Novedades de los inhibidores de DPP-4: saxagliptin/metformin XR

Dr. Chih Hao Chen Ku, FACE
Servicio de Endocrinología, Hospital San Juan de Dios
Departamento de Farmacología y Toxicología Clínica, Universidad de Costa Rica

EndoDrChen.com

Conflictos de interés

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

EndoDrChen.com

Agenda

- Hay diferencias entre inhibidores de DPP-4?
- Saxagliptin/metformin XR, diferencias
- Cuál es la importancia de la formulación?
- Seguridad cardiovascular y datos en ICC

EndoDrChen.com

Inhibidores de DPP-4

- Sitagliptina
- Vildagliptina
- Linagliptina
- Saxagliptina
- Alogliptin

- Hay alguna diferencia entre ellas?

EndoDrChen.com

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: omariglitptina

EndoDrChen.com

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

EndoDrChen.com

Diferencias cinéticas

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

EndoDrChen.com

Otras diferencias

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

EndoDrChen.com

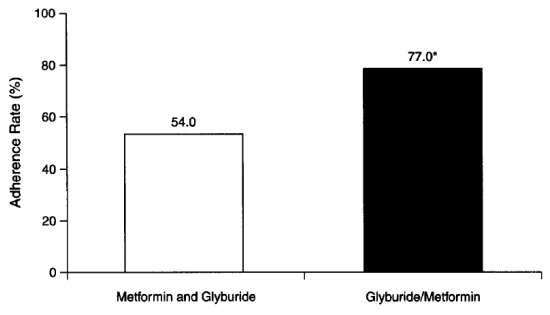
ADHERENCIA A MEDICAMENTOS

EndoDrChen.com

Adherencia

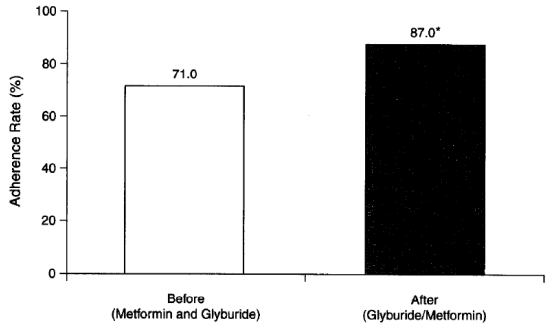
- Pacientes con DM-2 con muchísima frecuencia son polimedicados
- Entre más número de medicamentos, menor adherencia
  - Efectos adversos
  - Interacciones
  - Costos
  - Confusión/olvido

EndoDrChen.com



EndoDrChen.com

Melikian C. Clin Ther. 2002;24:460



EndoDrChen.com

Melikian C. Clin Ther. 2002;24:460

Adherencia e impacto clínico

Nonadherence Measure	Nonadherent Patients, %	No. of Patients	Odds Ratio (95% Confidence Interval)			
			All-Cause Mortality		All-Cause Hospitalization	
			Unadjusted	Adjusted*	Unadjusted	Adjusted*
Summary measure	21.3	11 532	1.49 (1.22-1.81)	1.81 (1.46-2.23)	1.27 (1.15-1.42)	1.58 (1.38-1.81)
Antihypertensives	19.1	6217	1.54 (1.20-1.97)	1.58 (1.22-2.05)	1.39 (1.21-1.60)	1.44 (1.24-1.67)
Statins	24.8	6486	1.60 (1.21-2.13)	2.07 (1.54-2.80)	1.17 (1.01-1.36)	1.39 (1.18-1.63)
Oral hypoglycemics	20.3	7883	1.25 (0.97-1.62)	1.39 (1.07-1.82)	1.31 (1.16-1.49)	1.38 (1.21-1.58)

EndoDrChen.com

Ho PM. Arch Intern Med. 2006;166:1836

Por lo tanto…

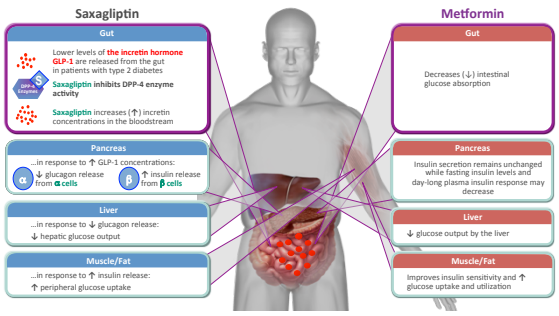
- Esquemas de tratamiento simplificados pueden mejorar la adherencia
- Menor número de tabletas
- Menor cantidad de tomas diarias de la tableta

EndoDrChen.com

SAXAGLIPTINA/METFORMINA XR

EndoDrChen.com

Saxagliptin/metformin XR: mecanismos de acción complementarios

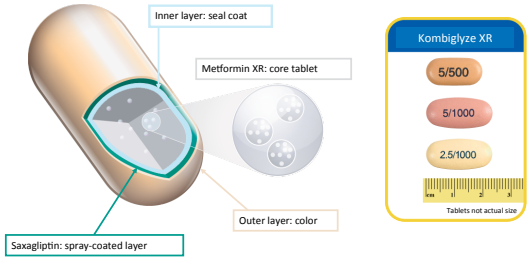


GLP=glucagon-like peptide; DPP=dipeptidyl peptidase.

