



# DIABETES

Madrid, 2 de octubre 2019

5º CURSO AVANZADO



RedGDPS Madrid

#redgdpsmadrid

ESCENARIOS CLÍNICOS  
EN DM TIPO 2 PARA  
MÉDICOS DE FAMILIA

“Casos de la práctica  
diaria”



# DIABETES

## E

# INSUFICIENCIA CARDIACA



Diabetes Mellitus

TOMO V - NUM. 615 | Oficina de la ciudad de México. No.  
calle de Hidalgo, número 14. | MEXICO, SABADO 12 DE OCTUBRE DE 1918

# PASAN YA DE MIL LOS CASOS DE "INFLUENZA ESPAÑOLA" QU SE REGISTRAN EN LA CAPIT

SOLAMENTE SE TIENE NOTICIA DE DOS DEFUNCIONES

Porque la Pandemia, tan Gra-  
no en las Ciudades de la  
Frontera, en México  
es Benigna

VENTE MIL ATACADOS, EN  
NUEVO LEÓN

Amenazan con  
Declararse en  
Huelga Todos  
los Maestros

Está Obliga  
la Entend  
la Aceptad  
la Paz

Si el H. Ayuntamiento no  
les Cobre los Adelados Co-  
respondientes a sus Sarcos  
Las Notas de los  
Gastrales Duran O  
Ayuntamiento,

Insuficiencia Cardiaca

## MAGNITUD DEL PROBLEMA

Diabetes Mellitus

### NORTH AMERICA & CARIBBEAN

Half the global diabetes healthcare spending occurs in this region



1 in 7 adults in this region is at risk of type 2 diabetes

### EUROPE

USD 1 in every USD 4 of the global diabetes healthcare spending occurs in this region



1 in 6 live births is affected by hyperglycaemia in pregnancy

### WESTERN PACIFIC

1 in 3 adults with diabetes lives in this region  
1 in 3 deaths attributable to diabetes happen in this region



### MIDDLE EAST AND NORTH AFRICA

1 in 9 live births are affected by hyperglycaemia in pregnancy

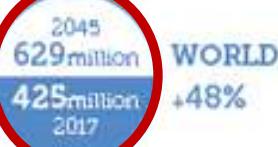
1 out of 2 deaths due to diabetes were in people under the age of 60



### SOUTH AND CENTRAL AMERICA

2 out of 5 people with diabetes were undiagnosed

Only 4% of global healthcare expenditure for diabetes spent in this region



### AFRICA

2 out of 3 people with diabetes are undiagnosed

3 out of 4 deaths due to diabetes were in people under the age of 60



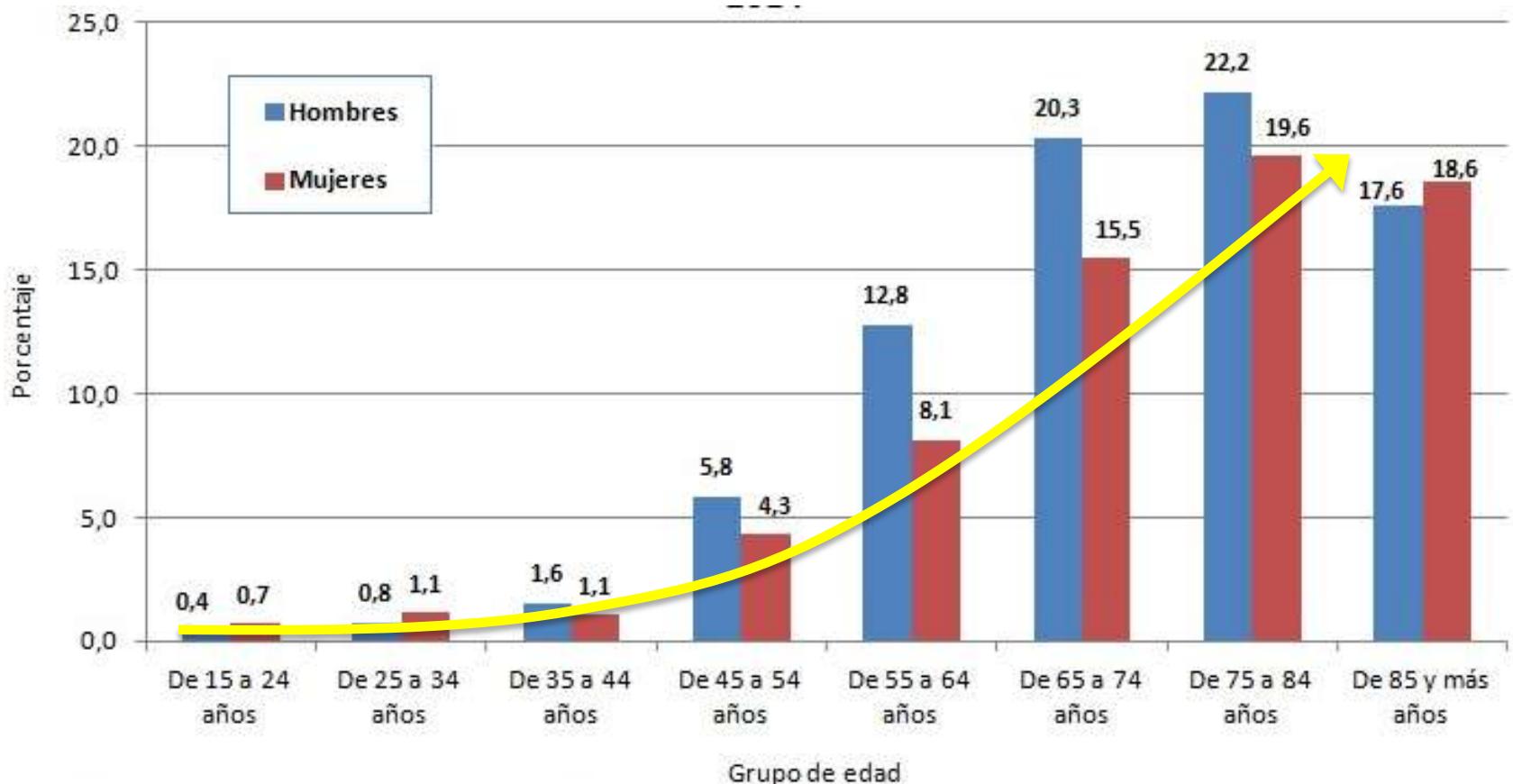
### SOUTH-EAST ASIA

1 in 5 adults with diabetes lives in this region

1 in 4 live births is affected by hyperglycaemia in pregnancy



## Porcentaje de pacientes con DM segun sexo y grupo de edad en España 2014



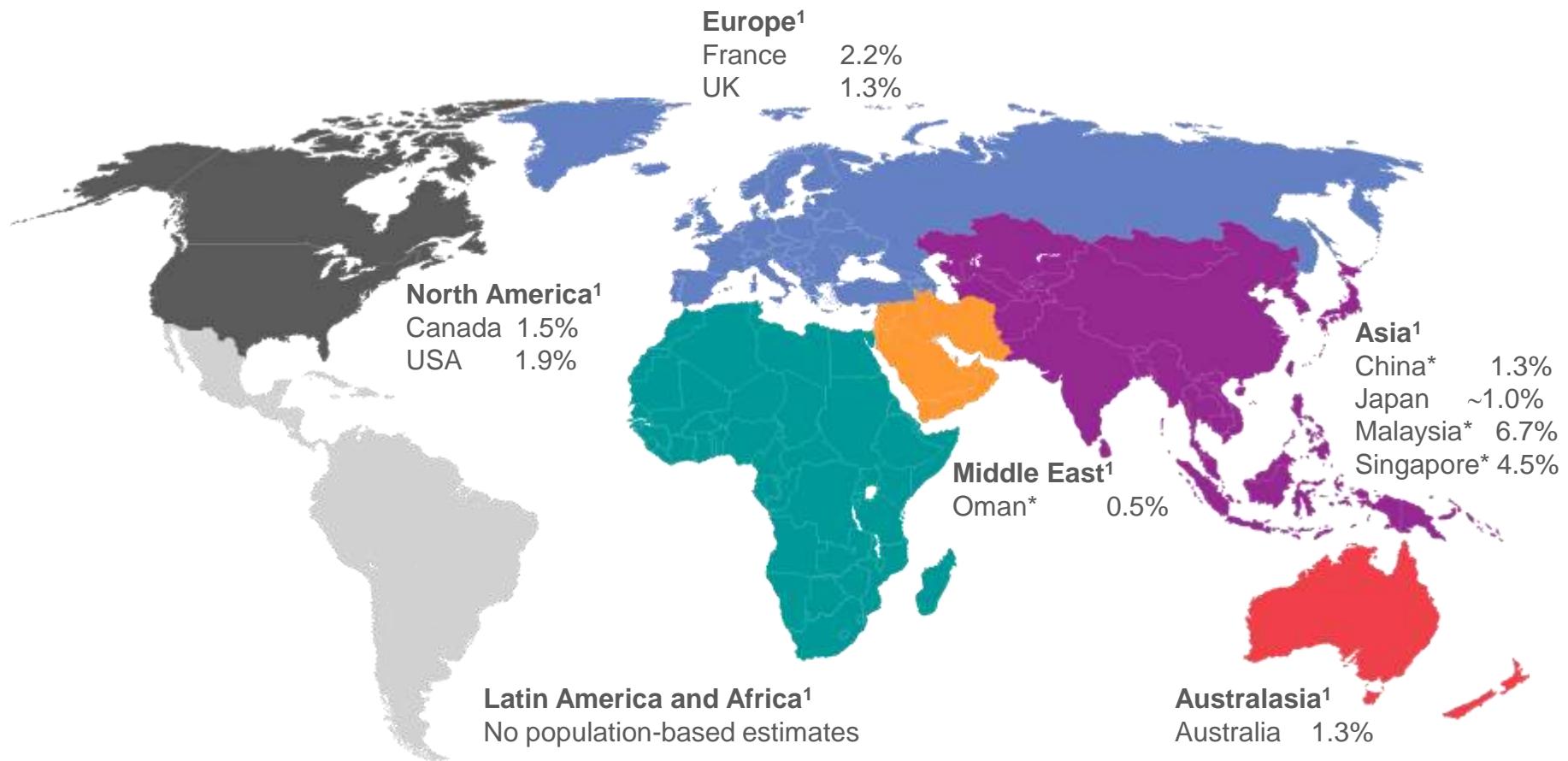
Fuente: INE: Inebase. Encuesta Europea de Salud (EES), 2014.

## MAGNITUD DEL PROBLEMA

Diabetes Mellitus

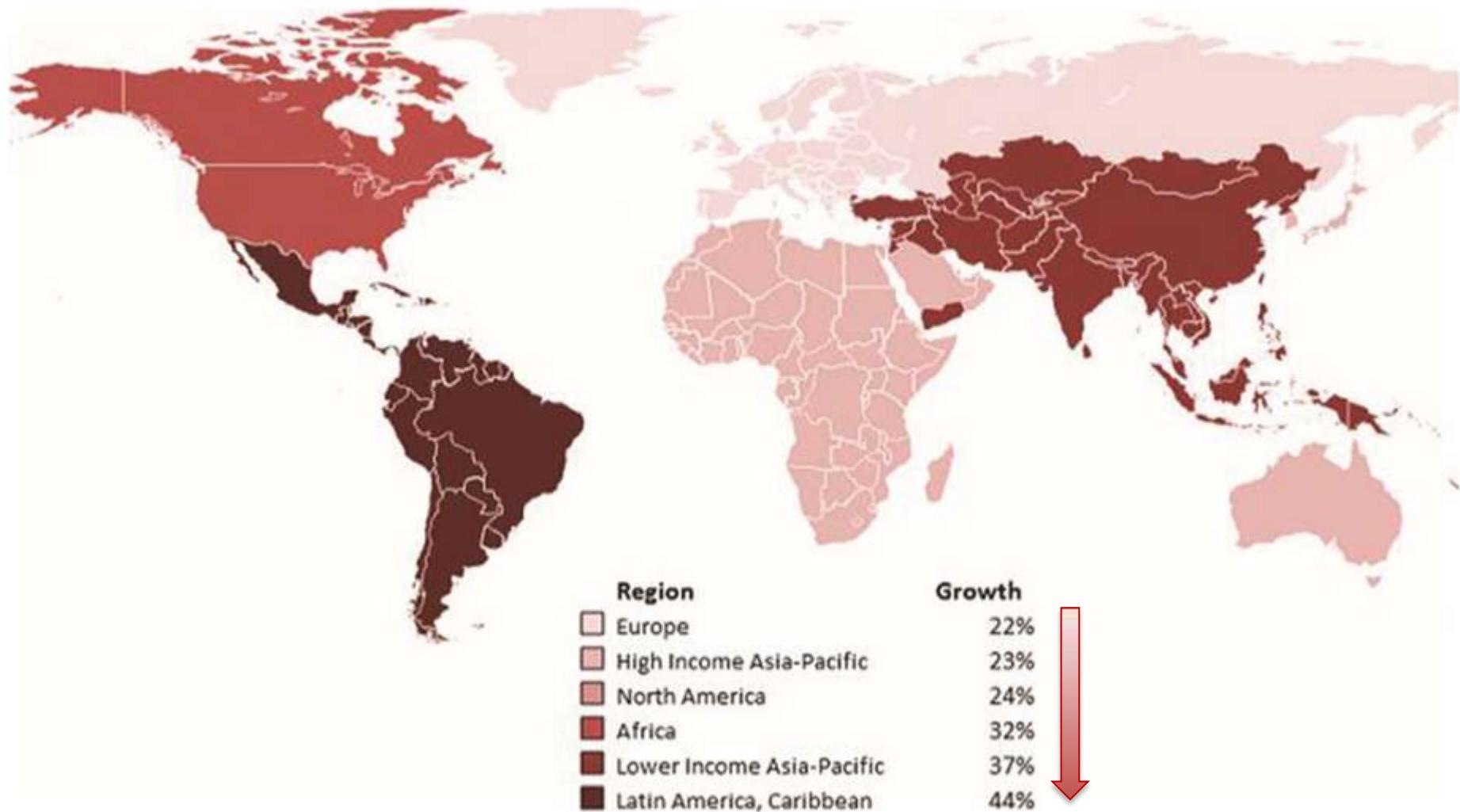
Insuficiencia Cardiaca

## Prevalencia de Insuficiencia Cardiaca en diferentes países

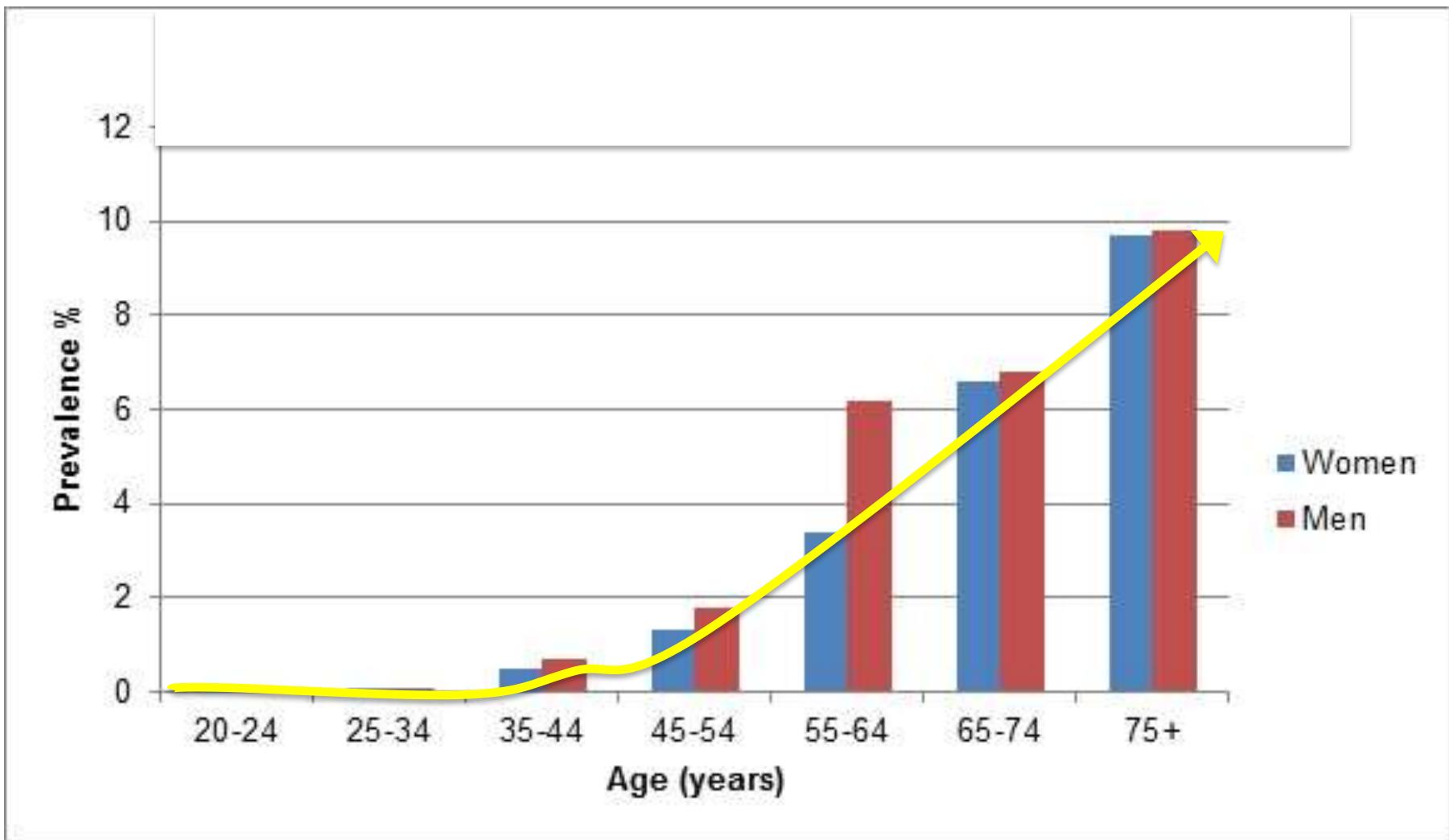


Adapted from Ponikowski P et al. European Society of Cardiology. Heart failure - Preventing disease and death worldwide. 2014. Available at: [https://www.escardio.org/static\\_file/Escardio/Subspecialty/HFA/WHFA-whitepaper-15-May-14.pdf](https://www.escardio.org/static_file/Escardio/Subspecialty/HFA/WHFA-whitepaper-15-May-14.pdf) (accessed Oct 2015)

## Incremento de la prevalencia de Insuficiencia cardiaca



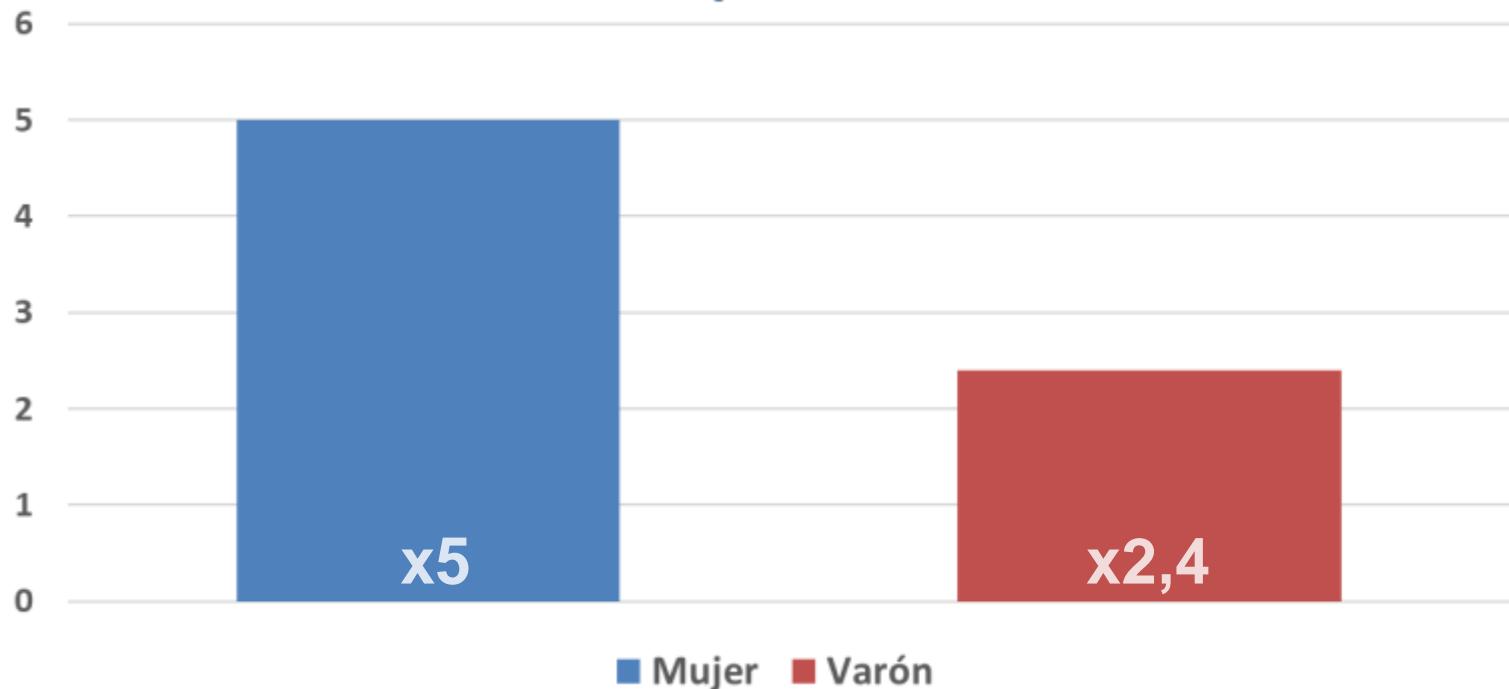
## Porcentaje de pacientes con IC segun sexo y grupo de edad



