SGLT2i: Η 1η επιλογή στη θεραπεία των ασθενών με Καρδιακή Ανεπάρκεια ανεξαρτήτου κλάσματος εξώθησης

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Epidemiology

There is an urgent unmet medical need for people living with HF

More than 60 million people worldwide are living with HF[1]

HF is one of the leading causes of hospitalization[2,3] and the **number 1 cause of hospitalization in patients over 65 years old**[4]

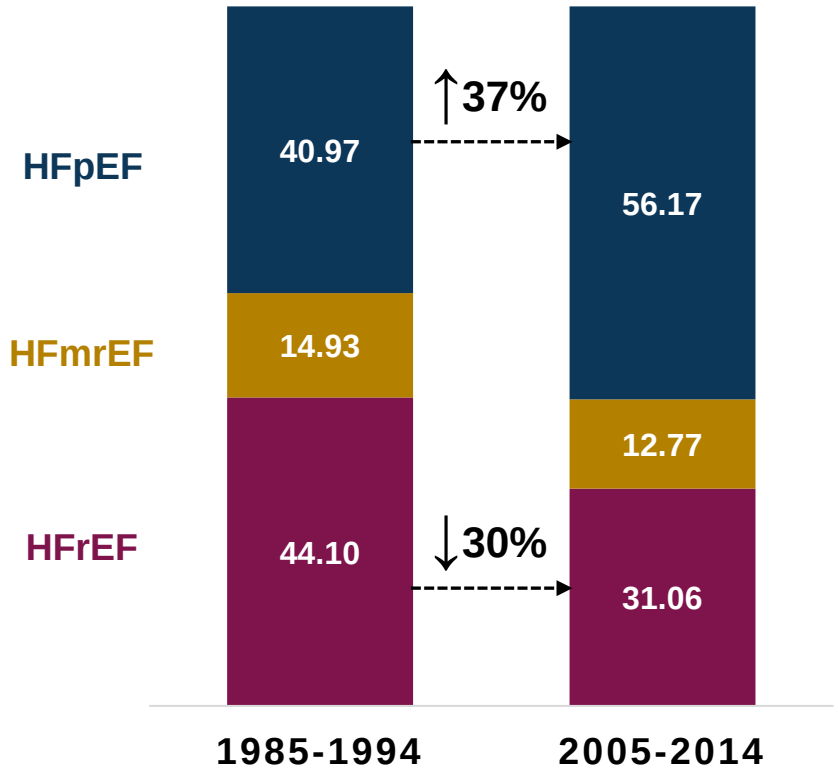
Hospital readmission rates after HHF are as high as **~30%** within 90 days[5]

Approximately **30%** of patients who are hospitalized with HF **die within 1 year**[6]

1. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. *Lancet.* 2017;390:1211; 2. Blecker S *et al. J Am Coll Cardiol.* 2013;61:1259; 3. Ambrosy AP *et al. J Am Coll Cardiol.* 2014;63:1123; 4. Azad N, Lemay G. *J Geriatr Cardiol.* 2014;11:329; 5. Fonarow GC *et al. J Am Coll Cardiol.* 2007;50:768; 6. Shah KS *et al. J Am Coll Cardiol.* 2017;70:2476.

HFpEF Prevalence Rising

Percentage of Patients Within Each LVEF Category[1,a]



Reasons for Increased HFpEF Prevalence[2]

Increasing Life Expectancy and Aging of the Population

- Global population is rapidly aging
- Rate of HFpEF among patients with HF increases with age
- Increase in comorbidities associated with aging

Epidemic of Cardiac and Non-cardiac Comorbidities

- Improved survival after onset of CAD
- Rate of AF increasing due to an aging general population and increased longevity
- Increasing incidence of obesity, metabolic syndrome, and diabetes

Increased Clinical Recognition

- Improved diagnostic techniques
- Development of diagnostic guidelines

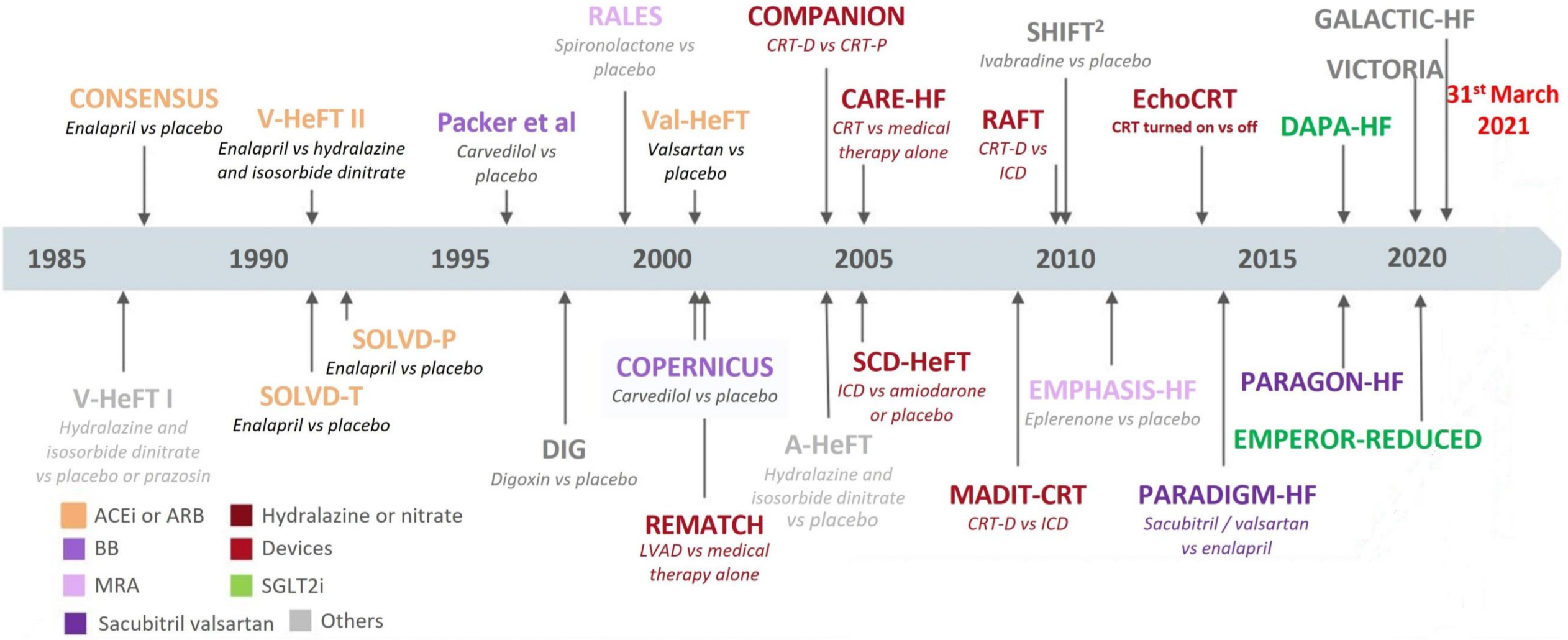
[a]HF prevalence data for 894 outpatients with new onset HF from the community based, Framingham Study over 3 decades (1985-2014). LVEF categories were defined as HFrEF (EF <40%), HF with mid-range EF (EF 40-<50%), and HFpEF (EF ≥50%).

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

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

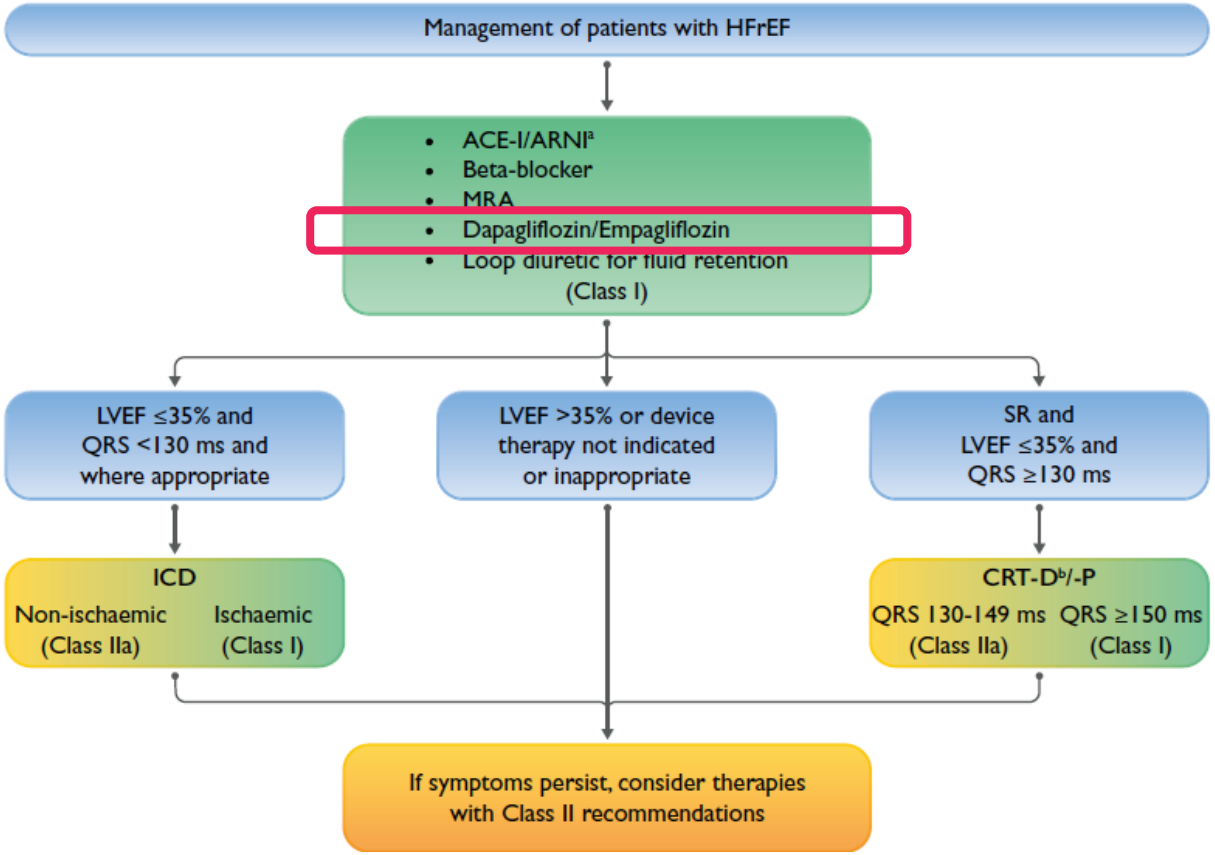
Trials history

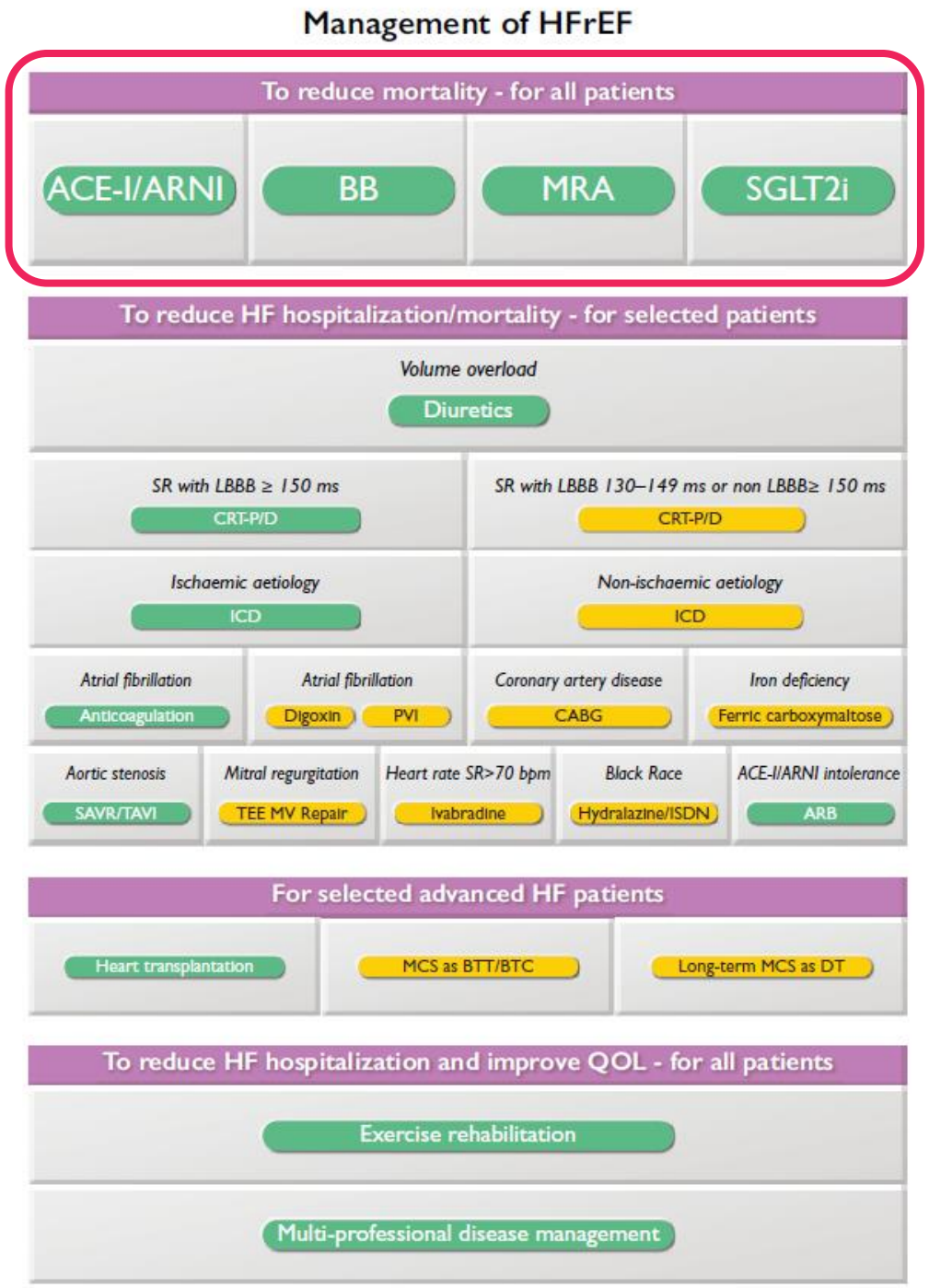
In 2021, we had **34 years** of heart failure therapy to consider



2023 Focused update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad195)

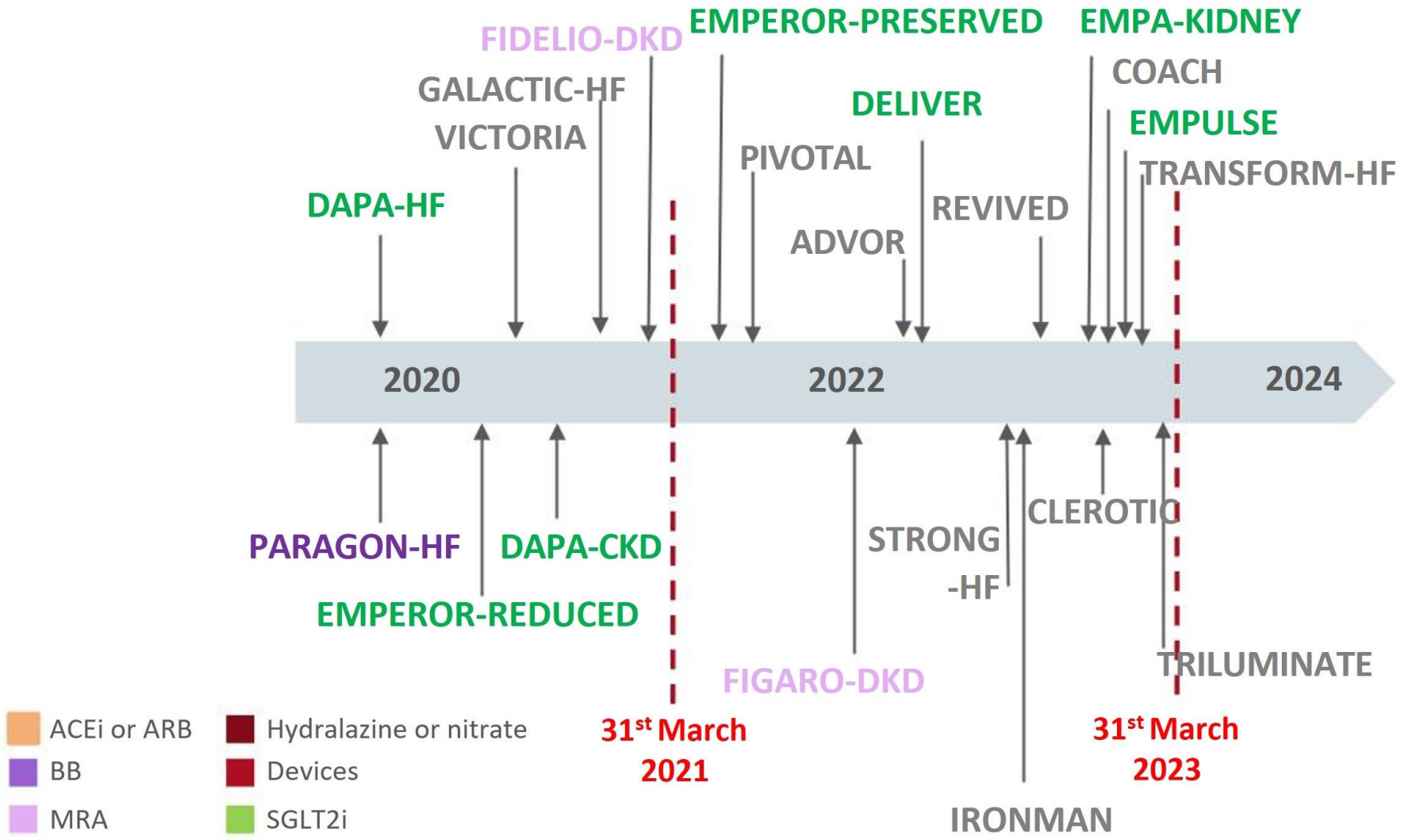
2021 ESC Heart Failure Guidelines





*Class of recommendation. †Level of evidence.
ACEi, angiotensin-converting enzyme inhibitor; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist.
McDonagh TA *et al. Eur Heart J.* 2021;42:3599.

