Centro Cardiológico
Dr. Fernández de Soria

NOVEDADES TERAPEUTICAS EN DIABETES MELLITUS

Dr. Fdez de Soria

Centro Cardiológico-Hospital Clideba

Abril 2017

INTRODUCCION

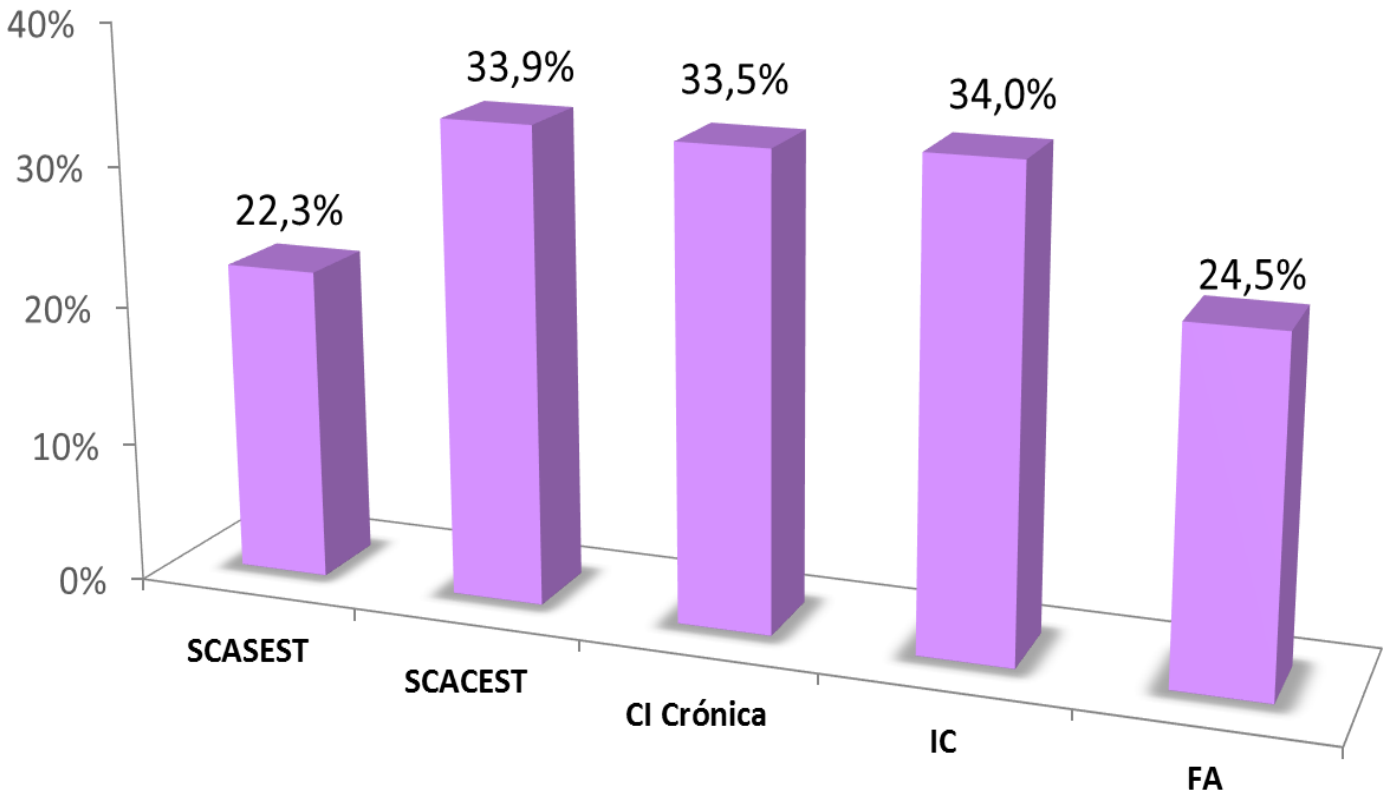
Centro Cardiológico
Dr. Fernández de Soria

- La diabetes mellitus es uno de los factores más prevalentes en los pacientes con cardiopatías en España.[1-4]
- La presencia de diabetes en sí misma aumenta el riesgo de complicaciones cardiovasculares.[5]
- El 75% de la mortalidad a largo plazo de los pacientes con diabetes es de causa cardiovascular.[6]
- La insuficiencia cardiaca y la cardiopatía isquémica son las cardiopatías con mayor morbimortalidad en los pacientes con diabetes.[5]

1. Barrabes et al. REC. 2015; 68: 98-106; 2. Zamorano et al. REC. 2014; 6: 538-544; 3. Comín-Colet et al. REC. 2014; 67: 283-293; 4. Gómez-Doblas et al. REC. 2014; 67: 259-269; 5. Abu-Assi et al. Rev Esp Cardiol. 2016; 69: 11-18; 6. Cordero et al. Am J Cardiol. 2016 (en prensa);

Prevalencia de la Diabetes Mellitus en las cardiopatías

Centro Cardiológico
Dr. Fernández de Soria



CI: Cardiopatía isquémica
IC: Insuficiencia cardíaca
FA: Fibrilación auricular
SCASEST, Síndrome coronario agudo sin elevación de ST
SCACEST: Síndrome coronario agudo con elevación del segmento ST

Barrabes et al. REC. 2015; 68: 98-106.
Zamorano et al. REC. 2014; 6: 538-544.
Comín-Colet et al. REC. 2014; 67: 283-293.
Gómez-Doblas et al. REC. 2014; 67: 259-269.

Necesidades a cubrir en el paciente DM2 con FRCV

Centro Cardiológico Dr. Fernández de Soria

- Para cubrir las necesidades en el tratamiento del paciente con DM2 con FRCV deberíamos disponer de un antidiabético que:[1]
  - pueda usarse en todas las fases de la enfermedad
  - produzca un descenso significativo de la HbA_{1c}
  - tenga un efecto sostenido
  - tenga una buena tolerabilidad
  - no induzca hipoglucemias
  - promueva la pérdida de peso
  - **Seguridad a nivel C.V.**
  - **Reduzca la morbi-mortalidad C.V.**

Centro Cardiológico
Dr. Fernández de Soria

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 14, 2007 VOL. 356 NO. 24

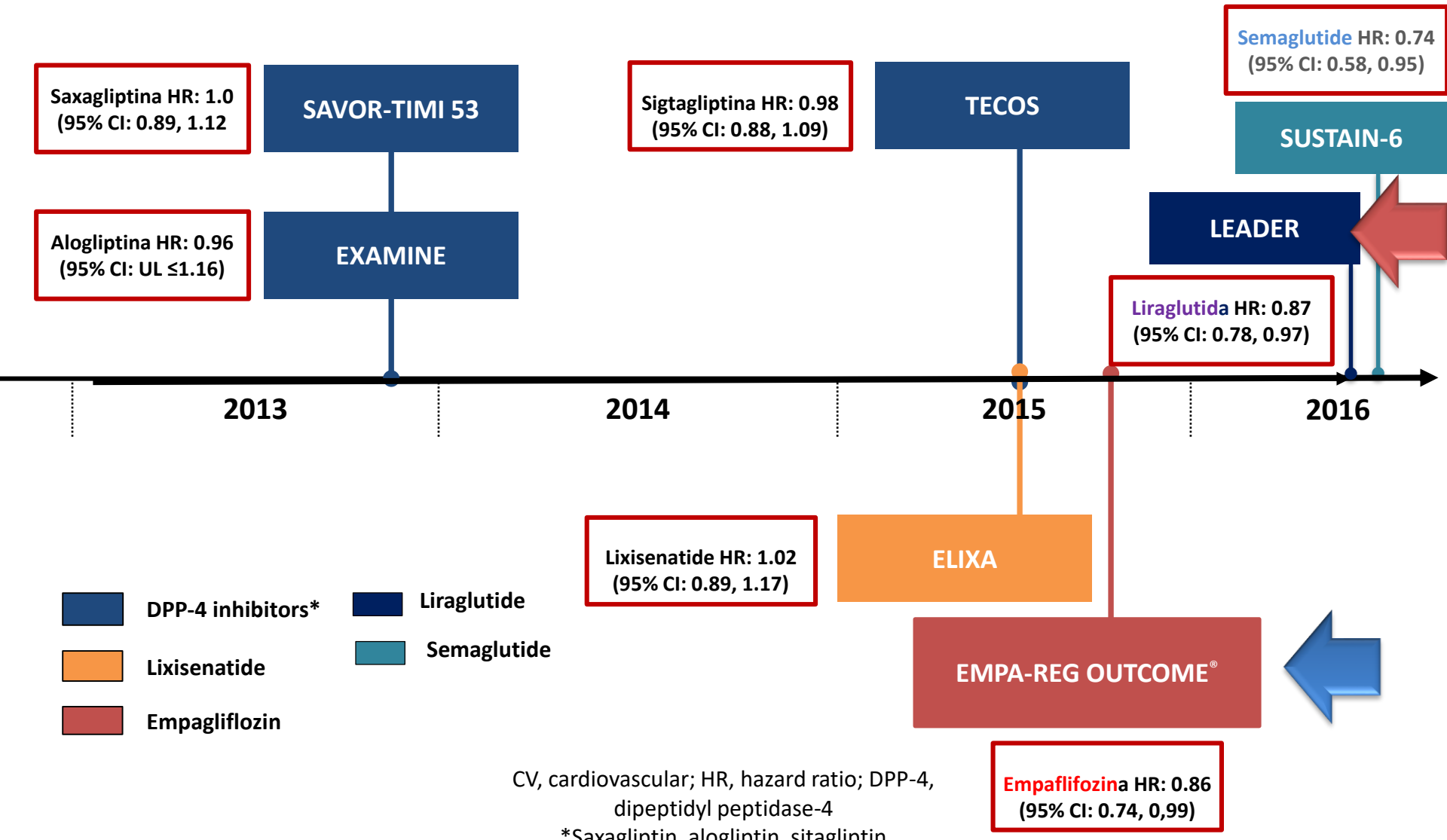
Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Seguridad a nivel Cardiovascular

Los ensayos de los nuevos agentes hipoglucemiantes han mostrado neutralidad en la variable primaria C.V.

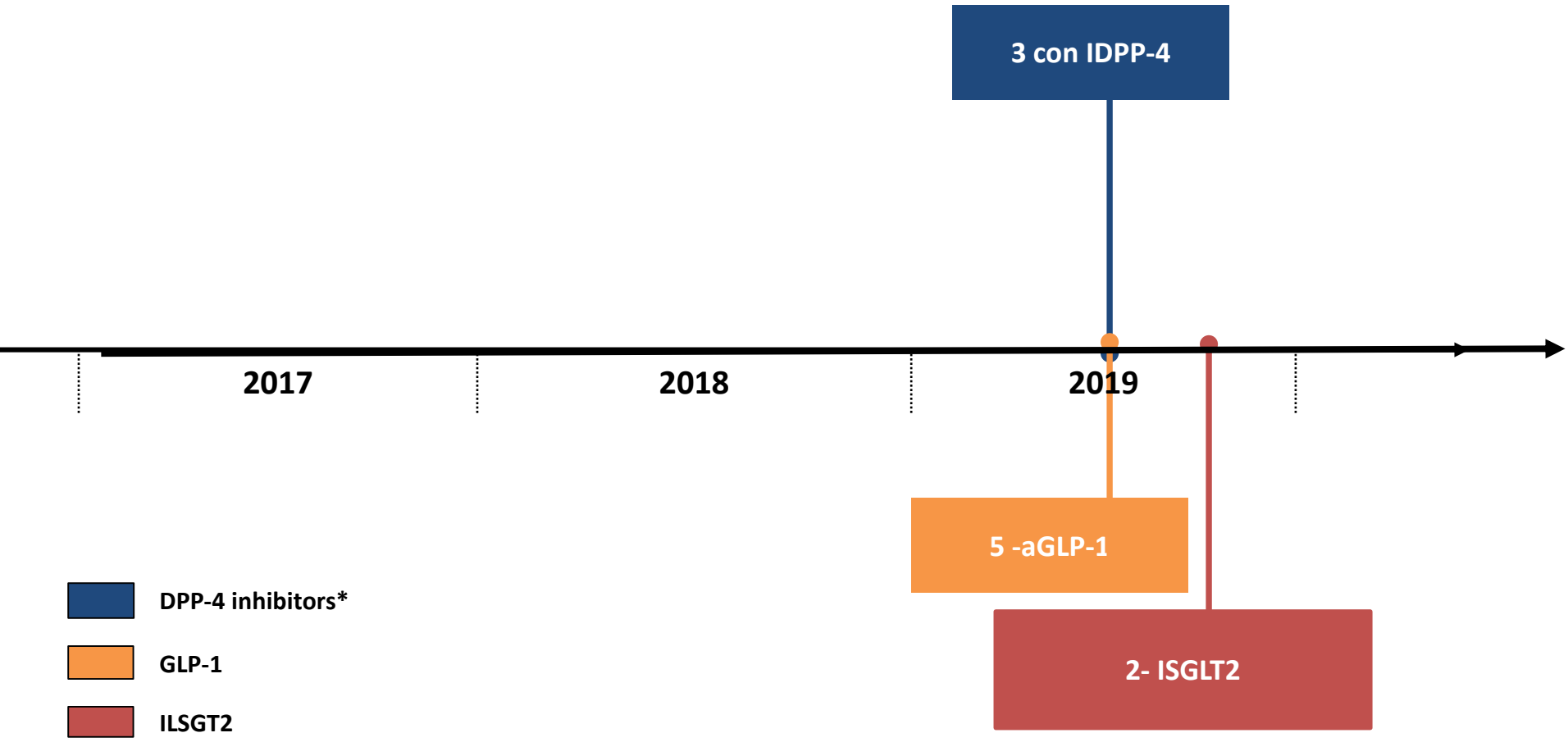
Centro Cardiológico Dr. Fernández de Soria



CV, cardiovascular; HR, hazard ratio; DPP-4, dipeptidyl peptidase-4
*Saxagliptin, alogliptin, sitagliptin
Adapted from Johansen OE. World J

10 ensayos de los nuevos agentes hipoglucemiantes están en marcha con más de 80.000 pacientes

Centro Cardiológico
Dr. Fernández de Soria



ESTUDIOS CON REDUCCION DE LA MORTALIDAD C.V. EN DM tipo II

-Resultados del ensayo con ISGLT2:
EMPAREG –OUTCOME

-Resultados ensayos con aGLP1:

