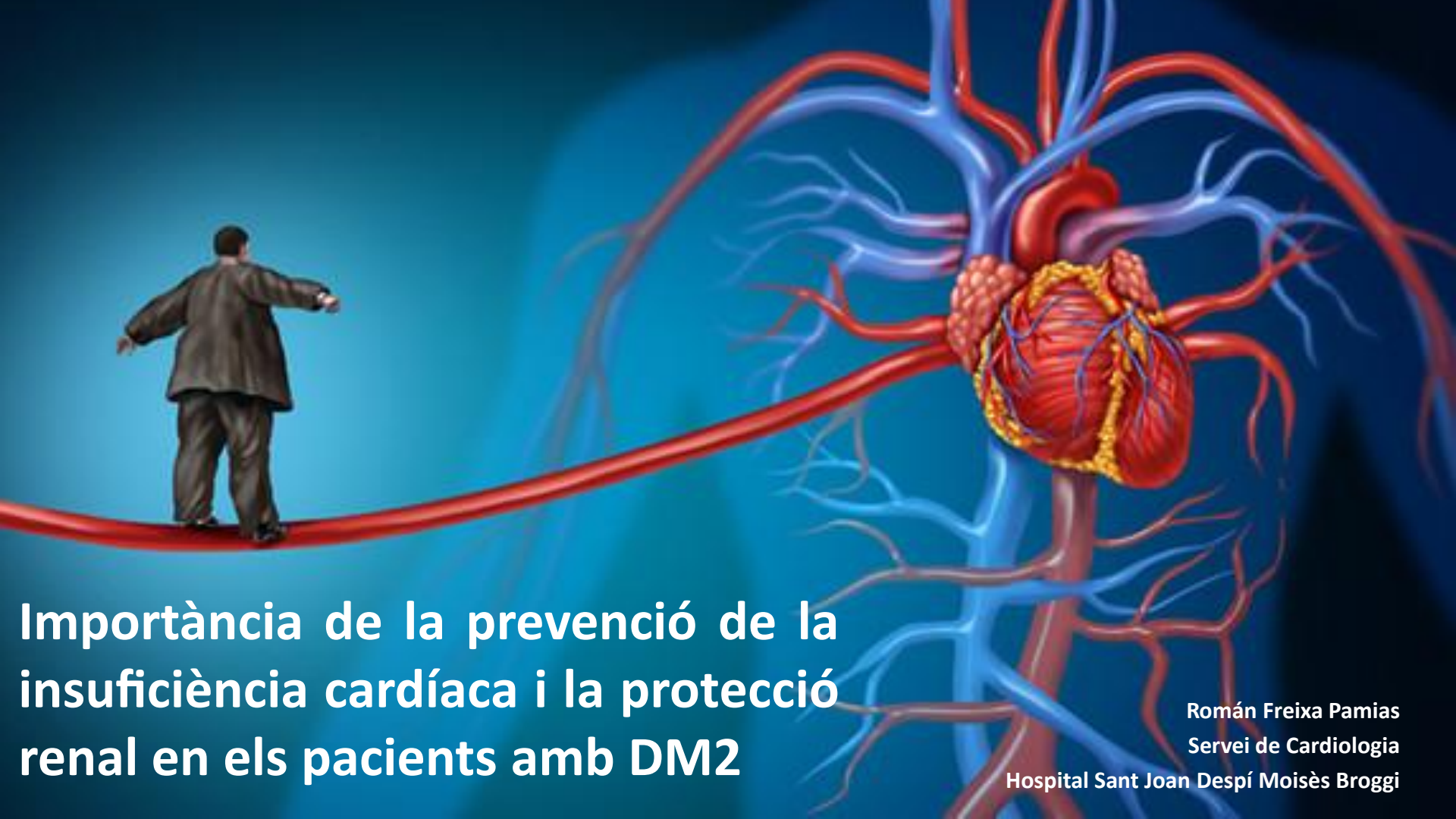
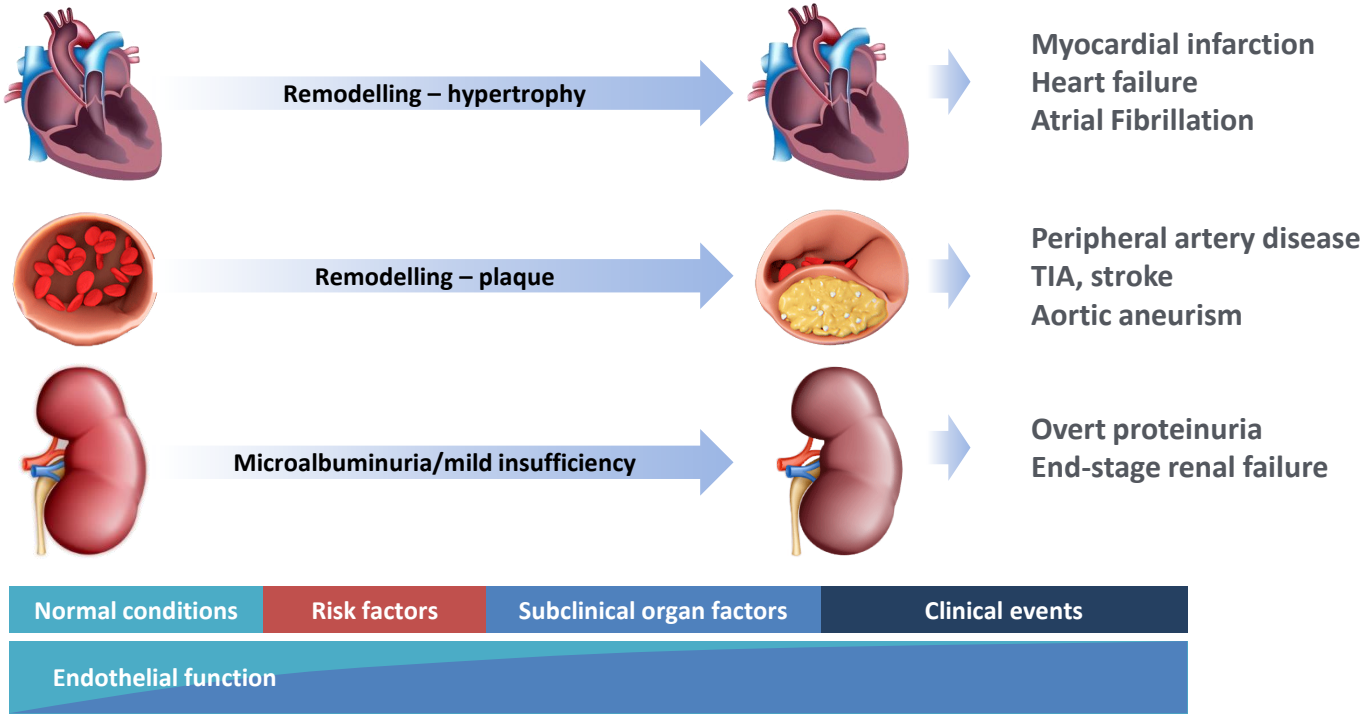


Importància de la prevenció de la insuficiència cardíaca i la protecció renal en els pacients amb DM2

Román Freixa Pamias
Servei de Cardiologia
Hospital Sant Joan Despí Moisès Broggi

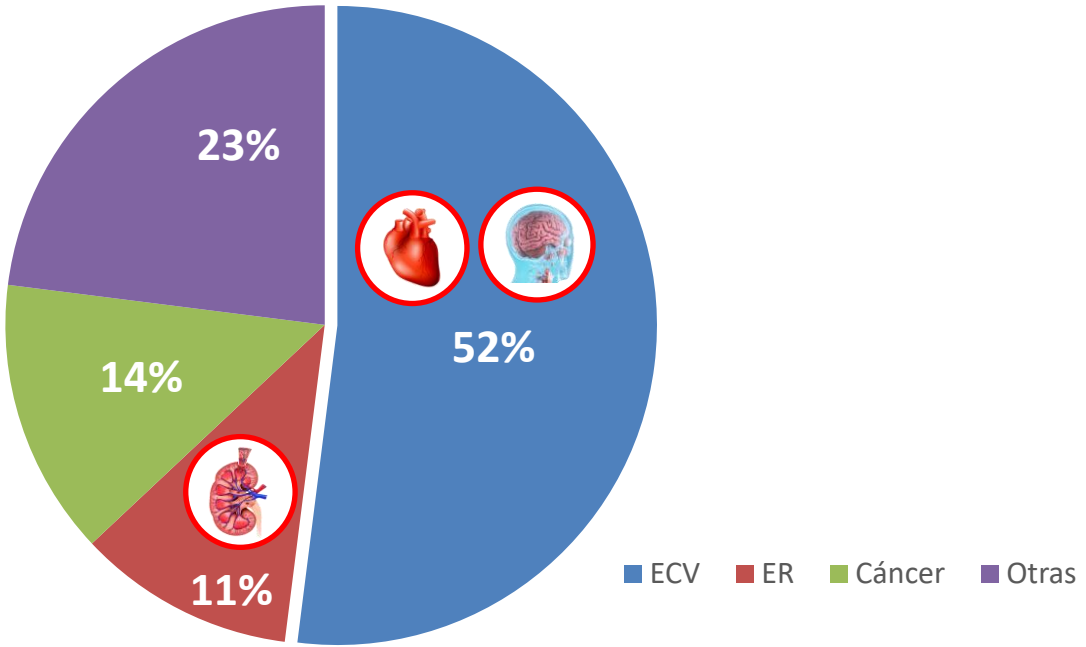
DIABETES: Endothelial dysfunction is common to microvascular and macrovascular events



Versari et al. Diabetes Care 2009;32(suppl 2):S314-321.

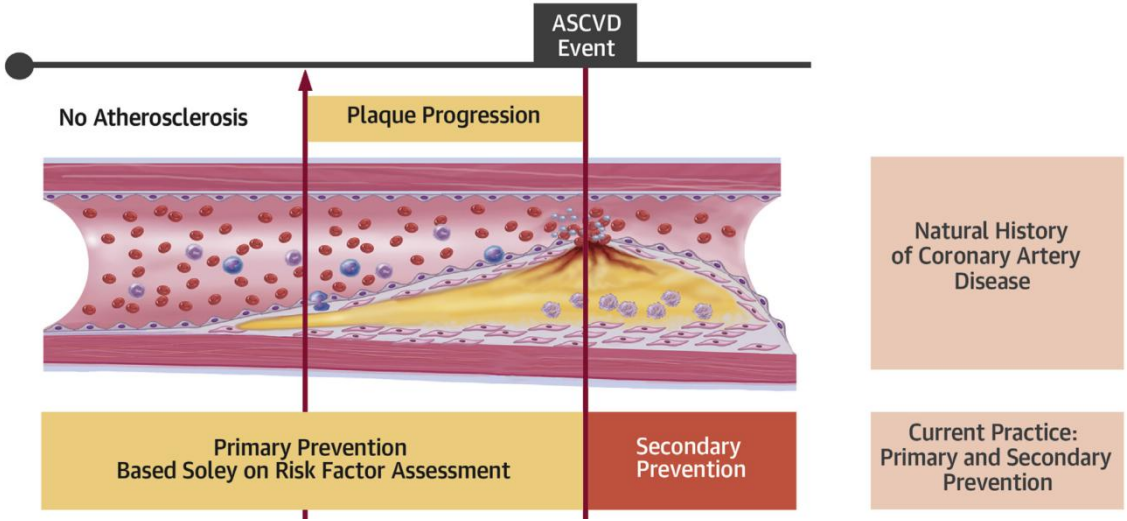
Abordaje del riesgo cardiovascular en el paciente diabético

La enfermedad CV es la principal causa de muerte en pacientes con DM2



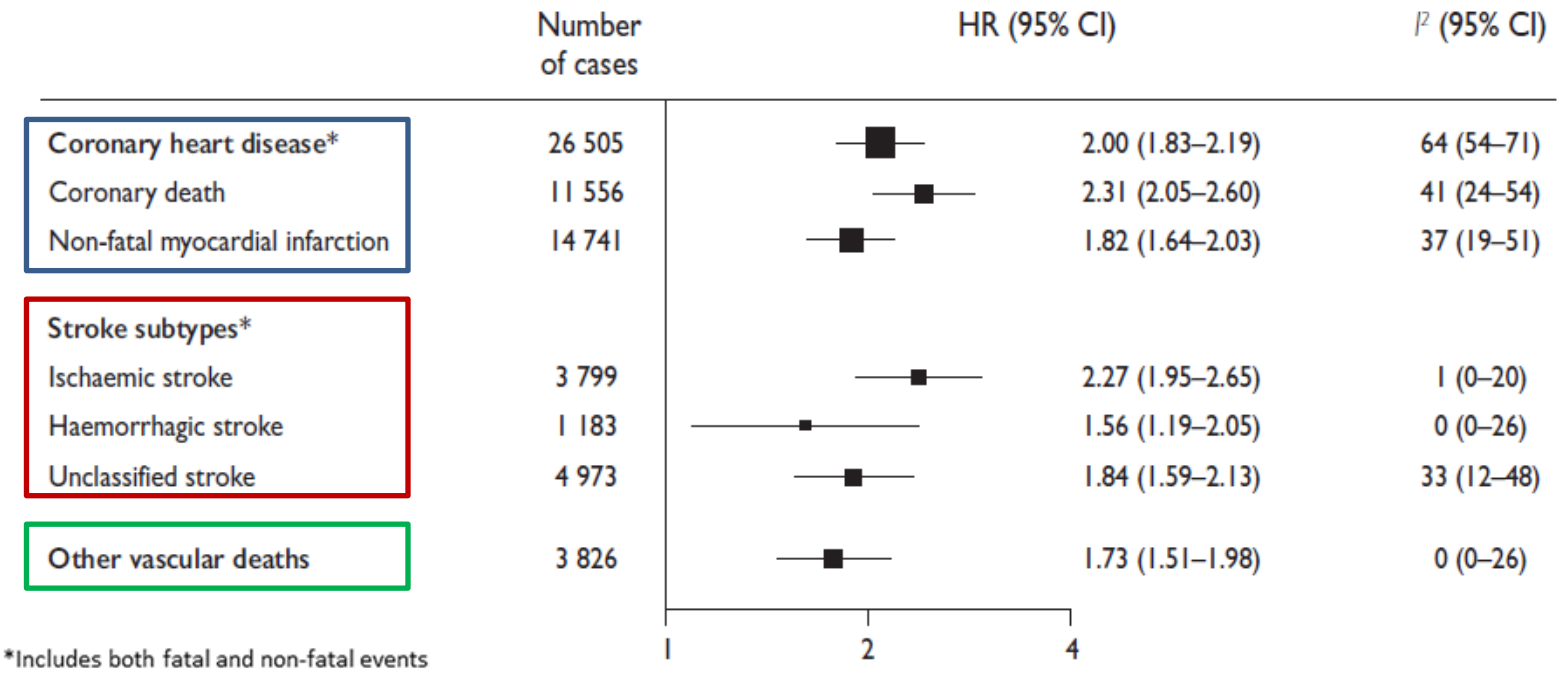
DM2: diabetes mellitus tipo 2, ECV: enfermedad cardiovascular, ER: enfermedad renal Morrish NJ *et al. Diabetologia* 2001;44 Suppl 2:S14

Atherosclerosis timeline



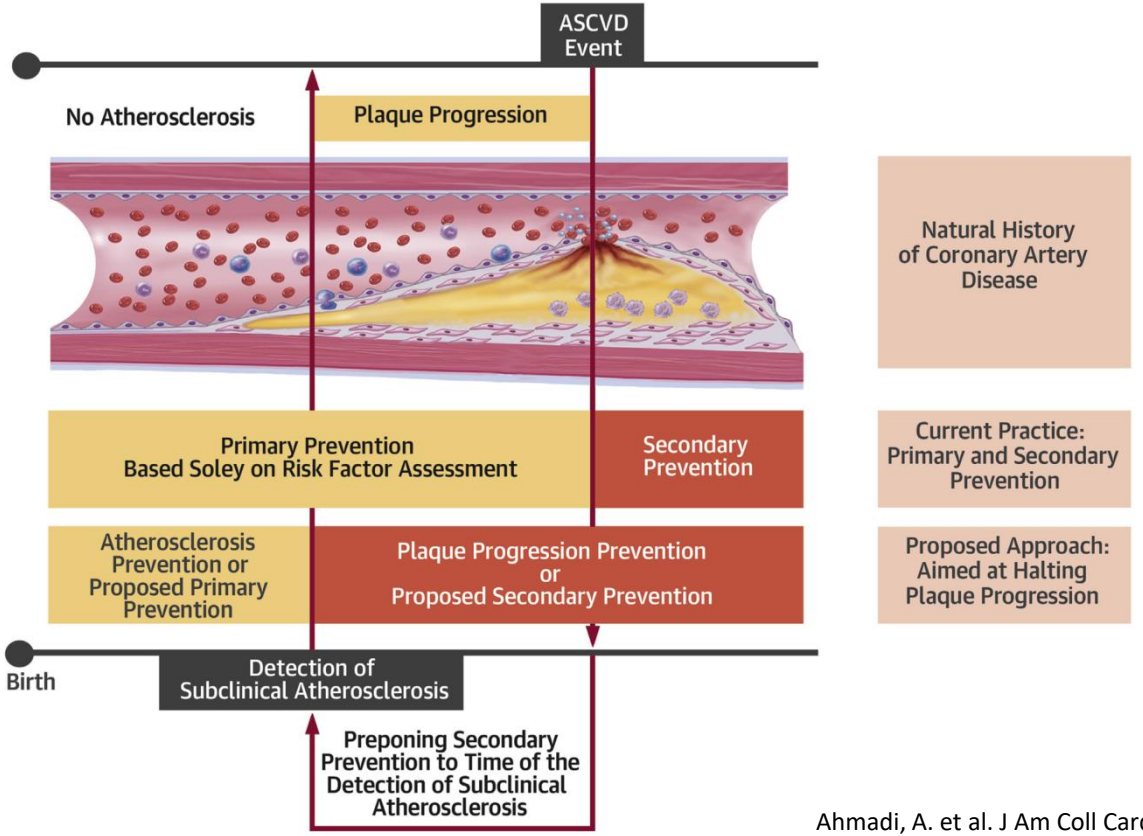
Ahmadi, A. et al. J Am Coll Cardiol. 2019;74(12):1608–17.