Amazing progress in heart failure



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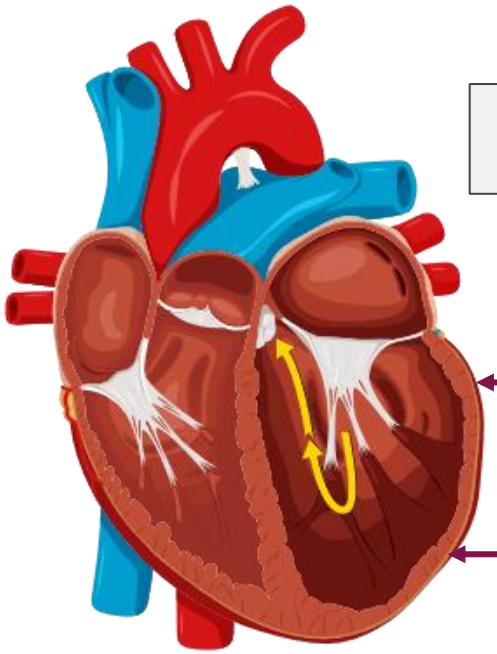
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad195)

Pathophysiology

Differences in HF Pathophysiology[1-3]

HFrEF

LV contraction is reduced resulting in inadequate cardiac output**.**



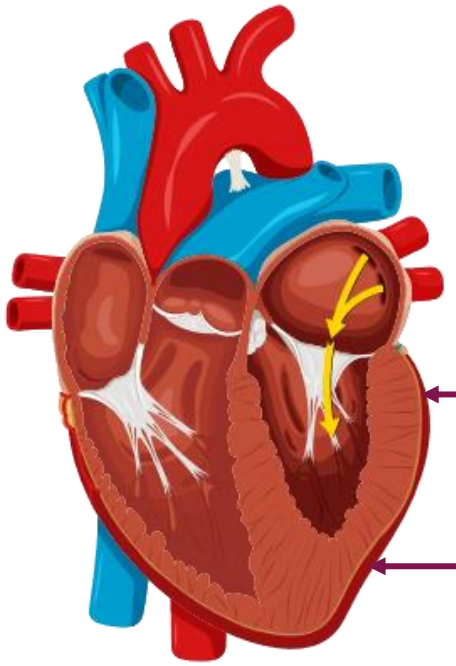
~2/3 of cases are due to CAD

- **LVEF ≤40%**
- **LV dilation**

- **Abnormal contractility**
- **LV remodeling**

HFpEF

LV filling is reduced so that, even though LVEF is normal, cardiac output is reduced**.**



Substantial pathophysiologic heterogeneity

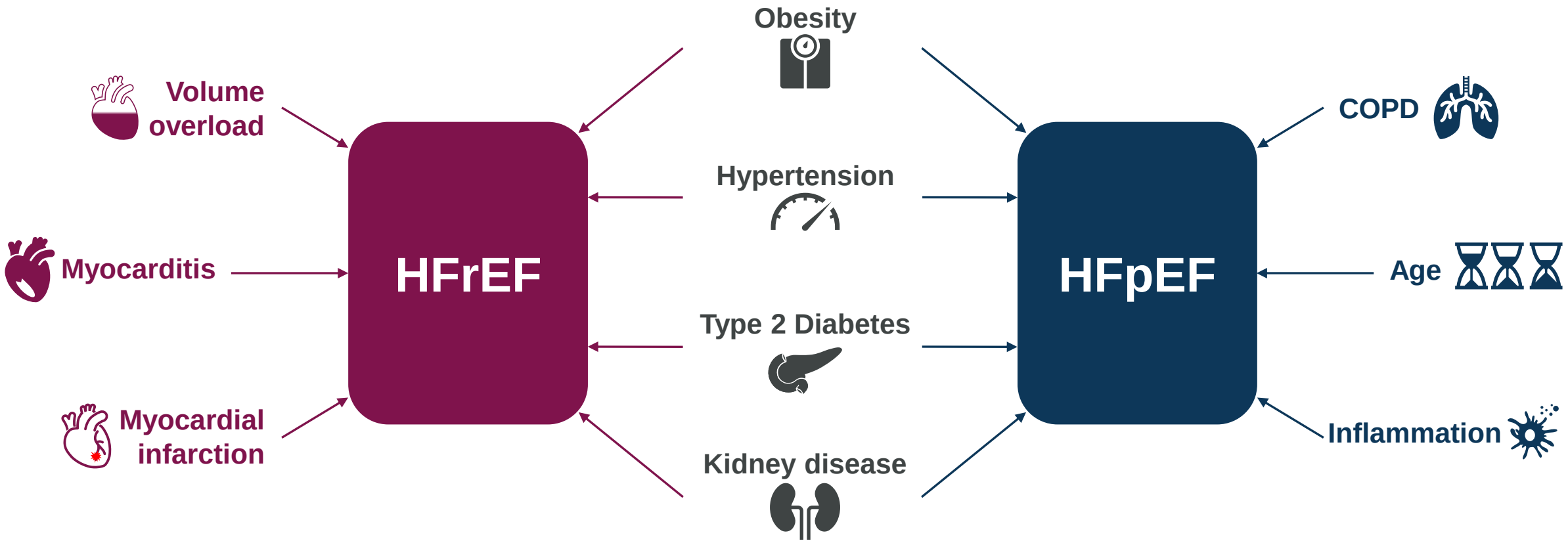
- **Normal LVEF (≥50%)**
- **No LV dilation**

- **Stiff, thickened walls**
- **Normal contractility**
- **Concentric LV hypertrophy**

CAD = coronary artery disease; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HTN = hypertension; LV = left ventricular; LVEF = left ventricular ejection fraction.

1. Bloom MW et al. *Nat Rev Dis Primers.* 2017;3:17058; 2. Borlaug BA. *Nat Rev Cardiol*. 2014;11:507-515; 3. Redfield MM. *N Engl J Med*. 2016;375:1868-1877.

HFrEF and HFpEF Share Many Comorbidities and Risk Factors, While Others Differ



COPD = chronic obstructive pulmonary disease; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

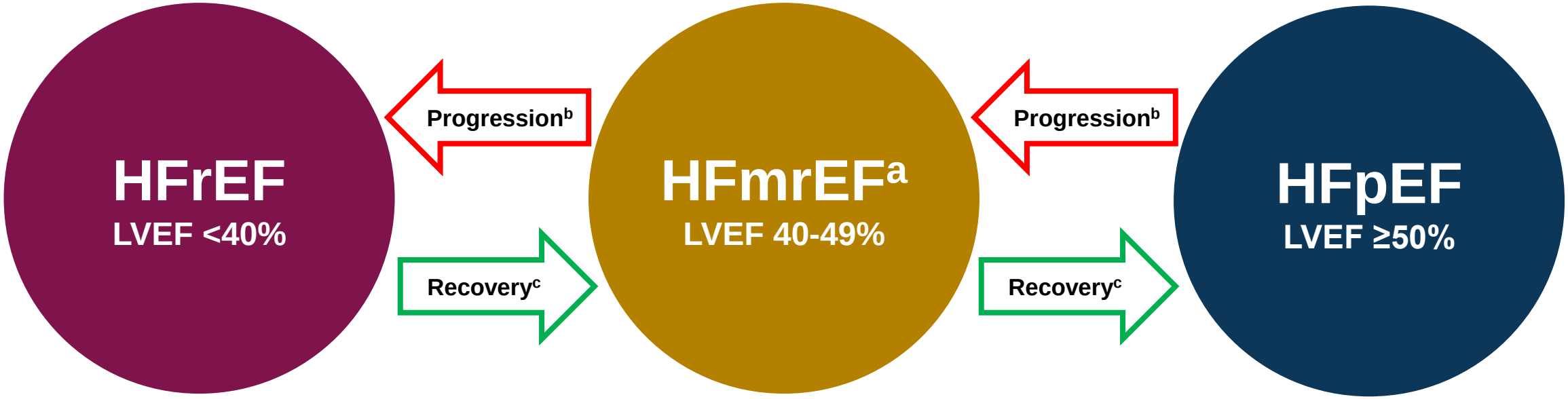
Simmonds SJ et al. *Cells*. 2020;9:242.

HF, CKD, and T2D Are Often Comorbid

CKD = chronic kidney disease; HF = heart failure; M = million; T2D = type 2 diabetes.

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. *Lancet.* 2018;392:1789-1858; 2. Ronco C et al. *J Am Coll Cardiol.* 2008;52:1527-1539; 3. Jager KJ et al. *Nephrol Dial Transplant*. 2019;34:1803-1805; 4.Birkeland KI et al. *Diabetes Obes Metab.* 2020:22:1607-1618; 5. IDF Diabetes Atlas, 9th edition. https://diabetesatlas.org/atlas/ninth-edition/. Accessed November 1, 2022; 6. Parving HH et al. *Kidney Int.* 2006;69:2057-2063.

Changes in LVEF Occur Over Time and Are Associated With Specific Patient Characteristics



Factors associated with progression[b]:

Diabetes, ischemic heart disease, lack of specialized HF follow-up, higher NT-proBNP levels

Factors associated with recovery[c]:

Younger age, female, lower HF severity, shorter HF duration, fewer comorbidities

Data from patients with ≥2 EF measurements in the SwedeHF study (N=4942) between May 2000 and December 2012.

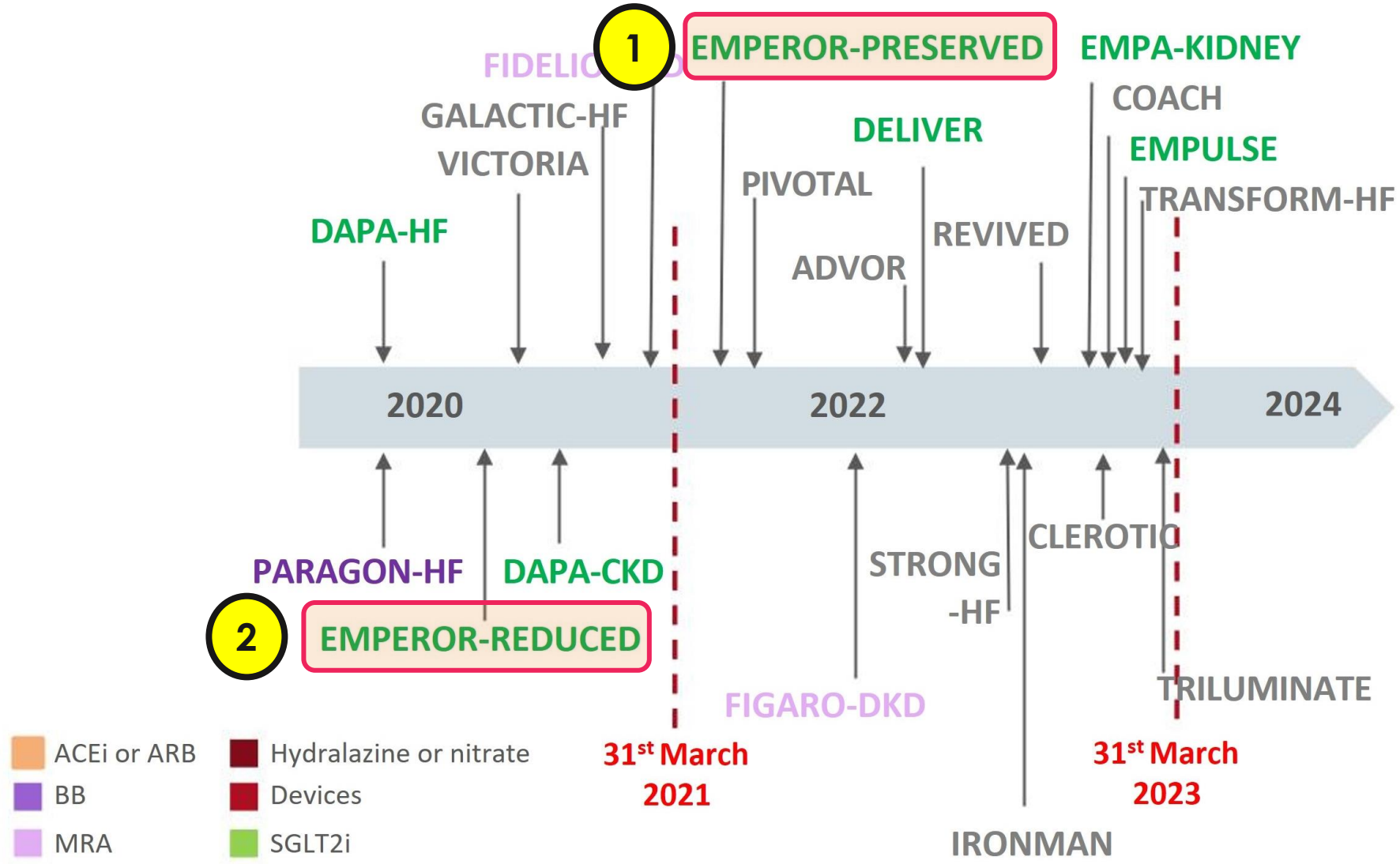
[a]Reference uses the term HF with midrange EF (EF 40-49%) for this group; [b]EF decrease; [c]EF increase.

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; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

Savarese G et al. *JACC Heart Fail*. 2019;7:306-317.

Empa studies

Amazing progress in heart failure



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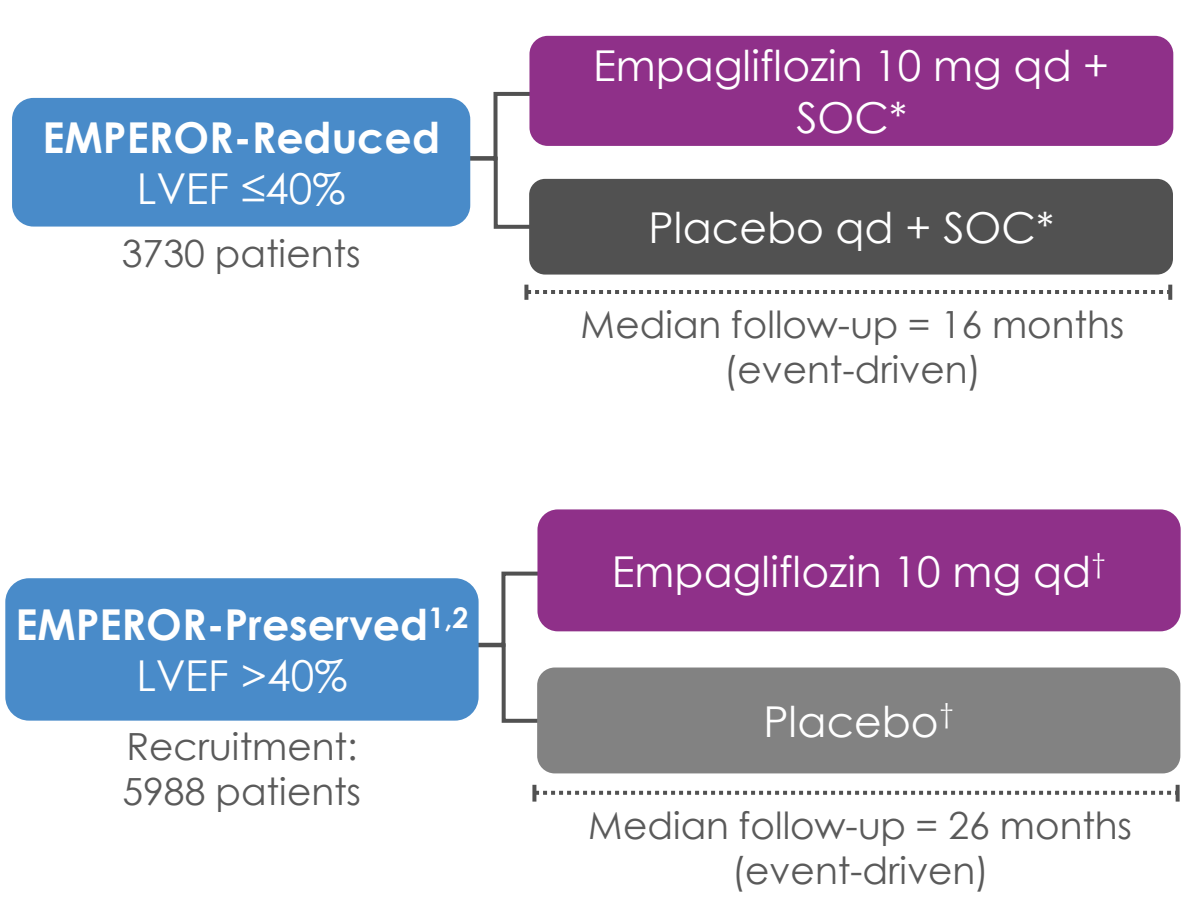
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad195)

EMPEROR TRIALS Study Design[1–3]



