SGLT2 inhibitors: the panacea for heart failure

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Declaration for Dushen Tharmaratnam

I have the following financial interest or relationship/s to disclose with regard to the subject matter of this presentation:

Consulting fees/speaker fees: Astra Zeneca

Research contracts: nil

Clinical trial steering committee: nil

Owner/stockholder of healthcare company/ies: nil

Other: nil

Structure of talk

Background to the use of SGLT2 inhibitors in heart failure

Current NICE/guideline recommendations for use of SGLT2 inhibitors in various types of heart failure

- Evidence base for usage in HFrEF (Heart Failure with Reduced Ejection Fraction)
- Evidence base for usage in HFmrREF (Heart Failure with Mid-range Ejection Fraction)
- Evidence base for usage in HFpEF (Heart Failure with Preserved Ejection Fraction)

The inter-related conditions of diabetes, heart failure and chronic kidney disease (CKD)

Conclusions

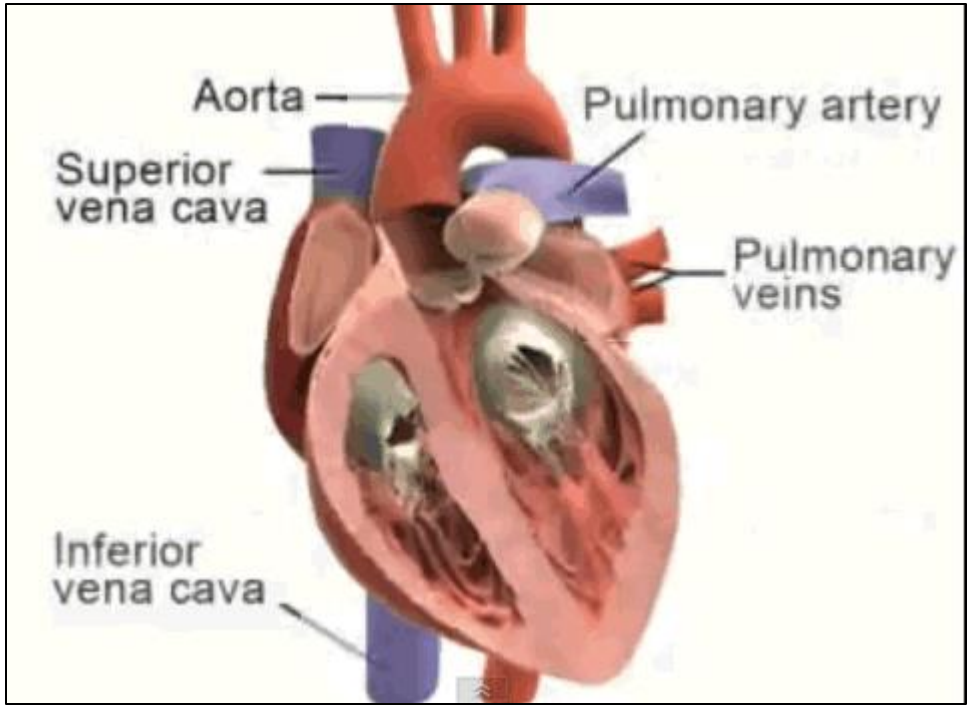
Background to the use of SGLT2 inhibitors in heart failure

Will be talking about Dapagliflozin and Empagliflozin as relevant to heart failure, in their chronological trial order

Will not be talking about Sotagliflozin, which in May 2023, became the third SGLT2 inhibitor to be approved by the U.S. Food and Drug Administration (FDA) for the treatment of HF, but

- Is not licensed in the UK for HF
- Is a combined SGLT1/SGLT2 inhibitor

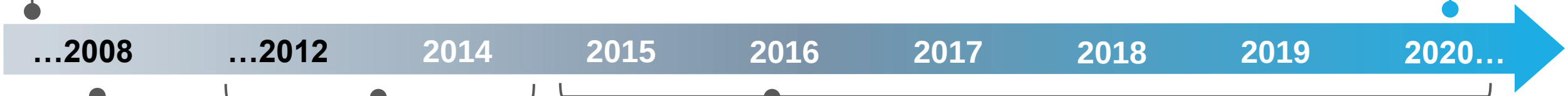
Will not be talking about Canagliflozin or Ertugliflozin- not licensed in HF



SGLT2 inhibitors have been established in type 2 diabetes since 2012[1,2]

Dapagliflozin is the first licensed SGLT2 inhibitor for HFrEF patients with or without T2D[2]

Concerns of CV risk for previous generation anti-hyperglycaemic treatments[3,4]



EMA & FDA mandate safety trials for all newer anti-hyperglycaemic treatments in diabetes patients, to demonstrate **safety from a CV perspective[3]**

Launch of 3 SGLT2 inhibitors (dapagliflozin, empagliflozin, canagliflozin), initially **developed to improve glycaemic control in T2D[1]**

- **Landmark CVOTs for SGLT2 inhibitors** completed in patients with T2D – DECLARE-TIMI-58, EMPA-REG OUTCOME, CANVAS-Program, VERTIS CV[5-8]
- Unexpectedly demonstrated CV benefits, including reduction in the risk of hHF[3,5-7]

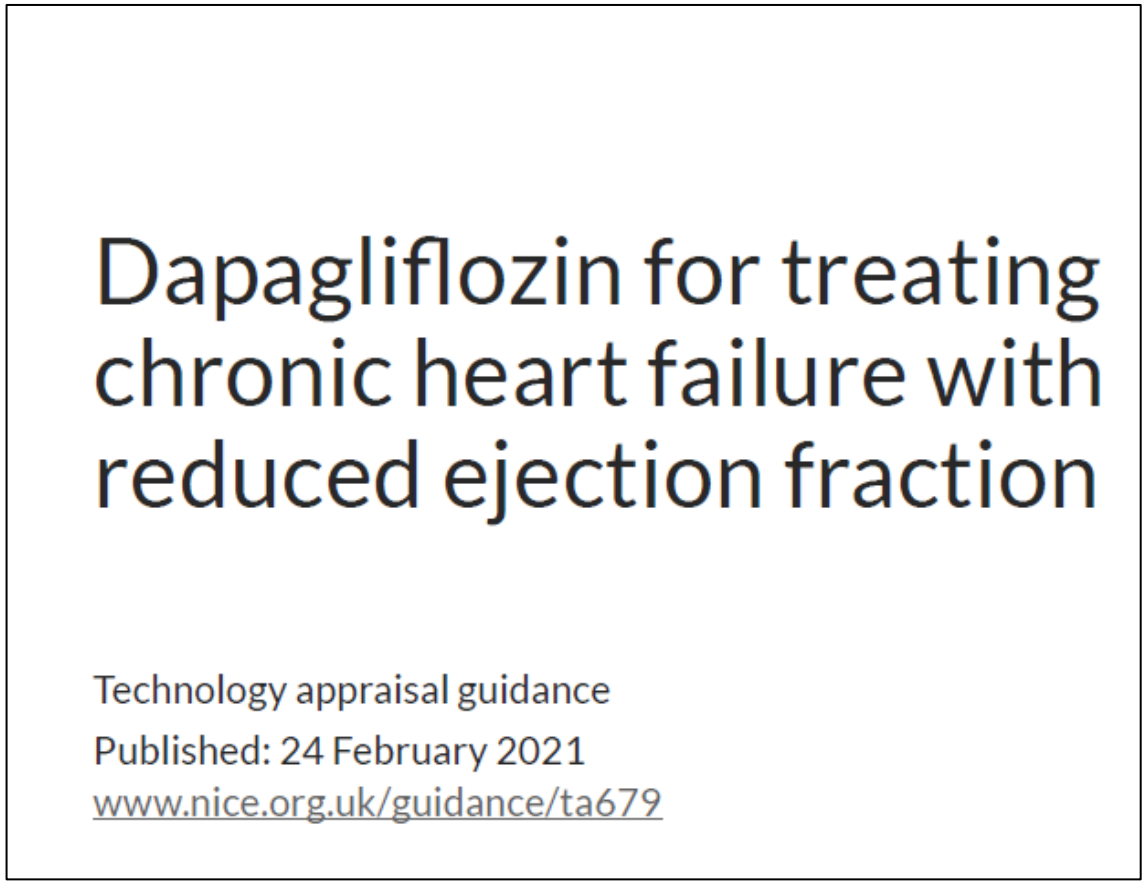
Results varied for each CVOT due to different trial designs and patient populations[5-7]

Results led to further clinical trials for SGLT2 inhibitors in the **treatment of heart failure <u>with and without</u> T2D, including the landmark trial published in Nov 2019: DAPA-HF[3,9]**

CV, cardiovascular; CVOT, cardiovascular outcomes trials; CVRM, cardio-renal-metabolic; EMA, European Medicines Agency; FDA, Food and Drug Administration; SGLT2, sodium-glucose co-transporter-2; T2D, type 2 diabetes.

References: 1. Choi, C. Molecules. 2016; 21:1136. 2. Forxiga 10mg film-coated tablets. Summary of Product Characteristics. November 2020. 3. Cowie MR & Fisher M. Nat Rev Cardiol. 2020. [Epub ahead of print]. 4. Nissen SE. Eur Heart J. 2010;31:773-776. 5. Zinman B et al. N Engl J Med. 2015;373:2117-2128. 6. Neal B, et al. N Engl J Med. 2017;377:644-657. 7. Wiviott SD, et al. 2019;380:347-357. 8. Cannon CP, et al. Am Heart J. 2018;206:11-23. 9. McMurray JJV et al. N Engl J Med. 2019;381:1995-2008.

Which led to the first NICE TA in HFrEF for SGLT2 inhibitors:



NICE has recommended dapagliflozin as an option for treating chronic symptomatic heart failure (HFrEF)[1]

Dapagliflozin is recommended as an option for treating symptomatic chronic heart failure with reduced ejection fraction in adults, only if it is used as an add-on to optimised standard care with:

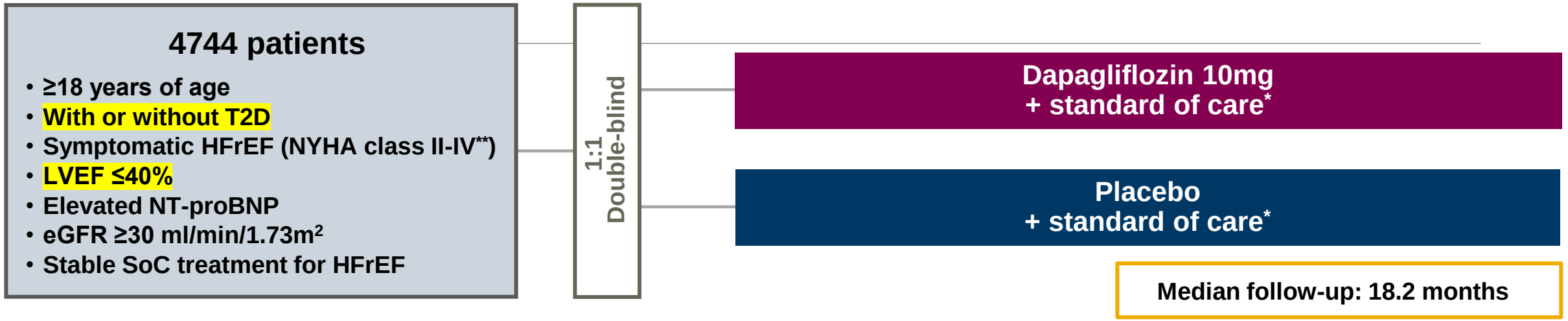
- **ACE inhibitors or ARBs, with beta blockers, and, if tolerated, MRAs, or**
- **Sacubitril valsartan, with beta blockers, and, if tolerated, MRAs**

Start treatment of symptomatic heart failure with reduced ejection fraction with dapagliflozin on the advice of a heart failure specialist.
Monitoring should be done by the most appropriate HCP

ACE: angiotensin-converting enzyme; ARB, angiotensin-2 receptor blockers; HCP, healthcare professional; MRA, mineralocorticoid receptor antagonist; NICE, National Institute for Health and Care Excellence; TAG, Technology Appraisal Guidance.

1. NICE Technology Appraisal Guidance: TA679 (24th February 2021). Dapagliflozin for treating heart failure with reduced ejection fraction. Publication date: February 2021. Available from: https://www.nice.org.uk/guidance/ta679. Last accessed March 2021.

