UNIVERSITÀ DEL PIEMONTE ORIENTALE

AOU AL
Azienda Ospedaliero-Universitaria
di ALESSANDRIA

SGLT2 INIBITORI: SOLI O BEN ACCOMPAGNATI?

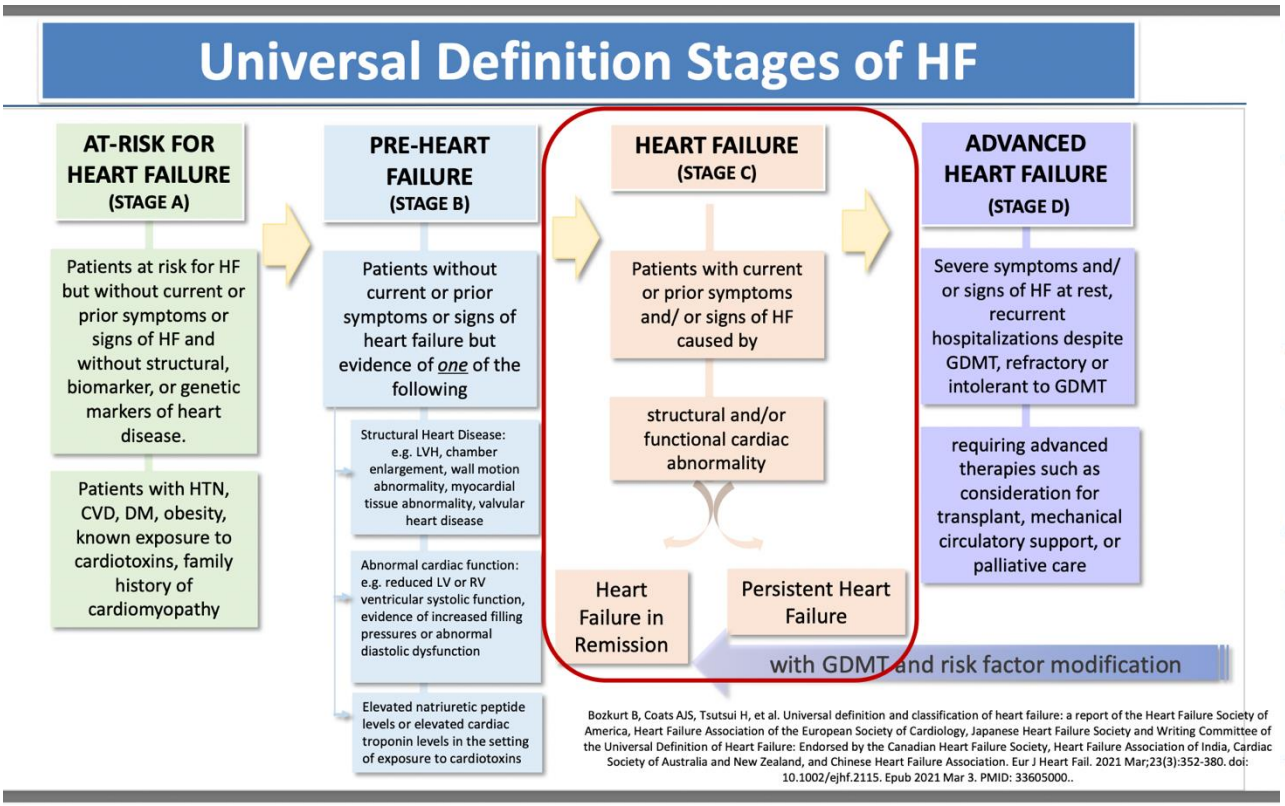
IL CUORE INFRANTO

Gioel Gabrio Secco, MD PhD
Head of Interventional Cardiology Unit – AOU Alessandria
University of Eastern Piedmont

dichiara di NON aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

Heart failure: definition and epidemiology



HF with reduced EF (HFrEF):

- HF with LVEF ≤ 40%

HF with mildly reduced EF (HFmrEF):

- HF with LVEF 41-49%

HF with preserved EF (HFpEF):

- HF with LVEF ≥ 50%

HF with improved EF (HFimpEF):

- HF with a baseline LVEF ≤ 40%, a ≥ 10 point increase from baseline LVEF, and a second measurement of LVEF > 40%

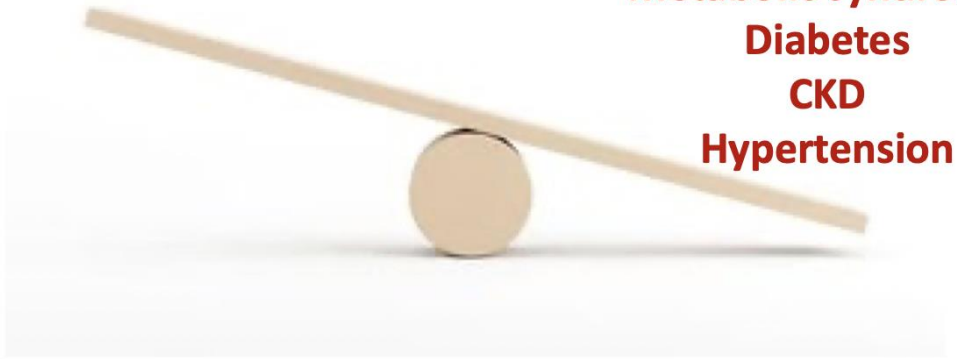
Figure 3. New classification of HF according to LVEF.

ESC Guidelines 2021 HF

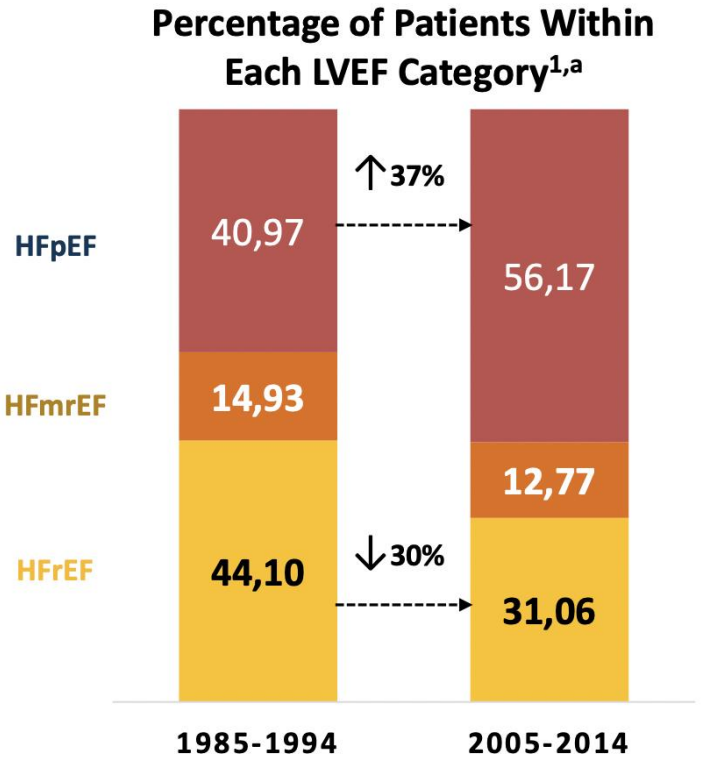
Heart failure: definition and epidemiology

Rising Prevalence of HFpEF

LV dysfunction / HF
post-MI
Prevalence of CAD



Aging
Obesity,
Metabolic syndrome,
Diabetes
CKD
Hypertension

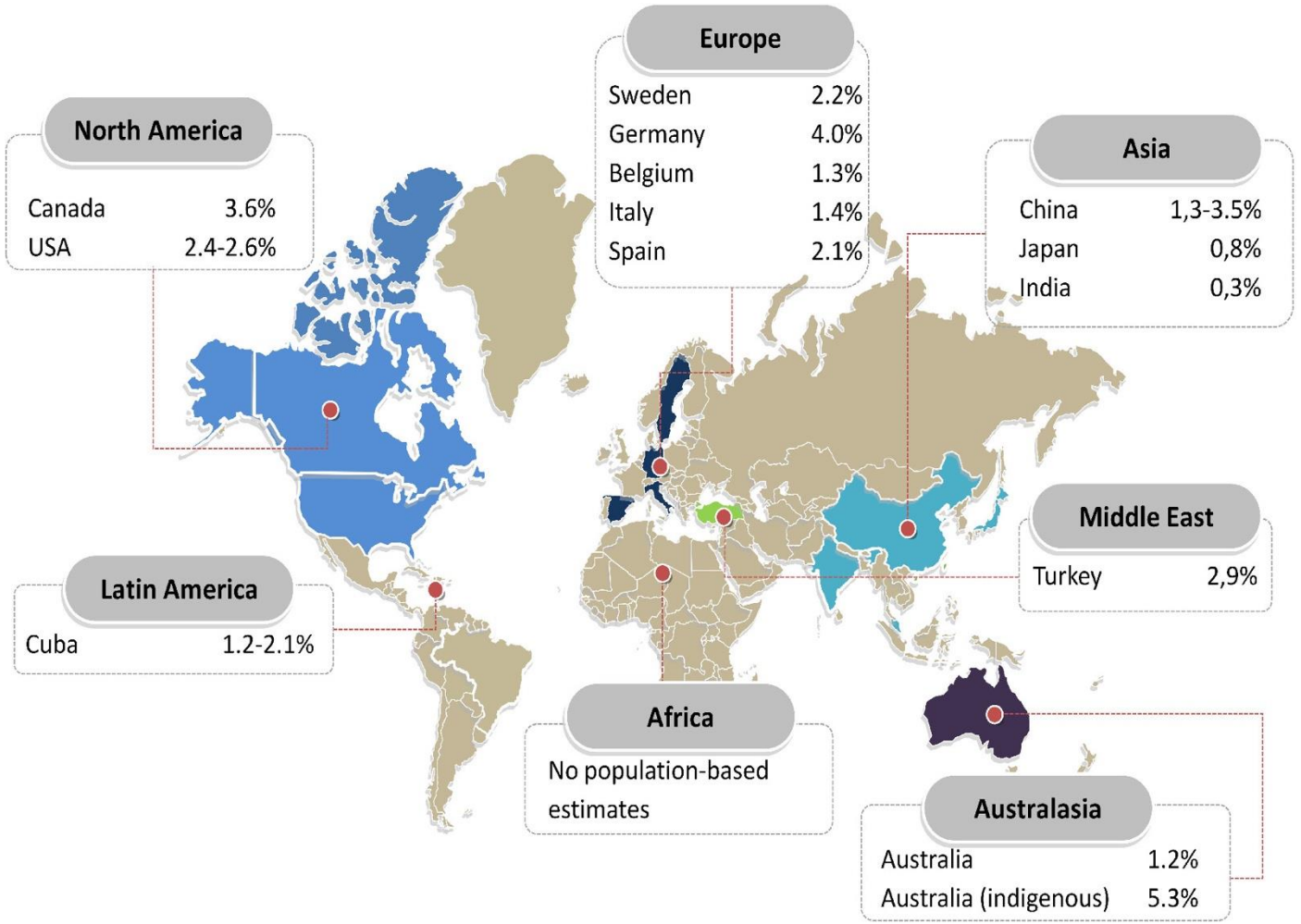


[a]HF prevalence data for 894 outpatients with new onset HF from the community based, Framingham Study over 3 decades (1985-2014). LVEF categories were defined as HFrEF (EF <40%), HF with mid-range EF (EF 40-<50%), and HFpEF (EF ≥50%).

AF = atrial fibrillation; CAD = coronary artery disease; EF = ejection fraction; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction.

