



UNIVERSITÀ DEL PIEMONTE ORIENTALE



AOU AL

Azienda Ospedaliero-Universitaria
di ALESSANDRIA

SGLT2 INIBITORI: SOLI O BEN ACCOMPAGNATI?

IL CUORE INFRANTO

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University of Eastern Piedmont*



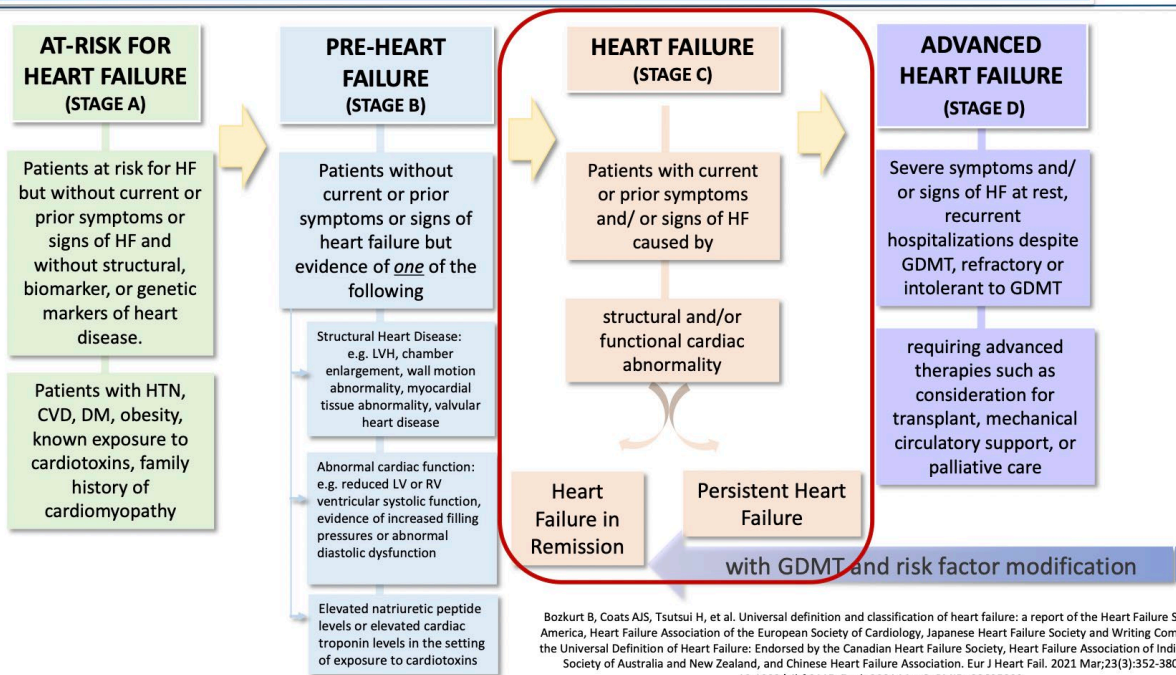
dichiara di NON aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche

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



Universal Definition Stages of HF



HF with reduced EF (HFrEF):

- HF with LVEF $\leq 40\%$

HF with mildly reduced EF (HFmrEF):

- HF with LVEF 41-49%

HF with preserved EF (HFpEF):

- HF with LVEF $\geq 50\%$

HF with improved EF (HFimpEF):

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

Figure 3. New classification of HF according to LVEF.

Heart failure: definition and epidemiology



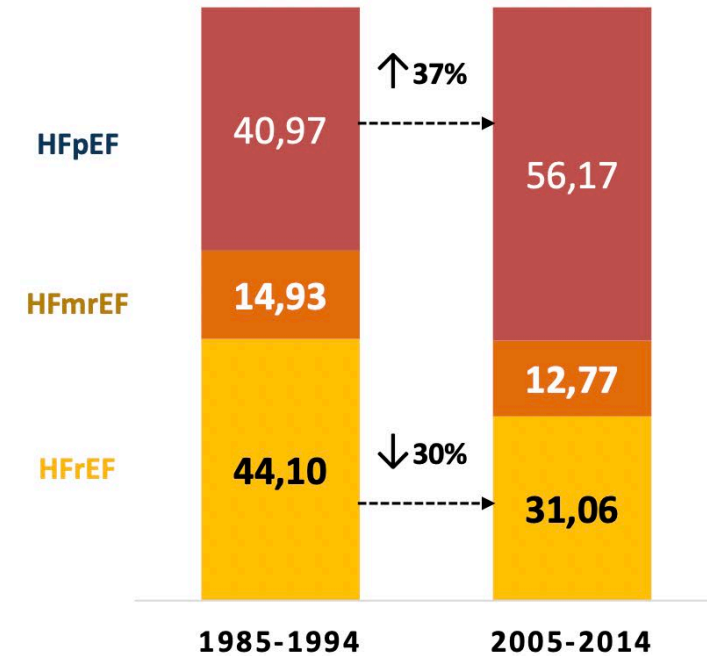
Rising Prevalence of HFpEF

LV dysfunction / HF
post-MI
Prevalence of CAD



Aging
Obesity,
Metabolic syndrome,
Diabetes
CKD
Hypertension

Percentage of Patients Within
Each LVEF Category^{1,a}

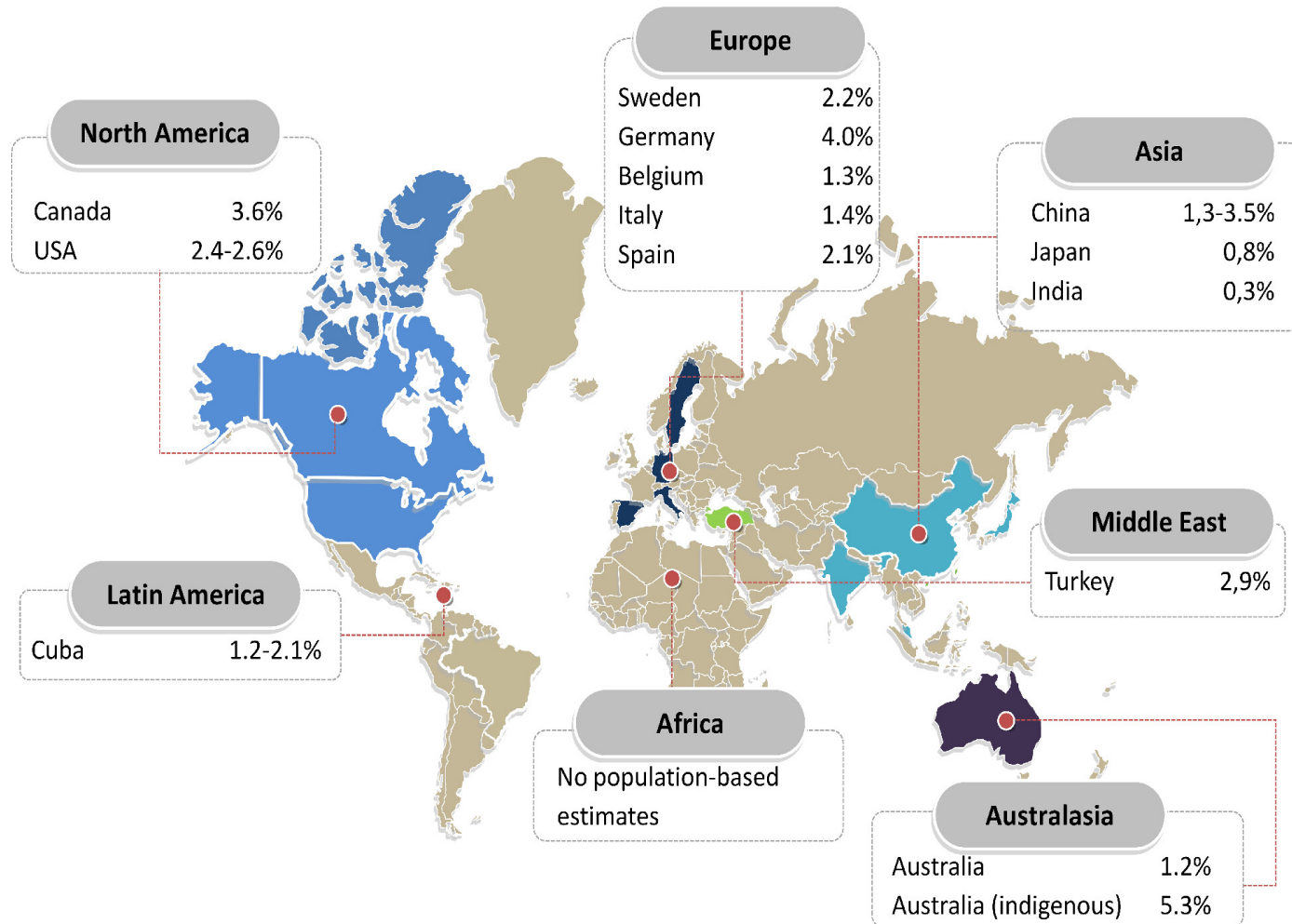


^aHF prevalence data for 894 outpatients with new onset HF from the community based, Framingham Study over 3 decades (1985-2014). LVEF categories were defined as HFrEF (EF <40%), HF with mid-range EF (EF 40-~50%), and HFpEF (EF ≥50%).

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.