DAPA-HF trial– assessed dapagliflozin in HFrEF patients with or without T2D[1,2]



Primary endpoint

- **Composite: CV death or worsening HF** (defined as hHF or urgent HF visit)

Secondary endpoints

- Time to first occurrence of either of the components of the composite: **CV death or hHF**
- Total number of **(first and recurrent) hHF and CV death**
- Change from baseline measured at 8 months in the **total symptom score of the KCCQ**
- Time to first occurrence of any of the components of the composite: **≥50% sustained decline in eGFR or reaching ESRD or renal death**
- Time to **death from any cause**

*Patients were treated according to regional standard of care for HF. Dose reduction or discontinuation of standard of care therapy was discouraged unless all other measures failed. Changes in standard of care medications was at the discretion of the investigator. **Experience with dapagliflozin in NYHA class IV is limited.

CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; hHF, hospitalisation for heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; SoC, standard of care; T2D, type 2 diabetes.

References: 1. McMurray JJV, et al. N Engl J Med. 2019;381:1995-2008. 2. McMurray JJV, et al. Eur J Heart Fail. 2019;21:665-675.

Patient baseline characteristics[1]

Characteristic	Dapagliflozin (n=2373)	Placebo (n=2371)
Mean age (years)	66	67
Sex; male	76%	77%
Race; White: Asian: Black: Other:	70% 23% 5% 2%	71% 24% 4% 1%
Body mass index (kg/m²)	28	28
Mean eGFR (mL/min/1.73m²) Rate of <60 mL/min/1.73m²	66 41%	66 41%
NYHA; II: III: IV:	68% 32% 1%	67% 32% 1%

Characteristic	Dapagliflozin (n=2373)	Placebo (n=2371)
Mean LVEF	31%	31%
Median NT-proBNP (pg/ml)	1428	1446
Medical history; Hospitalisation for HF: Atrial Fibrillation: T2D: New diagnosis of T2D*:	 47% 39% 42% 3%	 48% 38% 42%
Principal cause of HF; Ischaemic: Non-ischaemic: Unknown:	 56% 36% 8%	 57% 35% 8%

*3% of patients had previously undiagnosed diabetes, which was defined as a glycated haemoglobin level of ≥48 mmol/mol, measured at both screening and randomisation.

eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; T2D, type 2 diabetes.

Reference: 1. McMurray JJV, et al. N Engl J Med. 2019; 381:1995-2008.

Concomitant background treatments for patients in DAPA-HF[1,2]

HF medication	% of patients on treatment	
	Dapagliflozin (n=2373)	Placebo (n=2371)
Diuretic	93%	94%
BB	96%	96%
ACEi	56%	56%
ARB	28%	27%
MRA	72%	71%
ARNI (sacubitril-valsartan)	11%	11%
Digitalis	19%	19%
Glucose-lowering medication*		
Biguanide	51%	52%
Sulfonylurea	23%	21%
DPP4i	16%	15%
GLP-1 RA	1%	1%
Insulin	28%	27%

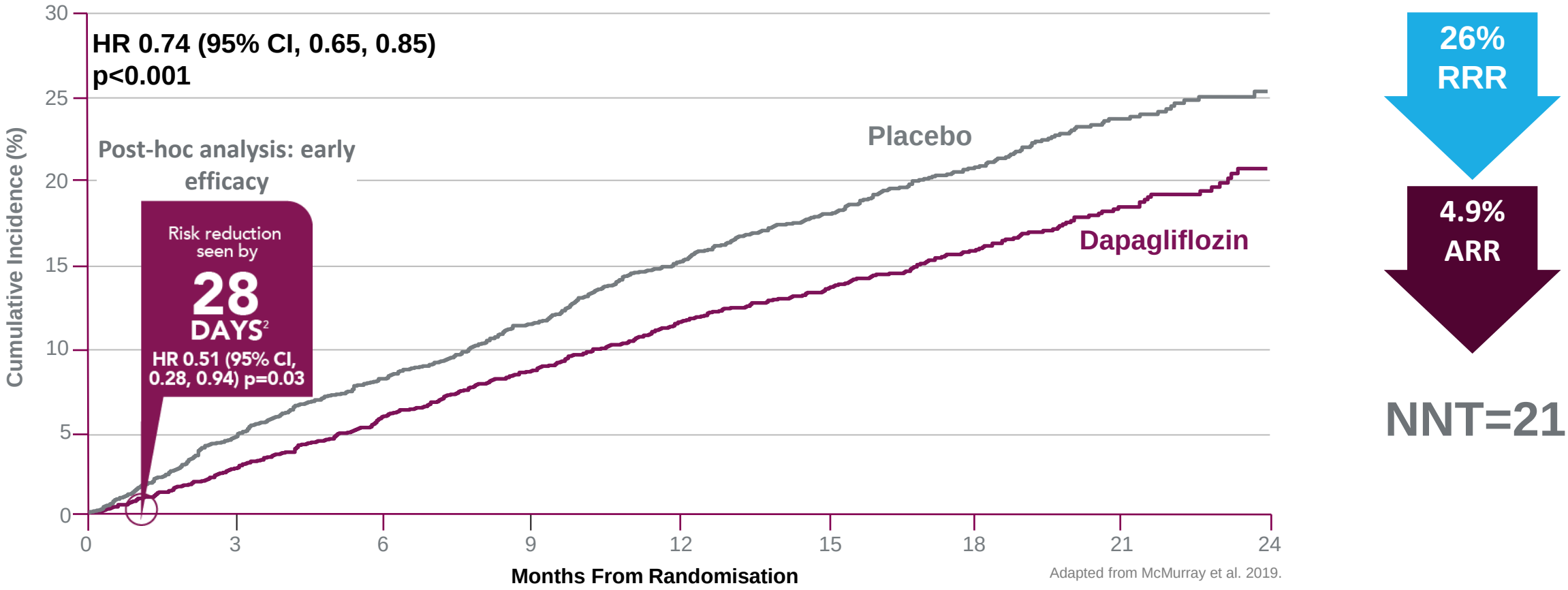
*Glucose-lowering medications are listed only for the patients who had a history of diabetes at baseline.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BB, beta blocker; DPP4i, dipeptidyl peptidase 4 inhibitor; GLP1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; MRA, mineralocorticoid receptor antagonist.

References: 1. McMurray JJV, et al. N Engl J Med. 2019;381:1995-2008. 2. Docherty KF, et al. Eur Heart J. 2020;41:2379-2392.

On top of standard of care, dapagliflozin 10mg reduces the risk of CV death or worsening HF[1*]

Primary endpoint: composite of CV death or worsening HF[1,2*]



Adapted from McMurray et al. 2019.

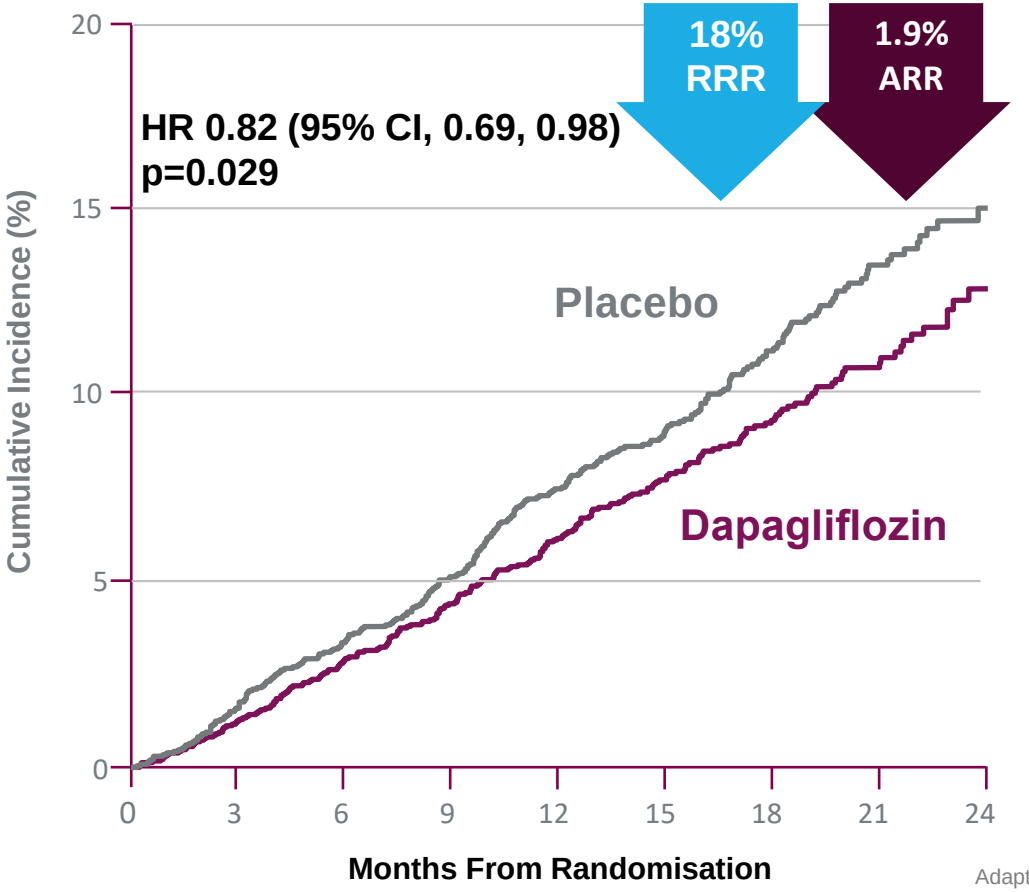
*Worsening HF is defined as hHF or urgent HF visit requiring IV therapy.

ARR, absolute risk reduction; CI, confidence interval; CV, cardiovascular; HF, heart failure; hHF, hospitalisation for heart failure; HR, hazard ratio; IV, intravenous; NNT, number needed to treat; RRR, relative risk reduction.

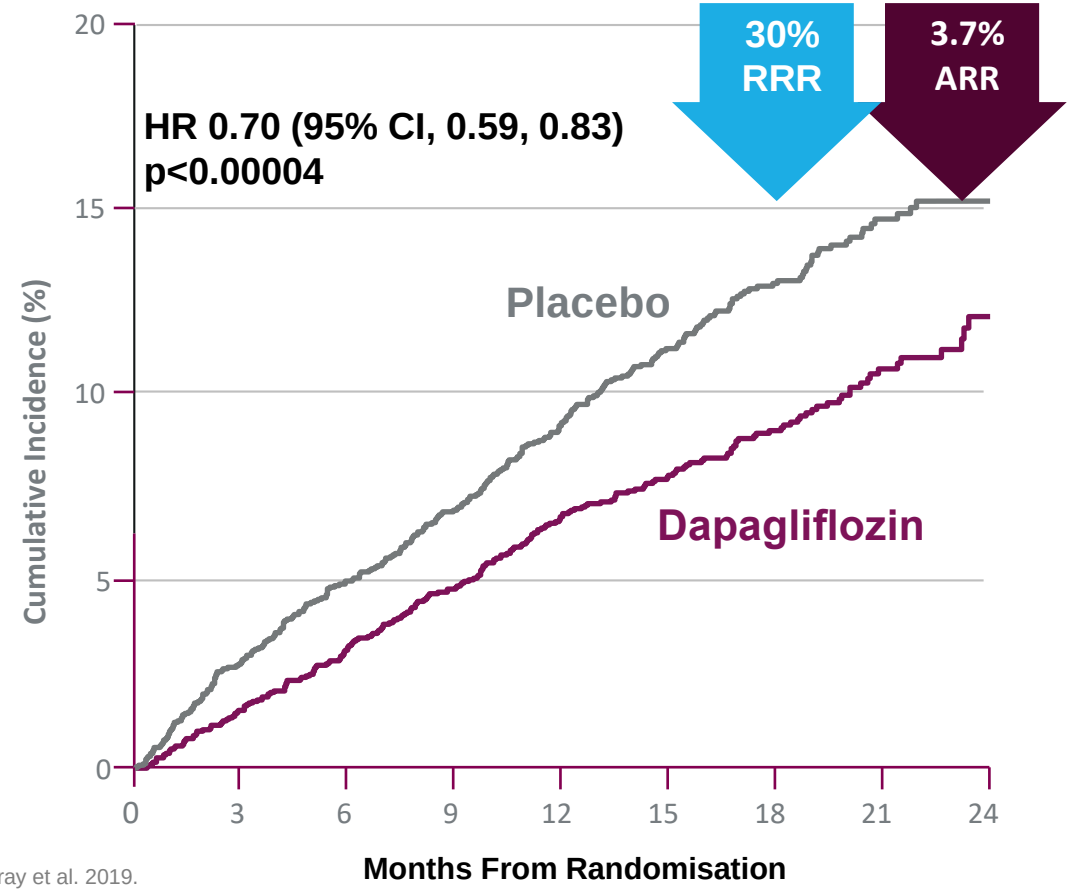
References: 1. McMurray JJV et al. N Engl J Med. 2019;381:1995-2008. 2. Sabatine MS et al. Presented at: AHA Scientific Sessions; November 16-18, 2019; Philadelphia, PA.

