



Eficacia y seguridad de terapia basada en incretinas

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Introducción

- 2 estrategias muy diferentes de modular el sistema de incretinas
 - Eficacia
 - Otros parámetros más allá de hba1c
 - Efectos adversos
- Farmacológicamente, mucho de la diferencia se puede explicar por las concentraciones alcanzadas del GLP-1 o su agonista

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Agenda

- Eficacia de inhibidores de DPP-4
- Eficacia de análogos de GLP-1
- Seguridad
- Diferencias entre agentes

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EFICACIA

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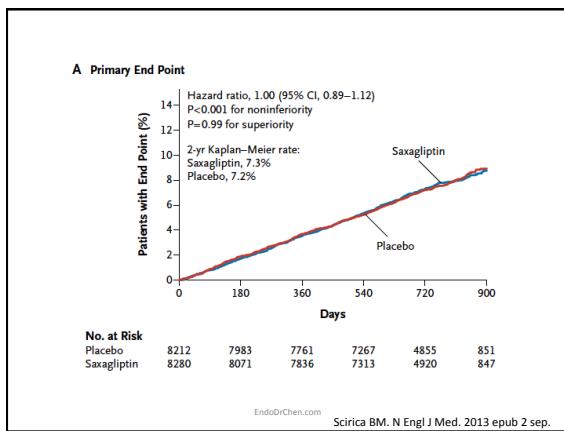
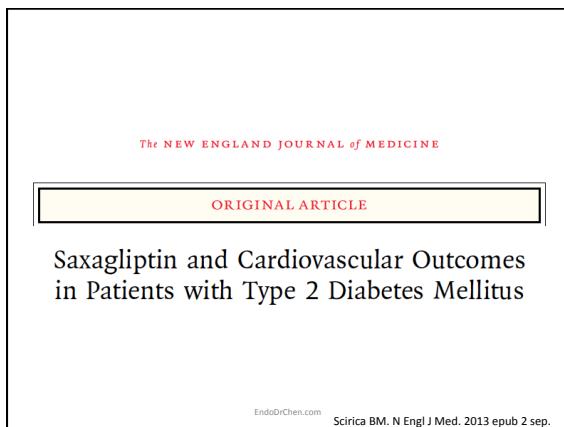
Eficacia

- Cuáles son los parámetros que nos han dicho que mejora el sistema de incretinas?
- Cómo valoramos su eficacia?
 - Antidiabético: reducción de Hba1c
 - Preservación de células beta?
 - Efectos beneficiosos cardiovasculares?

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EVENTOS CARDIOVASCULARES

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End Point	Saxagliptin (N=8280)	Placebo (N=8212)	Hazard Ratio (95% CI)	P Value
Cardiovascular death, myocardial infarction, or stroke: primary efficacy end point	613 (7.3)	609 (7.2)	1.00 (0.89–1.12)	0.99
Cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, heart failure, or coronary revascularization: secondary efficacy end point	1059 (12.8)	1034 (12.4)	1.02 (0.94–1.11)	0.66
Death from any cause	420 (4.9)	378 (4.2)	1.11 (0.96–1.27)	0.15
Death from cardiovascular causes	269 (3.2)	260 (2.9)	1.03 (0.87–1.22)	0.72
Myocardial infarction	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
Hospitalization for unstable angina	97 (1.2)	81 (1.0)	1.19 (0.89–1.60)	0.24
Hospitalization for heart failure	289 (3.5)	228 (2.8)	1.27 (1.07–1.51)	0.007
Hospitalization for coronary revascularization	423 (5.2)	459 (5.6)	0.91 (0.80–1.04)	0.18
Doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine >6.0 mg/dl (530 µmol/liter)	194 (2.2)	178 (2.0)	1.08 (0.88–1.32)	0.46
Hospitalization for hypoglycemia	53 (0.6)	43 (0.5)	1.22 (0.82–1.83)	0.33

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Intrepretación de los datos de ICC

- Definición:
 - Requiere hospitalización o estar en el servicio de emergencias por al menos 12 horas
 - Manifestaciones que incluyen 1 de lo siguientes:
 - Disnea, ortopnea, disnea paroxística nocturna, edema, crepitaciones basales, ingurgitación yugular, evidencia radiológica de ICC
 - Y
 - Uso de diuréticos intravenosos, inotrópicos o vasodilatadores, aumento de dosis de agentes intravenosos, uso de intervención mecánica o quirúrgica orientado a ICC
 - Biomarcadores son de apoyo pero no son parte del diagnóstico

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ICC

- El aumento de hospitalización por ICC se presentó en el cuartilo que tenía niveles mayores de BNP al enrolamiento, no en el momento de la ICC
- En otros subrupos no hubo aumento de ICC
- Según se mencionó, al parecer BNP basal fue mayor en pacientes que hicieron ICC
- Abre nuevas posibilidades de vías de investigación

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ICC

- Aún así, el aumento del riesgo absoluto es de 0.7%
- NNH 142 pacientes por 2.1 años

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End Point	Saxagliptin (N=8280)	Placebo (N=8212)	P Value ^a
	no. (%)		
Thrombocytopenia	55 (0.7)	65 (0.8)	0.36
Lymphocytopenia	49 (0.6)	40 (0.5)	0.40
Severe infection	590 (7.1)	576 (7.0)	0.78
Opportunistic infection	21 (0.3)	35 (0.4)	0.06
Hypersensitivity reaction	93 (1.1)	89 (1.1)	0.82
Bone fracture	241 (2.9)	240 (2.9)	1.00
Skin reaction	228 (2.8)	232 (2.8)	0.81
Renal abnormality	483 (5.8)	418 (5.1)	0.04
Any hypoglycemia†	1264 (15.3)	1104 (13.4)	<0.001
Major	177 (2.1)	140 (1.7)	0.047
Minor	1172 (14.2)	1028 (12.5)	0.002
Cancer	327 (3.9)	362 (4.4)	0.15

