CVOT: quiénes, por qué y cuándo?

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

EndoDrChen.com

Agenda

- Por qué es necesario?
- Diferencia entre estudios por metas de Hba1c y agentes específicos
- Evidencia más reciente en seguridad cardiovascular
  - Inhibidores de DPP-4
  - Análogos de GLP-1
  - Inhibidores de SGLT-2
- Cuáles son estos mecanismos?

EndoDrChen.com

METAS DE HBA1C E IMPACTO CARDIOVASCULAR

EndoDrChen.com

Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials

Study	Microvasc		CVD		Mortality	
UKPDS	↓	↓	↔	↓	↔	↓
DCCT / EDIC*	↓	↓	↔	↓	↔	↔
ACCORD	↓		↔		↑	
ADVANCE	↓		↔		↔	
VADT	↓		↔		↔	

Initial Trial

Long Term Follow-up

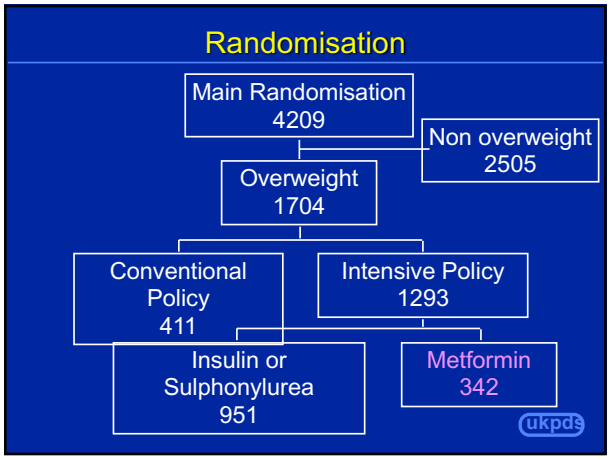
* in T1DM

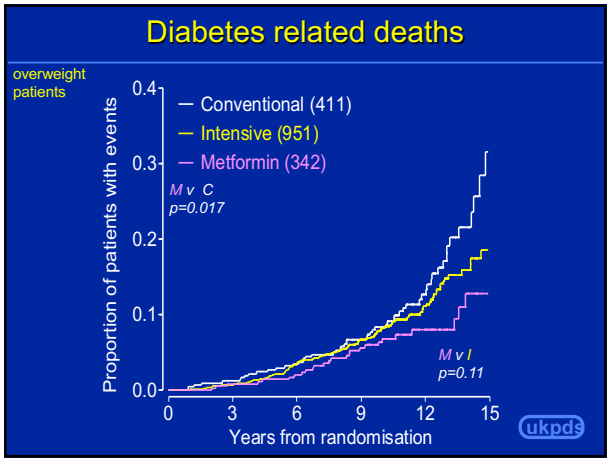
UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:854.
Holman RR et al. *N Engl J Med*. 2008;359:1577. DCCT Research Group. N Engl J Med 1993;329:977.
Nathan DM et al. *N Engl J Med*. 2005;353:2643. Gerstein HC et al. *N Engl J Med*. 2008;358:2545.
Patel A et al. N Engl J Med 2008;358:2560. Duckworth W et al. N Engl J Med 2009;360:129. (erratum: Moritz T. *N Engl J Med* 2009;361:1024)

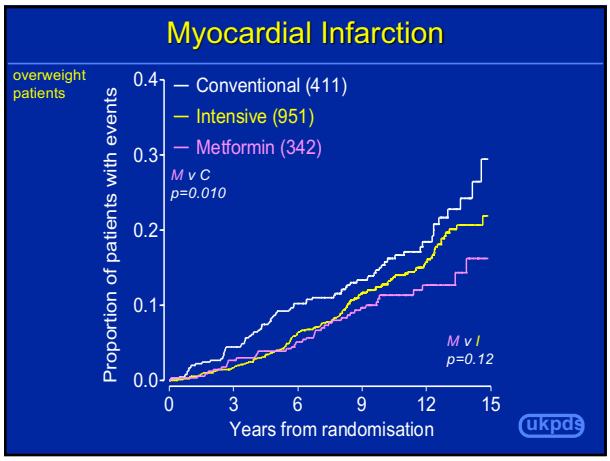
EndoDrChen.com

EVALUACIÓN DE AGENTES ESPECÍFICOS

EndoDrChen.com

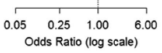

Randomisation
Main Randomisation
4209
Non overweight
2505
Overweight
1704
Conventional
Policy
411
Intensive Policy
1293
Insulin or
Sulphonylurea
951
Metformin
342
ukpds


Diabetes related deaths
overweight
patients
Proportion of patients with events
0.4
0.3
0.2
0.1
0.0
Conventional (411)
Intensive (951)
Metformin (342)
M v C
p=0.017
M v I
p=0.11
0
3
6
9
12
15
Years from randomisation
ukpds


Myocardial Infarction
overweight
patients
Proportion of patients with events
0.4
0.3
0.2
0.1
0.0
Conventional (411)
Intensive (951)
Metformin (342)
M v C
p=0.010
M v I
p=0.12
0
3
6
9
12
15
Years from randomisation
ukpds

Metanálisis: mortalidad CV

Author(s) and Year	SU alive (N)	SU deaths (N)	Non-SU alive (N)	Non-SU deaths (N)	Odds Ratios [95% CI]
Evans et al., 2006	5308	373	2248	38	4.16 [2.97 , 5.83]
Johnson et al., 2005	2899	320	862	61	1.56 [1.17 , 2.07]
Schramm et al., 2011	57757	3942	42513	827	3.51 [3.25 , 3.79]
Schramm et al., 2011	5278	961	2737	169	2.95 [2.49 , 3.49]
Sillars et al., 2010	396	137	503	81	2.15 [1.58 , 2.91]
RE Model					2.72 [1.95 , 3.79]

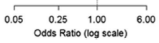


Forst T. Diabetes Vasc Dis Res. 2013;10:302

Metanálisis: mortalidad total

Author(s) and Year	SU alive (N)	SU deaths (N)	Non-SU alive (N)	Non-SU deaths (N)	Odds Ratios [95% CI]
Eurich et al., 2005	958	667	139	69	1.40 [1.03 , 1.90]
Evans et al., 200					.09 , 4.67]
Fisman et al., 20					.30 , 1.86]
Gosmanova et a					.85 , 1.40]
Gulliford & Latin					.04 , 2.90]
Hsiao et al., 201					.92 , 1.57]
Kahler et al., 20					.13 , 1.51]
Meier & Deifuss,					.38 , 1.78]
Pantalone et al.,					.12 , 3.82]
Roussel et al., 2					.39 , 2.03]
Schramm et al., 2011	54683	7016	41792	1548	3.46 [3.27 , 3.67]
Schramm et al., 2011	5033	1206	2693	213	3.03 [2.60 , 3.53]
Sillars et al., 2010	289	244	398	186	1.81 [1.42 , 2.30]
RE Model					1.92 [1.48 , 2.49]

Casi todos los estudios incluidos son cohortes y casos controles, por lo que la población incluida es heterogénea! Sigue siendo difícil sacar conclusiones al respecto



Forst T. Diabetes Vasc Dis Res. 2013;10:302

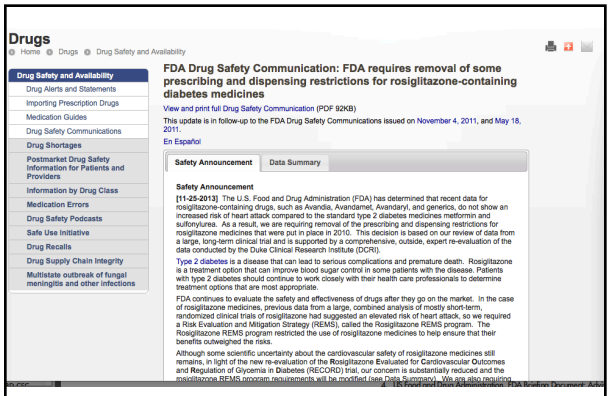
JUSTIFICACIÓN DE LOS ESTUDIOS: POR QUÉ CADA VEZ HAY MÁS?

