Empagliflozin, the first successful result for heart failure with preserved ejection fraction

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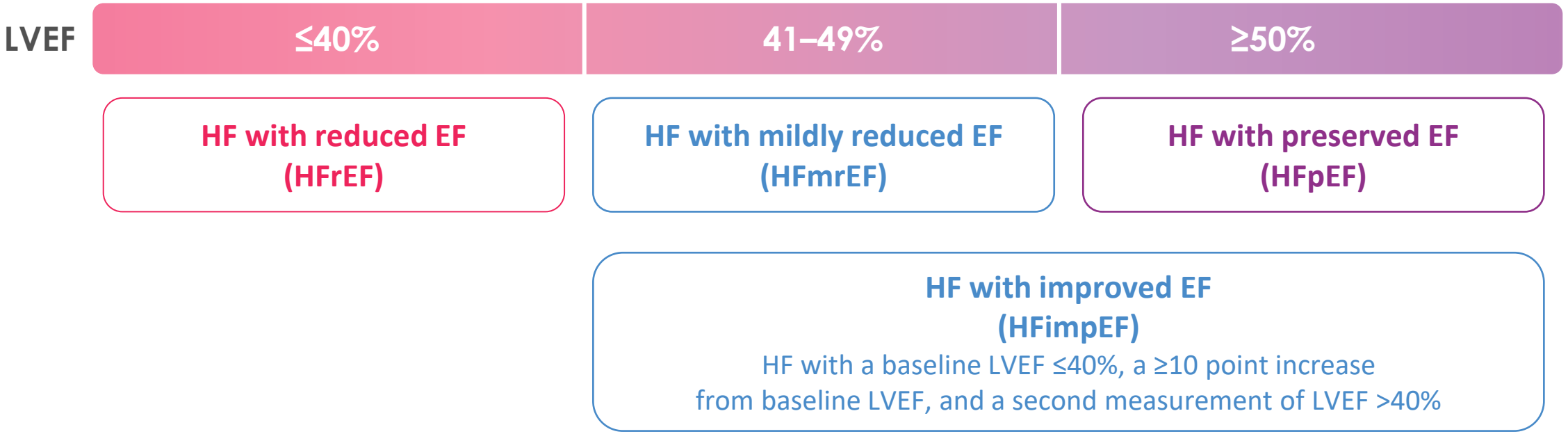
The classification based on LVEF includes two new definitions: HFmrEF and HFimpEF



EF, ejection fraction; HF, heart failure; LVEF, left ventricular ejection fraction.
Bozkurt B et al. Eur J Heart Fail 2021;23:352.

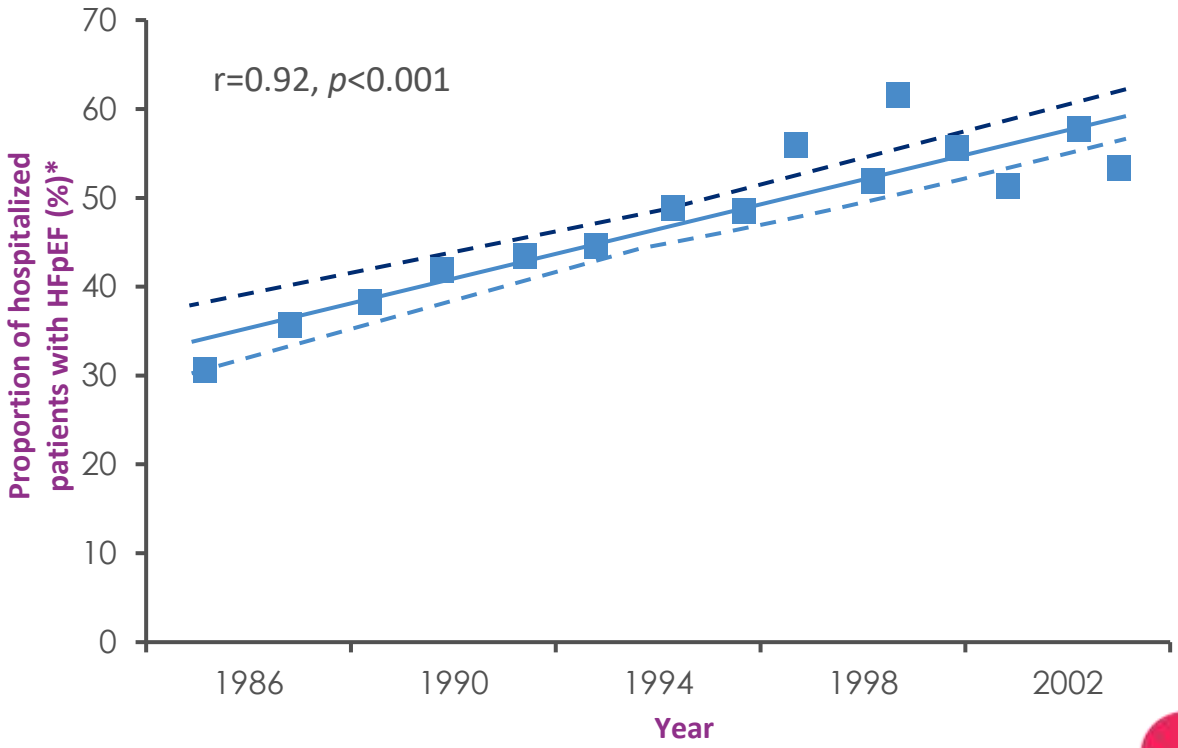
Approximately 50% of patients with heart failure have a preserved ejection fraction (HFpEF)

The total prevalence of HF (HFrEF and HFpEF) is 1–3%

Epidemiological cohort studies reporting the incidence of HFpEF[1]

Study	Mean age at entry (years)	12-year cumulative incidence of HF (%)	Proportion with HFpEF (%)
Cardiovascular Health Study	73	13.7	53.3
Framingham Heart Study	58	6.7	46.5
PREVEND	49	4.2	36.9

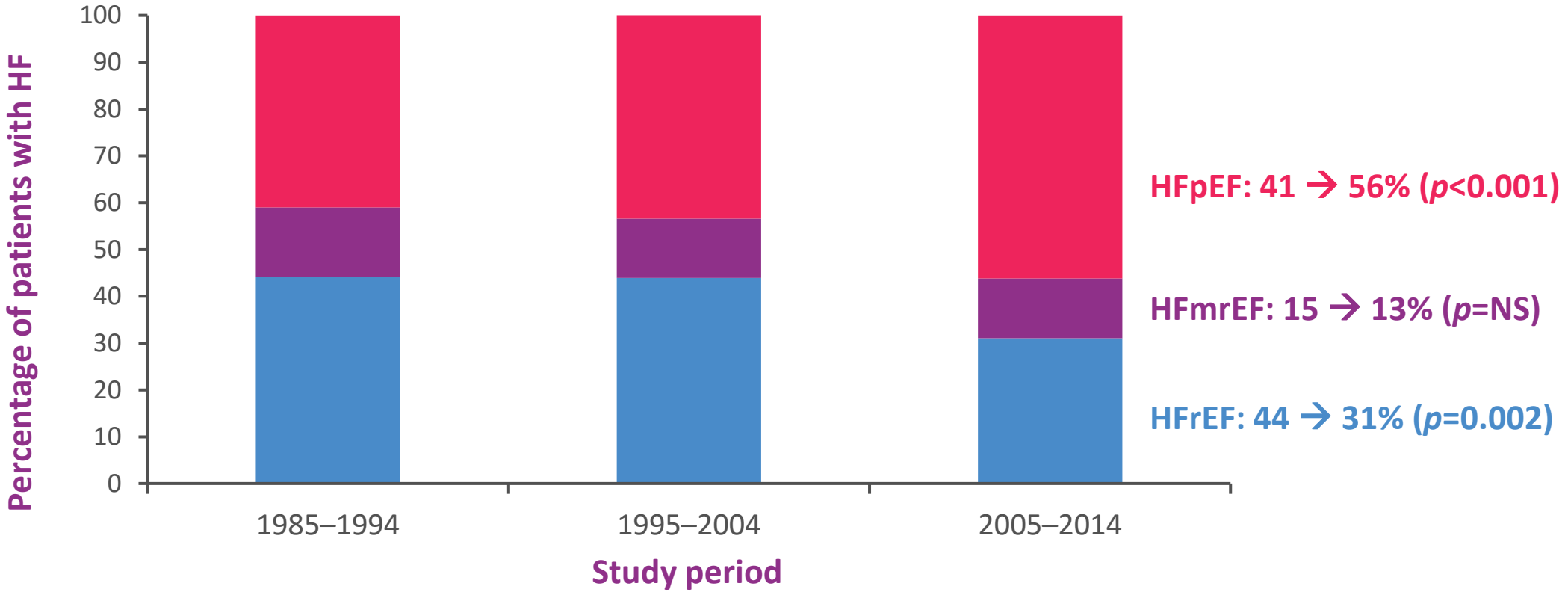
Proportion of patients with HFpEF (%)[2]



*The solid line represents the regression line for the relation between the year of admission and the percentage of patients with HFpEF. The dashed lines indicate the 95% CIs.
CI, confidence interval; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.
1. Dunlay SM et al. Nat Rev Cardiol. 2017;14:591. 2. Owan T et al. N Engl J Med. 2006;355:251.

The proportion of Heart Failure patients with preserved EF has significantly increased over time

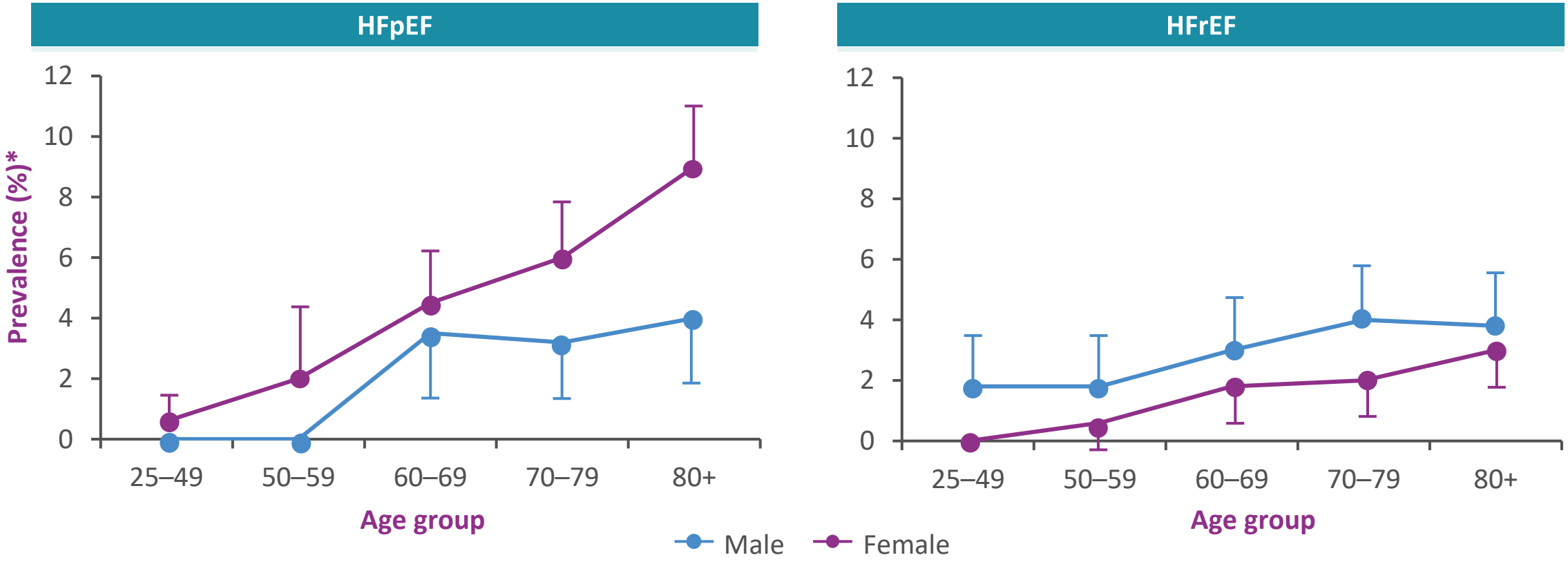
Framingham study participants with new-onset HF (n=894) over 3 decades



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; NS, not significant.
Vasan R et al. JACC Cardiovasc Imaging. 2018;11:1.

The prevalence of HFpEF increases with age and is higher in females than in males

EPICA project, Portugal: 551 patients with congestive heart failure in 1998

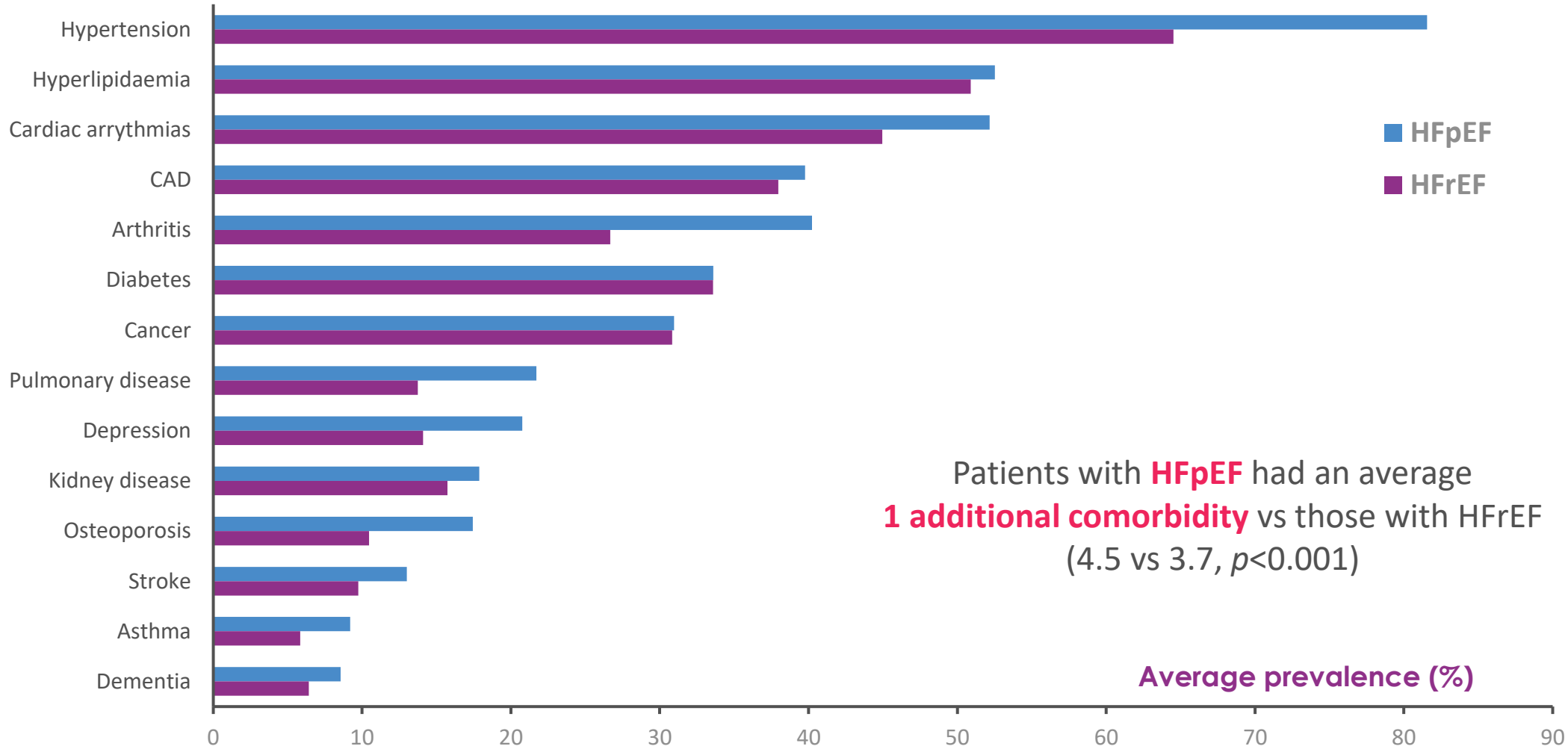


*Error bars represent the 95% CIs.

