



Tavola rotonda 3

## SGLT2 INIBITORI NEL PAZIENTE CON SCOMPENSO CARDIACO - Il problema -

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#### Disclosures

Nothing to be declared.

## Classification of HF

Type of	HF	HFrEF	HFmrEF	HFpEF
٩	1	Symptoms ± Signs <sup>a</sup>	Symptoms ± Signs <sup>a</sup>	Symptoms ± Signs <sup>a</sup>
ERI	2	LVEF ≤40%	LVEF 41-49% <sup>b</sup>	LVEF ≥50%
CRIT	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 <sup>c</sup>

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; LV = left ventricle; LVEF = left ventricular ejection fraction.

<sup>a</sup>Signs may not be present in the early stages of HF (especially in HFpEF) and in optimally treated patients.

<sup>b</sup>For the diagnosis of HFmrEF, the presence of other evidence of structural heart disease (e.g. increased left atrial size, LV hypertrophy or echocardiographic measures of impaired LV filling) makes the diagnosis more likely.

For the diagnosis of HFpEF, the greater the number of abnormalities present, the higher the likelihood of HFpEF.

## Diagnosis & Management



McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021 Aug 27:ehab368.

# Pharmacological treatments of HFrEF

Recommendations	<b>Class</b> <sup>a</sup>	Level <sup>b</sup>
An ACE-I is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death. <sup>110–113</sup>	1	A
A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death. <sup>114–120</sup>	1	A
An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death. <sup>121,122</sup>	1	Α
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death. <sup>108,109</sup>	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. <sup>105</sup>	I	В

McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021 Aug 27:ehab368.

## 2008 FDA Guidance

#### **Guidance for Industry**

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

> U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER)

> > December 2008 Clinical/Medical

To establish the safety of a new antidiabetic therapy to treat type 2 diabetes, sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk.  $\rightarrow$  CVOTs (Cardiovascular Outcome Trials).

- Independent cardiovascular endpoints (should include MACE) committee.
- Patients at higher risk of cardiovascular events (s.a. relatively advanced disease, elderly, renal impairment).
- Sponsors should perform a meta-analysis of the important cardiovascular events across phase 2 and phase 3 controlled clinical trials and explore similarities and/or differences in subgroups (e.g., age, sex, race), if possible.

#### CVOTs Timeline



Cefalu WT, Kaul S, Gerstein HC, et al. Cardiovascular Outcomes Trials in Type 2 Diabetes: Where Do We Go From Here? Reflections From a *Diabetes Care* Editors' Expert Forum. Diabetes Care Jan 2018;41:14-31.

#### **EMPA-REG OUTCOME**



- Patients with T2DM, ≥18 years of age and high cardiovascular risk, BMI ≤45 Kg/m<sup>2</sup>, eGFR ≥30 ml/min/1.73m<sup>2</sup>.
- Mean age: 63.1 years; female: 28.5%; Median observation time: 3.1 years

#### **EMPA-REG OUTCOME**



Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med 2015; 373:2117-2128.

#### **EMPA-REG OUTCOME**



Event	Placebo (N = 2333)	Empagliflozin, 10 mg (N = 2345)	Empagliflozin, 25 mg (N=2342)	Pooled Empagliflozin (N = 4687)
		number of pa	tients (percent)	
Any adverse event	2139 (91.7)	2112 (90.1)	2118 (90.4)	4230 (90.2)†
Severe adverse event	592 (25.4)	536 (22.9)	564 (24.1)	1100 (23.5)‡
Serious adverse event				
Any	988 (42.3)	876 (37.4)	913 (39.0)	1789 (38.2)†
Death	119 (5.1)	97 (4.1)	79 (3.4)	176 (3.8)§
Adverse event leading to discontinuation of a study drug	453 (19.4)	416 (17.7)	397 (17.0)	813 (17.3)§
Confirmed hypoglycemic adverse event¶				
Any	650 (27.9)	656 (28.0)	647 (27.6)	1303 (27.8)
Requiring assistance	36 (1.5)	33 (1.4)	30 (1.3)	63 (1.3)
Event consistent with urinary tract infection	423 (18.1)	426 (18.2)	416 (17.8)	842 (18.0)
Male patients	158 (9.4)	180 (10.9)	170 (10.1)	350 (10.5)
Female patients	265 (40.6)	246 (35.5)	246 (37.3)	492 (36.4)‡
Complicated urinary tract infection**	41 (1.8)	34 (1.4)	48 (2.0)	82 (1.7)
Event consistent with genital infection ††	42 (1.8)	153 (6.5)	148 (6.3)	301 (6.4)†
Male patients	25 (1.5)	89 (5.4)	77 (4.6)	166 (5.0)†
Female patients	17 (2.6)	64 (9.2)	71 (10.8)	135 (10.0)†
Event consistent with volume depletion ‡	115 (4.9)	115 (4.9)	124 (5.3)	239 (5.1)
Acute renal failure	155 (6.6)	121 (5.2)	125 (5.3)	246 (5.2)§
Acute kidney injury	37 (1.6)	26 (1.1)	19 (0.8)	45 (1.0)‡
Diabetic ketoacidosis¶¶	1 (<0.1)	3 (0.1)	1 (<0.1)	4 (0.1)
Thromboembolic event∭	20 (0.9)	9 (0.4)	21 (0.9)	30 (0.6)
Bone fracture	91 (3.9)	92 (3.9)	87 (3.7)	179 (3.8)

Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med 2015; 373:2117-2128.

## CANVAS Program



 T2DM, ≥30 years of age with history of CV disease (65.6%) or ≥ 50 years of age with 2 or more CV risk factors (34.4%), eGFR >30 ml/min/1.73m<sup>2</sup>.

• Mean age: 63.3 years; women: 35.8%; median follow-up: 2.4 years.

Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017 Aug 17;377:644-657.

## CANVAS Program





Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017 Aug 17;377:644-657.