1. Verspohl EJ. *Pharmacol Ther* 2009;124:113-138.

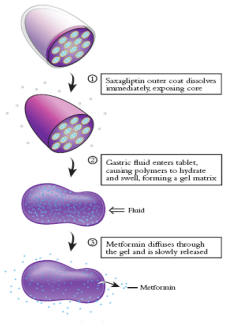
EndoDrChen.com

saxagliptin and metformin HCl XR: Fixed-Dose Combination Therapy Tablets



EndoDrChen.com

Release of Saxagliptin and Metformin XR



Adapted from Data on File, 2009; Hussein et al, 2005

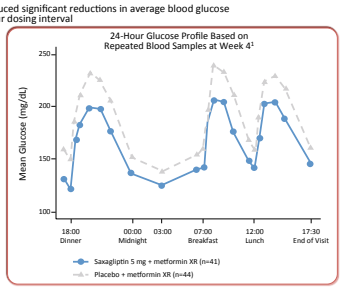
EndoDrChen.com

Saxagliptin/metformin XR Improved Glycemic Control Over 24 Hours

- Saxagliptin/metformin XR produced significant reductions in average blood glucose concentrations over the 24-hour dosing interval

Study Design[1]

- Phase 3, 4-week, multicenter, multinational, randomized, double-blind, placebo-controlled
- Adults (18–77 years) with type 2 diabetes
- Inadequate control for ≥8 weeks with metformin IR 1500–2550 mg/day or metformin XR 2000 mg/day
- A1C 7%–10%
- Saxagliptin 5 mg vs placebo as add-on to OL metformin XR (1500–2000 mg) taken once daily with the evening meal



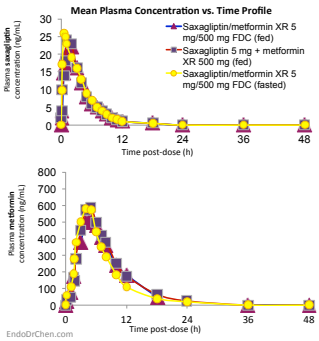
FPG=fasting plasma glucose; PPG=postprandial glucose; DPP=dipeptidyl peptidase; IR=immediate release; OL=open label.

1. Stenlöf K et al. *Curr Med Res Opin* 2010;26(10):2355-2363.

EndoDrChen.com

Saxagliptin/metformin XR is Bioequivalent to Single Components Saxagliptin and Metformin XR tablets

These studies demonstrated that in healthy subjects the saxagliptin metformin XR combination tablets are bioequivalent (same exposure) to coadministration of corresponding doses of saxagliptin and metformin XR as individual tablets under fed conditions



EndoDrChen.com

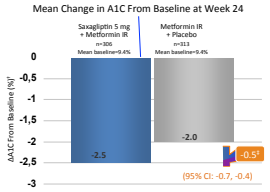
Boulton et al *Clin Drug Investig* 2011; 31 (9)

Saxagliptin + metformin IR vs metformin IR

Pacientes vírgenes de tratamiento

EndoDrChen.com

Treatment-Naive: A1C*



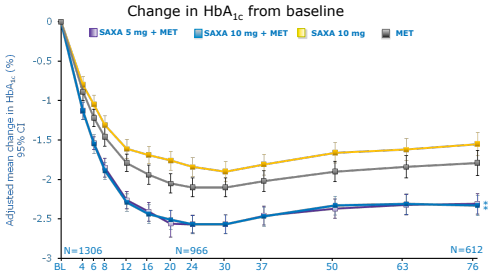
- Mean daily metformin IR doses at Week 24 were 1790 mg for saxagliptin 5 mg + metformin IR and 1817 mg for metformin IR + placebo[1]
- The proportion of patients discontinued or rescued for metformin IR alone, saxagliptin 10 mg, saxagliptin 5 mg + metformin IR, and saxagliptin 10 mg + metformin IR was 10.1%, 21.2%, 7.5%, and 5.9%, respectively[1]
- Incidence of reported hypoglycemia§ was 3.4% in treatment-naive patients given saxagliptin 5 mg + metformin IR and 4.0% in patients given metformin IR + placebo
- Adverse reactions with saxagliptin 5 mg + metformin IR reported in ≥5% of patients and more commonly than in patients treated with metformin IR + placebo were headache (7.5% vs 5.2%) and nasopharyngitis (6.9% vs 4.0%)

* Intent-to-treat population using last observation on study, or last observation prior to pioglitazone rescue therapy for patients needing rescue.
† Least squares mean adjusted for baseline value.
‡ $P<0.0001$ compared to metformin IR + placebo.
§ A concurrent glucose measurement was not required or was normal in some patients. Therefore, it is not possible to conclusively determine that all these reports reflected true hypoglycemia.
IR=immediate release; CI=confidence interval.

1. Jadzinsky M et al. *Diabetes Obes Metab* 2009;11:611-622.

EndoDrChen.com

Initial combination with metformin: 76-week extension



*Post hoc p<0.0001 vs both SAXA 10 mg and MET alone.
MET: metformin; SAXA: saxagliptin.

