



20<40 **Rising Stars**
de la Fundación redGDPS

III Jornada Nacional
Rising Stars

Barcelona, 5-6 | 4 | 2019



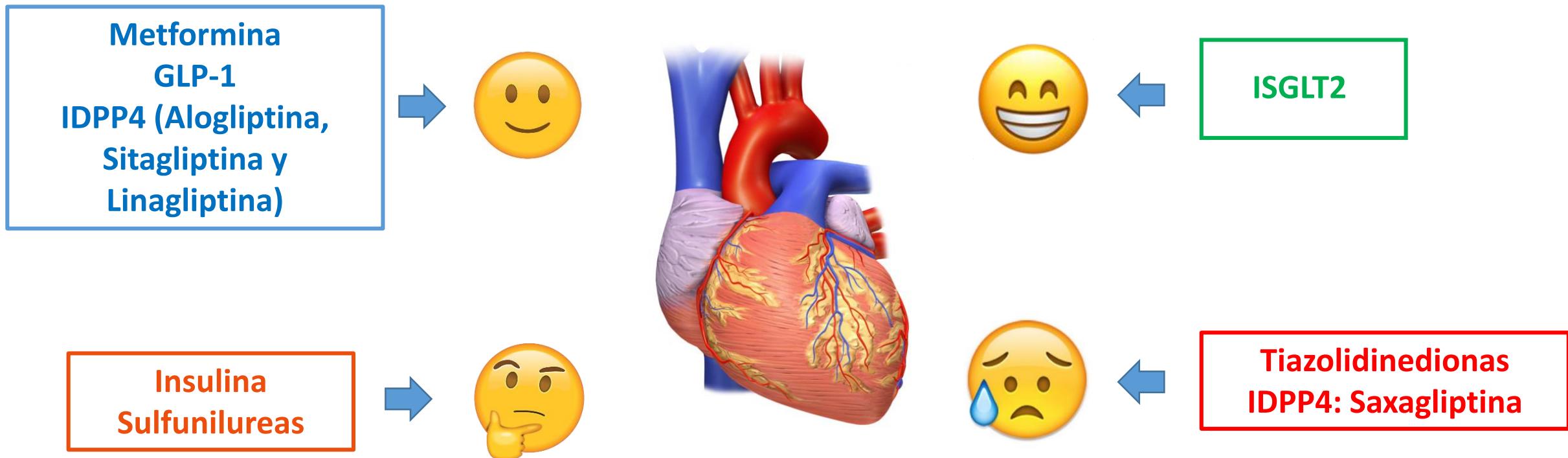
Evidencia del tratamiento antidiabético en insuficiencia cardiaca

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Moderador: Patxi Ezkurra Loiola



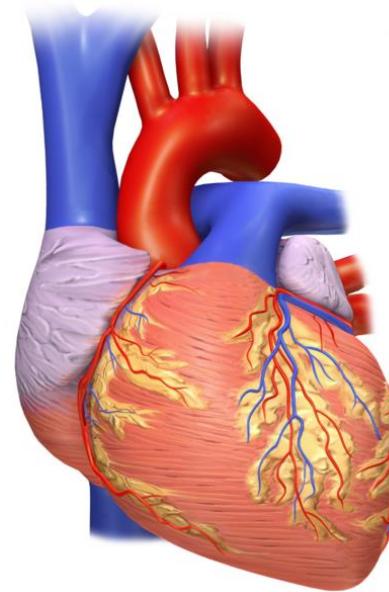
20<40 Rising Stars
de la Fundación redGDPS

Antidiabéticos e insuficiencia cardiaca



Antidiabéticos e insuficiencia cardíaca

Metformina
GLP-1
IDPP4 (Alogliptina,
Sitagliptina y
Linagliptina)



Antidiabéticos e insuficiencia cardiaca



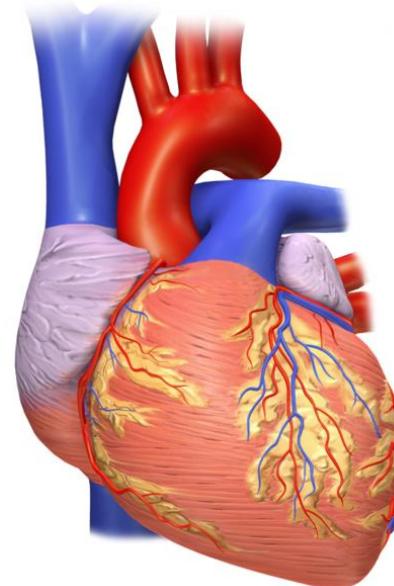
Metformina



Utilización de glucosa por miocardiocitos



Esteatosis cardiaca



Fibrosis miocárdica



Protege de la apoptosis

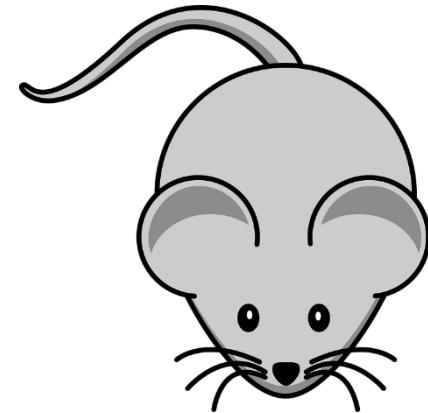


Antidiabéticos e insuficiencia cardiaca



Metformina

Efectos protectores demostrados en modelos animales. ⁽¹⁾



No tiene ensayos clínicos aleatorizados en insuficiencia cardiaca.