LEADER y SUSTAIN

Efectos de los iSGLT2 : modula los factores de riesgo cardiovascular

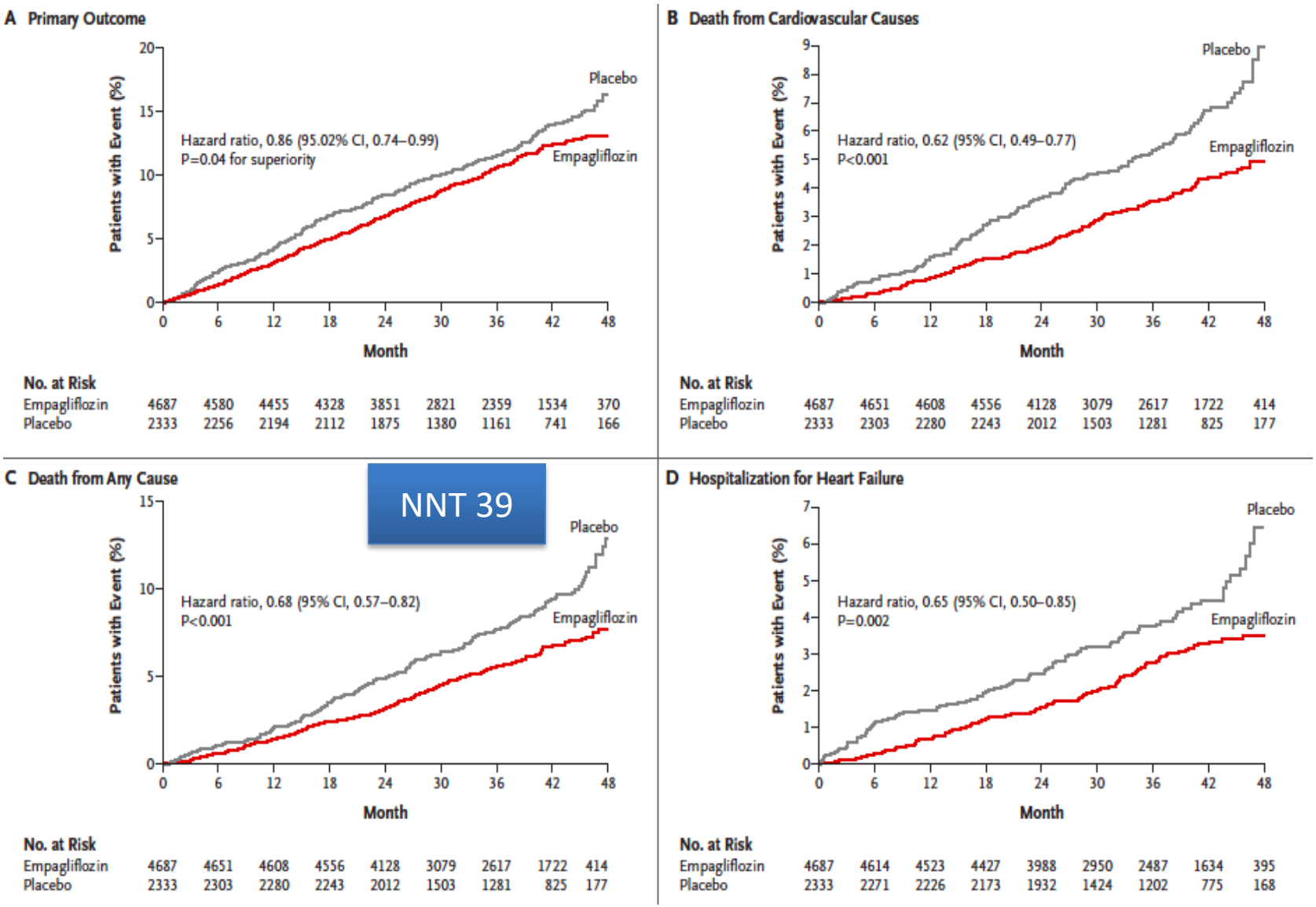
Centro Cardiológico Dr. Fernández de Soria

CV, cardiovascular; TG, triglycerides

Inzucchi SE, et al. Diab Vasc Dis Res 2015;12:90–100

Seguridad CV de empagliflozina: Ensayo EMPA-REG OUTCOME .N England J Med 2015;373:2117

Centro Cardiológico Dr. Fernández de Soria



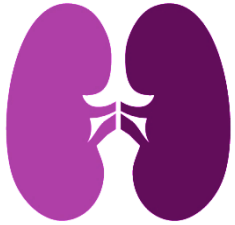
Bernard Zinman et al. N Engl J Med 2015; 373:2117-2128.

EMPA-REG OUTCOME®: ofrece una nueva perspectiva

Centro Cardiológico Dr. Fernández de Soria

T2D

Empagliflozina añadida al tratamiento de referencia redujo el riesgo CV y la mortalidad en adultos con DM2 y ECV establecida

14%	38%	32%	35%	39%
				
↓ 3P-MACE[1]	↓ CV death[1]	↓ All-cause mortality[1]	↓ HF hospitalisations[1]	↓New or worsening nephropathy*,[2]

El comportamiento de las dos dosis de empagliflozina (10 y 25 mg) fue similar

*Defined as new onset of macroalbuminuria, doubling of serum creatinine (accompanied by eGFR [MDRD] ≤45 ml/min/1.73m2), initiation of renal replacement therapy or death due to renal disease; 3P-MACE, 3-point major adverse cardiovascular events

1. Zinman B *et al. N Engl J Med* 2015;373:2117; 2. Wanner C *et al. N Engl J Med* 2016 (submitted)

For internal use only. Strictly confidential. Do not copy or distribute externally.

(NNT) para prevenir una muerte en pacientes con alto riesgo C.V.

Centro Cardiológico Dr. Fernández de Soria

Simvastatin[1] for 5.4 years

30

High CV risk
5% diabetes, 26% hypertension

Ramipril[2] for 5 years

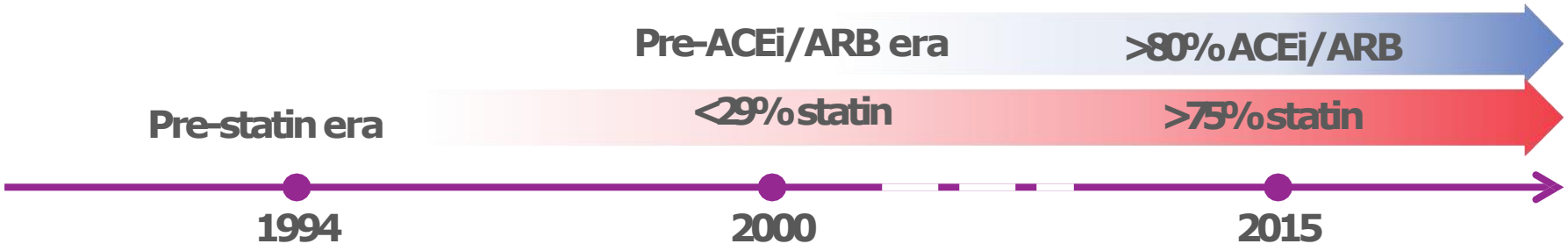
56

High CV risk
38% diabetes, 46% hypertension

Empagliflozin for 3 years

39

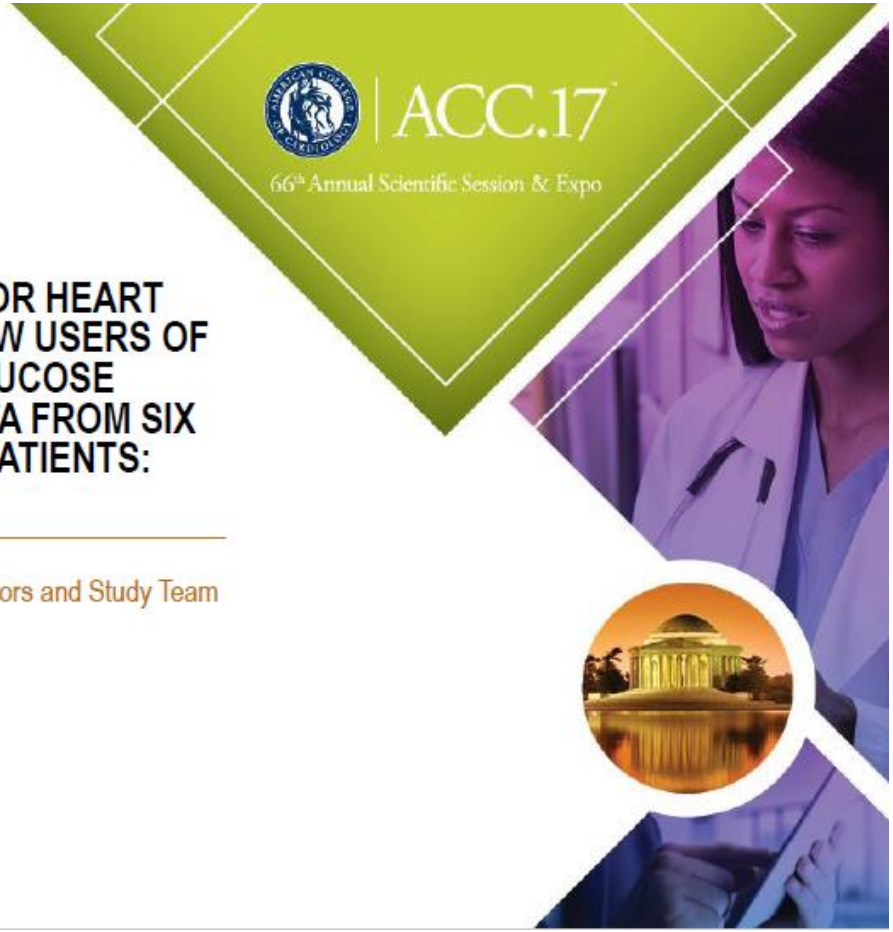
T2DM with high CV risk
92% hypertension



1. 4S investigator. Lancet 1994; 344: 1383-89, http://www.trialresultscenter.org/study2590-4S.htm;
2. HOPE investigator N Engl J Med 2000;342:145-53, http://www.trialresultscenter.org/study2606-HOPE.htm

Centro Cardiológico
Dr. Fernández de Soria

VIDA REAL



LOWER RATES OF HOSPITALIZATION FOR HEART FAILURE AND ALL-CAUSE DEATH IN NEW USERS OF SGLT-2 INHIBITORS VERSUS OTHER GLUCOSE LOWERING DRUGS – REAL WORLD DATA FROM SIX COUNTRIES AND MORE THAN 300,000 PATIENTS: THE CVD-REAL STUDY

Mikhail Kosiborod, MD on behalf of the CVD-REAL Investigators and Study Team

WASHINGTON, DC
FRI • SAT • SUN
MARCH 17 – 19, 2017

Estudio CVD-REAL:vida real

Centro Cardiológico Dr. Fernández de Soria

- El estudio CVD-REAL se trata de un **estudio observacional de cohortes.**
- En los estudios observacionales de cohortes, los pacientes son seguidos en el tiempo hasta que padecen (o no) un evento determinado.
- **A partir de bases de datos de distintos países, se evaluaron los efectos de los iSGLT-2 en pacientes que inician estos fármacos, frente a pacientes que inician cualquier otro antidiabético-**
- El periodo de estudio abarca desde la primera comercialización de un iSGLT-2 entre los países participantes.*
- **66th Annual Scientific Session of the American College of Cardiology, March 17–19, 2017**

* Primera fecha de la primer comercialización de iSGLT-2: Noviembre de 2012 en adelante (varía según base de datos)

Bases de datos de las que proceden los pacientes

Centro Cardiológico
Dr. Fernández de Soria

Variable primaria

hIC

EEUU

- Truven Health MarketScan Claims and Encounters and linked Medicare Supplemental and Coordination of Benefits (Medicare Supplemental) databases

Noruega

- Linked Prescribed Drug, National Patient and Cause of Death Registries

Suecia

- Linked Prescribed Drug, National Patient and Cause of Death Registries

Dinamarca

- Linked Prescribed Drug, National Patient and Cause of Death Registries

Reino Unido

Clinical Practice Research Datalink (CPRD) dataset

- The Health Improvement Network (THIN) dataset

Alemania

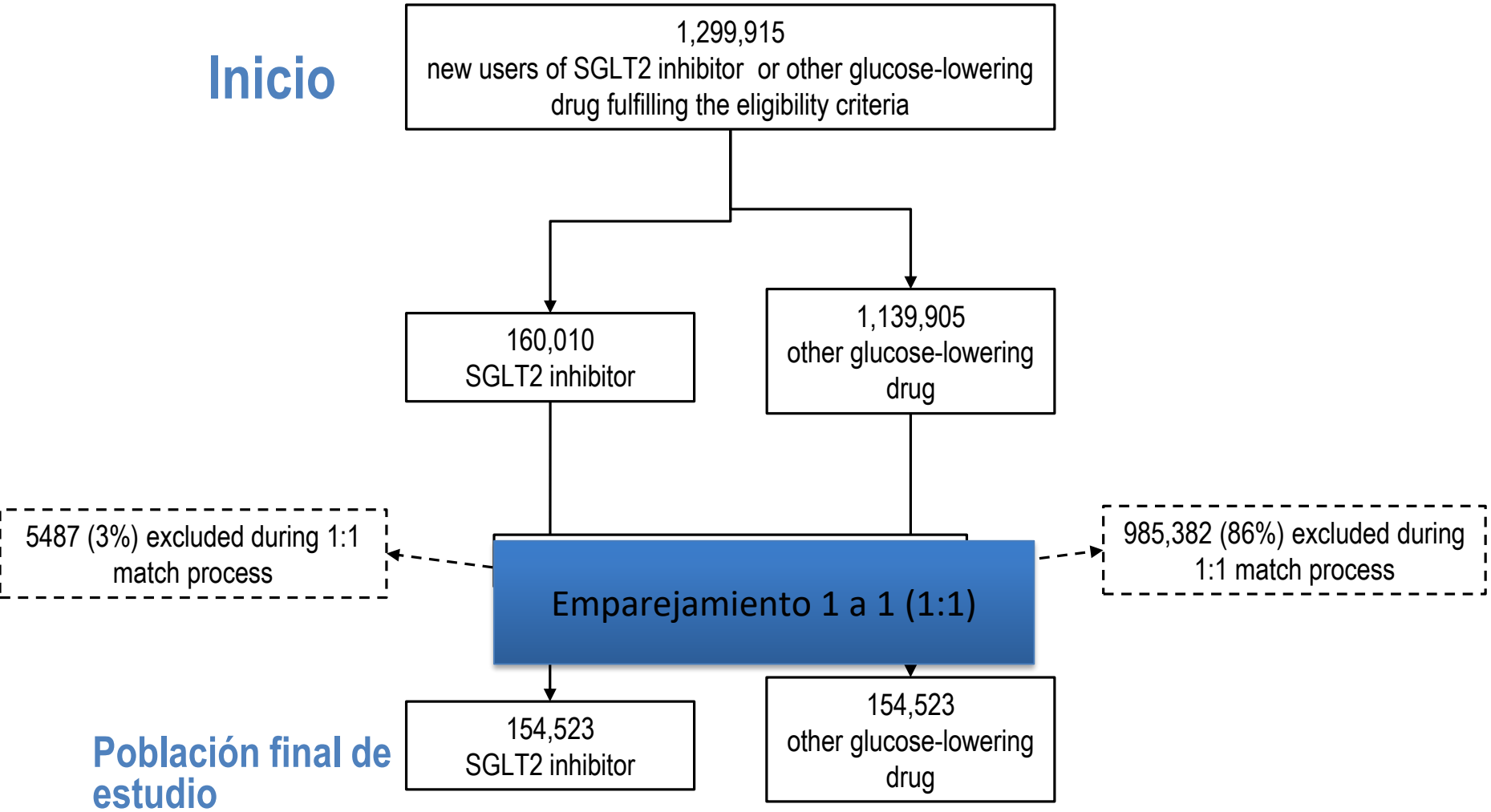
- Diabetes-Patienten-Verlaufsdokumentation (Diabetes Prospective Follow-Up; DPV)

