Role of SGLT2 Inhibitors in Heart Failure

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Outlines

- SGLTs & SGLT2 inhibitors
- Cardiovascular protection mechanisms of SGLT2 inhibitors
- Evidence for SGLT2 inhibitors in heart failure
- Treatment goals for heart failure & role of SGLT2 inhibitors

Sodium Glucose Co-transpoters (SGLTs)

- **SGLT2 is the glucose transporter, reabsorbs approximately 90% of glucose in the proximal tubule**
- **Little glucose excreted in the urine through sodium glucose co-transporters (SGLTs)**
- **Type 2 diabetes is a dysregulation of glucose homeostasis characterized by persistent hyperglycaemia, impaired β-cell function, and insulin resistance**
- **SGLT2 is a therapeutic target for the management of type 2 diabetes**

Various types of SGLTs

Transporter	Substrate	Distribution
SGLT1	Glucose, galactose	Intestine, trachea, kidney, heart, brain, testis, and prostate
SGLT2	Glucose Galactose	Kidney, brain, liver, thyroid, muscle, and heart
SGLT4	Glucose and mannose	Intestine, kidney, liver, brain, lung, trachea, uterus, and pancreas
SGLT5	Not known	Kidney
SGLT6	Myo-inositol, glucose	Brain, kidney, and intestine
SMIT1	Myo-inositol, glucose	Brain, heart, kidney, and lung

- **Two types of SGLTs, SGLT1 and SGLT2, important for the reabsorption of filtered glucose from the kidney with different functions**

SGLT2 vs SGLT1

SGLT2

- High-capacity transporter, but low affinity for glucose.
- One molecule of glucose is co-transported for each Na^+ ion.
- About 90% of renal glucose reabsorption is carried out by SGLT2 in first segment of the proximal tubule.
- Major transporter of glucose in the kidney.

SGLT1

- Low-capacity transporter, but high affinity for glucose.
- One molecule of glucose is co-transported for 2 Na^+ ions.
- About 10% of renal glucose reabsorption is carried out by SGLT1 located in the third segment of the proximal tubule.
- Major transporter of glucose in the intestines.

SGLT2 inhibitors

MOA of SGLT2 inhibition:

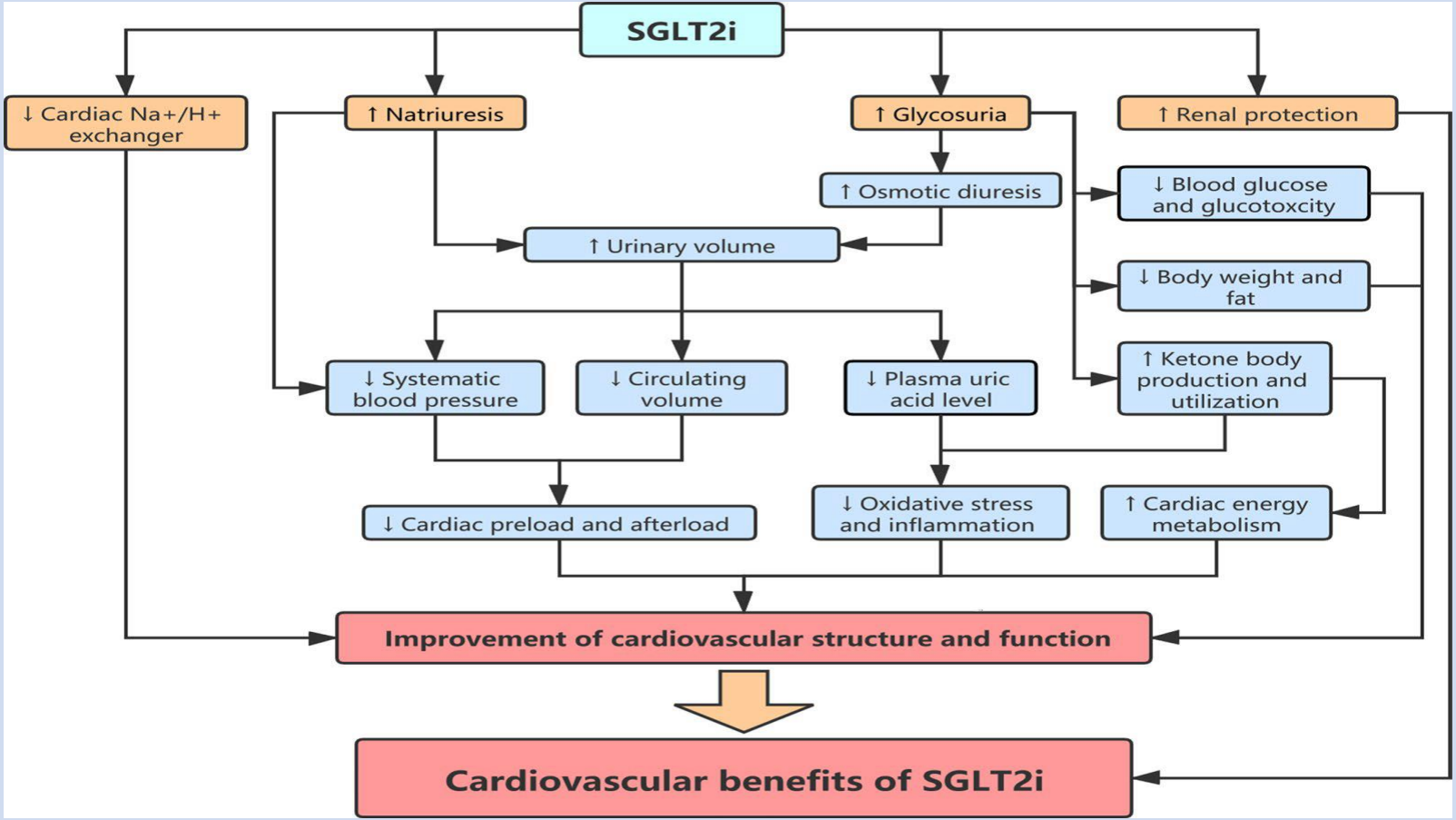
- **SGLT2 inhibitors block transport of glucose by SGLT2 competing with glucose for binding sites**
- **They reduce the T_{max} of glucose reabsorption in the proximal tubule, leading to urinary glucose excretion at a lower threshold concentration**

Potential benefits of SGLT2 inhibitors:

- **Lowers plasma glucose**
- **Weight loss**
- **Improves β-cell function and insulin resistance**
- **Lowers blood pressure**

Cardiovascular protection mechanisms of SGLT2 inhibitors

- **Multiple direct & indirect mechanisms**
- **Improve many aspects : hemodynamics, metabolism, oxidative stress & inflammation**
- **Cardiovascular benefits are not related to anti-hyperglycemic effect of SGLT2i.**


SGLT2i
↓ Cardiac Na+/H+ exchanger
↑ Natriuresis
↑ Glycosuria
↑ Renal protection
↑ Osmotic diuresis
↓ Blood glucose and glucotoxcity
↑ Urinary volume
↓ Body weight and fat
↓ Systematic blood pressure
↓ Circulating volume
↓ Plasma uric acid level
↑ Ketone body production and utilization
↓ Cardiac preload and afterload
↓ Oxidative stress and inflammation
↑ Cardiac energy metabolism
Improvement of cardiovascular structure and function
Cardiovascular benefits of SGLT2i

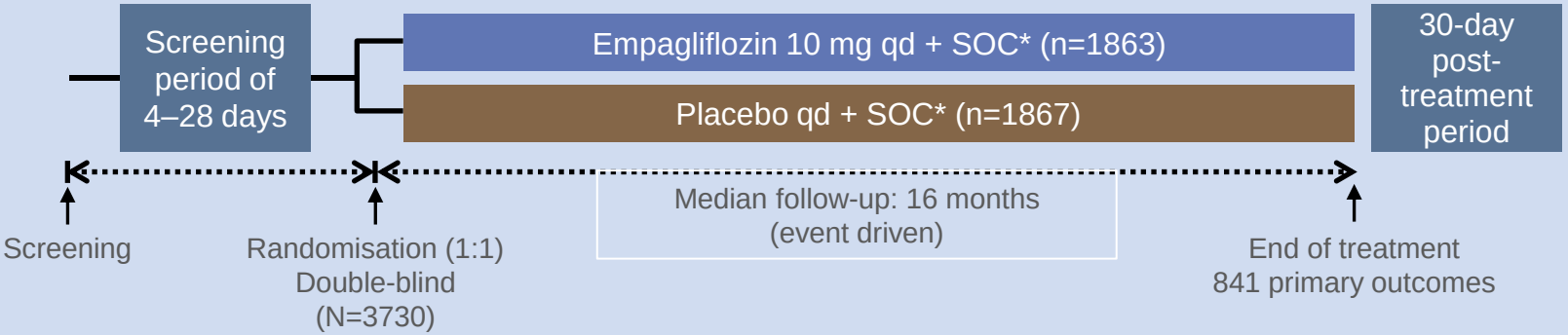
Cardiovascular benefits

- Glycemic control & attenuation of glucotoxicity
- Natriuresis, diuresis & reduction in plasma volume
- Reduction in BP
- Amelioration of endothelial dysfunction & vascular stiffness
- Improvement of cardiac energy metabolism
- Inhibition of cardiac Na+/H+ (attenuation of cardiac remodeling & fibrosis)
- Improvements in cardiac structure & function
- Attenuation of inflammation
- Reduction in serum uric acid level

Evidence for SGLT2 inhibitors in heart failure

EMPEROR-Reduced : trial design

Aim: to investigate the safety and efficacy of empagliflozin versus placebo, on top of SOC,* in patients with HFrEF with or without diabetes



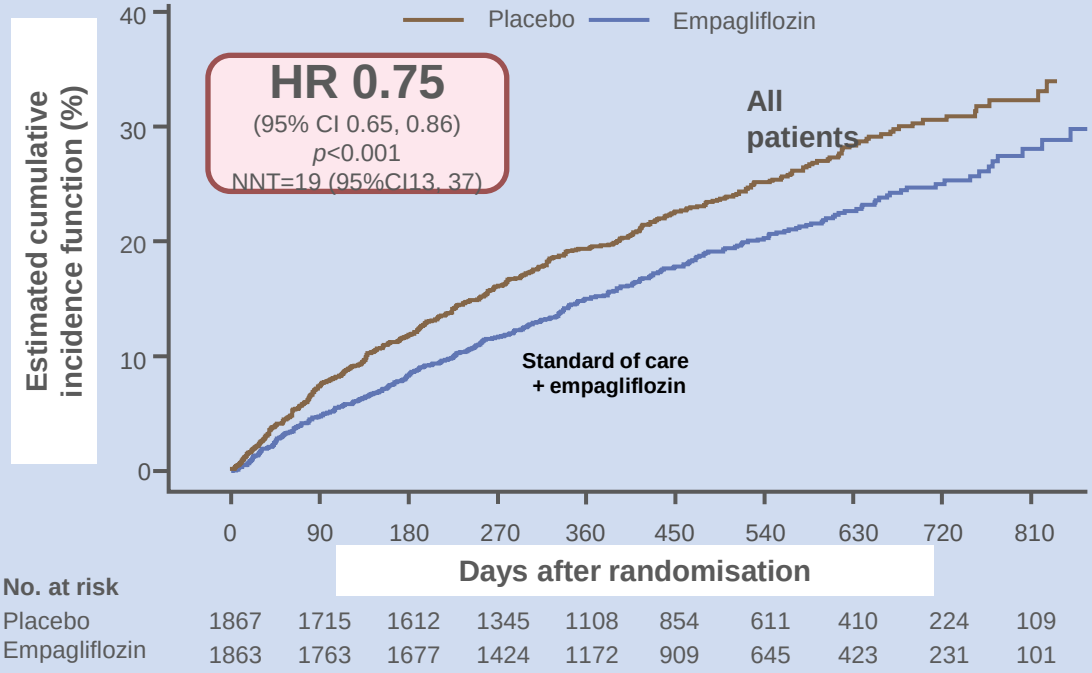
Composite primary outcome†	•	Time to first event of adjudicated CV death or adjudicated HHF
Secondary outcomes†	•	First and recurrent adjudicated HHF events
	•	Rate of the decline in the eGFR during double-blind treatment

*Guideline-directed medical therapy; †Included in a hierarchical testing procedure HHF, hospitalisation for heart failure; SOC, standard of care

1. ClinicalTrials.gov. NCT03057977 (accessed Aug 2020); 2. Packer M *et al. Eur J Heart Fail* 2019;21:1270; 3. Packer M *et al. N Engl J Med* 2020;383:1413

EMPEROR-Reduced - early and sustained benefits from empagliflozin on CV outcomes* 12 days after randomization

Primary composite of first adjudicated CV death or HHF



No. 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	NNT†
25%	19

Combined risk of death, HHF or an emergent/urgent heart failure visit requiring intravenous treatment[3]

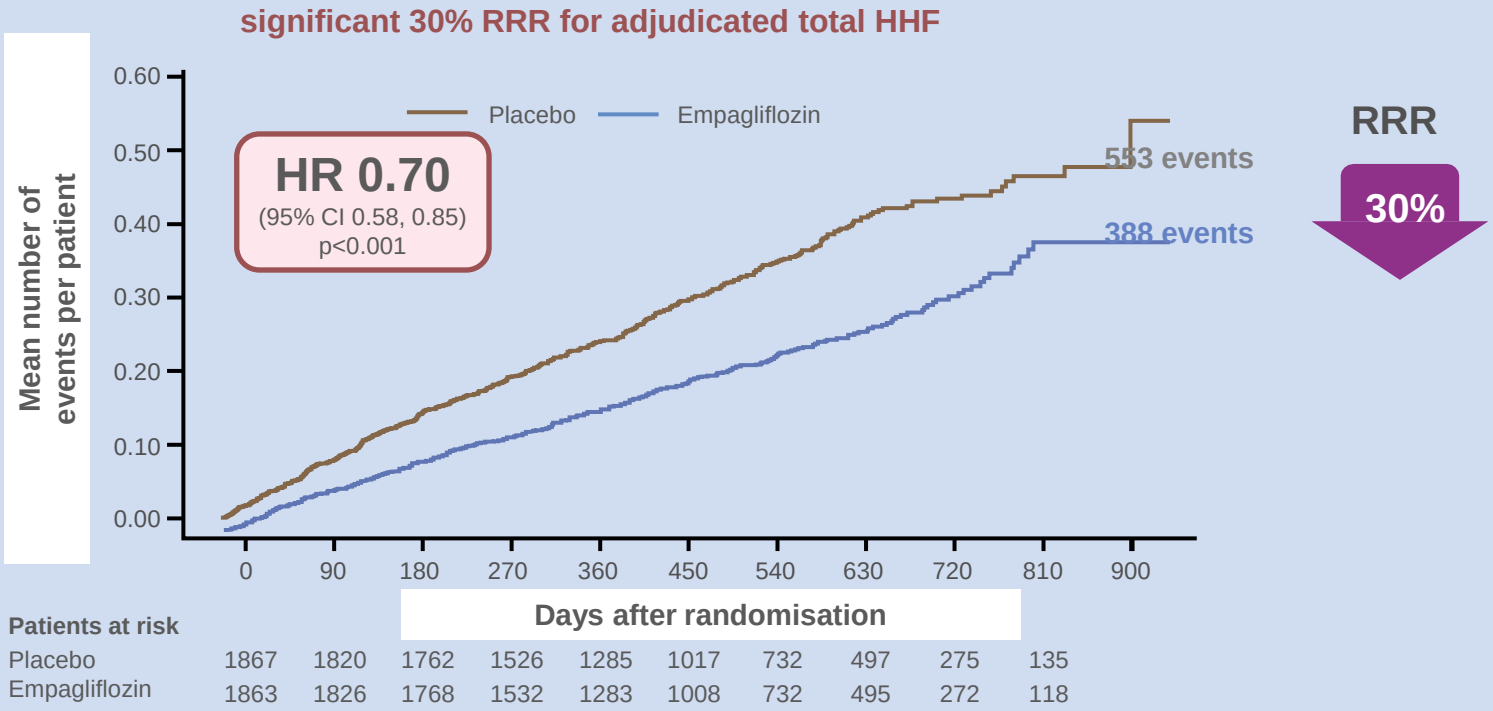
Statistical significance:

- Reached **12 days after randomization**
- Sustained from day 34

HHF, hospitalisation for heart failure; NNT, number needed to treat; PY, patient-years; RRR, relative risk reduction

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.

