Update on Saxagliptin/ Metformin XR in type 2 diabetes

Dr. Chih Hao Chen Ku, FACE
Endocrinology Department, San Juan de Dios Hospital
Pharmacology and Clinical Toxicology Department, University of Costa Rica

Conflicts of interest

- Speaker: Astra Zeneca, Abbott Nutrition, Novartis Oncology, Novo Nordisk, Merck Sharp & Dohme, Roche, Glaxo SmithKline, Sanofi Aventis, Genzyme, Bayer
- Advisory Board: Novartis Oncology, Sanofi Aventis, Astra Zeneca, Novo Nordisk
- Clinical research: Astra Zeneca, Novartis Pharma Logistics Inc., Merck Sharp & Dohme, Glaxo SmithKline, Organon, Boehringer Ingelheim, Roche

Agenda

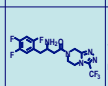
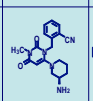
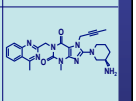
- Are there any differences betweeen DPP4 inhibitors?
- Update on clinical data
  - Chronic kidney disease
  - Proteinuria
  - New metformin guidelines
- Update on cardiovascular safety

DPP4 inhibitors

- Sitagliptin
- Vildagliptin
- Linagliptin
- Saxagliptin
- Alogliptin
- Gemigliptin

- Are there any relevant clinical differences?

DPP4 inhibitors pharmacokinetic and molecular differences[a]

Chemical class	β-Fenetilaminas[1]	Cianopirrolidinas[5,7]		Aminopiperidina[9]	Xantina[3]
Name	Sitagliptina[2]	Vildagliptina[6]	Saxagliptina[8]	Alogliptina[10]	Linagliptina[12]
Molecular structure[3]					
DPP-4 inhibitory activity (IC_{50})	~18 nM[1]	5.3 nM[4]	3.4 nM[4]	6.9 nM[11]	~1 nM[3]
Half life	12.4 hours	~2–3 hours	2.5 hours(original drug)[8] 3.1 hours(metabolite)[8]	21 hours	$T_{1/2}$ eficaz ~12 h[12] $T_{1/2}$ terminal ~100 h[12]

[a]Los estudios farmacodinámicos se realizaron en diferentes sistemas de ensayo y no deben compararse.

DPP-4 = dipeptidil peptidasa-4.

1. Kim D y cols. *J Med Chem.* 2005;48:141–151. **2.** JANUVIA WPC. **3.** Thomas L y cols. *J Pharmacol Exp Ther.* 2008;325:175–182. **4.** Matsuyama-Yokono A y cols. *Biochem Pharmacol.* 2008;76:98–107. **5.** Villhauer EB y cols. *J Med Chem.* 2003;46:2774–2789. **6.** EUSPC for Galvus. **7.** Augeri DJ y cols. *J Med Chem.* 2005;48:5025–5037. **8.** EUSPC for Onglyza. **9.** Feng J y cols. *J Med Chem.* 2007;50:2297–2300. **10.** EUSPC for Vipidia. **11.** Lee B y cols. *Eur J Pharmacol.* 2008;589:306–14. **12.** EUSPC for Trajenta.

5

Pharmacokinetic characteristics of DPP4 inhibitors[a]

	T_{max} absorption (mediana)	Bioavailability	Half life ($t_{1/2}$) at clinically relevant doses	Distribution	Metabolism	Elimination
Sitagliptina (Merck)[1]	1–4 hours	~87%	12.4 hours	38% binded to proteins	~16% metabolized	Renal 87% (79% intact)
Vildagliptina (Novartis)[2]	1.7 hours	85%	~2–3 hours	9.3% binded to proteins	69% metabolizaded mainly renal (inactive metabolite)	Renal 85% (23% intact)
Saxagliptina (BMS/AZ)[3]	2 hours(4 hours active metabolite)	≥75%[4]	2.5 hours (original drug) 3.1 hours(metabolite)	Very low protein binding	Liver (active metabolite) CYP3A4/5	Renal 75% (24% as original drug; 36% as active metabolite)
Alogliptina (Takeda)[5]	1-2 hours	100%	~21 hours	20–30% binded to proteins	<7% metabolized	Renal 76% (60–70% intact)
Linagliptina (BI)[6]	1.5 hours	~30%	$T_{1/2}$ eficaz ~12 horas $T_{1/2}$ terminal >100 horas	Protein binding depending upon concentration: 1 nM: 99% (DPP-4) ≥30 nM: 75%–89%	~13% metabolizaded	Feces80% Renal 5%

[a]Los estudios farmacodinámicos se realizaron en diferentes sistemas de ensayo y no deben compararse.

DPP-4 = dipeptidil peptidasa-4.

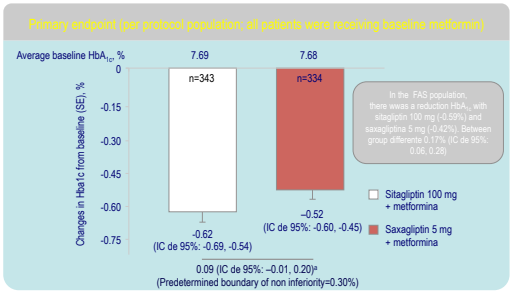
1. JANUVIA WPC. 2. EUSPC for Galvus. 3. EUSPC for Onglyza. 4. EPAR for Onglyza. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001035/WC500044319.pdf. Accessed November 11, 2012A. 5. EUSPC for Vipidia. 6. EUSPC for Trajenta.

