HFpEF Masterclasses
In centers of expertise

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FRANCE

7th November 2024 - DAY 1
8th November 2024 - DAY 2

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Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2i) for the treatment of patients with heart failure with preserved ejection fraction (HFpEF)

Disclosures:

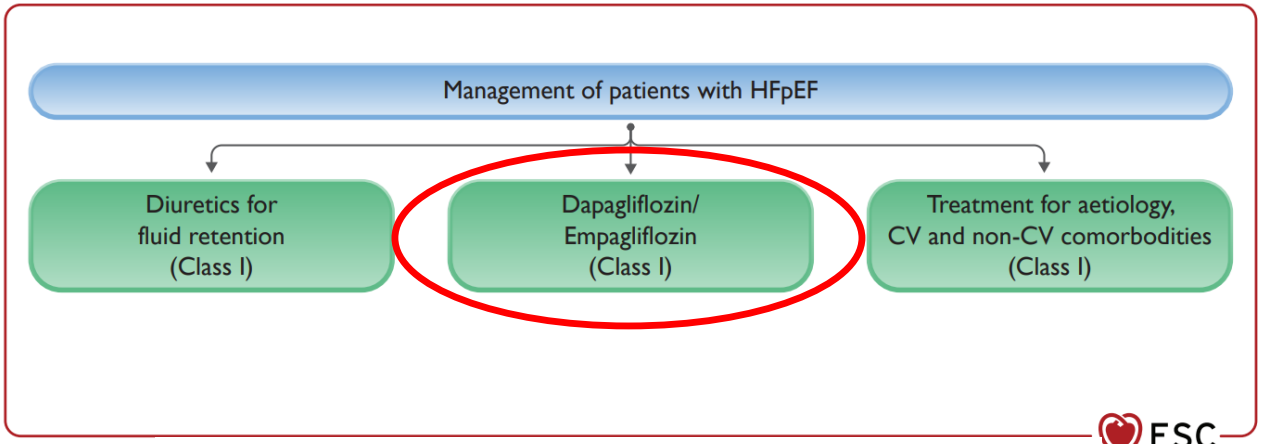
- **Congress / travel fees:** Bayer, Servier, Astra Zeneca
- Collaborations with advocacy groups: none
- Grants: none
- Personal fees (honoraria, consulting fees, lecture fees): none
- Intellectual property (eg, patents, copyrights, royalties): none
- Stock or share ownership: none

SGLT2 inhibitors in HFpEF

ESC European Society of Cardiology
European Heart Journal (2023) **44**, 3627–3639
https://doi.org/10.1093/eurheartj/ehad195

ESC GUIDELINES

2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure



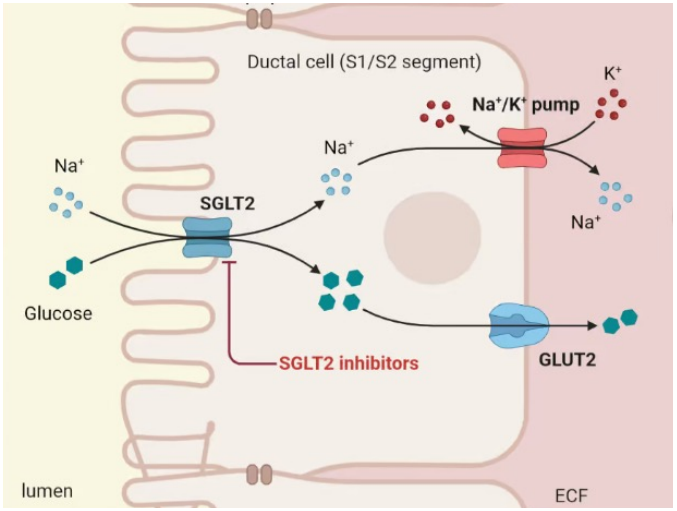
Recommendation	Class[a]	Level[b]
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFpEF to reduce the risk of HF hospitalization or CV death.[c] [6,8]	I	A