EMPEROR-Reduced : adjudicated total HHF*



*Total HHF was evaluated with the use of a joint frailty model that accounted for informative censoring because of CV death HHF, hospitalisation for heart failure; RRR, relative risk reduction

Packer M *et al. N Engl J Med* 2020;383:1413

EMPEROR-Reduced: empagliflozin significantly reduced the risk of CV death or HHF in patients with HFrEF with or without diabetes

Primary composite outcome

CV death or HHF

↓ **25% RRR**
HR 0.75 (95% CI 0.65, 0.86)
p<0.001

Secondary outcomes

Total first and recurrent HHF events

↓ **30% RRR**
HR 0.70 (95% CI 0.58, 0.85)
p<0.001

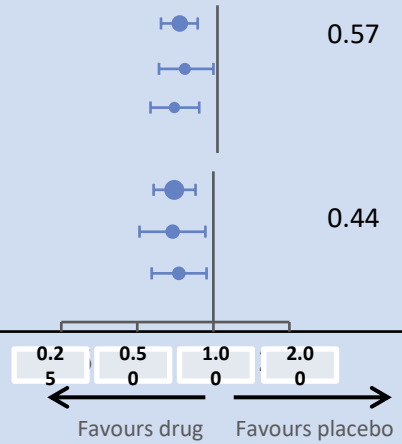
Rate of eGFR decline (difference per year vs placebo)

+1.73 ml/min/1.73 m^2
(95% CI 1.10, 2.37)
p<0.001

HHF, hospitalisation for heart failure; RRR, relative risk reduction
Packer M *et al*. *N Engl J Med* 2020;383:1413

EMPEROR-Reduced: subgroup analysis by diabetes status showed consistent effects on primary composite and key secondary outcomes

	Empagliflozin (n=1863)		Placebo (n=1867)				*p*-value for interaction
	n with event/N analysed (%)	Rate per 100 PY	n with event/N analysed (%)	Rate per 100 PY	HR (95% CI)	HR (95% CI)	
Time to first event of adjudicated HHF or CV death							
Overall	361/1863 (19.4)	15.77	462/1867 (24.7)	21.00	0.75 (0.65, 0.86)		0.57
No diabetes	161/936 (17.2)	13.93	197/938 (21.0)	17.59	0.78 (0.64, 0.97)		
Diabetes	200/927 (21.6)	17.66	265/929 (28.5)	24.55	0.72 (0.60, 0.87)		
First and recurrent HHF (number of events)							
Overall	388/1863	–	553/1867	–	0.70 (0.58, 0.85)		0.44
No diabetes	167/936	–	216/938	–	0.76 (0.57, 1.01)		
Diabetes	221/927	–	337/929	–	0.65 (0.50, 0.85)		



HHF, hospitalisation for heart failure; PY, patient-years

Anker SD *et al. Circulation* 2021;143:337

EMPEROR-Reduced: Select Safety Data in patients with and without diabetes

	Empagliflozin (n=1863)	Placebo (n=1863)
	n/N (%)	n/N (%)
Confirmed hypoglycaemic episode*		
Normoglycaemic	1/304 (0.3)	1/302 (0.3)
Pre-diabetes	6/632 (0.9)	5/635 (0.8)
Diabetes	20/927 (2.2)	22/926 (2.4)
Severe hypoglycaemic episode†		
Normoglycaemic	0/304	0/302
Pre-diabetes	0/632	0/635
Diabetes	6/927 (0.6)	7/926 (0.8)
Diabetic ketoacidosis		
Normoglycaemic	0/304	0/302
Pre-diabetes	0/632	0/635
Diabetes	0/927	0/926

No cases of diabetic ketoacidosis
No severe hypoglycaemic episodes in patients without diabetes
No difference vs placebo in diabetes-related adverse events

*Defined as hypoglycaemic AEs with a plasma glucose value of ≤70 mg/dl or that required assistance; †Defined as a hypoglycaemic episode requiring assistance
AE, adverse event. Anker SD *et al. Circulation* 2021;143:337

EMPEROR-Reduced: Select Safety Data in patients with and without CKD

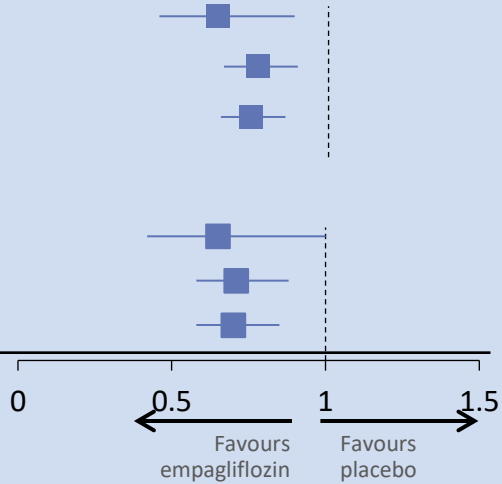
	Empagliflozin n/N (%)	Placebo n/N (%)
Serious AE		
No prevalent CKD	310/879 (35.3)	381/865 (44.0)
Prevalent CKD	462/981 (47.1)	513/995 (51.6)
AE leading to discontinuation of trial drug		
No prevalent CKD	124/879 (14.1)	116/865 (13.4)
Prevalent CKD	198/981 (20.2)	210/995 (21.1)
Acute renal failure*		
No prevalent CKD	52/879 (5.9)	62/865 (7.2)
Prevalent CKD	123/981 (12.5)	130/995 (13.1)

As expected, AE rates (including serious AEs and AEs leading to discontinuation) were higher in patients with prevalent CKD

*Narrow standardised MedDRA query 'acute renal failure' from MedDRA version 23
AE, adverse event; CKD, chronic kidney disease
Zannad F *et al. Circulation* 2021;143:310

EMPEROR-Reduced: subgroup analysis by neprilysin inhibitor use showed consistent effects on primary composite and key secondary outcomes

	Empagliflozin n/N (%)	Placebo n/N (%)	HR (95% CI)
Time to CV death or HHF*			
Neprilysin inhibitor	51/340 (15.0)	93/387 (24.0)	0.64 (0.45, 0.89)
No neprilysin inhibitor	310/1523 (20.9)	369/1480 (24.9)	0.77 (0.66, 0.90)
All patients	361/1863 (19.4)	462/1867 (24.7)	0.75 (0.65, 0.86)
First and recurrent HHF† (no. of events)			
Neprilysin inhibitor	70	121	0.65 (0.42, 1.00)
No neprilysin inhibitor	318	432	0.71 (0.58, 0.88)
All patients	388	553	0.70 (0.58, 0.85)



*Treatment by neprilysin inhibitor interaction: *p*=0.31; †Treatment by neprilysin inhibitor interaction: *p*=0.72

HHF, hospitalisation for heart failure

Packer M *et al. Eur Heart J* 2021;42:671; Packer M *et al. N Engl J Med* 2020;383:1413

EMPEROR-Reduced: adverse events according to use of neprilysin inhibitor

	No neprilysin inhibitor (n=2999)		Neprilysin inhibitor (n=727)	
	Placebo (n=1476)	Empagliflozin (n=1523)	Placebo (n=387)	Empagliflozin (n=340)
Serious adverse events	702 (47.6)	631 (41.4)	194 (50.1)	141 (41.5)
Hypotension	124 (8.4)	132 (8.7)	39 (10.1)	44 (12.9)
Symptomatic hypotension	75 (5.1)	76 (5.0)	28 (7.2)	30 (8.8)
Volume depletion	144 (9.8)	146 (9.6)	40 (10.3)	51 (15.0)
Hyperkalaemia	98 (6.6)	89 (5.8)	29 (7.5)	20 (5.9)
Hypokalaemia	24 (1.6)	30 (2.0)	5 (1.3)	5 (1.5)
Worsening kidney function	141 (9.6)	143 (9.4)	51 (13.2)	32 (9.4)
Acute kidney injury	38 (2.6)	25 (1.6)	17 (4.4)	10 (2.9)
Confirmed hypoglycaemia	22 (1.5)	22 (1.4)	6 (1.6)	5 (1.5)

Data are shown as n (%).
Shown are adverse events while on study medication and recorded up to 7 days following discontinuation of the study medications
Packer M *et al. Eur Heart J* 2021;42:671

Summary of EMPEROR-Reduced

SGLT2 inhibitors improved cardiovascular outcomes (composite primary endpoint of CV death or HHF) in patients with HFrEF[1,2]

Subgroup analyses confirmed that the effect of SGLT2 inhibitors on CV outcomes was consistent across subgroups of patients with HFrEF, including with or without diabetes,[3,4] with or without CKD,[5,6] and with or without different types of background HFrEF medical therapy[7–9]

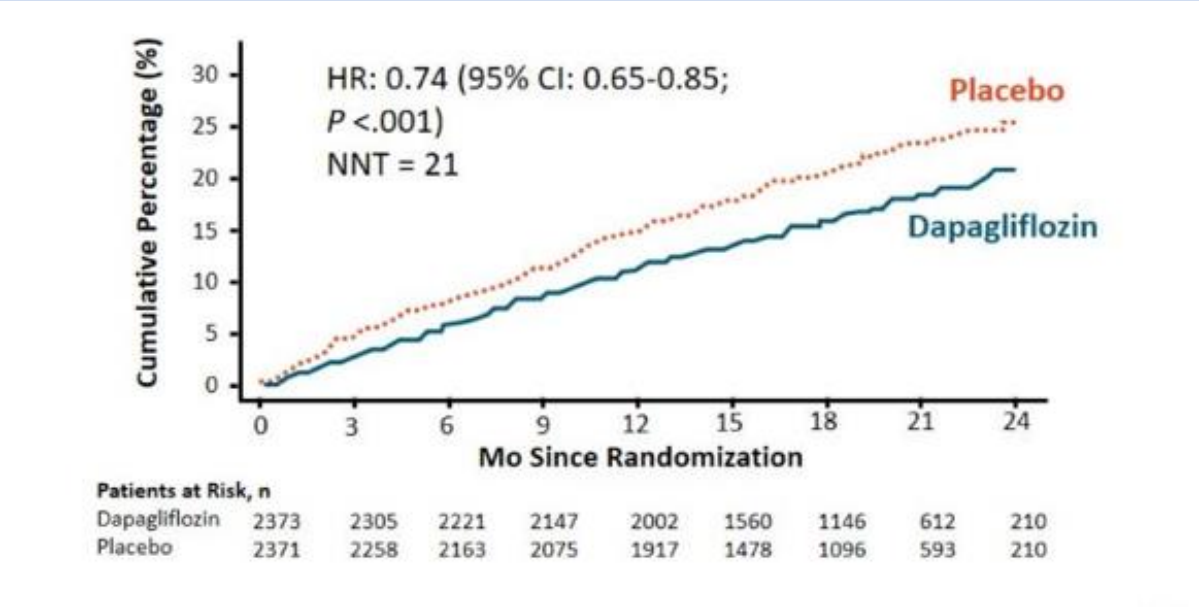
CKD, chronic kidney disease; HHF, hospitalisation for heart failure; SGLT2, sodium-glucose co-transporter-2

1. McMurray J *et al. N Engl J Med* 2019;381:1995; 2. Packer M *et al. N Engl J Med* 2020;383:1413; 3. Anker SD *et al. Circulation* 2021;143:337; 4. Zannad F *et al. Lancet* 2020;396:819; 5. Zannad F *et al. Circulation* 2021;143:310; 6. Jhund PS *et al. Circulation* 2021;143:298; 7. Packer M *et al. Eur Heart J* 2021;42:671; 8. Ferreira JP *et al. J Am Coll Cardiol* 2021;77:1397; 9. Docherty KF *et al. Eur Heart J* 2020;41:2379

DAPA-HF : Primary Composite Outcome

- Randomized, double-blind, international phase III trial in patients with HF and reduced ejection fraction (N = 4744)