## CANVAS Program



Event	Canagliflozin	Placebo	P Value
	event rate per 10	00 patient-yr	
All serious adverse events	104.3	120.0	0.04
Adverse events leading to discontinuation	35.5	32.8	0.07
Serious and nonserious adverse events of interest recorded in the CANVAS Program			
Acute pancreatitis (adjudicated)	0.5	0.4	0.63
Cancer			
Renal cell	0.6	0.2	0.17
Bladder	1.0	1.1	0.74
Breast	3.1	2.6	0.65
Photosensitivity	1.0	0.3	0.07
Diabetic ketoacidosis (adjudicated)	0.6	0.3	0.14
Amputation	6.3	3.4	<0.001
Fracture (adjudicated):			
All	15.4	11.9	0.02
Low-trauma	11.6	9.2	0.06
Venous thromboembolic events	1.7	1.7	0.63
Infection of male genitalia§	34.9	10.8	<0.001
Serious and nonserious adverse events of interest collected in CANVAS alone¶			
Osmotic diuresis	34.5	13.3	<0.001
Volume depletion	26.0	18.5	0.009
Hypoglycemia	50.0	46.4	0.20
Acute kidney injury	3.0	4.1	0.33
Hyperkalemia	6.9	4.4	0.10
Urinary tract infection	40.0	37.0	0.38
Mycotic genital infection in women	68.8	17.5	< 0.001
Severe hypersensitivity or cutaneous reaction	8.5	6.1	0.17
Hepatic injury	7.4	9.1	0.35
Renal-related (including acute kidney injury)	19.7	17.4	0.32

Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017 Aug 17;377:644-657.

#### DECLARE-TIMI 58



T2DM, ≥ 40 years of age with established CV disease or with ≥1 traditional CV risk factors (men ≥ 55 years of age; women ≥ 60 years of age), eGFR >60 ml/min/1.73m<sup>2</sup>.

• Mean age: 63.9 years; women: 37.4%; median follow-up: 4.2 years.

Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019 Jan 24;380:347-357.

#### DECLARE-TIMI 58





Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019 Jan 24;380:347-357.

#### DECLARE-TIMI 58

Outcome	Dapag (N=	(liflozin 8582)	Pla/ (N=	cebo 8578)	Hazard Ra	atio (95% CI)	P Value
	no. (%)	rate/1000 patient-yr	no. (%)	rate/1000 patient-yr		a a	
Cardiovascular death or hospitalization for heart failure	417 (4.9)	12.2	496 (5.8)	14.7	⊢●⊣	0.83 (0.73-0.95)	0.005
MACE	756 (8.8)	22.6	803 (9.4)	24.2	He	0.93 (0.84-1.03)	0.17
≥40% decrease in eGFR to <60 ml/min/1.73 m <sup>2</sup> , ESRD, or death from renal or cardiovascular cause	370 (4.3)	10.8	480 (5.6)	14.1	+.●-1	0.76 (0.67-0.87)	
Death from any cause	529 (6.2)	15.1	570 (6.6)	16.4	<b>⊢●</b>	1 0.93 (0.82-1.04)	
Hospitalization for heart failure	212 (2.5)	6.2	286 (3.3)	8.5	<b>⊢−●</b> −−1	0.73 (0.61-0.88)	
Myocardial infarction	393 (4.6)	11.7	441 (5.1)	13.2	<b>⊢●</b>	0.89 (0.77-1.01)	
Ischemic stroke	235 (2.7)	6.9	231 (2.7)	6.8	F	1.01 (0.84-1.21)	
Death from cardiovascular cause	245 (2.9)	7.0	249 (2.9)	7,1	H	0.98 (0.82-1.17)	
Death from noncardiovascular cause	211 (2.5)	6.0	238 (2.8)	6.8	<b>⊢●</b>	0.88 (0.73-1.06)	
≥40% decrease in eGFR to <60 ml/min/1.73 m <sup>2</sup> , ESRD, or death from renal cause	127 (1.5)	3.7	238 (2.8)	7.0	<b>⊢</b> ●	0.53 (0.43-0.66)	
				0.4	0 0.50	1.0 1.5	
					Dapagliflozin Better	Placebo Better	

		1400 U	101 1010-0010	
Event	Dapagliflozin (N = 8574)	Placebo (N = 8569)	Hazard Ratio (95% CI)	P Value
	no. (	%)		
Serious adverse event	2925 (34.1)	3100 (36.2)	0.91 (0.87–0.96)	<0.001
Adverse event leading to discontinuation of trial regimen	693 (8.1)	592 (6.9)	1.15 (1.03–1.28)	0.01
Major hypoglycemic event	58 (0.7)	83 (1.0)	0.68 (0.49-0.95)	0.02
Diabetic ketoacidosis	27 (0.3)	12 (0.1)	2.18 (1.10-4.30)	0.02
Amputation	123 (1.4)	113 (1.3)	1.09 (0.84-1.40)	0.53
Fracture	457 (5.3)	440 (5.1)	1.04 (0.91-1.18)	0.59
Symptoms of volume depletion	213 (2.5)	207 (2.4)	1.00 (0.83-1.21)	0.99
Acute kidney injury	125 (1.5)	175 (2.0)	0.69 (0.55-0.87)	0.002
Genital infection	76 (0.9)	9 (0.1)	8.36 (4.19–16.68)	< 0.001
Urinary tract infection	127 (1.5)	133 (1.6)	0.93 (0.73-1.18)	0.54
Cancer	481 (5.6)	486 (5.7)	0.99 (0.87–1.12)	0.83
Bladder cancer	26 (0.3)	45 (0.5)	0.57 (0.35-0.93)	0.02
Breast cancer	36 (0.4)	35 (0.4)	1.02 (0.64-1.63)	0.92
Hypersensitivity	32 (0.4)	36 (0.4)	0.87 (0.54-1.40)	0.57
Hepatic event	82 (1.0)	87 (1.0)	0.92 (0.68-1.25)	0.60

Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019 Jan 24;380:347-357.

