)	89 (~89)

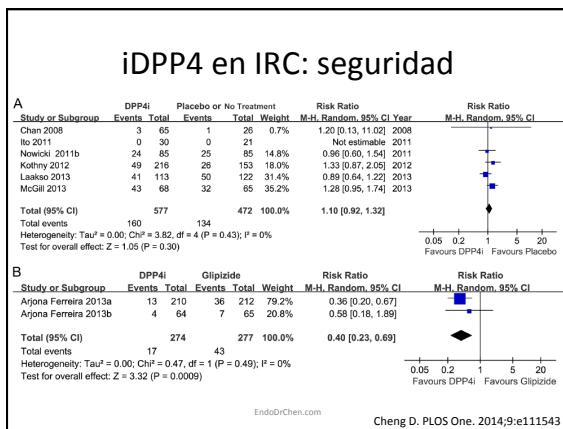
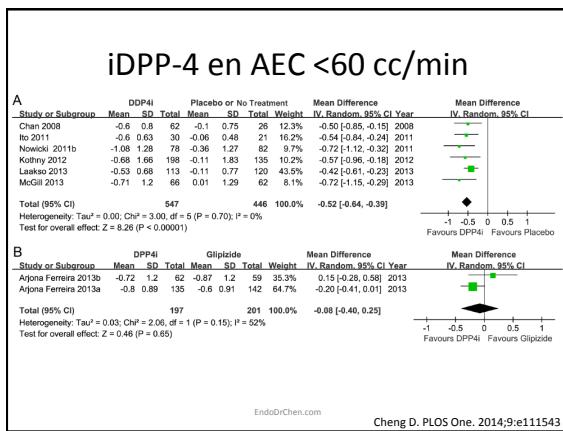
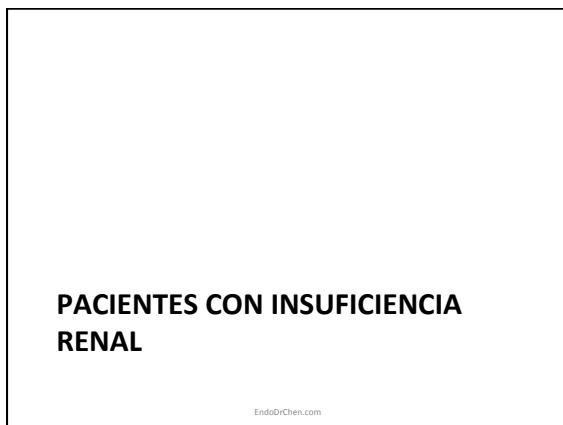
<sup>a</sup> Los estudios farmacodinámicos se realizaron en diferentes sistemas de ensayo y no deben compararse.  
DPP-4 = dipeptidil peptidasa 4; FAP = proteína de activación de fibroblastos n.

1. Adaptación autorizada por Alba M y cols. *Curr Med Res Opin*. 2009;25:2507-2514. 2. Kim D y cols. *J Med Chem*. 2005;48:141-151. 3. Lee B y cols. *Eur J Pharmacol*. 2008;589:306-313. 4. Tardivo A y cols. *Diabetologia*. 2010;53:2043-2041. 5. European Public Assessment Report for Vildagliptin. Available at: [http://www.emea.europa.eu/humomedics/PDFs-EU/monographs/H\\_1030-en.pdf](http://www.emea.europa.eu/humomedics/PDFs-EU/monographs/H_1030-en.pdf). Accessed November 11, 2014. 6. Thomasset y cols. *J Pharmacol Exp Ther*. 2006;315:176-182. 7. Covington R y cols. *Clin Ther*. 2008;30:499 -512. 8. Heise T y cols. *Diabetes Obes Metab*. 2009;11:786-794. 53

## Caso clínico #2

- Femenina de 60 años de edad, está siendo tratada con sitagliptina/metformin 50/1000 mg bid
- En laboratorios de control se ha documentado que su creatinina ha aumentado gradualmente y está en 1.3 mg/dl
- AEC 45 cc/min, HbA1c 6.6%
- Qué decisión terapéutica tomarán?