EndoDrChen.com

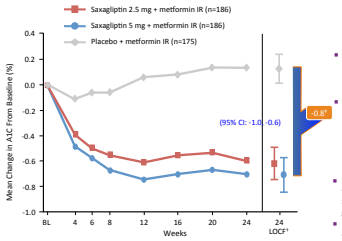
Pfützner , A. et al. *Diabetes, Obesity and Metabolism* 13: 567–576, 2011

Saxagliptin + metformin IR vs placebo + metformin IR

Pacientes no controlados con metformin

EndoDrChen.com

Uncontrolled on Metformin Monotherapy: A1C*



- A1C reduction with saxagliptin 5 mg + metformin IR was -0.7%[2] (baseline=8.1%, n=186) at Week 24, vs an increase of +0.1% with placebo + metformin IR (baseline=8.1%, n=175)
- A1C reduction with saxagliptin 2.5 mg + metformin IR was -0.6%[2] (baseline=8.1%, n=186) at Week 24
- Mean daily metformin IR doses at Week 24 were 1897 mg, 1872 mg, and 1870 mg for saxagliptin 5 mg + metformin IR, saxagliptin 2.5 mg + metformin IR, and placebo + metformin IR, respectively[1]
- The proportion of patients who discontinued or who were rescued in the saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo + metformin IR groups was 15%, 13%, and 27%, respectively
- Incidence of reported hypoglycemia[§] was 5.8% with saxagliptin 5 mg + metformin IR and 7.8% with saxagliptin 2.5 mg + metformin IR, vs 5% with placebo + metformin IR

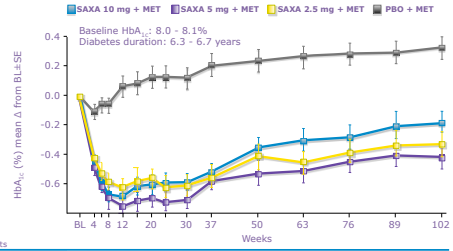
* Includes patients with a baseline and Week 24 value.
† Week 24 (LOCF) includes intent-to-treat population using last observation on study or last observation prior to pioglitazone rescue therapy for patients needing rescue. Mean change from baseline is adjusted for baseline value.
‡ P<0.0001 vs metformin + placebo at Week 24.

§ A concurrent glucose measurement was not required or was normal in some patients. Therefore, it is not possible to conclusively determine that all reports reflected true hypoglycemia.
IR=immediate release; BL=baseline; LOCF=last observation carried forward; CI=confidence interval

RadioDrChen.com

1. DeFronzo RA et al. *Diabetes Care*. 2009;32(9):1649-1655.

Saxagliptin added to metformin: 102-week extension HbA1c mean change from baseline

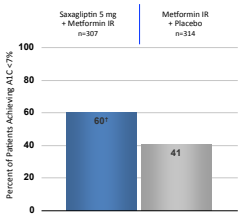


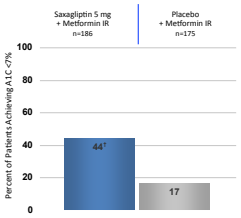
Patients								
SAXA 2.5 mg + MET	192	152	117	105	96	79	67	21
SAXA 5 mg + MET	191	146	116	99	89	70	58	25
SAXA 10 mg + MET	181	140	124	111	93	80	68	32
PBO + MET	179	111	72	60	52	33	25	15

BL: Baseline; MET: Metformin; PBO: Placebo; SAXA: Saxagliptin.

Ravichandran S, et al. *Diabetologia* 2009; 52(Suppl. 1):S60 [Abstract]. Presented as an Oral Presentation at the European Association for the Study of Diabetes Congress, Vienna, Austria, September 2009 [Presentation no. 132]

Patients Achieving A1C <7% at Week 24*





- Patients achieving A1C <7% with saxagliptin 2.5 mg, 5 mg, 10 mg + metformin IR was 37%, 44% and 44% vs 17 % placebo + metformin IR ; *P* <0.0001 at Week 24.

* Intent-to-treat population using last observation on study, or last observation prior to pioglitazone rescue therapy for patients needing rescue.
† *P*<0.05 compared to placebo + metformin IR.
IR=immediate release.

1. Jadzinsky M et al. *Diabetes Obes Metab*. 2009;11:611-622.
2. DeFronzo RA et al. *Diabetes Care*. 2009;32(9):1649-1655.

kombiglyze XR
(saxagliptin and metformin HCl extended-release) tablets

Changes in Other Parameters

- Decrease in body weight in patients given Kombiglyze XR was similar to that in patients given metformin IR alone
- Saxagliptin plus metformin IR was not associated with significant changes from baseline in fasting serum lipids compared to metformin IR alone

IR=immediate release.

