Empagliflozin

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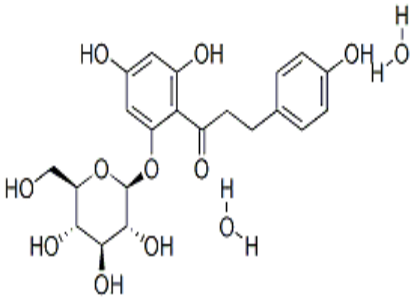
Evolution of clinical use of SGLT2i

- 1835: French chemists isolated a substance, phlorizin, from the **bark of apple trees**.

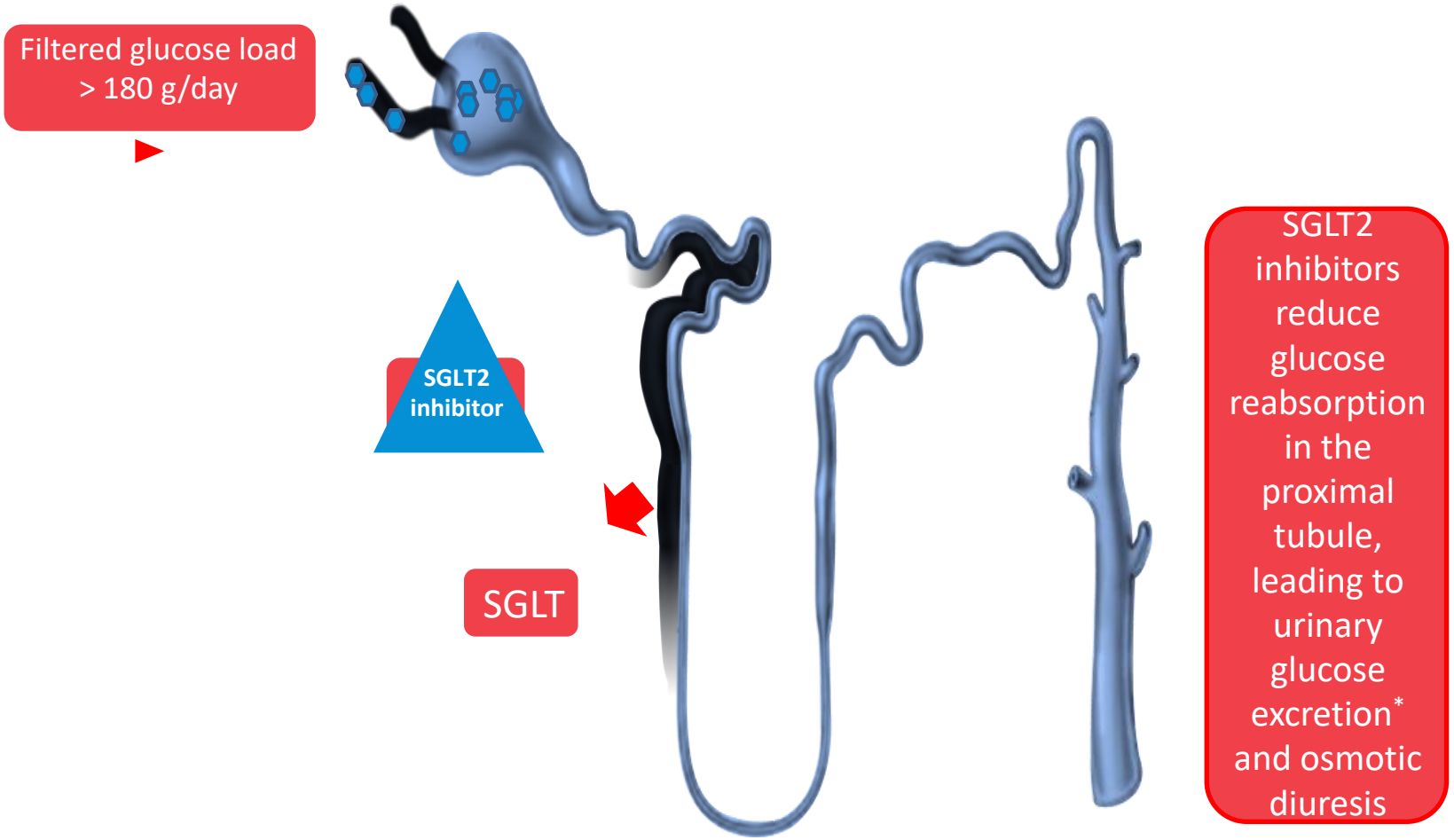
- 1856: German scientist Joseph von Mering demonstrated that **phlorizin caused glucosuria.**

- Patients/families described with familial renal glucosuria
- 90's: The human SGLT2 cloned and protein characterized

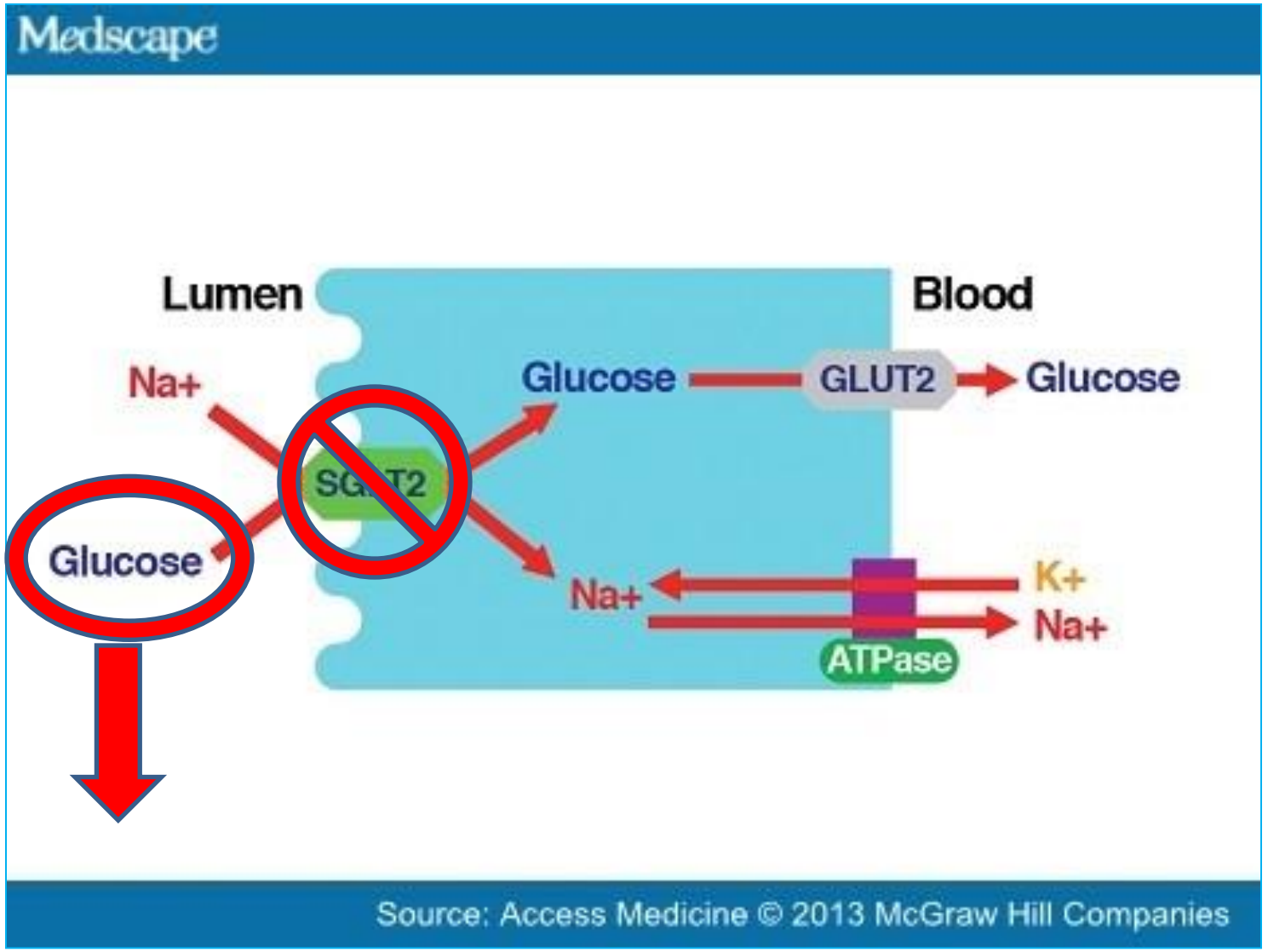


Diabetes Metab Res Rev 2005; 21: 31–38.

SGLT2 Inhibitors Mechanism of Action



1. Bakris et al. Kidney Int 2009;75;1272–7.


Medscape
Lumen
Blood
Na+
Glucose
GLUT2
Glucose
SGLT2
Glucose
Na+
K+
Na+
ATPase
Source: Access Medicine © 2013 McGraw Hill Companies

DM

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[§]	or GLP-1-RA	or Insulin[§]	or GLP-1-RA
or Insulin[§]	or Insulin[§]		or Insulin[§]		

SGLT2 inhibitors have been shown to impact CV risk factors in patients with T2DM

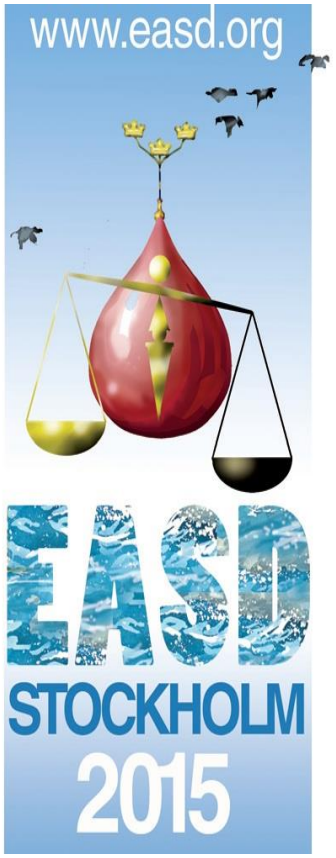
SGLT2i with background Metformin	Empagliflozin 10 mg[1]	Canagliflozin 100 mg[2]	Dapagliflozin 10 mg[3]
HbA1c, %	-0.70	-0.73	-0.84
Weight, kg	-2.08	-3.3	-2.9
Systolic Blood Pressure , mmHg	-4.5	-3.5	-5.1
Diastolic Blood Pressure, mmHg	-2.1	-1.8	-1.8

1.Häring Hu et al. Diabetes care. 2014 Jun 1;37(6):1650-9.
2.Lavalle-González et al.Diabetologia. 2013 Dec 1;56(12):2582-92.
3.Bailey CJ et al.The Lancet. 2010 Jun 26;375(9733):2223-33.

Is there any cardiovascular benefit of SGLT2 inhibitor therapy?

EMPA-REG Trial

EMPA-REG OUTCOME was presented at EASD 2015

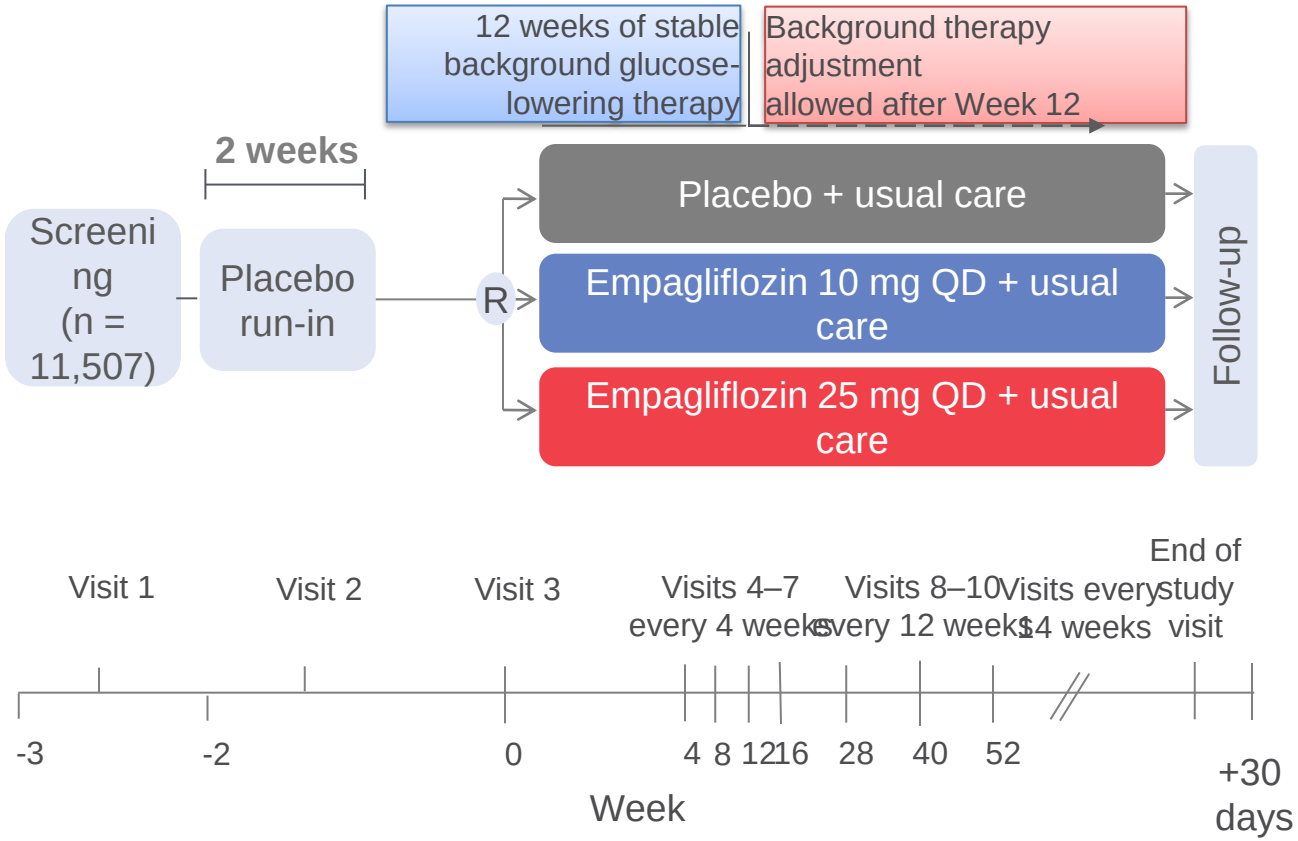


EMPA-REG OUTCOME®

EMPA-REG OUTCOME®: Study design

Aim **Compound-specific**

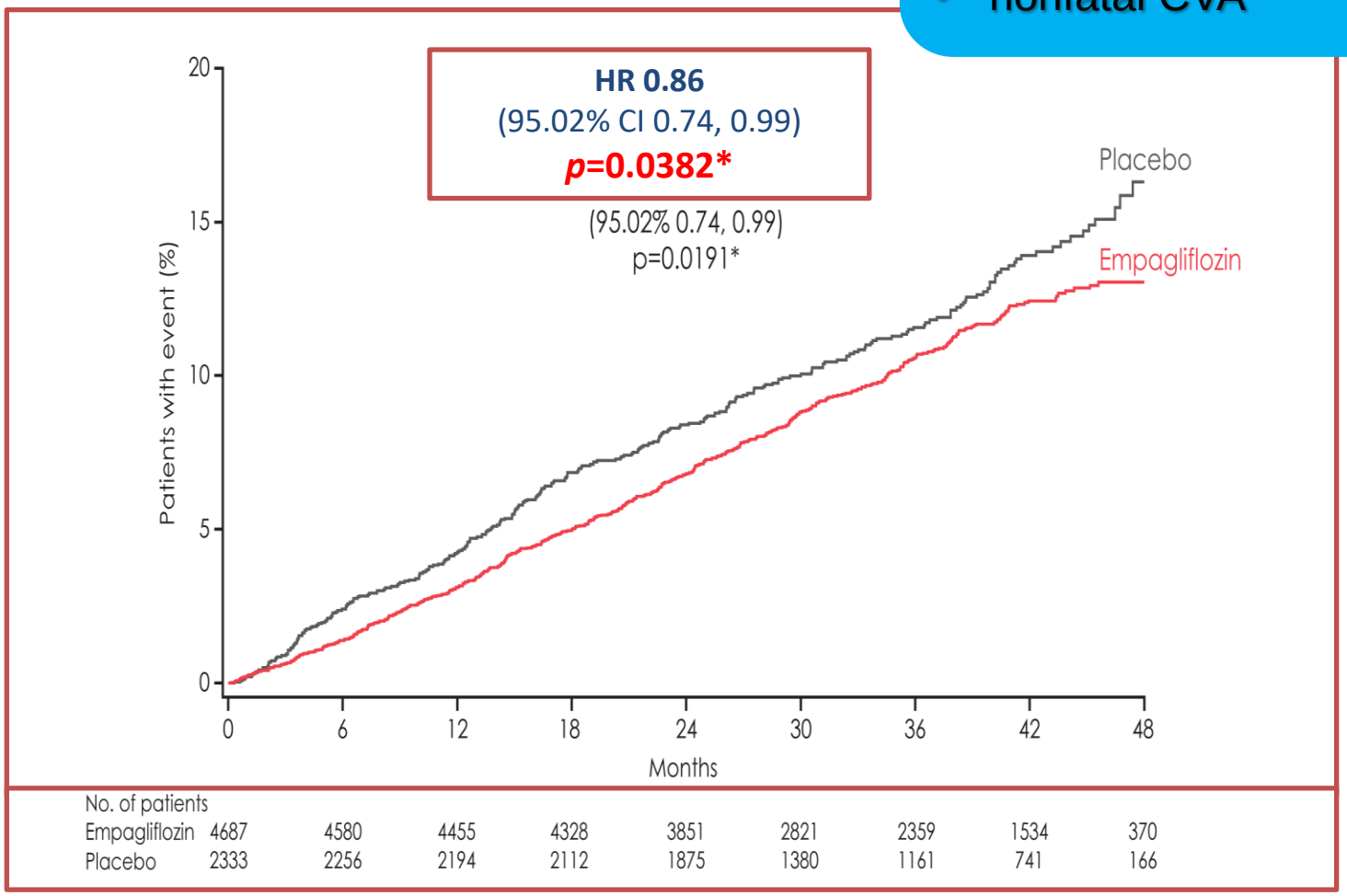
To determine CV safety of empagliflozin vs placebo + usual care for glycaemic control and CV risk in patients with **T2D and high CV risk**



Zinman et al. Cardiovasc Diabetol 2014;13:102.

Primary outcome: 3-point MACE

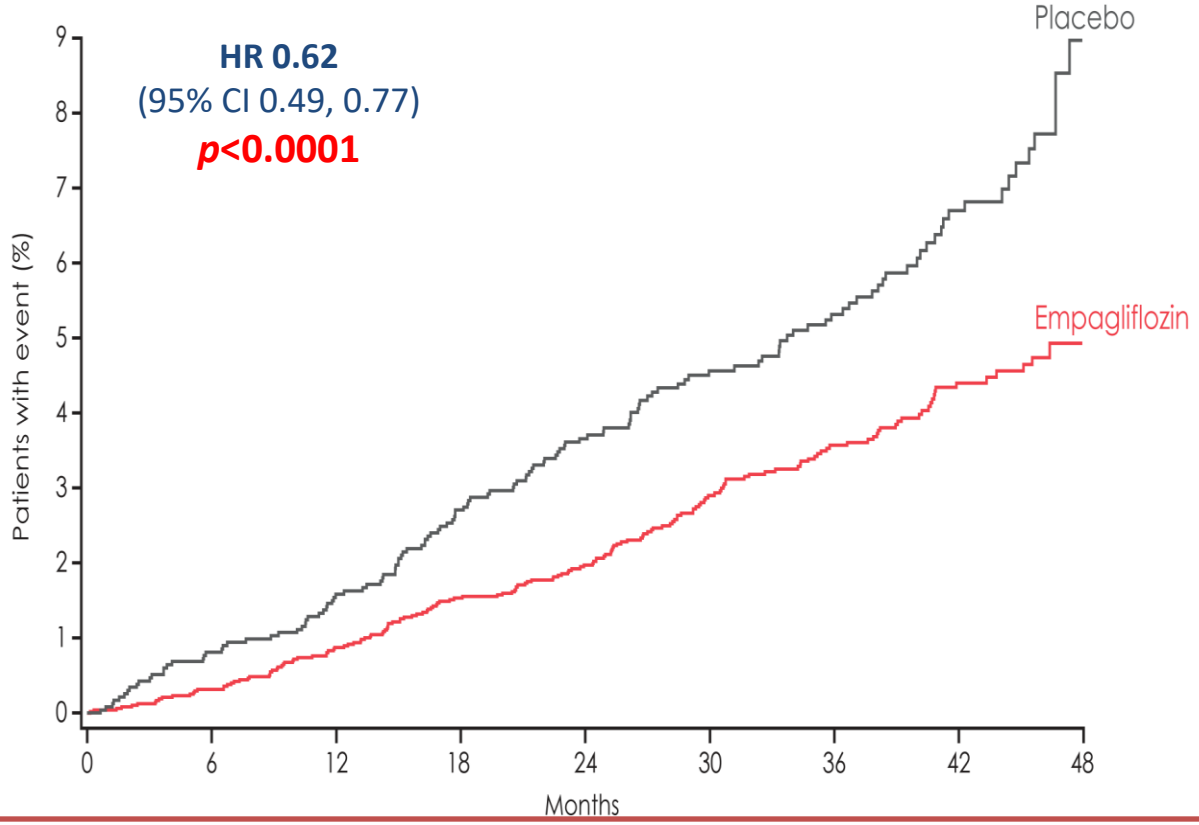
Composite of death from
- cardiovascular causes,
- nonfatal MI,
- nonfatal CVA



Cumulative incidence function. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio.

* Two-sided tests for superiority were conducted (statistical significance was indicated if p≤0.0498)

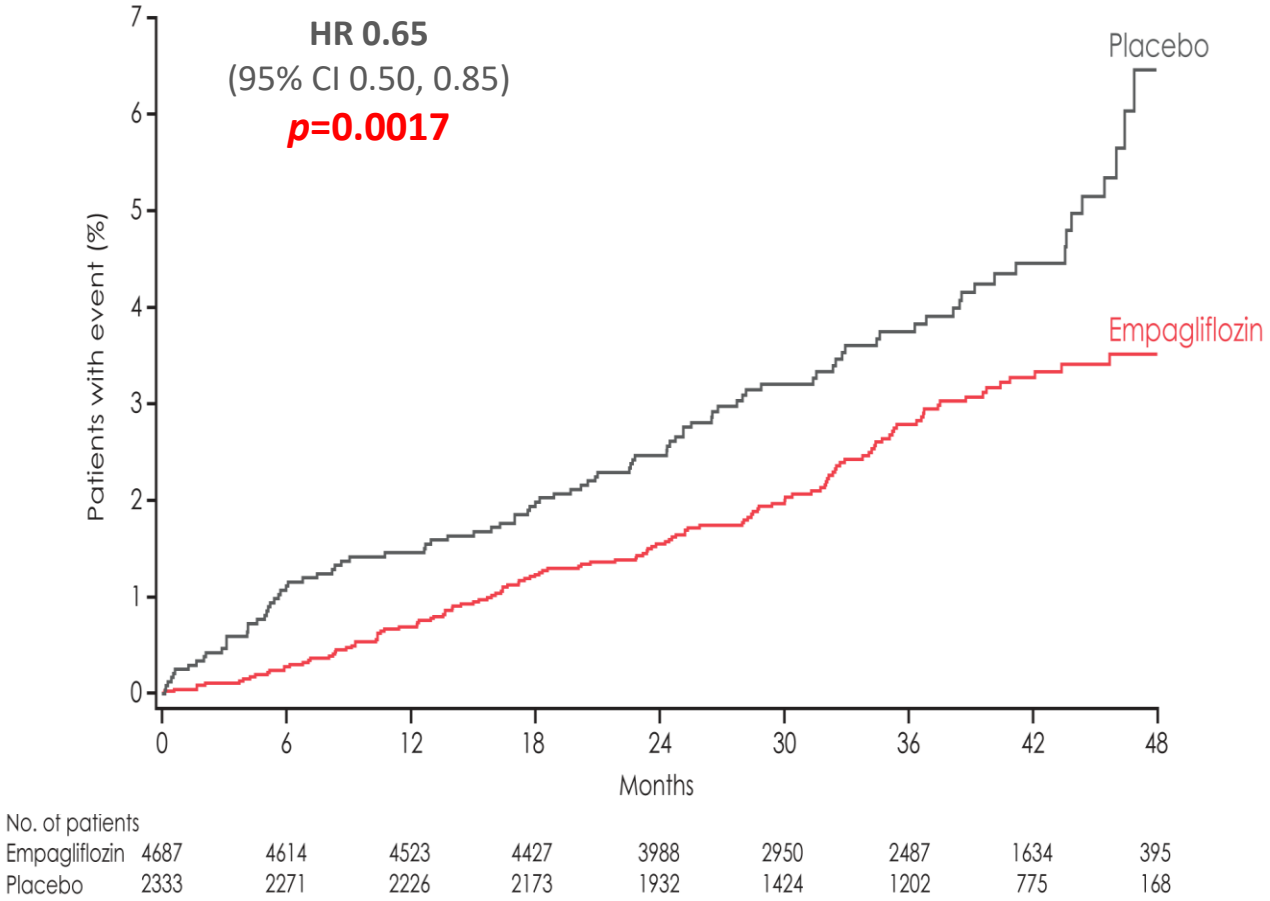
CV death



No. of patients									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Cumulative incidence function. HR, hazard ratio

Hospitalization for heart failure



Cumulative incidence function. HR, hazard ratio

EMPA-REG OUTCOME®: Therapeutic considerations

- Empagliflozin, as used in this trial, for 3 years in 1,000 patients with type 2 diabetes at high CV risk:
  - 25 lives saved (82 vs 57 deaths)
    - 22 fewer CV deaths (59 vs 37)
  - 14 fewer hospitalizations for heart failure (42 vs 28)
  - 53 additional genital infections (22 vs 75)

Summary

- SGLT2 Inhibitors were developed as T2DM therapies with a novel glucose lowering mechanism
- In addition to improving glucose control they were associated with weight reduction and no increased risk of hypoglycemia
- Cardiovascular safety studies demonstrated not only CV safety but remarkable CV outcome benefit

ACCUMULATED CV DATA FROM SGLT2I OUTCOMES TRIAL

Published: 2020.