On top of standard of care, dapagliflozin 10mg achieved a statistically significant reduction in each component of the primary endpoint[1]

CV death[1,2]



Worsening HF[1,2*]



Adapted from McMurray et al. 2019.

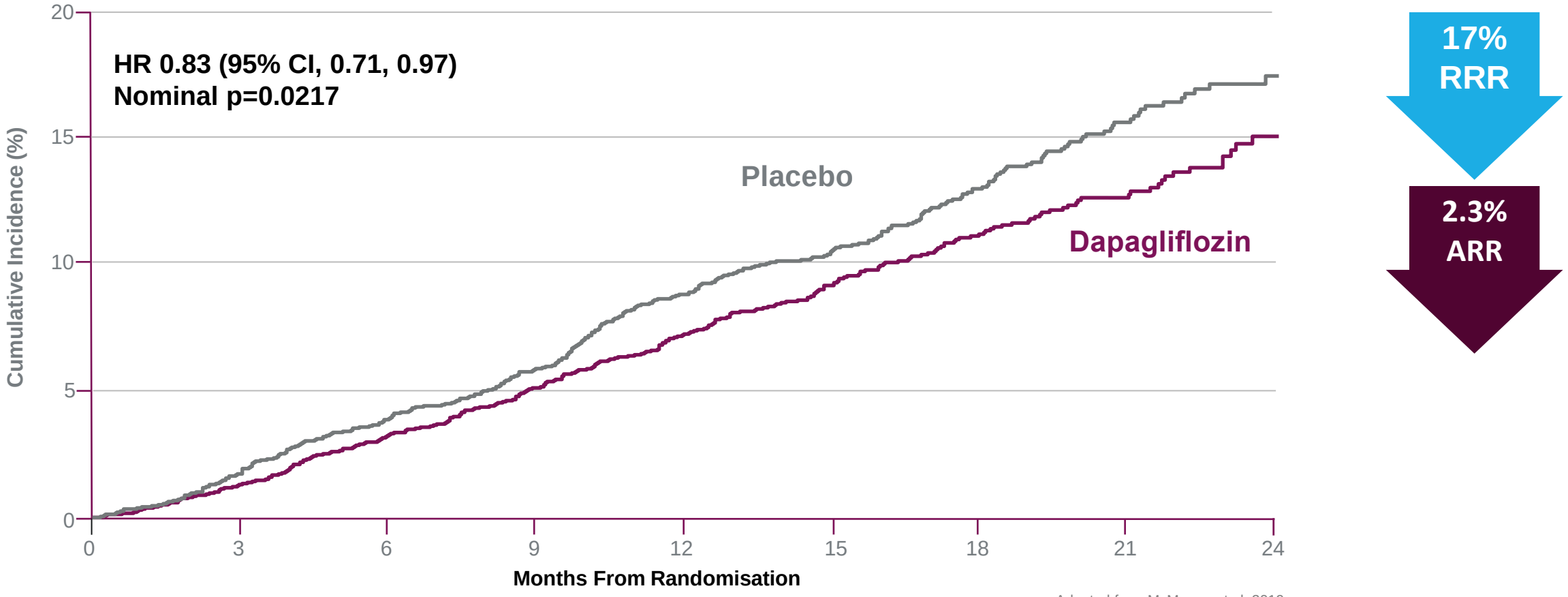
*Worsening HF is defined as hHF or urgent HF visit requiring IV therapy.

ARR, absolute risk reduction; CI, confidence interval; CV, cardiovascular; HF, heart failure; hHF, hospitalisation for heart failure; HR, hazard ratio; IV, intravenous; RRR, relative risk reduction.

References: 1. McMurray JJV et al. N Engl J Med. 2019;381:1995-2008. 2. McMurray J. Presented at: ESC Congress; August 31-September 4, 2019; Paris, France.

On top of standard of care, dapagliflozin 10mg reduces the risk of all-cause mortality[1*]

Secondary endpoint: all-cause mortality[1,2*]



Adapted from McMurray et al. 2019.

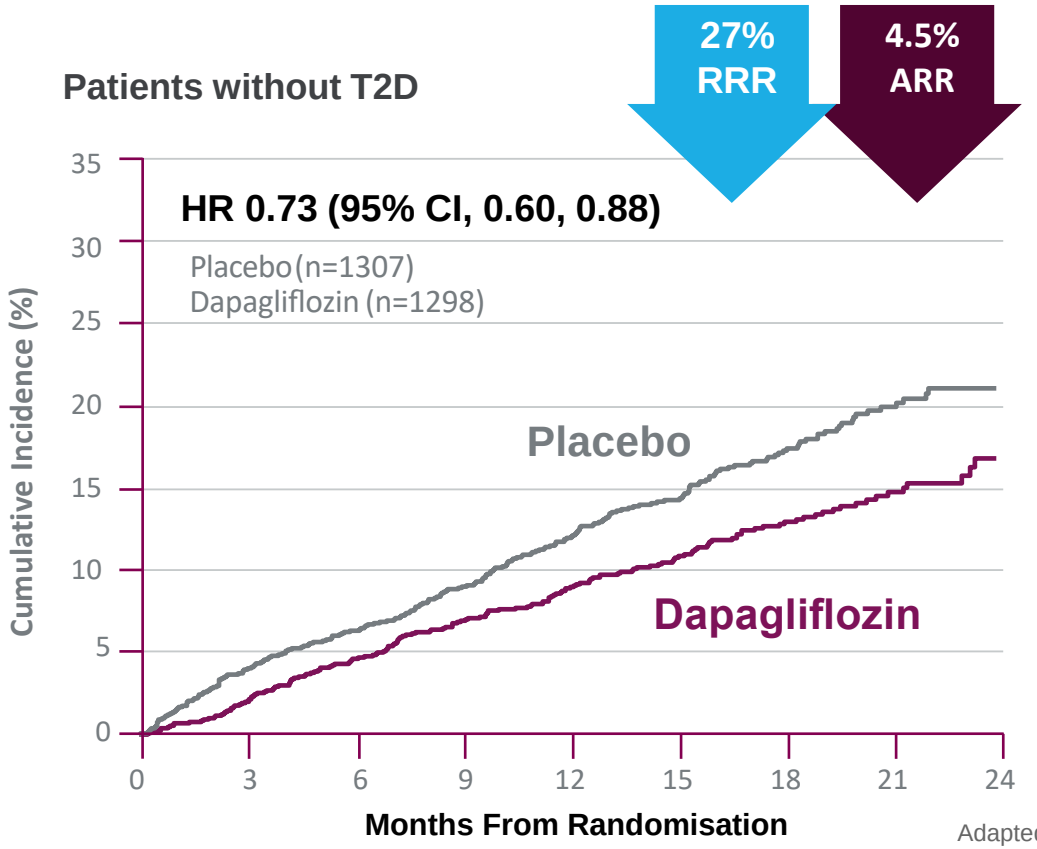
ARR, absolute risk reduction; CI, confidence interval; HR, hazard ratio; RRR, relative risk reduction.

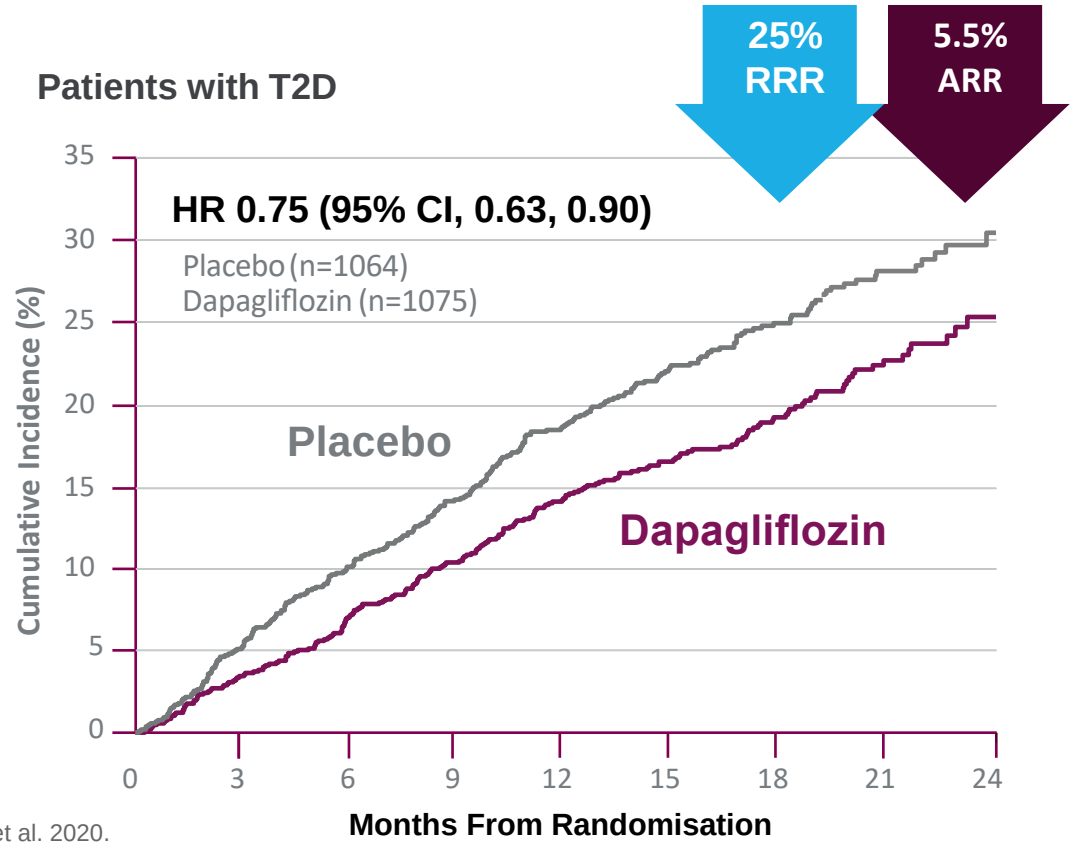
*Due to the hierarchical testing strategy, all-cause mortality was nominally significant.

References: 1. McMurray JJV et al. N Engl J Med. 2019;381:1995-2008. 2. Forxiga 10mg film-coated tablets. Summary of Product Characteristics. November 2020.

On top of standard of care, proven efficacy in patients with and without T2D[1,2]

Prespecified subgroup analysis: composite of CV death or worsening HF by diabetes status[1,2*]





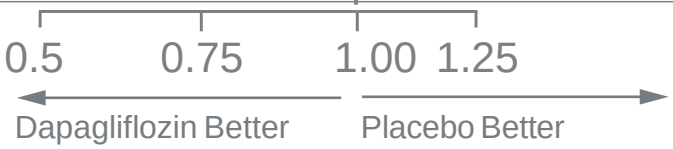
Adapted from Petrie et al. 2020.
Interaction P value: 0.80**

*Worsening HF is defined as hHF or urgent HF visit requiring IV therapy. **A non-significant result for an interaction test can be interpreted as consistency of effect across the subgroup.
ARR, absolute risk reduction; CI, confidence interval; HF, heart failure; hHF, hospitalisation for heart failure; HR, hazard ratio; IV, intravenous; RRR, relative risk reduction; T2D, type 2 diabetes.
References: 1. Petrie MC, et al. JAMA. 2020;323:1353-1368. 2. McMurray JJV et al. N Engl J Med. 2019;381:1995-2008.

On top of standard of care, dapagliflozin 10mg reduces the risk of first and recurrent hHF events[1]

Prespecified secondary analysis

Time-to-first event	HR or RR (95% CI)	*P*-value
Secondary endpoint: CV death or hHF	0.75 (0.65–0.85)	<0.0001
Recurrent events analysis		
CV death or hHF**	0.75 (0.65–0.88)	0.0002
hHF*	0.71 (0.61–0.82)	<0.0001
CV death*	0.81 (0.67–0.98)	0.0282



Adapted from Ponikowski & Jhund, 2020.

*Pre-specified analysis using the Joint Frailty Model. **Analysed by the semi-parametric proportional rates model (Lin-Wei-Yang-Yang method).
CI, confidence interval; CV, cardiovascular; hHF, hospitalisation for heart failure; HR, hazard ratio; RR, rate ratio.
Reference: 1. Ponikowski P & Jhund PS. Presented at: ACC.20/WCC Scientific Sessions; March 28-30, 2020; Virtual Congress.

What is the Kansas City Cardiomyopathy Questionnaire (KCCQ)?