1. Vasan RS et al. *JACC Cardiovasc Imaging*. 2018;11:1-11; 2. Oktay AA et al. *Curr Heart Fail Rep*. 2013;10:401-410.

Heart failure: definition and epidemiology

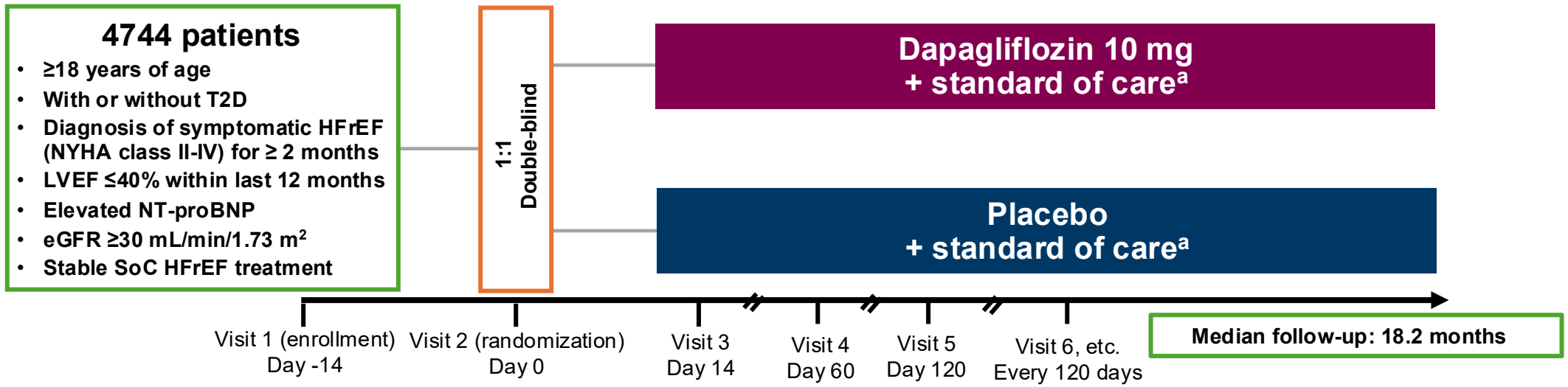


An estimated 64.3 million people are living with heart failure worldwide. In developed countries, the prevalence of ***known*** heart failure is generally estimated at 1% to 2% of the general adult population

The incidence of heart failure in European countries and the USA ranges widely from 1 to 9 cases per 1000 person-years

Amy Groenewengen et al. European Journal of Heart Failure, 2020

Dapaglifozin in HF with reduced EF: DAPA-HF



Primary Endpoint

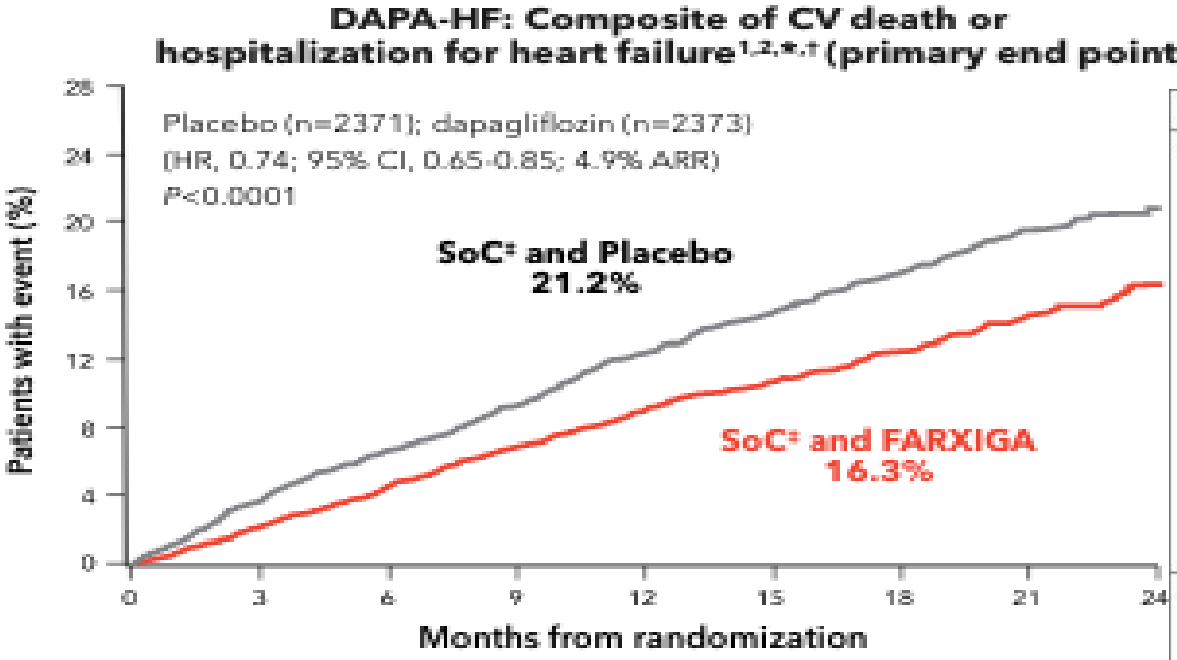
- Time to first occurrence of any of the components of the composite: CV death or hHF or an urgent HF visit

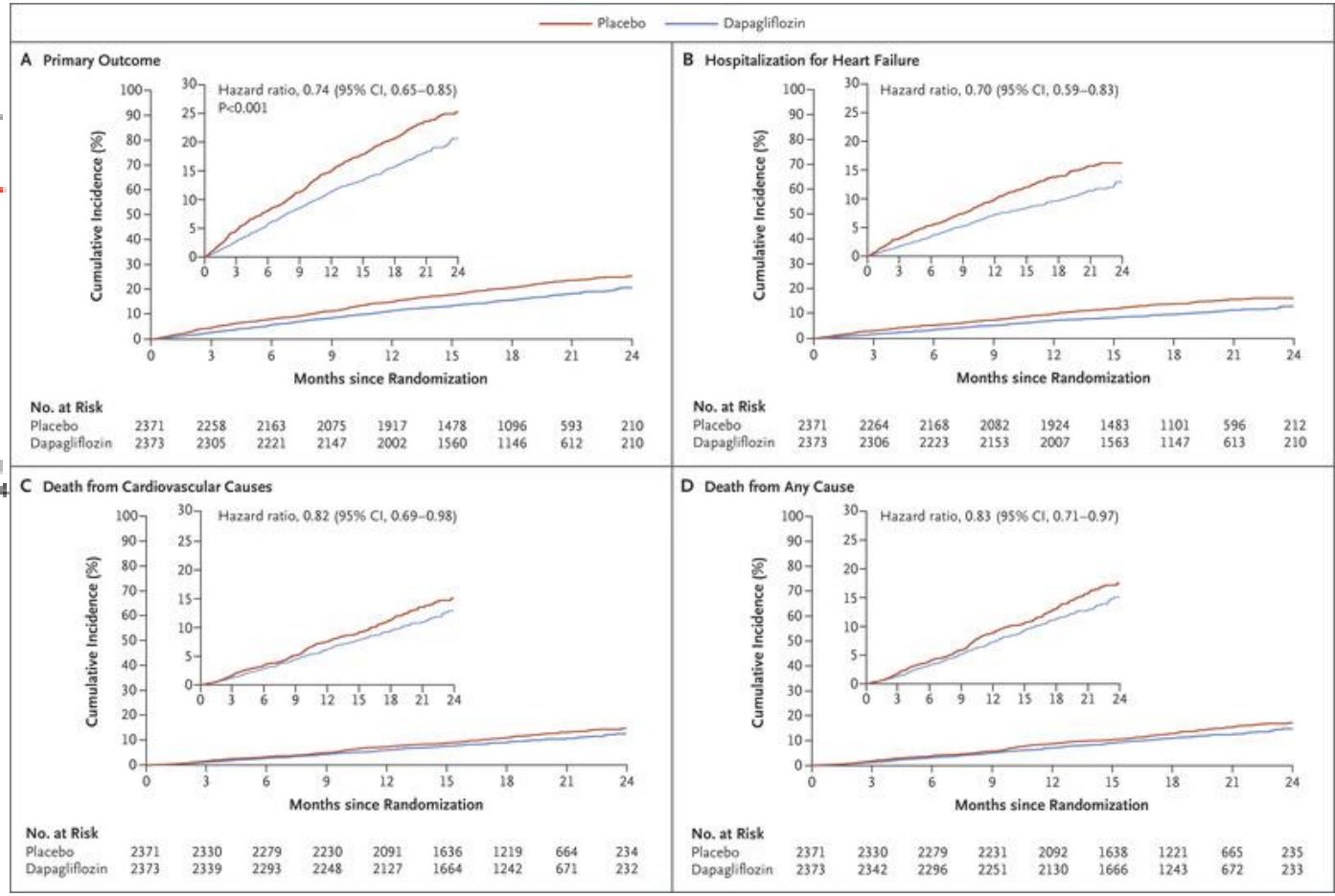
Secondary Endpoints

- 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[b] or renal death
- Time to death from any cause

McMurray JJV et al. DAPA-HF trial. N Engl J Med. 2019

Dapaglifozin in HF with reduced EF: DAPA-HF





NNT=21

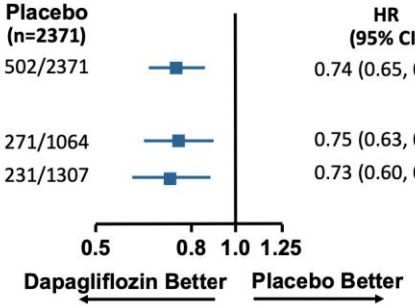
↓ 26 % RRR

McMurray JJV et al. DAPA-HF trial. N Engl J Med. 2019

Dapaglifozin in HF with reduced EF: DAPA-HF

No diabetes/diabetes subgroup: Primary endpoint

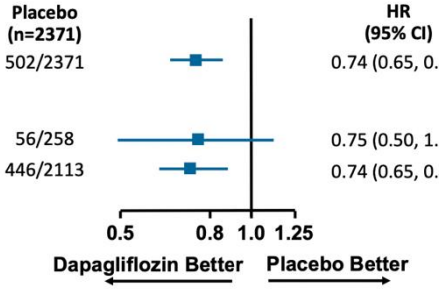
	Dapagliflozin (n=2373)	Placebo (n=2371)	HR (95% CI)
All patients	386/2373	502/2371	0.74 (0.65, 0.85)
Type 2 diabetes at baseline*			
Yes	215/1075	271/1064	0.75 (0.63, 0.90)
No	171/1298	231/1307	0.73 (0.60, 0.88)



*Defined as history of type 2 diabetes or HbA1c ≥6.5% at both enrollment and randomization visits.

ARNI/no ARNI *post hoc* subgroup: Primary endpoint

	Dapagliflozin (n=2373)	Placebo (n=2371)	HR (95% CI)
All patients	386/2373	502/2371	0.74 (0.65, 0.85)
Angiotensin Receptor Neprilysin Inhibitor (ARNI)			
Yes	41/250	56/258	0.75 (0.50, 1.13)
No	345/2123	446/2113	0.74 (0.65, 0.86)



Kansas City Cardiomyopathy Questionnaire (KCCQ)

Total Symptom Score (TSS): Change from baseline to 8 months

Treatment	Change
Dapagliflozin	**+6.1** ± 18.6
Placebo	**+3.3** ± 19.2

Difference
2.8 points (95% CI 1.6, 4.0)
p<0.001*

Increase in score indicates an improvement

Worsening renal function endpoint

Composite of: Sustained* ≥50% reduction in eGFR, end-stage renal disease (ESRD) or death from renal causes

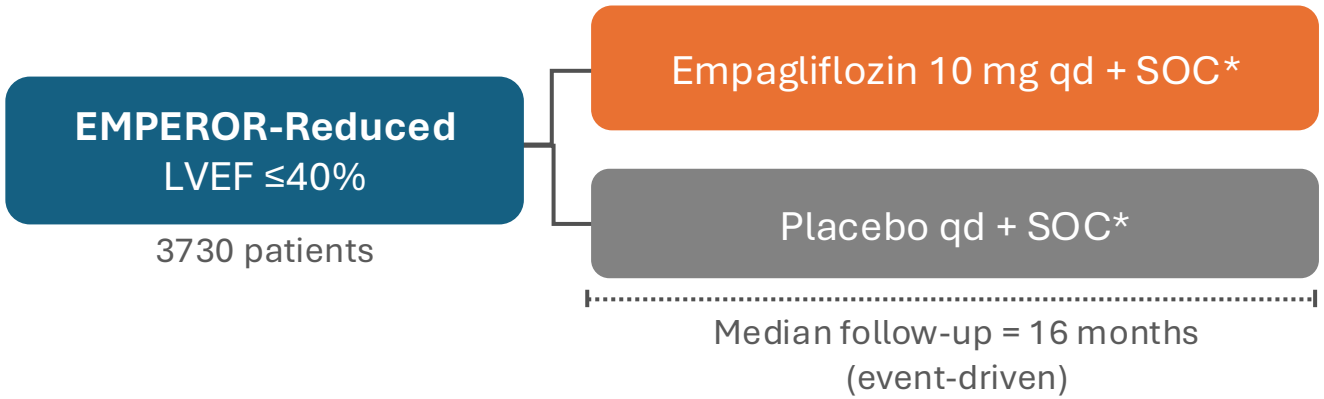
Treatment	No. (%)
Dapagliflozin	28 (1.2)
Placebo	39 (1.6)