6

DPP4 inhibitors

- How do we give them?
  - OD: sitagliptin, linagliptin, saxagliptin, alogliptin
  - Bid: vildagliptin
  - weekly: omariglitptin
- Clinical efficacy:
  - Very few direct comparative data
  - Indirect comparison show similar efficacy

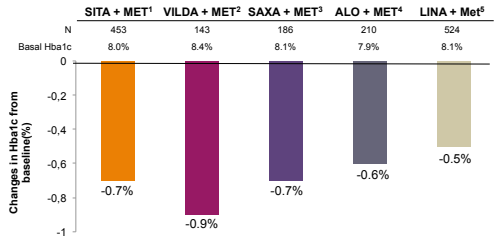
Saxagliptin was non inferior compared to sitagliptin on Hba1c reduction at 18 weeks[1]



aDiferencia en el cambio ajustado desde el inicio *vs.* sitagliptina + metformina.
IC = intervalo de confianza; FAS = análisis de grupo completo; EE = error estándar.
1. Scheen AJ y cols. *Diabetes Metab Res Rev.* 2010;26:540-549.

HbA1c reduction

*DPP-4 inhibitors (added to metformin)**



- ALO = alogliptina; DPP-4 = dipeptidil peptidasa-4; HbA1c = hemoglobina A1c; LINA = linagliptina; MET = metformina; SAXA = saxagliptina; SITA = sitagliptina; VILDA = vildagliptina
- 1. Charbonnel B, et al. *Diabetes Care* 2006;29:2638-2643. 2. Bosi E, et al. *Diabetes Care* 2007;30:809-895. 3. DeFronzo R, et al. *Diabetes Care* 2009;32:1649-1655. 4. Nauck MA, et al. *Int J Clin Pract* 2009;64:46-55. 5. Taskinen MR et al. *Diabetes, Obesity and Metabolism* 2010;13:65-74.

Pharmacokinetic differences

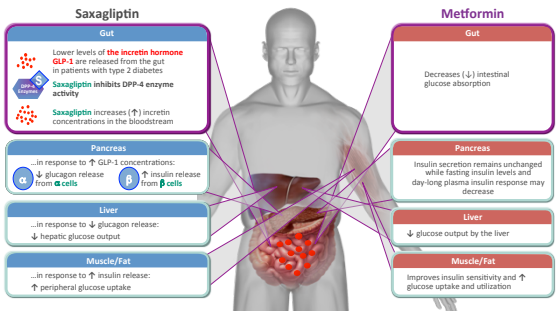
- Cytochrome substrate:
  - CYP3A4: saxagliptin
  - Interaction with potent CYP3A4 inducers or inhibitors suck as ketoconazole

Other differences

- Cardiovascular safety:
  - Published trials: SAVOR, EXAMINE, TECOS
  - Ongoing: CAROLINA
- Fixed dose combination:
  - Metformin rapid release: sitagliptin, vildagliptin, linagliptin
  - Metformin XR: saxagliptin

SAXAGLIPTIN/METFORMINA XR

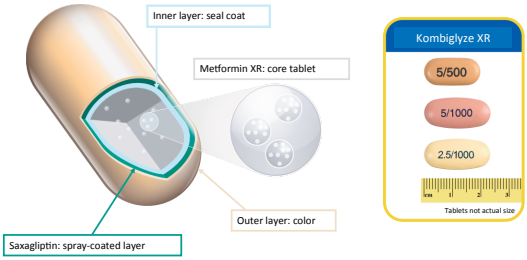
Saxagliptin/metformin XR: complementary mechanism of action



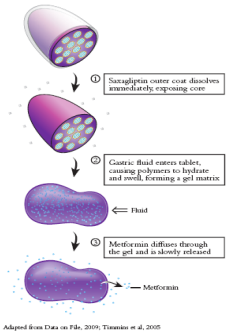
GLP=glucagon-like peptide; DPP=dipeptidyl peptidase.

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

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



Release of Saxagliptin and Metformin XR



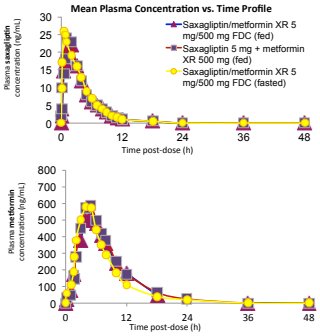
Adapted from Data on File, 2009; Timmins et al, 2005

Saxagliptin/metformin XR

- Phase III program was developed using saxagliptin/metformin immediate release
- Combination of saxagliptin with metformin IR or XR showed the same therapeutic effects

Saxagliptin/metformin XR 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

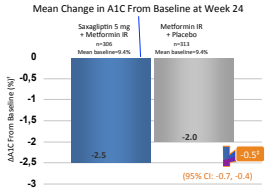


Boulton et al *Clin Drug Investig* 2011; 31 (9)

Saxagliptin + Metformin IR

Treatment-naïve patients

Treatment-Naive: A1C*

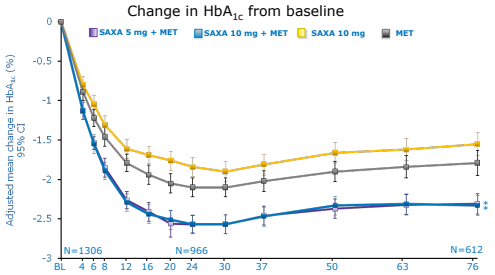


- Mean daily metformin IR doses at Week 24 were 1790 mg for saxagliptin 5 mg + metformin IR and 1817 mg for metformin IR + placebo[1]
- The proportion of patients discontinued or rescued for metformin IR alone, saxagliptin 10 mg, saxagliptin 5 mg + metformin IR, and saxagliptin 10 mg + metformin IR was 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.