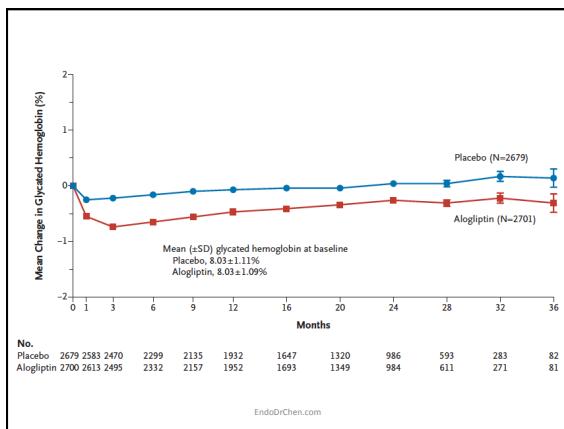
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ORIGINAL ARTICLE

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. Bergenfelz, 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. Cushman, 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 ^a
no. (%)				
Primary end point ^t	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)	345 (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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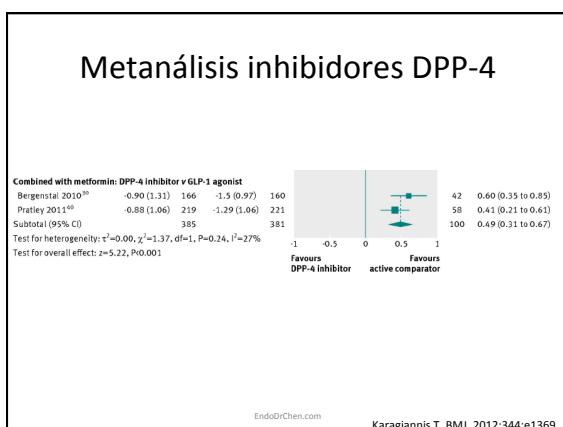
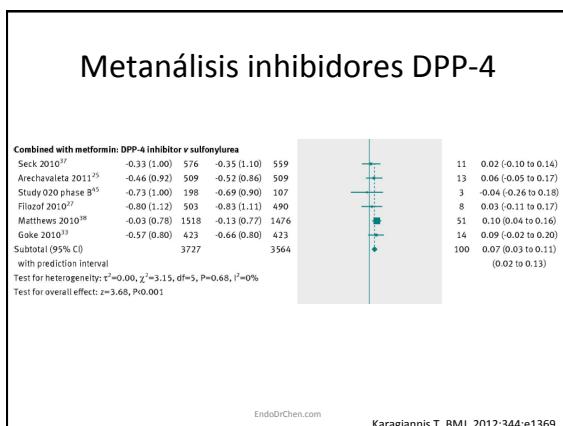
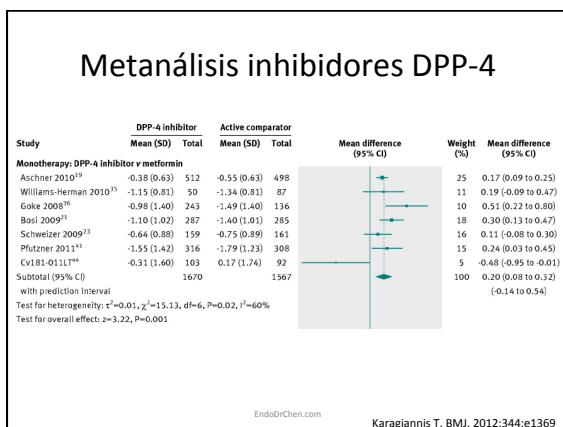
Análogos GLP-1

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

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EFICACIA HBA1C

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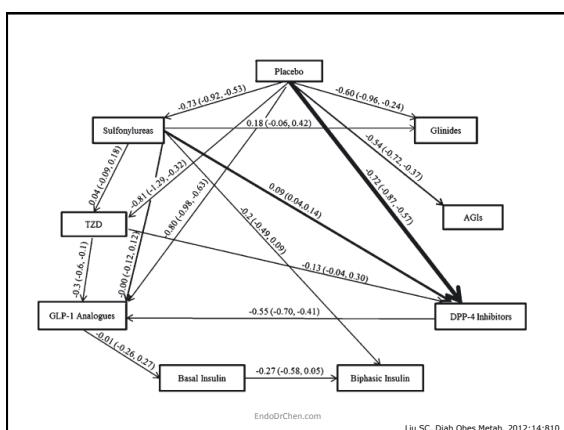


Network metanálisis de terapia segunda línea

Agente	ΔHbA1c (95% IC)
Inhibidores α -glucosidasa	0,66 (0,42-0,90)
Sulfonilureas	0,82 (0,70-0,95)
Glinidas	0,71 (0,43-1,01)
Glitazonas	0,82 (0,66-0,98)
Inhibidores de DPP-4	0,69 (0,61-0,79)
Análogos GLP-1	1,02 (0,86-1,17)
Insulina Basal	0,88 (0,56-1,21)
Insulina Bifásica	1,07 (0,69-1,46)

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Liu SC. Diab Obes Metab. 2012;14:810

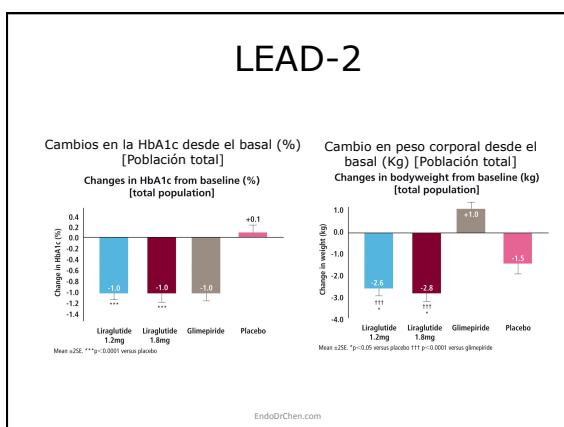
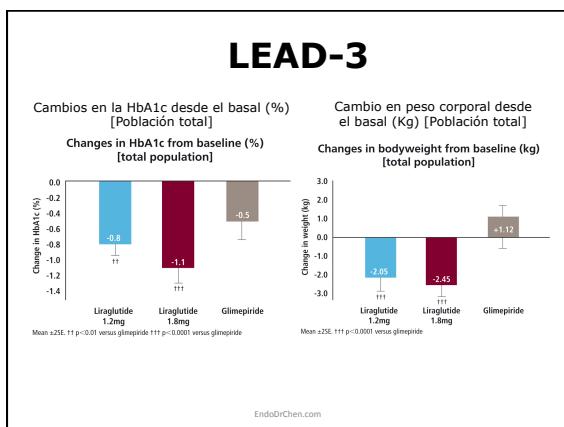