Variables secundarias

1) Mortalidad por todas las causas y 2) variable hIC o mortalidad

Propensity Score: Resumen del proceso

Centro Cardiológico
Dr. Fernández de Soria



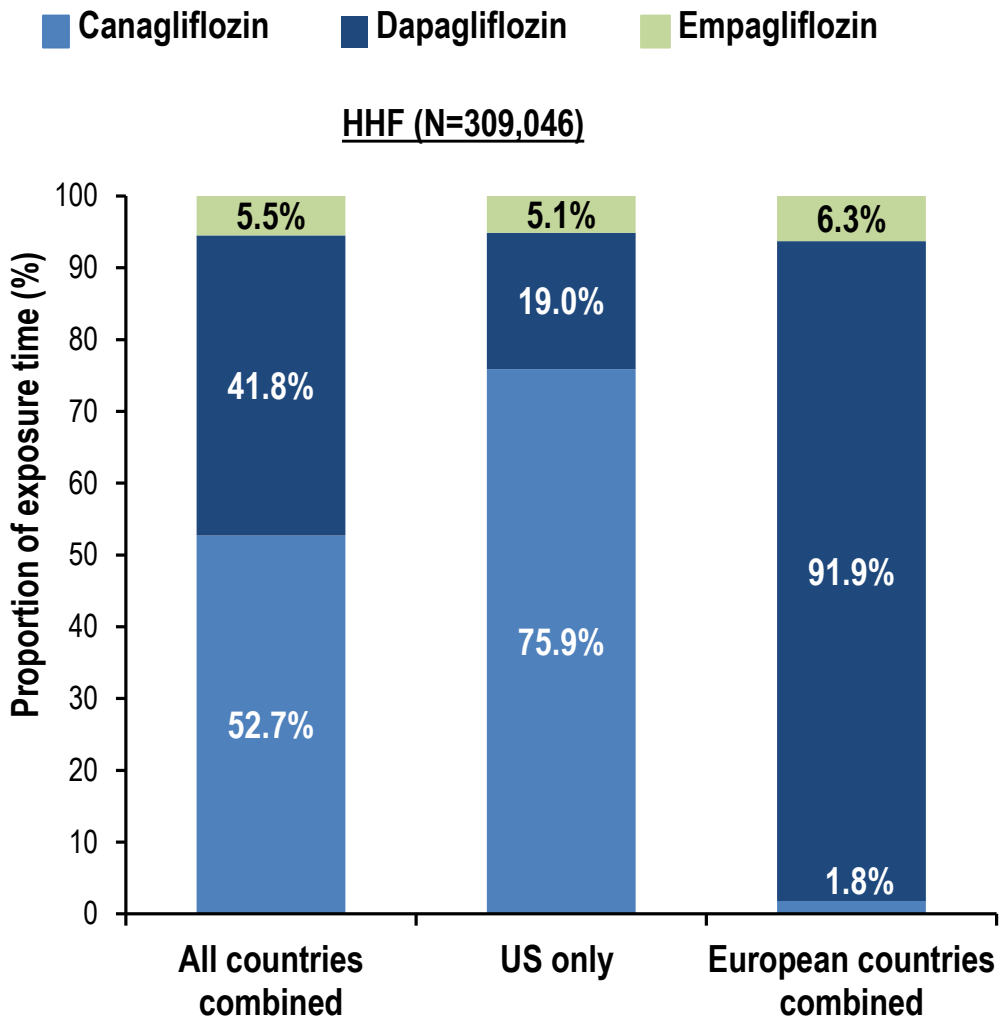
Características basales de la población de estudio muy similares

Centro Cardiológico Dr. Fernández de Soria

	SGLT2 inhibitor* N=154,523	Other glucose-lowering drug* N=154,523
Age (years), mean (SD)	57.0 (9.9)	57.0 (10.1)
Women	68,419 (44.3)	68,770 (44.5)
Established cardiovascular disease†	20,043 (13.0)	20,302 (13.1)
Acute myocardial infarction	3792 (2.5)	3882 (2.5)
Unstable angina	2529 (1.6)	2568 (1.7)
Heart failure	4714 (3.1)	4759 (3.1)
Atrial fibrillation	5632 (3.6)	5698 (3.7)
Stroke	6347 (4.1)	6394 (4.1)
Peripheral arterial disease	5239 (3.4)	5229 (3.4)
Microvascular disease	42,214 (27.3)	42,221 (27.3)
Chronic kidney disease	3920 (2.5)	4170 (2.7)

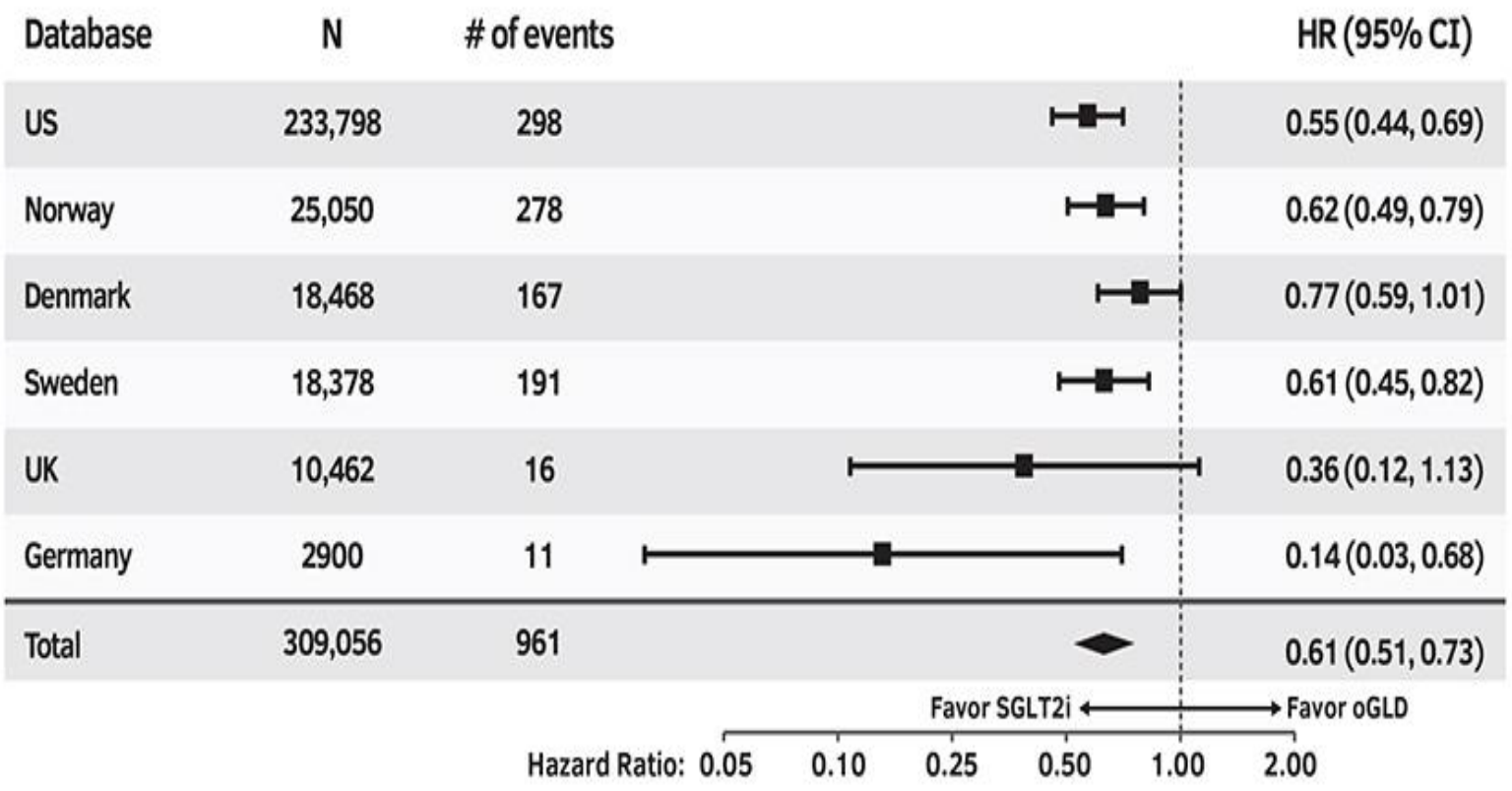
*Data are n (%) unless otherwise stated; †Myocardial infarction, unstable angina, stroke, heart failure, transient ischemic attack, coronary revascularization or occlusive peripheral artery disease

Contribution of SGLT-2 inhibitor: Cohort 1 HHF



Hospitalización por Insuficiencia Cardíaca

Centro Cardiológico
Dr. Fernández de Soria



- 39%

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

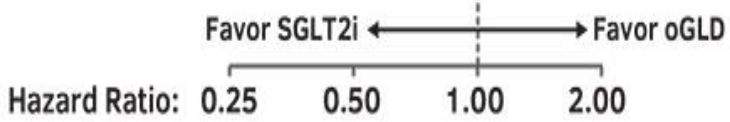
Heterogeneity p-value: 0.17

Data are on treatment, unadjusted.

Mortalidad por todas las causas

Centro Cardiológico
Dr. Fernández de Soria

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)



- 51%

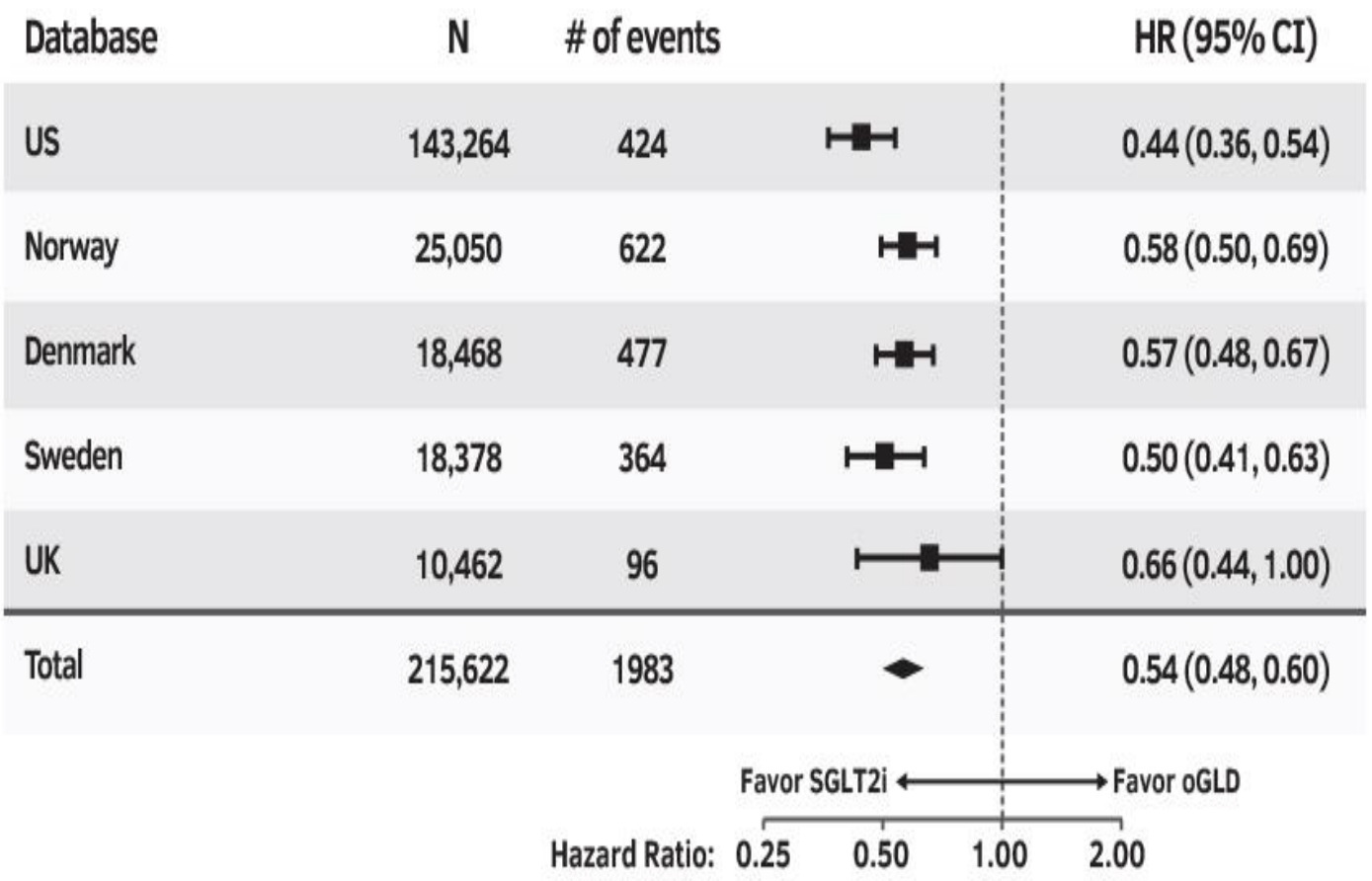
P-value for SGLT2i vs other glucose-lowering drug: <0.001

Heterogeneity p-value: 0.09

Data are on treatment, unadjusted.

hIC o Mortalidad por cualquier causa

Centro Cardiológico
Dr. Fernández de Soria



- 46%

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

Heterogeneity p-value: 0.17

Data are on treatment, unadjusted.

Fortalezas estudio CVD-REAL: vida real:

Centro Cardiológico Dr. Fernández de Soria

- Gran análisis contemporáneo de la **práctica clínica habitual** del mundo real en **seis países**, sobre la base de una muestra bien adaptada de más de **300.000 pacientes** con DM2 y cerca de 200.000 pacientes-año de seguimiento.
- Esta evidencia en vida real, **complementa** la producida en los ensayos clínicos.
- La mayoría de los pacientes **no tenían antecedentes de ECV establecida** al inicio y durante el estudio.
- Los **efectos** observados **permanecieron inalterados** después de un ajuste multivariable adicional, así como después de múltiples análisis de sensibilidad.
- Los resultados fueron **consistentes en todos los países**,

  independientemente de la variabilidad geográfica en los sistemas de salud y la diferencia en el uso de los inhibidores de SGLT-2 entre países.