EndoDrChen.com

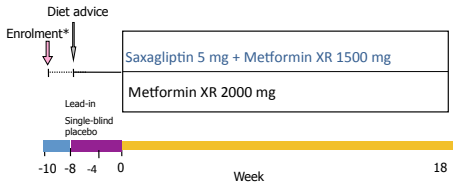
Saxagliptin + Metformin XR

Comparado con aumento de dosis de Metformin XR

EndoDrChen.com

kombiglyze XR
(saxagliptin and metformin HCl extended-release) tablets

Saxagliptin + Metformin XR vs. Metformin XR Uptitration



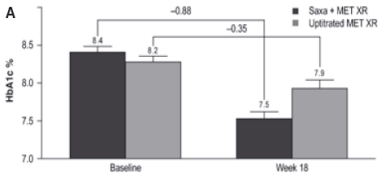
* Patients with type 2 diabetes with inadequate glycemic control defined as HbA1c >6.5 % and ≤10.5% (at randomization), on a stable dose (≥850 mg and ≤1500mg) of metformin IR or XR therapy for at least 8 weeks will enter an 8 week lead-in period. Patients on a stable dose (1500mg) of metformin XR will enter a 4 week lead-in period.

Fonseca, V et al *Diabetes, Obesity and Metabolism* 14: 365–371, 2012.

EndoDrChen.com

Saxagliptin + Metformin XR vs. Metformin XR Uptitration

Mean HbA1c at baseline and week 18

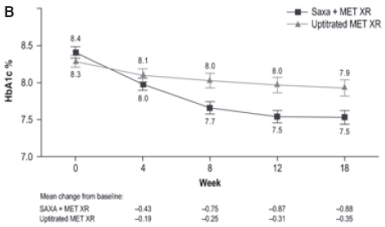


Adjusted mean change from baseline HbA1c, was −0.88% for saxagliptin + metformin XR and −0.35% for uptitrated metformin XR; the between-group difference was−0.52% (p *< 0.0001)*

Fonseca, V et al *Diabetes, Obesity and Metabolism* 14: 365–371, 2012. EndoDrChen.com

Saxagliptin + Metformin XR vs. Metformin XR Uptitration

Mean change in HbA1c over 18 weeks of treatment (LOCF)



From week 8 through week 18, decreases in mean HbA1c were greater in patients receiving saxagliptin + metformin XR than in those receiving uptitrated metformin XR

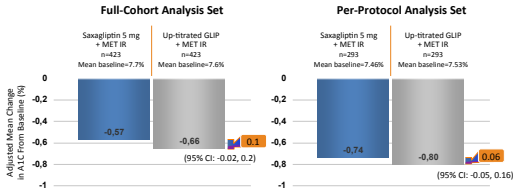
Fonseca, V et al *Diabetes, Obesity and Metabolism* 14: 365–371, 2012. EndoDrChen.com

Saxagliptin + Metformin IR

Comparado con GLIPIZIDE + Metformin IR

EndoDrChen.com

A1C at Week 52[1]



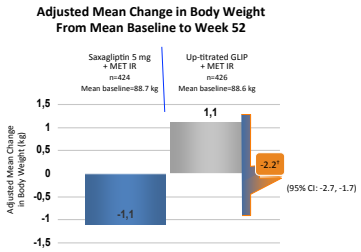
- The upper limit of this 95% CI met the predefined criterion for non-inferiority of <0.35%. Thus, saxagliptin 5 mg + MET IR was non-inferior to up-titrated GLIP + MET IR
- A conclusion of non-inferiority of saxagliptin to up-titrated GLIP may be limited to patients with baseline A1C comparable to those in the trial (91% of patients had baseline A1C <9%)
- Mean final GLIP dose in the titrated arm was 14.7 mg/day; 50% of patients received 20 mg/day
- The proportion of patients who discontinued due to lack of efficacy by Week 52 in the saxagliptin + MET IR group and the up-titrated GLIP + MET IR group was 15.3% and 12.0%, respectively[2]

MET IR=metformin immediate release; GLIP=glipizide; CI=confidence interval.

1. Göke B et al. *Int J Clin Pract*. 2010;64(12):1619-1631.
2. Data on file, SAXA 070. Bristol-Myers Squibb Company. Princeton, NJ.

EndoDrChen.com

Add-On to MET IR Versus GLIP + MET IR: Body Weight*

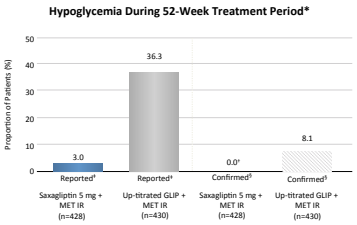


* Safety analysis set.
† *P*<0.0001 vs up-titrated GLIP + MET IR.
MET IR=metformin immediate release; GLIP=glipizide; CI=confidence interval.

Göke B et al. *Int J Clin Pract* 2010;64(12):1619-1631.

EndoDrChen.com

Add-On to MET IR Versus GLIP + MET IR: Hypoglycemia



Reported Hypoglycemia:

- **13 patients in the saxagliptin 5 mg + MET IR group reported 19 hypoglycemic events**
- **156 patients in the up-titrated GLIP + MET IR group reported 750 hypoglycemic events**

‡ Reported hypoglycemia events were a combination of reports of either signs or symptoms consistent with hypoglycemia with or without documented glucose levels or reported low glucose levels without any symptoms. Therefore, it is not possible to conclusively determine that all these reports reflected true hypoglycemia.