## MAGNITUD DEL PROBLEMA

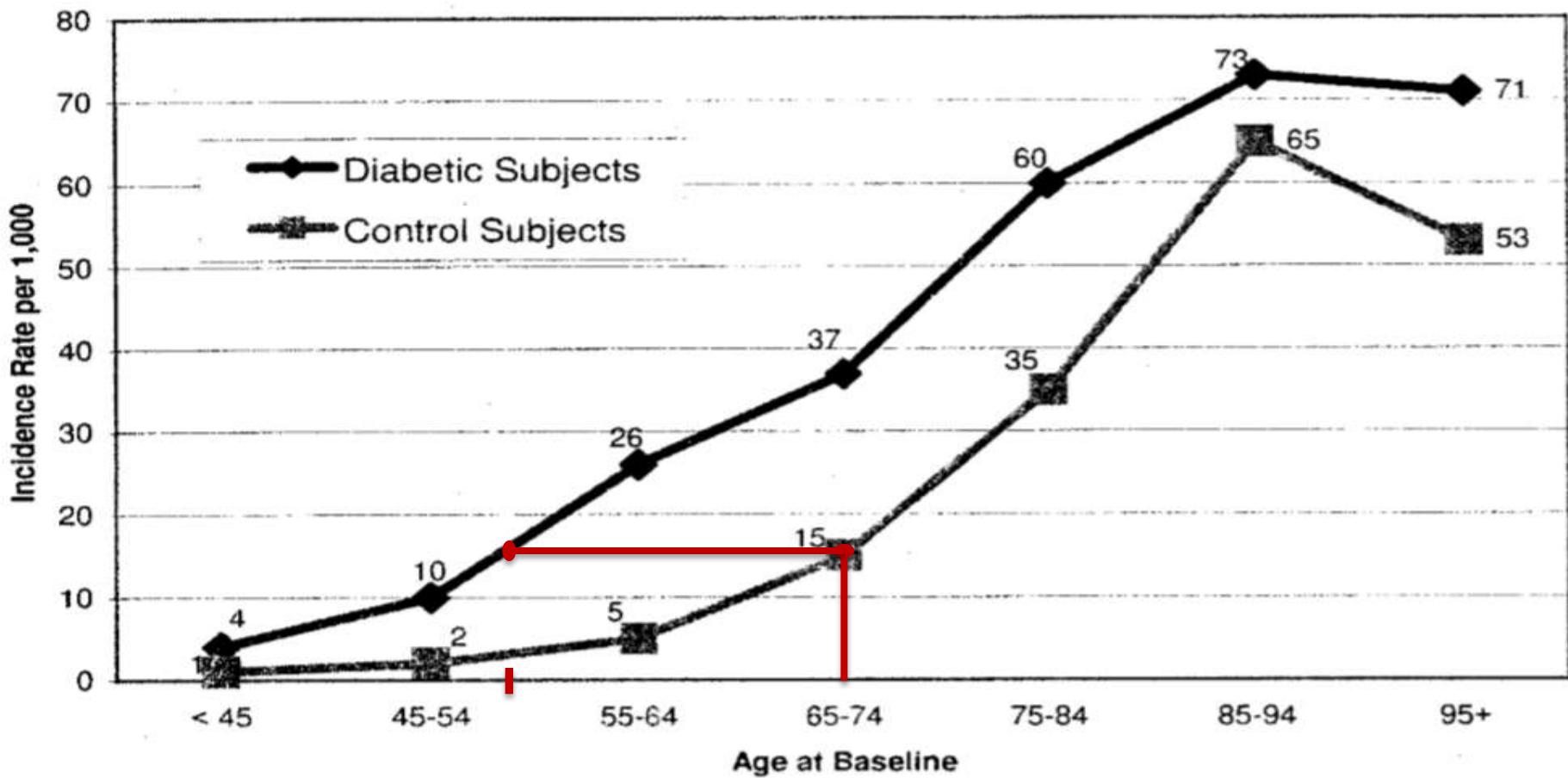


## Incremento del riesgo de presentar IC en el paciente DM



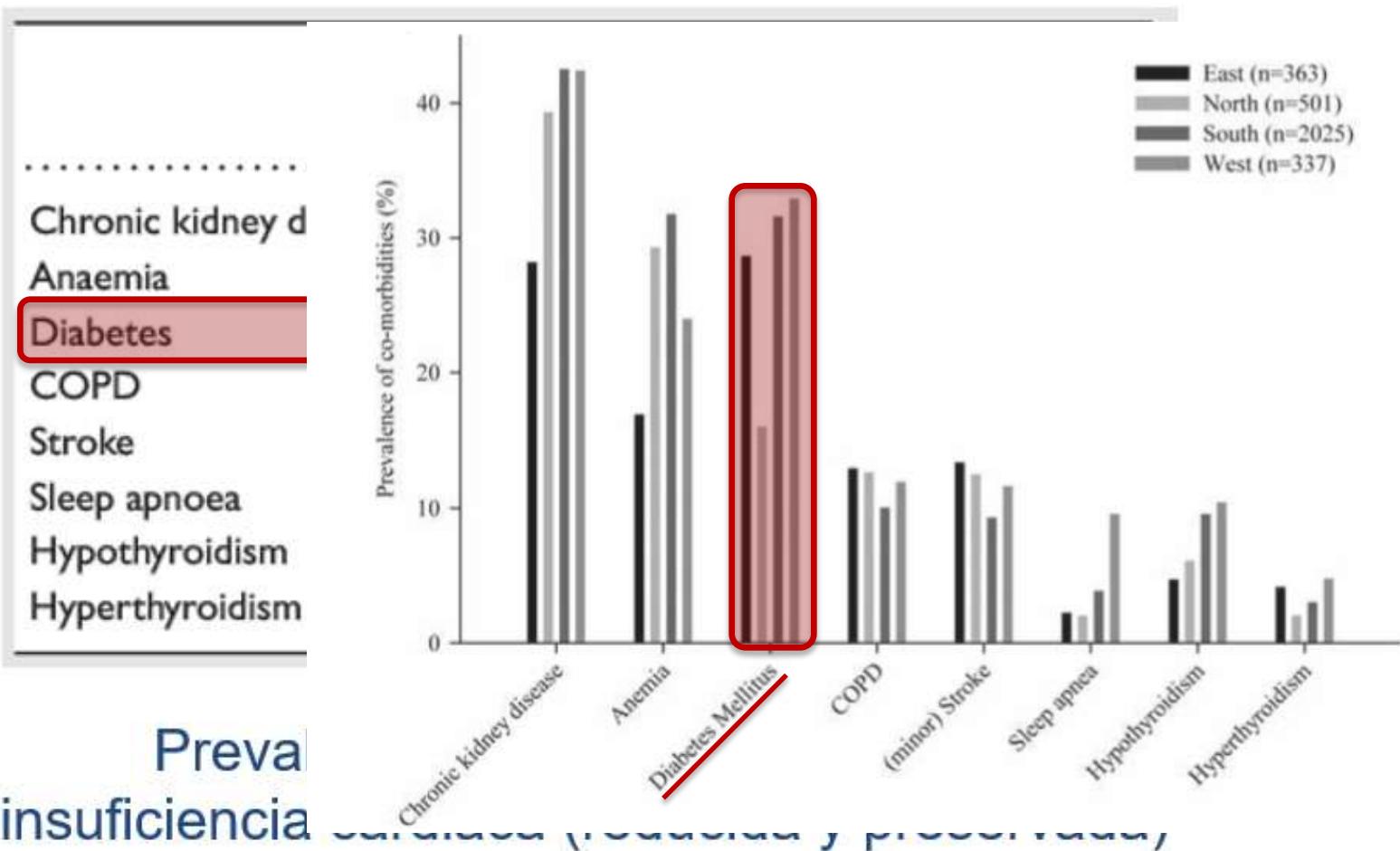
Nichols GA, Gullion CM, et al. The incidence of congestive heart failure in type 2 diabetes: an update. Diabetes Care. 2004;27:1879–1884.

## Incidencia anual de Insuficiencia Cardiaca (/1000 pacientes)



Nichols GA, Gullion CM, et al. The incidence of congestive heart failure in type 2 diabetes: an update. Diabetes Care. 2004;27:1879–1884.

## PREVALENCIAS



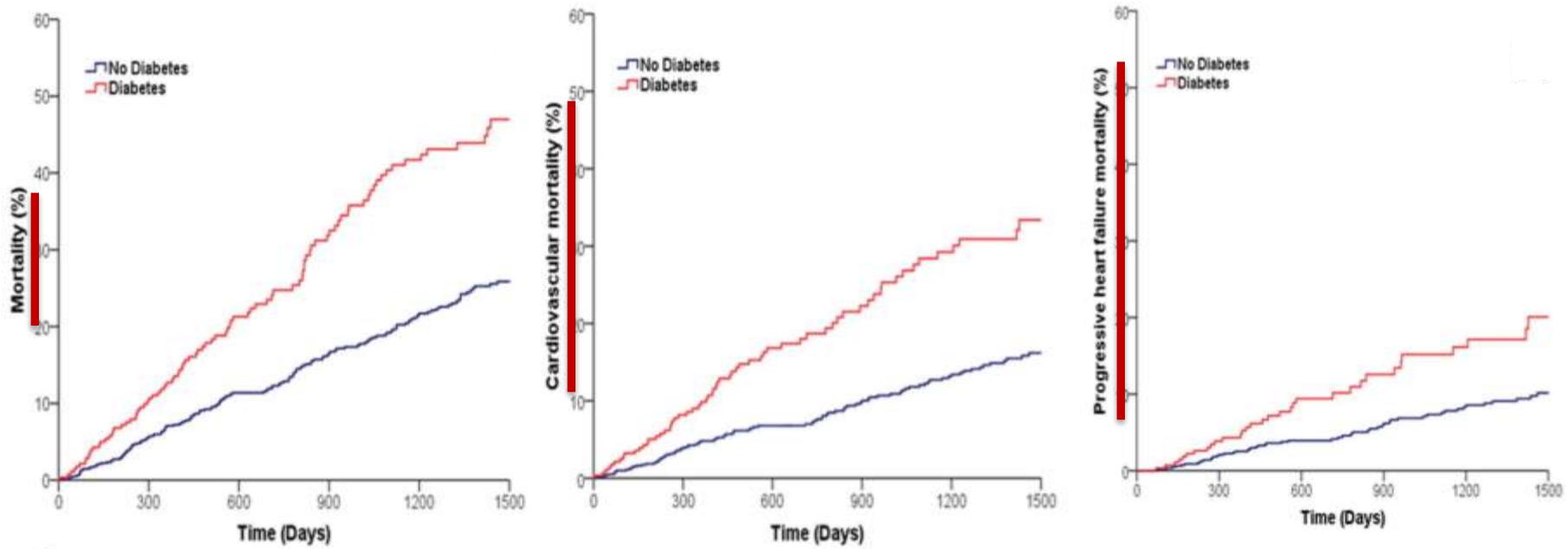
Preva  
insuficiencia

## PREVALENCIAS

<b>Cardiovascular outcome</b>	<b>Studies</b>	<b>N</b>	<b>Rate<sup>a</sup> (%)</b>	<b>95% confidence interval (%)</b>
Stroke	39	3,901,505	7.6	6.6–8.6
Myocardial infarction	13	3,518,833	10.0	7.5–12.5
Angina pectoris	4	354,743	14.6	12.0–17.3
<u>Heart failure</u>	14	601,154	14.9	13.0–16.7
Atherosclerosis	4	1153	29.1	21.7–36.4
Coronary artery disease	42	3,833,200	21.2	20.3–22.2
Cardiovascular disease (any)	53	4,289,140	32.2	30.0–34.4

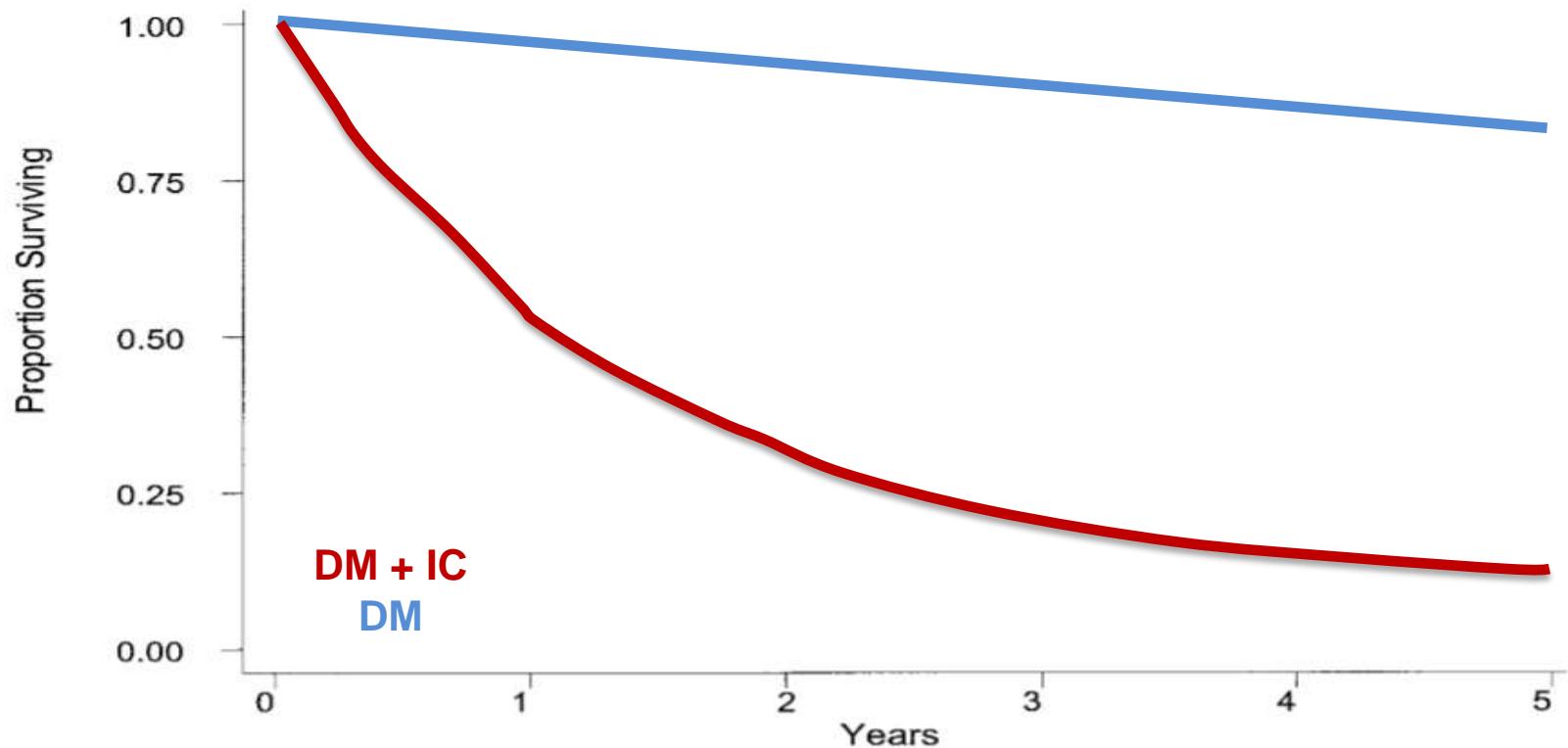
Tasas de prevalencia de comorbilidades cardiovasculares en el paciente con DM2

## PRONÓSTICO



Mortalidad en pacientes con Insuficiencia Cardiaca en relación a la presencia o no de DM

## PRONÓSTICO



Supervivencia en pacientes con DM en relación a la presencia o no de Insuficiencia Cardiaca

# ¿Magnitud del problema para Medicina Interna?

Tabla 3 Hospitalizaciones en pacientes con diabetes tipo 2 y enfermedad cardiovascular en España (año 2015). Análisis agrupado por servicios de medicina interna, otros servicios médicos y servicios quirúrgicos

	Medicina interna (212.013)		Otros servicios médicos (227.271)		Servicios quirúrgicos (179.904)	
	n	%	n	%	n	%
Enfermedad cardiovascular	107.428	42,3	106.160	41,8*	40.124	15,8*
Cardiopatía isquémica	16.792	28,9	34.163	58,8*	7.164	12,3*
<u>Insuficiencia cardiaca congestiva</u>	69.709	55,6	47.077	37,5*	8.596	6,9*
Enfermedad cerebrovascular	26.248	40,8	29.878	46,4*	8.216	12,8*
Enfermedad arterial periférica	16.320	28,6**	18.226	32,0**	22.435	39,4

ORIGINAL

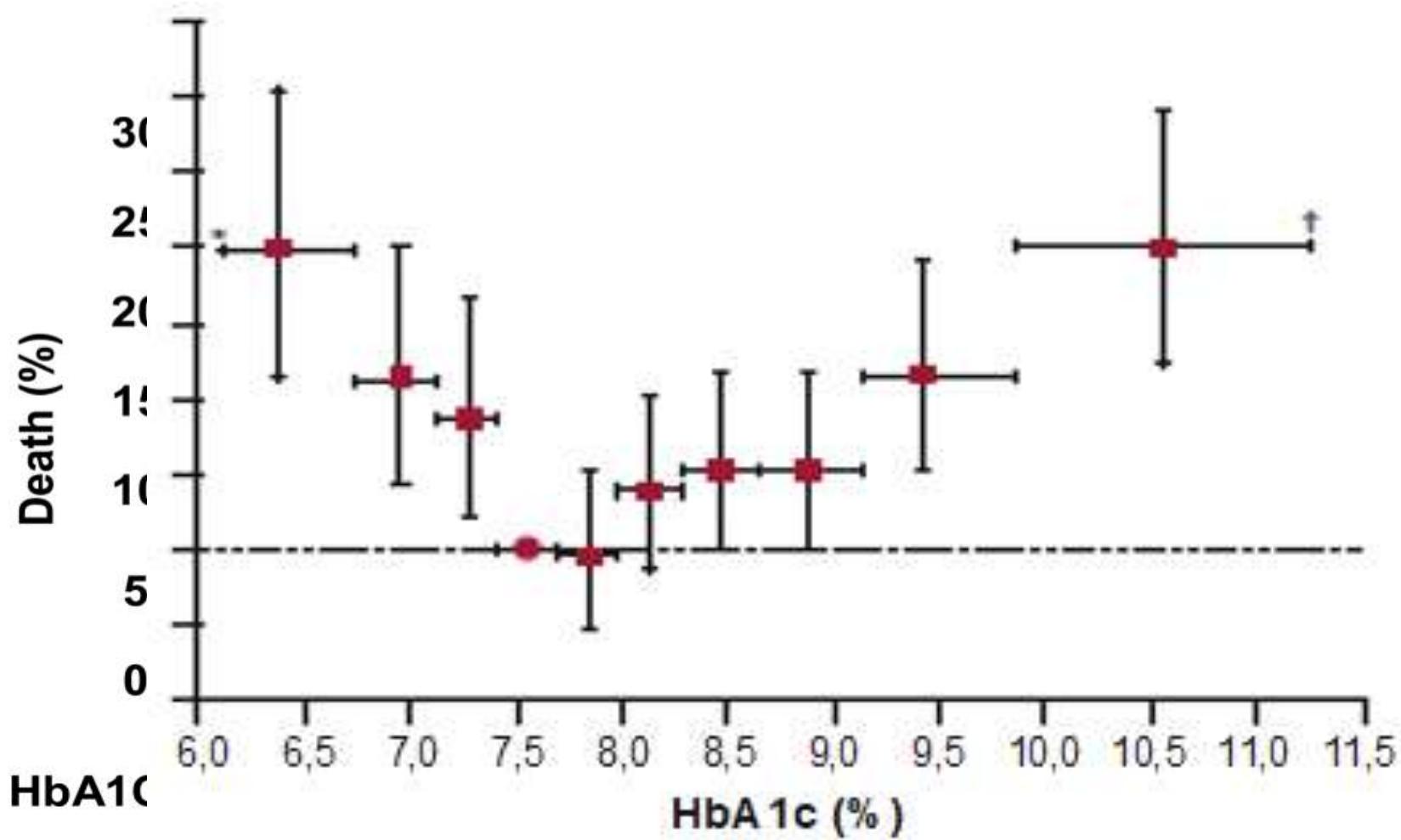
## Análisis de las hospitalizaciones por enfermedad cardiovascular en población diabética en España