ESTUDIOS CON REDUCCION DE LA MORTALIDAD C.V. EN DM tipo II

Resultados de los ensayos GLP1:

LEADER y SUSTAIN

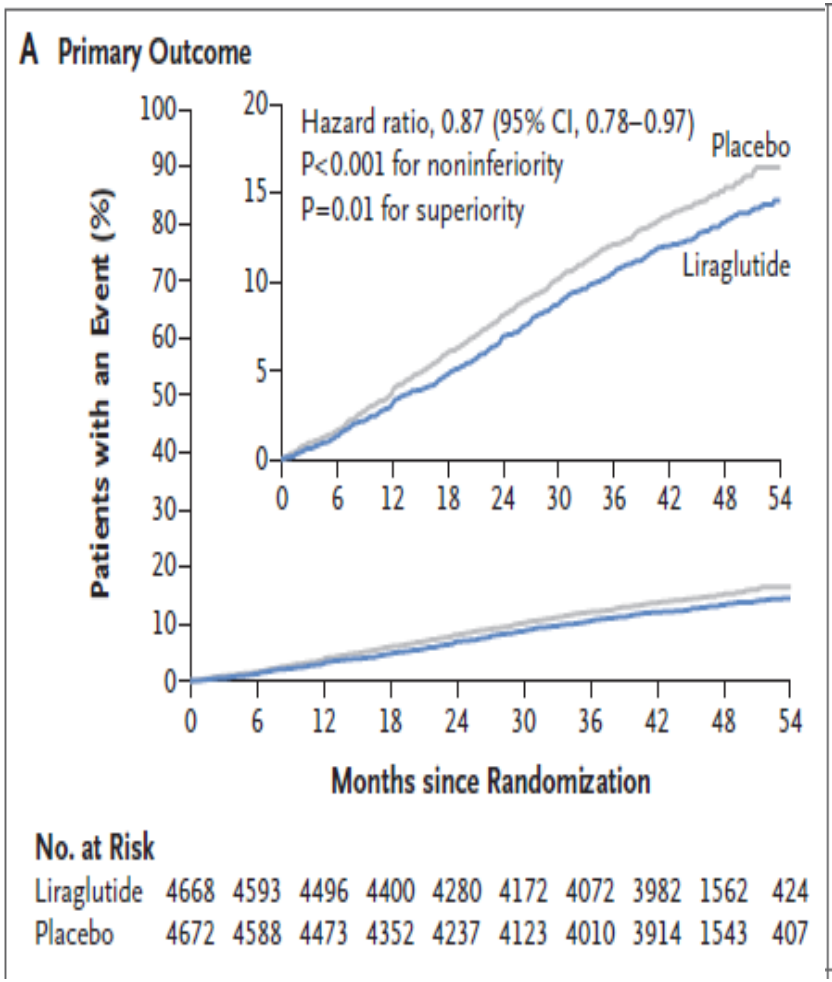
Efectos de los aGLP1 : modula los factores de riesgo cardiovascular

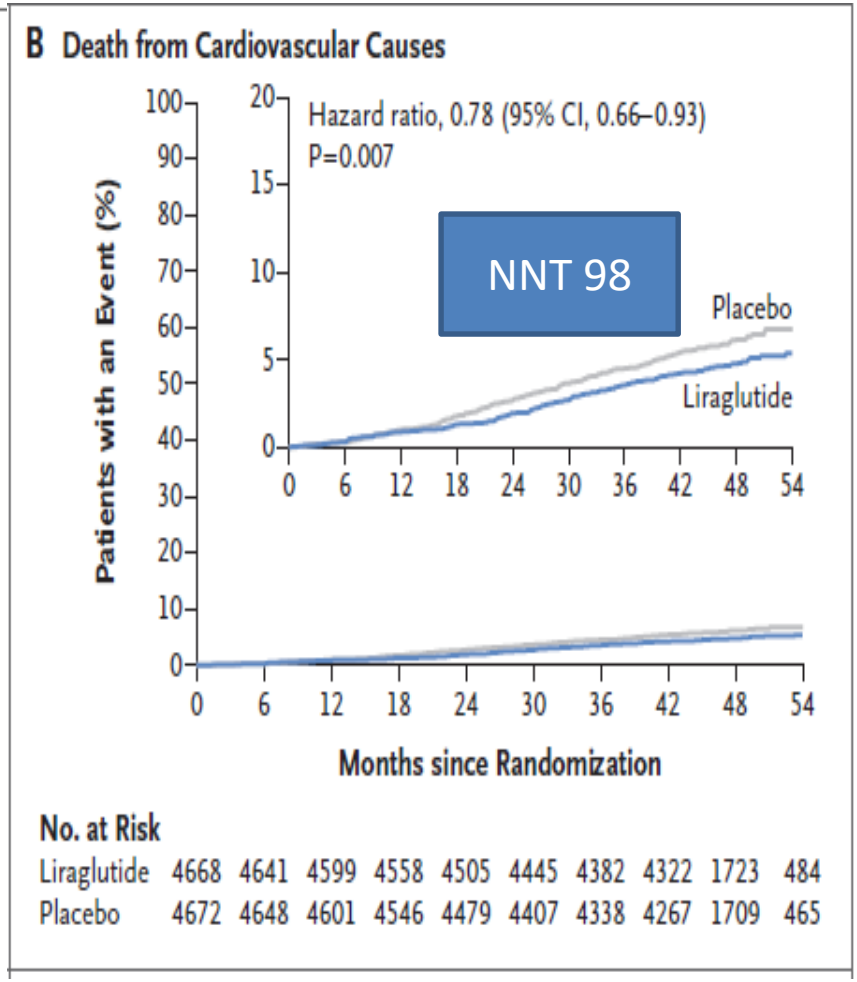
Centro Cardiológico Dr. Fernández de Soria

CV, cardiovascular; TG, triglycerides

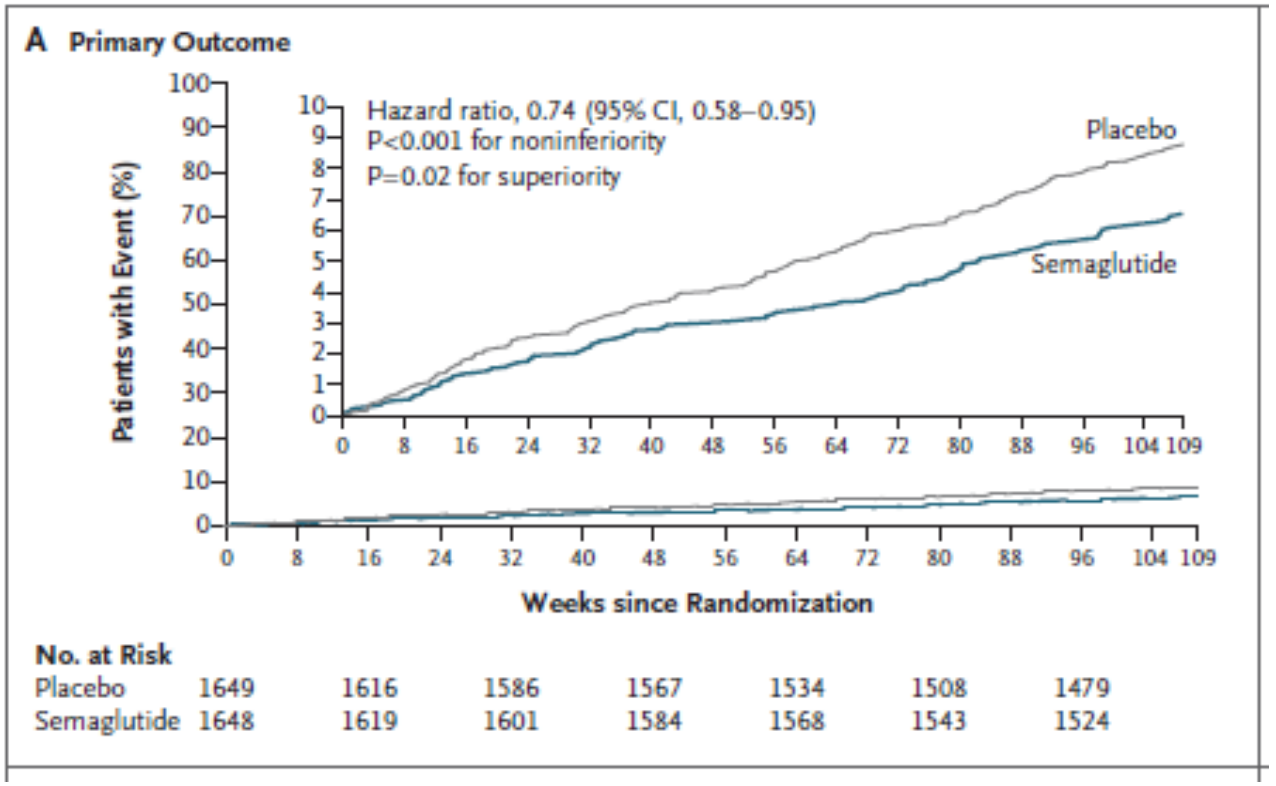
Inzucchi SE, et al. Diab Vasc Dis Res 2015;12:90–100

ESTUDIO LEADER: N Engl J Med. 2016;375:311



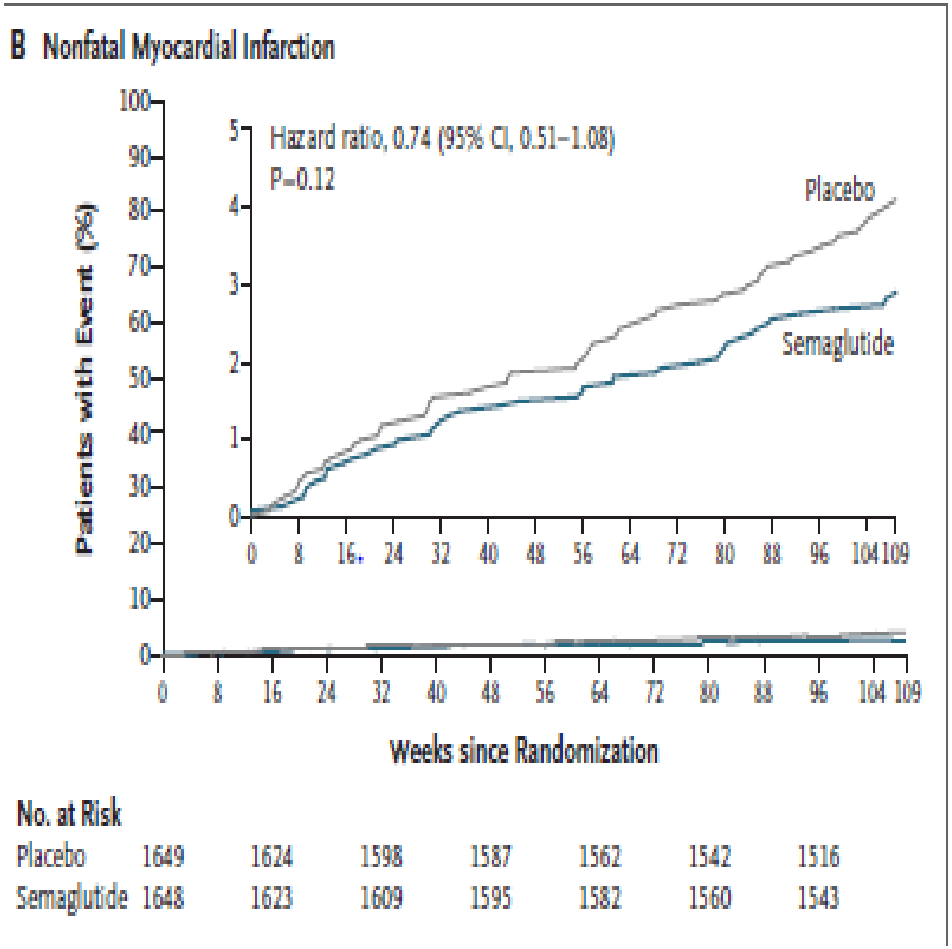


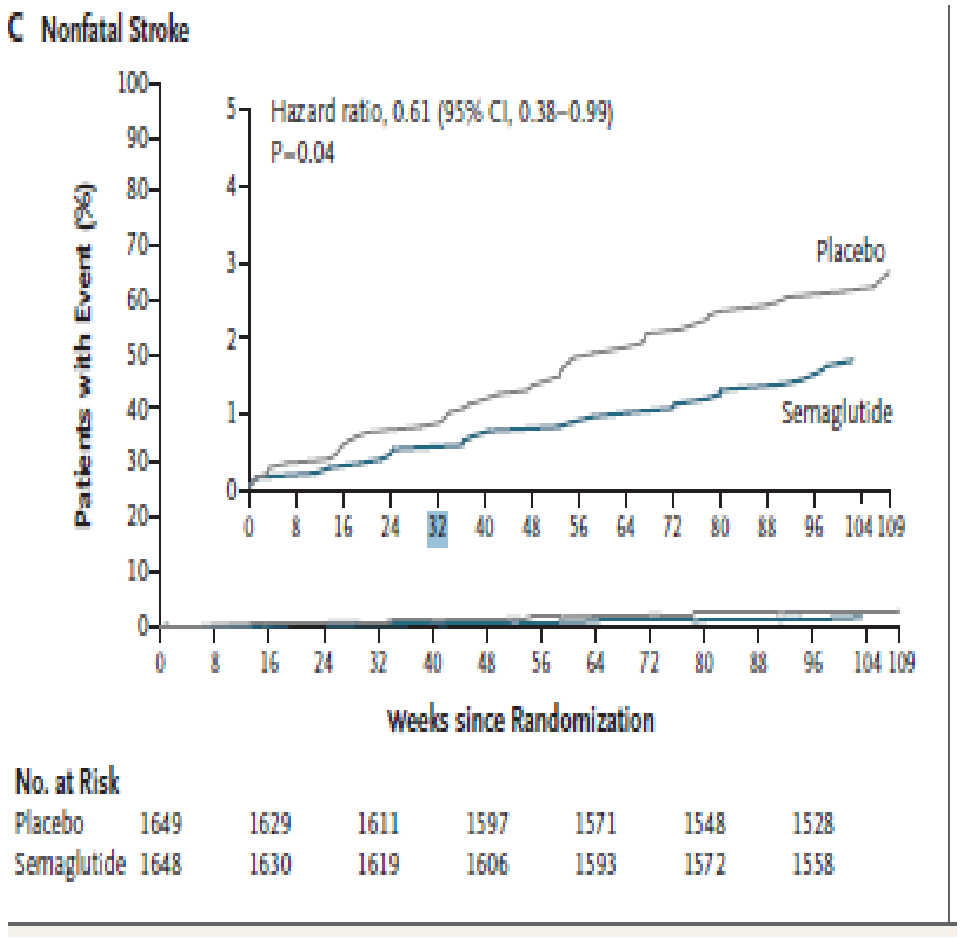
ESTUDIO SUSTAIN: N Engl J Med 2016;375:1834