Overview:

- Validated, **self-administered 23-item questionnaire** designed to measure **health status** from the perspective of a patient with HF[1]
- Quantifies symptoms, disease impact on physical and social function, and quality of life over the prior 2 weeks[1]

Interpretation:

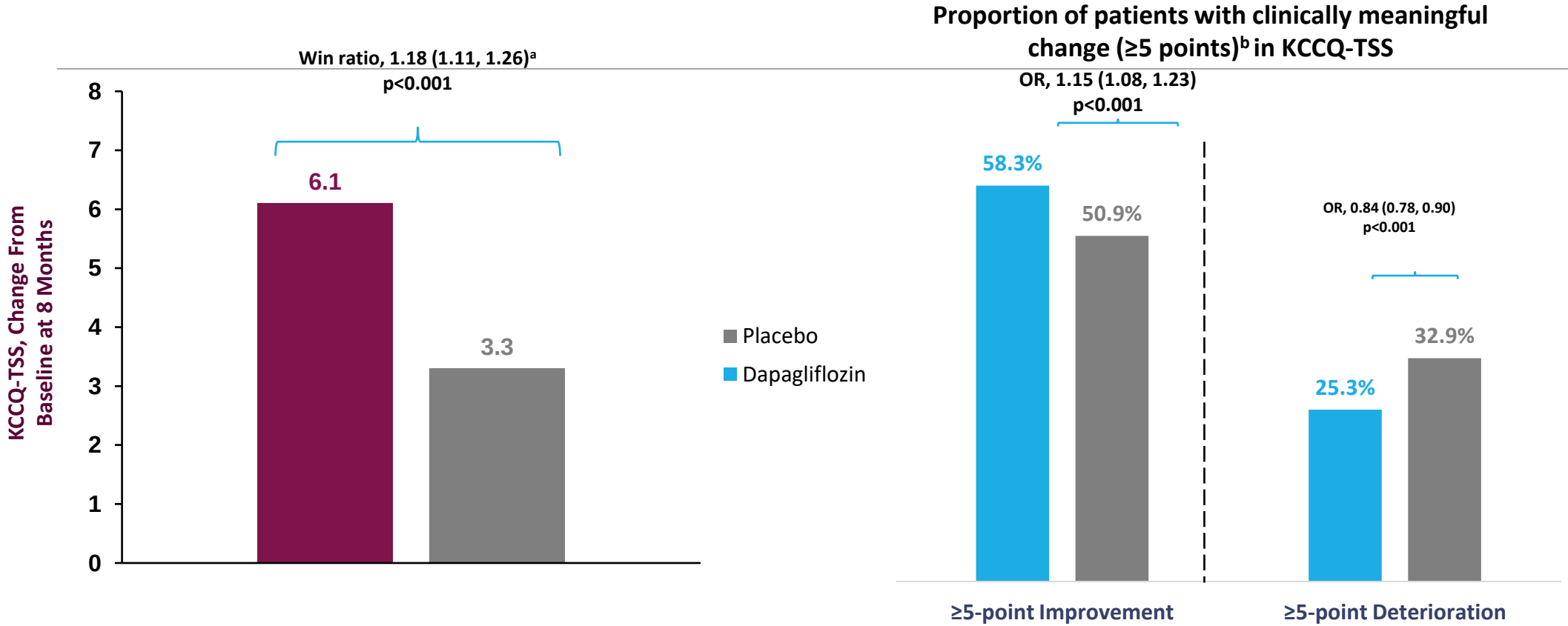
- Scores reported as 0-100 with higher scores reflecting better health status[1]
- A change of **5 or more points on the KCCQ is considered clinically meaningful**[2]

KCCQ, Kansas City Cardiomyopathy Questionnaire; HF, heart failure.

References: 1. Green CP, et al. J Am Coll Cardiol. 2000;35:1245-1255. 2. Kosiborod MN, et al. Circulation. 2020;141:90-99.

In a post-hoc analysis Dapagliflozin 10mg demonstrated a clinically meaningful* improvement in symptoms and quality of life vs. placebo[1]

Quality of life was measured by KCCQ-OSS which was a post hoc analysis



Patients on dapagliflozin were 18% more likely to have symptom benefit (improvement in KCCQ-TSS) compared to placebo

Symptom improvement was more common and deterioration was less common with dapagliflozin

[a]Win ratio >1 indicates superiority of dapagliflozin over placebo; [b]Taking account of death.
KCCQ-TSS = Kansas City Cardiomyopathy Questionnaire Total Symptom Score; OR = odds ratio.
McMurray JJV et al. *N Engl J Med*. 2019;381:1995-2008, Kosiborod MN, et al. Circulation. 2020;141:90-99.

DAPA-HF confirms the well-established safety and tolerability profile of dapagliflozin 10mg[1-3]

Safety profile in DAPA-HF[2,3]	Dapagliflozin (n=2368)	Placebo (n=2368)
AE leading to treatment discontinuation (%)	4.7	4.9
Adverse events of interest (%)		
Volume depletion	7.5	6.8
Renal AE	6.5	7.2
Amputation	0.5	0.5
Major hypoglycaemia	0.2	0.2
Diabetic ketoacidosis	0.1	0.0
Fournier's gangrene	0	<0.1
UTI (%, collected as SAE)	0.5	0.7

The overall safety profile of dapagliflozin in patients with HF was consistent with the known safety profile of dapagliflozin.[1]

Increased risk of mild genital infections (0.3% vs 0%) – counsel patients on risk, signs/symptoms and appropriate genital hygiene

AE, adverse event; HF, heart failure; SAE, serious adverse event; UTI, urinary tract infection.

References: 1. Forxiga 10mg film-coated tablets. Summary of Product Characteristics. November 2020. 2. McMurray JJV, et al. N Engl J Med. 2019;381:1995-2008. 3. McMurray JJV, et al. N Engl J Med. 2019;381:1995-2008 (suppl.). 4. Wiviott SD, et al. N Engl J Med 2019; 380:347-357.

EMPEROR-Reduced Trial

Effect of Empagliflozin on Cardiovascular and Renal Events in Heart Failure With a Reduced Ejection Fraction

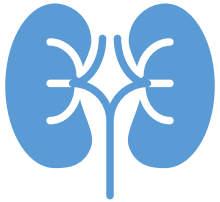
Published in New England Journal of Medicine, August 2020

EMPEROR-Reduced Trial

- Double-blind, placebo-controlled, randomized trial of 3730 patients in 565 centers in 20 countries

- Men and women with mild, moderate or severe heart failure due to poor systolic function of the left ventricle, who were already receiving all appropriate treatments for heart failure
- With and without type 2 diabetes (50% had T2DM, vs DAPA-HF 42%)
- Randomly assigned to placebo or empagliflozin 10 mg once daily, which was added to existing treatment. Study medication was continued for median of 16 months (up to 34 months)
- This was the second large-scale trial of a SGLT2 inhibitor in patients with a reduced ejection fraction. DAPA-HF previously reported positive results with dapagliflozin, but EMPEROR-Reduced trial studied many patients with more advanced disease (mean LVEF of 27% vs 31%)

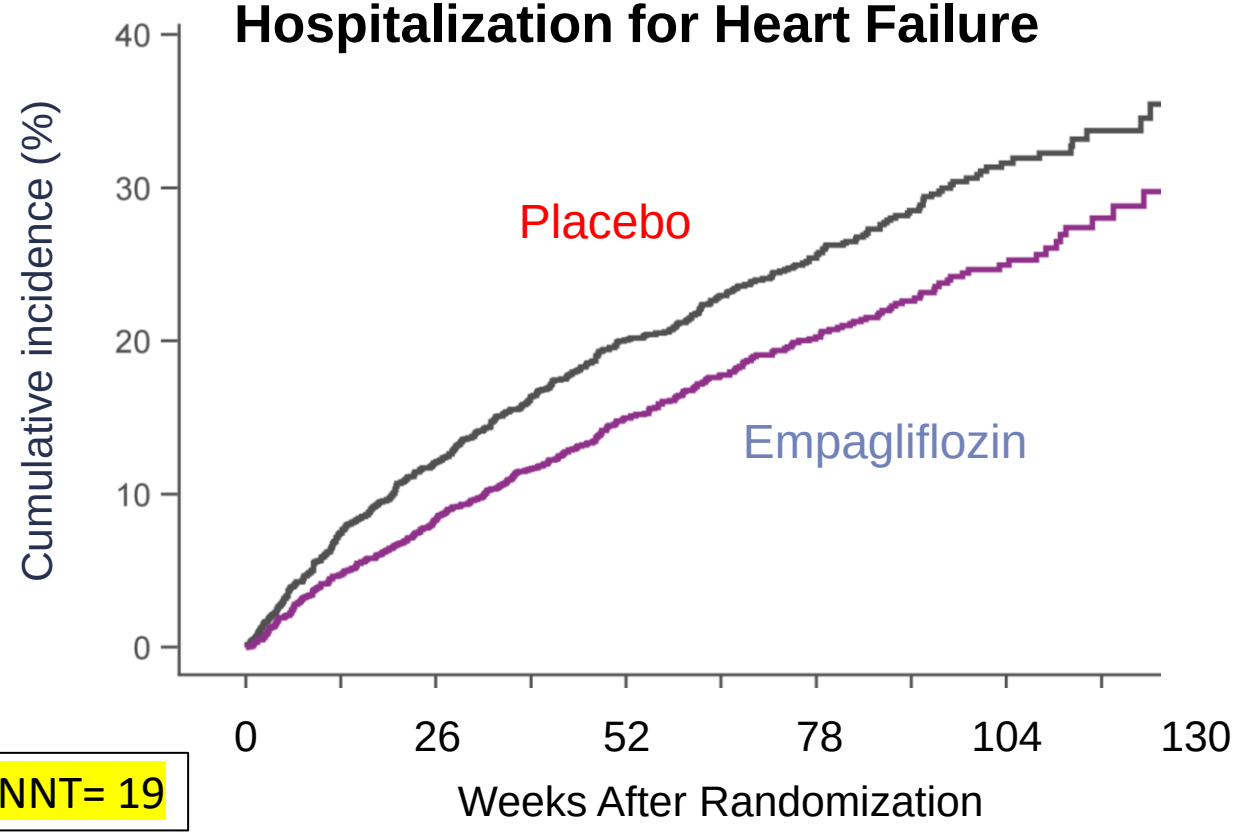
SGLT2 Inhibition With Empagliflozin Is Effective in Heart Failure With a Reduced Ejection Fraction With or Without Diabetes

 **Primary Endpoint** Composite of cardiovascular death or heart failure hospitalization	**25% ↓ in risk** **P < 0.001**
 **First Secondary Endpoint** Total (first and recurrent heart failure hospitalizations)	**30% ↓ in risk** **P < 0.001**
 **Second Secondary Endpoint** Slope of decline in glomerular filtration rate over time	**P < 0.001** **(50% ↓ in renal events)**

Also achieved success on composite renal endpoint, KCCQ clinical summary score, and total number of hospitalizations for any reason (all nominal P < 0.01)

Empagliflozin Prevented Both Serious Heart Failure and Serious Kidney Failure Events

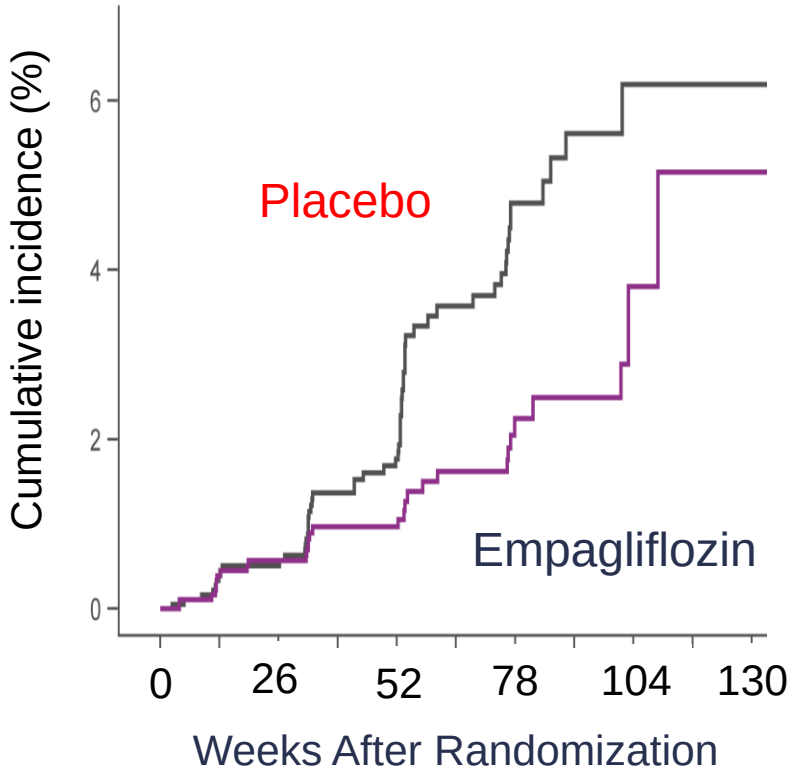
Cardiovascular Death or Hospitalization for Heart Failure