Initial combination with metformin: 76-week extension



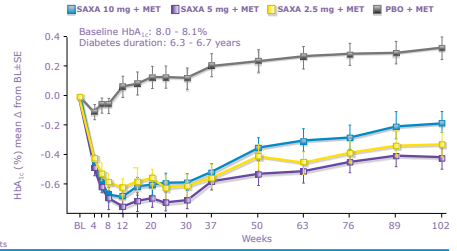
*Post hoc p<0.0001 vs both SAXA 10 mg and MET alone.
MET: metformin; SAXA: saxagliptin.

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

Saxagliptin + Metformin IR

Uncontrolled on metformin patients

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

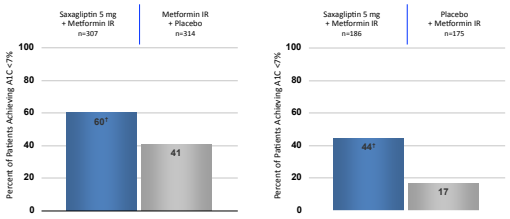


Patients								
SAXA 2.5 mg + MET	192	152	117	105	96	79	67	21
SAXA 5 mg + MET	191	146	116	99	89	70	58	25
SAXA 10 mg + MET	181	140	124	111	93	80	68	32
PBO + MET	179	111	72	60	52	33	25	15

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.

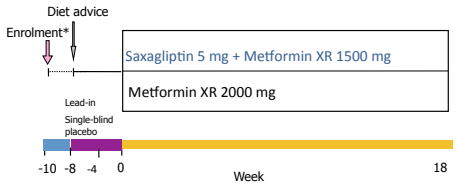
* Intent-to-treat population using last observation on study, or last observation prior to pioglitazone rescue therapy for patients needing rescue.
† *P*<0.05 compared to placebo + metformin IR.
IR=immediate release.

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

Saxagliptin + Metformin XR

Compared to Uptitrating Metformin XR

Saxagliptin + Metformin XR vs. Metformin XR Uptitration

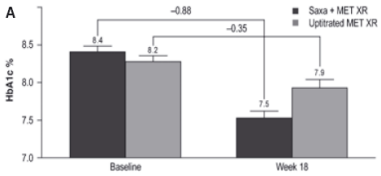


* Patients with type 2 diabetes with inadequate glycemic control defined as HbA1c >6.5 % and ≤10.5% (at randomization), on a stable dose (≥850 mg and ≤1500mg) of metformin IR or XR therapy for at least 8 weeks will enter an 8 week lead-in period. Patients on a stable dose (1500mg) of metformin XR will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

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

Saxagliptin + Metformin XR vs. up tration metformin XR

Mean HbA1c at baseline and week 18



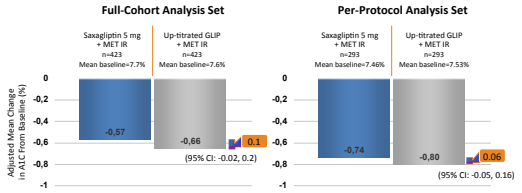
Adjusted mean change from baseline HbA1c, was −0.88% for saxagliptin + metformin XR and −0.35% for uptitrated metformin XR; the between-group difference was−0.52% (p < *0.0001)*

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

Saxagliptin + Metformin IR

Compared to GLIPIZIDE + Metformin IR

A1C at Week 52[1]

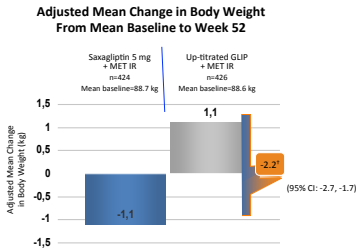


- The upper limit of this 95% CI met the predefined criterion for non-inferiority of <0.35%. Thus, saxagliptin 5 mg + MET IR was non-inferior to up-titrated GLIP + MET IR
- A conclusion of non-inferiority of saxagliptin to up-titrated GLIP may be limited to patients with baseline A1C comparable to those 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.

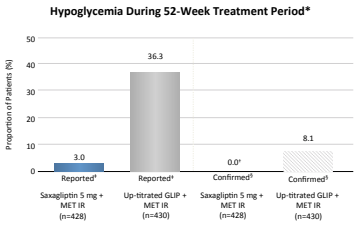
Add-On to MET IR Versus GLIP + MET IR: Body Weight*



* 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.