§ Confirmed hypoglycemia was defined as a fingerstick glucose ≤50 mg/dL with associated symptoms.

* Safety analysis set.
† *P*<0.0001 vs up-titrated GLIP + MET IR group.
‡ MET IR=metformin immediate release; GLIP=glipizide.

Göke B et al. *Int J Clin Pract* 2010;64(12):1619-1631.

EndoDrChen.com

Saxagliptin + Metformin IR + Insulin

Vs Placebo + Metformin + Insulin

EndoDrChen.com

kombiglyze XR
(saxagliptin and metformin HCl extended-release) tablets

Demographic and Baseline Characteristics (cont)

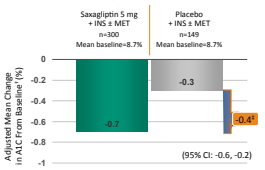
Characteristic	Saxagliptin 5 mg + INS (n=304)	MET IR + Placebo (n=151)
MTDDI, units (range)	53.6 (19–150)	55.3 (30–149)
Insulin type, n (%)		
No premixed	115 (38)	69 (46)
Intermediate acting and long acting	9 (3)	8 (5)
Intermediate acting, alone	54 (18)	32 (21)
Long-acting, alone	52 (17)	29 (19)
Any premixed	189 (62)	82 (54)
Premixed alone	182 (60)	76 (50)
Intermediate acting and premixed	4 (1)	4 (3)
Long acting and premixed	3 (1)	2 (1)
Patients taking MET, n (%)	209 (69)	105 (70)
MET dose, mean (range), mg	1805.4 (250–3000)	1861.1 (850–3000)

INS=insulin; MET=metformin; IR=immediate release; MTDDI=mean total daily dose of insulin.

Barnett AH, et al. *Curr Med Res Opin* 2012. doi:10.1185/03007995.2012.665046.

EndoDrChen.com

Change in A1C at Week 24*

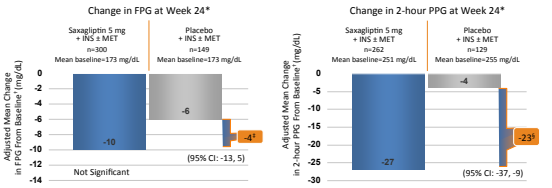


- Similar mean reductions in A1C versus placebo were observed for patients treated with saxagliptin 5 mg + INS alone and saxagliptin 5 mg + INS ± MET (-0.4% and -0.4%, respectively)
- The proportion of patients who discontinued for lack of glycemic control or who were rescued for meeting prespecified glycemic criteria in the saxagliptin 5 mg + INS ± MET group and the placebo + INS ± MET group was 23% and 32%, respectively

* Intent-to-treat population using last observation on study or last observation prior to INS rescue therapy for patients needing rescue.
† Least squares mean adjusted for baseline value and MET use at baseline.
‡ P<0.0001 compared to placebo + INS ± MET.
INS=insulin; MET=metformin; CI=confidence interval.

Barnett AH, et al. *Curr Med Res Opin* 2012. doi:10.1185/03007995.2012.665046.

EndoDrChen.com



- * Intent-to-treat population using last observation on study or last observation prior to INS rescue therapy for patients needing rescue.
- † Least squares mean adjusted for baseline value and MET use at baseline.
- ‡ Difference compared to placebo + INS ± MET was not statistically significant.
- § *P*<0.05 compared to placebo + INS ± MET.

INS=insulin; MET=metformin; FPG=fasting plasma glucose; PPG=postprandial glucose; CI=confidence interval.

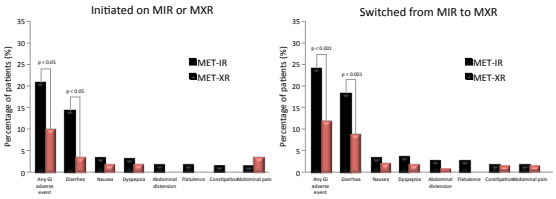
Barnett AH, et al. *Curr Med Res Opin* 2012. doi:10.1185/03007995.2012.665048

EndoDrChen.com

Seguridad y tolerabilidad

EndoDrChen.com

Metformin XR and Metformin IR clinical data: Tolerability



Patients who were initiated on MET-XR or who were switched from MIR to MXR experienced fewer GI adverse events on comparable doses of metformin

GI, gastrointestinal; MET, metformin; MET-IR, immediate-release metformin; MET-XR, extended-release metformin.

Blonde L, *et al. Curr Med Res Opin* 2004;20:565–72.

EndoDrChen.com

Gastrointestinal Adverse Events in ≥5% Patients Treated With Saxagliptin and Metformin IR

- In patients treated with the combination of saxagliptin and metformin IR, either in treatment-naive patients or in patients uncontrolled on metformin monotherapy, diarrhea was the only gastrointestinal-related event that occurred in ≥5% in any treatment group across both studies

Treatment-Naive[1]

	Patients (%)	
	Saxagliptin 5 mg + Metformin IR (n=320)	Metformin IR + Placebo (n=328)
Diarrhea	6.9%	7.3%

Uncontrolled on Metformin Monotherapy[2]

	Patients (%)		
	Saxagliptin 5 mg + Metformin IR (n=191)	Saxagliptin 2.5 mg + Metformin IR (n=192)	Placebo + Metformin IR (n=179)
Diarrhea	5.8%	9.9%	11.2%

IR=immediate release.