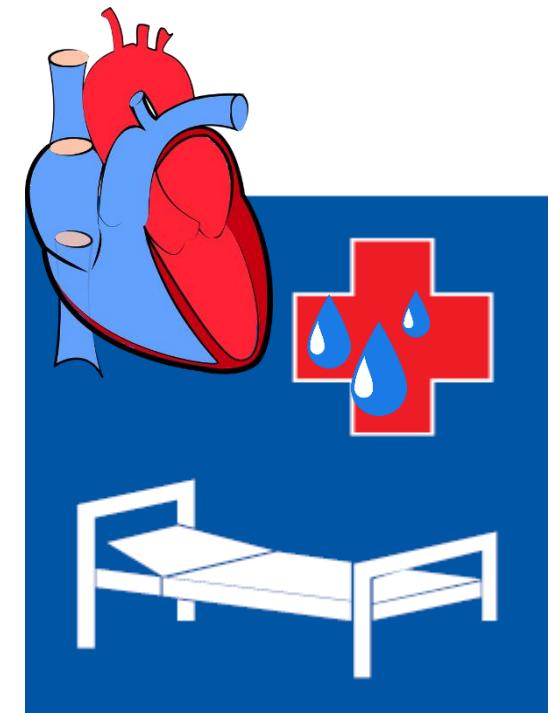
En estudio observacionales se asoció a disminución de mortalidad frente a sulfunilureas. ⁽²⁾

Antidiabéticos e insuficiencia cardiaca



GLP-1

GLP1	Ensayo clínico
Lixisenatide	ELIXA
Liraglutide	LEADER
Semaglutide	SUSTAIN 6
Exenatide	EXSCEL



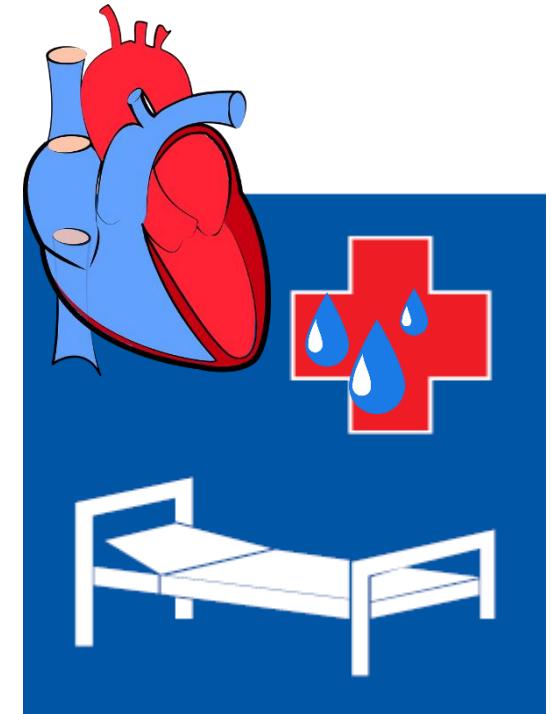
Antidiabéticos e insuficiencia cardiaca



GLP-1

Dos ensayos clínicos en IC: Sin efecto en función ventricular ^(3,4)

GLP1	Ensayo clínico
Lixisenatide	ELIXA
Liraglutide	LEADER
Semaglutide	SUSTAIN 6
Exenatide	EXSCEL



3- Jorsal A, Kistorp C, Holmager P, et al. Effect of liraglutide, a glucagon-like peptide-1 analogue, on left ventricular function in stable chronic heart failure patients with and without diabetes (LIVE) – a multicentre, double-blind, randomised, placebo-controlled trial. *Eur J Heart Fail* 2017;19:69–77.