Research

JAMA Cardiology | Original Investigation

Association of SGLT2 Inhibitors With Cardiovascular and Kidney Outcomes in Patients With Type 2 Diabetes

A Meta-analysis

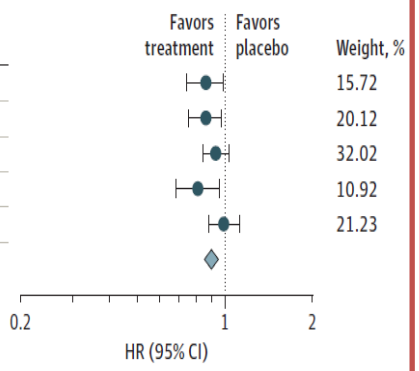
Darren K. McGuire, MD, MHSc; Weichung J. Shih, PhD; Francesco Cosentino, MD, PhD; Bernard Charbonnel, MD; David Z. I. Cherney, MD, PhD; Samuel Dagogo-Jack, MD, DSc; Richard Pratley, MD; Michelle Greenberg, BSc; Shuai Wang, PhD; Susan Huyck, DrPH; Ira Gantz, MD; Steven G. Terra, PharmD; Urszula Masiukiewicz, MD; Christopher P. Cannon, MD

Effects of SGLT2 Inhibitors on Major Adverse Cardiovascular Events—Composite of Myocardial Infarction, Stroke, or Cardiovascular Death

Ertugliflozin

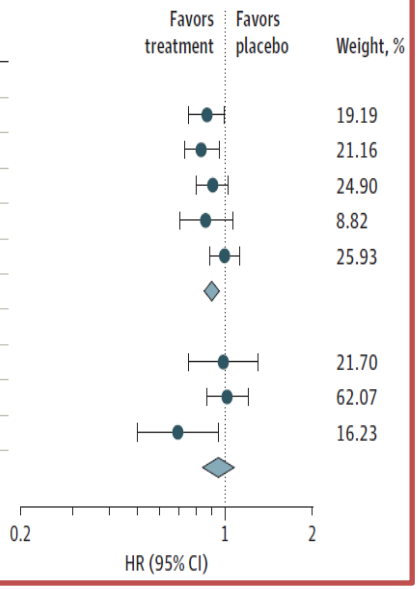
A Overall MACEs

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	490/4687	37.4	282/2333	43.9	0.86 (0.74-0.99)
CANVAS program	NA/5795	26.9	NA/4347	31.5	0.86 (0.75-0.97)
DECLARE-TIMI 58	756/8582	22.6	803/8578	24.2	0.93 (0.84-1.03)
CREDENCE	217/2202	38.7	269/2199	48.7	0.80 (0.67-0.95)
VERTIS CV	735/5499	40.0	368/2747	40.3	0.99 (0.88-1.12)
Fixed-effects model (Q = 5.22; *df* = 4; *P* = .27; I^2 = 23.4%)					0.90 (0.85-0.95)



B MACEs by ASCVD status

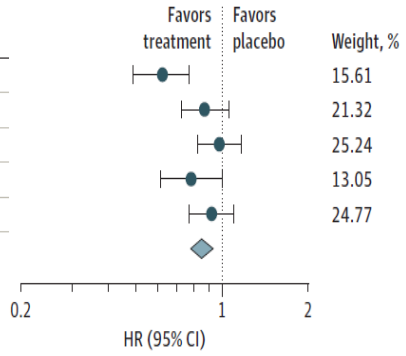
	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
Patients with ASCVD					
EMPA-REG OUTCOME	490/4687	37.4	282/2333	43.9	0.86 (0.74-0.99)
CANVAS program	NA/3756	34.1	NA/2900	41.3	0.82 (0.72-0.95)
DECLARE-TIMI 58	483/3474	36.8	537/3500	41.0	0.90 (0.79-1.02)
CREDENCE	155/1113	55.6	178/1107	65.0	0.85 (0.69-1.06)
VERTIS CV	735/5499	40.0	368/2747	40.3	0.99 (0.88-1.12)
Fixed-effects model (Q = 4.53; *df* = 4; *P* = .34; I^2 = 11.8%)					0.89 (0.84-0.95)
Patients without ASCVD					
CANVAS program	NA/2039	15.8	NA/1447	15.5	0.98 (0.74-1.30)
DECLARE-TIMI 58	273/5108	13.4	266/5078	13.3	1.01 (0.86-1.20)
CREDENCE	62/1089	22.0	91/1092	32.7	0.68 (0.49-0.94)
Fixed-effects model (Q = 4.59; *df* = 2; *P* = .10; I^2 = 56.5%)					0.94 (0.83-1.07)



Effects of SGLT2 Inhibitors on Cardiovascular Death

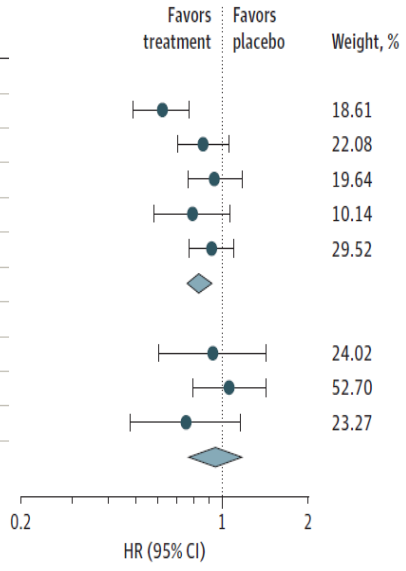
A Overall CV death

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	172/4687	12.4	137/2333	20.2	0.62 (0.49-0.77)
CANVAS program	NA/5795	11.6	NA/4347	12.8	0.87 (0.72-1.06)
DECLARE-TIMI 58	245/8582	7.0	249/8578	7.1	0.98 (0.82-1.17)
CREDENCE	110/2202	19.0	140/2199	24.4	0.78 (0.61-1.00)
VERTIS CV	341/5499	17.6	184/2747	19.0	0.92 (0.77-1.10)
Fixed-effects model (Q = 11.22; *df* = 4; *P* = .02; I^2 = 64.3%)					0.85 (0.78-0.93)



B CV death by ASCVD status

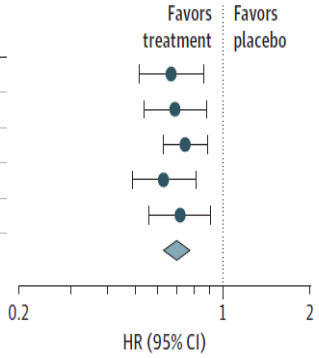
	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
Patients with ASCVD					
EMPA-REG OUTCOME	172/4687	12.4	137/2333	20.2	0.62 (0.49-0.77)
CANVAS program	NA/3756	14.8	NA/2900	16.8	0.86 (0.70-1.06)
DECLARE-TIMI 58	153/3474	10.9	163/3500	11.6	0.94 (0.76-1.18)
CREDENCE	75/1113	25.7	93/1107	32.4	0.79 (0.58-1.07)
VERTIS CV	341/5499	17.6	184/2747	19.0	0.92 (0.77-1.10)
Fixed-effects model (Q = 9.10; *df* = 4; *P* = .06; I^2 = 56.1%)					0.83 (0.76-0.92)
Patients without ASCVD					
CANVAS program	NA/2039	6.5	NA/1447	6.2	0.93 (0.60-1.43)
DECLARE-TIMI 58	92/5108	4.4	86/5078	4.1	1.06 (0.79-1.42)
CREDENCE	35/1089	12.2	47/1092	16.4	0.75 (0.48-1.16)
Fixed-effects model (Q = 1.65; *df* = 2; *P* = .44; I^2 = 0.0%)					0.95 (0.77-1.17)



Effects of SGLT2 Inhibitors on Hospitalization for Heart Failure

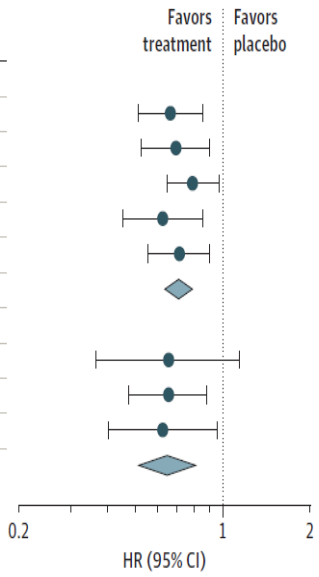
A Overall HHF

	Treatment		Placebo			Favors treatment	Favors placebo	Weight, %
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)			
EMPA-REG OUTCOME	126/4687	9.4	95/2333	14.5	0.65 (0.50-0.85)			16.09
CANVAS program	NA/5795	5.5	NA/4347	8.7	0.67 (0.52-0.87)			17.10
DECLARE-TIMI 58	212/8582	6.2	286/8578	8.5	0.73 (0.61-0.88)			33.72
CREDENCE	89/2202	15.7	141/2199	25.3	0.61 (0.47-0.80)			16.01
VERTIS CV	139/5499	7.3	99/2747	10.5	0.70 (0.54-0.90)			17.08
Fixed-effects model ($Q=1.39$; $df=4$; $P=.85$; $I^2=0.0\%$)					0.68 (0.61-0.76)			



B HHF by ASCVD status

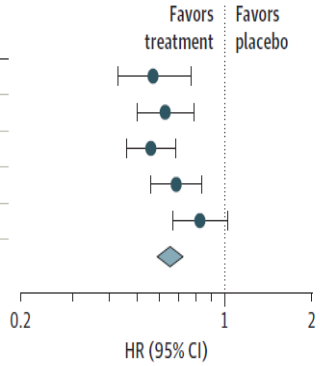
	Treatment		Placebo			Favors treatment	Favors placebo	Weight, %
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)			
Patients with ASCVD								
EMPA-REG OUTCOME	126/4687	9.4	95/2333	14.5	0.65 (0.50-0.85)			19.62
CANVAS program	NA/3756	7.3	NA/2900	11.3	0.68 (0.51-0.90)			17.13
DECLARE-TIMI 58	151/3474	11.1	192/3500	14.1	0.78 (0.63-0.97)			29.66
CREDENCE	59/1113	20.6	92/1107	33.2	0.61 (0.44-0.85)			12.74
VERTIS CV	139/5499	7.3	99/2747	10.5	0.70 (0.54-0.90)			20.84
Fixed-effects model ($Q=1.97$; $df=4$; $P=.74$; $I^2=0.0\%$)					0.70 (0.62-0.78)			
Patients without ASCVD								
CANVAS program	NA/2039	2.6	NA/1447	4.2	0.64 (0.35-1.15)			16.38
DECLARE-TIMI 58	61/5108	3.0	94/5078	4.6	0.64 (0.46-0.88)			55.07
CREDENCE	30/1089	10.6	49/1092	17.5	0.61 (0.39-0.96)			28.56
Fixed-effects model ($Q=0.03$; $df=2$; $P=.99$; $I^2=0.0\%$)					0.63 (0.50-0.80)			



Effects of SGLT2 Inhibitors on Kidney-Related Outcomes

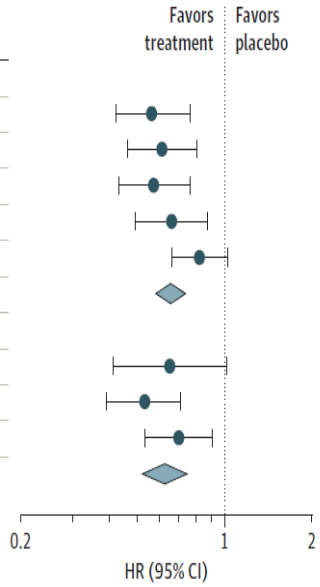
A Overall kidney outcomes

	Treatment		Placebo				
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)	Favors treatment / Favors placebo	Weight, %
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)		11.51
CANVAS program	NA/5795	5.5	NA/4347	9.0	0.60 (0.47-0.77)		18.66
DECLARE-TIMI 58	127/8582	3.7	238/8578	7.0	0.53 (0.43-0.66)		24.77
CREDENCE	153/2202	27.0	224/2199	40.4	0.66 (0.53-0.81)		25.28
VERTIS CV	175/5499	9.3	108/2747	11.5	0.81 (0.64-1.03)		19.79
Fixed-effects model ($Q = 7.96$; $df = 4$; $P = .09$; $I^2 = 49.7\%$)					0.62 (0.56-0.70)		



B Kidney outcomes by ASCVD status

	Treatment		Placebo				
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)	Favors treatment / Favors placebo	Weight, %
Patients with ASCVD							
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)		16.67
CANVAS program	NA/3756	6.4	NA/2900	10.5	0.59 (0.44-0.79)		19.23
DECLARE-TIMI 58	65/3474	4.7	118/3500	8.6	0.55 (0.41-0.75)		18.06
CREDENCE	69/1113	24.1	102/1107	36.5	0.64 (0.47-0.87)		17.37
VERTIS CV	175/5499	9.3	108/2747	11.5	0.81 (0.64-1.03)		28.66
Fixed-effects model ($Q = 6.09$; $df = 4$; $P = .19$; $I^2 = 34.4\%$)					0.64 (0.56-0.72)		
Patients without ASCVD							
CANVAS program	NA/2039	4.1	NA/1447	6.6	0.63 (0.39-1.02)		15.72
DECLARE-TIMI 58	62/5108	3.0	120/5078	5.9	0.51 (0.37-0.69)		37.41
CREDENCE	84/1089	29.9	122/1092	44.3	0.68 (0.51-0.89)		46.87
Fixed-effects model ($Q = 1.86$; $df = 2$; $P = .40$; $I^2 = 0.0\%$)					0.60 (0.50-0.73)		



Conclusion

- Study results suggest that:
- The SGLT2 inhibitor class of medications favorably affects risk for CV outcomes in patients with T2D
- Empagliflozin is associated with reduced risk for CV death
- Across the class, there are robust and consistent associations with reduction in risk for HHF, independent of baseline ASCVD status or kidney function.
- These data support contemporary society recommendations to prioritize the use of SGLT2 inhibitors with demonstrated outcomes, independent of glucose control considerations, in patients with **T2D with or at high risk for CV and kidney complications.**

What is the explanation for the reduction in CV death?

No difference in rates of MI or CVA

Only 10% with HF at baseline

Diuretics (excepting aldosterone antagonists) have not been shown to reduce mortality

What is the explanation for the reduction in CV death?

Related to modest BP reduction (~4 mmHg)?

Related to modest weight loss (~2 kg)?

Unidentified mechanism?

whether **glycemic status** influences
the magnitude of their benefits on **heart failure** and **renal** events

?

Circulation

ORIGINAL RESEARCH ARTICLE

Effect of Empagliflozin on Cardiovascular and Renal Outcomes in Patients With Heart Failure by Baseline Diabetes Status

Results From the EMPEROR-Reduced Trial

JACC Journals › JACC › Archives › Vol. 77 No. 3 Previous | Next

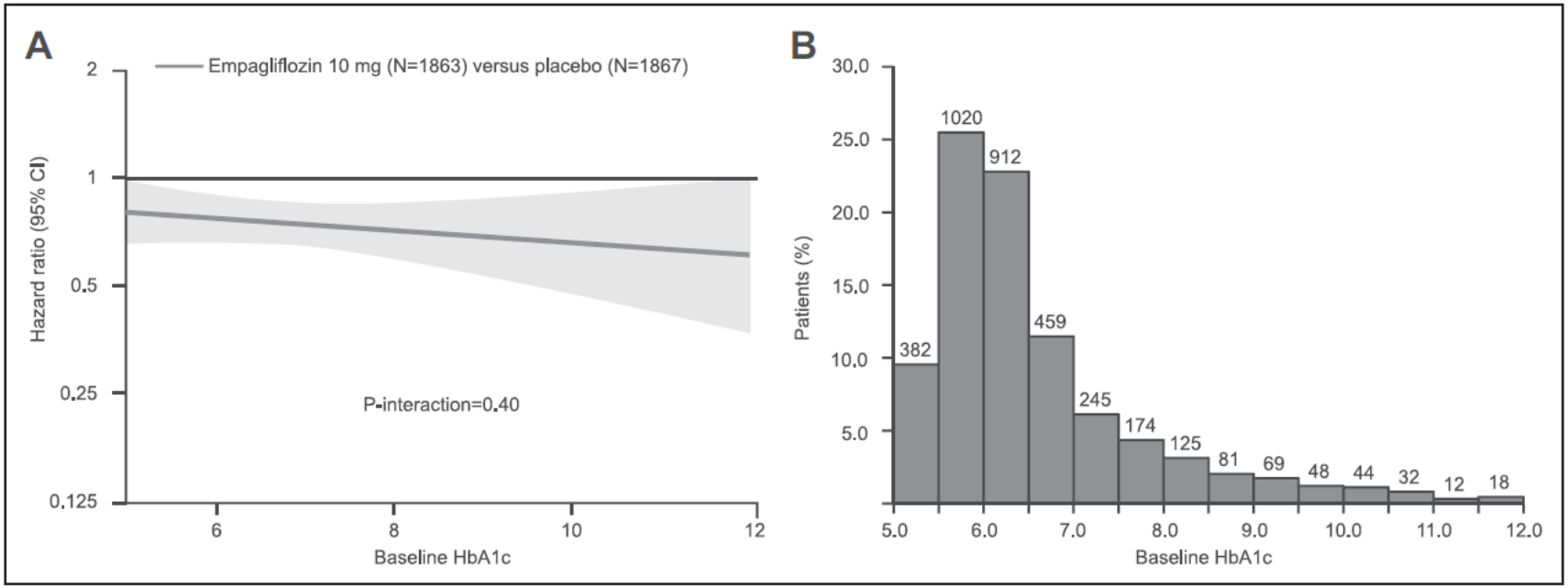
Randomized Trial of Empagliflozin in Nondiabetic Patients With Heart Failure and Reduced Ejection Fraction

Original Investigation

Carlos G. Santos-Gallego, Ariana P. Vargas-Delgado, Juan Antonio Requena-Ibanez, Alvaro Garcia-Ropero, Donna Mancini, Sean Pinney, Frank Macaluso, Samantha Sartori, Merce Roque, Fernando Sabatel-Perez, ... SEE ALL AUTHORS

J Am Coll Cardiol. 2021 Jan, 77 (3) 243–255

Effect of empagliflozin on the primary outcome of EMPEROR-Reduced



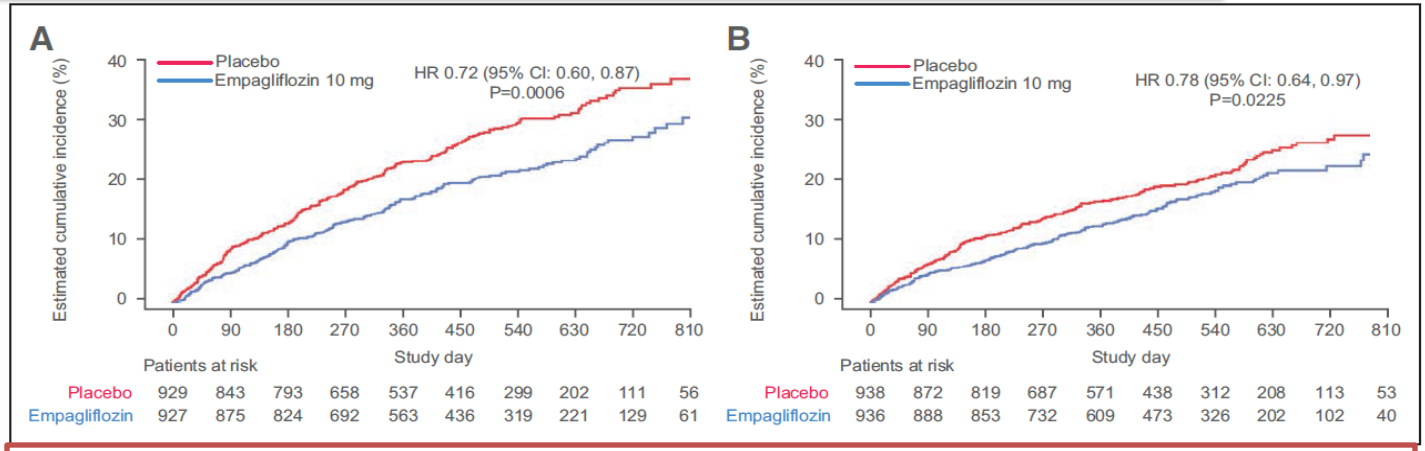
Circulation

ORIGINAL RESEARCH ARTICLE

Effect of Empagliflozin on Cardiovascular and Renal Outcomes in Patients With Heart Failure by Baseline Diabetes Status

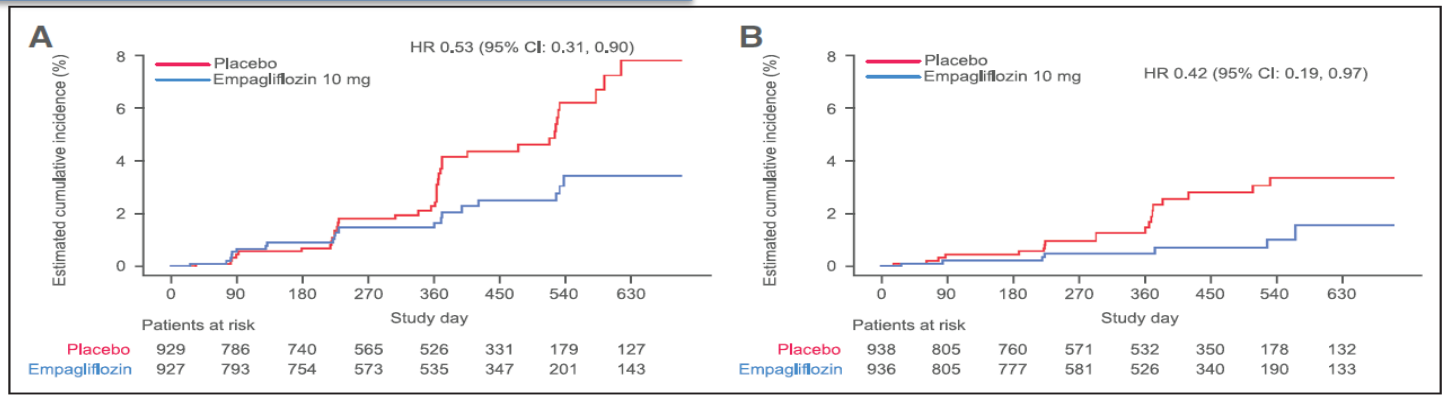
Results From the EMPEROR-Reduced Trial

first event of either cardiovascular death or heart failure hospitalization



(**A**) patients **with** diabetes and (**B**) patients **without** diabetes

Effect of empagliflozin on renal composite



improved

cardiovascular and renal outcomes

In patients with **HFrEF**,

independent of baseline **DM** status and across the continuum of **HbA1c**.

EMPEROR-Reduced

Empagliflozin➔ HFrEF +/- DM

- reduced cardiovascular death
- heart failure (HF) hospitalization
- total HF hospitalizations,
- slowed the progressive decline in kidney function in patients with

JACC Journals › JACC › Archives › Vol. 77 No. 3

Randomized Trial of Empagliflozin in Nondiabetic Patients With Heart Failure and Reduced Ejection Fraction

Original Investigation

Carlos G. Santos-Gallego, Ariana P. Vargas-Delgado, Juan Antonio Requena-Ibanez, Alvaro Garcia-Ropero, Donna Mancini, Sean Pinney, Frank Macaluso, Samantha Sartori, Merce Roque, Fernando Sabatel-Perez, ... SEE ALL AUTHORS

J Am Coll Cardiol. 2021 Jan, 77 (3) 243–255

assess the effect of empagliflozin in nondiabetic HFrEF patients

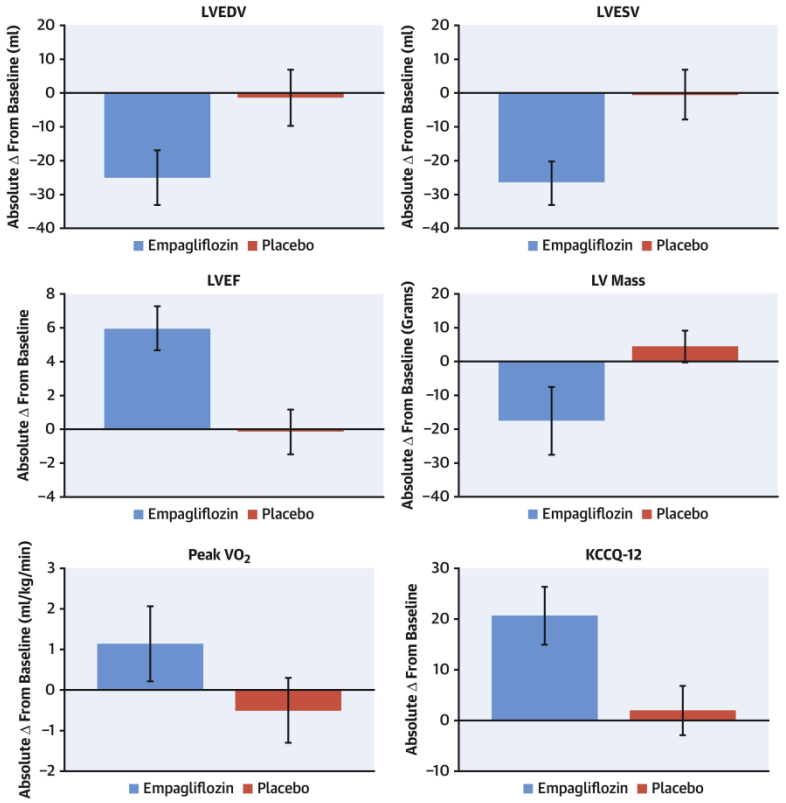
- left ventricular (LV) function and volumes,
- functional capacity,
- quality of life (QoL)

- double-blind, placebo-controlled trial,
- nondiabetic HFrEF patients (n = 84)
- randomized to empagliflozin 10 mg daily or placebo for 6 months.