Hazard ratio (95% CI)
0.71 (0.44, 1.16)
p=0.17

ESRD consisted of sustained eGFR below 15 ml/min/1.73m^2, sustained dialysis or kidney transplantation

McMurray JJV et al. DAPA-HF trial. N Engl J Med. 2019

Empaglifozin in HF with reduced EF: EMPEROR Reduced



COMPOSITE PRIMARY ENDPOINT

Time to first event of adjudicated CV death or adjudicated HHF

SECONDARY ENDPOINTS

- **First and recurrent adjudicated HHF events**
- **Slope of change in eGFR (CKD-EPI) from baseline**

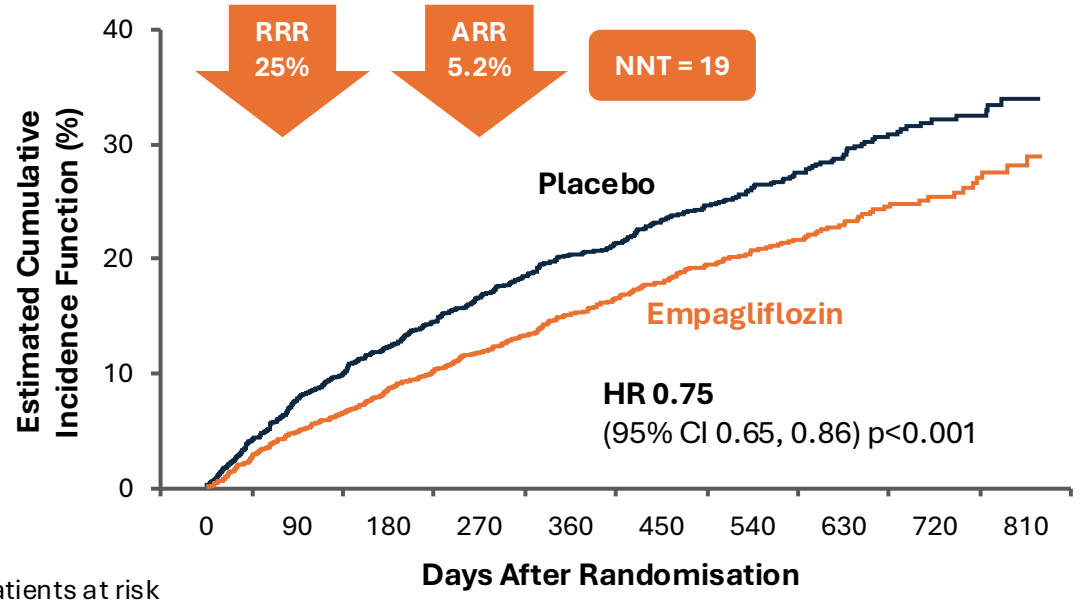
Liao et al. Cardiovascular Diabetology 2024

Paker et al. Circulation. 2021

Butler et al. European Heart Journal 2021

Empaglifozin in HF with reduced EF: EMPEROR Reduced

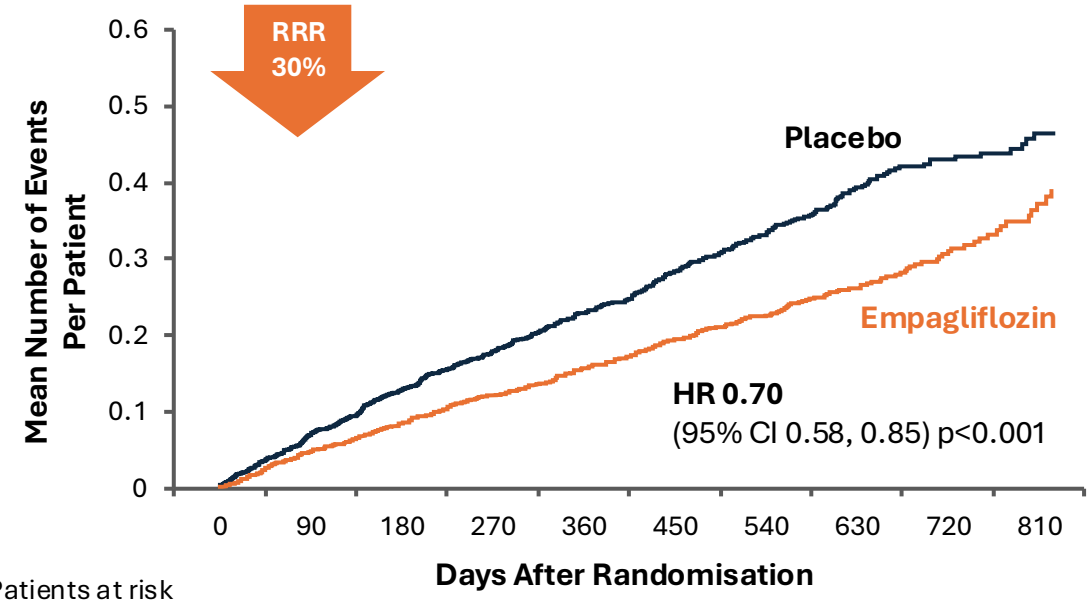
First Adjudicated CV Death or Hospitalisation for Heart Failure



Patients at risk

Placebo	1867	1715	1612	1345	1108	854	611	410	224	109
Empagliflozin	1863	1763	1677	1424	1172	909	645	423	231	101

Adjudicated Total Hospitalisations for Heart Failure (First and Recurrent)



Patients at risk

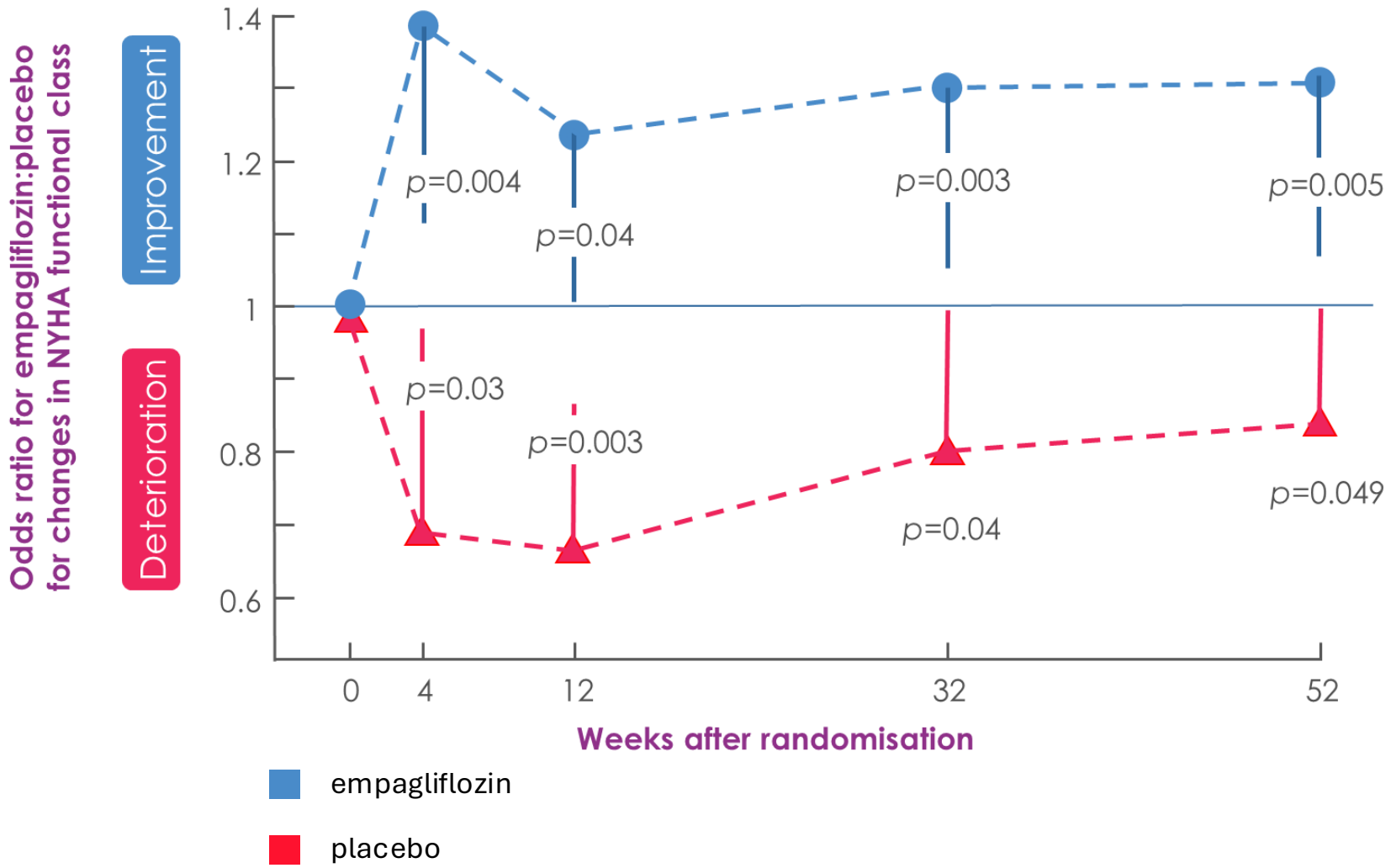
Placebo	1867	1820	1762	1526	1285	1017	732	497	275	135
Empagliflozin	1863	1826	1768	1532	1283	1008	732	495	272	118

Liao et al. Cardiovascular Diabetology 2024

Paker et al. Circulation. 2021

Butler et al. European Heart Journal 2021

Empaglifozin in HF with reduced EF: EMPEROR Reduced



Liao et al. Cardiovascular Diabetology 2024

Paker et al. Circulation. 2021

Butler et al. European Heart Journal 2021

Empaglifozin in HF with preserved EF: EMPEROR Preserved

Aim: To investigate the safety and efficacy of empagliflozin versus placebo in patients with HF with **preserved ejection fraction**

Population: T2D and non-T2D, aged ≥18 years, chronic HF, and eGFR ≥20 mL/min/1.73m^2

EMPEROR-Preserved
LVEF >40%

5988 patients

- Empagliflozin 10 mg OD
- Placebo

Median follow-up 26.2 months

Confirmatory endpoints

PRIMARY ENDPOINT

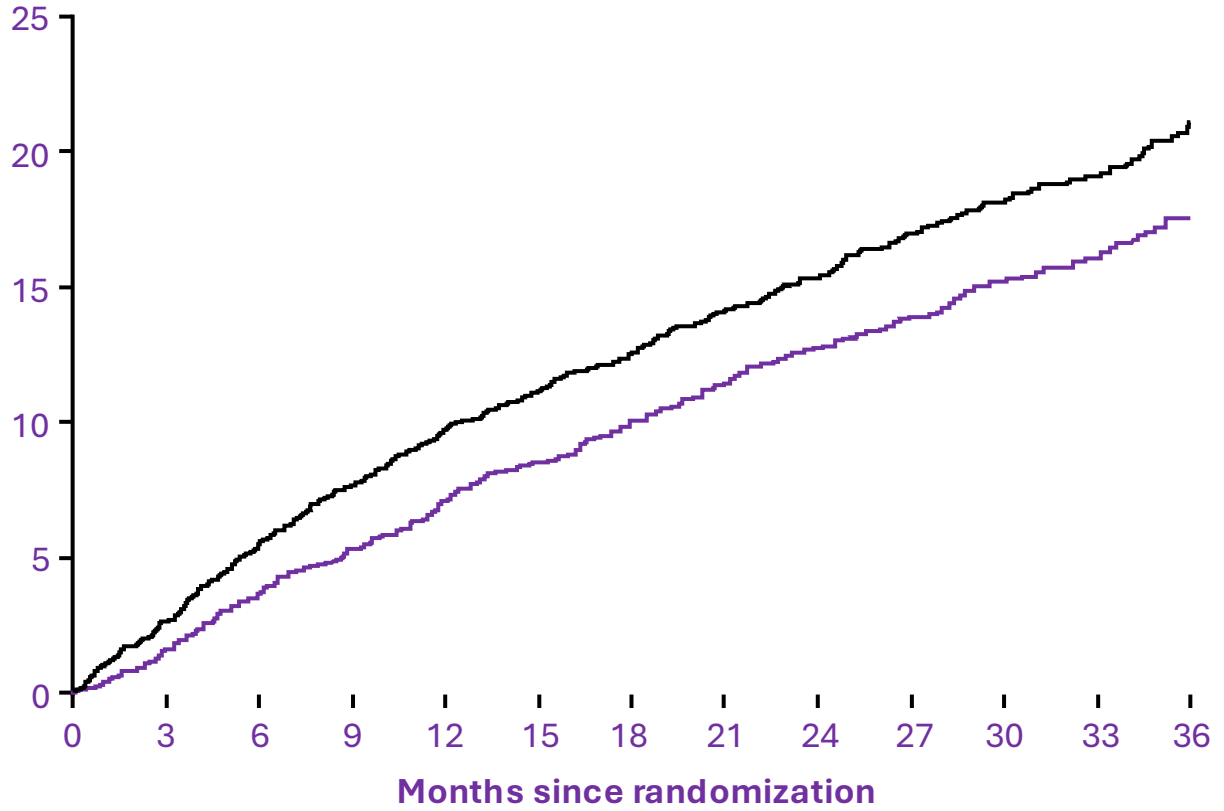
Time to cardiovascular death or hospitalization for heart failure

SECONDARY ENDPOINT

- **First and recurrent adjudicated HHF events**
- **Slope of change in eGFR (CKD-EPI) from baseline**

Anker S et al. N Engl J Med. 2021;385:1451.