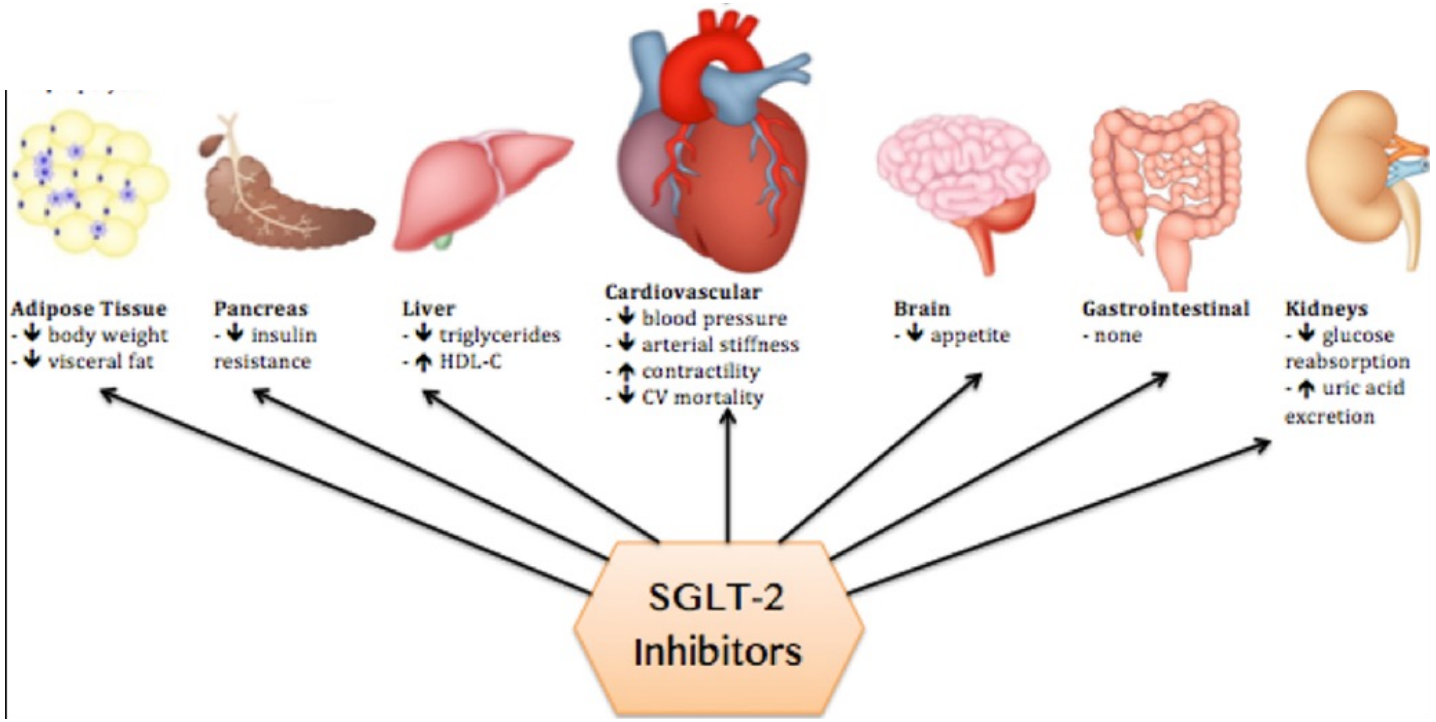
- [a]Class of recommendation; [b]Level of evidence; [c]This recommendation is based on the reduction of the primary composite endpoint used in the DELIVER and EMPEROR-Preserved trials and in a meta-analysis. However, it should be noted that there was a significant reduction only in HF hospitalizations and no reduction in CV death.
- CV = cardiovascular; ESC = European Society of Cardiology; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; SGLT2 = sodium-glucose cotransporter

- **Mechanisms of action**
- **Efficacy**
- **Safety / tolerance**

- **Next speakers: comorbidities (CKD, Afib etc), amyloidosis**

SGLT2 inhibitors in HFpEF: machanism of action





- Increased glucosuria and natriuresis
- Reduced plasma volume / blood pressure
- Reduced visceral fat / insulin resistance

Sajja AP, et al. J Cardiovasc Pharmacol Ther. 2019 (modified)