EndoDrChen.com

Revaluación de los datos de RECORD

	Rosiglitazone	Metformin/sulfonylurea	HR (95% CI)
DCRI CEC results (original definitions)			
CV (or unknown cause) death, MI, or stroke	181 (8.3%)	188 (8.4%)	0.95 (0.78-1.17)
CV (or unknown cause) death	88 (4.0%)	96 (4.3%)	0.90 (0.68-1.21)
MI	68 (3.1%)	60 (2.7%)	1.13 (0.80-1.59)
Stroke	50 (2.3%)	63 (2.8%)	0.79 (0.54-1.14)
All death	139 (6.3%)	160 (7.2%)	0.86 (0.68-1.08)
Original RECORD CEC results (original definitions)			
CV (or unknown cause) death, MI, or stroke	154 (6.9%)	165 (7.4%)	0.93 (0.74-1.15)
CV (or unknown cause) death	60 (2.7%)	71 (3.2%)	0.84 (0.59-1.18)
MI	64 (2.9%)	56 (2.5%)	1.14 (0.80-1.63)
Stroke	46 (2.1%)	63 (2.8%)	0.72 (0.49-1.06)
All death	136 (6.1%)	157 (7.0%)	0.86 (0.68-1.08)

Mahaffey KW. Am Heart J. 2013;166:240



Drugs

Home › Drugs › Drug Safety and Availability

- Drug Safety and Availability
- Drug Alerts and Statements
- Importing Prescription Drugs
- Medication Guides
- Drug Safety Communications
- Drug Shortages
- Postmarket Drug Safety Information for Patients and Providers
- Information by Drug Class
- Medication Errors
- Drug Safety Podcasts
- Safe Use Initiative
- Drug Recalls
- Drug Supply Chain Integrity
- Multistate outbreak of fungal meningitis and other infections

FDA Drug Safety Communication: FDA requires removal of some prescribing and dispensing restrictions for rosiglitazone-containing diabetes medicines

View and print full Drug Safety Communication (PDF 92KB)

This update is in follow-up to the FDA Drug Safety Communications issued on November 4, 2011, and May 18, 2011.

En Español

Safety Announcement | Data Summary

Safety Announcement

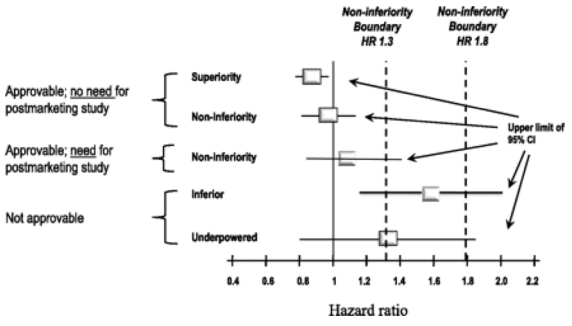
[11-25-2013] The U.S. Food and Drug Administration (FDA) has determined that recent data for rosiglitazone-containing drugs, such as Avandia, Avandamet, Avandaryl, and generics, do not show an increased risk of heart attack compared to the standard type 2 diabetes medicines metformin and sulfonylurea. As a result, we are requiring removal of the prescribing and dispensing restrictions for rosiglitazone medicines that were put in place in 2010. This decision is based on our review of data from a large, long-term clinical trial and is supported by a comprehensive, outside, expert re-evaluation of the data conducted by the Duke Clinical Research Institute (DCRI).

Type 2 diabetes is a disease that can lead to serious complications and premature death. Rosiglitazone is a treatment option that can improve blood sugar control in some patients with the disease. Patients with type 2 diabetes should continue to work closely with their health care professionals to determine treatment options that are most appropriate.

FDA continues to evaluate the safety and effectiveness of drugs after they go on the market. In the case of rosiglitazone medicines, previous data from a large, combined analysis of mostly short-term, randomized clinical trials of rosiglitazone had suggested an elevated risk of heart attack, so we required a Risk Evaluation and Mitigation Strategy (REMS), called the Rosiglitazone REMS program. The Rosiglitazone REMS program restricted the use of rosiglitazone medicines to help ensure that their benefits outweighed the risks.

Although some scientific uncertainty about the cardiovascular safety of rosiglitazone medicines still remains, in light of the new re-evaluation of the **R**osiglitazone **E**valuated for **C**ardiovascular **O**utcomes and **R**egulation of **G**lycemia in **D**iabetes (RECORD) trial, our concern is substantially reduced and the rosiglitazone REMS program requirements will be modified (see Data Summary). We are also requiring

Requerimientos de seguridad cardiovascular por FDA

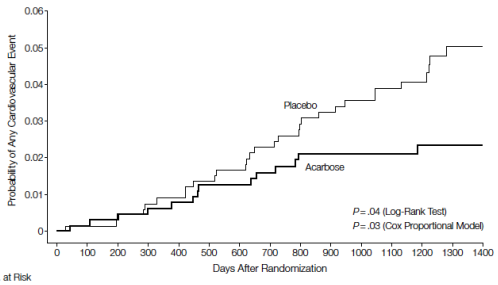


ESTUDIOS CON DESENLACES CARDIOVASCULARES

EndoDrChen.com

EL RETO EN INTERPRETAR SUBGRUPOS O ANÁLISIS POST HOC: ACARBOSA

Acarbosa: sobrevida libre de enfermedad cardiovascular

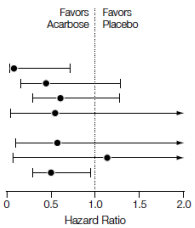


No. at Risk														
Placebo	686	675	667	658	643	638	633	627	615	611	604	519	424	332	232
Acarbose	682	659	635	622	608	601	596	590	577	567	558	473	376	286	203

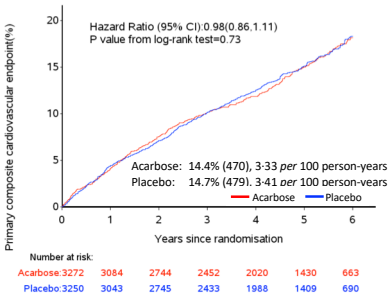
Chiasson JL. JAMA. 2003;290:486

STOP-NIDDM

	No. Experiencing Event: Acarbose (n=682)	Placebo (n=686)	Hazard Ratio (95% CI)	P Value
Coronary Heart Disease				
Myocardial Infarction	1	12	0.09 (0.01-0.72)	.02
Angina	5	12	0.45 (0.16-1.28)	.13
Revascularization Procedures	11	20	0.61 (0.29-1.26)	.18
Cardiovascular Death	1	2	0.55 (0.05-6.11)	.63
Congestive Heart Failure*	0	2	---	---
Cerebrovascular Event or Stroke	2	4	0.56 (0.10-3.07)	.51
Peripheral Vascular Disease	1	1	1.14 (0.07-18.30)	.93
Any Cardiovascular Event	15	32	0.51 (0.28-0.95)	.03