Hazard ratios for vascular outcomes in people with vs. without diabetes mellitus at baseline, based on analyses of 530 083 patients.



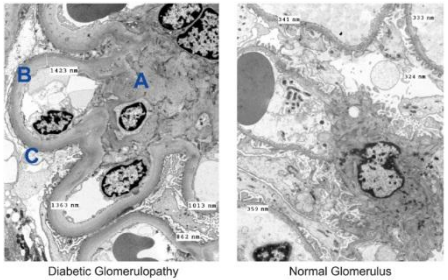
Emerging Risk Factors Collaboration. Lancet 2010;375:2215-2222.
ESC Guidelines on Diabetes, pre-diabetes and cardiovascular diseases in collaboration with EASD. EHJ 2019

Prevention Based on Detection of Subclinical Atherosclerosis Should Result in Reduced Coronary Events



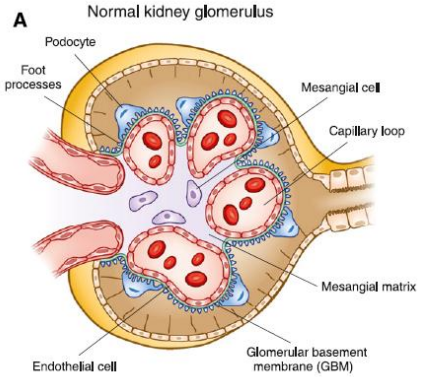
Ahmadi, A. et al. J Am Coll Cardiol. 2019;74(12):1608–17.

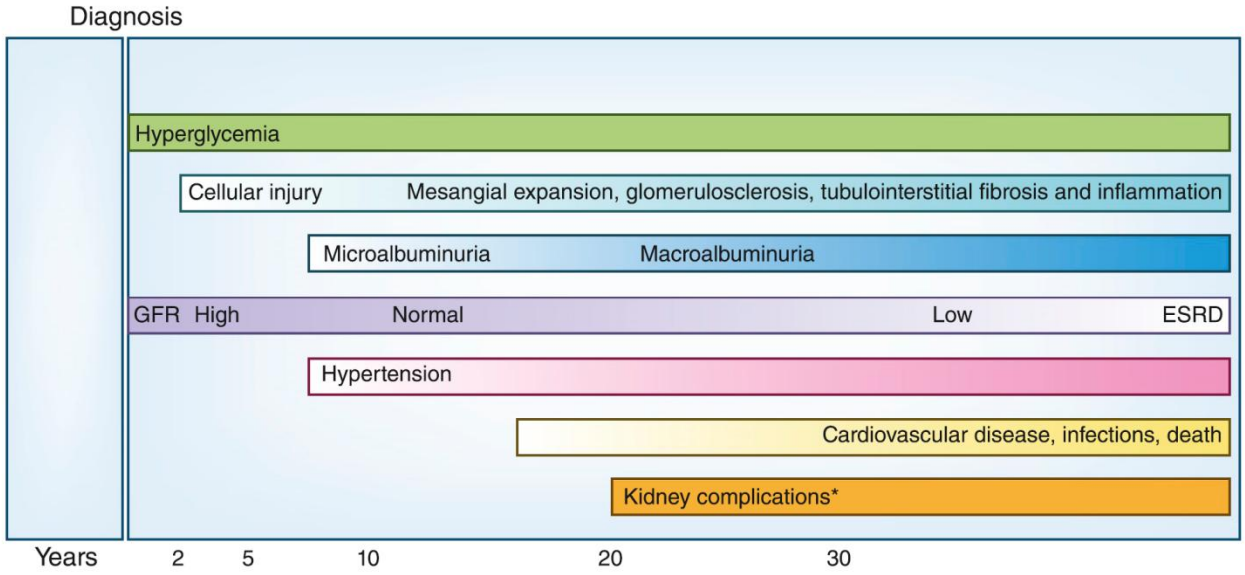
Diabetic Kidney Disease

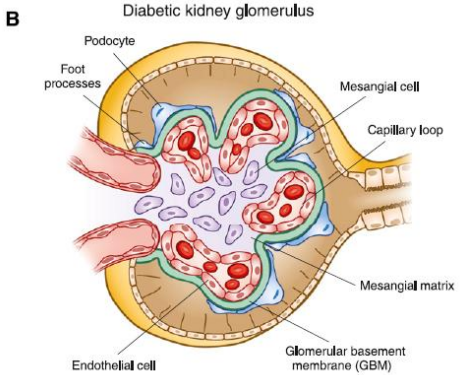


Diabetic Glomerulopathy

Normal Glomerulus



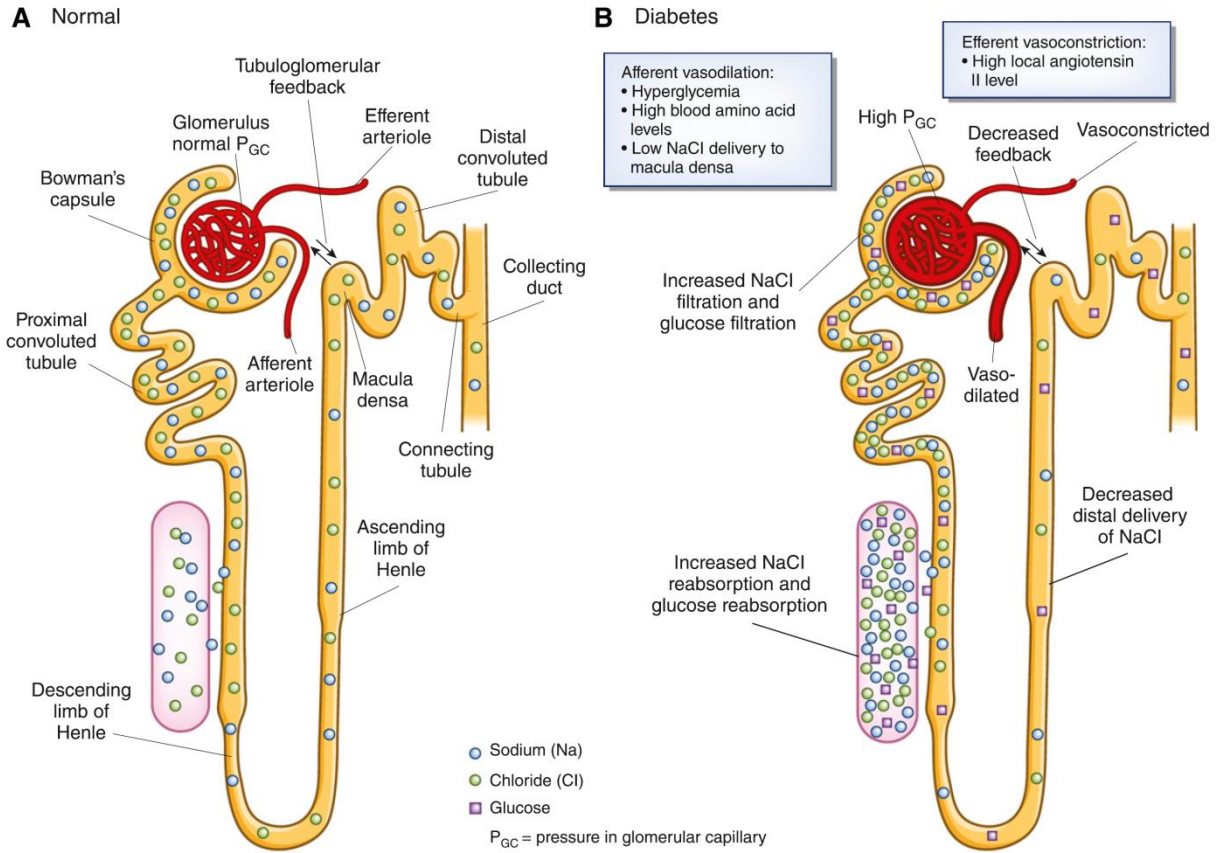




*Kidney complications: anemia, bone and mineral metabolism, retinopathy, and neuropathy

Alicic. Clin J Am Soc Nephrol 2017;12:2032 2045

Normal and diabetic nephron with altered renal hemodynamics



Chronic kidney disease classification by estimated glomerular filtration rate and albuminuria

eGFR (mL/min/1.73 m^2)	Albuminuria categories (albumin:creatinine ratio spot urine)			
	A1 (<3 mg/mmol)	A2 (3–30 mg/mmol)	A3 (>30 mg/mmol)	
G1 (≥90)	No CKD	G1 A2	G1 A3	Increasing risk↓
G2 (60–89)	No CKD	G2 A2	G2 A3	
G3a (45–59)	G3a A1	G3a A2	G3a A3	
G3b (30–44)	G3b A1	G3b A2	G3b A3	
G4 (15–29)	G4 A1	G4 A2	G4 A3	
G5 (<15)	G5 A1	G5 A2	G5 A3	
	Increasing risk→			

KDIGO 2012 Clinical Practice Guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013;3:1150

CV risk categories in patients with DM & continuum vascular risk

Moderate Risk

Young patients
(T1DM <35 y or T2DM <50 y)
with **DM duration <10 years, without other risk factors**

High Risk

DM duration ≥ 10 years
without target organ damage
plus any other **additional risk factor**

Very High Risk

DM and established CVD

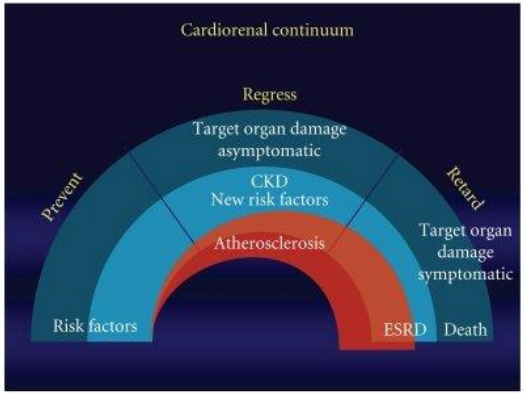
or **other target organ damage**

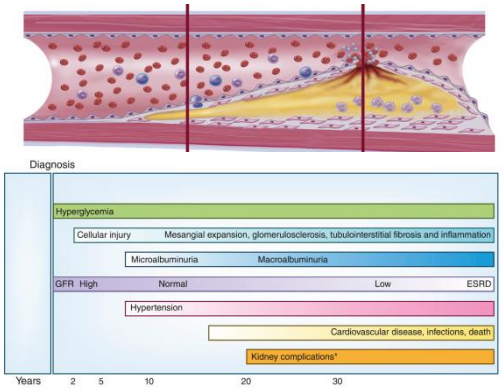
- Proteinuria
- Renal impairment eGFR <30 mL/min/1.73 m^2
- Left ventricular hypertrophy
- Retinopathy.

or **3 or more major risk factors**

- Age
- Hypertension
- Dyslipidemia
- Smoking
- Obesity

or **early onset T1DM of long duration (>20 y)**

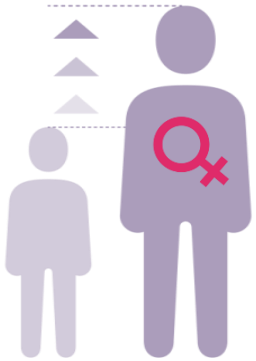




Cosentino F et al. Eur Heart J 2019;00:1-69. Piepoli MF et al. Eur Heart J 2016;37:2315-2381

Abordaje del riesgo cardiovascular en el paciente diabético

Personas con DM: mayor riesgo de insuficiencia cardiaca



Las personas con **diabetes** tienen un **riesgo 2 a 5 veces** mayor de desarrollar **IC**[1]

En pacientes con **IC establecida**, la **diabetes** confiere una probabilidad **60-80% mayor de muerte CV y de mortalidad por todas las causas**[2,3*]

1. Kannel WB, Hjortland M, Castelli WP. Am J Cardiol. 1974; 34(1):29-34. 2. Cubbon RM, Adams B, Rajwani A, et al. Diab Vasc Dis Res. 2013; 10(4):330-6. 3. MacDonald MR, Petrie MC, Varyani F, et al. Eur Heart J. 2008; 29(11):1377-85.

Magnitud del problema en España

1.300.000 personas con IC

IC= **3,8% gasto sanitario**

Causa más frecuente de hospitalización en >65 años.

Cuarta causa de mortalidad
(>17000 en 2011)

>100.000 hospitalizaciones anuales

El **50%** de los pacientes ingresados son **>75 años** y múltiples **comorbilidades**

Mortalidad intrahospitalaria: 10%
Mortalidad al año: 16%
Mortalidad a los 5 años : 50%

El 20-25% reingresos Hospital <30 días

Dos visitas a urgencias por año (50% ingresan)

Montes-Santiago et al Med Clin 2014; 142 (supl 1):3-8

Epidemiologia IC.

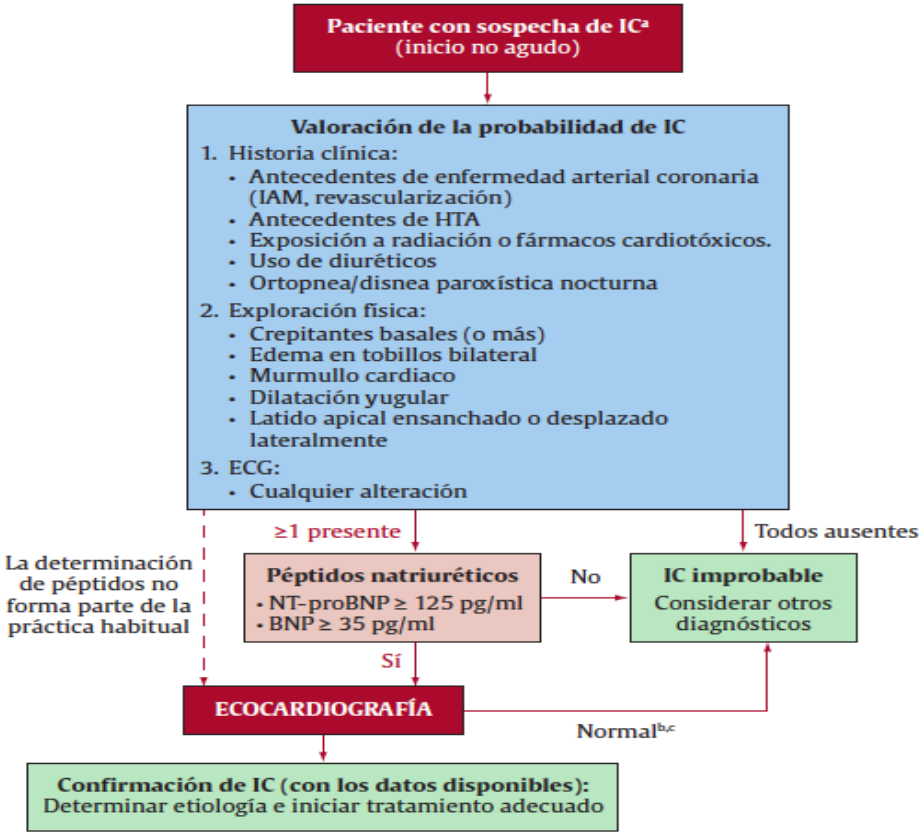
Estudio PRICE 2008: Prevalencia de la **insuficiencia cardiaca* en España, según sexo y edad,** en la población **>45 años**[2]

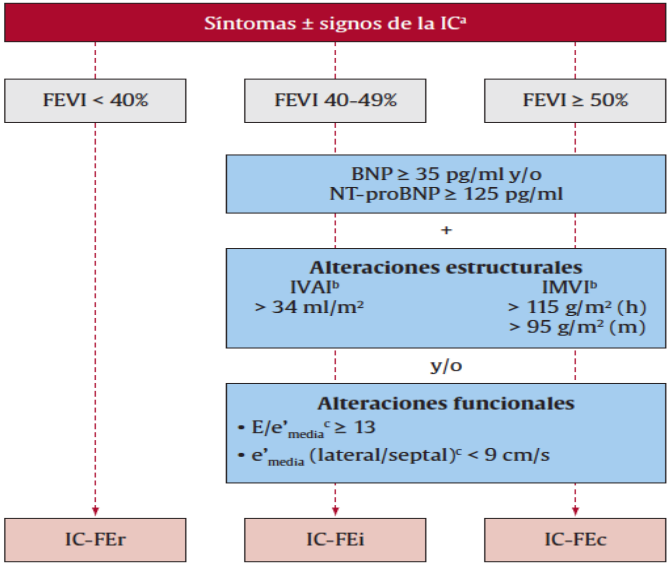
45 - 54 años	1,3%
55 - 64 años	5,5%
65 - 74 años	8%
> 75 años	16,1%
Total	6,8%

* Fracción de eyección conservada en un 50% de los casos.