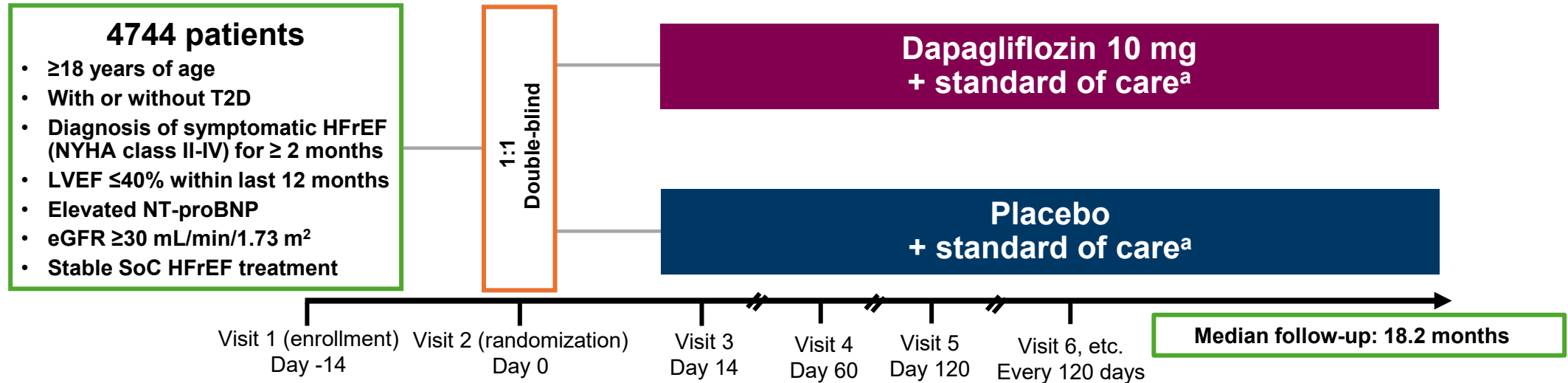
Heart failure: definition and epidemiology



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

Dapagliflozin 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

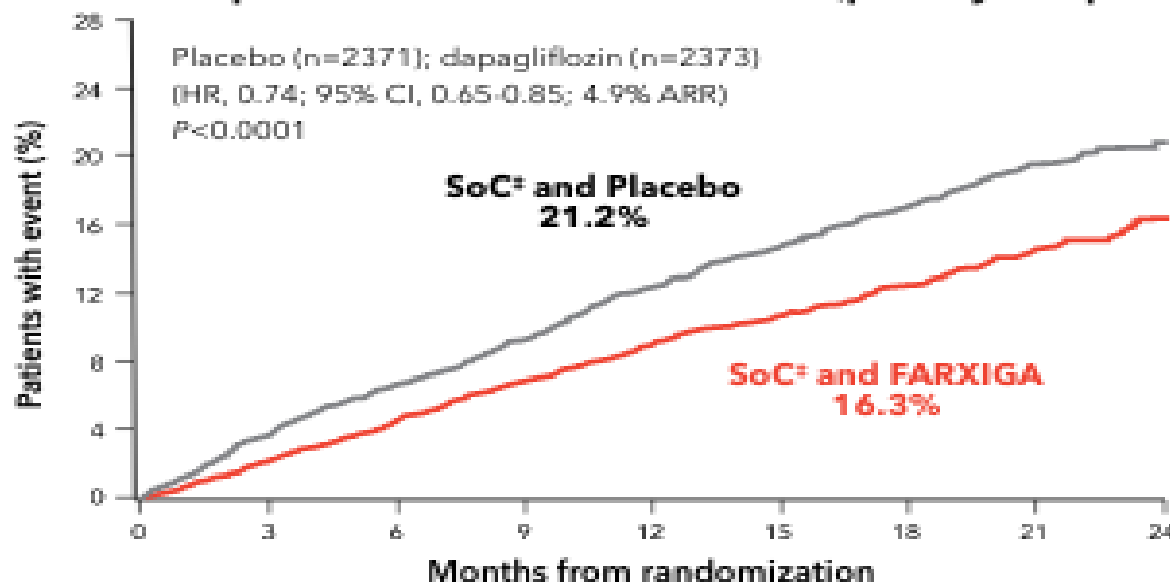
Secondary Endpoints

- 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

Dapagliflozin in HF with reduced EF: DAPA-HF

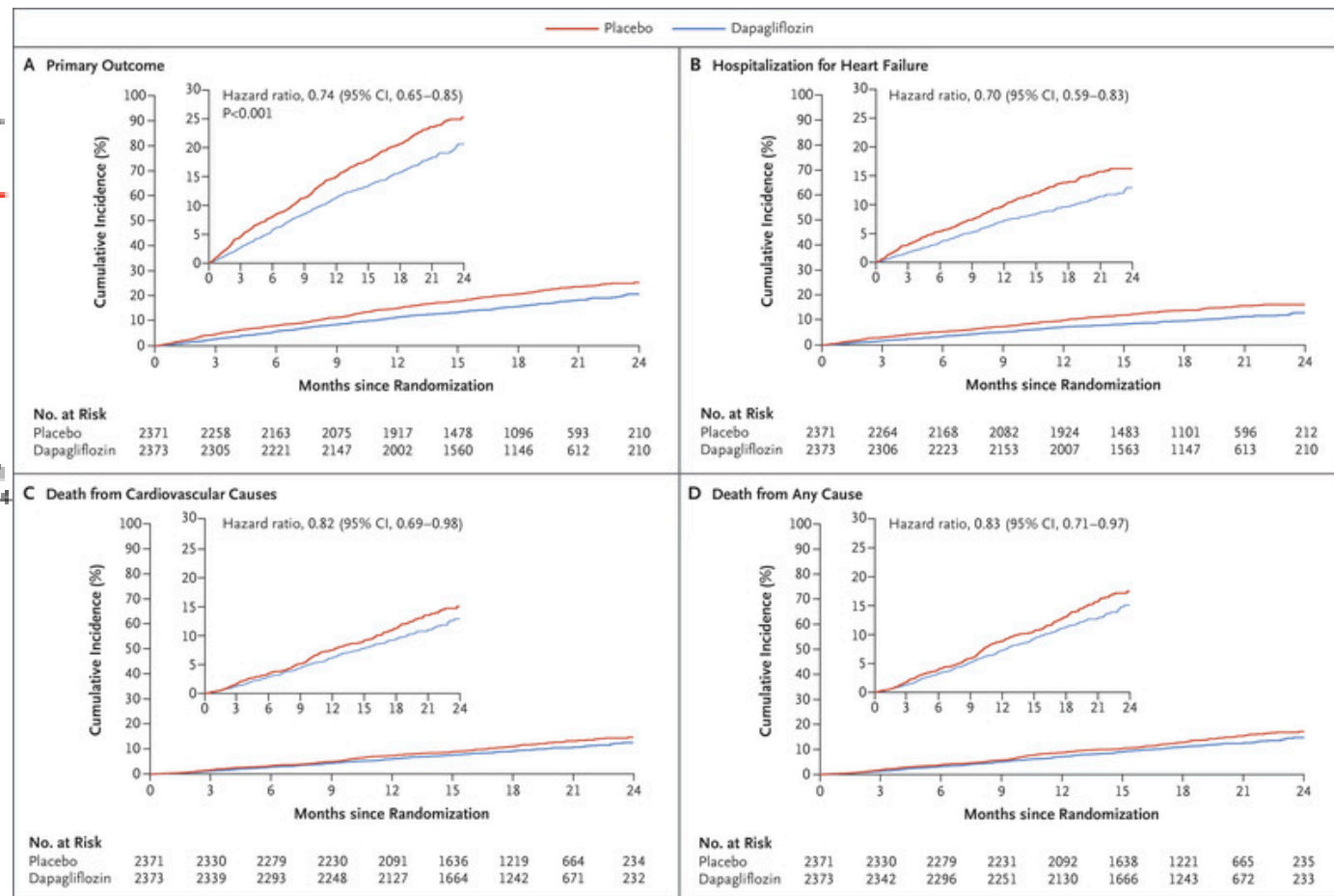


DAPA-HF: Composite of CV death or hospitalization for heart failure^{1,2,*†} (primary end point)



 **NNT=21**

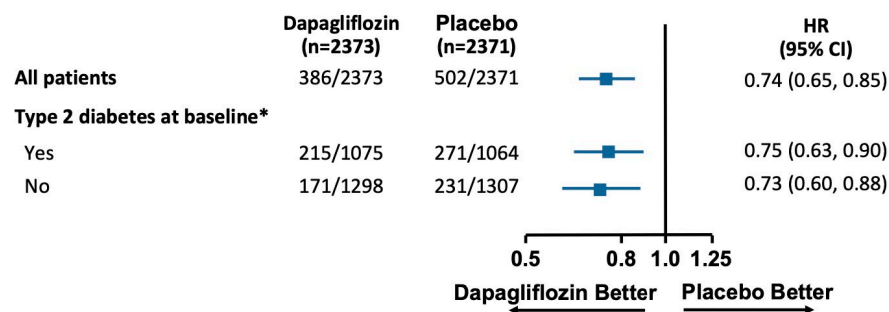
**↓ 26%
RRR**



Dapagliflozin in HF with reduced EF: DAPA-HF

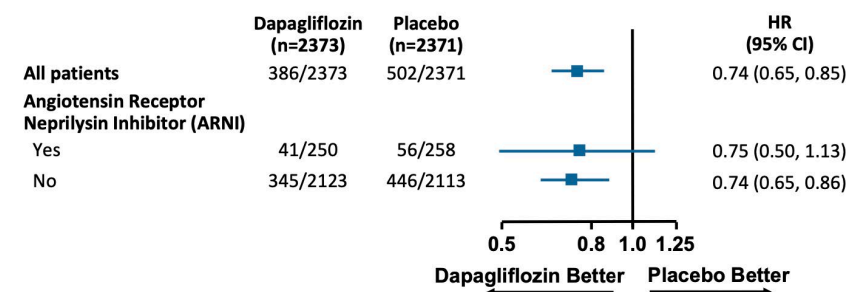


No diabetes/diabetes subgroup: Primary endpoint



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

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



Kansas City Cardiomyopathy Questionnaire (KCCQ)

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

Treatment	Change
Dapagliflozin	+6.1 $\pm$ 18.6
Placebo	+3.3 $\pm$ 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

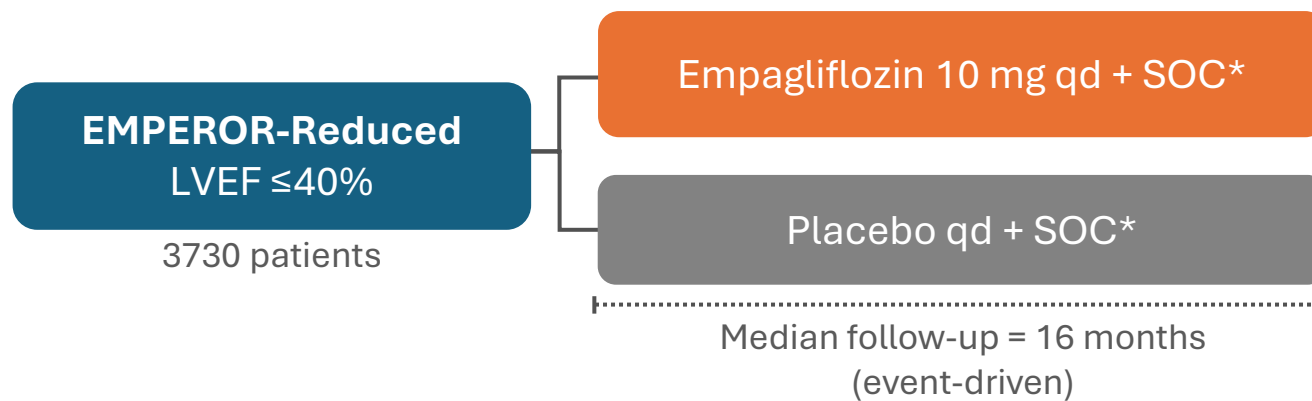
Composite of: Sustained* $\geq 50\%$ reduction in eGFR, end-stage renal disease (ESRD) or death from renal causes

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/1.73m², sustained dialysis or kidney transplantation