Chiasson JL. JAMA. 2003;290:486



Study Design

Multicenter, randomized, active-controlled, single-blind CV outcome trial (NCT00700856)

Screening period	Randomized, double-blind short-term treatment period

- T2DM for at least 2 year,
- Age 50 to 75 years,
- On metformin ≥2g/day, HbA1c ≥ 7.0% and ≤ 9.0% BMI 20-45 kg/m²
- No acute CV events in the past 6 mo

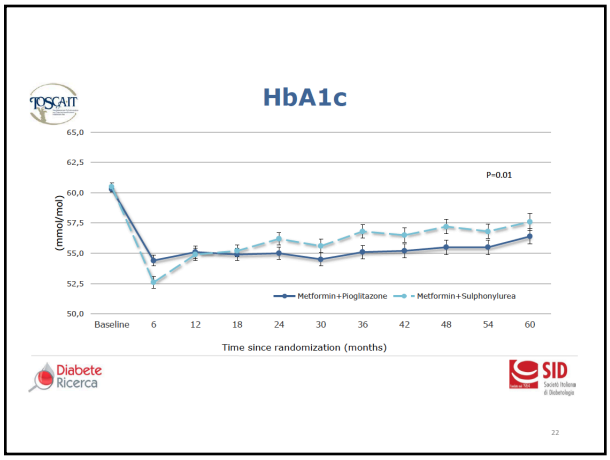
Metformin + Pioglitazone

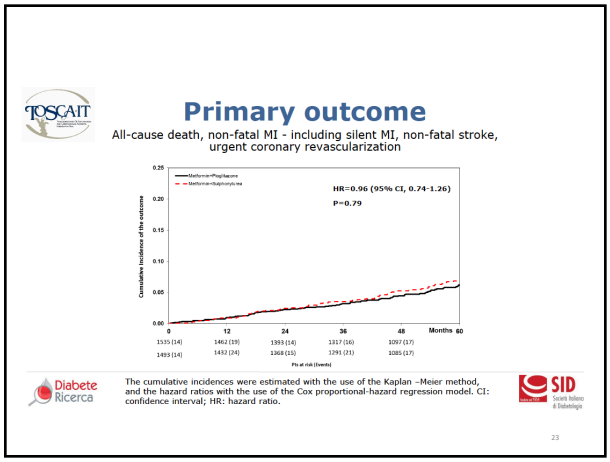
Metformin + Sulphonylureas

0 — EoT

HbA1c, glycated haemoglobin; BMI, body mass index; DAPA, dapagliflozin; FPG, fasting plasma glucose; MET, metformin; SAXA, saxagliptin; SITA, sitagliptin

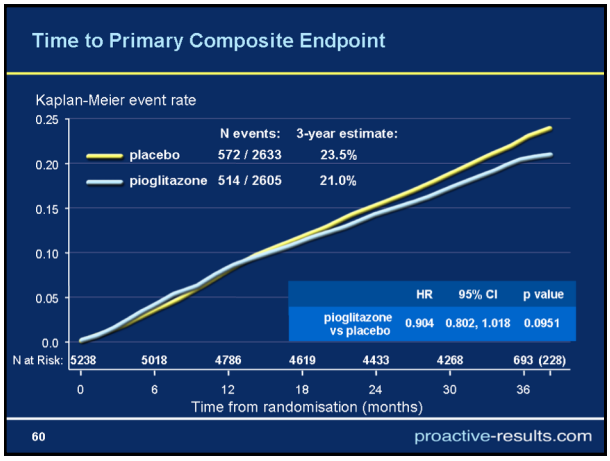
21

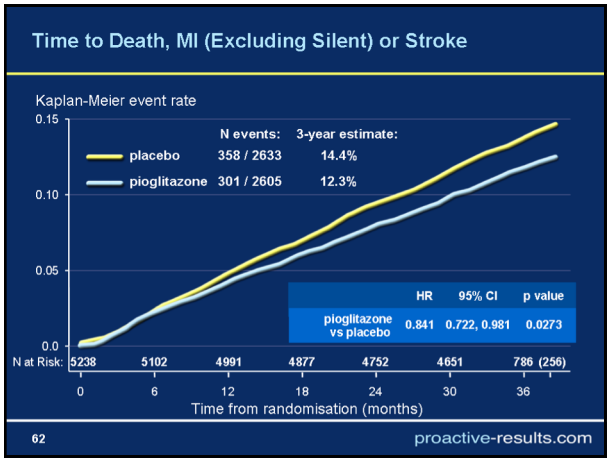


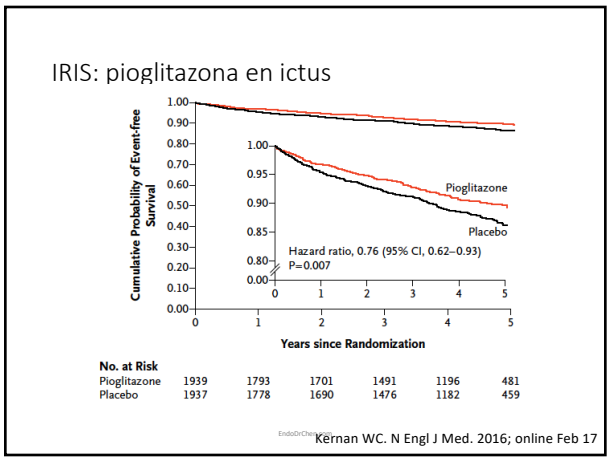


PIOGLITAZONA

24


Time to Primary Composite Endpoint
Kaplan-Meier event rate
N events: 3-year estimate:
placebo 572 / 2633 23.5%
pioglitazone 514 / 2605 21.0%
HR 95% CI p value
pioglitazone vs placebo 0.904 0.802, 1.018 0.0951
0.25
0.20
0.15
0.10
0.05
0.0
N at Risk: 5238 5018 4786 4619 4433 4268 693 (228)
0 6 12 18 24 30 36
Time from randomisation (months)
60
proactive-results.com

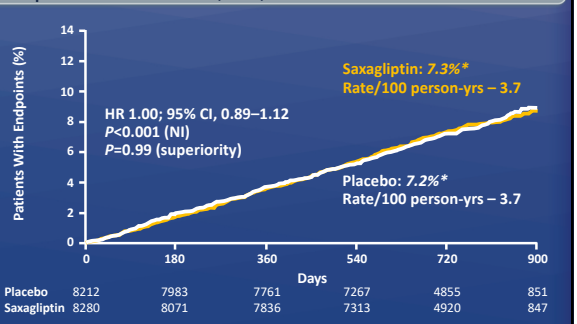

Time to Death, MI (Excluding Silent) or Stroke
Kaplan-Meier event rate
N events: 3-year estimate:
placebo 358 / 2633 14.4%
pioglitazone 301 / 2605 12.3%
HR 95% CI p value
pioglitazone vs placebo 0.841 0.722, 0.981 0.0273
0.15
0.10
0.05
0.0
N at Risk: 5238 5102 4991 4877 4752 4651 786 (256)
0 6 12 18 24 30 36
Time from randomisation (months)
62
proactive-results.com


IRIS: pioglitazona en ictus
Cumulative Probability of Event-free Survival
Pioglitazone
Placebo
Hazard ratio, 0.76 (95% CI, 0.62–0.93)
P=0.007
Years since Randomization
No. at Risk
Pioglitazone 1939 1793 1701 1491 1196 481
Placebo 1937 1778 1690 1476 1182 459
Kernan WC. N Engl J Med. 2016; online Feb 17

INHIBIDORES DE DPP-4

EndoDrChen.com

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



*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.