1.Sayago-Silva I, et al. Rev Esp Cardiol (Engl Ed). 2013 Aug;66(8):649-56
2.Anguita Sánchez M, et al. Rev Esp Cardiol. 2008 Oct;61(10):1041-9.

Diagnóstico Insuficiencia Cardiaca





Ponikowski P, 2016 ESC Guidelines HF. Eur J Heart Fail. 2016;18:891-975

La IC sintomática sólo es la punta del iceberg

Visible

IC sintomática
(Prevalencia **>60ª** es del **11,8%**)

IC refractaria

ICFEPreservada / **IC Sistólica**
(Prev >60ª es **4,9%**) (Prev >60ª es **3,3%**)

IC no reconocida
- (15-20% pacientes >65 años atendidos en AP por dísnea de esfuerzo)
- En **>60 años un 27,7%** tienen **IC no reconocida** (**22,9% ICFEp y 4,8% ICFEr**)

Disfunción VI asintomática
- **DV Sistólica (5,5%, varones >80 años)**
- **DV Diastólica (36%, en >80ª es >50%)**

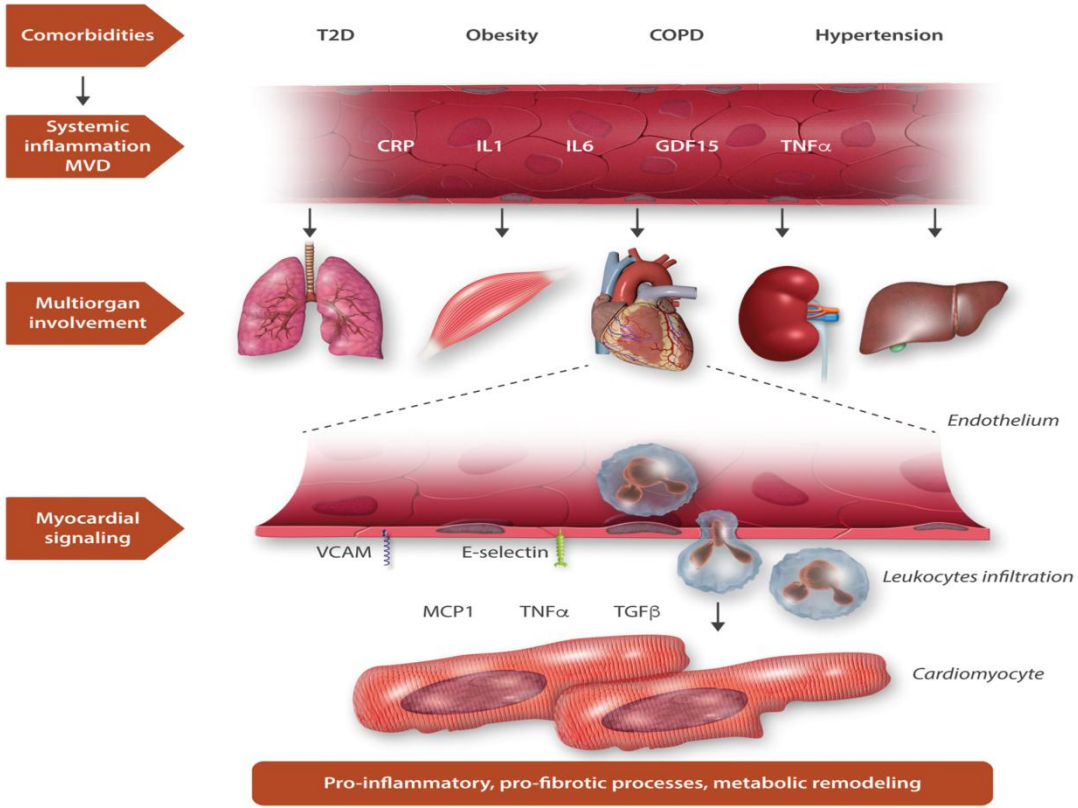
Hipertrofia ventricular izquierda, Cardiopatía isquémica, Diabetes mellitus, Valvulopatías, Aterosclerosis, Tóxicos, Hipertensión arterial, Obesidad, Senilidad ……

Invisible

Estado Preclínico de la Insuficiencia Cardiaca

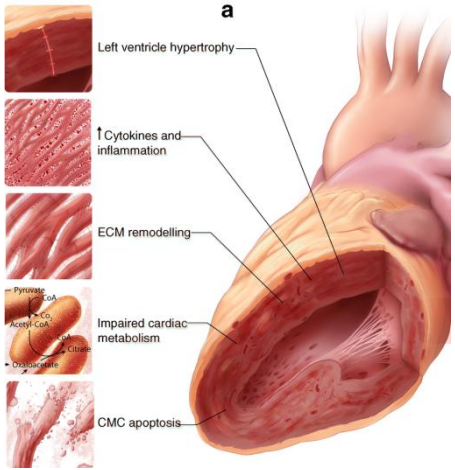
Van Riet EJHF 2016;18:242-252
Ponikowski P ESC HF Eur Heart J. 2016;37:2129–2200
Plastic iceberg J Kottke May 2018 National Geographic

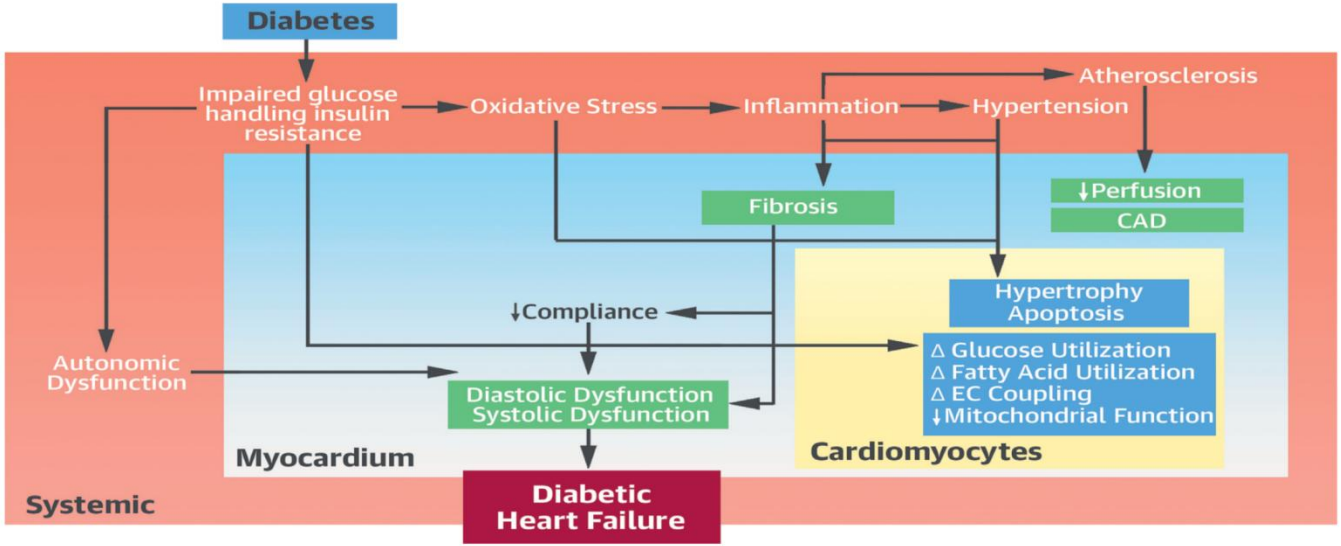
Insuficiencia Cardiaca ICFEP



M Rech. Cardiovascular Research 2018;114 (6):782–793

DM2 e Insuficiencia Cardiaca:



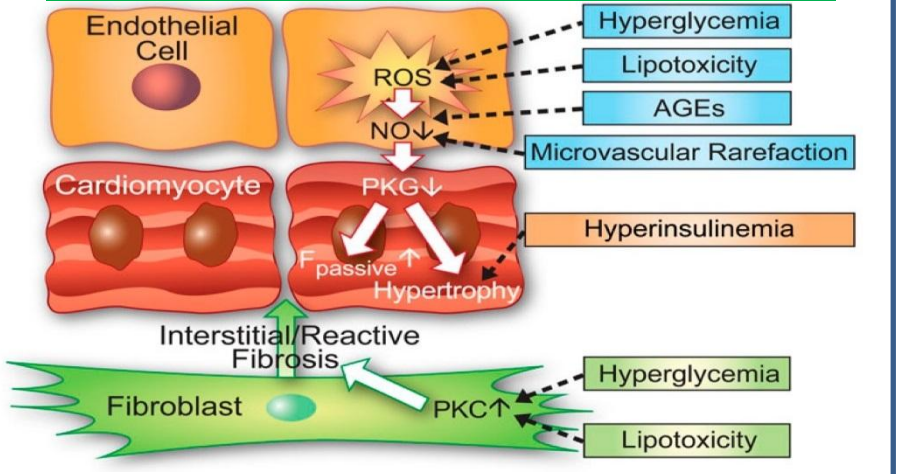


J Am Coll Cardiol. 2018;71(3):339–51.

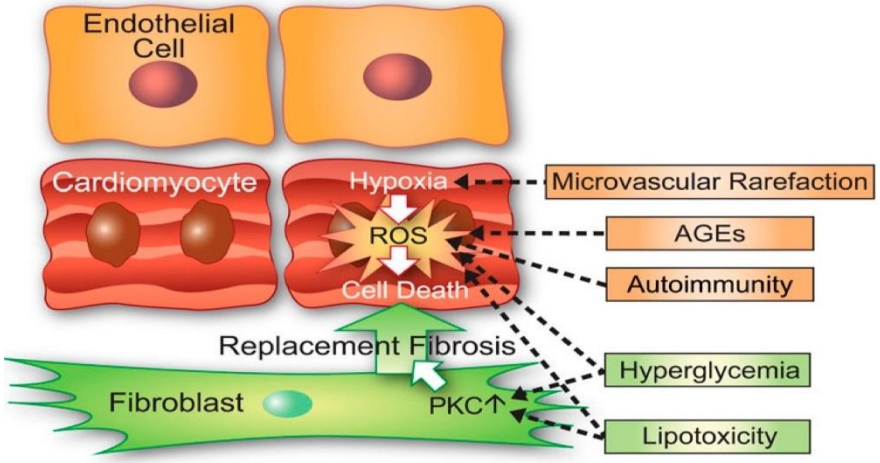
DM2 e Insuficiencia Cardiaca:

Clinical diabetic cardiomyopathy: a two-faced disease with restrictive and dilated phenotypes

MCD restrictiva
fenotipo FE conservada

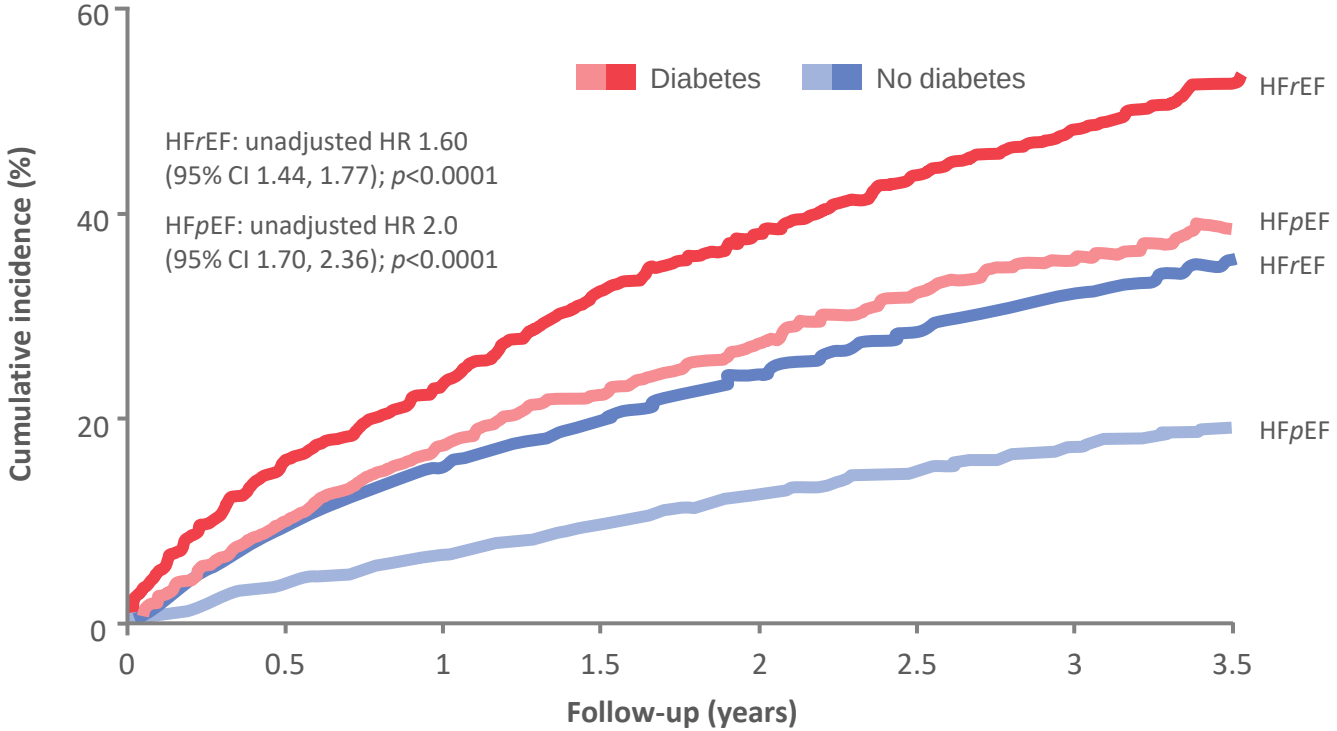


MCD dilatada
fenotipo FE reducida



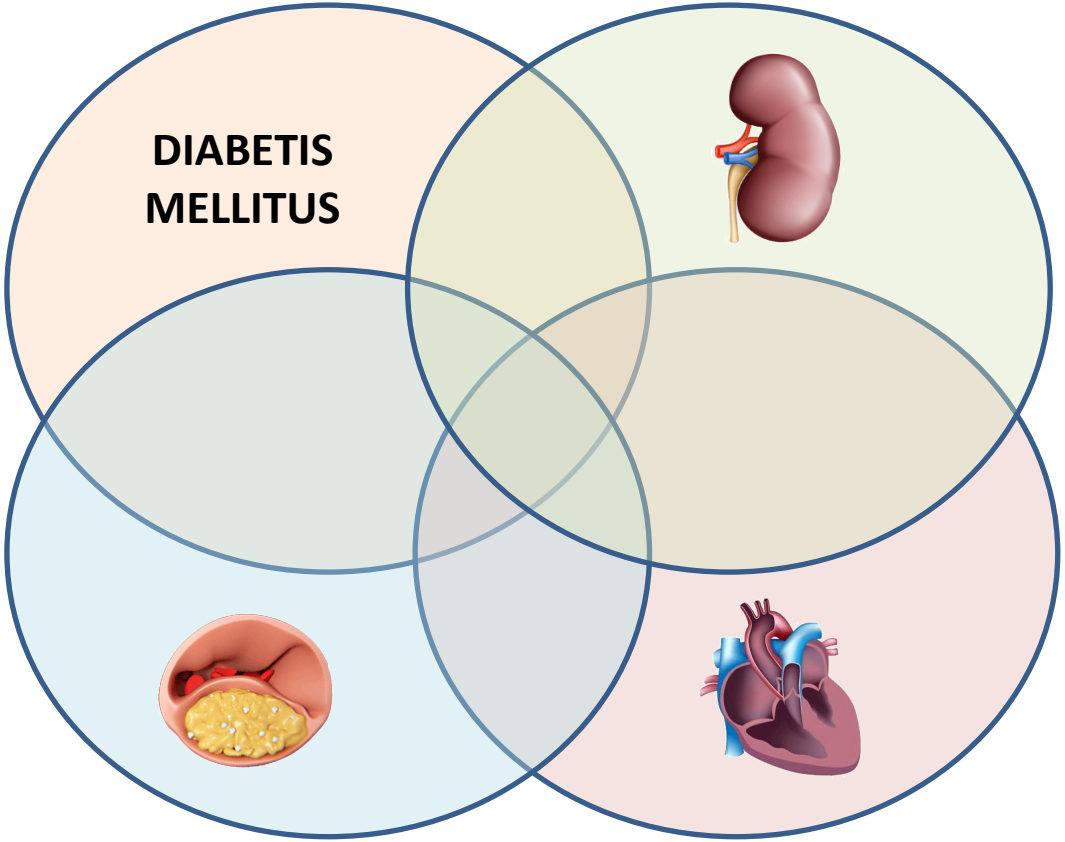
Seferovic et al. Eur Heart J. 2015; 36: 1.718-1.727.