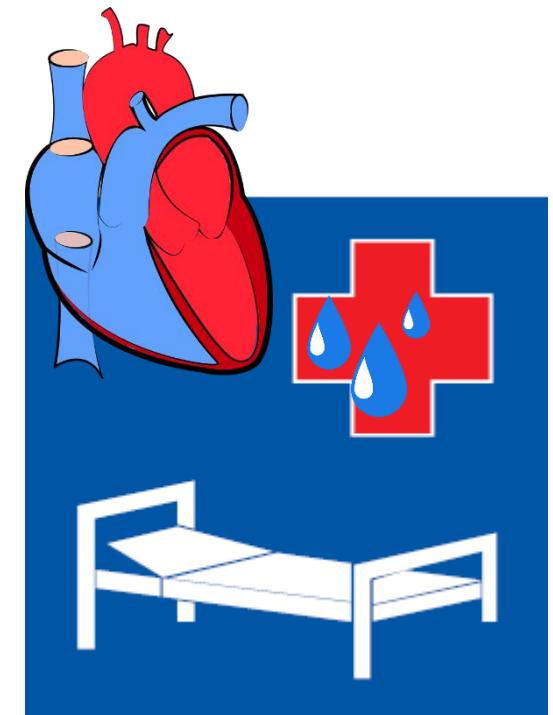
4-Margulies KB, Hernandez AF, Redfield MM, et al. NHLBI Heart Failure Clinical Research Network. Effects of liraglutide on clinical stability among patients with advanced heart failure and reduced ejection fraction: a randomized clinical trial. *JAMA* 2016;316:500–508

Antidiabéticos e insuficiencia cardiaca



IDPP4

IDPP4	Ensayo clínico
Alogliptina	EXAMINE
Sitagliptina	TECOS
Linagliptina	CARMELINA



Antidiabéticos e insuficiencia cardiaca



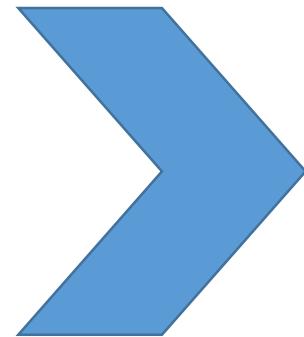
Insulina
Sulfonilureas



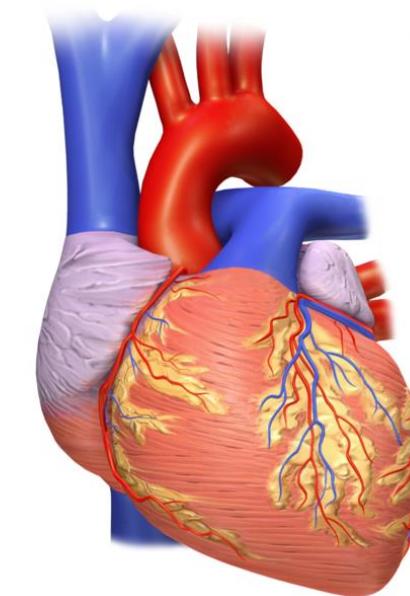
Retención de Sodio



Glucosuria



Retención
hídrica



Antidiabéticos e insuficiencia cardiaca



Insulina
Sulfunilureas

Table 2. Adjusted HRs for Composite and Individual Cardiovascular Outcomes by ADM Class Among 132 737 Insured Adults With Type 2 Diabetes^a

ADM Class	Composite Cardiovascular Outcome ^b		Individual Cardiovascular Outcomes, HR (95% CI)			
	No. of Events (%)	HR (95% CI)	Congestive Heart Failure	Stroke	Ischemic Heart Disease	Peripheral Artery Disease
DPP-4 inhibitors	543 (1.9)	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
GLP-1 receptor agonists	104 (0.9)	0.78 (0.63-0.96)	0.65 (0.42-1.02)	0.65 (0.44-0.97)	0.91 (0.67-1.24)	0.90 (0.42-1.95)
SGLT-2 inhibitors	34 (0.6)	0.81 (0.57-1.53)	0.54 (0.24-1.22)	0.56 (0.26-1.12)	1.18 (0.74-1.87)	1.11 (0.33-3.65)
TZDs	132 (1.8)	0.92 (0.76-1.11)	0.93 (0.63-1.36)	0.73 (0.51-1.05)	0.95 (0.71-1.28)	1.67 (0.94-2.97)
<u>Basal insulin</u>	721 (4.4)	2.03 (1.81-2.27)	2.33 (1.90-2.87)	1.77 (1.44-2.19)	1.92 (1.59-2.32)	2.92 (1.96-4.35)
<u>SFUs</u>	1946 (3.1)	1.36 (1.23-1.49)	1.47 (1.23-1.75)	1.28 (1.08-1.52)	1.35 (1.16-1.57)	1.65 (1.16-2.36)

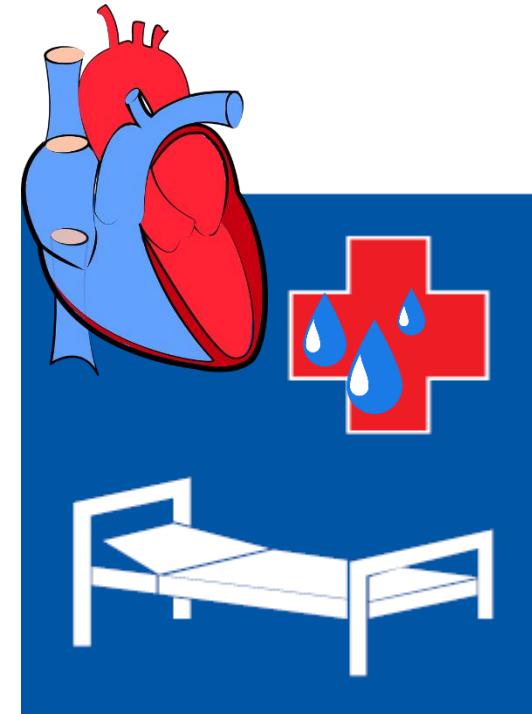
Antidiabéticos e insuficiencia cardiaca



Insulina
Sulfonilureas

No tiene ensayos clínicos
randomizados en
insuficiencia cardiaca

¿?