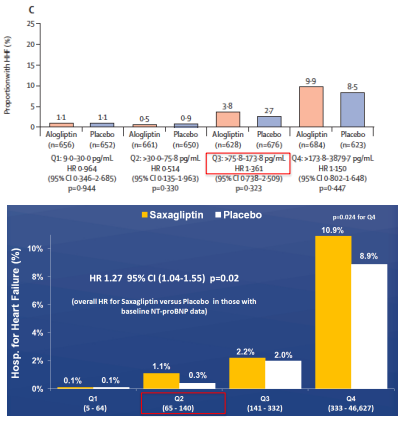
Scirica BM, et al. *N Engl J Med.* 2013.10.1056/NEJMoa1307684.
Bristol-Myers Squibb AstraZeneca

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	--	--	--

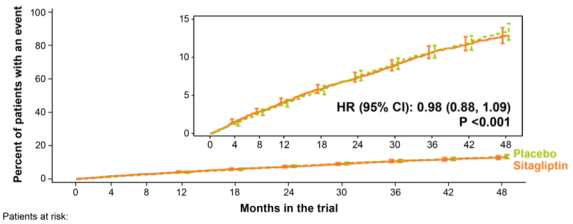
*Analysis includes all cardiovascular deaths, including those that followed heart failure that were not counted in the analysis of the composite endpoint.

Zannad F. Lancet. 2015. Online Mar 15



Primary Composite Cardiovascular Outcome*

PP Analysis for Non-inferiority



Patients at risk:

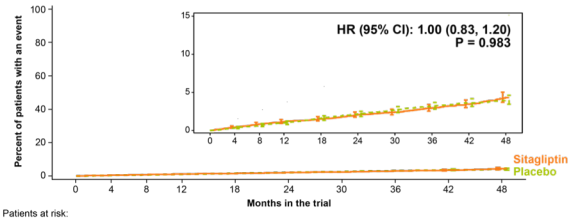
Sitagliptin	7,257	6,857	6,519	6,275	5,931	5,616	3,919	2,896	1,748	1,028
Placebo	7,266	6,846	6,449	6,165	5,803	5,421	3,780	2,743	1,690	1,005

** CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina*

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

Hospitalization for Heart Failure*

ITT Analysis

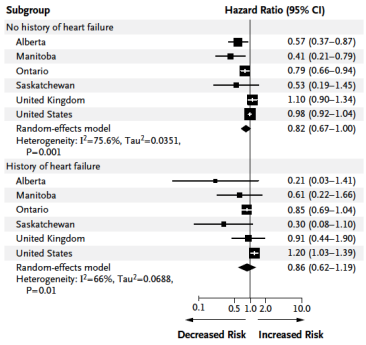


Patients at risk:										
Sitagliptin	7,332	7,189	7,036	6,917	6,780	6,619	4,728	3,515	2,175	1,324
Placebo	7,339	7,204	7,025	6,903	6,712	6,549	4,599	3,443	2,131	1,315

** Adjusted for history of heart failure at baseline*

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

CNODES



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

ANÁLOGOS GLP-1

EndoDrChen.com

ADA 2015 Scientific Sessions

ELIXA: Cardiovascular Outcomes for Lixisenatide Vs Placebo

No increased risk for lixisenatide vs placebo for:

	Lixisenatide	Placebo
Primary composite outcome: CV death, nonfatal MI, nonfatal stroke, hospitalization for UA	13.4%	13.2%
	HR=1.02 (95% CI: 0.89-1.17)	
Primary outcome plus hospitalization for heart failure	HR=0.97 (95% CI: 0.85-1.10)	
Hospitalization for heart failure	HR=0.96 (95% CI: 0.75-1.23)	
All-cause mortality	HR=0.94 (95% CI: 0.78-1.13)	

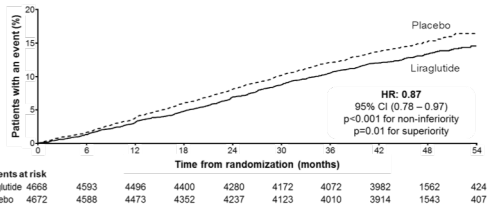
ELIXA=Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With Lixisenatide
HR=hazard ratio

EndoDrChen.com

Pfeffer MA, et al. Presented at the American Diabetes Association 75th Scientific Sessions. June 5-9, 2015, Boston, Massachusetts.

Primary outcome

CV death, non-fatal myocardial infarction, or non-fatal stroke

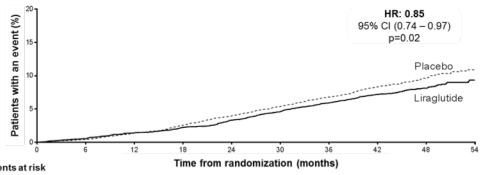


Patients at risk										
Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; CV: cardiovascular; HR: hazard ratio.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-5Y24. June 13 2016, New Orleans, LA, USA.

All-cause death

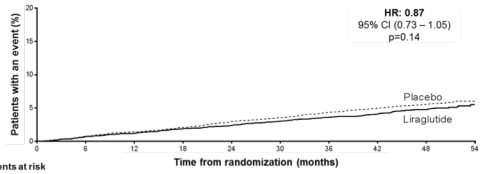


Patients at risk										
Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4268	1709	465

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; HR: hazard ratio.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-5Y24. June 13 2016, New Orleans, LA, USA.

Hospitalization for heart failure



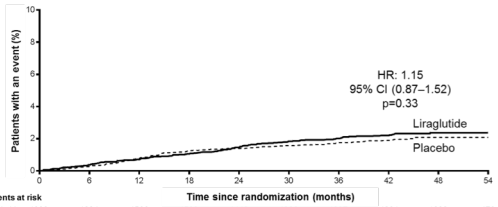
Patients at risk										
Liraglutide	4668	4612	4550	4483	4414	4337	4258	4185	1662	467
Placebo	4672	4612	4540	4464	4372	4288	4187	4107	1647	442

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; HR: hazard ratio.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-5Y24. June 13 2016, New Orleans, LA, USA.

Time to first eye event

Photocoagulation or treatment with intravitreal agents, vitreous hemorrhage or blindness



Patients at risk										
Liraglutide	4668	4624	4566	4509	4442	4366	4297	4231	1689	473
Placebo	4672	4636	4565	4489	4417	4339	4264	4188	1681	454

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; HR: hazard ratio.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-5Y24. June 13 2016, New Orleans, LA, USA.