Empagliflozin in HF with reduced EF: EMPEROR Reduced



COMPOSITE PRIMARY ENDPOINT

Time to first event of adjudicated CV death or adjudicated HHF

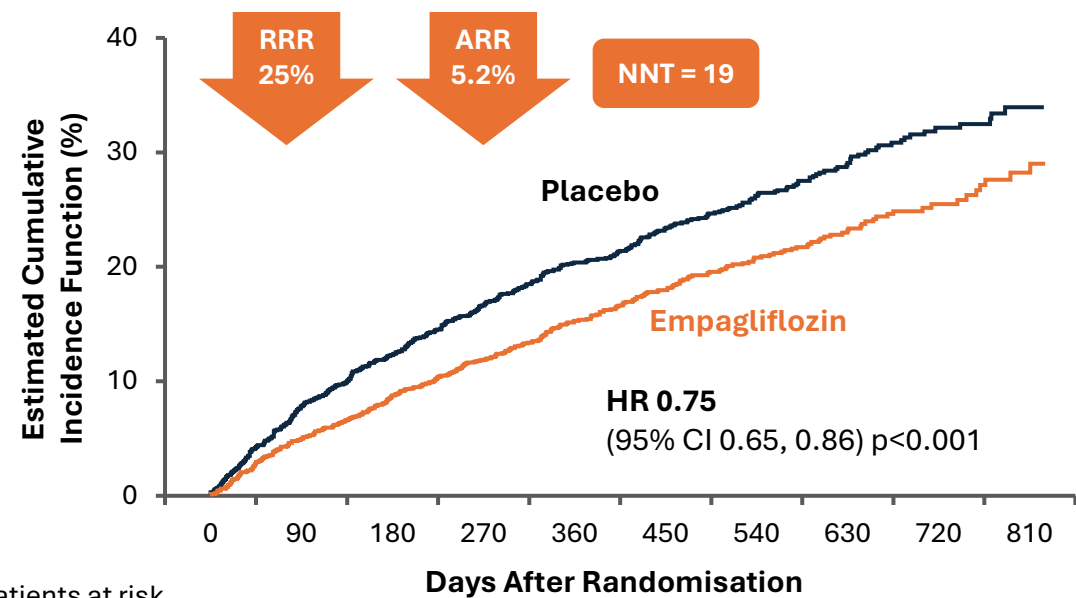
SECONDARY ENDPOINTS

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

Empagliflozin in HF with reduced EF: EMPEROR Reduced



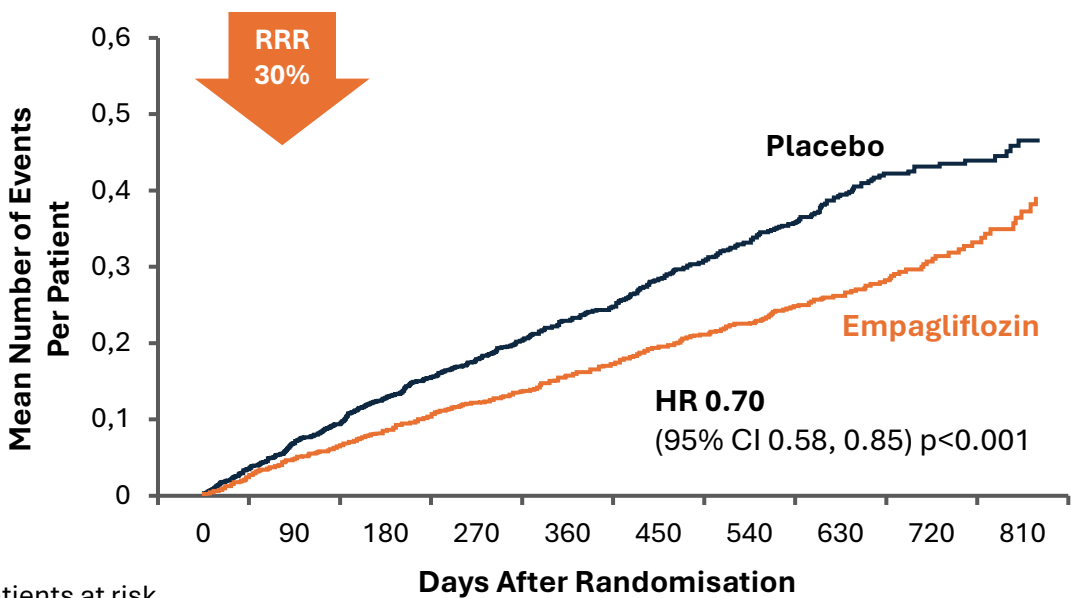
First Adjudicated CV Death or Hospitalisation for Heart Failure



Patients at risk

	0	90	180	270	360	450	540	630	720	810
Placebo	1867	1715	1612	1345	1108	854	611	410	224	109
Empagliflozin	1863	1763	1677	1424	1172	909	645	423	231	101

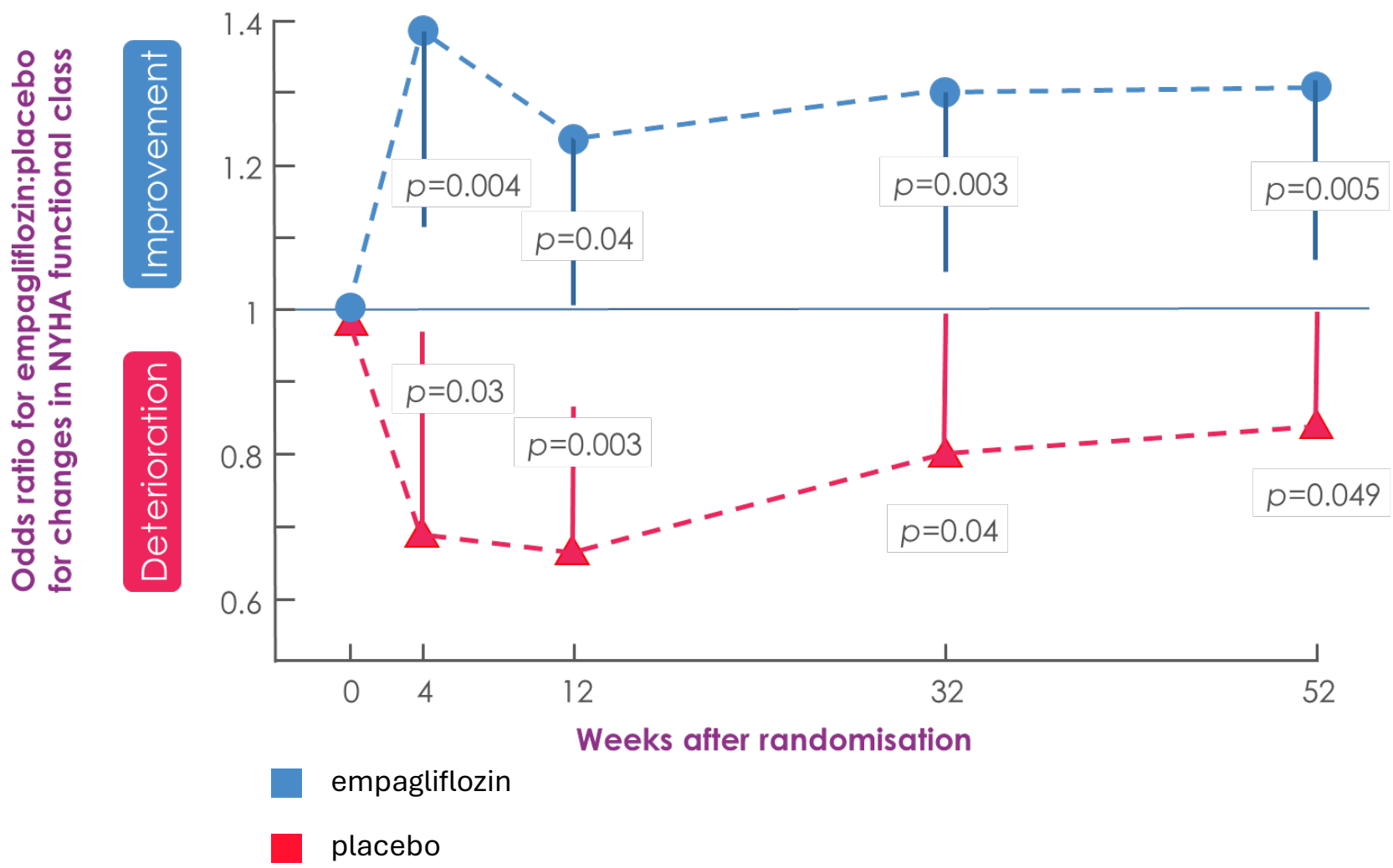
Adjudicated Total Hospitalisations for Heart Failure (First and Recurrent)



Patients at risk

	0	90	180	270	360	450	540	630	720	810
Placebo	1867	1820	1762	1526	1285	1017	732	497	275	135
Empagliflozin	1863	1826	1768	1532	1283	1008	732	495	272	118

Empagliflozin in HF with reduced EF: EMPEROR Reduced

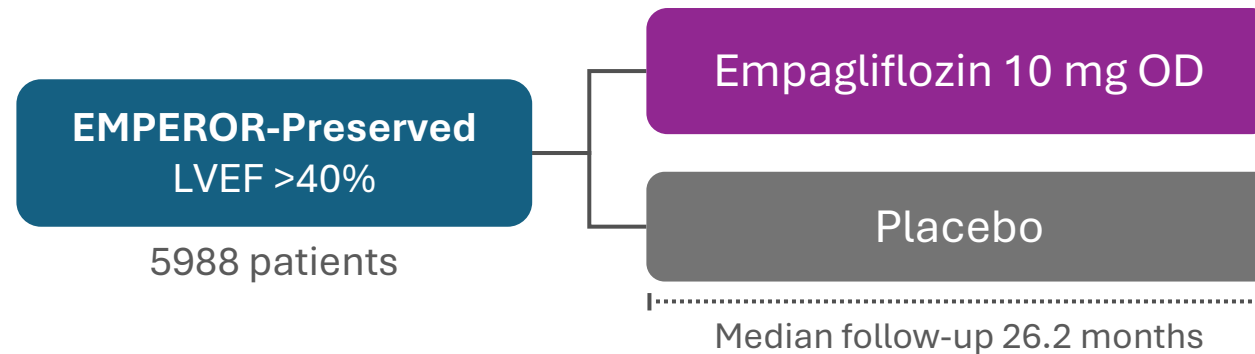


Empagliflozin in HF with preserved EF: EMPEROR Preserved



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 $\text{eGFR} \geq 20 \text{ mL/min/1.73m}^2$