Endpoint:

- LV end-diastolic and -systolic volume (CMR). changes in LV mass,
- LV ejection fraction,
- peak oxygen consumption in the cardiopulmonary exercise test,
- 6-min walk test,
- quality of life.

CENTRAL ILLUSTRATION: Empagliflozin in Nondiabetic Patients With Heart Failure With Reduced Ejection Fraction Improves Cardiac Function, Adverse Remodeling, and Exercise Capacity: A Randomized Control Trial



Santos-Gallego, C.G. et al. J Am Coll Cardiol. 2021;77(3):243-55.

- significant reduction of LV end-diastolic volume (−25.1 ± 26.0 ml vs. −1.5 ± 25.4 ml; $p < 0.001$)
- LV end-systolic volume (−26.6 ± 20.5 ml vs. −0.5 ± 21.9 ml for ; $p < 0.001$).
- reductions in LV mass (−17.8 ± 31.9 g vs. 4.1 ± 13.4 g, for ; $p < 0.001$)
- LV sphericity,
- improvements in LV ejection fraction (6.0 ± 4.2 vs. −0.1 ± 3.9; $p < 0.001$).
- improvements in peak O_2 consumption (1.1 ± 2.6 ml/min/kg vs. −0.5 ± 1.9 ml/min/kg for empagliflozin vs. placebo, respectively; $p = 0.017$), oxygen uptake efficiency slope (111 ± 267 vs. −145 ± 318; $p < 0.001$),
- 6-min walk test (81 ± 64 m vs. −35 ± 68 m; $p < 0.001$)
- quality of life (Kansas City Cardiomyopathy Questionnaire-12: 21 ± 18 vs. 2 ± 15; $p < 0.001$).

Conclusions

Empagliflozin administration to nondiabetic HFrEF patients significantly improves

- LV volumes,
- LV mass,
- LV systolic function,
- functional capacity,
- quality of life

the effect of the drug on

inpatient and outpatient events that reflect worsening heart failure

reduced the risk and total number of inpatient and outpatient

worsening heart failure events,
with benefits seen early after initiation of treatment
and sustained for the duration of double-blind therapy.

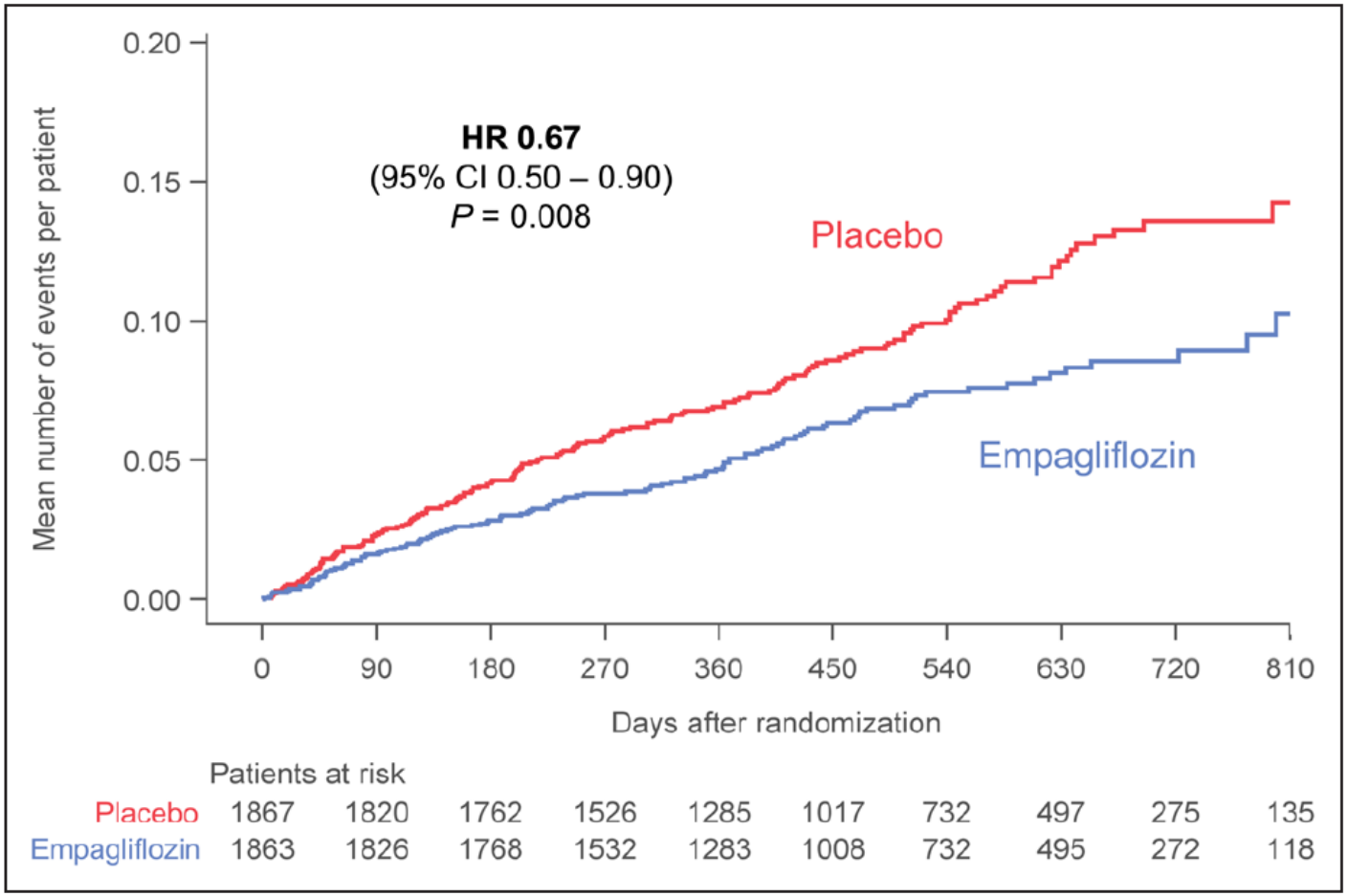
Circulation

ORIGINAL RESEARCH ARTICLE

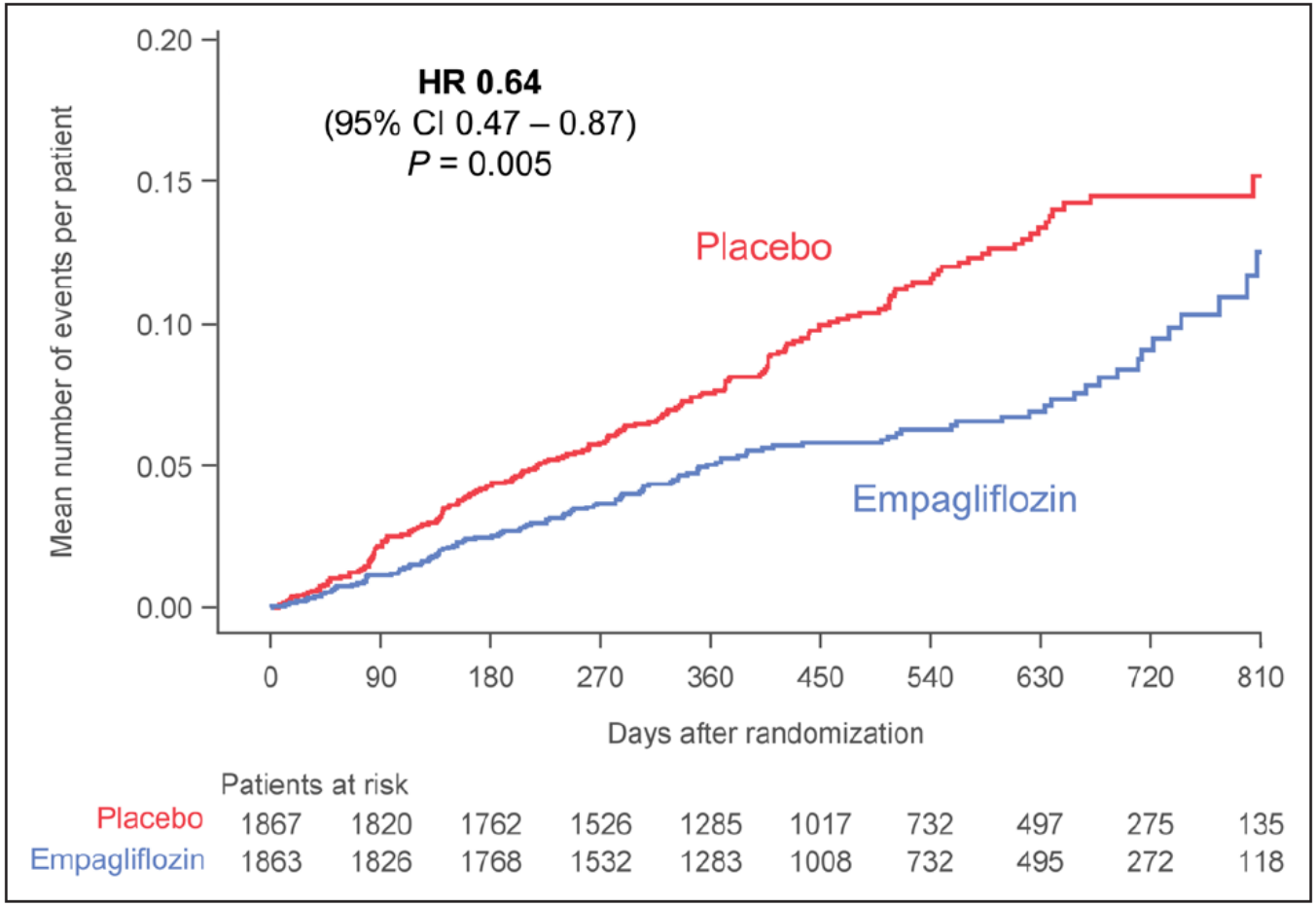
Effect of Empagliflozin on the Clinical Stability of Patients With Heart Failure and a Reduced Ejection Fraction

The EMPEROR-Reduced Trial

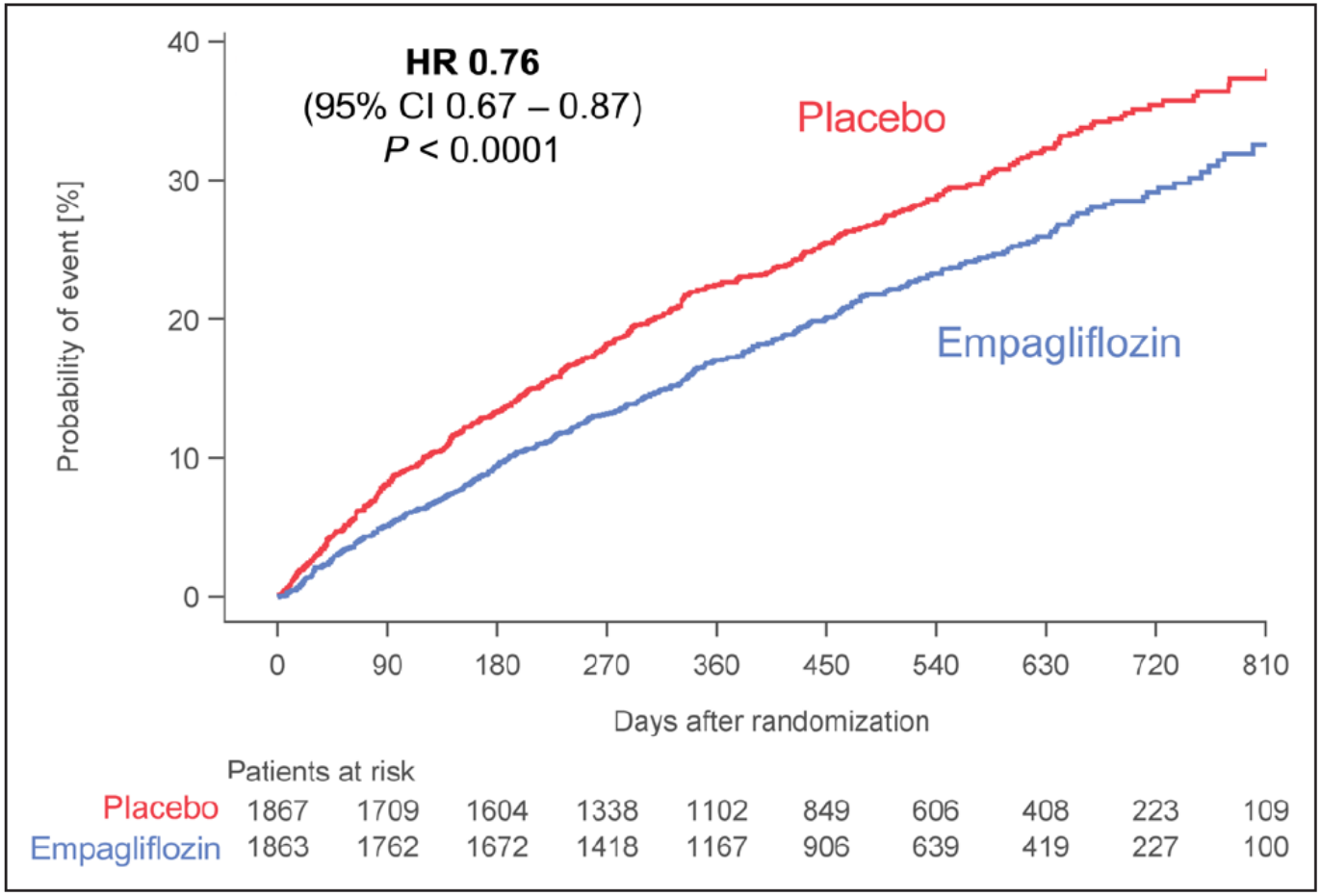
Total (first and recurrent) adjudicated heart failure hospitalizations requiring admission to CCU/ ICU

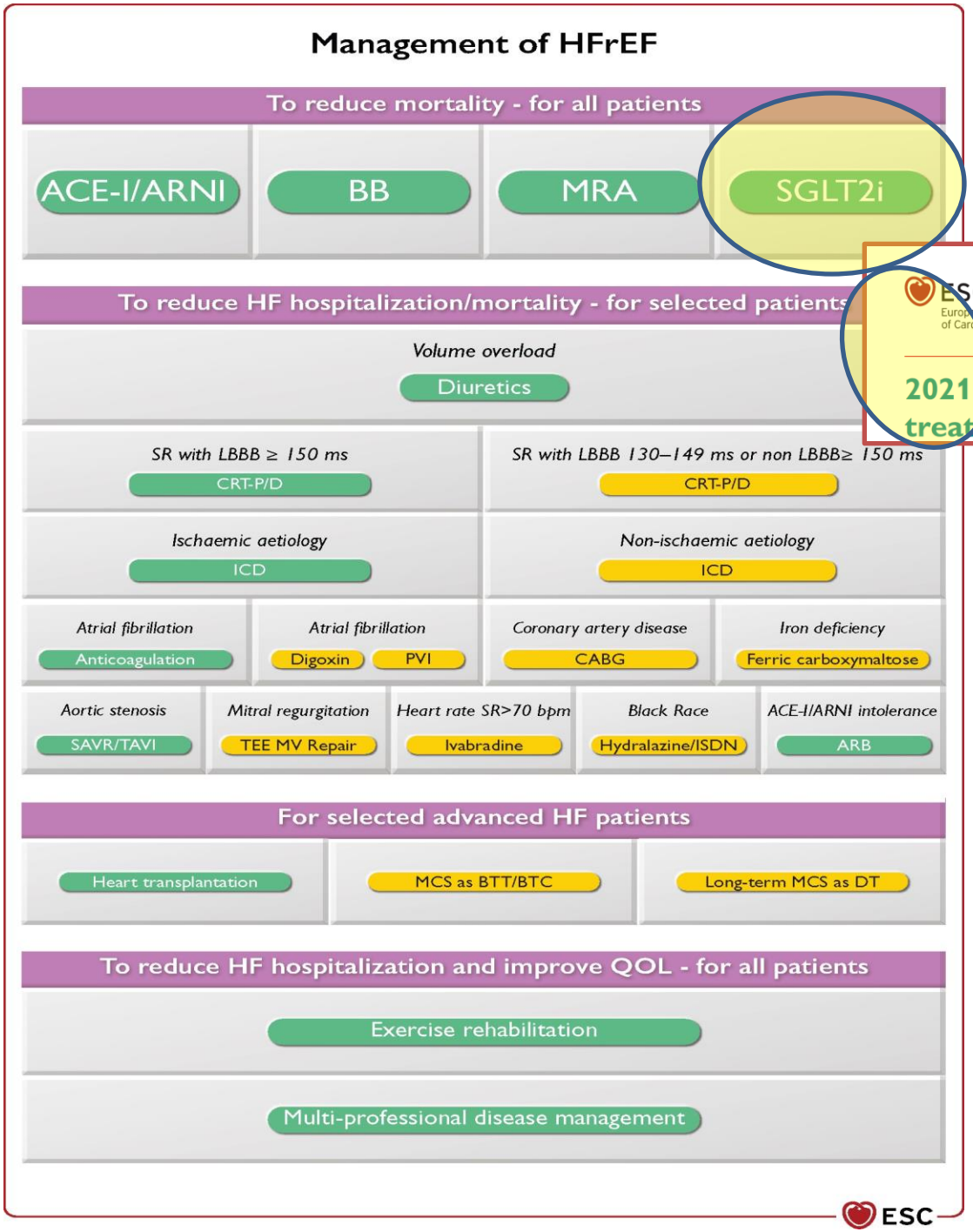


Total (first and recurrent) adjudicated hospitalization for heart failure requiring intravenous vasopressor or positive inotropic drug



Time-to-first-event analysis of all-cause mortality, heart failure hospitalization, or emergent/urgent care visit for worsening heart failure





ESC GUIDELINES

ESC European Society of Cardiology

European Heart Journal (2021) 00, 1–128
doi:10.1093/eurheartj/ehab368

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

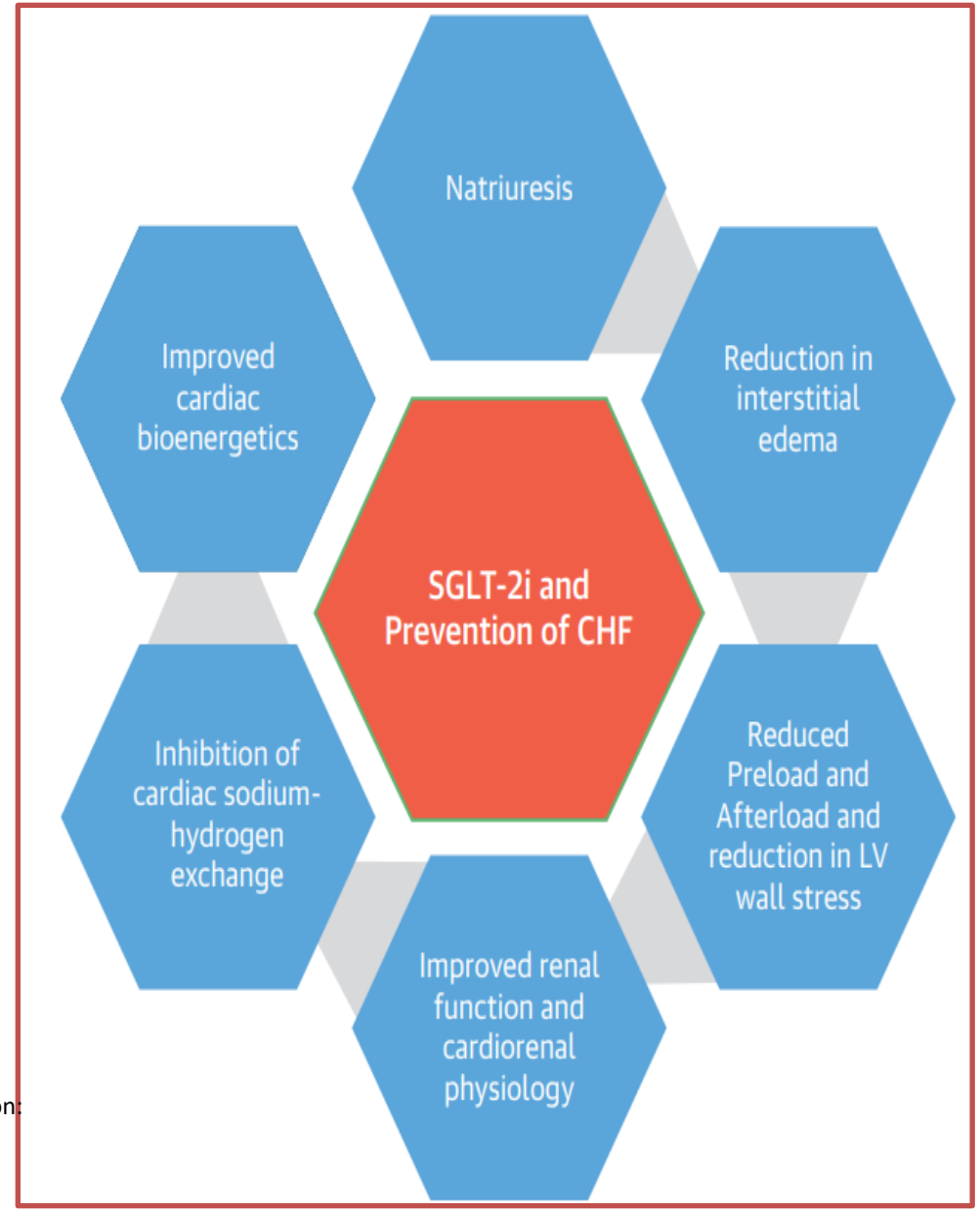
ESC European Society of Cardiology

OXFORD UNIVERSITY PRESS

MECHANISTIC INSIGHTS FOR CV BENEFITS

Summary of mechanistic insights for CV benefits of SGLT2i

Proposed Mechanisms of Benefit of SGLT-2i in Heart Failure



Farkouh ME, Verma S. Prevention of heart failure with SGLT-2 inhibition: insights from CVD-REAL.

(Empagliflozin Evaluation by Measuring Impact on Hemodynamics in Patients With Heart failure)

- improve outcomes in those with HF and reduced ejection fraction(+/- DM).
- prevent heart failure (HF) hospitalizations in patients with type 2 diabetes.

Mechanisms of HF benefits remain unclear.
effects on hemodynamics (filling pressures) ?