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## Combinación con metformin

- Nuevos lineamientos para uso de metformin por FDA:
  - AEC >45 cc/min: uso seguro
  - AEC 30-45 cc/min: uso con precaución y la mitad de las dosis máximas
- Por lo tanto,
  - AEC mayores a 45 cc/min usar la dosis completa de metformin/DPP4
  - AEC 30-45 cc/min: usar la mitad de la dosis

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## OTROS PARÁMETROS METABÓLICOS

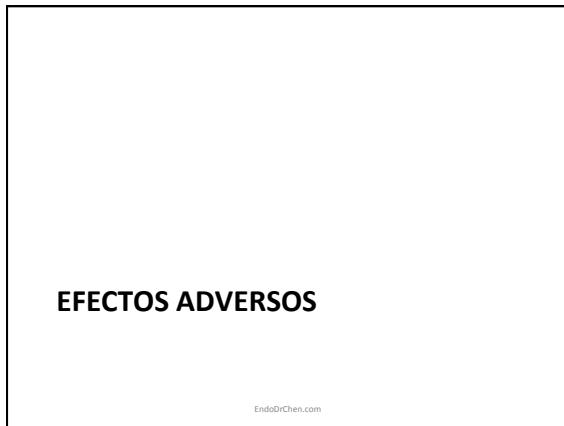
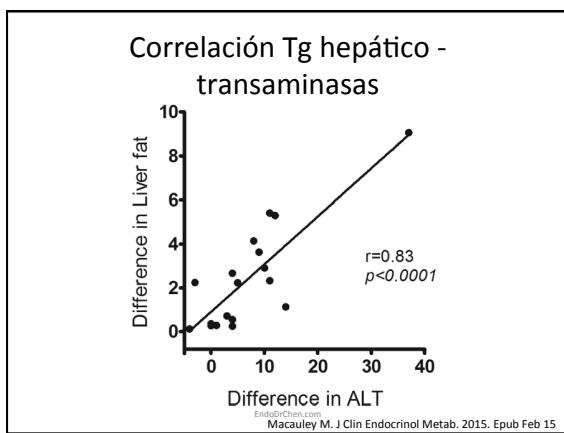
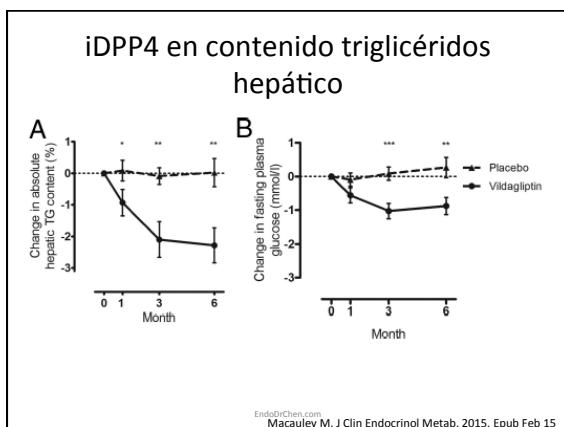
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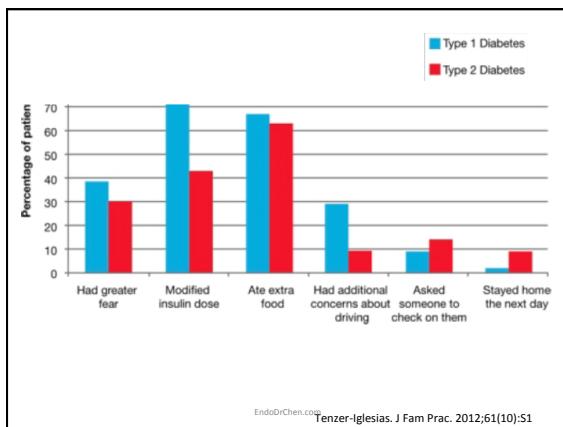
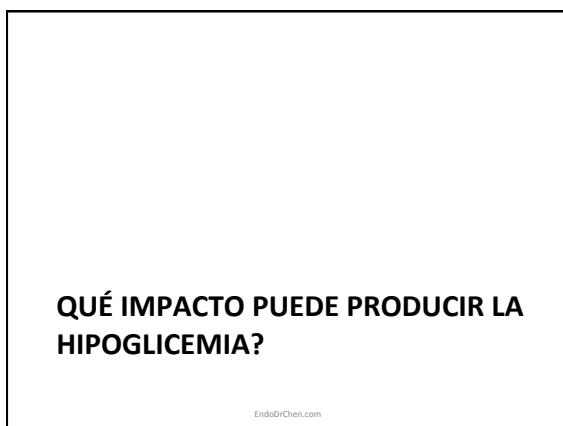
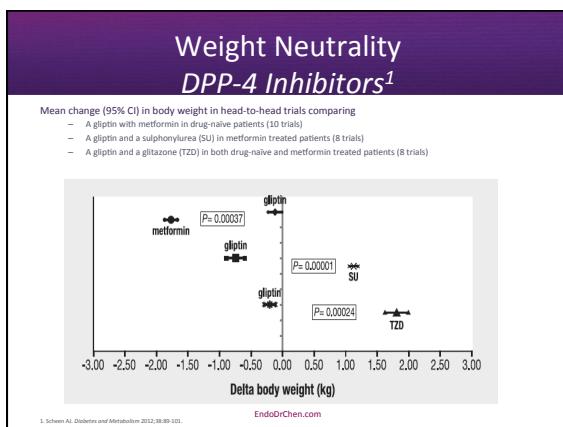
## Mejoría en función hepática