A. Zapatero-Gaviria<sup>a,\*</sup>, R. Gómez-Huelgas<sup>b</sup>, J. Canora-Lebrato<sup>a</sup>, J. Ena-Muñoz<sup>c</sup>, M. Romero-Sánchez<sup>a</sup>, M. Méndez-Bailón<sup>d</sup>, J. Marco-Martínez<sup>d</sup> y R. Barba-Martín<sup>e</sup>



## INFLUENCIA DE LA DM EN LA IC

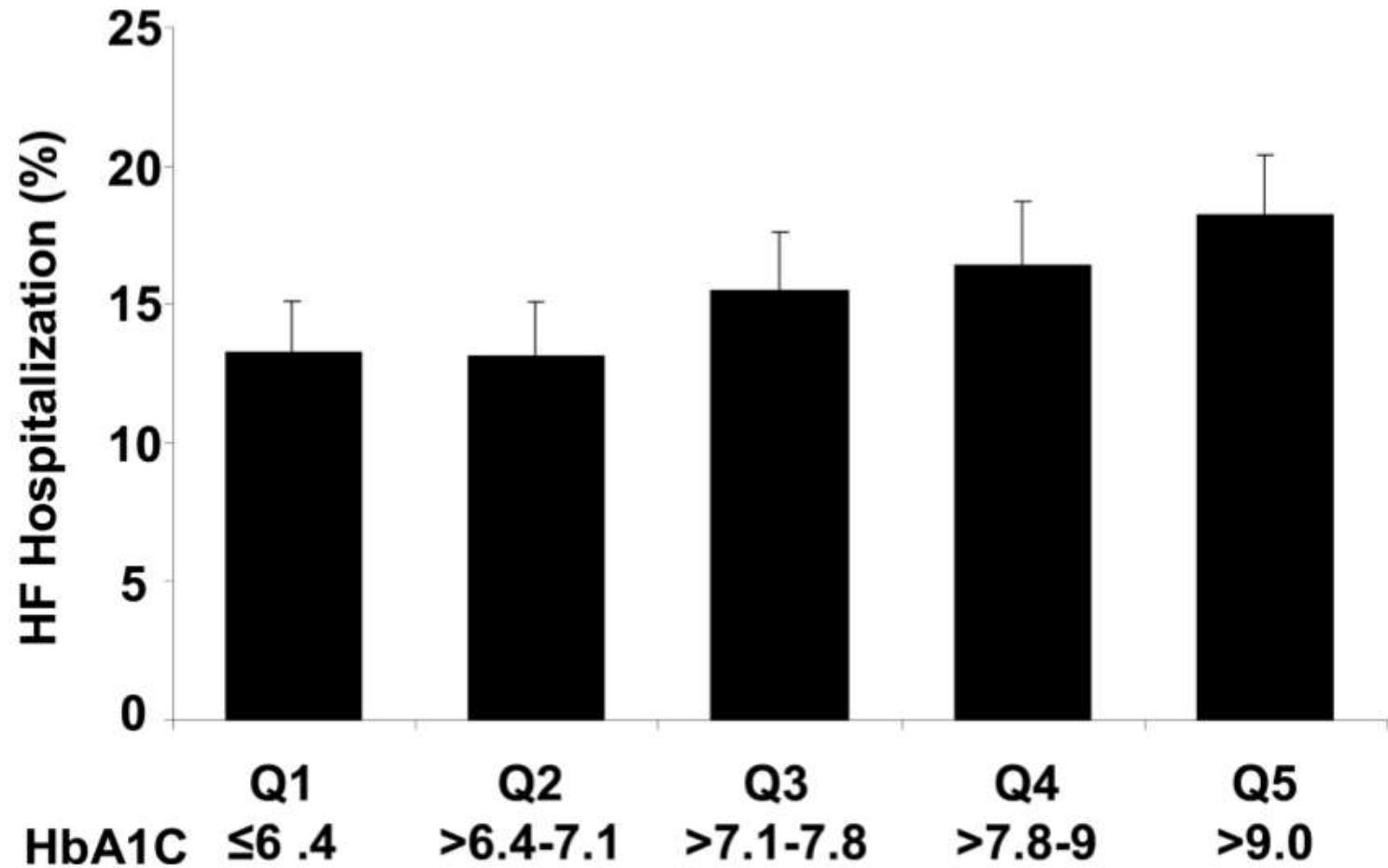
Control glucémico



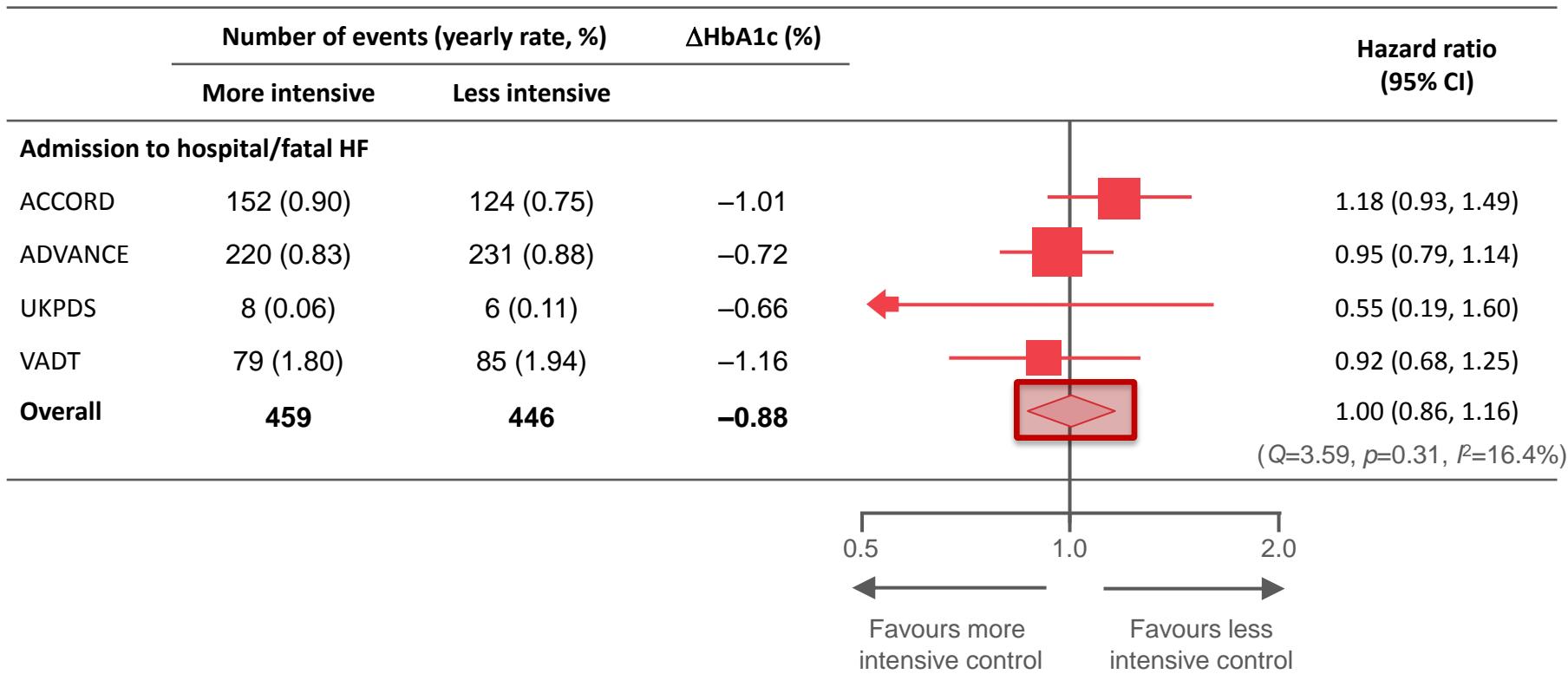
Mortalidad a los 2 años en pacientes con DM e IC según quintiles de HbA1c

Craig J Currie, et al. Lancet 2010; 375:481-89

D Aguilar et al. J Am Coll Cardiol. 2009 July 28; 54(5): 422–428.



Porcentaje de ingresos por IC en pacientes con DM en  
2 años de seguimiento según quintiles de HbA1c



Efecto del control glucémico intensivo sobre la insuficiencia cardiaca

## INFLUENCIA DE LA DM EN LA IC

Control glucémico

Efecto de los antidiabéticos

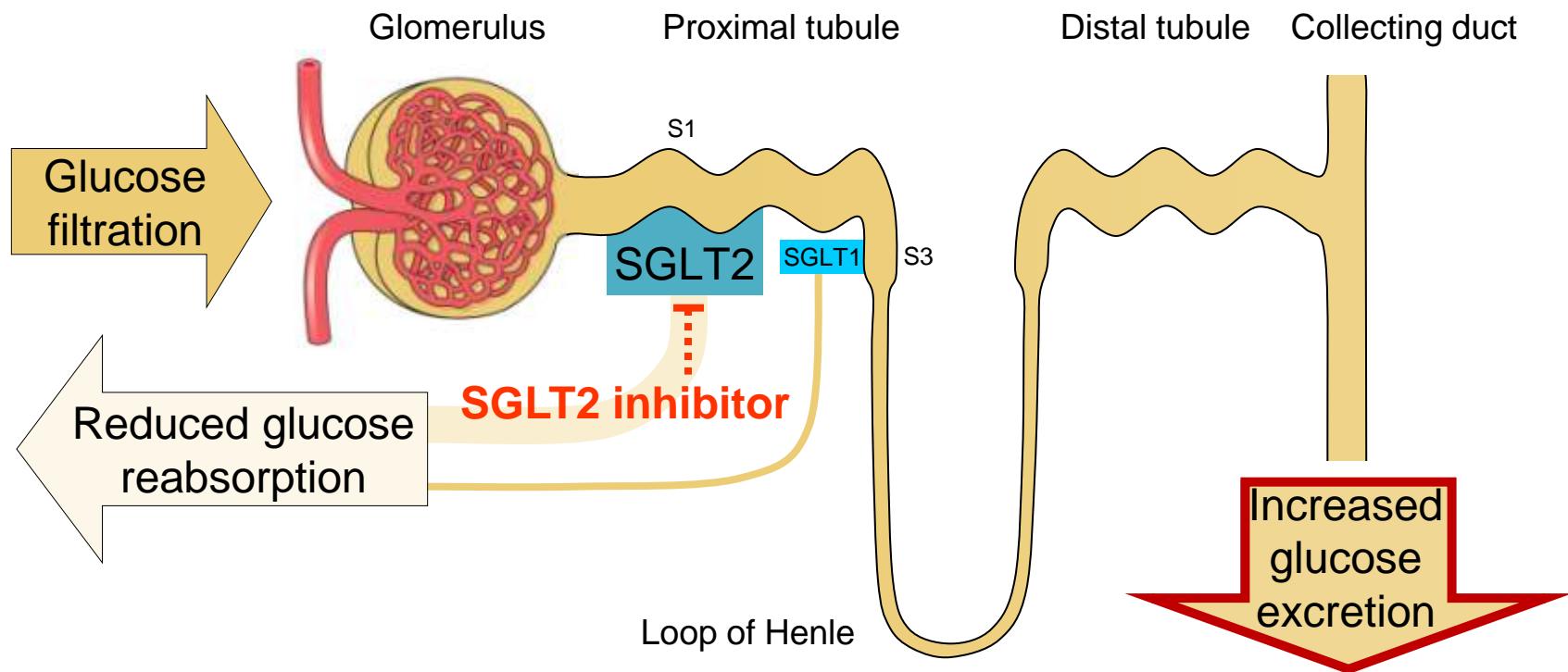
FARMACO	EFFECTO SOBRE IC
Metformina	●
Sulfonilureas	○
Insulina	●
Glitazonas	●
iDPP-4	
Sitagliptina-Linagliptina	●
Saxagliptina-Alogliptina	○
Vildagliptina	○
aGLP-1	●
iSGLT-2	?

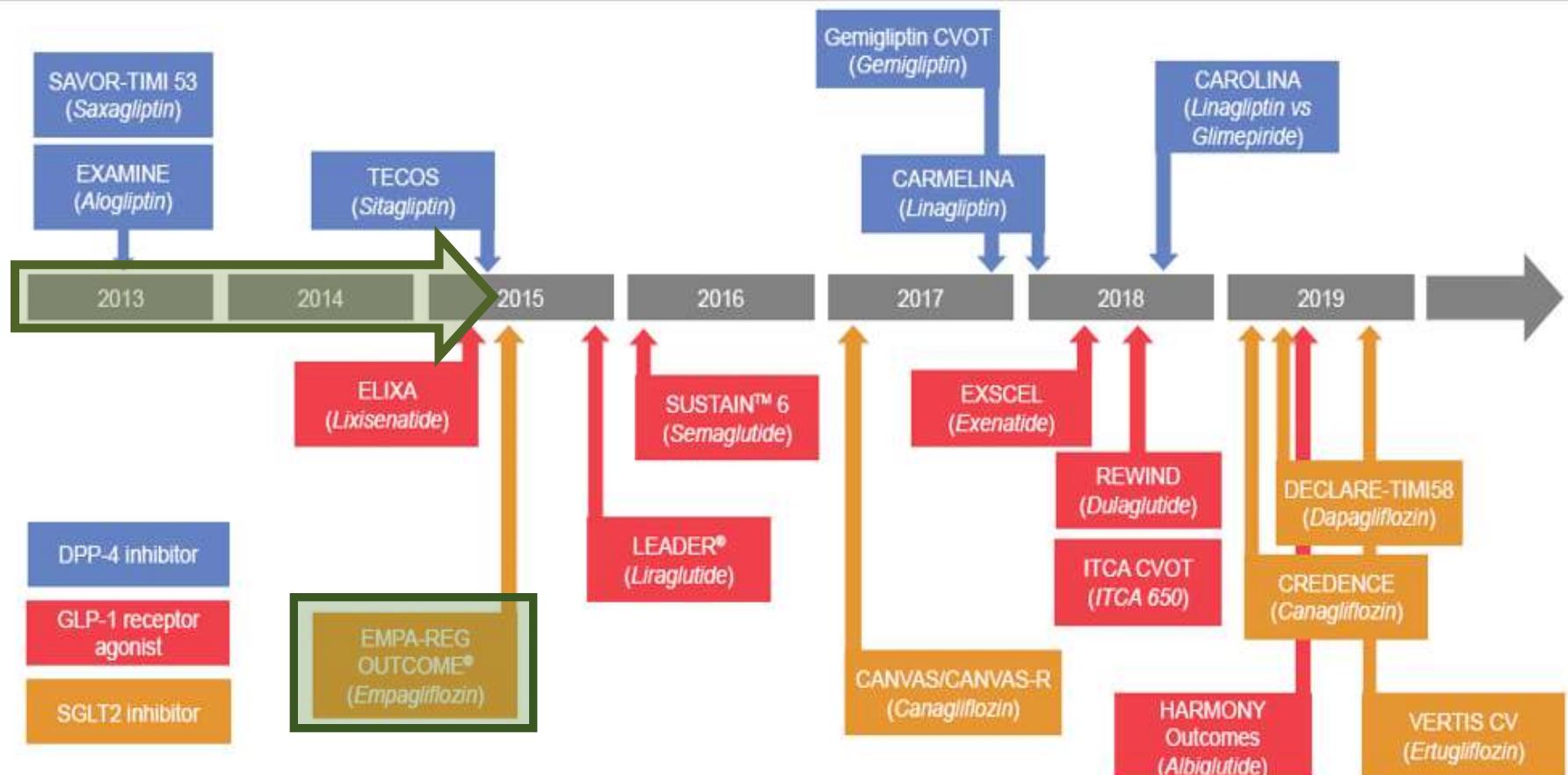
\*Meta-analysis; †As a secondary outcome in a CVOT, not in a dedicated HF trial with a study population selected for HF

1. Gilbert RE *et al.* Lancet 2015;385:2107; 2. Green JB *et al.* N Engl J Med 2015;373:232; 3. Pfeffer *et al.* ADA, 8 Jun 2015, Boston, USA (oral presentation); 4. ORIGIN Investigators. New Engl J Med 2012;367:319; 5. Zinman B *et al.* N Engl J Med 2015 (epub)