Empaglifozin in HF with preserved EF: EMPEROR Preserved



Patients at risk

Placebo	2991	2888	2786	2706	2627	2424	2066	1821	1534	1278	961	681	400
Empagliflozin	2997	2928	2843	2780	2708	2491	2134	1858	1578	1332	1005	709	402

RRR 21%

ARR 3.3%

NNT*= 31

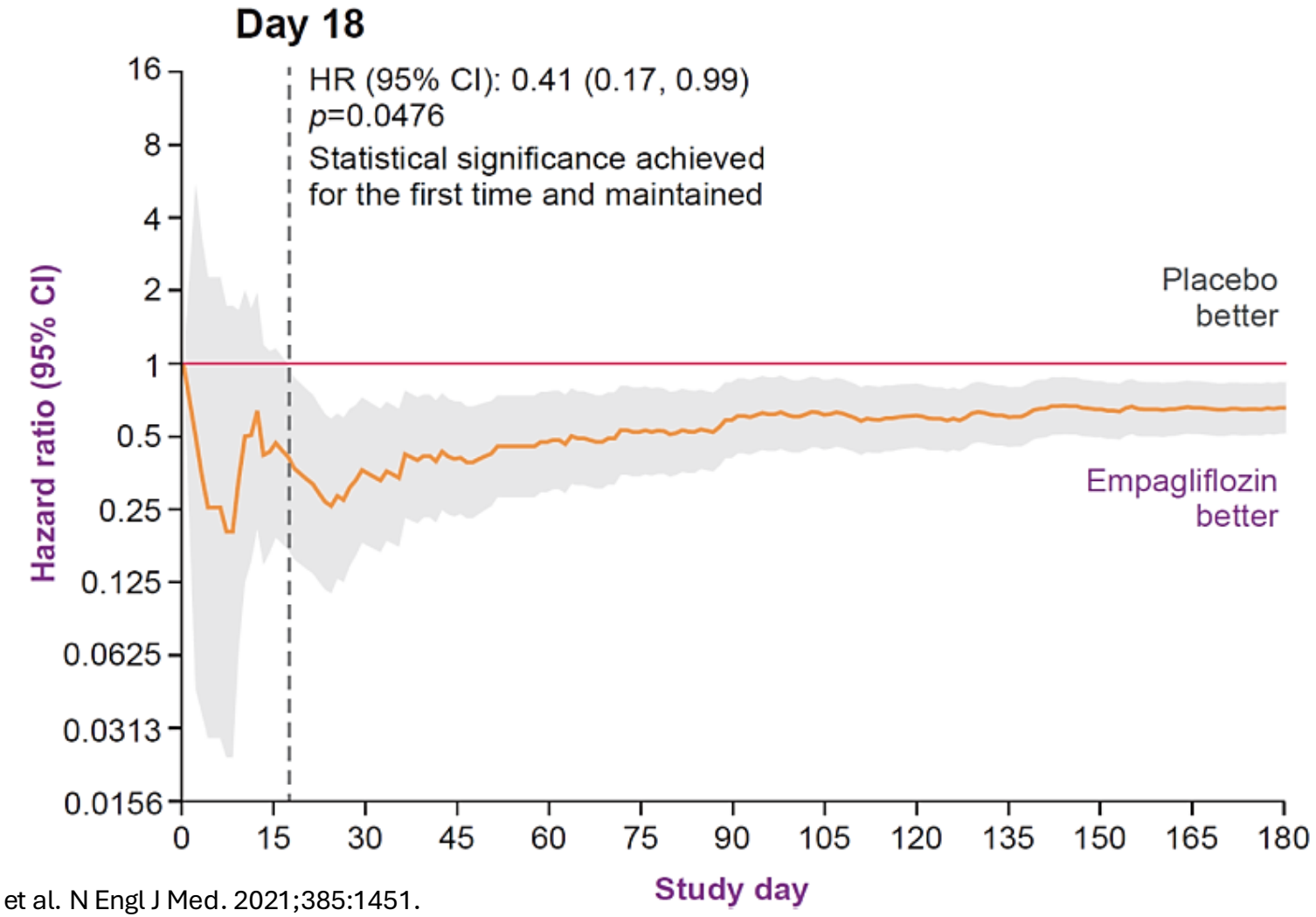
HR: 0.79
(95% CI: 0.69, 0.90)
p<0.001

Empagliflozin:
415 (13.8%) patients with event
Rate: 6.9/100 patient-years
Placebo:
511 (17.1%) patients with event
Rate: 8.7/100 patient-years

Anker S et al. N Engl J Med. 2021;385:1451.

Empaglifozin in HF with preserved EF: EMPEROR Preserved

Effect of empagliflozin vs placebo on time to cardiovascular death or heart failure hospitalization

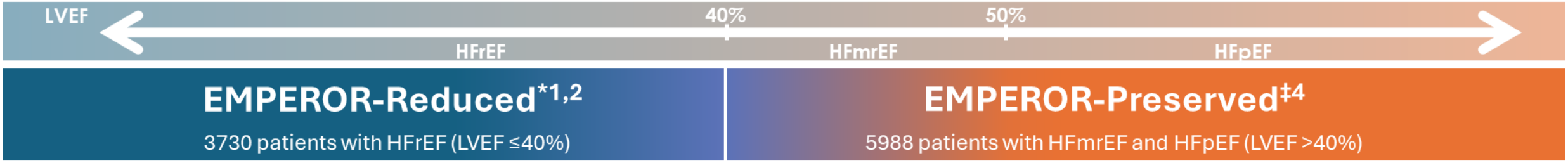


The Cox regression analysis achieved nominal statistical significance for separation between the empagliflozin and the placebo arms by **day 18** for time to cardiovascular death or HF hospitalization (hazard ratio at 18 days 0.41, 95% CI 0.17–0.99), and the statistical significance of this benefit was sustained from there on after which boundary of the upper CI remained below unity for the rest of the trial period.

Anker S et al. N Engl J Med. 2021;385:1451.

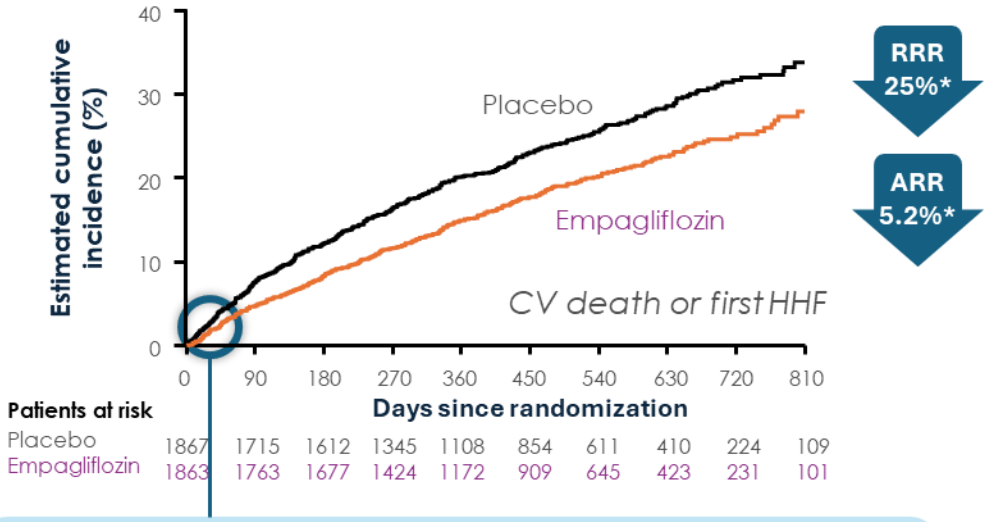
SGLT2 and HF: when?

Empagliflozin demonstrated early, significant and sustained reductions in the risk of CV death or first HHF across the LVEF spectrum compared with placebo



EMPEROR-Reduced*[1,2]

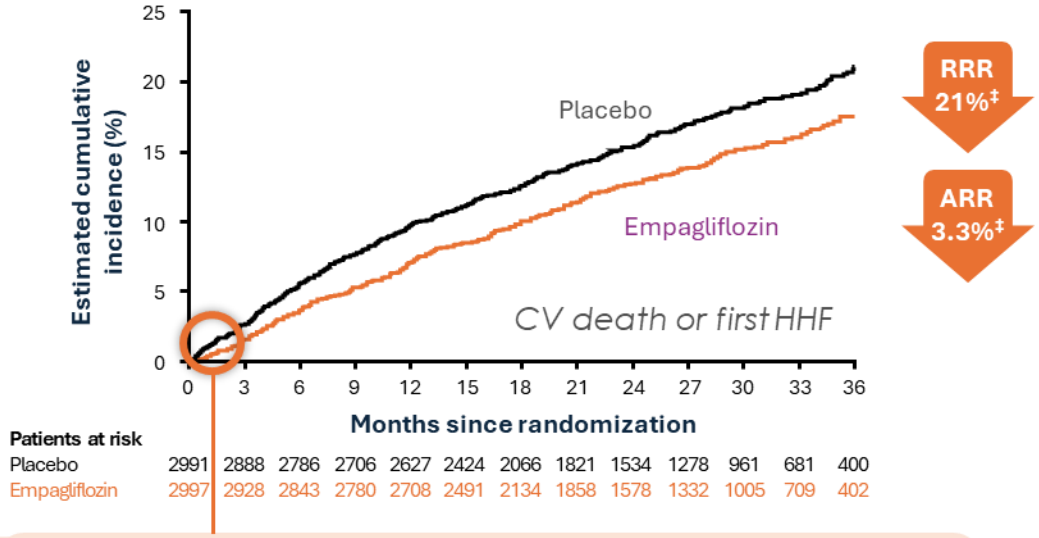
3730 patients with HFrEF (LVEF ≤40%)



Statistical significance:[†3]
Reached **12 days after randomization**
Sustained from day 34

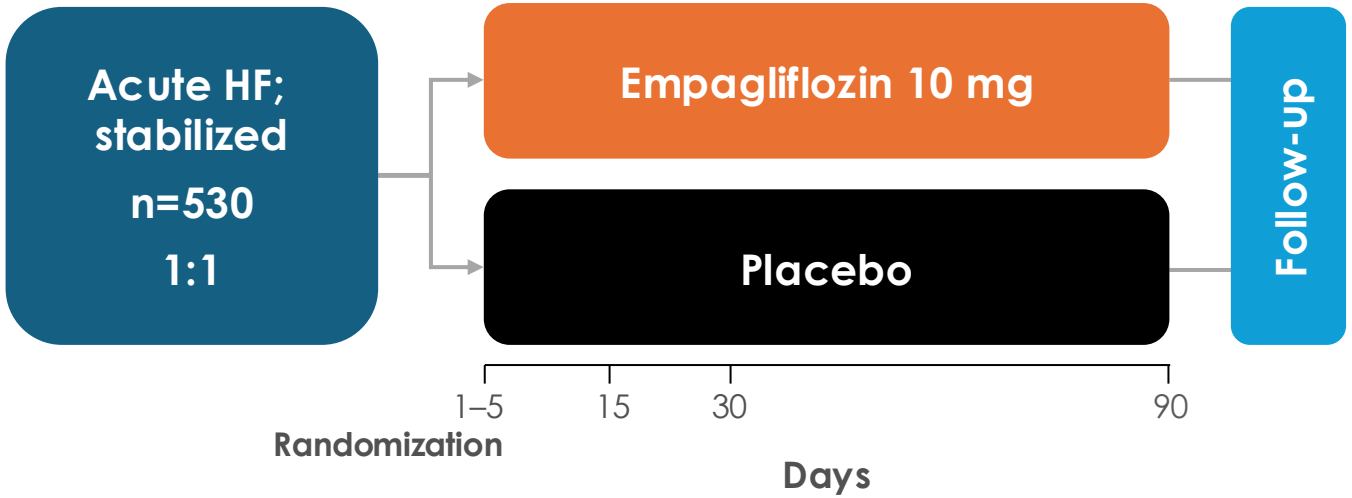
EMPEROR-Preserved‡[4]