#### Meta-analysis

	EMPA-REG OUTCOME <sup>1</sup>	CANVAS Program <sup>2</sup>	DECLARE-TIMI 583
Drug	Empagliflozin	Canagliflozin	Dapagliflozin
Doses analysed	10 mg, 25 mg (once daily)	100 mg, 300 mg (once daily)	10 mg (once daily)
Median follow-up time, years	3.1	2.4	4.2
Trial participants	7020	10142	17 160
Age, mean	63.1	63-3	63.9
Women	2004 (28.5%)	3633 (35.8%)	6422 (37.4%)
Patients with established atherosclerotic cardiovascular disease	7020 (100%)	6656 (65.6%)	6974 (40.6%)
Patients with a history of heart failure	706 (10.1%)	1461 (14.4%)	1724 (10.0%)
Patients with eGFR <60 mL/min per 1.73 m <sup>2</sup>	1819 (25.9%)	2039 (20.1%)	1265 (7·4%)

Data are n (%) unless otherwise specified. The CANVAS Program consisted of two trials, CANVAS and CANVAS-R, but are presented combined. eGFR=estimated glomerular filtration rate.

	Empaglifloz	in	Placebo		- 1			
	n with event/n	26	n with event/n	26	HR (95% CI)	F	wours empagliflozin	Favours placebo
Heart failure hospitalization or								
cardiovascular death								
All patients	265/4687	5.7	198/2333	8.5	0.66 (0.55-0.79)			
Heart failure at baseline								
No	190/4225	4.5	149/2089	7.1	0.63 (0.51-0.78)			
Yes	75/462	16.2	49/244	20.1	0.72 (0.50-1.04)			
Hospitalization for heart failure							~×	
All patients	126/4687	2.7	95/2333	4.1	0.65 (0.50-0.85)			
Heart failure at baseline								
No	78/4225	1.8	65/2089	3.1	0.59 (0.43-0.82)			
Yes	48/462	10.4	30/244	12.3	0.75 (0.48-1.19)			
Cardiovascular death								
All patients	172/4687	3.7	137/2333	5.9	0.62 (0.49-0.77)			
Heart failure at baseline							10 - 10 - 10 - 10 - 10 - 10 - 10 - 10 -	
No	134/4225	3.2	110/2089	5.3	0.60 (0.47-0.77)			
Yes	38/462	8.2	27/244	11.1	0.71 (0.43-1.16)			
All-cause mortality							822	
All patients	269/4687	5.7	194/2333	8.3	0.68 (0.57-0.82)			
Heart failure at baseline								
No	213/4225	5.0	159/2089	7.6	0.66 (0.51-0.81)			
Yes	56/462	12.1	35/244	14.3	0.79 (0.52-1.20)	-		
						0.25	0.50 1.	2.00
						3.1042423234	HR (95% C	D

1.Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019 Jan 5;393:31-39. 2. Fitchett D, Zinman B, Wanner C, et al. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial. Eur Heart J. 2016 May 14;37:1526-34.

#### Meta-analysis

Trials	Patients	Events	Treatment Events per 100 ptyrs	Placebo Events per 100 ptyrs	Weights			HR [95% CI]		Trials	Patients	Events	Treatment n/N	Placebo n/N	Weights			HR [95%	CIJ
SGLT2i										SGLT2i									
EMPA-REG OUTCO	ME 7020	221	0.9	1,4	24.0	<b>•</b> ••		0.65 [0.50, 0.85]		EMPA-REG OUTCO	ME 6968	152	81/4645	71/2323	20.9 🛥 👘			0.54 (0.40, 0	75]
CANVAS Program	10142	243	0.6	0.9	25.6			0.67 [0.52, 0.87]		CANVAS Program	10142	249	NA	NA	34.0	<u> </u>		0.60 [0.47, 0	,77]
DECLARE-TIMI 58	17160	498	0.6	0.8	50.4	<b>⊢</b> ∎→		0.73 [0.61, 0.88]		DECLARE-TIMI 58	17160	365	127/8582	238/8578	45.1 🛏 🔳	-		0.53 [0.43, 0	66]
Fixed Effects for Hi	fF (P-value<0.001	1				-		0.89 [0.61, 0.79]	<b>)</b>	Fixed Effects for SG	SLT2i (P-value<0	.001)			-			0.55 [0.48, 0	641
						r i	1	1							r	i	L.	_	
HHF -	-31%					0.50 1.00	1.50	2.00		Overa	ll kid	nev o	utcome	es -45°	70 0.40 0.50	1.00	1.50	2.00	
						Hazard R	atio					5				Hazard Ratio			

Modified: Zelniker TA, Wiviott SD, Raz I, et al. Comparison of the Effects of Glucagon-Like Peptide Receptor Agonists and Sodium-Glucose Cotransporter 2 Inhibitors for Prevention of Major Adverse Cardiovascular and Renal Outcomes in Type 2 Diabetes Mellitus. Circulation. 2019 Apr 23;139:2022-2031

	Effect of new g	lucose lowering dr	ugs on cardiovas	cular outcomes in p	lacebo-controlled tria
	3-point MACE	CV death	Myocardial infarction	Stroke	HF hospitalisation
SGLT-2 inhibitors	↓ Risk	↓ Risk Empagliflozin:38%	Neutral effect:	Neutral effect:	↓ Risk
Empagliflozin Canagliflozin Dapagliflozin	Empagliflozin:14% Canagliflozin: 14% Dapagliflozin: 17%*	Neutral effect: Canagliflozin, Dapagliflozin	All SGLT-2 inhibitors	All SGLT-2 inhibitors	Canagliflozin: 33% Dapagliflozin: 27%

Modified: Seferović PM, Coats AJS, Ponikowski P, et al. European Society of Cardiology/Heart Failure Association position paper on the role and safety of new glucose-lowering drugs in patients with heart failure. Eur J Heart Fail. 2020 Feb;22:196-213.



- 1. Provision of signed informed consent prior to any study specific procedures
- 2. Male or female, aged  $\geq 18$  years at the time of consent
- 3. Established documented diagnosis of symptomatic HFrEF (NYHA functional class II-IV)
- 4. LVEF≤40% (echocardiogram, radionuclide ventriculogram, contrast angiography or cardiac MRI ) within the last 12 months prior to enrolment
- 5. NT-proBNP ≥600 pg/ml (or if hospitalized for heart failure within the previous 12 months, NT-proBNP ≥400 pg/ml) at enrolment (visit 1). If concomitant atrial fibrillation at Visit 1, NT-proBNP must be ≥900 pg/ml (irrespective of history of heart failure hospitalization)
- 6. Patients should receive background standard of care for HFrEF
- eGFR ≥30 ml/min/1.73 m2 (CKD-EPI formula) at enrolment (visit 1)

McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019 Nov 21;381:1995-2008.