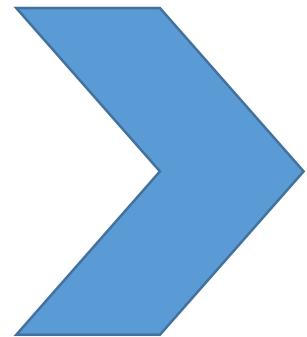
Antidiabéticos e insuficiencia cardiaca



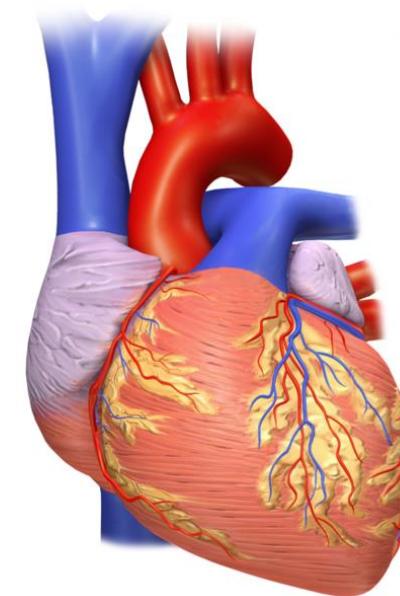
Tiazolidinedionas



Retención de Sodio



Retención
hídrica

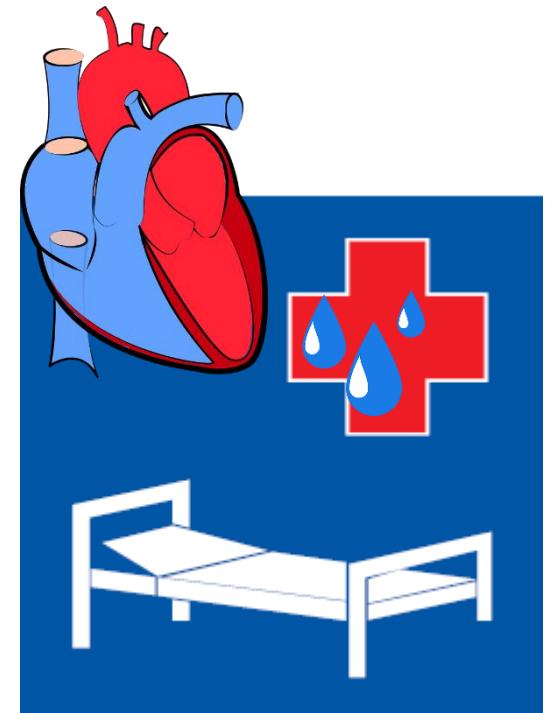


Antidiabéticos e insuficiencia cardiaca



Tiazolidinedionas
IDPP4: Saxagliptina

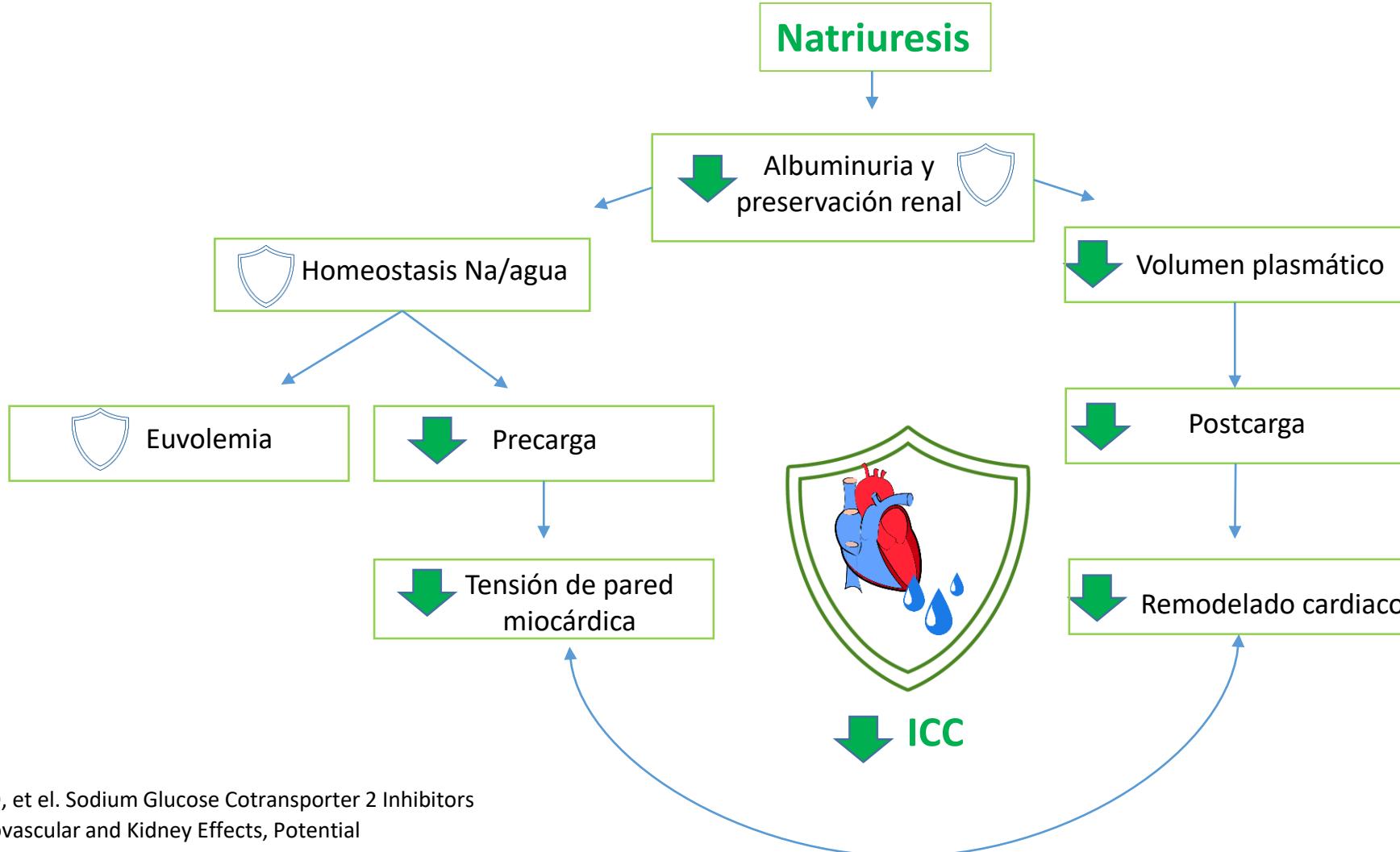
Farmaco	Ensayo clínico
Saxagliptina	SAVOR-TIMI 53