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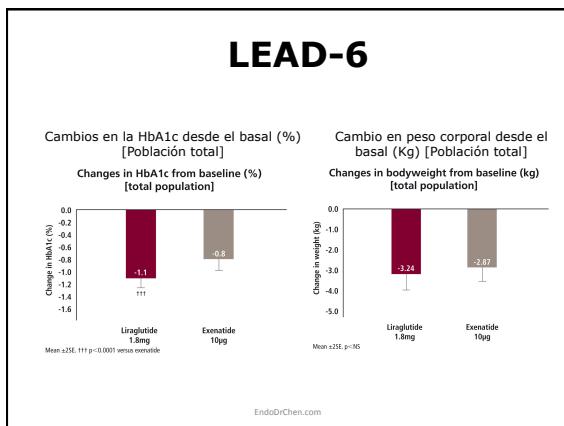
Liu SC. Diab Obes Metab. 2012;14:810

USO EN MONOTERAPIA

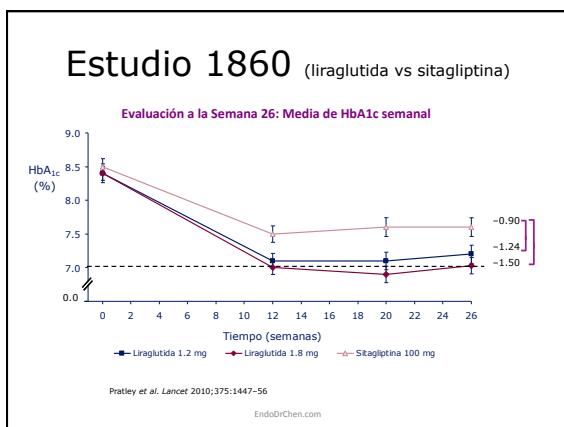
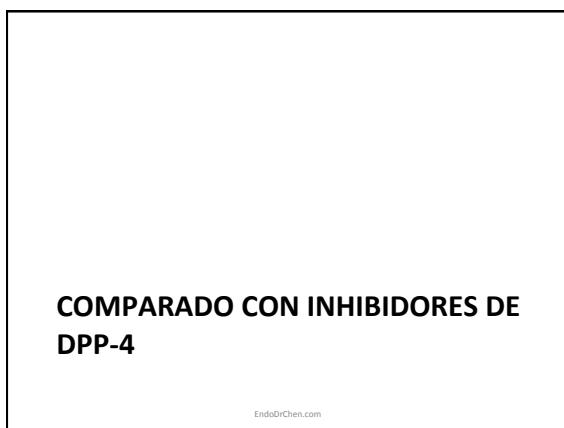
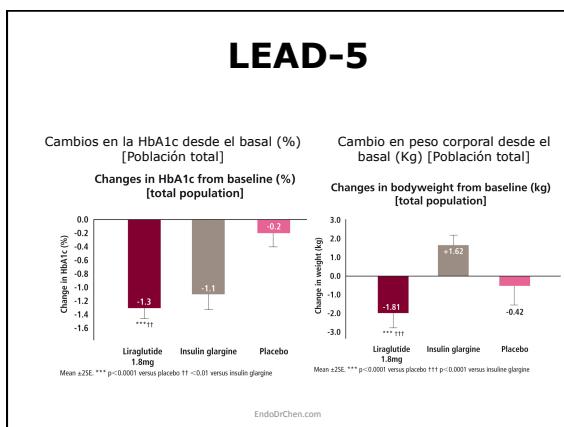
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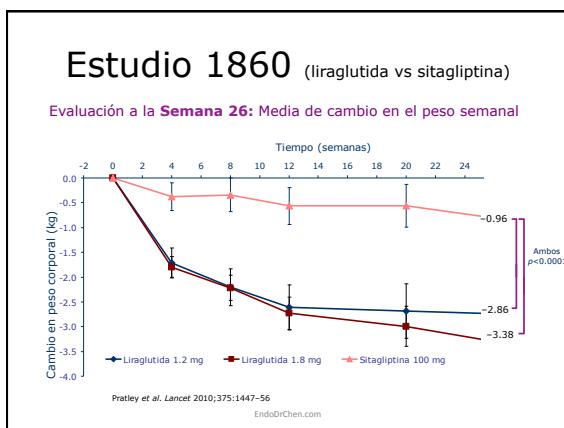
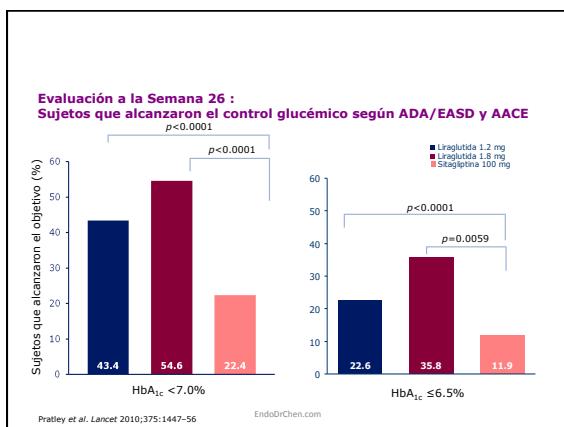












Estudios DURATION

Study	Change in HbA _{1c} , mean % (\pm SE)	Change in body weight, mean kg (\pm SE)
DURATION-1		
Exenatide q.w. 2 mg (n = 148)	-1.9 (\pm 0.1) *	-3.7 (\pm 0.5)
Exenatide 2 µg b.i.d. (n = 147)	-1.5 (\pm 0.1)	-3.6 (\pm 0.5)
DURATION-2		
Exenatide q.w. 2 mg (n = 160)	-1.6 (\pm 0.1)**	-2.3 (\pm 0.3)**
Sitagliptin q.d. 100 mg (n = 166)	-0.9 (\pm 0.1)	-0.8 (\pm 0.3)
Pioglitazone q.d. 45 mg (n = 165)	-1.2 (\pm 0.1)	+2.8 (\pm 0.3)
DURATION-3		
Exenatide q.w. 2 mg (n = 233)	-1.5 (\pm 0.1)**	-2.6 (\pm 0.3)**
Insulin glargina variable dose q.d. (n = 223)	-1.3 (\pm 0.2)	+1.4 (\pm 0.2)
DURATION-5		
Exenatide q.w. 2 mg (n = 129)	-1.6 (\pm 0.4)**	-2.3 (\pm 0.4)
Exenatide 5 µg o.i.d. (n = 125)	-0.9 (\pm 0.1)	-1.4 (\pm 0.4)

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Garber A. Exp Opin Invest Drugs. 2012;21(1):45

DURATION-6

- Exenatide semanal vs liraglutide
- Hba1c
 - -1.48% con liraglutide
 - -1.26% con exenatide
- Mayor pérdida de peso con liraglutide (-3.6 vs -2.7 kg)

EndoDrChen.com Buse JB. EASD 2011. Abstract 75.