1. Jadzinsky M et al. *Diabetes Obes Metab* 2009;11:611-622.
2. DeFronzo RA et al. *Diabetes Care* 2009;32(9):1649-1655.

EndoDrChen.com

Add-On to INS ± MET: Incidence of Adverse Events

Incidence of Adverse Events

	Patients (%)	
	Saxagliptin 5 mg + INS (± MET) (n=304)	Placebo + INS (± MET) (n=151)
Overall incidence of adverse events	56.9	59.6
Reported hypoglycemic events*†	18.4	19.9
Confirmed hypoglycemic events*‡	5.3	3.3

- Discontinuations due to adverse events occurred in 1.3% (4) in the saxagliptin arm, and 2.0% (3) in the placebo arm
- Use with Medications Known to Cause Hypoglycemia: When saxagliptin was used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia, the incidence of confirmed hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or with insulin. Therefore, a lower dose of the insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia when used in combination with KOMBIGLYZE XR.

* Prior to rescue.
† A concurrent glucose measurement was not required or was normal in some patients. Therefore, it is not possible to conclusively determine that all these reports reflected true hypoglycemia.
‡ Based on fingerstick glucose ≤50 mg/dL and associated symptoms.INS=insulin; MET=metformin.

1. Barnett AH, et al. *Curr Med Res Opin* 2012. doi:10.1185/03007995.2012.665046.

SEGURIDAD CARDIOVASCULAR

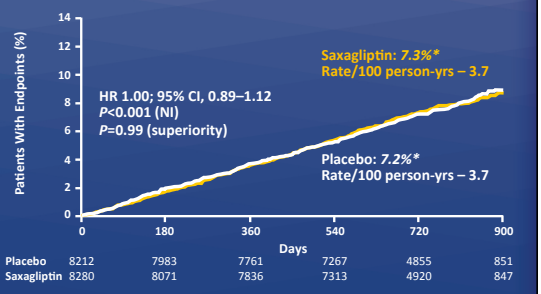
EndoDrChen.com

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

Confidential. For Internal Use Only. Not to be shared outside of the BMS/AZ Alliance Diabetes Collaborative Teams. Any potential promotional messaging/product claims are subject to regulatory review and approval and local promotional practices and policies.

Bristol-Myers Squibb AstraZeneca

Kaplan-Meier Rates of the Primary Composite Endpoint – CV Death, MI, or Stroke



Placebo	8212	7983	7761	7267	4855	851
Saxagliptin	8280	8071	7836	7313	4920	847

*K-M event rates are presented after 2 yrs.
HR: hazard ratio; K-M: Kaplan-Meier; Pbo: placebo; Saxa: saxagliptin
Scirica BM, et al. *N Engl J Med.* 2013.10.1056/NEJMoa1307684.

Bristol-Myers Squibb AstraZeneca

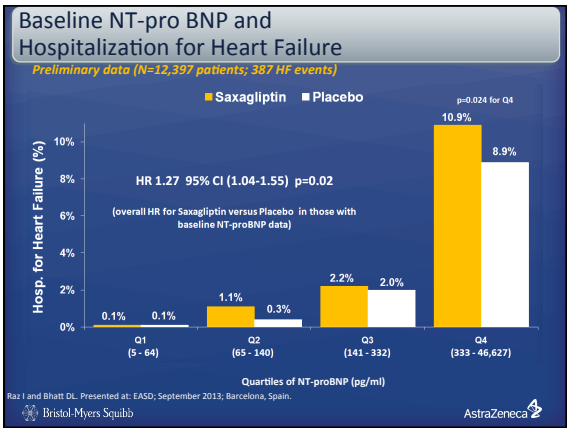
Individual Components of the Composite Endpoints

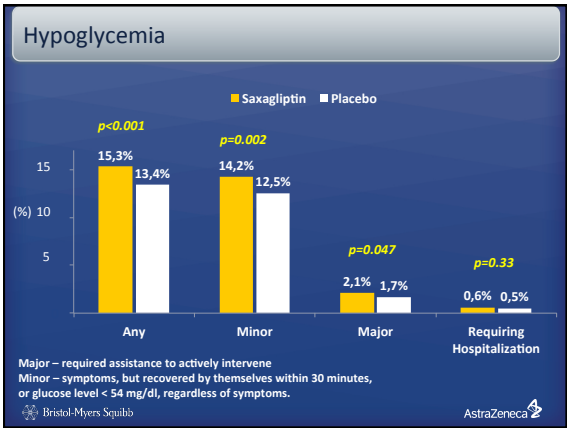
Efficacy endpoint	Saxagliptin n (%)* (N = 8,280)	Placebo n (%)* (N = 8,212)	HR (95% CI)	*P* value
CV death	269 (3.2)	260 (2.9)	1.03 (0.87–1.22)	0.72
MI	265 (3.2)	278 (3.4)	0.95 (0.80–1.12)	0.52
Ischemic stroke	157 (1.9)	141 (1.7)	1.11 (0.88–1.39)	0.38
Hosp for UA	97 (1.2)	81 (1.0)	1.19 (0.89–1.60)	0.24
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