Pioglitazona	PROactive
Rosiglitazona	RECORD



Antidiabéticos e insuficiencia cardiaca



ISGLT2



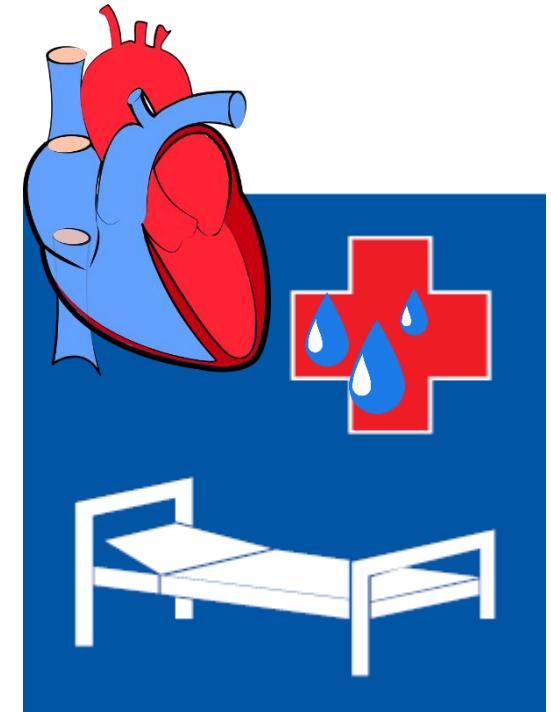
Adaptado: Heerspink H, Perkins B, Fitchett D, et al. Sodium Glucose Cotransporter 2 Inhibitors in the Treatment of Diabetes Mellitus Cardiovascular and Kidney Effects, Potential Mechanisms, and Clinical Applications. *Circulation*. 2016;134:752–772.

