¿Tienen interés clínico las diferencias de clase entre los fármacos DPP4i?

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Jefe Sección Medicina Interna HGUGM Madrid
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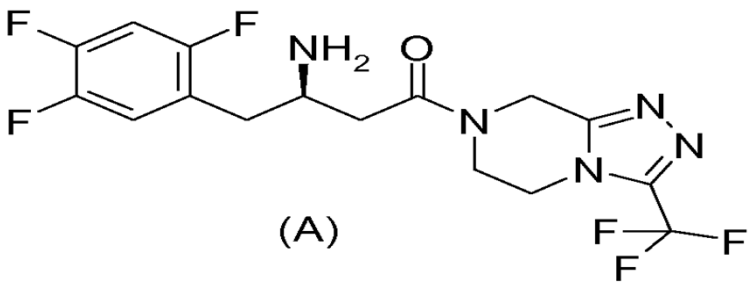
Departamento de Medicina Interna

Hospital General Universitario
GREGORIO MARAÑÓN
Madrid

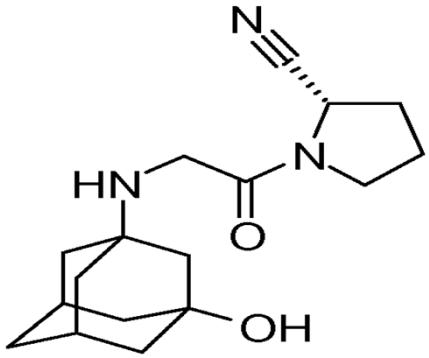
Junio 2017

DPP-4 Inh.

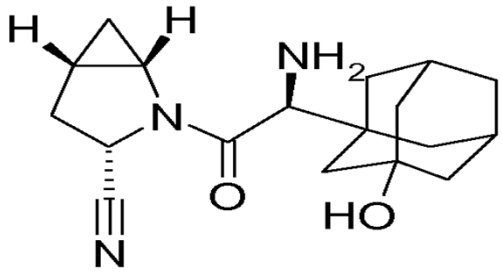


(A)

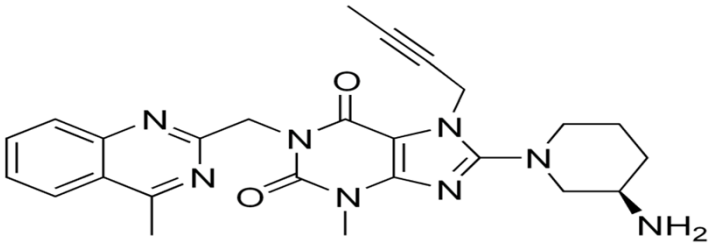
Sitagliptin 2007



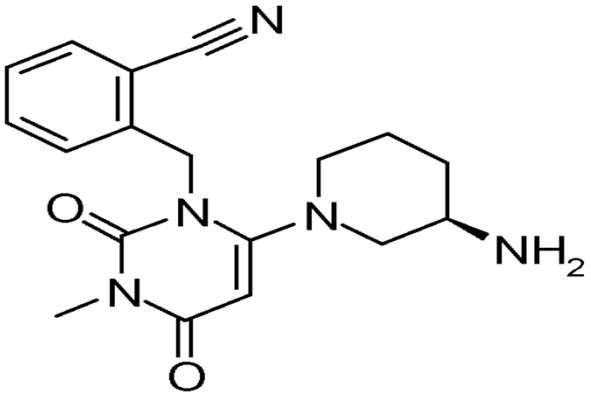
Vildagliptin



2009 Saxagliptin



Linagliptin 2011



Alogliptin 2013

Fechas de autorización de IDPP-4

DPP4i (aspectos comunes reflejados en Meta-Analisis)

- Mecanismo incretínico con reducción de glucosa postprandial y en menor grado de la basal con A1C reducción media: -0.74 (-0.85 to -0.62)
- Efecto neutro en peso y lípidos
- Antidiabéticos no inductores de hipoglucemia (similar a placebo)
- Efectos adversos raros (ADA 2017)
- Asentados en práctica clínica (experiencia de uso en mundo real)

Guia de Diabetes tipo 2 de la ADA 2017

Start with Monotherapy unless

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy **Metformin**

Lifestyle Management

EFFICACY*	high
HYPO RISK	low risk
WEIGHT	neutral/loss
SIDE EFFECTS	GI/lactic acidosis
COSTS*	low

If A1C target not achieved after approximately 3 months of mo
meant to denote any specific preference — choice dependent c

Dual Therapy **Metformin +**

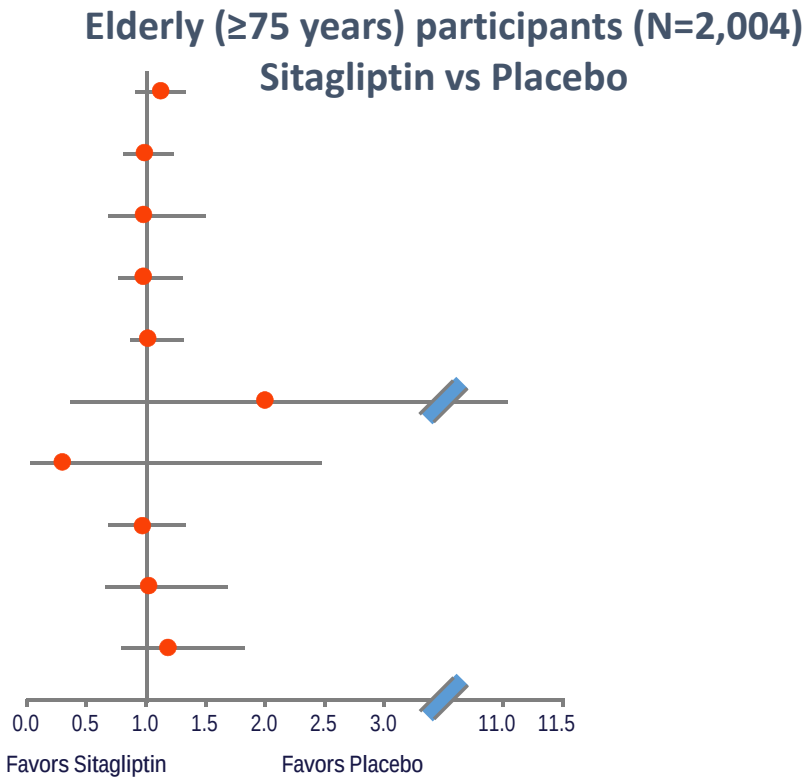
	Sulfonylurea	Thiazolidinedion
EFFICACY*	high	high
HYPO RISK	moderate risk	low risk
WEIGHT	gain	gain
SIDE EFFECTS	hypoglycemia	edema, HF, fxs
COSTS*	low	low

If A1C target not achieved after approximately 3 months of dua
meant to denote any specific preference — choice dependent c

	DPP-4 inhibitor
EFFICACY*	intermediate
HYPO RISK	low risk
WEIGHT	neutral
SIDE EFFECTS	rare
COSTS*	high