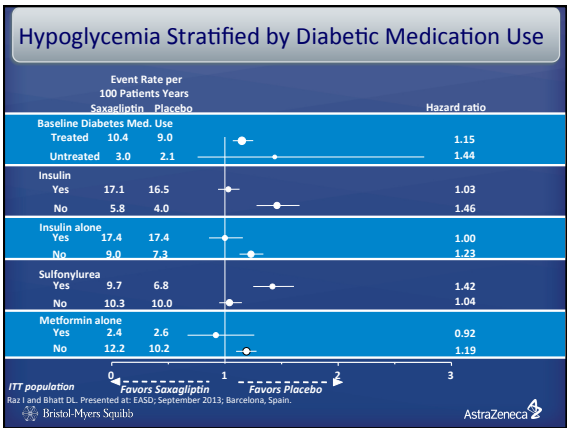
*K-M event rates are presented after 2 yrs.

Scirica BM, et al. *N Engl J Med.* 2013.10.1056/NEJMoa1307684.

Bristol-Myers Squibb AstraZeneca


Baseline NT-pro BNP and Hospitalization for Heart Failure
Preliminary data (N=12,397 patients; 387 HF events)
Saxagliptin
Placebo
p=0.024 for Q4
Hosp. for Heart Failure (%)
10%
8%
6%
4%
2%
0%
HR 1.27 95% CI (1.04-1.55) p=0.02
(overall HR for Saxagliptin versus Placebo in those with baseline NT-proBNP data)
0.1%
0.1%
1.1%
0.3%
2.2%
2.0%
10.9%
8.9%
Q1 (5 - 64)
Q2 (65 - 140)
Q3 (141 - 332)
Q4 (333 - 46,627)
Quartiles of NT-proBNP (pg/ml)
Raz I and Bhatt DL. Presented at: EASD; September 2013; Barcelona, Spain.
Bristol-Myers Squibb
AstraZeneca


Hypoglycemia
Saxagliptin
Placebo
(%)
15
10
5
p<0.001
15,3%
13,4%
p=0.002
14,2%
12,5%
p=0.047
2,1%
1,7%
p=0.33
0,6%
0,5%
Any
Minor
Major
Requiring Hospitalization
Major – required assistance to actively intervene
Minor – symptoms, but recovered by themselves within 30 minutes, or glucose level < 54 mg/dl, regardless of symptoms.
Bristol-Myers Squibb
AstraZeneca


Hypoglycemia Stratified by Diabetic Medication Use
Event Rate per 100 Patients Years
Saxagliptin Placebo
Hazard ratio
Baseline Diabetes Med. Use
Treated 10.4 9.0 1.15
Untreated 3.0 2.1 1.44
Insulin
Yes 17.1 16.5 1.03
No 5.8 4.0 1.46
Insulin alone
Yes 17.4 17.4 1.00
No 9.0 7.3 1.23
Sulfonylurea
Yes 9.7 6.8 1.42
No 10.3 10.0 1.04
Metformin alone
Yes 2.4 2.6 0.92
No 12.2 10.2 1.19
0
1
2
3
ITT population
Favors Saxagliptin
Favors Placebo
Raz I and Bhatt DL. Presented at: EASD; September 2013; Barcelona, Spain.
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. Cushman, M.D., and Faiez Zannad, M.D., Ph.D., for the EXAMINE Investigators*

EndoDrChen.com

End Point	Placebo (N=2679)	Alogliptin (N=2701)	Hazard Ratio for Alogliptin Group (95% CI)	P Value*
	no. (%)			
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

EndoDrChen.com

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

VIVIDD

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

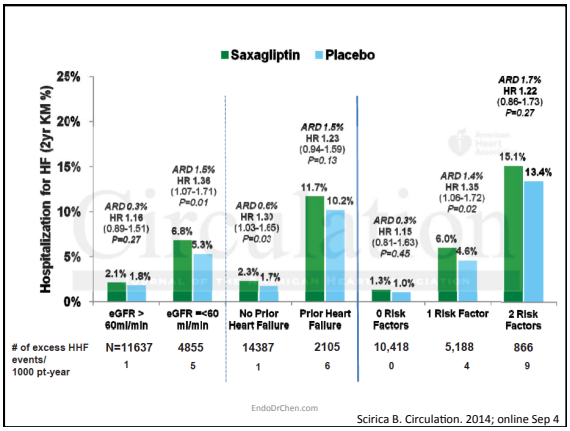
EndoDrChen.com

SAVOR e ICC

- Factores de riesgo:
  - Historia previa de falla cardíaca
  - AEC <60 cc/min
  - Microalbuminuria