	Baseline	1 month	3 months	6 months
<b>Total (n=224)</b>				
Body weight (kg)	62.9±13.5	62.4±11.8	63.9±13.5	63.4±14.3
AST (U/L)	28±17	27±17	26±14	28±16
ALT (U/L)	30±25	28±23	27±19	28±22
γGTP (U/L)	46±49	45±49	46±53	48±59
HbA1c (%)	7.9±1.2	7.5±1.0***	7.3±1.0***	7.2±1.0***
<b>With Liver injury (n=44)</b>				
Body weight (kg)	69.3±17.8	69.3±13.7	73.8±19.0	71.7±18.0
AST (U/L)	51±25	45±30*	42±24*	45±29*
ALT (U/L)	65±36	54±38**	49±30***	52±36**
γGTP (U/L)	84±74	76±71	82±91	88±102
HbA1c (%)	8.1±1.3	7.6±1.2***	7.4±1.1***	7.1±1.0***

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Kanazawa I. Med Sci Monit. 2014;20:1662



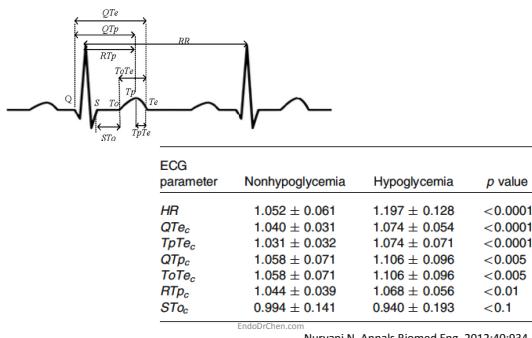


## Otras consecuencias

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

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

## Cambios ECG en hipoglicemia

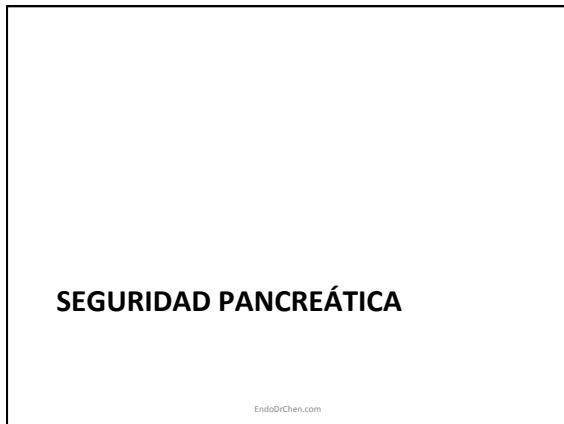
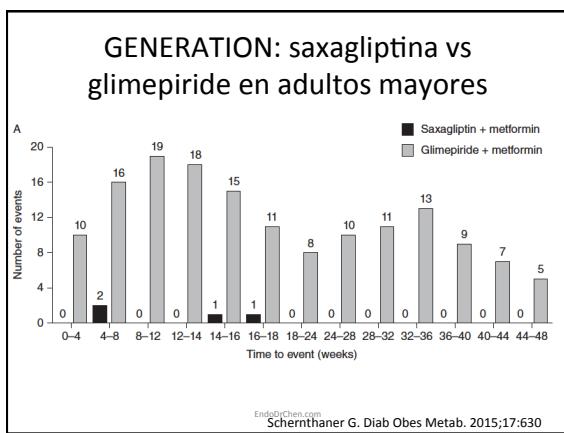
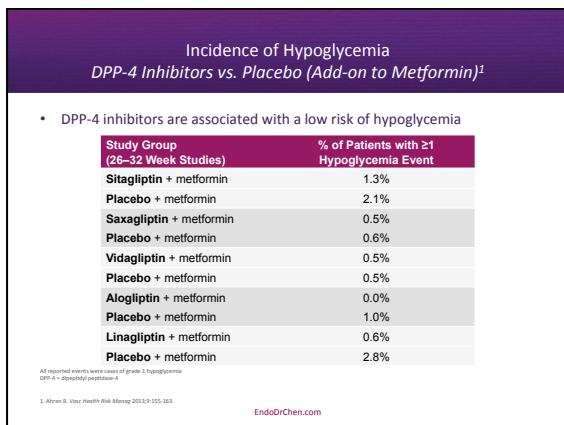


## Hipoglicemia e isquemia miocárdica

	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 ( $>100 \text{ mg} \cdot \text{dl}^{-1} \cdot \text{h}^{-1}$ )	50	9*	2

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

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Desouza C. Diabetes Care. 2003;26:1485



## Pancreatitis

- SAVOR, EXAMINE y TECOS evaluaron de forma prospectiva y de manera predefinida la incidencia de pancreatitis. No diferencias significativas.
- EMA y FDA se pronunciaron en cuanto a seguridad en riesgo de pancreatitis