SGLT2 inhibitors in HFpEF: efficacy

EMPEROR-Preserved

Empagliflozin 10mg vs placebo

DELIVER

Dapagliflozin 10mg vs placebo

LVEF > 40%

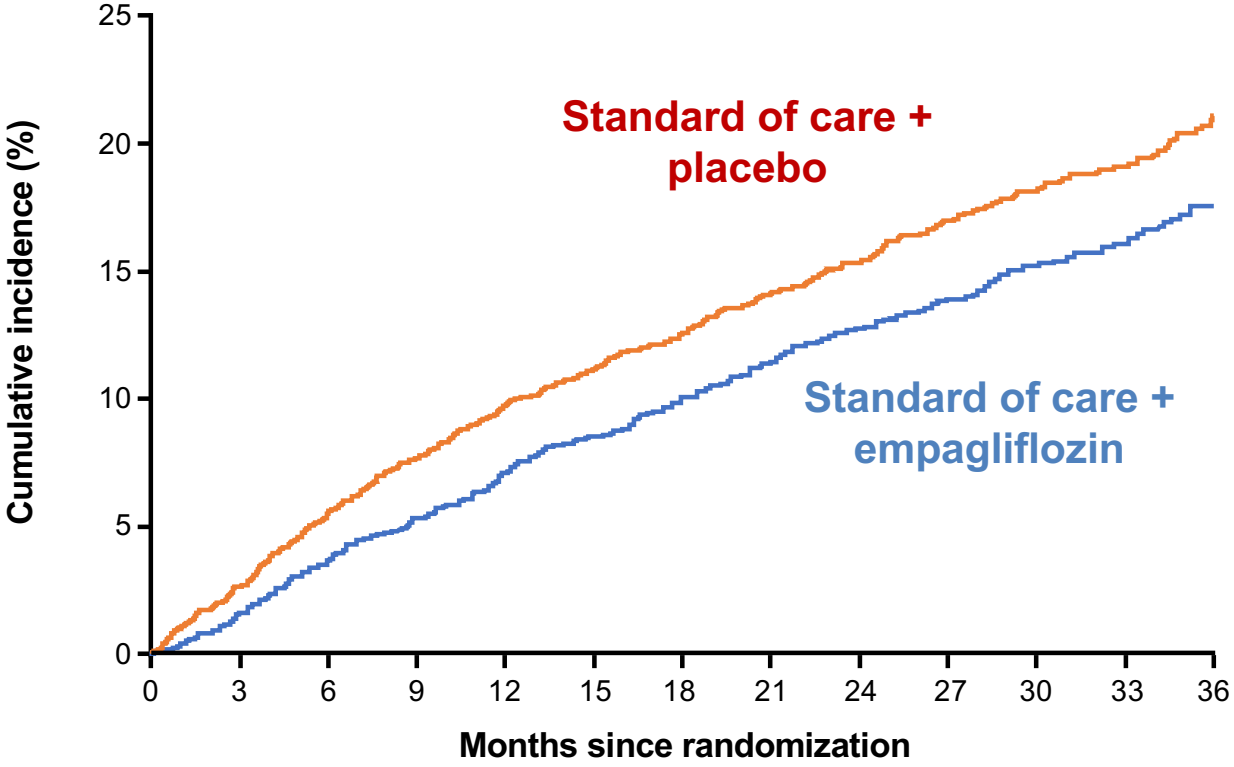
n=1156 (18%) with prior LVEF <40%

	N=5988	N=6263
LVEF>50% (%)	67.5	66.2
Age (y)	71.8±9.3	71.8±9.6
Female (%)	44.6	43.9
BMI (kg/m²)	29.77±5.8	29.8±6.1
NYHA 2 (%)	81.5	75.1
HF hospit < 12 months (%)	22.9	23
Afib (%)	51.1	57
Diabetes (%)	49.0	45,4
NT-proBNP (ng/l; IQR)	994 (501–1740)	1011.0 (623.0-1751.0)
eGFR (ml/min/1,73m²)	60.6±19.8	61±19

NEJM 2021;385:1451-1461; NEJM 2022;387:1089-1098 (modified)