DURATION-6

- Mayor incidencia de nódulos subcutáneos en exenatide semanal (10%) vs liraglutide (1%)

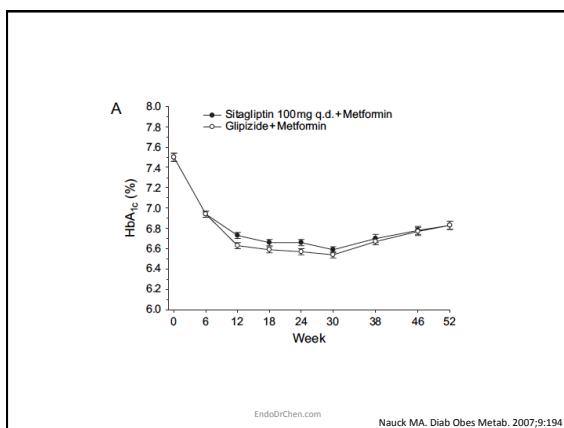
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Garber A. Exp Opin Invest Drugs. 2012;21(1):45

SOSTENIBILIDAD CONTROL A LARGO PLAZO

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Characteristic	Sitagliptin 100 mg q.d. + metformin (N = 588)	Glipizide + metformin (N = 584)
Age (years)	56.8 (9.3)	56.6 (9.8)
Sex, n (%)		
Male	336 (57.1)	358 (61.3)
Female	252 (42.9)	226 (38.7)
Race, n (%)		
Caucasian	432 (73.5)	434 (74.3)
Black	41 (7.0)	35 (6.0)
Hispanic	43 (7.3)	46 (7.9)
Asian	60 (6.5)	49 (8.4)
Other	22 (3.7)	20 (3.4)
Body weight (kg)	89.5 (17.4)	89.7 (17.5)
Body mass index (kg/m ²)	31.2 (6.0)	31.3 (5.2)
Duration of diabetes mellitus (years)	6.5 (6.1)	6.2 (5.4)
Use of OHA at screening, n (%)		
Dual therapy	177 (30.1)	159 (27.2)
Monotherapy	386 (65.6)	397 (68.0)
Absence	25 (4.3)	28 (4.8)
HbA _{1c} , % (range)	7.7 (0.9) (6.1–11.0)	7.6 (0.9) (5.8–10.5)
HbA _{1c} distribution at baseline, n (%)		
HbA _{1c} < 8%	375 (64.0)	381 (65.5)
HbA _{1c} ≥ 8 to <9%	151 (25.8)	141 (24.2)
HbA _{1c} ≥ 9%	60 (10.2)	60 (10.3)
FPG (mmol/l)	9.2 (2.3)	9.1 (2.3)

Nauck MA. Diab Obes Metab. 2007;9:194



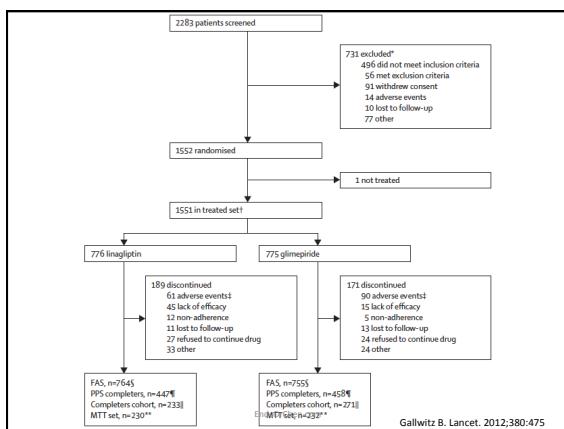
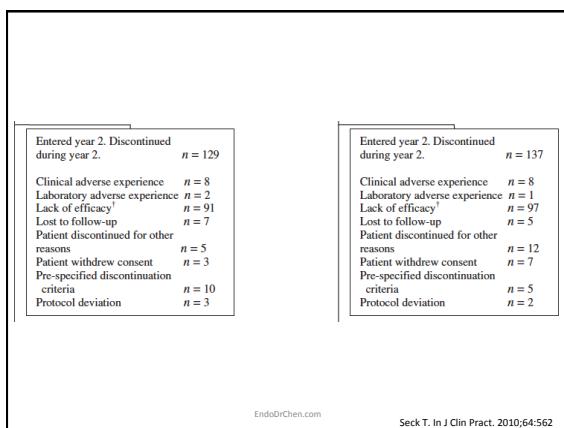
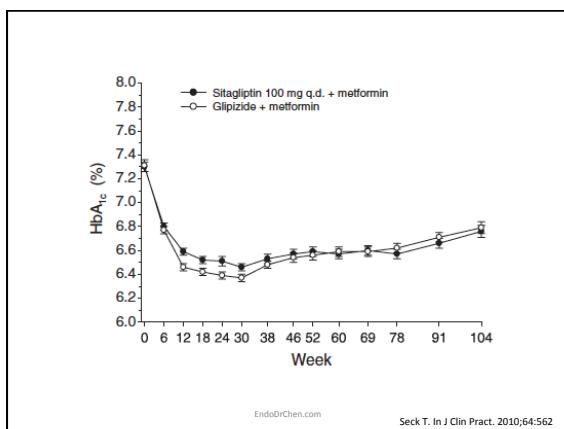
ORIGINAL PAPER