Confirmatory endpoints

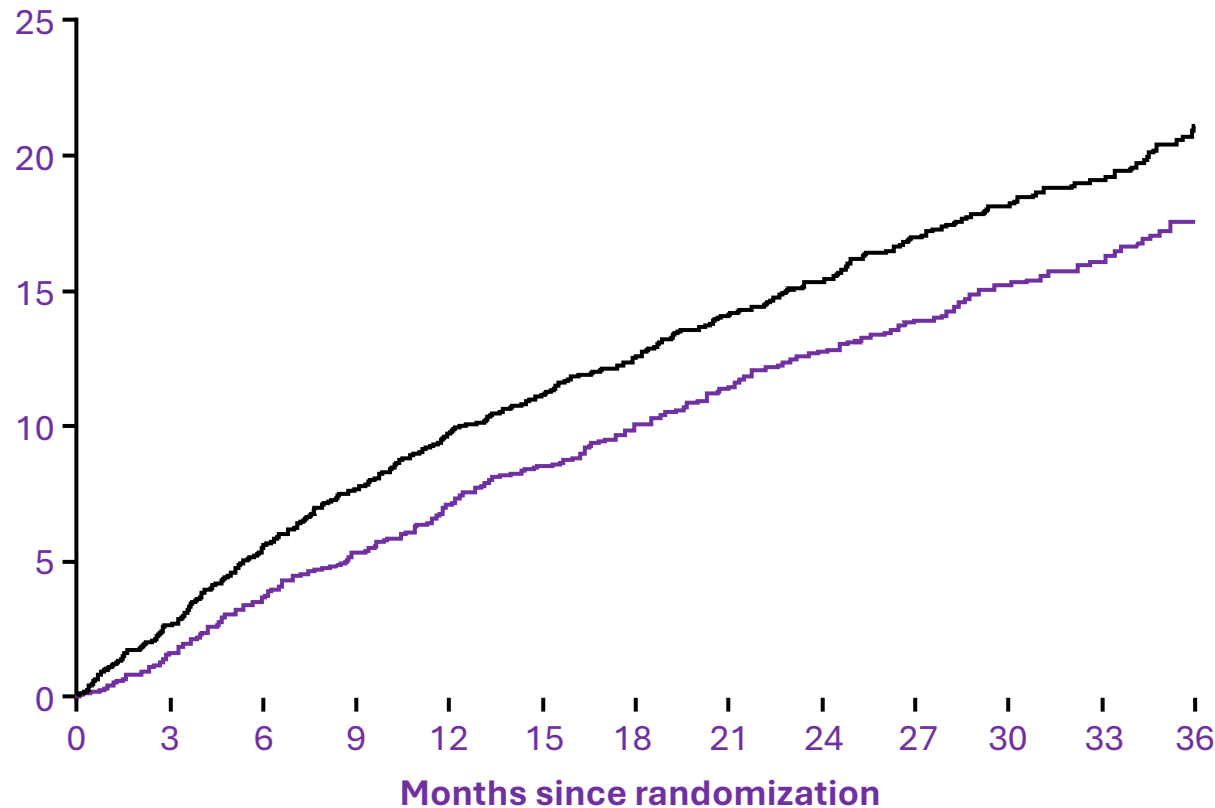
PRIMARY ENDPOINT

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

Empagliflozin 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:

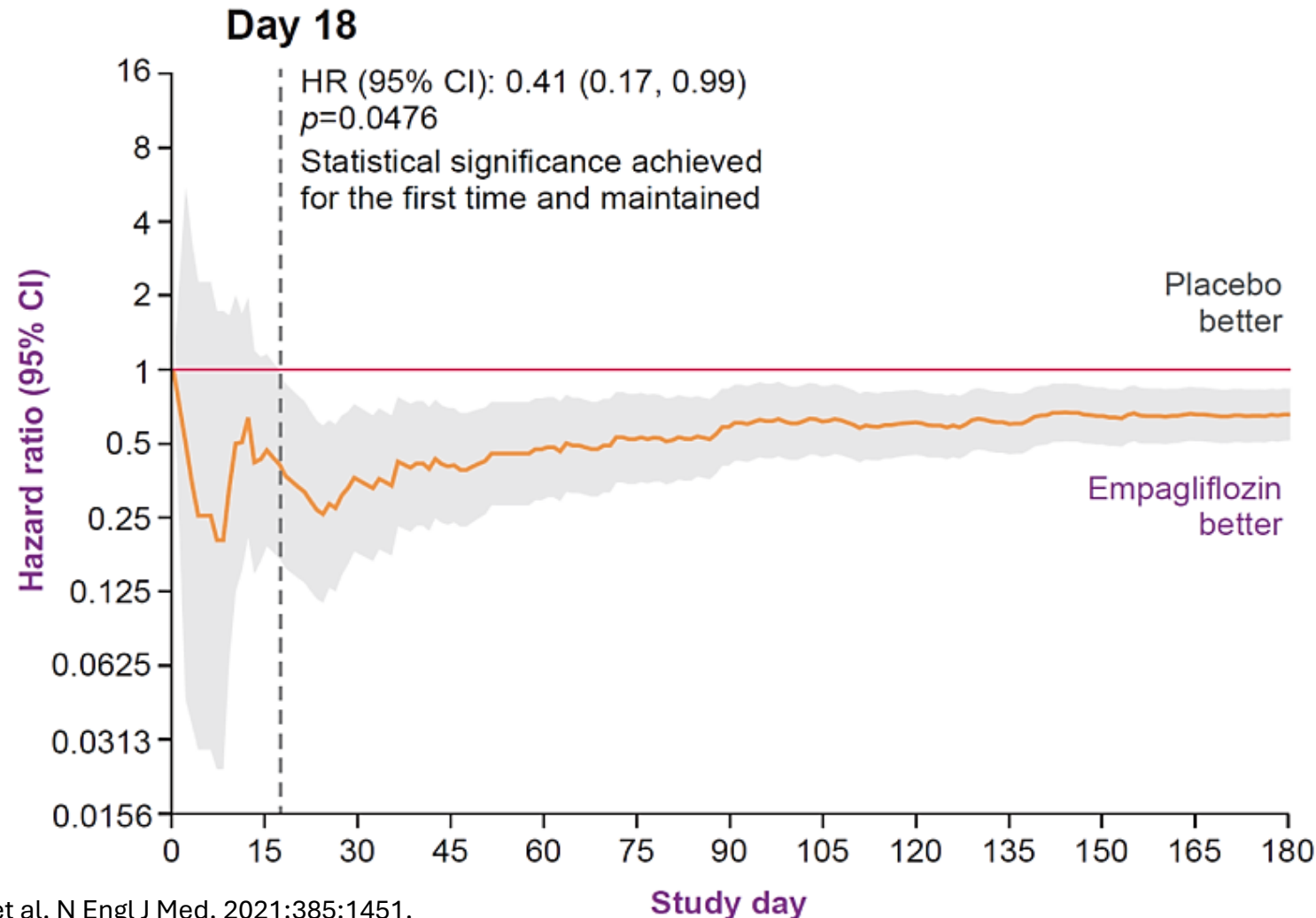
511 (17.1%) patients with event

Rate: 8.7/100 patient-years

Empagliflozin in HF with preserved EF: EMPEROR Preserved



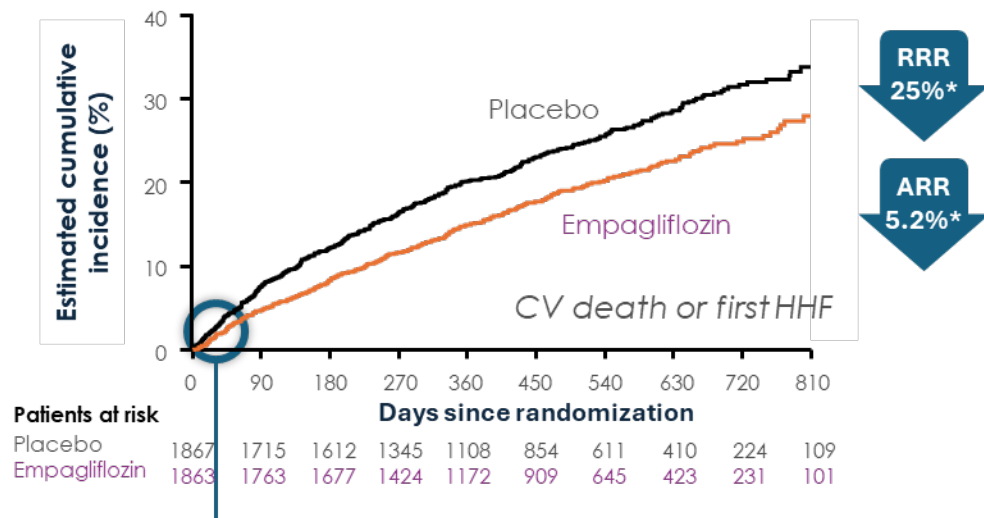
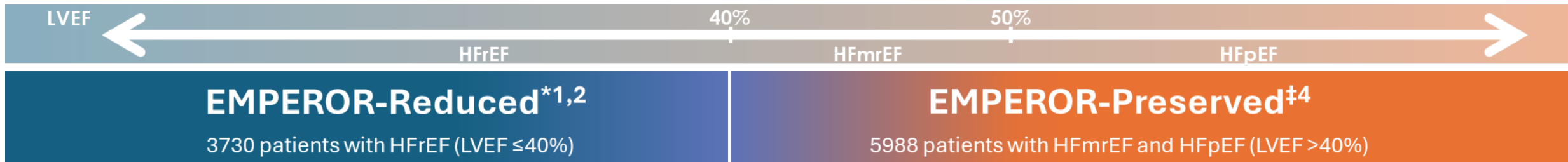
Effect of empagliflozin vs placebo on time to cardiovascular death or heart failure hospitalization



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.

SGLT2 and HF: when?