CI, confidence interval; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

Ceia F et al. Eur J Heart Fail. 2003;4:531.

Patients with HFpEF typically have more comorbidities than those with HFrEF



Patients with **HFpEF** had an average **1 additional comorbidity** vs those with HFrEF (4.5 vs 3.7, $p<0.001$)

Camilla Hage et al., J Card Fail. 2020 Dec;26(12):1050-1059

While most patients with HF die of CV causes, patients with HFpEF may die of more varied causes than those with HFrEF

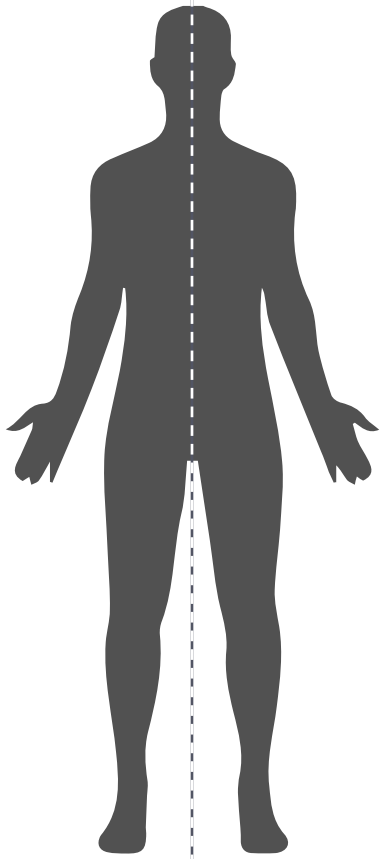
HFrEF

Cardiovascular: 80–85%

Worsening HF
Cardiogenic shock
Low output state

Sudden cardiac death
Ventricular tachyarrhythmia
Bradyarrhythmia

Other cardiovascular or non-cardiovascular: 15–20%



HFpEF

Cardiovascular: median 59%

Worsening HF
Restrictive cardiomyopathy
Right heart failure

Sudden death
Nonarrhythmic sudden death
Tachyarrhythmia
Bradyarrhythmia

Myocardial infarction

Vascular
Aortic aneurysm
Pulmonary embolism

Cerebrovascular
Intracranial haemorrhage
Ischaemic stroke

Non-cardiovascular: 20–30%

Renal
End-stage renal disease Renal ve nous congestion

Infection/sepsis

Malignancy

Respiratory
Respiratory failure
Pulmonary hypertension
Chronic obstructive pulmonary disease

Multisystem disease

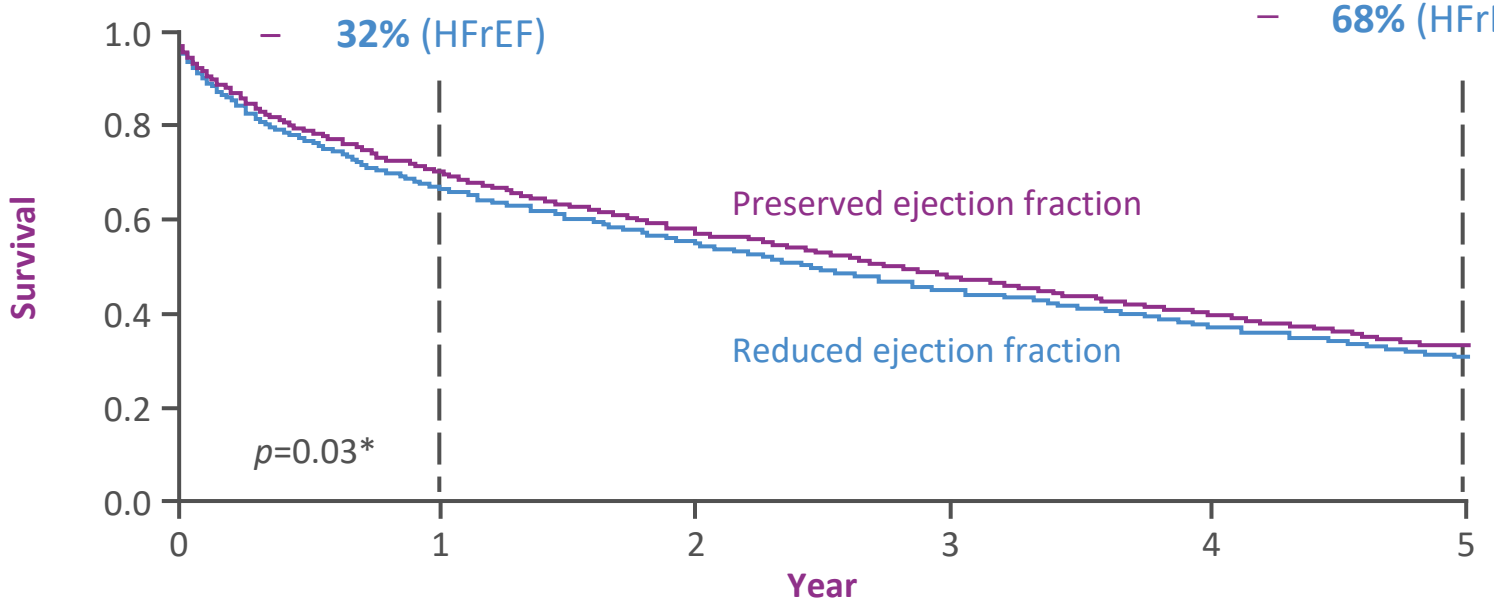
Multisystem organ failure

CV, cardiovascular; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.
Vaduganathan M et al. J Am Coll Cardiol. 2017; 69:556.

Mortality rate for patients with HFpEF is similar with HFrEF

1-year mortality rate:
- **29%** (HFpEF)
- **32%** (HFrEF)

5-year mortality rate:
- **65%** (HFpEF)
- **68%** (HFrEF)



No. at risk						
Reduced ejection fraction	2424	1637	1350	1049	813	604
Preserved ejection fraction	2166	1539	1270	1001	758	574

*Unadjusted hazard ratio for death in patients with HFpEF vs HFrEF: 0.96 (95% CI: 0.93, 1.00).
CI, confidence interval; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.
Owan T et al. N Engl J Med. 2006;355:3.

Patients with HFpEF suffer from poor outcomes, and there are no clinically proven therapies to date

- Hospitalization for HF (HHF) is the #1 cause of hospitalization in patients >65 years old[2]
- More than 50% of patients with HF suffer from HFpEF, and this proportion is significantly increasing[3]
- Approximately 30% of patients with HFpEF die within 1 year of HHF[4]

- No clinically proven therapies are available to reduce heart failure outcomes[1]
- Treatment options are limited to symptom control and treatment of comorbidities[1]

HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HHF, hospitalization for heart failure.

1. Butler J et al. J Am Coll Cardiol. 2014;2:97; 2. Azad N et al. J Geriatr Cardiol. 2014;11:329; 3. Vasan R et al. JACC Cardiovasc Imaging. 2018;11:1; 4. Owan TE et al. N Engl J Med. 2006;355:251.

Shifting the paradigm in the treatment of HFpEF,
started from striking result of EMPA-REG OUTCOME and completed with EMPEROR trial

EMPA-REG OUTCOME was the first* CVOT to show cardio-renal risk reduction with an antidiabetic agent

Raising new possibilities in T2D management

The NEW ENGLAND JOURNAL of MEDICINE

Empagliflozin, CV Outcomes, and Mortality in T2D

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

Patients with T2D and established CV disease

42 countries

7,020 patients

Empagliflozin or placebo given on top of standard of care

- Placebo
- Empagliflozin 10 mg
- Empagliflozin 25 mg

3.1 years median observation time

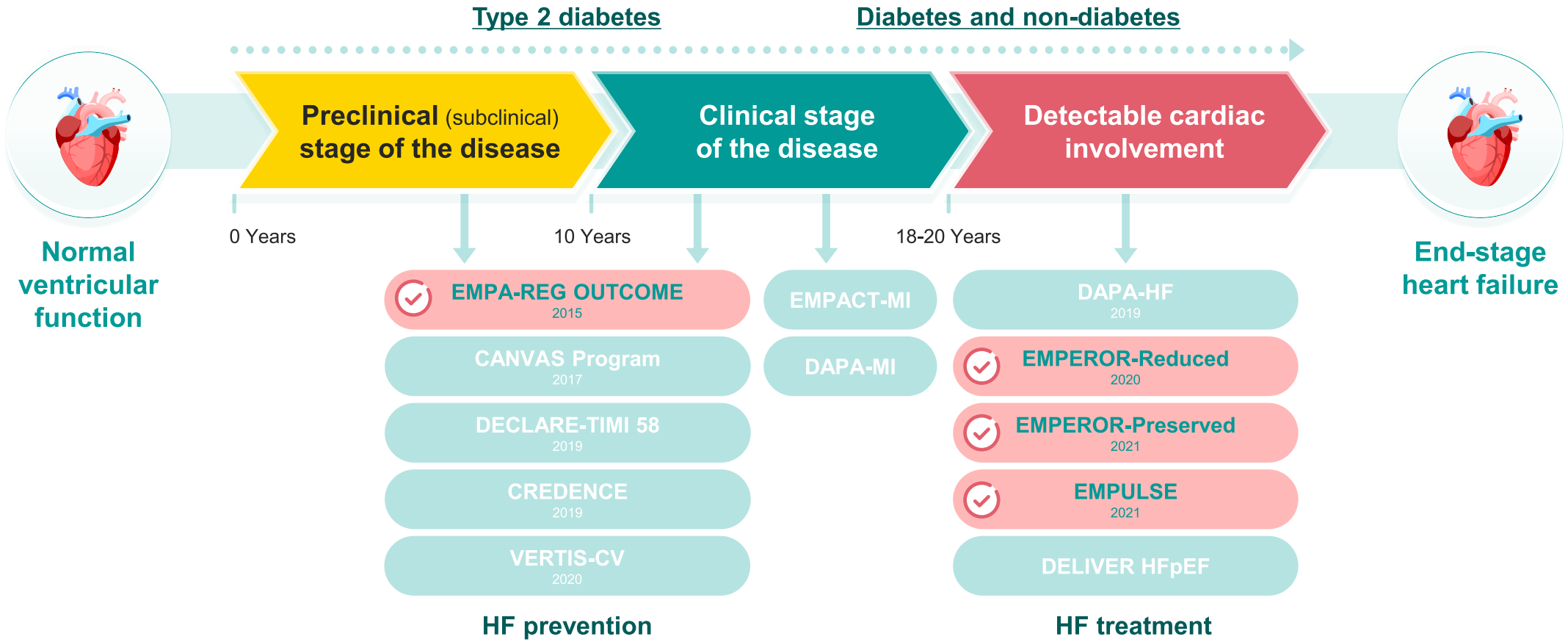
Significant relative risk reduction

3P-MACE	CV Death	All-cause Mortality
14%	38%	32%

HHF	Nephropathy*
35%	39%

*New or worsening nephropathy, a composite of: progression to macroalbuminuria, doubling of serum creatinine, initiation of RRT, or renal death; †≥40% decline in eGFR, RRT, or renal death
3P-MACE, 3-point major adverse CV event; CV, CV; CVOT, CV outcomes trial; eGFR, estimated glomerular filtration rate; HHF, hospitalisation for HF; RRT, renal replacement therapy;
1. Zinman, et al. N Engl J Med 2015;373:2117–28. 2. Wanner, et al. N Engl J Med 2016;375:323–4. 'Sep 2015 EMPA-REG outcome 기준'
자디앙정은 심혈관계 질환을 동반한 제2형 당뇨병 환자의 심혈관 사건 발생, 심혈관 사망, 모든 원인으로 인한 사망 및 신장질환 위험 감소로 국내 허가 받지 않았습니다

Journey of SGLT2 inhibitor in heart failure



Dates indicate the year of publication of primary results from each trial. HF, heart failure; SGLT2, sodium-glucose co-transporter-2. ※ The off-label use is for investigational purposes only and has not been approved by the relevant authorities.

Bhatt DL, et al. Cell Metab 2019;30:847

자디앙은 급성 비보상성 심부전 환자 또는 심근경색 환자의 심부전 및 사망 위험 감소로 국내 허가받지 않았습니다

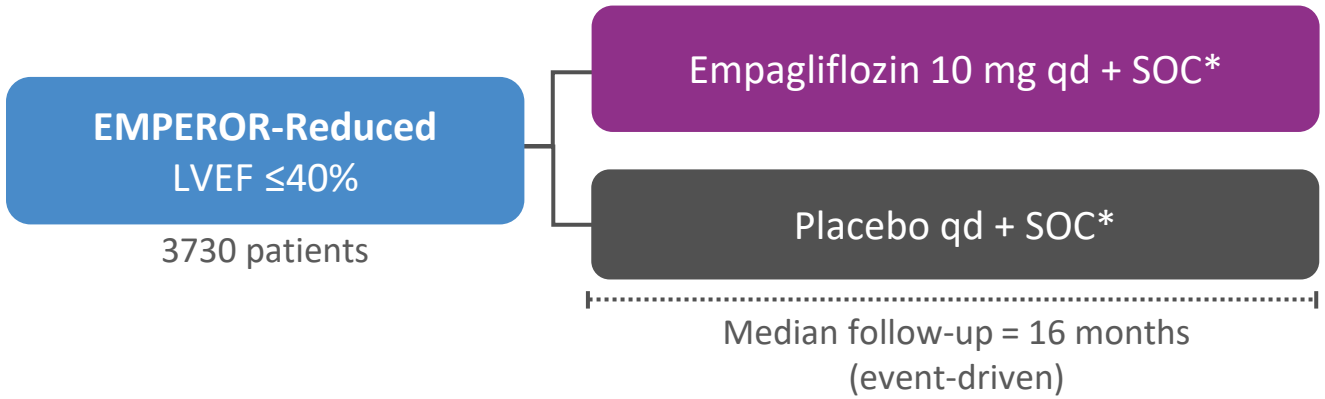
The 2nd paradigm shift; EMPEROR-Reduced

Phase III randomised double-blind placebo-controlled trial

Aim: To investigate the safety and efficacy of empagliflozin versus placebo on top of guideline-directed medical therapy in patients with HF with **reduced ejection fraction**

Population: T2D and non-T2D, aged ≥18 years, chronic HF (NYHA class II–IV)

Study design[1–3]



Confirmatory endpoints[1,2]

COMPOSITE PRIMARY ENDPOINT

Time to first event of adjudicated CV death or adjudicated HHF

SECONDARY ENDPOINTS

- **First and recurrent adjudicated HHF events**
- **eGFR slope: change from baseline**