Centro Cardiológico
Dr. Fernández de Soria

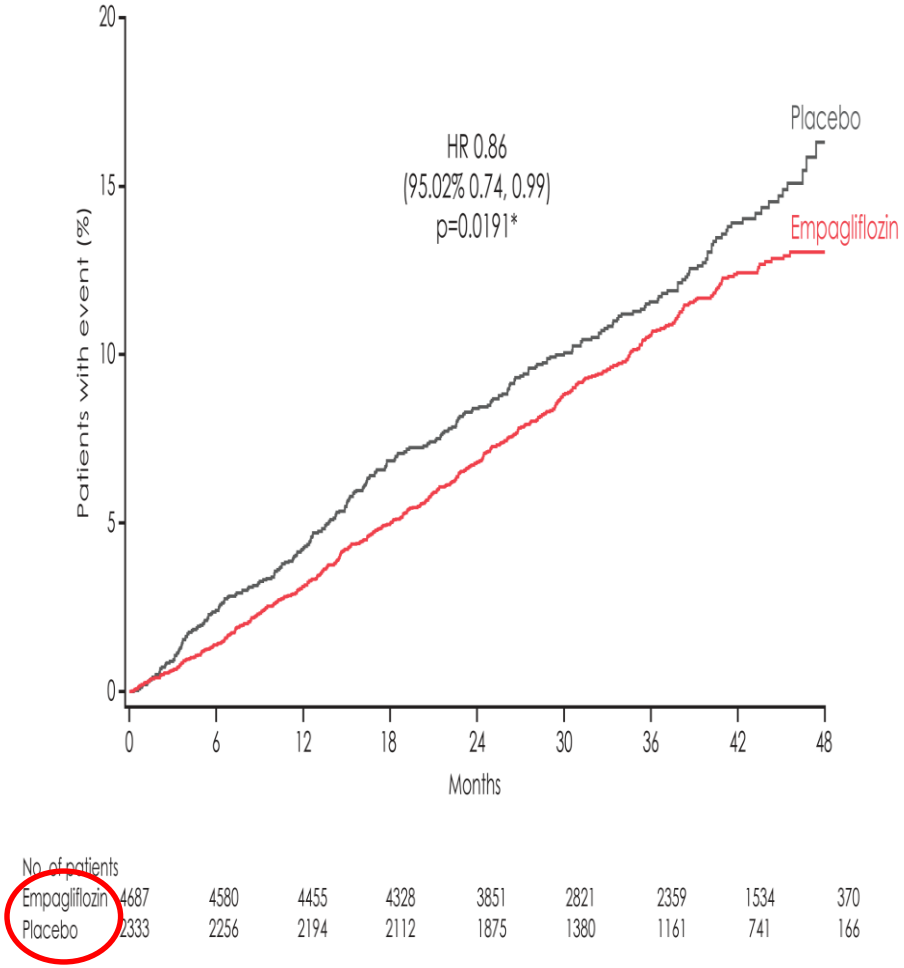
ESTUDIO SUSTAIN

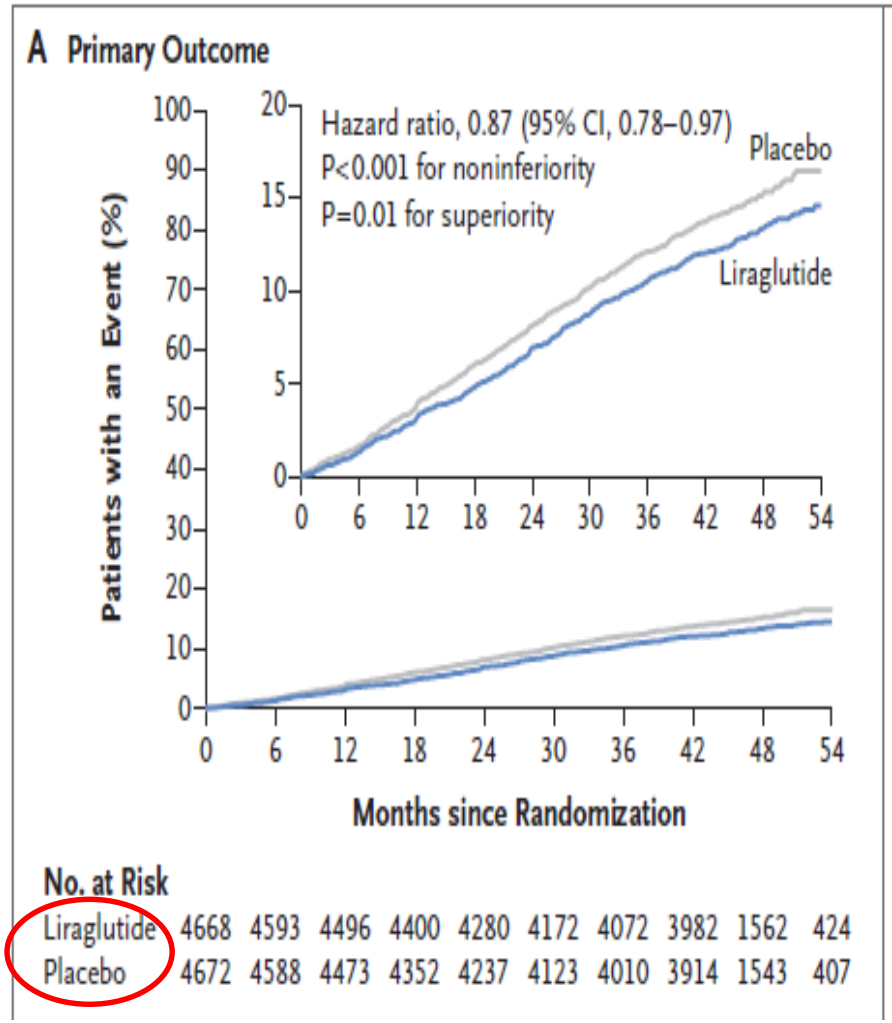




Diferencia de cronología en los Eventos C.V. (mortalidad CV, IAM no fatal e ictus no fatal)

Centro Cardiológico
Dr. Fernández de Soria





Estimación de Kaplan-Meier. HR: cociente de riesgos

EMPA-REG OUTCOME® Y LEADER:

como

se ha traducido sus resultados en las guías de práctica clínica?

Centro Cardiológico Dr. Fernández de Soria

EASD European Association for the Study of Diabetes

American Diabetes Association®

Canadian Diabetes Association

International Diabetes Federation

AACE American Association of Clinical Endocrinologists

ENDOCRINE SOCIETY

AMERICAN COLLEGE of CARDIOLOGY

American Heart Association®

EUROPEAN SOCIETY OF CARDIOLOGY®

ESH

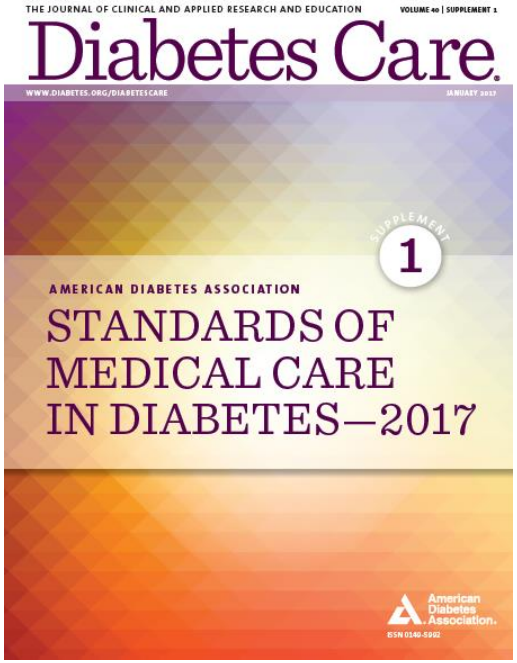
Wonca

AMERICAN ACADEMY OF FAMILY PHYSICIANS

STRONG MEDICINE FOR AMERICA

ADA (American Diabetes Association) Standards of Medical Care in Diabetes (Dec 2016) –

Centro Cardiológico Dr. Fernández de Soria



"Based on the results of two large clinical trials, a recommendation was added to consider **empagliflozin or liraglutide** in patients with established cardiovascular disease to reduce the risk of mortality."
[...]
"A section was added describing the cardiovascular outcome trials that demonstrated benefits of **empagliflozin and liraglutide** in certain high-risk patients with diabetes."

CDA (Canadian Diabetes Association): Update of Clinical Practice Guidelines for the Prever and Management of Diabetes in Canada (Nov 2016*)

Centro Cardiológico Dr. Fernández de Soria

Can J Diabetes 40 (2016) 484–486

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

Canadian Diabetes Association

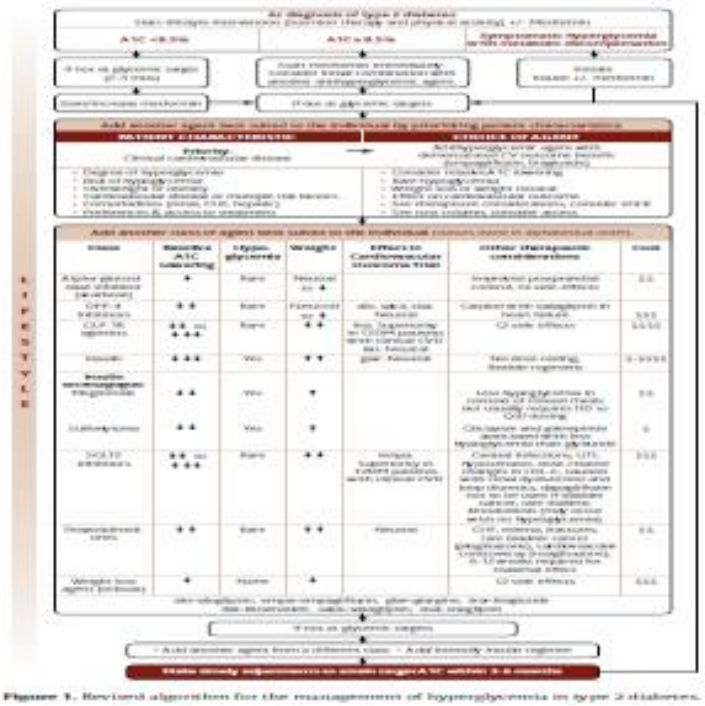
CJD

Policies, Guidelines, and Consensus Statements

Pharmacologic Management of Type 2 Diabetes: 2016 Interim Update

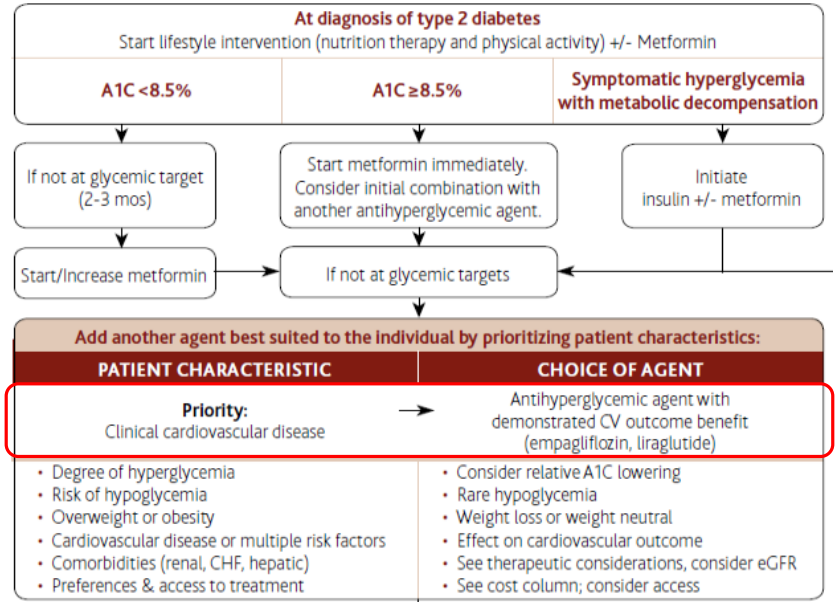
Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this commentary was prepared by Gillian Booth MD, FRCPC, Lorraine Lipscombe MD, MSc, FRCPC, Sonia Butalia MD, MSc, FRCPC, Kaberi Dasgupta MD, MSc, FRCPC, Dean Eurich PhD, MSc, Ronald Goldenberg MD, FRCPC, FACE, Nadia Khan MD, MSc, FRCPC, Lori MacCallum BScPhm, PharmD, CDE, Baiju Shah MD, PhD, FRCPC, Scot Simpson BScPhm, PharmD, MSc, Robyn L. Houlden MD, FRCPC on behalf of the Steering Committee for the Canadian Diabetes Association 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada



EMPA-REG OUTCOME and LEADER Study

In adults with type 2 diabetes with clinical cardiovascular disease in whom glycemic targets are not met, an antihyperglycemic agent with demonstrated cardiovascular outcome benefit should be added to reduce the risk of major cardiovascular events (Grade 1, Level 1A for empagliflozin (2); Grade 1, Level 1A for liraglutide if age ≥50 years (3); Grade D, Consensus for liraglutide if age <50 years).



*Canadian Diabetes Association Treatment Guidelines updated to include CV risk reduction information for Empagliflozin and Liraglutide, 13 Nov 2016

2016 European Guidelines on cardiovascular disease prevention in clinical practice

Centro Cardiológico
Dr. Fernández de Soria

Recommendations for management of diabetes

Recommendations	Class[a]	Level[b]	Ref[c]
Lifestyle changes including smoking cessation, low fat diet, high fibre diet, aerobic physical activity, and strength training are recommended.	I	A	387
Reduction in energy intake is recommended to patients to help achieve lower weight or prevent weight gain.	I	B	387
A target HbA1c for the reduction in risk of CVD and microvascular complications in DM of <7.0% (<53 mmol/mol) is recommended for the majority of non-pregnant adults with either type 1 or type 2 DM.	I	A	388, 389
For patients with a long duration of DM, the elderly, frail, or those with existing CVD, a relaxing of the HbA1c targets (i.e. less stringent) should be considered.	IIa	B	389
A target HbA1c of ≤6.5% (≤48 mmol/mol) should be considered at diagnosis or early in the course of type 2 DM in patients, who are not frail and do not have CVD.	IIa	B	389
When screening for DM in individuals with or without CVD, assessment of HbA1c (which can be done non-fasting) or fasting blood glucose should be considered. An oral glucose tolerance test can be offered when there is still doubt.	IIa	A	390
Metformin is recommended as first-line therapy, if tolerated and not contra-indicated, following evaluation of renal function.	I	B	391
Avoidance of hypoglycaemia and excessive weight gain should be considered and individual approaches (with respect to both treatment targets and drug choices) should be considered in patients with advanced disease.	IIa	B	389, 392, 393
In patients with type 2 DM and CVD, the use of an SGLT2 inhibitor should be considered early in the course of the disease to reduce CV and total mortality.	IIa	B	394
Lipid lowering agents (principally statins) are recommended to reduce CV risk in all patients with type 2 or type 1 DM above the age of 40 years.	I	A	371, 372

2016 ESC Guidelines for the diagnosis and Treatment of acute and chronic heart failure

Centro Cardiológico Dr. Fernández de Soria

Recommendations to prevent or delay the development of overt heart failure or prevent death before the onset of symptoms

Recommendations	Class [a]	Level [b]	Ref [c]
Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life.	I	A	126, 129, 150, 151
Treatment with statins is recommended in patients with or at high-risk of CAD whether or not they have LV systolic dysfunction, in order to prevent or delay the onset of HF and prolong life.	I	A	137–140, 152
Counselling and treatment for smoking cessation and alcohol intake reduction is recommended for people who smoke or who consume excess alcohol in order to prevent or delay the onset of HF.	I	C	131–134
Treating other risk factors of HF (e.g. obesity, dysglycaemia) should be considered in order to prevent or delay the onset of HF.	IIa	C	130, 141, 153–155
Empagliflozin should be considered in patients with type 2 diabetes in order to prevent or delay the onset of HF and prolong life.	IIa	B	130
ACE-I is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction in order to prevent or delay the onset of HF and prolong life.	I	A	5, 144, 145
ACE-I is recommended in patients with asymptomatic LV systolic dysfunction without a history of myocardial infarction, in order to prevent or delay the onset of HF.	I	B	5

DOCUMENTO S.E.C. Nov 2016

Centro Cardiológico
Dr. Fernández de Soria

Seguridad CV y beneficio clínico en la reducción de eventos CV (eficacia CV) en los estudios clínicos

Eficacia CV	Seguridad CV	Reducción A1C	< Hipoglucemias
Empagliflozina (iSGLT2)	Empagliflozina (iSGLT2)	iSGLT2	iSGLT2
Metformina	Metformina	Metformina	Metformina
Liraglutida (aGLP1) Semaglutida (aGLP1)	Liraglutida (aGLP1) Semaglutida (aGLP1)	aGLP1	aGLP1
	IDPP-4 (sitagliptina)	IDPP-4	IDPP-4
	Gliclazida (SU)	Gliclazida (SU)	
	Insulina	Insulina	