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**

EXCLUSION CRITERIA

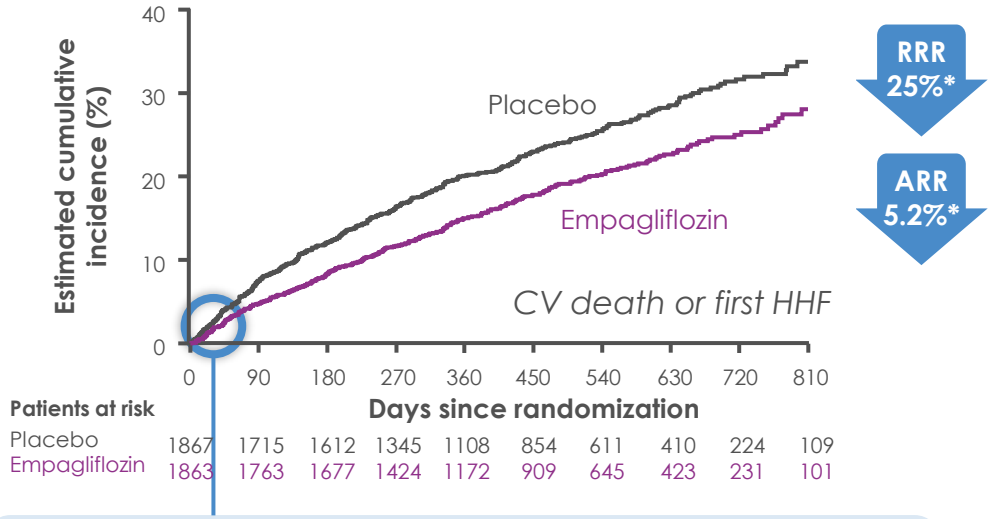
- **eGFR <20 mL/min/1.73 m^2 or requiring dialysis**

The cutoff for patients with AF is doubled in EMPEROR-Reduced & Preserved
See slides notes for abbreviations
Packer M et al. Eur J Heart Fail 2019;21:1270
DOI: 10.1056/NEJMoa2022190
ClinicalTrials.gov. NCT03057951; 2. Butler J et al. ESC-HF 2018; poster P972

Empagliflozin demonstrated early, significant and sustained reductions in the risk of CV death or first HHF across the LVEF spectrum compared with placebo[1–4]

EMPEROR-Reduced*[1,2]

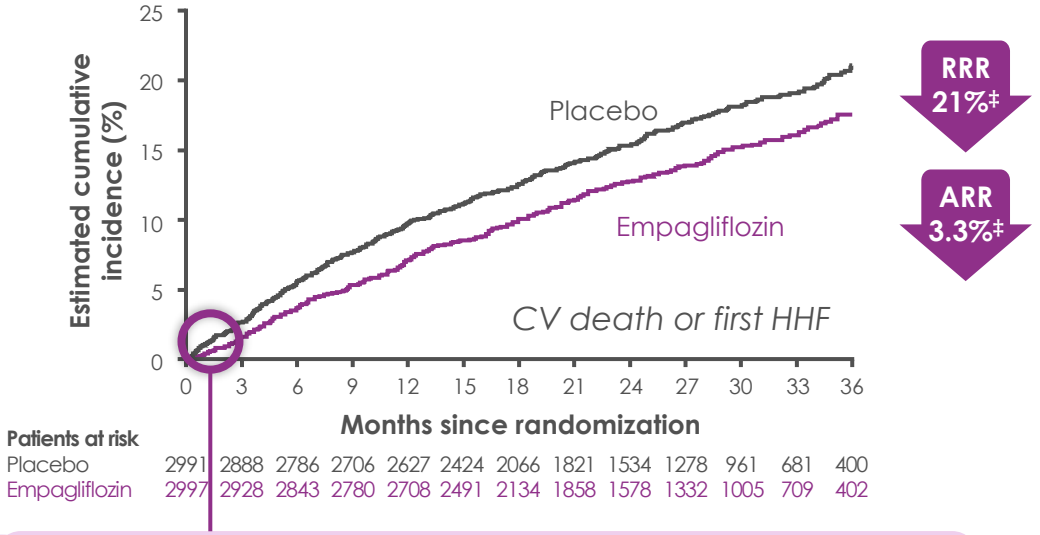
3730 patients with HFrEF (LVEF ≤40%)



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

EMPEROR-Preserved‡[4]

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



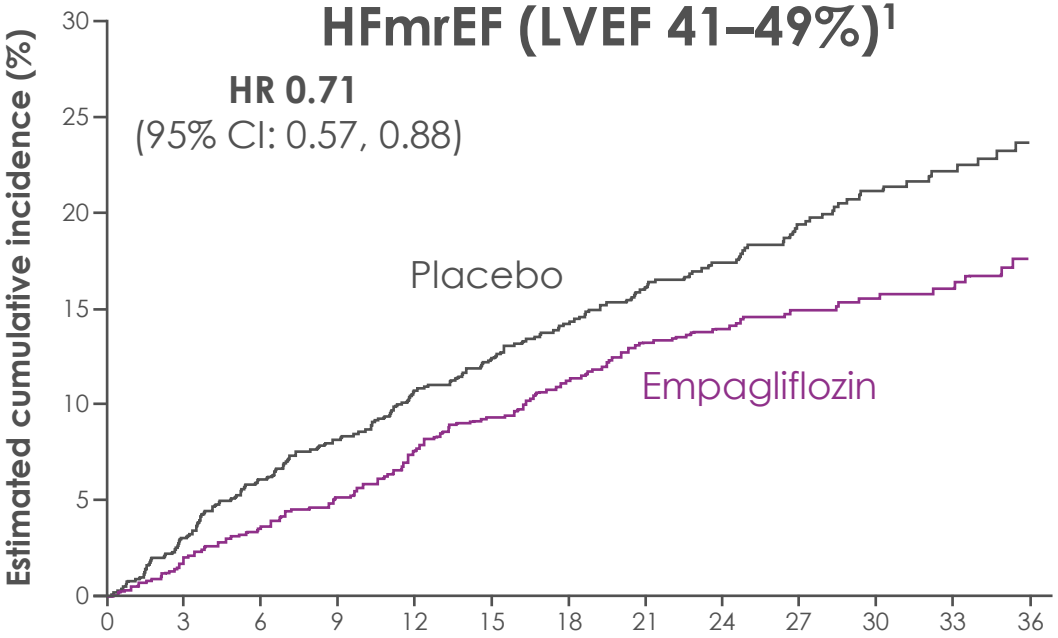
Statistical significance:[5]
Reached **18 days after randomization**
Sustained for the duration of the follow-up period

*Patients received empagliflozin 10 mg or placebo OD. The median follow-up was 16 months. For CV death or first HHF, HR (95% CI): 0.75 (0.65, 0.86); $p<0.001$; NNT=19. †Combined risk of death, HHF or an emergent or urgent HF visit requiring IV treatment.[3] ‡Patients received empagliflozin 10 mg or placebo OD. The median follow-up was 26.2 months. For CV death or first HHF, HR (95% CI): 0.79 (0.69, 0.90); $p<0.001$; NNT=31. Abbreviations in slide notes. 1. Packer M *et al. N Engl J Med*. 2020;383:1413; 2. Butler J *et al. Eur J Heart Fail.* 2020;22:1991; 3. Packer M *et al. Circulation*. 2021;143:326; 4. Anker SD *et al. N Engl J Med.* 2021;385:1451; 5. Butler J *et al. Eur J Heart Fail*. 2022;24:245.

EMPEROR-Preserved: Effect of empagliflozin on CV death or HHF was consistent between patients with HFmrEF or HFpEF

Primary composite endpoint: Time to first event of adjudicated CV death or HHF

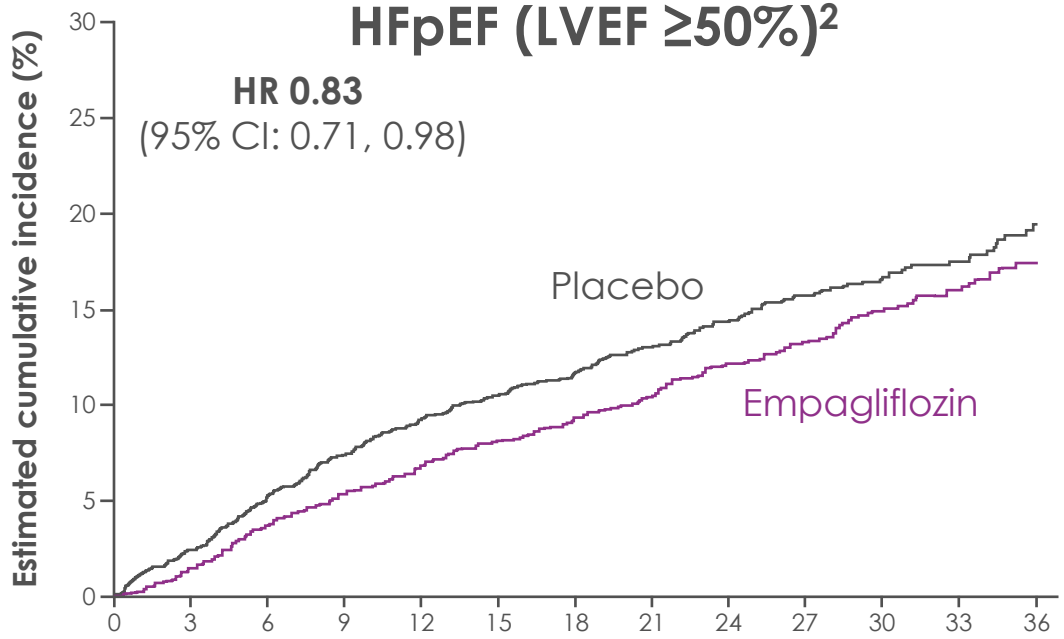
HFmrEF (LVEF 41–49%)[1]



Patients at risk[1,2]

Placebo	998	945	906	880	848	794	689	601	513	422	322	228	136
Empagliflozin	995	968	945	927	897	834	726	625	524	450	335	246	136

HFpEF (LVEF ≥50%)[2]



2003	1943	1880	1826	1779	1630	1377	1220	1021	856	639	453	264
2002	1960	1898	1853	1811	1657	1408	1233	1054	882	670	463	266

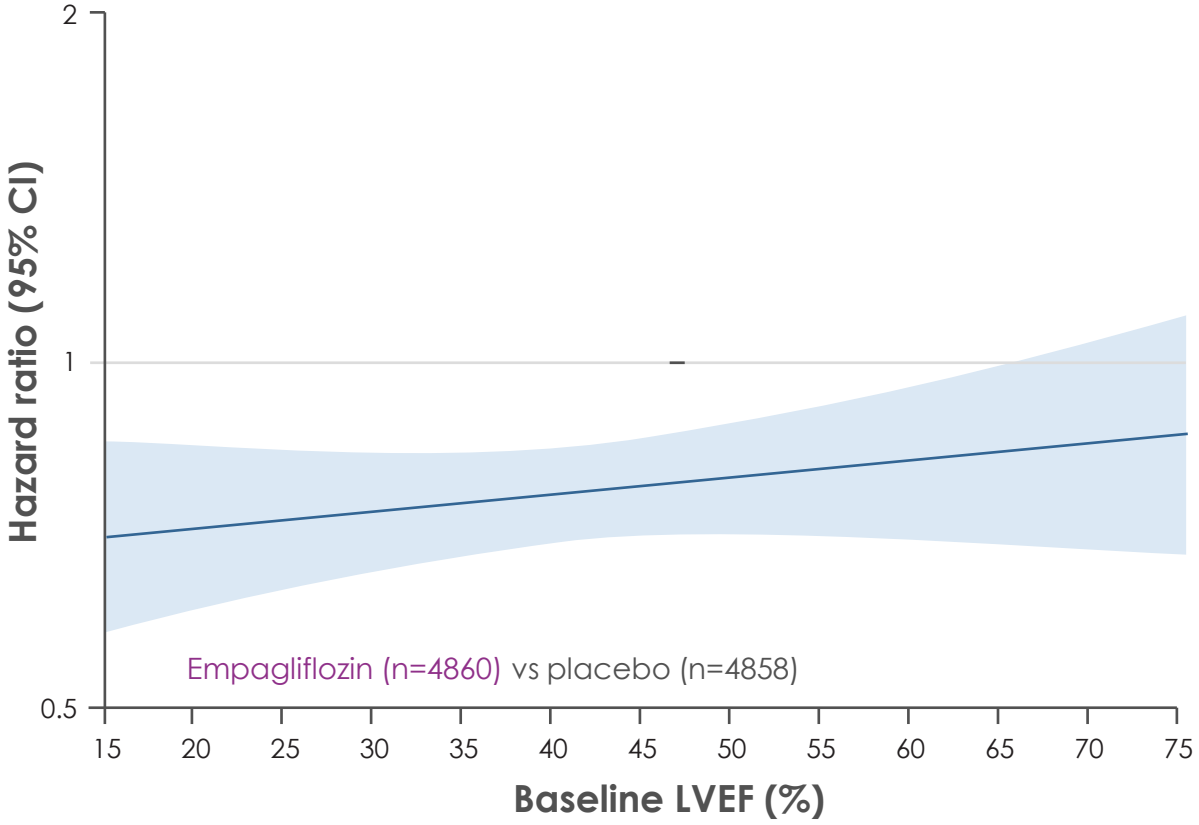
Interaction: *p*=0.27[2]

CI, confidence interval; CV, cardiovascular; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HHF, hospitalization for heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction.

1. Boehringer Ingelheim data on file; 2. Anker S *et al.* Presented at AHA 2021 Scientific Sessions, 13–15 November 2021.

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

Primary composite endpoint: Time to first event of adjudicated CV death or HHF



Interaction: *p*=0.30

SmPC

4.1 Therapeutic indications

Type 2 diabetes mellitus

Jardiance is indicated in adults and children aged 10 years and above for the treatment of insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise
- as monotherapy when metformin is considered inappropriate due to intolerance
- in addition to other medicinal products for the treatment of diabetes

For study results with respect to combination of therapies, effects on glycaemic control, cardiovascular and renal events, and the populations studied, see sections 4.4, 4.5 and 5.1.

Heart failure

Jardiance is indicated in adults for the treatment of symptomatic chronic heart failure.

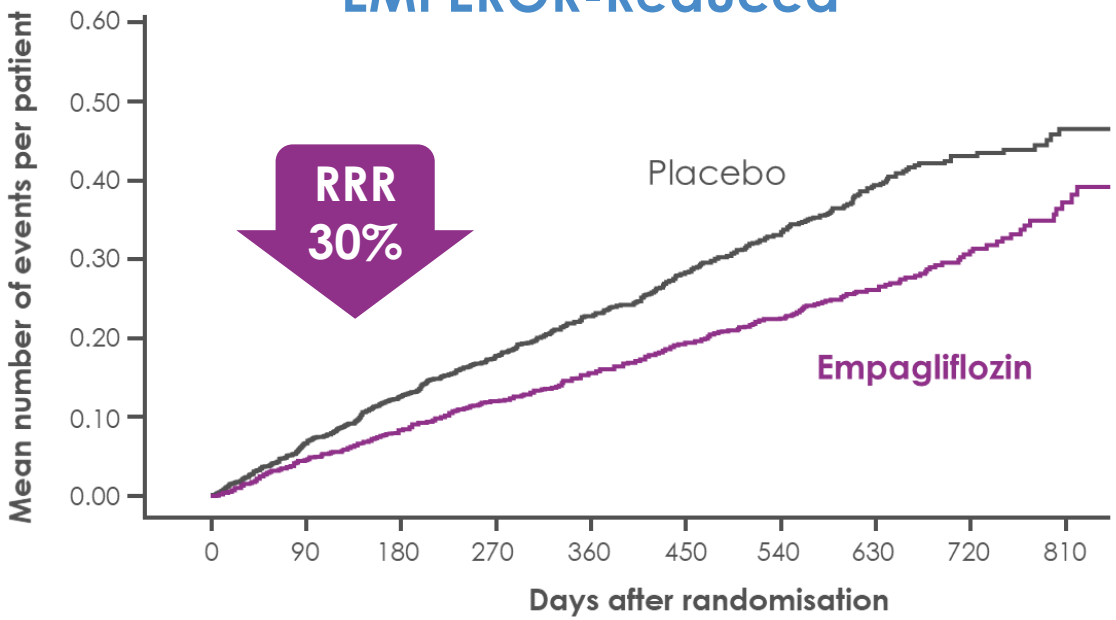
Chronic kidney disease

Jardiance is indicated in adults for the treatment of chronic kidney disease.

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. Butler J *et al. Eur Heart J.* 2022;43:416.