Cox regression model including covariates age, baseline eGFR, geographic region, baseline diabetes status, sex, LVEF and treatment

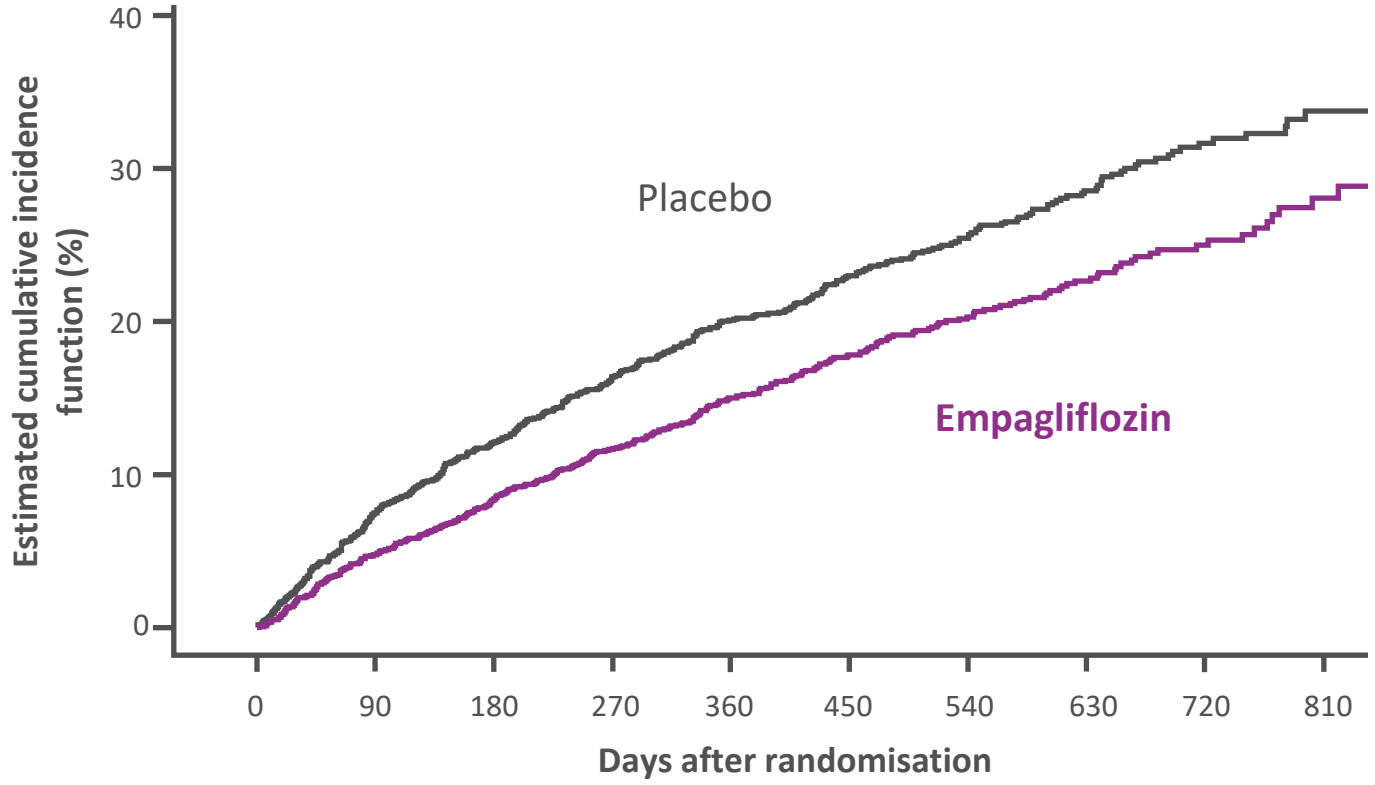
CV, cardiovascular; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; ARR, absolute risk reduction; RRR, relative risk reduction. NNT: Number needed to treat

Milton Packer et al., N Engl J Med. 2020 Oct 8;383(15):1413-1424.

자디앙은 심박출률이 감소된 심부전 환자의 신기능 감소 지연으로 국내 허가받지 않았습니다

Empagliflozin reduced the risk of cardiovascular death or hospitalization for heart failure by 25% in patient with HFrEF vs. placebo

Primary endpoint: 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

RRR 25%

ARR 5.2%

NNT = 19

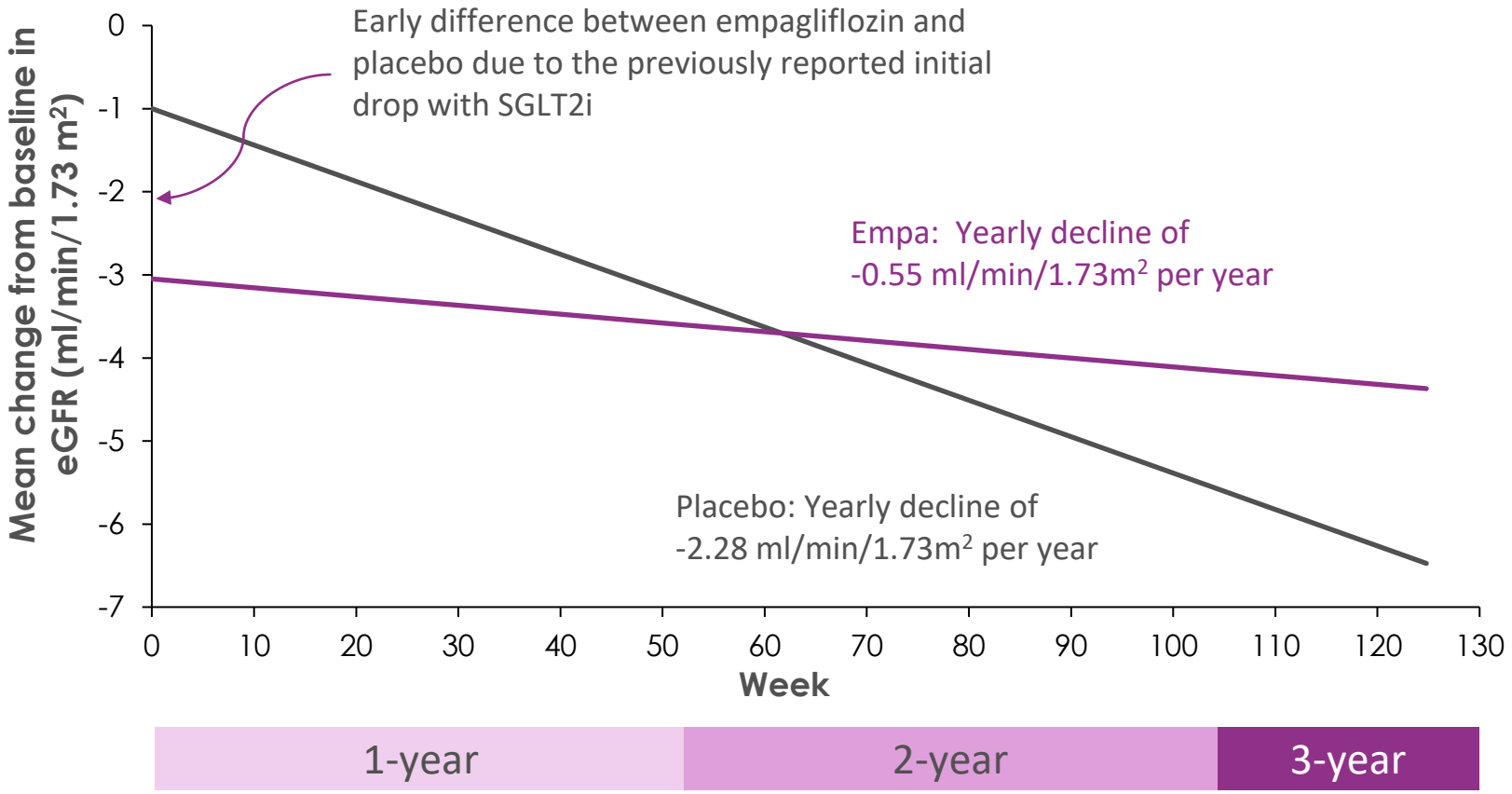
HR 0.75
(95% CI 0.65, 0.86)
p<0.001

Empagliflozin:
361 patients with event
Rate: 15.8/100 patient-years
Placebo:
462 patients with event
Rate: 21.0/100 patient-years

Cox regression model including covariates age, baseline eGFR, geographic region, baseline diabetes status, sex, LVEF and treatment
CV, cardiovascular; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; ARR, absolute risk reduction; RRR, relative risk reduction. NNT: Number needed to treat
Milton Packer et al., N Engl J Med. 2020 Oct 8;383(15):1413-1424

Empagliflozin reduced the kidney event in HFrEF by slowing the decline in kidney function over time

Key secondary endpoint: eGFR slope



eGFR Slope = **rate of decline**

eGFR slope is a measure for **long-term renal function**

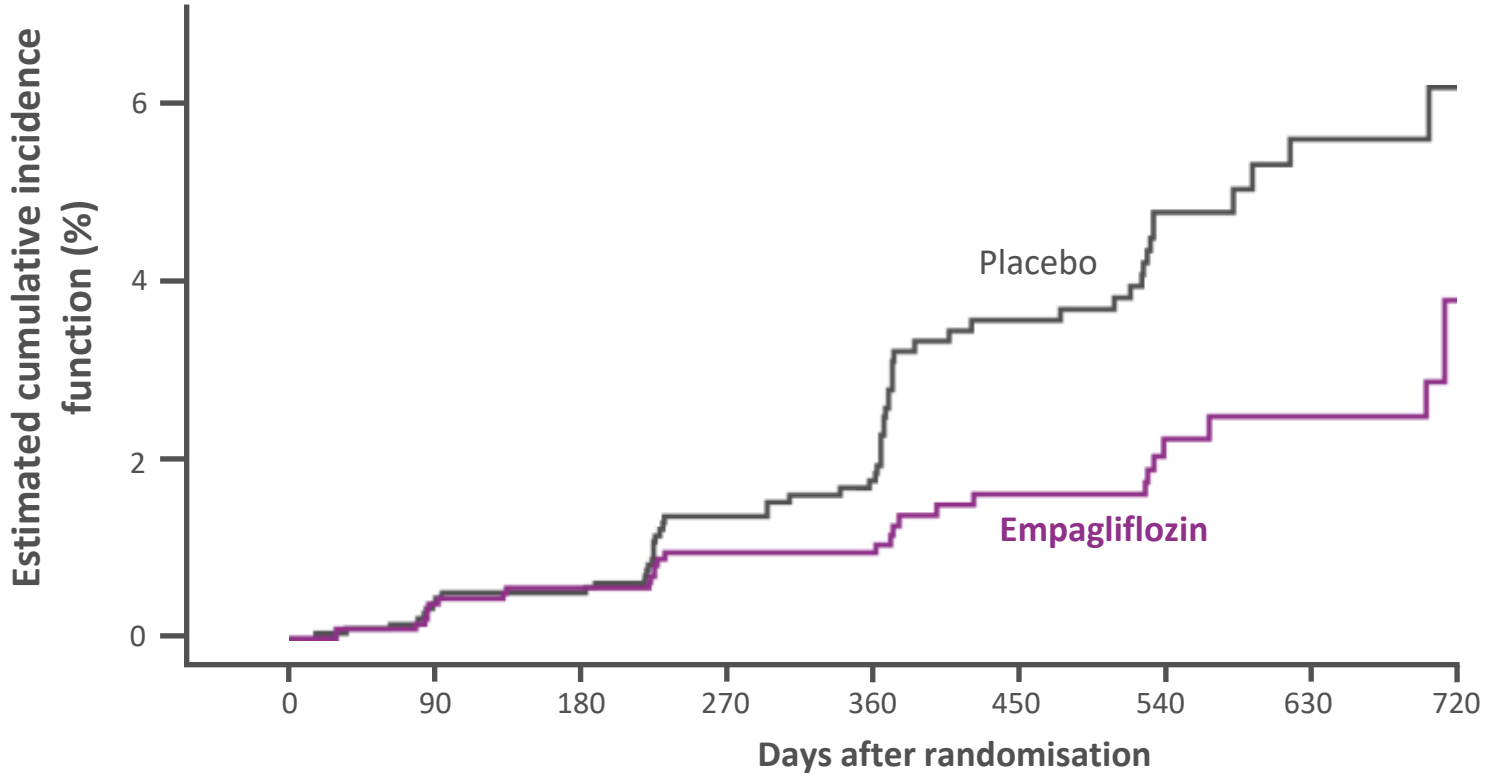
+1.73
eGFR slope difference
ml/min/1.73 m2 per year
p<0.001

eGFR slope is analyzed based on on-treatment data using a random coefficient model including age and baseline eGFR as linear covariates and sex, region, baseline LVEF, baseline diabetes status, and baseline by time and treatment by time interactions as fixed effects; the model allows for randomly varying slope and intercept between patients. eGFR, estimated glomerular filtration rate; SGLT2i, sodium-glucose co-transporter-2 inhibitor.

Milton Packer et al., N Engl J Med. 2020 Oct 8;383(15):1413-1424. 자디앙은 심부전환자의 신장기능 악화 지연 및 신장 사건 발생 감소 목적으로 허가 받지 않았습니다

Empagliflozin reduced the risk of renal outcomes by 50% in patient with HFrEF

Composite renal endpoint (end-stage kidney disease or sustained profound decrease in eGFR)



Patients at risk									
Placebo	1867	1592	1501	1136	1058	681	357	259	76
Empagliflozin	1863	1599	1532	1155	1062	687	391	276	78

RRR 50%

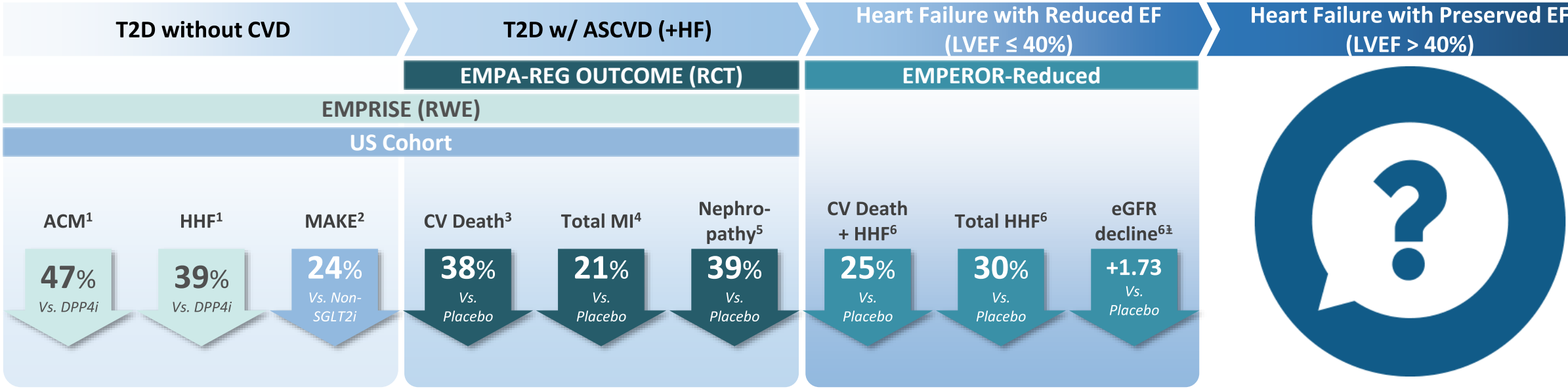
ARR 1.5%

HR 0.50
(95% CI 0.32, 0.77)

Empagliflozin:
30 patients with event
Rate: 1.6/100 patient-years
Placebo:
58 patients with event
Rate: 3.1/100 patient-years

Composite renal endpoint is defined as chronic dialysis, renal transplant, sustained reduction of ≥40% eGFR or sustained eGFR <15 ml/min/1.73 m2 for patients with eGFR ≥30 ml/min/1.73 m2 at baseline (<10 ml/min/1.73 m2 for patients with eGFR <30 ml/min/1.73 m2 at baseline). Dialysis is regarded as chronic if the frequency of dialysis is twice or more per week for at least 90 days. Cox regression model including covariates age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, and baseline LVEF. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; PY, patient years. ARR, absolute risk reduction; RRR, relative risk reduction. Milton Packer et al., N Engl J Med. 2020 Oct 8;383(15):1413-1424. 자디앙은 심부전환자의 신장기능 악화 지연 및 신장 사건 발생 감소 목적으로 허가 받지 않았습니다

Jardiance, starting as an anti-diabetic drug with consistent cardiorenal benefit, turned out to be HFrEF medication. Then what would be the NEXT?