5988 patients with HFmrEF and HFpEF (LVEF >40%)



Statistical significance:[5]
Reached **18 days after randomization**
Sustained for the duration of the follow-up period

Early Empaglifozin in HF: the EMPULSE trial

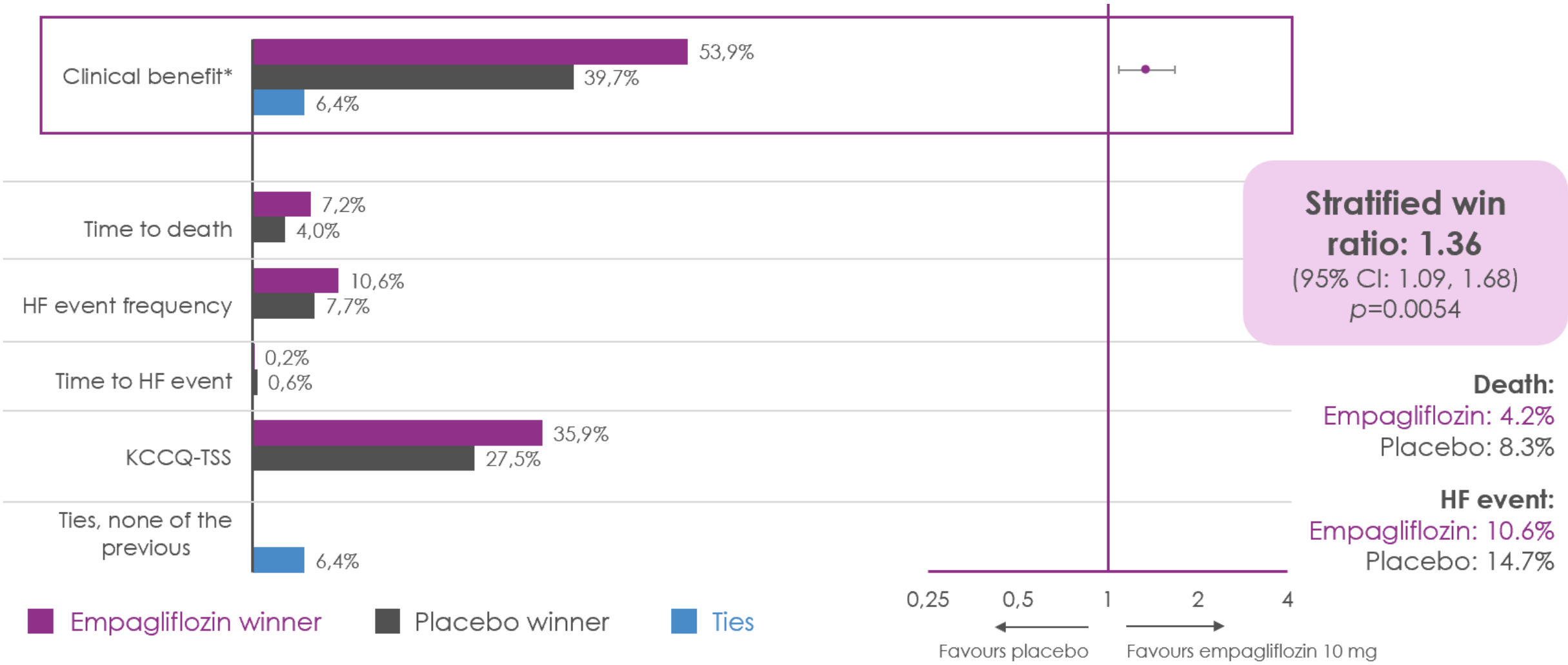


Median time from hospital admission to randomization was **3 days**

Primary endpoint

- **Clinical benefit evaluated with a win ratio based on a composite of:**
  - Death
  - Number of HFEs (including HHFs, urgent HF visits and unplanned outpatient visits)
  - Time to first HFE
  - ≥5-point difference in the KCCQ-TSS change from baseline after 90 days of treatment

Early Empaglifozin in HF: the EMPULSE trial



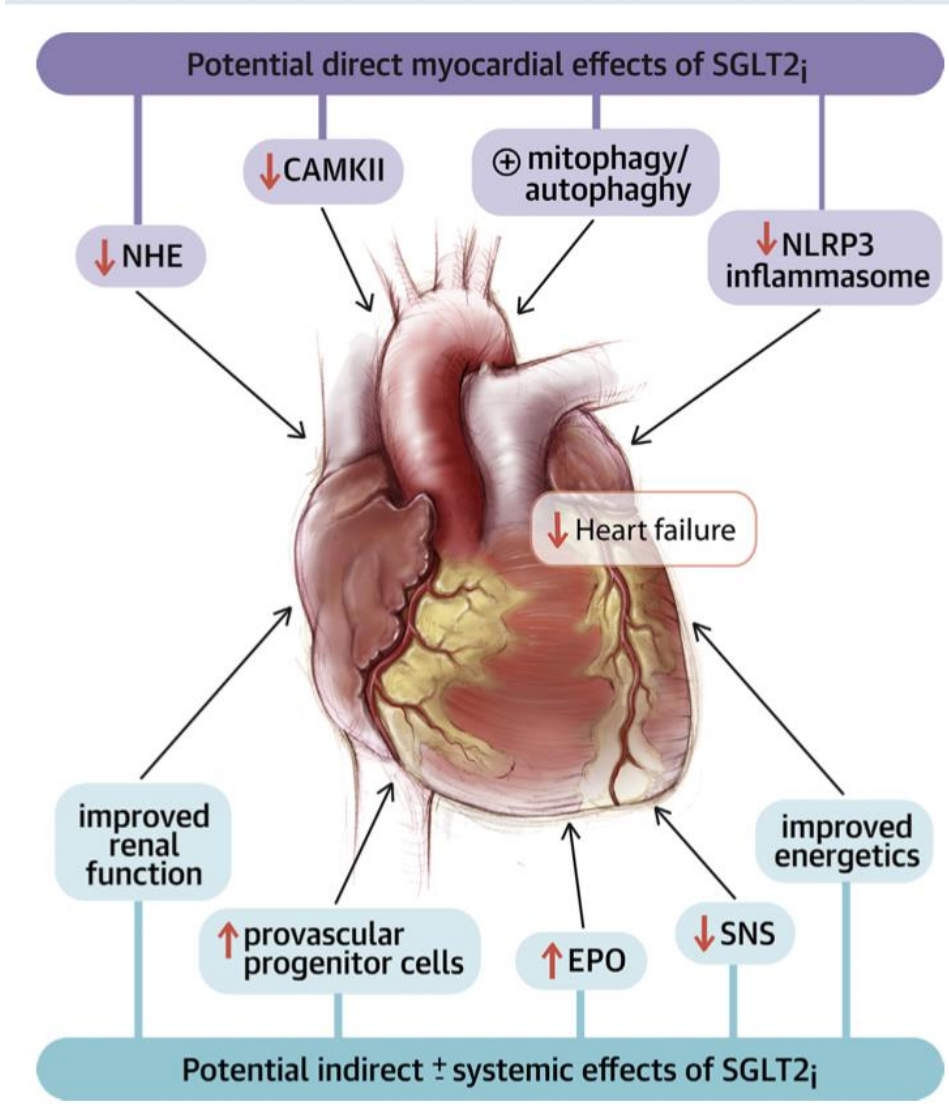
Stratified win ratio: 1.36
(95% CI: 1.09, 1.68)
p=0.0054

Death:
Empagliflozin: 4.2%
Placebo: 8.3%

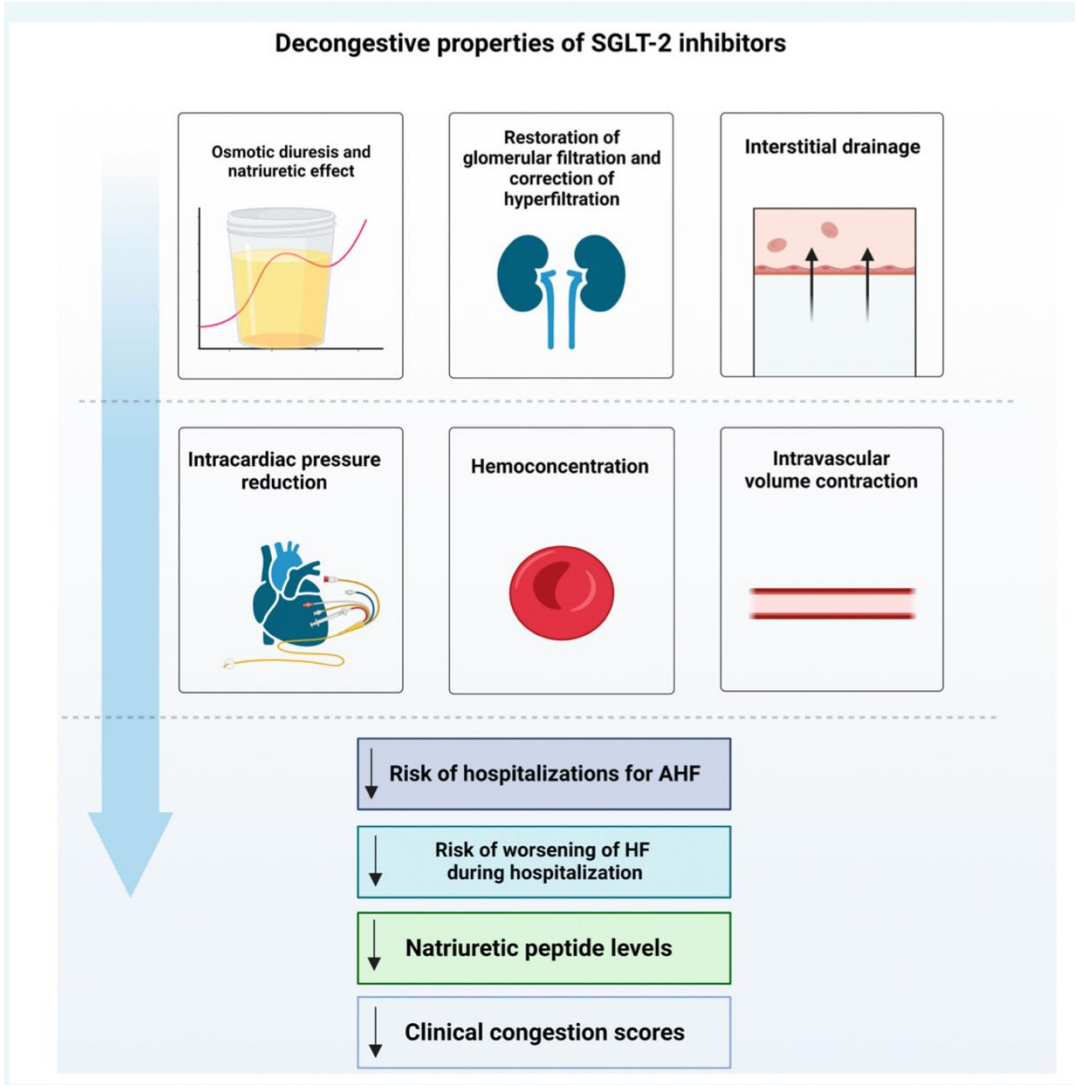
HF event:
Empagliflozin: 10.6%
Placebo: 14.7%