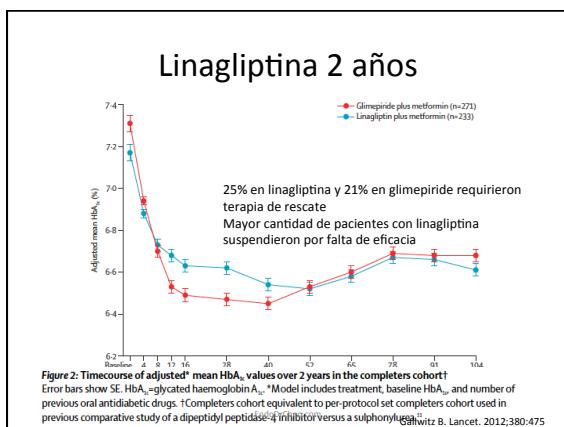
THE INTERNATIONAL JOURNAL OF
CLINICAL PRACTICE

Safety and efficacy of treatment with sitagliptin or glipizide in patients with type 2 diabetes inadequately controlled on metformin: a 2-year study

T. Seck,¹ M. Nauck,² D. Sheng,¹ S. Sunga,¹ M. J. Davies,¹ P. P. Stein,¹ K. D. Kaufman,¹ J. M. Amatruda³ for the Sitagliptin Study 024 Group*

EndoDrChen.com Seck T. In J Clin Pract. 2010;64:562

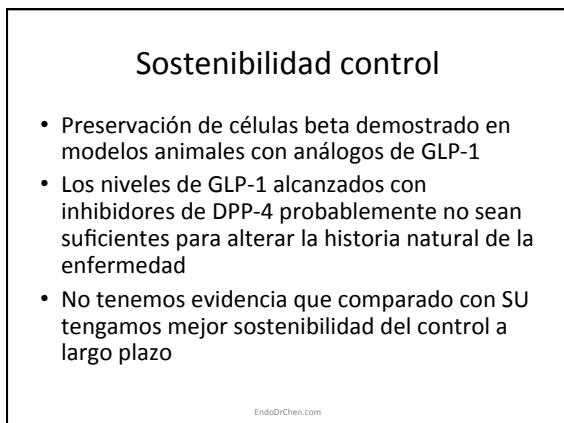


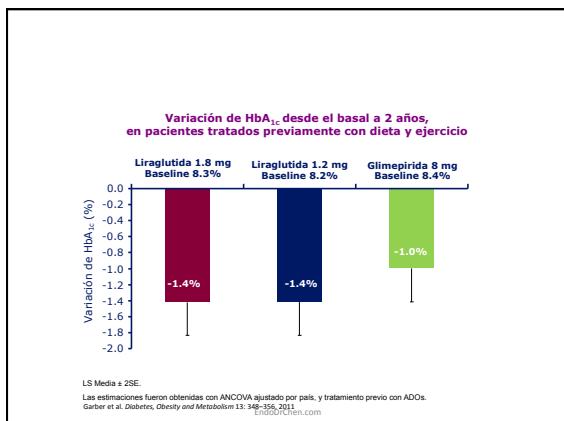
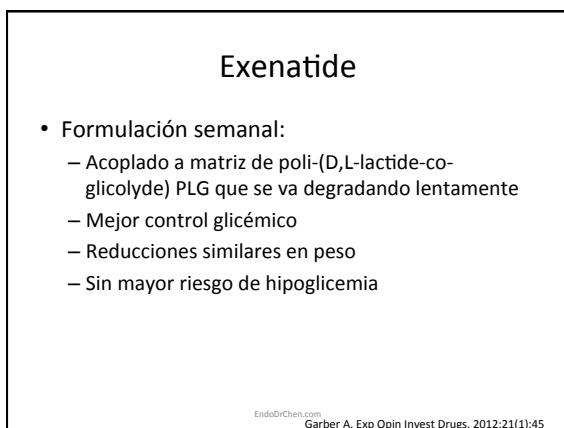
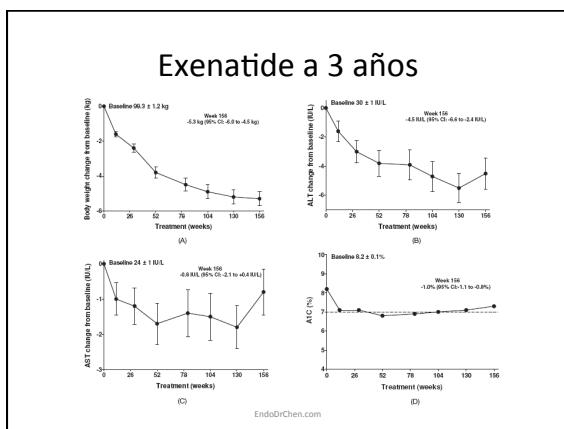