# DATOS DE LOS ISGLT-2 SOBRE

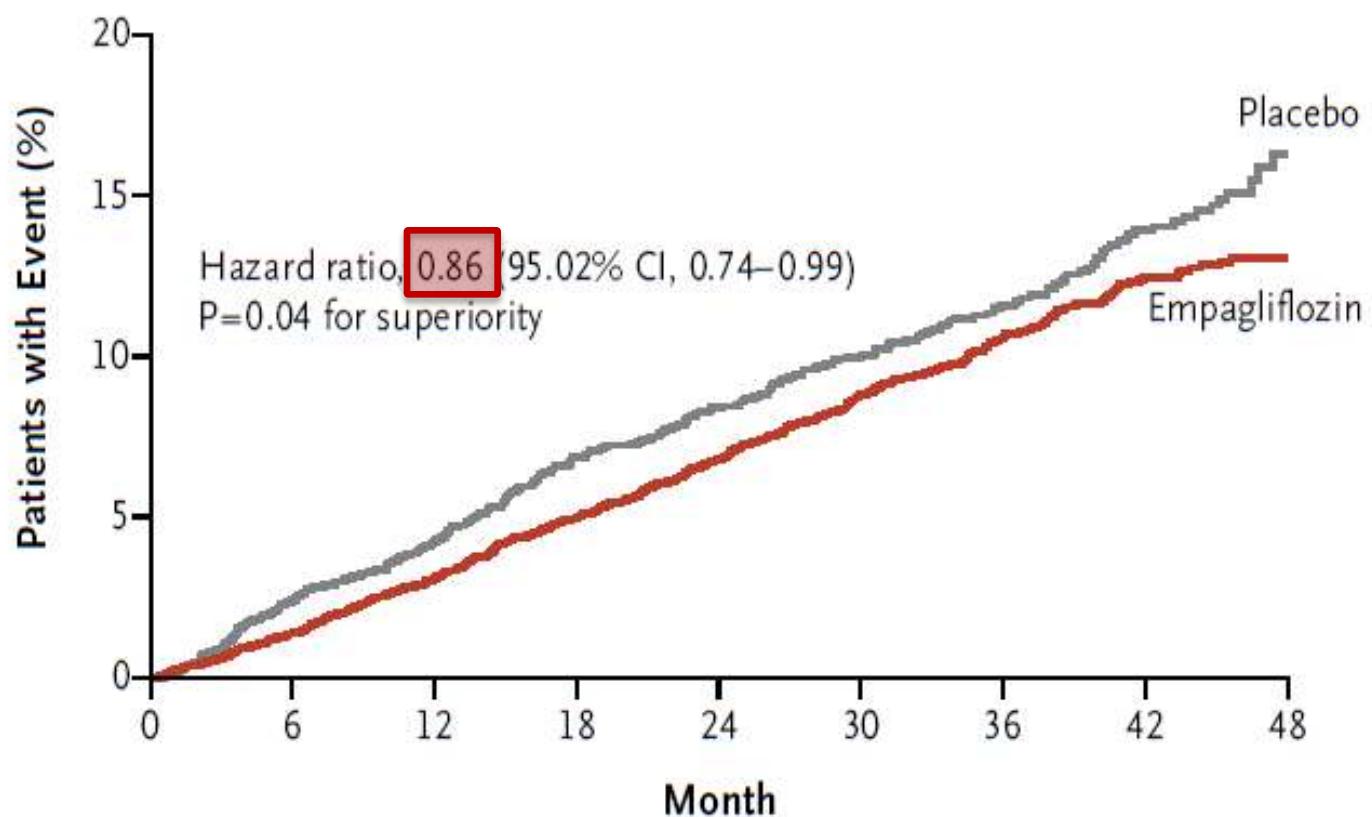
# LA INSUFICIENCIA CARDIACA



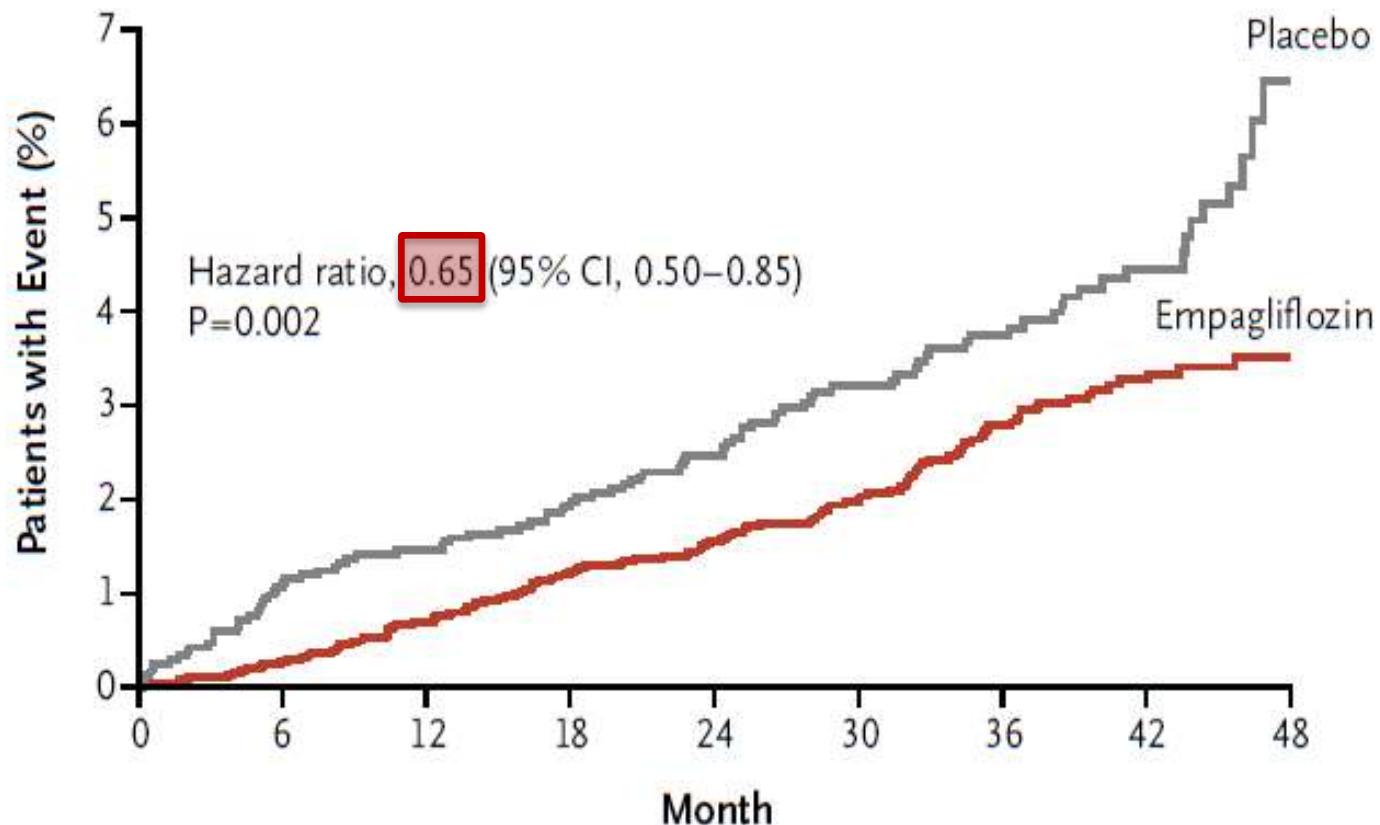




### Primary Outcome

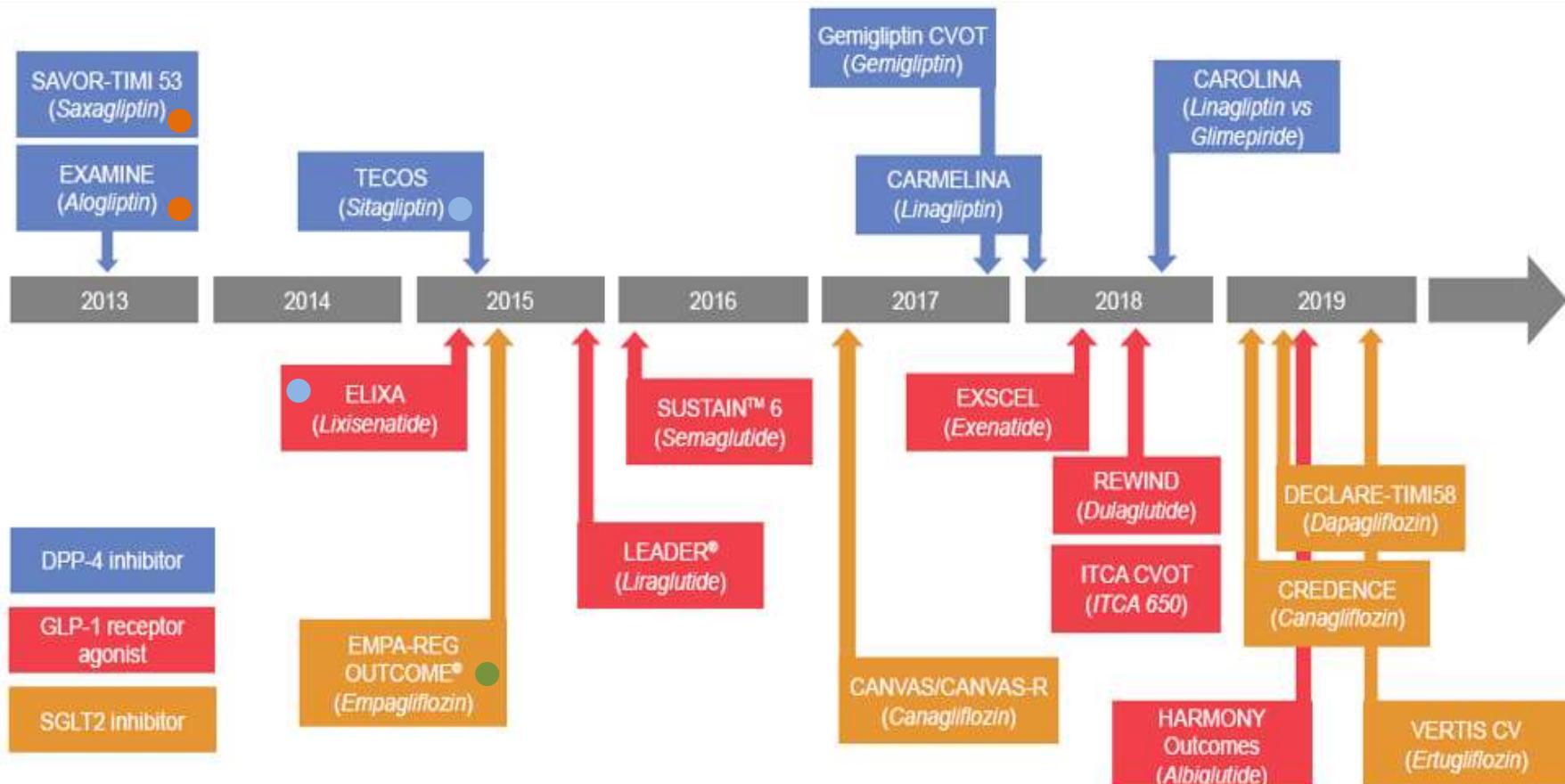


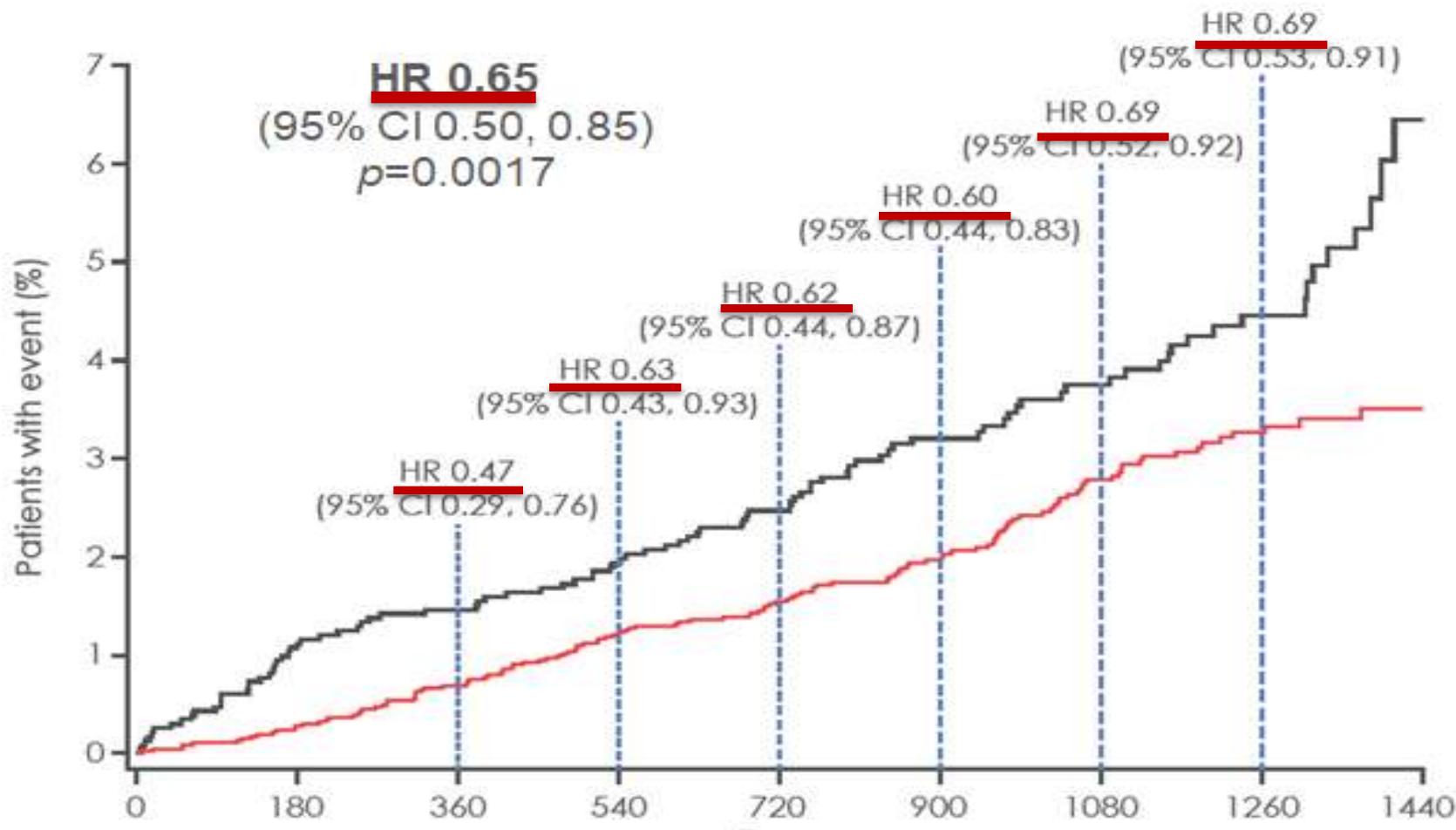
## Hospitalization for Heart Failure

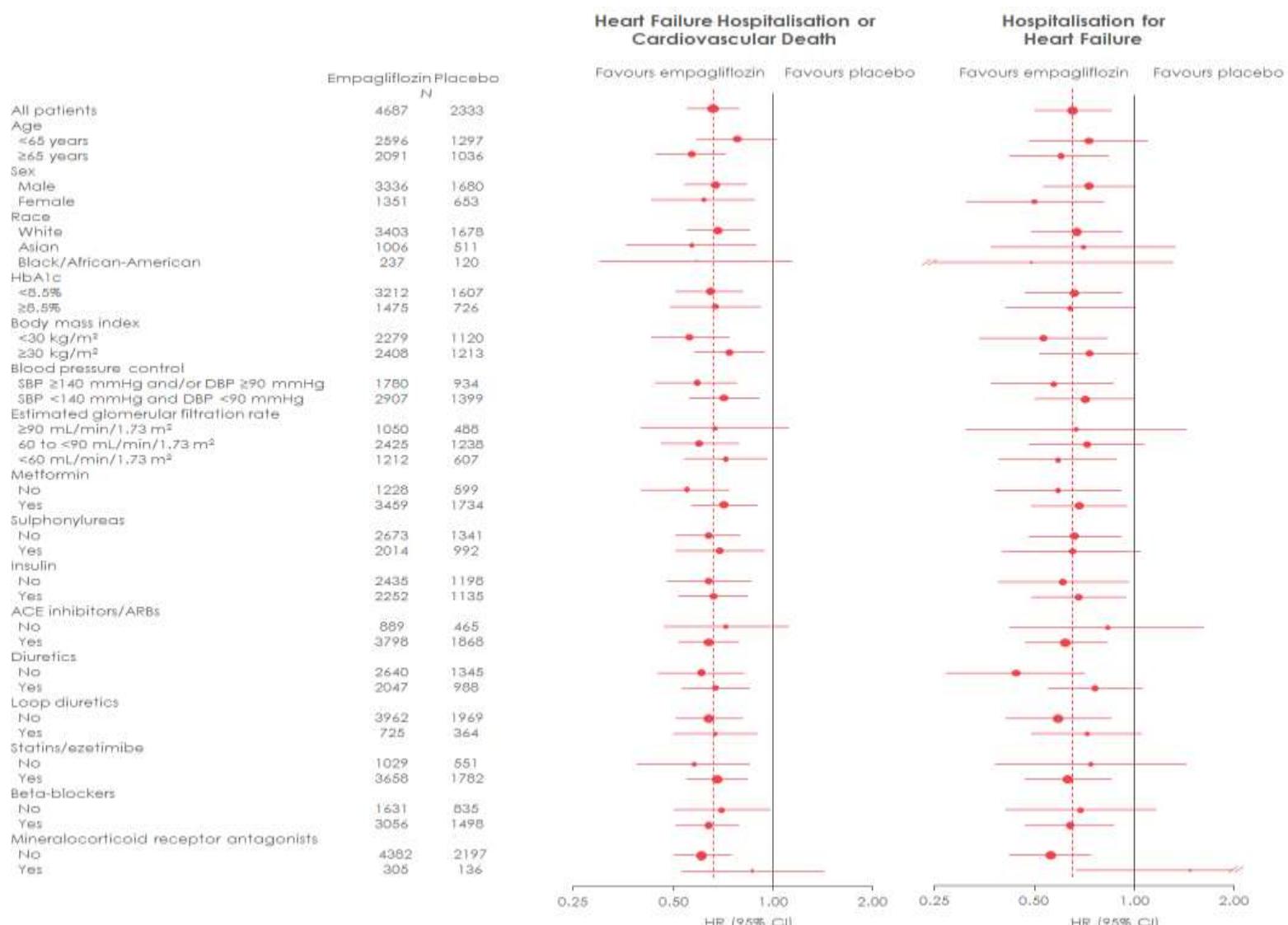


Zinman B, et al. *N Engl J Med.* 2015 Nov 26;373(22):2117-28

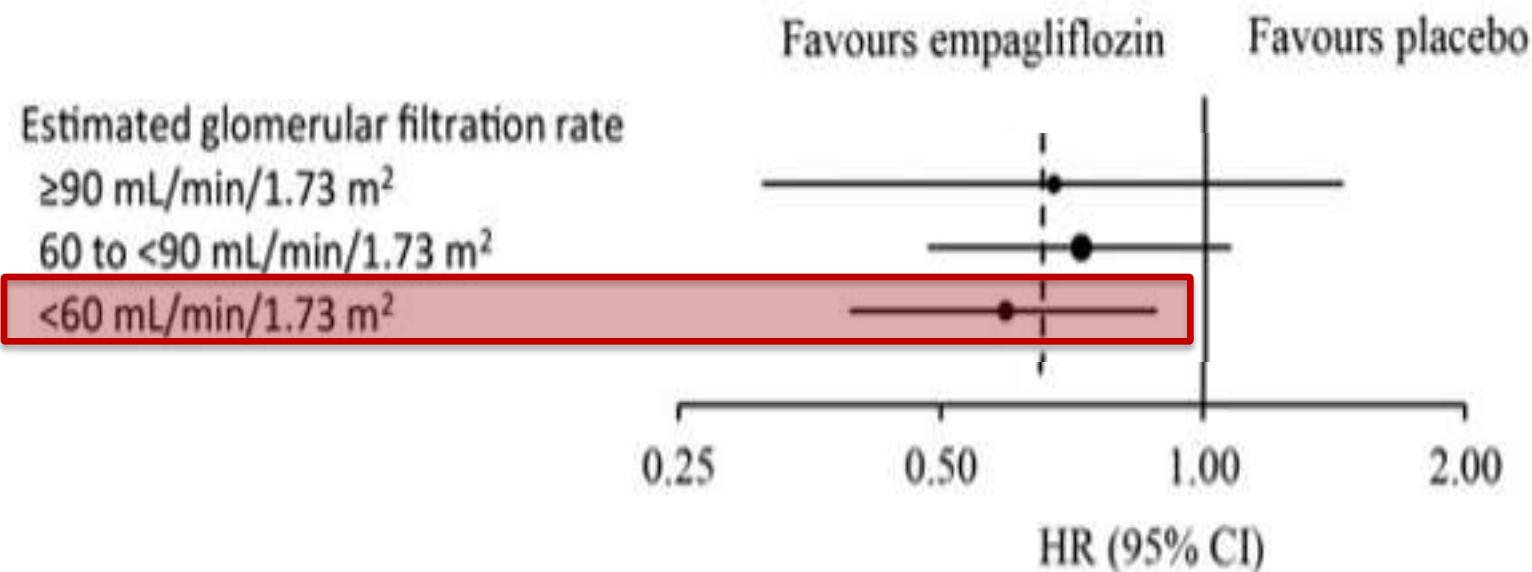
# INSUFICIENCIA CARDIACA





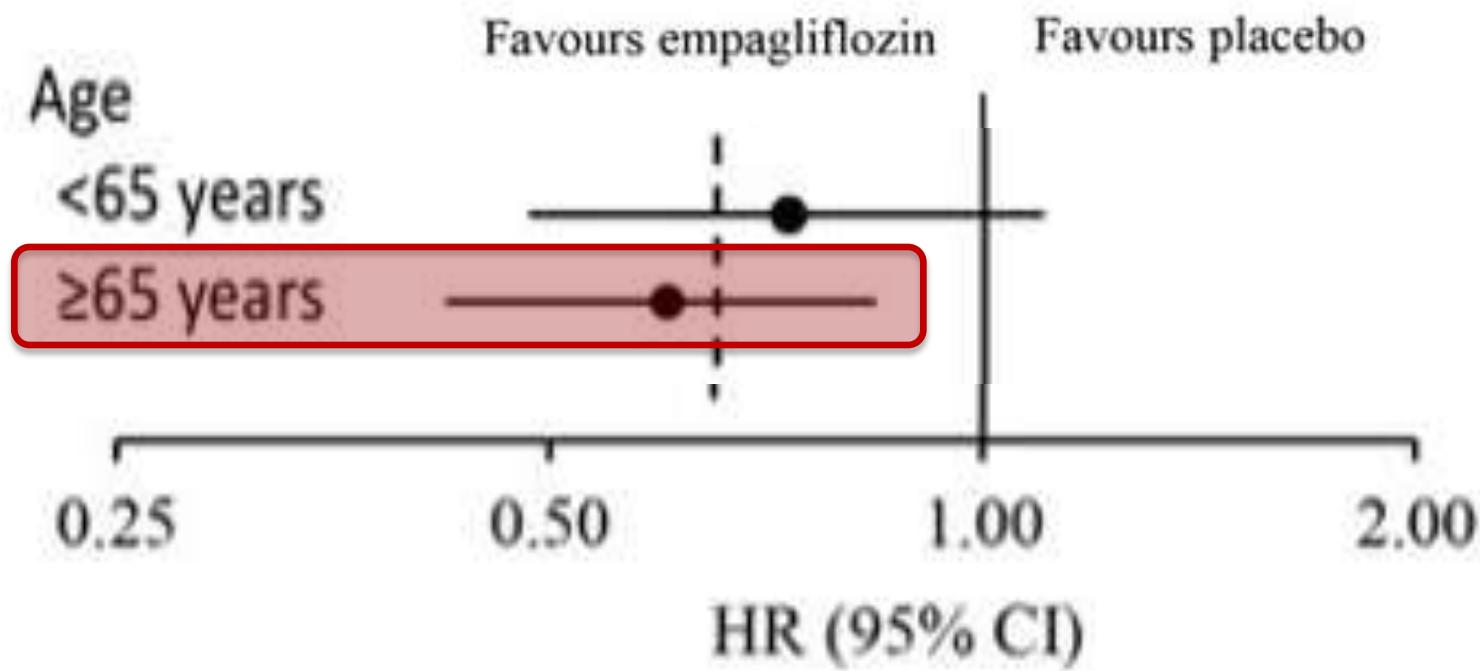


## Hospitalization for heart failure



Reducción de ingresos por IC en EMPA-REG según FGe

## Hospitalization for heart failure



Reducción de ingresos por IC en EMPA-REG según edad

### Hospitalization for heart failure

All patients

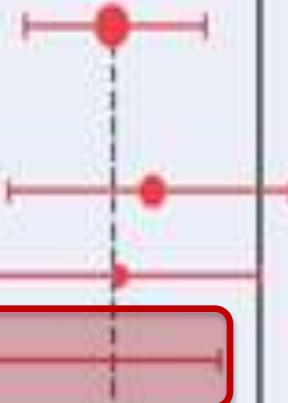
Age at baseline, years

<65

65 to <75

≥75

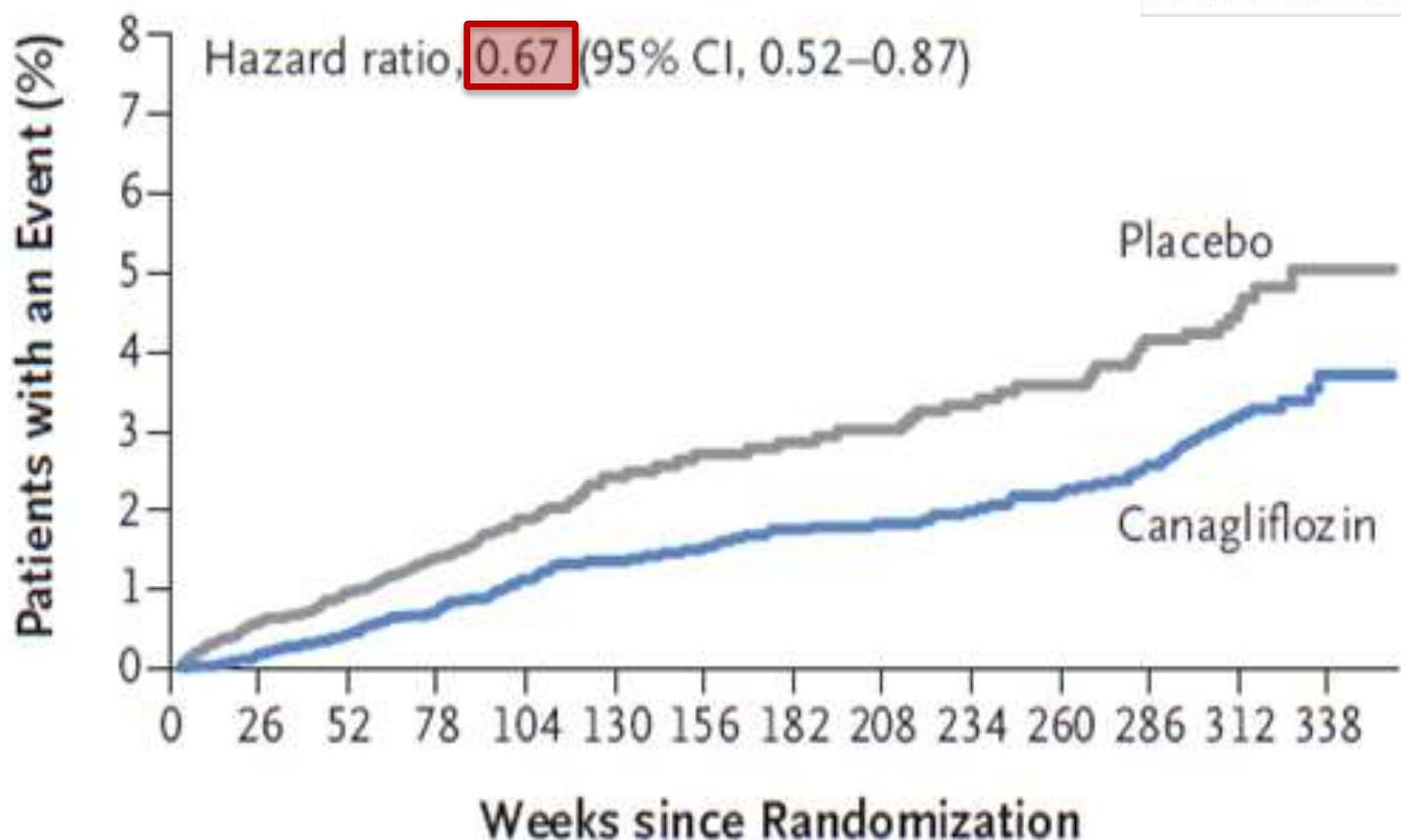
HR  
(95% CI)



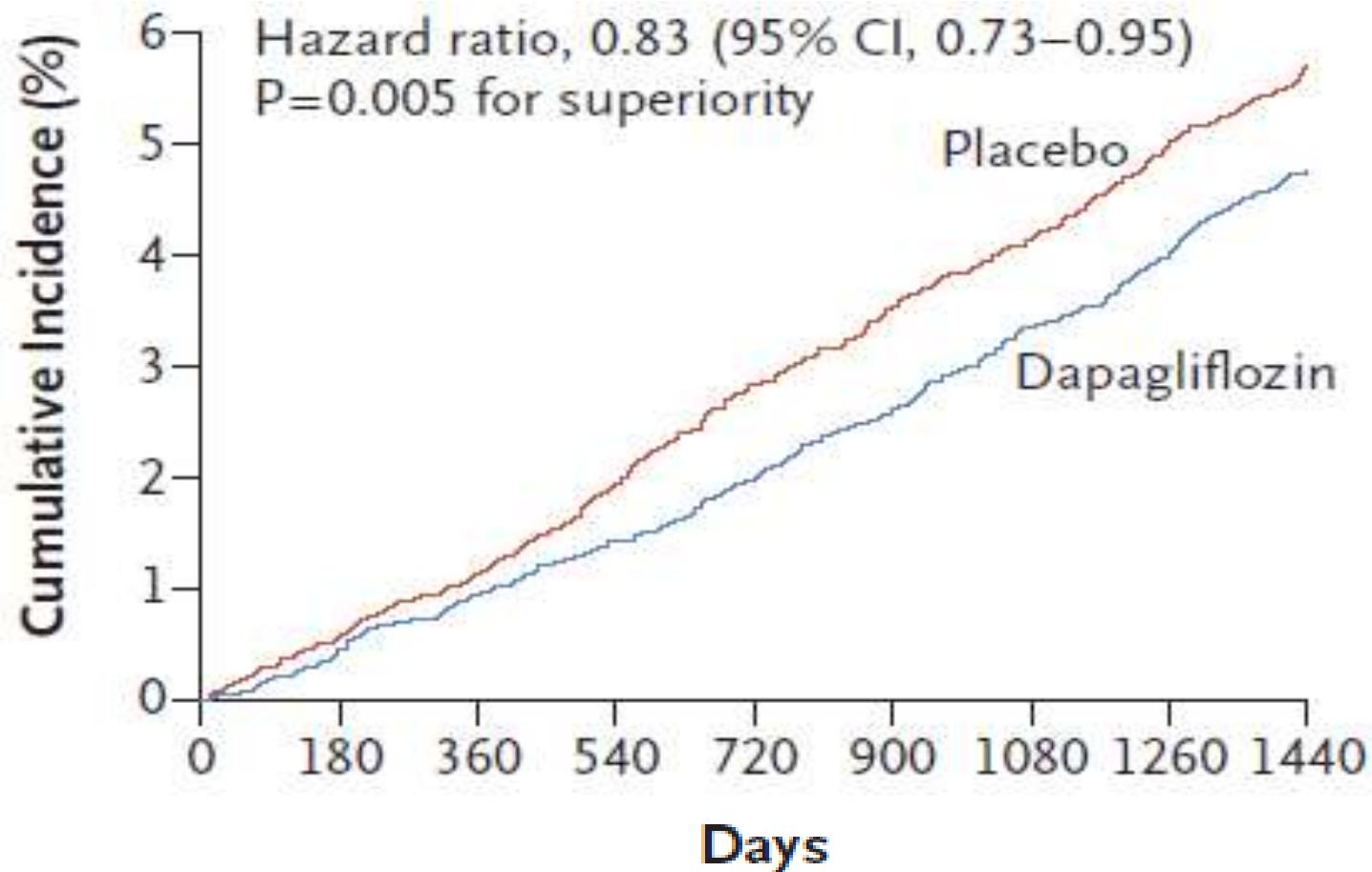
Reducción de ingresos por IC en EMPA-REG según edad  
(<65, 65-75 y > 75 años)



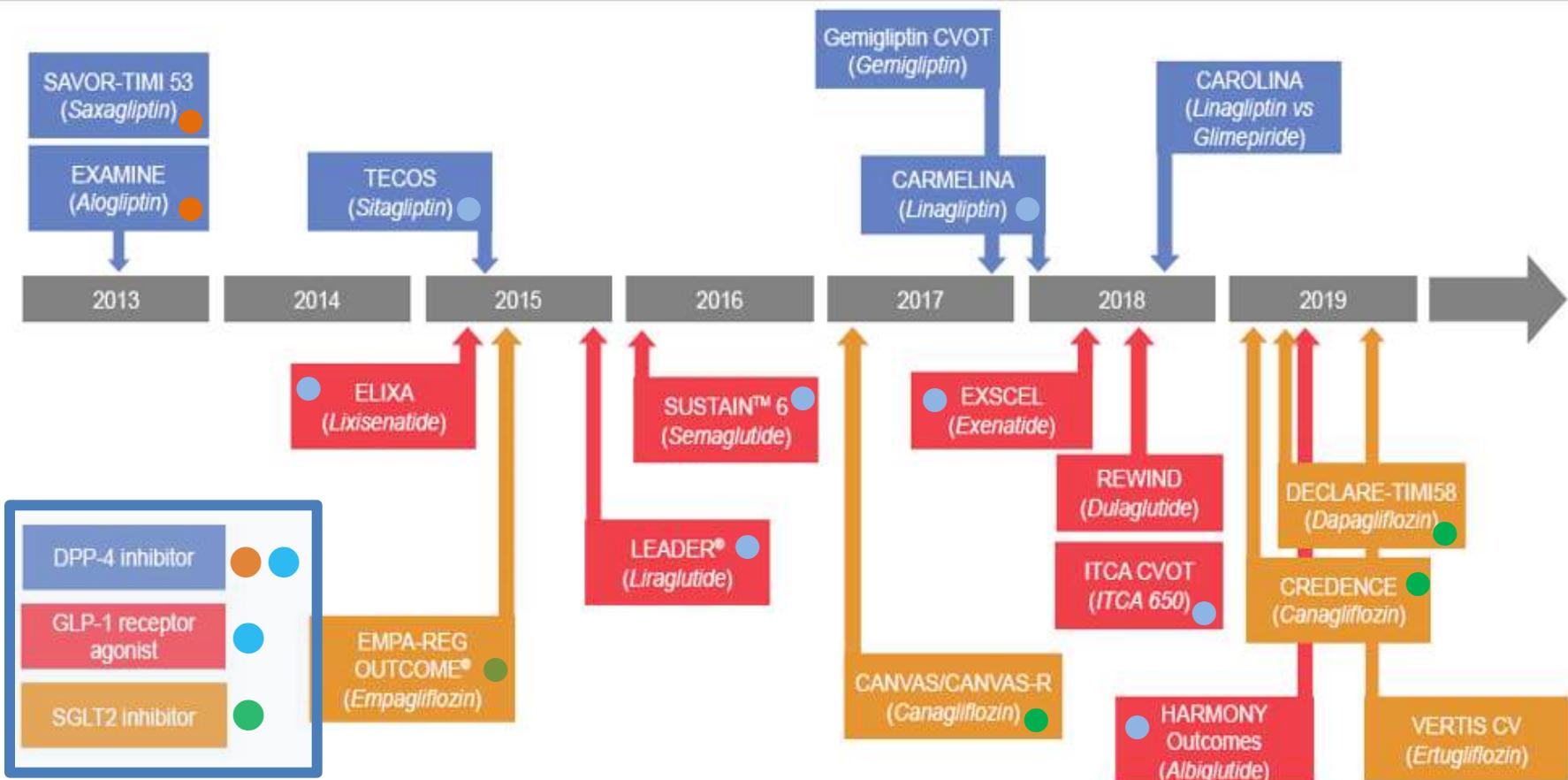
## Hospitalization for Heart Failure



## Cardiovascular Death or Hospitalization for Heart Failure



# INSUFICIENCIA CARDIACA



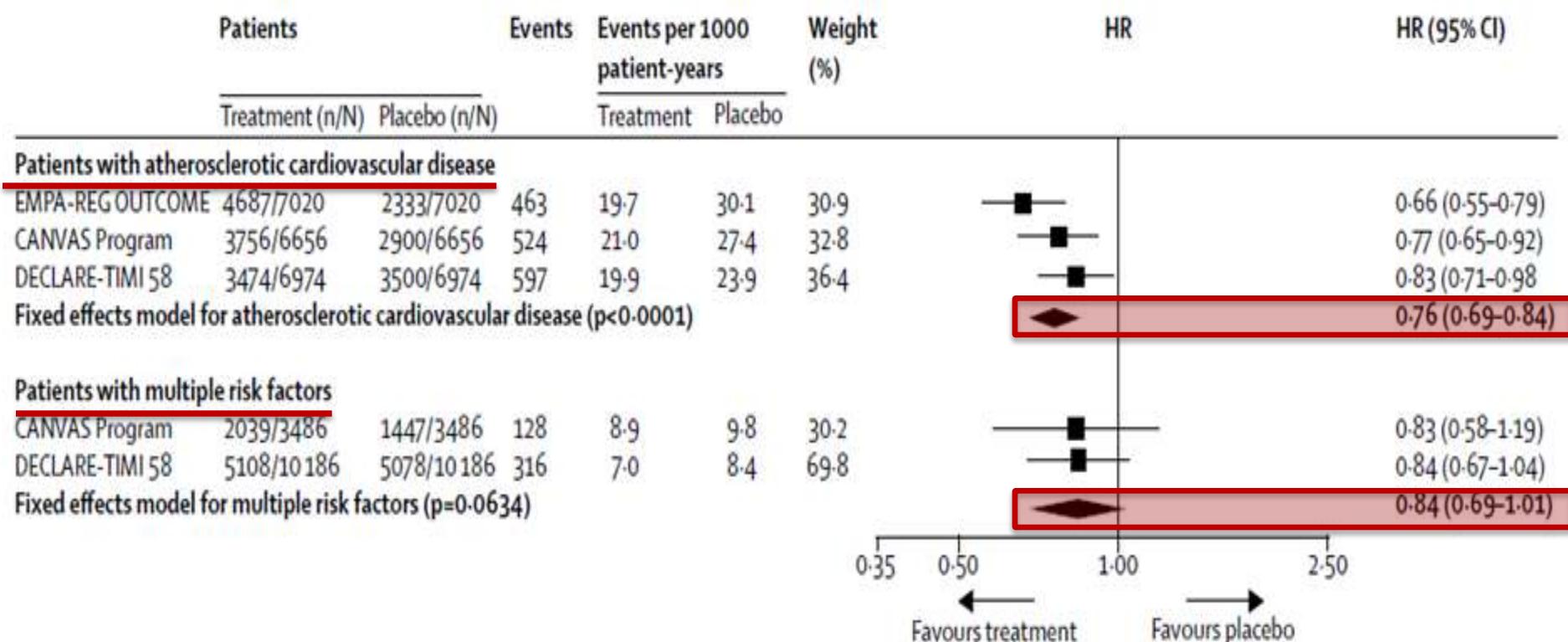
# SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

Thomas A Zelniker, Stephen D Wiviott, Itamar Raz, Kyungah Im, Erica L Goodrich, Marc P Bonaca, Ofri Mosenzon, Eri T Kato, Avivit Cahn, Remo H M Furtado, Deepak L Bhatt, Lawrence A Leiter, Darren K McGuire, John P H Wilding, Marc S Sabatine

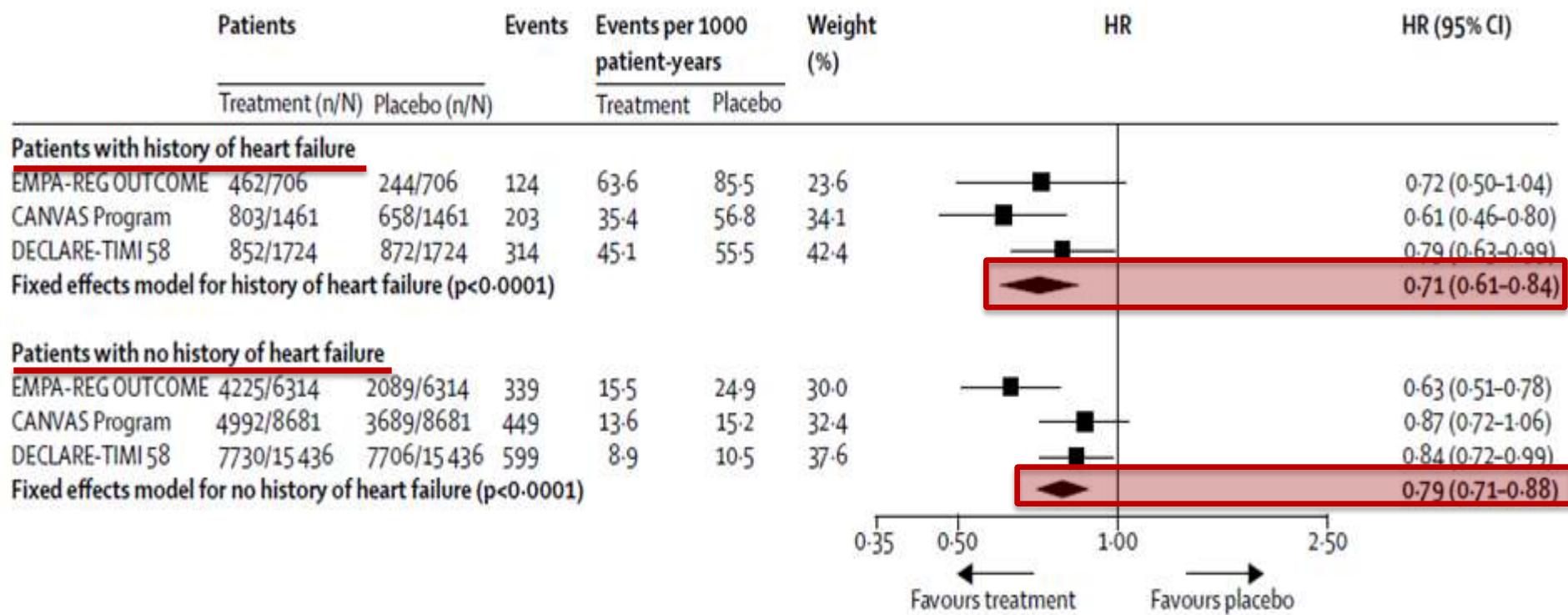
	EMPA-REG OUTCOME <sup>1</sup>	CANVAS Program <sup>2</sup>	DECLARE-TIMI 58 <sup>3</sup>
Drug	Empagliflozin	Canagliflozin	Dapagliflozin
Doses analysed	10 mg, 25 mg (once daily)	100 mg, 300 mg (once daily)	10 mg (once daily)
Median follow-up time, years	3·1	2·4	4·2
Trial participants	7020	10142	17160
Age, mean	63·1	63·3	63·9
Women	2004 (28·5%)	3633 (35·8%)	6422 (37·4%)
Patients with established atherosclerotic cardiovascular disease	7020 (100%)	6656 (65·6%)	6974 (40·6%)
Patients with a history of heart failure	706 (10·1%)	1461 (14·4%)	1724 (10·0%)
Patients with eGFR <60 mL/min per 1·73 m <sup>2</sup>	1819 (25·9%)	2039 (20·1%)	1265 (7·4%)

Data are n (%) unless otherwise specified. The CANVAS Program consisted of two trials, CANVAS and CANVAS-R, but are presented combined. eGFR=estimated glomerular filtration rate.