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**

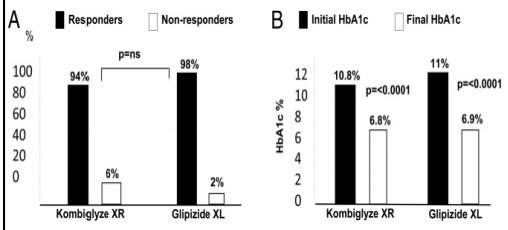
‡ Reported hypoglycemia events were a combination of reports of either signs or symptoms consistent with hypoglycemia with or without documented glucose levels or reported low glucose levels without any symptoms. Therefore, it is not possible to conclusively determine that all these reports reflected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

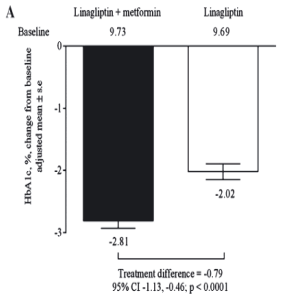
Göke B et al. *Int J Clin Pract* 2010;64(12):1619-1631.

Saxagliptin/metformin vs glipizide XL in very hyperglycemic patients



Amblee A. *J Clin Endocrinol Metab.* 2016;101:2528

Baseline Hba1c 8.5-12%

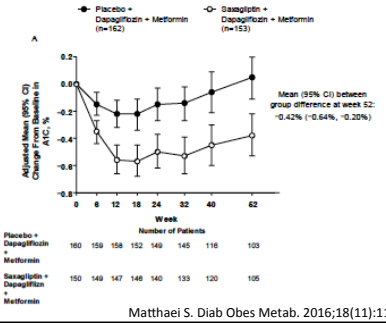


Ross SA. *Diab Obes Metab.* 2015;17:136-44.

Saxagliptin + Metformin IR + Dapagliflozin

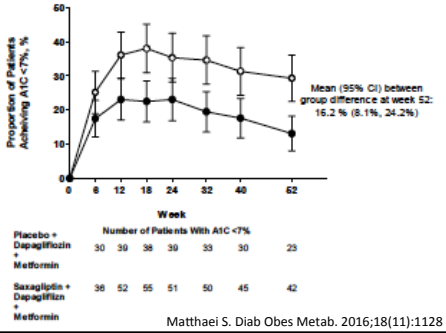
Vs Placebo + Metformin + Dapagliflozin
Third line treatment

Saxa vs placebo in patients with metformin + dapagliflozin



Matthaei S. Diab Obes Metab. 2016;18(11):1128

Saxa vs placebo in patients receiving metformin + dapagliflozin



Matthaei S. Diab Obes Metab. 2016;18(11):1128

Saxagliptin + Metformin IR + Insulin

Vs Placebo + Metformin + Insulin

Third line treatment

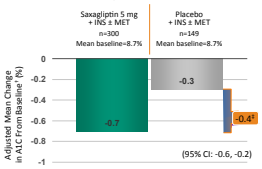
Demographic and Baseline Characteristics (cont)

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.

Change in A1C at Week 24*

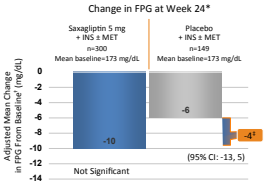


- Similar mean reductions in A1C versus placebo were observed for patients treated with saxagliptin 5 mg + INS alone and saxagliptin 5 mg + INS ± MET (-0.4% and -0.4%, respectively)
- The proportion of patients who discontinued for lack of glycemic control or who were rescued for meeting prespecified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

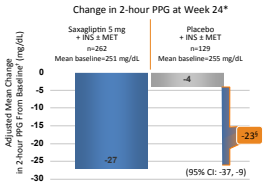
* Intent-to-treat population using last observation on study or last observation prior to INS rescue therapy for patients needing rescue.
† Least squares mean adjusted for baseline value and MET use at baseline.
‡ *P*<0.0001 compared to placebo + INS ± MET.
INS=insulin; MET=metformin; CI=confidence interval.

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

Change in FPG at Week 24*



Change in 2-hour PPG at Week 24*



- 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:10.1185/03007995.2012.665046.

Adding DPP-4i to insulin

Analysis 5.2. Comparison 5 Insulin monotherapy versus insulin plus DPP-4 inhibitor, Outcome 2 HbA1c (change from baseline).

Review: Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control

Comparison: 5 Insulin monotherapy versus insulin plus DPP-4 inhibitor

Outcome: 2 HbA1c (change from baseline)

Study or subgroup	Insulin + DPP-4 inhibitor N	Mean(SD)	Insulin mono N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Barnett 2013	95	-0.65 (0.9089)	46	-0.28 (0.9089)		2.9 %	-0.37 [-0.69, -0.05]
Hong 2012	61	-0.63 (0.19)	63	-0.22 (0.11)		97.1 %	-0.41 [-0.46, -0.36]
Total (95% CI)	**156**		**109**			**100.0 %**	**-0.41 [-0.46, -0.35]**

Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.06, df = 1 (P = 0.81); I^2 =0.0%

Test for overall effect: Z = 14.82 (P < 0.00001)