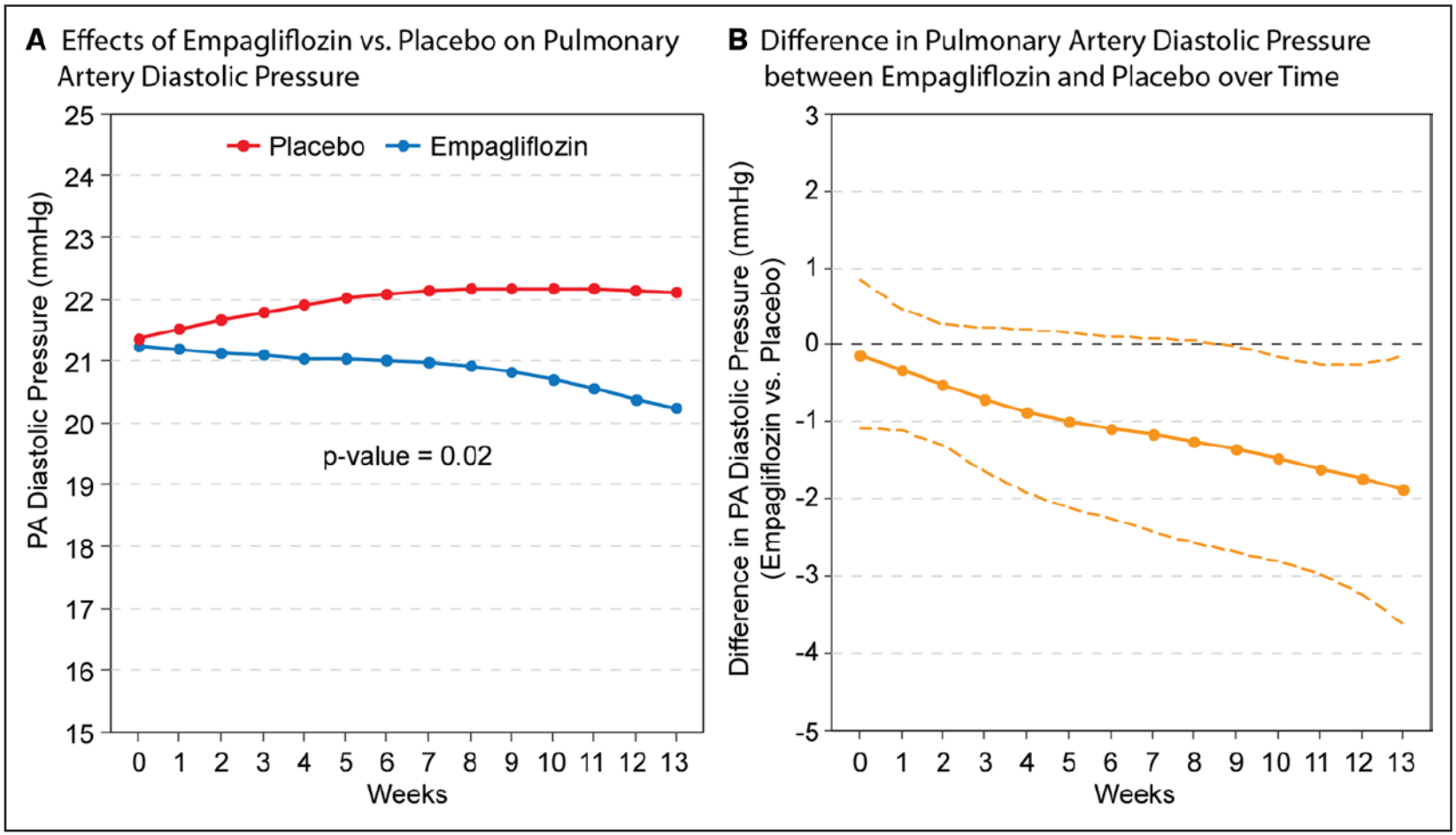
Circulation

ORIGINAL RESEARCH ARTICLE

Empagliflozin Effects on Pulmonary Artery Pressure in Patients With Heart Failure

Results From the EMBRACE-HF Trial

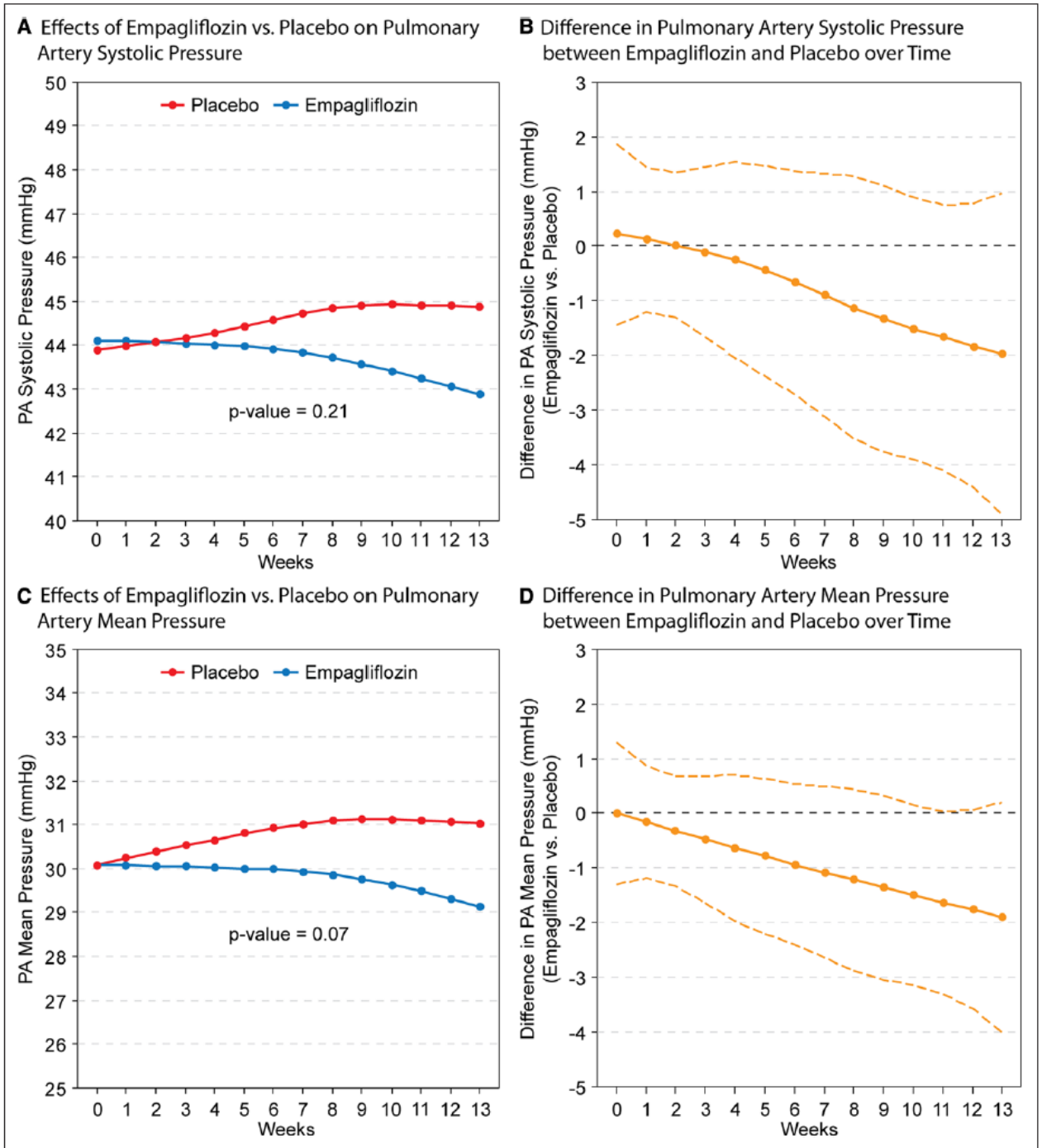
Effects of empagliflozin vs placebo on the primary end point of PA diastolic pressure.

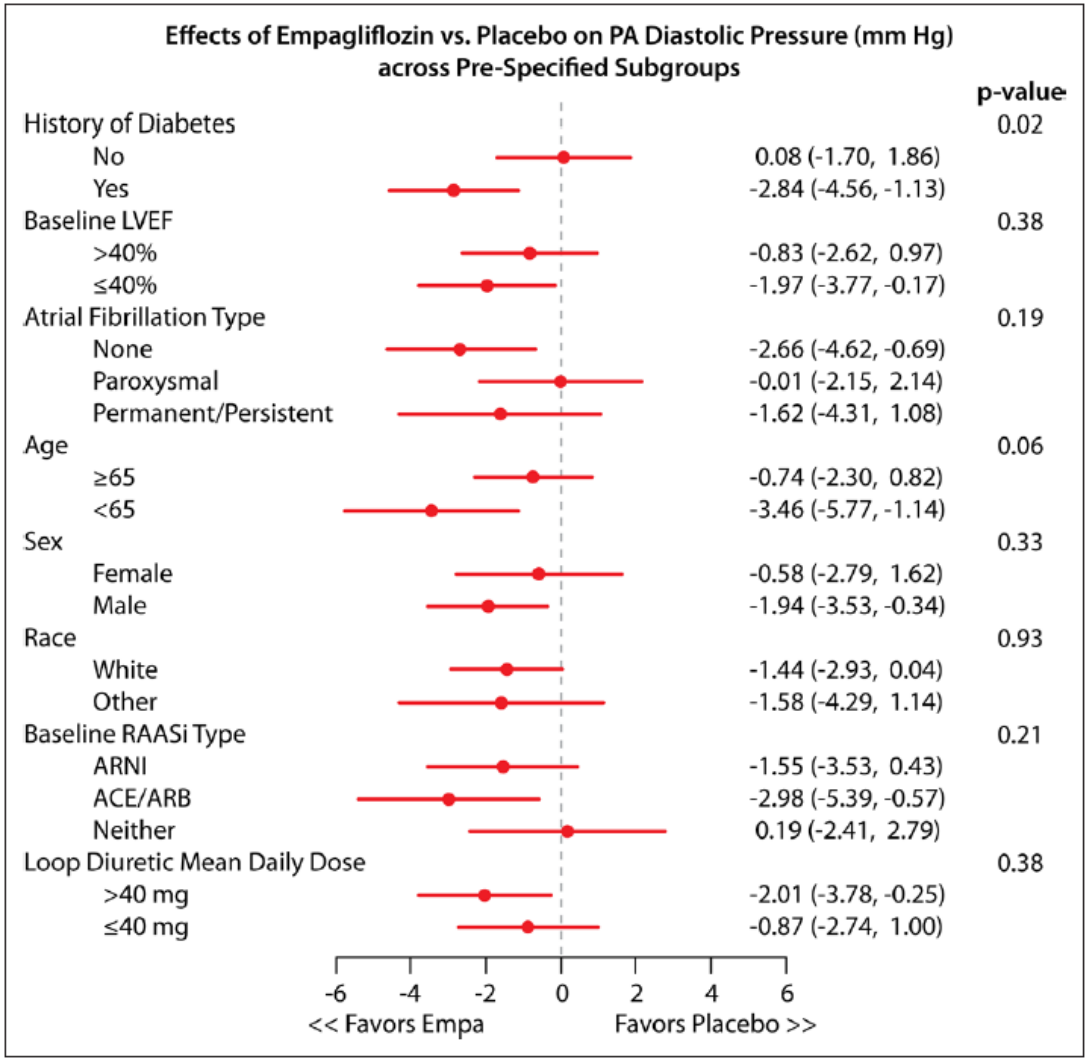


secondary end points of

PA systolic pressures

Mean-PA pressures.




Effects of Empagliflozin vs. Placebo on PA Diastolic Pressure (mm Hg)
across Pre-Specified Subgroups
p-value
History of Diabetes
0.02
No
0.08 (-1.70, 1.86)
Yes
-2.84 (-4.56, -1.13)
Baseline LVEF
0.38
>40%
-0.83 (-2.62, 0.97)
≤40%
-1.97 (-3.77, -0.17)
Atrial Fibrillation Type
0.19
None
-2.66 (-4.62, -0.69)
Paroxysmal
-0.01 (-2.15, 2.14)
Permanent/Persistent
-1.62 (-4.31, 1.08)
Age
0.06
≥65
-0.74 (-2.30, 0.82)
<65
-3.46 (-5.77, -1.14)
Sex
0.33
Female
-0.58 (-2.79, 1.62)
Male
-1.94 (-3.53, -0.34)
Race
0.93
White
-1.44 (-2.93, 0.04)
Other
-1.58 (-4.29, 1.14)
Baseline RAASi Type
0.21
ARNI
-1.55 (-3.53, 0.43)
ACE/ARB
-2.98 (-5.39, -0.57)
Neither
0.19 (-2.41, 2.79)
Loop Diuretic Mean Daily Dose
0.38
>40 mg
-2.01 (-3.78, -0.25)
≤40 mg
-0.87 (-2.74, 1.00)
-6
-4
-2
0
2
4
6
<< Favors Empa
Favors Placebo >>

Empagliflozin ➔ rapid reductions in PA pressures that were amplified over time and appeared to be independent of loop diuretic management.

Circulation

2020

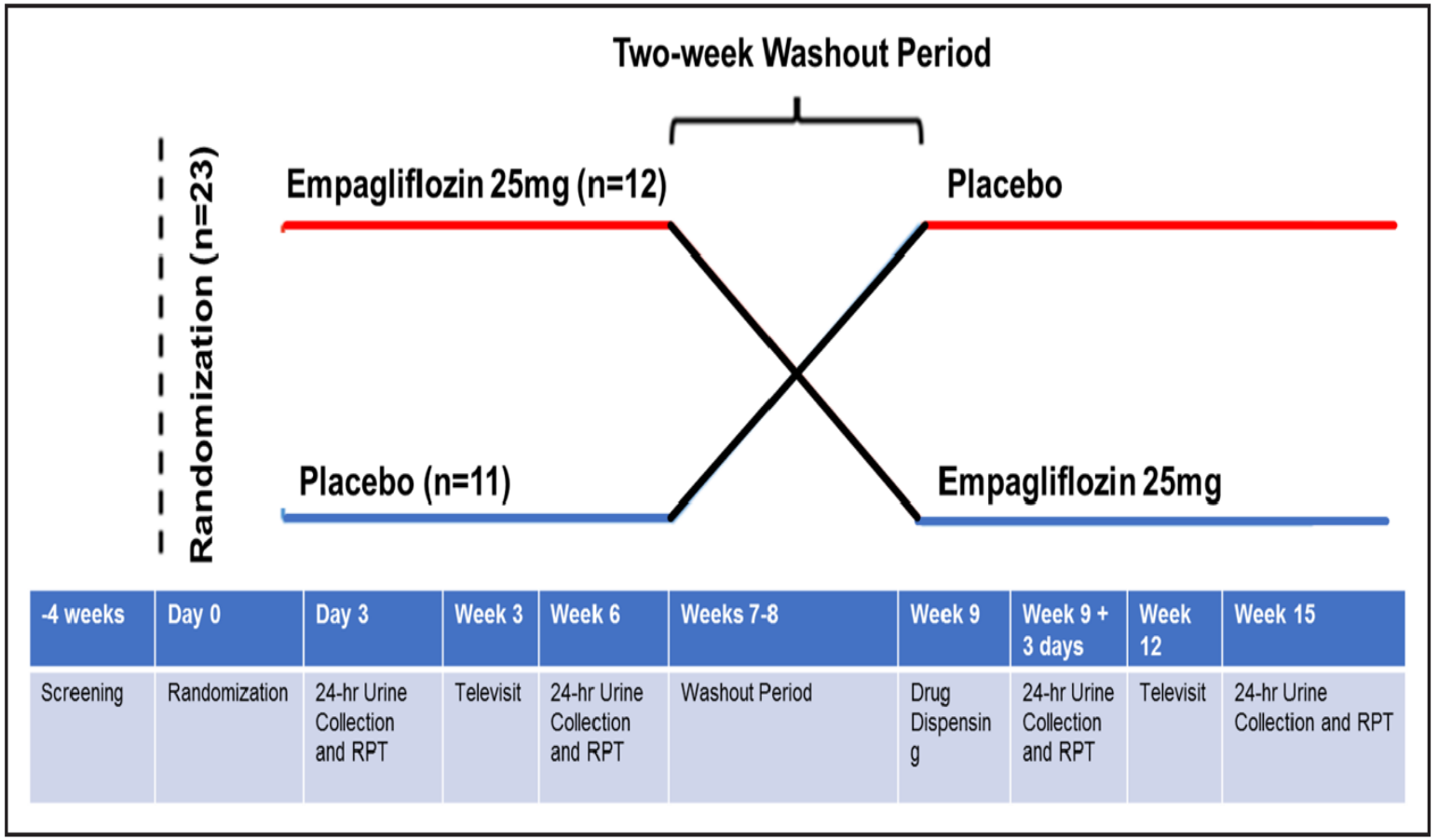
ORIGINAL RESEARCH ARTICLE

Renal and Cardiovascular Effects of SGLT2 Inhibition in Combination With Loop Diuretics in Patients With Type 2 Diabetes and Chronic Heart Failure

The RECEDE-CHF Trial

Circulation. 2020;142:1713–1724. DOI: 10.1161/CIRCULATIONAHA.120.048739

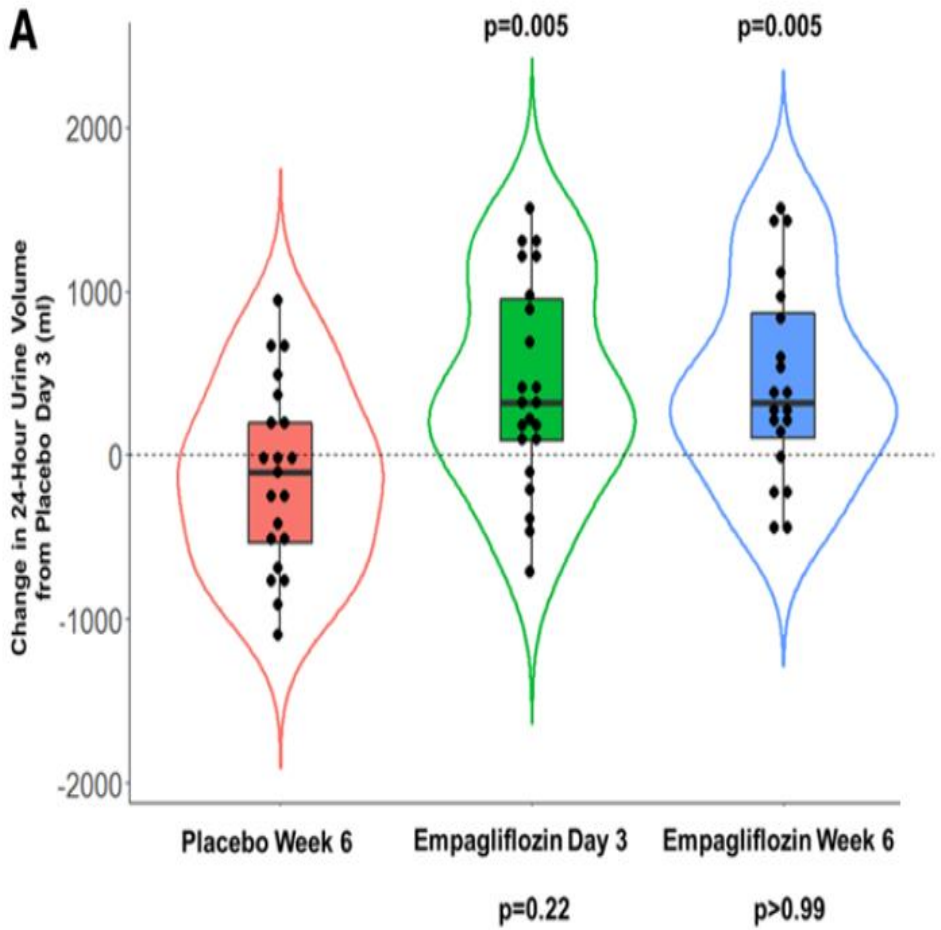
The RECEDE-CHF (SGLT2 Inhibition in Combination With Diuretics in Heart Failure) study design



-4 weeks	Day 0	Day 3	Week 3	Week 6	Weeks 7-8	Week 9	Week 9 + 3 days	Week 12	Week 15
Screening	Randomization	24-hr Urine Collection and RPT	Televisit	24-hr Urine Collection and RPT	Washout Period	Drug Dispensing	24-hr Urine Collection and RPT	Televisit	24-hr Urine Collection and RPT

Circulation. 2020;142:1713–1724. DOI: 10.1161/CIRCULATIONAHA.120.048739

Change in urine volume



Circulation. 2020;142:1713–1724. DOI: 10.1161/CIRCULATIONAHA.120.048739

RECEDE-CHF Trial Conclusion

- In patients with T2DM and HF taking regular furosemide, 6 weeks of treatment with empagliflozin caused a significant increase in 24-hour urine volume without an increase in urinary sodium compared with placebo.
- Empagliflozin also caused a significant increase in electrolyte-free water clearance, significant weight loss, and reduced loop diuretic requirement.
- These findings, combined with a reduction in serum uric acid and no significant renal impairment or electrolyte disturbance, provide further insight into the mechanism of the diuretic effect of empagliflozin and suggest that the combination of loop diuretic and SGLT2 inhibition could have a beneficial role in HF.

Circulation. 2020;142:1713–1724. DOI: 10.1161/CIRCULATIONAHA.120.048739

Circulation

2021

ORIGINAL RESEARCH ARTICLE

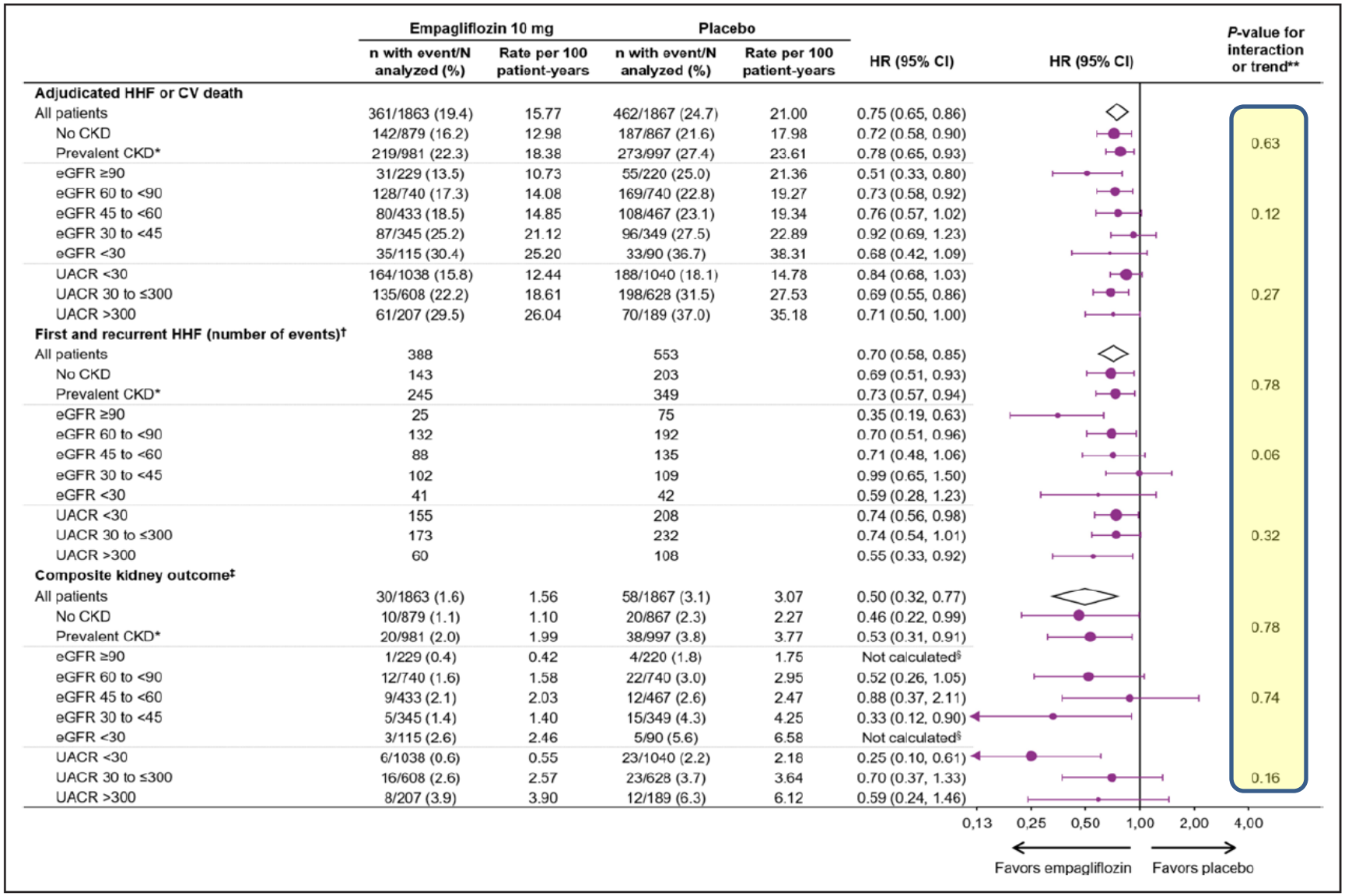
Cardiac and Kidney Benefits of Empagliflozin in Heart Failure Across the Spectrum of Kidney Function

Insights From EMPEROR-Reduced

aim to study the effect of empagliflozin on cardiovascular and kidney outcomes across the spectrum of kidney function.