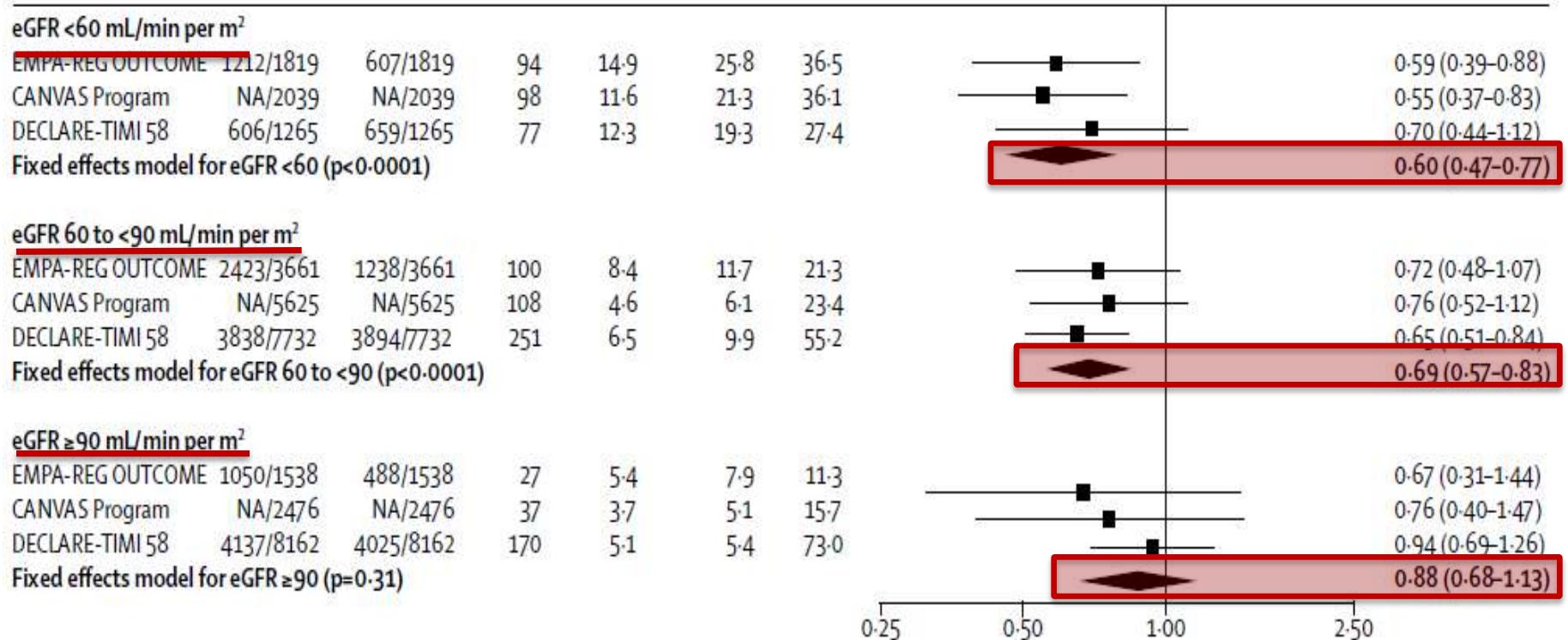
**Table:** Randomised controlled phase 3/4 clinical trials of sodium-glucose cotransporter-2 inhibitors



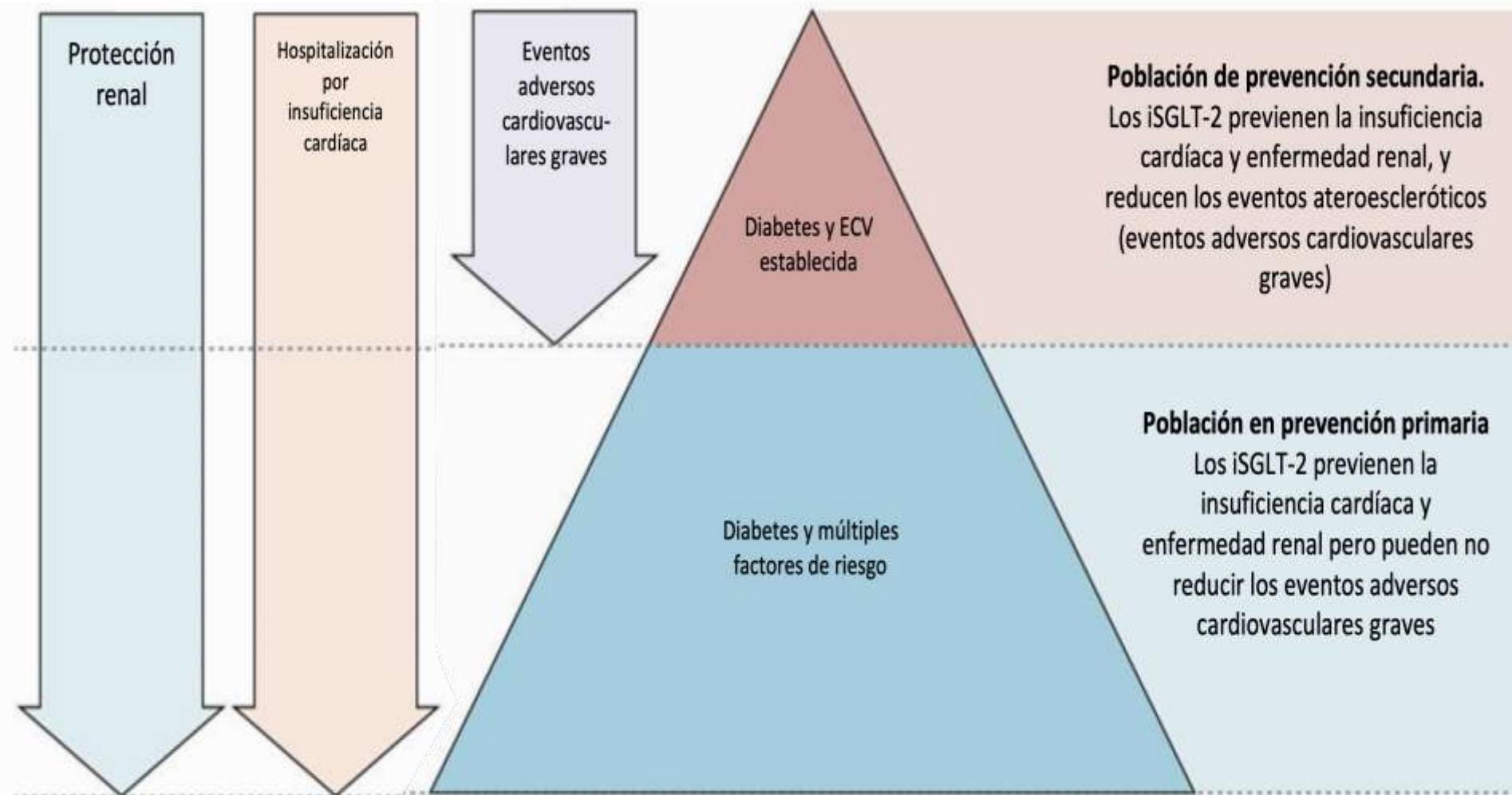
Reducción de ingresos por IC y muerte cardiovascular  
según nivel de prevención cardiovascular



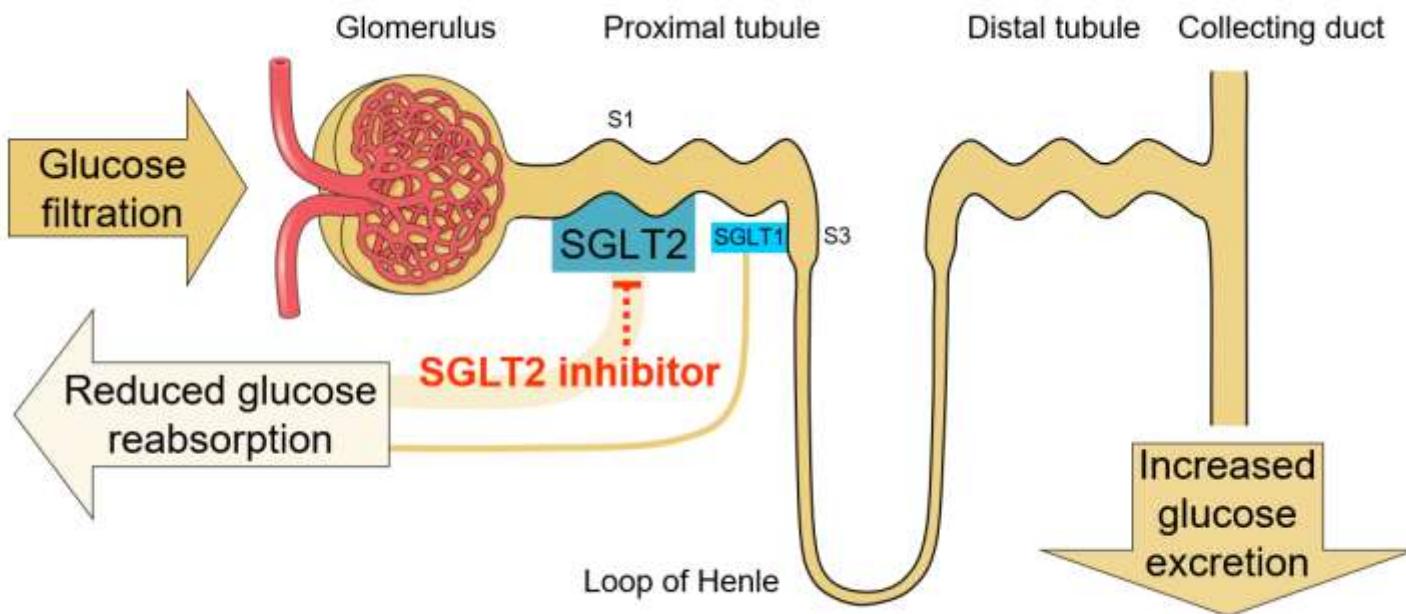
Reducción de ingresos por IC y muerte cardiovascular  
según antecedentes de Insuficiencia Cardiaca



Reducción de ingresos por IC y muerte cardiovascular  
según Filtrado Glomerular estimado

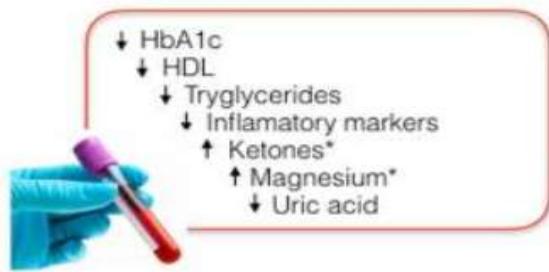
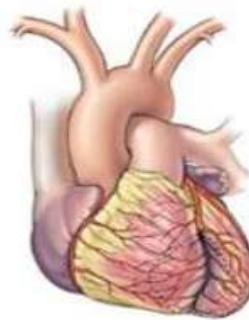
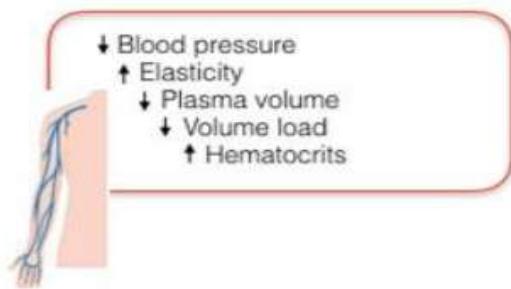


# ¿Explicación del beneficio en IC?

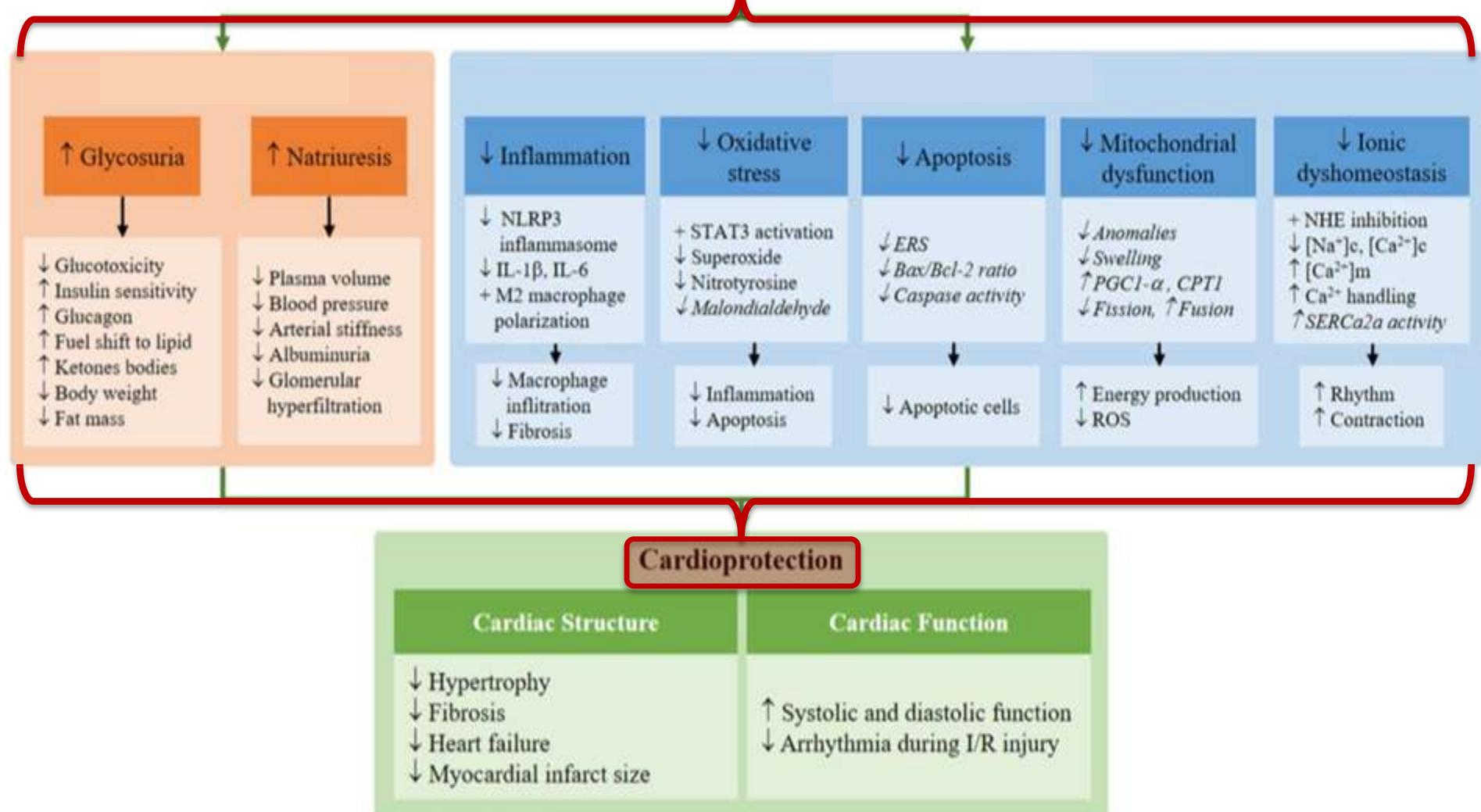


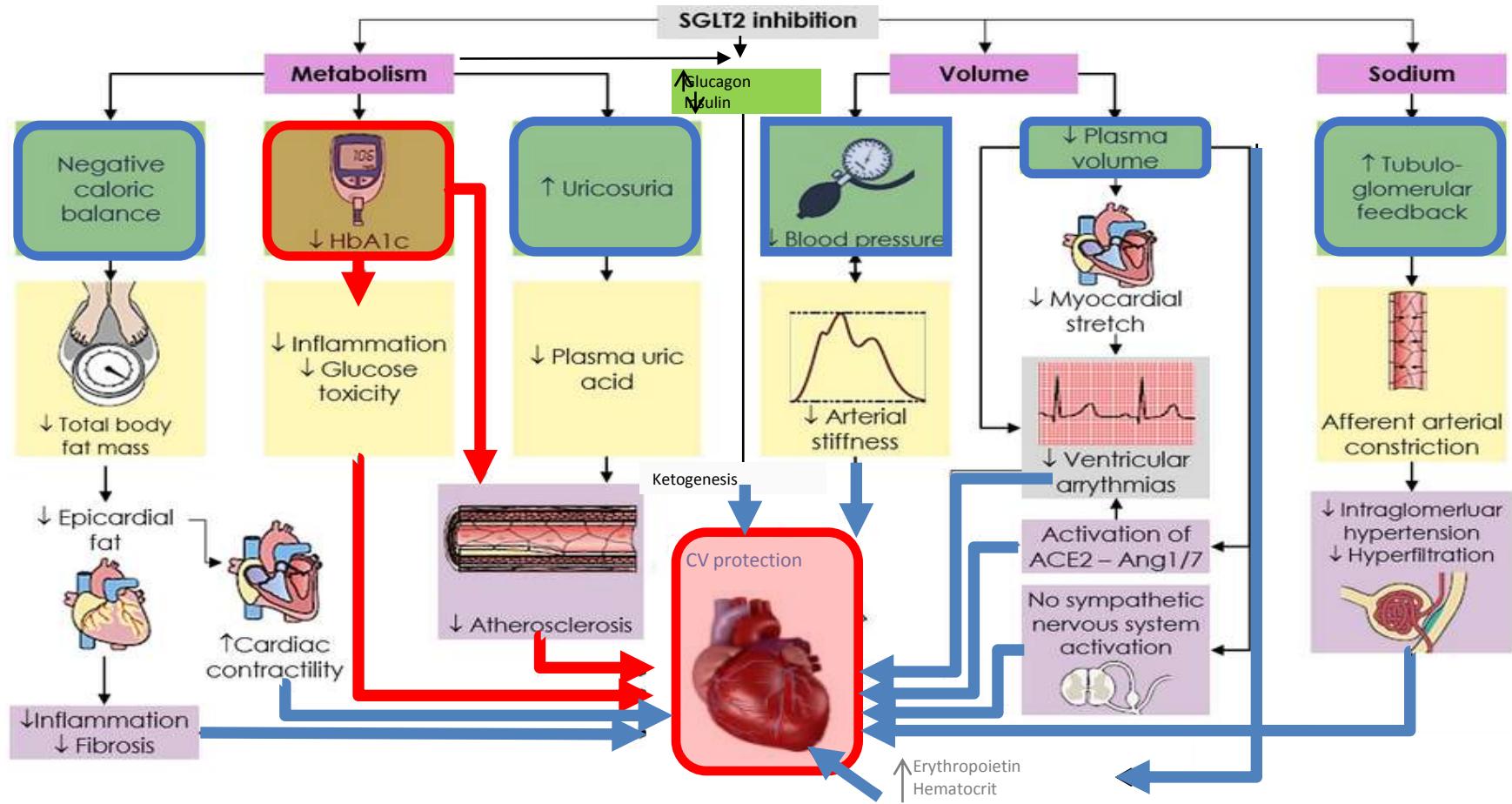
Wright EM. Am J Physiol Renal Physiol 2001;280:F10–8; Lee YJ, et al. Kidney Int Suppl 2007;106:S27–35. Wright EM, et al. J Intern Med 2007;261:32–43.