Antidiabéticos e insuficiencia cardiaca



ISGLT2

Farmaco	Ensayo clínico
Empagifozina	EMPA-REG OUTCOME
Canaglifocina	CANVAS
Dapaglifozina	DECLARE



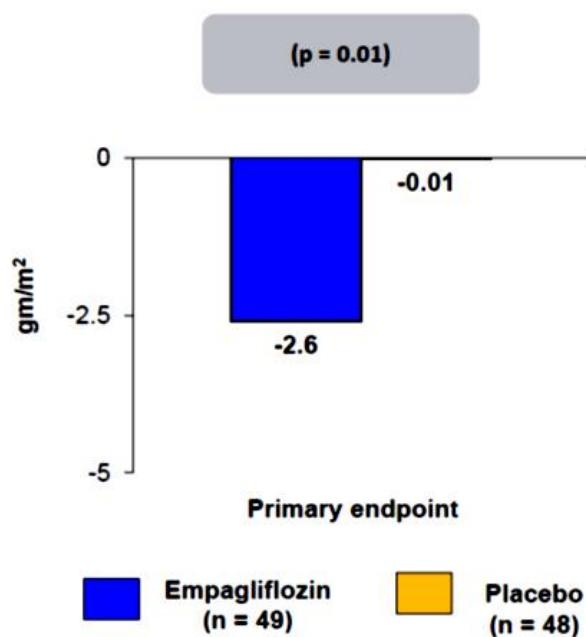
EMPA-HEART

#AHA18



AMERICAN
COLLEGE of
CARDIOLOGY

Trial description: Patients with type 2 diabetes mellitus (DM2) and stable CAD with or without HF were randomized in a 1:1 fashion to either empagliflozin 10 mg daily or placebo. Patients were followed for 6 months.



RESULTS

- Primary endpoint, change in LV mass index, empagliflozin vs. placebo: -2.6 vs. -0.01 g/m^2 , $p = 0.01$
- Change in systolic BP: -7.9 vs. -0.7 mm Hg, $p = 0.003$
- Change in LV end-systolic volume index : -1.0 vs. 0.04 ml/m^2 , $p = 0.36$, change in LVEF: 2.2% vs. -0.01%, $p = 0.07$

CONCLUSIONS

- Empagliflozin results in salutary effects on LV remodeling at 6 months among patients with DM2 and stable CAD but normal EF and without a clear history of HF (only 6% had known HF in this trial)

Presented by Dr. Subodh Verma at AHA 2018

CONFERENCE COVERAGE

CVD-REAL 2: Lower mortality, CV risks with SGLT-2i vs. DPP-4i treatment in T2DM

Publish date: July 17, 2018

By [Sharon Worcester](#); MDedge News

REPORTING FROM ADA 2018

ORLANDO – Initiation of treatment with a sodium-glucose cotransporter 2 (SGLT2) inhibitor is associated with significantly lower risks of death, cardiovascular events, and stroke, compared with initiation of dipeptidyl peptidase-4 (DPP-4) inhibitor treatment in patients with type 2 diabetes mellitus, according to findings from the CVD-REAL 2 study.



Heart Failure and Cardiomyopathies

COMPARATIVE EFFECTIVENESS AND SAFETY OF EMPAGLIFLOZIN: AN INTERIM ANALYSIS FROM THE EMPAGLIFLOZIN COMPARATIVE EFFECTIVENESS AND SAFETY (EMPRISE) STUDY

Moderated Poster Contributions

Heart Failure and Cardiomyopathies Moderated Poster Theater, Poster Hall, Hall F

Sunday, March 17, 2019, 3:45 p.m.-3:55 p.m.