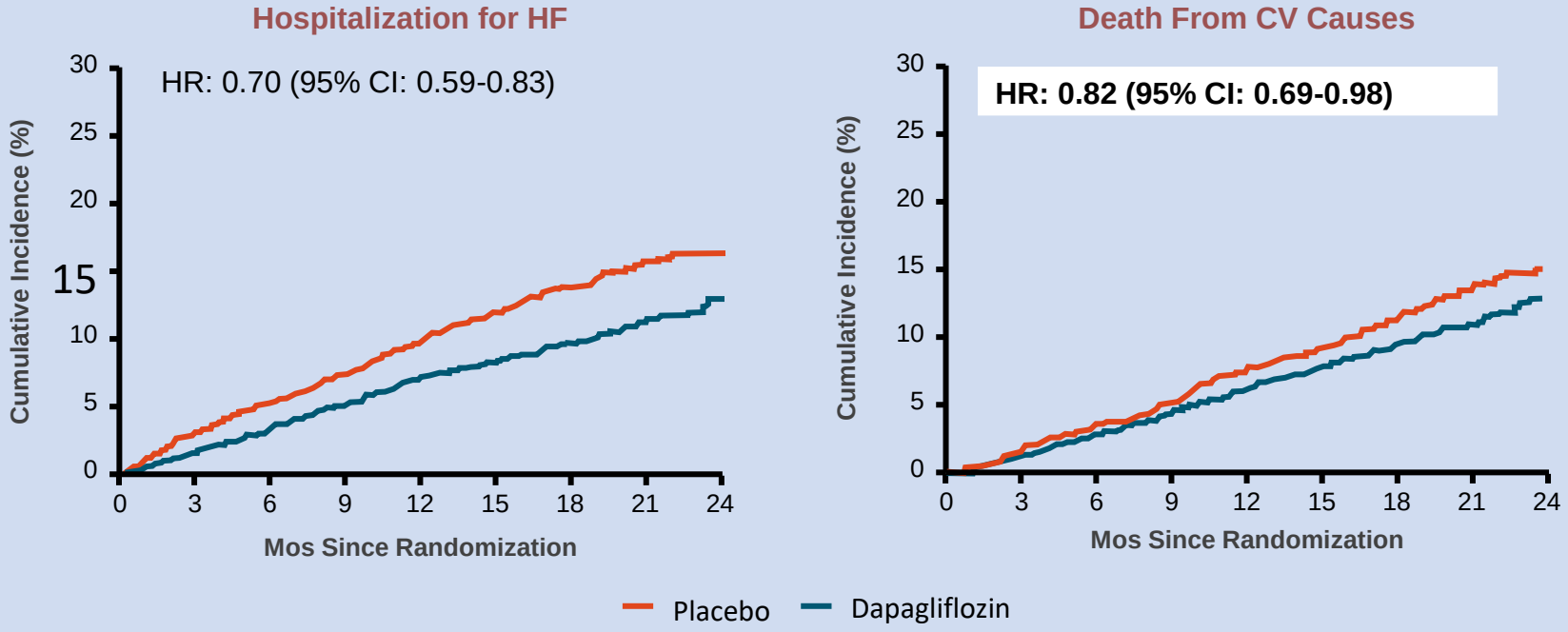
Primary outcome: CV death, HF Hospitalization, or urgent visit for HF



McMurray:NEJM 2019

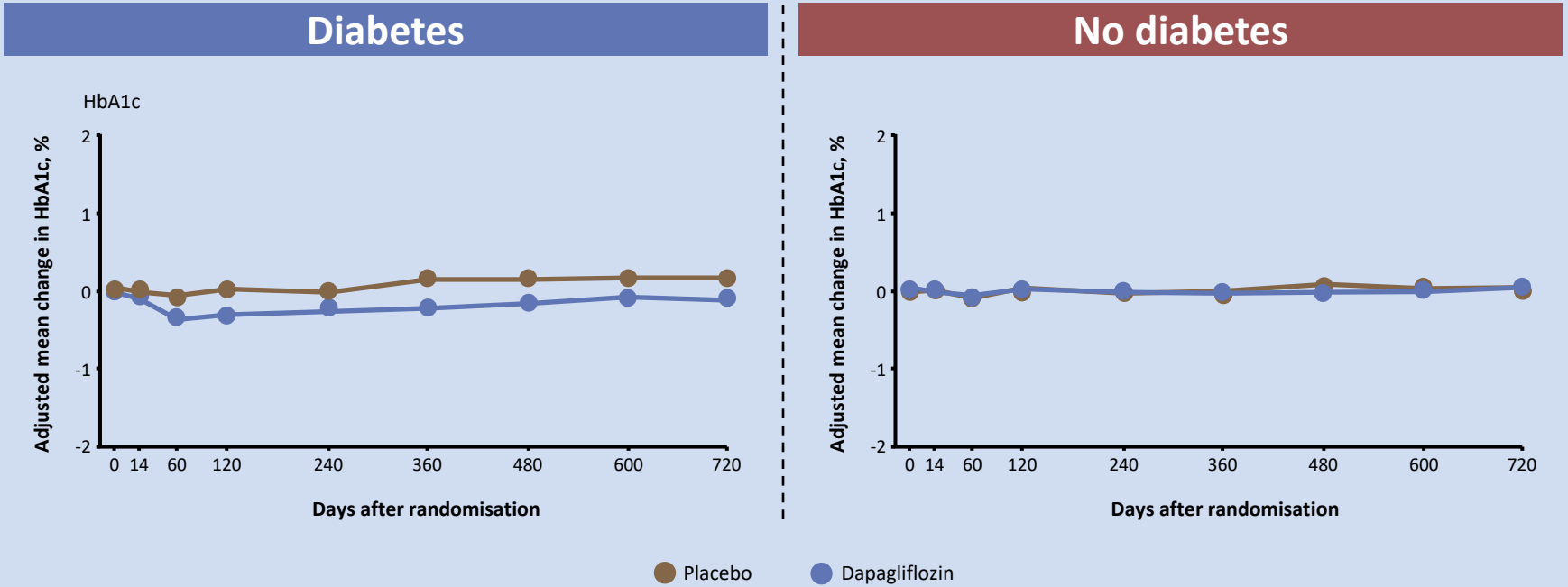
DAPA-HF: Components of Primary Outcomes

- Randomized, double-blind, international phase III trial in patients with HF and reduced ejection fraction (N = 4744)



McMurray. NEJM. 2019;381:1995. NCT03036124.

DAPA-HF: there was no effect on HbA1c in patients without diabetes



p-value for interaction <0.001, HbA1c, glycated haemoglobin

Petrie MC *et al. JAMA* 2020;323:1353

DAPA-HF: dapagliflozin significantly reduced the risk of worsening heart failure* or CV death in patients with HFrEF with or without diabetes

Primary composite outcome

Worsening HF* or CV death

↓26% RRR

HR 0.74 (95% CI 0.65, 0.85)
p<0.001

Secondary outcomes

HHF or CV death

↓25% RRR

HR 0.75 (95% CI 0.65, 0.85)
p<0.001

Total HHF and CV death events

↓25% RRR

HR 0.75 (95% CI 0.65, 0.88)
p<0.001

KCCQ total symptom score

1.18 rate ratio

(95% CI 1.11, 1.26)
p<0.001

Composite kidney outcome

HR 0.71
(95% CI 0.44, 1.16)
NA†

All-cause mortality

HR 0.83
(95% CI 0.71, 0.97)
NA†

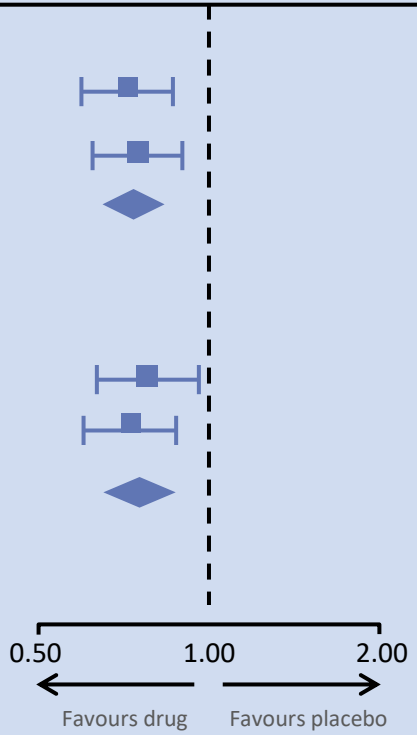
*Unplanned HHF or urgent visit resulting in intravenous therapy for HF; †NA denotes not applicable because *p*-values for efficacy outcomes are reported only for outcomes that were included in the hierarchical testing strategy

HHF, hospitalisation for heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; NA, not applicable; RRR, relative risk reduction

McMurray J *et al. N Engl J Med* 2019;381:1995

Meta-analysis: beneficial effects on HHF or CV death seen regardless of diabetes status

First HHF or CV death	SGLT2 inhibitor n with event/N analysed (%)	Placebo n with event/N analysed (%)	HR (95% CI)
With diabetes			
EMPEROR-Reduced	200/927 (21.6)	265/929 (28.5)	0.72 (0.60, 0.87)
DAPA-HF	215/1075 (20.0)	271/1064 (25.5)	0.75 (0.63, 0.90)
Subtotal			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)	231/1307 (17.7)	0.73 (0.60, 0.88)
Subtotal			0.75 (0.65, 0.87)
Test for overall treatment effect, $p<0.0001$ Test for heterogeneity of effect, $p=0.65$			
Test for treatment by subgroup interaction, $p=0.81$			



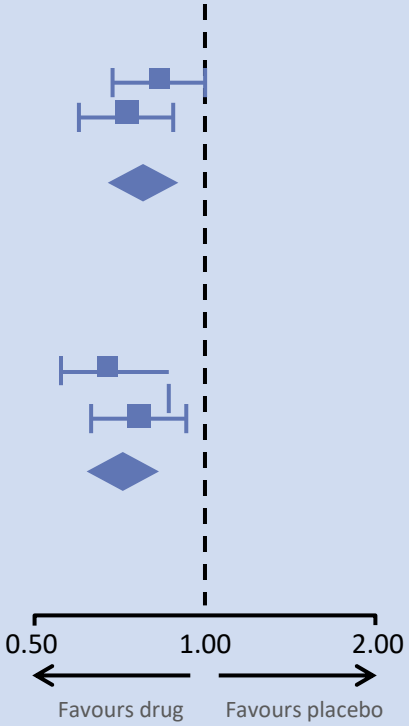
Comparison of studies should be interpreted with caution due to differences in study design, populations and methodology

HHF, hospitalisation for heart failure; SGLT2, sodium-glucose co-transporter-2

Zannad F *et al. Lancet* 2020;396:819

Meta-analysis: beneficial effects on first HHF or CV death were consistent in patients with eGFR < and ≥60 ml/min/1.73 m²

First HHF or CV death	SGLT2 inhibitor	Placebo	HR (95% CI)
	n with event/N analysed (%)		
eGFR: <60 ml/min/1.73 m²			
EMPEROR-Reduced	202/893 (22.6)	237/906 (26.2)	0.83 (0.69, 1.00)
DAPA-HF	191/962 (19.9)	254/964 (26.3)	0.72 (0.59, 0.86)
Subtotal			0.77 (0.68, 0.88)
Test for overall treatment effect, *p*=0.0001 Test for heterogeneity of effect, *p*=0.29			
eGFR: ≥60 ml/min/1.73 m²			
EMPEROR-Reduced	159/969 (16.4)	224/960 (23.3)	0.67 (0.55, 0.83)
DAPA-HF	195/1410 (13.8)	248/1406 (17.6)	0.76 (0.63, 0.92)
Subtotal			0.72 (0.62, 0.82)
Test for overall treatment effect, *p*<0.0001 Test for heterogeneity of effect, *p*=0.38			
Test for treatment by subgroup interaction, *p*=0.44			



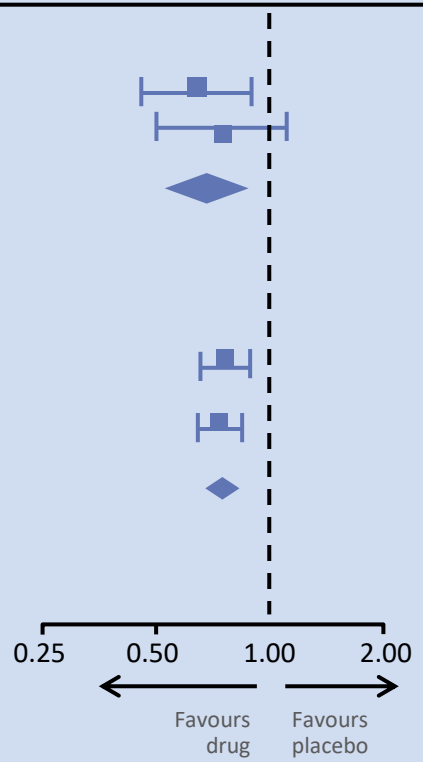
Comparison of studies should be interpreted with caution due to differences in study design, populations and methodology

HHF, hospitalisation for heart failure; SGLT2, sodium-glucose co-transporter-2

Zannad F *et al. Lancet* 2020;396:819

Meta-analysis: beneficial effects on first HHF or CV death seen regardless of use of ARNi

First HHF or CV death	SGLT2 inhibitor	Placebo	HR (95% CI)
	n with event/N analysed (%)		
Receiving ARNi			
EMPEROR-Reduced	51/340 (15.0)	93/387 (24.0)	0.64 (0.45, 0.89)
DAPA-HF	41/250 (16.4)	56/258 (21.7)	0.75 (0.50, 1.13)
Subtotal			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			
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)	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 subgroup interaction, p=0.50			



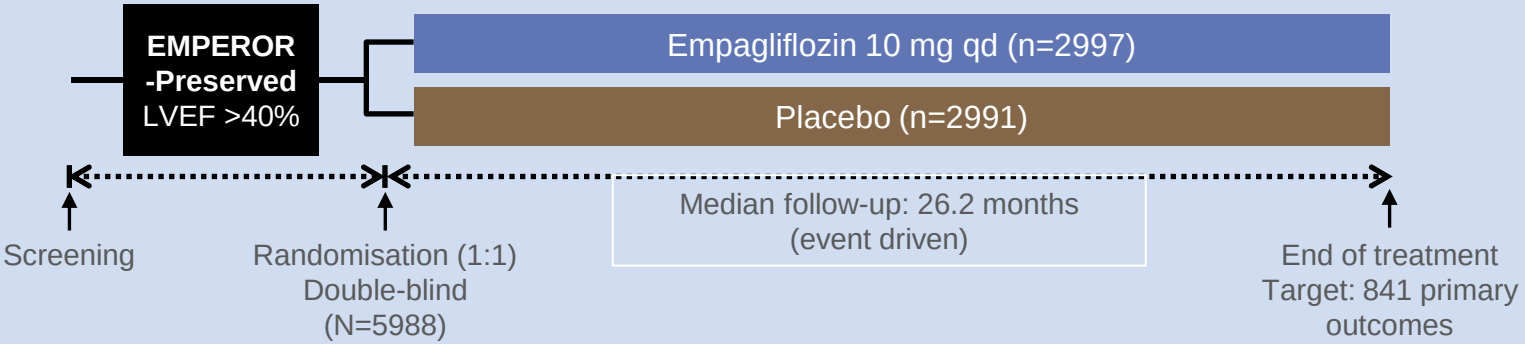
Comparison of studies should be interpreted with caution due to differences in study design, populations and methodology