Eur J ofHF 2020 Dec;22(12):2383-2392

EMPEROR-Preserved: reduction in CV death or HHF in patients with HFpEF



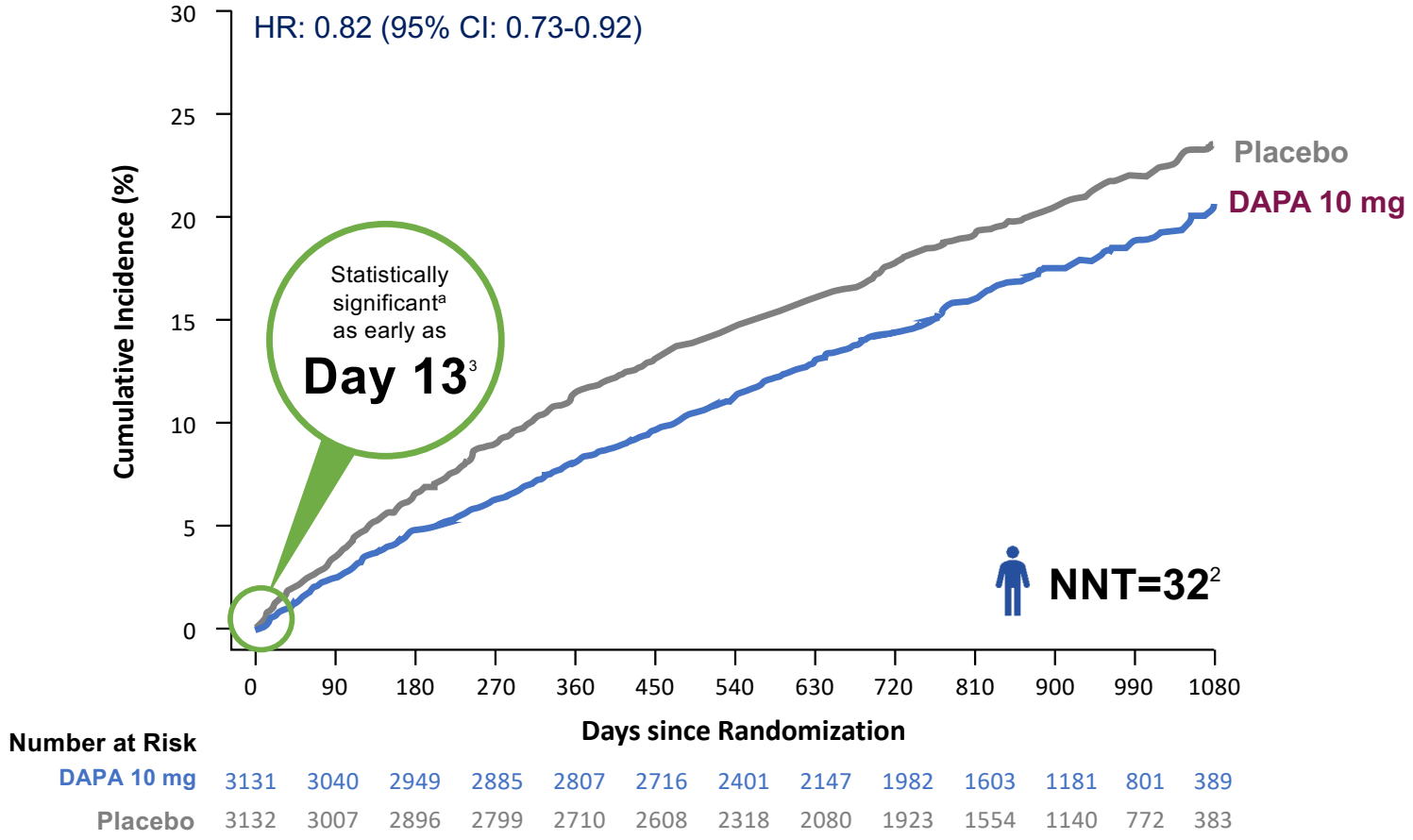
	RRR	ARR	NNT*
All pts	21%	3.3%	31

HR: 0.79
(95% CI: 0.69, 0.90)
p<0.001

*During a median trial period of 26 months.