EndoDrChen.com

Scirica B. Circulation. 2014; online Sep 4



EndoDrChen.com

Scirica B. Circulation. 2014; online Sep 4

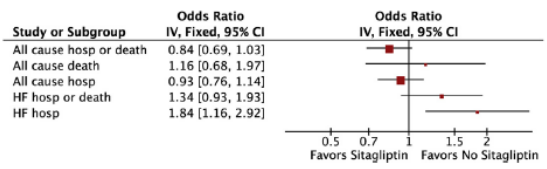
Sitagliptina e ICC

Outcome	Agent	Exposed Cases/Total Exposed	Unexposed Cases/Total Unexposed	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)	p Value*
All-cause death or hospital admission	Sitagliptin	113/1,588	4,024/43,846	0.75 (0.62-0.92)	0.84 (0.69-1.03)	0.10
	Metformin	756/10,734	3,381/34,700	0.64 (0.59-0.70)	0.78 (0.71-0.85)	<0.001
	Insulin	800/7,149	3,337/38,285	1.37 (1.25-1.50)	1.16 (1.05-1.28)	0.004
	Sulfonylurea	673/7,710	3,464/37,724	0.94 (0.86-1.03)	1.10 (1.00-1.23)	0.043
	Other	109/1,429	4,028/44,005	0.81 (0.67-1.00)	0.95 (0.77-1.17)	0.64
All-cause death	Sitagliptin	19/274	389/4,193	0.73 (0.45-1.18)	1.16 (0.68-1.97)	0.59
	Metformin	66/1,530	342/2,937	0.33 (0.25-0.44)	0.52 (0.37-0.71)	<0.001
	Insulin	142/1,411	266/3,056	1.18 (0.95-1.47)	1.11 (0.84-1.47)	0.46
	Sulfonylurea	73/1,247	335/3,220	0.53 (0.41-0.69)	0.83 (0.61-1.14)	0.25
	Other	13/214	395/4,253	0.63 (0.36-1.12)	0.87 (0.46-1.63)	0.66
All-cause hospital admission	Sitagliptin	112/1,489	3,964/43,274	0.80 (0.6-0.98)	0.93 (0.76-1.14)	0.46
	Metformin	750/10,556	3,326/34,207	0.65 (0.59-0.71)	0.79 (0.71-0.87)	<0.001
	Insulin	795/7,215	3,281/37,548	1.34 (1.23-1.47)	1.13 (1.03-1.25)	0.014
	Sulfonylurea	669/7,683	3,407/37,080	0.93 (0.85-1.03)	1.08 (0.97-1.19)	0.15
	Other	109/1,277	3,967/43,486	0.93 (0.76-1.13)	1.06 (0.86-1.31)	0.56
HF-related hospital admission or death	Sitagliptin	37/409	1,109/12,172	0.99 (0.70-1.41)	1.34 (0.93-1.92)	0.12
	Metformin	154/2,556	992/10,025	0.53 (0.44-0.64)	0.70 (0.57-0.86)	0.001
	Insulin	217/2,126	929/10,455	1.20 (1.01-1.42)	1.02 (0.84-1.24)	0.81
	Sulfonylurea	156/2,063	990/10,518	0.76 (0.63-0.92)	0.92 (0.75-1.13)	0.41
	Other	21/302	1,125/12,279	0.74 (0.47-1.16)	0.85 (0.53-1.36)	0.50
HF-related hospital admission	Sitagliptin	25/200	799/8,862	1.47 (0.95-2.27)	1.84 (1.16-2.92)	0.01
	Metformin	106/1,378	718/7,684	0.76 (0.60-0.96)	0.87 (0.66-1.12)	0.28
	Insulin	113/1,114	711/7,948	1.19 (0.94-1.50)	0.97 (0.75-1.27)	0.83
	Sulfonylurea	103/1,067	721/7,995	1.09 (0.86-1.39)	1.11 (0.84-1.45)	0.47
	Other	14/147	810/8,905	0.98 (0.56-1.72)	1.08 (0.59-1.96)	0.81

EndoDrChen.com

Weir D. JACC: Heart Failure. 2014

Sitagliptina e ICC



EndoDrChen.com

Weir D. JACC: Heart Failure. 2014

Análisis

- Con estos datos e ICC
  - Saxagliptina: SAVOR
  - Alogliptina: EXAMINE
  - Vildagliptina: VIVIDD
  - Sitagliptina: estudio de Weir et al
- Será un efecto de clase?
- A la espera de TECOS y CAROLINA
- Conducta actual

EndoDrChen.com

SEGURIDAD PANCREÁTICA

EndoDrChen.com

Pancreatitis

- SAVOR y EXAMINE 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

EndoDrChen.com

Conclusiones

- Los inhibidores de DPP-4 en general son una clase donde es difícil diferenciar entre los agentes
- Saxagliptin/metformin XR es la única formulación combinada que permite administrarlo una vez al día
- Falta de adherencia se asocia a mayor morbilidad
- Precaución en pacientes con historia de falla cardíaca, insuficiencia renal o proteinuria

EndoDrChen.com

Preguntas…
chenku2409@gmail.com
EndoDrChen.com

EndoDrChen.com