HHF, hospitalisation for heart failure; SGLT2, sodium-glucose co-transporter-2

Zannad F *et al. Lancet* 2020;396:819

EMPEROR-Preserved: a randomised, double-blind, placebo-controlled, phase III trial in patients with HFpEF

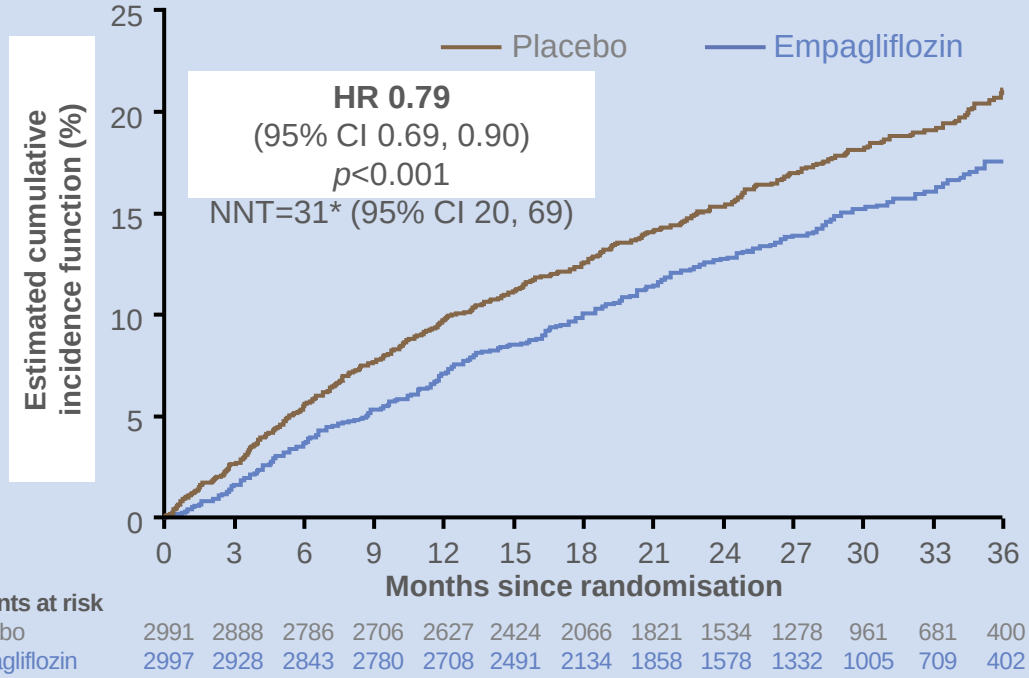
Aim: to investigate the safety and efficacy of empagliflozin versus placebo in patients with HF with preserved ejection fraction



Composite primary outcome	•	Time to first event of adjudicated CV death or adjudicated HHF
Secondary outcomes	•	First and recurrent adjudicated HHF
	•	Slope of change in eGFR (CKD-EPI) from baseline

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; HHF, hospitalisation for heart failure
Anker S *et al. N Engl J Med* 2021;385:1451

EMPEROR-Preserved: empagliflozin demonstrated a 21% RRR in the composite primary endpoint of CV death or first HHF event



511 events

Rate: 8.7/100 PY

415 events

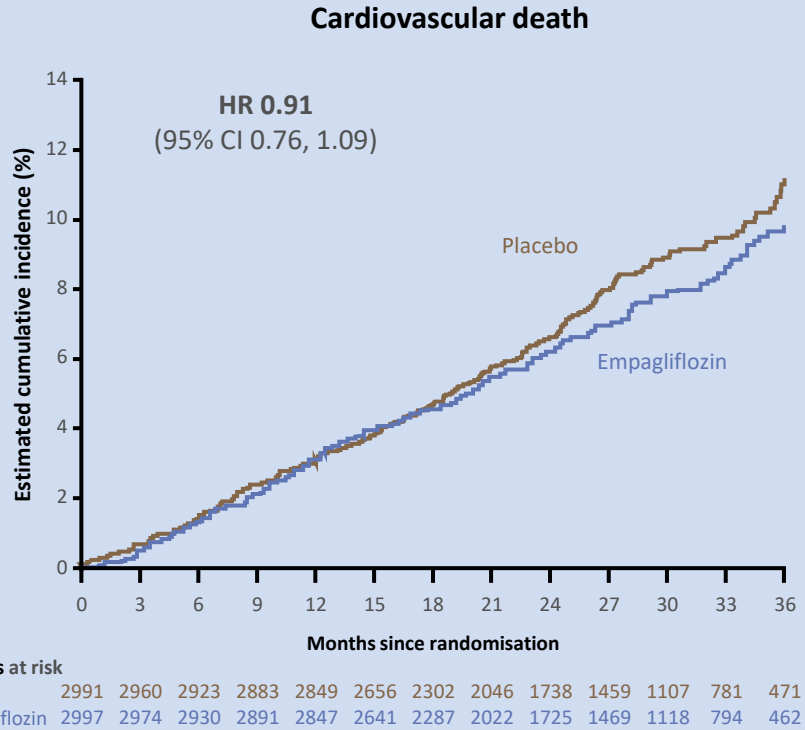
Rate: 6.9/100 PY

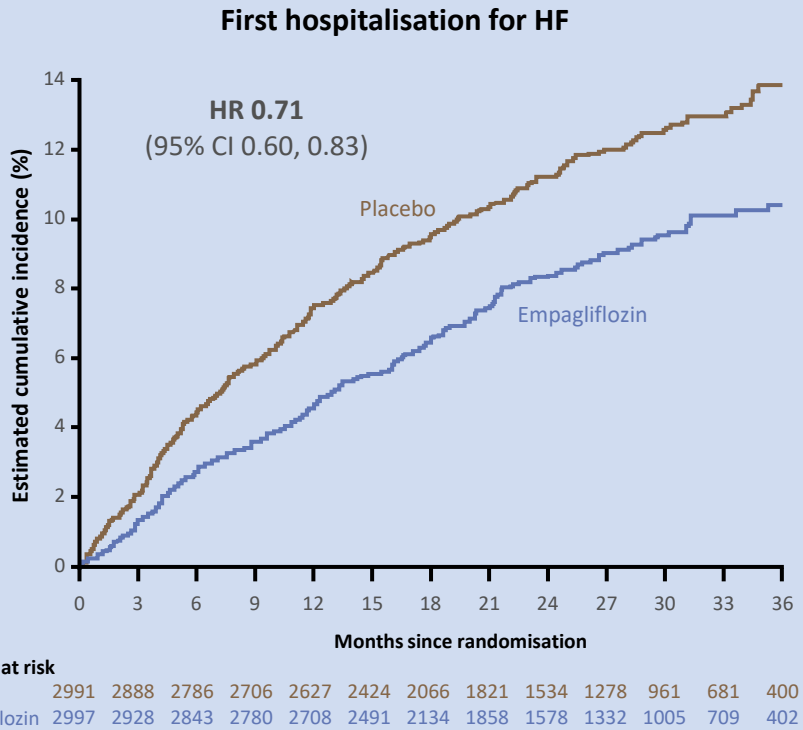
*During a median trial period of 26 months

HHF, hospitalisation for heart failure; NNT, number needed to treat; PY, patient-years; RRR, relative risk reduction

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

EMPEROR-Preserved: effects on individual components of the primary endpoint (CV death or first HHF event)

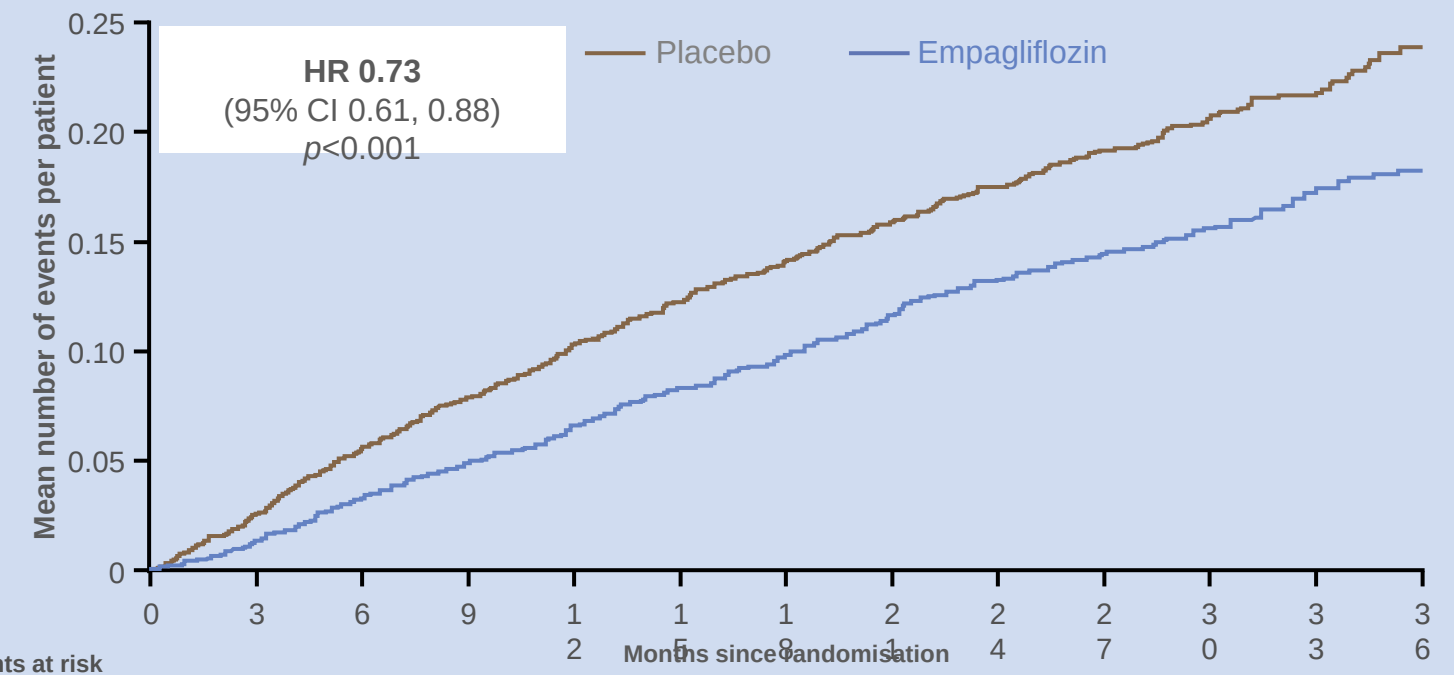




HHF, hospitalisation for heart failure

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

EMPEROR-Preserved: empagliflozin demonstrated a 27% RRR in total (first & recurrent) HHF, a key secondary endpoint



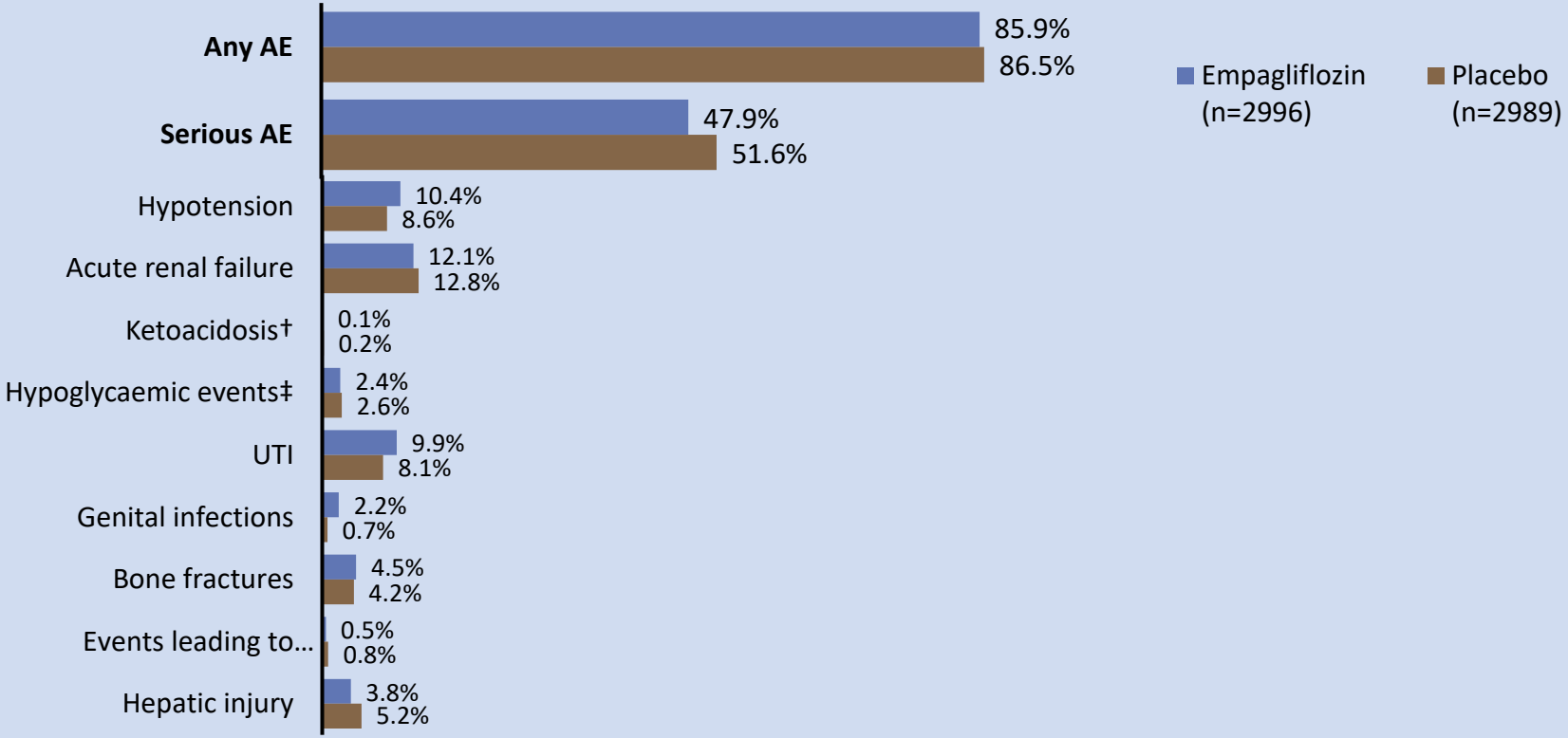
Placebo: 541 patients with event

Empagliflozin: 407 patients with event

HHF, hospitalisation for heart failure; RRR, relative risk reduction

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

EMPEROR-Preserved: selected adverse events of interest



*Investigator-defined events; †All events occurred in patients with diabetes mellitus at baseline; ‡Hypoglycaemic AEs with a plasma glucose value of ≤70 mg/dl (≤3.9 mmol/l) or that required assistance. AE, adverse event; UTI, urinary tract infection