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

DELIVER- Primary Composite of CV Death, hHF or Urgent HF Visit



18 % RRR

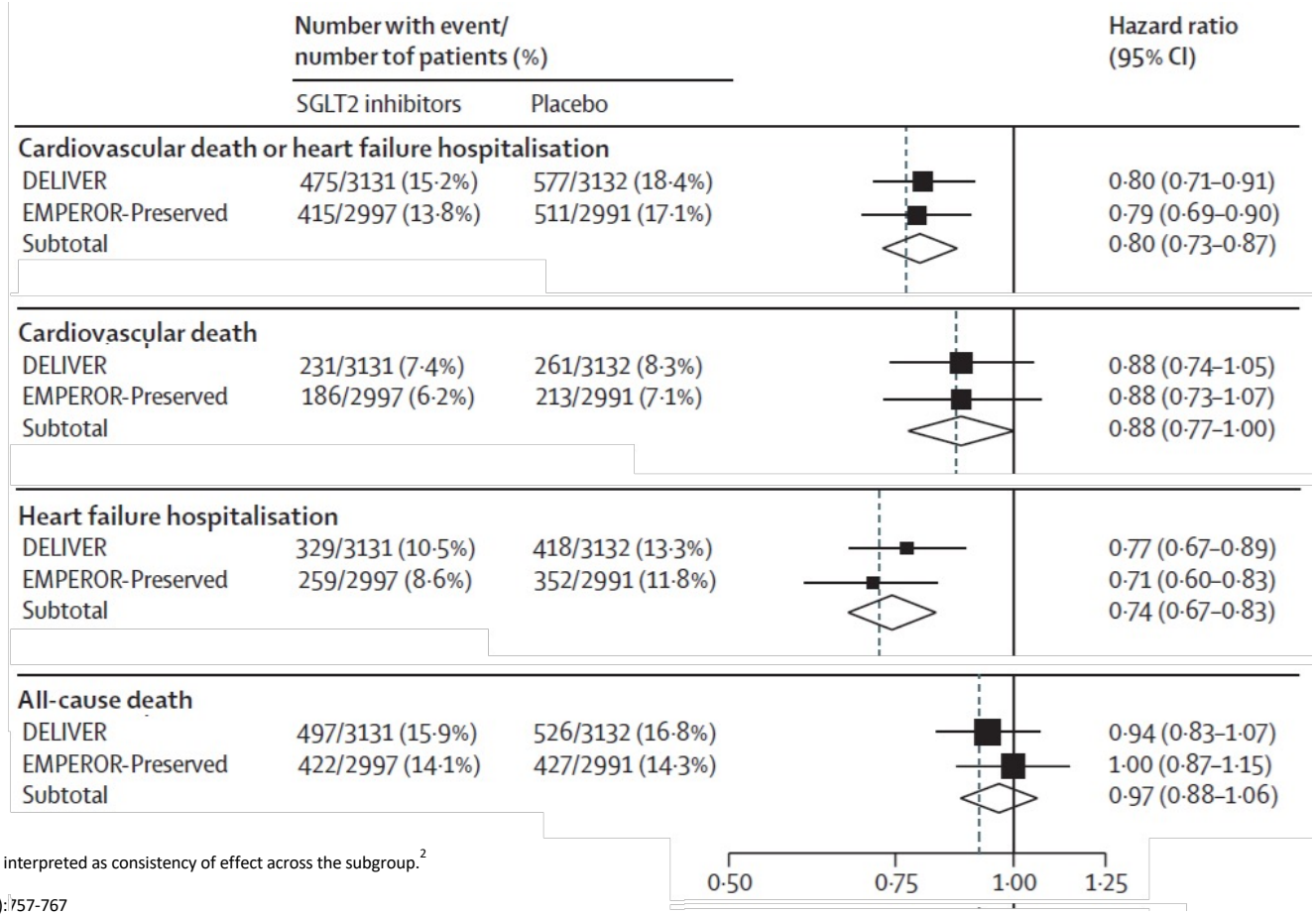
3.1% ARR
p=0.0008[2]

[a]Nominal significance at Day 13 (HR, 0.45; 95% CI, 0.20-0.99; p=0.046), with sustained statistical significance starting at Day 15.
Solomon SD et al. *N Engl J Med*. 2022;387(12):1089-1098; Vaduganathan et al. *JAMA Cardiol*. 2022 Dec 1;7(12):1259-1263.