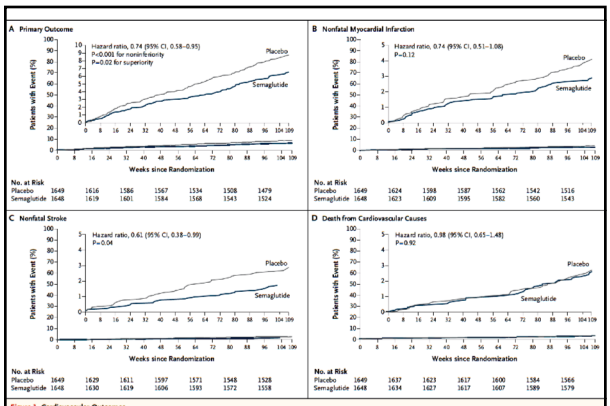


Figure 1. Cardiovascular Outcomes.

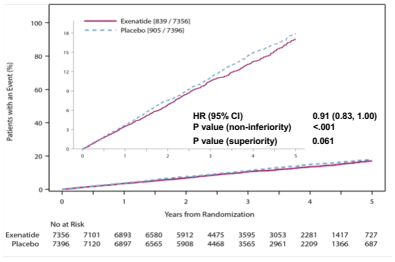
Shown are Kaplan–Meier plots of the primary outcome (a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) (Panel A), nonfatal myocardial infarction (Panel B), nonfatal stroke (Panel C), and death from cardiovascular causes (Panel D). The trial included a planned observation period of 109 weeks for all patients (a 104-week treatment period with a 5-week follow-up period). In Panel C, there were no events in the semaglutide group after week 104. Insets show the same data on an expanded y axis.

Table 2. Primary and Secondary Cardiovascular and Microvascular Outcomes.

Outcome	Semaglutide (N = 1648)		Placebo (N = 1649)		Hazard Ratio (95% CI)*	P Value
	no. (%)	*no./100 person-yr*	*no. (%)*	*no./100 person-yr*		
Primary composite outcome†	108 (6.6)	3.24	146 (8.9)	4.44	0.74 (0.58–0.95)	<0.001 for noninferiority; 0.02 for superiority
Expanded composite outcome‡	199 (12.1)	6.17	264 (16.0)	8.36	0.74 (0.62–0.89)	0.002
All-cause death, nonfatal myocardial infarction, or nonfatal stroke	122 (7.4)	3.66	158 (9.6)	4.81	0.77 (0.61–0.97)	0.03
Death						
From any cause	62 (3.8)	1.82	60 (3.6)	1.76	1.05 (0.74–1.50)	0.79
From cardiovascular cause	44 (2.7)	1.29	46 (2.8)	1.35	0.98 (0.65–1.48)	0.92
Nonfatal myocardial infarction	47 (2.9)	1.40	64 (3.9)	1.92	0.74 (0.51–1.08)	0.12
Nonfatal stroke	27 (1.6)	0.80	44 (2.7)	1.31	0.61 (0.38–0.99)	0.04
Hospitalization for unstable angina pectoris	22 (1.3)	0.65	27 (1.6)	0.80	0.82 (0.47–1.44)	0.49
Revascularization	83 (5.0)	2.50	126 (7.6)	3.85	0.65 (0.50–0.86)	0.003
Hospitalization for heart failure	59 (3.6)	1.76	54 (3.3)	1.61	1.11 (0.77–1.61)	0.57
Retinopathy complications§	50 (3.0)	1.49	29 (1.8)	0.86	1.76 (1.11–2.78)	0.02
New or worsening nephropathy¶	62 (3.8)	1.86	100 (6.1)	3.06	0.64 (0.46–0.88)	0.005

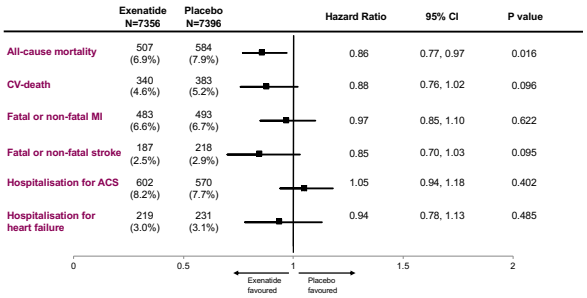
* Hazard ratios and P values were estimated with the use of a Cox proportional-hazards model with the study treatments as fixed factors and stratified according to all combinations of stratification factors used in the randomization.
† The primary composite outcome was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.
‡ The expanded composite outcome included death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, revascularization (coronary or peripheral), and hospitalization for unstable angina or heart failure.
§ Retinopathy complications include vitreous hemorrhage, onset of diabetes-related blindness, and the need for treatment with an intravitreal agent or retinal photocoagulation.
¶ New or worsening nephropathy includes persistent macroalbuminuria, persistent doubling of the serum creatinine level and a creatinine clearance of less than 45 ml per minute per 1.73 m^2 of body-surface area (according to the Modification of Diet in Renal Disease criteria), or the need for continuous renal-replacement therapy.

Primary Composite Cardiovascular Outcome
Intention-to-Treat Analysis for Non-inferiority & Superiority

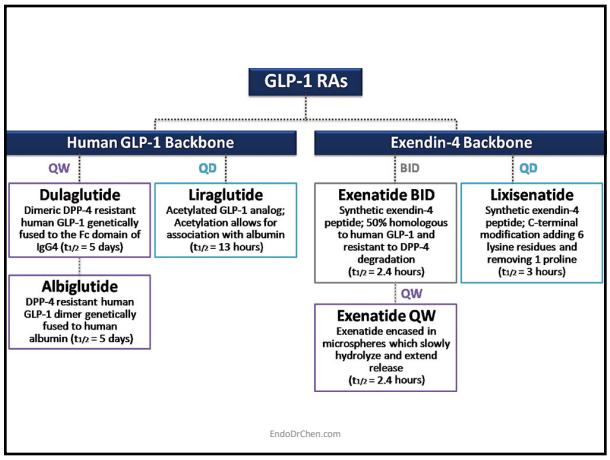


EXSCEL

Forest Plot of Secondary Endpoints (Intention-to-Treat Analysis)



EXSCEL



ANALOGOS GLP-1

- En resume…
  - No todos son iguales
  - Liraglutide y semaglutide reducen MACE, pero parece que aumentan retinopatía diabética
  - No tienen efecto sobre falla cardíaca

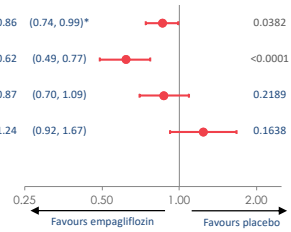
EndoDrChen.com

INHIBIDORES DE SGLT-2

EndoDrChen.com

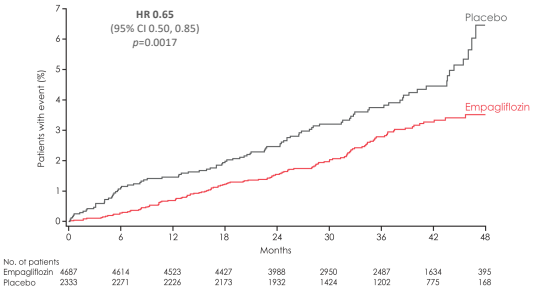
CV death, MI and stroke

	Patients with event/analysed Empagliflozin	Placebo	HR	(95% CI)	*p*-value
3-point MACE	490/4687	282/2333	0.86	(0.74, 0.99)*	0.0382
CV death	172/4687	137/2333	0.62	(0.49, 0.77)	<0.0001
Non-fatal MI	213/4687	121/2333	0.87	(0.70, 1.09)	0.2189
Non-fatal stroke	150/4687	60/2333	1.24	(0.92, 1.67)	0.1638