Characteristic	Dapagliflozin (N = 2373)	Placebo (N = 2371)
NYHA functional classification — no. (%)		
11	1606 (67.7)	1597 (67.4)
111	747 (31.5)	751 (31.7)
IV.	20 (0.8)	23 (1.0)
Heart rate — beats/min	71.5±11.6	71.5±11.8
Systolic blood pressure — mm Hg	122.0±16.3	121.6±16.3
Left ventricular ejection fraction — %	31.2±6.7	30.9±6.9
Median NT-proBNP (IQR) — pg/ml	1428 (857–2655)	1446 (857–2641)

#### Mean age: 66.3 yrs Women: 23.4%

Characteristic	Dapagliflozin (N=2373)	Placebo (N = 2371)
Heart failure medication — no. (%)		
Diuretic	2216 (93.4)	2217 (93.5)
ACE inhibitor	1332 (56.1)	1329 (56.1)
ARB	675 (28.4)	632 (26.7)
Sacubitril–valsartan	250 (10.5)	258 (10.9)
Beta-blocker	2278 (96.0)	2280 (96.2)
Mineralocorticoid receptor antagonist	1696 (71.5)	1674 (70.6)
Digitalis	445 (18.8)	442 (18.6)

#### 41.8% diabetics Median f-u: 18.2 m

McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019 Nov 21;381:1995-2008.



McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019 Nov 21;381:1995-2008.





McMurray J. Presented at: AHA Scientific Sessions; November 16-18, 2019; Philadelphia, PA;
 McMurray JJV et al. Online protocol. *N Engl J Med.* 2019.

Safety outcomes						
Discontinuation due to adverse event - no./total no. (%)	111/2368 (4.7)		116/2368 (4.9)	÷.	$\rightarrow$	0.79
Adverse events of interest no./total no. (%)						
Volume depletion	178/2368 (7.5)	-2	162/2368 (6.8)	174	=2	0.40
Renal adverse event	153/2368 (6.5)	-0	170/2368 (7.2)	<del>71</del> 1		0.36
Fracture	49/2368 (2.1)		50/2368 (2.1)	<u>114</u>		1.00
Amputation	13/2368 (0.5)	-	12/2368 (0.5)	22	-	1.00
Major hypoglycemia**	4/2368 (0.2)	-	4/2368 (0.2)	15	-	NA
Diabetic ketoacidosis††	3/2368 (0.1)	-2	0	<b>**</b>	=	NA
Fournier's gangrene	0	-÷.;	1/2368 (<0.1)	+	-÷.	NA



- 1. Age  $\geq 18$  years at screening. For Japan only: Age  $\geq 20$  years at screening
- 2. Men or women
- 3. Patients with CHF diagnosed for at least 3 months before Visit 1, and currently in NYHA functional class II, III or IV
- 4. Chronic heart failure with a reduced left ventricular ejection fraction (LVEF), defined as LVEF  $\leq 40\%$
- 5. In addition to LVEF  $\leq$  40%, patients must have at least one of the following :
  - a) If EF  $\geq$ 36% to  $\leq$ 40%: elevated NT-proBNP at Visit 1  $\geq$ 2500 pg/ml for patients without AF, OR  $\geq$ 5000 pg/ml for patients with AF, analyzed at the Central Laboratory,
  - b) If EF  $\geq$ 31% to  $\leq$ 35%: elevated NT-proBNP at Visit 1  $\geq$ 1000 pg/ml for patients without AF, OR  $\geq$ 2000 pg/ml for patients with AF, analyzed at the Central Laboratory,
  - c) If EF $\leq$ 30%: elevated NT-proBNP at Visit 1  $\geq$ 600 pg/ml for patients without AF, OR  $\geq$ 1200 pg/ml for patients with AF, analyzed at the Central Laboratory
  - d) For EF≤ 40% and documented hospitalization for heart failure within 12 months prior to visit 1, elevated NT-proBNP at Visit 1 ≥600pg/ml for patients without AF and ≥1200 pg/ml for patients with AF
- 6. Appropriate dose of medical therapy for heart failure
- 7. Appropriate use of medical devices such as ICD or CRT
- 8. Body mass index (BMI) < 45 kg/m2 at Visit 1 (screening)
- 9. Signed and dated written ICF (informed consent) in accordance with GCP and local regulations, prior to admission to the trial

Characteristic	Empagliflozin (N = 1863)	Placebo (N=1867)
Left ventricular ejection fraction		
Mean value	27.7±6.0	27.2±6.1
Value of ≤30% — no. (%)	1337 (71.8)	1392 (74.6)
NT-proBNP		
Median value (IQR) — pg/ml	1887 <mark>(1077–3429)</mark>	1926 (1153–3525)
Value of ≥1000 pg/ml — no./total no. (%)	1463/1862 (78.6)	1488/1866 (79.7)
Estimated glomerular filtration rate		
Mean value — ml/min/1.73 m <sup>2</sup>	61.8±21.7	62.2±21.5
Value of <60 ml/min/1.73 m <sup>2</sup> — no./total no. (%)	893/1862 (48.0)	906/1866 (48.6)

#### Mean age: 66.9 yrs Women: 24%

#### 49.8% diabetics Median f-u: 16 m

Characteristic	Empagliflozin (N=1863)	Placebo (N = 1867)
Heart failure medication — no. (%)		
Renin–angiotensin inhibitor§		
Without neprilysin inhibitor	1314 (70.5)	1286 (68.9)
With neprilysin inhibitor	340 (18.3)	387 (20.7)
Mineralocorticoid receptor antagonist	1306 (70.1)	1355 (72.6)
Beta-blocker	1765 (94.7)	1768 (94.7)

Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020 Oct 8;383:1413-1424.





Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020 Oct 8;383:1413-1424.