Ancianos y DPP4i

Outcome	HR (95% CI)	*P* value
4-point MACE	1.10 (0.89, 1.36)	0.40
3-point MACE	1.01 (0.81, 1.26)	0.94
Hospitalization for heart failure	0.99 (0.65, 1.49)	0.94
Hospitalization for heart failure or death	1.00 (0.77, 1.29)	0.99
All-cause mortality	1.05 (0.83, 1.32)	0.71
Pancreatitis	2.01 (0.36, 11.04)	0.42
Pancreatic malignancy	0.28 (0.03, 2.50)	0.25
Overall malignancy	0.95 (0.67, 1.36)	0.78
Severe hypoglycemia	1.03 (0.62, 1.71)	0.92
Bone fracture	1.21 (0.78, 1.85)	0.40



TECOS CV Safety Trial: Primary and Key Secondary Outcomes in the Elderly vs Nonelderly Cohorts

Bethel MA et al. Assessing the Safety of Sitagliptin in Older Participants in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS). Diabetes Care 2017

Riesgo de fracturas y uso de i-DPP-4

Exposure	No. of cases (N = 229 145)†	No. of controls (N = 229 145)†	Crude OR (95% CI)	Adjusted OR (95% CI) (‡)
Never NIAD use	217 623	218 194	1.03 (0.99–1.06)	1.10 (1.06–1.14)
Past NIAD use	3631	2815	1.33 (1.25–1.41)	1.12 (1.05–1.20)
Current NIAD use excluding incretin use	6993	7209	Reference	Reference
Distant DPP4-I use (>365 days before the index date)	112	121	0.95 (0.74–1.24)	0.95 (0.72–1.25)
Past DPP4-I use (183–365 days before index date)	181	186	1.00 (0.81–1.23)	0.96 (0.77–1.20)
Recent DPP4-I use (92–182 days before the index date)	131	168	0.80 (0.64–1.01)	0.76 (0.59–0.97)*
Current DPP4-I use (1–91 days before the index date)	219	232	0.97 (0.81–1.17)	0.97 (0.79–1.18)
By sex				
Males	103	94	1.10 (0.83–1.46)	1.14 (0.84–1.54)
Females	116	138	0.88 (0.69–1.13)	0.86 (0.66–1.12)
By age on index date				
<50 years	17	14	1.19 (0.58–2.47)	1.16 (0.54–2.50)
50–59 years	50	51	1.07 (0.71–1.61)	1.06 (0.68–1.64)
60–69 years	64	65	0.97 (0.68–1.39)	0.97 (0.67–1.42)
70–79 years	49	58	0.83 (0.56–1.22)	0.89 (0.59–1.36)
80 + years	39	44	0.96 (0.62–1.48)	0.92 (0.58–1.44)

No existió aumento de riesgo con iDPP-4

Abbreviations: OR: odds ratio; CI: confidence interval, DPP4-I: dipeptidyl peptidase 4 inhibitor; GLP-1 RA: glucagon-like peptide-1 receptor agonist.
Never NIAD use: no NIAD prescription before the index date.
Past NIAD use: most recent NIAD prescription over 91 days before index date.
Current NIAD use: most recent NIAD prescription within 91 days before index date.
*Statistically significant ($P < 0.05$).
†The numbers do not sum to the total number of fractures because GLP-1 RA exposure is not shown.
‡Adjusted for history of cancer, COPD, fracture, alcoholism, rheumatoid arthritis, secondary osteoporosis, hyperthyroidism, retinopathy, neuropathy, heart failure and use of GLP-1 RA, glucocorticoids, statins, anxiolytics, hypnotics, antidepressants, antipsychotics, anti-Parkinson drugs, beta-blockers, thiazide diuretics, RAAS inhibitors, loop diuretics and antiarrhythmics.

Driessen JHM et al: Pharmacoepidemiol Drug Saf 24:1017-1025; 2015

Dipeptidyl Peptidase-4 Inhibitors, Peripheral Arterial Disease, and Lower Extremity Amputation Risk in Diabetic Patients

Chun-Chin Chang, MD,[a,b,c] Yung-Tai Chen, MD,[c,d] Chien-Yi Hsu, MD,[b,c,e] Yu-Wen Su, MD,[f] Chun-Chih Chiu, MD,[b,g]

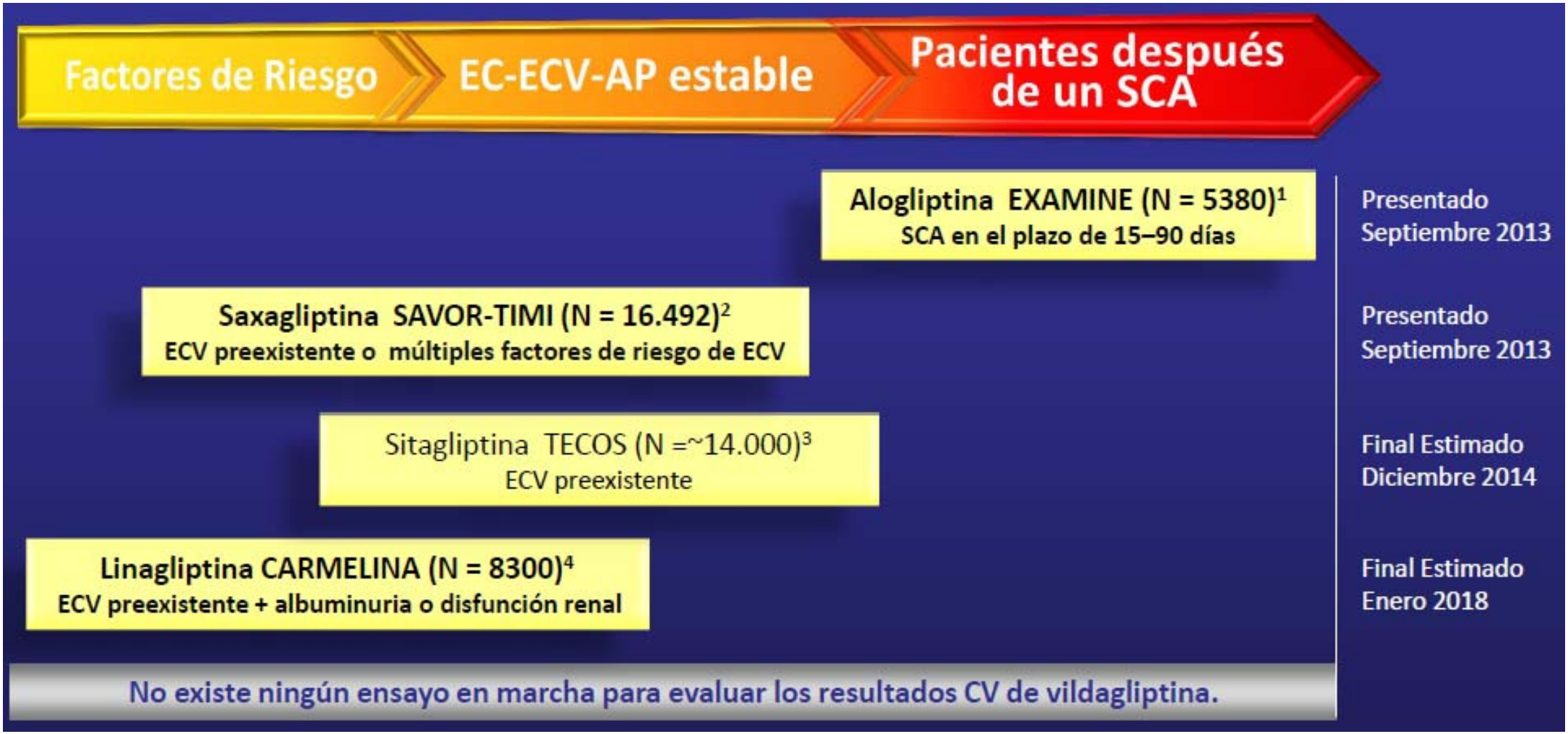
Amputation for peripheral arterial disease as outcome	169	255,277	0.662	252	248,396	1.015	0.65 (0.54-0.79)	<.001