‡ Difference of eGFR mean slope change per year — ml/min/1.73 m2. The eGFR slope is analyzed on the basis of on-treatment data, using a random intercept–random slope model including age, baseline eGFR, and baseline left ventricular ejection fraction as linear covariates and sex, geographic region, baseline diabetes status, and baseline-by-time and treatment by-time interactions as fixed effects; the model allows for randomly varying slope and intercept between patients

1. Elisabetta Patorno et al., Diabetes Obes Metab. 2022;24:442–454 2. Yan Xie et al., Diabetes Care 2020;43:2785–2795 3. Bernard Zinman et al., N Engl J Med 2015;373:2117-28. 4. Darren K McGuire et al., Lancet Diabetes Endocrinol 2020; 8: 949–59 5. Christoph Wanner et al., N Engl J Med 2016;375:323-34 6. Milton Packer et al., N Engl J Med. 2020 Oct 8;383(15):1413-1424

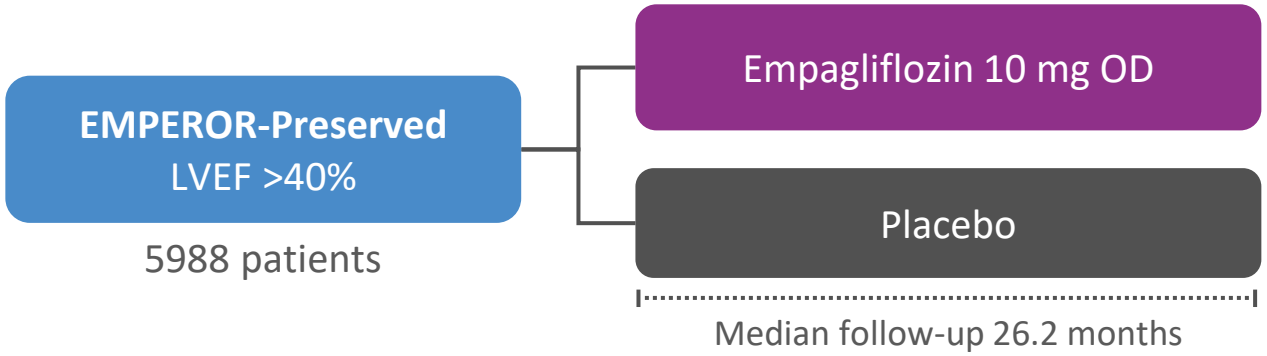
Assess the efficacy and safety of empagliflozin vs. placebo,
in patients with **Heart Failure with preserved Ejection Fraction**

The 3rd paradigm shift; EMPEROR-Preserved

Phase III trial* in patients with HFpEF

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 (NYHA class II–IV)



COMPOSITE PRIMARY ENDPOINT

- **Time to first event of adjudicated CV death or adjudicated HHF**

CONFIRMATORY KEY SECONDARY ENDPOINTS

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

*Randomized, double-blind, placebo-controlled trial.
CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HHF, hospitalization for heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OD, once daily; T2D, type 2 diabetes.
Stefan D Anker et al., N Engl J Med. 2021 Oct 14;385(16):1451-1461
자디앙은 심박출률이 보존된 심부전 환자의 신기능 감소 지연으로 국내 허가받지 않았습니다

EMPEROR-Preserved: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria

• Age ≥18 years
• Chronic HF NYHA class II–IV
• **LVEF >40%**
• **NT-proBNP:**
  • **>300 pg/mL** in patients without AF
  • **>900 pg/mL** in patients with AF
• **Structural changes in the heart** (increases in left atrial size or left ventricular mass) **or HHF within 12 months of screening**
	• MI, coronary artery bypass graft surgery or other major CV surgery, stroke or TIA ≤90 days before visit
	• Heart transplant recipient, or listed for heart transplant
	• Acute decompensated HF
	• SBP ≥180 mmHg at randomization
	• Symptomatic hypotension and/or SBP <100 mmHg
	• **eGFR <20 mL/min/1.73 m^2** or requiring dialysis

AF, atrial fibrillation; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HHF, hospitalization for heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; TIA, transient ischaemic attack.

Stefan D Anker et al., N Engl J Med. 2021 Oct 14;385(16):1451-1461

EMPEROR-Preserved: Characteristics of patients at baseline (1 of 2)

	Empagliflozin (n=2997)	Placebo (n=2991)
Age, years, mean ± SD	71.8±9.3	71.9±9.6
Women, n (%)	1338 (44.6)	1338 (44.7)
Race, n (%)		
White	2286 (76.3)	2256 (75.4)
Black	133 (4.4)	125 (4.2)
Asian *(including 103 Korean patient)*	413 (13.8)	411 (13.7)
Other or missing	165 (5.5)	199 (6.7)
NYHA functional class, n (%)		
Class I	3 (0.1)	1 (<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)
BMI, kg/m^2	29.77±5.8	29.90±5.9
Heart rate, bpm	70.4±12.0	70.3±11.8
Systolic BP, mmHg	131.8±15.6	131.9±15.7
LVEF, %	54.3±8.8	54.3±8.8
>40 to <50%, n (%)	995 (33.2)	988 (33.0)
≥50 to <60%, n (%)	1028 (34.3)	1030 (34.4)
≥60%, n (%)	974 (32.5)	973 (32.5)

SD, standard deviation.

Stefan D Anker et al., N Engl J Med. 2021 Oct 14;385(16):1451-1461

EMPEROR-Preserved: Characteristics of patients at baseline (2 of 2)

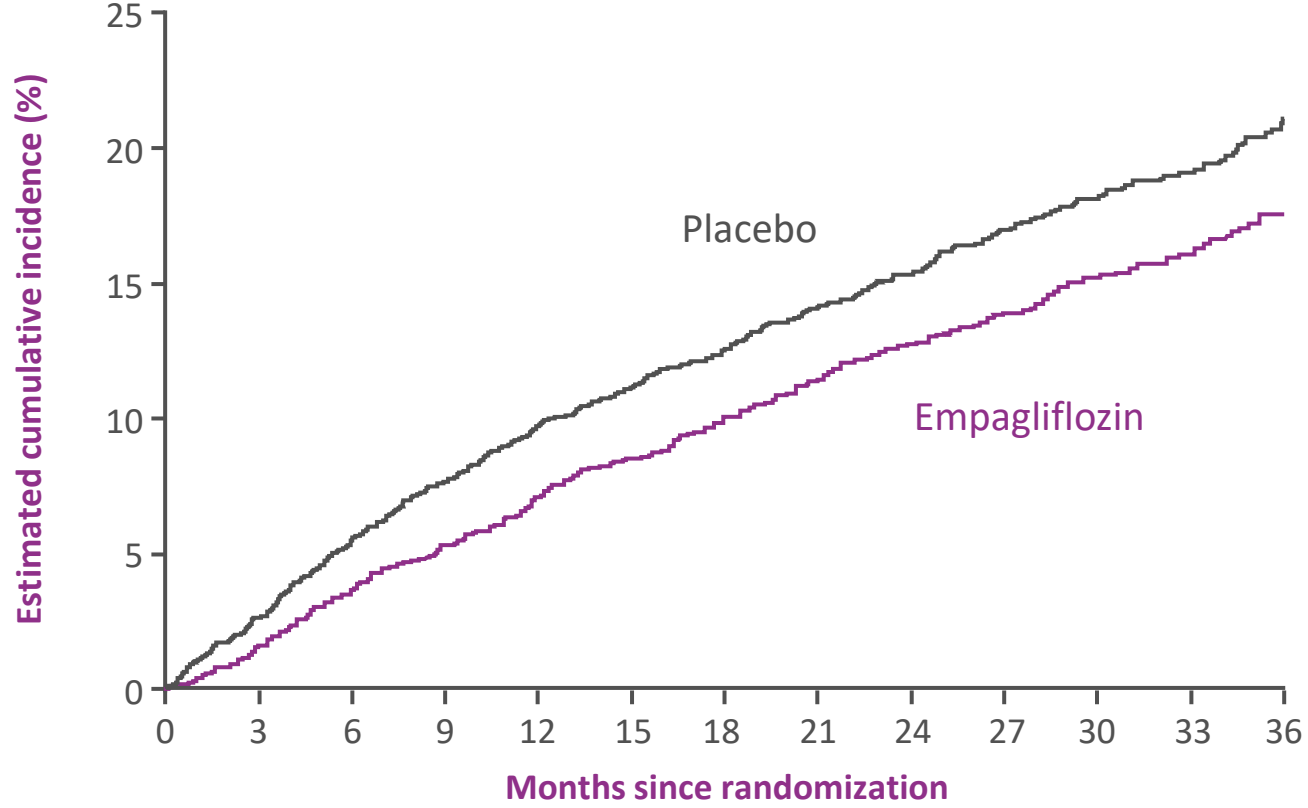
	Empagliflozin (n=2997)	Placebo (n=2991)
NT-proBNP, pg/mL, median (IQR)	994 (501, 1740)	946 (498, 1725)
Aetiology of HF, n (%)		
Ischaemic	1079 (36.0)	1038 (34.7)
Non-ischaemic	1917 (64.0)	1953 (65.3)
CV history, n (%)		
HHF <12 months	699 (23.3)	670 (22.4)
Atrial fibrillation	1543 (51.5)	1514 (50.6)
Diabetes mellitus	1466 (48.9)	1472 (49.2)
Hypertension	2721 (90.8)	2703 (90.4)
eGFR, mL/min/1.73 m^2, mean ± SD	60.6±19.8	60.6±19.9
<60 mL/min/1.73 m^2, n (%)	1504/2997 (50.2)	1484/2989 (49.6)
CV medications, n (%)		
RAASi ± neprilysin inhibitor*	2428 (81.0)	2404 (80.4)
MRA	1119 (37.3)	1125 (37.6)
Beta blocker	2598 (86.7)	2569 (85.9)
Digitalis glycosides	293 (9.8)	263 (8.8)
Aspirin	1240 (41.4)	1272 (42.5)
Statins	2042 (68.1)	2089 (69.8)

SD, standard deviation.

Stefan D Anker et al., N Engl J Med. 2021 Oct 14;385(16):1451-1461

Empagliflozin demonstrated a clinically meaningful 21% RRR in the composite primary endpoint of CV death or HHF

Primary endpoint: First adjudicated CV death or hospitalisation for heart failure



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

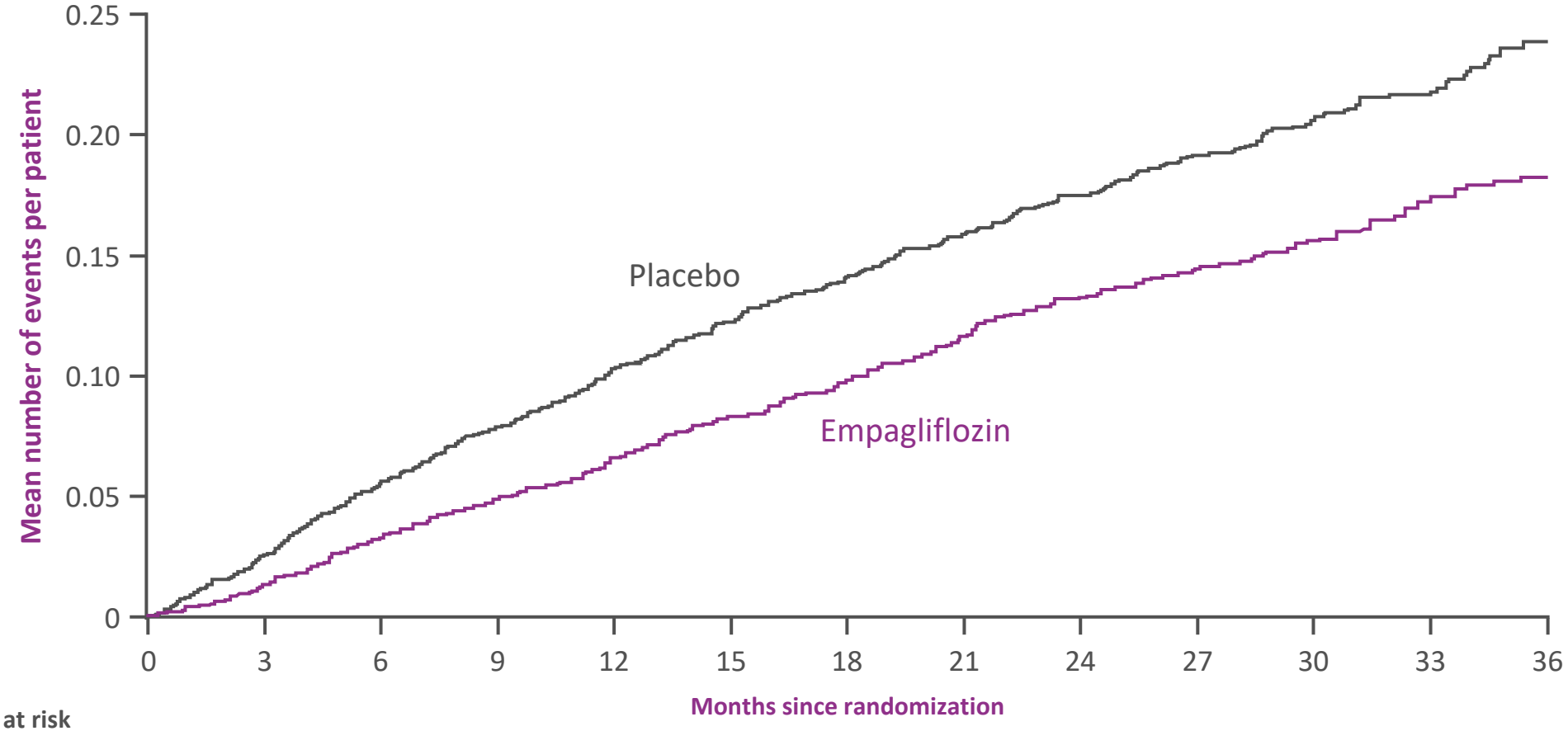
Placebo:
511 (17.1%) patients with event
Rate: 8.7/100 patient-years

*During a median trial period of 26 months. ARR, absolute risk reduction; CI, confidence interval; CV, cardiovascular; HHF, hospitalization for heart failure; HR, hazard ratio; NNT, number needed to treat; RRR, relative risk reduction.