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

EMPEROR-Preserved: summary

Primary outcome

- Empagliflozin significantly reduced the relative risk of CV death or first HHF by 21% in patients with LVEF >40%*
  - A consistent and clinically meaningful benefit was observed across all prespecified patient subgroups

Secondary outcomes

- Empagliflozin significantly reduced the relative risk of HHF, including first and recurrent events, by 27%
- Empagliflozin slowed the decline in kidney function

Safety

- Overall safety data for empagliflozin were consistent with findings in patients with HFrEF
  - UTIs and genital infections were reported more frequently in the empagliflozin group
  - No between-group difference in the frequency of hypoglycaemia and ketoacidosis

*During a median trial period of 26 months
HHF, hospitalisation for heart failure; UTI, urinary tract infection
Anker S *et al. N Engl J Med* 2021;385:1451

DELIVER Study Design

Randomized, double-blind, placebo-controlled trial testing that dapagliflozin would reduce CV death or worsening HF in patients with HF: mildly reduced or preserved ejection fraction

- Age ≥ 40 years
- NYHA class II-IV
- LVEF > 40% (including prior LVEF ≤ 40%)

Eligibility Criteria

- Structural Heart Disease (LVH or LA Enlargement)
- Elevated Natriuretic Peptides (> 300 pg/ml or 600 pg/ml in AFF)
- Either Ambulatory or Hospitalized for Heart Failure

Double-blind Treatment period

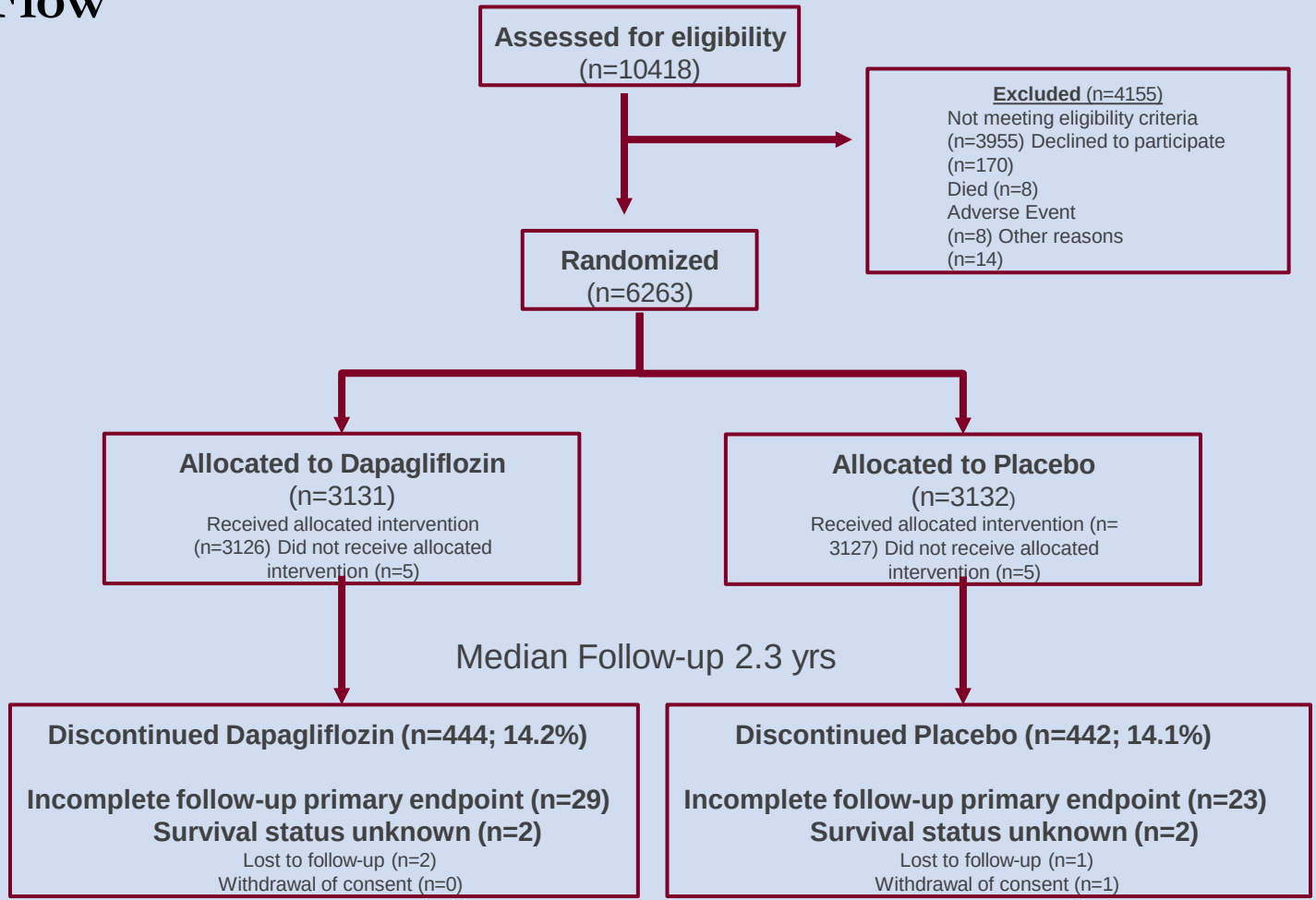
Dapagliflozin 10mg once daily

Event Driven (1117 estimated events)

Placebo

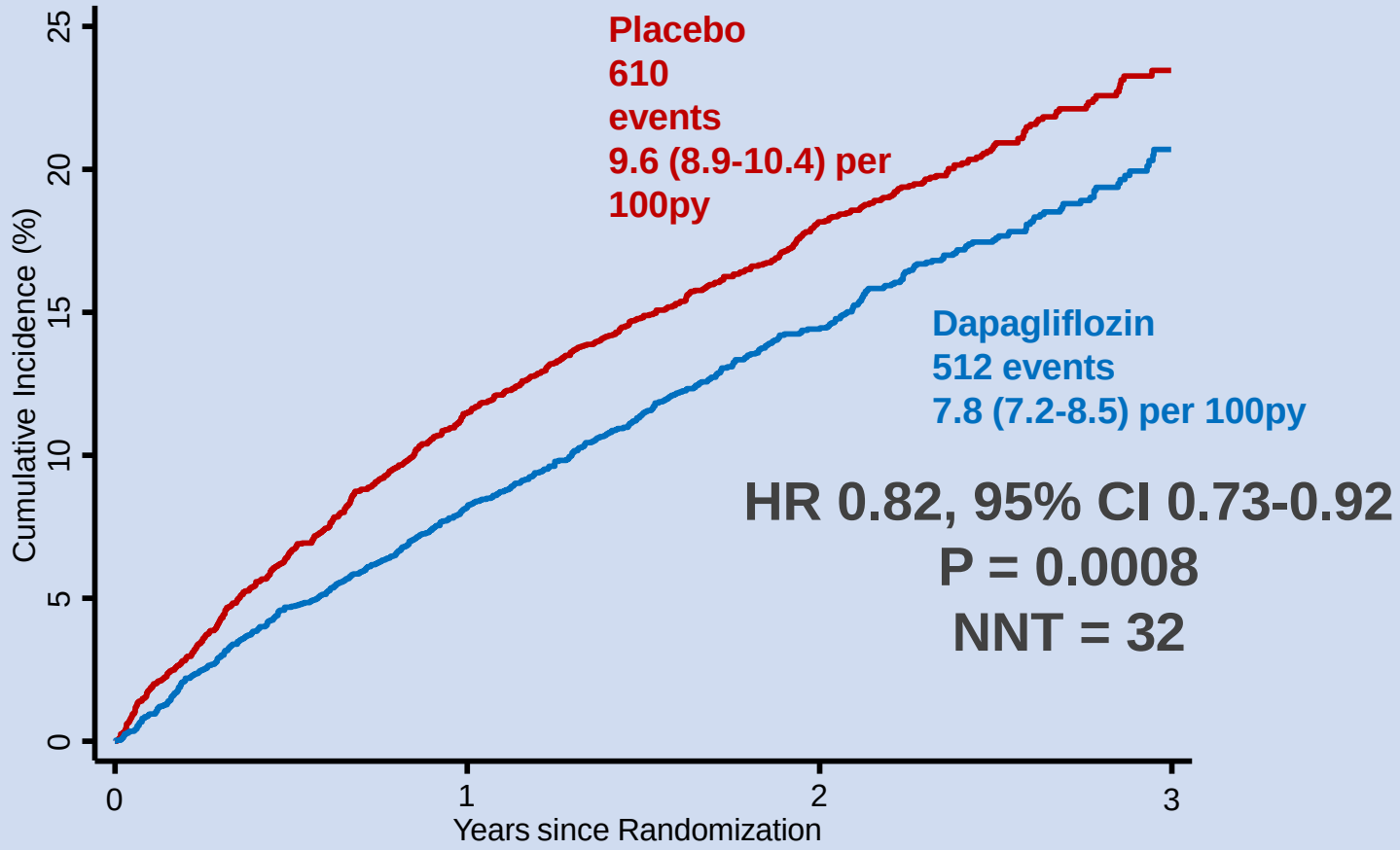
Solomon et al. Eur J Heart Fail 2021

Patient Flow



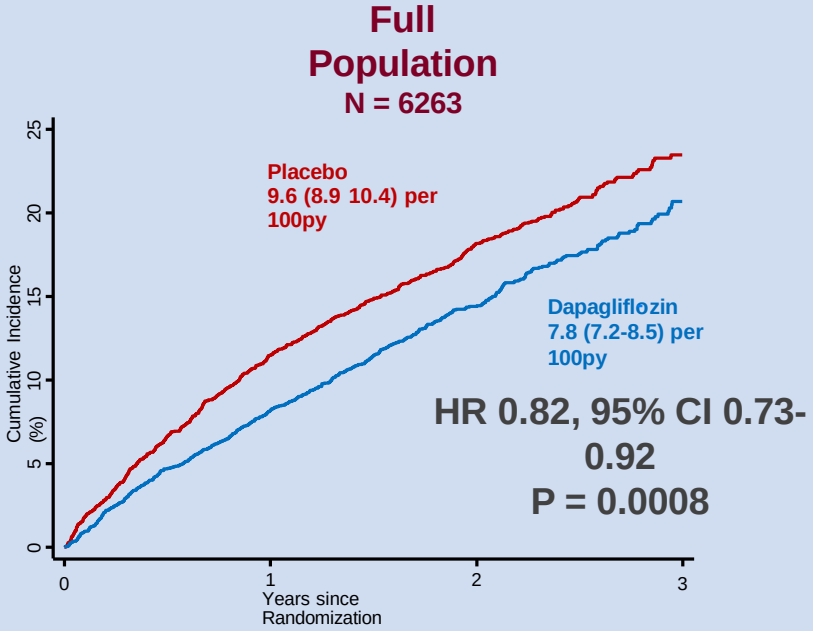
Primary Endpoint: CV Death or Worsening HF