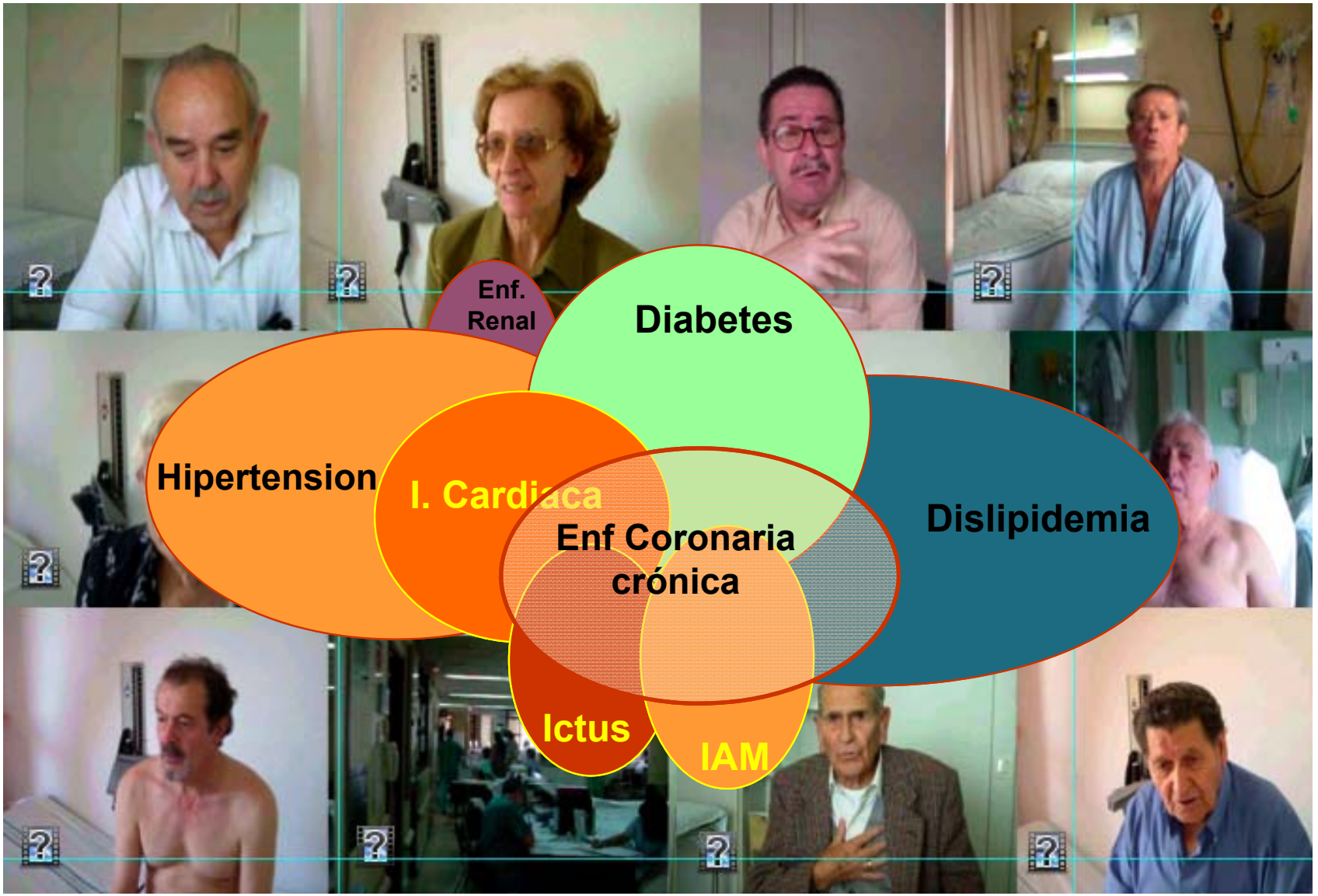
CI = confidence interval; DPP-4i = dipeptidyl peptidase-4 inhibitor.
*Per 10^3 person-years.

CONCLUSIONS: This large-scale nationwide population-based cohort study is the first to demonstrate that treatment with DPP-4 inhibitors is associated with lower risk of peripheral arterial disease occurrence and limb amputation in patients with type 2 diabetes mellitus.

• *The American Journal of Medicine (2017) 130, 348-355*

Ensayos con DPP-4i en seguridad cardiovascular




Enf.
Renal
Diabetes
Hipertension
I. Cardiaca
Enf Coronaria
crónica
Dislipidemia
Ictus
IAM

European Journal of Internal Medicine xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

European Journal of Internal Medicine

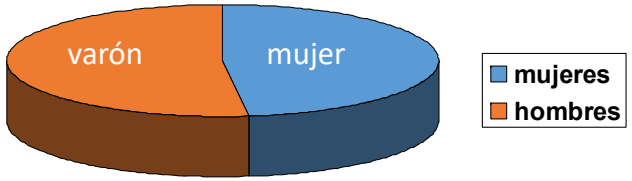
journal homepage: www.elsevier.com/locate/ejim

Original Article

Hyperglycemia management in patients admitted to internal medicine in Spain: A point-prevalence survey examining adequacy of glycemic control and guideline adherence

Hospitalización del paciente con DM2 en M.Interna

Pacientes con DM Hospitalizados en Servicios de Med. Interna



30 - 40% de los pacientes en M.I.

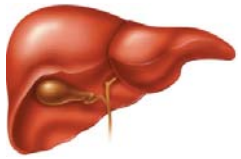
Perfil medio

N: 1000

- Edad media 76 años (76 - 85)
- Duracion DM 10.9 años, Tipo 2 (94 %)
- Estancia Hospitalaria: 12,1 dias
- A1c disponible 56.3% (average 7,1%)
- Comorbilidad (Media Charlson 4)
- FG 61,3 ml/m (> 60 ml/m 44%)