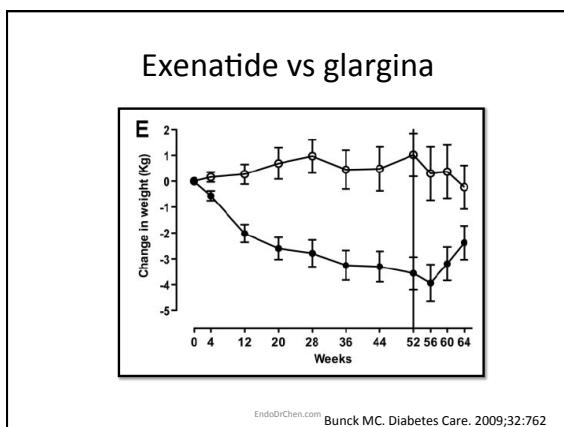
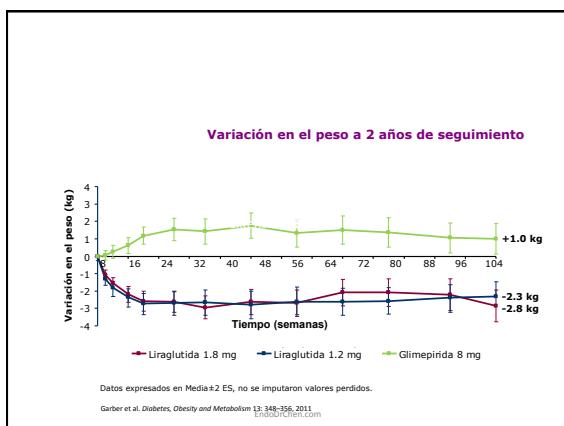
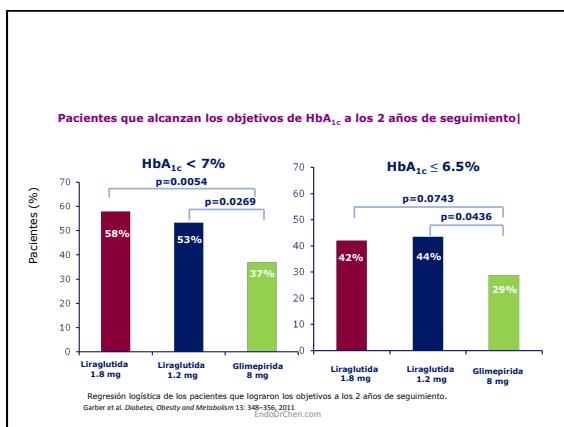
	Linagliptin	Glimepiride	Difference (linagliptin-glimepiride)		
			Adjusted* mean (SE, %)	CI	p value
HbA_{1c} in full analysis set (LOCF)					
n	764	755
Mean at baseline (SE, %)	7.69% (0.03)	7.69% (0.03)
Change from baseline					
Mean (SE, %)	-0.21% (0.03)	-0.41% (0.03)
Adjusted* mean (SE, %)	-0.16% (0.03)	-0.36% (0.03)	0.20% (0.05)	0.09-0.30†	0.0004‡
HbA_{1c} in PPS completers (OC)					
n	477	458
Mean at baseline (SE, %)	7.43% (0.04)	7.53% (0.04)
Change from baseline					
Mean (SE, %)	-0.37% (0.04)	-0.61% (0.04)
Adjusted* mean (SE, %)	-0.35% (0.04)	-0.53% (0.04)	0.17% (0.05)	0.07-0.28†	0.0001‡
HbA_{1c} in the completers cohort					
n	233	271
Mean at baseline (SE, %)	7.17% (0.04)	7.31% (0.04)
Change from baseline					
Adjusted* mean (SE, %)	-0.56% (0.03)	-0.63% (0.03)	0.08% (0.04)	0.00-0.15§	0.0468¶

HbA_{1c}=glycated haemoglobin A_{1c}. LOCF=last observation carried forward. PPS=per-protocol set. OC=observed cases.
*Model includes treatment, baseline HbA_{1c}, and number of previous oral antidiabetic drugs. †97.5% CI. ¶p<0.0125, one-sided. §95% CI. ¶p<0.05, two-sided.

Gallwitz B. Lancet. 2012;380:475







Exenatide vs glargina

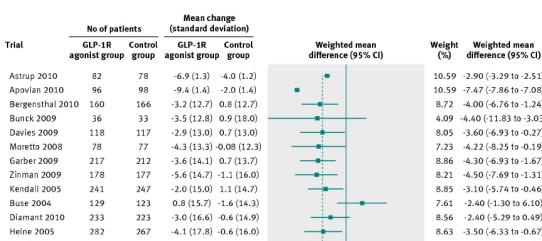
	Pre-treatment (week -2)	On-drug		Off-drug		On-drug rate to pre-treatment (week 52)		Off-drug rate to pre-treatment (week 56)	
		On-drug (week 52)	Off-drug (week 56)	Geometric mean	Geometric difference	P	Geometric mean	Geometric difference	P
First phase									
Insulin glargina	5.4 ± 0.6	6.1 ± 0.5	6.1 ± 0.6	1.17 ± 0.06			1.13 ± 0.05		
Exenatide	5.4 ± 0.6	9.4 ± 1.0	5.0 ± 0.6	1.78 ± 0.11	1.53 ± 0.11	<0.0001	1.00 ± 0.05	0.90 ± 0.06	0.1188
Second phase									
Insulin glargina	77.4 ± 8.8	80.7 ± 6.9	86.2 ± 9.1	1.08 ± 0.05			1.10 ± 0.05		
Exenatide	78.5 ± 8.3	235.6 ± 23.0	79.5 ± 9.1	3.05 ± 0.22	2.85 ± 0.22	<0.0001	1.01 ± 0.04	0.92 ± 0.06	0.1906
Abs									
Insulin glargina	20.0 ± 2.5	24.8 ± 2.2	21.4 ± 2.5	1.31 ± 0.07			1.03 ± 0.08		
Exenatide	19.7 ± 2.1	62.2 ± 7.0	22.0 ± 2.6	3.19 ± 0.24	2.46 ± 0.20	<0.0001	1.12 ± 0.06	1.08 ± 0.10	0.4052

EndoDrChen.com Bunck MC. Diabetes Care. 2009;32:762

OTROS FACTORES DE RIESGO CV

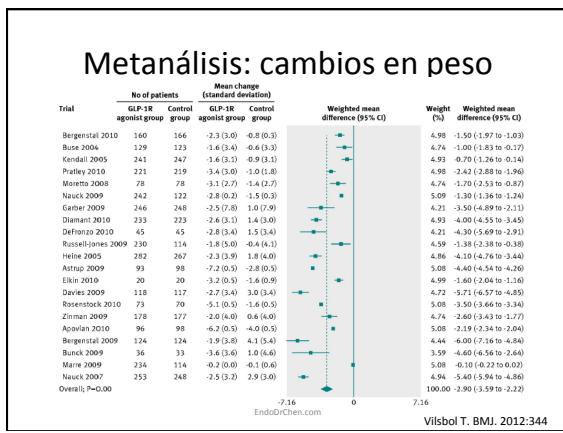
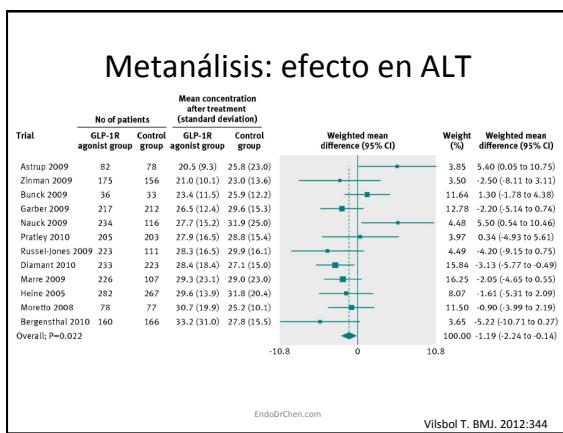
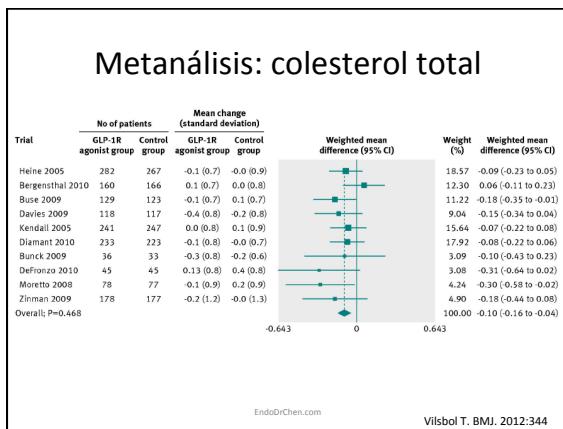
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Metanálisis: presión arterial sistólica