NNT= 19

Hazard ratio 0.75 (25% reduction in risk)
(95% CI 0.65, 0.86), P < 0.0001

Composite Renal Endpoint



Hazard ratio 0.50 (50% reduction in risk)
(95% CI 0.32, 0.77), P = 0.0019

EMPEROR-Reduced: Safety

	Empagliflozin (n=1863)	Placebo (n=1863)
Serious adverse events	772 (41.4)	896 (48.1)
Related to cardiac disorder	**500 (26.8)**	**634 (34.0)**
Related to worsening renal function	**59 (3.2)**	**95 (5.1)**
Selected adverse events of interest		
Volume depletion	197 (10.6)	184 (9.9)
Hypotension	176 (9.4)	163 (8.7)
Symptomatic hypotension	106 (5.7)	103 (5.5)
Hypoglycemia	27 (1.4)	28 (1.5)
Ketoacidosis	0 (0.0)	0 (0.0)
Urinary tract infections	91 (4.9)	83 (4.5)
Genital tract infections	31 (1.7)	12 (0.6)
Bone fractures	45 (2.4)	42 (2.3)
Lower limb amputations	13 (0.7)	10 (0.5)

NICE TA773 (March 2022): Empagliflozin for treating chronic heart failure with reduced ejection fraction

Empagliflozin is recommended as an option for treating symptomatic chronic heart failure with reduced ejection fraction in adults, only if it is used as an add-on to optimised standard care with:

- an angiotensin-converting enzyme (ACE) inhibitor or angiotensin 2 receptor blocker (ARB), with a beta blocker and, if tolerated, a mineralocorticoid receptor antagonist (MRA), or
- Sacubitril valsartan with a beta blocker and, if tolerated, an MRA

The 4 foundational classes of medication in HFrEF

Sacubitril/valsartan (Entresto)
Beta-blockers (Bisoprolol/Carvedilol)
Mineralocorticoid antagonists (Spironolactone and Eplerenone)
SGLT2 inhibitors (Empagliflozin and Dapagliflozin)

The EMPEROR-Reduced trial (Empagliflozin) and the DAPA-HF trial (Dapagliflozin) led to this 4th class of medication (SGLT2 inhibitors) being incorporated into international/NICE guidelines for the treatment of patients with chronic heart failure and reduced ejection fraction, whether or not they have diabetes.

In heart failure, both are licensed as 10mg once daily, require no dose adjustment, and are well tolerated

There is now compelling evidence that SGLT2 inhibitors should be started as soon as possible

Sequencing of these 4 treatment classes in HFrEF: current practice

Morbidity and mortality benefits are rapid: Start all four foundational treatments (ACEi/ARB/ARNI, BB, MRA, SGLT2i) within 2-4 weeks

- Evidence for efficacy and safety of this approach (STRONG-HF study, Lancet Dec 2022)

Treatment benefit of each drug class is independent of that produced by other agents

Even low starting doses of foundational therapies have substantial therapeutic benefits

- This approach should take precedence over uptitration of any individual drug class to target doses

Starting certain drugs first can influence patients' tolerating introduction of the next drug

- Appropriate sequencing can enhance the tolerability of agents started later in the sequence (e.g. diuretic effect of SGLT2-inhibitors can facilitate tolerating introduction of beta-blockers etc)

Aim to achieve rapid initiation of all four foundational therapies within 4 weeks; up-titration follows thereafter[1,2]

European Heart Journal (July 2024): SGLT2 inhibitors should be first-line treatment in heart failure with reduced ejection fraction

ESC European Society of Cardiology

SGLT2 inhibitors should be first line treatment in heart failure with reduced ejection fraction

Pro	Contra
DAPA-HF and EMPEROR-Reduced demonstrate early and sustained reduction of CV death/HF hospitalizations	Only patients failing on GRMT were enrolled in DAPA-HF and EMPEROR-Reduced
SGLT2i are among the four foundational drugs for HFrEF and can add to the efficacy of the other three	Inconsistent effect of SGLT2i on mortality; most HF hospitalizations not prevented
When all foundational drugs are started within one week, the ordering does not matter	DAPA-MI failed to show SGLT2i reduced HF or all-cause hospitalizations or deaths
SGLT2i do not require dose adjustment or uptitration; the starting dose of these drugs is the target dose	All-cause hospitalizations are more important drivers of healthcare costs, HF causes <30% of all admissions
Modeling analyses suggest greatest benefit when SGLT2i are initiated first	Effect of SGLT2i on morbidity/mortality modest versus β-blocker, MRA or ARNI
SGLT2i can facilitate the safety and tolerability of other foundational drugs for HF	Many patients in trials had few symptoms and little symptom benefit from SGLT2i
	Adjusting diuretics may have a similar effect as SGLT2i on symptoms/congestion

EUR HEART J, VOLUME 45, ISSUE 25, 1 JULY 2024, PAGES 2186–2196, HTTPS://DOI.ORG/10.1093/EURHEARTJ/EHAE300

SGLT2 inhibitors in HFpEF/HFmrEF

FEW PHARMACOLOGIC TREATMENT OPTIONS ARE AVAILABLE FOR PATIENTS WITH HEART FAILURE WITH MILDLY REDUCED OR PRESERVED EJECTION FRACTION, WHICH REPRESENTS ABOUT HALF OF OUR PATIENTS WITH HEART FAILURE

Disclaimer- will not talk about Finerenone (non-steroidal MRA) in HFpEF/HFmrEF (FINEARTS-HF trial, NEJM 2024)

Definition of HFpEF (ESC criteria)

HFpEF = LVEF ≥50%, &

- Symptoms ± signs of HF, and
- Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides

HFmrEF = LVEF 41–49%, &

- Symptoms ± signs of HF
- *"For the diagnosis of HFmrEF, the presence of other evidence of structural heart disease (e.g. increased left atrial size, LV hypertrophy, or echocardiographic measures of impaired LV filling) makes the diagnosis more likely"*

EMPEROR-Preserved Trial (NEJM, 2021)

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

Double-blind controlled trial- randomly assigned 5988 patients with class II–IV heart failure and an ejection fraction of more than 40% to receive empagliflozin (10 mg once daily) or placebo, in addition to usual therapy. The primary outcome was a composite of cardiovascular death or hospitalization for heart failure

- *Encompassed patients with mid-range ejection fraction (HFmrEF , LVEF 41%+)*
- *Baseline patient characteristics: mean LVEF of 54%; and 49% with type 2 DM*
- *Mean age 72; 45% female, and 51% with atrial fibrillation*

EMPEROR-Preserved trial results

RESULTS

Primary endpoint, CV death or HF hospitalization, for empagliflozin vs. placebo: 13.8% vs. 17.1% (HR = 0.79 95% CI 0.69 –0.9; $p < 0.001$)

CV death: 7.3% vs. 8.2% ($p>0.05$); HF hospitalization: 8.6% vs. 11.8% (HR 0.71, 95% CI 0.60-0.83); All-cause mortality: 13.4% vs. 14.2% ($p > 0.05$)

Composite renal outcome: 3.6% vs. 3.7% ($p > 0.05$)

CONCLUSIONS

Empagliflozin is superior to placebo in improving HF outcomes among patients with HFpEF (EF>40%)

The benefit was largely driven by reduction in HF hospitalization without significant difference on mortality

HF hospitalization reduction was seen in patients with and without diabetes

Uncomplicated genital (1.9% vs 0.4%) and urinary tract infections (9.9% vs 8.1%) and hypotension (10.4% vs 8.6%) were reported more frequently with empagliflozin than placebo

NICE TA929 (Nov 23): Empagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction

Empagliflozin is recommended, within its marketing authorisation, as an option for treating symptomatic chronic heart failure with preserved or mildly reduced ejection fraction in adults

Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction (DELIVER trial)

LEADING TO NICE TA902 (JUNE 2023): DAPAGLIFLOZIN FOR TREATING CHRONIC HEART FAILURE WITH PRESERVED OR MILDLY REDUCED EJECTION FRACTION

DELIVER trial (NEJM, 2022)

Background/rationale: the previous year Empagliflozin, was found to reduce the risk of cardiovascular death and heart failure hospitalization in the EMPEROR-Preserved trial

Uncertainty remains regarding efficacy in specific groups of patients with HF with mildly reduced or preserved ejection fraction:

- Those in the highest part of the ejection fraction range, where there has been concern about attenuation of the treatment effect
- Those initiated on treatment during or soon after hospitalization, where limited data are available
- Those with a previously reduced ejection fraction that has improved to > 40%, a group that has been excluded from prior trials

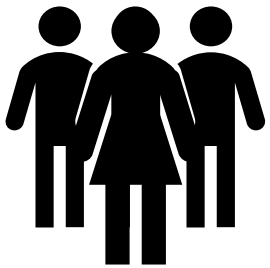
DELIVER Study Design

Randomized, double-blind, placebo-controlled trial testing the hypothesis that dapagliflozin would reduce cardiovascular death or worsening heart failure in patients with heart failure and mildly reduced or preserved ejection fraction

Eligibility Criteria

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

AFF, atrial fibrillation and flutter; LA, left atrium; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; NYHA, New York Heart Association.
Solomon SD, et al. Eur J Heart Fail. 2021. 23(7):1217-1225.

DELIVER Baseline Characteristics

Well Balanced Between Treatment Groups

	Dapagliflozin N=3131	Placebo N=3132
Age (years)	71.8 ± 9.6	71.5 ± 9.5
Female Sex	43.6%	44.2%
Baseline LVEF (%)	54.0 ± 8.6	54.3 ± 8.9
LVEF < 60%	70.3%	69.3%
HF with Improved EF (Prior LVEF ≤ 40%)	18.3%	18.5%
Race		
White	70.7%	71.0%
Black	2.6%	2.5%
Asian	20.1%	20.6%
Other	6.6%	5.9%
Geographic Region		
Europe and Saudi Arabia	47.7%	48.2%
Asia	19.4%	19.8%
Latin America	19.2%	18.5%
North America	13.7%	13.5%
NYHA Class at Baseline		
II	73.9%	76.6%
III/IV	26.1%	23.4%
KCCQ Total Symptom Score	70 ± 23	70 ± 22

EF, ejection fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire.

DELIVER Baseline Characteristics (2)