Clinical outcomes in patients by

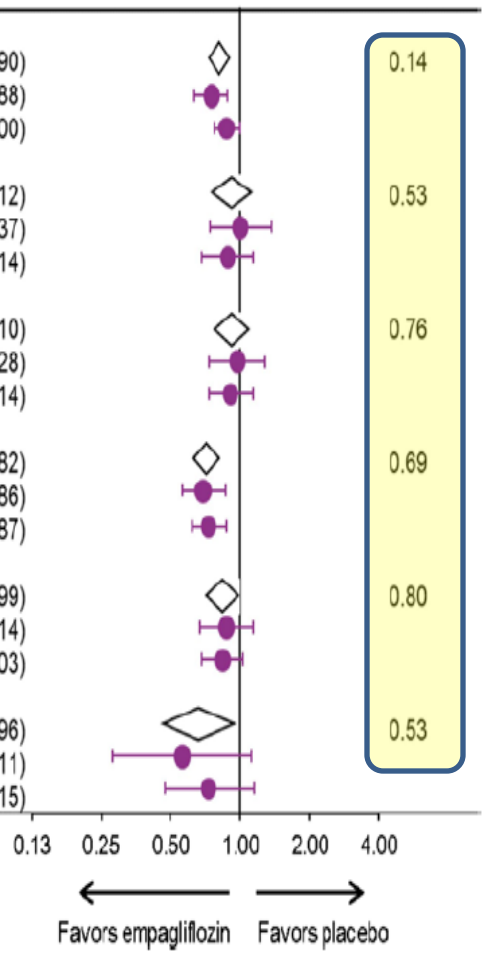
CKD status ， eGFR ， urinary albumin-to-creatinine ratio



	Empagliflozin 10 mg		Placebo			*P*-value for interaction or trend**
	n with event/N analyzed (%)	Rate per 100 patient-years	n with event/N analyzed (%)	Rate per 100 patient-years	HR (95% CI)	
Adjudicated HHF or CV death						
All patients	361/1863 (19.4)	15.77	462/1867 (24.7)	21.00	0.75 (0.65, 0.86)	
No CKD	142/879 (16.2)	12.98	187/867 (21.6)	17.98	0.72 (0.58, 0.90)	0.63
Prevalent CKD*	219/981 (22.3)	18.38	273/997 (27.4)	23.61	0.78 (0.65, 0.93)	
eGFR ≥90	31/229 (13.5)	10.73	55/220 (25.0)	21.36	0.51 (0.33, 0.80)	
eGFR 60 to <90	128/740 (17.3)	14.08	169/740 (22.8)	19.27	0.73 (0.58, 0.92)	
eGFR 45 to <60	80/433 (18.5)	14.85	108/467 (23.1)	19.34	0.76 (0.57, 1.02)	0.12
eGFR 30 to <45	87/345 (25.2)	21.12	96/349 (27.5)	22.89	0.92 (0.69, 1.23)	
eGFR <30	35/115 (30.4)	25.20	33/90 (36.7)	38.31	0.68 (0.42, 1.09)	
UACR <30	164/1038 (15.8)	12.44	188/1040 (18.1)	14.78	0.84 (0.68, 1.03)	
UACR 30 to ≤300	135/608 (22.2)	18.61	198/628 (31.5)	27.53	0.69 (0.55, 0.86)	0.27
UACR >300	61/207 (29.5)	26.04	70/189 (37.0)	35.18	0.71 (0.50, 1.00)	
First and recurrent HHF (number of events)†						
All patients	388		553		0.70 (0.58, 0.85)	
No CKD	143		203		0.69 (0.51, 0.93)	0.78
Prevalent CKD*	245		349		0.73 (0.57, 0.94)	
eGFR ≥90	25		75		0.35 (0.19, 0.63)	
eGFR 60 to <90	132		192		0.70 (0.51, 0.96)	
eGFR 45 to <60	88		135		0.71 (0.48, 1.06)	0.06
eGFR 30 to <45	102		109		0.99 (0.65, 1.50)	
eGFR <30	41		42		0.59 (0.28, 1.23)	
UACR <30	155		208		0.74 (0.56, 0.98)	
UACR 30 to ≤300	173		232		0.74 (0.54, 1.01)	0.32
UACR >300	60		108		0.55 (0.33, 0.92)	
Composite kidney outcome‡						
All patients	30/1863 (1.6)	1.56	58/1867 (3.1)	3.07	0.50 (0.32, 0.77)	
No CKD	10/879 (1.1)	1.10	20/867 (2.3)	2.27	0.46 (0.22, 0.99)	0.78
Prevalent CKD*	20/981 (2.0)	1.99	38/997 (3.8)	3.77	0.53 (0.31, 0.91)	
eGFR ≥90	1/229 (0.4)	0.42	4/220 (1.8)	1.75	Not calculated§	
eGFR 60 to <90	12/740 (1.6)	1.58	22/740 (3.0)	2.95	0.52 (0.26, 1.05)	
eGFR 45 to <60	9/433 (2.1)	2.03	12/467 (2.6)	2.47	0.88 (0.37, 2.11)	0.74
eGFR 30 to <45	5/345 (1.4)	1.40	15/349 (4.3)	4.25	0.33 (0.12, 0.90)	
eGFR <30	3/115 (2.6)	2.46	5/90 (5.6)	6.58	Not calculated§	
UACR <30	6/1038 (0.6)	0.55	23/1040 (2.2)	2.18	0.25 (0.10, 0.61)	
UACR 30 to ≤300	16/608 (2.6)	2.57	23/628 (3.7)	3.64	0.70 (0.37, 1.33)	0.16
UACR >300	8/207 (3.9)	3.90	12/189 (6.3)	6.12	0.59 (0.24, 1.46)	

Additional clinical outcomes by CKD status

	Empagliflozin 10 mg		Placebo				
	n with event/N analyzed (%)	Rate per 100 patient-years	n with event/N analyzed (%)	Rate per 100 patient-years	HR (95% CI)	HR (95% CI)	*P*-value for interaction
All-cause hospitalization							
All patients	703/1863 (37.7)	36.62	814/1867 (43.6)	45.23	0.81 (0.73, 0.90)		0.14
No prevalent CKD	266/879 (30.3)	28.10	330/867 (38.1)	37.71	0.75 (0.63, 0.88)		
Prevalent CKD*	422/981 (43.0)	42.92	464/997 (46.5)	49.46	0.87 (0.77, 1.00)		
CV death							
All patients	187/1863 (10.0)	7.55	202/1867 (10.8)	8.13	0.92 (0.75, 1.12)		0.53
No prevalent CKD	81/879 (9.2)	6.89	79/867 (9.1)	6.84	1.00 (0.74, 1.37)		
Prevalent CKD*	106/981 (10.8)	8.17	121/997 (12.1)	9.13	0.88 (0.68, 1.14)		
All-cause mortality							
All patients	249/1863 (13.4)	10.06	266/1867 (14.2)	10.71	0.92 (0.77, 1.10)		0.76
No prevalent CKD	96/879 (10.9)	8.17	96/867 (11.1)	8.32	0.97 (0.73, 1.28)		
Prevalent CKD*	153/981 (15.6)	11.79	168/997 (16.9)	12.68	0.91 (0.73, 1.14)		
Composite kidney outcome†, CV death or HHF							
All patients	370/1863 (19.9)	19.95	492/1867 (26.4)	27.81	0.71 (0.62, 0.82)		0.69
No prevalent CKD	147/879 (16.7)	16.67	198/867 (22.8)	23.87	0.69 (0.56, 0.86)		
Prevalent CKD*	223/981 (22.7)	22.98	292/997 (29.3)	31.18	0.73 (0.62, 0.87)		
Composite kidney outcome† or all-cause mortality							
All patients	265/1863 (14.2)	13.37	305/1867 (16.3)	15.60	0.84 (0.71, 0.99)		0.80
No prevalent CKD	102/879 (11.6)	10.97	109/867 (12.6)	12.14	0.87 (0.67, 1.14)		
Prevalent CKD*	163/981 (16.6)	15.53	194/997 (19.5)	18.41	0.84 (0.68, 1.03)		
Acute kidney injury‡							
All patients	46/1863 (2.5)	1.89	67/1867 (3.6)	2.76	0.66 (0.45, 0.96)		0.53
No prevalent CKD	13/879 (1.5)	1.13	22/867 (2.5)	1.95	0.56 (0.28, 1.11)		
Prevalent CKD*	33/981 (3.4)	2.58	45/997 (4.5)	3.48	0.73 (0.47, 1.15)		



eGFR Slope Analyses by CKD Status, eGFR, and UACR Categories at Baseline

Slope of change in eGFR per year*, mean±SE	Empagliflozin	Placebo	Absolute difference (95% CI)	*P* Value	*P* value for interaction
All patients (N=3726)	–0.55±0.23	–2.28±0.23	1.73 (1.10–2.37)	<0.001	
By prevalent CKD status†					
No prevalent CKD (n=1744)	–0.93±0.33	–3.33±0.33	2.41 (1.49–3.32)	<0.001	0.045
Prevalent CKD (n=1976)	–0.22±0.32	–1.33±0.32	1.11 (0.23–1.98)	0.013	
By eGFR (CKD-EPI) category, mL/(min·1.73 m^2)					*P* Value for trend
≥90 (n=449)	–2.20±0.63	–4.17±0.66	1.96 (0.16–3.76)	0.033	0.033
60 to <90 (n=1478)	–0.72±0.36	–3.21±0.36	2.49 (1.49–3.49)	<0.001	
45 to <60 (n=900)	0.03±0.47	–1.59±0.45	1.62 (0.35–2.89)	0.013	
30 to <45 (n=693)	0.05±0.54	–0.38±0.54	0.43 (–1.06 to 1.93)	0.57	
<30 (n=204)	–0.17±0.92	–0.80±1.18	0.63 (–2.31 to 3.56)	0.68	
By UACR category, mg/g					*P* Value for trend
Normoalbuminuria (<30) (n=2076)	–0.04±0.30	–2.13±0.31	2.09 (1.24–2.93)	<0.001	0.29
Microalbuminuria (30 to <=300) (n=1235)	–1.12±0.40	–2.35±0.40	1.23 (0.14–2.33)	0.028	
Macroalbuminuria (>300) (n=396)	–1.47±0.71	–2.87±0.72	1.40 (–0.58 to 3.37)	0.166	

Empagliflozin had a beneficial effect on the

- key efficacy outcomes and slowed the rate of kidney function decline
- in patients with and without CKD,
- regardless of the severity of kidney impairment at baseline.

Circulation

ORIGINAL RESEARCH ARTICLE

Effect of Empagliflozin on Left Ventricular Volumes in Patients With Type 2 Diabetes, or Prediabetes, and Heart Failure With Reduced Ejection Fraction (SUGAR-DM-HF)

reduce the risk of heart failure hospitalization and cardiovascular death in HFrEF

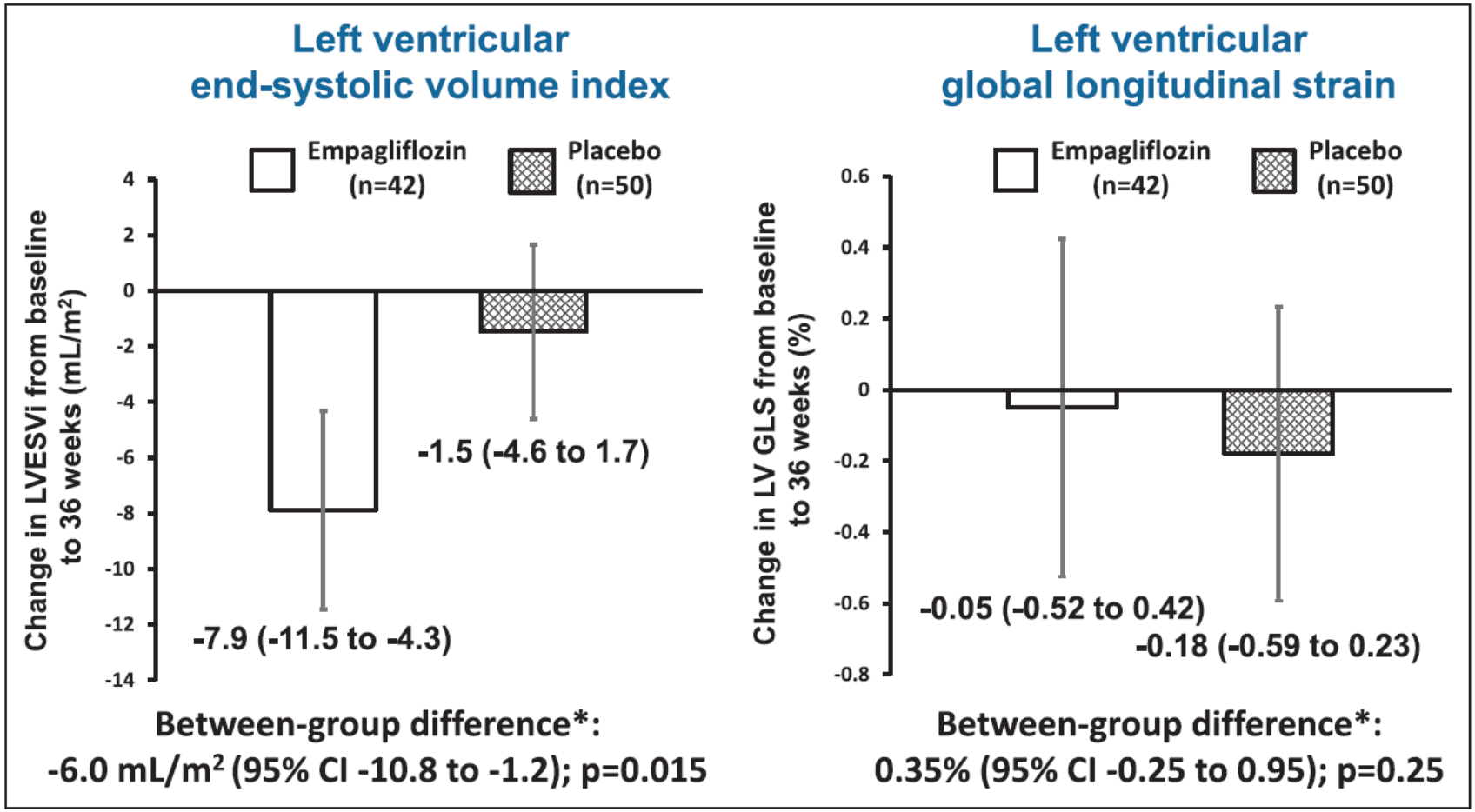
- effects on cardiac structure and function in HFrEF ?

- double-blind, placebo-controlled trial (the SUGAR-DM-HF trial
- Diabetes Mellitus, or Prediabetes,
- HF + NYHA functional class II to IV with a LVEF ≤40%
- randomly assigned 1:1 to empagliflozin 10 mg once daily or placebo,
- The primary outcomes were change from baseline to 36 weeks in
- LV end-systolic volume
- indexed to body surface area and LV global longitudinal strain both measured using
- cardiovascular magnetic resonance. Secondary efficacy outcomes included other
- cardiovascular magnetic resonance measures (LV end-diastolic volume index, LV
- ejection fraction), diuretic intensification, symptoms (Kansas City Cardiomyopathy
- Questionnaire Total Symptom Score, 6-minute walk distance, B-lines on lung
- ultrasound, and biomarkers (including N-terminal pro-B-type natriuretic peptide

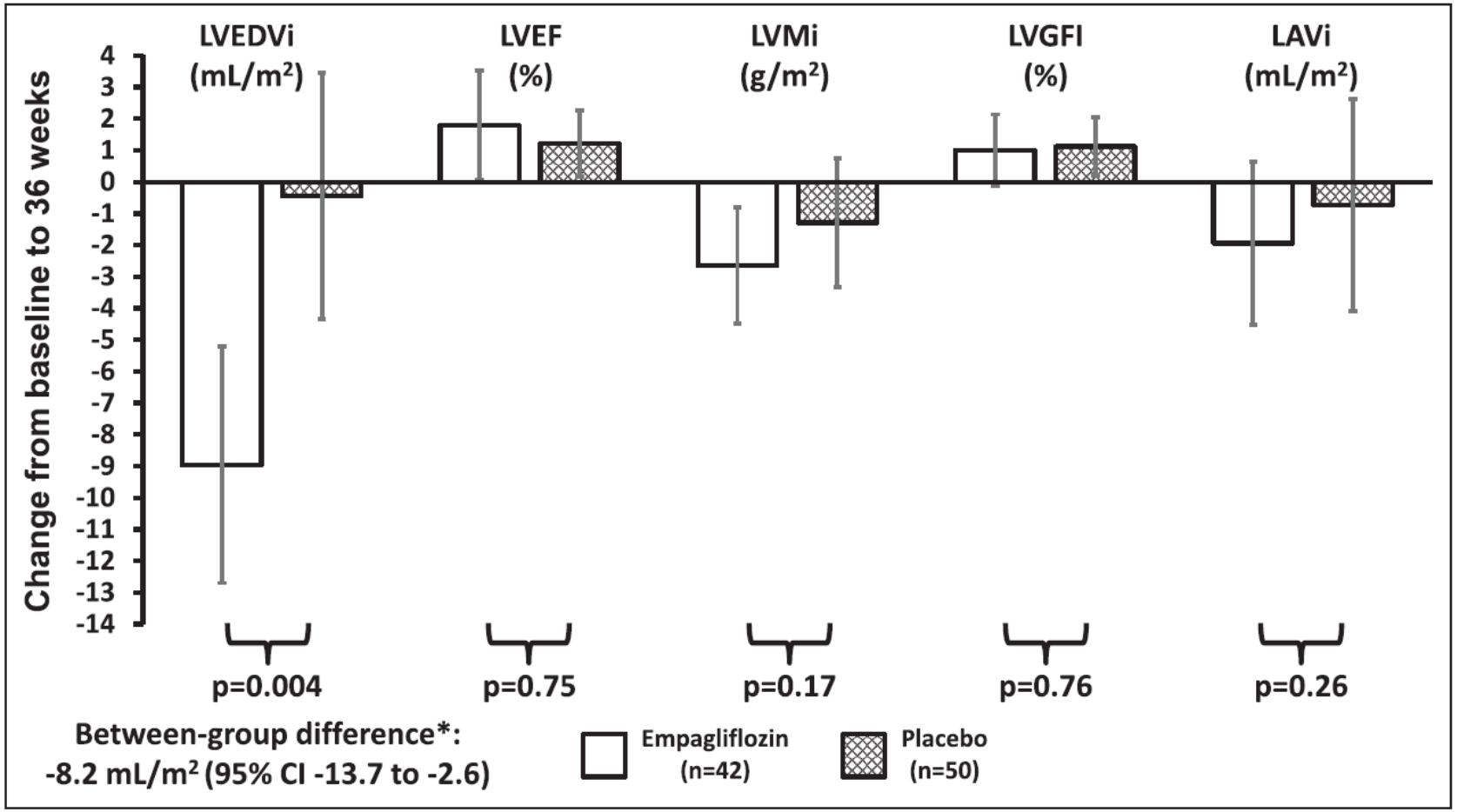
Table 2. Change in CMR Parameters with Empagliflozin 10 mg/d or Placebo From Baseline to Week 36

Variable*	Empagliflozin				Placebo				Between-group difference (95% CI)†	*P* value
	n	Baseline	Week 36	Change	n	Baseline	Week 36	Change		
Coprimary CMR outcomes										
LV end-systolic volume index,‡ mL/m²	42	80.8 (37.2)	72.9 (37.0)	–7.9 (11.8)	50	76.6 (29.3)	75.2 (29.2)	–1.5 (11.3)	–6.0 (–10.8 to –1.2)	0.015
LV global longitudinal strain,§ %	42	–7.04 (2.11)	–7.09 (2.11)	–0.05 (1.57)	50	–7.79 (2.54)	–7.97 (2.31)	-0.18 (1.49)	0.35 (–0.25 to 0.95)	0.25
Secondary CMR outcomes										
LV end-diastolic volume index,‡ mL/m²	42	114.7 (37.0)	105.7 (37.6)	–9.0 (12.4)	50	111.4 (29.2)	110.9 (28.3)	–0.4 (14.1)	–8.2 (–13.7 to –2.6)	0.004
LV ejection fraction, %	42	31.7 (9.9)	33.5 (10.3)	1.8 (5.7)	50	33.0 (9.5)	34.2 (9.7)	1.2 (3.8)	0.3 (–1.7 to 2.3)	0.75
LV mass index,‡ g/m²	42	61.2 (16.1)	58.6 (16.2)	–2.7 (6.1)	50	65.4 (19.6)	64.1 (18.3)	–1.3 (7.3)	–1.9 (–4.7 to 0.8)	0.17
LV global function index, %	42	23.4 (7.7)	24.4 (7.9)	1.0 (3.8)	50	23.6 (7.4)	24.8 (7.5)	1.1 (3.3)	–0.2 (–1.7 to 1.2)	0.76
Left atrial volume index,‡ mL/m²	42	40.5 (13.3)	38.6 (13.5)	–1.9 (8.5)	50	43.7 (12.5)	43.0 (11.9)	–0.7 (12.1)	–2.4 (–6.5 to 1.8)	0.26
Myocardial blood flow,‖ mL/g/min	32	0.80 (0.18)	0.81 (0.24)	0.01 (0.22)	37	0.85 (0.24)	0.93 (0.30)	0.08 (0.27)	–0.08 (–0.20 to 0.04)	0.17
Extracellular volume fraction, %	32	31.8 (4.5)	31.0 (4.7)	–0.8 (3.5)	36	31.6 (4.8)	31.0 (5.1)	–0.7 (3.5)	0.004 (–1.7 to 1.7)	1.00
Exploratory CMR outcomes										
LV end-systolic volume, mL	42	157.5 (68.1)	142.3 (70.9)	–15.1 (24.0)	50	152.9 (58.4)	150.1 (57.7)	–2.8 (23.7)	–11.9 (–21.9 to –1.9)	0.021
LV end-diastolic volume, mL	42	224.8 (72.2)	207.5 (75.3)	–17.3 (24.8)	50	222.7 (60.1)	222.1 (59.3)	–0.6 (29.2)	–16.4 (–27.8 to –5.0)	0.005
LV mass, g	42	121.2 (36.5)	116.1 (37.1)	–5.1 (12.7)	50	131.9 (44.9)	129.5 (42.9)	–2.5 (14.8)	–3.8 (–9.6 to 1.9)	0.19
Left atrial volume, mL	42	79.0 (24.3)	75.5 (26.3)	–3.5 (17.2)	50	87.9 (27.5)	86.3 (25.6)	–1.5 (24.1)	–5.1 (–13.4 to 3.2)	0.22

Change in primary cardiovascular magnetic resonance outcomes from baseline to week 36.



Change in secondary cardiovascular magnetic resonance outcomes from baseline to week 36.



empagliflozin

- reduced LVESV-index by 6.0 (95% CI, –10.8 to –1.2) mL/m2 (*P*=0.015).
- reduced LVEDV-index by 8.2 (95% CI, –13.7 to –2.6) mL/m2 (*P*=0.0042)
- reduced N-terminal pro-BNP by 28% (2%– 47%), *P*=0.038.

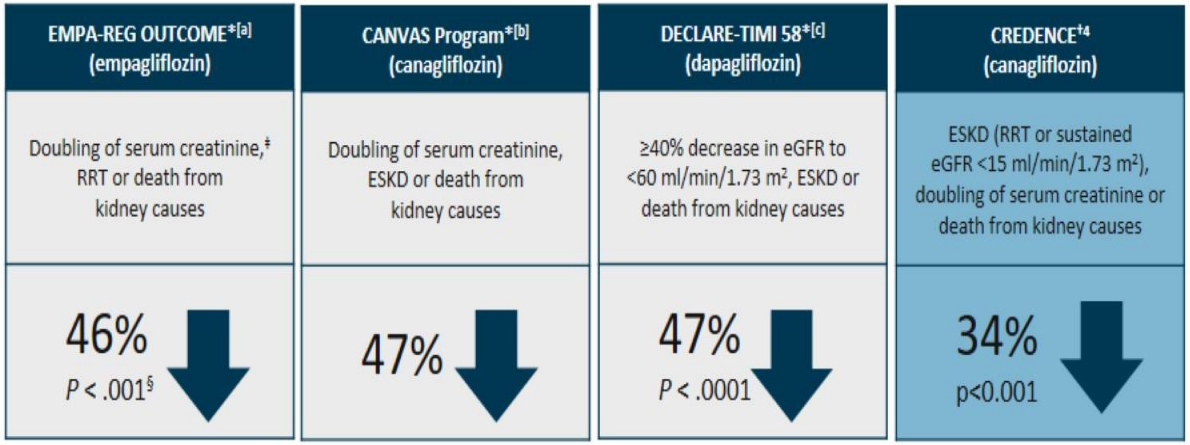
There was no difference in

- LV global longitudinal strain.
- other cardiovascular magnetic resonance measures,
- diuretic intensification,
- Kansas City Cardiomyopathy Questionnaire Total Symptom Score,
- 6-minute walk distance,
- B-lines.

- Favorable reverse LV remodeling may be a mechanism reduce heart failure
- hospitalization and mortality in HFrEF

ACCUMULATED RENAL DATA FROM SGLT2I OUTCOMES TRIALS

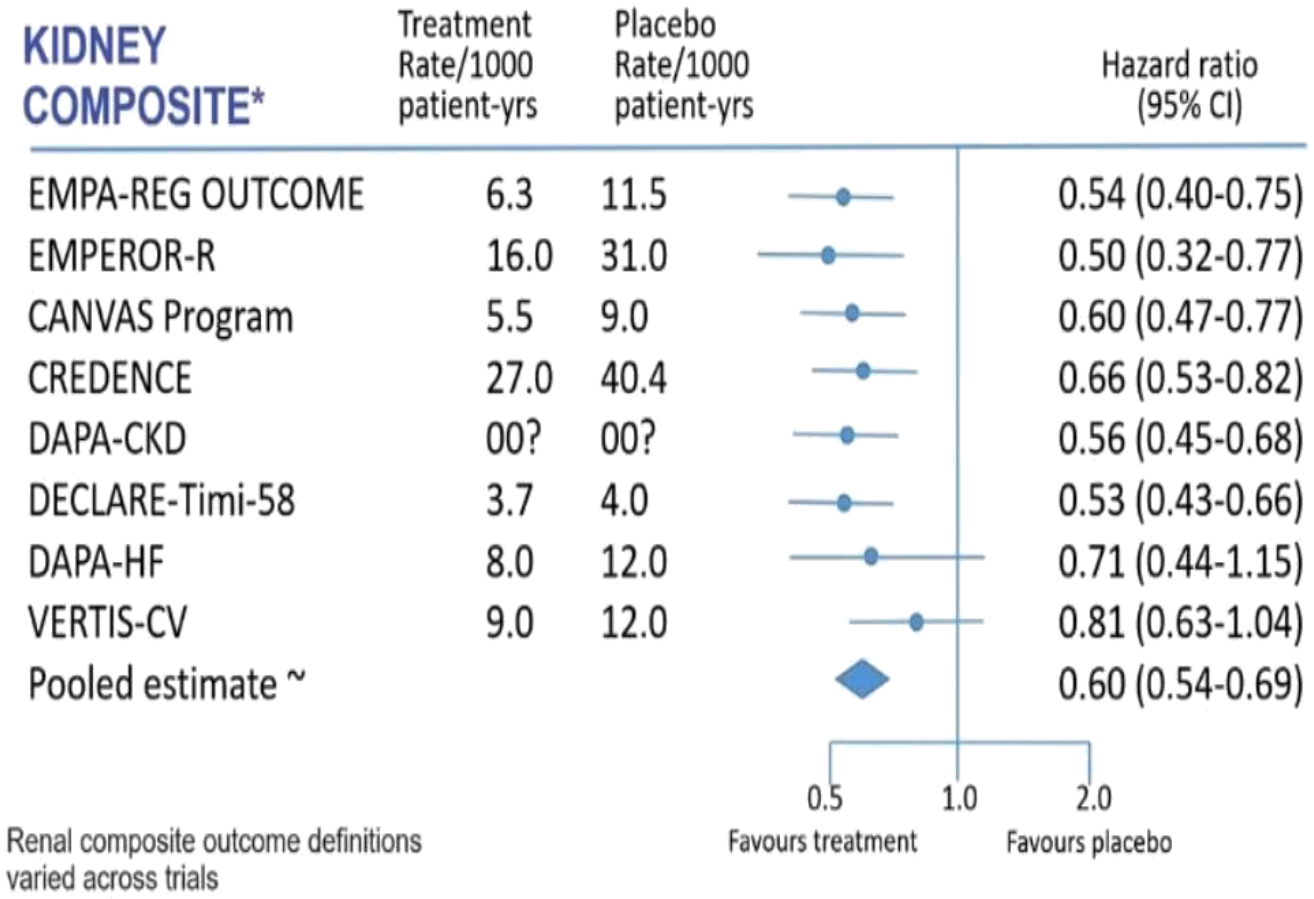
Kidney Outcomes in SGLT2 Inhibitor CV and Cardio-Renal Outcome Trials



*Exploratory analyses; †Prespecified outcome; ‡Accompanied by eGFR ≤45 ml/min/1.73 m²; §Nominal *P* value.

a. Wanner C et al. *N Engl J Med.* 2016;375:323; b. Perkovic V et al. *Lancet Diabetes Endocrinol.* 2018;6:691;
c. Mosenzon O et al. *Lancet Diabetes Endocrinol.* 2019;7:606; d. Perkovic V et al. *N Engl J Med*. 2019;380:2295.