ENA J et al (Estudio MIDIA) EJIM 2015

Seguridad y Comorbilidad

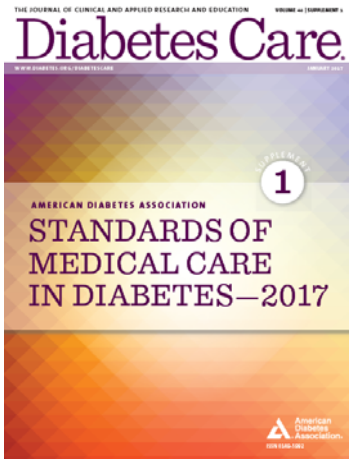


Principales diferencias entre iDPP-4

	Sitagliptina[1]	Vildagliptina[2]	Saxagliptina[3]	Linagliptina[4]	Alogliptina[5]
Seguridad Cardiovascular a Largo Plazo	TECOS: No Inferioridad	Estudio NO Realizado	SAVOR-TIMI 53: No Inferioridad	Pendiente de Resultados	EXAMINE: No Inferioridad
Hospitalización por Insuficiencia Cardíaca	Hazard Ratio: 0.98 (0.81-1.19)	Estudio NO Realizado	Hazard Ratio: 1.27 (1.07-1.51)	Pendiente de Resultados	Hazard Ratio: 1.19 (0.90-1.58)
Uso en insuficiencia hepática leve y moderada	Sí	No debe usarse, incluyendo pacientes con ALT o AST > 3 LSN pre-tratamiento	Sí, precaución en insuf, hepática moderada	Sí, pero falta experiencia clínica	Sí
Uso en insuficiencia hepática severa	No estudiada, tener precaución		No recomendado	Sí, pero falta experiencia clínica	No recomendado
Uso en insuficiencia renal leve /moderada	Sí *	Sí *	Sí *	Sí	Sí *
Uso en insuficiencia renal severa	Sí *	Sí *	Sí *	Sí	Sí* Experiencia limitada
Uso en Insuficiencia Renal Terminal (ESRD)/ Hemodiálisis (HD)	Sí *	Sí, precaución / limitada experiencia en HD, ESRD: *	No recomendado	Sí	Sí* Experiencia limitada
Uso en ancianos >65 años	Sí	Sí	Sí	Sí, pero falta experiencia > 80 años	Sí, precaución insuf, renal
Autorización EMA/FDA	EMA/FDA	EMA	EMA/FDA	EMA/FDA	EMA/FDA
Indicaciones de uso #	7	6	6	4	5

Diabetes e Insuficiencia Cardiaca

Diabetes and Heart Failure
As many as 50% of patients with type 2 diabetes may develop heart failure (112).



EUROPEAN SOCIETY OF CARDIOLOGY®

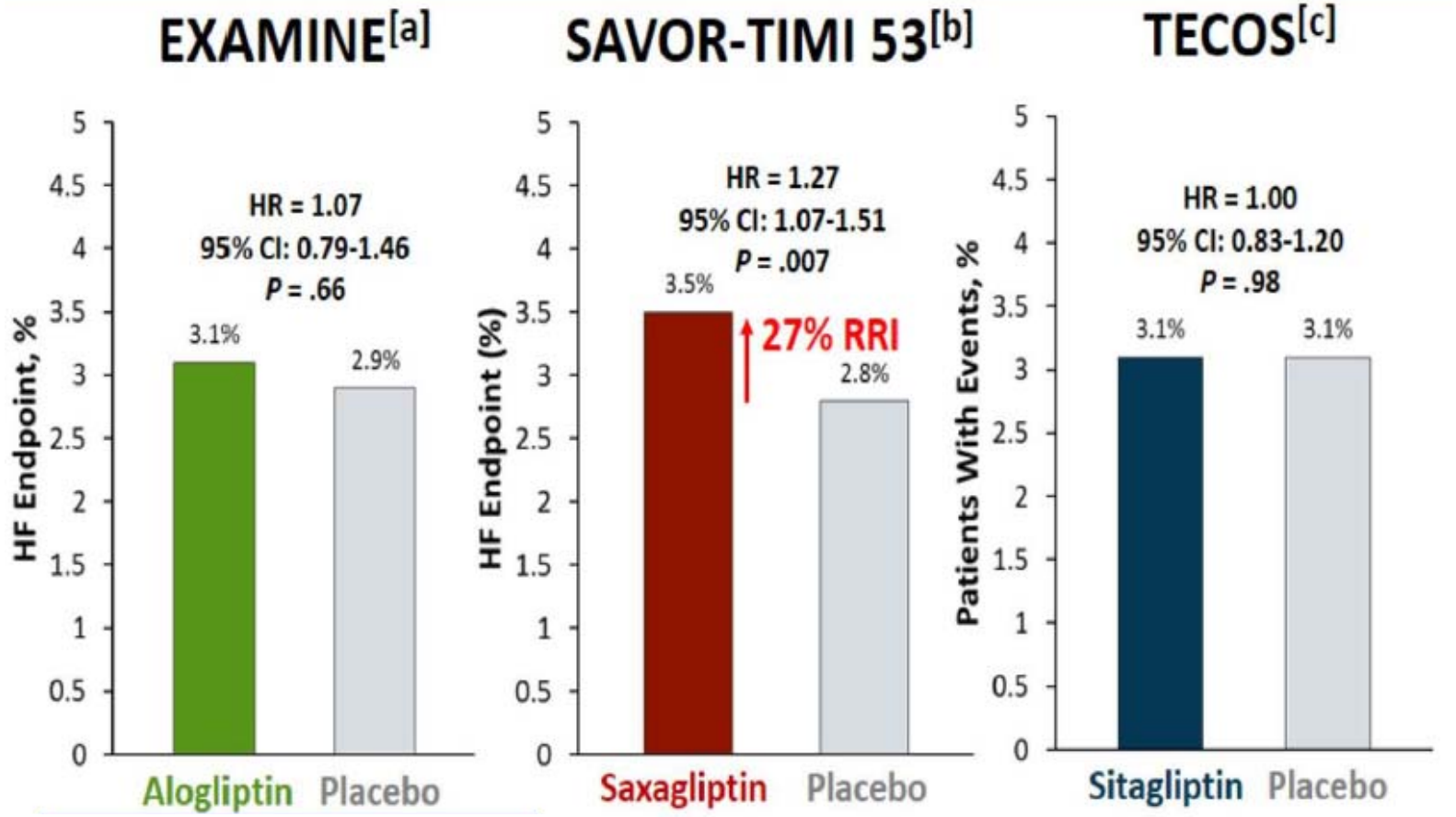
European Journal of Heart Failure (2017) 19, 43–53
doi:10.1002/ejhf.633

REVIEW

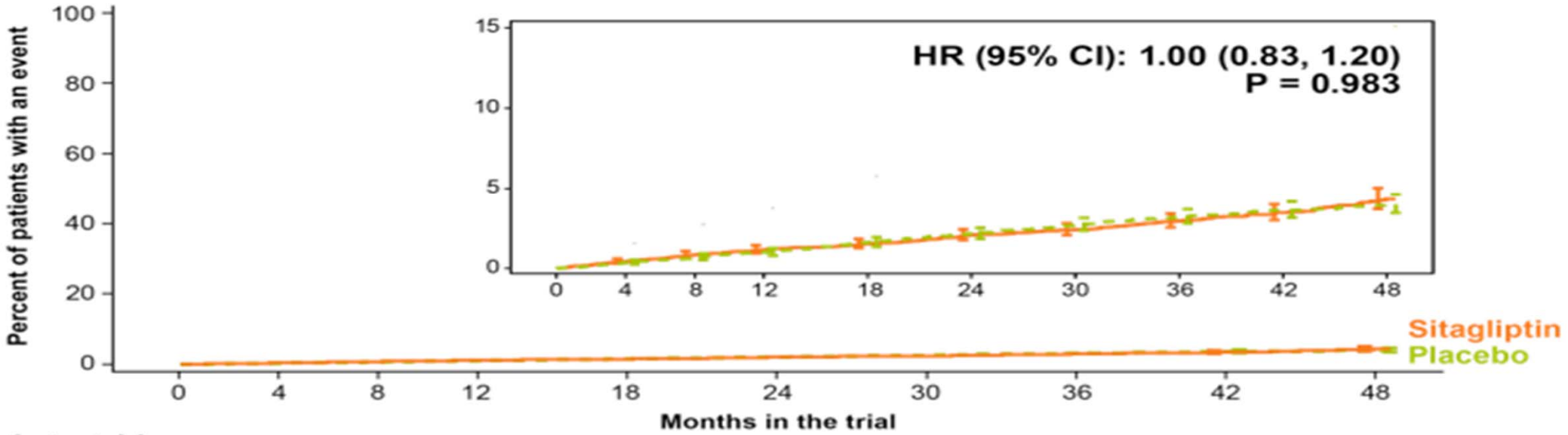
Heart failure outcomes in clinical trials of glucose-lowering agents in patients with diabetes