Subgroup	Empagliflozin no. of patients wit	Placebo h events/total	no.			Haz	ard Ratio	(95% CI)		
Overall	361/1863	462/1867			H	■-1				0.75 (0.65-0.86)
Baseline diabetes status										
Diabetes	200/927	265/929			н					0.72 (0.60–0.87)
No diabetes	161/936	197/938								0.78 (0.64-0.97)
Baseline use of ARNi										
No	310/1523	369/1480			H					0.77 (0.66–0.90)
Yes	51/340	93/387								0.64 (0.45-0.89)
			0.125	0.25	0.5	1.0	2.0	4.0	8.0	
			E	Empaglific	ozin Bette	r	Placeb	o Better		

#### Selected adverse events of interest

Hypotension	176 (9.4)	163 (8.7)
Symptomatic hypotension	106 (5.7)	103 (5.5)
Volume depletion	197 (10.6)	184 (9.9)
Ketoacidosis	0 (0.0)	0 (0.0)
Hypoglycemic events*	27 (1.4)	28 (1.5)
In patients with type 2 diabetes	20 (2.2)	22 (2.4)
In patients without type 2 diabetes	7 (0.7)	6 (0.6)
Urinary tract infections	91 (4.9)	83 (4.5)
Complicated urinary tract infections	19 (1.0)	15 (0.8)
Genital infections	31 (1.7)	12 (0.6)
Complicated genital infections	6 (0.3)	5 (0.3)
Bone fractures	45 (2.4)	42 (2.3)
Events leading to lower limb amputation	13 (0.7)	10 (0.5)

Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020 Oct 8;383:1413-1424.

# Comparison

	EMPEROR-Reduced N=3730			
Median follow-up (mo)	≈16	≈18		
Inclusion criteria	<ul> <li>LVEF ≤30% and NT-pro8NP ≥600 pg/ mL (without AF) and ≥1200 pg/mL (with AF)</li> <li>LVEF 31%-35% and NT-pro8NP ≥1000 pg/mL (without AF) and ≥2000 pg/mL (with AF)</li> <li>LVEF 36%-40% and NT-pro8NP ≥2500 pg/mL (without AF) and ≥5000 pg/mL (without AF)</li> <li>LVEF ≤40% and HHF in past 12 mo and NT-pro8NP ≥600 pg/mL (without AF) and ≥1200 pg/mL (with AF)</li> <li>eGFR ≥20 mL-min<sup>-1</sup>, 1.73 m<sup>3</sup></li> </ul>	<ul> <li>LVEF ≤40% and NT-proBNP ≥600 pg/mL (without AF) or ≥900 pg/ml (with AF)</li> <li>LVEF ≤40% and HHF in past 12 mo and NT-proBNP ≥400 pg/mL (without AF) or ≥900 pg/mL (with AF)</li> <li>eGFR ≥30 mL-min<sup>-1</sup>-1.73 m<sup>3</sup></li> </ul>		
Demographics and key clinical history of the	placebo groups*			
Age, y	66.5	66.5		
Women, %	24.4	23.0		
Body mass index, kg/m <sup>2</sup>	27.8	28.1		
eGFR, mL-min <sup>-1</sup> -1.73 m <sup>-2</sup>	62.2	65.5		
Diabetes, %	49.8	41.8		
Atrial fibrillation, %	37.8	38.0		
Features of heart failure in the placebo group	is			
Left ventricular ejection fraction (%)	27.2	30.9		
Median NT-proBNP, pg/mL	1926	1446		
Ischemic cardiomyopathy, %	50.7	57.3		
HHF in previous 12 mo, %	30.7	27.4		
NYHA class IVIII/IV, %	75.0/24.4/0.6	67.4/31.7/1.0		
Baseline heart failure therapies of the placebo	o groups, %			
ACE inhibitor or angiotensin receptor blocker without ARNI	68.9	82.8		
β-Blocker	94.7	96.2		
MRA	72.6	70.6		
ARNI	20.7	10.9		
Implantable cardioverter-defibrillator	31.8	26.1		
Cardiac resynchronization therapy	11.9	6.9		
Placebo event rates/100 patient-years, %				
Cardiovascular death or HHF	21.0	15.3		
HHE	15.5	9.8		
Cardiovascular death	8.1	7.9		
All-cause mortality	10.7	9.5		

Verma S, McGuire DK, Kosiborod MN. Two Tales: One Story: EMPEROR-Reduced and DAPA-HF. Circulation. 2020 Dec 8;142:2201-2204.

#### Meta-analysis

A All-cause mortality	Sec. 12, 144							(11)(2)(1)(1)
	SGI T2 inhibitor	Placebo						HR (95% CI)
EMPEROR-Reduced DAPA-HF Total	249/1863(13-4%) 276/2373(11-6%)	266/1867 (14-2%) 329/23/1 (13-9%)					Į.	0-92 (0-77-1-10) 0-83 (0-71-0-97) 0-87 (0-77-0-98)
Test for heterogeneity of effect p=0-39			0.25	0.50	075	100	1-25	
B Cardiovascular death	Number with event/n	umber of patients {%}						HR (95% CI)
	SGLT2 Inhibitor	Placebo						
EMPEROR-Reduced DAPA-HF Total	187/1863 (10-0%) 227/2373 (9-6%)	202/1867 (10-8%) 273/2371 (11-5%)					-	0-92 (075-1-12) 0-82 (0-69-0-98) 0-86 (0-76-0-98)
Test for overall treatment effect p=0-027 Test for heterogeneity of effect p=0-40			0.25	0-50	075	1-00	1.25	
C First hospitalisation for heart failure of	r cardiovascular death Number with event/n	umber of patients (%)			$\frown$			HR (95% CI)
	5GLT2 Inhibitor	Placebo						
EMPEROR-Reduced DAPA-HF Total	361/1863 (19-4%) 386/23/3 (16-3%)	462/1867 (24-7%) 502/2371 (21-2%)			-			0-75 (0-65-0-86) 0-74 (0-65-0-85) 0-74 (0-68-0-82)
Test for overall treatment effect p=0.0001 Test for heterogeneity of effect p=0.89			0.25	0.5	075	1-00	1.25	
D First hospitalisation for heart failure	Number with event/n	umber of patients (%)						HR (95% CI)
	SGLT2 Inhibitor	Placebo						
EMPEROR-Reduced DAPA-HF Total	246/1863 (13.2%) 231/23/3 (9-7%)	342/1867(18-3%) 318/2371(13-4%)		14- 17- 1	-			0-69 (0-59-0-81) 0-70 (0-59-0-83) 0-69 (0-62-0-78)
Test for heterogeneity of effect p=0-90			0.25	050	075	1-00	1-25	
E First kidney outcome composite	Number with event/n	umber of patients (%)						HR (95% CI)
	SGLT2 Inhibitor	Placebo						
EMPEROR-Reduced DAPA-HF Total Total	18/1863 (1-0%) 28/2373 (1-2%)	33/1867 (1-8%) 39/2371 (1-6%)	-			-	-	0-52 (0-29-0-92) 0-71 (0-44-1-16) 0-62 (0-43-0-90)
Test for heterogeneity of effect p=0-042			0.25	0.10	075	1.00	1.25	
F All (first and recurrent) hospitalisation	n for heart failure or card Number with event/n	lovascular death umber of patients (%)						RR (95% CI)
·	SGLT2 Inhibitor	Placebo		-+				
EMPEROR-Reduced DAPA-HF Total	575/1863 (30-9%) 567/2373 (23-9%)	753/1867 (40-3%) 742/23/1 (31-3%)			1			0-76 (0-65-0-89) 0-75 (0-65-0-88) 0-75 (0-68-0-84)
Test for overall treatment effect p=0-0001 Test for heterogeneity of effect p=0-91	5		0.25	0.50	074	1.00	1-25	