*Composite of death, number of HFEs (including HHFs, urgent HF visits and unplanned outpatient visits), time to first HFE and ≥5 point difference in the KCCQ-TSS change from baseline after 90 days of treatment

Heart failure: why SGLT2 inhibitors



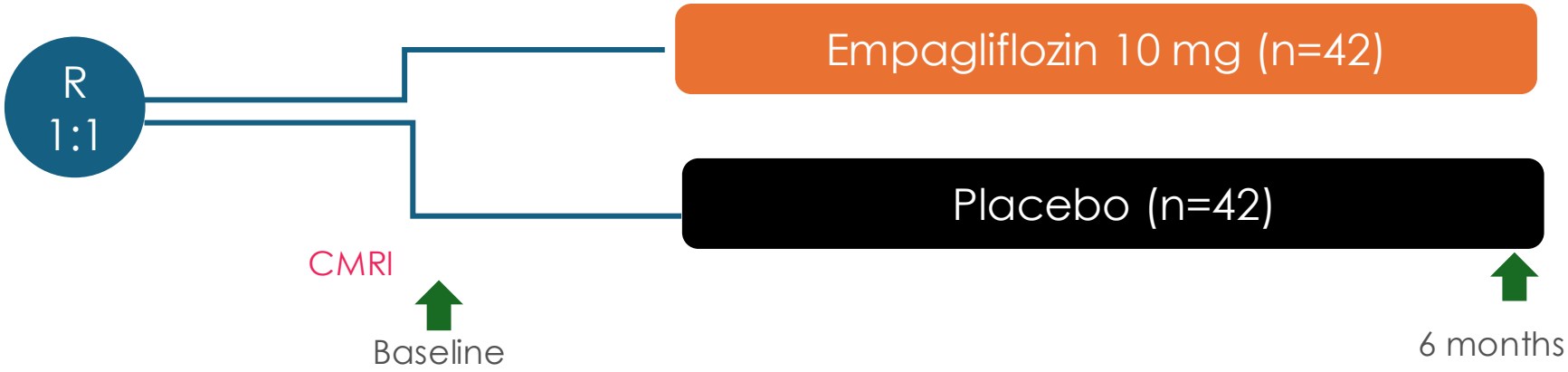
J. Biegus et al. European Journal of Heart Failure 2023;



ACC: JUNE BASIC TO TRANSLATIONAL SCIENCE 2020

Empaglifozin and cardiac remodeling

EMPA-TROPISM evaluated the effects of empagliflozin on LV remodelling in non-diabetic patients with HFrEF



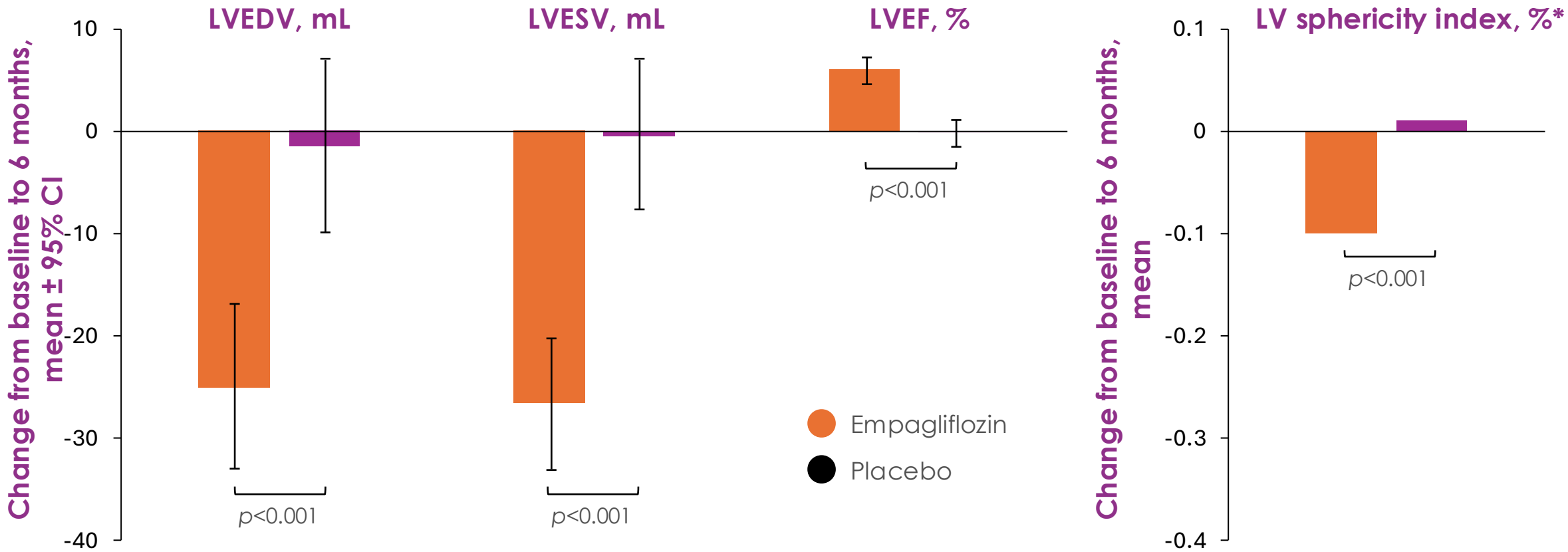
Inclusion criteria & selected baseline characteristics

- Adult patients (>18 years)
- HF (NYHA II–III)
- LVEF <50%
- Stable symptoms and medical therapy
- Patients with diabetes were **excluded**

	Empagliflozin	Placebo
Age, years (mean)	64.2	59.9
Male, % of patients	64	64
LVEDV, mL (mean)	219.8	210.4
LVESV, mL (mean)	143.6	135.1
LVEF, % (mean)	36.2	36.5

Empaglifozin and cardiac remodeling

Empagliflozin is associated with reverse LV remodelling and LVEF improvement in HFrEF without T2D



Mean (SD) at:	LVEDV, mL		LVESV, mL		LVEF, %		LV sphericity index, %*	
Baseline	219.8±75.8	210.4±68.9	143.6±66.3	135.1±54.8	36.2±8.2	36.5±8.0	0.62±0.16	0.58±0.12
6 months	194.7±69.7	208.9±72.8	117.0±60.0	134.5±58.9	42.2±9.2	36.3±8.5	0.52±0.11	0.59±0.13

Heart failure and functional MR: SGLT2i the EFFORT Trial

- Patients with HF (LVEF 35-50%) NYHA II or III with or without DM and substantial MR (EROA >0.1 cm2) despite OMT
- Randomization to receive ertugliflozin or placebo in addition to OMT
- The primary end point was change in EROA of functional MR from baseline to 12 months follow-up. Secondary end points included changes in RV, LV ESVi and EDVi index, LAVI, LV GLS and NT-proBNP

Medical therapy at baseline

Heart failure medication		
ACE inhibitor	4 (6.2)	3 (4.8)
ARB	24 (36.9)	25 (39.7)
ARNI	28 (43.1)	27 (42.9)
Diuretic	54 (83.1)	45 (71.4)
Beta-blocker	54 (83.1)	53 (84.1)
Aldosterone antagonist	35 (53.8)	33 (52.4)

Etiology of MR and echo at baseline

Cause of functional MR		
Ischemic	27 (41.5)	21 (33.3)
Nonischemic	38 (58.5)	42 (66.7)
Mechanism of MR		
Ventricular	56 (86.2)	47 (74.6)
Atrial	9 (13.8)	16 (25.4)
Echocardiographic measure		
End-systolic dimension, mm	48.4±10.4	46.9±9.8
End-diastolic dimension, mm	62.5±8.4	60.6±7.8
Left atrial dimension, mm	50.8±10.6	51.2±12.0
Left atrial volume index, mL/m^2	80.7±46.0	81.4±58.8
End-systolic volume index, mL/m^2	56.4±29.9	54.2±22.9
End-diastolic volume index, mL/m^2	93.7±37.5	89.9±29.2
Ejection fraction, %	41.9±8.3	42.4±7.5
GLS, %	−12.9±3.7	−12.0±2.9
Regurgitant volume, mL	36.9±23.1	33.7±17.0
EROA, cm^2	0.20±0.12	0.20±0.10
>0.10 to <0.20	41 (63.1)	40 (63.5)
≥0.20 to <0.40	18 (27.7)	19 (30.2)
≥0.40	6 (9.2)	4 (6.3)

Kang et al; Circulation 2024.

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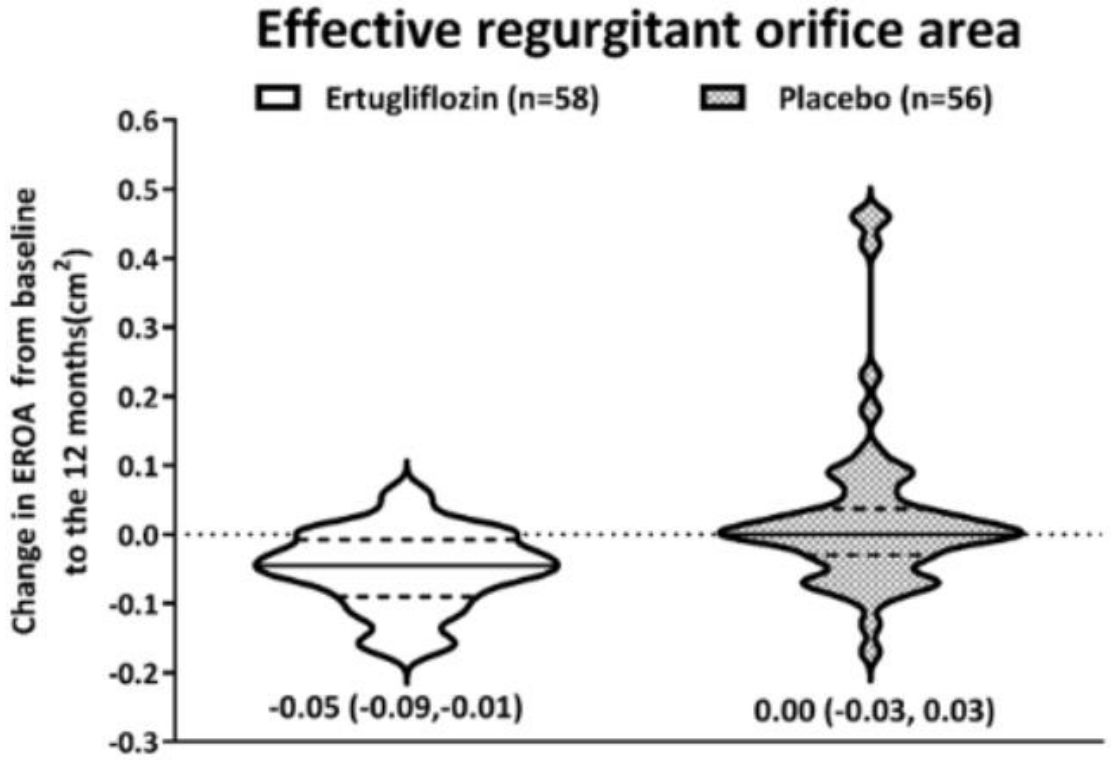