Test for subgroup differences: Not applicable

-1 -0.5 0 0.5 1

Favours insulin+DPP-4 Favours insulin mono

Vos RC. Cochrane Datab Syst Rev. 2016;9:CD006992

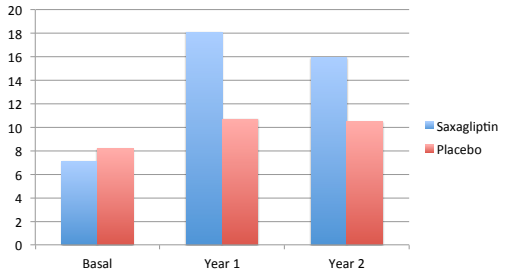
GLYCEMIC INSTABILITY

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

Glycaemic instability

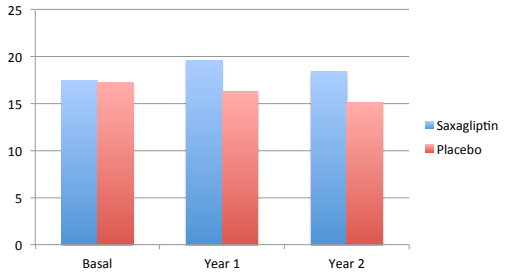
- Initiation of new antidiabetic drugs for > 3 months
- Increase in oral antidiabetic agents or >25% of insulin dose for more than 3 months
- Adding new insulin therapy for more than 3 months
- Increase of Hba1c >0.5% after randomization

SAVOR: patients with hba1c <6.5%



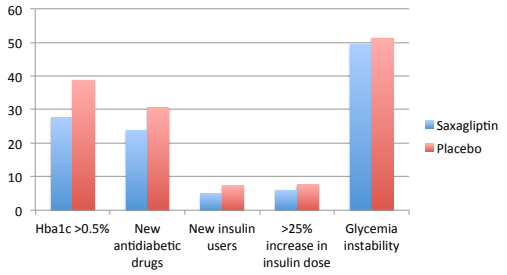
Leibowitz G. Diab Obes Metab. 2015, early on line.

SAVOR: patients with hba1c 6.5-7%



Leibowitz G. Diab Obes Metab. 2015, early on line.

SAVOR: patients with glycaemic instability



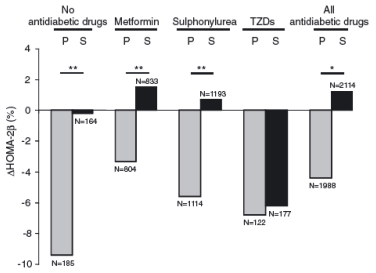
Leibowitz G. Diab Obes Metab. 2015, early on line.

Predictors of glycaemic instability

- Asian origin
- Younger age at diagnosis
- Longer duration of DM
- Smoking
- High hba1c levels
- Higher eGFR
- Low HDL
- Baseline treatment with SU or TZD

Leibowitz G. Diab Obes Metab. 2015, early on line.

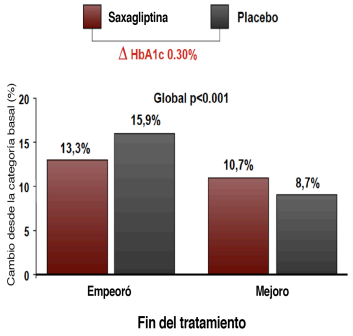
HOMA beta



Leibowitz G. Diab Obes Metab. 2015, early on line.

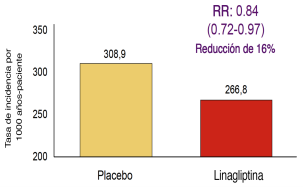
ADDITIONAL BENEFITS: KIDNEY AND LIVER

Saxagliptin improved UACR ratio in SAVOR



- Perrone G, et. al. *Nutrition, Metabolism & Cardiovascular Disease*. 2016;26:361-3733

Linagliptin and renal endpoints



Eventos renales	306	448
Tiempo en riesgo, años	991	1679
Pacientes, n	1961	3505

Microalbuminuria, macroalbuminuria, enfermedad renal crónica (ERC) (CR en suero >2. 8 mg/dl), empeoramiento de ERC (reducción >50% en TFGe desde él valor basal, insuficiencia renal aguda, muerte por todas las causas.

- Perrone G, et. al. *Nutrition, Metabolism & Cardiovascular Disease*. 2016;26:361-3733

Metformin combination

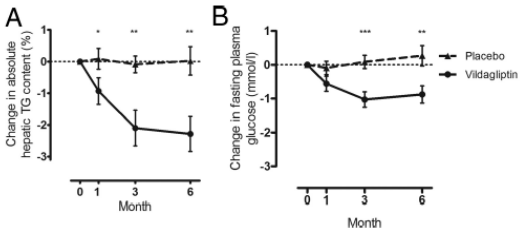
- New guidelines of metformin use by FDA:
  - CrCl >45 cc/min: safe, use usual dose
  - CrCl 30-45 cc/min: use with caution and half the maximal dose
- Therefore,
  - CrCl > 45 cc/min use usual dose of metformin/ DPP4i
  - CrCl 30-45 cc/min: use half the dose of metformin/DPP4i (except linagliptin)

Improvement in liver function

	Baseline	1 month	3 months	6 months
Total (n=224)				
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***
With Liver injury (n=44)				
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***