Risk of CV death or HHF in patients with diabetes versus non-diabetes

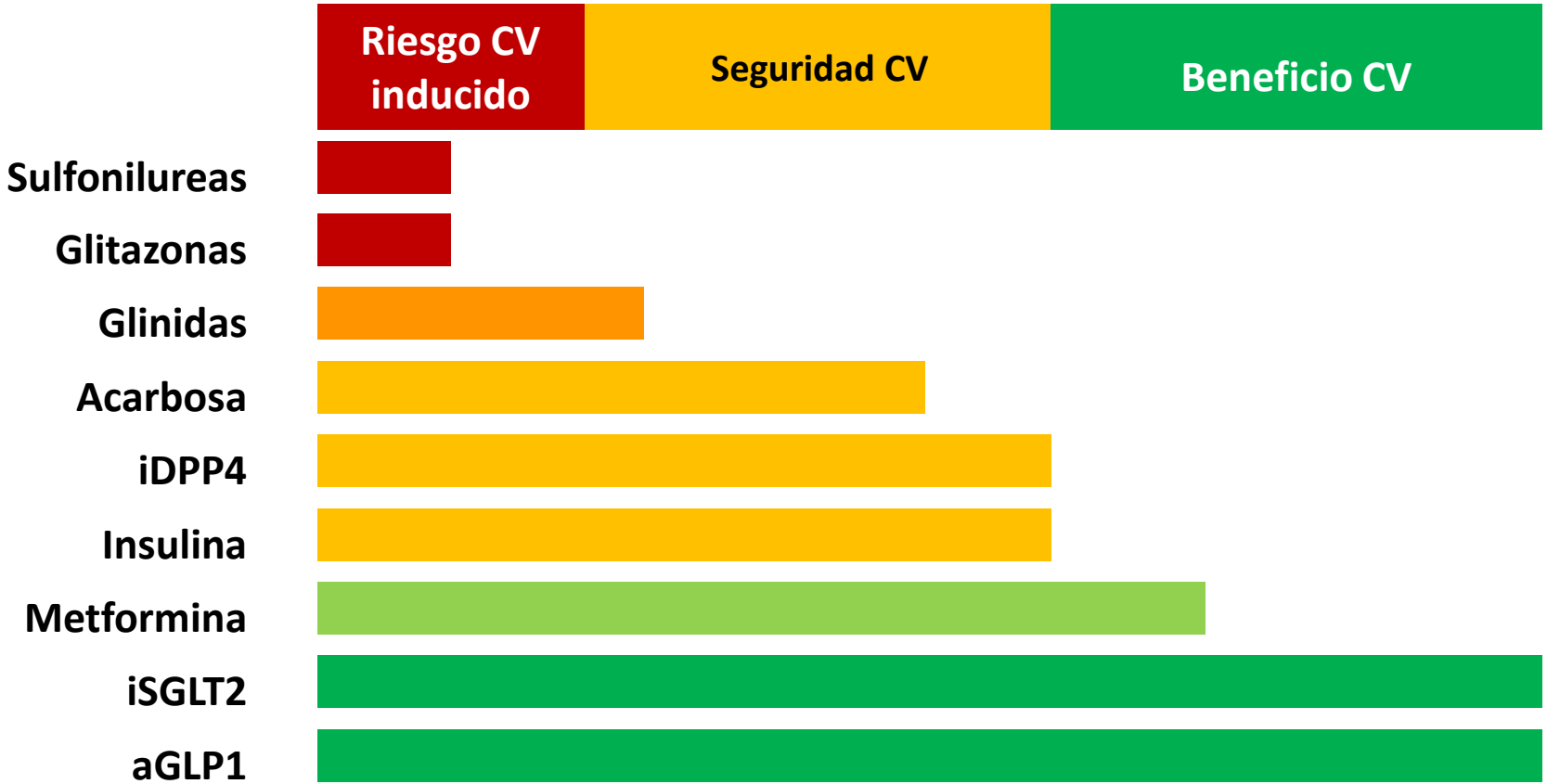


MacDonald MR *et al. Eur Heart J* 2008;29:1377

Tractaments antidiabetics i PROTECCIÓ CARDIORENAL



Tratamiento de la DM2 en Prevención Secundaria



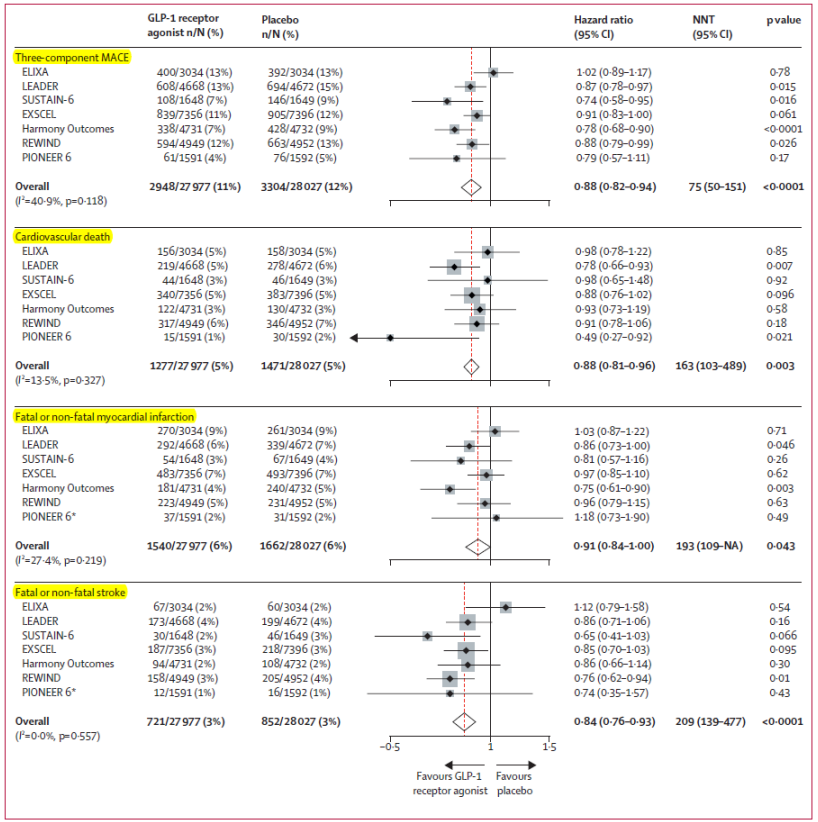
Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes (56.004 participants)

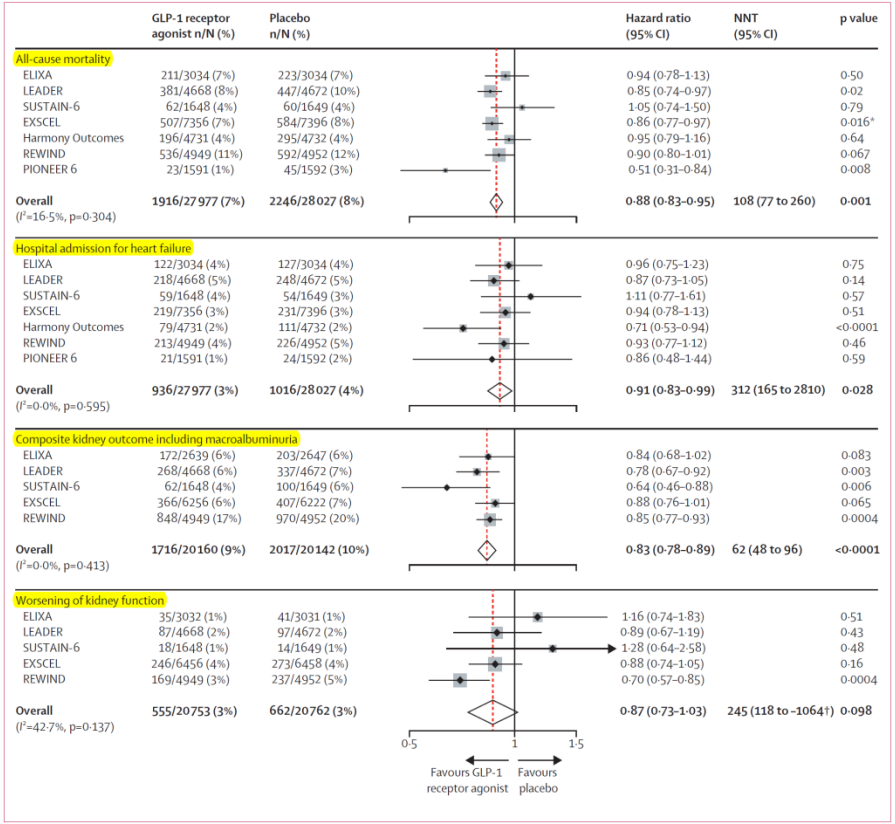
	ELIXA (n=6068)[7]	LEADER (n=9340)[8,14]	SUSTAIN-6 (n=3297)[9]	EXSCEL (n=14752)[11]	Harmony Outcomes (n=9463)[10]	REWIND (n=9901)[12,13]	PIONEER 6 (n=3183)[14]
Drug	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Albiglutide	Dulaglutide	Semaglutide (oral)
Structural basis	Exendin-4	Human GLP-1	Human GLP-1	Exendin-4	Human GLP-1	Human GLP-1	Human GLP-1
Administration route	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Oral
Dose	20 µg per day	1·8 mg per day	0·5 or 1 mg per week	2 mg per week	30 or 50 mg per week	1·5 mg per week	14 mg per day
Age (years)	60 (10)	64 (7)	65 (7)	62 (9)	64 (7)	66 (7)	66 (7)
Sex							
Men	4207 (69%)	6003 (64%)	2002 (61%)	9149 (62%)	6569 (69%)	5312 (54%)	2176 (68%)
Women	1861 (31%)	3337 (36%)	1295 (39%)	5603 (38%)	2894 (31%)	4589 (46%)	1007 (32%)
Ethnic origin							
White	4576 (75%)	7238 (77%)	2736 (83%)	11175 (76%)	6583 (70%)	7498 (76%)	2300 (72%)
Other	1492 (25%)	2102 (23%)	561 (17%)	3577 (24%)	2880 (30%)	2403 (24%)	883 (28%)
BMI (kg/m^2)	30·1 (5·6)	32·5 (6·3)	32·8 (6·2)	32·7 (6·4)	32·3 (5·9)	32·3 (5·7)	32·3 (6·5)
Diabetes duration (years)	9·2 (8·2)	12·8 (8·0)	13·9 (8·1)	13·1 (8·3)	14·2 (8·8)	10·6 (7·2)	14·9 (8·5)
HbA_{1c} (%)	7·7 (1·3)	8·7 (1·6)	8·7 (1·5)	8·1 (1·0)	8·7 (1·5)	7·3 (1·1)	8·2 (1·6)
Established cardiovascular disease	6068 (100%)	7598 (81%)	2735 (83%)	10782 (73%)	9463 (100%)	3114 (31%)	2695 (85%)
History of heart failure	1358 (22%)	1667 (18%)	777 (24%)	2389 (16%)	1922 (20%)	853 (9%)	388 (12%)
Systolic blood pressure (mm Hg)	129 (17)	136 (18)	136 (17)	135 (17)	135 (17)	137 (17)	136 (18)
eGFR (mL/min per 1·73 m^2)*	78 (21)	80 (NR)	80 (61–92)	77 (61–92)	79 (25)	75 (24)	74 (21)
Glucose-lowering drugs used							
Insulin	2374 (39%)	4169 (45%)	1913 (58%)	6838 (46%)	5597 (59%)	2363 (24%)	1930 (61%)
Biguanides	4021 (66%)	7144 (76%)	2414 (73%)	11295 (77%)	6969 (74%)	8037 (81%)	2463 (77%)
Sulfonylurea	2004 (33%)	4733 (51%)	1410 (43%)	5401 (37%)	2725 (29%)	4552 (46%)	1027 (32%)
Thiazolidinedione	95 (2%)	575 (6%)	76 (2%)	579 (4%)	194 (2%)	168 (2%)	118 (4%)
DPP-4 inhibitor	NA	6 (<1%)	5 (<1%)	2203 (15%)	1437 (15%)	88 (1%)	2 (<1%)
SGLT2 inhibitor	NA	NA	5 (<1%)	77 (1%)	575 (6%)	12 (<1%)	305 (10%)

Numerical data are mean (SD) or n (%), unless otherwise specified. GLP-1=glucagon-like peptide-1. eGFR=estimated glomerular filtration rate. NR=not reported. DPP-4=dipeptidyl peptidase-4. SGLT2=sodium-glucose co-transporter-2. *eGFR data are median (IQR) for SUSTAIN-6 and EXSCEL.