Empagliflozin reduced first and recurrent HHF in both EMPEROR-Reduced[1] and EMPEROR-Preserved[2]

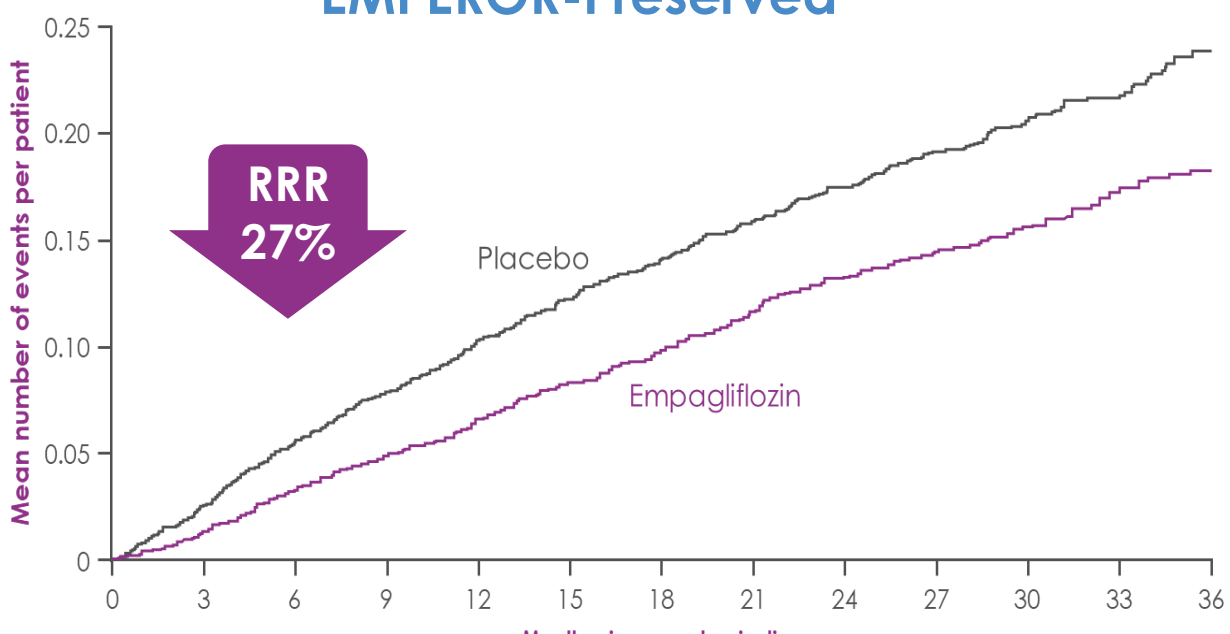
EMPEROR-Reduced[1]



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

HR 0.70
(95% CI 0.58, 0.85)
p<0.001

EMPEROR-Preserved[2]



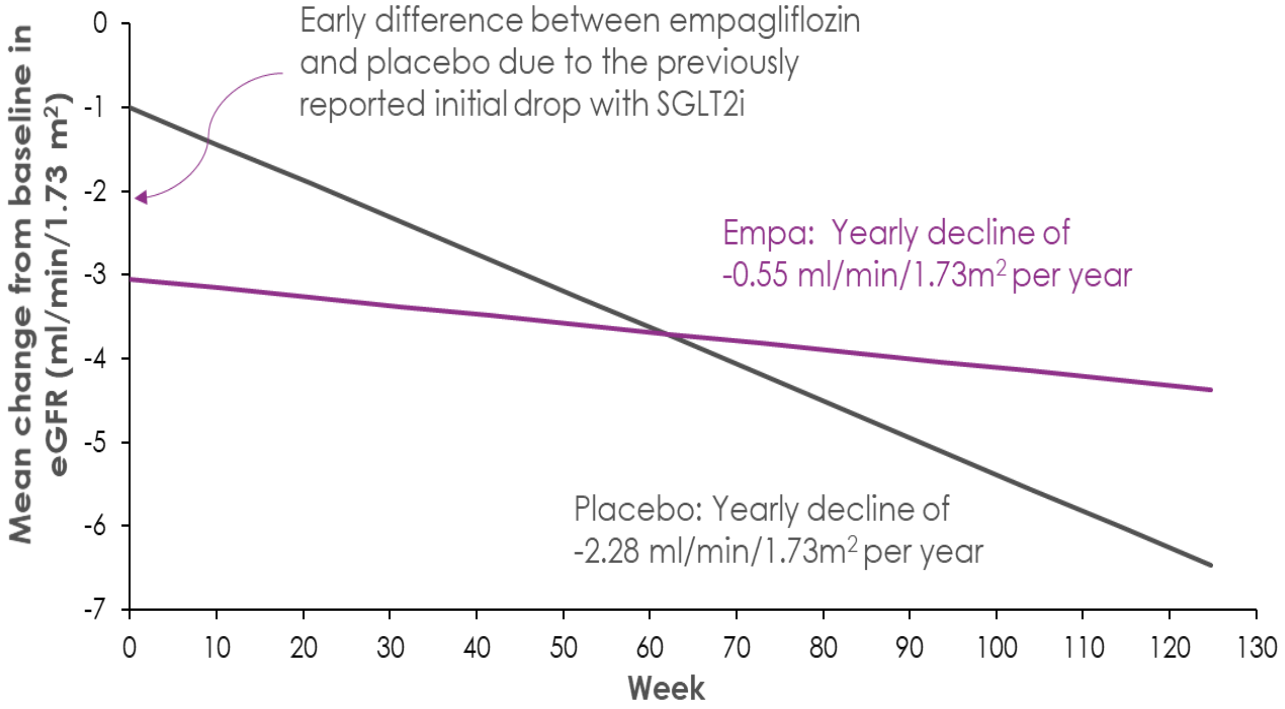
Patients at risk													
Placebo	2991	2945	2901	2855	2816	2618	2258	1998	1695	1414	1061	747	448
Empagliflozin	2997	2962	2913	2869	2817	2604	2247	1977	1684	1429	1081	765	446

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

1. Packer M *et al. N Engl J Med.* 2020;383:1413; 2. Anker S *et al. N Engl J Med*. 2021;385:1451

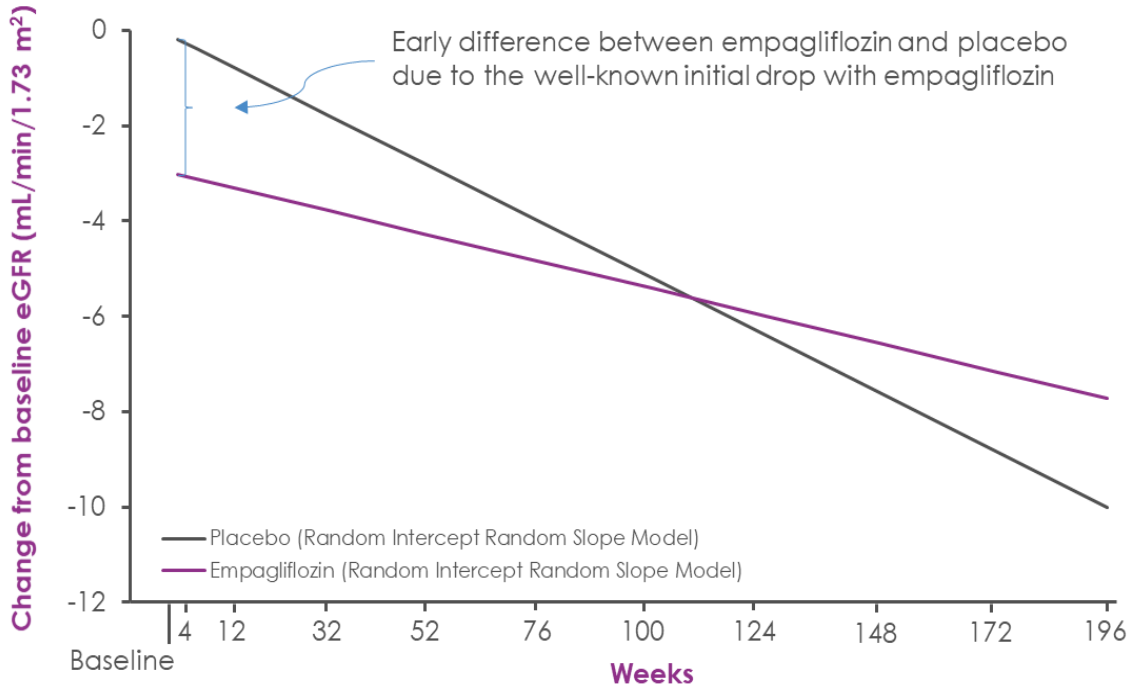
Empagliflozin significantly reduced the decline in eGFR slope compared with placebo (secondary endpoint), slowing the decline in kidney function

EMPEROR-Reduced[1]



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

EMPEROR-Preserved[2]



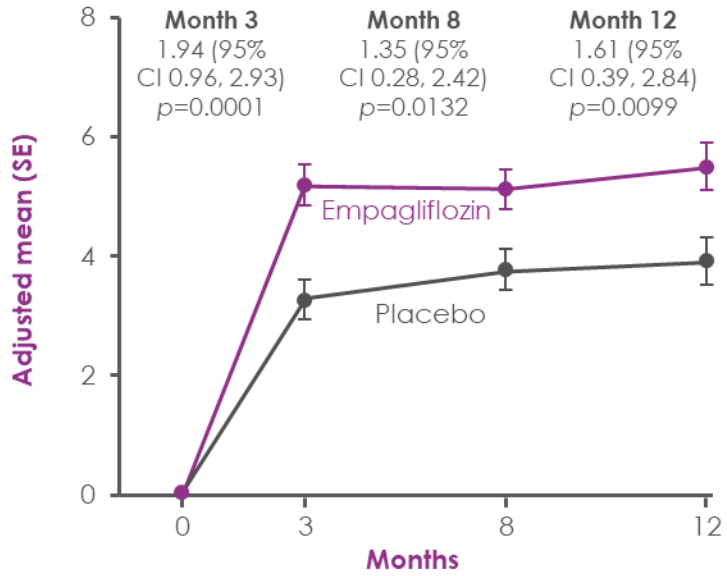
+1.36
eGFR slope difference
ml/min/1.73 m2 per year
p<0.001

1. Packer M *et al. N Engl J Med.* 2020;383:1413; 2. Anker S *et al. N Engl J Med*. 2021;385:1451

EMPEROR: Early and sustained improvements in KCCQ with empagliflozin

Emperor-Reduced

KCCQ-CSS

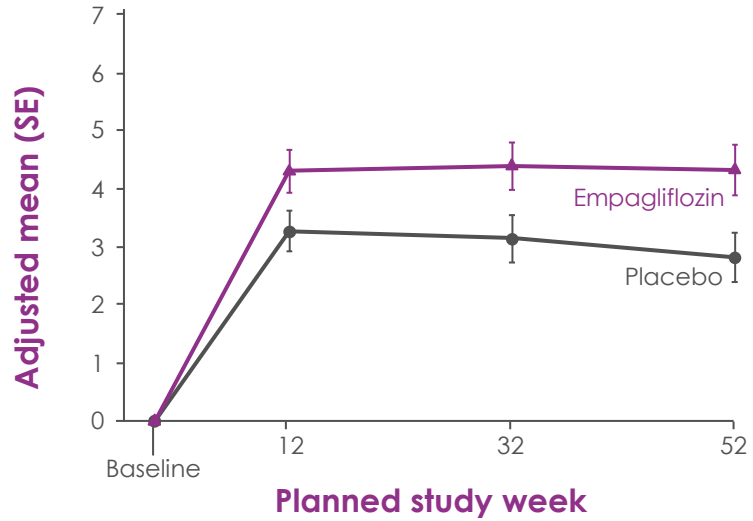


Placebo	1753	1732	1568	1218
Empagliflozin	1776	1755	1618	1239

Emperor Preserved

KCCQ-CSS

Difference (CI) empa vs pla*	1.03 (0.32, 1.74) p=0.0044	1.24 (0.44, 2.04) p=0.0025	1.50 (0.64, 2.36) p=0.0007



No. with data at visit

Placebo	2867	2817	2576	2457
Empagliflozin	2884	2846	2616	2473

*Least-squares mean difference was estimated following adjustment for baseline KCCQ score, eGFR, age, region, sex, diabetes status and LVEF.
CI, confidence interval; CSS, Clinical Summary Score; eGFR, estimated glomerular filtration rate; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; OSS, Overall Summary Score; TSS, Total Symptom Score.
Butler J *et al. Circulation.* 2022;145:184.

EMPEROR-Preserved and EMPEROR-Reduced both met their key prespecified endpoints

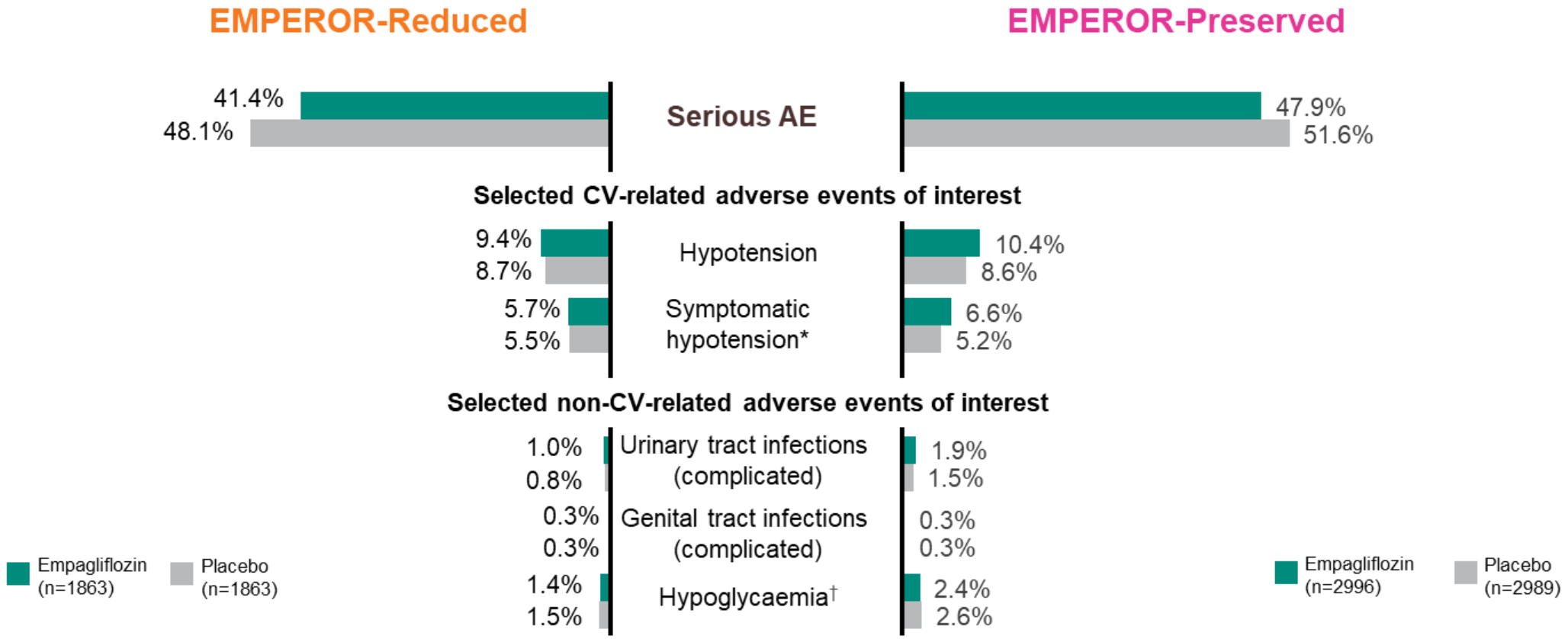
	EMPEROR-Reduced[1]	EMPEROR-Preserved[2]
Primary endpoint: Adjudicated CV death or HHF	✓	✓
Key secondary endpoint: Adjudicated first and recurrent HHF	✓	✓
Key secondary endpoint: eGFR slope	✓	✓

CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure.

1. Packer M *et al. N Engl J Med.* 2020;383:1413; 2. Anker S *et al. N Engl J Med*. 2021;385:1451.

Enhanced safety

AE rates similar between the empagliflozin and placebo treatment arms



*Investigator-defined events. †Hypoglycaemic AEs with a plasma glucose value of ≤70 mg/dL (3.9 mmol/L) or that required assistance. Packer M *et al. N Engl J Med.* 2020;383:1413; Anker S *et al. N Engl J Med.* 2021;385:1451.

Guidelines implementation – management strategies

Three fundamental changes in approach to heart failure treatment are highlighted in recent Society recommendations[1–3]

1

Order and sequence of therapies

There is no fixed order and no preference for the sequence used

2

Initiation *vs* dose titration

Prioritize initiation over up-titration of dose

3

Speed matters

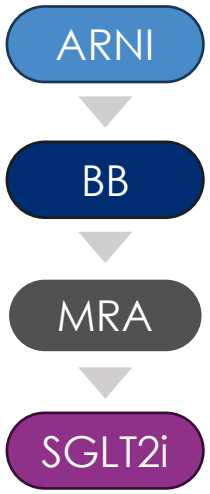
We have been too slow in introducing life-saving therapies in the past

1. Heidenreich PA *et al. J Am Coll Cardiol.* 2022;79:e263; 2. Metra M *et al. Eur J Heart Fail.* 2023;25:1115; 3. McDonagh T, Metra M. 2023 Focused update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Presented at ESC 2023.