David H. Fitchett[1]*, Jacob A. Udell[2], and Silvio E. Inzucchi[3]

HOSPITALIZACIÓN POR IC



Hospitalización por IC (sitagliptina Estudio TECOS)



Patients at risk:										
Sitagliptin	7,332	7,189	7,036	6,917	6,780	6,619	4,728	3,515	2,175	1,324
Placebo	7,339	7,204	7,025	6,903	6,712	6,549	4,599	3,443	2,131	1,315

** Adjusted for history of heart failure at baseline*

Green JB et al. NEJM 2015; DOI: 10.1056/NEJMoa1501352

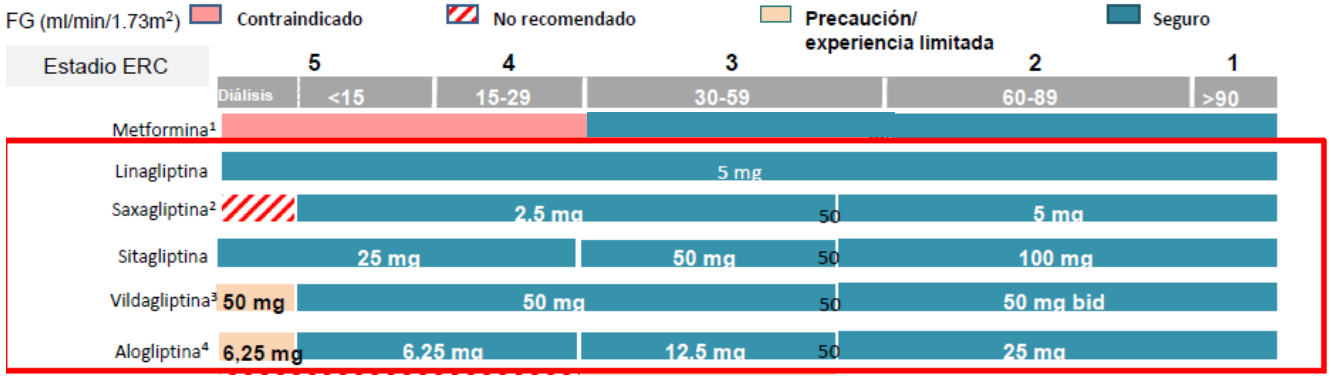
Seguridad Cardiovascular respecto a IC de los iDPP4

Molécula	Estudio	Objetivo 1º MACE	↑ Hospitalización Insuf. Cardíaca
Sitagliptina	TECOS[1]	No inferioridad MACE	Seguridad confirmada
Vildagliptina	NO realizado	NO realizado	No realizado
Saxagliptina	SAVOR-TIMI	No inferioridad MACE	AUMENTA ↑27% P=0.007
Linagliptina	CAROLINA CARMELINA[3]	Pendiente de resultados	Pendiente resultados
Alogliptina	EXAMINE	No inferioridad MACE	No inferioridad

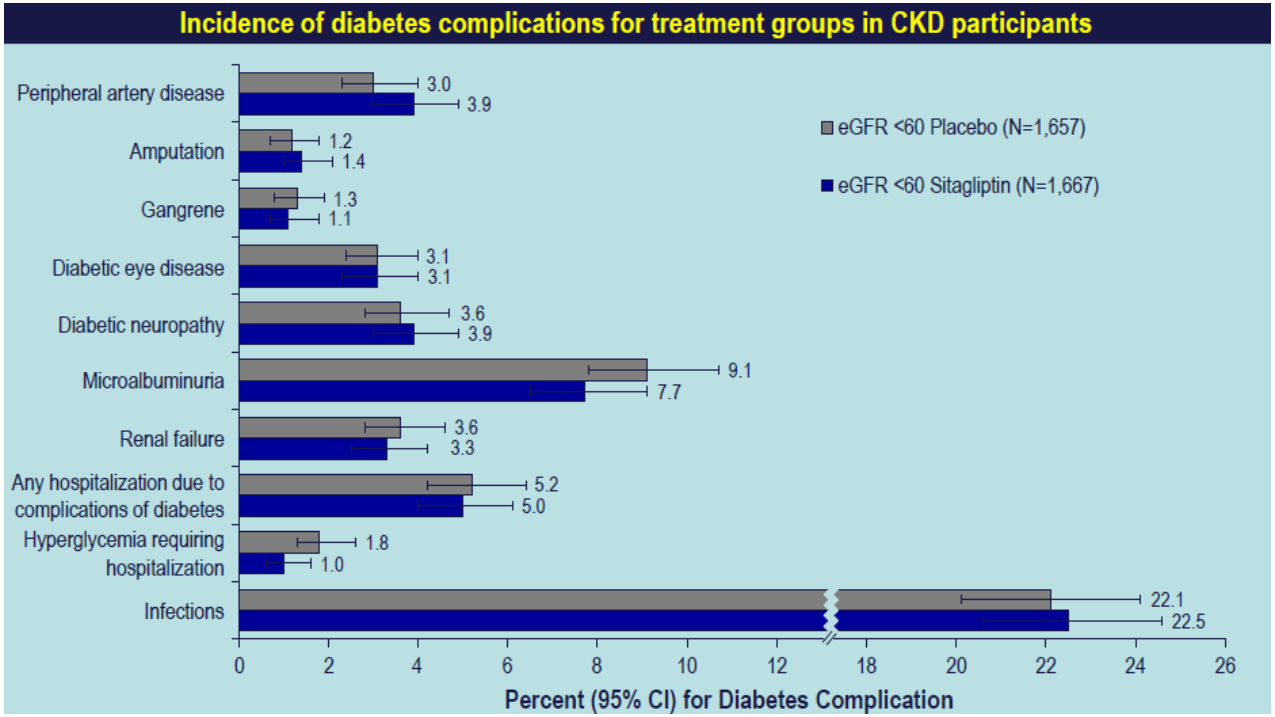
"At the present time these data suggest that if a DPP-4 inhibitor is to be used in type 2 diabetic patients with HF, sitagliptin would be the one to use".

Harold Lebovitz Heart Failure: A Major Cardiovascular Complication of Diabetes Mellitus.Current Diabetes Reports Dec 2016

Tratamiento antidiabético en paciente con IR



Eventos en estudio TECOS (sitagliptin vs placebo) según Filtrado Glomerular



AJKD
Original Investigation

Safety and Efficacy of Incretin-Based Therapies in Patients With Type 2 Diabetes Mellitus and CKD: A Systematic Review and Meta-analysis

Patricia M. Howse, BSc,[1] Lyudmila N. Chibrikova, PhD,[2] Laurie K. Twells, PhD,[1,2] Brendan J. Barrett, MD, MSc, FRCPC,[1] and John-Michael Gamble, PhD[2]

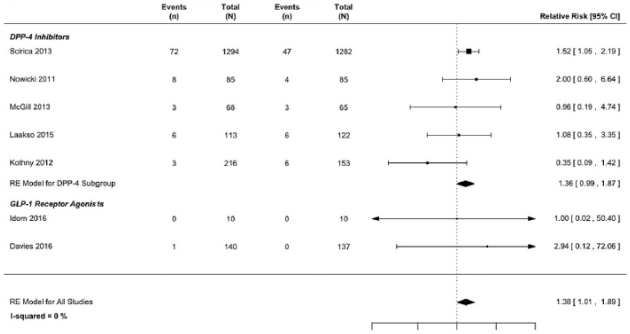
Background: The pharmacokinetics and pharmacodynamics of antidiabetic therapies for patients with type 2 diabetes are often altered in the context of chronic kidney disease (CKD).