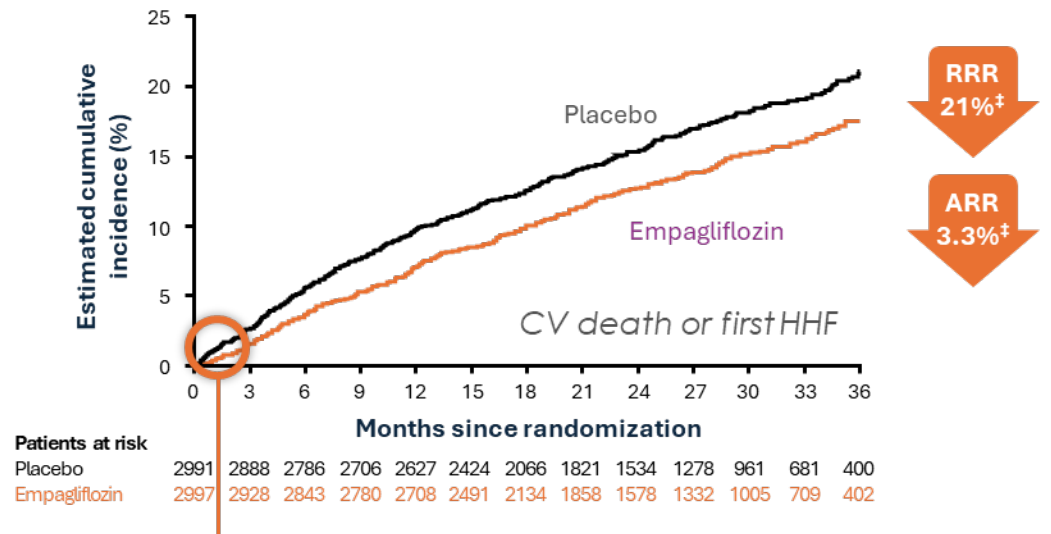
Empagliflozin demonstrated early, significant and sustained reductions in the risk of CV death or first HHF across the LVEF spectrum compared with placebo



Statistical significance:^{†3}

Reached **12 days after randomization**

Sustained from day 34

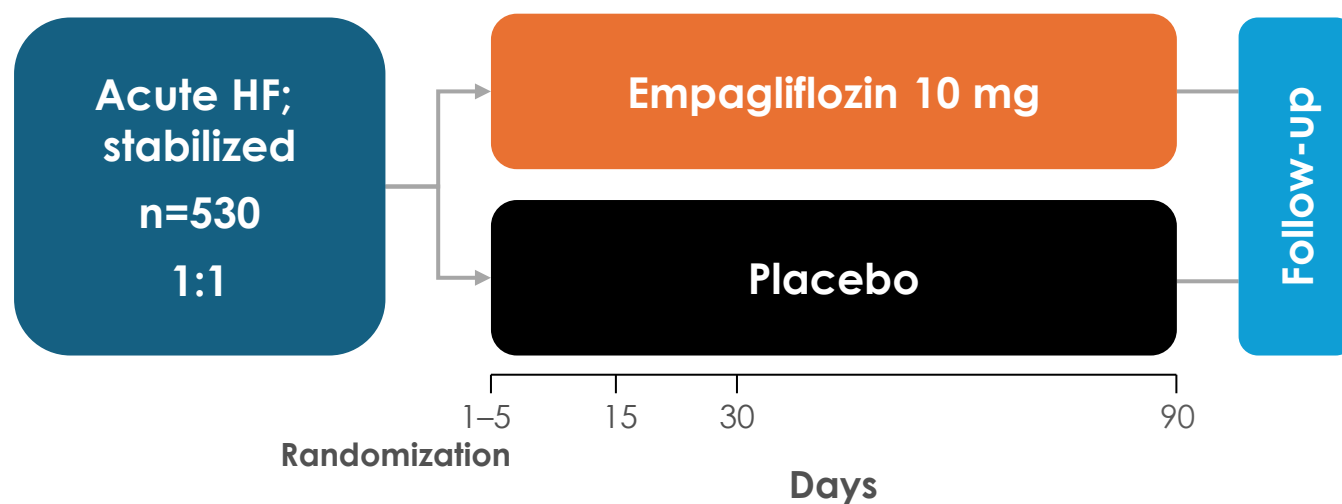


Statistical significance:⁵

Reached **18 days after randomization**

Sustained for the duration of the follow-up period

Early Empagliflozin in HF: the EMPULSE trial

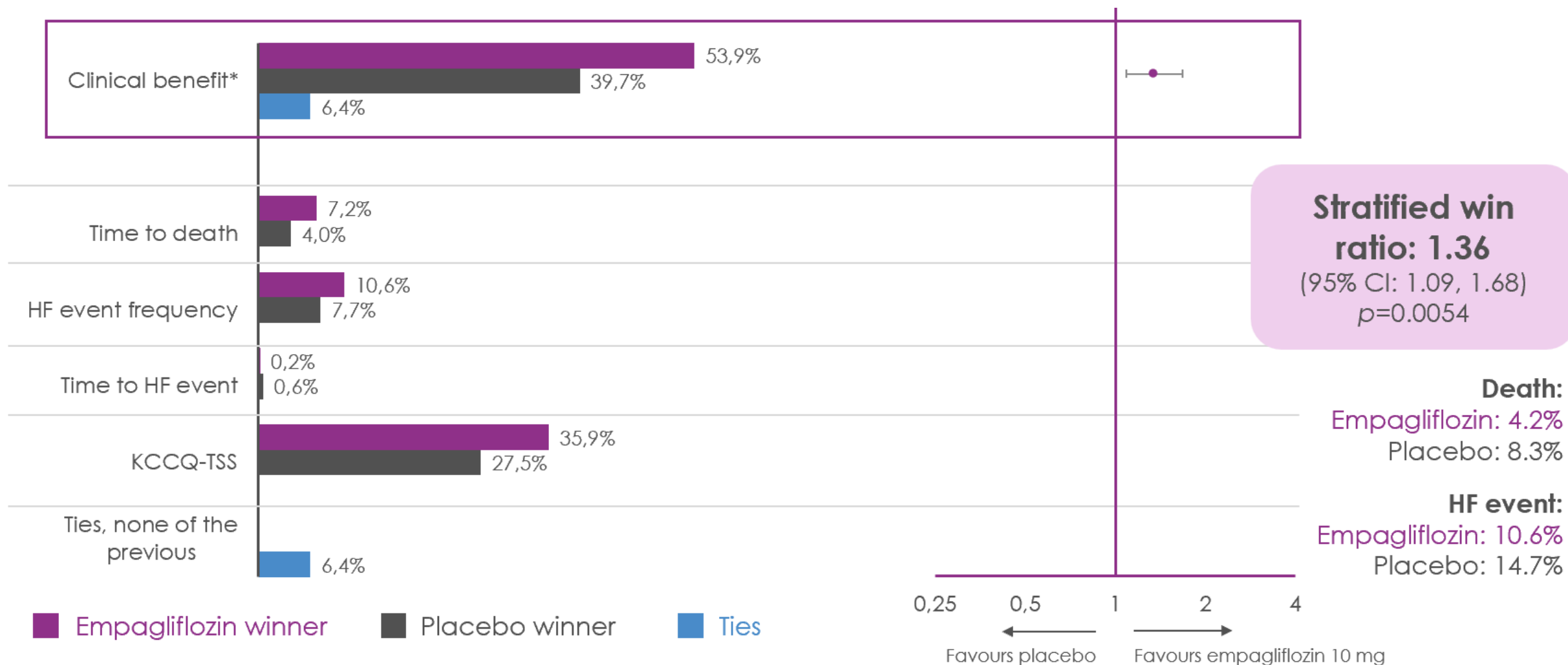


Median time from hospital admission
to randomization was **3 days**

Primary endpoint

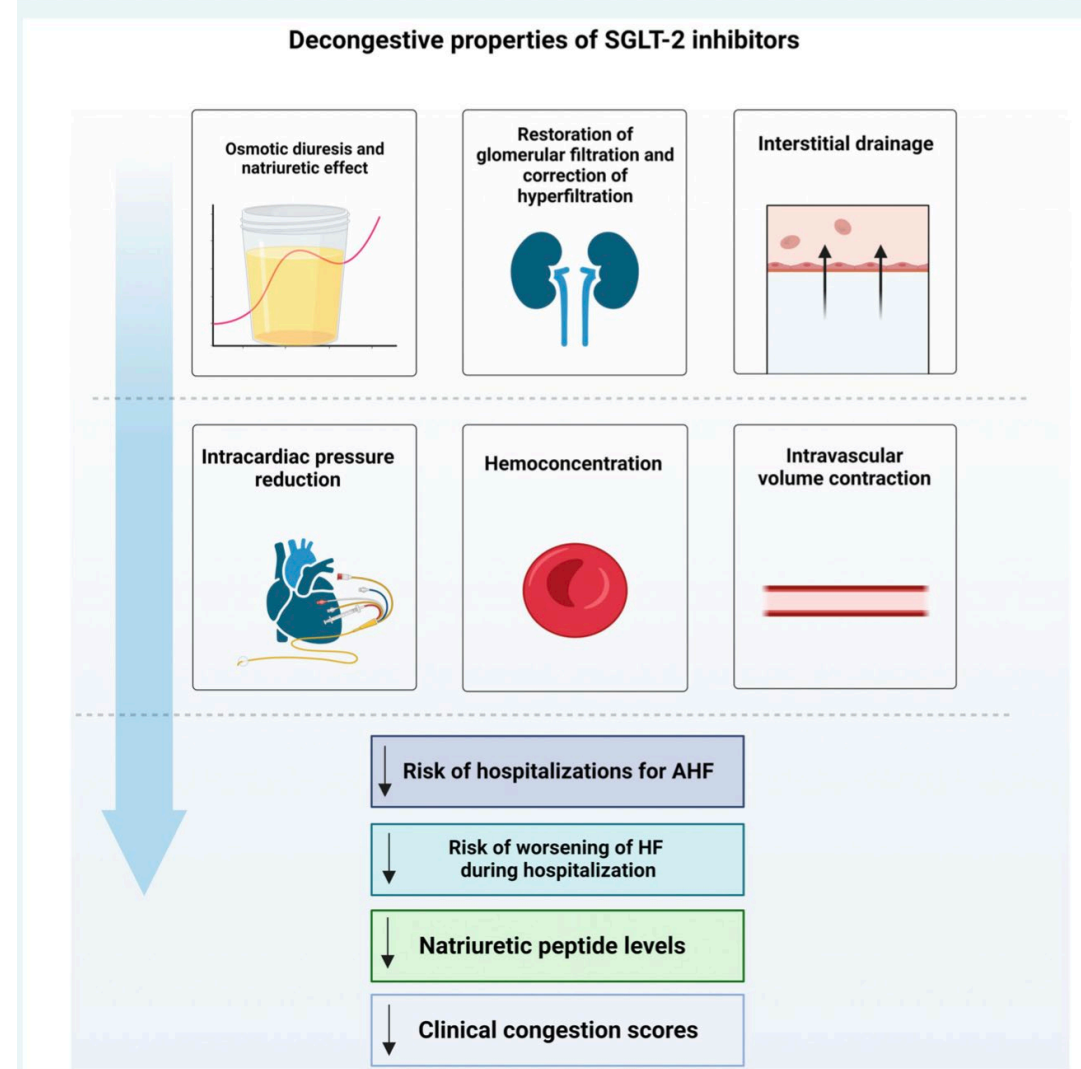
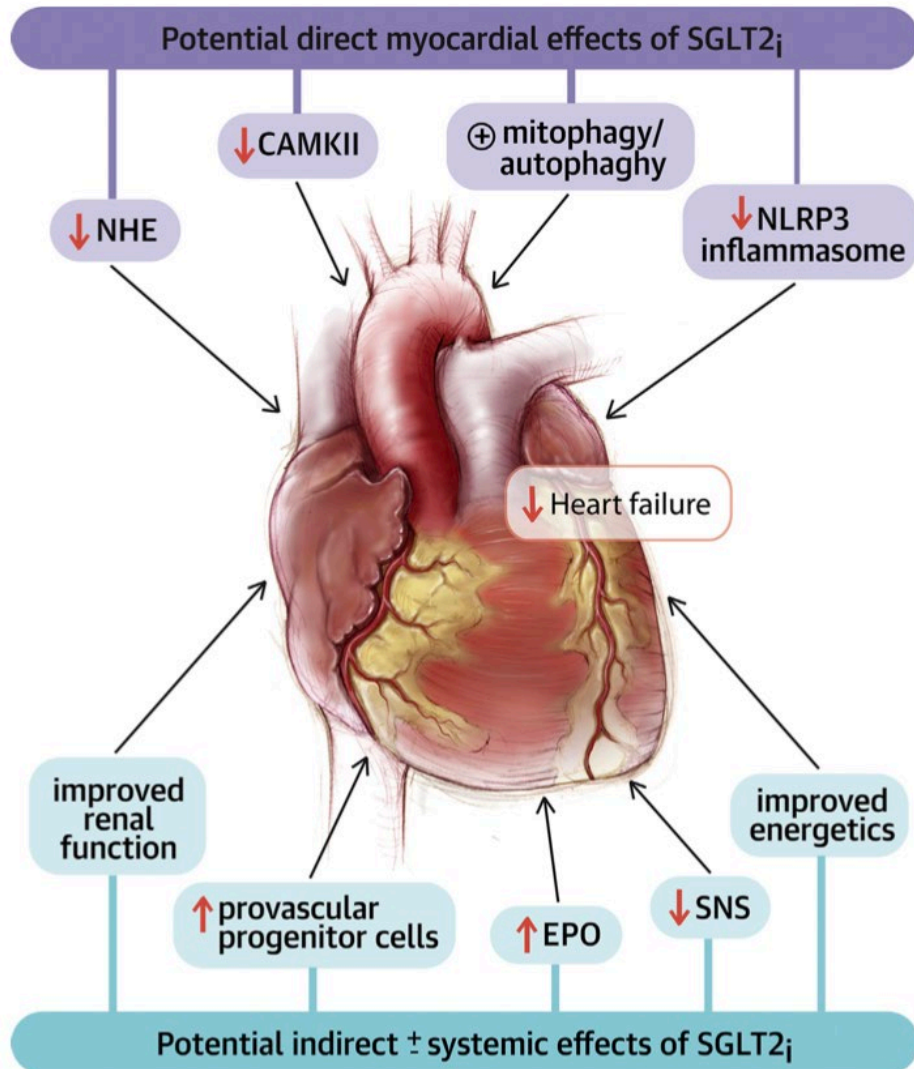
- Clinical benefit evaluated with a win ratio based on a composite of:
 - Death
 - Number of HFEs (including HHFs, urgent HF visits and unplanned outpatient visits)
 - Time to first HFE
 - ≥ 5 -point difference in the KCCQ-TSS change from baseline after 90 days of treatment