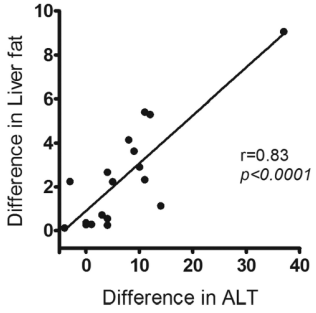
Kanazawa I. Med Sci Monit. 2014;20:1662

Liver triglyceride content and DPP4i



Macauley M. J Clin Endocrinol Metab. 2015. Epub Feb 15

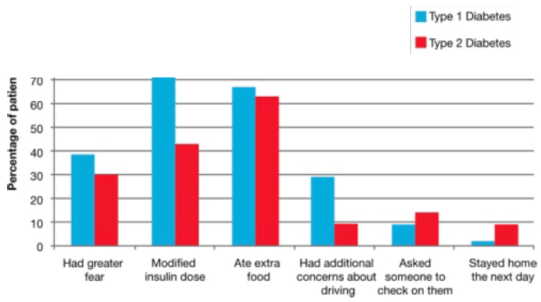
Correlation of intrahepatic triglyceride content and ALT



Macauley M. J Clin Endocrinol Metab. 2015. Epub Feb 15

Safety and tolerability

WHAT'S THE CLINICAL IMPACT OF HYPOGLYCEMIA?



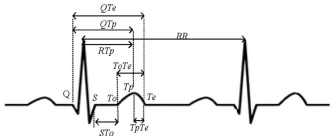
Tenzer-Iglesias. J Fam Prac. 2012;61(10):S1

Hypoglycemia

- Anxiety
- Depression
- Healthcare resources
- Cost
- Poor treatment adherence
- Car accidents
- Fractures

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

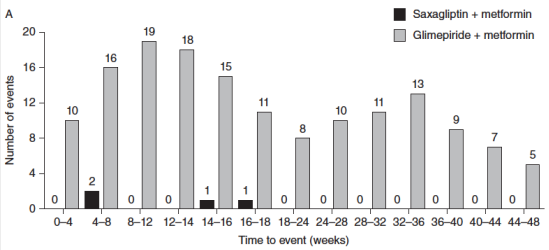
Hypoglycemia and ECG changes



ECG parameter	Nonhypoglycemia	Hypoglycemia	*p* value
HR	1.052 ± 0.061	1.197 ± 0.128	<0.0001
QTe_c	1.040 ± 0.031	1.074 ± 0.054	<0.0001
$TpTe_c$	1.031 ± 0.032	1.074 ± 0.071	<0.0001
QTp_c	1.058 ± 0.071	1.106 ± 0.096	<0.005
$ToTe_c$	1.058 ± 0.071	1.106 ± 0.096	<0.005
RTp_c	1.044 ± 0.039	1.068 ± 0.056	<0.01
STo_c	0.994 ± 0.141	0.940 ± 0.193	<0.1

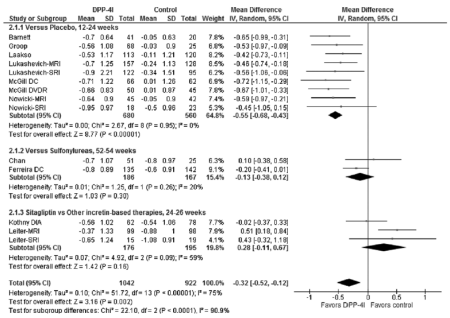
Nuryani N. Annals Biomed Eng. 2012;40:934

GENERATION: saxagliptin vs glimepiride in elderly



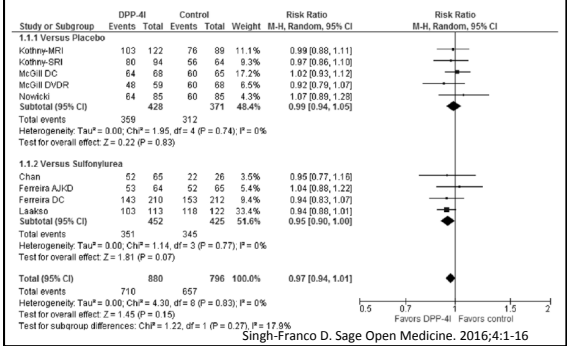
Schernthaner G. Diab Obes Metab. 2015;17:630

DPP4i in stage 3-5 CKD: Hba1c



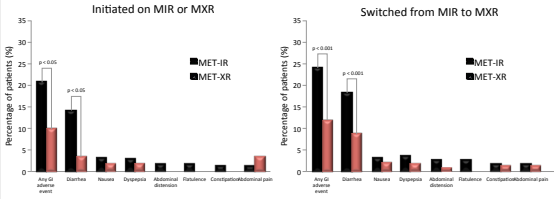
Singh-Franco D. Sage Open Medicine. 2016;4:1-16

DPP4i in stage 3-5 CKD: AEs



Singh-Franco D. Sage Open Medicine. 2016;4:1-16

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.