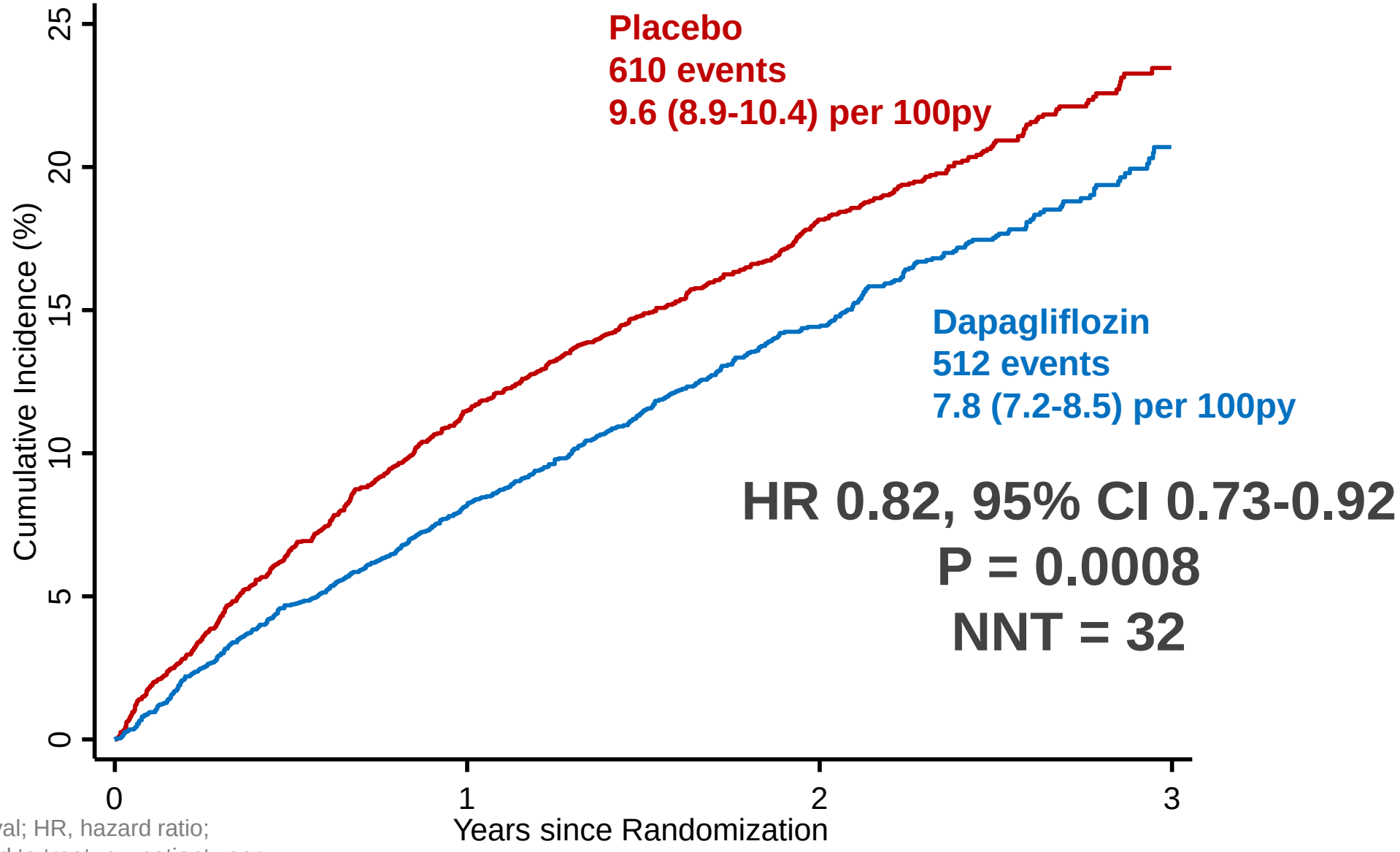
Well Balanced Between Treatment Groups

	Dapagliflozin N=3131	Placebo N=3132
NT-proBNP without AFF (ECG) (pg/ml)	729 [472, 1299]	704 [467, 1265]
NT-proBNP with AFF (ECG) (pg/ml)	1408 [956, 2256]	1387 [966, 2180]
Prior HF Hospitalization	40.6%	40.5%
Atrial Fibrillation/Flutter at Enrollment	42.4%	42.1%
Type 2 Diabetes	44.7%	44.9%
eGFR (mL/min/1.73m^2)	61.2 ± 19.0	60.9 ± 19.3
eGFR < 60 mL/min/1.73m^2	48.4%	49.6%
Medications		
Loop diuretics	76.7%	76.9%
ACEi	36.5%	36.7%
ARB	36.2%	36.4%
Sacubitril-valsartan	5.3%	4.3%
β-blocker	82.8%	82.5%
MRA	42.8%	42.4%

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro b-type natriuretic peptide.

Primary Endpoint: CV Death or Worsening HF

Full Population

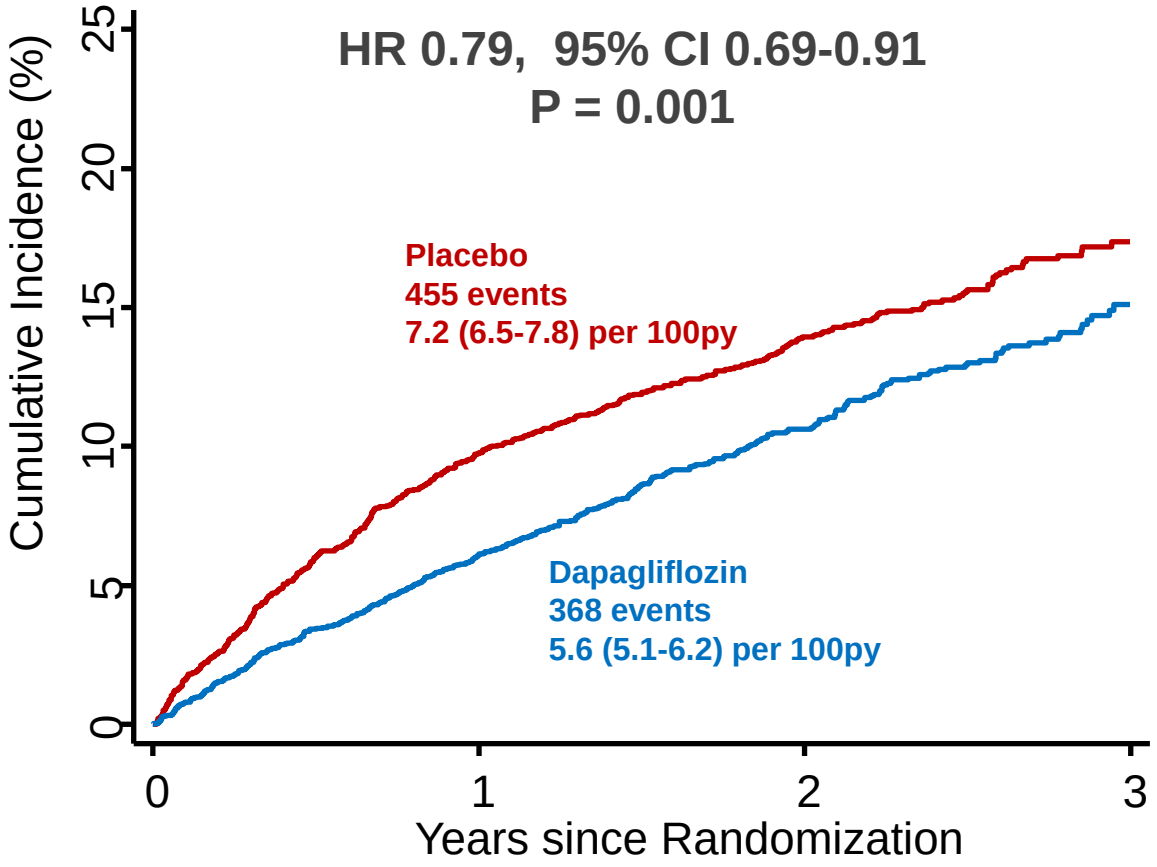


CI, confidence interval; HR, hazard ratio;
NNT, number needed to treat; py, patient year.

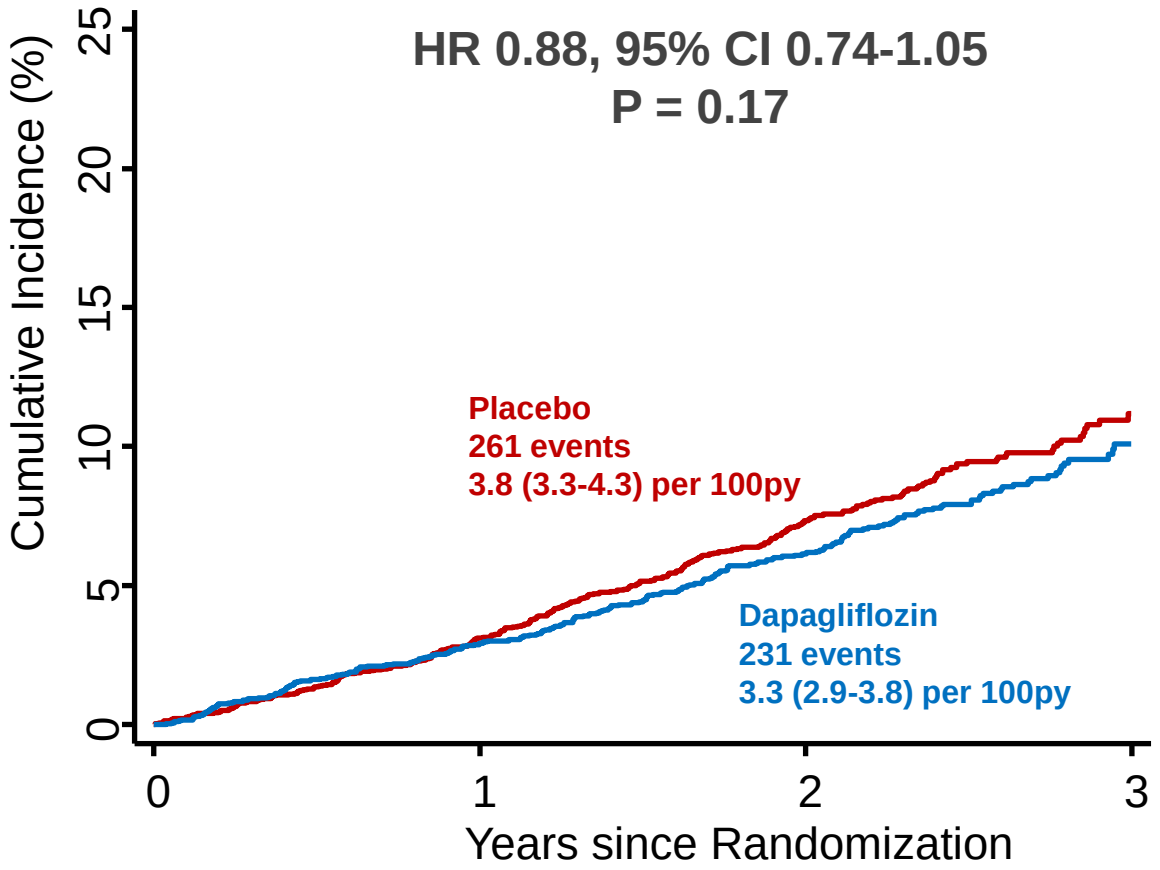
Components of Primary Endpoint

Full Population

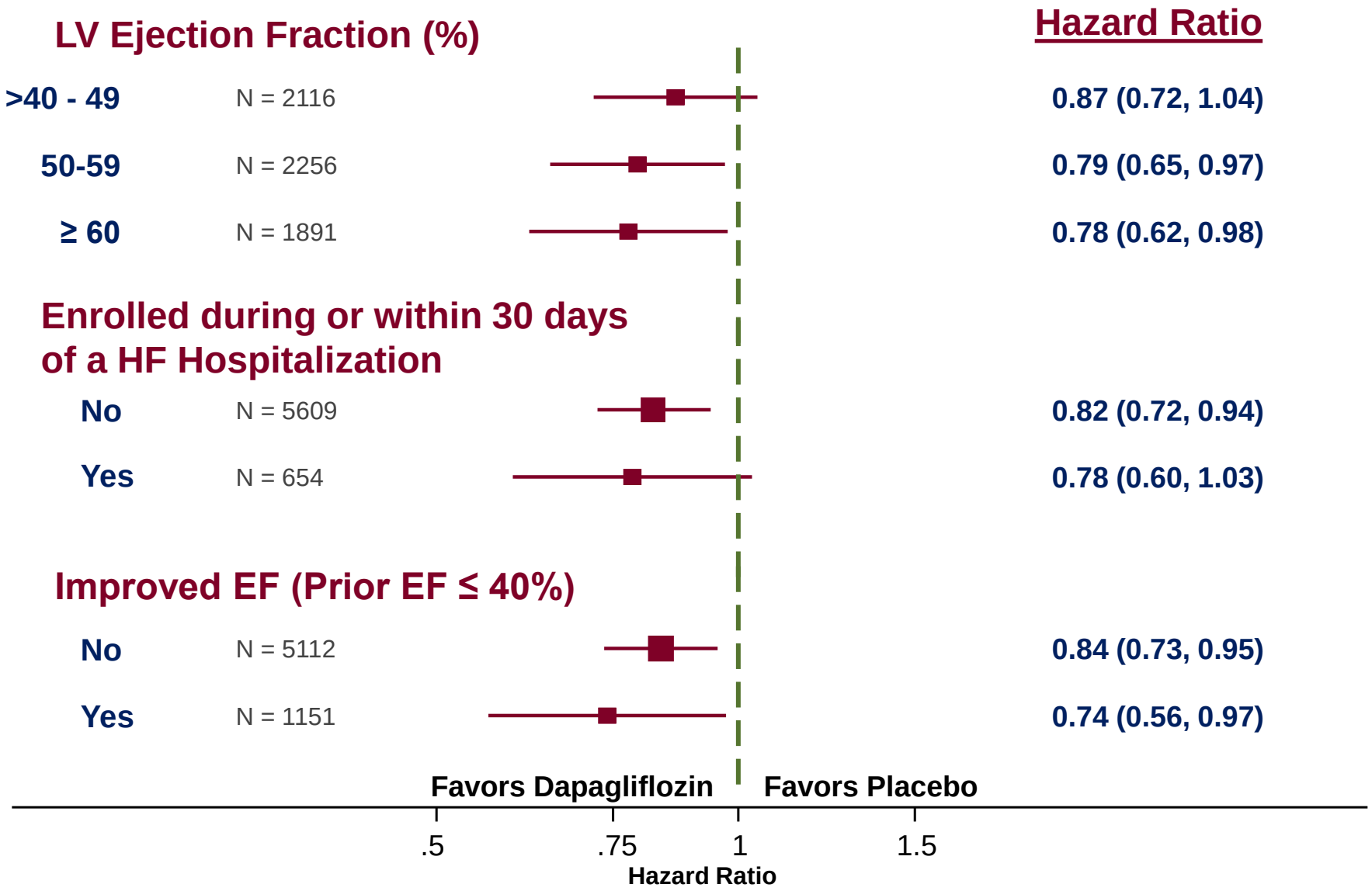
Worsening Heart Failure (HF Hospitalization + Urgent HF Visit)