Lancet Diabetes Endocrinol 2019 http://dx.doi.org/10.1016/S2213-8587(19)30249-9

Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in T2DM





In patients with type 2 diabetes, GLP-1 receptor agonists reduced three-component MACE and its individual components, as well as all-cause mortality and risk of hospital admission for heart failure. Treatment with a GLP-1 receptor agonist also reduced the risk of worsening kidney function, due mainly to a decrease in development of macroalbuminuria. These benefits were obtained without an increase in risk of severe hypoglycaemia, pancreatic adverse effects, or thyroid cancer

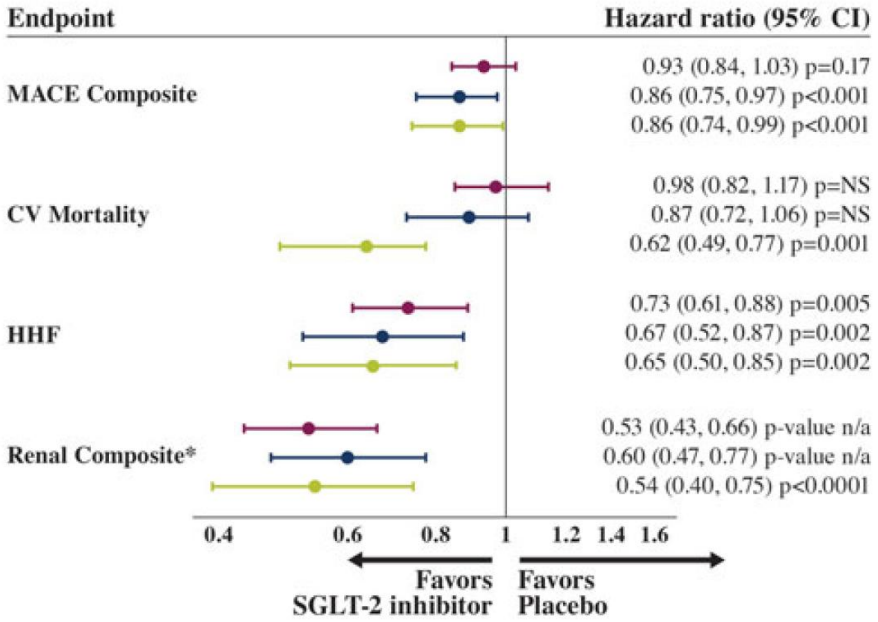
Cardiovascular Outcome Trials with SGLT-2 Inhibitors

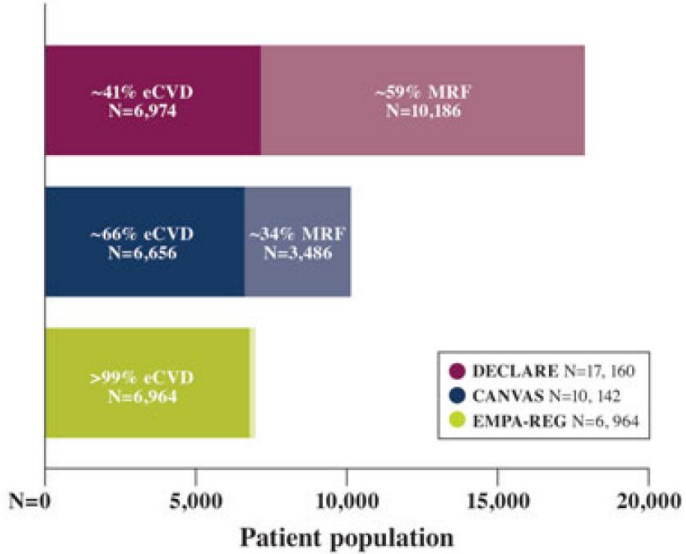
STUDIES	SGLT-2 Inhibitor Daily Dose vs Comparator	SGLT-2i vs Placebo or Comparator, N	History of CVD Patients %	Primary CV Composite Outcome*	CV death	Hospit. for Heart Failure (HHF)	CV death or HHF	All-Cause Mortality	Stroke (Fatal or Nonfatal)	Myocardial Infarction (Fatal or Nonfatal)
EMPA-REG OUTCOME (FU 3,1 years)	Empagliflozin 10 or 25 mg vs placebo	4687 vs 2333	99%	0.86 (0.74–0.99); *P*=0.04	0.62 (0.49–0.77); P<0.001	0.65 (0.50–0.85); P=0.002	0.66 (0.55–0.79); P<0.001	0.68 (0.57–0.82); P<0.001	1.18 (0.89–1.56); P=0.26	0.87 (0.70–1.09); P=0.23
CANVAS Program (FU 2,4 years)	Canagliflozin 100–300 mg vs placebo	5795 vs 4347	65%	0.86 (0.75–0.97); P=0.02	0.87 (0.72–1.06); NS	0.67 (0.52–0.87)†	0.78 (0.67–0.91) p=0,002	0.87 (0.74–1.01); NS	0.90 (0.71–1.15); NS	0.85 (0.69–1.05); NS
DECLARE-TIMI 58 (FU 4,2 years)	Dapagliflozin 10 mg vs placebo	8582 vs 8578	41%	0,93 (0,84-1,03) p=0,17	0,98 (0,82-1,17) NS	0,73 (0,61-0,88)	0,83 (0,73-0,95) P=0,005	0,93 (0,82-1,04) NS	1,01 (0,84-1,21) NS	0,89 (0,77-1,01) NS

*Cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke.
†Not considered statistically significant on the basis of the prespecified hypothesis testing sequence

Scheen. Circulation Research 2018;122:1439-1459
Wiviott SD. N Engl J Med 2018 DOI: 10.1056/NEJMoa1812389

Risk of cardiovascular or renal events for patients in the EMPA-REG (empagliflozin), CANVAS (canagliflozin), and DECLARE (dapagliflozin)



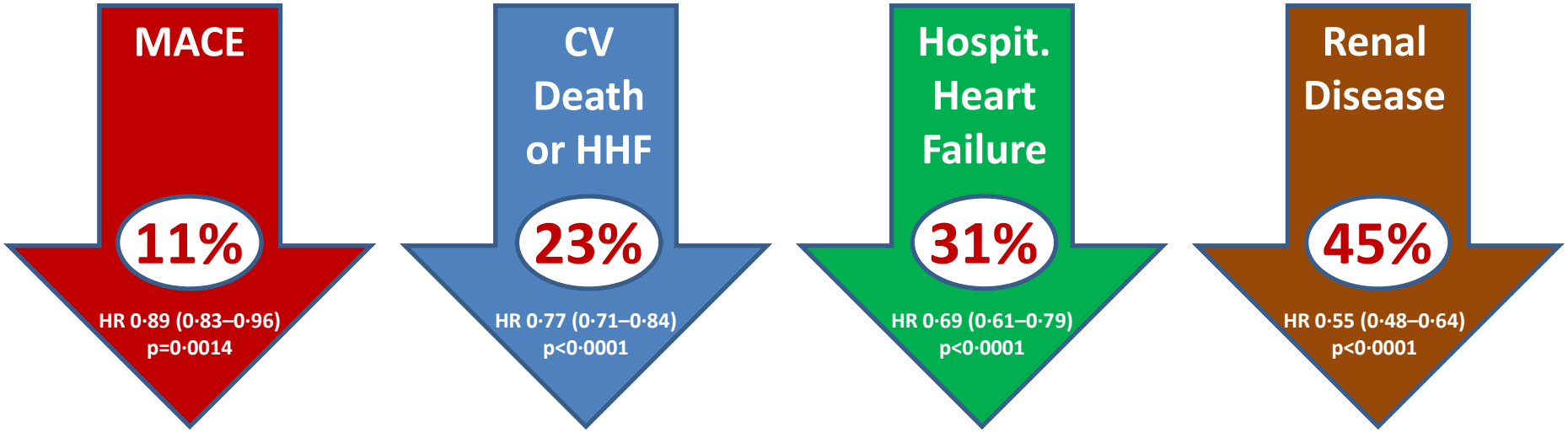


Woo et al. CURRENT MEDICAL RESEARCH AND OPINION 2019
https://doi.org/10.1080/03007995.2019.1576479

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

We included data from three identified trials and 34.322 patients (60·2% with established atherosclerotic cardiovascular disease), with 3342 MACE, 2028 cardiovascular deaths or hospitalisations for heart failure events, and 766 renal composite outcomes

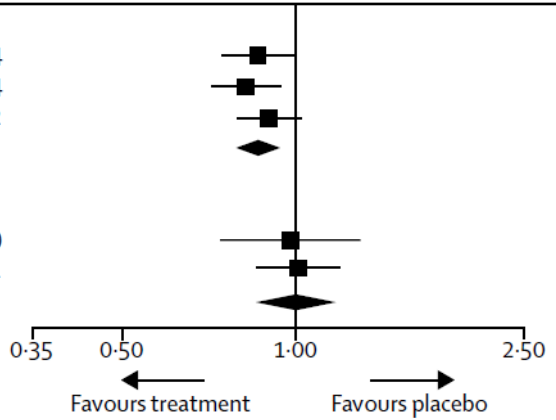


Zelniker TA, Wiviott SD, Sabatine M. Lancet November 10, 2018, doi.org/10.1016/S0140-6736(18)32590-X

Meta-analysis of SGLT2i trials on the composite of myocardial infarction, stroke, and cardiovascular death (MAJOR ADVERSE CARDIOVASCULAR EVENTS) stratified by the presence of Established atherosclerotic cardiovascular disease

MACE

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo		
Patients with atherosclerotic cardiovascular disease							
EMPA-REG OUTCOME	4687/7020	2333/7020	772	37·4	43·9	29·4	0·86 (0·74–0·99)
CANVAS Program	3756/6656	2900/6656	796	34·1	41·3	32·4	0·82 (0·72–0·95)
DECLARE-TIMI 58	3474/6974	3500/6974	1020	36·8	41·0	38·2	0·90 (0·79–1·02)
Fixed effects model for atherosclerotic cardiovascular disease (p=0·0002)							**0·86 (0·80–0·93)**
Patients with multiple risk factors							
CANVAS Program	2039/3486	1447/3486	215	15·8	15·5	25·9	0·98 (0·74–1·30)
DECLARE-TIMI 58	5108/10 186	5078/10 186	539	13·4	13·3	74·1	1·01 (0·86–1·20)
Fixed effects model for multiple risk factors (p=0·98)							**1·00 (0·87–1·16)**



Zelniker TA, Wiviott SD, Sabatine M. Lancet November 10, 2018
http://dx.doi.org/10.1016/S0140-6736(18)32590-X

Meta-analysis of SGLT2i trials on HOSPITALISATION FOR HEART FAILURE stratified by the presence of Established atherosclerotic cardiovascular disease

Hospitalización por Insuficiencia Cardíaca

Diabéticos con Enfermedad CV aterosclerótica establecida

↓ 29%

HR 0,71 (95% IC 0,62-0,82)

Diabéticos con múltiples factores de riesgo

↓ 36%

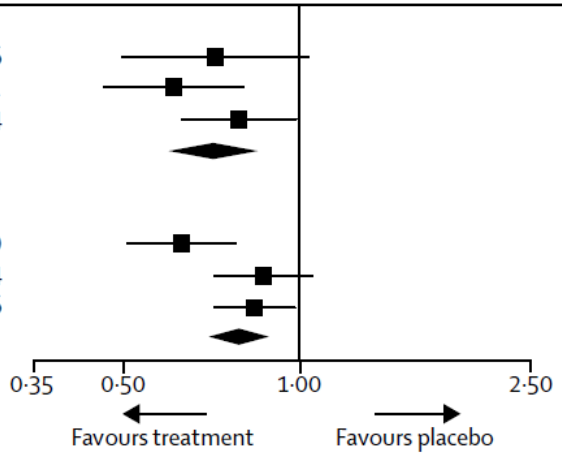
HR 0,64 (95% IC 0,48-0,85)

Zelniker TA, Wiviott SD, Sabatine M. Lancet November 10, 2018
http://dx.doi.org/10.1016/S0140-6736(18)32590-X

Meta-analysis of SGLT2i trials on hospitalisation for heart failure and cardiovascular death stratified by HISTORY OF HEART FAILURE

CV Death or HHF

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo			
Patients with history of heart failure								
EMPA-REG OUTCOME	462/706	244/706	124	63·6	85·5	23·6		0·72 (0·50–1·04)
CANVAS Program	803/1461	658/1461	203	35·4	56·8	34·1		0·61 (0·46–0·80)
DECLARE-TIMI 58	852/1724	872/1724	314	45·1	55·5	42·4		0·79 (0·63–0·99)
Fixed effects model for history of heart failure (p<0·0001)								**0·71 (0·61–0·84)**
Patients with no history of heart failure								
EMPA-REG OUTCOME	4225/6314	2089/6314	339	15·5	24·9	30·0		0·63 (0·51–0·78)
CANVAS Program	4992/8681	3689/8681	449	13·6	15·2	32·4		0·87 (0·72–1·06)
DECLARE-TIMI 58	7730/15 436	7706/15 436	599	8·9	10·5	37·6		0·84 (0·72–0·99)
Fixed effects model for no history of heart failure (p<0·0001)								**0·79 (0·71–0·88)**

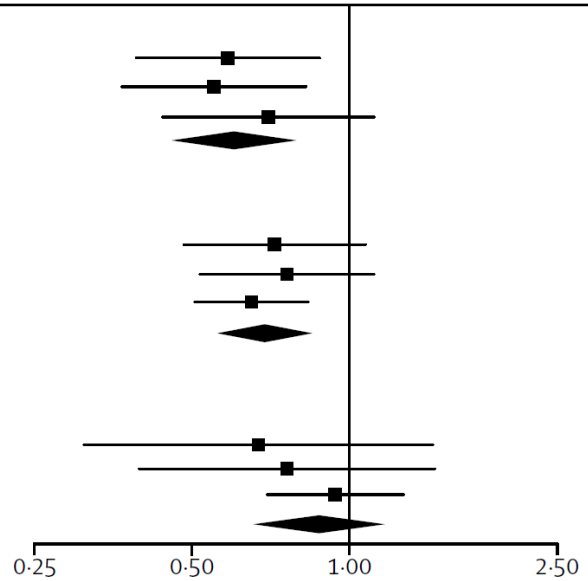


Zelniker TA, Wiviott SD, Sabatine M. Lancet November 10, 2018
http://dx.doi.org/10.1016/S0140-6736(18)32590-X

Meta-analysis of SGLT2i trials on the hospitalisation for heart failure stratified by the eGFR levels

Hospitalisation for Heart Failure

eGFR <60 mL/min per m²							
EMPA-REG OUTCOME	1212/1819	607/1819	94	14·9	25·8	36·5	0·59 (0·39–0·88)
CANVAS Program	NA/2039	NA/2039	98	11·6	21·3	36·1	0·55 (0·37–0·83)
DECLARE-TIMI 58	606/1265	659/1265	77	12·3	19·3	27·4	0·70 (0·44–1·12)
Fixed effects model for eGFR <60 (p<0·0001)							**0·60 (0·47–0·77)**
eGFR 60 to <90 mL/min per m²							
EMPA-REG OUTCOME	2423/3661	1238/3661	100	8·4	11·7	21·3	0·72 (0·48–1·07)
CANVAS Program	NA/5625	NA/5625	108	4·6	6·1	23·4	0·76 (0·52–1·12)
DECLARE-TIMI 58	3838/7732	3894/7732	251	6·5	9·9	55·2	0·65 (0·51–0·84)
Fixed effects model for eGFR 60 to <90 (p<0·0001)							**0·69 (0·57–0·83)**
eGFR ≥90 mL/min per m²							
EMPA-REG OUTCOME	1050/1538	488/1538	27	5·4	7·9	11·3	0·67 (0·31–1·44)
CANVAS Program	NA/2476	NA/2476	37	3·7	5·1	15·7	0·76 (0·40–1·47)
DECLARE-TIMI 58	4137/8162	4025/8162	170	5·1	5·4	73·0	0·94 (0·69–1·26)
Fixed effects model for eGFR ≥90 (p=0·31)							**0·88 (0·68–1·13)**



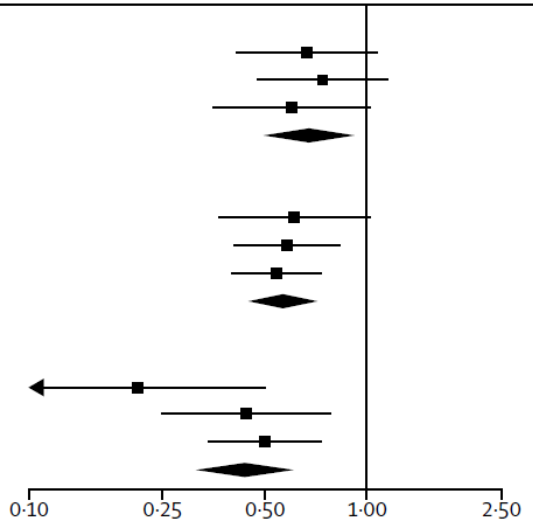
eGFR: estimated glomerular filtration rate

Zelniker TA, Wiviott SD, Sabatine M. Lancet November 10, 2018
http://dx.doi.org/10.1016/S0140-6736(18)32590-X

Meta-analysis of SGLT2i trials on the composite of WORSENING OF RENAL FUNCTION, END-STAGE RENAL DISEASE, OR RENAL DEATH

A

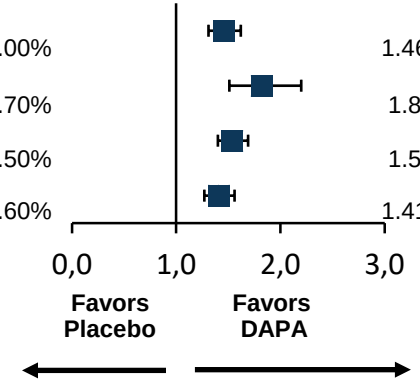
	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo			
eGFR <60 mL/min per m²								
EMPA-REG OUTCOME	1196/1801	605/1801	NA	NA	NA	33·5		0·66 (0·41–1·07)
CANVAS Program	NA/2039	NA/2039	83	11·4	15·1	39·6		0·74 (0·48–1·15)
DECLARE-TIMI 58	606/1265	659/1265	59	8·9	15·2	27·0		0·60 (0·35–1·02)
Fixed effects model for eGFR <60 (p=0·0054)								**0·67 (0·51–0·89)**
eGFR 60 to <90 mL/min per m²								
EMPA-REG OUTCOME	2406/3638	1232/3638	NA	NA	NA	16·8		0·61 (0·37–1·03)
CANVAS Program	NA/5625	NA/5625	118	4·6	7·4	34·4		0·58 (0·41–0·84)
DECLARE-TIMI 58	3838/7732	3894/7732	186	4·2	7·8	48·9		0·54 (0·40–0·73)
Fixed effects model for eGFR 60 to <90 (p<0·0001)								**0·56 (0·46–0·70)**
eGFR ≥90 mL/min per m²								
EMPA-REG OUTCOME	1043/1529	486/1529	NA	NA	NA	11·7		0·21 (0·09–0·53)
CANVAS Program	NA/2476	NA/2476	48	3·8	8·1	27·5		0·44 (0·25–0·78)
DECLARE-TIMI 58	4137/8162	4025/8162	120	2·5	4·9	60·8		0·50 (0·34–0·73)
Fixed effects model for eGFR ≥90 (p<0·0001)								**0·44 (0·32–0·59)**