DELIVER and EMPEROR-Preserved (N=12,251)

- Prespecified prior to unblinding of DELIVER
- Meta-analytic protocol registered with PROSPERO (CRD42022327527)
- Individual participant-level data from DELIVER used to harmonize endpoint definitions and subgroups

DELIVER and EMPEROR-Preserved Meta-Analysis: Cardiovascular Death, Hospitalizations for HF and All-cause Death

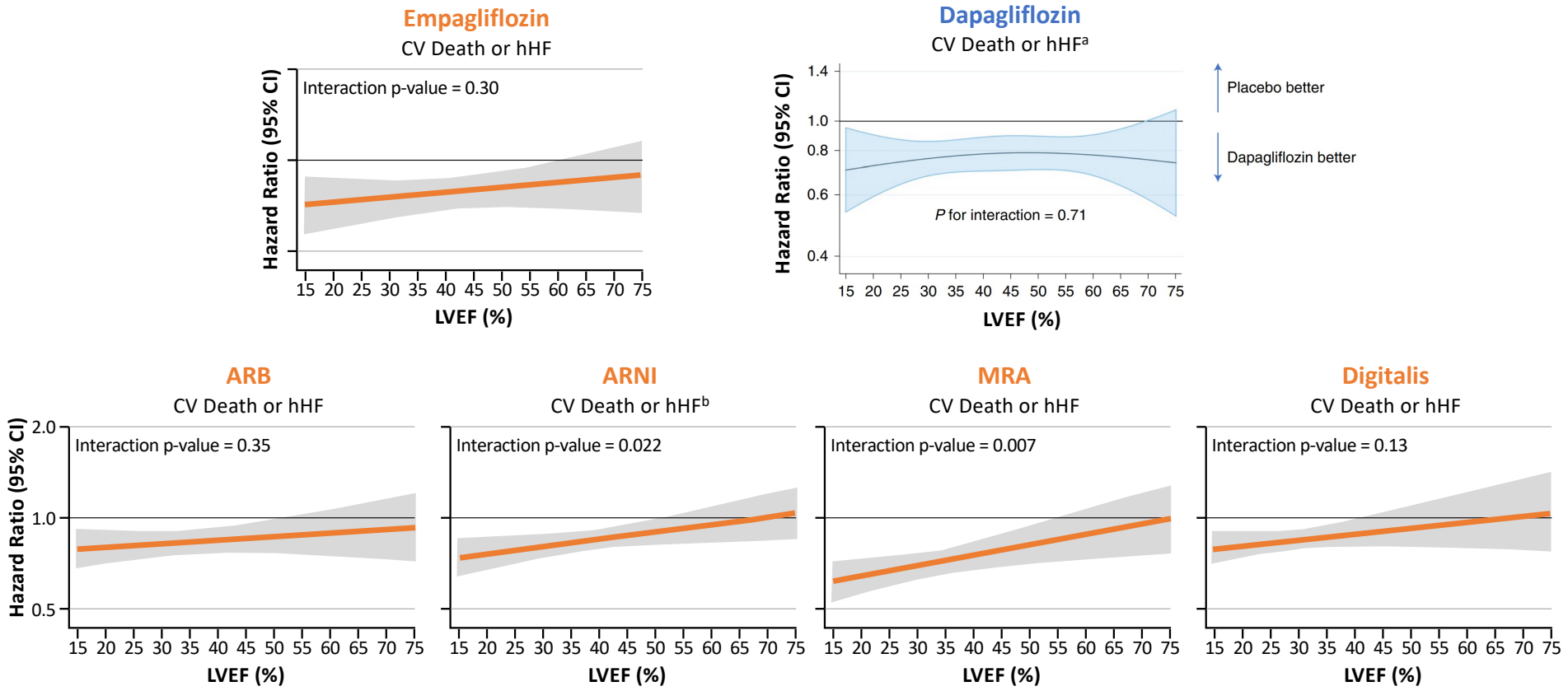


$P_{interaction}$>0.40[a] for all endpoints

[a]A non-significant result for an interaction test can be interpreted as consistency of effect across the subgroup.[2]