Stefan D Anker et al., N Engl J Med. 2021 Oct 14;385(16):1451-1461

EMPEROR-Preserved: adjudicated total HHF (first and recurrent)

Key secondary: Adjudicated total hospitalisations for heart failure (first and recurrent)



Patients at risk													
Placebo	2991	2945	2901	2855	2816	2618	2258	1998	1695	1414	1061	747	448
Empagliflozin	2997	2962	2913	2869	2817	2604	2247	1977	1684	1429	1081	765	446

RRR 27%

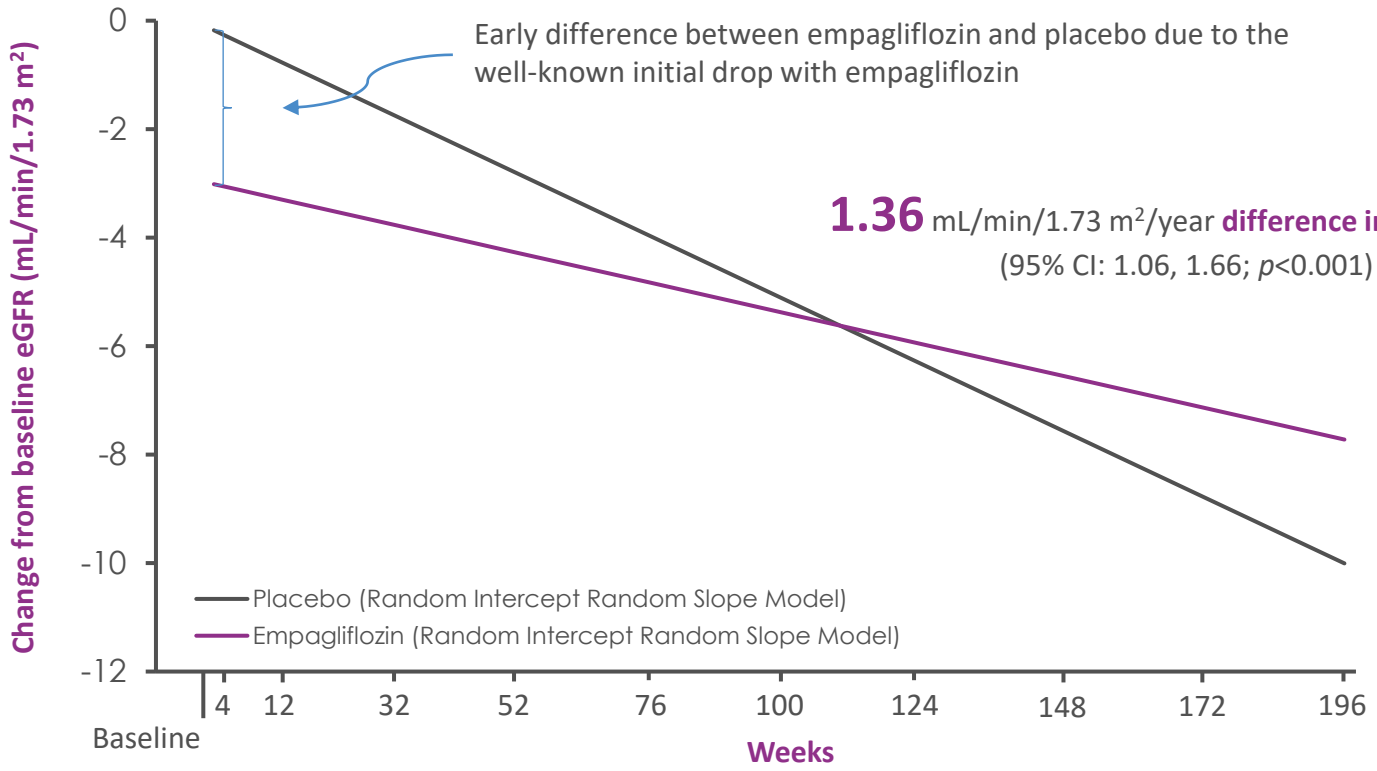
HR: 0.73
(95% CI: 0.61, 0.88)
p<0.001

Empagliflozin:
407 patients with event
Placebo:
541 patients with event

CI, confidence interval; HHF, hospitalization for heart failure; HR, hazard ratio; RRR, relative risk reduction.
Stefan D Anker et al., N Engl J Med. 2021 Oct 14;385(16):1451-1461

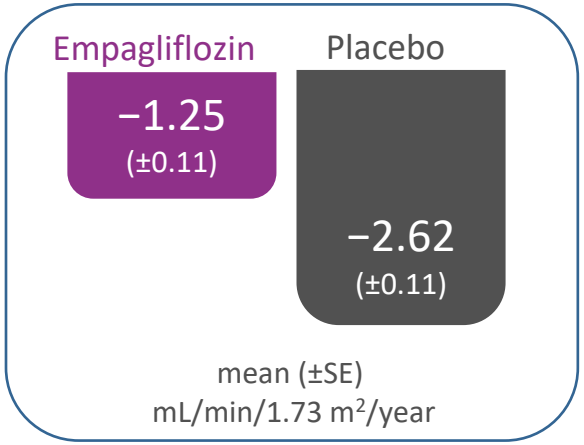
Empagliflozin reduced the risk of kidney event by significantly slowing the decline in kidney function

Key secondary endpoint: eGFR slope



1.36 mL/min/1.73 m²/year **difference in eGFR slope**
(95% CI: 1.06, 1.66; *p*<0.001)

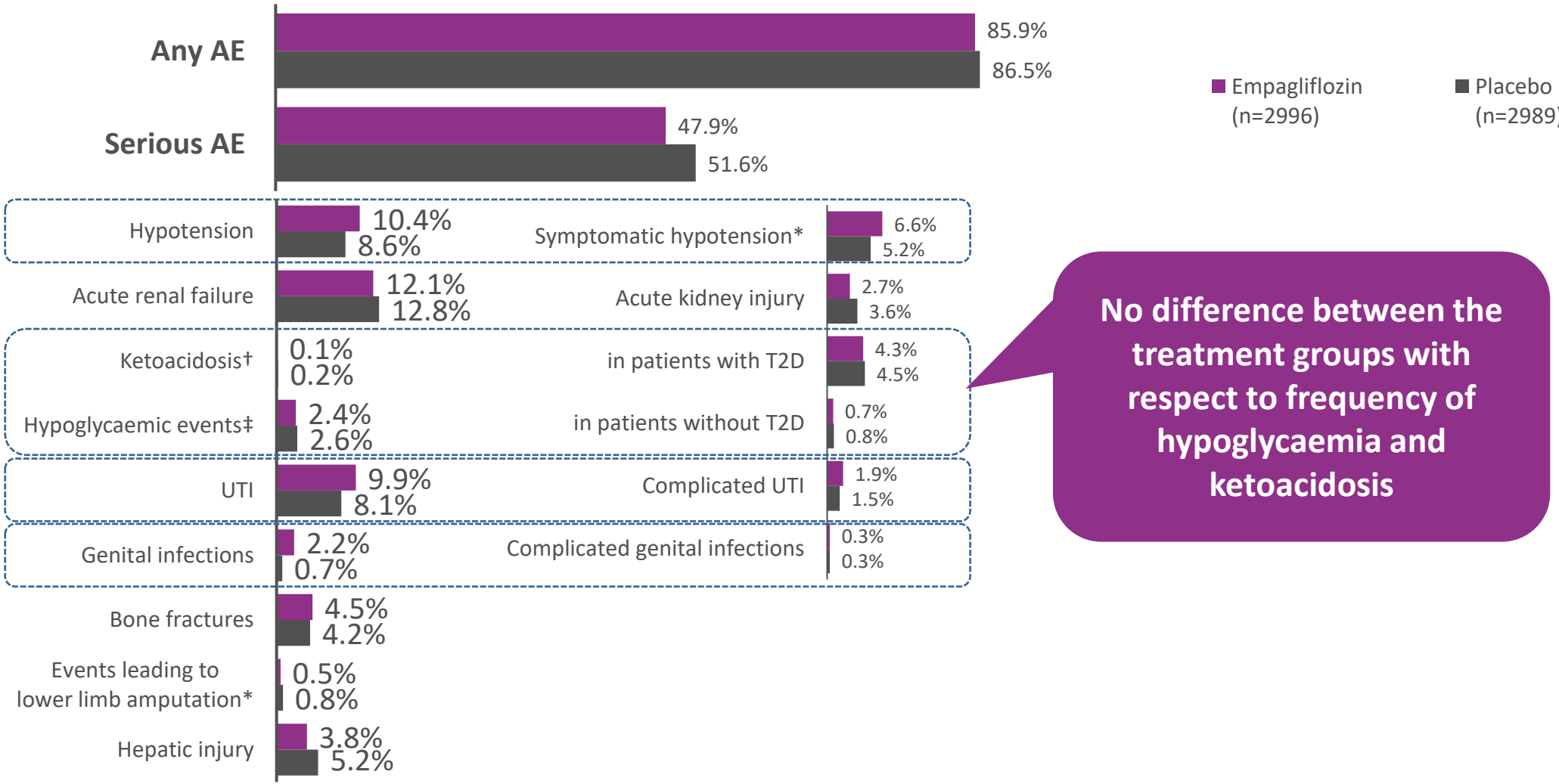
The rate of eGFR decline in patients tr eated with empagliflozin was half that of patients treated with placebo



eGFR slope = rate of decline (and is a measure for long-term renal function). eGFR slope is analysed based on on-treatment data using a random coefficient model including age, baseline eGFR and baseline LVEF as linear covariates and sex, region, baseline diabetes status, and baseline by time and treatment by time interactions as fixed effects; the model allows for randomly varying slope and intercept between patients.
CI, confidence interval; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; SE, standard error.

Stefan D Anker et al., N Engl J Med. 2021 Oct 14;385(16):1451-1461

EMPEROR-Preserved:
Selected adverse events of interest



No difference between the treatment groups with respect to frequency of hypoglycaemia and ketoacidosis

*Investigator-defined events. †All events occurred in patients with diabetes mellitus at baseline. ‡Hypoglycaemic AEs with a plasma glucose value of ≤70 mg/dL or that required assistance.
AE, adverse event; UTI, urinary tract infection.
Stefan D Anker et al., N Engl J Med. 2021 Oct 14;385(16):1451-1461 부작용 전문은 자디앙 제품설명서를 참고하여 주십시오

Empagliflozin is the first* approved chronic HF drug to significantly reduce the risk of CV death or HHF across the entire spectrum of ejection fractions

EMPEROR-Reduced[1]

CV death or HHF

RRR	ARR	NNT
25%	5.2%	19

EMPEROR-Preserved[2]

CV death or HHF

RRR	ARR	NNT
21%	3.3%	31

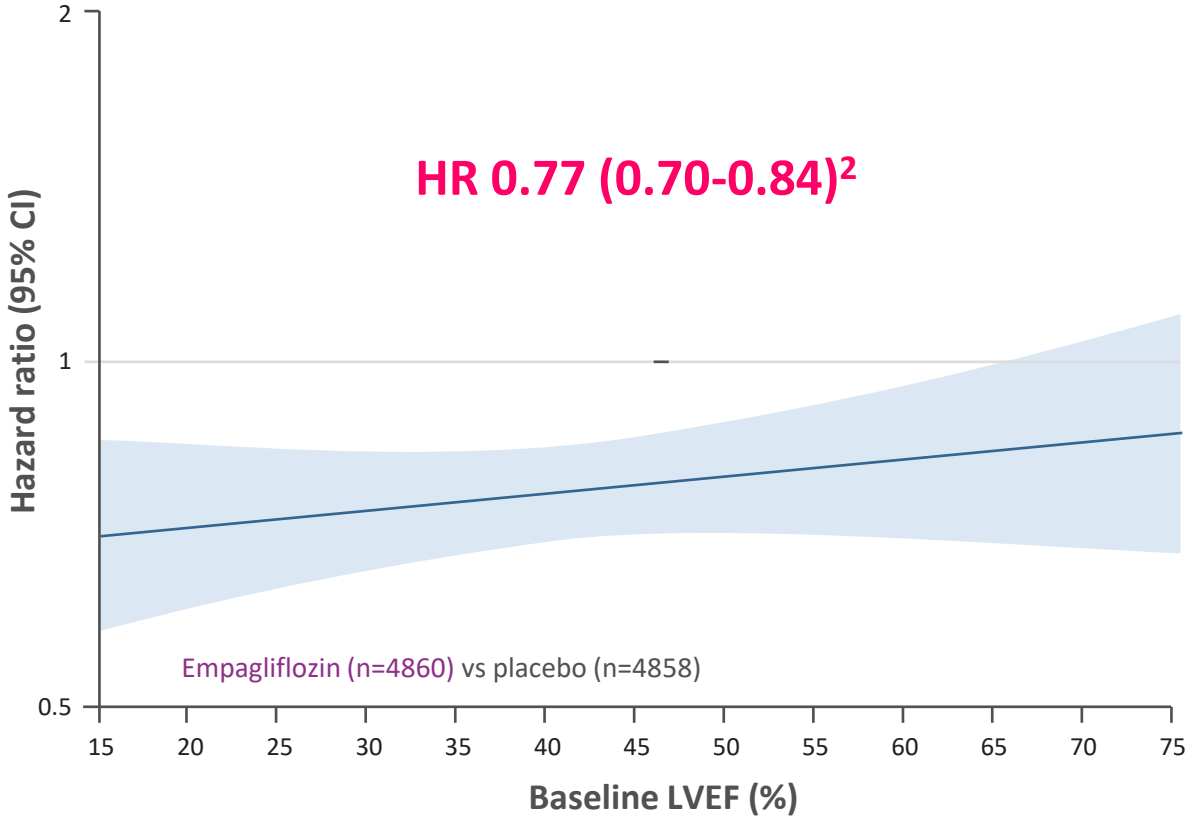
ARR, absolute risk reduction; CV, cardiovascular; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; LVEF, left ventricular ejection fraction; NNT, number needed to treat; RRR, relative risk reduction.