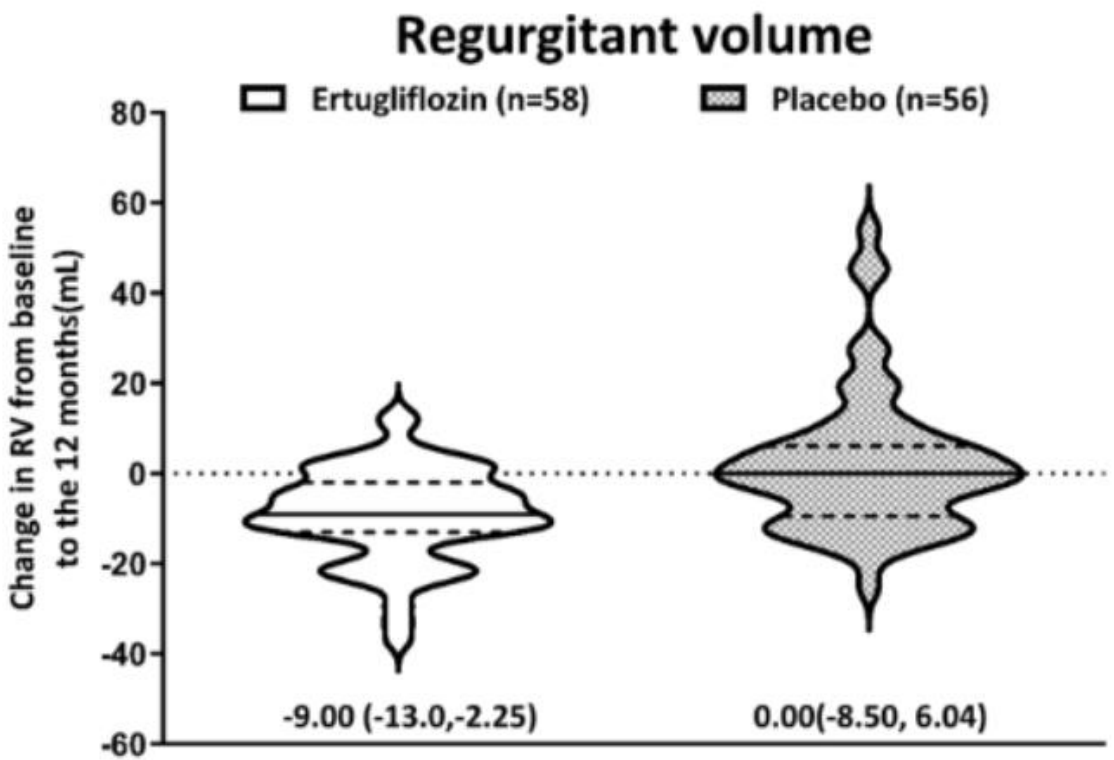

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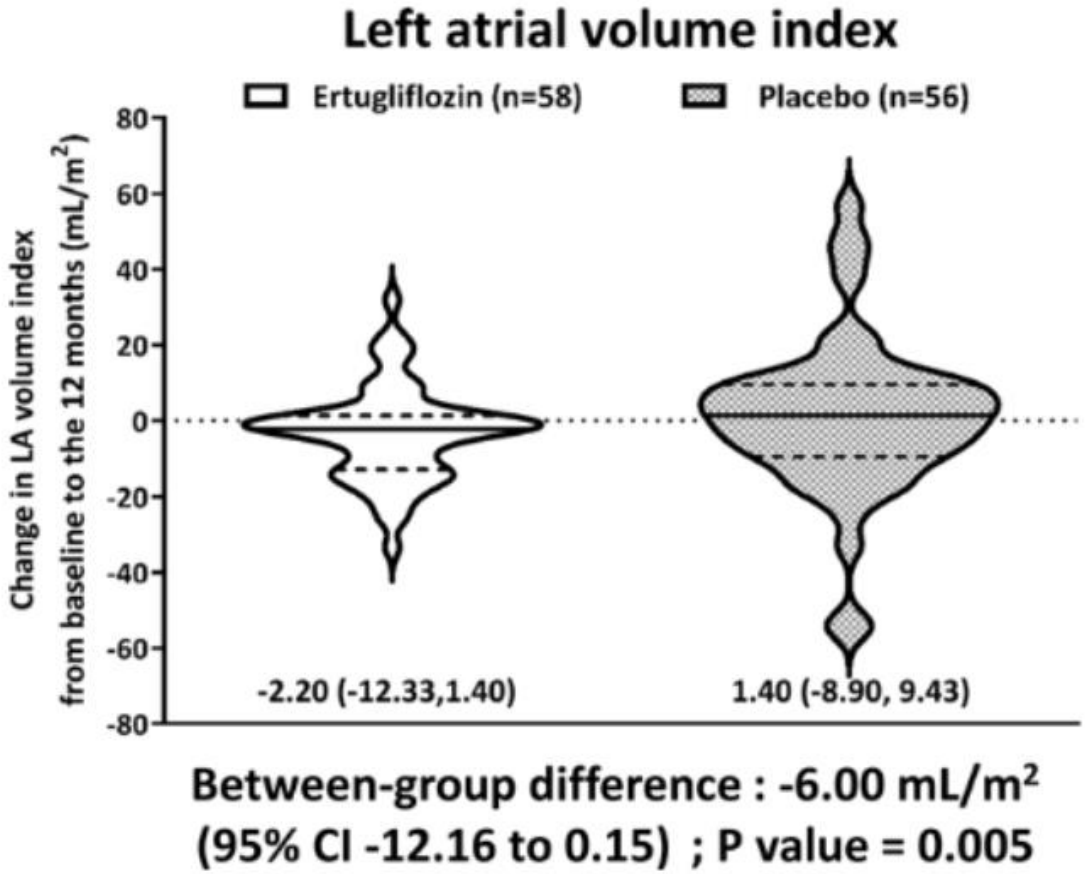
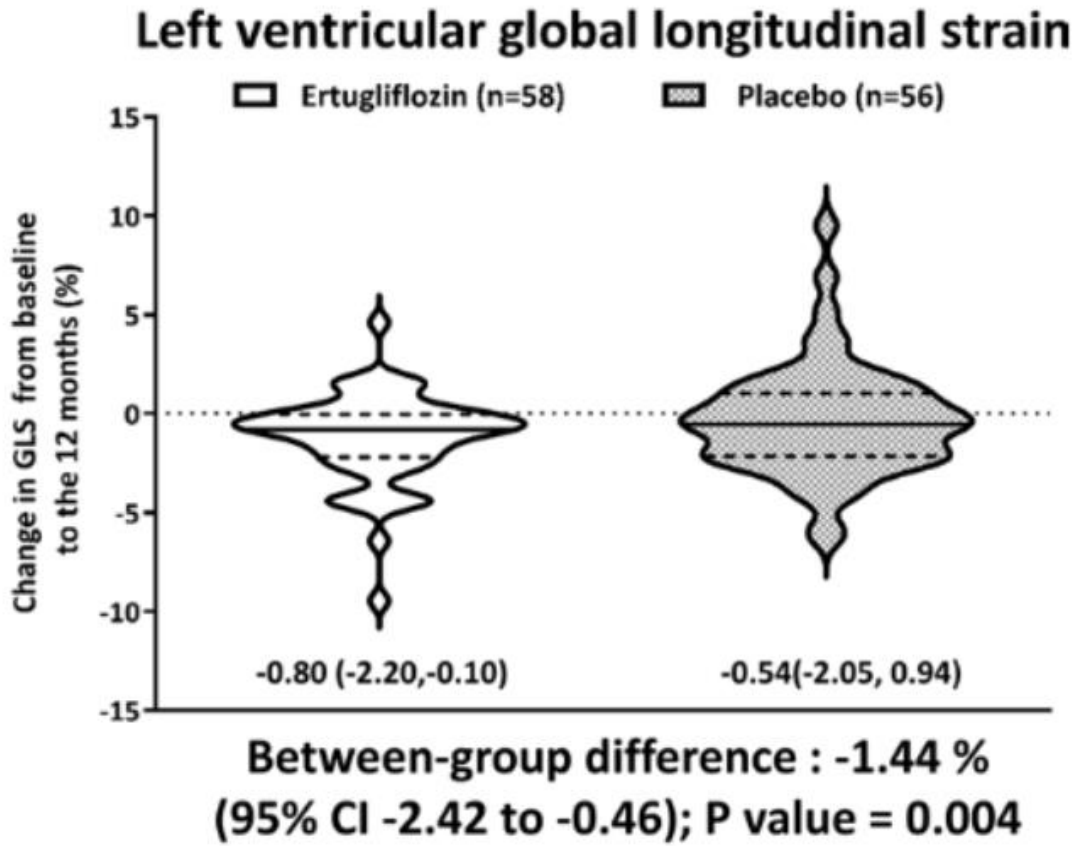




Kang et al; Circulation 2024.

Heart failure and functional MR: SGLT2i the EFFORT Trial

- Patients with HF (LVEF 35-50%) NYHA II or III with or without DM and substantial MR (EROA >0.1 cm2) despite OMT
- Randomization to receive ertugliflozin or placebo in addition to OMT
- The primary end point was change in EROA of functional MR from baseline to 12 months follow-up. Secondary end points included changes in RV, LV ESVi and EDVi index, LAVI, LV GLS and NT-proBNP

Table 3. Between-Group Differences of Primary End Point According to Subgroup

Subgroup	Number (%)	Mean difference (95% CI)	*P* value	$P_{interaction}$*
Diabetes				
Presence	15 (13.2)	−0.068 (−0.167 to 0.031)	0.174	0.878
Absence	99 (86.8)	−0.077 (−0.114 to −0.039)	<0.001	
Atrial fibrillation				
Presence	60 (52.6)	−0.073 (−0.122 to −0.024)	0.004	0.834
Absence	54 (47.4)	−0.080 (−0.132 to −0.029)	0.002	
LV ejection fraction				
<40%	46 (40.4)	−0.077 (−0.133 to −0.022)	0.007	0.970
≥40%	68 (59.6)	−0.076 (−0.122 to −0.030)	0.001	
Cause of MR				
Nonischemic	74 (64.9)	−0.072 (−0.116 to −0.028)	0.002	0.768
Ischemic	40 (35.1)	−0.084 (−0.144 to −0.023)	0.007	
Mechanism of MR				
Ventricular	91 (79.8)	−0.073 (−0.112 to −0.033)	<0.001	0.827
Atrial	23 (20.2)	−0.083 (−0.165 to −0.001)	0.048	
Severity of MR				
EROA <0.3	93 (81.6)	−0.058 (−0.096 to −0.020)	0.003	0.026
EROA ≥0.3	21 (18.4)	−0.160 (−0.241 to −0.079)	<0.001	
Use of ARNI				
Presence	48 (42.1)	−0.084 (−0.139 to −0.030)	0.003	0.721
Absence	66 (57.9)	−0.072 (−0.118 to −0.025)	0.003	

Kang et al; Circulation 2024.

SLGT2i and arrythmias

Effect of SGLT2i on Arrhythmias?

- To date no RCTs
- Studies reported inconsistent results

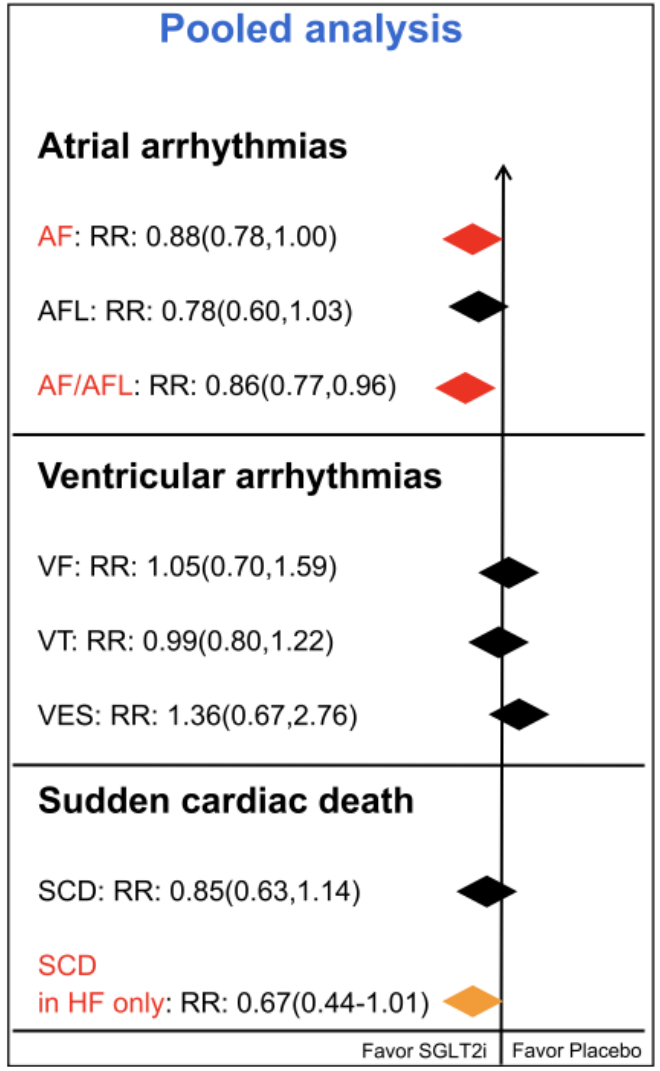
Baseline characteristics:

- Included studies: 33 RCTs
- Sample size: 88098
- Age: 64.9±9.4 yrs
- Male: 63.0%
- LVEF: 39.2±14.6%
- eGFR: 67.3±23.6 ml/min/1.73m²