Cardiovascular Death



Primary Endpoint in Prespecified Subgroups

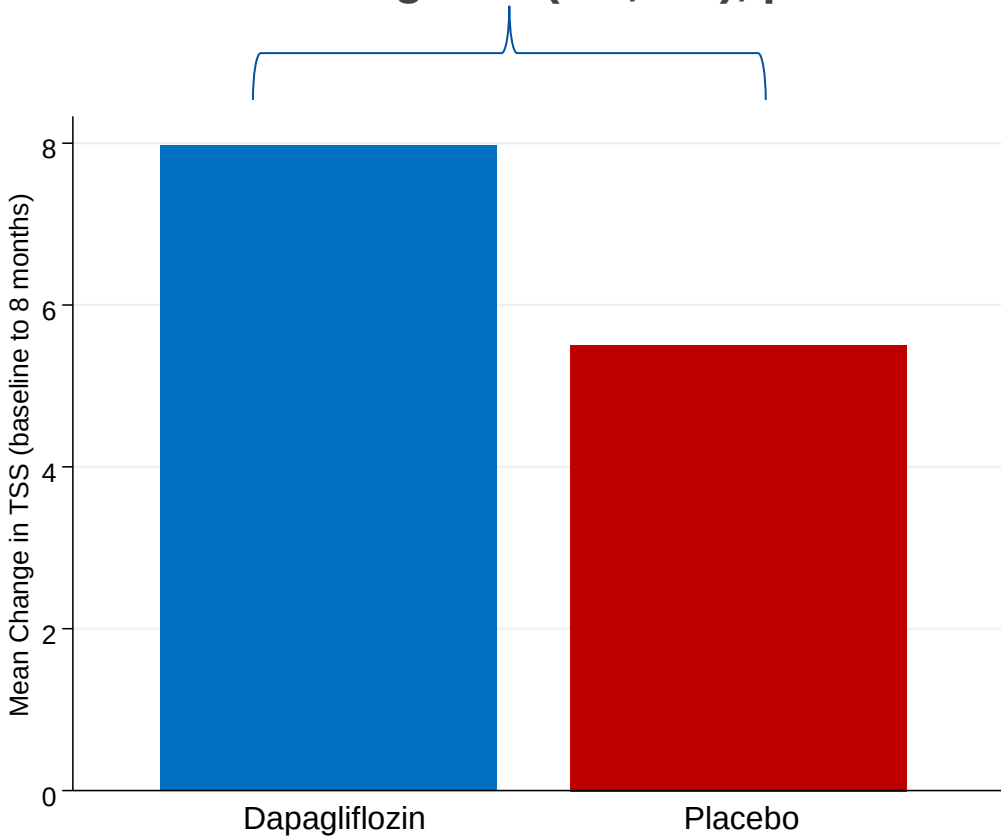


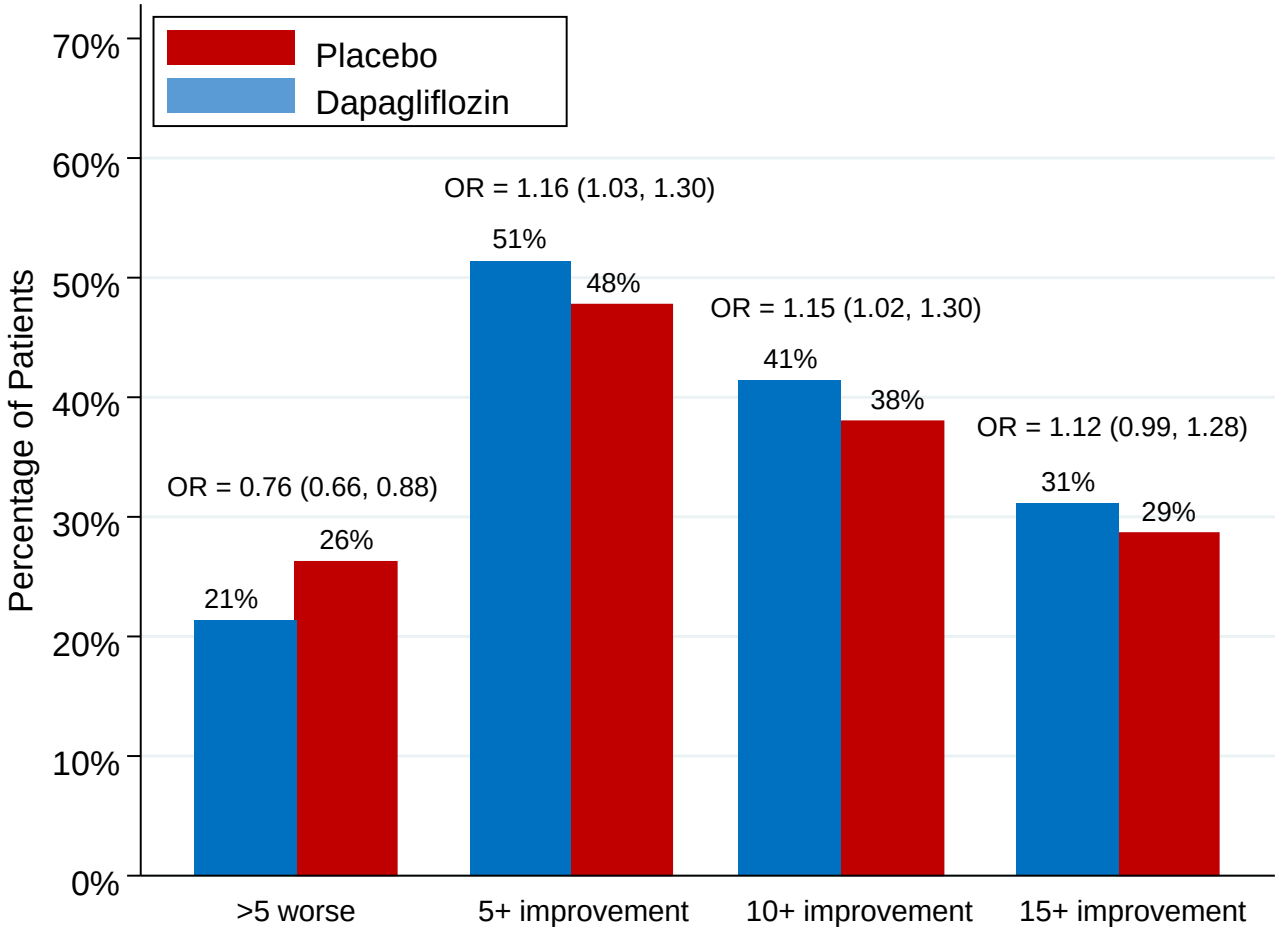
Secondary Endpoint: Improvement in KCCQ Total Symptom Score

Baseline to 8 months

Win Ratio* 1.11 (1.03, 1.21), p = 0.009

Mean Change 2.4 (1.5, 3.4), p < 0.001





*Primary Analysis Method in patients who reached 8 months prior to COVID-19 Pandemic

Adverse Events*

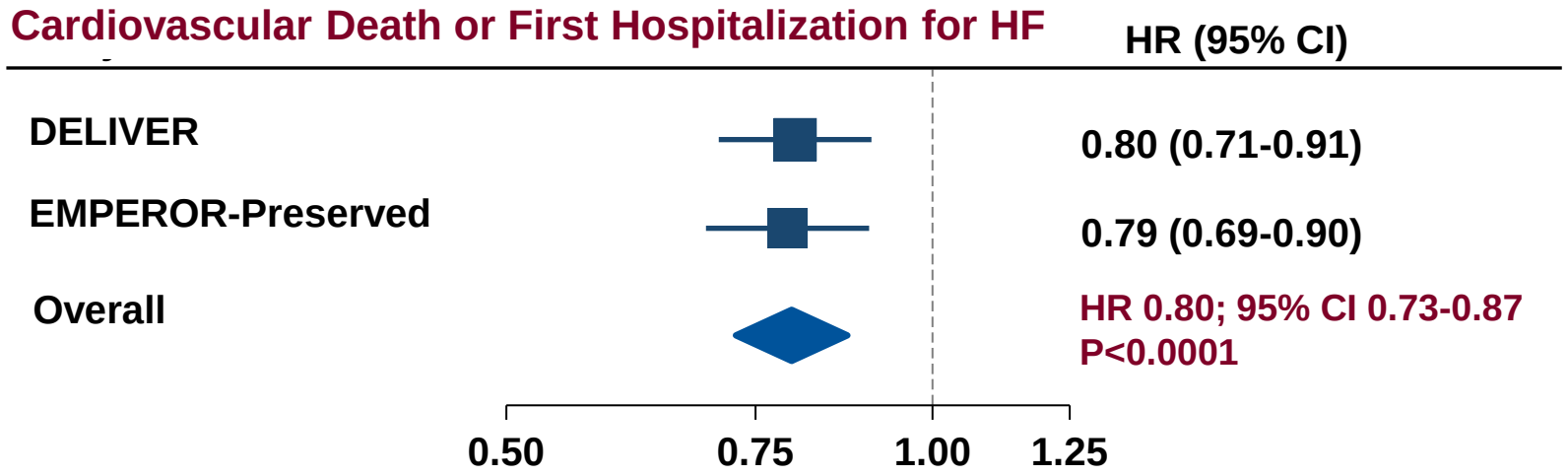
Serious Adverse Events and Adverse Events leading to treatment discontinuation and other selected adverse events

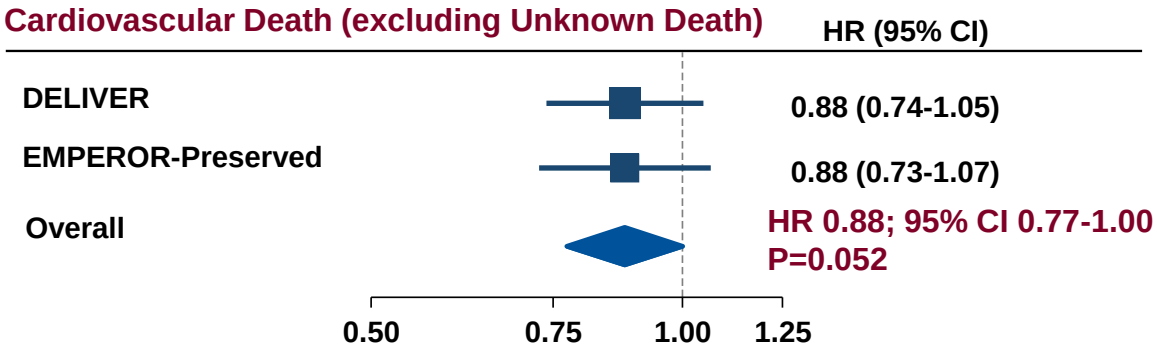
	Dapagliflozin* n=3126	Placebo* n=3127
Any SAE (including death)	1361 (43.5%)	1423 (45.5%)
Any AE leading to treatment discontinuation	182 (5.8%)	181 (5.8%)
Any AE leading to treatment interruption	436 (13.9%)	494 (15.8%)
Any amputation	19 (0.6%)	25 (0.8%)
Any definite or probable diabetic ketoacidosis	2 (0.1%)	0 (0.0%)
Any major hypoglycemic event	6 (0.2%)	7 (0.2%)
Events related to volume depletion	42 (1.3%)	32 (1.0%)
Renal Events	73 (2.3%)	79 (2.5%)

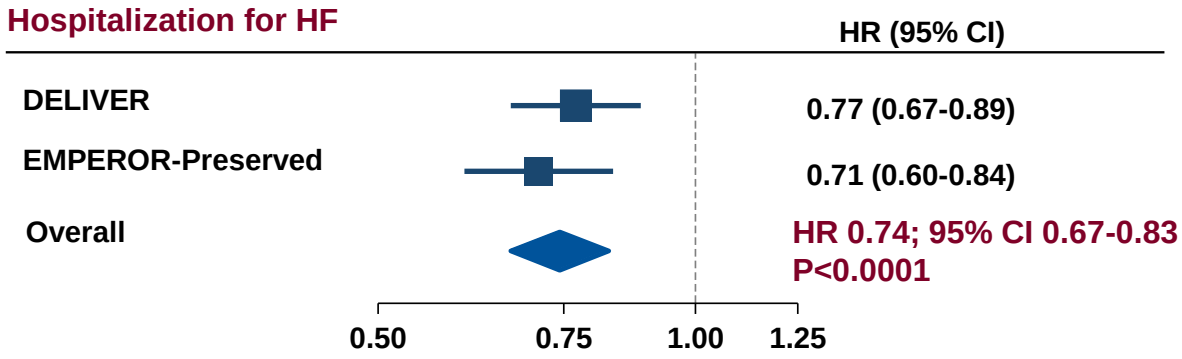
*On treatment (in patients receiving at least one dose and up to 30 days following last dose of IP)
AE, adverse event; IP, investigational product; SAE, serious adverse event.