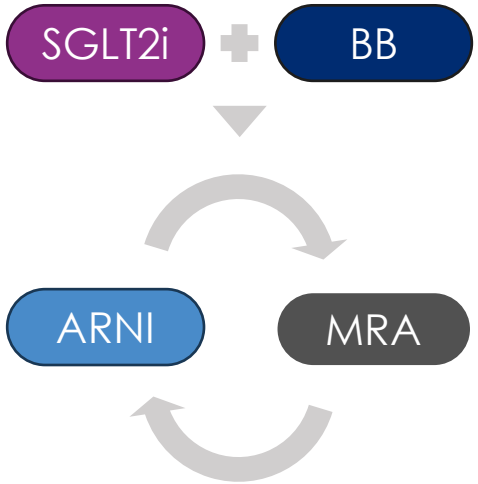
Order and Sequencing

Guidelines tell us *what* to do, but not *how* to do it

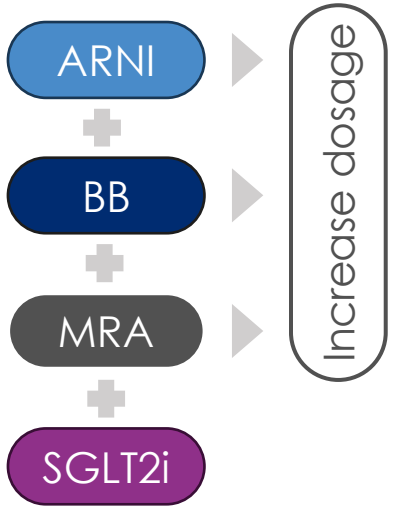
Traditional sequencing



Packer, McMurray



Greene *et al.*

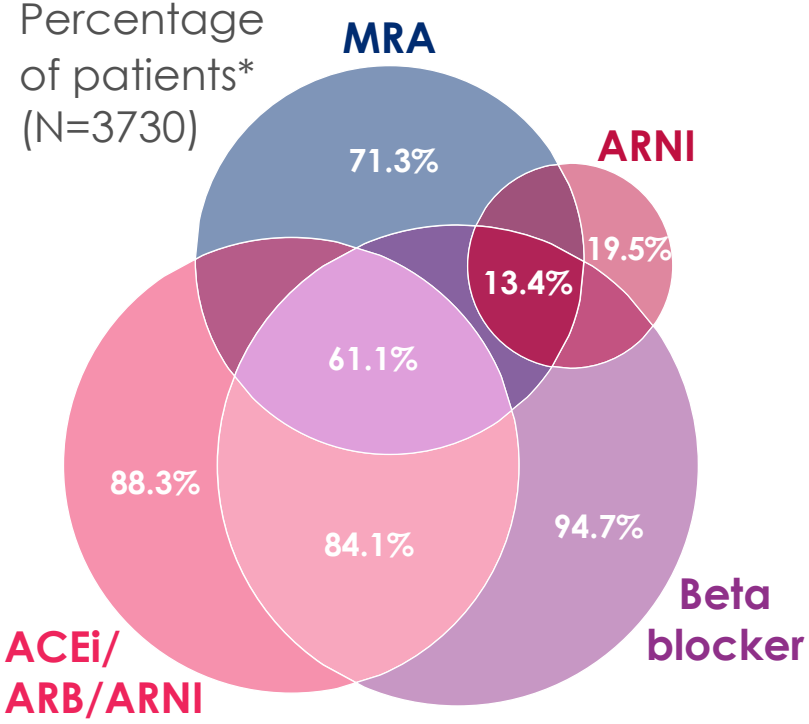


ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BB, beta blocker; BP, blood pressure; bpm, beats per minute; CKD, chronic kidney disease; GDMT, guideline-directed medical therapy; HK, hyperkalaemia; HR, heart rate; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose co-transporter-2 inhibitor. Adapted from Malgie J *et al. Heart Fail Rev.* 2023;28:1221. References cited: Rosano GMC *et al. Eur J Heart Fail*. 2021;23:872; Packer M, McMurray JJV. *Eur J Heart Fail.* 2021;23:882; Greene SJ *et al. JAMA Cardiol* 2021;6:743.

Empagliflozin can be combined effectively with other foundational HFrEF therapies

Background HF therapy at baseline (any dose)

Percentage of patients* (N=3730)



	N	HR (95% CI)	HR (95% CI)
Time to CV death or first HHF			
Overall	3730		**0.75** (0.65, 0.86)
Background HF treatment, any dose			
ACEi/ARB/ARNI + beta blocker	3138		**0.73** (0.62, 0.85)
ACEi/ARB/ARNI + beta blocker + MRA	2280		**0.73** (0.61, 0.88)
ARNI + beta blocker + MRA	501		**0.55** (0.35, 0.86)

*Percentages were calculated based on the number of patients receiving a specified HF therapy or combination of HF therapies at baseline.

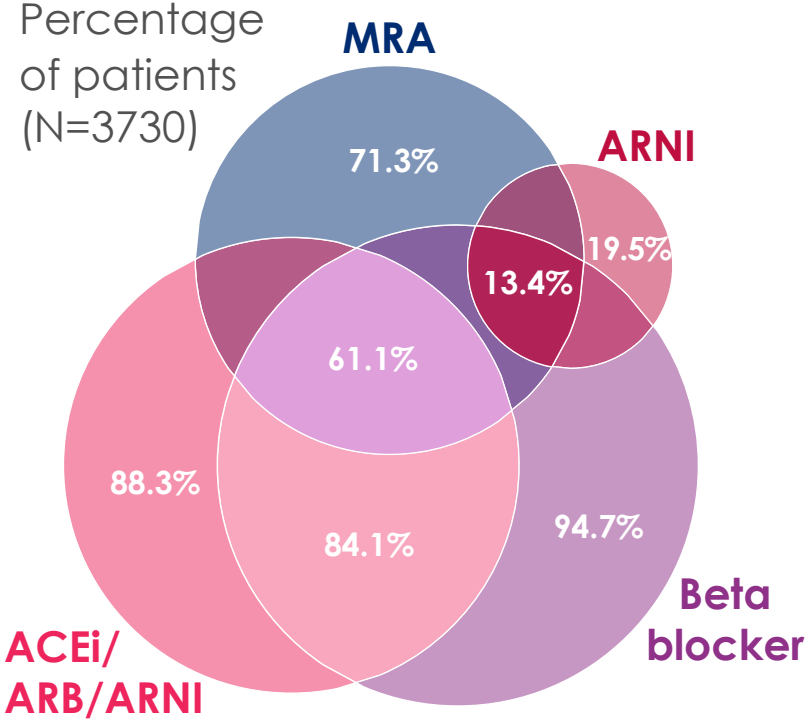
Verma S *et al. Lancet Diabetes Endocrinol.* 2022;10:35.

EMPEROR Reduced

Empagliflozin can be combined with other foundational HFrEF therapies with no impact on safety profile

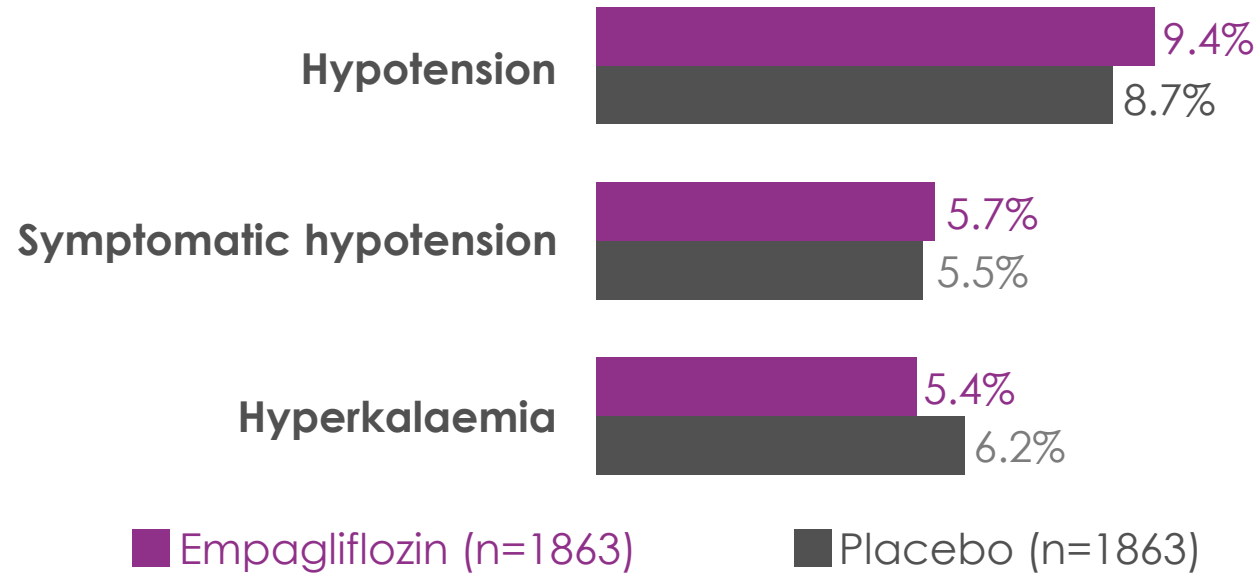
Background HF therapy at baseline (any dose)

Percentage of patients (N=3730)



Rates of **hypotension**, **symptomatic hypotension** and **hyperkalaemia** were largely similar in all background HF therapy subgroups

AE incidence (%) in the overall patient population



*Percentages were calculated based on the number of patients receiving a specified HF therapy or combination of HF therapies at baseline.

Verma S *et al. Lancet Diabetes Endocrinol.* 2022;10:35.

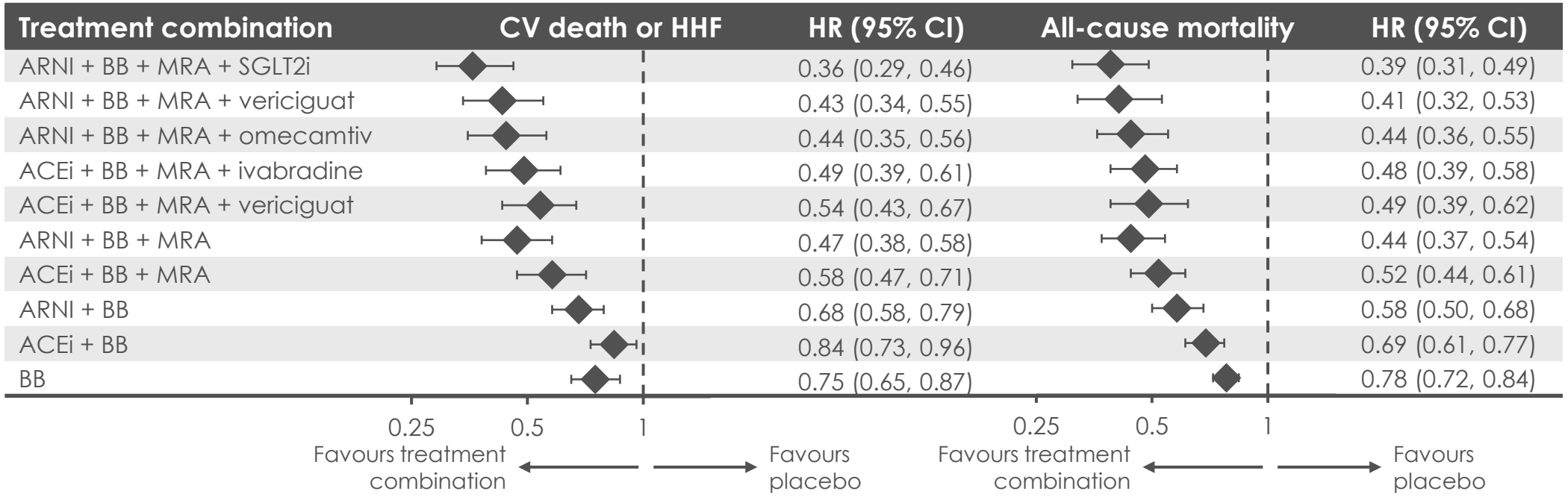
EMPEROR Reduced

Initiation or dose titration?

Patients with HFrEF may benefit from a comprehensive pharmacological approach

CV outcomes according to treatment combination in a large network meta-analysis (N=95 444)[1]

Treatment combination	CV death or HHF	HR (95% CI)	All-cause mortality	HR (95% CI)
ARNI + BB + MRA + SGLT2i		0.36 (0.29, 0.46)		0.39 (0.31, 0.49)
ARNI + BB + MRA + vericiguat		0.43 (0.34, 0.55)		0.41 (0.32, 0.53)
ARNI + BB + MRA + omecamtiv		0.44 (0.35, 0.56)		0.44 (0.36, 0.55)
ACEi + BB + MRA + ivabradine		0.49 (0.39, 0.61)		0.48 (0.39, 0.58)
ACEi + BB + MRA + vericiguat		0.54 (0.43, 0.67)		0.49 (0.39, 0.62)
ARNI + BB + MRA		0.47 (0.38, 0.58)		0.44 (0.37, 0.54)
ACEi + BB + MRA		0.58 (0.47, 0.71)		0.52 (0.44, 0.61)
ARNI + BB		0.68 (0.58, 0.79)		0.58 (0.50, 0.68)
ACEi + BB		0.84 (0.73, 0.96)		0.69 (0.61, 0.77)
BB		0.75 (0.65, 0.87)		0.78 (0.72, 0.84)



A **multidrug approach reduces the risk** of CV death and HHF for patients with HFrEF, supporting the use of a **comprehensive treatment over sequencing** of single agents with progressive titration to target doses[1,2]

Figure adapted from Tromp *et al.* 2022.[1] Each HF study was independently conducted, and no head-to-head HF studies have been completed that allow for direct comparison of the efficacy and/or safety of one drug vs another. ACEi, angiotensin-converting enzyme inhibitor; ARNI, angiotensin receptor–neprilysin inhibitor; BB, beta blocker; CI, confidence interval; CV, cardiovascular; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose co-transporter-2 inhibitor.

1. Tromp J *et al. J Am Coll Cardiol.* 2022;10:73; 2. Lam C *et al. Circulation.* 2020;142:1129.

Empagliflozin is given once daily at a single dose, with no titration required, down to an eGFR of 20 mL/min/1.73 m²

	Once daily	Single dose	No titration
SGLT2 inhibitors*[1,2]	✓	✓	✓
ACE inhibitors[3,4]	✗†	✗	✗
ARBs[5,6]	✗†	✗	✗
ARNIs[7]	✗	✗	✗
Mineralocorticoid receptor antagonists[8,9]	✓	✗	✗
Beta blockers[10,11]	✓	✗	✗
Loop diuretics[12,13]	✗†	✗	✗

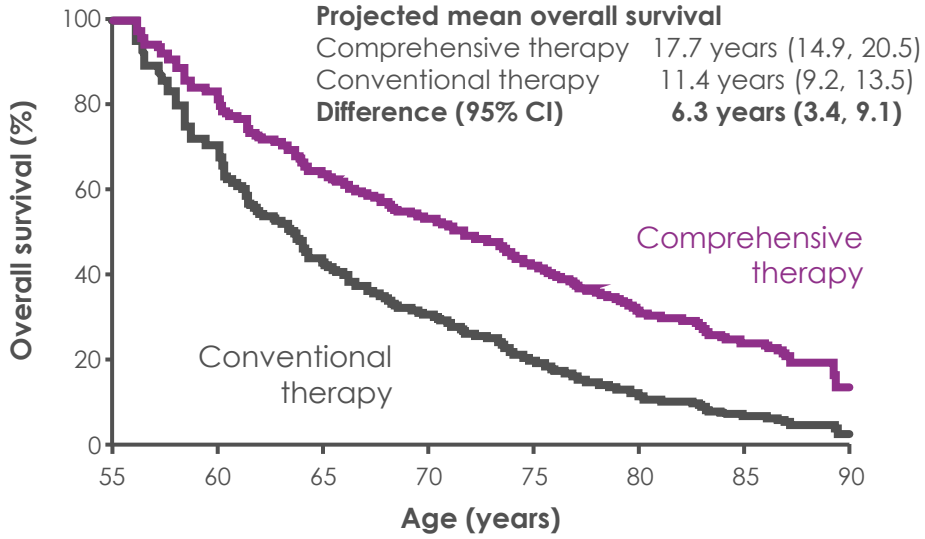
*For patients treated with empagliflozin who need tighter glycaemic control, the dose may be increased.[2] †Varies between drugs. Some ACE inhibitors, ARBs and loop diuretics are administered once per day in patients with HFrEF (LVEF ≤40%). 1. FORXIGA® Summary of Product Characteristics. AstraZeneca AB.; 2. Jardiance® Summary of Product Characteristics. Boehringer Ingelheim International GmbH; 3. VASOTEC™ Prescribing Information. Valeant Pharmaceuticals International, Inc.; 4. ALTACE® Prescribing Information. Pfizer Inc.; 5.DIOVAN® Prescribing Information. Novartis Pharmaceuticals Corporation.; 6. ATACAND® Prescribing Information. ANI Pharmaceuticals, Inc.; 7. ENTRESTO® Prescribing Information. Novartis Pharmaceuticals Corporation.; 8. ALDACTONE® Prescribing Information. Pfizer Inc.; 9. INSPRA® Prescribing Information. Pfizer Inc.; 10. Bisoprolol Summary of Product Characteristics. Accord Healthcare Limited.; 11. COREG CR Prescribing Information. GlaxoSmithKline.; 12. TOREM® Summary of Product Characteristics. Mylan.; 13. Furosemide Summary of Product Characteristics. Accord Healthcare Limited.