Early Empagliflozin in HF: the EMPULSE trial



*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

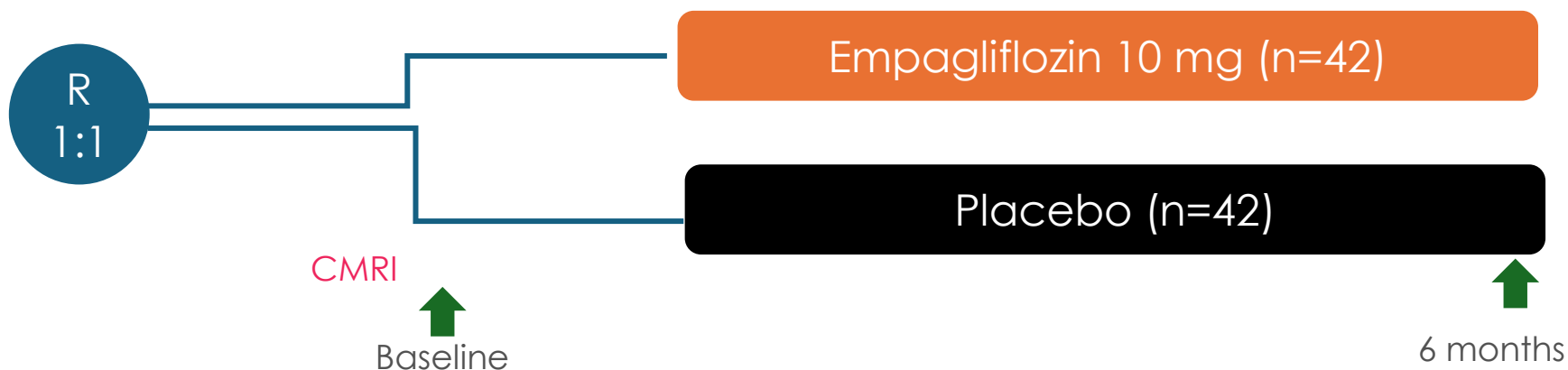
Heart failure: why SGLT2 inhibitors



Empagliflozin and cardiac remodeling



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



Inclusion criteria & selected baseline characteristics

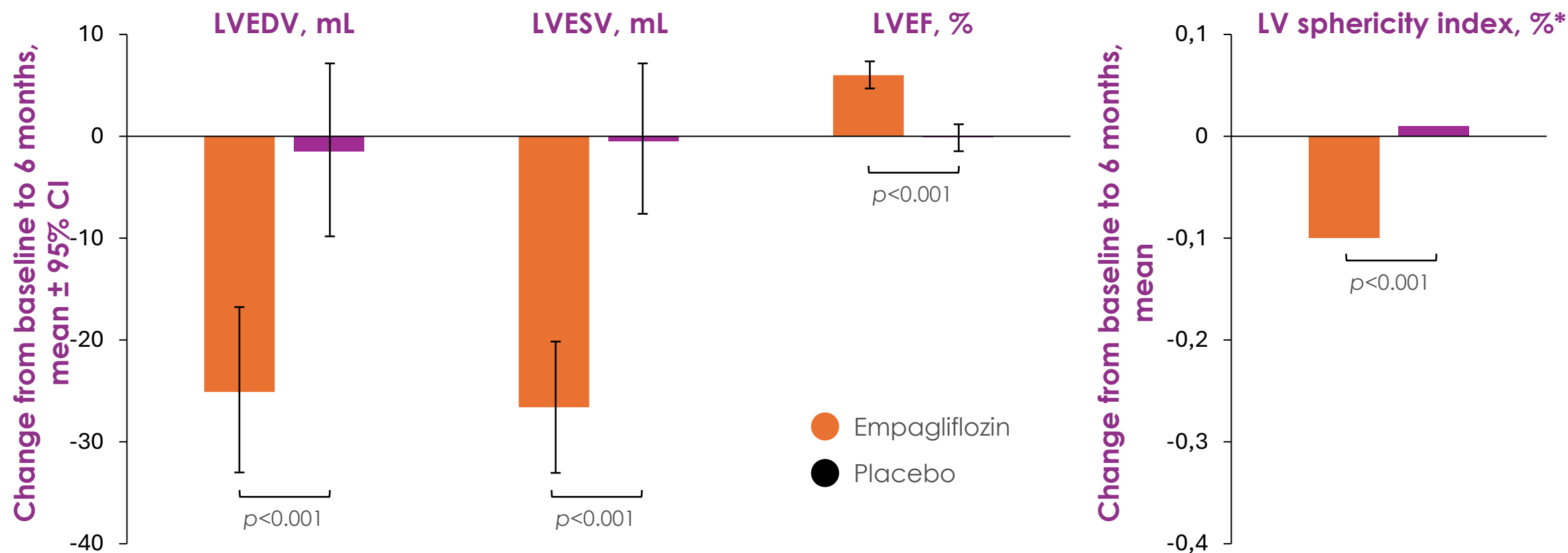
- Adult patients (>18 years)
- HF (NYHA II–III)
- LVEF <50%
- Stable symptoms and medical therapy
- Patients with diabetes were **excluded**

	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

Empagliflozin and cardiac remodeling



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



Mean (SD) at:

Baseline

6 months

219.8 $\pm$ 75.8 210.4 $\pm$ 68.9

194.7 $\pm$ 69.7 208.9 $\pm$ 72.8

143.6 $\pm$ 66.3 135.1 $\pm$ 54.8

117.0 $\pm$ 60.0 134.5 $\pm$ 58.9

36.2 $\pm$ 8.2 36.5 $\pm$ 8.0

42.2 $\pm$ 9.2 36.3 $\pm$ 8.5

0.62 $\pm$ 0.16 0.58 $\pm$ 0.12

0.52 $\pm$ 0.11 0.59 $\pm$ 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)