1. Milton Packer et al., N Engl J Med. 2020 Oct 8;383(15):1413-1424. 2. Stefan D Anker et al., N Engl J Med. 2021 Oct 14;385(16):1451-1461

자디앙정10mg에만 해당됩니다. * 2022년 5월 24일 식품의약품안전처 자디앙 10mg 허가 기준

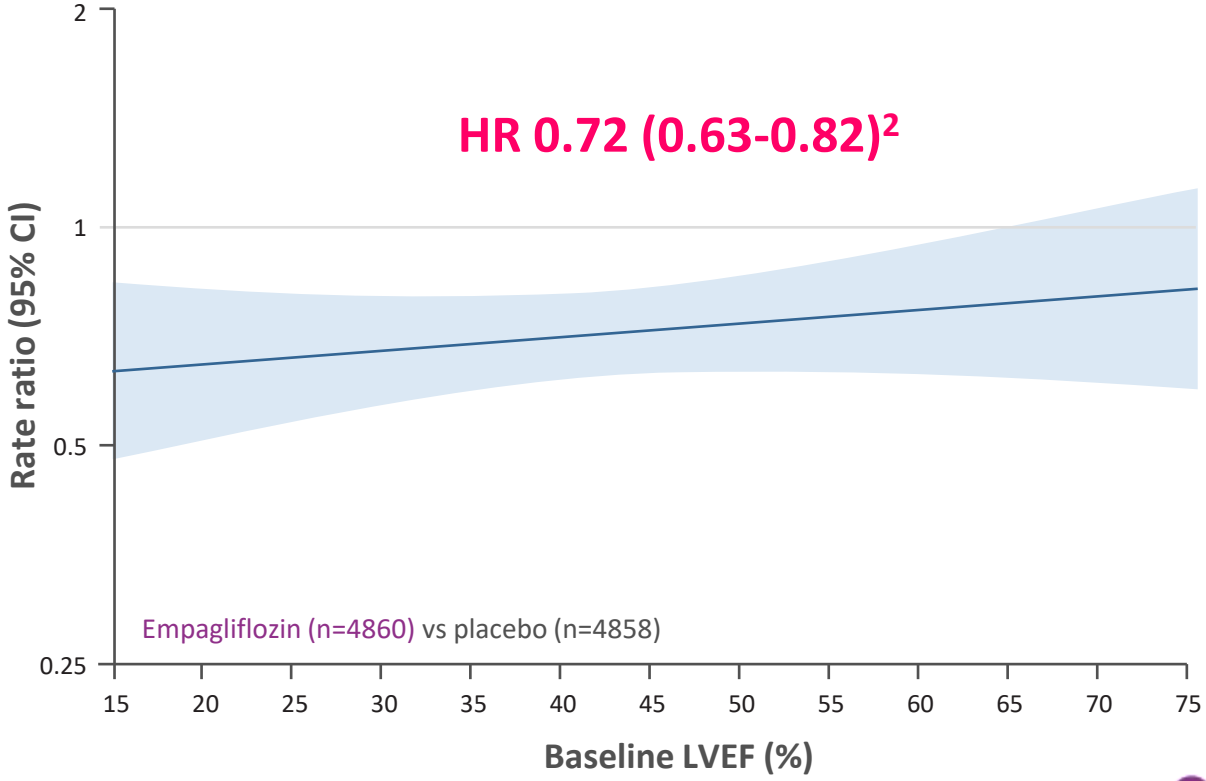
EMPEROR-Pooled: LVEF did not impact the effect of empagliflozin on CV death or first HHF[1]

Primary composite endpoint: Time to first CV death or HHF



Interaction: *p*=0.30

Key secondary endpoint: Total (first and recurrent) HHF



Interaction: *p*=0.35

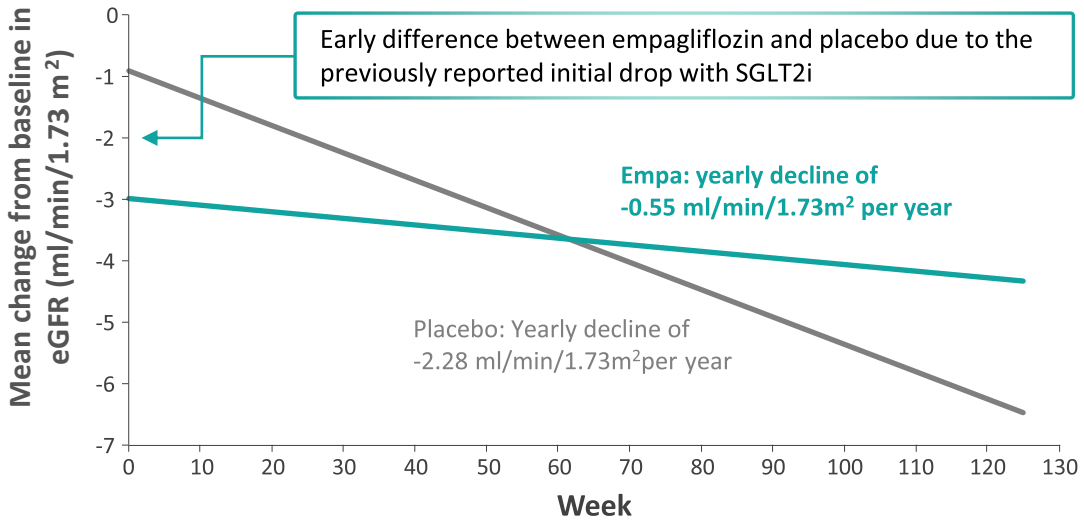
Ejection fraction analysed as a continuous variable based on the assumption that the relationship is linear (linear spline). Shaded areas represent the 95% CI.
CI, confidence interval; CV, cardiovascular; HHF, hospitalizations for heart failure; LVEF, left ventricular ejection fraction

1. Javed Butler et al., Eur Heart J. 2022 Feb 3;43(5):416-426. 2. João Pedro Ferreira et al., JAMA Cardiol. 2022 Sep 21. doi: 10.1001/jamacardio.2022.2924

Empagliflozin slowed the progression of kidney disease in the entire spectrum of LVEF in heart failure

eGFR Slope changes in Heart Failure

LVEF ≤40% (EMPEROR-Reduced[1])

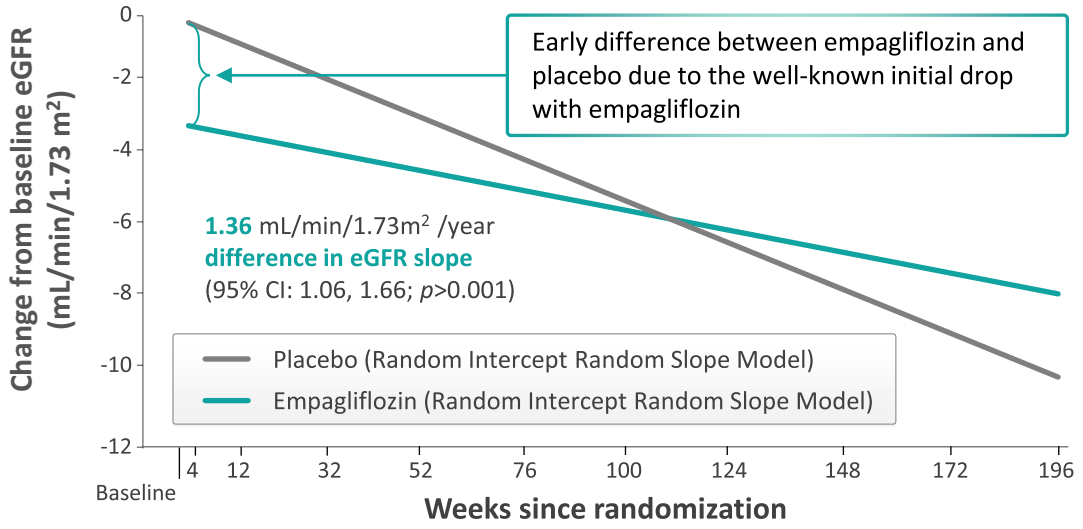


eGFR Slope = **rate of decline**

eGFR slope is a measure for **long-term renal function**

+1.73
eGFR slope difference
ml/min/1.73 m² per year
***p*<0.001**

LVEF >40% (EMPEROR-Preserved[2])



eGFR Slope = **rate of decline**

eGFR slope is a measure for **long-term renal function**

+1.36
eGFR slope difference
ml/min/1.73 m² per year
***p*<0.001**

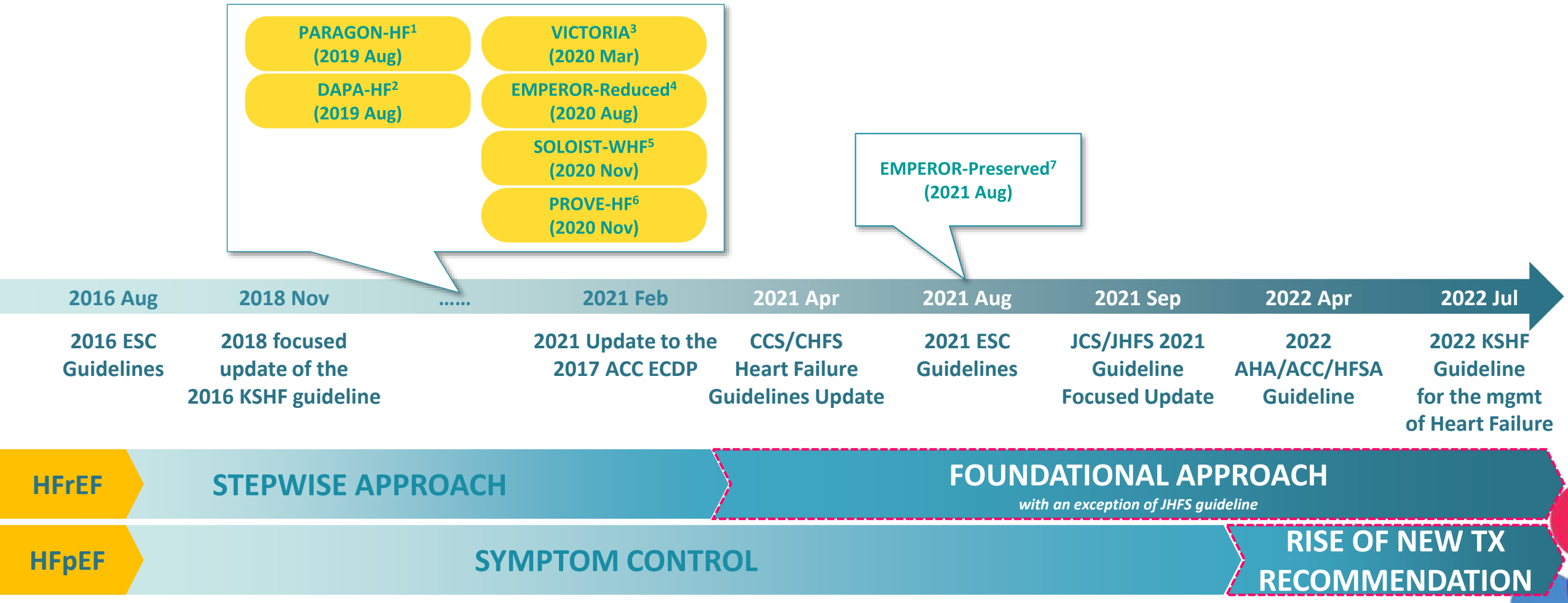
eGFR slope = rate of decline (and is a measure for long-term renal function). eGFR slope is analysed based on on-treatment data using a random intercept-random model including age, baseline eGFR and baseline LVEF as linear covariates and sex, region, baseline diabetes status, and baseline by time and treatment by time interactions as fixed effects; the model allows for randomly varying slope and intercept between patients. eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; SE, standard error.

1. Milton Packer et al., N Engl J Med. 2020 Oct 8;383(15):1413-1424 2. Stefan D Anker et al., N Engl J Med. 2021 Oct 14;385(16):1451-1461

자디앙은 심부전환자의 신장기능 악화 지연 및 신장 사건 발생 감소 목적으로 허가 받지 않았습니다. 자디앙 10mg에 대한 임상 데이터입니다.

Guidelines shifted toward to strong use of SGLT2 inhibitor in the treatment of heart failure…

Drastic shift in the paradigm of HFrEF & HFpEF with recent advances in clinical evidence in the treatment of Heart Failure made



1. Scott D Solomon et al., N Engl J Med. 2019 Oct 24;381(17):1609-1620 2. John J V McMurray et al., N Engl J Med. 2019 Nov 21;381(21):1995-2008 3. Paul W Armstrong et al., N Engl J Med. 2020 May 14;382(20):1883-1893 4. Milton Packer et al., N Engl J Med. 2020 Oct 8;383(15):1413-1424 5. Deepak L Bhatt et al., N Engl J Med. 2021 Jan 14;384(2):117-128 6. Sean P Murphy et al., JACC Heart Fail. 2021 Feb;9(2):127-136 7. Stefan D Anker et al., N Engl J Med. 2021 Oct 14;385(16):1451-1461

[2021 ESC HF Guideline]

Phenotypic approach to the management of HFrEF

To reduce mortality – for all patients

- **ACEi/ARNI**
- **BB**
- **MRA**
- **SGLT2i**

To reduce HF hospitalization/mortality – for selected patients

- Volume overload → **Diuretics**
- SR with LBBB ≥150 ms → **CRT-D/-P**
- SR with LBBB 130-149ms or non LBBB ≥150ms → **CRT-D/-P**
- Ischaemic aetiology → **ICD**
- Non-ischaemic aetiology → **ICD**
- AF → **Anticoagulation**
- AF → **Digoxin**
- **PVI**
- Coronary artery disease → **CABG**
- Iron deficiency → **Ferric carboxymaltose**
- Aortic stenosis → **SAVR/TAVI**
- Mitral regurgitation → **TEE MV repair**
- Heart rate SR>70bpm → **Ivabradine**
- Black race → **Hydralazine/ISDN**
- ACEi/ARNI intolerance → **ARB**

For selected advanced HF patients

- **Heart transplantation**
- **MCS as BTT/BTC**
- **Long-term MCS as DT**

To reduce HF hospitalization and improve QoL – for all patients

- **Exercise rehabilitation**
- **Multi-professional disease management**

Class I recommendations are shown in **green**; class IIa recommendations are shown in **orange**.

ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BB, beta blocker; BTC, bridge to candidacy; BTT, bridge to transplantation; CABG, coronary artery bypass graft; CRT-D/-P, cardiac resynchronization therapy with defibrillator/pacemaker; DT, destination therapy; ESC, European Society of Cardiology; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; LBBB, left bundle branch block; MCS, mechanical circulatory support; MRA, mineralocorticoid receptor antagonist; MV, mitral valve; PVI, pulmonary vein isolation; QoL, quality of life; SAVR, surgical aortic valve replacement; SGLT2i, sodium-glucose co-transporter-2 inhibitor; SR, sinus rhythm; TAVI, transcatheter aortic valve implantation; TEE, trans-oesophageal echocardiogram.

McDonagh TA, et al. Eur Heart J. 2021;42:3599.