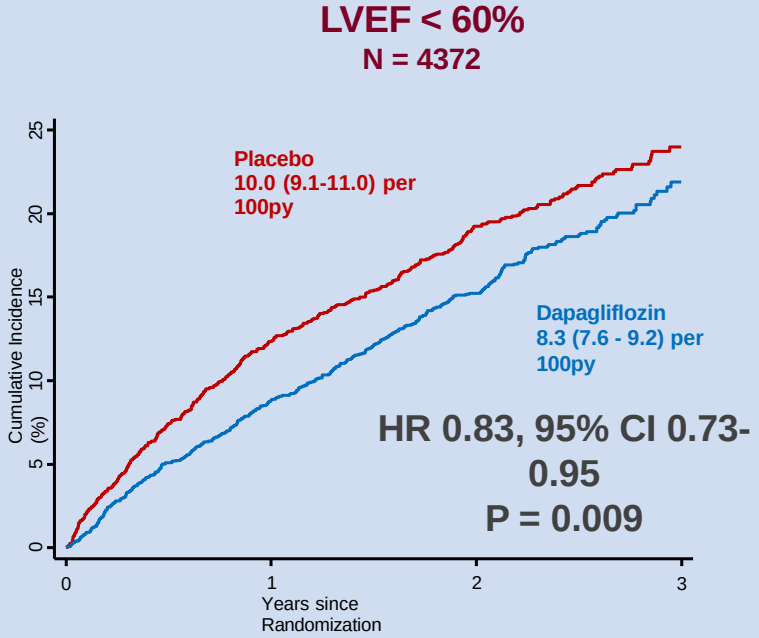
Full Population



ESC, 2022

Primary Endpoint in Full Population and LVEF < 60%
Dual Primary Analyses

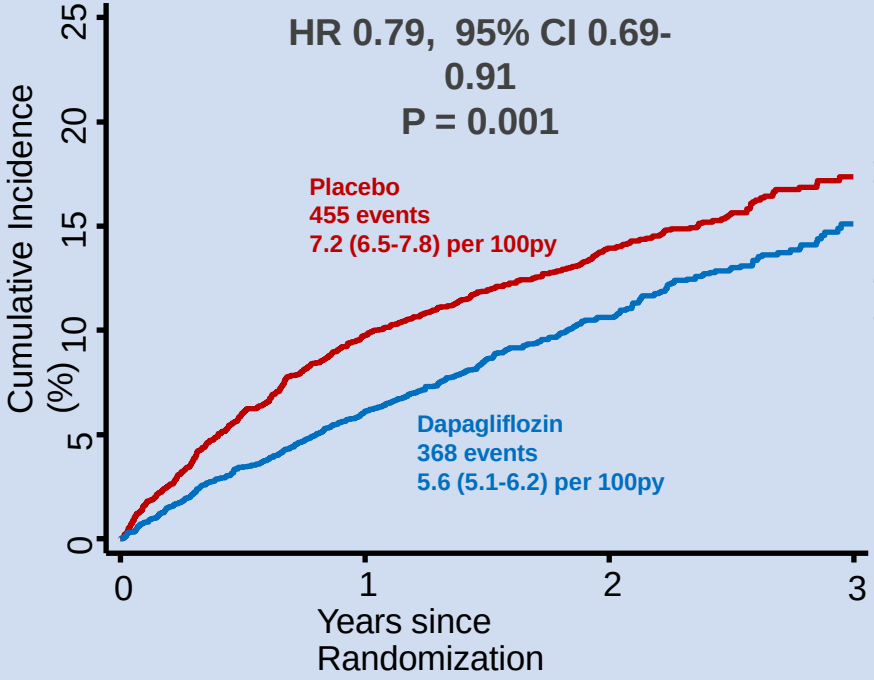




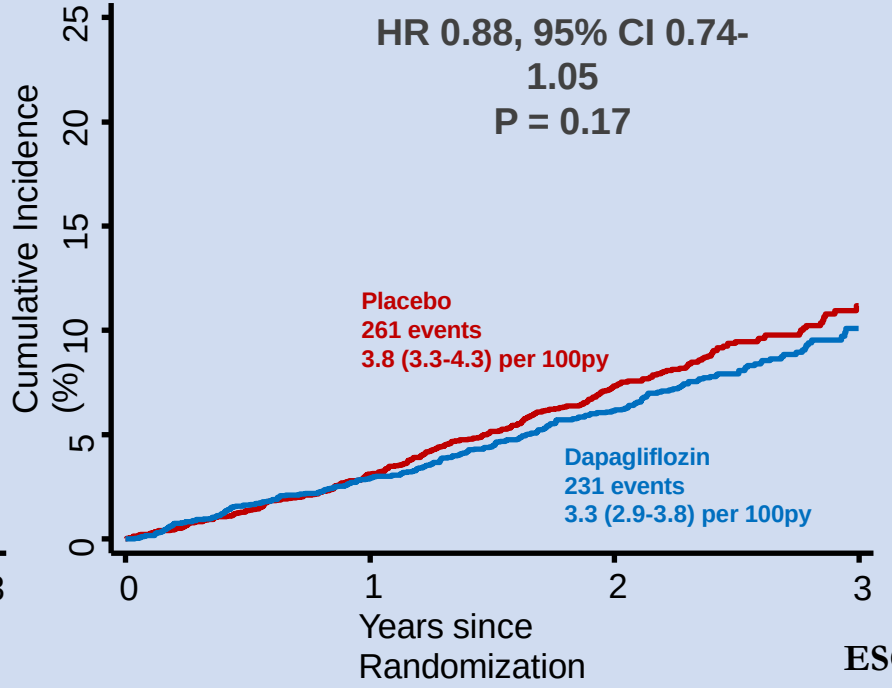
ESC, 2022

Components of Primary Endpoint (Full Population)

Worsening Heart Failure (HF Hospitalization + Urgent HF Visit)

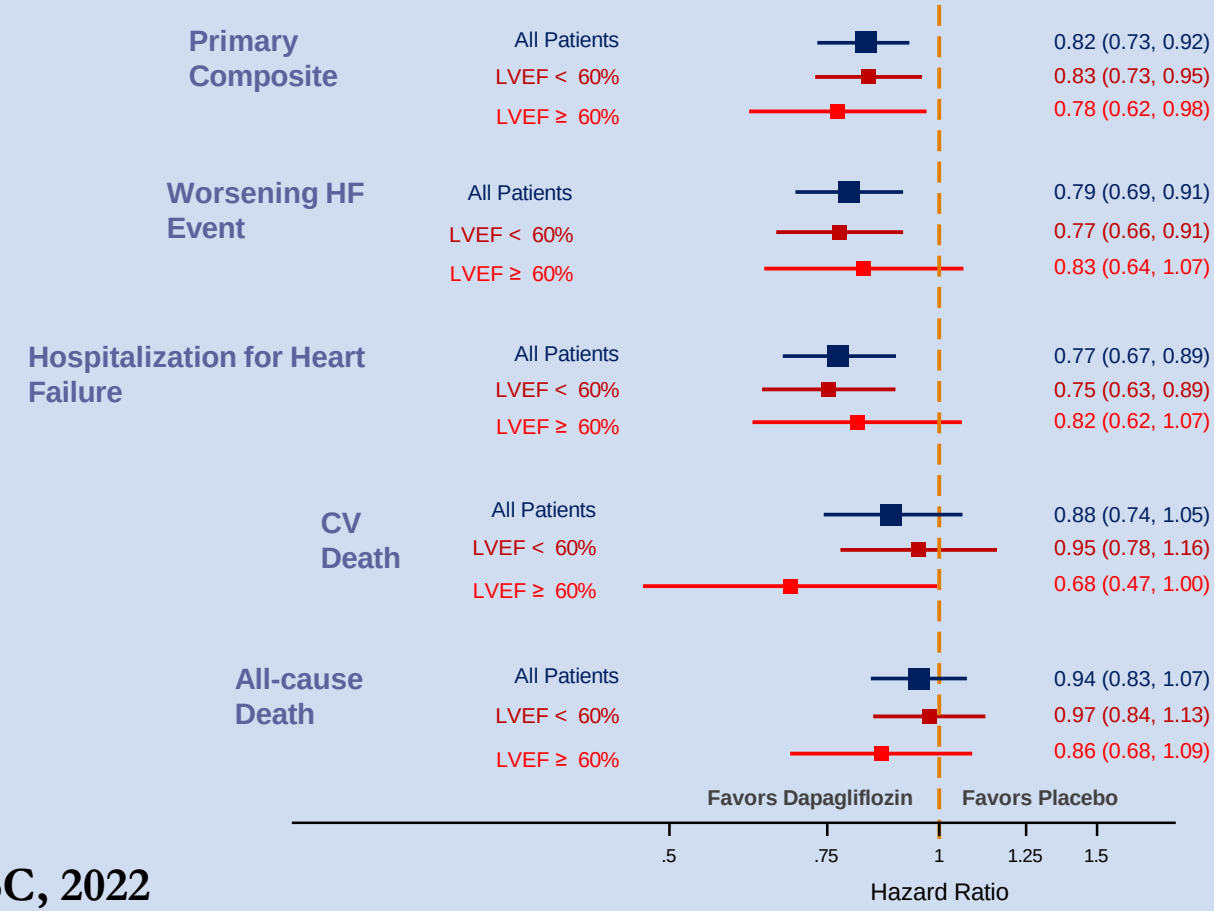


Cardiovascular Death



ESC, 2022

Outcomes by LVEF < 60% or LVEF ≥ 60%



All Patients N = 6263

LVEF < 60% N = 4372 (70%)

LVEF ≥ 60% N = 1891 (30%)

ESC, 2022

These data provide further evidence to support the use of an SGLT2 inhibitor as foundational therapy in patients with heart failure, regardless of care setting or ejection fraction

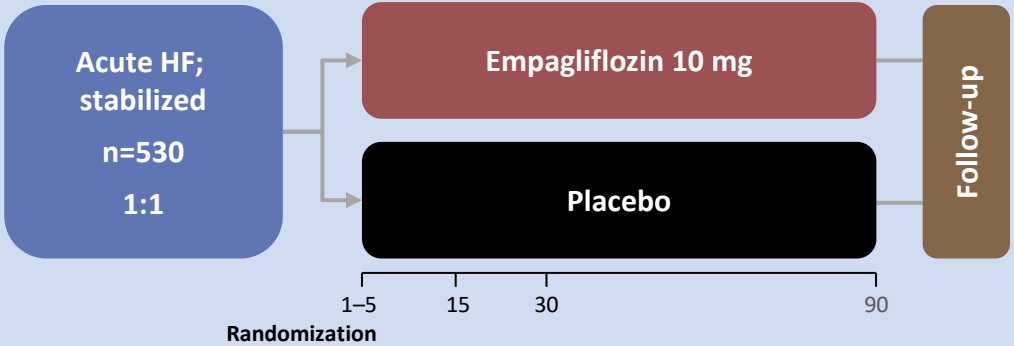
ESC, 2022

EMPULSE study in acute HF

- **Multinational randomized, double blind trial**
- **EMPULSE was specifically designed to prospectively address in hospital initiation of Empagliflozin in patients with acute HF regardless of LVEF or de-novo or decompensated chronic presentation**
- **Empagliflozin 10 mg OD vs placebo/ randomized in hospital when clinically stable/ treated for up to 90d**

Nature Medicine 28, 568-574 (2022)

EMPULSE studied the effect of empagliflozin in patients hospitalized for acute heart failure[1,2]



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

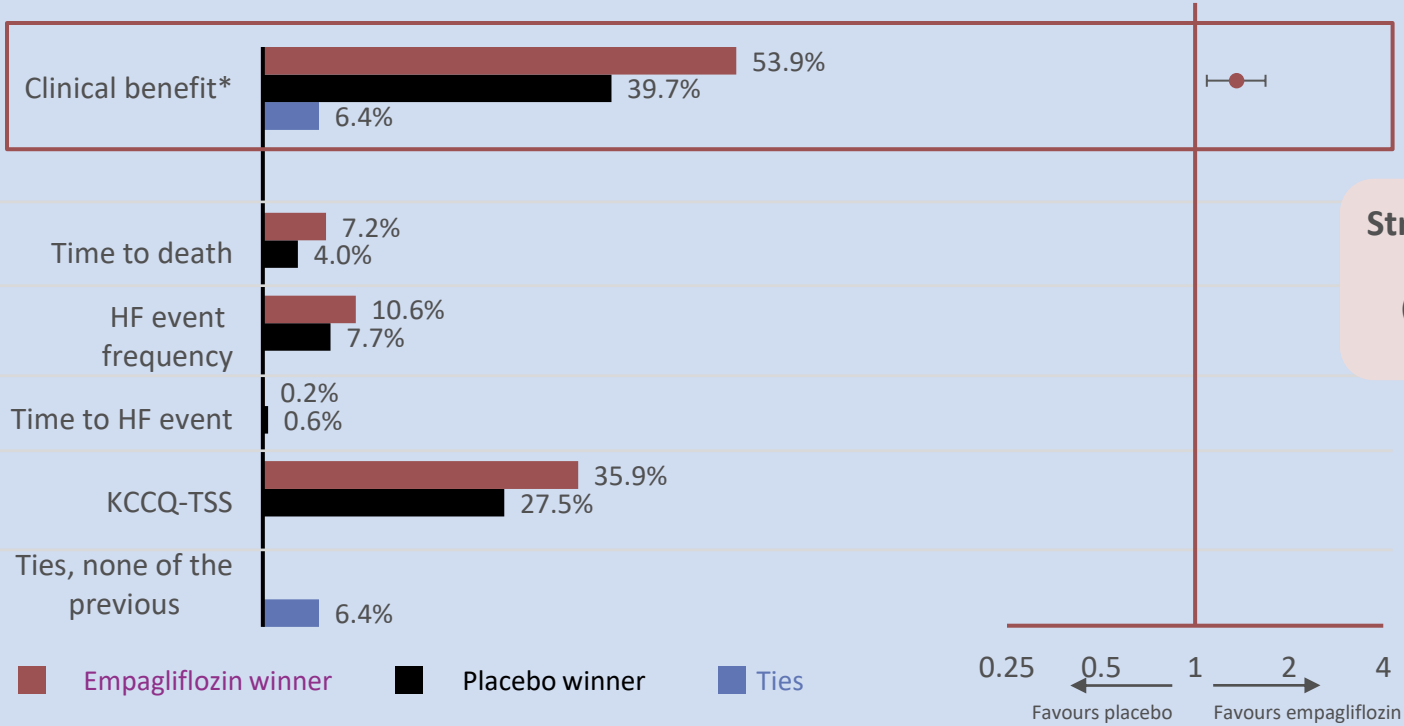
Primary endpoint

- **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

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. 2021;XX:XXX.[please update when available]

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



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

Empagliflozin: Superior in 53.9% of comparisons

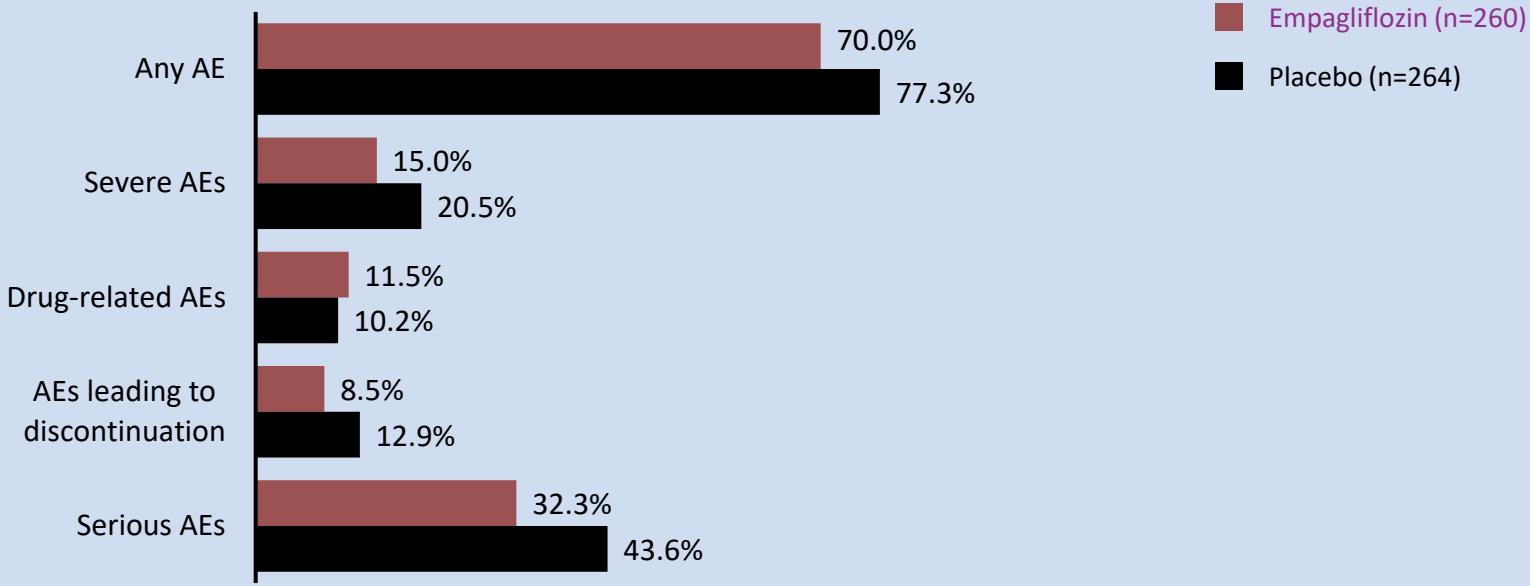
Placebo: Superior in 39.7% of comparisons

Numbers reflect percentage of comparisons. For the components of the win ratio these numbers do not reflect randomized comparisons. *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. CI, confidence interval; HF, heart failure; HFE, heart failure event; HHF, hospitalization for heart failure; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score. Voors AA et al. 2021;XX:XXX.[please update when available]

EMPULSE primary endpoint subgroup analysis

- The clinical benefits were consistent, regardless of whether patients presented with de novo or decompensated chronic HF
- The clinical benefits were independent of LVEF (including patients with HFrEF or HFpEF)

EMPULSE: Summary of adverse events (Safety outcome)



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. 2021;XX:XXX.[please update when available]

EMPULSE: Conclusions

Patients hospitalized for acute HF treated with empagliflozin were 36% more likely to experience a clinical benefit* versus patients on placebo

The clinical benefits were consistent in patients with HFrEF or HFpEF, and in patients with de novo or decompensated chronic heart failure

Empagliflozin was well tolerated, with overall safety data consistent with previous studies

*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; HHF, hospitalization for heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score.