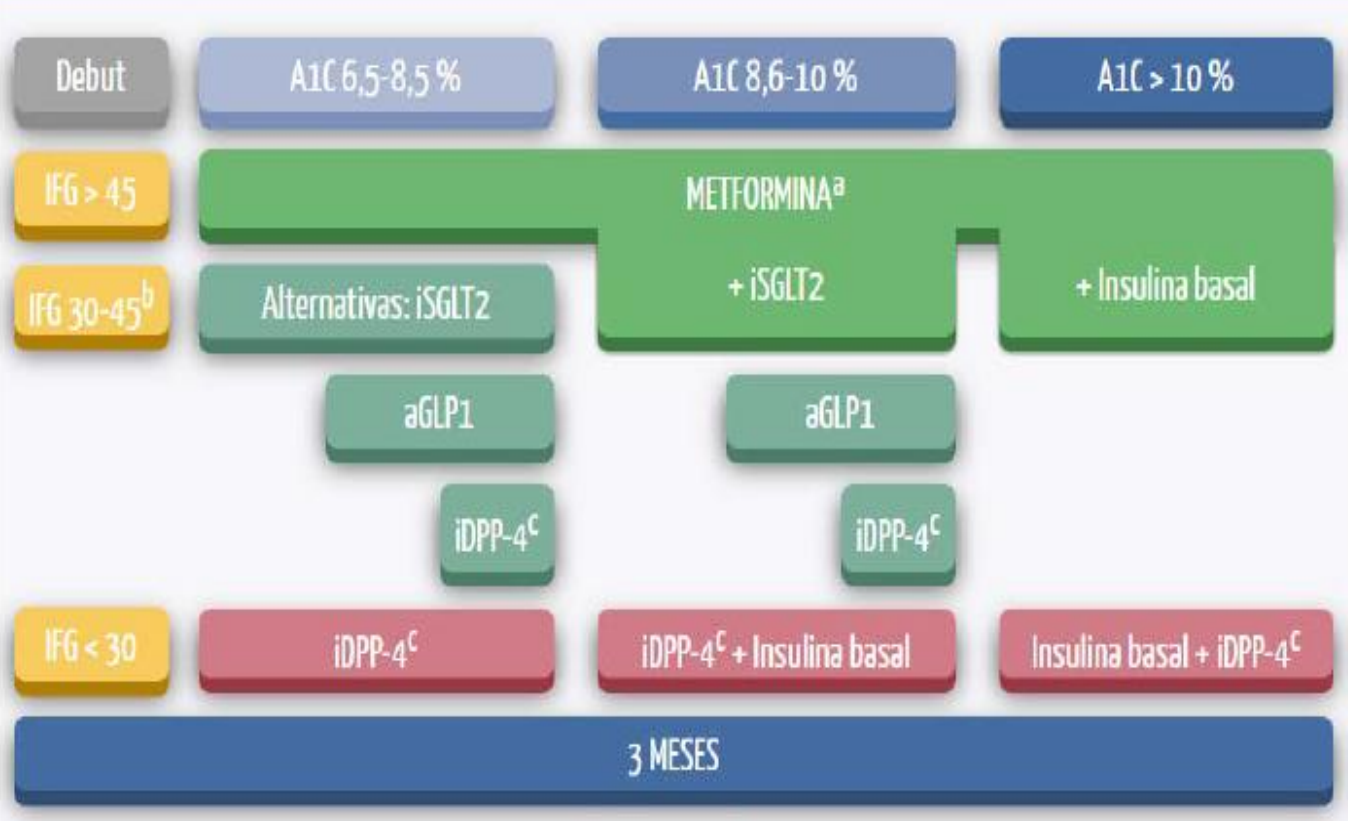
aGLP1: análogos del péptido semejante al glucagón tipo 1; CV: cardiovascular; iDPP-4: inhibidores de la enzima dipeptidilpeptidasa tipo 4; iSGLT2: inhibidores del cotransportador de sodio-glucosa tipo 2; SU: sulfonilureas.

DOCUMENTO S.E.C.

Centro Cardiológico
Dr. Fernández de Soria

Algoritmo 1 Algoritmo terapéutico del paciente con DM2 y cardiopatía

Estilo de vida (dieta, ejercicio físico, abstención tabáquica)
Control multifactorial (c-LDL < 70 mg/dL y TA < 130-140/80-85mmHg)
Revisión de la adherencia terapéutica y eventos de efectos perjudiciales de los antihiperglucemiantes en pacientes con tratamiento previo



CONCLUSION

- Los paciente diabéticos tienen > eventos C.V.
- No debemos conformarnos con el control metabólico.
- ¿Está justificado no ofrecer el beneficio demostrado?
- **Desde el 2015 sabemos que podemos obtener:**

  -Seguridad cardiovascular.

  -Eficacia en reducir eventos cardiovasculares.

  -Control de la HBA1C.

LA REVOLUCION YA HA EMPEZADO
Y HEMOS CRUZADO LA FRONTERA METABOLICA

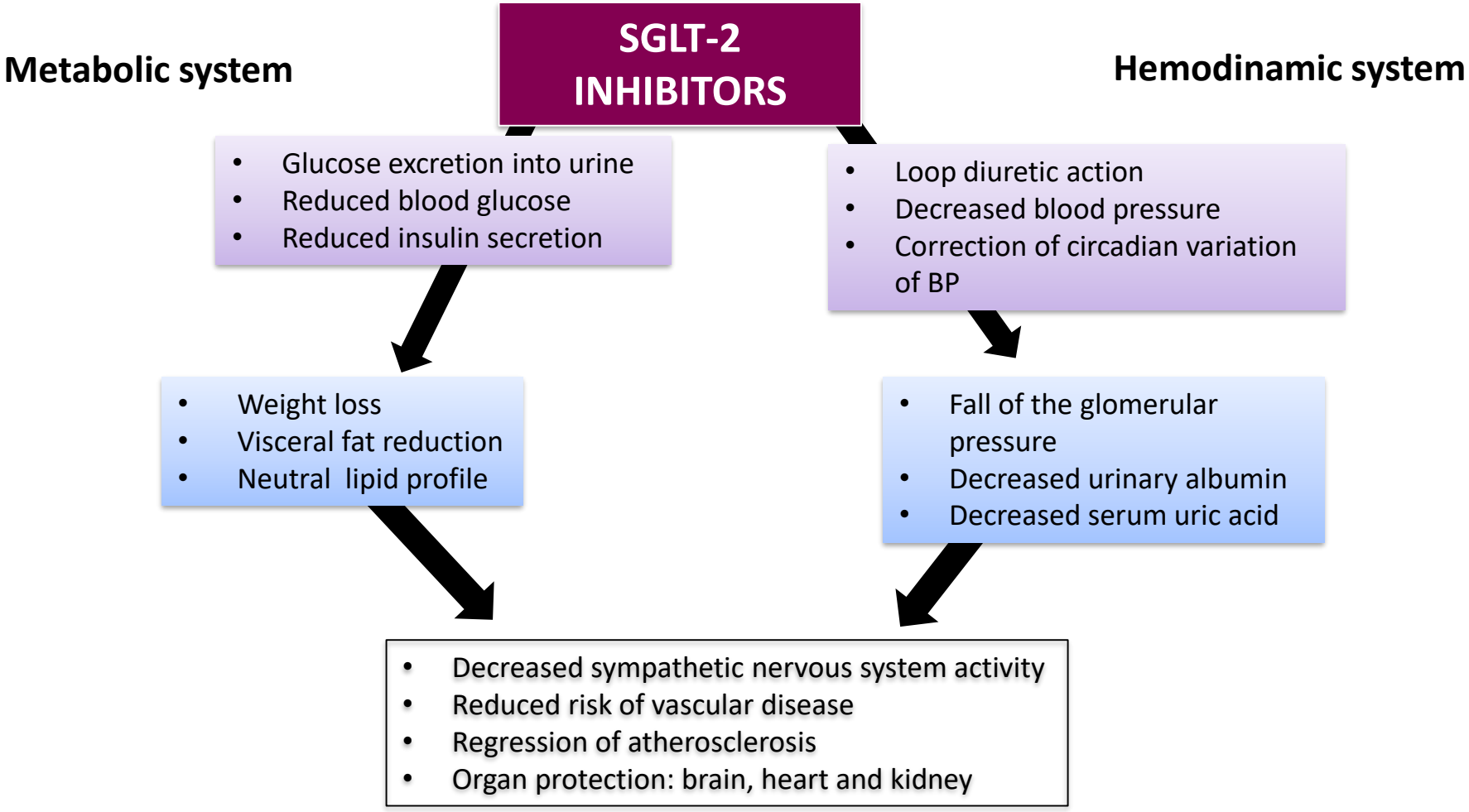
GRACIAS POR LA INVITACION

Centro Cardiológico
Dr. Fernández de Soria

Relación iSGLT2 y riesgo cardiovascular

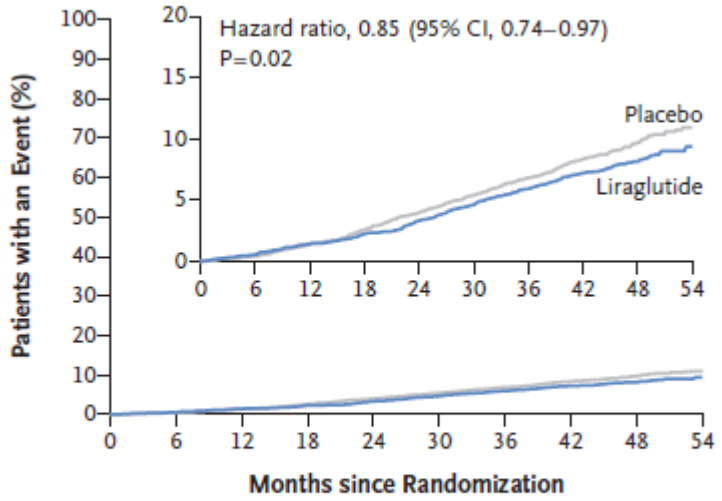
Centro Cardiológico Dr. Fernández de Soria

SGLT-2 inhibition can reduce cardiovascular risks in a multifaceted manner



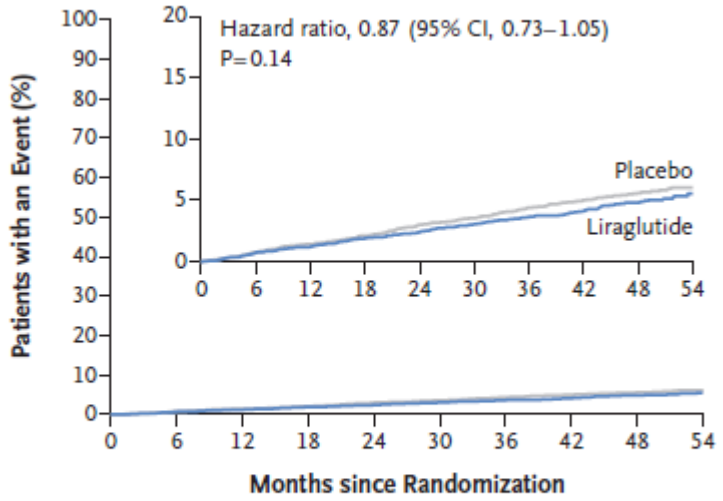
Kimura. Journal of the American Society of Hypertension 10(3) (2016) 271–278.

E **Death from Any Cause**



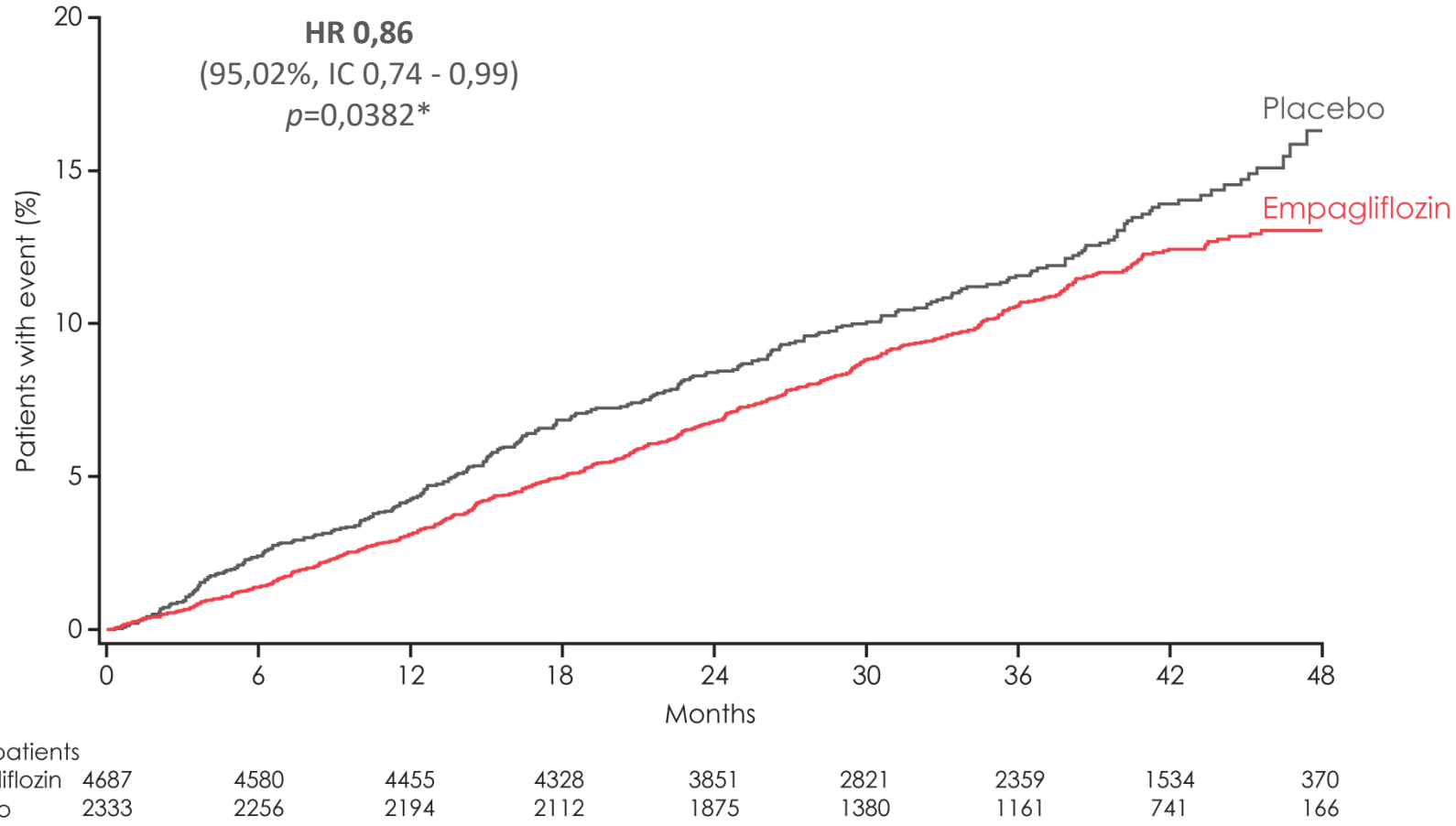
No. at Risk										
Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4268	1709	465

F **Hospitalization for Heart Failure**



No. at Risk										
Liraglutide	4668	4612	4550	4483	4414	4337	4258	4185	1662	467
Placebo	4672	4612	4540	4464	4372	4288	4187	4107	1647	442