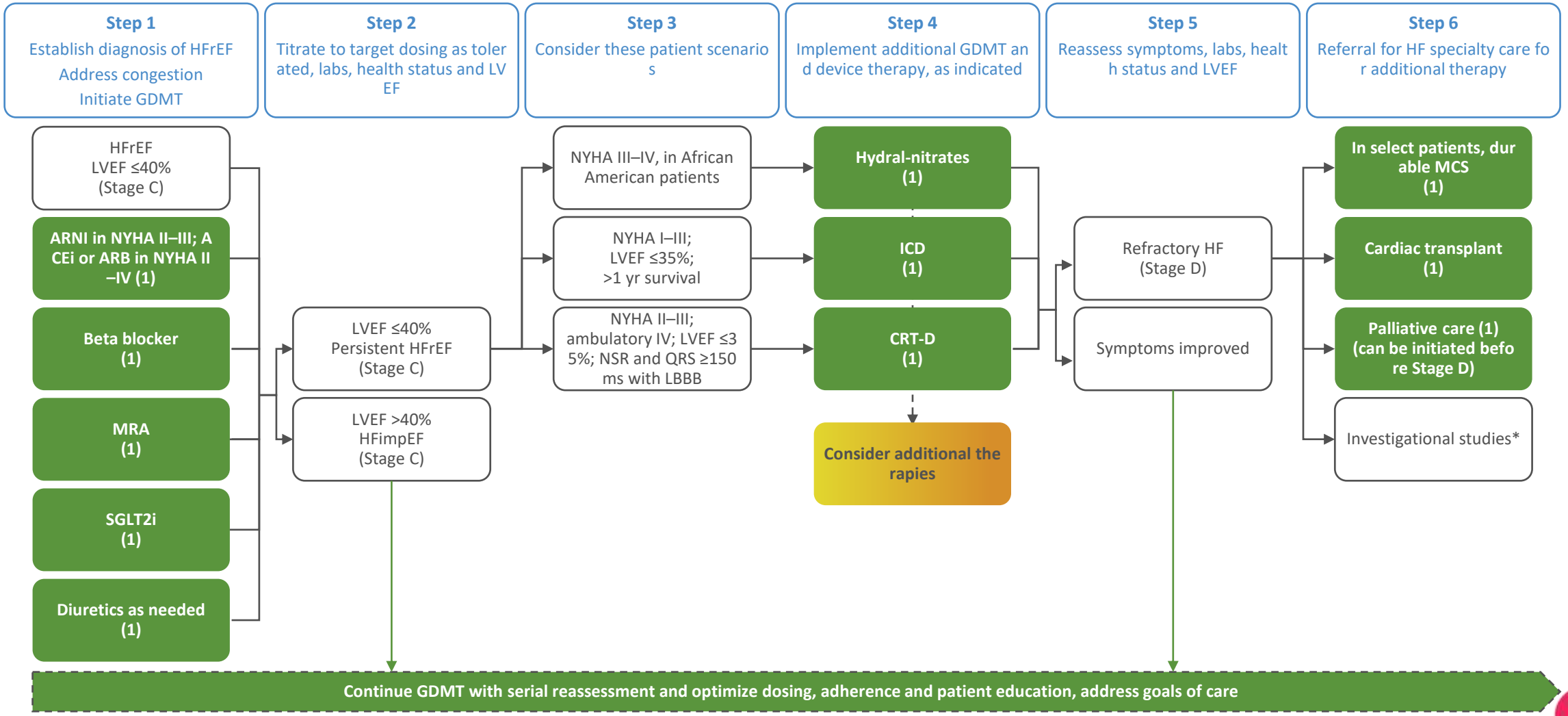
[2021 ESC HF Guideline]

Empagliflozin with Class I, Level of Evidence A RECOMMENDATION

Recommendations for the treatment of HFrEF	Class[a]	Level[b]
ACE-I is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
Beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.	I	A
MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	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.	I	B

McDonagh TA. et al, 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European Heart Journal 2021;00:1-128.

2022 AHA/ACC/HFSA Heart Failure Guideline also highlights the simultaneous initiation of GDMT (including SGLT2i)

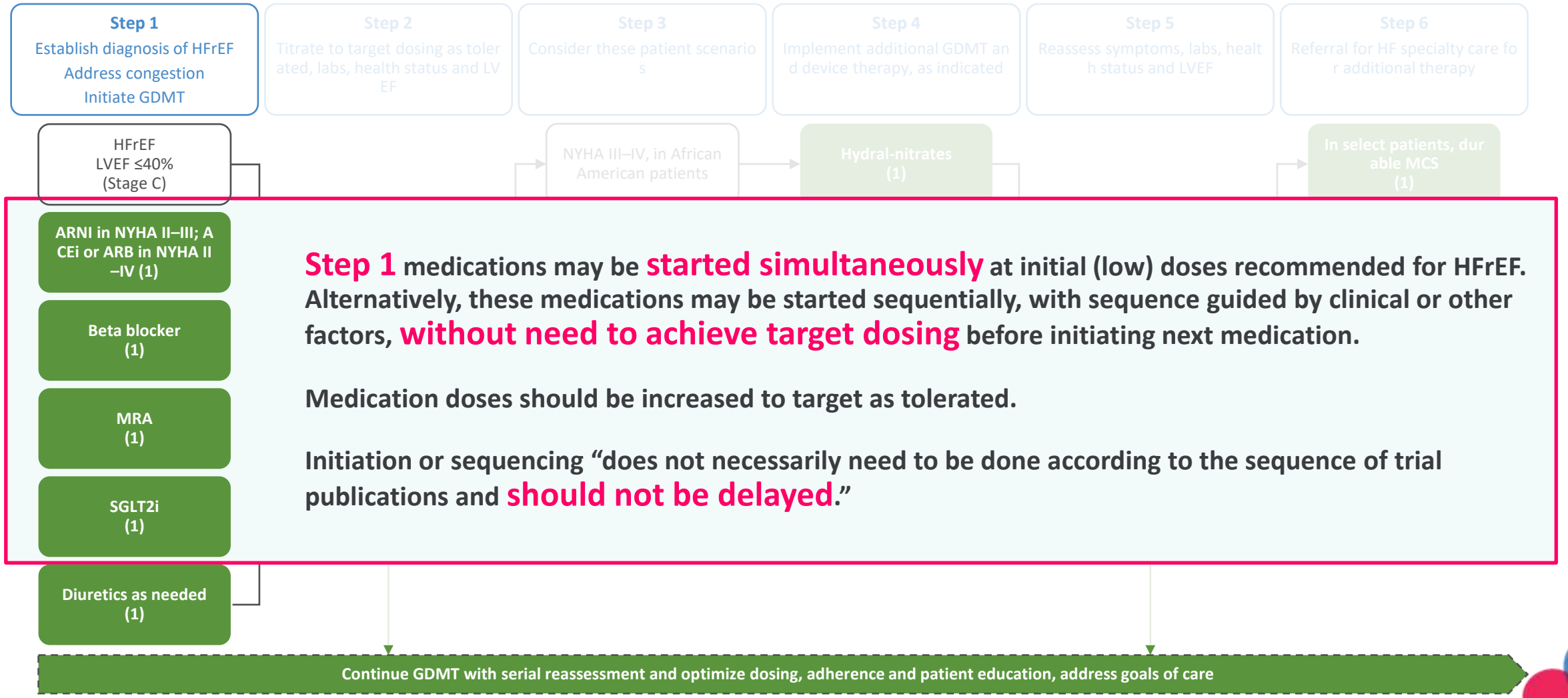


*Participation in investigational studies is appropriate for stage C, NYHA class II and III HF. See slide notes for abbreviations and definitions of classes of recommendation (COR) and levels of evidence (LOE).

Heidenreich PA et al. J Am Coll Cardiol. 2022; doi:10.1016/j.jacc.2021.12.012.

[2022 AHA/ACC/HFSA Heart Failure Guideline]

Step 1 treatments should be started simultaneously or sequentially without delay



*Participation in investigational studies is appropriate for stage C, NYHA class II and III HF. See slide notes for abbreviations and definitions of classes of recommendation (COR) and levels of evidence (LOE).

Heidenreich PA et al. J Am Coll Cardiol. 2022; doi:10.1016/j.jacc.2021.12.012.

[2022 AHA/ACC/HFSA Heart Failure Guideline]

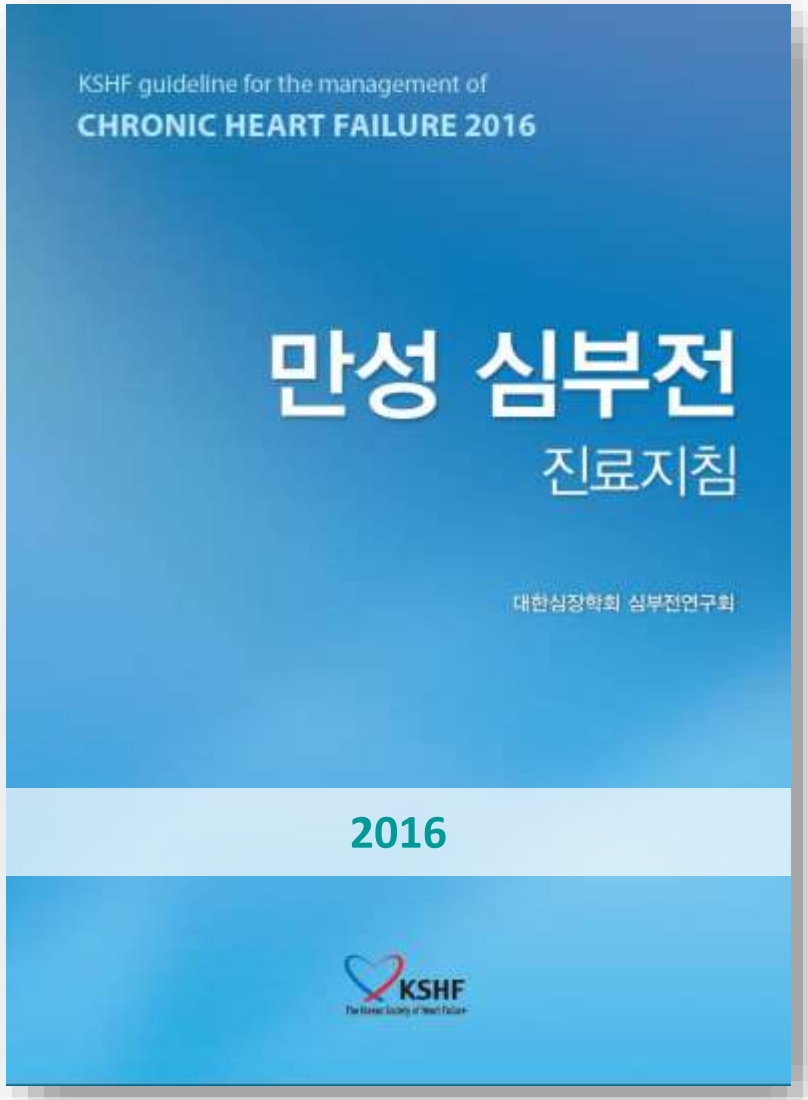
SGLT2 inhibitors have Class 1A recommendations, based on “high-quality evidence from >1 RCT”

	COR	LOE	RECOMMENDATIONS
SGLT2i	1	A	1. In patients with symptomatic chronic HFrEF, SGLT2i are recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes (1,2).
	Value Statement: Intermediate Value (A)		2. In patients with symptomatic chronic HFrEF, SGLT2i therapy provides intermediate economic value (3,4).
ARNi/ACEi /ARB	1	A	1. In patients with HFrEF and NYHA class II to III symptoms, the use of ARNi is recommended to reduce morbidity and mortality (1-5).
	1	A	2. In patients with previous or current symptoms of chronic HFrEF, the use of ACEi is beneficial to reduce morbidity and mortality when the use of ARNi is not feasible (6-13).
	1	A	3. In patients with previous or current symptoms of chronic HFrEF who are intolerant to ACEi because of cough or angioedema and when the use of ARNi is not feasible, the use of ARB is recommended to reduce monbidity and mortality (14-18).
Beta Blocker	1	A	1. In patients with HFrEF, with current or previous symptoms, use of 1 of the 3 beta blockers proven to reduce mortality (e.g., bisoprolol, carvedilol, sustained-release metoprolol succinate) is recommended to reduce mortality and hospitalizations (1-3).
MRA	1	A	1. In patients with HFrEF and NYHA class II to IV symptoms, an MRA (spironolactone or eplerenone) is recommended to reduce morbidity and mortality, if eGFR is >30 mL/min/1.73 m^2 and serum potassium is <5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely monitored thereafter to minimize risk of hyperkalemia and renal insufficiency (1-3).

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association; RCT, randomized controlled trial; SGLT2(i), sodium-glucose co-transporter-2 (inhibitor).

Heidenreich PA et al. J Am Coll Cardiol. 2022; doi:10.1016/j.jacc.2021.12.012.

2022 KSHF Guideline has newly adopted extended role of SGLT2 inhibitor in most advanced and proactive way



2016

2018

2022

[2022 KSHF Heart Failure Guideline]

Treatment strategy for the patient with HFrEF

* ARNI 또는 ACEI에 대한 내약성이 없는 경우 ARB를 대체제로 권고한다.
** 박출률 감소 심부전 환자에서 임상적 이득이 확인된 베타차단제

2022 KSHF Guideline for the Management of Heart Failure

[2022 KSHF Heart Failure Guideline]

Treatment strategy for the patient with HFrEF

HFrEF overall

핵심 권고사항

1. 박출률 감소 심부전 환자에서 안지오텐신수용체-네프릴리신억제제(ARNI) 또는 안지오텐신 전환효소억제제(내약성이 없는 경우 안지오텐신수용체차단제), 베타차단제, 염류코르티코이드 수용체 길항제(알도스테론 길항제)와 나트륨-포도당 공동수송체2(SGLT2) 억제제는 심혈관계 사망률과 심부전으로 인한 재입원을 감소시키므로, 표준치료로 사용해야 한다. (Class I, Level of Evidence A)
2. 표준약물 치료 후 심부전 증상이 개선되고 좌심실이 박출률이 40%이상으로 향상된 경우에도 표준약물 치료를 유지하는 것을 권고한다. (Class I, Level of Evidence B)

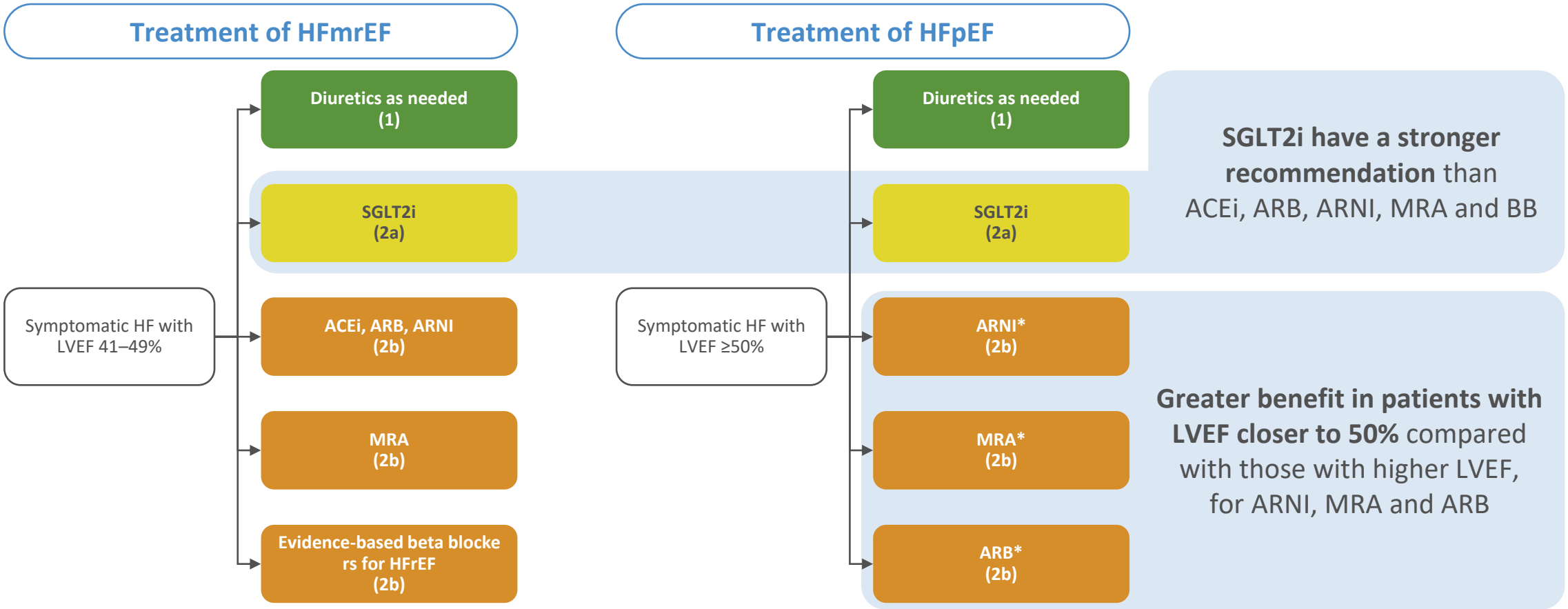
SGLT2i

핵심 권고사항

1. 당뇨병 동반유무와 관계없이 심부전으로 인한 입원 또는 심혈관계 사망을 감소시키기 위해 나트륨-포도당 공동수송체2(SGLT2) 억제제(empagliflozin 또는 dapagliflozin) 투여를 권고한다. (Class I, Level of Evidence A)

[2022 AHA/ACC/HFSA Heart Failure Guideline]

HFmrEF and HFpEF: SGLT2 inhibitors included in new treatment algorithms



*Greater benefit in patients with LVEF closer to 50%. Class and strength of recommendations: 2a: Moderate strength of recommendation; benefit >> risk. 2b: Weak recommendation; benefit ≥ risk. See slide notes for abbreviations and definitions of all classes of recommendation (COR) and levels of evidence (LOE).