INSUFICIENTE



## SGLT-2 Inhibitors





ACCORD      ADVANCE      VADT

# IMPACTO DE LA EVIDENCIA

# Primeras recomendaciones de guías clínicas en el empleo de iSGLT-2 en Insuficiencia Cardiaca



Guías 2016 de la Sociedad Europea de Cardiología para el diagnóstico y tratamiento de la IC<sup>2</sup>

*“Empagliflozina debe ser considerada en los pacientes con DM2 para prevenir o retrasar los eventos de IC y prolongar la supervivencia”*



Guías 2017 de la Sociedad canadiense cardiovascular para el manejo de IC<sup>1</sup>

*“Sugiere considerer el uso de empagliflozina en pacientes con DM2 y enfermedad CV establecida para prevenir eventos de IC”*

1. Ezekowitz JA et al. Can J Cardiol 2017;33:1342; 2. Ponikowski P et al. Eur Heart J 2016;37:2129

## ALGORITMO TERAPIA DM2 CENTRADO EN LAS COMPLICACIONES

Comorbilidad

MACE

MORTALIDAD CV

INSUFICIENCIA CARDIACA

ENFERMEDAD RENAL DIABÉTICA

ACV

+MET

30

Beneficio

Seguridad

Insuficiencia renal  
- FG límite para empleo.

Empagliflozina <sup>A</sup>  
Canagliflozina <sup>C</sup>  
45  
Liraglutida <sup>A</sup>  
Semaglutida <sup>1A</sup>  
15



Empagliflozina <sup>C</sup>  
45  
Liraglutida <sup>C</sup>  
15



Empagliflozina <sup>C</sup>  
Canagliflozina <sup>C</sup>  
45  
Dapagliflozina <sup>2†C</sup>  
60



Empagliflozina <sup>B</sup>  
Canagliflozina <sup>C</sup>  
45  
Dapagliflozina <sup>2†C</sup>  
60  
Liraglutida <sup>C</sup>  
Dulaglutida <sup>2C</sup>  
Semaglutida <sup>1C</sup>  
15



Semaglutida <sup>10</sup>  
15  
PIO # <sup>△</sup>

Dapagliflozina <sup>2C</sup>  
60  
Exenatida LAR <sup>A</sup>  
50  
Dulaglutida <sup>2C</sup>  
15  
IDPP4 <sup>A-C</sup>  
Lixisenatida <sup>A</sup>  
30  
PIO # <sup>A</sup>  
SU <sup>C</sup>  
30  
GLIN <sup>C</sup> <sup>△</sup>

Canagliflozina <sup>C</sup>  
45  
Dapagliflozina <sup>2C</sup>  
60  
orGLP1 <sup>IP</sup>  
IDPP4 <sup>A</sup>  
Lixisenatida <sup>A</sup>  
30  
PIO # <sup>A</sup>  
SU <sup>C</sup>  
30  
GLIN <sup>C</sup> <sup>△</sup>

orGLP1 <sup>IP</sup> <sup>A-C</sup>  
Sitagliptina <sup>A</sup>  
Lixisenatida <sup>A</sup>  
SU <sup>C</sup>  
30 <sup>△</sup>  
GLIN <sup>C</sup> <sup>△</sup>

Exenatida LAR <sup>C</sup>  
50  
IDPP4 <sup>A-C</sup>  
PIO # <sup>△</sup>  
SU <sup>C</sup>  
30 <sup>△</sup>  
GLIN <sup>C</sup> <sup>△</sup>

Liraglutida <sup>C</sup>  
15  
Canagliflozina <sup>C</sup>  
Empagliflozina <sup>C</sup>  
45  
Dapagliflozina <sup>2†C</sup>  
60  
orGLP1 <sup>IP</sup> <sup>A-C</sup>  
IDPP4 <sup>A-C</sup>  
Lixisenatida <sup>C</sup>  
SU <sup>C</sup>  
30  
GLIN <sup>C</sup> <sup>△</sup>

\*Ajuste de dosis en IR salvo Linagliptina:  
# No requiere ajuste de dosis en ERC; † Evidencia basada en estudios observacionales

(1) Aprobado por European Medicines Agency

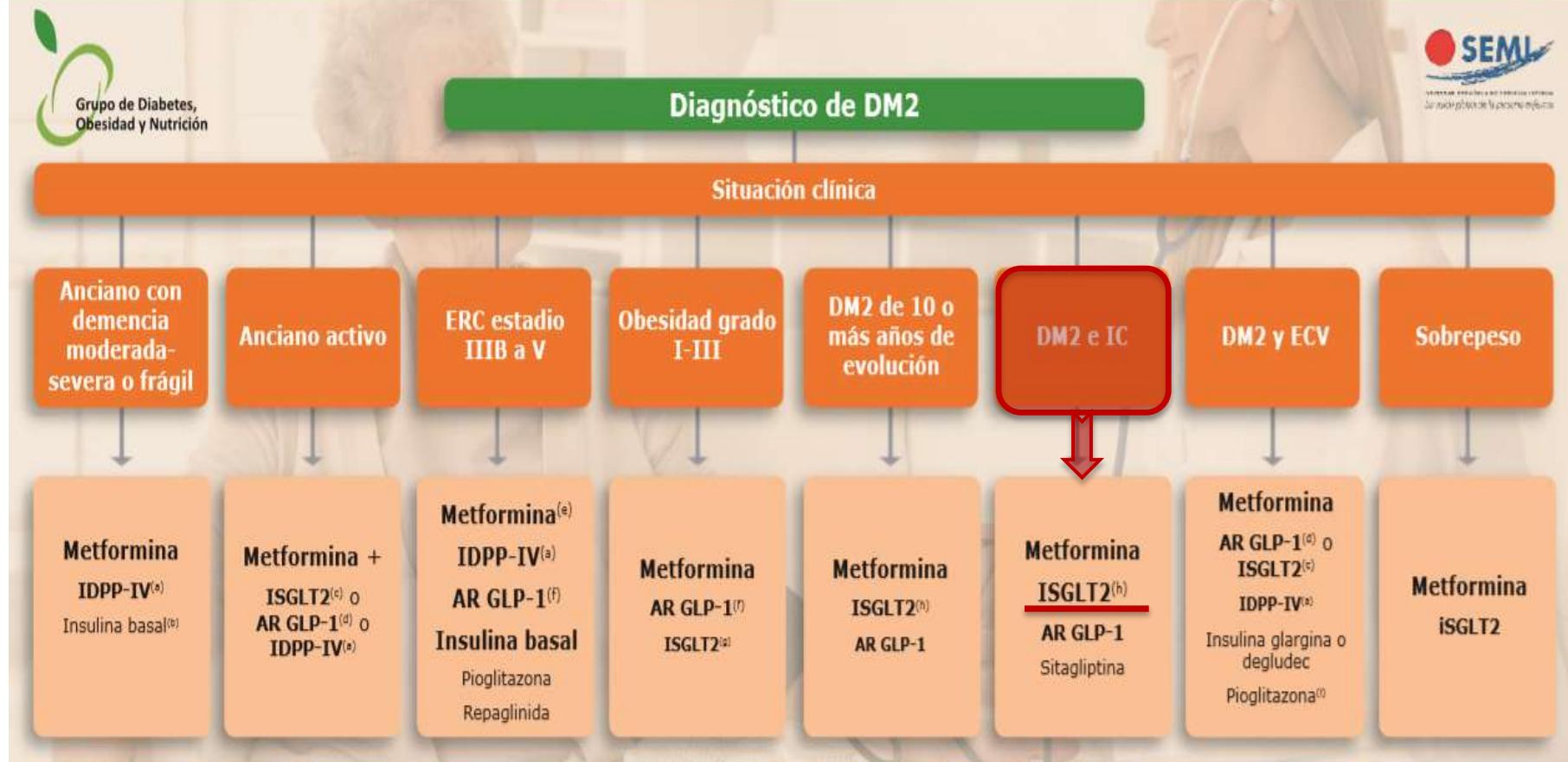
(2) Dulaglutida, dapagliflozina, y linagliptina no han finalizado ensayo de seguridad CV  
Vildagliptina no tiene ensayo de seguridad CV

⚠ Evitar si riesgo de hipoglucemias

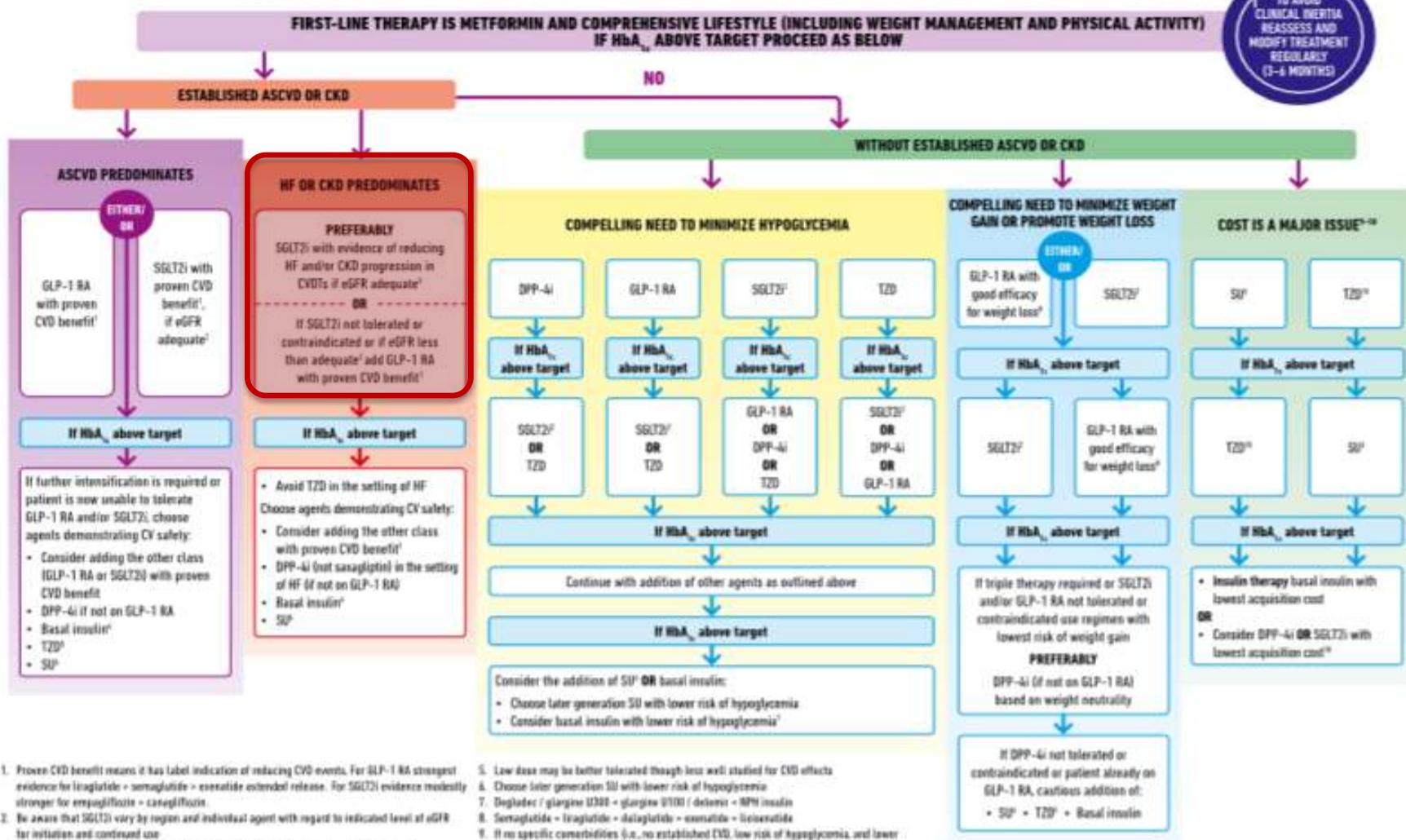
⚠ Contraindicado si Dx o sospecha de ICC

MACE: eventos CV mayores; CV: cardiovascular; ACV: accidente cerebrovascular; PIO: pioglitazona; SU: sulfonilurea; GLIN: repaglinida; FG: filtrado glomerular; DP: duración prolongada

# Algoritmo de tratamiento de la DM2 según la situación clínica



# GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH



1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for linagliptin > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.

2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use.

3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs.

4. Degludec or T100 glargin have demonstrated CVD safety.



HF or CKD predominates



**PREFERABLY**

SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate<sup>3</sup>

**OR**

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate<sup>2</sup> add GLP-1 RA with proven CVD benefit<sup>1,4</sup>

Dual Therapy	Metformin +					Lifestyle Management
	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 Inhibitor	GLP-1 receptor agonist	Insulin (basal)
<b>EFFICACY*</b>	high	high	intermediate	intermediate	high	highest
<b>HYPO RISK</b>	moderate risk	low risk	low risk	low risk	low risk	high risk
<b>WEIGHT</b>	gain	gain	neutral	loss	loss	gain
<b>SIDE EFFECTS</b>	hypoglycemia	edema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
<b>COSTS*</b>	low	low	high	high	high	high

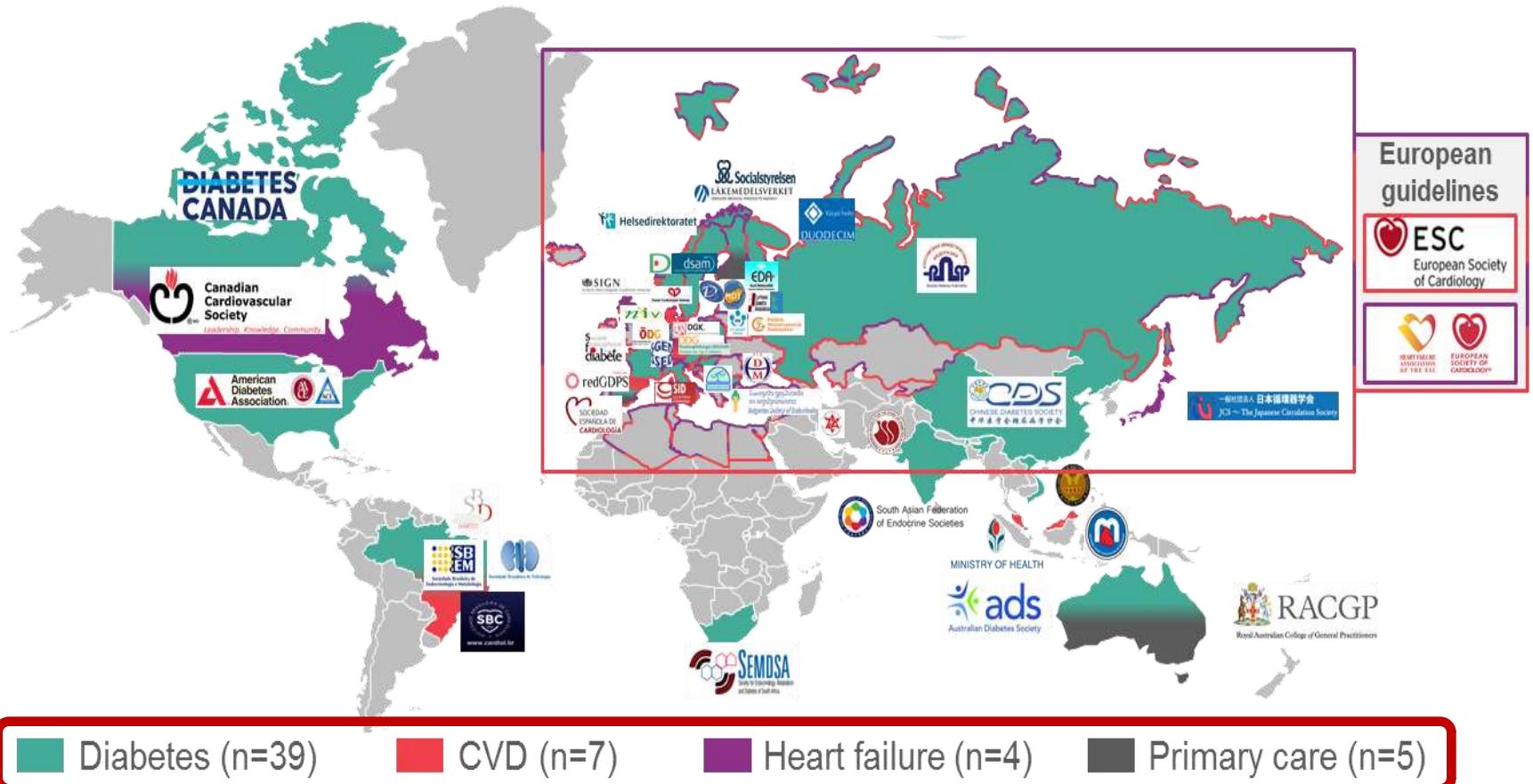
If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Davis J, et al. Diabetes Care 2018 Sep.

## 2016–2018 updates

55

Total number of guidelines incorporating  
EMPA-REG OUTCOME® data



Some guidelines have been developed across specialities  
CVD, cardiovascular disease

## ¿Manejo práctico?

¿Si añado un iSGLT-2.....  
Qué hago con el diurético?