Vaduganathan M et al. Lancet. 2022 Sep 3;400(10354):757-767

Benefit of SGLT2i is Consistent, With no Attenuation, Across LVEF

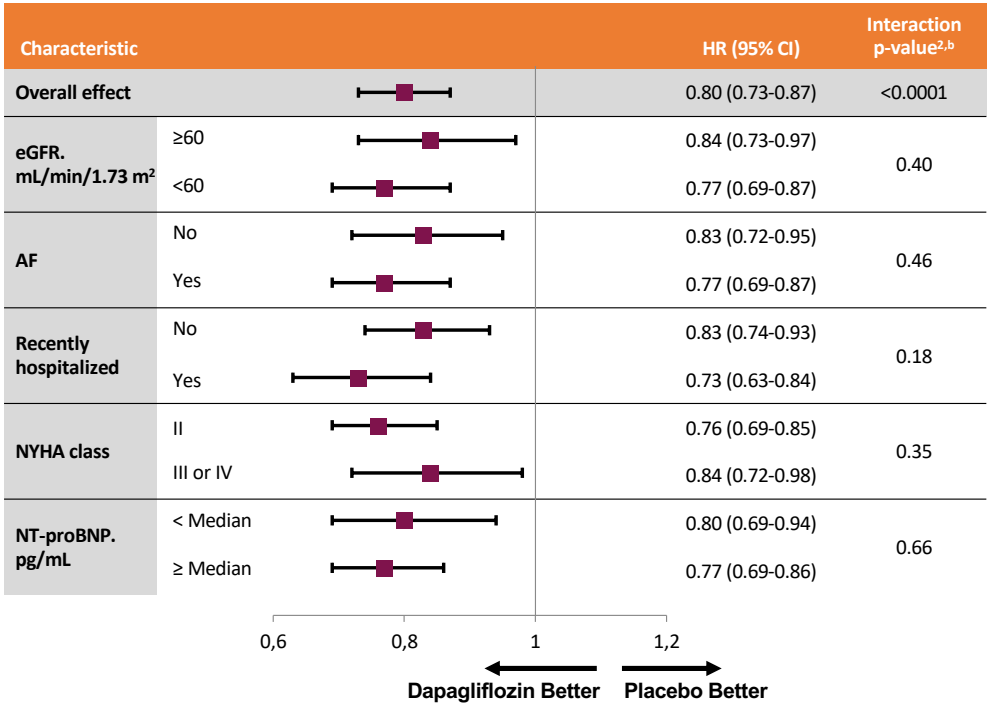


Differences among trial design, patient population, and treatment groups impact ability to directly compare results across different trials.

Kondo T et al. *Eur Heart J.* 2022;43(5):427-429; Jhund Nat Med 2022 Sep;28(9):1956-1964

DELIVER and EMPEROR-Preserved Meta-Analysis: Primary Composite Outcome[a] across Subgroups of Interest

Characteristic		HR (95% CI)	Interaction p-value[2,b]
Overall effect		0.80 (0.73-0.87)	<0.0001
LVEF. %	<50%	0.78 (0.67-0.90)	0.93
	50-59	0.79 (0.68-0.93)	
	≥60	0.81 (0.69-0.96)	
T2D	Yes	0.80 (0.71-0.90)	0.91
	No	0.79 (0.69-0.90)	
Age. yr	<65	0.85 (0.69-1.05)	0.50
	65-74	**0.81 (0.70-0.94)**	
	75-79	**0.70 (0.57-0.85)**	
	≥80	0.82 (0.69-0.98)	
Sex	Male	0.81 (0.72-0.91)	0.59
	Female	0.77 (0.67-0.89)	
Race	White	0.79 (0.71-0.87)	0.93
	Black	0.84 (0.55-1.29)	
	Asian	0.80 (0.64-1.00)	
	Other	0.89 (0.61-1.30)	
BMI. kg/m²	<30	0.79 (0.70-0.90)	0.98
	≥30	0.79 (0.70-0.90)	



[a]Cardiovascular Death or first hospitalizations for HF; [b]A non-significant result for an interaction test can be interpreted as consistency of effect across the subgroup.[3] HF = heart failure; HR = hazard ratio.