A Diabetes status								
	Number with event/n	umber of patients (%)						HR (95% CI)
	SGLT2 inhibitor	Placebo						
With diabetes								
EMPEROR-Reduced	200/927 (21-6%)	265/929 (28-5%)		-	-			0-72 (0-60-0-87)
DAPA-HF	215/10/5 (20-0%)	271/1064 (25-5%)				- 1		0.75 (0.63-0.90)
Subtotal						- X		0.74 (0.65-0-84)
Test for overall treatment effect p=0-0001 Test for heterogeneity of effect p=0-76								
Without diabetes								
EMPEROR-Reduced	161/936 (17-2%)	197/938 (21-0%)						0-78 (0-64-0-97)
DAPA-HF	171/1298 (13-2%)	233/1307 (17-7%)		-				0-73 (0-60-0-88)
Subtotal					~	• #		0.75 (0-65-0-87)
Test for overall treatment effect pc0-0001 Test for heterogeneity of effect p-0-65 Test for treatment by suborum interaction of	-0.81					0000		
test to a second by soughtup merecular p			0.25	050	0.75	1.00	1.25	
B Sex	Number with event/n	umber of patients (%)						HR (95% CI)
	SGLT2 inhibitor	Placebo						
Men						8		
EMPEROR-Reduced	294/1426 (20-6%)	353/1411 (25-0%)						0-80 (0-68-0-93)
DAPA-HF	307/1809 (17:0%)	406/1826 (22-2%)				2		073 (0-63-0-85)
Subtotal						. ¥		0-76 (0-68-0-85)
Test for overall treatment effect pc0-0001 Test for heterogeneity of effect p=0-41								
Women						1		
EMPEROR-Reduced	67/437 (15-3%)	109/456 (23-9%)			<u> </u>	1		0-59 (0-44-0-80)
DAPA-HF	79/564 (14-0%)	96/545 (17-6%)		-				0-79 (0-59-1-06)
Subtotal				-				0-68 (0-56-0-84)
Test for overall treatment effect p=0-0004 Test for heterogeneity of effect p=0-17 Test for treatment by suborcup interaction of	-0.37							
the second second by soughtup merecular p	-0.37		0.50	050	0.75	100	1.25	
			0.23	030	073	100	1.13	
CUSEOFARNI	Number with event/n	umber of patients (%)						HR (95% CI)
2	SGLT2 Inhibitor	Placebo						
Receiving ARNI								
EMPEROR-Reduced	51/340 (15-0)	93/387 (24-0)				- 8		0.64 (0-45-0-89)
DAPA-HF	41/250 (16-4)	55/258 (21-7)			-		-	0.75 (0.50-1.13)
Subtotal				-		- 1		0-68 (0-53-0-89)
Test for overall treatment effect p=0-0043 Test for heterogeneity of effect p=0-56								
Not receiving ARNI						1		
EMPEROR-Reduced	310/1523 (20-4)	369/1480 (24-9)				- *		0-77 (0-66-0-90)
DAPA-HF	345/2123 (16-3)	446/2113 (21-1)			_	- X		0-74 (0-65-0-86)
Subtotal								0.75 (0.68-0.84)
Test for overall treatment effect p=0-0001 Test for heterogeneity of effect p=0-71 Test for treatment by suborum interaction of	-0.60							
searches a carment of sondiroob interaction b			-		0.10		1	
			0-25	0-50	075	1.00	1.25	

Zannad F, Ferreira JP, Pocock SJ, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. Lancet. 2020 Sep 19;396:819-829.