EFFICACY AND TOLERABILITY SHOULD BE TRANSLATED TO ADHERENCE

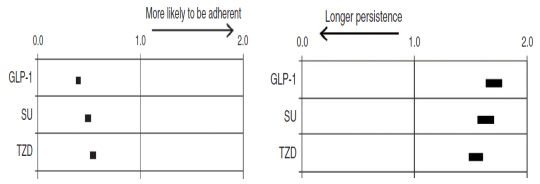
Adherence and clinical impact

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)

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

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

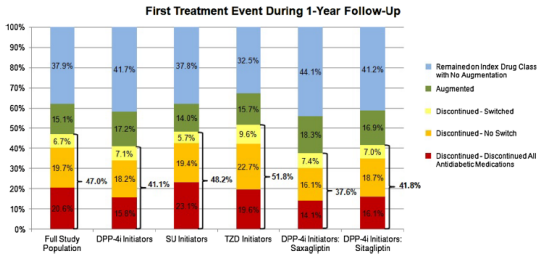
- Comparison of adherence and persistence for different antidiabetic drug classes
- Saxagliptin was the reference drug



- Curkendall SM et al. *Current Medical Research & Opinion 29;2013:1275–1286.*

EndoDrChen.com

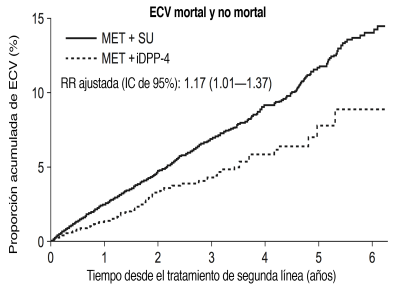
Treatment persistence



Farr AM. Adv Ther. 2014;31:1287

CARDIOVASCULAR SAFETY

iDPP-4 + metformina was associated with a lower risk of cardiovascular disease compared to SU + metformin

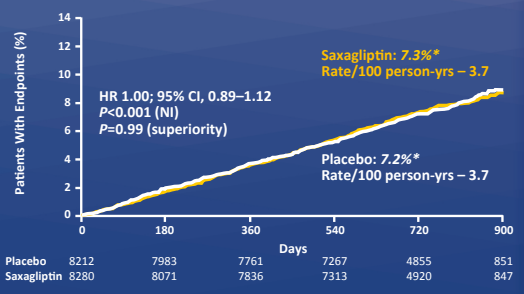


- Eriksson JW, et, al. *Diabetes Res Clin Pract.* 2016;117:39-47

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

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

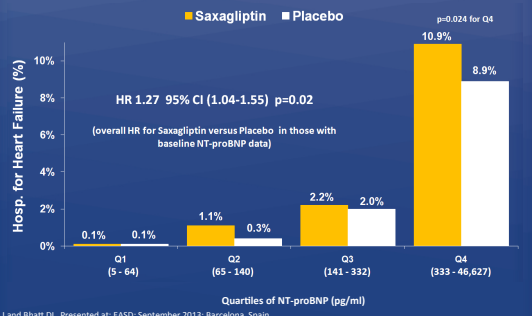
*K-M event rates are presented after 2 yrs.

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)



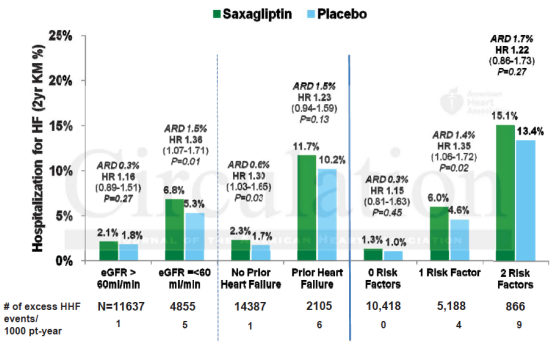
Raz I and Bhatt DL. Presented at: EASD; September 2013; Barcelona, Spain.

Bristol-Myers Squibb AstraZeneca

SAVOR and heart failure

- Risk factors:
  - Previous history of heart failure
  - GFR <60 cc/min
  - Microalbuminuria

Scirica B. Circulation. 2014; online Sep 4



Scirica B. Circulation. 2014; online Sep 4

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*

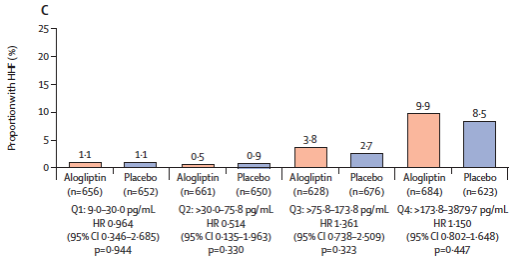
EXAMINE-análisis post hoc

	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	
$p_{interaction}$ 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	
$p_{interaction}$ 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)		1·00 (0·71-1·42)		1·76 (1·07-2·90)	
p value	0·220		0·996		0·026	
$p_{interaction}$ for treatment and history of heart failure	–	–	0·068	–	–	–

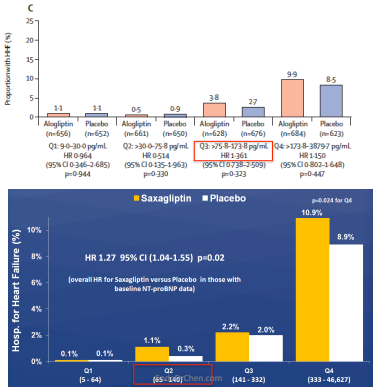
*Analysis includes all cardiovascular deaths, including those that followed heart failure that were not counted in the analysis of the composite endpoint.