Speed matters

Speed matters

Cross-trial analysis estimating the treatment effects of **comprehensive (ARNI, beta blocker, MRA and SGLT2 inhibitor)** versus **conventional (ACEi or ARB and beta blocker) therapy** in patients with HFrEF*

Implementing comprehensive therapy vs conventional therapy increased mean overall survival by 6.3 years



CV outcomes were improved by implementing comprehensive therapy vs conventional therapy

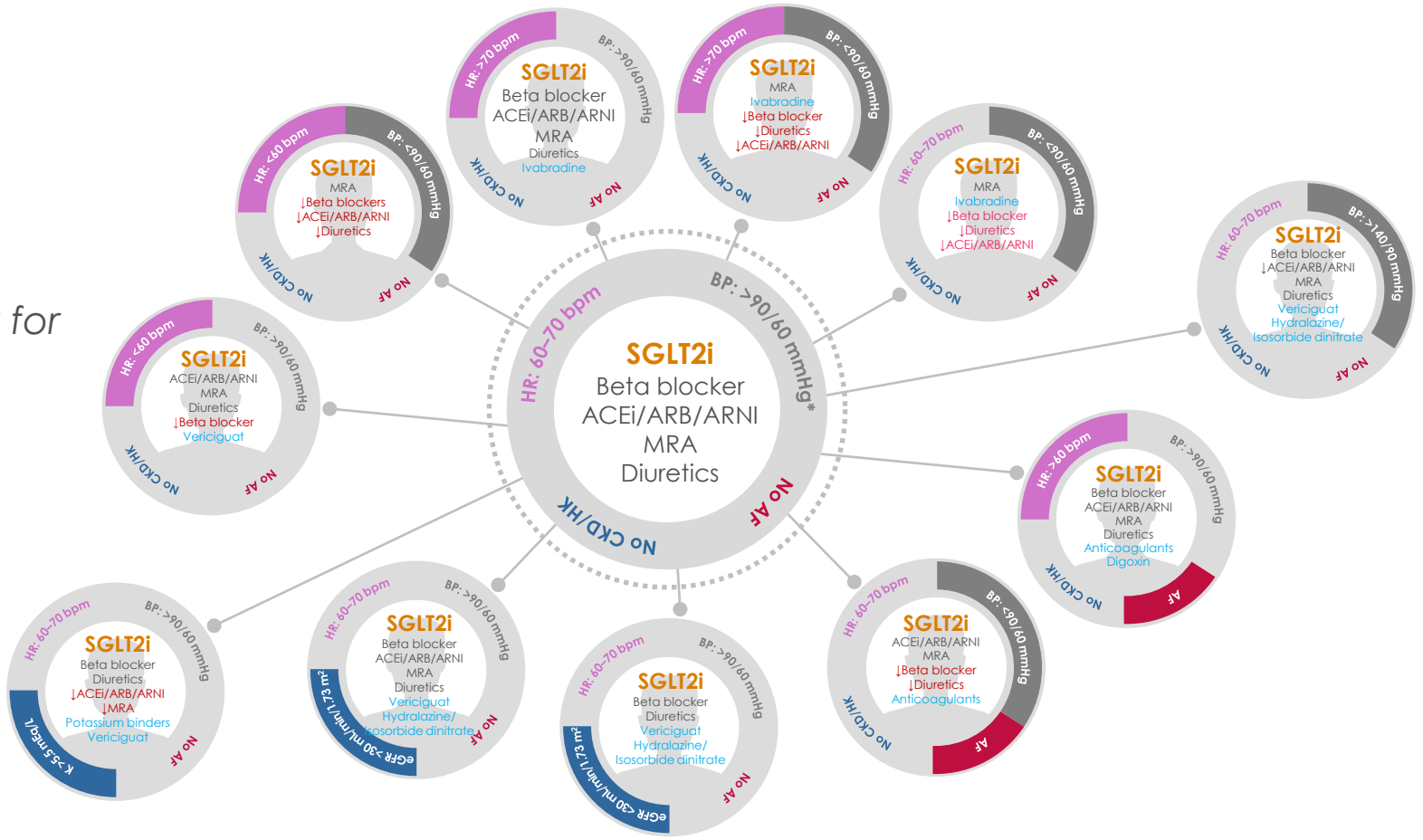
- *Trials: EMPHASIS-HF (n=2737); PARADIGM-HF (n=8399); DAPA-HF (n=4744). DAPA-HF is the only trial that enrolled patients on background ARNI (n=508).
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CI, confidence interval; CV, cardiovascular; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist; SGLT2, sodium-glucose co-transporter-2.

- Vaduganathan M *et al. Lancet.* 2020;396:121.

Combination drug treatment

SGLT2 inhibitors are the only foundational therapy that can be used without modification for the 11 HFrEF patient phenotypes below

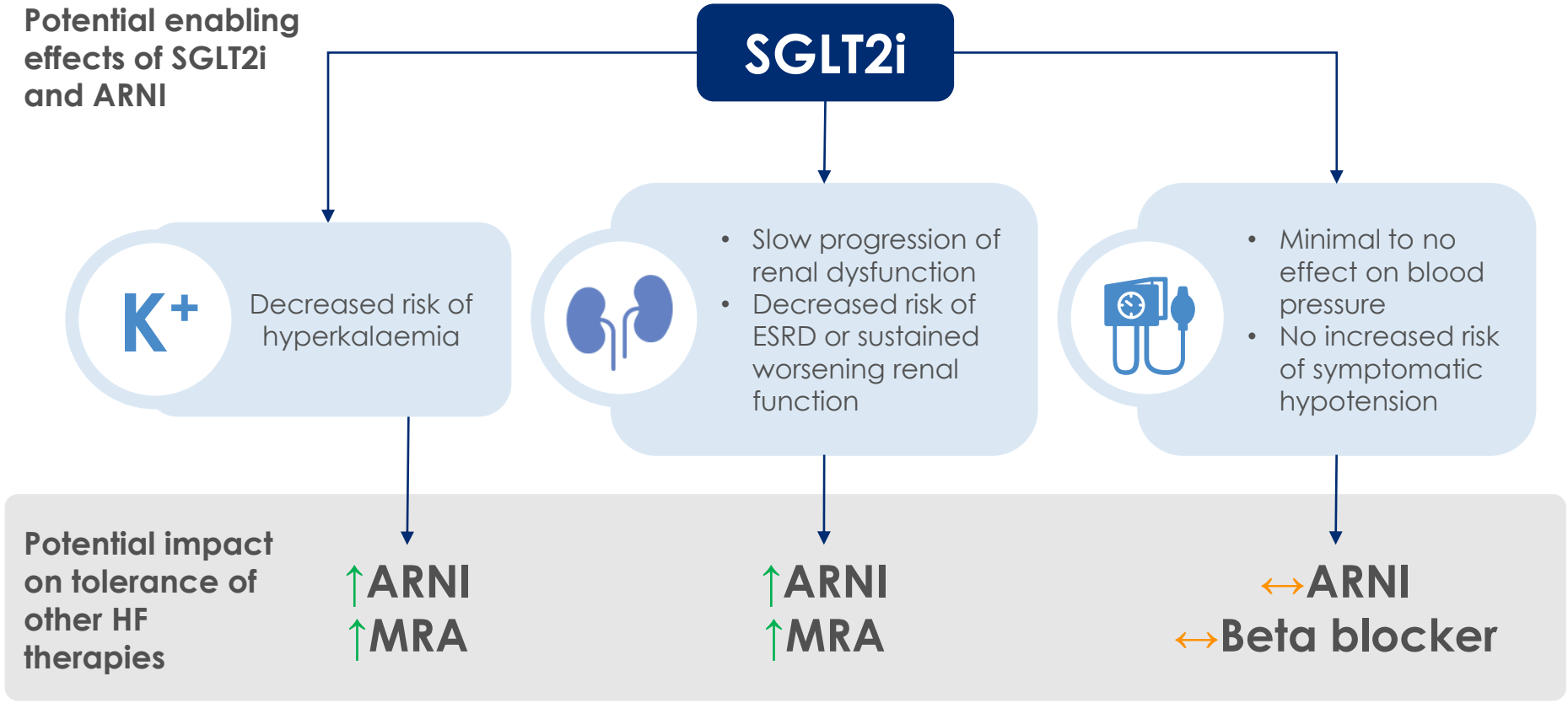
Tailoring of medical therapy for HFrEF according to clinical profiles (2021 consensus)



Grey = maintain (SGLT2i shown in orange); blue = add; red = reduce or discontinue.

*In patients with predominant chronic coronary syndrome, blood pressure threshold is 120/80 mmHg. ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BP, blood pressure; bpm, beats per minute; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; HK, hyperkalaemia; HR, heart rate; MRA, mineralocorticoid receptor antagonist; SGLT2(i), sodium-glucose co-transporter-2 (inhibitor). Rosano GMC *et al. Eur J Heart Fail.* 2021;23:872.

SGLT2 inhibitors may improve tolerance of other heart failure therapies

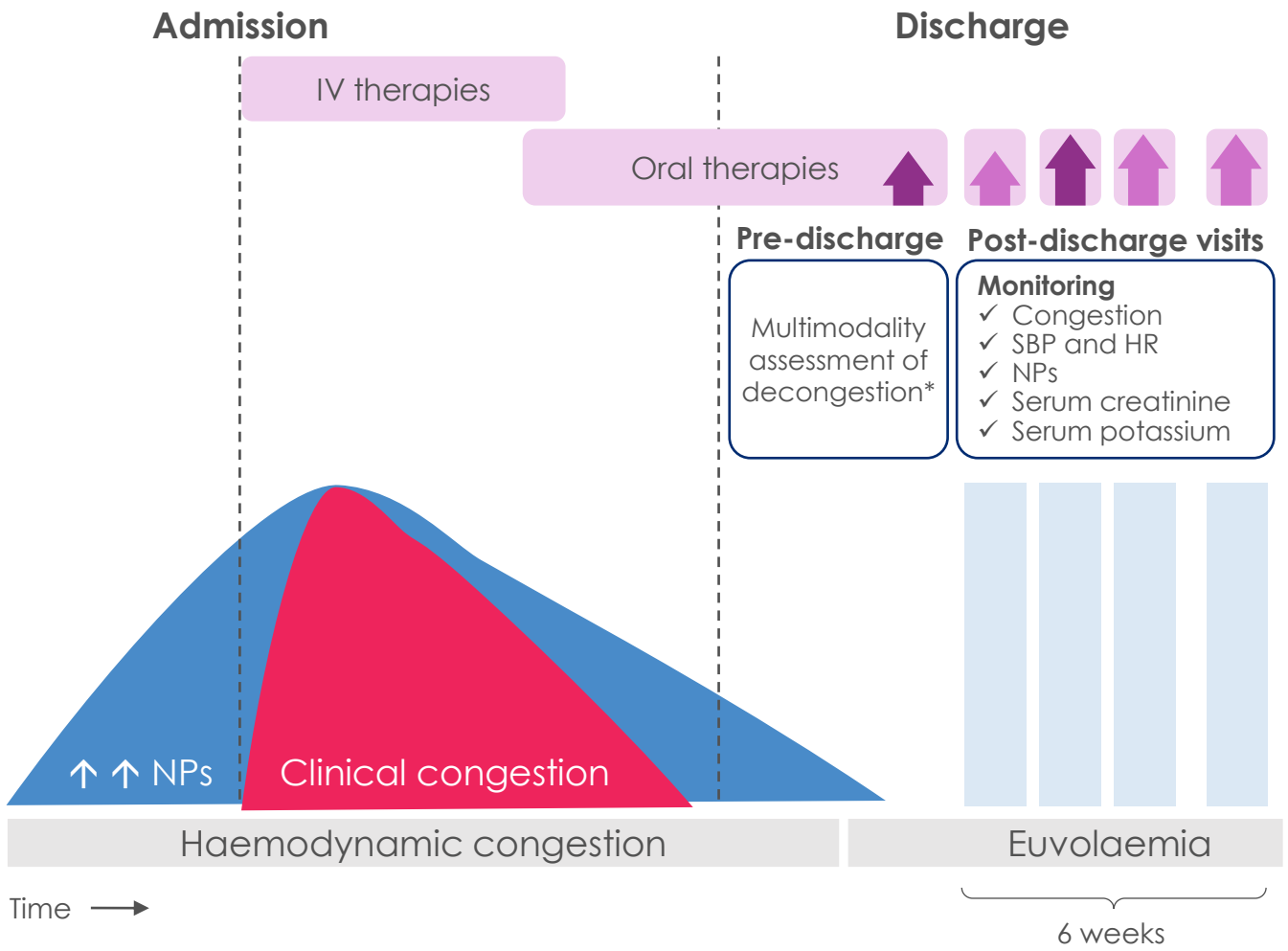


ARNI, angiotensin receptor–neprilysin inhibitor; ESRD, end-stage renal disease; HF, heart failure; MRA, mineralocorticoid receptor antagonist; SGLT2(i), sodium-glucose co-transporter-2 (inhibitor).

Greene SJ *et al. Eur J Heart Fail.* 2021;23:1525.

What to do during hospitalization

Hospitalization is a key opportunity to optimize GDMT in patients with HF



Optimal management of patients hospitalized for HF is critical:

1. May prevent re-HHF through early detection and effective treatment of residual or recurrent congestion
2. GDMT initiation at pre-discharge and titration to target doses in the early post-discharge period may improve short- and long-term outcomes
3. HHF presents an opportunity for implementation of GDMT

*This algorithm is not provided by ESC Guidelines, but it is a proposal from the authors.
ESC, European Society of Cardiology; GDMT, guideline-directed medical therapy; HF, heart failure; HHF, hospitalization for heart failure; HR, heart rate; IV, intravenous; NP, natriuretic peptide; SBP, systolic blood pressure. Metra M *et al. Eur J Heart Fail.* 2023; doi:10.1002/ejhf.2888.

Oral therapy should be initiated during hospitalization and promptly optimized around discharge

Recommendations for pre-discharge and early post-discharge follow-up of patients hospitalized for acute heart failure

ESC

Recommendations	Class	Level
An intensive strategy of initiation and rapid up-titration of evidence-based treatment **before discharge** and during frequent and careful **follow-up visits in the first 6 weeks** following a HF hospitalization is recommended to reduce the risk of HF rehospitalization or death.	I	B

- In STRONG-HF, the use of ACEi/ARB/ARNI, beta-blockers and MRA was evaluated in patients with HFrEF, HFmrEF and HFpEF.

- Although STRONG-HF was based only on triple therapy with neurohormonal modulators, this recommendation also includes empaglifozin or dapaglifozin based on recent evidence

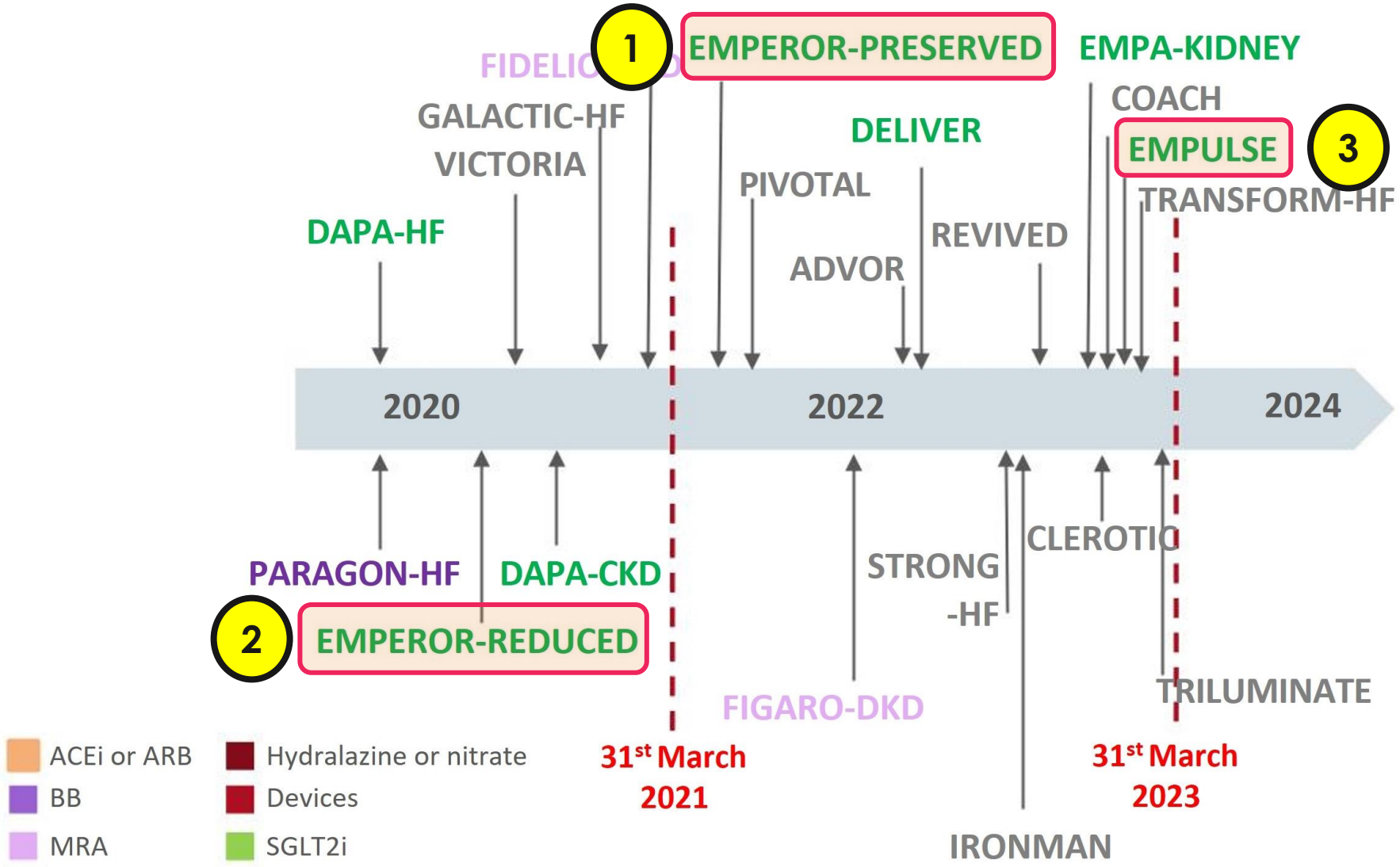
ESC

2023 Focused update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad195)

*Class of recommendation. †Level of evidence. ESC, European Society of Cardiology; HF, heart failure.