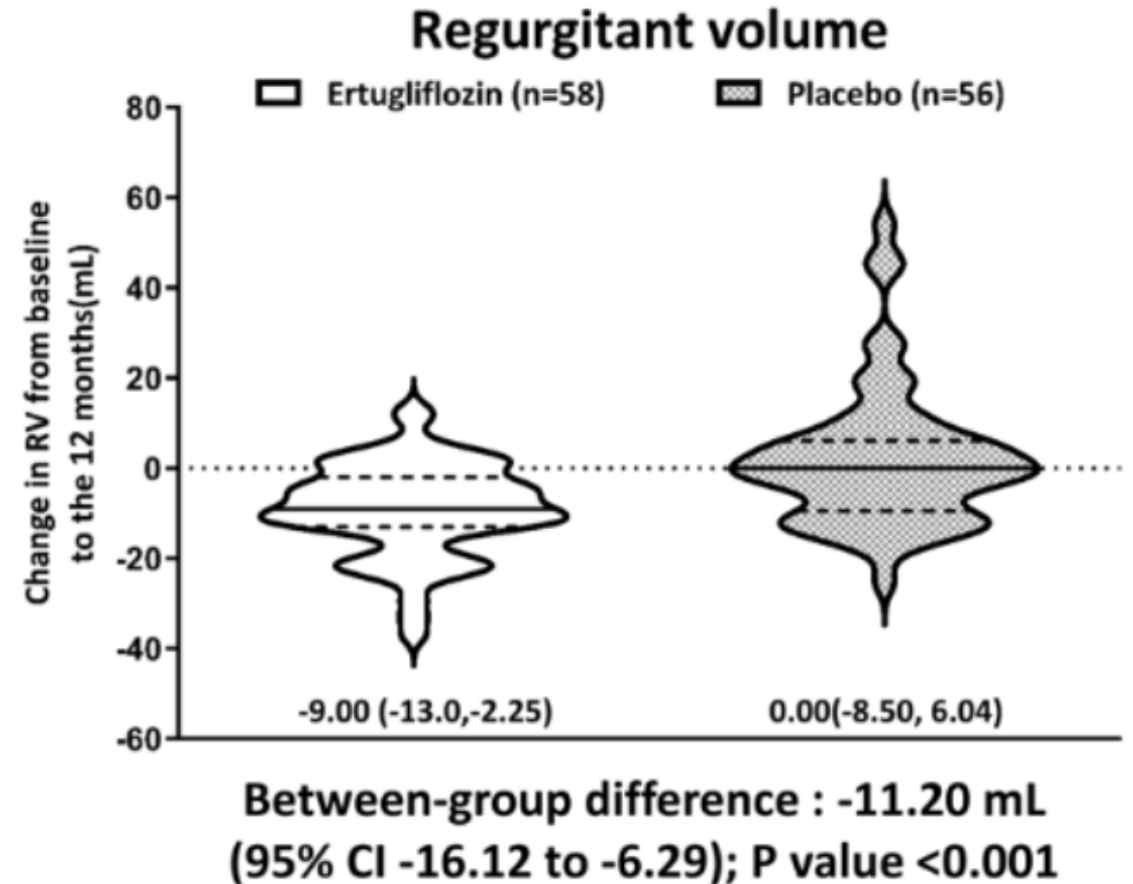
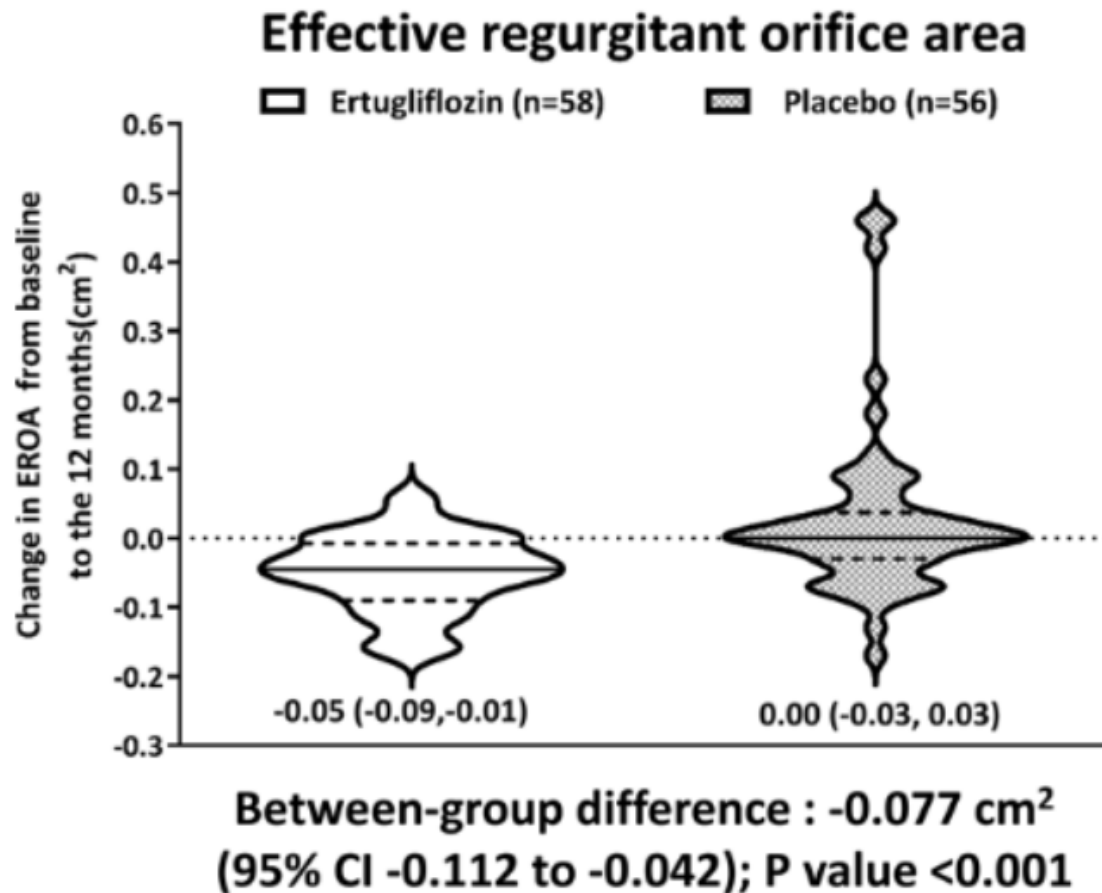
Etiology of MR and echo at baseline

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)

Heart failure and functional MR: SGLT2i the EFFORT Trial



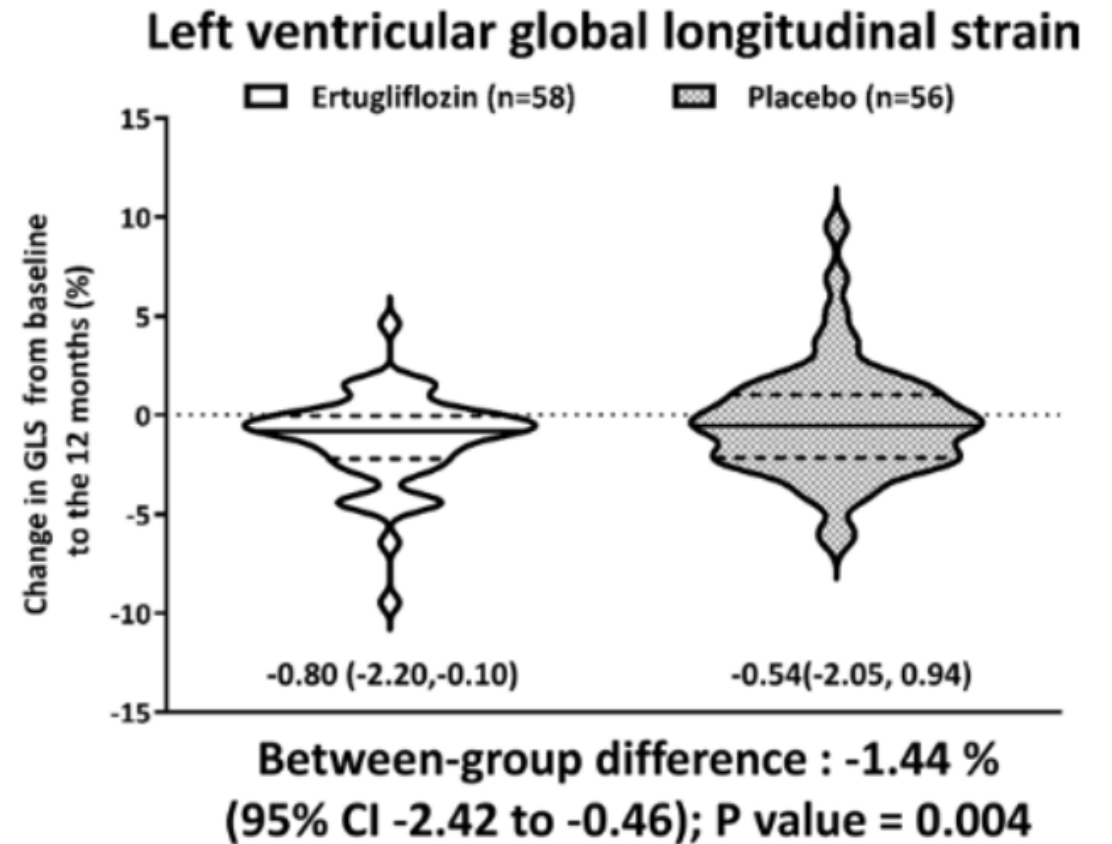
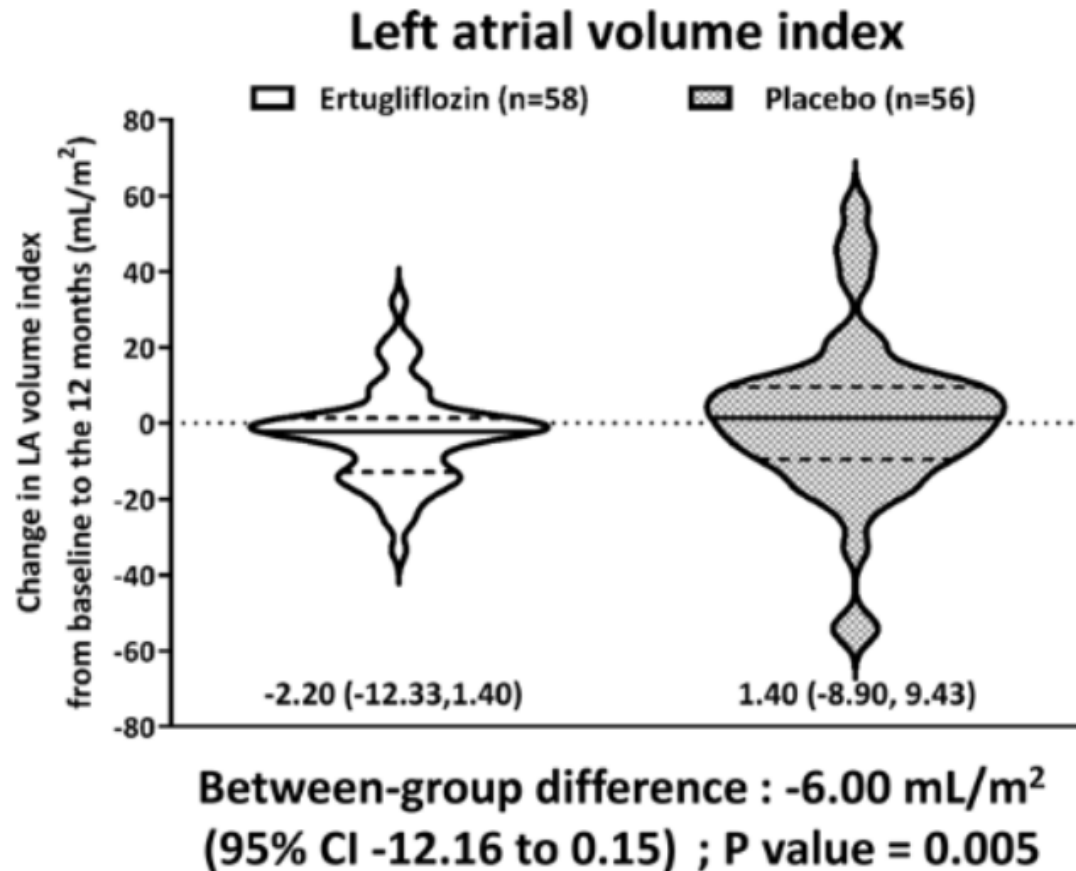
- Patients with HF (LVEF 35-50%) NYHA II or III with or without DM and substantial MR (EROA >0.1 cm²) despite OMT
 - Randomization to receive ertugliflozin or placebo in addition to OMT
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Heart failure and functional MR: SGLT2i the EFFORT Trial



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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	

SGLT2i and arrhythmias



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: $39.2 \pm 14.6\%$
- 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

Atrial arrhythmias

AF: RR: 0.88(0.78,1.00)

AFL: RR: 0.78(0.60,1.03)

AF/AFL: RR: 0.86(0.77,0.96)