Zannad F. Lancet. 2015. Online Mar 15

EXAMINE – post hoc analysis

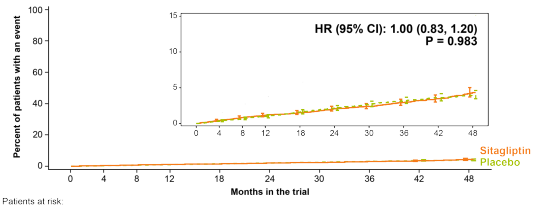


Zannad F. Lancet. 2015. Online Mar 15



TECOS: Hospitalization for Heart Failure*

ITT Analysis



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*

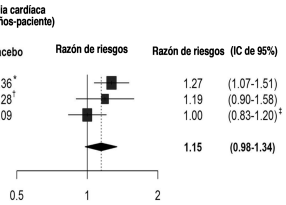
Green JB et al. NEJM 2015; DOI: 10.1056/NEJMoa1501352

Comparison

	SAVOR[1]	EXAMINE[2]	TECOS[3]
N	16492	5380	14724
Age	65.1	61	66
BMI	31.1	28.7	30.2
DM duration	10.3	7.3	11
Hba1c	8.0%	8.0%	7.3%
Caucasians	75.4%	72.5%	68%
Clinical setting	High CV risk	ACS	43% post IAM
History of HF	12.8%	27.8%	18%
Increase in hHF	0.7% (3.5-2.8%)	0.6% (3.9-3.3%)	0 (3.1-3.1%)
ACEi users	53.6%	82.5%	54%
ARB users	28.2%		28%

1. Scirica BM. N Engl J Med. 2013.
2.Zannad F. Lancet. 2015. Online Mar 15
3. Bethel MA. Diab Obes Metab. 2015;17:395

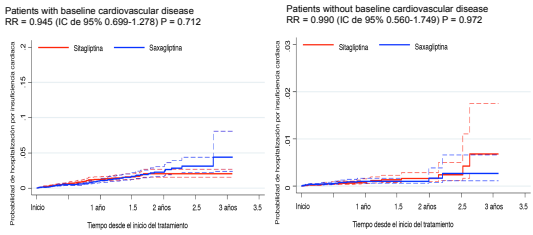
Meta analysis hospitalization for heart failure with DPP4 inhibitors



- iDPP4 = inhibidor de dipeptidil peptidasa-4; IC = insuficiencia cardíaca; TP = tasa de probabilidad
- Filion KB, *et al. Diabetes Care* 2016; 39:736-737

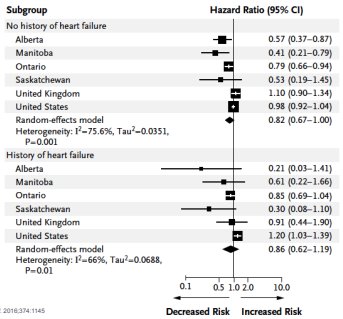
Observational study of 112,888 patients with saxagliptin and risk of hospitalization for heart failure

There was no increase in hospitalization for heart failure in patients treated with sitagliptin or saxagliptin, regardless or history of cardiovascular disease



- Fu et. al. *Diabetes Care*. 2016;29:726-734

CNODES



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

CNODES

Treatment†	Hospitalization for Heart Failure: Case Patients (N=23,205)	Hospitalization for Heart Failure: Controls (N=435,777)	Adjusted Hazard Ratio (95% CI)‡	I^2§
	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

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 aloglipitn

Pathophysiology of increased heart failure

- NPY and PYY are peptides that are metabolized by DPP4
- They stimulate Y1 receptors that increase BP and number of cardiac fibroblasts
- In animal models they have shown an increase in cardiac fibrosis

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 excretion	13%	4.5%	22%	13%	85%
Proportion excreted unchanged	79%	23%	24%	95%	~ 90%
Substrate for CYP3A4/5	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

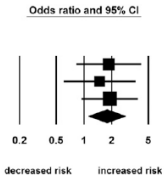
PANCREATIC SAFETY

Pancreatitis

- SAVOR, EXAMINE and TECOS evaluated prospectively and in a predefined manner the incidence of pancreatitis
- EMA and FDA issue an statement that there was no increase in risk of pancreatitis
- There is not enough data regarding pancreatic cancer

Pancreatitis and gliptins

Study name	Pancreatitis / Total		Statistics for each study			
	Gliptin	Placebo	Odds ratio	Lower limit	Upper limit	p-Value
SAVOR	17 / 8280	9 / 8212	1.875	0.835	4.209	0.128
EXAMINE	12 / 2701	8 / 2679	1.490	0.608	3.651	0.383
TECOS	23 / 7257	12 / 7266	1.922	0.956	3.865	0.067
TOTAL	52 / 18238	29 / 18157	1.786	1.133	2.816	0.013



Tkác I. Diabetes Care. Early online Sep 22

Conclusions

- DPP4 inhibitors are a very homogeneous class with small differences between agents
- Saxagliptin/metformin XR is the only formulation that may be given once daily
- DPP4 inhibitors may have some additional benefits in kidney and liver
- DPP4 inhibitors must be used with caution in patients with a prior history of heart failure, kidney disease or microalbuminuria

Questions…
chenku2409@gmail.com
EndoDrChen.com