Study Design: Systematic review and meta-analysis.

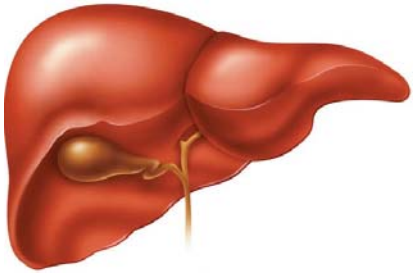
Setting & Population: Patients with type 2 diabetes and CKD.

Selection Criteria for Studies: 2 reviewers independently screened studies identified through bibliographic databases (Cochrane Library, PubMed, Embase, International Pharmaceutical Abstracts), clinical trial registries, and references from pertinent articles and clinical practice guidelines. Eligible studies included randomized controlled trials evaluating incretin-based therapy in adults with type 2 diabetes and estimated glomerular filtration rates < 60 mL/min/1.73 m^2.

Interventions: Incretin-based therapies (dipeptidyl peptidase 4 inhibitors and glucagon-like peptide 1 receptor agonists) compared to placebo or active antidiabetic therapies.



Conclusions: In patients with moderate or severe CKD, incretin-based therapies are effective in reducing HbA_{1c} levels. Hypoglycemic events are rare, and wide CIs for the association preclude any definitive conclusions. Likewise, wide CIs were observed for mortality, cardiovascular events, and end-stage renal disease.



Insuficiencia Hepática y DPP4i

	Sitagliptina[1]	Vildagliptina[2]	Saxagliptina[3]	Linagliptina[4]	Alogliptina[5]
Uso en insuficiencia hepática leve y moderada	Sí	No debe usarse, incluyendo pacientes con ALT o AST > 3 LSN pre-tratamiento	Sí, precaución en insuf, hepática moderada	Sí, pero falta experiencia clínica	Sí
Uso en insuficiencia hepática severa	No estudiada, tener precaución		No recomendado	Sí, pero falta experiencia clínica	No recomendado

Vildagliptina.

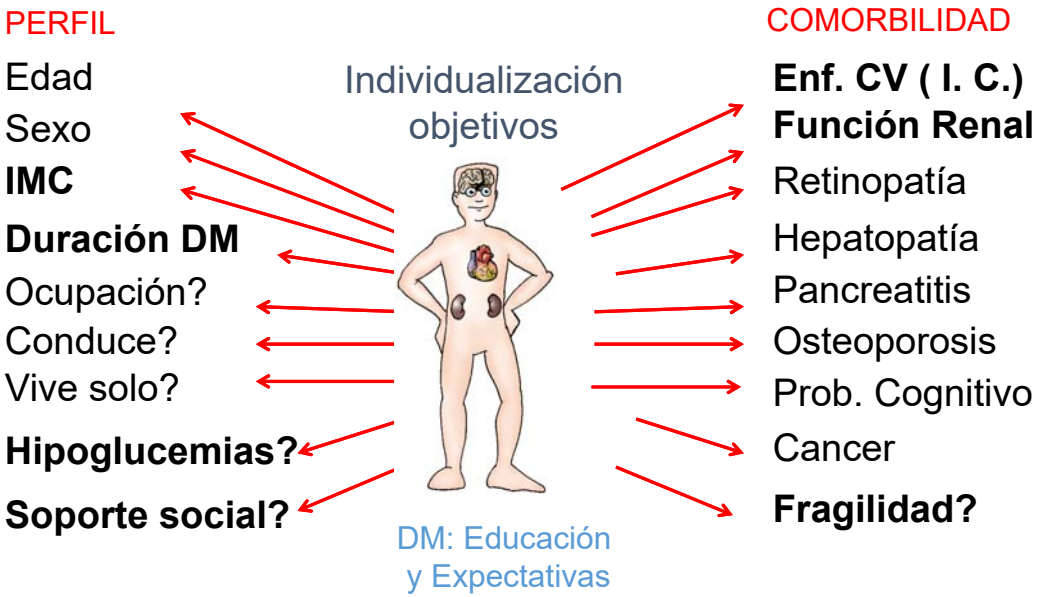
Se han notificado casos raros de disfunción hepática (incluyendo hepatitis).

Los pacientes fueron generalmente asintomáticos sin secuelas clínicas.

Debe realizarse un control de la función hepática antes de iniciar el tratamiento y monitorizarse ésta cada tres meses durante el primer año

Ficha técnica

Tratamiento del paciente con DM 2 (2017)



EASD 2016

iDPP-4: Indicaciones actuales en ficha técnica

	Sitagliptina[1]	Vildagliptina[2]	Saxagliptina[3]	Linagliptina[4]	Alogliptina [5]
Modo de administración: (vo: vía oral)	vo (1 al día)	vo (2 al día) ∞ vo (1 al día) §	vo (1 al día)	vo (1 al día)	vo (1 al día)
Monoterapia:	Sí***	Sí***	Sí***	Sí***	No
Asociado a MET:	Sí	Sí	Sí	Sí	Sí
Asociado a SU:	Sí	Sí	Sí	No	Sí
Asociado a GLIT:	Sí	Sí	Sí	No	Sí
Triple terapia con MET +SU:	Sí	Sí	Sí	Sí	No
Triple terapia con MET +GLIT:	Sí	No	No	No	Sí
Añadido a insulina:	Sí	Sí	Sí	Sí	Sí

Hospitalización del paciente con DM2 en M.Interna

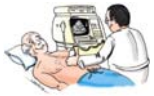
Management of Inpatient Hyperglycemia and Diabetes in Older Adults

Diabetes Care 2017;40:509–517 | DOI: 10.2337/dc16-0989

*" the two leading causes of hospital admissions in older adults with diabetes are **cardiovascular disorders** (coronary artery disease,angina, heart failure, and stroke) **and respiratory diseases** (pneumonia and chronic obstructive pulmonary disease)"*

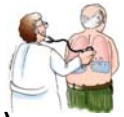
INGRESAN (CMBD) POR:

Complicaciones Cardiovasculares (IC) 25%



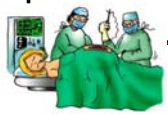
Infecciones Respiratorias 17%

Oncológicas 8 %



Infecciones urinarias y cutáneas (celulitis, pié..)