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Vilsbol T. BMJ. 2012:344



EFFECTOS ADVERSOS

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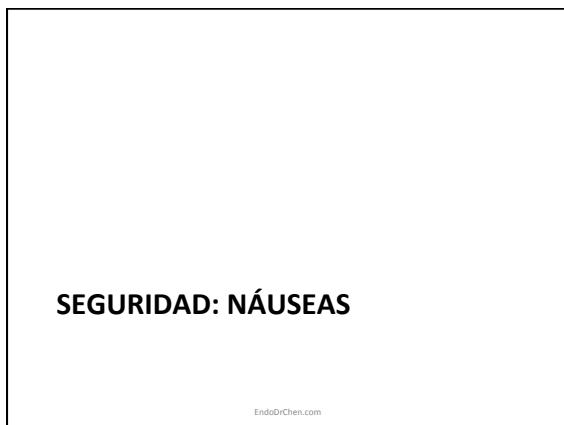
SEGURIDAD: PANCREATITIS

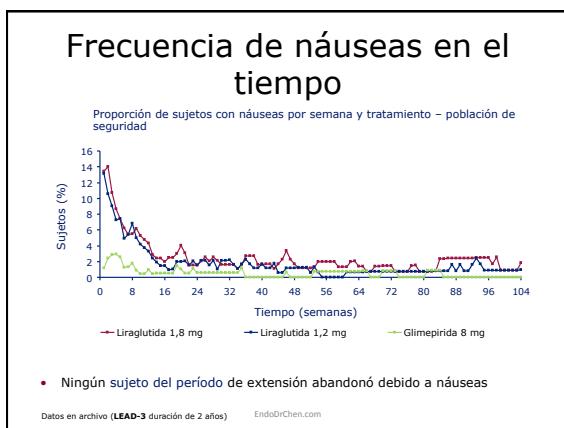
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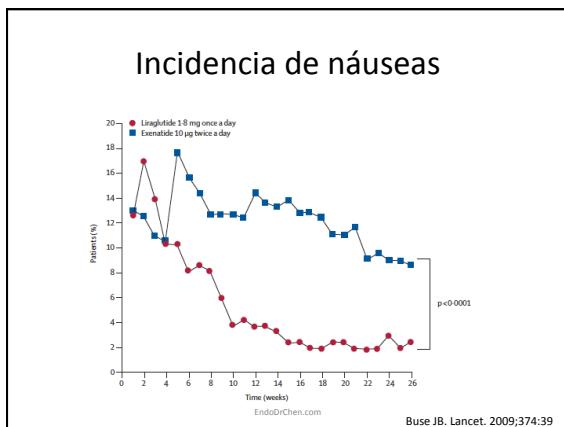
Pancreatitis

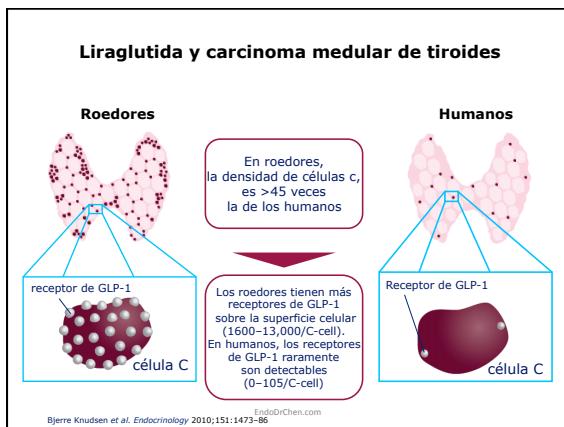
- SAVOR y EXAMINE evaluaron de forma prospectiva y de manera predefinida la incidencia de pancreatitis. No diferencias significativas.
- EMEA y FDA se pronunciaron en cuanto a seguridad en riesgo de pancreatitis

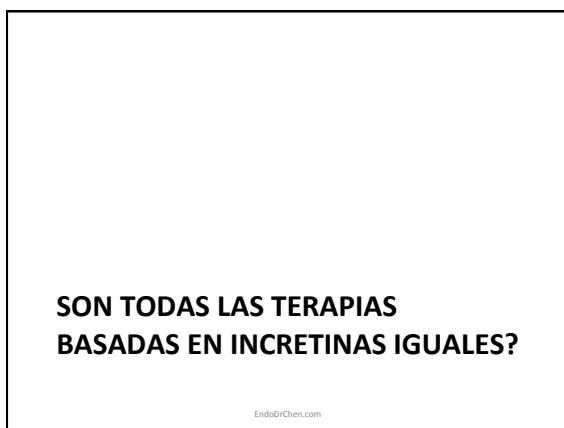
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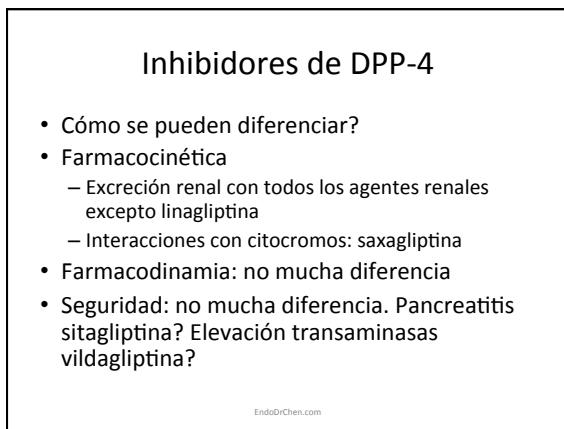