Antidiabéticos en insuficiencia cardíaca

Evidencia



Guías de
práctica clínica





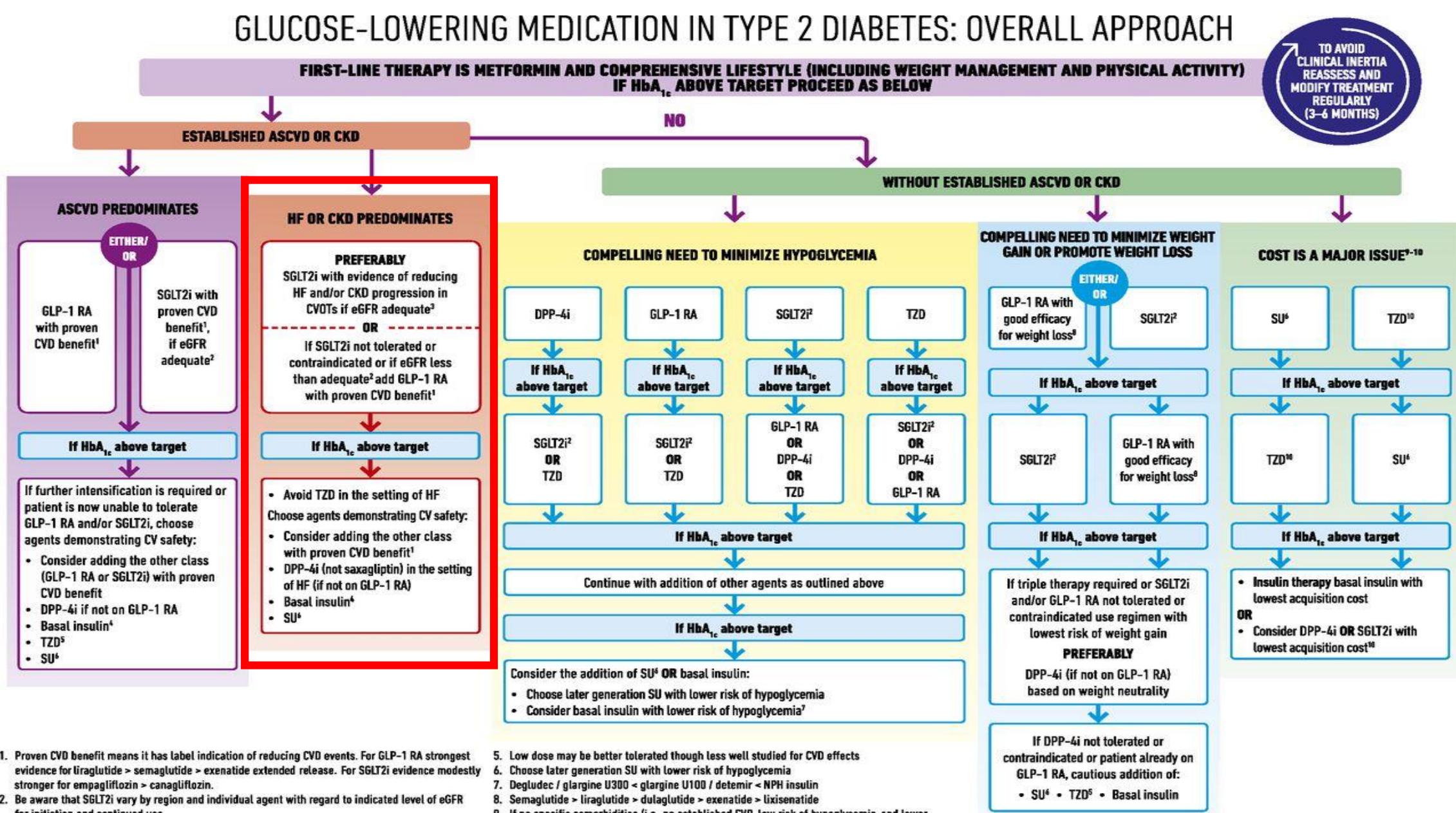
European Association
for the Study of Diabetes

Management of Hyperglycemia in Type 2 Diabetes 2018

A Consensus Report



GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH



CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHED ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD) OR CHRONIC KIDNEY DISEASE (CKD)



Use principles in Figure 1



Use metformin unless contraindicated or not tolerated

If not at HbA_{1c} target:

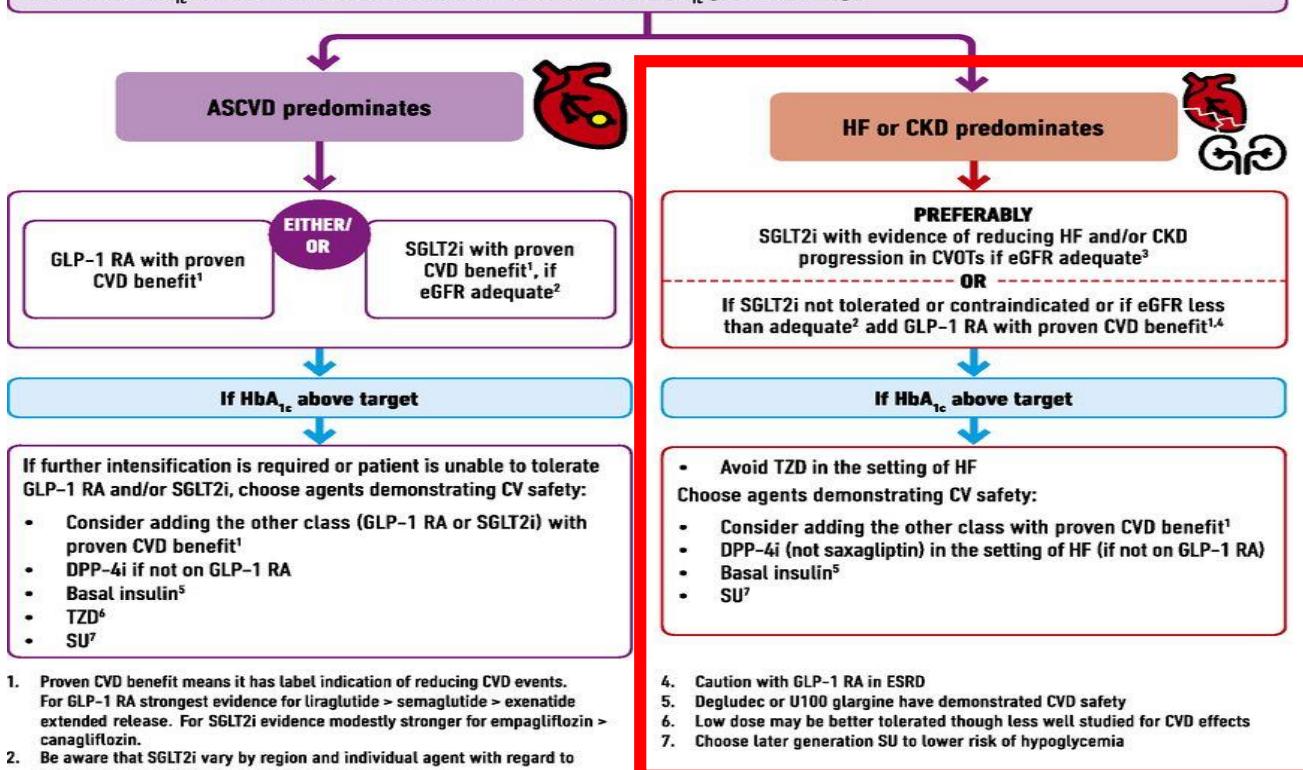
- Continue metformin unless contraindicated (remember to adjust dose/stop metformin with declining eGFR)
- Add SGLT2i or GLP-1 RA with proven cardiovascular benefit¹ (see below)