Hipoglucemias (más que por hiperglucemia)



Otras causas médico quirúrgicas

Medicina Interna

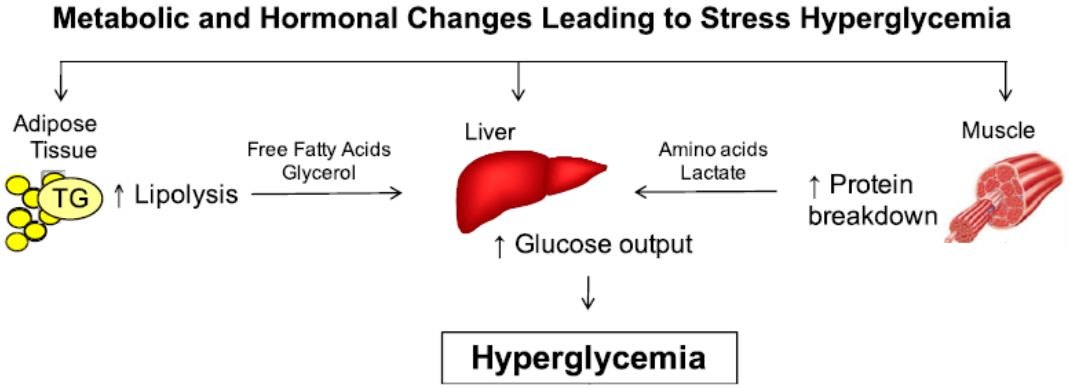
Médico de Familia

Diabetes Care Volume 40, April 2017

Management of Inpatient Hyperglycemia and Diabetes in Older Adults

Diabetes Care 2017;40:509–517 | DOI: 10.2337/dc16-0989

Guillermo E. Umpierrez and Francisco J. Pasquel



MEDICINA CLINICA
www.elsevier.es/medicinaclinica

Med Clin (Barc) 2009;132(12):465-475

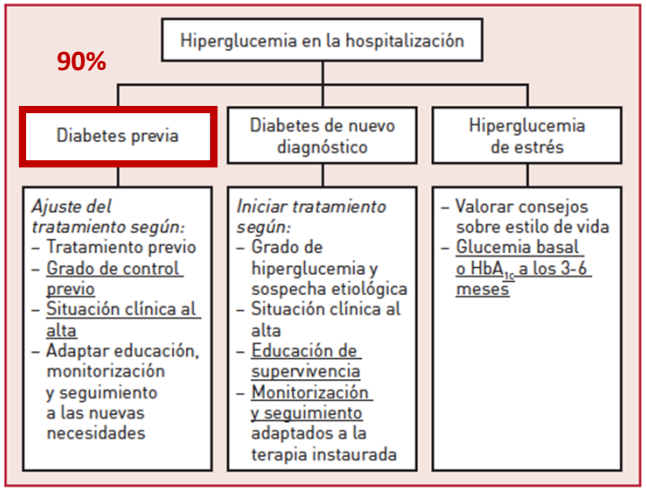
Conferencia de Consenso

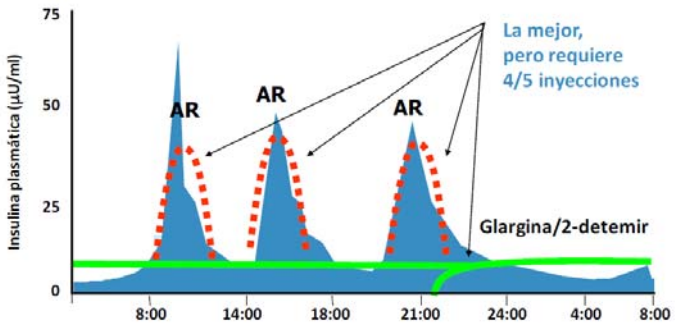
Tratamiento de la hiperglucemia en el hospital

Hospital management of hyperglycemia

Antonio Pérez Pérez [a,*], Pedro Conthe Gutiérrez [b], Manuel Aguilar Diosdado [a], Vicente Bertomeu Martínez [c], Pedro Galdos Anuncibay [d], Gonzalo García de Casasola [c], Ramón Gomis de Bárbara [a], José Luis Palma Gamiz [c], Manuel Puig Domingo [f] y Ángel Sánchez Rodríguez [b]

* En el paciente hospitalizado por lo general se recomienda retirada de Antidiabéticos orales





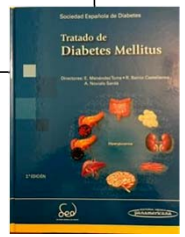
Indicadores de calidad en el informe de alta del paciente con diabetes

1-Determinación de la HbA_{1c} durante el ingreso
2-Incluir la función renal al alta (MDRD)
3-Situación clínica del paciente al alta y evolución previsible
4-Fijar los objetivos de control glucémico (HbA_{1c} y glucemias) y de otros factores de riesgo (lípidos, presión arterial, tabaco y reducción del peso)
5-Especificar el nivel de educación diabetológica y las necesidades pendientes de cubrir
6-Incluir recomendaciones individualizadas sobre la dieta y el ejercicio
7-Indicar los cambios efectuados en el tratamiento y su justificación
8-Especificar indicación y frecuencia de los controles glucémicos
9-Definir las necesidades de seguimiento: plazo de revisión y nivel asistencial (primaria, especializada)

✓ **Pautas sencillas para la transición al alta bajo control de A.Primaria**

Gestión eficiente del paciente diabético hospitalizado. Importancia del Informe de Alta en la continuidad asistencial

P. Conthe Gutiérrez, J. García Alegría



Tratado de DM 2017

Insulina basal + antidiabéticos en hospitalización?

Antidiabético oral	Uso en paciente hospitalizado
METFORMINA	✗
SULFONILUREAS	✗
PIOGLITAZONA	✗
AR-GLP1	✗
iSGLT2	✗
DPP4i	**?***

Management of Inpatient Hyperglycemia and Diabetes in Older Adults

Diabetes Care 2017;40:509–517 | DOI: 10.2337/dc16-0989

* Pasquel FJ et al. Lancet Diabetes Endocrinol. 2016;8587(16):1–9.

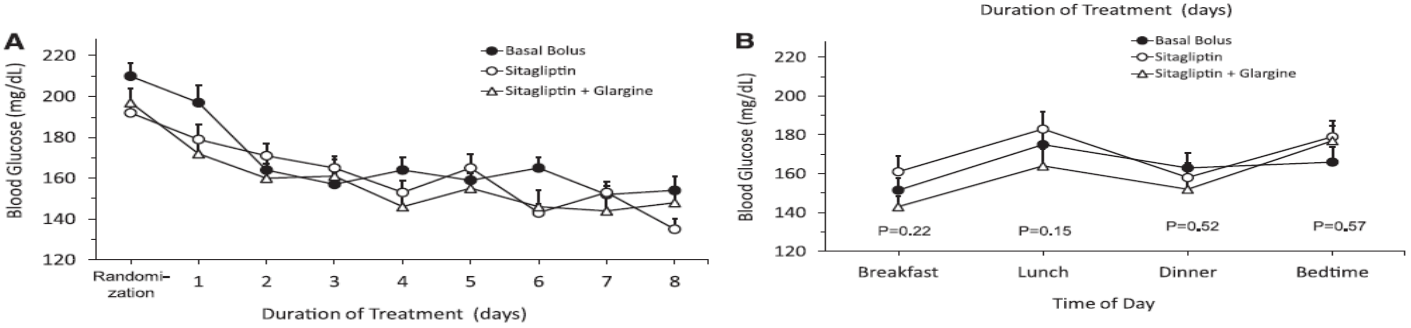
Antecedente del 2013

Safety and Efficacy of Sitagliptin Therapy for the Inpatient Management of General Medicine and Surgery Patients With Type 2 Diabetes

A pilot, randomized, controlled study

GUILLERMO E. UMPIERREZ, MD[1] FARNOOSH FARROKHI, MD[1]