Time to first kidney composite outcome



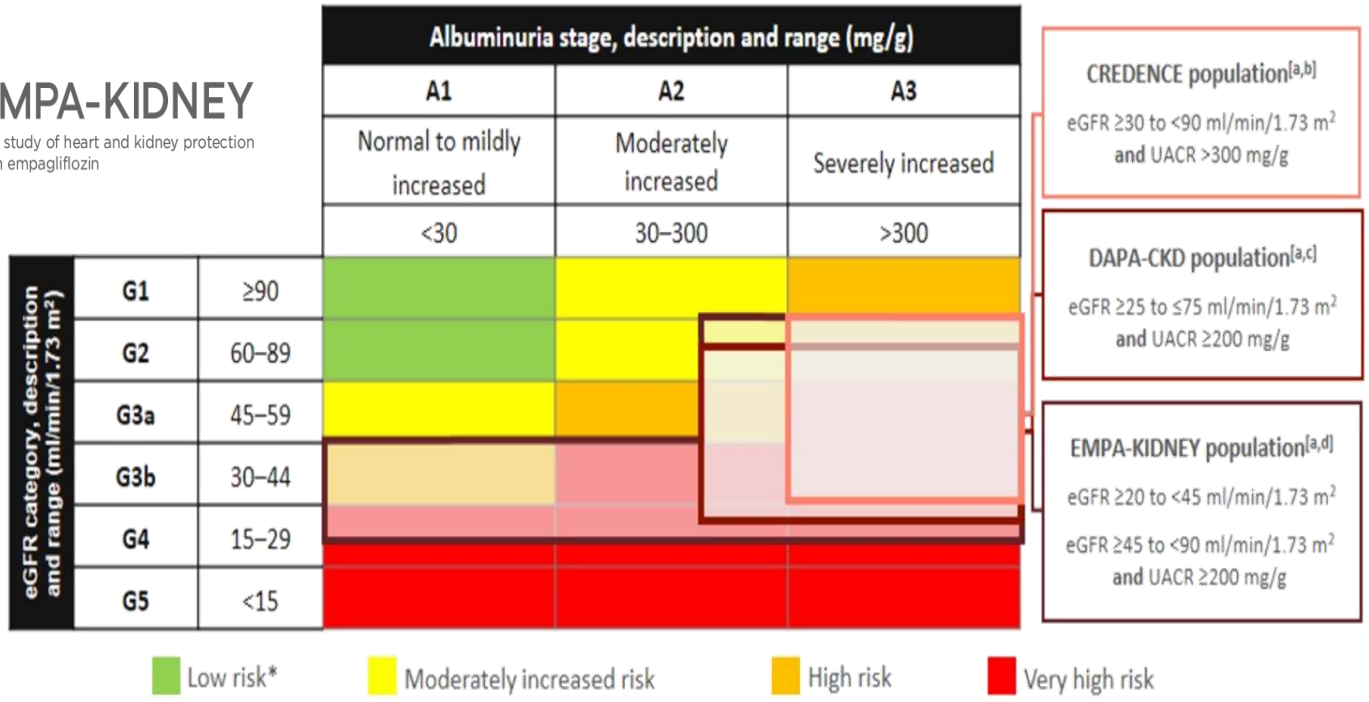
EMPEROR-Reduced Achieved All Three Hierarchically Specified Endpoints at P < 0.001

	**Primary Endpoint** Composite of cardiovascular death or heart failure hospitalization	**Achieved** **P < 0.001**
	**First Secondary Endpoint** Total (first and recurrent heart failure hospitalizations)	**Achieved** **P < 0.001**
	**Second Secondary Endpoint** Slope of decline in glomerular filtration rate over time	**Achieved** **P < 0.001**

Also achieved success on composite renal endpoint, KCCQ clinical summary score, and total number of hospitalizations for any reason (all nominal P < 0.01)

EMPA-KIDNEY is enrolling a broad CKD population

EMPA-KIDNEY
The study of heart and kidney protection with empagliflozin



*If no other markers of kidney disease, no CKD.
a. Levin A. *Kidney Int Suppl* 2013;3:1; b. Jardine MJ et al. *Am J Nephrol* 2017;46:462; c. ClinicalTrials.gov. NCT03036150; d. ClinicalTrials.gov. NCT03594110.

2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases

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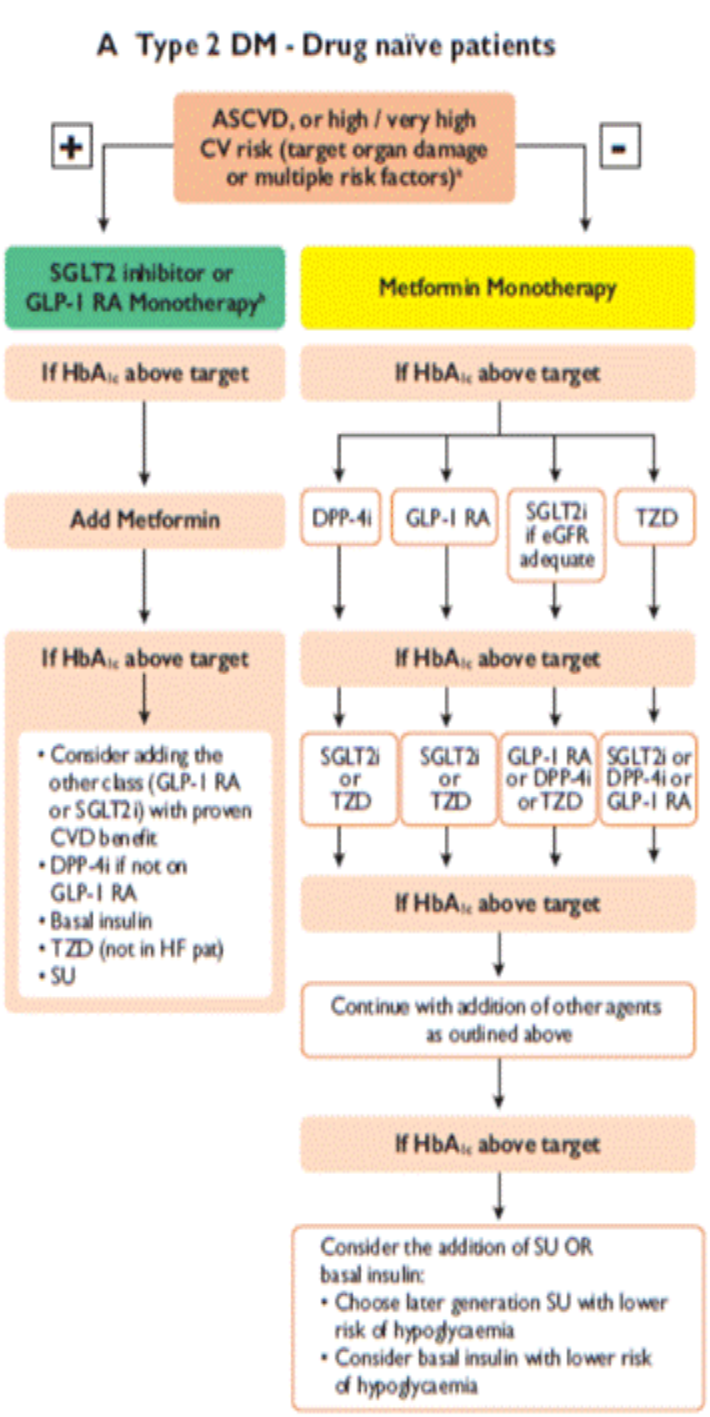

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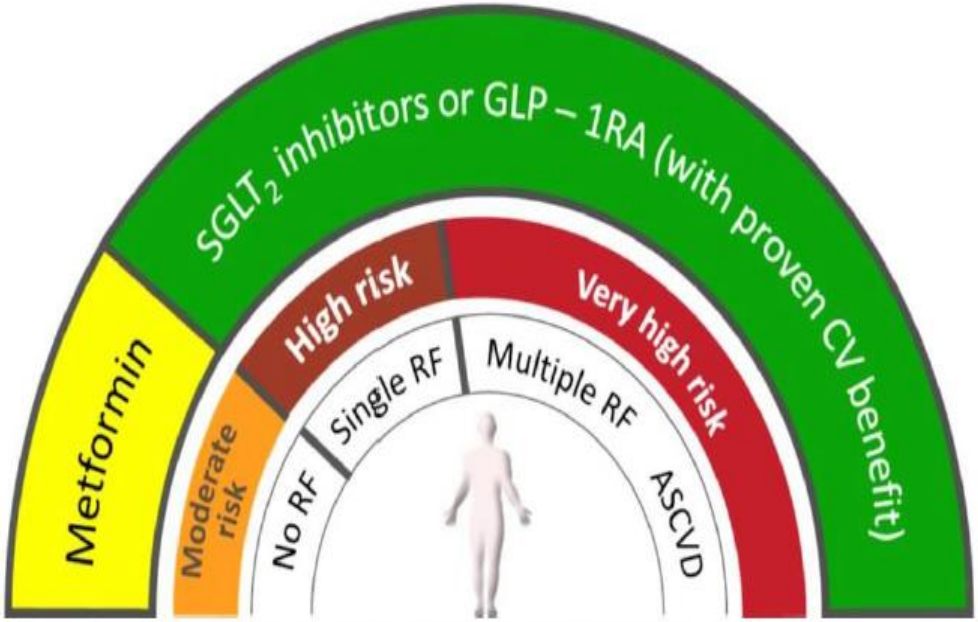
Treatment algorithm in patients with T2DM and ASCVD or high/very high CV risk - drug naïve

ESC Guidelines on Diabetes, pre-diabetes and cardiovascular diseases in collaboration with EASD (European Heart Journal 2019 - doi/10.1093/eurheartj/ehz486)

Cardiovascular risk stratification and baseline treatment recommendation to reduce cardiovascular risk in patients with T_2DM mellitus



Very high risk	Patients with DM **and** established CVD **or** other target organ damage[b] **or** three or more major risk factors **or** early onset T1DM of long duration (>20 years)
High risk	Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor
Moderate risk	Young patients (T1DM aged <35 years or T2DM aged <50 years) with DM duration <10 years, without other risk factors

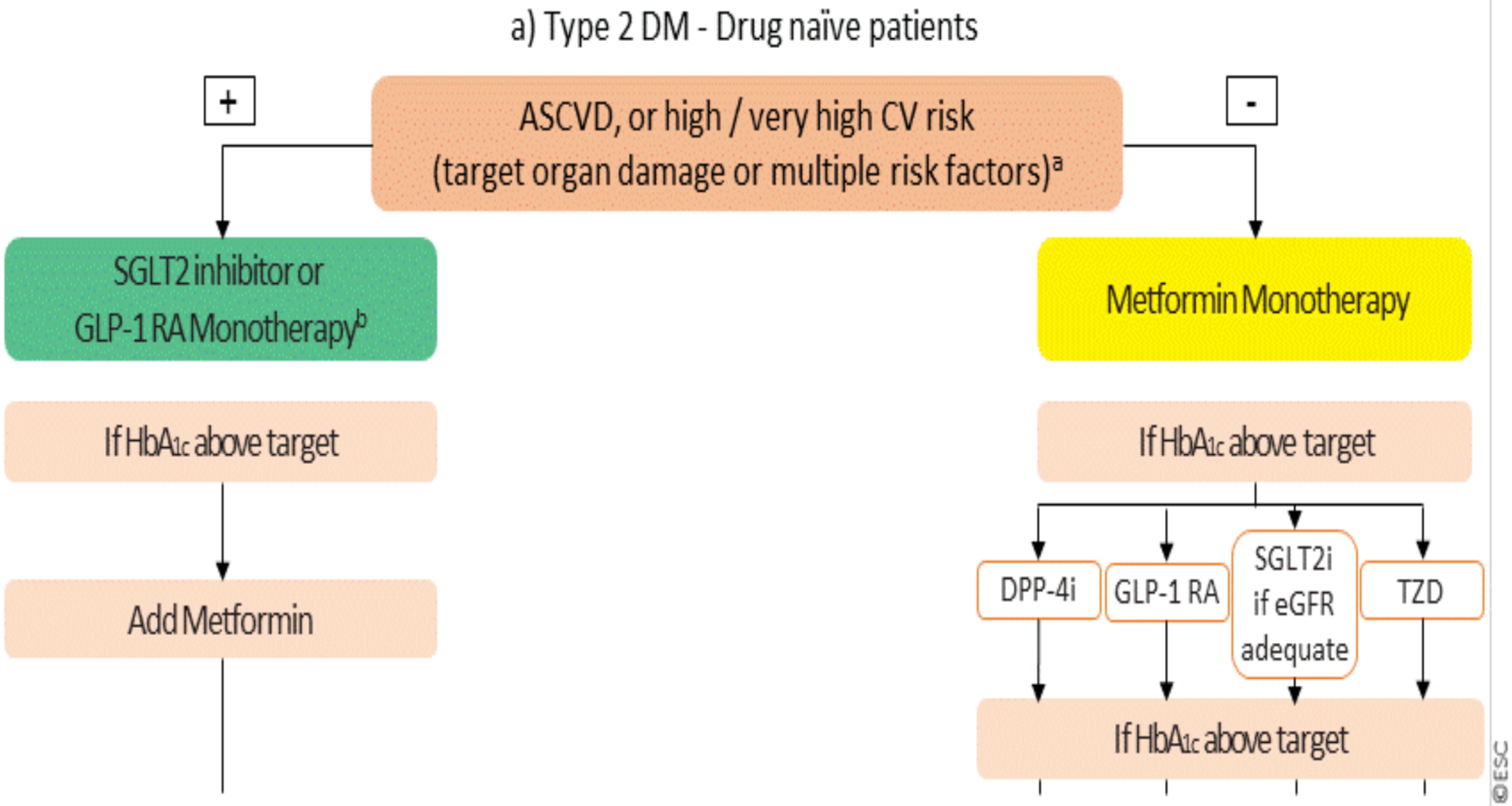
Marx N. *European Heart Journal*, ehaa174,

https://doi.org/10.1093/eurheartj/ehaa174

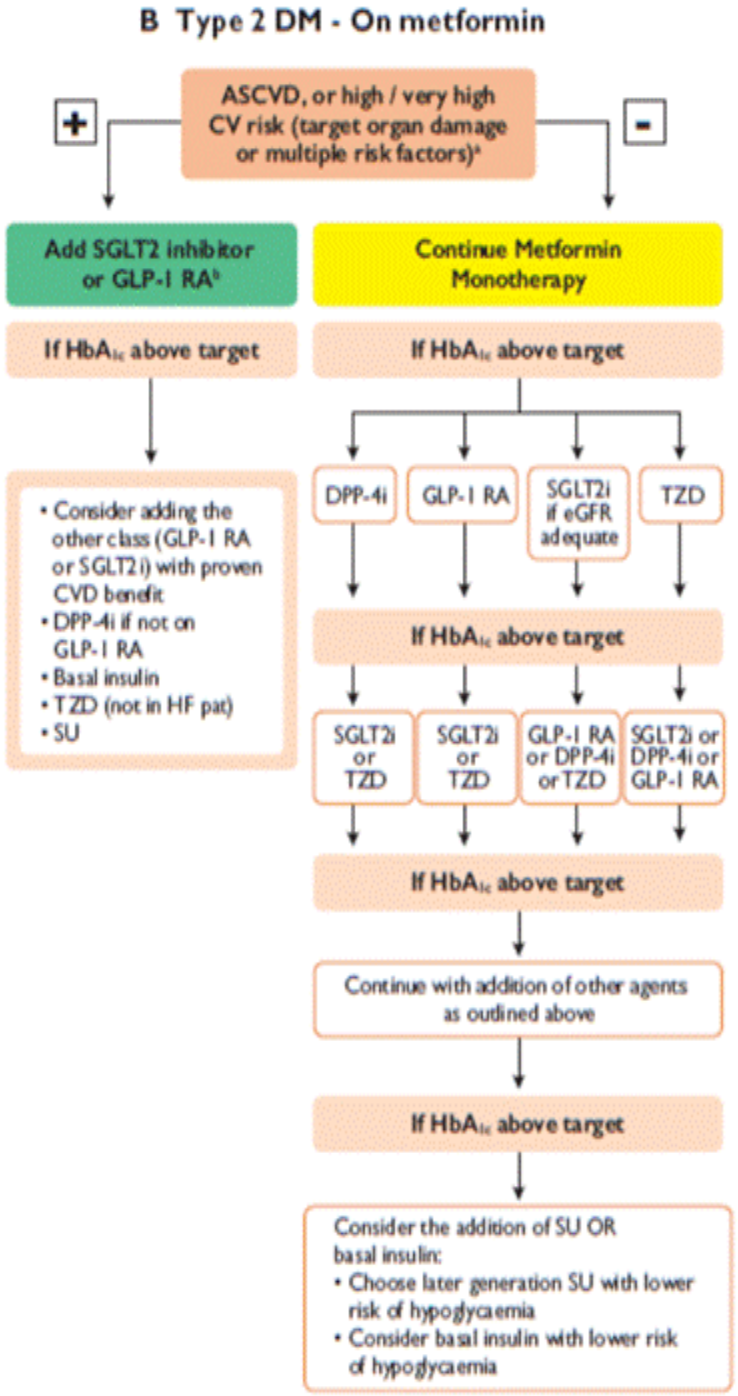
B: Proteinuria, renal impairment defined as eGFR<30 mL/min/1.73 m2, left ventricular hypertrophy, or retinopathy.
C:Age, hypertension, dyslipidemia, smoking, obesity

Treatment algorithm in patients with T2DM and ASCVD or high/very high CV risk - drug naïve (1)

ESC European Society of Cardiology



ESC Guidelines on Diabetes, pre-diabetes and cardiovascular diseases in collaboration with EASD (European Heart Journal 2019 - doi/10.1093/eurheartj/ehz486)



ESC
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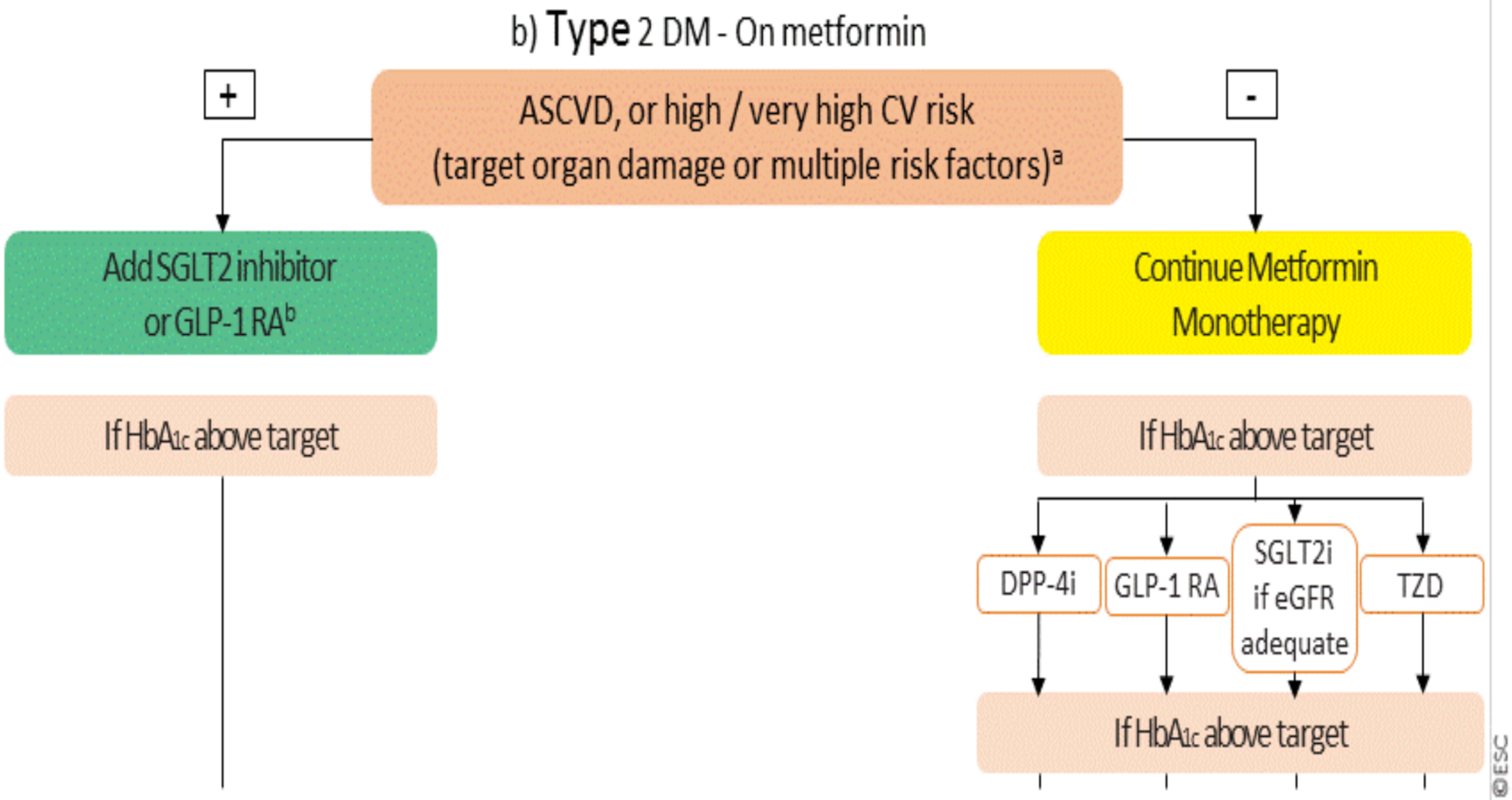
Treatment algorithm in patients with T2DM and ASCVD or high/very high CV risk - metformin treated

ESC Guidelines on Diabetes, pre-diabetes and cardiovascular diseases in collaboration with EASD (European Heart Journal 2019 - doi/10.1093/eurheartj/ehz486)

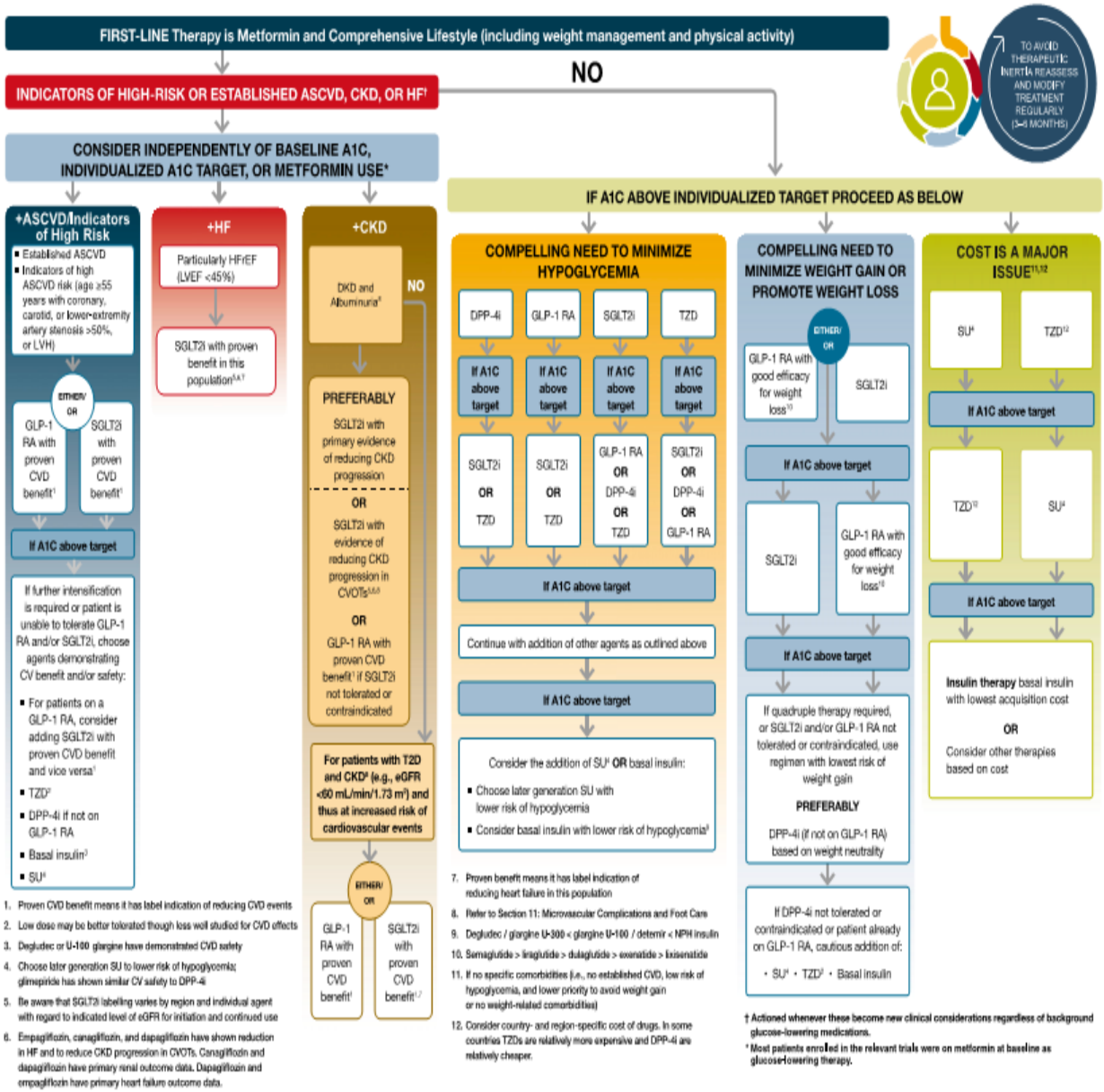
Treatment algorithm in patients with T2DM and ASCVD or high/very high CV risk - metformin treated (1)

ESC European Society of Cardiology



ESC Guidelines on Diabetes, pre-diabetes and cardiovascular diseases in collaboration with EASD (European Heart Journal 2019 - doi/10.1093/eurheartj/ehz486)

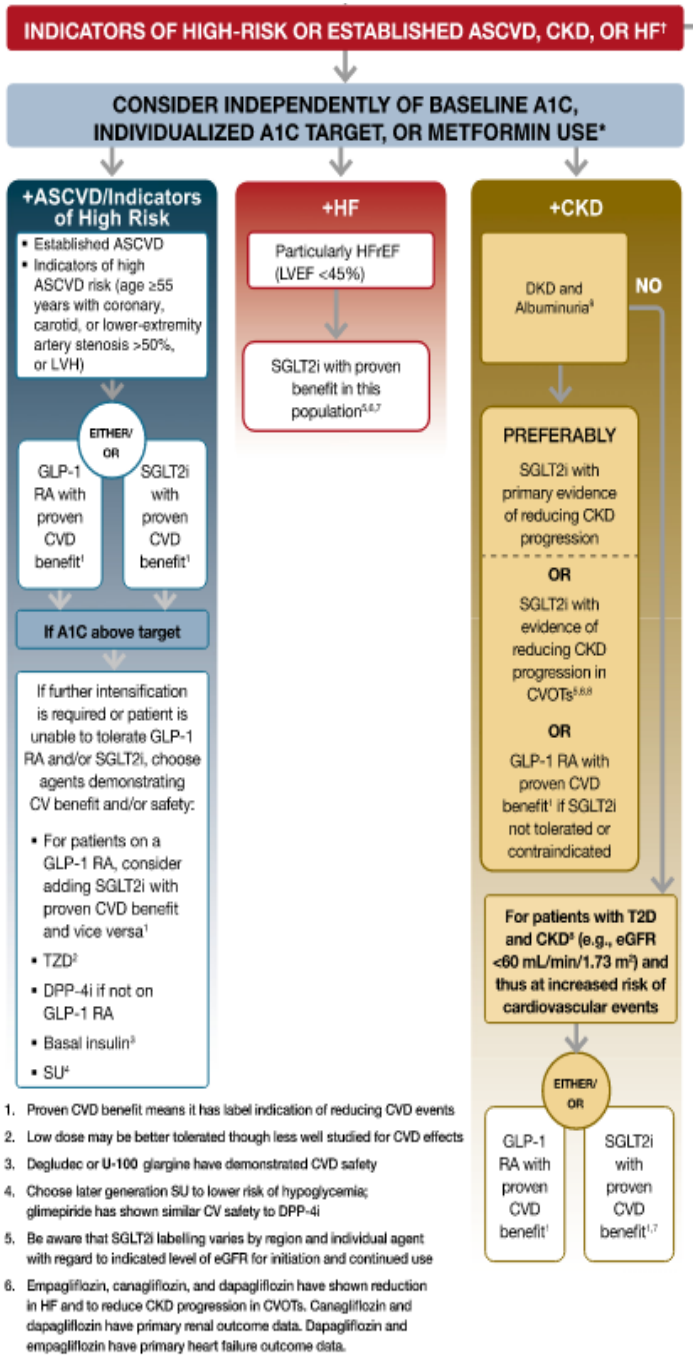
2021



1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though loss well studied for CVD effects
3. Degludec or U-100 glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.
7. Proven benefit means it has label indication of reducing heart failure in this population
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin
10. Semaglutide > lixisenatide > dulaglutide > exenatide > lixisenatide
11. 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)
12. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper.