- No hay datos suficientes para afirmar que hay aumento en riesgo de cáncer de páncreas

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## FRACTURAS

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Correlate	Adjusted Hazard Ratio (95% Confidence Interval)	P Value
Antidiabetic agents		
Sitagliptin	1.1 (0.8–1.4)	.7
Metformin	1.0 (0.8–1.2)	1.0
Sulfonylureas	1.3 (1.1–1.5)	.008
TZDs	1.2 (1.04–1.5)	.019
Insulin	2.1 (1.6–2.8)	<.001
Sociodemographic		
Age		
≤45 y	Reference	
46 to ≤60 y	1.7 (1.3–2.1)	<.001
>60 y	2.2 (1.7–2.9)	<.001
Female	1.2 (1.1–1.4)	<.008
Clinical and medication related		
Osteoporosis	1.5 (1.05–2.1)	.03
Loop diuretics	1.4 (1.03–1.8)	.03
Oral corticosteroids	1.3 (1.1–1.6)	.01

Majumdar SR. J Clin Endocrinol Metab. 2016;101:1963-69

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**EFICACIA Y SEGURIDAD TRADUCIDO  
EN ADHERENCIA**

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Saxagliptin is Associated with Increased Adherence and Persistence vs. GLP-1 Agonists, SUs or TZDS

- Comparison of adherence and persistence for different antidiabetic drug classes
- Saxagliptin was the reference drug

Drug Class	Adherence (approx.)
GLP-1	1.2
SU	0.8
TZD	0.8

Drug Class	Persistence (approx.)
GLP-1	1.8
SU	1.2
TZD	1.2

Corkendale SM et al. Current Medical Research & Opinion 29(2013)1275–1286. EndoDrChen.com

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**QUÉ DICEN LAS GUÍAS DE TRATAMIENTO?**