Scheduled basal bolus insulin therapy us-



Duration of Treatment (days)

Diabetes Care 36:3430–3435, 2013

Efficacy of sitagliptin for the hospital management of general medicine and surgery patients with type 2 diabetes (Sita-Hospital): a multicentre, prospective, open-label, non-inferiority randomised trial

Regímenes Bolo-basal o Basal Plus

VS

Basal + Sitagliptina

Francisco J Pasquel, Roma Gianchandani, Daniel J Rubin, Kathleen M Dungan, Isabel Anzola, Patricia C Gomez, Limin Peng, Israel Hodish, Tim Bodnar, David Wesorick, Vijay Balakrishnan, Kwame Osei, Guillermo E Umpierrez

Published online December 7, 2016 http://dx.doi.org/10.1016/S2213-8587(

Interpretation The trial met the non-inferiority threshold for the primary endpoint, because there was no significant difference between groups in mean daily blood glucose concentrations. Treatment with sitagliptin plus basal insulin is as effective and safe as, and a convenient alternative to, the labour-intensive basal–bolus insulin regimen for the management of hyperglycaemia in patients with type 2 diabetes admitted to general medicine and surgery services in hospital in the non-intensive-care setting.

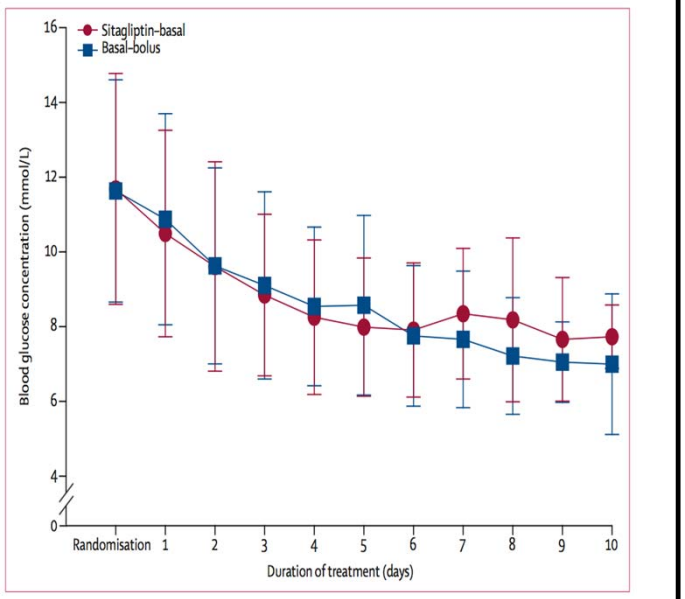


***Figure 2*: Mean daily blood glucose concentrations**
Data are mean (SD). Concentrations measured in patients treated with sitagliptin–basal (red circles) or basal–bolus regimens (blue squares).

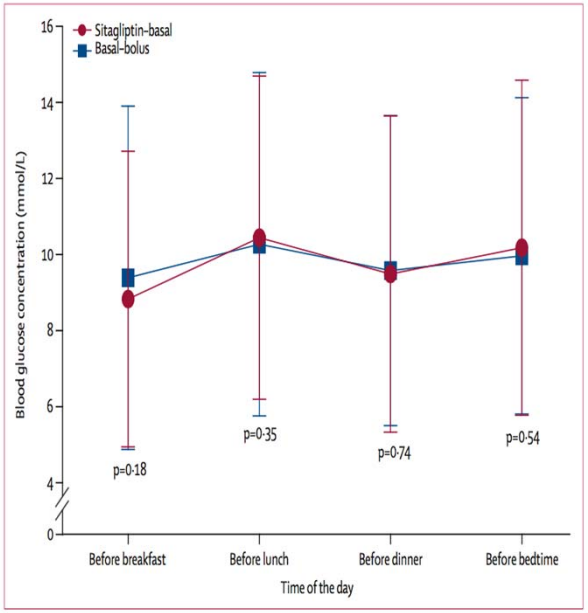


***Figure 3*: Mean blood glucose concentrations before meals and bedtime**
Data are mean (SD). Concentrations measured in patients treated with sitagliptin–basal (red circles) or basal–bolus regimens (blue squares).

SITA-HOSPITAL TRIAL

Umpierrez et al 2016

Primary Efficacy Outcome: differences in mean daily BG concentration between groups
Primary Safety Outcome: differences in hypoglycemia (BG < 70 mg/dl) between groups

Baseline Clinical Characteristics	**Sitagliptin + Basal**	**Basal Bolus**	**P value**
Number of patients	**138**	**139**	
Gender			0.36
Female, n (%)	59 (43)	52 (37)	
Male, n (%)	79 (57)	87 (63)	
Age, yrs	57 ± 11	57 ± 10	0.98
BMI, kg/m^2	35.4 ± 11	35.0 ± 10	0.80
Body weight, kg	104.4 ± 33	103.8 ± 31	0.97
Duration diabetes, yrs	10.2 ± 7	10.3 ± 8	0.85
Admission service			0.49
Medicine, n (%)	114 (**83**)	119 (**86**)	
Surgery, n (%)	24 (17)	20 (14)	
Hospital LOS, days median (min, max)	**4** (1, 50)	**4** (1, 68)	0.54

SITA-HOSPITAL TRIAL

Main Results	Sitagliptin + Basal	Basal Bolus	P-value
Total daily dose, U/day	24.1 ± 16.2	34.0 ± 20.1	**< 0.001**
Number of Injections			
injections/ day (day 2-10)	2.1 ± 1.4	2.9 ± 1.1	**< 0.001**

Hypoglycemia	Sitagliptin + Basal	Basal bolus	P-value
patients BG <70 mg/dl, n (%)	13 (9)	17 (12)	**0.45**
patients BG <40 mg/dl, n (%)	0 (0)	0 (0)	> 0.99

- Treatment with sitagliptin plus basal insulin **is a safe and effective regimen** for the management of hyperglycemia in patients with T2D.
- Our results indicate that treatment with **sitagliptin plus basal is a more convenient** alternative to basal bolus regimen in patients with T2D.

Umpierrez et al 2016

Dpp4i en paciente hospitalizado

- Insulina basal + **inhibidores de DPP4**

Tipo de iDPP4	Estudios con resultados favorables	Estudios en marcha	ADA 2017
Saxagliptina		NCT02182895	⚠*
Alogliptina			⚠*
Vildagliptina			N/A*
Linagliptina		NCT02004366	Sin datos
Sitagliptina	✓*		✓*

* Pasquel FJ et al. Lancet Diabetes Endocrinol. 2016;8587(16):1–9.

Editorial

Sitagliptin plus basal insulin: simplifying in-hospital diabetes treatment?

*Michael A Nauck, Juris J Meier
Division of Diabetology, Medical Department I, St. Josef-Hospital

Conclusión

Se han evidenciado diferencias significativas entre los fármacos DPP4 I que pueden ser relevantes en la práctica clínica:

.- En cuanto a seguridad demostrada en el paciente con Insuficiencia Cardiaca y Enf. Cardiovascular

.- En cuanto al paciente que presente Insuficiencia Hepática y/o Insuficiencia Renal

.- En cuanto a la experiencia clínica global en uso clínico con las distintas moléculas del grupo DPP4i

.-En cuanto a evidencias de su posible utilización eficiente en el paciente hospitalizado (con Insulina)

fin