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

* Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.



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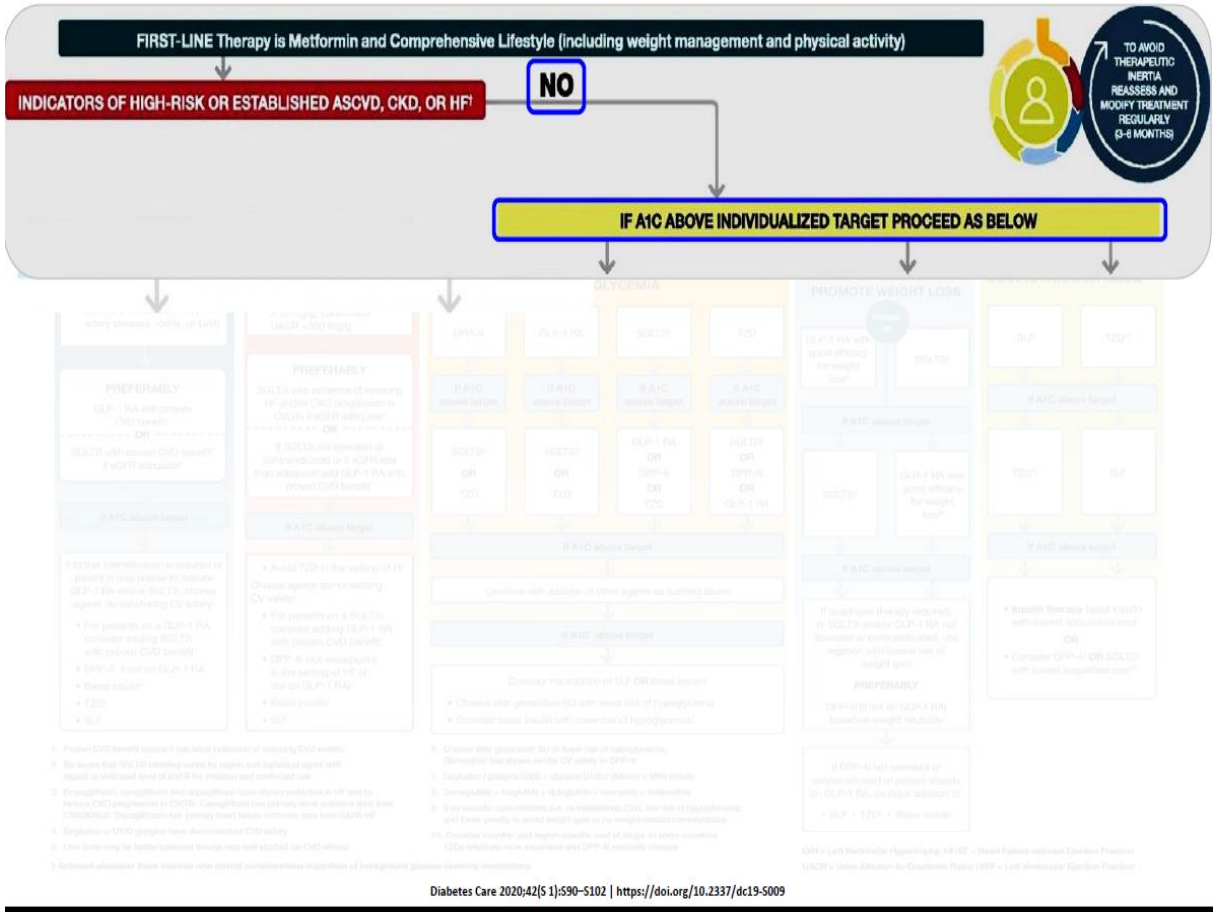
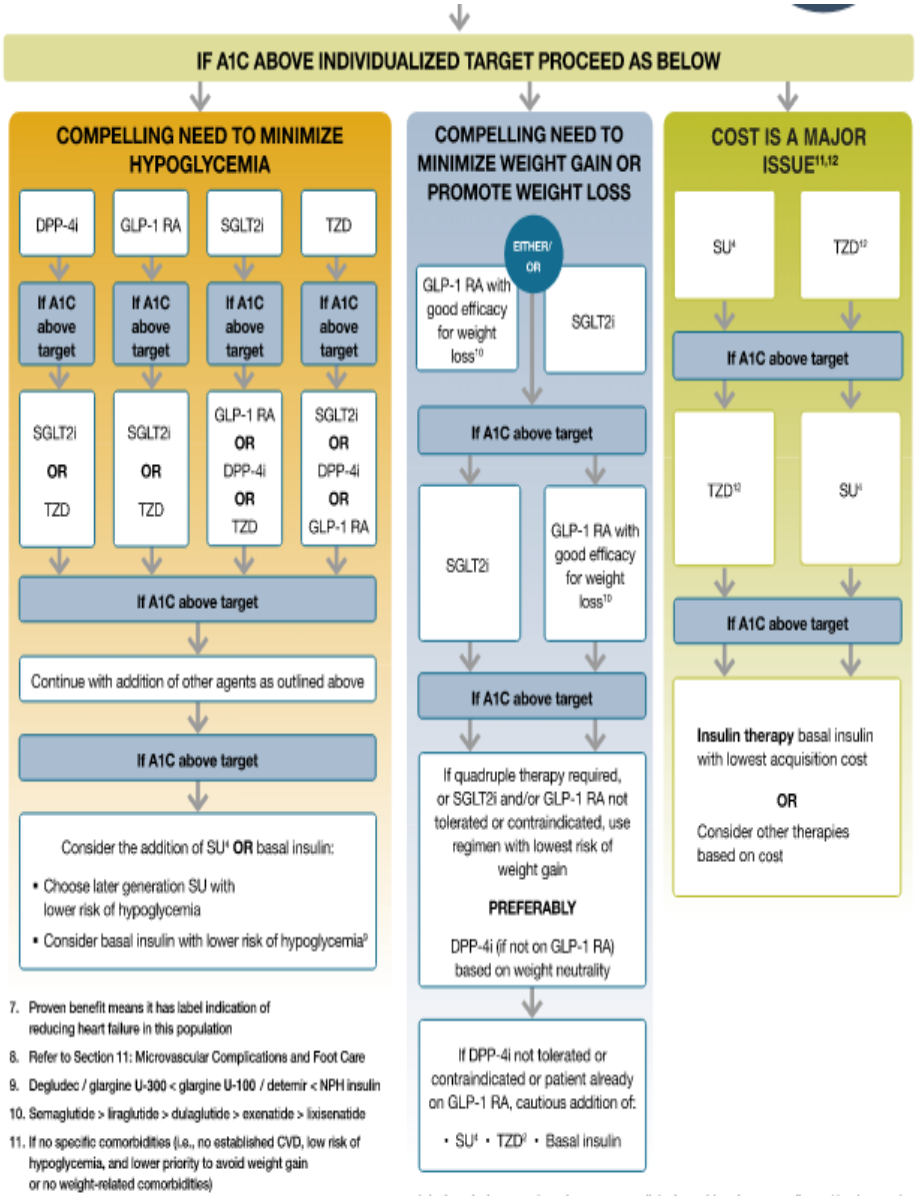


Diabetes Care 2020;42(S 1):S90–S102 | https://doi.org/10.2337/dc19-S009



7. Proven benefit means it has label indication of reducing heart failure in this population
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin
10. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
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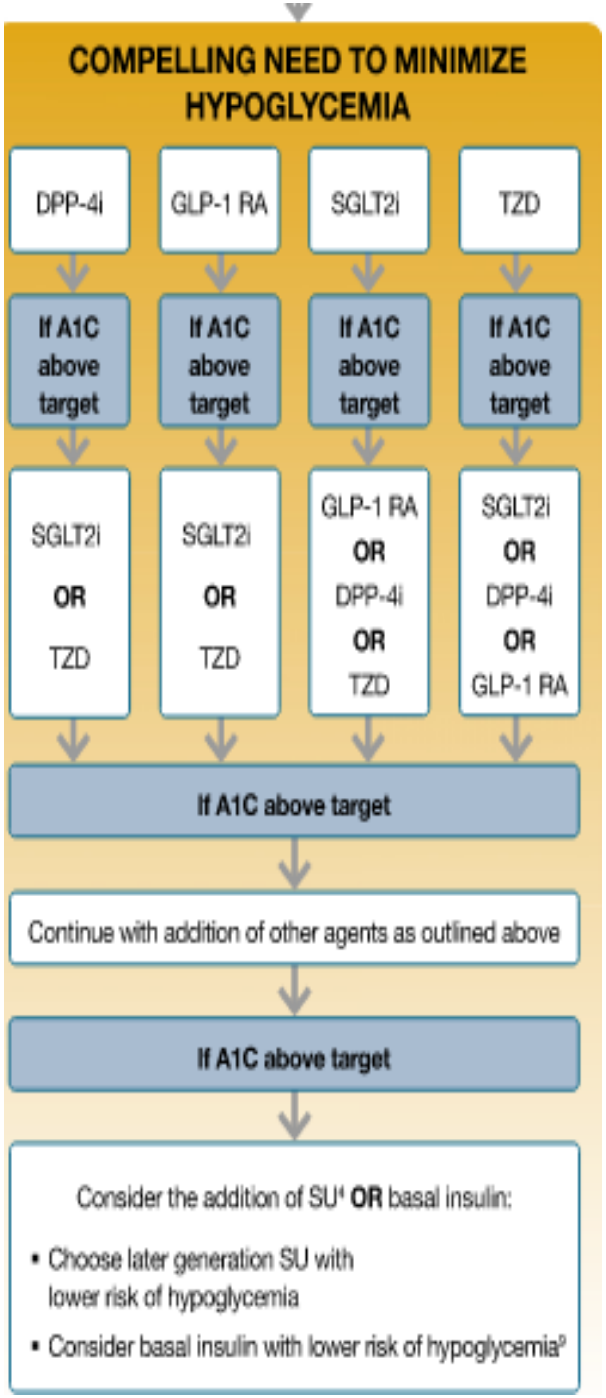
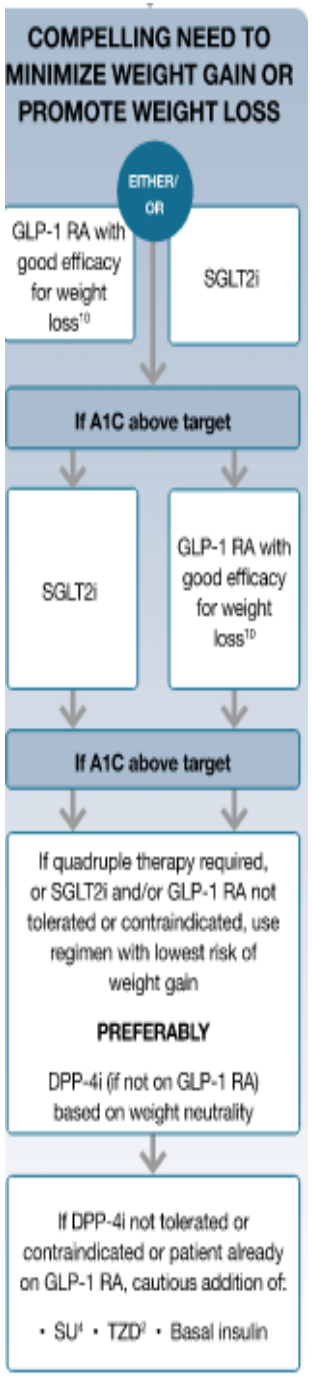
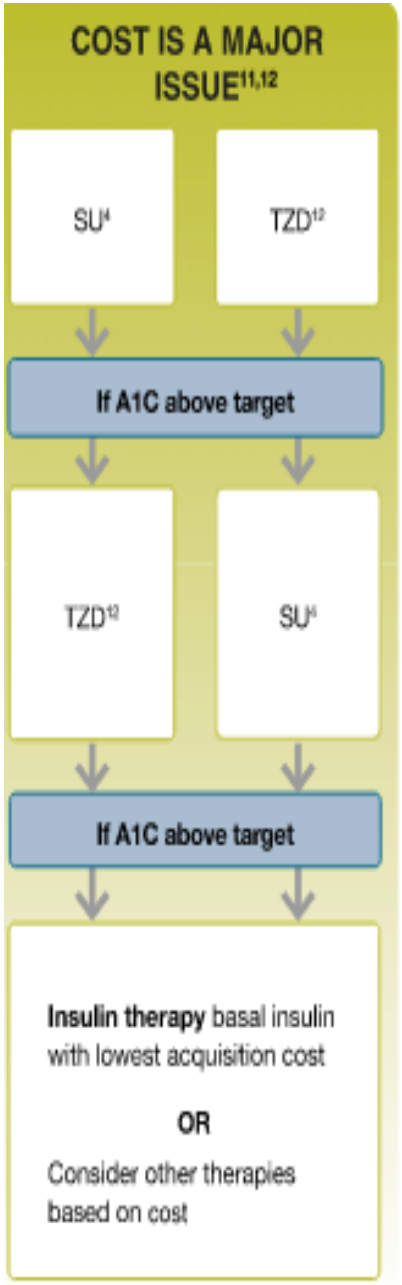

COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA
DPP-4i
GLP-1 RA
SGLT2i
TZD
If A1C above target
If A1C above target
If A1C above target
If A1C above target
SGLT2i OR TZD
SGLT2i OR TZD
GLP-1 RA OR DPP-4i OR TZD
SGLT2i OR DPP-4i OR GLP-1 RA
If A1C above target
Continue with addition of other agents as outlined above
If A1C above target
Consider the addition of SU[4] OR basal insulin:
• Choose later generation SU with lower risk of hypoglycemia
• Consider basal insulin with lower risk of hypoglycemia[9]


COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS
EITHER/ OR
GLP-1 RA with good efficacy for weight loss[10]
SGLT2i
If A1C above target
SGLT2i
GLP-1 RA with good efficacy for weight loss[10]
If A1C above target
If quadruple therapy required, or SGLT2i and/or GLP-1 RA not tolerated or contraindicated, use regimen with lowest risk of weight gain
PREFERABLY
DPP-4i (if not on GLP-1 RA) based on weight neutrality
If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:
• SU[4] • TZD[7] • Basal insulin


COST IS A MAJOR ISSUE[11,12]
SU[4]
TZD[12]
If A1C above target
TZD[12]
SU[4]
If A1C above target
Insulin therapy basal insulin with lowest acquisition cost
OR
Consider other therapies based on cost

EMPAVER - Highlights

- **Oral: in the morning, with or without food**
- **10 mg once daily; may increase to 25 mg once daily**

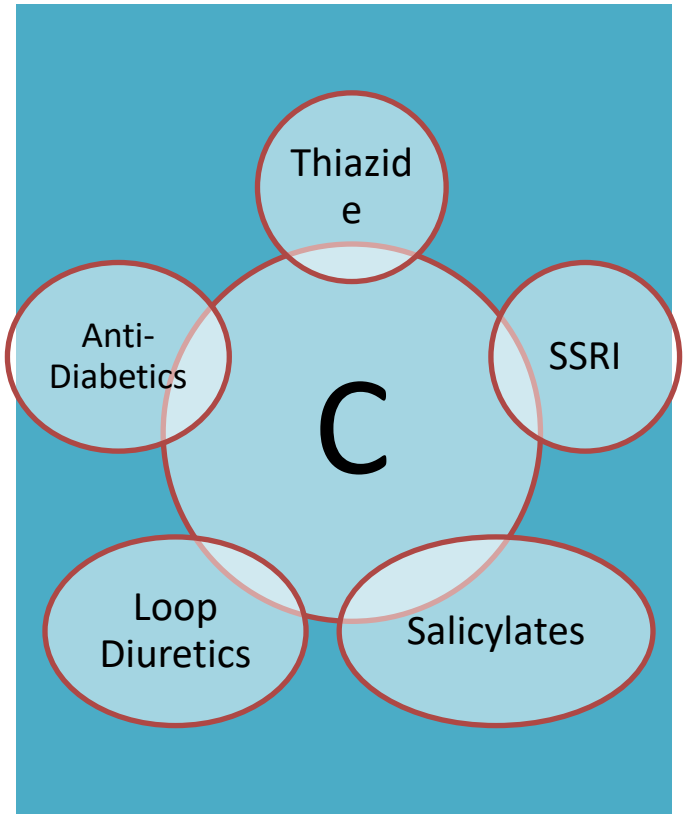
Dosing in Renal impairment

- **eGFR ≥45:** No dosage adjustment necessary.
- **eGFR 30 to <45:** Empagliflozin in diabetic patients with CVD and renal impairment (eGFR 30 to <60) may be associated with decreases in incident or worsening nephropathy as well as decreased cardiovascular mortality.
- **eGFR <30:** Use is contraindicated.
- **ESRD, dialysis:** Use is contraindicated.

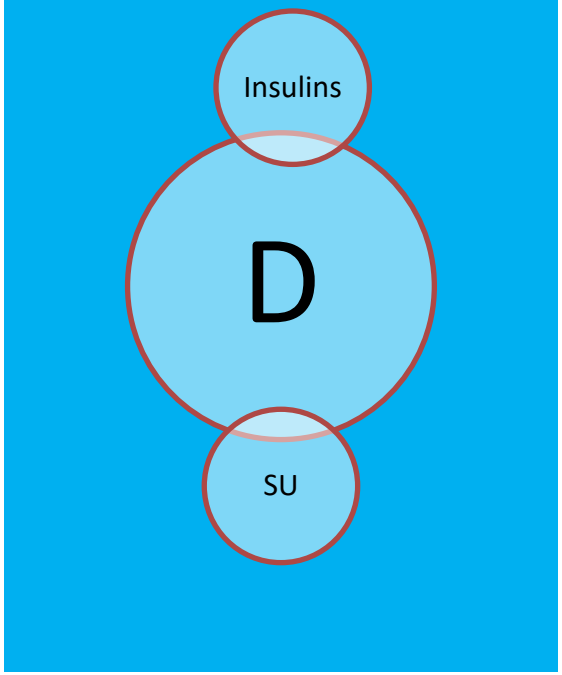
Dosing in Hepatic impairment

- No dose adjustment necessary

Drug interaction



Reduced dose of insulin and/or insulin secretagogues may be needed



Risk C: Monitor therapy Risk D: Consider therapy modification

Summary

- SGLT2 inhibitors were developed and approved:
- As T2D therapies with a novel glucose lowering mechanism
- For People with reasonably good kidney function

- The **EMPA-REG** OUTCOME was the first of a series of SGLT2i trials that changed treatment guidelines for **endocrinologists, cardiologists and nephrologists**

- Today➔ SGLT2 inhibitors have moved:
- **Reduce CV risk & Improve CV outcome**
- **a solid kidney drug , "highly efficient"** in individuals with poor kidney function

- SGLT2 inhibitors have a **significant and clinically relevant** impact across the spectrum of kidney function in DKD/CKD

Thanks for your attention

ESC European Society of Cardiology

European Journal of Heart Failure (2021) **23**, 68–78
doi:10.1002/ejhf.2066

RESEARCH ARTICLE

Effects of empagliflozin on renal sodium and glucose handling in patients with acute heart failure (EMPA-RESPONSE-AHF)

Eva M. Boorsma[1†], Joost C. Beusekamp[1†], Jozine M. ter Maaten[1], Sylwia M. Figarska[1], A.H. Jan Danser[2], Dirk J. van Veldhuisen[1], Peter van der Meer[1], Hiddo J.L. Heerspink[1], Kevin Damman[1], and Adriaan A. Voors[1*]

[1]University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; and [2]Department of Internal Medicine, Division of Pharmacology, Erasmus University Medical Center Rotterdam, Rotterdam, The Netherlands

Received 12 September 2020; revised 1 November 2020; accepted 23 November 2020; online publish-ahead-of-print 16 December 2020

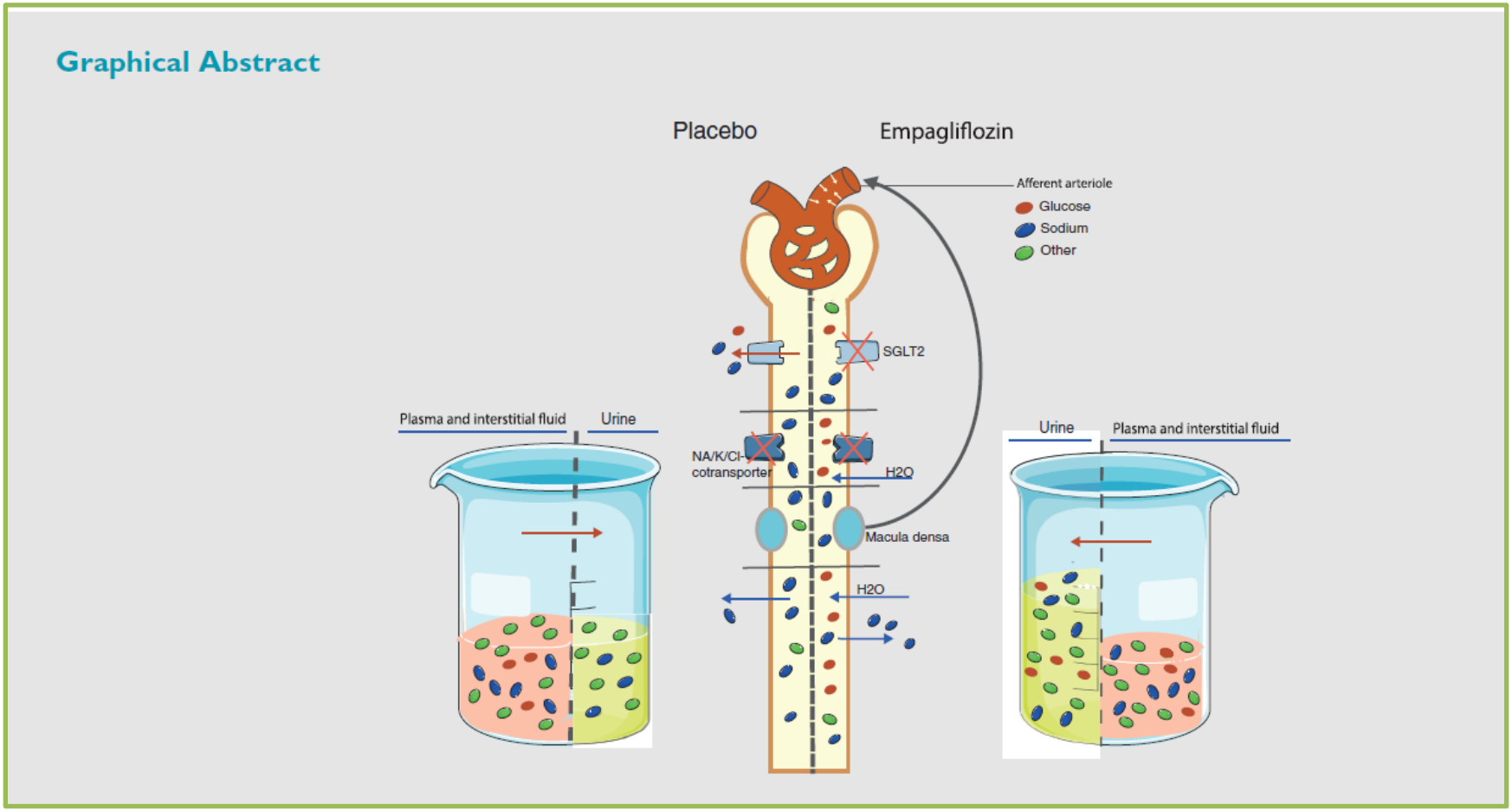
- This study was sub-study EMPA-RESPONSE-AHF.
- within 24 h of an acute HF admission to either empagliflozin
- 10 mg/day (*n* = 40) or placebo (*n* = 39) for 30 days.