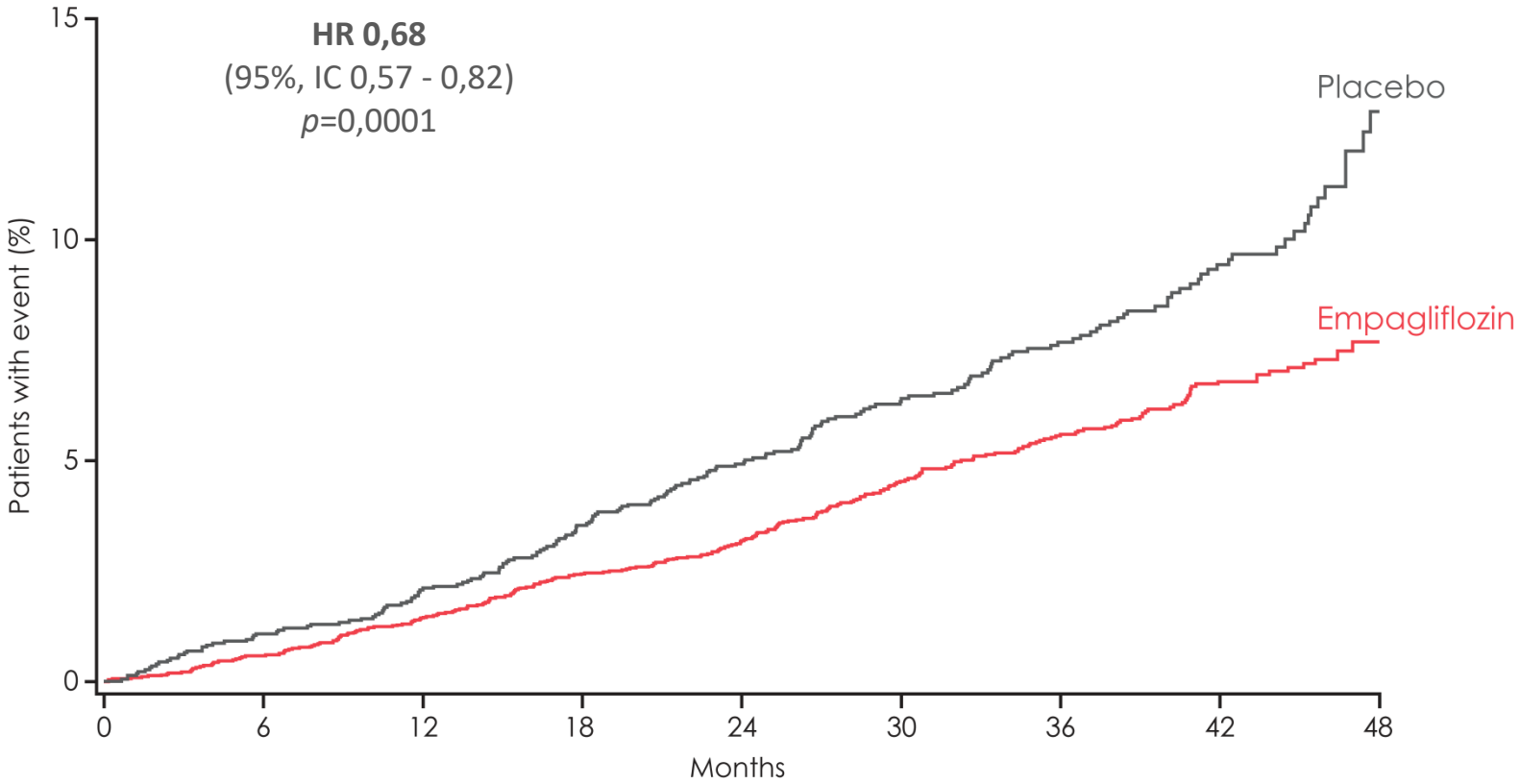
Criterio de valoración principal: AACG de 3 puntos(mortalidad CV, IAM no fatal e ictus no fatal)



Función de incidencias acumuladas. AACG: acontecimiento adverso cardiovascular grave; HR: cociente de riesgos.

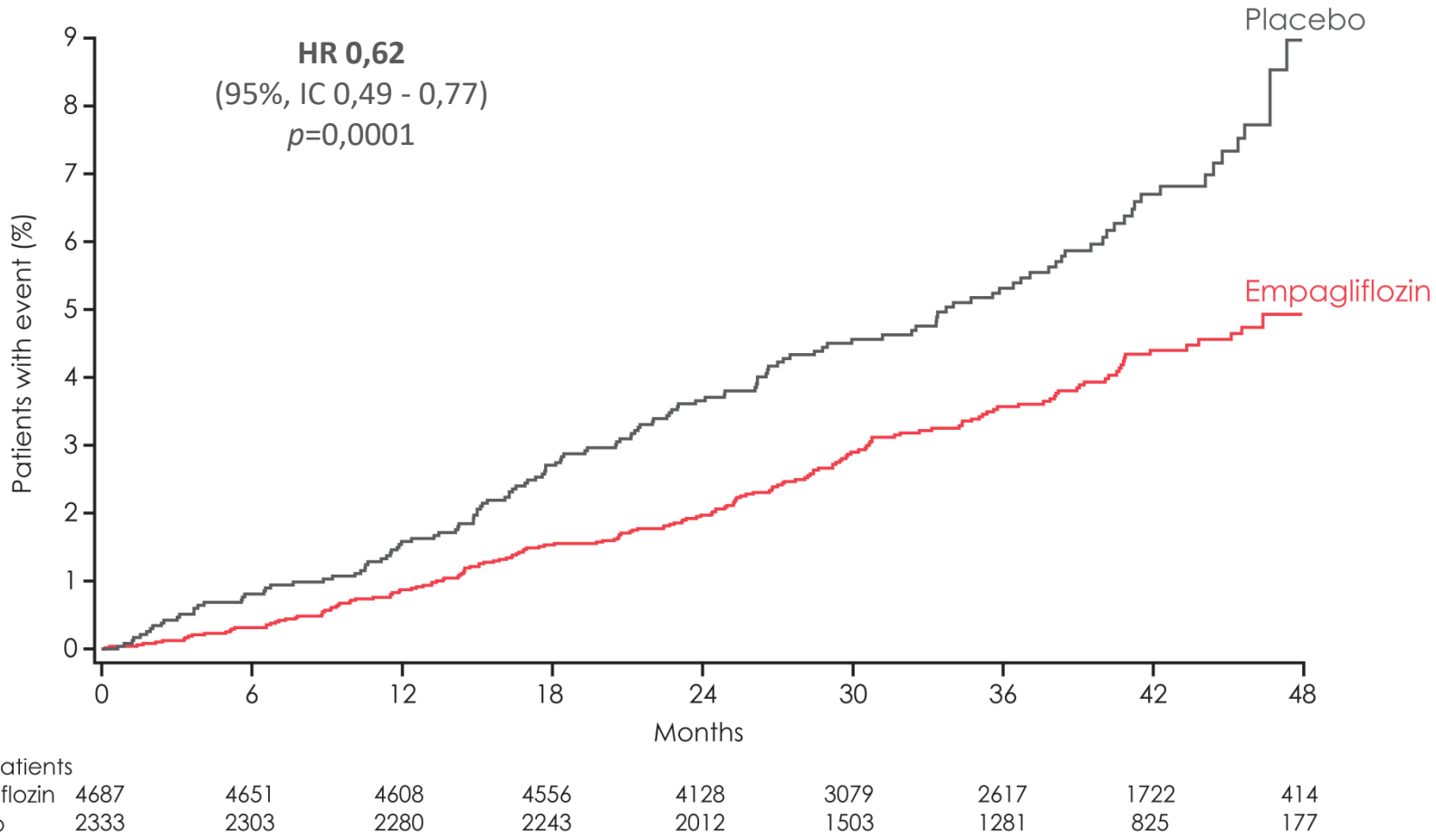
* Se realizaron pruebas bilaterales de superioridad (la significación estadística se indicó cuando p≤0,0498)

Mortalidad por todas las causas



Estimación de Kaplan-Meier. HR: cociente de riesgos

Muerte cardiovascular

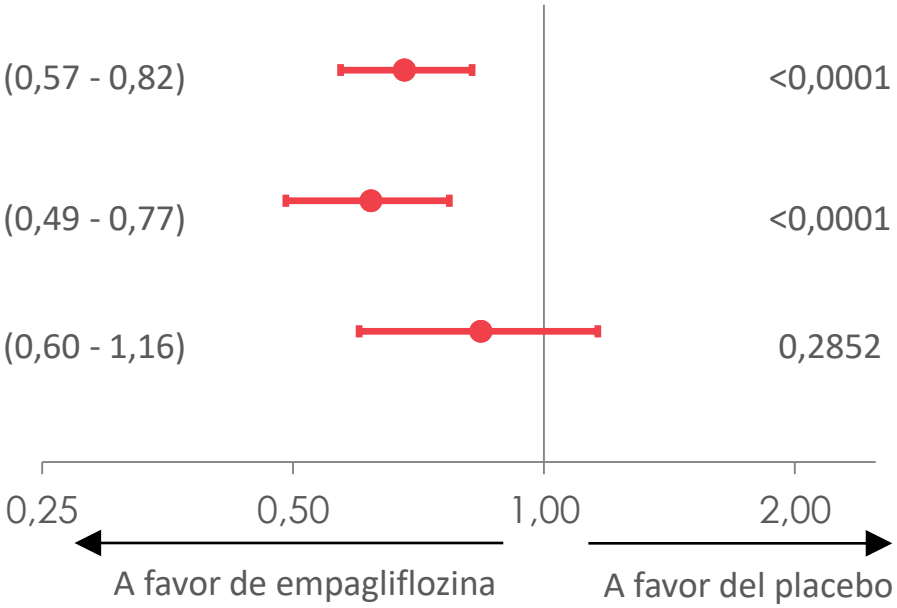


Función de incidencias acumuladas. HR: cociente de riesgos

Mortalidad por todas las causas, muerte CV y muerte no CV

Centro Cardiológico Dr. Fernández de Soria

	Pacientes con acontecimiento/analizados Empagliflozina	Placebo	HR	IC 95%	*p*-valor
Mortalidad por todas las causas	269/4687	194/2333	0,68	(0,57 - 0,82)	<0,0001
Muerte CV	172/4687	137/2333	0,62	(0,49 - 0,77)	<0,0001
Muerte no CV	97/4687	57/2333	0,84	(0,60 - 1,16)	0,2852

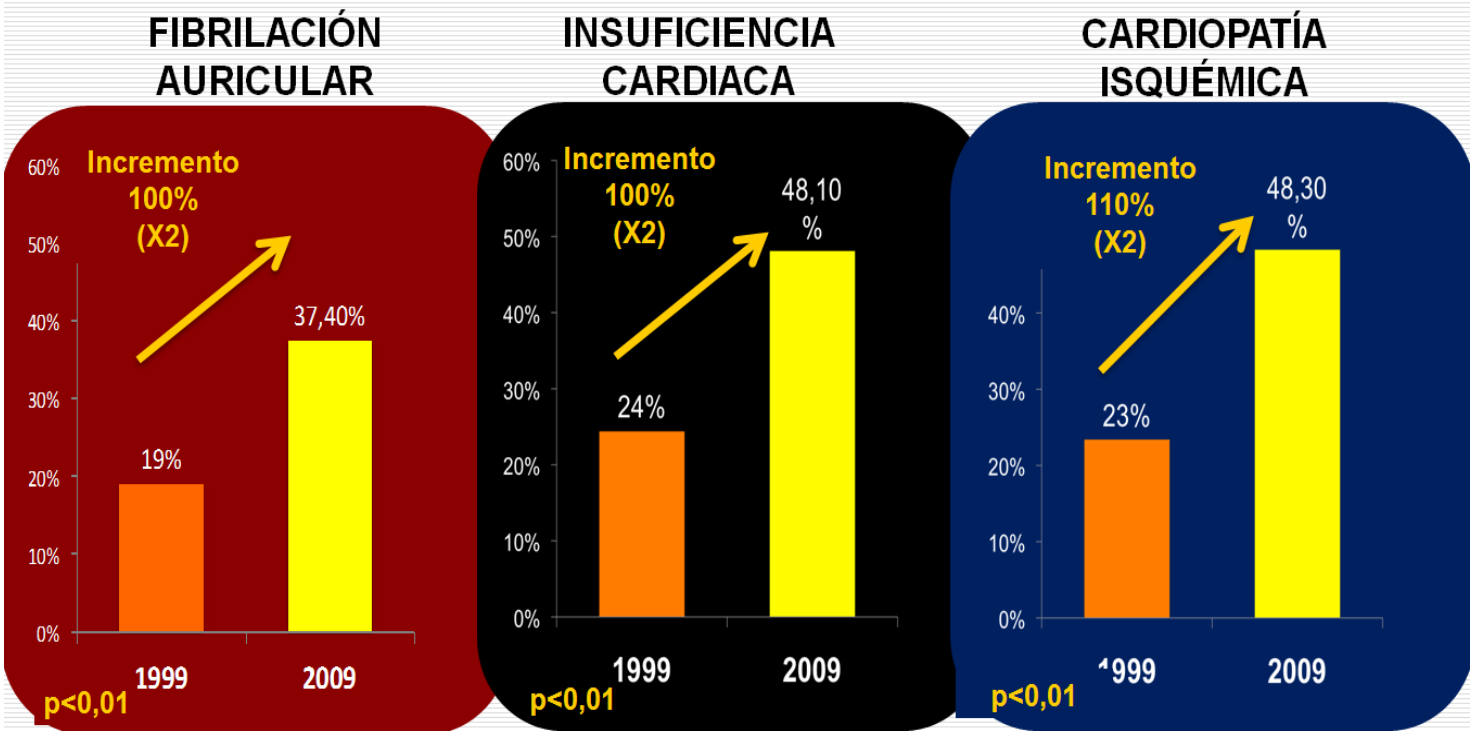


Análisis de regresión de Cox. CV: cardiovascular; HR: cociente de riesgos

Diabetes y ECV

Centro Cardiológico
Dr. Fernández de Soria

En la última década se ha observado una evolución de la prevalencia de DM en pacientes con cardiopatías

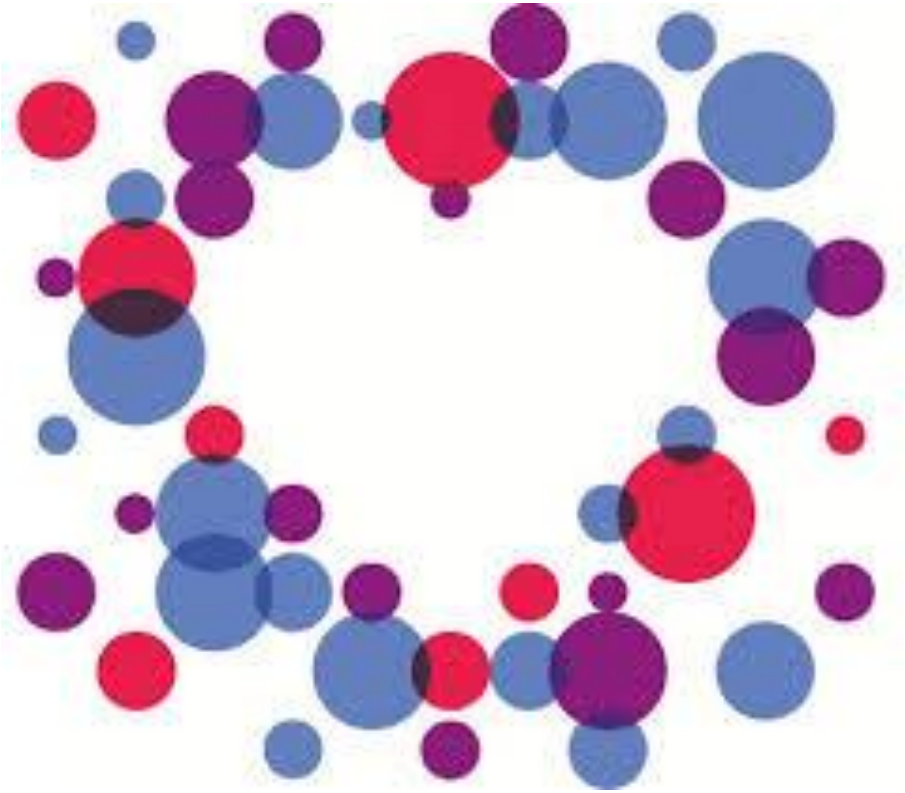


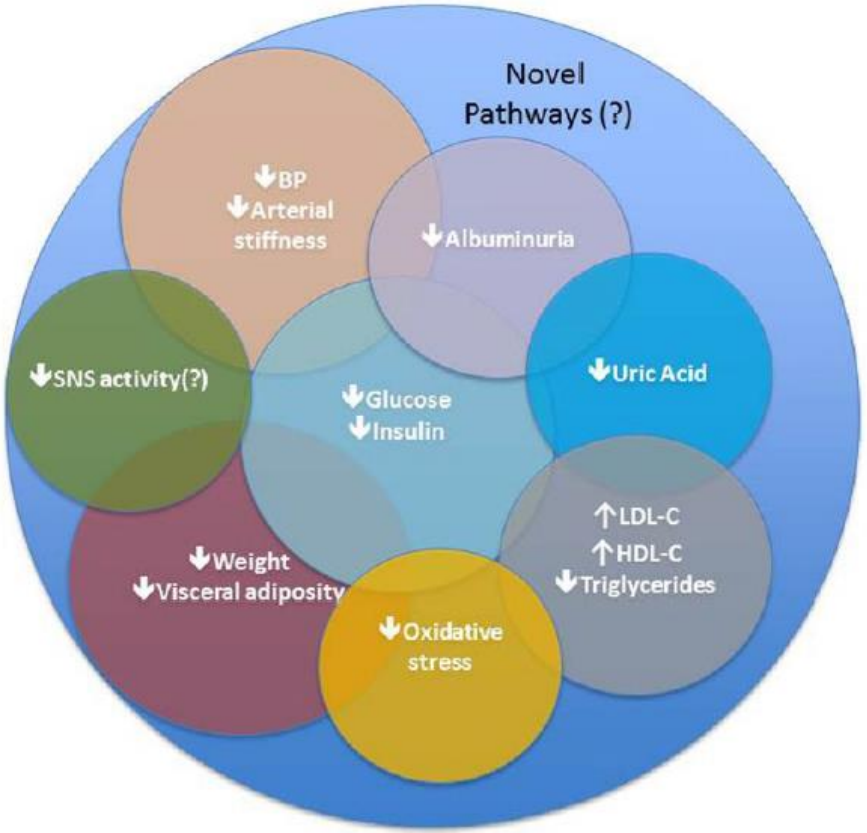
CARDIOTENS 1999-2009

Cordero et al. World J Cardiol. 2013; 26: 288-294.
Rodríguez-Mañero et al. Rev Port Cardiol. 2013; 32: 103-109.