Ventricular arrhythmias

VF: RR: 1.05(0.70,1.59)

VT: RR: 0.99(0.80,1.22)

VES: RR: 1.36(0.67,2.76)

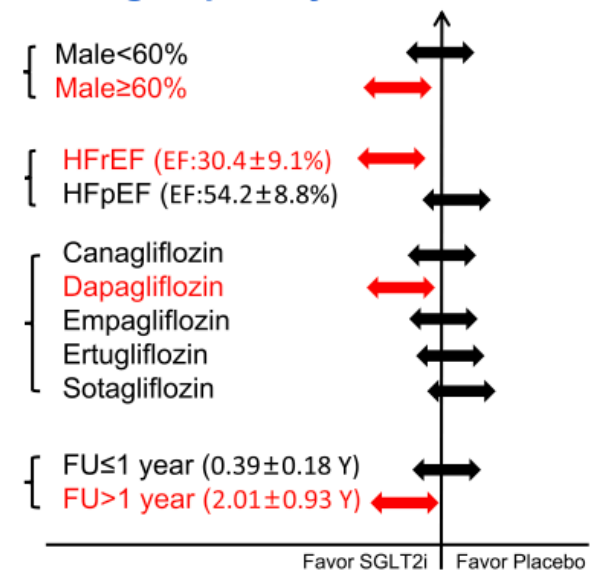
Sudden cardiac death

SCD: RR: 0.85(0.63,1.14)

SCD
in HF only: RR: 0.67(0.44-1.01)

Favor SGLT2i | Favor Placebo

Subgroup analyses for AF



Meta-regression for AF: Gender & LVEF

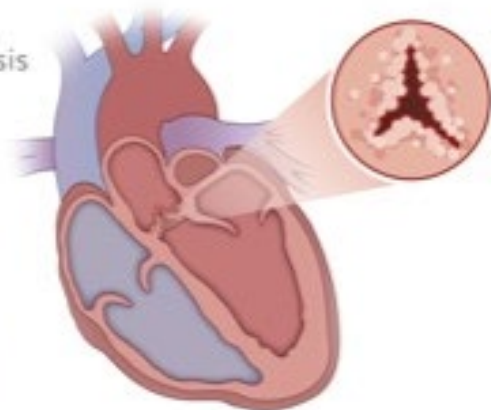
Variables	Effect of SGLT2i on AF			
	Coef.	Z value	P value	Log RR 95%CI
Male, %	-0.021	-2.34	0.019	-0.039 to -0.0035
LVEF, %	0.024	2.62	0.009	0.006 to 0.04

SLGT2i and TAVI: DAPA TAVI trial



Patients

- 1222 adults in primary analysis
- Mean age: 82 years
- Men: 51%; Women 49%



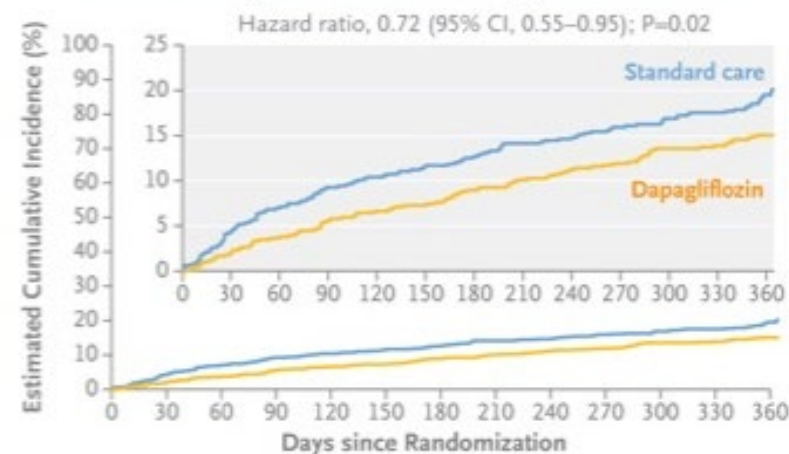
Dapagliflozin + Standard Care



Standard Care

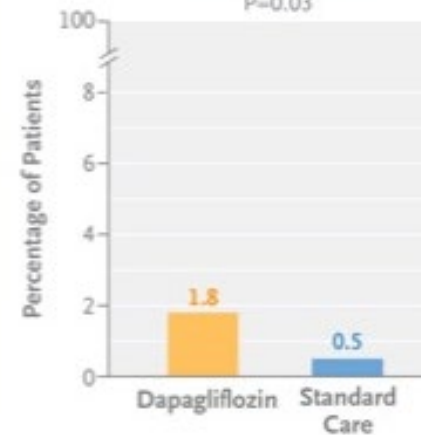


Death from Any Cause or Worsening of Heart Failure



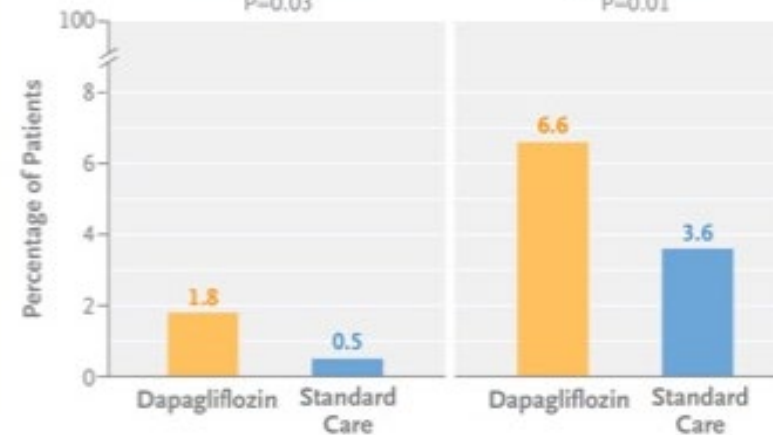
Genital infection

P=0.03



Hypotension

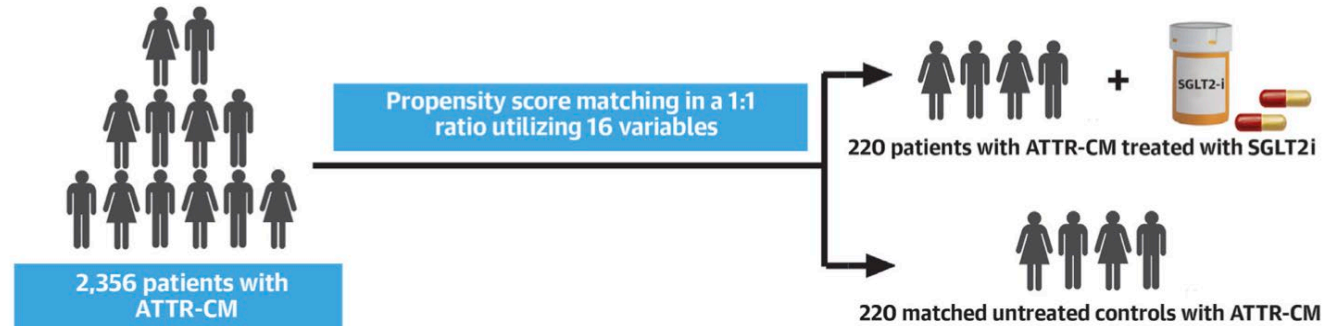
P=0.01



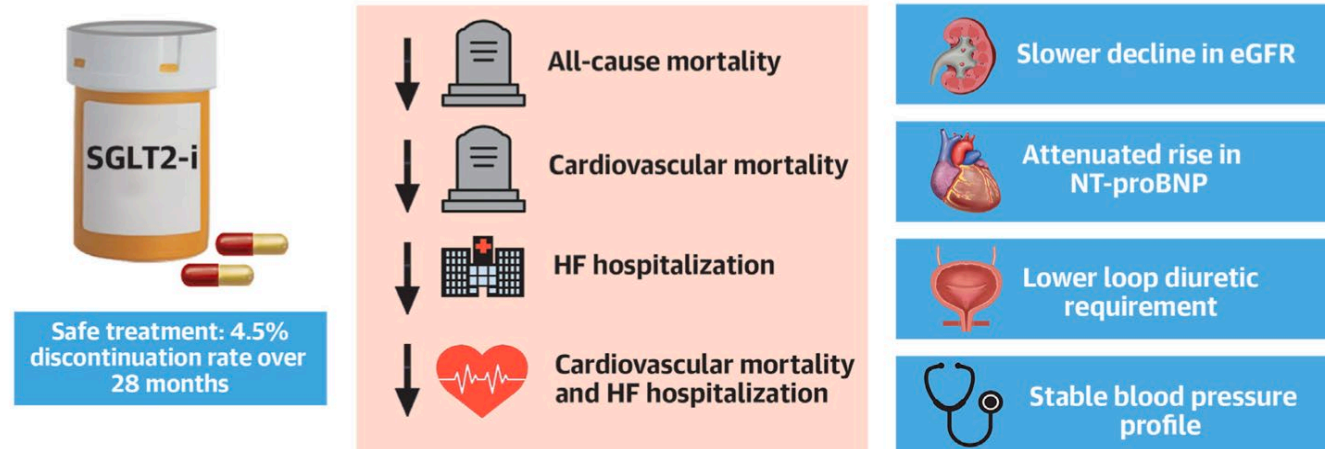
SGLT2i and amyloid cardiomyopathy



Study Design and Population



Main Findings



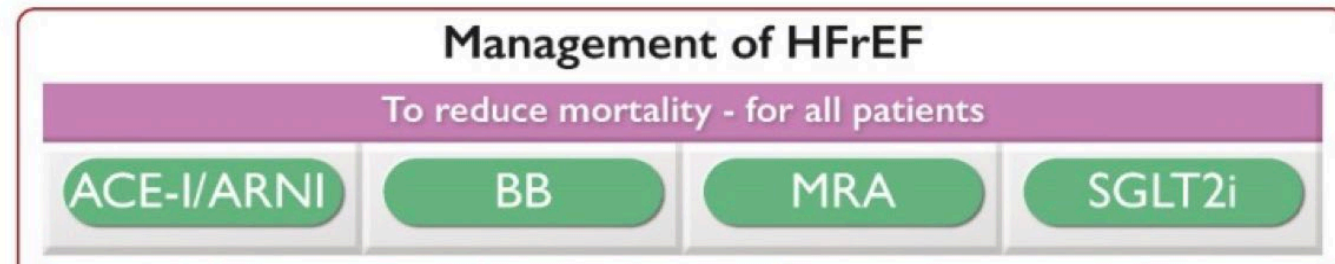
SGLT2 inhibitors: what the guidelines and consensus suggest



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

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

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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

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SGLT2-i		Class ^a	Level ^b
		I	A



- ❖ SGLT2i are a cornerstone of HF therapy
- ❖ There may be a benefit in early administration of SGLT2i
- ❖ SGLT2i seems to be beneficial in a wide 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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