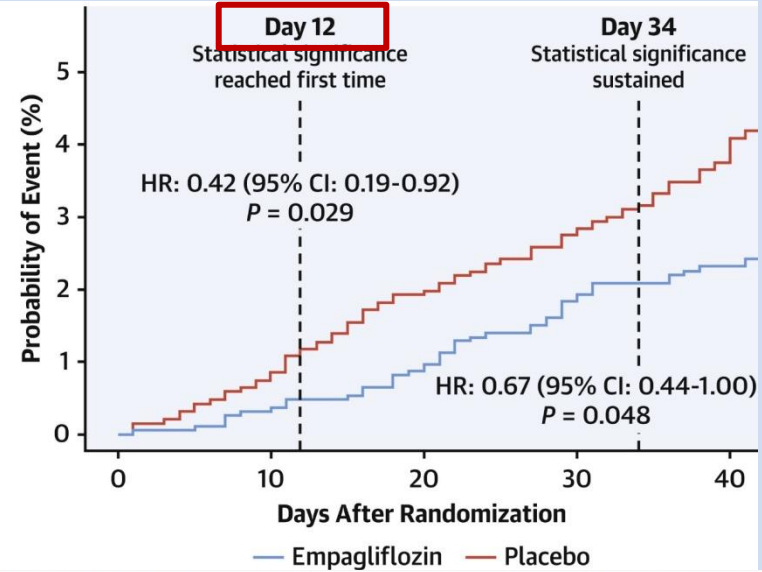
Voors AA et al. 2021;XX:XXX.[please update when available]

Early benefits with empagliflozin were observed in both EMPEROR-Reduced and EMPEROR-Preserved

ACROSS HF

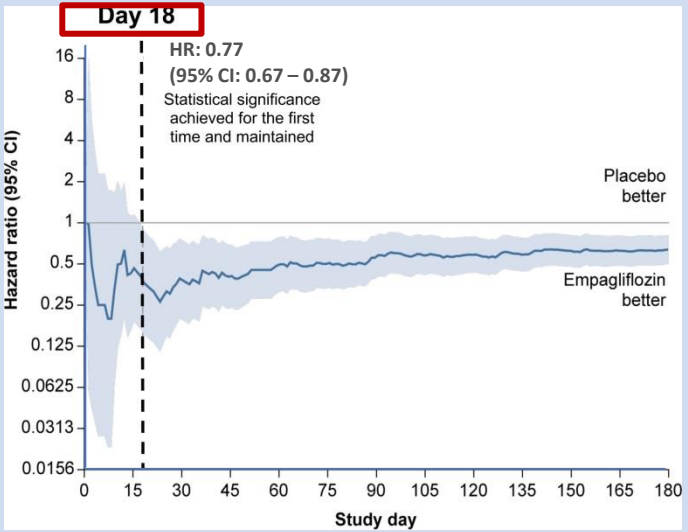
EMPEROR-Reduced

Combined risk of death, HHF or an emergent/urgent heart failure visit requiring intravenous treatment



EMPEROR-Preserved

Combined risk of CV death, HHF or an emergent/urgent heart failure visit requiring intravenous treatment

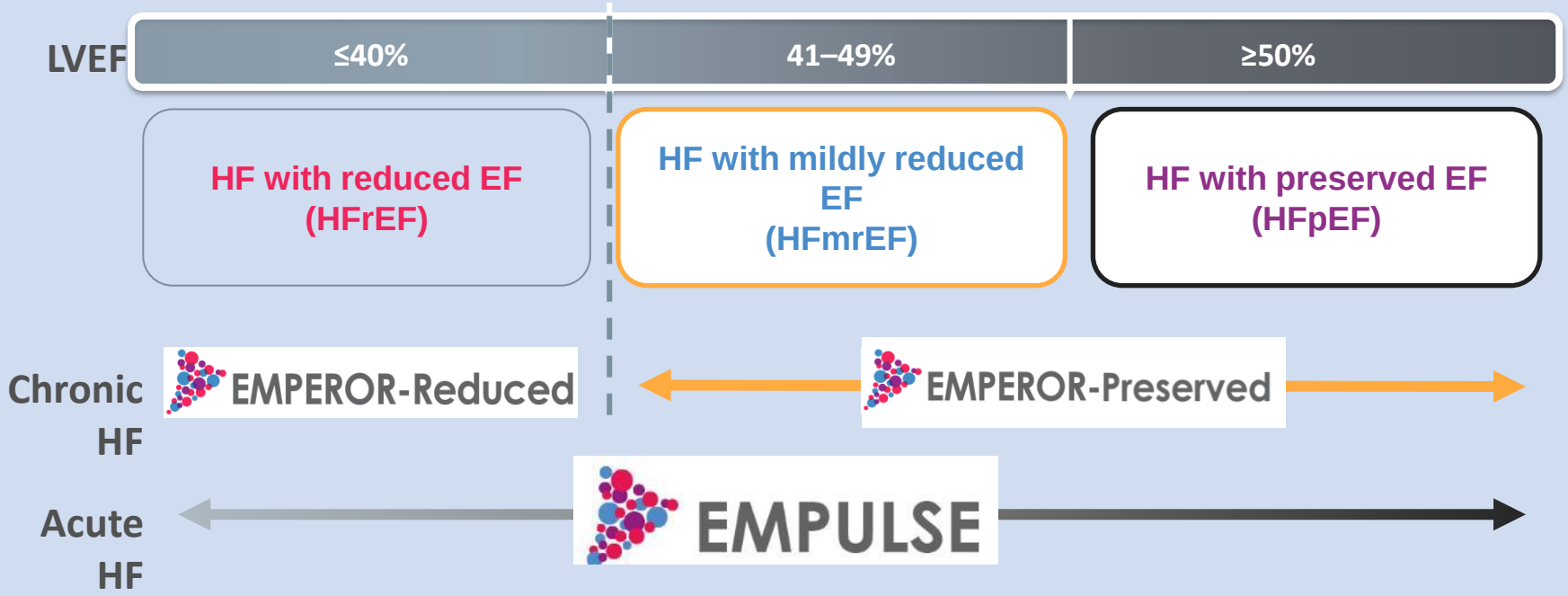


Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[108,109]	I	A

CV, cardiovascular; HHF, hospitalization for heart failure.

1. Packer M *et al. Circulation.* 2021;143:326; 2. Packer M *et al. Circulation*. 2021; doi:10.1161/CIRCULATIONAHA.121.056824.

Empagliflozin across a broad range of patients with heart failure, regardless of ejection fraction

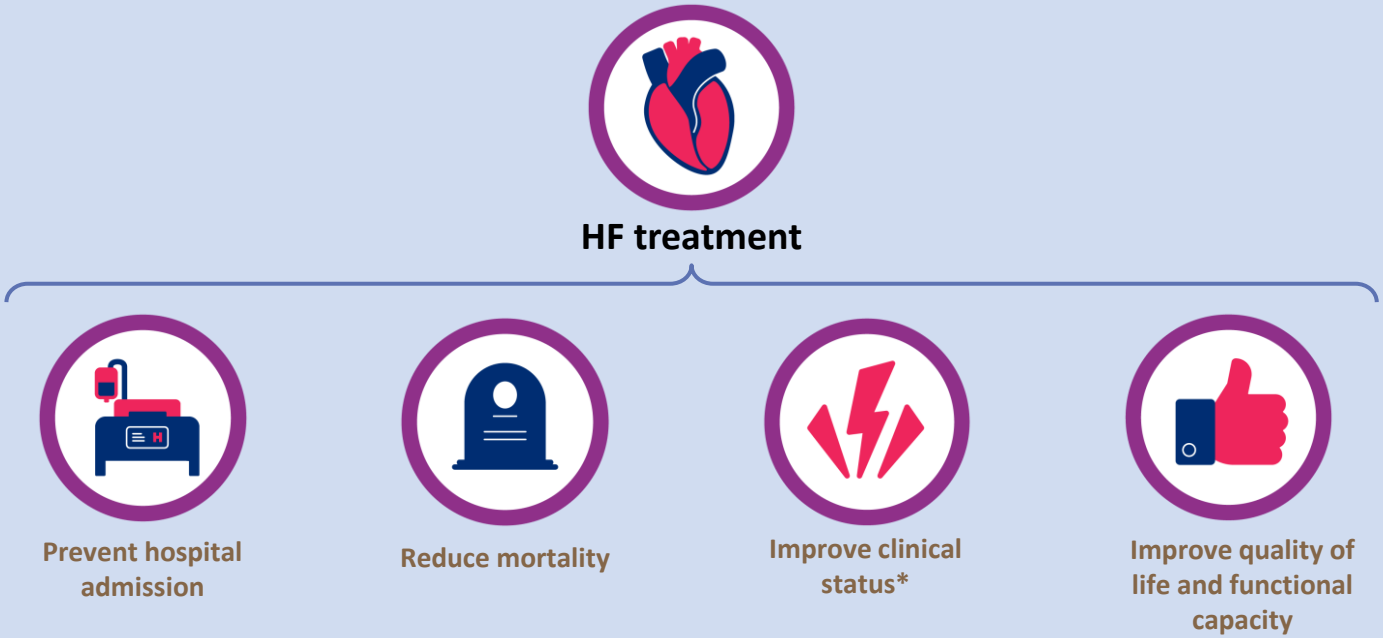


EF, ejection fraction; HF, heart failure; LVEF, left ventricular ejection fraction.

1. Packer M, et al. N Engl J Med. DOI: 10.1056/NEJMoa2022190; 2. Anker S *et al. N Engl J Med.* 2021; DOI: 10.1056/NEJMoa210703

What are the treatment goals for Heart Failure and what is the role of SGLT2 inhibitors?

Treatment of patients with Heart Failure 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]

1. Ponikowski P *et al. Eur J Heart Fail*. 2016;18:891; 2. Yancy CW *et al. J Am Coll Cardiol.* 2017;70:776.

ESC, CCS/CHFS and AHA/ACC/HFSA Guidelines: SGLT2 inhibitors are considered a foundational treatment in HFrEF[1–3]

HFrEF treatment

Foundational therapy

RAAS inhibitors	Beta blockers	MRAs	SGLT2 inhibitors

ACC, American College of Cardiology; AHA, American Heart Association; CCS, Canadian Cardiovascular Society; CHFS, Canadian Heart Failure Society; ESC, European Society of Cardiology; HFrEF, heart failure with reduced ejection fraction; HFSA, Heart Failure Society of America; MRA, mineralocorticoid receptor antagonist; RAAS, renin-angiotensin-aldosterone system; 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.