Zelniker TA, Wiviott SD, Sabatine M. Lancet November 10, 2018
http://dx.doi.org/10.1016/S0140-6736(18)32590-X

Dapaglflozin increased the likelihood of patients improving in albuminuria category, regardless of baseline UACR

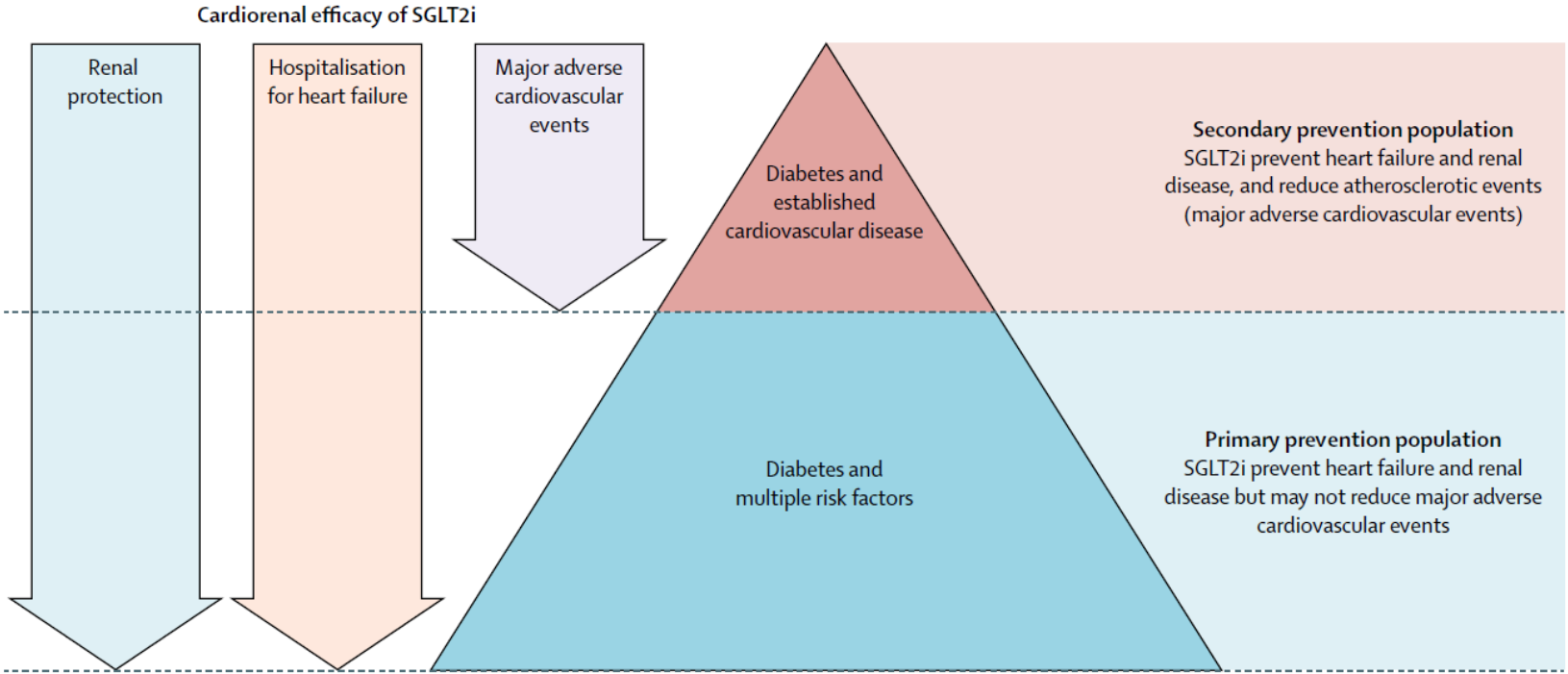
	Dapagliflozin		Placebo			
	n/N (%)	KM Event Rate	n/N (%)	KM Event Rate	Hazard Ratio (95% CI)	Cox p-value
Endpoints						
Improvement from baseline						
Micro to Normo	774/2017 (38.4)	38.90%	576/2013 (28.6)	29.00%	1.46 (1.31, 1.62)	<0.0001
Macro to Normo/Micro	282/594 (47.5)	48.10%	175/575 (30.4)	31.70%	1.82 (1.51, 2.2)	<0.0001
Macro to Normo/Micro or Micro to Normo	1056/2611 (40.4)	41.00%	751/2588 (29.0)	29.50%	1.54 (1.4, 1.69)	<0.0001
Micro/Macro to Normo	809/2611 (31.0)	31.50%	604/2588 (23.3)	23.60%	1.41 (1.27, 1.56)	<0.0001



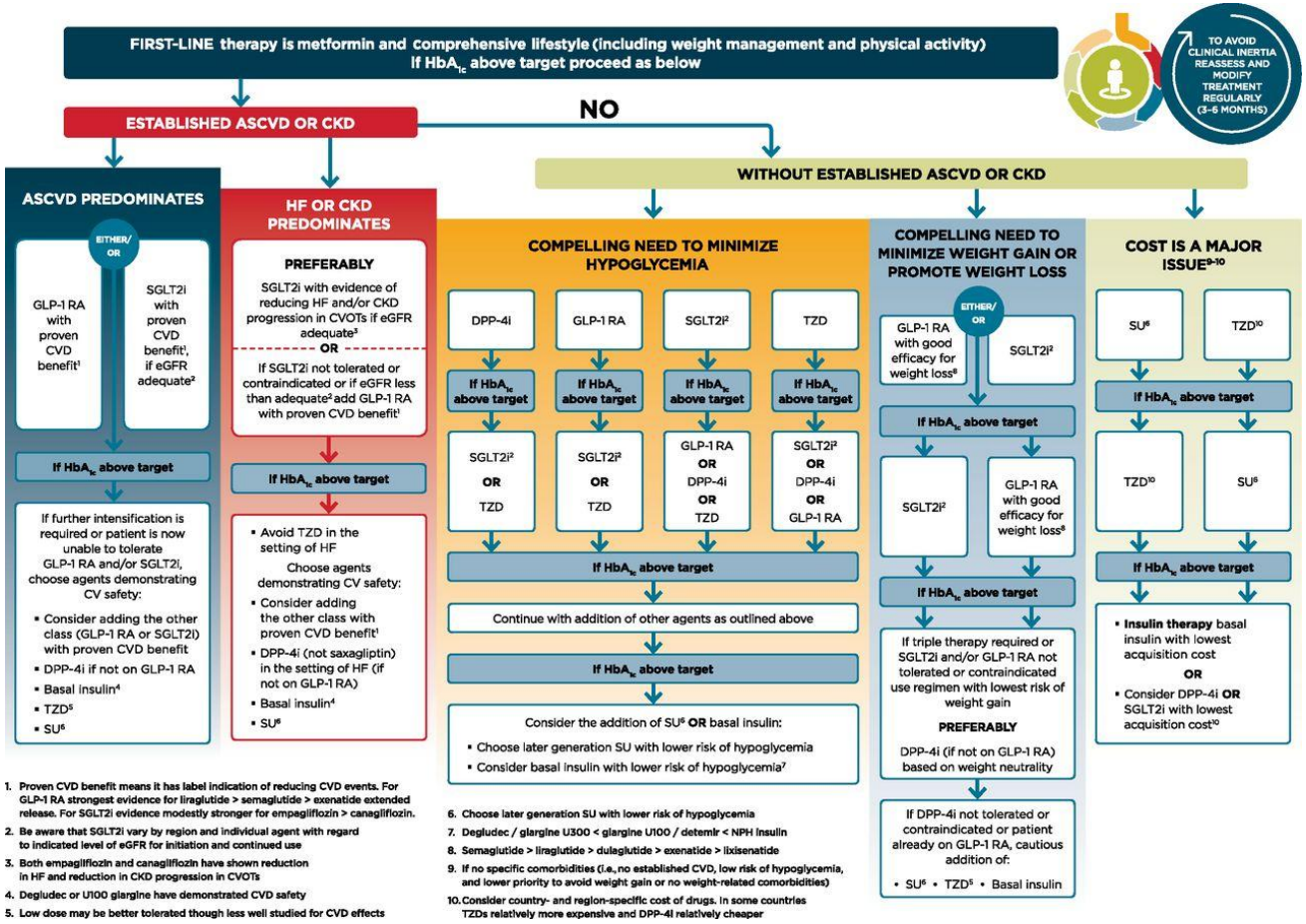
Definitions of Albuminuria Categories	
Macroalbuminuria	UACR ≥300 mg/g
Microalbuminuria	UACR ≥30 to <300 mg/g
Normoalbuminuria	UACR <30 mg/g

Raz I et al. Presented at: ADA 79th Scientific Sessions; June 7-11, 2019; San Francisco, CA. 244-OR.

Cardiorenal benefits of SGLT2i in different patient populations



Verma S. Lancet November 10, 2018
http://dx.doi.org/10.1016/S0140-6736(18)32824-1



1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > 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 U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

American Diabetes Association Diabetes Care 2019

Recommendations for glucose-lowering treatment for patients with diabetes

Recommendations	Class[a]	Level[b]
SGLT2 inhibitors		
Empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with T2DM and CVD, or at very high/high CV risk,[c] to reduce CV events.[306,308,309,311]	I	A
Empagliflozin is recommended in patients with T2DM and CVD to reduce the risk of death.[306]	I	B
GLP1-RAs		
Liraglutide, semaglutide, or dulaglutide are recommended in patients with T2DM and CVD, or at very high/high CV risk,[c] to reduce CV events.[176,299–300,302–303]	I	A
Liraglutide is recommended in patients with T2DM and CVD, or at very high/high CV risk,[c] to reduce the risk of death.[176]	I	B
Biguanides		
Metformin should be considered in overweight patients with T2DM without CVD and at moderate CV risk.[146,149]	IIa	C
Insulin		
Insulin-based glycaemic control should be considered in patients with ACS with significant hyperglycaemia (>10 mmol/L or >180 mg/dL), with the target adapted according to comorbidities.[260–262]	IIa	C
Thiazolidinediones		
Thiazolidinediones are not recommended in patients with HF.	III	A
DPP4 inhibitors		
Saxagliptin is not recommended in patients with T2DM and a high risk of HF.[291]	III	B

ESC Guidelines on Diabetes, pre-diabetes and cardiovascular diseases in collaboration with EASD. EHJ 2019

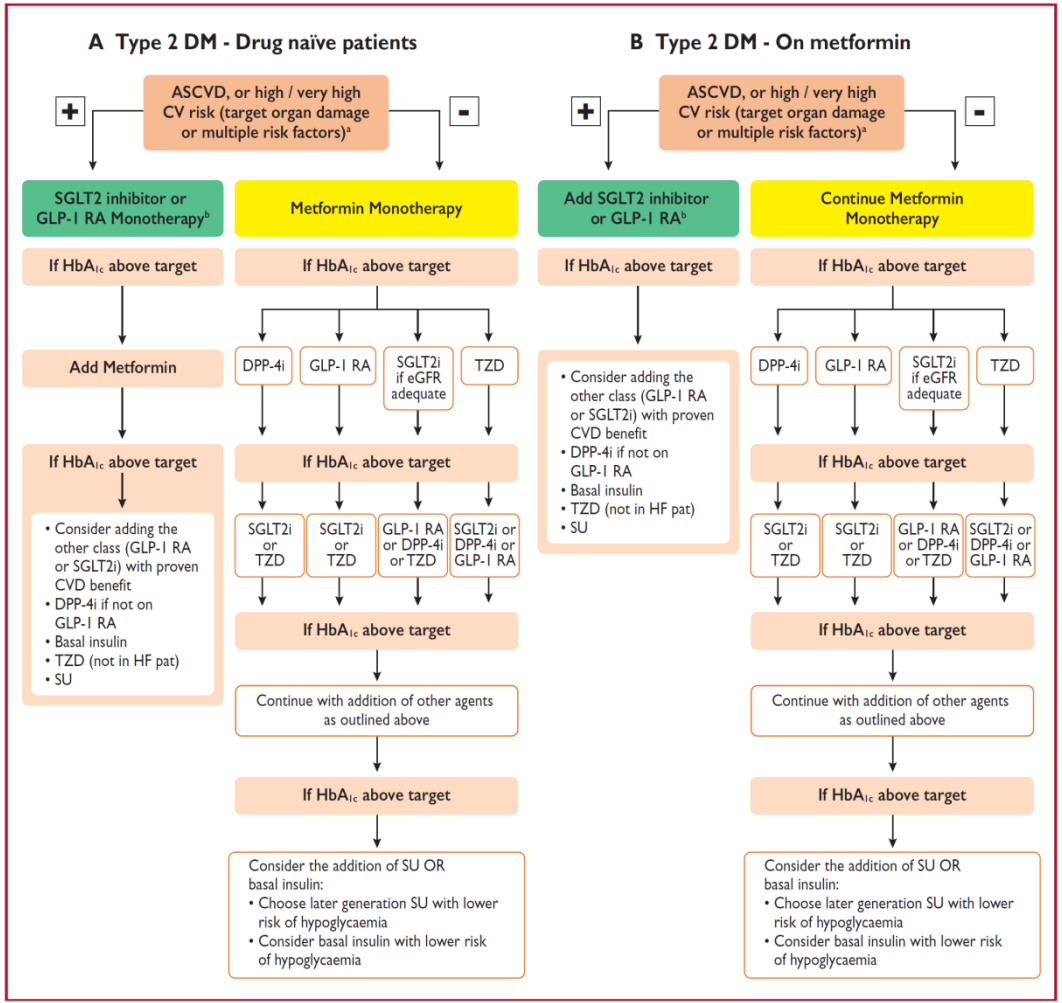
Recommendations for the treatment of patients with diabetes to reduce heart failure risk

Recommendations	Class[a]	Level[b]
SGLT2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin) are recommended to lower risk of HF hospitalization in patients with DM.[306,311,496]	I	A
Metformin should be considered for DM treatment in patients with HF, if the eGFR is stable and >30 mL/min/1.73 m^2.[484,485]	IIa	C
GLP1-RAs (lixisenatide, liraglutide, semaglutide, exenatide, and dulaglutide) have a neutral effect on the risk of HF hospitalization, and may be considered for DM treatment in patients with HF.[158,176,297,299,300,303,498,499]	IIb	A

Recommendations for the prevention and management of chronic kidney disease in patients with diabetes

Treatment with an SGLT2 inhibitor (emplagliflozin, canagliflozin, or dapagliflozin) is associated with a lower risk of renal endpoints and is recommended if eGFR is 30 to <90 mL/min/1.73 m^2).[306,311,313,496]	I	B
Treatment with the GLP1-RAs liraglutide and semaglutide is associated with a lower risk of renal endpoints, and should be considered for DM treatment if eGFR is >30 mL/min/1.73m^2.[176,299]	IIa	B

ESC Guidelines on Diabetes, pre-diabetes and cardiovascular diseases in collaboration with EASD. EHJ 2019