- daily Na + Glu during the first 96 h and at day 30.
- 76 (range 38–89) years old , 33% had DM.
- Loop diuretics during the first 96 h was similar in both groups.

Empagliflozin

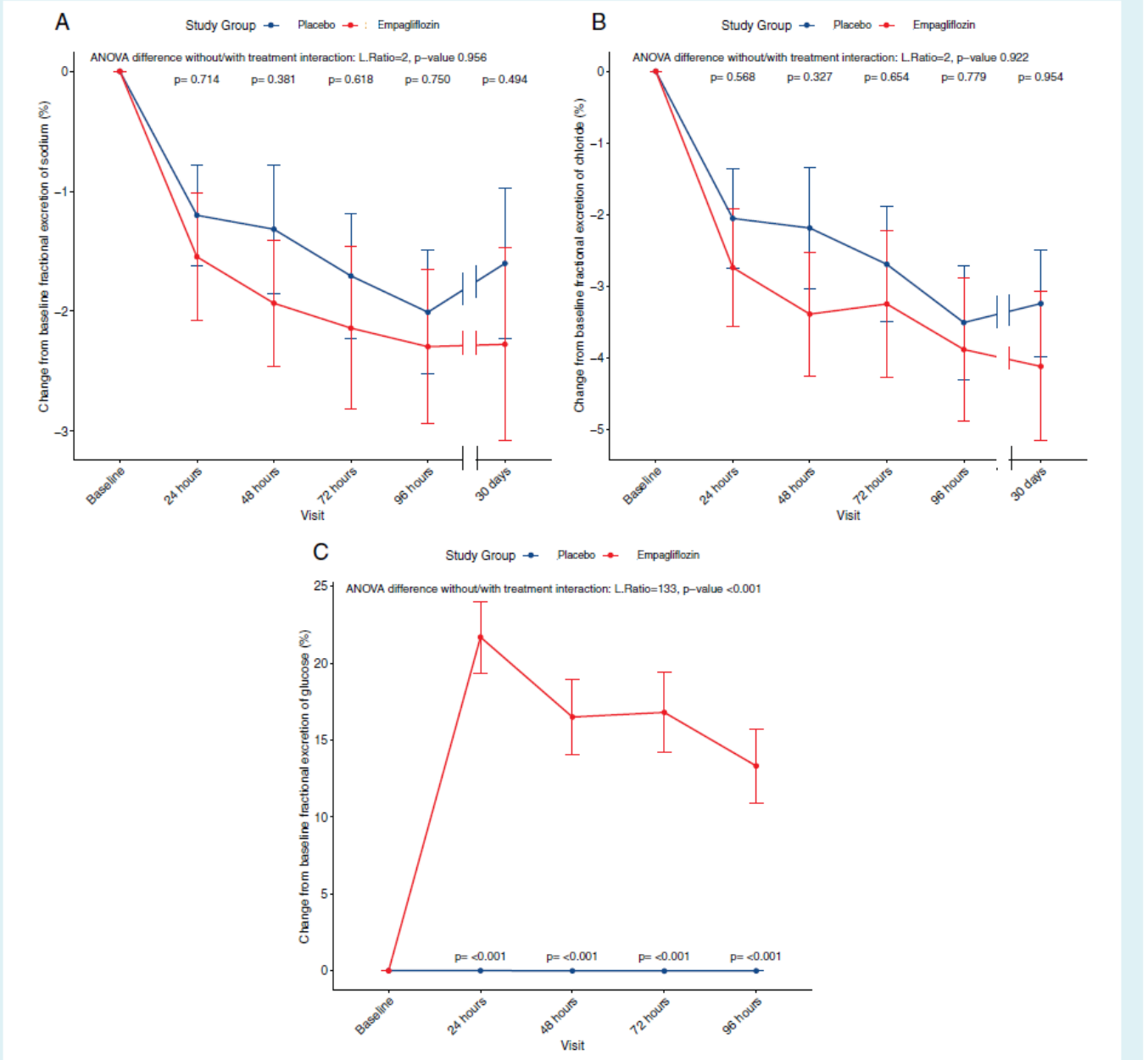
- increased fractional glucose excretion with a peak after 24 h
- without affecting plasma glucose concentration,
- fractional Na and Cl excretion and urinary osmolality remained unchanged (*P* >0.3 for all).
- Increased plasma osmolality (delta osmolality at 72 h: 5±8 vs. 2±5 mOsm/kg; *P* = 0.049).
- there was an early decline in estimated GFR with empagliflozin vs. placebo which recovered within 30 days.

changes in urinary and plasma volume and osmolality



SGLT2- inhibition ➔ Glu + more water in nephrons ➔ increased electrolyte free water Excretion➔ plasma osmolality increased + total volume of plasma and interstitial fluid is decreased.

excretion of sodium (*A*), chloride (*B*) glucose (*C*)

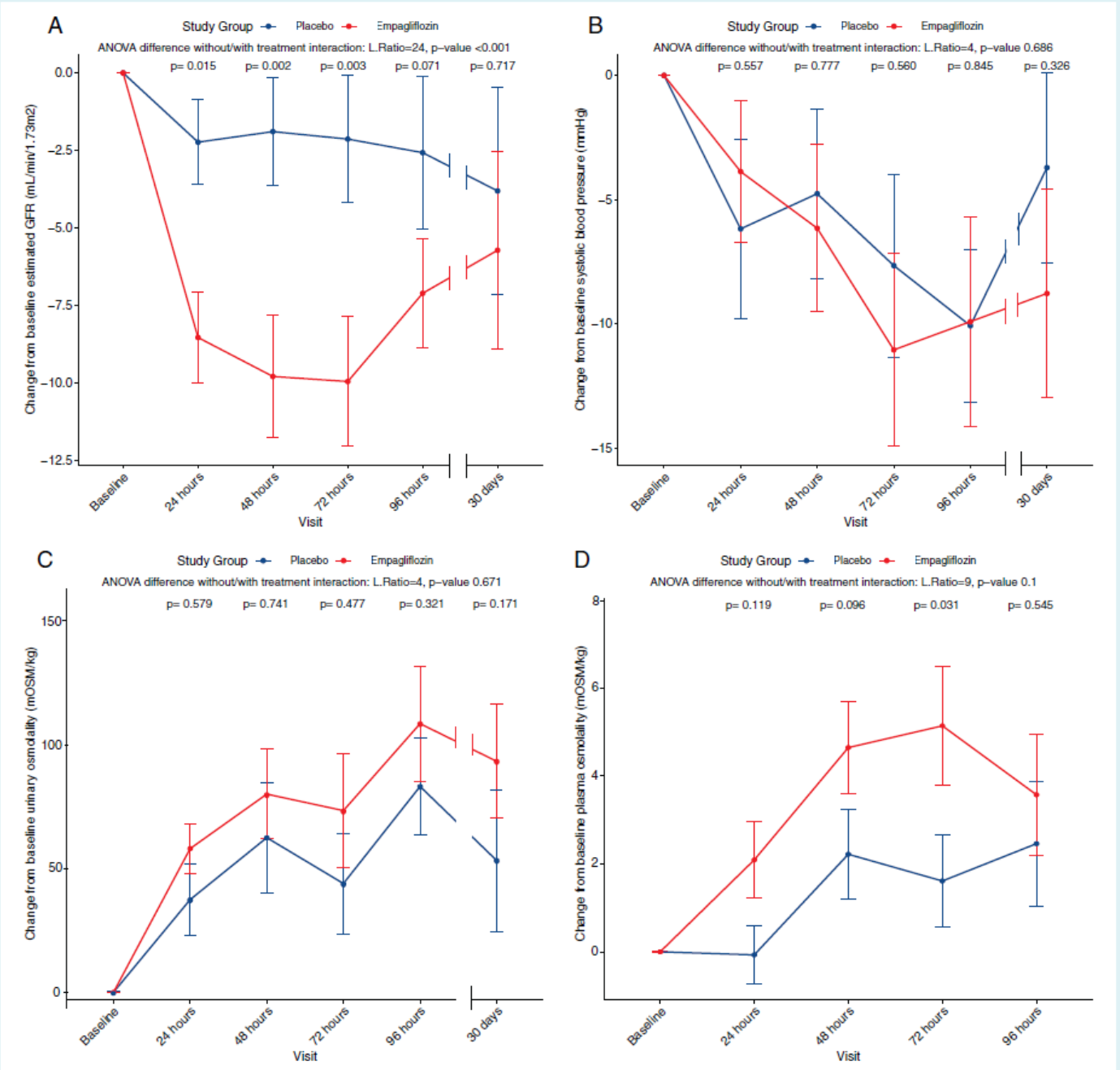


GFR (*A*),

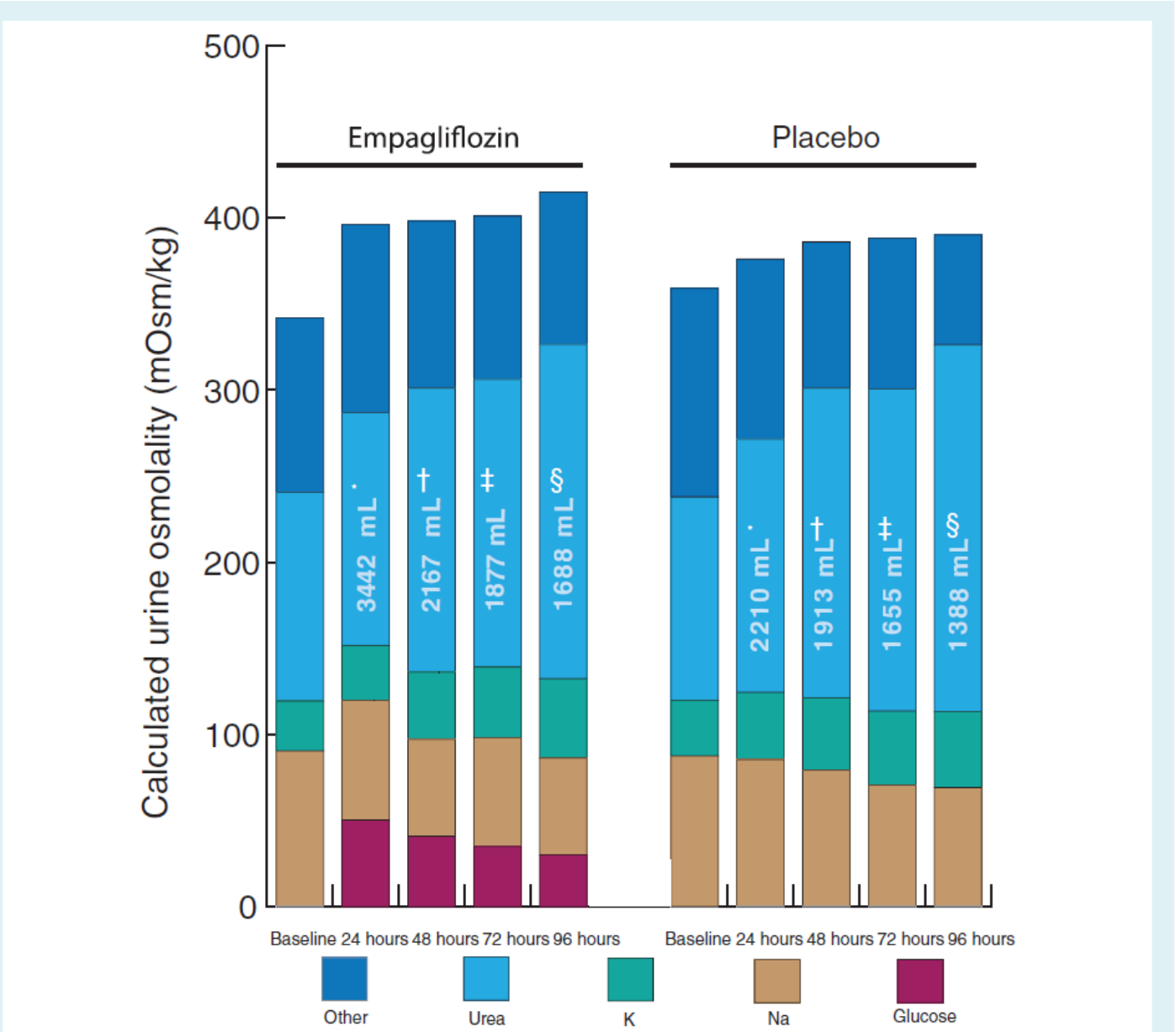
systolic BP (*B*),

urine osmolality (*C*)

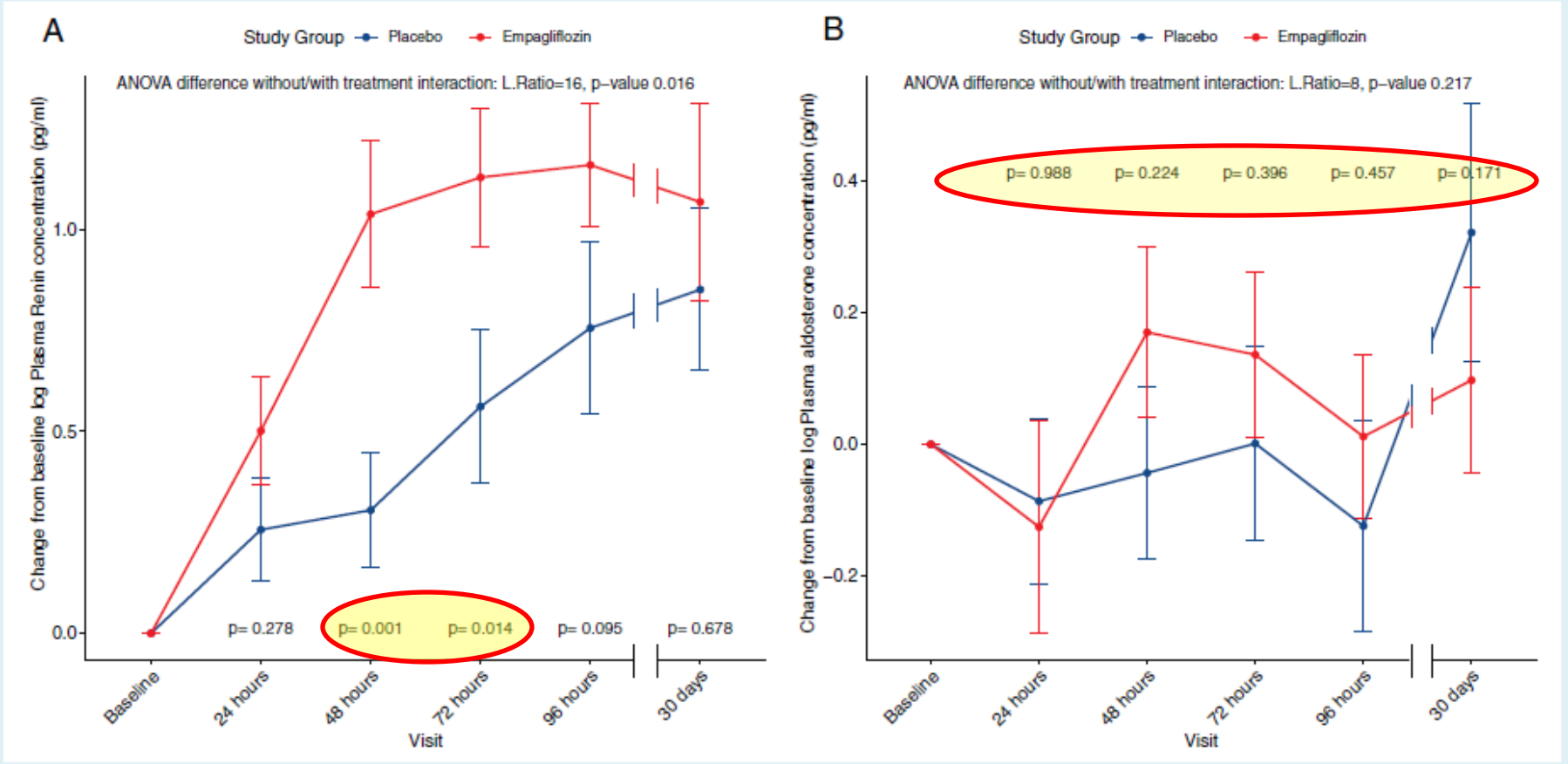
plasma osmolality (*D*)



Composites of urinary molecules making up osmolality



Delta renin (*A*) - Delta aldosterone (*B*)



In acute HF ➔ empagliflozin

- increased fractional glucose excretion and plasma osmolality,
- without affecting fractional sodium excretion or urine osmolality
- temporary decline in estimated glomerular filtration rate.

empagliflozin ➔ stimulates osmotic diuresis through increased glycosuria rather than natriuresis in patients with acute HF.

JACC: Cardiovascular Imaging
Volume 14, Issue 2, February 2021, Pages 393-407

Original Research

Empagliflozin Ameliorates Diastolic Dysfunction and Left Ventricular Fibrosis/Stiffness in Nondiabetic Heart Failure: A Multimodality Study

Carlos G. Santos-Gallego MD, Juan Antonio Requena-Ibanez MD, Rodolfo San Antonio MD, Alvaro Garcia-Ropero MD, Kiyotake Ishikawa MD, Shin Watanabe MD, Belen Picatoste PhD, Ariana P. Vargas-Delgado MD, Eduardo J. Flores-Umanzor MD, Javier Sanz MD, Valentin Fuster MD, PhD, Juan J. Badimon PhD

effect of empagliflozin on diastolic function in a nondiabetic heart failure with reduced ejection fraction (HFrEF) scenario and on the pathways causing diastolic dysfunction.

empagliflozin

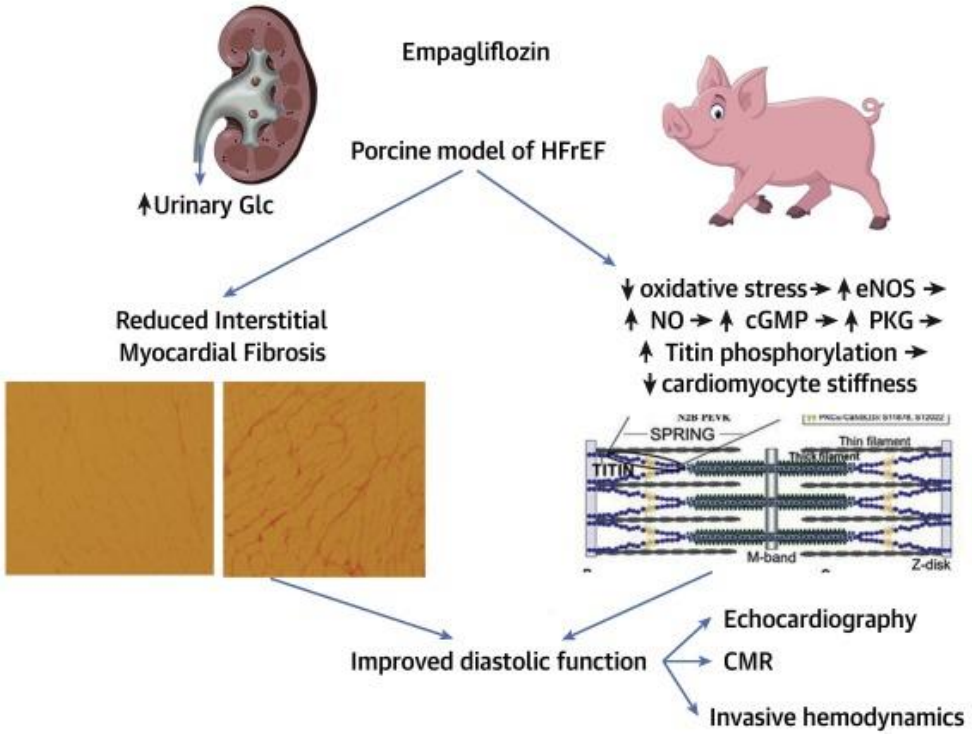
- ameliorates adverse cardiac remodeling,
- enhances myocardial energetics,
- improves left ventricular systolic function in a nondiabetic porcine model of HF.

Whether empagliflozin also improves diastolic function?

- Hypothetically, empagliflozin would improve diastolic function in HF mediated both by a reduction in interstitial myocardial fibrosis and an improvement in cardiomyocyte stiffness (titin phosphorylation).

- HF was induced in nondiabetic pigs by 2-h balloon occlusion of proximal left anterior descending artery

CENTRAL ILLUSTRATION: Empagliflozin Improves Sarcomere Relaxation in Isolated Cardiomyocytes



Santos-Gallego, C.G. et al. J Am Coll Cardiol Img. 2021;14(2):393–407.

significantly improved diastolic function at 2 months

- TTE➔ (higher e' and color M-mode propagation velocity, lower E/e' ratio, myocardial performance Tei index, isovolumic relaxation time, and left atrial size) + strain imaging (strain imaging diastolic index, strain rate at isovolumic relaxation time and during early diastole, and untwisting),

- CMR ➔ (higher peak filling rate, larger first filling volume).

- **Invasive hemodynamics** ➔ improved **diastolic function** (better peak LV pressure rate of decay (–dP/dt), shorter **Tau**, lower **end-diastolic pressure-volume** relationship (EDPVR), and reduced **filling** pressures).

- Empagliflozin reduced interstitial myocardial fibrosis at the imaging, histological and molecular level.

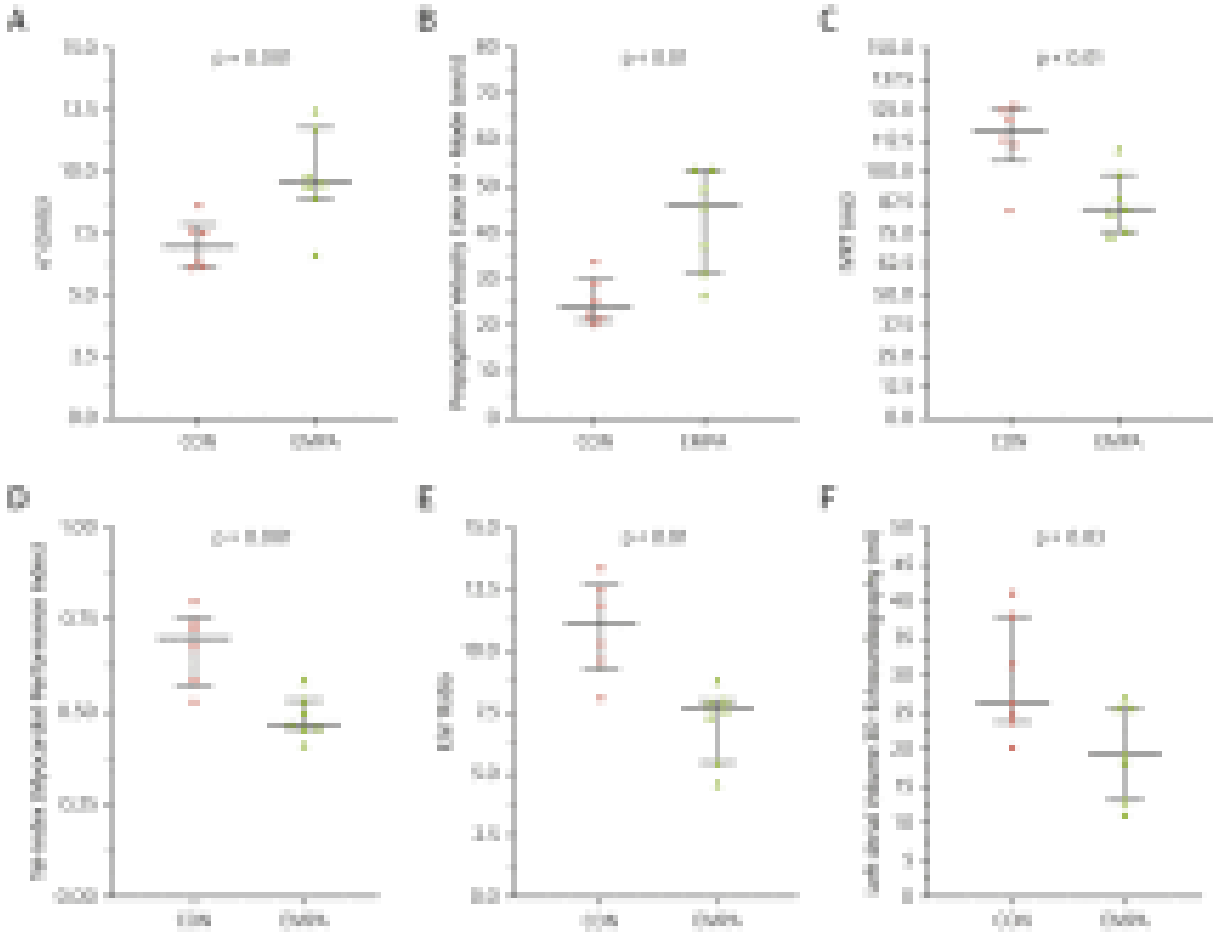
- Empagliflozin improved nitric oxide signaling (endothelial nitric oxide synthetase [eNOS] activity, nitric oxide [NO] availability, cyclic guanosine monophosphate (cGMP) content, protein kinase G [PKG] signaling)

- enhanced titin phosphorylation (which is responsible for cardiomyocyte stiffness).

- isolated cardiomyocytes exhibited better relaxation in empagliflozin-treated animals. Myocardial consumption of glucose and ketone bodies negatively and positively correlated with diastolic function, respectively.

Empagliflozin

- ameliorates diastolic function in a nondiabetic HF porcine model,
- mitigates histological and molecular remodeling,
- reduces both left ventricle and cardiomyocyte stiffness.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