#### Meta-analysis

5GLT2 inhibitor 153/577 (26-5) 195/1124 (17-3) e 208/1286 (16-2) 191/1249 (15-3)	Placebo 177/574 (30-8) 279/1127 (24-8)	L 2	5				079 (0-64-0-99)
153/577 (26-5) 195/1124 (17-3) e 208/1286 (16-2) 191/1249 (15-3)	177/574 (30-8) 279/1127 (24-8)		1	-			079 (0-64-0-99)
153/577 (26-5) 195/1124 (17-3) 8 208/1286 (16-2) 191/1249 (15-3)	177/574 (30-8) 279/1127 (24-8)		-	5			079 (0-64-0-99)
195/1124 (17-3) e 208/1286 (16-2) 191/1249 (15-3)	279(1127 (24-8)			5	100		
e 208/1286 (16-2) 191/1249 (15-3)							0-67 (0-56-0-80
e 208/1286 (16-2) 191/1249 (15-3)	~						0.72 (0-62-0-82
e 208/1286 (16-2) 191/1249 (15-3)	2						
208/1286 (16-2) 191/1249 (15-3)					22		
191/1249 (15:3)	285/1293 (22-0)		1				071(0-60-0-85
	223/1244 (17-9)						0-84 (0-69-1-01
					3 <u>1</u>		0-77 (0-67-0-87
0-48							
		0-25	0.50	0.75	1-00	1.25	
							22202220000000
Number with eventy	number of patients (%)						HR (95% CI)
SGLIZINNIDION	Pracedo				- 57		-
202/893 (22-6)	737/906 (26-2)						0-83 (0-69-1-00
191/962 (19-9)	254/964 (26-3)			-	2 8		072 (0-59-0-86
					e 8		0-77 (0-68-0-8
159/969 (16-4)	224/960 (23:3)			-			0-67 (0-55-0-83
195/1410 (13-8)	248/1405 (17-6)			_			076 (0-63-0-92
							0.72 (0-62-0-8
9.99		0.55	670	0.21	+ 00	-1-	
		4-25	0.50	0.75	1-00	1.25	
Number with event/	number of patients (%)						HR (95% CI)
SGLT2 inhibitor	Placebo						
220/1309/1571	200/1401/21-25		12	-			071/0-50-0-84
190/1606/11-8	289/1597 (18-1)						0-63 (0-52-0-75
			5				0-67 (0-59-0-71
							(
141/464 (30-4)	163/466 (35-0)						0-83 (0-66-1-04
196/767 (25-6)	213/774 (27:5)			1000	<u> </u>		0-90 (0-74-1-09
2012/02/22/0	2010/02/02/02			-			0-87 (0-75-1-0:
0.0027							
0,0007			-	and the second sec			
	0-48           Number with event/i           SGLT2 (nhibitor           202/993 (22-6)           191/962 (19-9)           159/969 (16-4)           195/969 (16-4)           195/91410 (13-8)           0-44           Number with event/i           5GLT2 inhibitor           220/1399 (15-7)           190/1666 (11-8)           141/464 (30-4)           196/767 (25-6)           0-0087	Number with event/number of patients (%)           SGLT2 inhibitor         Placebo           202/893 (22-6)         237/966 (26-2)           191/962 (19-9)         254/964 (26-3)           159/969 (16-4)         224/960 (23-3)           159/969 (16-4)         224/960 (23-3)           159/969 (16-4)         224/960 (23-3)           159/969 (16-4)         224/960 (23-3)           159/969 (16-4)         224/960 (23-3)           159/1401 (13-8)         248/1406 (17-6)           9-44         SGLT2 inhibition         Placebo           220/1399 (157)         299/1401 (21-3)           190/1606 (11-8)         289/1597 (18-1)           141/464 (30-4)         163/466 (35-9)           196/767 (25-6)         213/774 (27-5)	0-48           Number with event/ number of patients (%)         2025           SGLT2 (nhlbitor         Placebo           202/893 (22-6)         237/906 (26-2)           191/962 (19-9)         254/964 (26-3)           159/969 (16-4)         224/960 (23-3)           159/969 (16-4)         224/960 (23-3)           159/969 (16-4)         224/960 (23-3)           159/969 (16-4)         224/960 (23-3)           159/969 (16-4)         224/960 (23-3)           159/969 (16-4)         224/960 (23-3)           0-25         0-25           Number with event/ number of patients (%)         0-25           SGLT2 inhlbitor         Placebo           220/1399 (157)         299/1401 (21-3)           190/1606 (11-8)         289/1597 (18-1)           141/464 (30-4)         163/466 (35-0)           196/767 (25-6)         213/774 (27-5)	0-48           Number with event/number of patients (%)         volume           SGLT2 (nhlbitor         Placebo           202/893 (22-6)         737/906 (26-2)           191/962 (19-9)         254/964 (26-3)           159/969 (16-4)         224/960 (23-3)           159/969 (16-4)         224/960 (23-3)           159/969 (16-4)         224/960 (23-3)           0-44         0-25           0-44         0-25           220/1399 (157)         299/1401 (21-3)           190/1666 (11-8)         289/1597 (18-1)           141/464 (30-4)         163/466 (35-0)           141/464 (30-4)         163/466 (35-0)           0-0087         0-25	0-48 0-25 0-50 0.75 Number with event/ number of patients (%) SGLT2 (nhlbitor Placebo 202/893 (22-6) 237/906 (26-2) 191/962 (19-9) 254/964 (26-3) 159/969 (16-4) 224/960 (23-3) 159/969 (16-4) 224/960 (23-3) 195/1410 (13-6) 248/1406 (07-6) 0-44 0-25 0-50 0-75 Number with event/ number of patients (%) SGLT2 inhlbitor Placebo 220/1399 (157) 299/1401 (21-3) 190/1666 (11-8) 289/1597 (18-1) 141/464 (30-4) 163/466 (35-0) 196/767 (25-6) 213/774 (27-5)	0-48 Number with event/number of patients (%) SGLT2 (nhlbitor Placebo 202/893 (22-6) 237/966 (26-2) 191/962 (19-9) 254/964 (26-3) 159/969 (16-4) 224/960 (23-3) 159/969 (16-4) 224/960 (23-3) 159/969 (16-4) 224/960 (23-3) 159/969 (16-4) 224/960 (23-3) 0-25 0-50 0-75 1-00 Number with event/number of patients (%) SGLT2 inhlbition Placebo 220/1399 (157) 299/1401 (21-3) 190/1606 (11-8) 299/1401 (21-3) 190/1606 (11-8) 299/1401 (21-3) 190/1606 (11-8) 163/466 (35-0) 141/464 (30-4) 163/466 (35-0) 196/767 (25-6) 213/774 (27-5) 0-25 0-50 0-75 1-00	0-48 Number with event/ number of patients (%) SGLT2 (nhlbitor Placebo 202/893 (22-6) 237/906 (26-2) 191/962 (19-9) 254/964 (26-3) 159/969 (16-4) 224/960 (23-3) 159/969 (16-4) 224/960 (23-3) 159/969 (16-4) 224/960 (23-3) 159/969 (16-4) 224/960 (23-3) 0-25 0-50 0-75 1.00 1.25 Number with event/ number of patients (%) SGLT2 (nhlbitior Placebo 220/1399 (157) 299/1401 (21-3) 190/1606 (11-8) 289/1597 (18-1) 141/464 (30-4) 163/466 (35-9) 196/767 (25-6) 213/774 (27-5) 0-0087

	EMPEROR-Redu	ced	DAPA-HF	
	Empagliflozin (n=1863)	Placebo (n=1867)	Dapagliflozin (n=2373)	Placebo (n=2371)
Serious adverse events	772 (41.4%)	896 (48·1%)	846 (35:7%)	951(40-2%)
Any renal adverse event	175 (9·4%)	192 (10·3%)	141 (6.0%)	158 (6.7%)
Volume depletion	197 (10.6%)	184 (9.9%)	170 (7.2%)	153 (6.5%)
Ketoacidosis	0	0	3 (0.1%)	0
Severe hypoglycaemic events	6 (0.3%)	7 (0.4%)	4 (0·2%)	4 (0.2%)
Bone fractures	45 (2·4%)	42 (2:3%)	48 (2.0%)	47 (2-0%)
Lower limb amputation	13 (0.7%)	10 (0.5%)	13 (0.5%)	12 (0.5%)
Fournier's Gangrene	1 (0.1%)	0	0	1(0.1%)

Zannad F, Ferreira JP, Pocock SJ, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. Lancet. 2020 Sep 19;396:819-829.