Heidenreich PA et al. J Am Coll Cardiol. 2022; doi:10.1016/j.jacc.2021.12.012.

[2022 AHA/ACC/HFSA Heart Failure Guideline]

HFmrEF and HFpEF: Guidelines emphasize role of SGLT2 inhibitors in decreasing HF hospitalizations and CV mortality

COR	LOE	Recommendations for HF with mildly reduced ejection fraction
2a	B-R	1. In patients with HFmrEF, **SGLT2i** can be beneficial in decreasing HF hospitalizations and cardiovascular mortality
2b	B-NR	2. Among patients with current or previous symptomatic HFmrEF (LVEF 41–49%), use of evidence-based beta blockers for HFrEF, ARNI, ACEi or ARB, and MRAs may be considered to reduce the risk of HF hospitalization and cardiovascular mortality, particularly among patients with LVEF on the lower end of this spectrum

COR	LOE	Recommendations for HF with preserved ejection fraction
1	C-LD	1. Patients with HFpEF and hypertension should have medication titrated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent morbidity
2a	B-R	2. In patients with HFpEF, **SGLT2i** can be beneficial in decreasing HF hospitalizations and cardiovascular mortality
2a	C-EO	3. In patients with HFpEF, management of AF can be useful to improve symptoms
2b	B-R	4. In selected patients with HFpEF, MRAs may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum
2b	B-R	5. In selected patients with HFpEF, the use of ARB may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum
2b	B-R	6. In selected patients with HFpEF, ARNI may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum
3: No benefit	B-R	7. In patients with HFpEF, routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or QoL is ineffective

ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CV, cardiovascular; 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; MRA, mineralocorticoid receptor antagonist; QoL, quality of life; SGLT2(i), sodium-glucose co-transporter-2 (inhibitor).

Heidenreich PA et al. J Am Coll Cardiol. 2022; doi:10.1016/j.jacc.2021.12.012.

[2022 KSHF Heart Failure Guideline]

Treatment strategy for the patient with HFmrEF and HFpEF

Treatment of HFmrEF

핵심 권고사항

1. 이뇨제는 울혈이 있는 환자에서 증상 및 증후를 경감시키기 위해서 사용해야 한다. (Class I, Level of Evidence C)
2. 나트륨-포도당 공동수송체2(SGLT2) 억제제(empagliflozin 또는 dapagliflozin)는 당뇨병 유무와 관계없이 심부전으로 인한 입원 또는 심혈관계 사망을 감소시키기 위해 투여하는 것을 권고한다. (Class I, Level of Evidence B)
3. 안지오텐신수용체-네프릴리신 억제제(ARNI)는 심부전으로 인한 입원 또는 심혈관계 사망을 줄이기 위해 투여하는 것은 타당하다. (Class IIa, Level of Evidence B)
4. 안지오텐신전환효소억제제 또는 안지오텐신수용체차단제는 심부전으로 인한 입원 또는 심혈관계 사망을 감소시키기 위해 사용하는 것을 고려할 수 있다. (Class IIb, Level of Evidence C)
5. 베타차단제는 박출률 경도 감소 심부전 환자에서 심부전으로 인한 입원 또는 심혈관계 사망을 줄이기 위해서 사용하는 것을 고려할 수 있다. (Class IIb, Level of Evidence C)
6. 염류코르티코이드 수용체 길항제(알도스테론 길항제)는 심부전으로 인한 입원 또는 심혈관계 사망을 줄이기 위해서 사용하는 것이 도움이 될 수 있다. (Class IIa, Level of Evidence B)

Treatment of HFpEF

핵심 권고사항

1. 동반 질환(고혈압, 심방세동 등의 심혈관계 질환 및 당뇨병, 신부전 등의 비심혈관계 질환)에 대한 선별 검사와 치료가 필요하다. (Class I, Level of Evidence C)
2. 울혈 증상이 있는 경우 이뇨제 치료가 필요하다. (Class I, Level of Evidence C)
3. 나트륨-포도당 공동수송체2(SGLT2) 억제제(empagliflozin 또는 dapagliflozin)는 당뇨병 유무와 관계없이 심부전으로 인한 입원 또는 심혈관계 사망을 감소시키기 위해 투여하는 것을 권고한다. (Class I, Level of Evidence B)
4. 안지오텐신수용체-네프릴리신 억제제(ARNI)는 심부전으로 인한 입원 또는 심혈관계 사망을 줄이기 위해서 투여하는 것은 도움이 될 수 있다. (Class IIa, Level of Evidence B)
5. 안지오텐신수용체차단제 또는 안지오텐신전환효소억제제는 심부전으로 인한 입원 또는 심혈관계 사망을 감소시키기 위해 사용을 고려할 수 있다. (Class IIb, Level of Evidence C)
6. 베타차단제는 심혈관계 사망을 감소시키기 위해 사용을 고려할 수 있다. (Class IIb, Level of Evidence C)
7. 염류코르티코이드 수용체 길항제(알도스테론 길항제)는 심부전으로 인한 입원 또는 심혈관계 사망을 감소시키기 위해 사용을 고려할 수 있다. (Class IIb, Level of Evidence C)

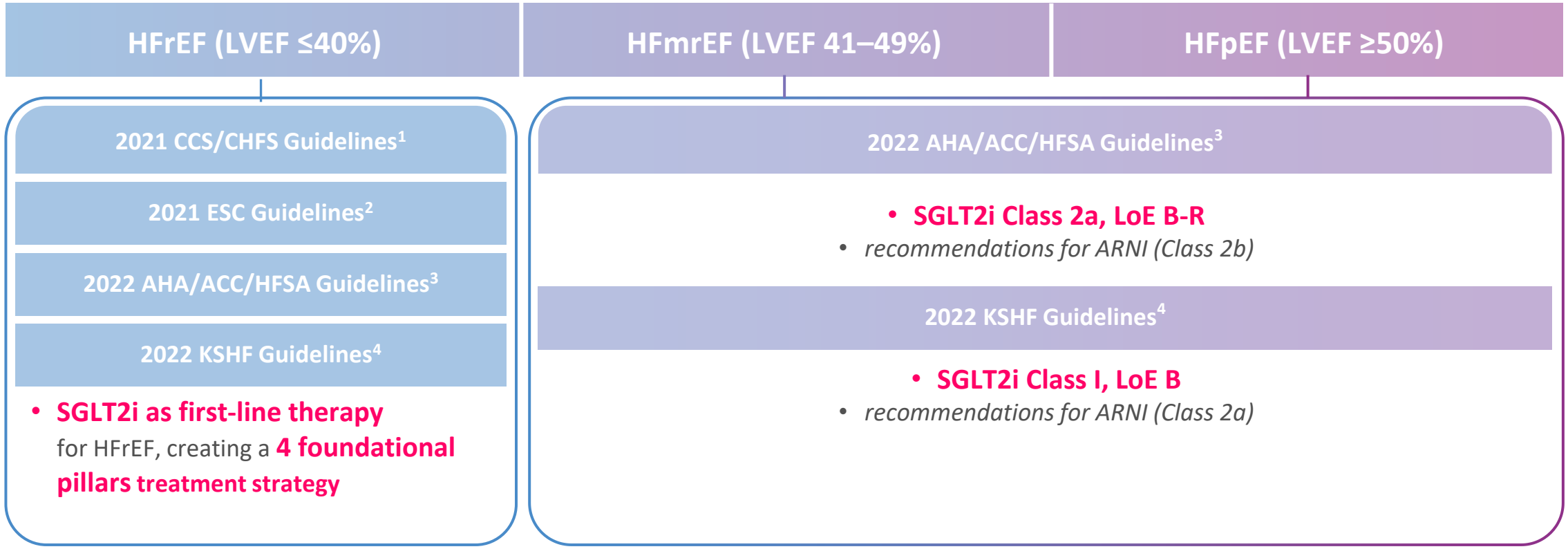
[2022 AHA/ACC/HFSA Heart Failure Guideline]

Recommendations for Patients at Risk for HF (Stage A: Primary Prevention)

COR	LOE	RECOMMENDATIONS
1	A	1. In patients with hypertension, blood pressure should be controlled in accordance with GDMT for hypertension to prevent symptomatic HF (1-9).
1	A	2. In patients with type 2 diabetes and either established CVD or at high cardiovascular risk, SGLT2i should be used to prevent hospitalizations for HF (10-12).
1	B-NR	3. In the general population, healthy lifestyle habits such as regular physical activity, maintaining normal weight, healthy dietary patterns, and avoiding smoking are helpful to reduce future risk of HF (13-21).

Paul A Heidenreich et al., Circulation. 2022 Apr 1. 2022 AHA/ACC/HFSA Heart Failure Guideline

Recommendations for SGLT2 inhibitors in HF: Summary



ACC, American College of Cardiology; ACEi, angiotensin-converting enzyme inhibitor; AHA, American Heart Association; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BB, beta blocker; CCS, Canadian Cardiovascular Society; CHFS, Canadian Heart Failure Society; ESC, European Society of Cardiology; KSHF, Korean Society of Heart Failure; 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; HFSA, Heart Failure Society of America; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; SGLT2, sodium-glucose co-transporter-2. 1. McDonald M et al. Can J Cardiol. 2021;37:531; 2. McDonagh TA et al. Eur Heart J. 2021;42:3599; 3. Heidenreich PA et al. J Am Coll Cardiol. 2022; doi:10.1016/j.jacc.2021.12.012. 4. 2022 KSHF Guideline for the Management of Heart Failure

Empagliflozin[13] is a simple chronic HF treatment to implement, with consistent efficacy across patient subgroups and a favourable safety profile

Efficacy

- Clinically meaningful RRR for CV death or HHF across the LVEF spectrum[1,2]
- Clinical benefit in acute HF once stabilized[3]

Consistency

- CV and renal benefits consistent across multiple subgroups[1–12]
- Including prespecified LVEF categories[4]
- Including in patients with de novo or chronic HF[3]

Safety profile

- Safety data consistent with previous findings[1–3]
- Protected the kidney by significantly slowing the decline in kidney function[1,2]
- Inpatient initiation was well tolerated[3]

Implementation

- Once-daily single dose[13]
- No titration required[13]
- Can be combined with other foundational HF therapies[1,2]
- Can be initiated in hospital after stabilization[3] and down to eGFR of 20mL/min/1.73m^2 [13]

Supported by strong cost-effective profile; 660원/일 or 19,800원/월 (인정비급여 기준)

CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HHF, hospitalization for heart failure; LVEF, left ventricular ejection fraction; RRR, relative risk reduction.

1. Milton Packer et al., N Engl J Med. 2020 Oct 8;383(15):1413-1424. 2. Stefan D Anker et al., N Engl J Med. 2021 Oct 14;385(16):1451-1461. 3. Adriaan A Voors et al., Nat Med. 2022 Mar;28(3):568-574. 4. Javed Butler et al., Eur Heart J. 2022 Feb 3;43(5):416-426. 5. Michael Böhm et al., J Am Coll Cardiol. 2021 Sep 28;78(13)1337-1348. 6. Milton Packer et al., J Am Coll Cardiol. 2021 Mar 23;77(11):1381-1392. 7. João Pedro Ferreira et al., J Am Coll Cardiol. 2021 Mar 23;77(11):1397-1407. 8. João Pedro Ferreira et al., J Am Coll Cardiol. 2022 Mar 29;79(12):1129-1137. 9. Milton Packer et al., Circulation. 2021 Jan 26;143(4):326-336. Supplemental Material. 10. Milton Packer et al., Circulation. 2021 Oct 19;144(16):1284-1294. 11. Javed Butler et al., Eur Heart J. 2021 Mar 31;42(13):1203-1212. 12. Javed Butler et al., Circulation. 2022 Jan 18;145(3):184-193. 13. 자디앙®정10밀리그램 제품정보. 식품의약품안전처의약품안전나라.https://nedrug.mfds.go.kr/ (accessed on 2023-01-31). 자디앙정은 만성 심부전 환자의 신장 질환 위험 감소 및 신기능 감소 지연 목적으로 국내 허가 받지 않았습니다

Case: 77-year old Female with AF

2018.7 ER visit
CC> DOE with chest discomfort
Hospital course>
V/S 150/80-120
ECG: AF with RVR
CPA: cardiomegaly, but no apparent
CCTA: insignificant
→ Started lasix

1st OPD Visit>
BP 154/90-83, still dypneic, minimal rale
TTE:
1. non-valvular AF with low normal LV systolic function (LVEF=53%)
2. Both atrial enlargement
3. Mild to moderate TR, mild MR

→Valsartan/HCT 80/12.5mg qd, bisoprolol 2.5mg qd, lasix 40mg qd, apixaban 5mg bid

2nd OPD Visit>
Says doing fine
BP 122/84-82
→ Ditto

Case: 77-year old Female with AF

SBP(mmHg) 136 DBP(mmHg) 99 PR(회/min) 80
괜찮다

Ass>
non-valvular a.fib with low normal LV systolic function (LVEF= 53%)
mild to moderate TR, mild MR

ditto

SBP(mmHg) 127 DBP(mmHg) 88 PR(회/min) 85
no sx.

lab: ok

Ass>
non-valvular a.fib with low normal LV systolic function (LVEF= 53%)
mild to moderate TR, mild MR

ditto 잘 지낸다

Ass>
non-valvular a.fib with low normal LV systolic function (LVEF= 53%)
mild to moderate TR, mild MR

stop lasix

SBP(mmHg) 131 DBP(mmHg) 85 PR(회/min) 85
lasix 끊으니까 숨차하심

Ass>
non-valvular a.fib with low normal LV systolic function (LVEF= 53%)
mild to moderate TR, mild MR

add lasix

SBP(mmHg) 135 DBP(mmHg) 93 PR(회/min) 101
HR 80

Ass>
non-valvular a.fib with low normal LV systolic function (LVEF= 53%)
mild to moderate TR, mild MR
R/O HEpEF

SGLT2i

SBP(mmHg) 125 DBP(mmHg) 76 PR(회/min) 87
숨이 안차니까 살것 같다
감사하다

"I feel like I'm alive because I can breathe."

Ass>
non-valvular a.fib with low normal LV systolic function (LVEF= 53%)
mild to moderate TR, mild MR
R/O HEpEF

ditto

"Just because a patient says they are okay doesn't mean there are no symptoms. They may simply be adapting and getting by."