**¿Cuál es el estado de volumen?**

**Euvolemia**

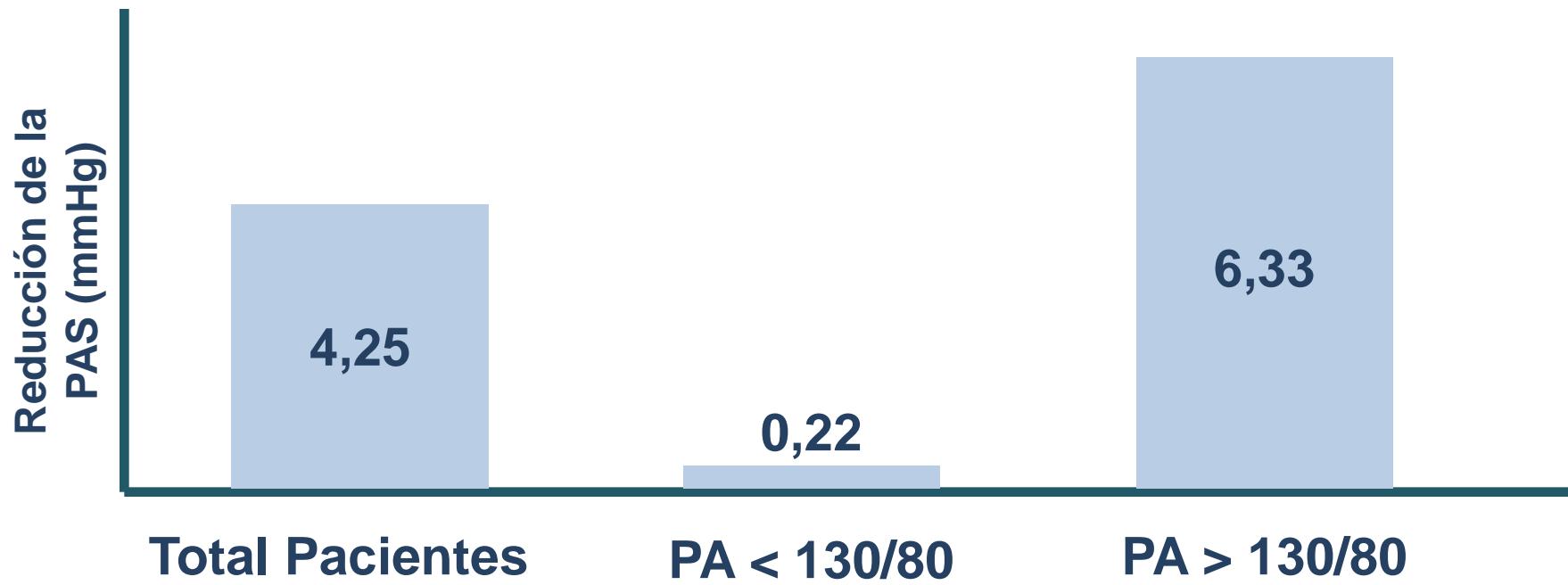
**¿Cuál es el nivel de presión arterial?**

- Tiacidas:
  - Continuar diuréticos y monitorizar
- Diuréticos de asa:
  - Considerar reducir la dosis en un 50% y monitorizar presión arterial y peso
    - Si estable, continuar tratamiento
    - Si aumenta la PA: aumentar diurético
    - Si disminuye, suspender diuréticos

# Empagliflozin Reduces Blood Pressure in Patients With Type 2 Diabetes and Hypertension

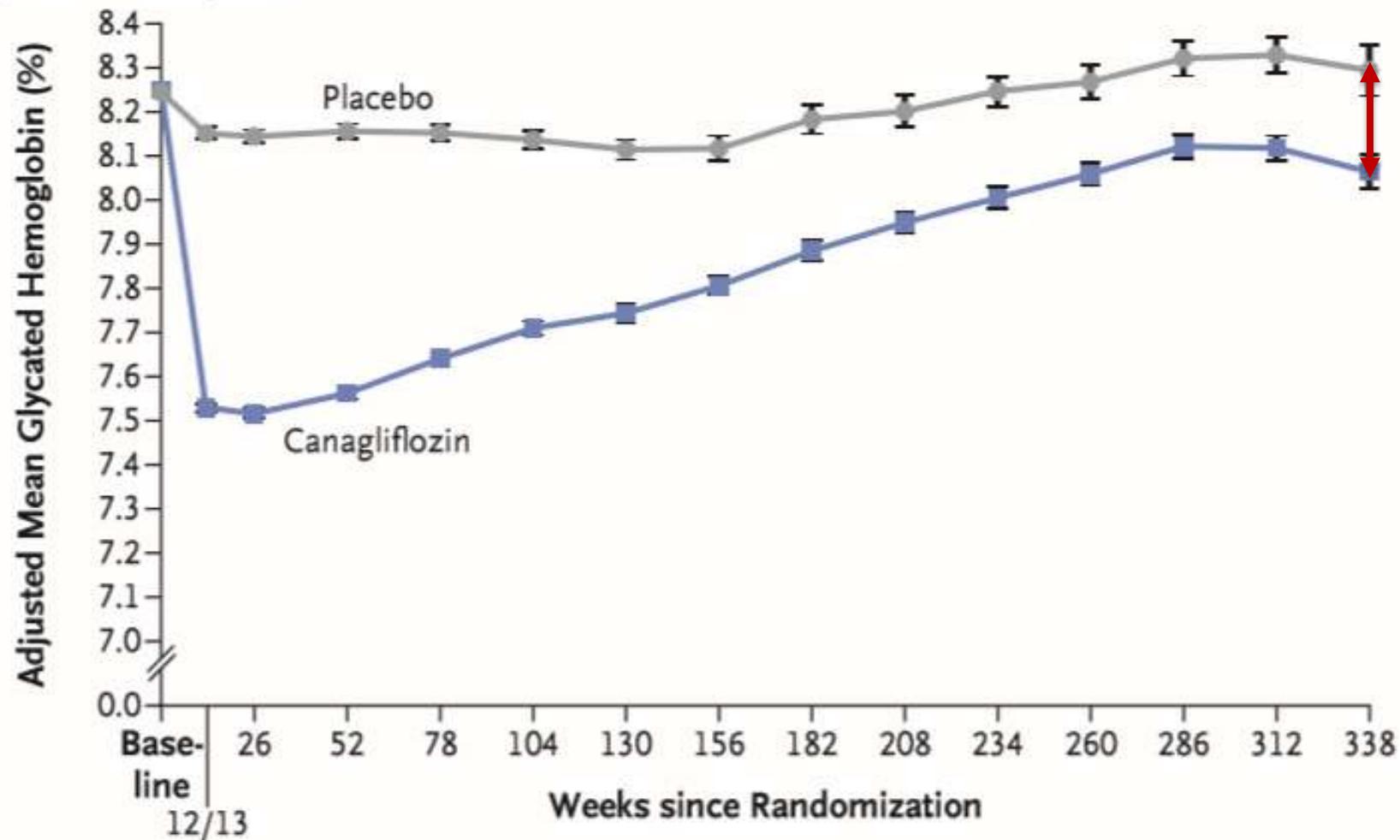
*Diabetes Care* 2015;38:420–428 | DOI: 10.2337/dc14-1096

Ikkka Tikkannen,<sup>1</sup> Kirsi Narko,<sup>2</sup>  
Cordula Zeller,<sup>3</sup> Alexandra Green,<sup>4</sup>  
Afshin Salsali,<sup>5</sup> Uli C. Broedl,<sup>5</sup> and  
Hans J. Woerle,<sup>5</sup> on behalf of the  
*EMPA-REG BP Investigators*



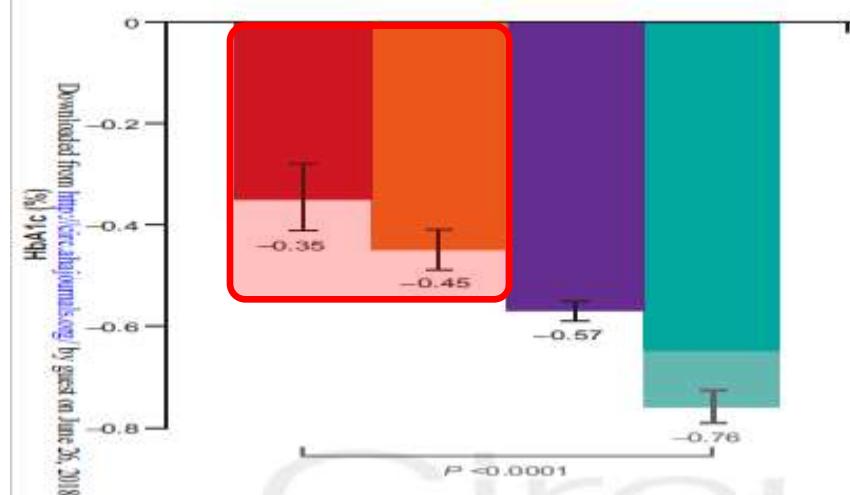
¿Beneficio solo en el Diabético?

## Glycated Hemoglobin

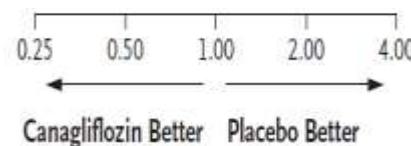


█ eGFR <45 mL/min/1.73 m<sup>2</sup>  
 █ eGFR 45-<60 mL/min/1.73 m<sup>2</sup>  
 █ eGFR 60-<90 mL/min/1.73 m<sup>2</sup>  
 █ eGFR ≥90 mL/min/1.73 m<sup>2</sup>

**A. HbA<sub>1c</sub>**



Subgroup	Canagliflozin no. of participants per 1000 patient-yr	Placebo no. of participants per 1000 patient-yr	Hazard Ratio (95% CI)	P Value
All patients	26.9	31.5	0.86 (0.75–0.97)	0.20
eGFR				



eGFR <60 mL/min per m<sup>2</sup>

EMPA-REG OUTCOME	1212/1819	607/1819	94	14.9	25.8	36.5
CANVAS Program	NA/2039	NA/2039	98	11.6	21.3	36.1
DECLARE-TIMI 58	606/1265	659/1265	77	12.3	19.3	27.4

Fixed effects model for eGFR <60 ( $p<0.0001$ )

eGFR 60 to <90 mL/min per m<sup>2</sup>

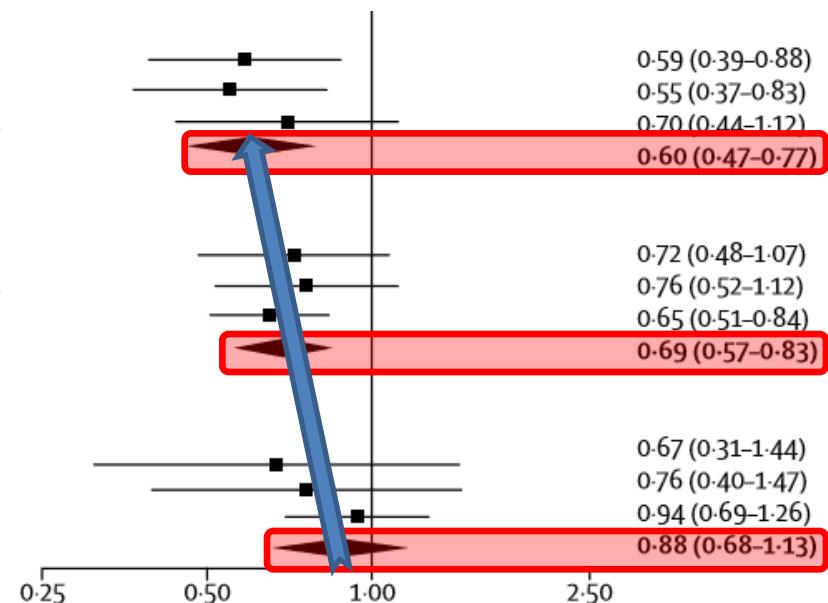
EMPA-REG OUTCOME	2423/3661	1238/3661	100	8.4	11.7	21.3
CANVAS Program	NA/5625	NA/5625	108	4.6	6.1	23.4
DECLARE-TIMI 58	3838/7732	3894/7732	251	6.5	9.9	55.2

Fixed effects model for eGFR 60 to <90 ( $p<0.0001$ )

eGFR ≥90 mL/min per m<sup>2</sup>

EMPA-REG OUTCOME	1050/1538	488/1538	27	5.4	7.9	11.3
CANVAS Program	NA/2476	NA/2476	37	3.7	5.1	15.7
DECLARE-TIMI 58	4137/8162	4025/8162	170	5.1	5.4	73.0

Fixed effects model for eGFR ≥90 ( $p=0.31$ )



# ¿Futuro de los iSGLT2 en IC?

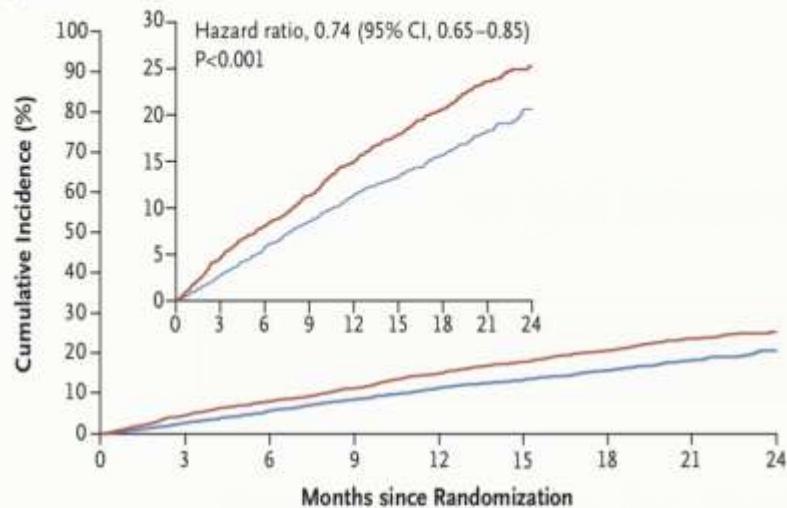
EMPEROR-Pre

EMPERIAL-Pre

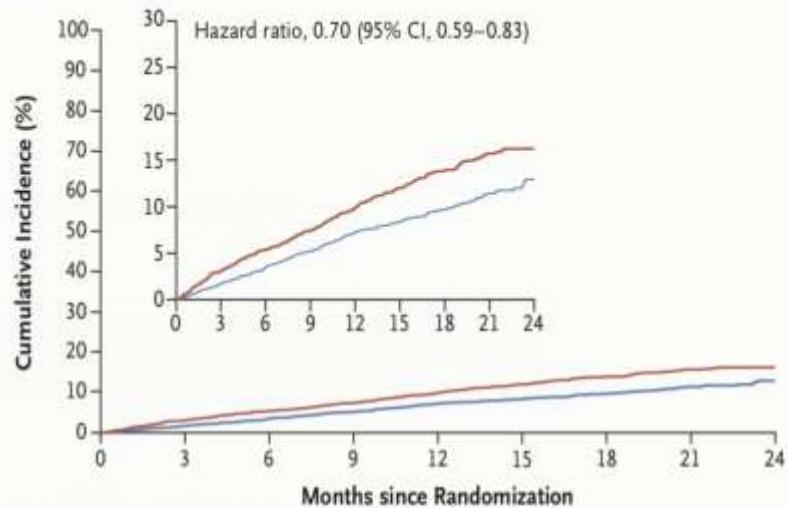
Dapa-HF

EMPEROR-Re

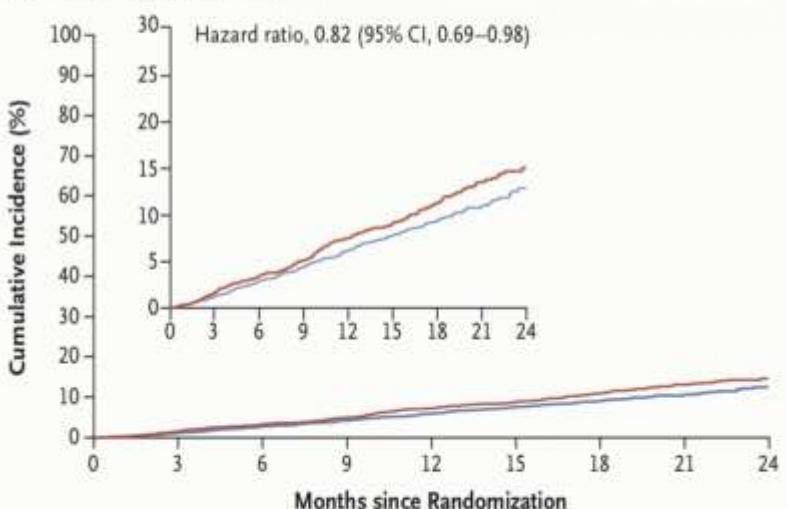
EMPERIAL-Re

**A Primary Outcome****No. at Risk**

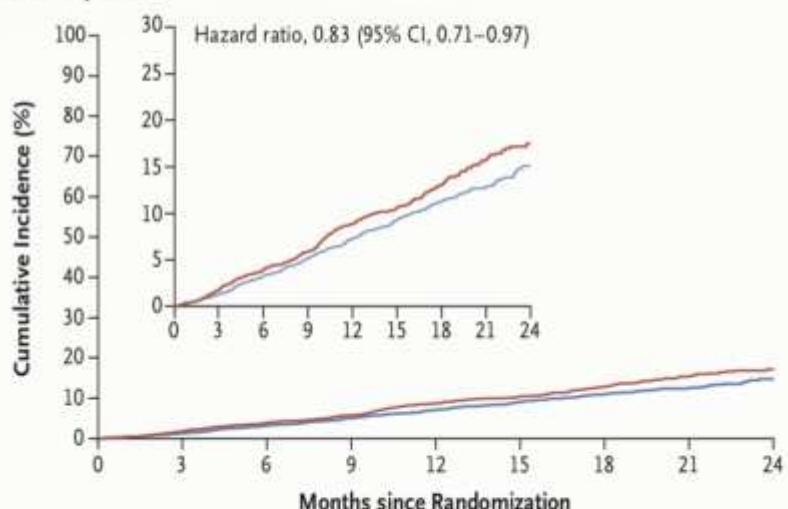
	0	3	6	9	12	15	18	21	24
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210
Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210

**B Hospitalization for Heart Failure****No. at Risk**

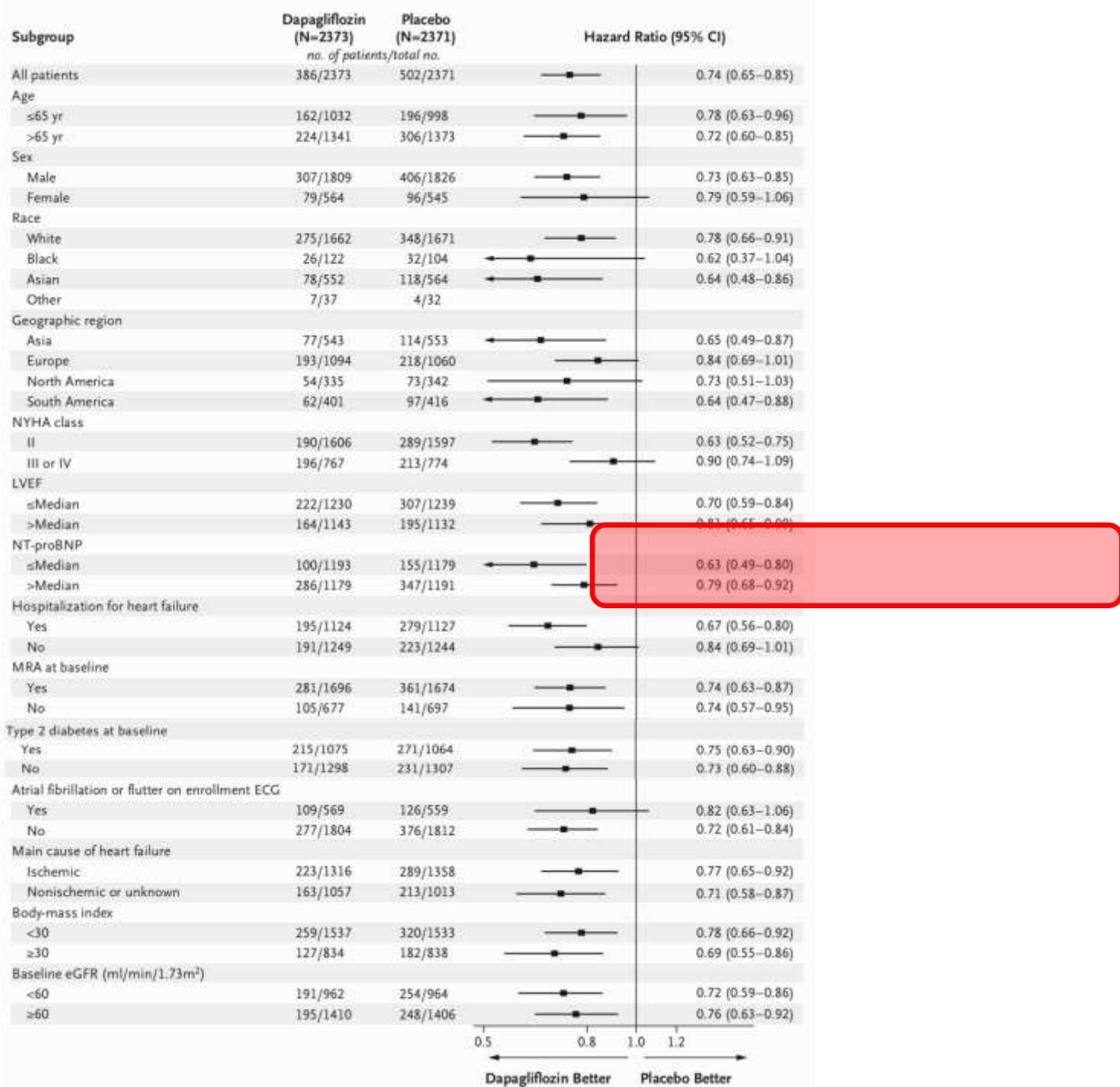
	0	3	6	9	12	15	18	21	24
Placebo	2371	2264	2168	2082	1924	1483	1101	596	212
Dapagliflozin	2373	2306	2223	2153	2007	1563	1147	613	210

**C Death from Cardiovascular Causes****No. at Risk**

	0	3	6	9	12	15	18	21	24
Placebo	2371	2330	2279	2230	2091	1636	1219	664	234
Dapagliflozin	2373	2339	2293	2248	2127	1664	1242	671	232

**D Death from Any Cause****No. at Risk**

	0	3	6	9	12	15	18	21	24
Placebo	2371	2330	2279	2231	2092	1638	1221	665	235
Dapagliflozin	2373	2342	2296	2251	2130	1666	1243	672	233



**20 mill**



**50-100 mill**



**Diabetes Mellitus**

**55 mill**

**XXI**

**Insuficiencia Cardiaca**

**40 mill**



[...] Al principio tiene una extraña sensación de invulnerabilidad –una suerte de egotismo–, luego cae de repente en la cuenta de que, lejos de ser un mero espectador, forma parte del objetivo; de que, de producirse bajas, él podría contarse entre ellas»



*Gracias!!!*