DELIVER and EMPEROR-Preserved Meta-Analysis:

↓ 20% (13-27%) Relative Risk Reduction of Primary Endpoint with Consistent Reductions in Both Components



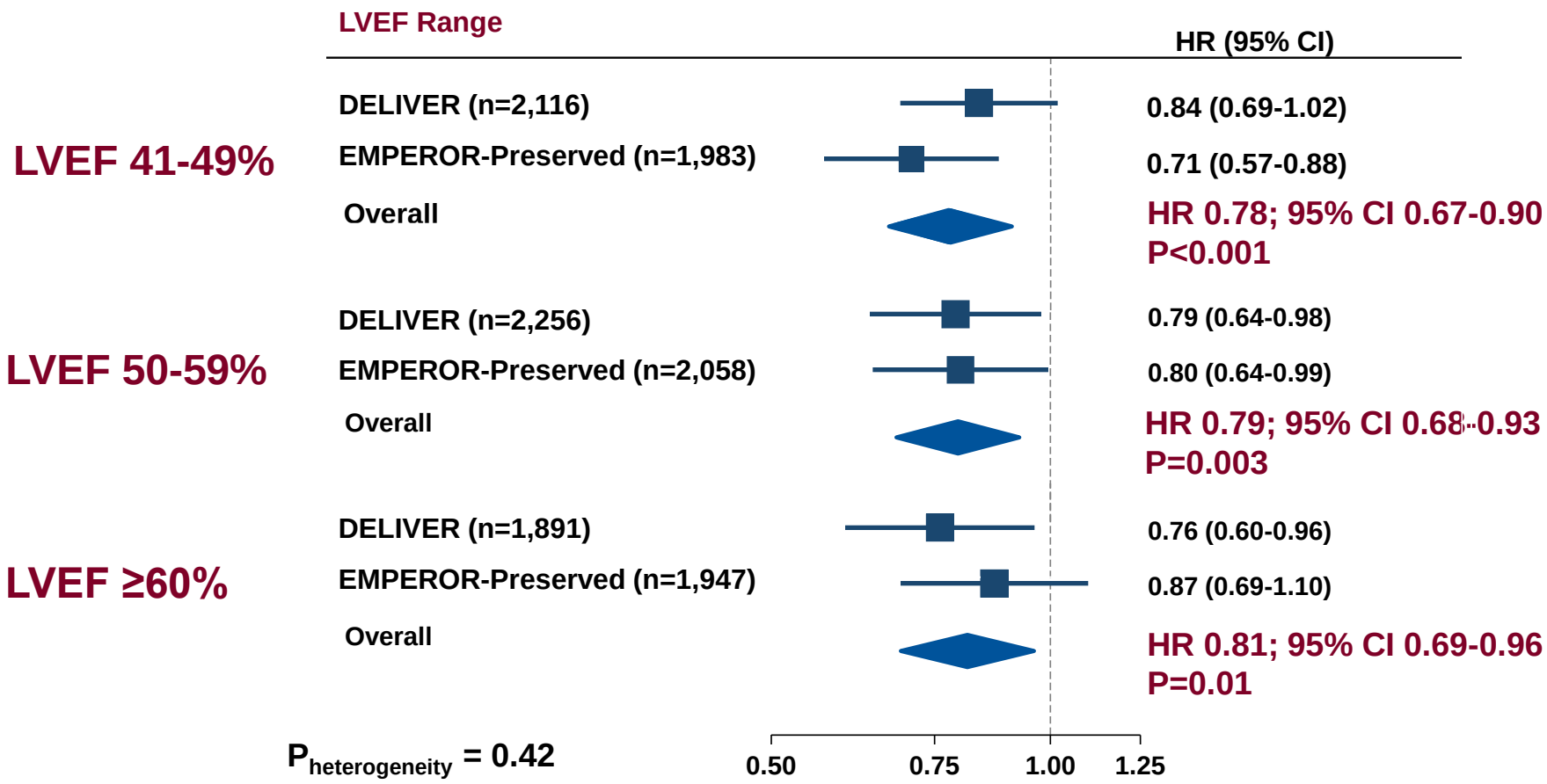




$P_{heterogeneity}$ >0.40 for all endpoints

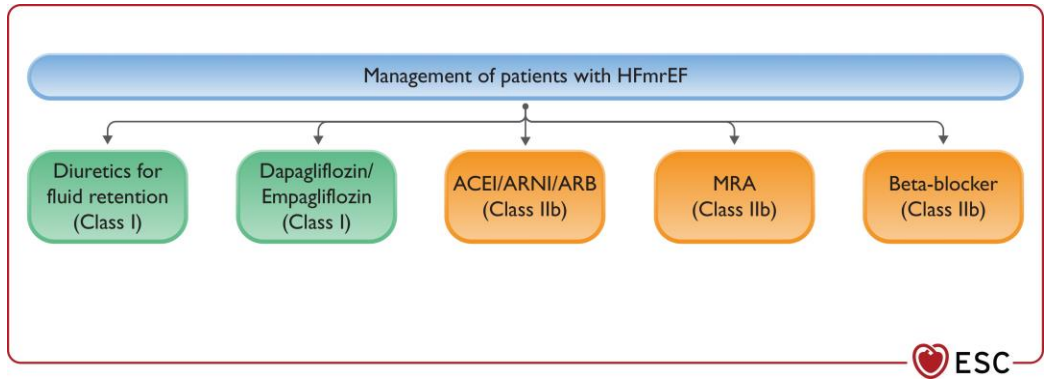
DELIVER and EMPEROR-Preserved Meta-Analysis:

Consistent Reductions in Primary Endpoint Across LVEF Range, Including Among LVEF ≥60%

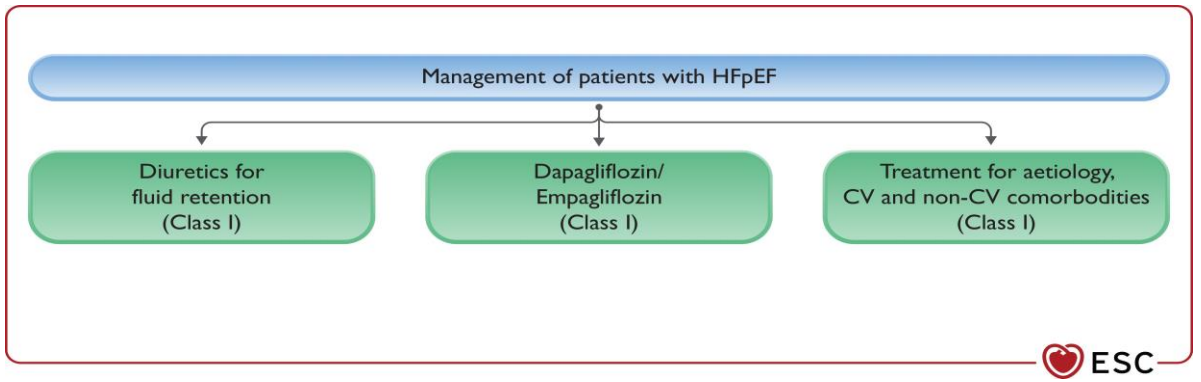


2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC

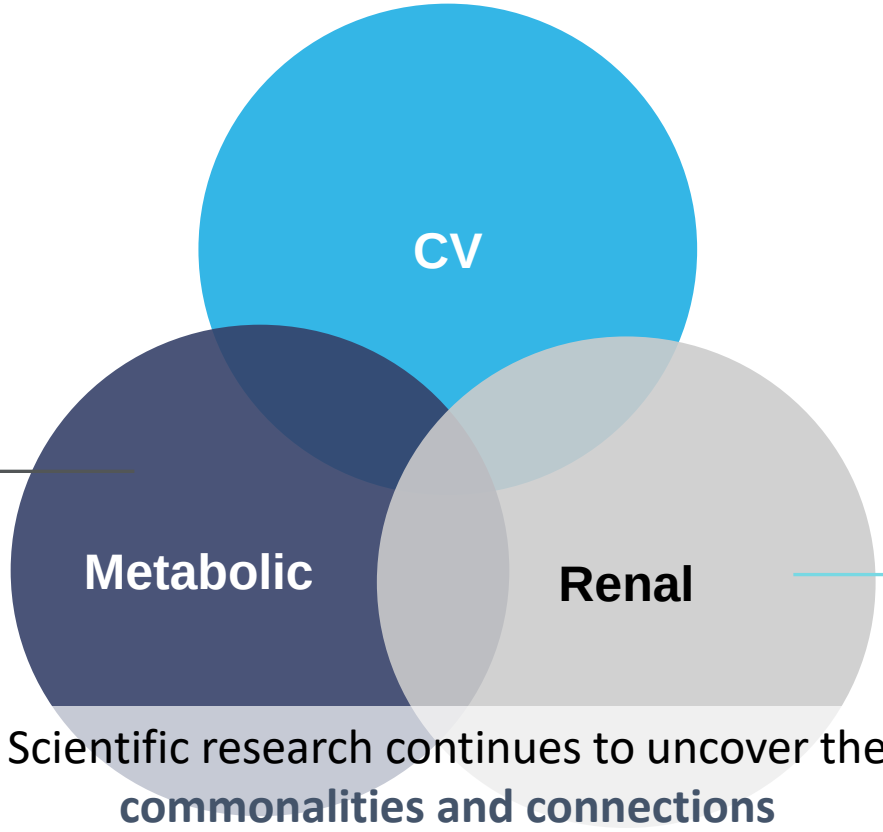
- AN SGLT2 INHIBITOR (DAPAGLIFLOZIN OR EMPAGLIFLOZIN) IS RECOMMENDED IN PATIENTS WITH HFMREF TO REDUCE THE RISK OF HF HOSPITALIZATION OR CV DEATH (CLASS 1A)



- AN SGLT2 INHIBITOR (DAPAGLIFLOZIN OR EMPAGLIFLOZIN) IS RECOMMENDED IN PATIENTS WITH HFPEF TO REDUCE THE RISK OF HF HOSPITALIZATION OR CV DEATH (CLASS 1A)



Shared risk factors exist between cardiovascular, renal and metabolic diseases that need to be jointly addressed to help improve patient outcomes[1-3]



2-5 times more likely to develop HF if you have T2D[4]

CKD affects up to **50% of HF** patients[3]

Scientific research continues to uncover the **commonalities and connections** between cardiovascular, renal and metabolic disease areas[1-3]

CKD, chronic kidney disease; HF, heart failure; T2D, type 2 diabetes.

References: 1. House AA, et al. Kidney Int . 2019;95:1304-1317. 2. Sowers JR. Kidney International. 2007;71:719-720. 3. Mullens, W, et al. Eur J Heart Fail. 2020;22:584-603. 4. Nichols GA, et al. Diabetes Care. 2001;24:1614-1619.

Fostering an integrated approach to managing these inter-related conditions:

CAREME UK

The Cardio-Renal-Metabolic (CaReMe) partnership (CaReMe UK) is a collaboration between five of the UK's national professional societies focused on improving management of people with Cardiovascular, Renal and Metabolic Disorders

CaReMe UK was established in 2019 and brings together a panel of primary and secondary care experts from the British Cardiovascular Society, the Association of British Clinical Diabetologists, the UK Kidney Association, the Primary Care Cardiovascular Society and the Primary Care Diabetes Society

CVRM-UK

"As cardiometabolic conditions continue to rise with a substantial impact on the quality of life of patients, causing frequent hospitalisations, and premature death, it is clear a new model of specialty training and care delivery in the cardiometabolic disease space is needed"

CVRM UK aims:

To support this separate subspeciality with the aim to provide comprehensive training to healthcare professionals

The training will be delivered by high-quality educational meetings and resources

Conclusions

- In patients with HF with reduced ejection fraction, SGLT2 inhibitors reduce the risk of cardiovascular death AND risk of recurrent heart failure hospitalization/worsening heart failure
- In patients with HF with mildly reduced or preserved ejection fraction, SGLT2 inhibitors reduce the risk of cardiovascular death or worsening heart failure (mainly driven by the latter)
  - These findings were consistent across prespecified subgroups, including those defined according to left ventricular ejection fraction, with no attenuation in the highest LVEF group
  - Dapagliflozin was equally effective in patients with recent HF hospitalization and those with prior reduced ejection fraction that had improved to over 40% (DELIVER trial)
- A comprehensive meta-analysis confirmed robust benefits of SGLT2 in heart failure with mildly reduced or preserved EF, including among patients with LVEF ≥60%

The totality of evidence supports prioritizing the use of SGLT2 inhibitors in all types of heart failure, irrespective of patient phenotype or care setting

SGLT2 inhibitors: The panacea in heart failure!