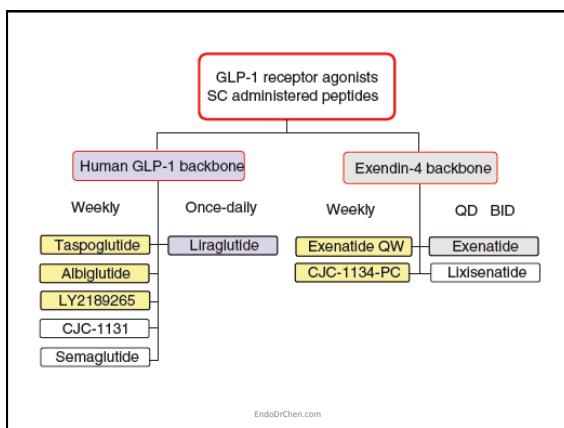


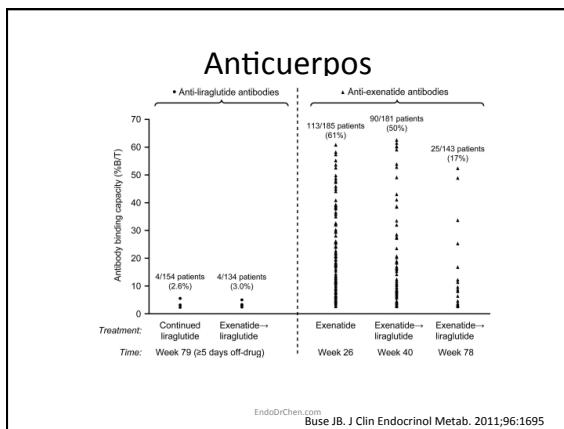


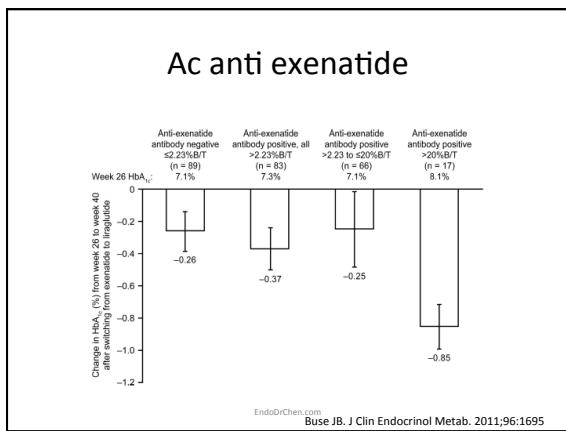
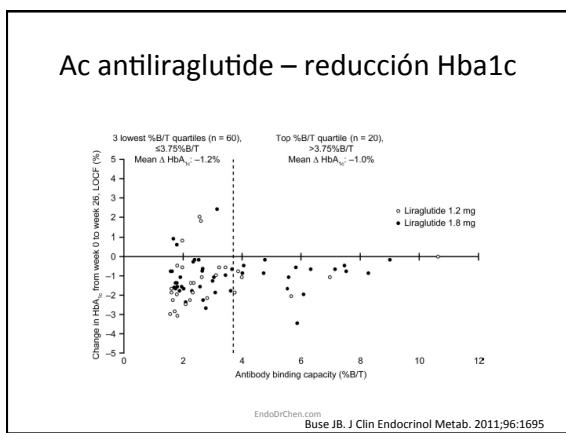
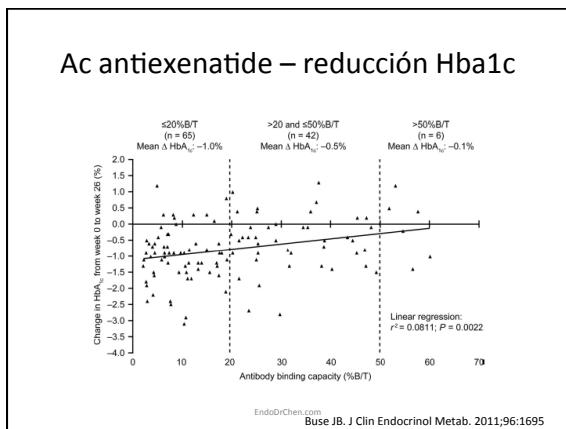
Diferencias entre inhibidores de DPP-4

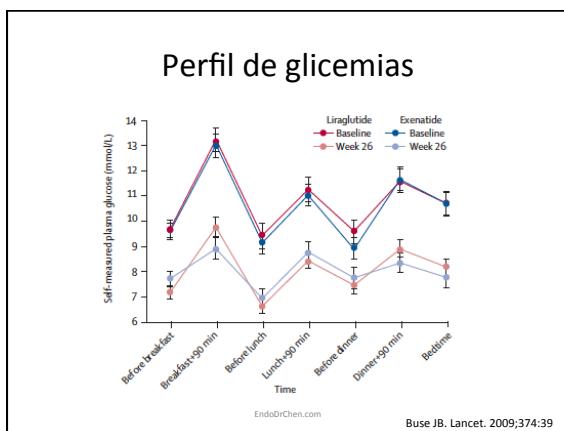
- En la práctica clínica, realmente no hay mucha diferencia y no hay un claro factor diferenciador para escoger entre los diferentes agentes
- Únicamente tener cuidado con AEC y ajustar la dosis en caso necesario

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Diferencias entre análogos GLP-1

- Hay diferencias en pérdida de peso, náuseas
- Los de acción prolongada tienden a actuar más sobre glicemia en ayunas y los de acción corta sobre postprandiales
- Menos náuseas con liraglutide
- Antigenicidad

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Conclusiones

- La terapia basada en increatinas no aumentan el riesgo de eventos cardiovasculares
- Reducción de hba1c mayor con análogos de GLP-1 vs inhibidores de DPP-4
- Mayor pérdida de peso con análogos de GLP-1 pero aumenta el riesgo de náuseas
- Perfil de todos los inhibidores de DPP-4 similar, pero no así con los análogos de GLP-1

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