- 1. Age  $\geq$  18 years at screening. For Japan only: Age  $\geq$  20 years
- 2. Male or female patients.
- 3. Patients with chronic HF diagnosed for at least 3 months before Visit 1, and currently in HF NYHA class II-IV
- 4. Chronic HF with preserved EF defined as LVEF > 40 %
- Elevated NT-proBNP > 300 pg/ml for patients without AF, OR > 900 pg/ml for patients with AF, analysed at the Central laboratory at Visit 1
- 6. Patients must have at least one of the following evidence of HF:
  - a. Structural heart disease (left atrial enlargement and/or left ventricular hypertrophy) documented by echocardiogram at Visit 1 or within 6 months prior to Visit 1, OR
  - b. Documented HHF within 12 months prior to Visit 1
- 7. Oral diuretics, if prescribed to patient according to local guidelines and discretion of the Investigator, should be stable for at least 1 week prior to Visit 2 (Randomisation)
- 8. Body Mass Index (BMI) < 45 kg/m<sup>2</sup> at Visit 1
- 9. Signed and dated written ICF in accordance with GCP and local legislation prior to admission to the trial.

Characteristic	Empagliflozin (N = 2997)	Placebo (N=2991)
NYHA functional classification no. (76)	100000000000	No. Contraction
Class I	3 (0.1)	3 (-(0,1)
Class II	2432 (81.1)	2451 (81.9)
Class III	552 (18.4)	531 (17.8)
Class IV	10 (0.3)	8 (0.3)
Left ventricular ejection fraction.		
Mean left ventricular ejection fraction %	54.3+8.8	54.3+8.8
Left ventricular ejection fraction >40% to <50% no. (%)§	995 (33.2)	988 (33.0)
Left ventricular ejection fraction a50% to <60% - no. (%)	1028 (34.3)	1030 (34.4)
Left ventricular ejection fraction a60% no. (%)	974 (32.5)	973 (32.5)
Median NT-proBNP (interquartile range) pg/ml	994 (501-1240)	946 (498-1725)
Heart failure category no. (%)		
Ischemic	1079 (36.0)	1038 (34 7)
Nonischemic	1917 (64.0)	1953 (65.3)

#### Mean age: 71.8 yrs Women: 44.6%

#### Median f-u: 26.2 m

Characteristic	Empagliflozin (N = 2997)	Placebo (N = 2991)
Cardiovascular history — no. (%)		
Hospitalization for heart failure during previous 12 mo	659 (23.3)	620 (22.4)
Atrial fibrillation	1543 (51.5)	1514 (50.6)
Diabetes mellitus	1466 (48.9)	1472 (49.2)
Hypertension	2721 (90.8)	2703 (90.4)
Mean eGF8 — ml/min/1.73 m <sup>2</sup>	60.6±19.8	60.6±19.9
eGFR -:60 ml/min/1.73 m <sup>2</sup> no./total no. (%)	1504/2997 (50.2)	1484/2989 (49.6)





Anker SD, Butler J, Filippatos G, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021 Aug 27.

Subgroup	Empagliflozin no. of patients with	Placebo events/total no.	Hazard Ratio (95% CI)		
Overall	415/2997	511/2991	HEH	0.79 (0.69-0.90)	
Diabetes at baseline		a destruction of the second			
Yes	239/1466	291/1472		0.79 (0.67-0.94)	
No	176/1531	220/1519	- <b>a</b> -	0.78 (0.64-0.95)	
LVEF at baseline			· · · · · · · · · · · · · · · · · · ·		
<50%	145/995	193/988		0.71 (0.57-0.88)	
≥50% to <60%	138/1028	173/1030	<b>—</b>	0.80 (0.64-0.99)	
≥60%	132/974	145/973	<b>⊢</b> ∎	0.87 (0.69-1.10)	
		0.25	0.50 1.00	2.00	
		Em	Empagliflozin Better Placebo Better		

Subgroup	Empagliflozin	Placebo	Hazard Ratio (95% CI)	
	no. of patients with	events/total no.		3-19-19-19-19-19-18-18-
Hospitalization for heart failure ≤12 mo				
No	258/2298	319/2321		0.81 (0.68-0.95)
Yes	157/699	192/670	<b>⊢</b> ∎ -	0.73 (0.59-0.90)
NYHA class at baseline			MC 104	
11	275/2435	361/2452		0.75 (0.64-0.87)
III or IV	140/562	150/539		0.86 (0.68-1.09)
NT-proBNP at baseline (calculated by atrial fibrillation/flutter status)				
<median< td=""><td>126/1477</td><td>168/1508</td><td></td><td>0.76 (0.61-0.96)</td></median<>	126/1477	168/1508		0.76 (0.61-0.96)
≥Median	288/1516	341/1476	<u> </u> −	0.78 (0.67-0.91)
Use of ACE-inhibitor, ARB, or ARNI at bas	seline			
No	90/569	121/587		0.75 (0.57-0.99)
Yes	325/2428	390/2404	H-100-1	0.80 (0.69-0.93)
Use of MRA at baseline		10 10		
No	233/1878	306/1866		0.73 (0.62-0.87)
Yes	182/1119	205/1125		0.87 (0.71-1.06)
		0.25	0.50 1.00	2.00

#### Which, When, How to use?

• Naive patient

• Chronic heart failure

• Worsening heart failure