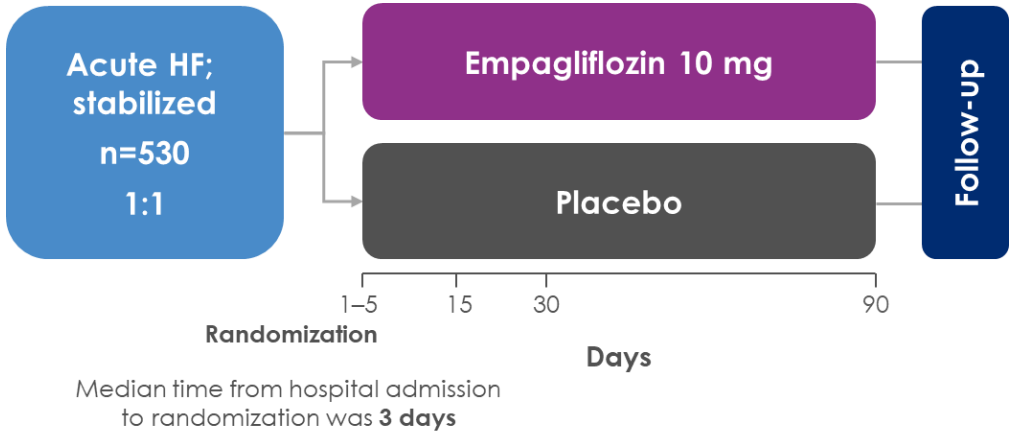
EMPULSE Study

EMPULSE complements the EMPEROR trials in examining the effect of empagliflozin across the whole LVEF spectrum in hospital setting



2023 Focused update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad195)

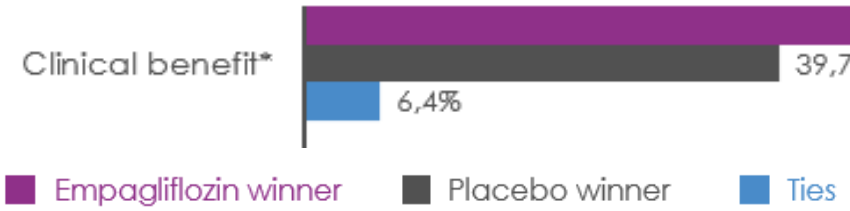
EMPULSE: acute HF patients treated with empagliflozin were 36% more likely to experience a clinical benefit than those who received placebo

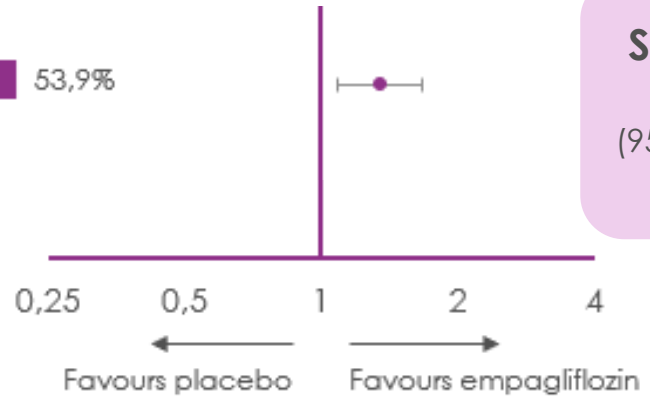


Median time from hospital admission to randomization was **3 days**

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
  - Change from baseline in KCCQ-TSS after 90 days of treatment





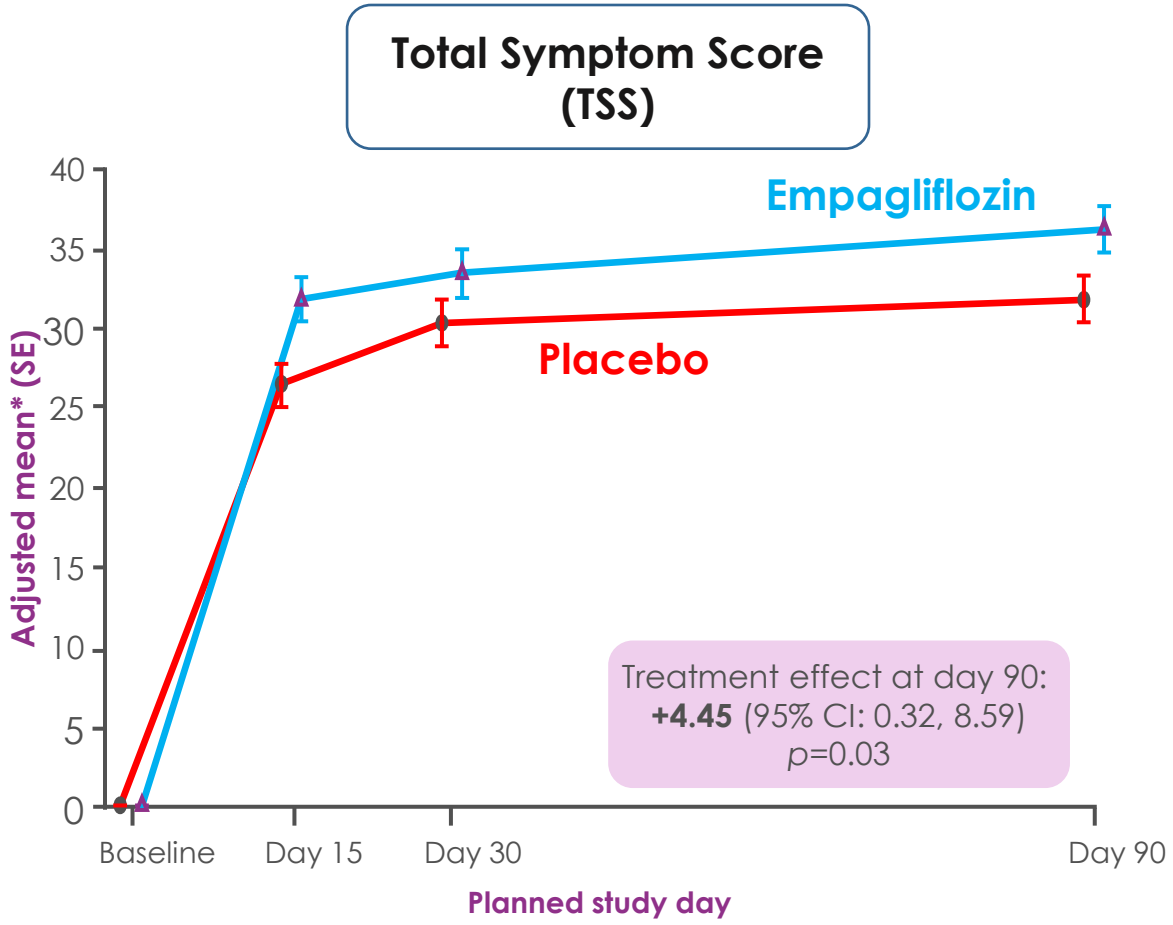
Stratified win ratio: 1.36
(95% CI: 1.09, 1.68)
p=0.0054

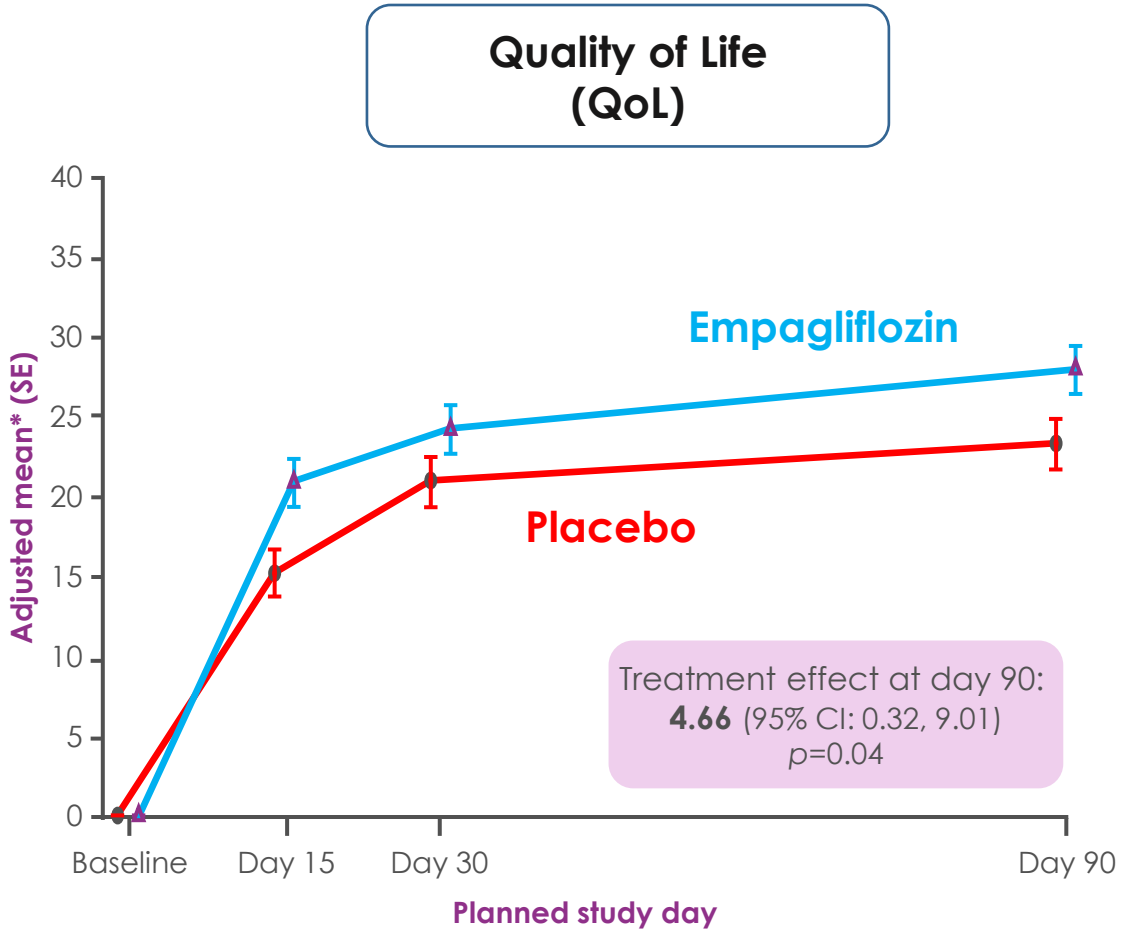
Empagliflozin:
Superior in 53.9% of comparisons

Placebo:
Superior in 39.7% of comparisons

CV, cardiovascular; HF, heart failure; HFE, heart failure event; HHF, hospitalization for heart failure; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; NT-proBNP, N-terminal prohormone of brain natriuretic peptide. 1. Tromp J *et al. Eur J Heart Fail.* 2021;23:826; 2. Voors AA et al. *Nat Med* 2022; doi.org/10.1038/s41591-021-01659-1

Effects of empagliflozin on KCCQ score in patients hospitalized for acute HF





*Adjusted least-square mean; CI, confidence interval; KCCQ, Kansas City Cardiomyopathy Questionnaire; SE, standard error; TSS, Total Symptom Score; QoL, quality of life

Kosiborod M *et al. Circulation.* 2022; doi:10.1161/CIRCULATIONAHA.122.059725.

Stabilization criteria

All of the following criteria must apply for inclusion

1

Systolic BP ≥100 mmHg and no symptoms of hypotension in the preceding **6 hours**

2

No increase in IV diuretic dose for **6 hours** prior to randomization

3

No IV vasodilators including nitrates within the last **6 hours** prior to randomization

4

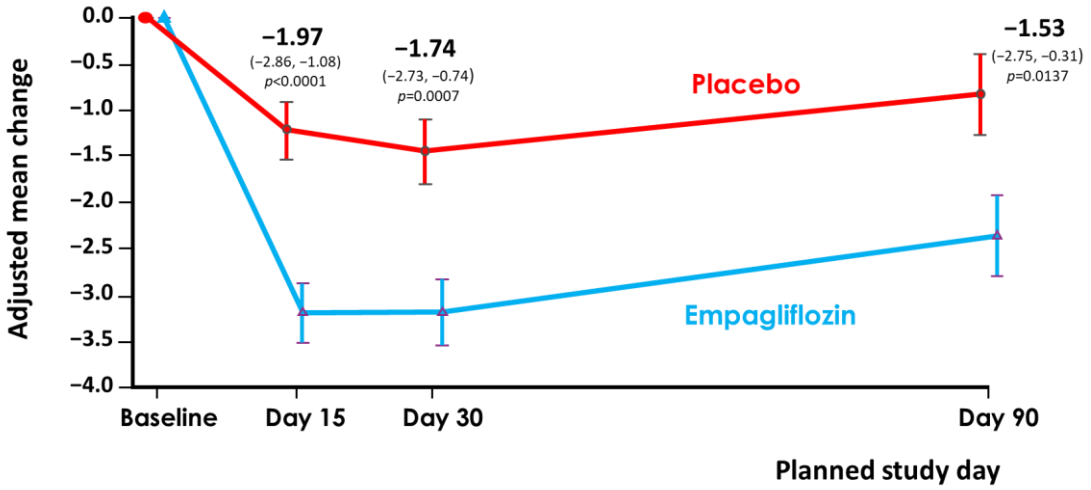
No IV inotropic drugs for **24 hours** prior to randomization

BP, blood pressure.

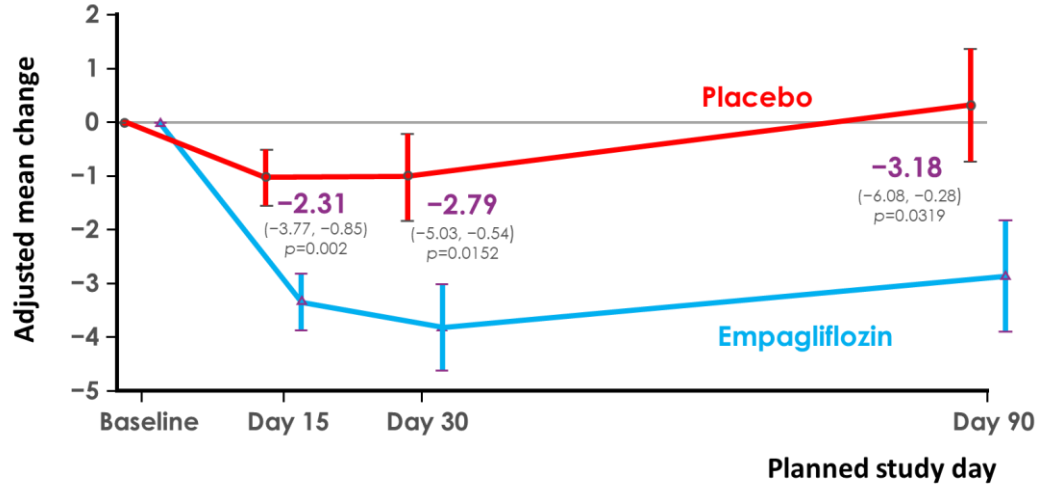
Tromp J *et al. Eur J Heart Fail.* 2021; doi:10.1002/ejhf.2137.

Impact of empagliflozin on decongestion in patients hospitalized for acute HF

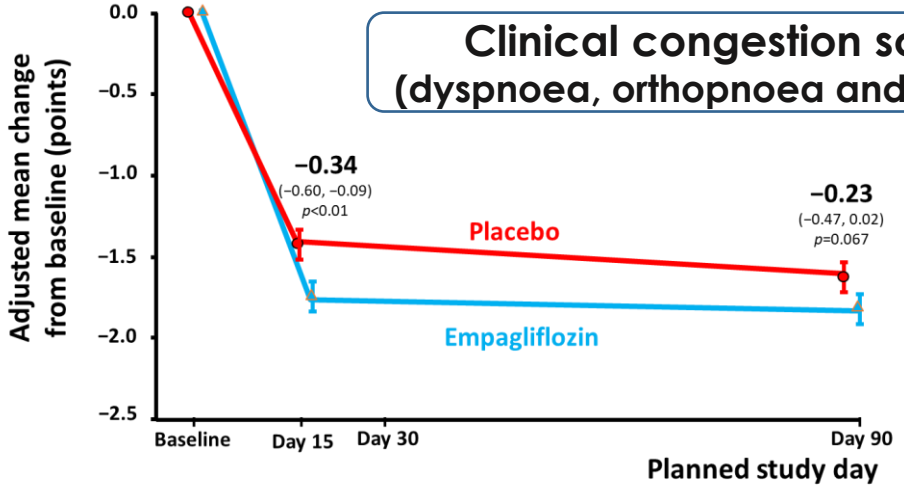
Body weight (kg)



Body weight per mean daily diuretic dose*



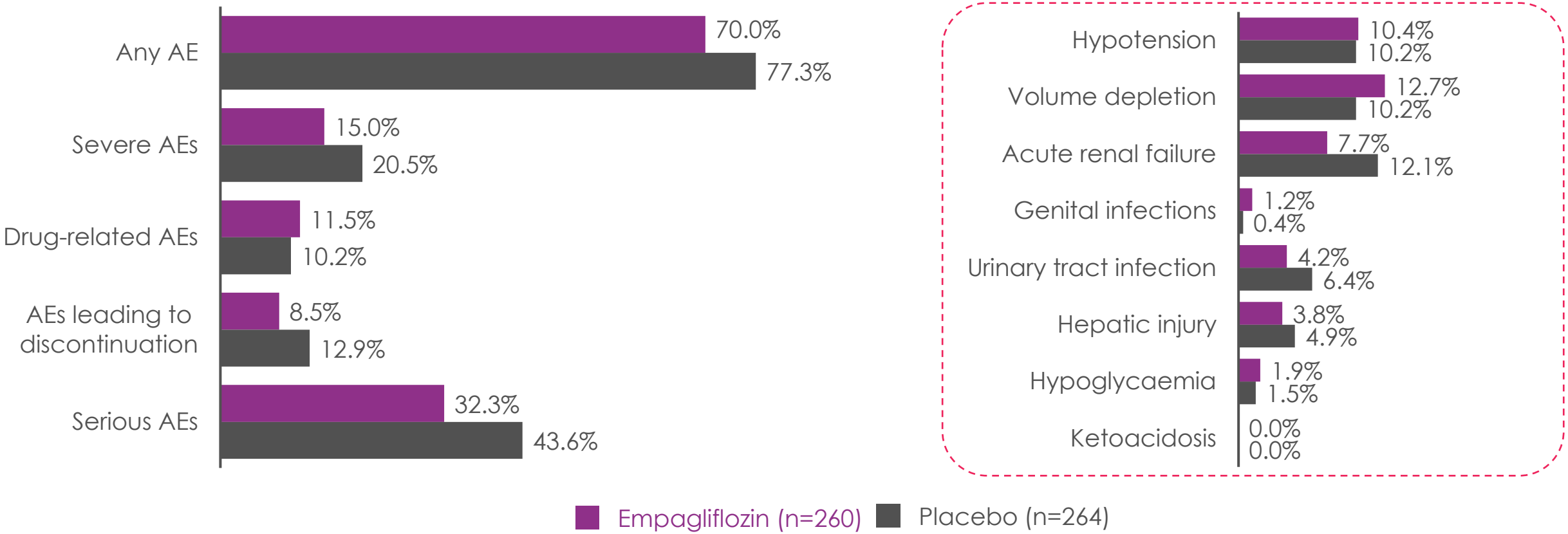
Clinical congestion score (dyspnoea, orthopnoea and fatigue)



clinical congestion score (0-3 point scale)	
absence	0
seldom	1
frequent	2
continuous	3

*The units of weight changes per mean daily loop diuretic dose are presented in kg/40 mg of intravenous furosemide (or 80 mg of oral furosemide) or equivalent. The equivalent to 40 mg of furosemide was defined as 20 mg of torasemide or 1 mg of bumetanide. CI, confidence interval. Biegus J et al. Eur.Heart J 2022, 00: 1-11

Adverse event rates were similar between the empagliflozin and placebo treatment arms in the EMPULSE trial[1,2]



Percentages calculated using total number of patients per treatment as the denominator. A patient may be counted in more than one seriousness criterion.
AE, adverse event.