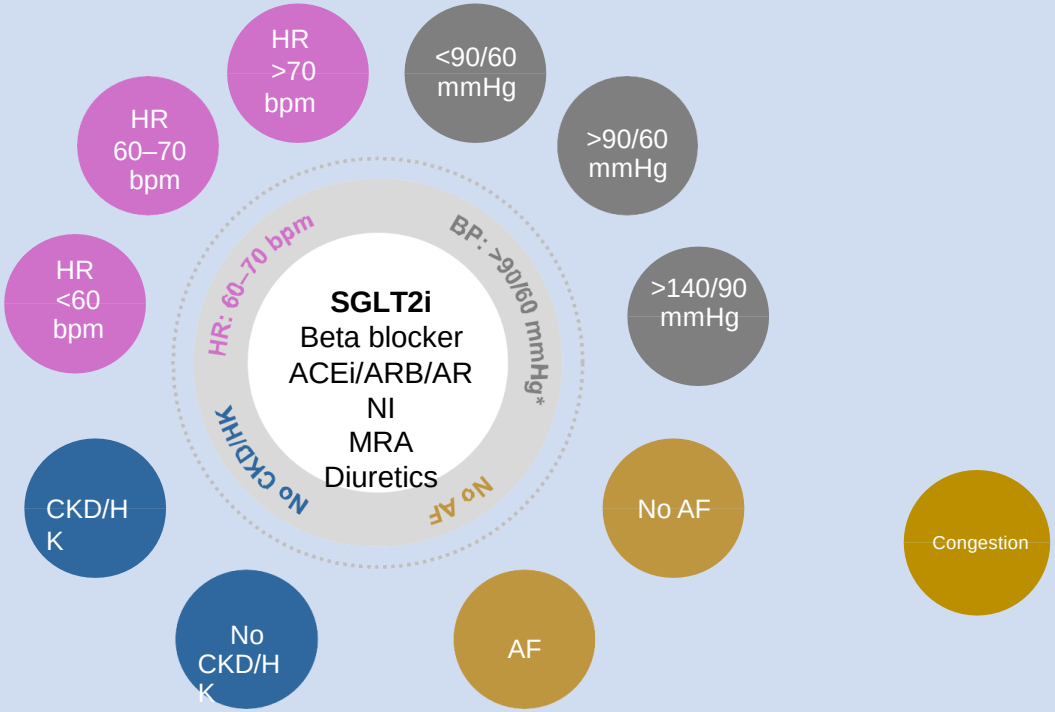
The HFA-ESC consensus document highlights key characteristics that should be considered in the management of HFrEF

ESC European Society of Cardiology
European Journal of Heart Failure (2021) 23, 872–881
doi:10.1002/ejhf.2206
POSITION PAPER

Patient profiling in heart failure for tailoring medical therapy. A consensus document of the Heart Failure Association of the European Society of Cardiology

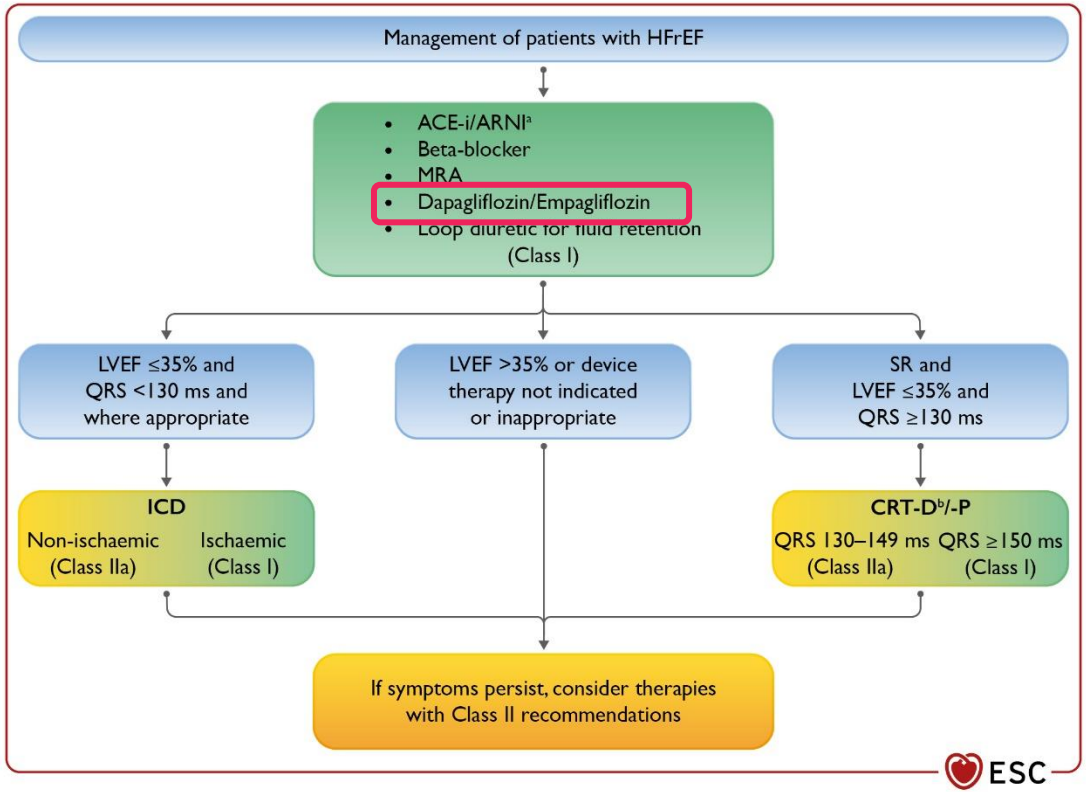
1. Clinical profile
2. Co-morbidities
3. Baseline cardiovascular risk

The HFA-ESC consensus document recommends **maintaining SGLT2i** across all phenotypes listed



*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; HFA- ESC, Heart Failure Association of the European Society of Cardiology; HFrEF, heart failure with reduced ejection fraction; HK, hyperkalaemia; HR, heart rate; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose co- transporter-2 inhibitor.

Rosano GMC *et al. Eur J Heart Fail.* 2021;23:872.

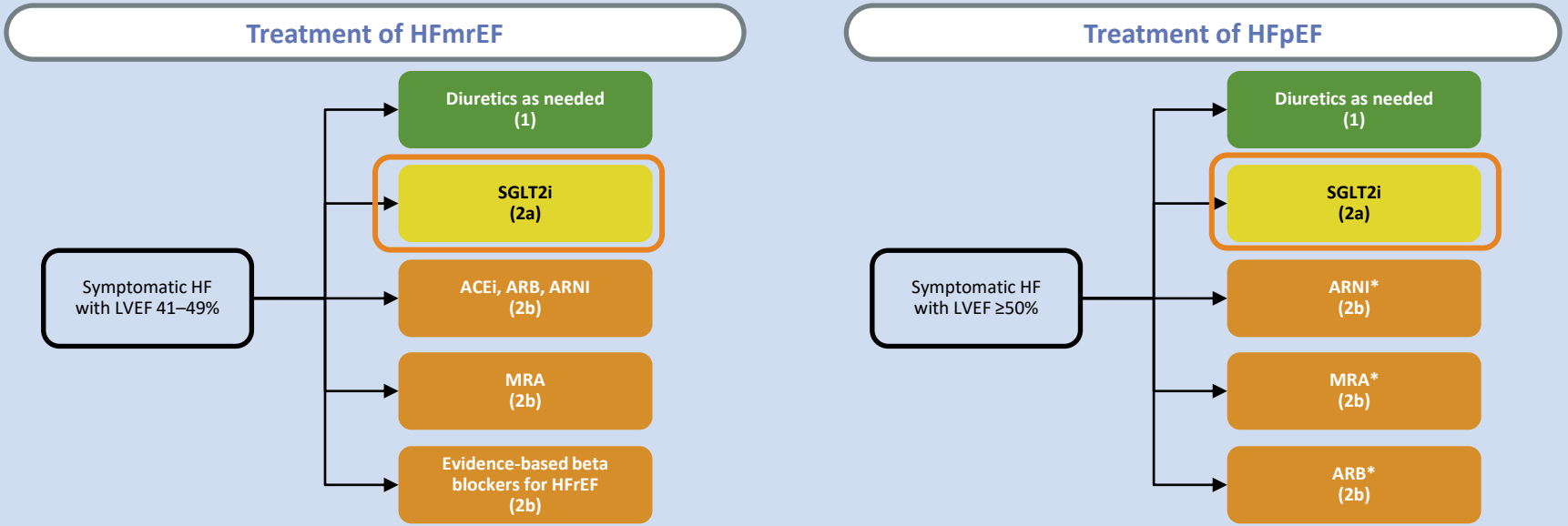


Therapeutic algorithm of Class I Therapy Indications for a patient with heart failure with reduced ejection fraction

ACE-I = angiotensin-converting enzyme inhibitor; ARNI = angiotensin receptor-neprilysin inhibitor; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy with pacemaker; ICD = implantable cardioverter-defibrillator; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist; QRS = Q, R, and S waves (on a 12-lead electrocardiogram); SR = sinus rhythm.
[a]As a replacement for ACE-I.
[b]Where appropriate. Class I=green. Class IIa=Yellow.

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure
(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab368)

AHA/ACC/HFSA Guidelines:[1] SGLT2 inhibitors "can be beneficial" in decreasing hospitalizations and CV mortality in HFmrEF and HFpEF



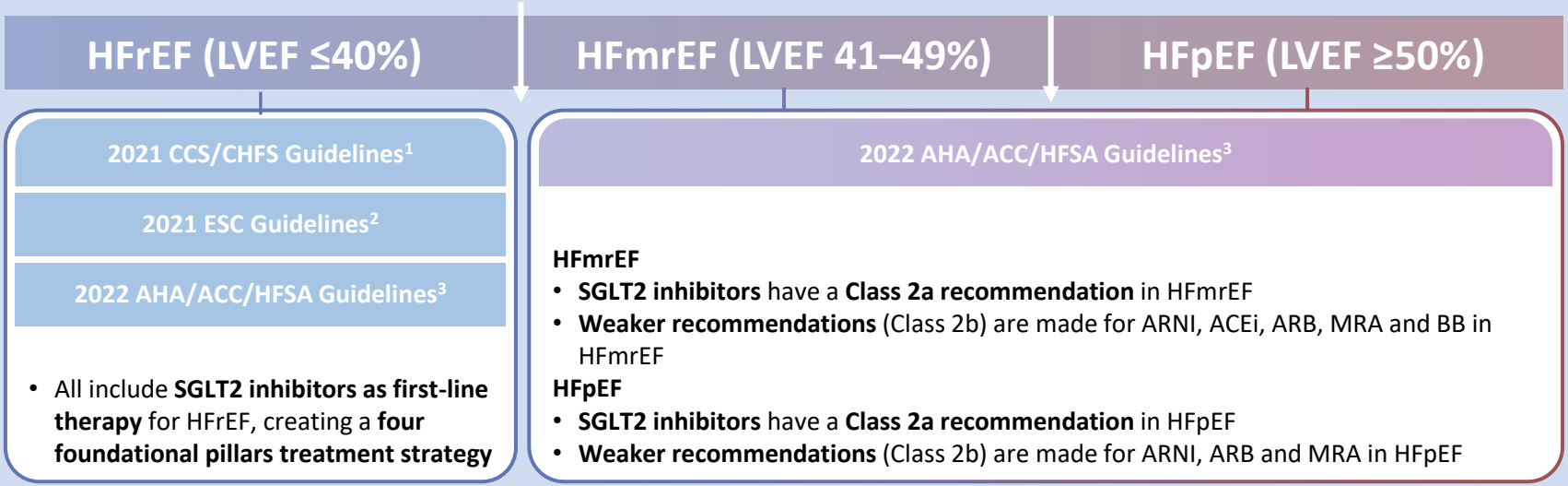
The CCS/CHFS[2] and ESC Guidelines[3] do not include guidance on the use of SGLT2 inhibitors in HFmrEF and HFpEF as they were published before the disclosure of EMPEROR-Preserved

*Greater benefit in patients with LVEF closer to 50%..

1. Heidenreich PA *et al. J Am Coll Cardiol.* 2022; doi:10.1016/j.jacc.2021.12.012; 2. McDonald M *et al. Can J Cardiol.* 2021;37:531; 3. McDonagh TA *et al. Eur Heart J.* 2021;42:3599.

Recommendations for SGLT2 inhibitors in HF: Overview

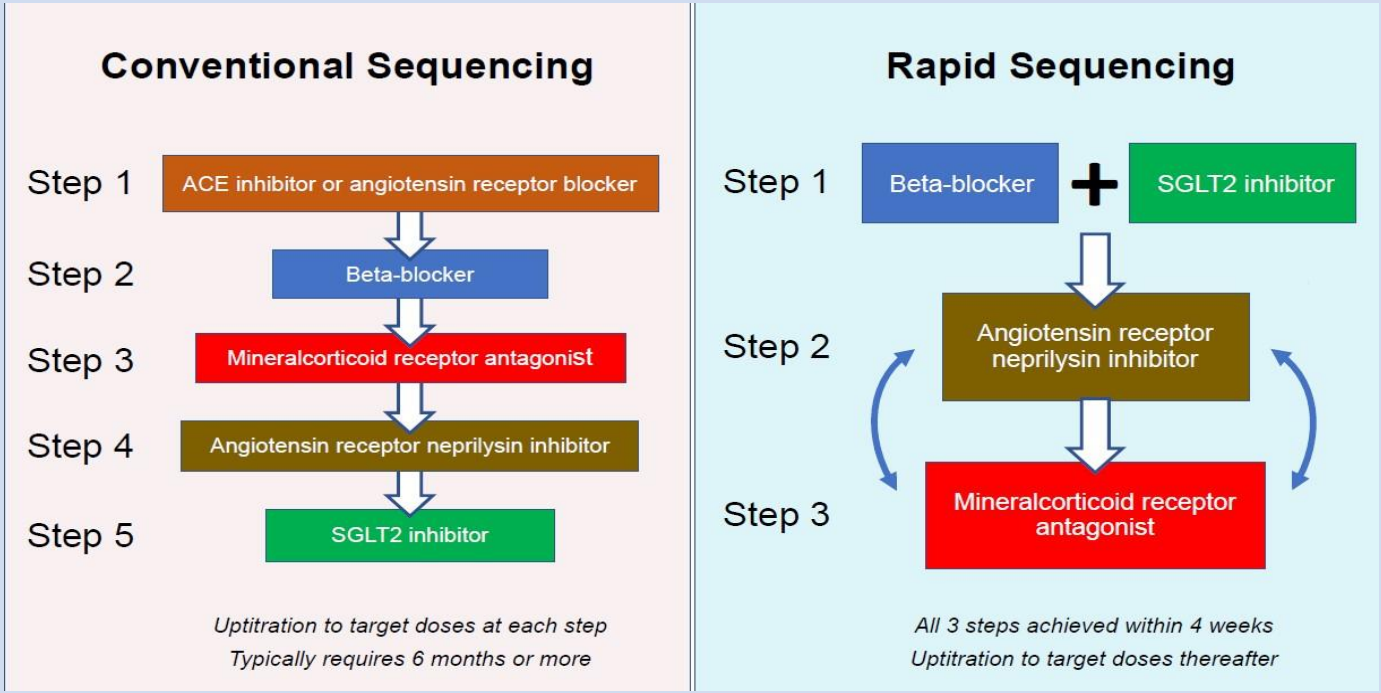
- Only the AHA/ACC/HFSA Guidelines were published AFTER disclosure of the EMPEROR-Preserved trial



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; 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.

Novel Sequencing Strategies – Dual Start



Eur J Heart Fail. 2021 Mar 11. doi: 10.1002/ejhf.2149

Conclusion

- **SGLT2 inhibitors were developed as anti-diabetic agents but cumulating evidence has shown their beneficial effects on CV system.**
- **Therapeutic spectrum of SGLT2i are extended to non-diabetic patients since CV benefits are independent of glycemic control.**
- **Extensive clinical studies demonstrated that SGLT2i reduced the risk of CV death & hospitalization for HF in broad range of patients with HF.**
- **This was supported that their role as a foundational Rx for HF irrespective of EF or care setting.**
- **The use of SGLT2i is also safe in patients with CKD.**

Thank You