Bloqueo de **ISGLT2;modula**

los factores de riesgo C.V.



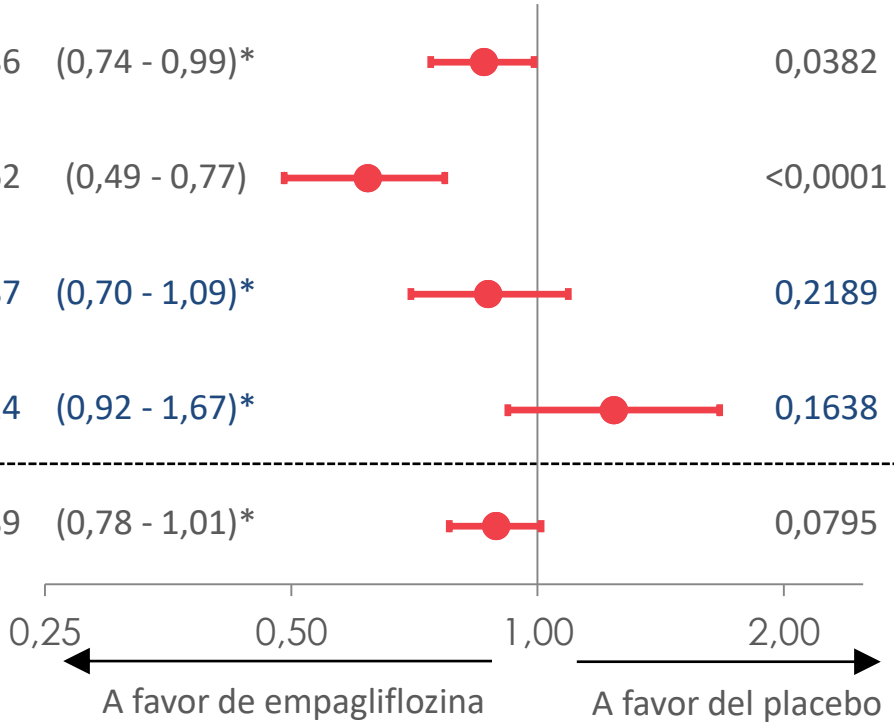


Adapted from Inzucchi SE,Zinman, B, Wanner, C et al. Diab Vasc Dis Res 2015;12:90-100

AACG de 3 puntos y AACG de 4 puntos

Centro Cardiológico Dr. Fernández de Soria

	Pacientes con acontecimiento/analizados Empagliflozina	Placebo	HR	(IC 95%)	*p*-valor
AACG de 3 puntos	490/4687	282/2333	0,86	(0,74 - 0,99)*	0,0382
Muerte CV	172/4687	137/2333	0,62	(0,49 - 0,77)	<0,0001
Infarto de miocardio no mortal	213/4687	121/2333	0,87	(0,70 - 1,09)*	0,2189
Accidente cerebrovascular no mortal	150/4687	60/2333	1,24	(0,92 - 1,67)*	0,1638
AACG de 4 puntos	599/4687	333/2333	0,89	(0,78 - 1,01)*	0,0795



Análisis de regresión de Cox. AACG: acontecimiento adverso cardiovascular grave; HR: cociente de riesgos; CV, cardiovascular
*IC 95.02%

Población del estudio CVD-REAL

Centro Cardiológico
Dr. Fernández de Soria

- Los pacientes del estudio CVD-REAL son diabéticos tipo II que iniciaron **un nuevo tratamiento** con (en adición a la terapia de base que tuviesen):
  -iSGLT-2 (dapagliflozina, empagliflozina y canagliflozina)
  -Cualquier otro antidiabético (iDPP4, sulfos, pioglitazona, insulina, etc)

- Para garantizar que los pacientes son **verdaderos iniciadores** del nuevo tratamiento antidiabético, solo fueron seleccionados aquellos con los que se contaba con su información clínica al menos 1 año en la BD.

Objetivos del estudio

Centro Cardiológico
Dr. Fernández de Soria

Objetivo primario

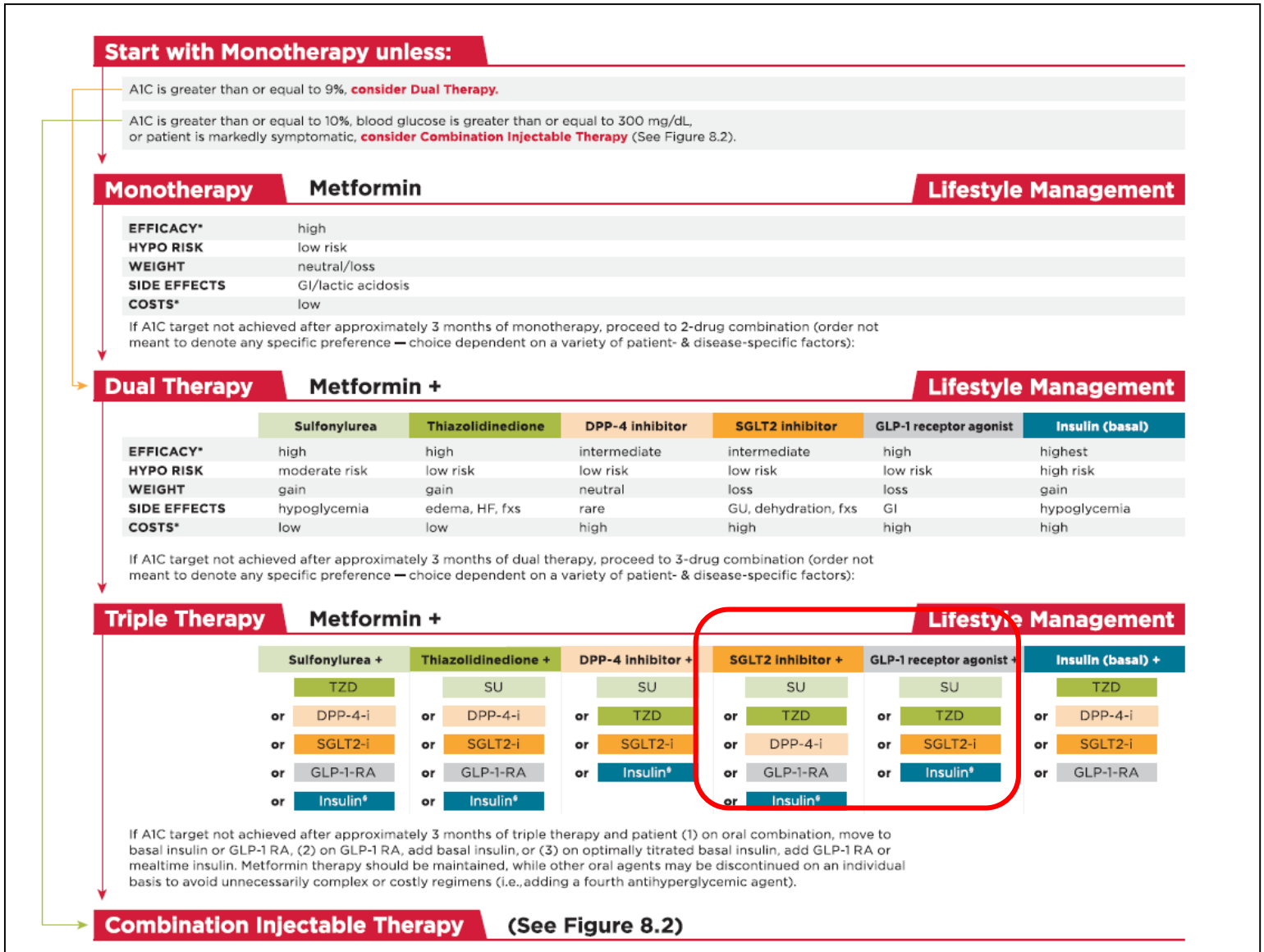
- Comparar el riesgo de hospitalizaciones por insuficiencia cardiaca (hIC) en pacientes con DM2 que inician nuevo tratamiento con iSGLT2 frente a aquellos que inician cualquier otro antidiabético.

Objetivo secundario

- Comparar el riesgo de mortalidad por todas las causas
- Comparar el riesgo de hIC o mortalidad por todas las causas entre los 2 grupos de tratamiento

ADA (American Diabetes Association) Standards of Medical Care in Diabetes (Dec 2016)

Centro Cardiológico Dr. Fernández de Soria



Start with Monotherapy unless:

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

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

Monotherapy **Metformin** **Lifestyle Management**

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

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Dual Therapy **Metformin +** **Lifestyle Management**

	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
EFFICACY*	high	high	intermediate	intermediate	high	highest
HYPO RISK	moderate risk	low risk	low risk	low risk	low risk	high risk
WEIGHT	gain	gain	neutral	loss	loss	gain
SIDE EFFECTS	hypoglycemia	edema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
COSTS*	low	low	high	high	high	high

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Triple Therapy **Metformin +** **Lifestyle Management**

Sulfonylurea +	Thiazolidinedione +	DPP-4 inhibitor +	SGLT2 inhibitor +	GLP-1 receptor agonist +	Insulin (basal) +
TZD	SU	SU	SU	SU	TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or SGLT2-i	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin[6]	or GLP-1-RA	or Insulin[6]	or GLP-1-RA
or Insulin[6]	or Insulin[6]		or Insulin[6]		

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

Combination Injectable Therapy **(See Figure 8.2)**

ADA (American Diabetes Association) Standards of Medical Care in Diabetes (Dec 2016)

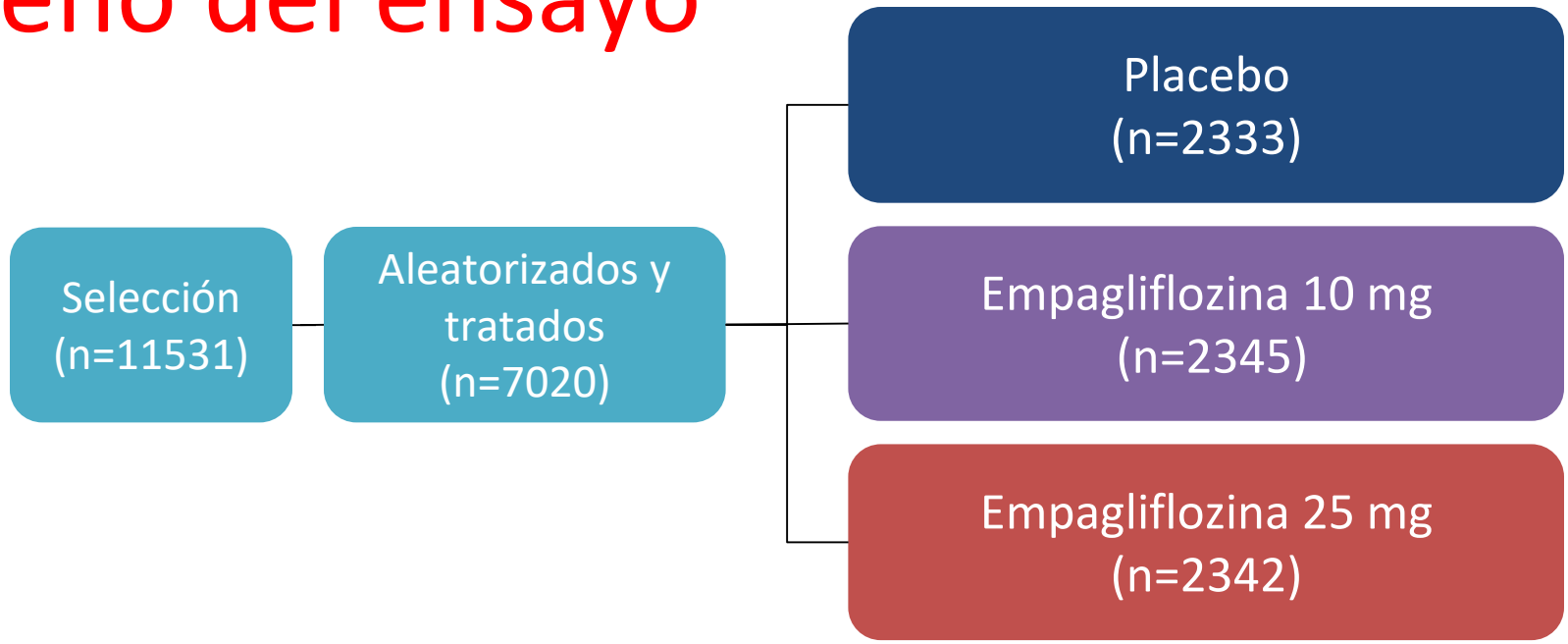
PHARMACOLOGIC THERAPY FOR TYPE 2 DIABETES (p: S65)

In patients with long-standing suboptimally controlled type 2 diabetes and established atherosclerotic cardiovascular disease, **empagliflozin or liraglutide** should be considered as they have been shown to reduce cardiovascular and all-cause mortality when added to standard care. Ongoing studies are investigating the cardiovascular benefits of other agents in these drug classes. B

DIABETIC KIDNEY DISEASE (p: S90)

The glucose-lowering effects of SGLT2 inhibitors are blunted with reduced eGFR, but the renal and cardiovascular benefits of empagliflozin, compared with placebo, were not reduced among trial participants with baseline eGFR 30–59 mL/min/1.73 m^2, compared with participants with baseline eGFR $\geq$60 mL/min/1.73 m^2 (19,28).

Diseño del ensayo



- Se suministró la medicación del estudio junto con el tratamiento convencional
- Asignación de tratamiento con doble enmascaramiento
- El ensayo debía continuar hasta que al menos 691 pacientes experimentaran un acontecimiento establecido como criterio principal de valoración

ESTUDIO LEADER