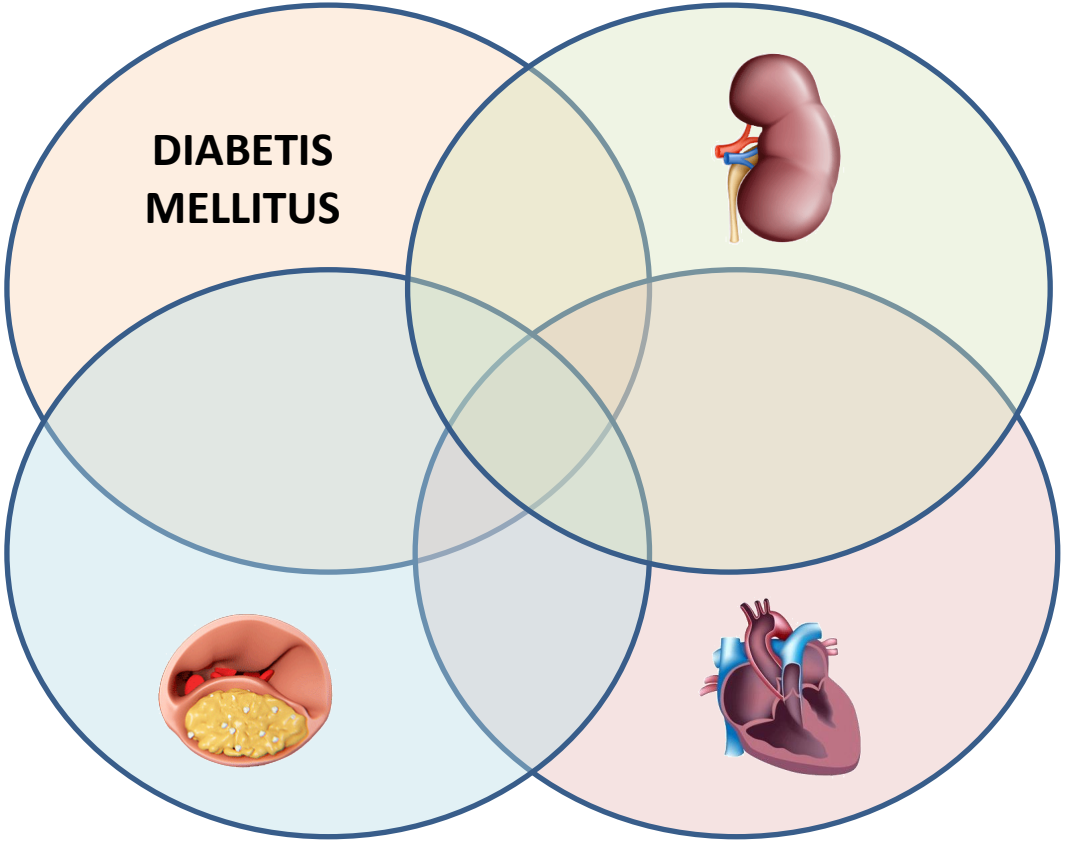
ESC Guidelines on Diabetes, pre-diabetes and cardiovascular diseases in collaboration with EASD. EHJ 2019

Abordaje integral DM2 en paciente con ECV o muy alto riesgo

* Semaglutida no se encuentra comercializada en España

Grupo de trabajo de Diabetes y Obesidad. Sociedad Española de Cardiología. Disponible en: https://secardiologia.es/cientifico/grupos-de-trabajo/diabetes (febrero 2019)

Tractaments antidiabetics i TRACTAMENT MALALTIES CARDIO-RENALS



All-Cause Mortality, Cardiovascular Events, and Renal Outcomes in the CREDENCE Trial

Study design and participants

4401 patients with T2DM & UACR >300 mg/g

62 years

eGFR 57

UACR 927 mg/g

Intervention

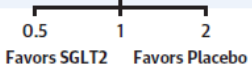
Stable on maximum dose tolerated ACEi or ARB for 4 weeks

Canagliflozin Placebo

Conclusion

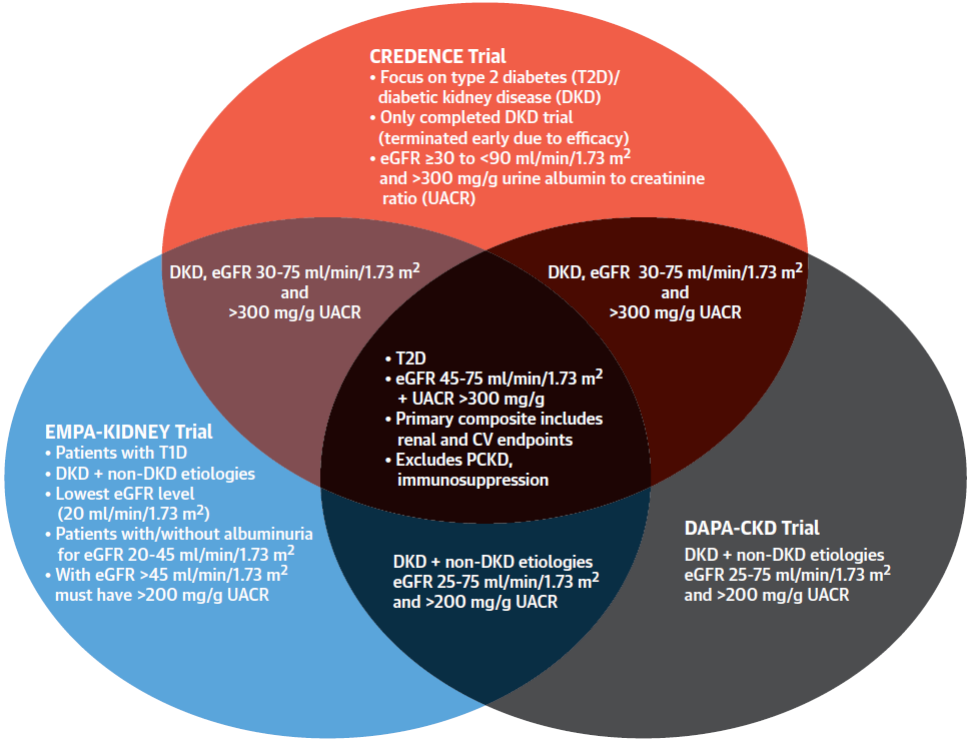
In patients with type 2 diabetes and kidney disease, canagliflozin reduces the risk of kidney failure and cardiovascular events

Outcome	Total Events	Participants	Canagliflozin	Placebo	CREDENCE	HR [95%-CI]	IRR in 1,000 pts. Over 3 yrs [95%-CI]	NNT Over 3 yrs [95%-CI]
			events per 1,000 patient years					
Primary Outcome								
dSCr, ESKD, Renal or CV Death	585	4,401	43.2	61.2		0.70 [0.59-0.82]	-54.0 [-79.4 to -28.6]	19 [13 to 35]
All-Cause Mortality								
All-Cause Mortality	369	4,401	29.0	35.0		0.83 [0.68-1.02]	-18.0 [-37.6 to 1.6]	56 [27 to ∞]
Renal Outcomes								
Renal Composite	377	4,401	27.0	40.4		0.66 [0.53-0.81]	-40.2 [-60.6 to -19.8]	25 [17 to 51]
ESKD	281	4,401	20.4	29.4		0.68 [0.54-0.86]	-27.0 [-44.5 to -9.5]	38 [23 to 106]
dSCr	306	4,401	20.7	33.8		0.60 [0.48-0.76]	-39.3 [-57.6 to -21.0]	26 [18 to 48]
Cardiovascular Outcomes								
Cardiovascular Mortality	250	4,401	19.0	24.4		0.78 [0.61-1.00]	-16.2 [-32.3 to -0.0]	62 [31 to ∞]
MACE	486	4,401	38.7	48.7		0.80 [0.67-0.95]	-30.0 [-53.3 to -6.7]	34 [19 to 150]
Hospitalization for Heart Failure	230	4,401	15.7	25.3		0.61 [0.47-0.8]	-28.8 [-44.7 to -12.9]	35 [23 to 78]



PERKOVIC N Engl J Med 2019; 380:2295-2306
Cherney, D.Z. et al. J Am Coll Cardiol. 2019;74(20):2511–24

Areas of Overlap for Clinical Trials With Sodium-Glucose Cotransporter-2 Inhibitors in Patients With Chronic Kidney Disease



Cherney, D.Z. et al. J Am Coll Cardiol. 2019;74(20):2511–24.

iSGLT2 en el Tractament de la Insuficiència Cardíaca (Amb o Sense Diabetis)

IC amb funció sistòlica reduïda

DAPAHF

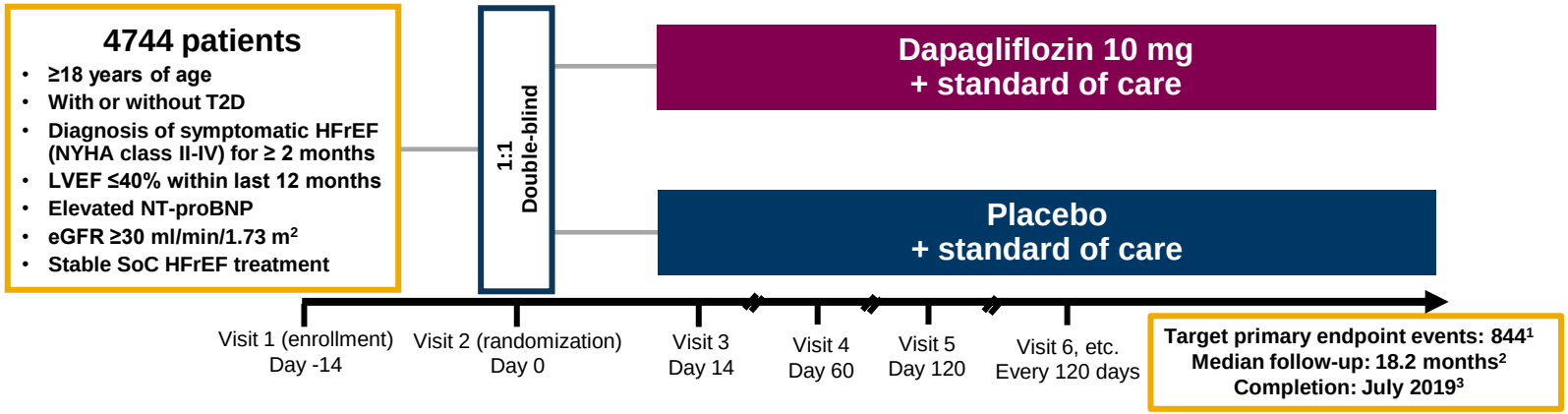
EMPEROR-Reduced

IC amb funció sistòlica preservada

DELIVER

EMPEROR-Preserved

DAPA-HF: Assessing Dapagliflozin in Patients with Chronic HFrEF With or Without T2D[1-4]



Primary Endpoint

- Time to first occurrence of any of the components of the composite: CV death or hHF or an urgent HF visit

Secondary Endpoints

- Time to first occurrence of either of the components of the composite: CV death or hHF
- Total number of (first and recurrent) hHF and CV death
- Change from baseline measured at 8 months in the total symptom score of the KCCQ
- Time to first occurrence of any of the components of the composite: ≥50% sustained decline in eGFR or reaching ESRD or renal death
- Time to death from any cause

CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESRD = end stage renal disease; HbA1c = glycated hemoglobin; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; hHF = hospitalization for heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro B-type natriuretic peptide; NYHA = New York Heart Association; SoC = standard of care; T2D = type 2 diabetes.

1. McMurray JJV et al. Article and supplementary appendix. *Eur J Heart Fail.* 2019;21:665-675; 2. McMurray J. Presentation at: European Society of Cardiology Congress. September 1, 2019; Paris, France; 3. Study NCT03036124. ClinicalTrials.gov website. Accessed August 19, 2019. 4. McMurray JJV et al. *Eur J Heart Fail*. 2019;doi: 10.1002/ejhf.1548. Accessed July 16, 2019.

Key Baseline Characteristics and baseline treatment

Characteristic	Dapagliflozin (n=2373)	Placebo (n=2371)
Mean age (yr)	66	67
Male (%)	76	77
NYHA class II/III/IV (%)	68/31/1	67/32/1
Mean LVEF (%)	31	31
Median NT pro BNP (pg/mL)	1428	1446
Mean systolic BP (mmHg)	122	122
Ischaemic aetiology (%)	55	57
Mean eGFR (mL/min/1.73m^2)	66	66
Prior diagnosis T2D (%)	42	42
Any baseline T2D (%)[a]	45	45

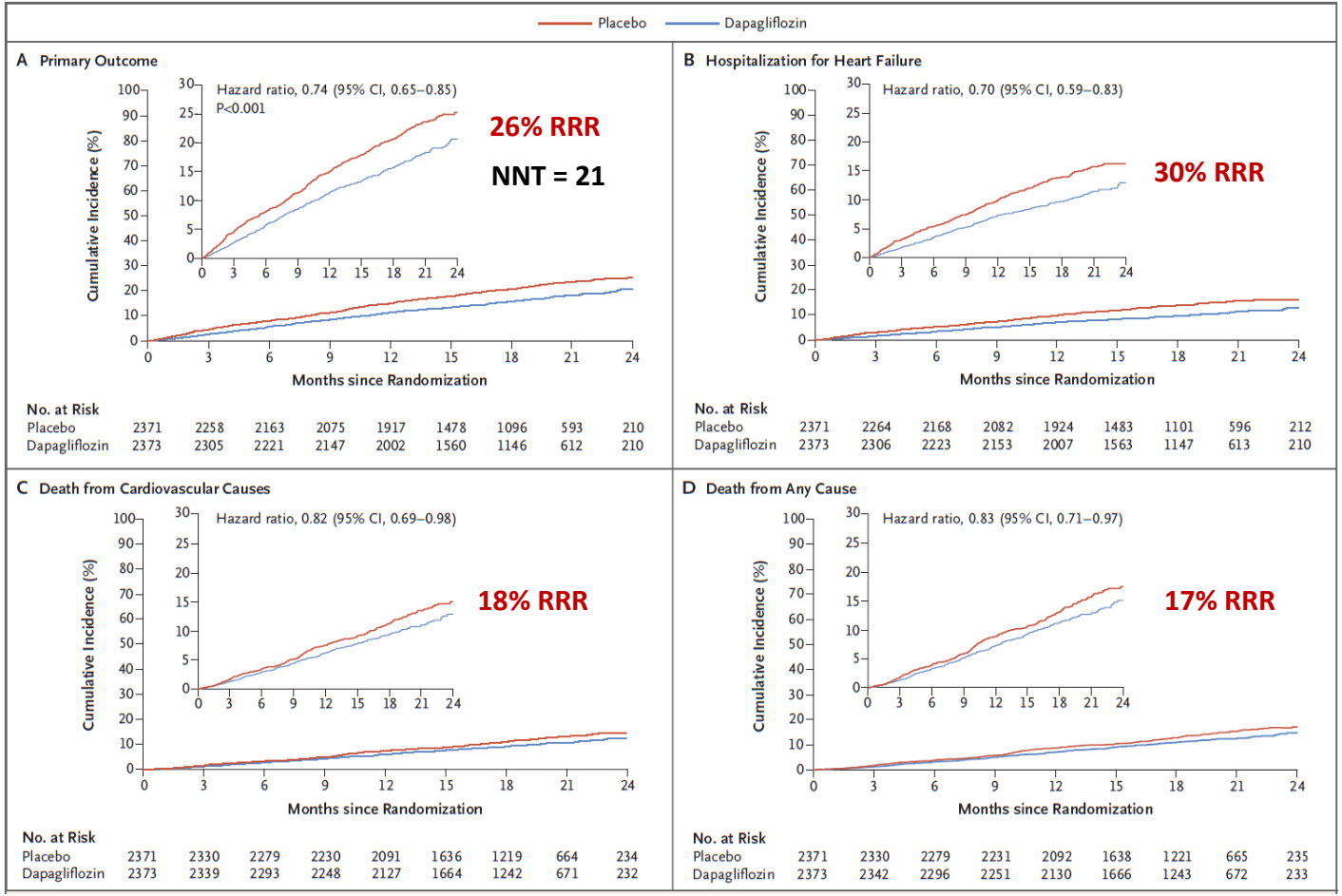
Treatment (%)	Dapagliflozin (n=2373)	Placebo (n=2371)
Diuretic	93	94
ACE-inhibitor/ARB/ARNI	94	93
ACE inhibitor	56	56
ARB	28	27
Sacubitril/valsartan	11	11
Beta-blocker	96	96
MRA	71	71
ICD*	26	26
CRT**	8	7

[a] Includes 82 dapagliflozin and 74 placebo patients with previously undiagnosed diabetes i.e. two HbA1c ≥6.5% (≥48 mmol/mol). ICD or CRT-D; **CRT-P or CRT-D

BP = blood pressure; eGFR = estimated glomerular filtration rate; NT pro BNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; LVEF = left ventricular ejection fraction; T2D = type 2 diabetes. ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; MRA = mineralocorticoid receptor antagonist; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator

McMurray J. Presentation at: European Society of Cardiology Congress. September 1, 2019; Paris, France.