EndoDrChen.com

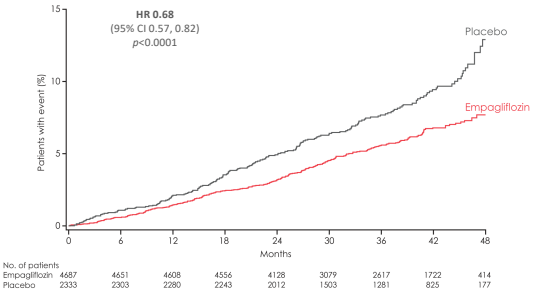
Hospitalisation for heart failure



Cumulative incidence function. HR, hazard ratio

50

All-cause mortality

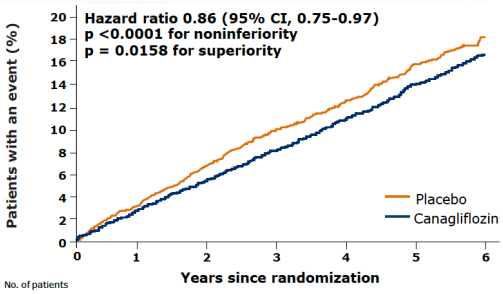


Kaplan-Meier estimate. HR, hazard ratio

51

Primary MACE Outcome

CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke



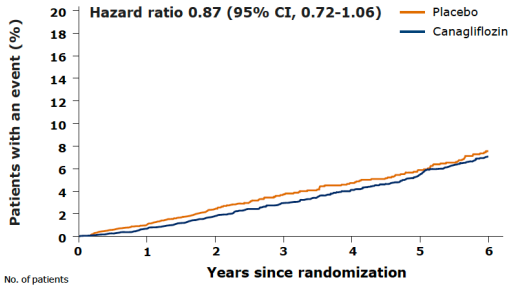
No. of patients

Placebo	4347	4153	2942	1240	1187	1120	789
Canagliflozin	5795	5566	4343	2555	2460	2363	1661

Intent-to-treat analysis

CANVAS Program

CV Death Component of Primary Outcome



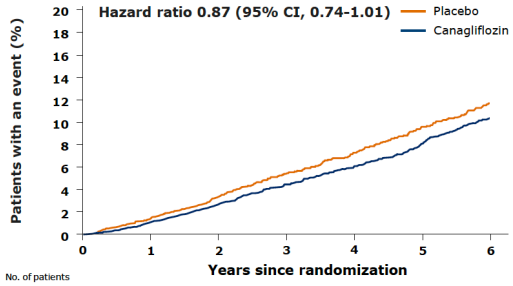
No. of patients

Placebo	4347	4279	3119	1356	1328	1292	924
Canagliflozin	5795	5723	4576	2761	2710	2651	1904

Intent-to-treat analysis

CANVAS Program

All-Cause Mortality



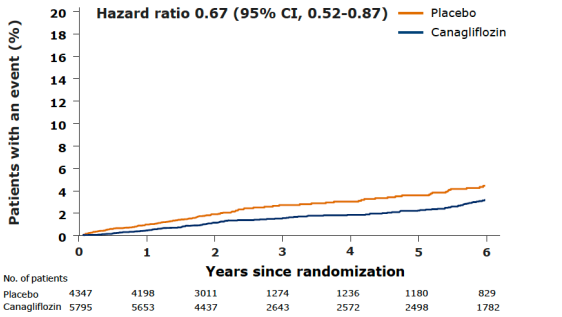
No. of patients

Placebo	4347	4279	3119	1356	1328	1292	924
Canagliflozin	5795	5723	4576	2761	2710	2651	1904

Intent-to-treat analysis

CANVAS Program

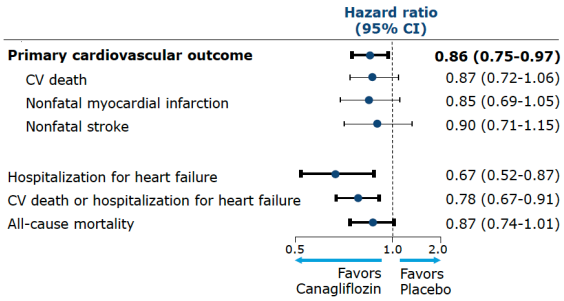
Hospitalization for Heart Failure



Intent-to-treat analysis

CANVAS Program

Summary



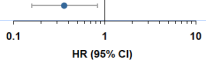
Intent-to-treat analysis

CANVAS Program

Eventos CV - dapagliflozina

Components of Endpoints

Event	Pts with Event: Dapa N=5936	Pts with Event: Control N=3403	Hazard Ratio vs. Control (95% CI)
CV Death	20 / 3825	18 / 2200	0.70 (0.36, 1.36)
MI	30 / 5244	33 / 3014	0.57 (0.34, 0.95)
Stroke	25 / 4227	18 / 2412	1.00 (0.54, 1.86)
Unstable Angina	26 / 4592	20 / 2697	0.87 (0.48, 1.59)
Unplanned Coronary Revasc	58 / 5525	55 / 3153	0.73 (0.50, 1.07)
Hosp. for Heart Failure	10 / 2576	16 / 1780	0.36 (0.16, 0.84)

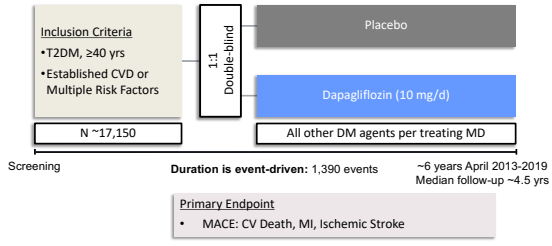


Stratified by study. Only trials with at least one positively adjudicated event included in analysis.
Cox Proportional Hazards Model.

EndoDrChen.com

CORE - 118

DECLARE - Dapagliflozin Effects on CardiovascuLAR Events



CV; cardiovascular; DM, diabetes mellitus; MI, myocardial infarction; T2DM, type 2 diabetes mellitus.
https://clinicaltrials.gov/ct2/show/NCT01730534
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM379659.pdf

58

DECLARE: Primary and Secondary Outcomes

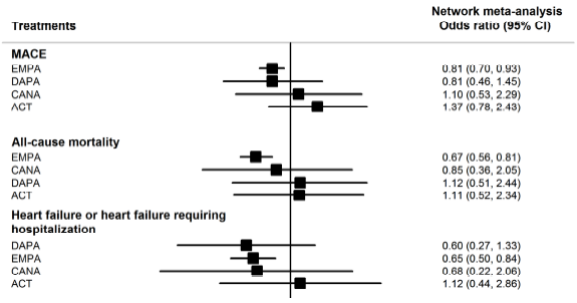
Primary Outcome

- Time to first event included in the composite endpoint of CV death, MI or ischemic stroke