Voors AA et al. *Nat Med* 2022; doi.org/10.1038/s41591-021-01659-1

Considerations for implementation of SGLT2 inhibitors in the hospital setting

I'm concerned about my patient's age

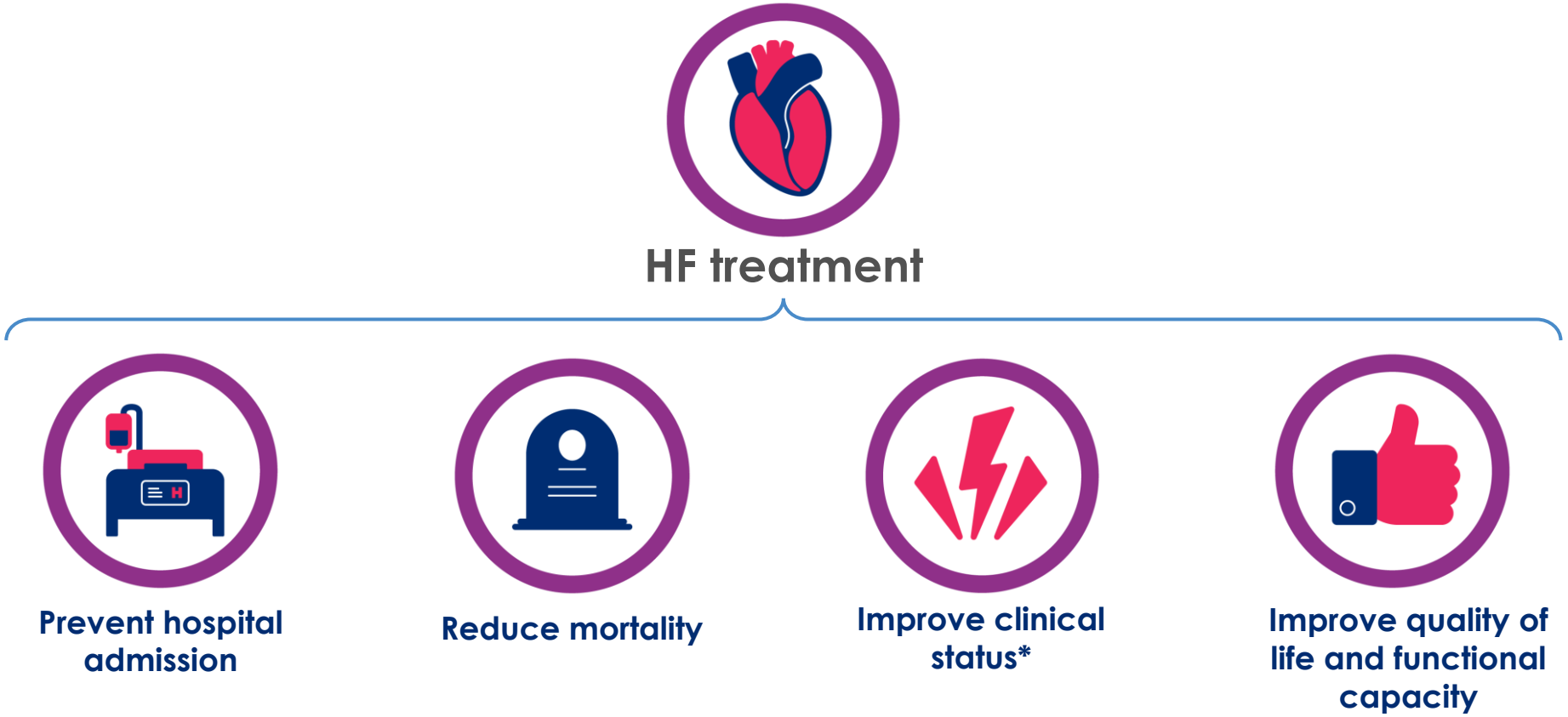
I'm concerned about my patient's blood pressure

I'm concerned about my patient's kidney function

Empagliflozin

SGLT2, sodium-glucose co-transporter-2.

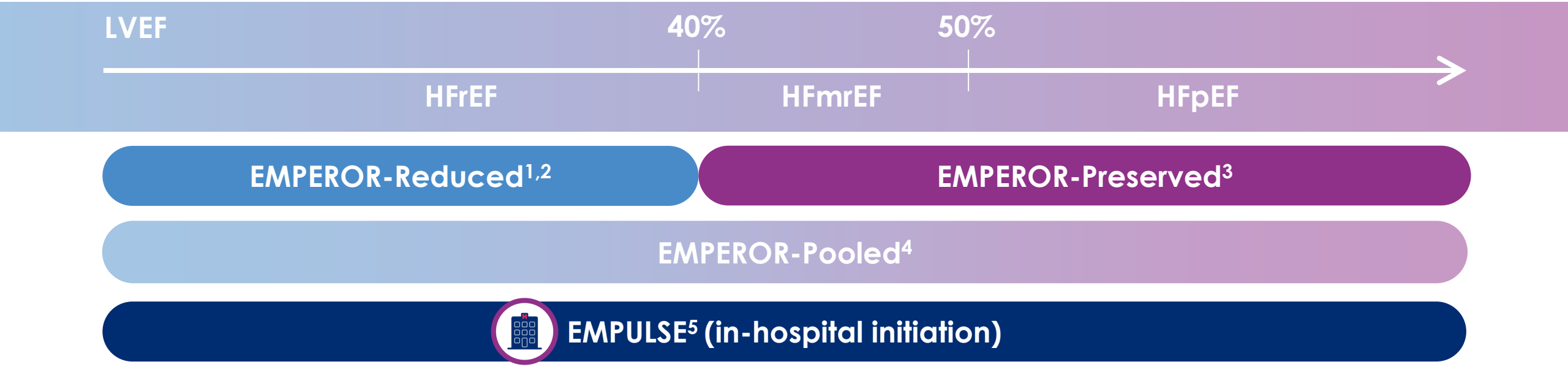
Treatment of patients with HF has multiple goals[1,2]



*Clinical status includes (but is not limited to) heart rate, heart rhythm, respiratory rate, oxygen saturation, blood pressure, weight, fluid balance, HF symptoms and renal function.[1]

HF, heart failure. 1. McDonagh TA *et al. Eur Heart J*. 2021;42:3599; 2. Heidenreich PA *et al. J Am Coll Cardiol.* 2022;79:e263.

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



ESC

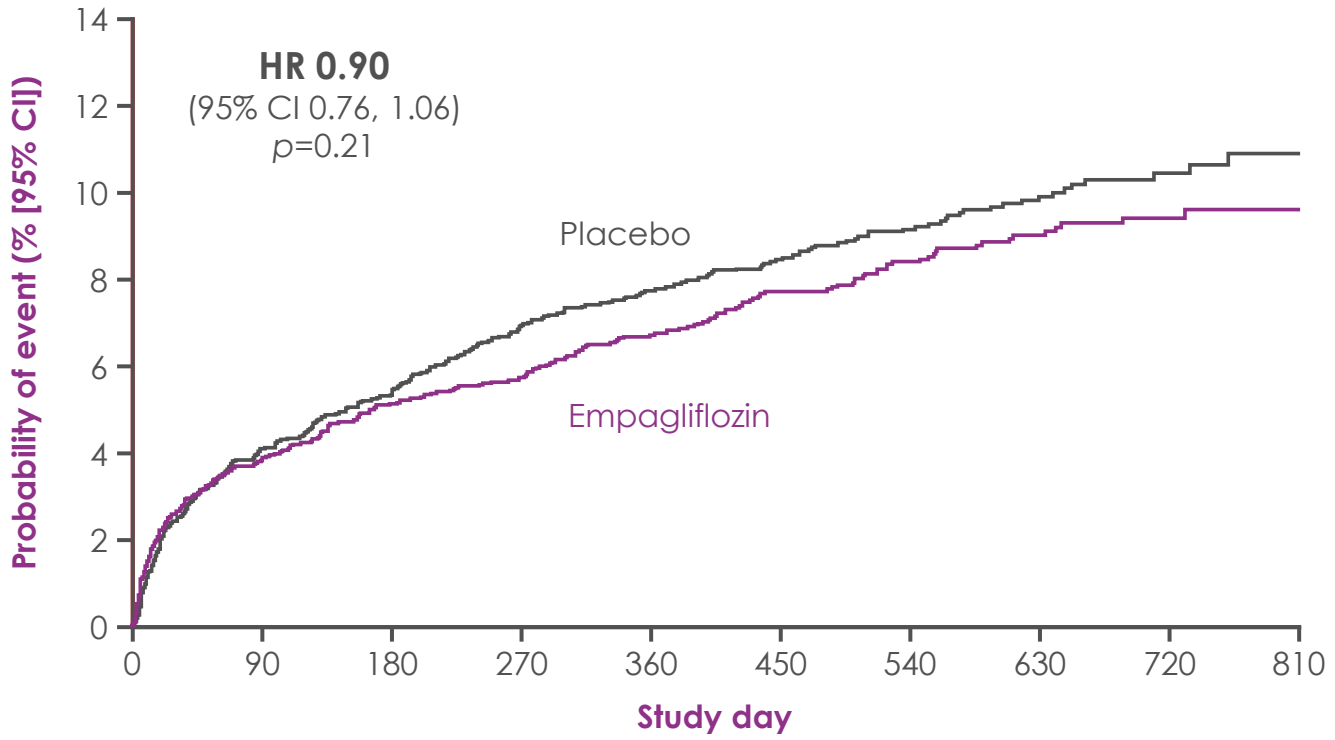
SGLT2is as empagliflozin is recommended as 1st line treatment in patients across the entire spectrum of LVEF to reduce the risk of HF hospitalization or CV death **(Class IA recommendation)[6]**

*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 and change from baseline in KCCQ-TSS after 90 days of treatment. HF, heart failure; HFE, heart failure event; 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; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; LVEF, left ventricular ejection fraction. 1. Packer M *et al. N Engl J Med*. 2020;383:1413; 2. Butler J *et al. Eur J Heart Fail.* 2020;22:1991; 3. Anker SD *et al. N Engl J Med.* 2021;385:1451; 4. Butler J *et al. Eur Heart J.* 2022;43:416; 5. Voors AA *et al. Nat Med.* 2022;28:568. 6. McDonagh TA *et al. Eur Heart J.* 2023; doi.org/10.1093/eurheartj/ehad195

3η ΚΑΡΔΙΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ Α.Π.Θ.

Ευχαριστώ πολύ

EMPACT-MI
Time to first HHF or all-cause mortality (primary endpoint)



Patients at risk

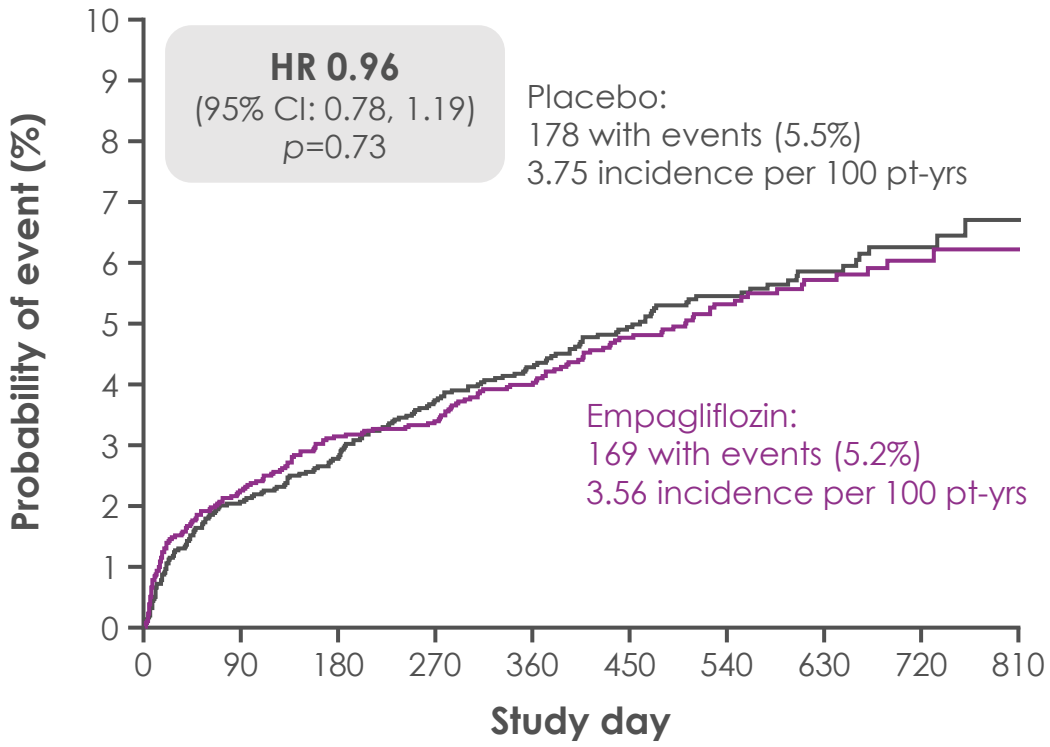
Placebo	3262	3092	3044	2832	2486	2071	1556	1040	551	137
Empagliflozin	3260	3111	3060	2881	2532	2107	1566	1048	531	134

HHF, hospitalisation for heart failure
Butler J *et al. N Engl J Med* 2024; doi: 10.1056/NEJMoa2314051

Components of primary endpoint

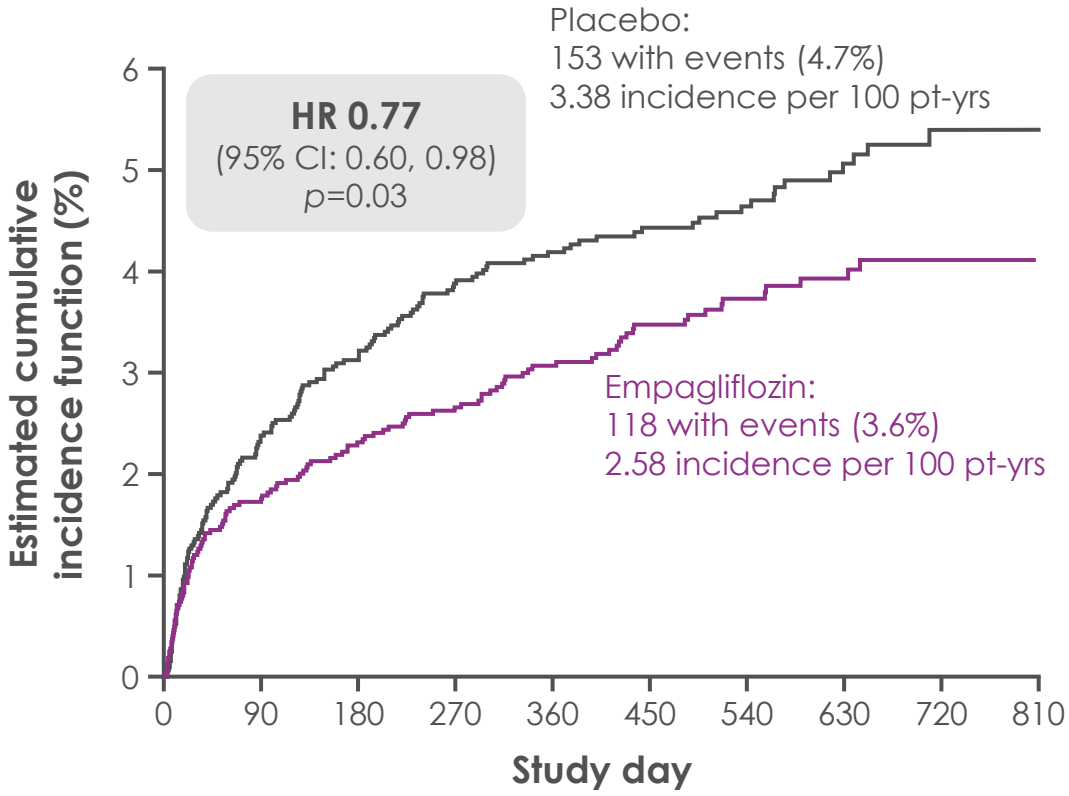
Time to all-cause mortality

347 deaths: 263 (76%) CV death; 84 (24%) non-CV death



No. at risk										
Placebo	3262	3186	3159	2975	2632	2207	1660	1111	593	148
Empagliflozin	3260	3177	3148	2995	2639	2218	1658	1119	572	153

Time to first HHF



	3262	3092	3044	2832	2486	2071	1556	1040	551	137
	3260	3111	3060	2881	2532	2107	1566	1048	531	134

Butler J *et al.* ACC 2024; oral presentation.