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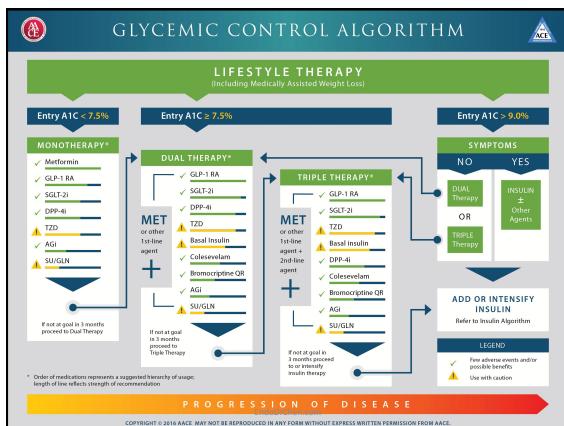
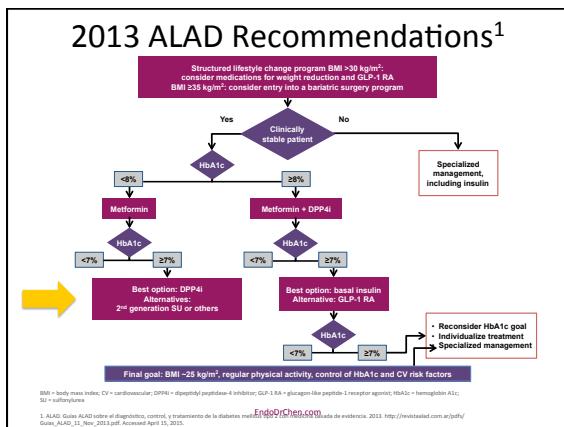
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**PROFILES OF ANTIDIABETIC MEDICATIONS**

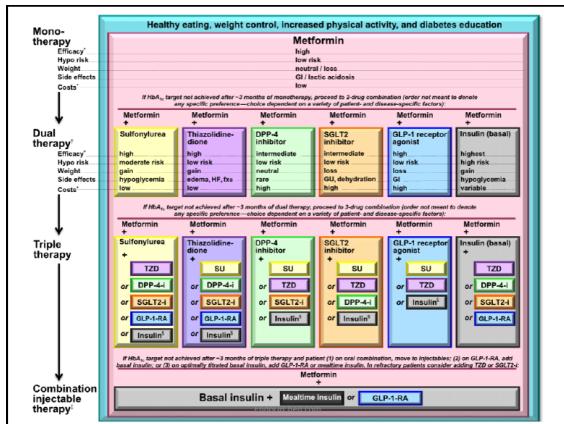
	MET	GLP-1 RA	SGLT-2i	DPP-4i	AGI	TZD (immediate dose)	SU	GLN	COL	SVL	BCR-QR	INSULIN	PRALI
HYPOTHYROIDISM	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/Severe	Mild	Neutral	Neutral	Moderate to Severe	Neutral	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Neutral	Gain	Loss	Neutral
RENAL/GU	Contraindicated in GFR < 45 mL/min or indicated Ckd > 3	Excessive Not Effective in GFR < 45 mL/min or indicated Ckd > 3	Not Effective in GFR < 45 mL/min or indicated Ckd > 3	Neutral	Neutral	Moderate	Neutral	Mild	Moderate	Moderate	Neutral	Moderate	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Mild	Mild	Moderate	Moderate	Neutral	Moderate	Neutral
CHF	Neutral	Neutral	Neutral	Neutral	Moderate	Neutral	Mild	Mild	Neutral	Neutral	Neutral	Neutral	Neutral
ASCVD	Benefit	Neutral	Possible Benefit	Neutral	Neutral	Neutral	?	?	Neutral	Safe	Neutral	Neutral	Neutral
BONE	Neutral	Neutral	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

LEGEND

- Few adverse events or possible benefits
- Use with caution
- Likelihood of adverse effects
- Uncertain effect

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## Conclusiones

- Los inhibidores de DPP-4 en general son una clase donde es difícil diferenciar entre los agentes
- Entre más alto Hba1c basal, mayor reducción
- Con Hba1c menor a 8%, eficacia similar a otros grupos terapéuticos
- Precaución con falla cardíaca (presencia de IRC, BNP alto) especialmente con saxagliptina y alogliptina
- Grupo terapéutico sumamente seguro

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**Preguntas...**  
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