Secondary Outcomes

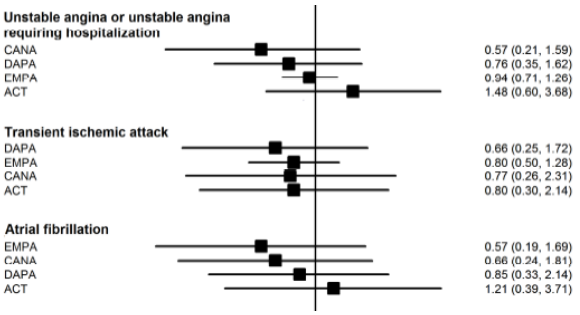
- Time to first event of:
  - Hospitalization for congestive heart failure
  - The composite endpoint of CV death, MI, ischemic stroke, hospitalization for HF, hospitalization for unstable angina or hospitalization for any revascularization
- Time to all-cause mortality
- Body weight from baseline

Metanálisis cardiovascular



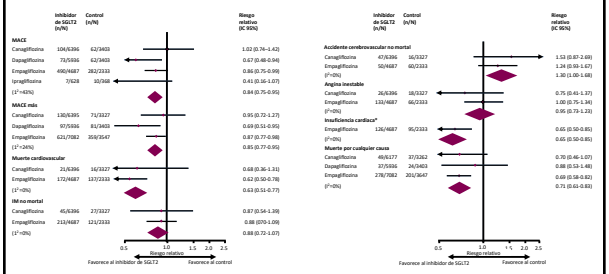
Tang H. Am J Cardiol. 2016; early online.

Metanálisis cardiovascular



Tang H. Am J Cardiol. 2016; early online.

Los datos del metaanálisis sugieren una protección neta contra eventos cardiovasculares con inhibidores de SGLT-2

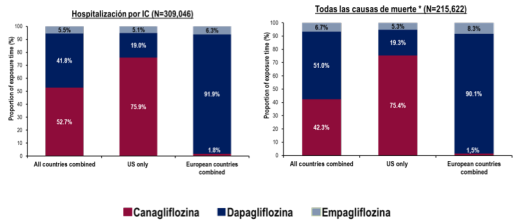


Wu JH, et al. *Lancet Diabetes Endocrinol* 2016;4:411–9

EVIDENCIAS EN LA VIDA REAL

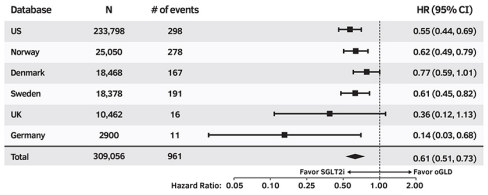
EndoDrChen.com

Contribución de los iSGLT2



*Data shown are for all-cause death; data for HHF or all-cause death are similar

Hospitalización por Insuficiencia Cardiaca Punto final primario



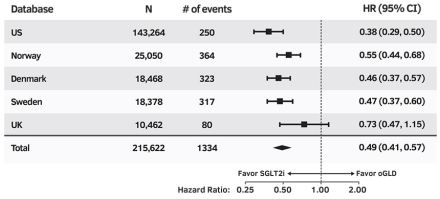
Database	N	# of events	HR (95% CI)
US	233,798	298	0.55 (0.44, 0.69)
Norway	25,050	278	0.62 (0.49, 0.79)
Denmark	18,468	167	0.77 (0.59, 1.01)
Sweden	18,378	191	0.61 (0.45, 0.82)
UK	10,462	16	0.36 (0.12, 1.13)
Germany	2900	11	0.14 (0.03, 0.68)
Total	309,056	961	0.61 (0.51, 0.73)

Para el punto final primario de hospitalización por insuficiencia cardíaca hubo con el uso desde el inicio de iSGLT2 de un 39% (hazard ratio [HR], 0.61; p < 0.001) reducción significativa .

Heterogeneity p-value: 0.17

P-value for SGLT2 inhibitor vs other glucose-lowering drug: <0.001

Todas las causas de muerte – Punto final secundario



Database	N	# of events	HR (95% CI)
US	143,264	250	0.38 (0.29, 0.50)
Norway	25,050	364	0.55 (0.44, 0.68)
Denmark	18,468	323	0.46 (0.37, 0.57)
Sweden	18,378	317	0.47 (0.37, 0.60)
UK	10,462	80	0.73 (0.47, 1.15)
Total	215,622	1334	0.49 (0.41, 0.57)

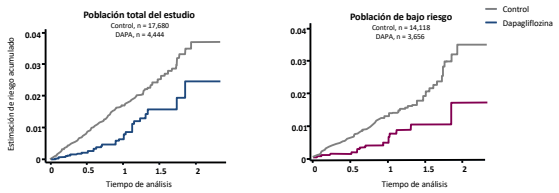
Punto final secundario de muerte por cualquier causa, los iSGLT2 también fueron asociados con una incidencia de 51% menos de muerte por cualquier causa (HR, 0.49; p < 0.001)

Heterogeneity p-value: 0.09

P-value for SGLT2i vs other glucose-lowering drug: <0.001

Estudio de la base de datos THIN del Reino Unido: Mortalidad por cualquier causa

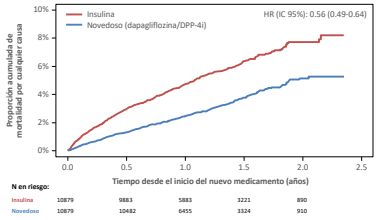
- Los datos de la vida real de un estudio de cohortes abiertas de la base de datos THIN, sugieren que la dapagliflozina puede estar asociada a una disminución de la mortalidad por cualquier causa, independientemente de la condición inicial de ECV



Toulis KA, et al. *J Clin Endocrinol Metab* 2017;[publicación electrónica previa a la impresión]

Registros nacionales suecos: Mortalidad por cualquier causa de los medicamentos hipoglucemiantes novedosos en comparación con insulina

Los medicamentos hipoglucemiantes novedosos se asociaron a un menor riesgo de mortalidad por cualquier causa en comparación con insulina



N en riesgo:

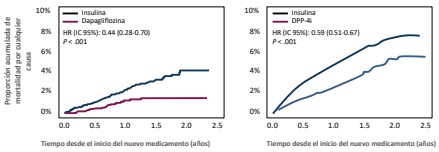
Insulina	10879	9883	5883	3221	890
Novedoso	10879	10482	6455	3324	910

Nystrõm et al. *Diabetes Obes Metab* 2017 [En impresión]
IC, intervalo de confianza; DPP-4i, inhibidor de la dipeptidil peptidasa IV; HR, cociente de riesgos instantáneos; SGLT-2i, inhibidor del cotransportador de sodio-glucosa 2

68

Registros nacionales suecos: Mortalidad por cualquier causa de dapagliflozina e inhibidores de DPP-4 en comparación con insulina

- **Dapagliflozina se asoció con un 56% menos riesgo de mortalidad por cualquier causa en comparación con insulina**
- **Los inhibidores de DPP-4 se asociaron con un 41% menos riesgo de mortalidad por cualquier causa en comparación con insulina**



Nystrõm et al. *Diabetes Obes Metab* 2017 [En impresión]
IC, intervalo de confianza; DPP-4i, inhibidor de la dipeptidil peptidasa IV; HR, cociente de riesgos instantáneos

69

CÓMO SE EXPLICA EL BENEFICIO CARDIOVASCULAR?