If at HbA_{1c} target:

- If already on dual therapy, or multiple glucose-lowering therapies and not on an SGLT2i or GLP-1 RA, consider switching to one of these agents with proven cardiovascular benefit¹ (see below)

OR reconsider/lower individualized target and introduce SGLT2i or GLP-1 RA

OR reassess HbA_{1c} at 3-month intervals and add SGLT2i or GLP-1 RA if HbA_{1c} goes above target



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

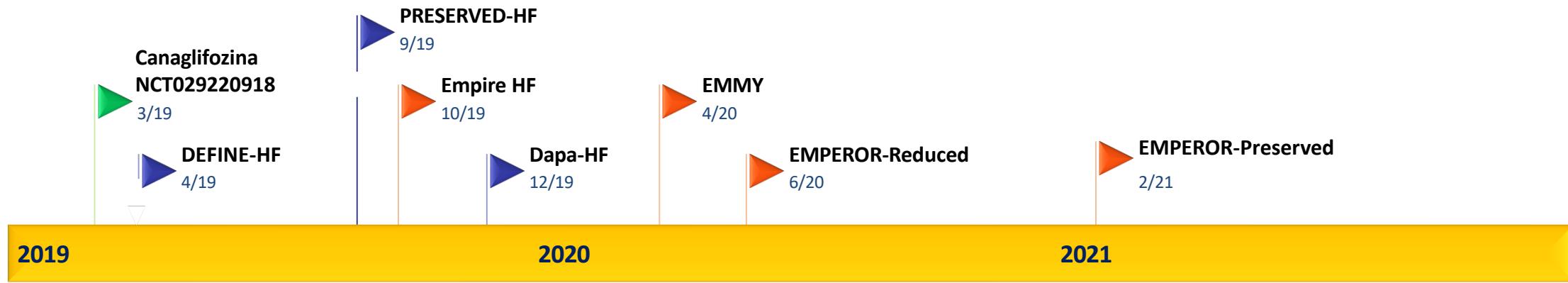
3. Both empagliflozin and canagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs

Antidiabéticos e insuficiencia cardiaca



¿Qué novedades nos esperan?

Ensayos clínicos en paciente con insuficiencia cardiaca por concluir



- Canaglifozina
- Dapaglifozina
- Empaglifozina

Ensayos clínicos en pacientes con insuficiencia cardiaca por concluir

	Ensayo clínico	n	Objetivo	Duración	Características
► Canaglifozina	EMPEROR-Reduced	2850	Muerte CVA Hospitalización IC	38 meses	FE reducida
► Dapaglifozina	EMPEROR-Preserved	4126	Muerte CVA Hospitalización IC	38 meses	FE preserva
► Empaglifozina	Empire HF	189	NT -proBNP	90 días	FE reducida
	EMMY	476	NT -proBNP	26 semanas	Con IAM
	REDECE-CHF	34	Cambios en volumen urinario	6 semana	Combinado con tto diurético
	Canaglifozina (NCT02920918)	88	Cambios capacidad ejercicio aeróbico	12 semanas	
	Dapa-HF	4500	Muerte CVA, Hospitalización IC, Visitas a urgencias IC	3 años	
	DEFINE-HF	250	NT -proBNP	12 semanas	Con DM
	PRESERVED-HF	320	NT -proBNP	Control a las 6 y 12 semanas	Con DM y prediabetes
	REFORM	56	Cambios en ventrículo izquierdo y volumen diastólico por RMN	1 año	Finalizo 2017, no publicado.

Antidiabéticos e insuficiencia cardiaca

Conclusiones

- Faltarán ensayos clínicos aleatorizados en fármacos como la metformina que ha mostrado efectos favorables en ensayos experimentales.
- Los ensayos de seguridad cardiovascular han sido de gran utilidad para establecer la relación entre antidiabéticos e insuficiencia cardiaca.
- El futuro próximo (transcurso de 2019) depara importantes estudios clínicos aleatorizados diseñados específicamente para valorar IC.



Gracias por su
atención!!!