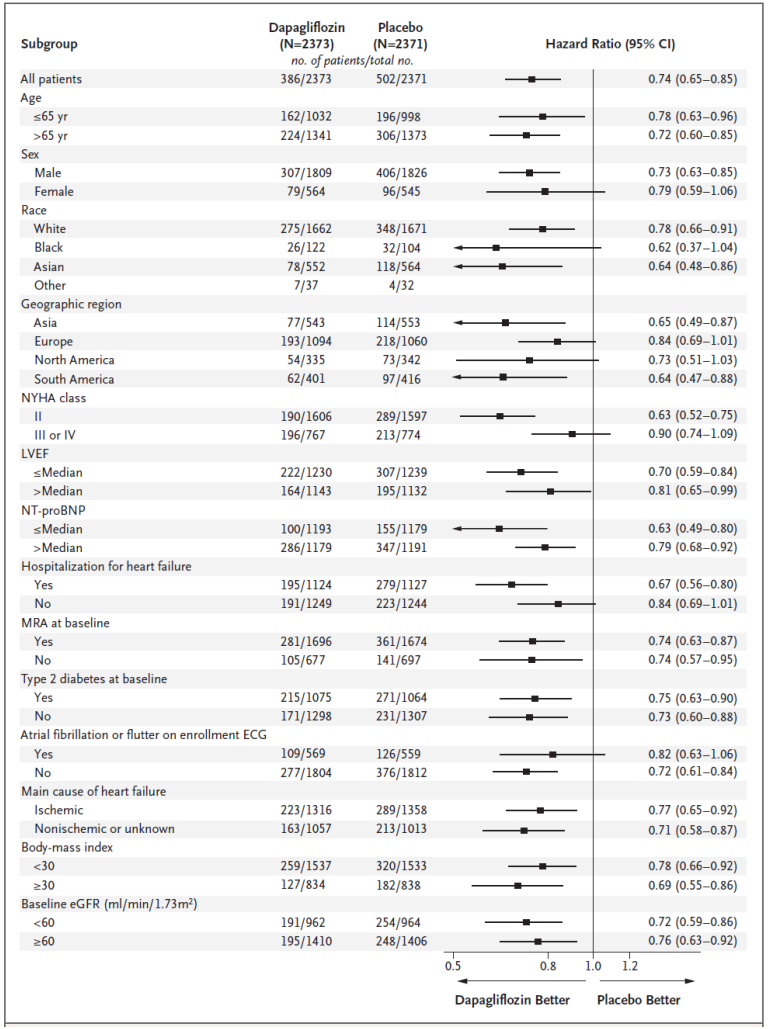
DAPAHF



J.J.V. McMurray September 19, 2019, at NEJM.org.

DAPAHF

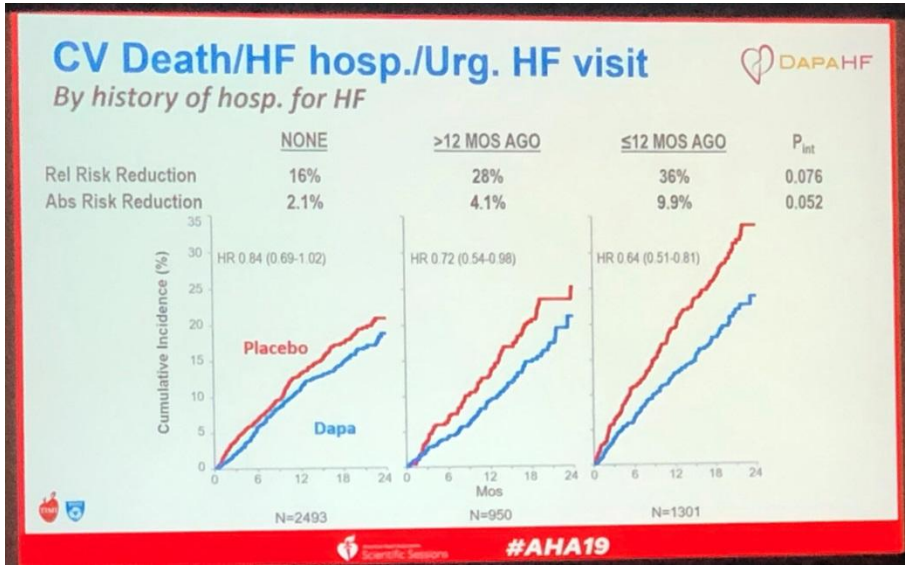
Primary Composite Outcome, According to Prespecified Subgroup

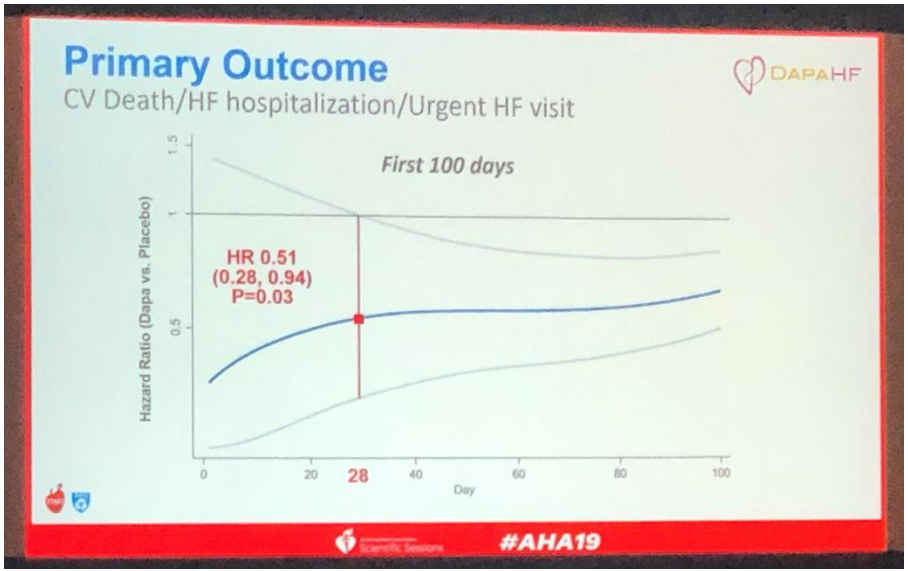


Subgroup	Dapagliflozin (N=2373)	Placebo (N=2371)	Hazard Ratio (95% CI)
	no. of patients/total no.		
All patients	386/2373	502/2371	0.74 (0.65–0.85)
Age			
≤65 yr	162/1032	196/998	0.78 (0.63–0.96)
>65 yr	224/1341	306/1373	0.72 (0.60–0.85)
Sex			
Male	307/1809	406/1826	0.73 (0.63–0.85)
Female	79/564	96/545	0.79 (0.59–1.06)
Race			
White	275/1662	348/1671	0.78 (0.66–0.91)
Black	26/122	32/104	0.62 (0.37–1.04)
Asian	78/552	118/564	0.64 (0.48–0.86)
Other	7/37	4/32	
Geographic region			
Asia	77/543	114/553	0.65 (0.49–0.87)
Europe	193/1094	218/1060	0.84 (0.69–1.01)
North America	54/335	73/342	0.73 (0.51–1.03)
South America	62/401	97/416	0.64 (0.47–0.88)
NYHA class			
II	190/1606	289/1597	0.63 (0.52–0.75)
III or IV	196/767	213/774	0.90 (0.74–1.09)
LVEF			
≤Median	222/1230	307/1239	0.70 (0.59–0.84)
>Median	164/1143	195/1132	0.81 (0.65–0.99)
NT-proBNP			
≤Median	100/1193	155/1179	0.63 (0.49–0.80)
>Median	286/1179	347/1191	0.79 (0.68–0.92)
Hospitalization for heart failure			
Yes	195/1124	279/1127	0.67 (0.56–0.80)
No	191/1249	223/1244	0.84 (0.69–1.01)
MRA at baseline			
Yes	281/1696	361/1674	0.74 (0.63–0.87)
No	105/677	141/697	0.74 (0.57–0.95)
Type 2 diabetes at baseline			
Yes	215/1075	271/1064	0.75 (0.63–0.90)
No	171/1298	231/1307	0.73 (0.60–0.88)
Atrial fibrillation or flutter on enrollment ECG			
Yes	109/569	126/559	0.82 (0.63–1.06)
No	277/1804	376/1812	0.72 (0.61–0.84)
Main cause of heart failure			
Ischemic	223/1316	289/1358	0.77 (0.65–0.92)
Nonischemic or unknown	163/1057	213/1013	0.71 (0.58–0.87)
Body-mass index			
<30	259/1537	320/1533	0.78 (0.66–0.92)
≥30	127/834	182/838	0.69 (0.55–0.86)
Baseline eGFR (ml/min/1.73m²)			
<60	191/962	254/964	0.72 (0.59–0.86)
≥60	195/1410	248/1406	0.76 (0.63–0.92)

J.J.V. McMurray
September 19, 2019, at NEJM.org.

Benefit of dapaglifozin seen as early as 28 days after initiation of treatment.
Effect on primary outcome is even greater in individuals with recent hospitalizations

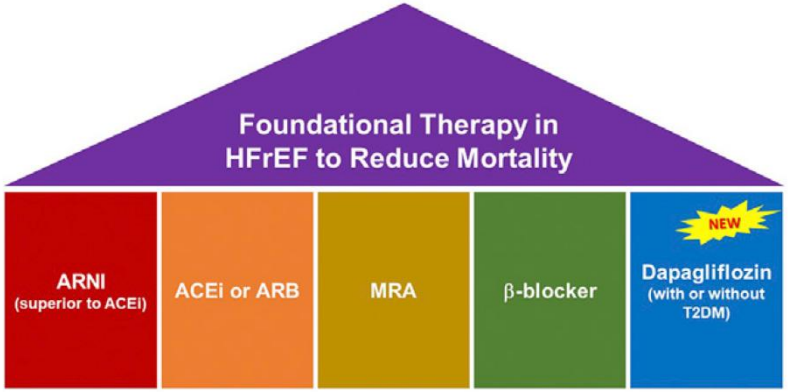




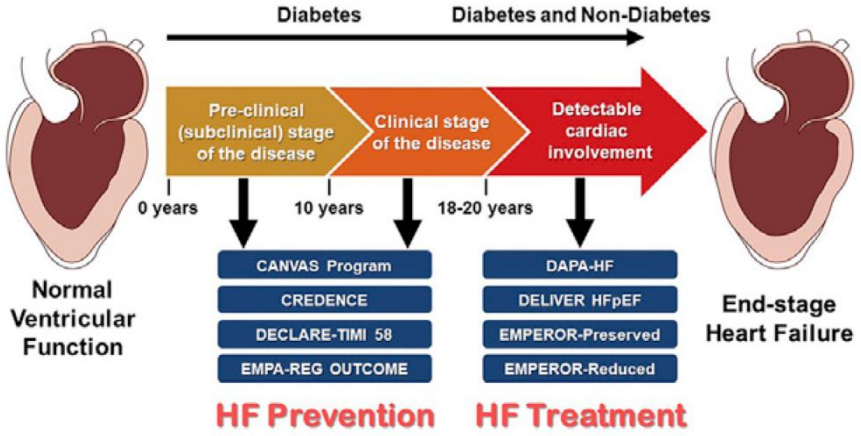
AHA 2019

The DAPA-HF Trial: A Momentous Victory in the War against Heart Failure

Deepak L. Bhatt,[1,*] Subodh Verma,[2] and Eugene Braunwald[1]



The Story of SGLT2 inhibition in Heart Failure



DL. Bhatt. Cell Metabolism 30, November 5, 2019

CONCLUSIONS

La diabetis mellitus produeix efectes deleteris en el la bomba (insuficiència cardíaca), conductes (aterosclerosi) i filtres (malaltia renal). La malaltia Cardiovascular és la principal causa de mort en pacients amb DM2

Gran part de l'enfocament (i de l'èxit) s'ha centrat en reduir les complicacions ateroscleròtiques, la insuficiència cardíaca i malaltia renal segueixen sent complicacions importants i en augment en pacients diabètics

L'abordatge dels pacients amb Diabetis mellitus ha evolucionat en les darreres dècades d'un objectiu glucocèntric a un altre centrat en avaluar el risc cardio-vascular-renal i administrar els fàrmacs que hagin demostrat benefici pronòstic i de prevenció de la malaltia cardiovascular.

CONCLUSIONS

Es recomana el tractament amb arGLP1 i iSGLT2 a pacients Diabètics tipus 2 amb alt risc o molt alt risc CV per a reduir events cardiovasculars majors

En pacients DM2, es recomana administrar tractament amb iSGLT2 amb l'objectiu de reduir el risc d' hospitalització per Insuficiència cardíaca, així com la prevenció del dany renal (filtrat glomerular entre 30 i 90 mL/min/1,73m^2)

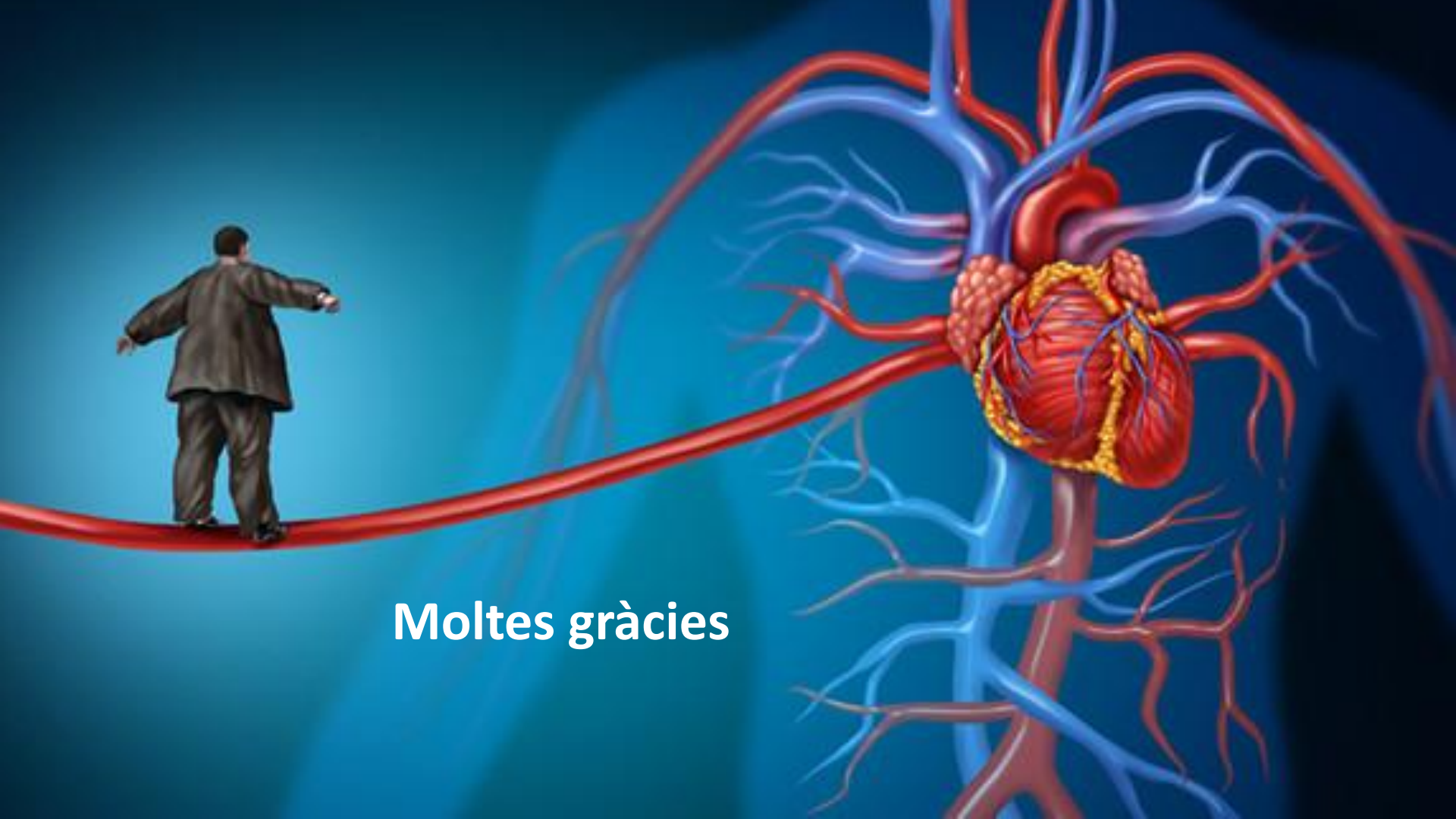
Es pot considerar utilitzar arGLP1 en pacients diabètics amb l'objectiu de prevenir el dany renal (FG>30 mL/min/1,73m^2) i tenen un efecte neutre en la reducció d'hospitalitzacions per IC

CONCLUSIONS

La Canaglifozina (CREDENCE) ha resultat efectiva en el tractament de Diabètics amb malaltia renal crònica (Reducció 30% endpoint primari, NNT 19 en 3 anys). Estem pendents de nous estudis (malalts diabètics i no diabètics) amb Dapaglifozina (DAPA-CKD) i Empaglifozina (EMPA-KIDNEY)

La Dapaglifozina (DAPA HF) ha resultat efectiva en el tractament de pacients amb insuficiència cardíaca amb funció sistòlica reduïda (45% DM, Reducció 26% endpoint primari, NNT 21 en 2 anys). Hi ha altres estudis en marxa per avaluar el paper de iSGLT2 en població ICFEP i ICFER (Deliver, Emperor-Reduced, Emperor-Preserved)

El tractament amb iSGLT2 hauria de considerar-se actualment com un tractament de primera línia després de la Metformina, en una àmplia majoria de pacients diabètics, com a tractament protector cardiorenal.


Moltes gràcies