FDA Drug Safety Communication: FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood

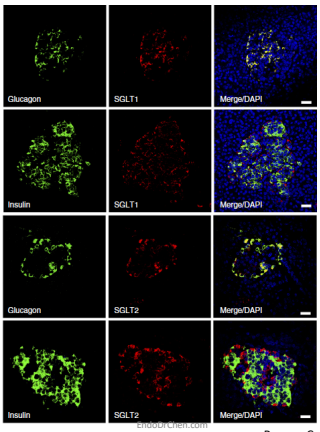
[05-15-2015]

Safety Announcement

The U.S. Food and Drug Administration (FDA) is warning that the type 2 diabetes medicines canagliflozin, dapagliflozin, and empagliflozin may lead to ketoacidosis, a serious condition where the body produces high levels of blood acids called ketones that may require hospitalization. We are continuing to investigate this safety issue and will determine whether changes are needed in the prescribing information for this class of drugs, called sodium-glucose cotransporter-2 (SGLT2) inhibitors.

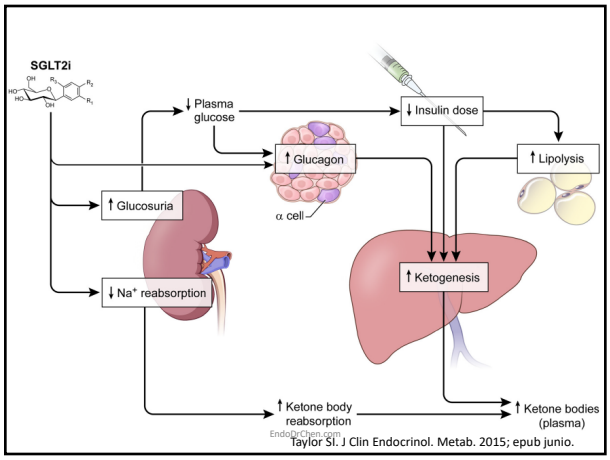
Patients should pay close attention for any signs of ketoacidosis and seek medical attention immediately if they experience symptoms such as difficulty breathing, nausea, vomiting, abdominal pain, confusion, and unusual fatigue or sleepiness. Do not stop or change your diabetes medicines without first talking to your prescriber. Health care professionals should evaluate for the presence of acidosis, including ketoacidosis, in patients experiencing these signs or symptoms; discontinue SGLT2 inhibitors if acidosis is confirmed; and take appropriate measures to correct the acidosis and monitor sugar levels.

EndoDrChen.com



EndoDrChen.com

Bonner C. Nat Med. 2015;21(5):512



Taylor SI. J Clin Endocrinol. Metab. 2015; epub junio.

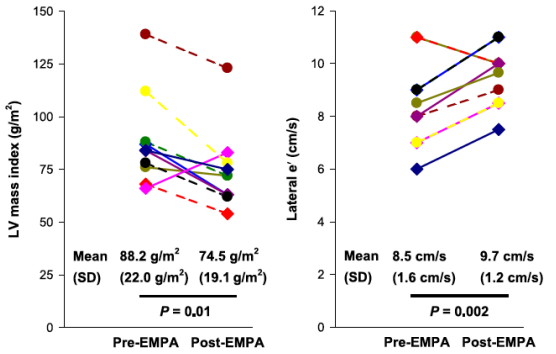
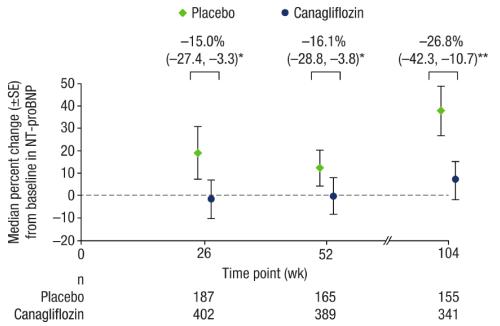
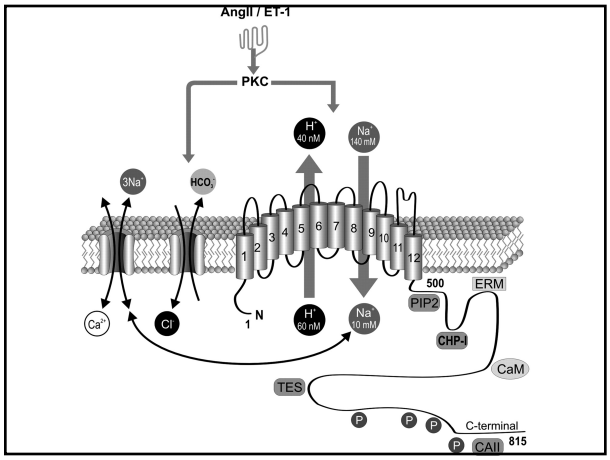


Figure 1—LV mass index and lateral e′ at baseline (Pre-EMPA) and at the 3-month follow-up (Post-EMPA). A total of 10 patients were evaluated with each patient denoted by a specific color. e′, early lateral annular tissue Doppler velocity; EMPA, empagliflozin.

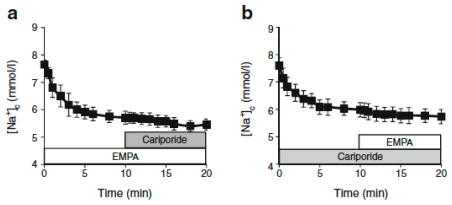
Verma S. Diabetes Care. 2016. online sep 27



Januzzi JL. JACC. 2017. Online June 8.

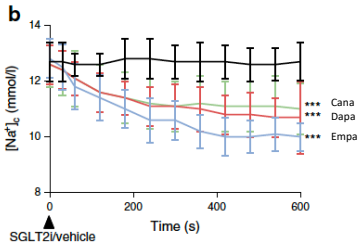


Efecto en Na^+-H^+



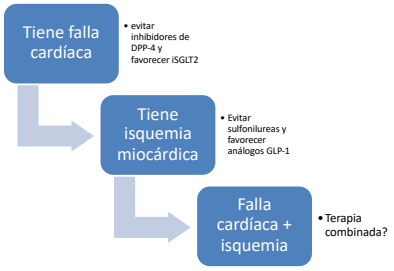
Baartscheer A. Diabetologia. 2016; online oct 16.

Bloqueo intercambiador Na^+/H^+



Uthman L. Diabetologia. Online 2 dic 2017

Cómo escoger agentes



EndoDrChen.com

Combinación análogo GLP1 + iSGLT2

- DURATION8
  - Exenatide semanal: -1.54 kg
  - Dapagliflozina: -2.19 kg
  - Exenatide semanal + dapagliflozina: -3.41 kg
- Por qué efectos menores a los esperados?
- Papel de glucagon?
- No hay estudios con desenlaces CV con combinación

EndoDrChen.com

Conclusiones

- Tenemos mejor evidencia de eficacia y seguridad de antidiabéticos
- Beneficio
  - Pioglitazona: MACE
  - iSGLT2: hospitalización por falla cardíaca, mortalidad total
  - Análogos GLP-1: MACE y mortalidad total, no todos son iguales, tener cuidado con retinopatía
- No hay datos suficientes con otras combinaciones

EndoDrChen.com

PREGUNTAS…

Puede descargar la presentación en:

www.EndoDrChen.com

chenku2409@gmail.com