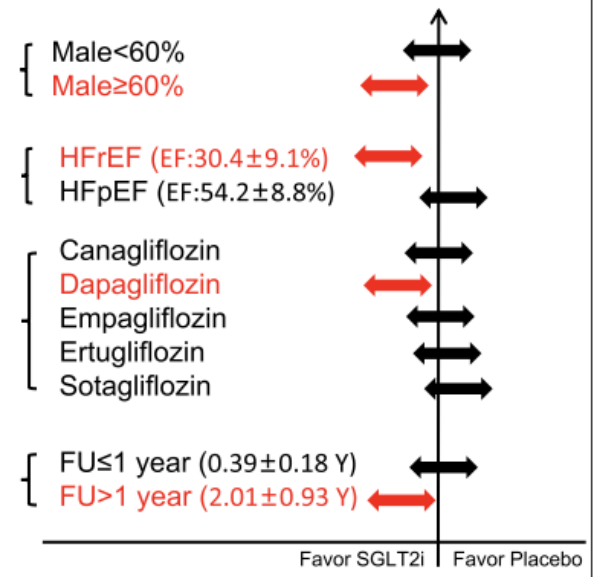
Strengths of our study:

- Large sample size
- Subgroup/regression/sensitivity analyses, TSA
- Statistical power

Pooled analysis



Subgroup analyses for AF

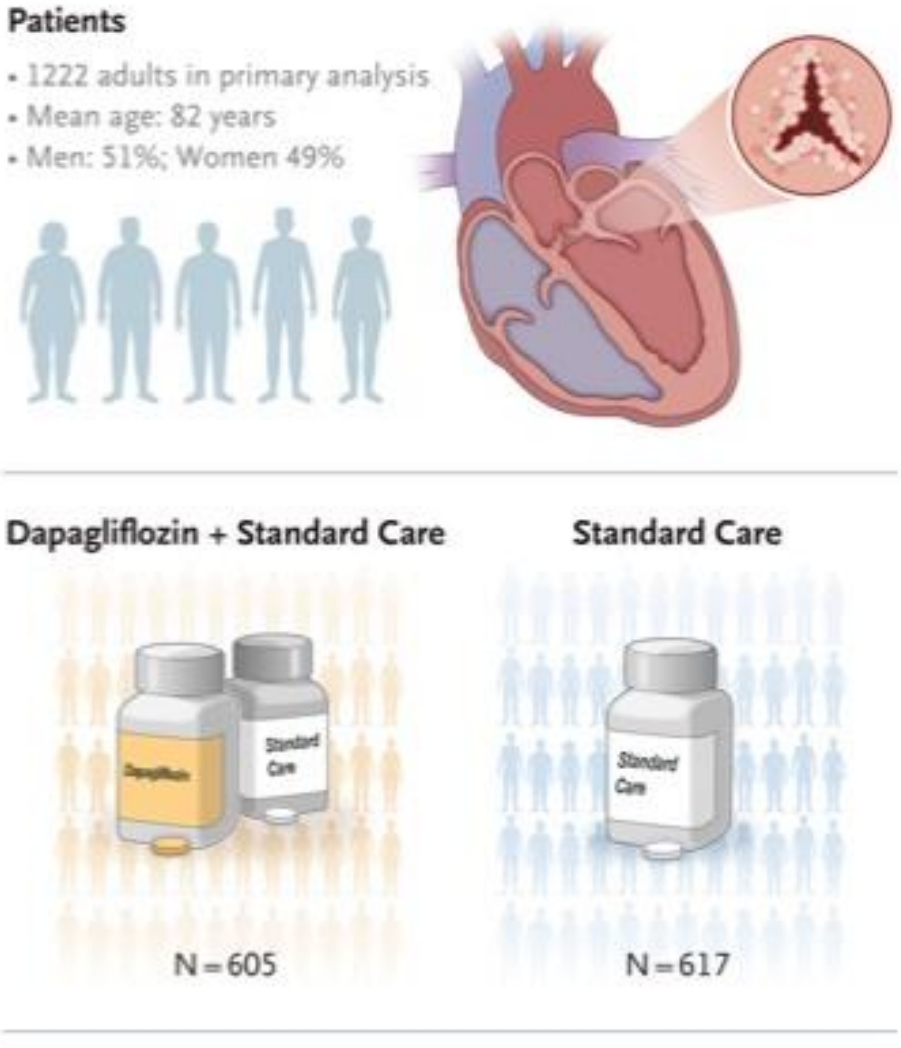


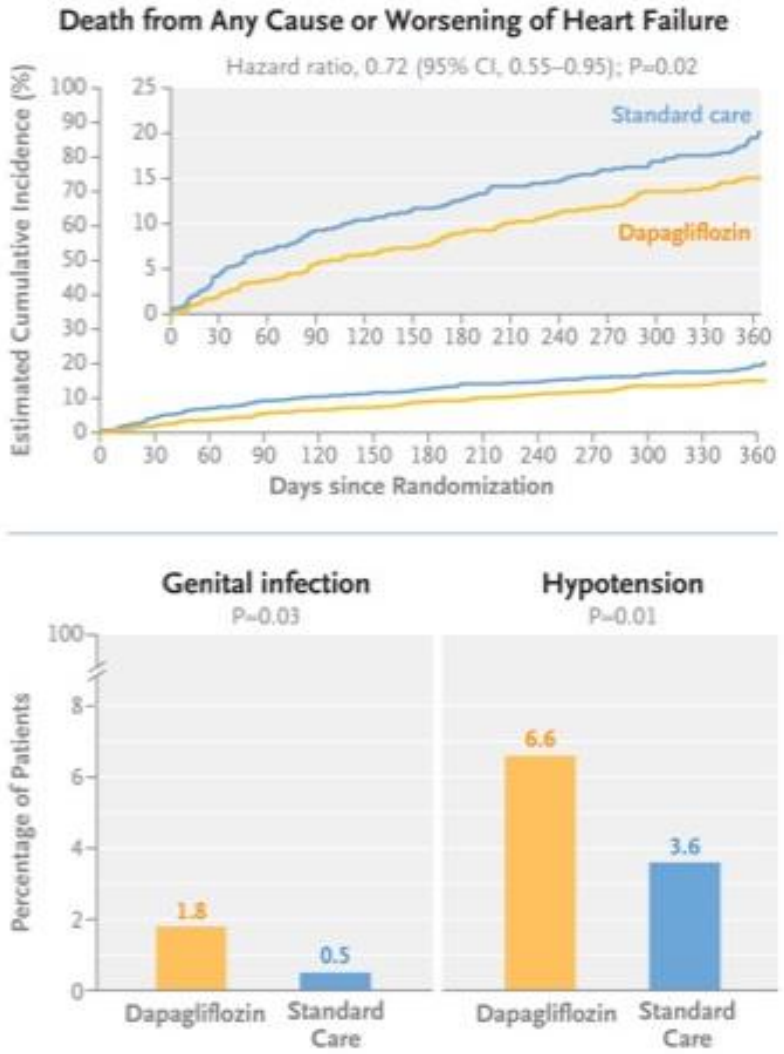
Meta-regression for AF: Gender & LVEF

Variables	Effect of SGLT2i on AF			
	Coef.	Z value	P value	Log RR 95%CI
Male, %	-0.021	-2.34	0.019	-0.039 to -0.0035
LVEF, %	0.024	2.62	0.009	0.006 to 0.04

Liao et al. Cardiovascular Diabetology 2024

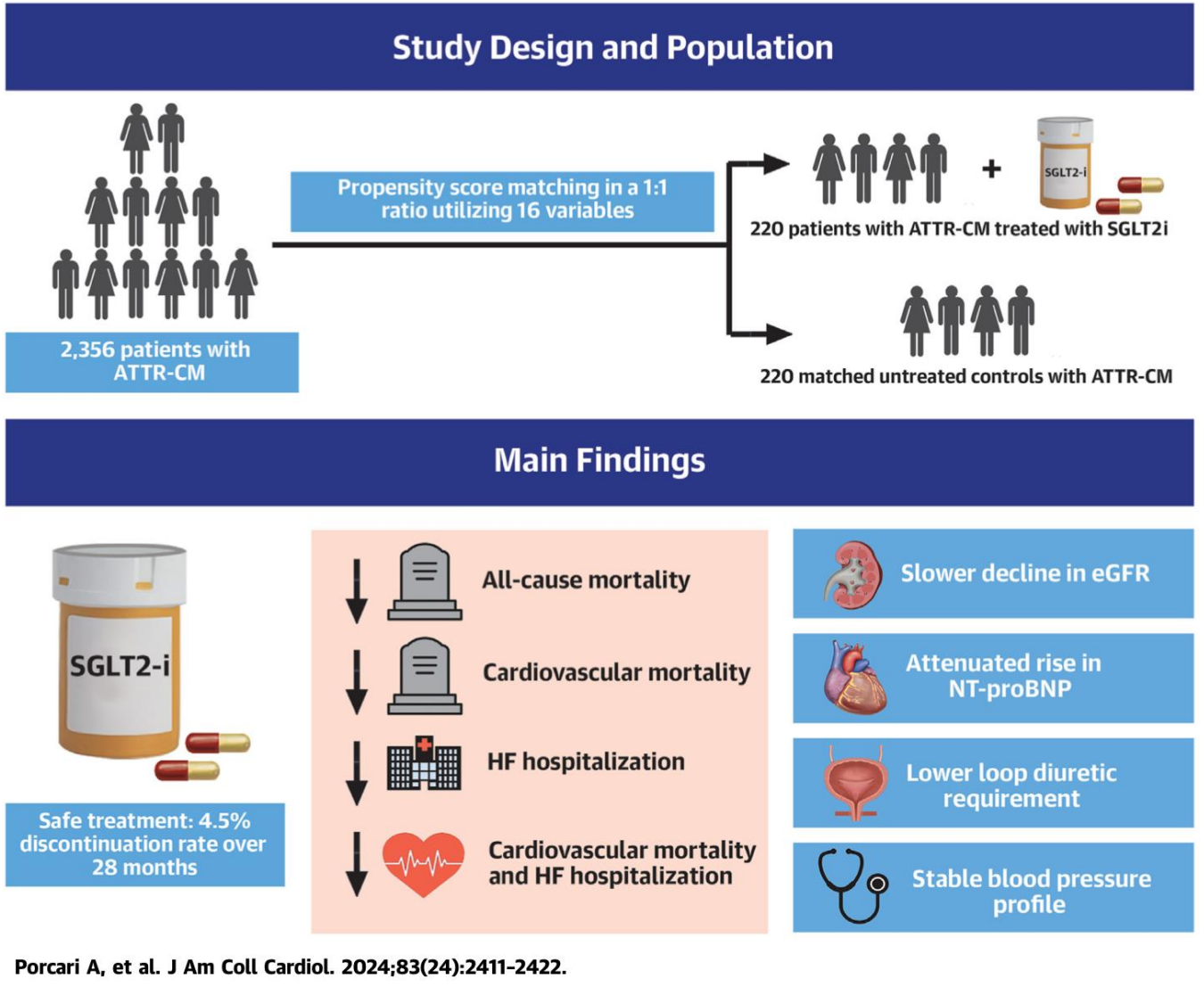
SLGT2i and TAVI: DAPA TAVI trial





DAPA TAVI; NEJM 2025

SLGT2i and amyloid cardiomyopathy



Porcari A, et al. J Am Coll Cardiol. 2024;83(24):2411-2422.

SGLT2 inhibitors: what the guidelines and consensus suggest

Pharmacological treatments indicated in patients with (NYHA class II–IV) heart failure with reduced ejection fraction (LVEF ≤40%)

Recommendations	Class[a]	Level[b]
An ACE-I is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[110–113]	I	A
A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.[114–120]	I	A
An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[121,122]	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[108,109]	I	A
Sacubitril/valsartan is recommended as a replacement for an ACE-I in patients with HFrEF to reduce the risk of HF hospitalization and death.[105]	I	B

SGLT2 inhibitors: what the guidelines and consensus suggest

Table 3 **Definition of heart failure with reduced ejection fraction, mildly reduced ejection fraction and preserved ejection fraction**

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF ≤40%	LVEF 41–49%[b]	LVEF ≥50%
	3	–	–	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c]

SGLT2-i

Class[a]	Level[b]
I	A

CONCLUSIONS

- SGLT2i are a cornerstone of HF therapy
- There may be a benefit in early administration of SGLT2i
- SLGT2i seems to be beneficial in a wild spectrum of both HFrEF and HFpEF
- There still are niche where SGLT2i are underused

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Thank you for your attention

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