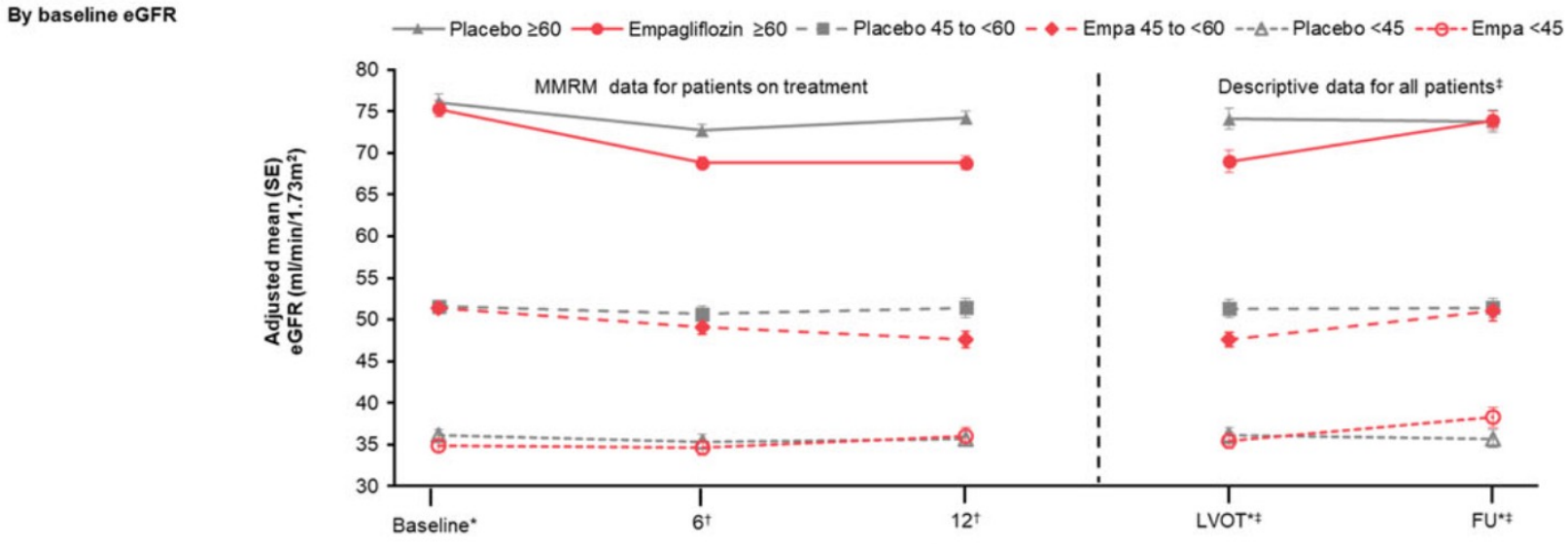
1. Vaduganathan M et al. Lancet. 2022 Sep 3;400(10354):757-767; 2. Vaduganathan M. Presented at: ESC Congress; August 26-29. 2022; Barcelona. Spain; 3. Alosh M et al. *J Biopharm Stat*. 2015;25(6):1161-1178.

Safety[a] of SGLT2 Inhibitors in Patients with HFmrEF/HFpEF[1,2]

Event, n (%)	DELIVER[1]		EMPEROR-Preserved[2]	
	Dapagliflozin N=3126	Placebo N=3127	Empagliflozin N=2996	Placebo N=2989
Any serious adverse event	1361 (43.5%)	1423 (45.5%)	1436 (47.9%)	1543 (51.6%)
Amputation	19 (0.6%)	25 (0.8 %)	16 (0.5%)	23 (0.8%)
Diabetic ketoacidosis	2 (0.1%)	0 (0.0 %)	4 (0.1%)	5 (0.2%)
Hypoglycaemia	6 (0.2 %)	7 (0.2 %)	73 (2.4%)	78 (2.6%)
Renal	73 (2.3 %)	79 (2.5 %)	363 (12.1%)	384 (12.8%)

Solomon SD et al. *NEJM* 2022;387(12):1089-1098; Anker SD et al. *NEJM* 2021;385(16):1451-1461

Kidney function after initiation of SGLTi



Patients analyzed, n						
eGFR category	≥60	Placebo	132	130	127	124	124
		Empagliflozin	131	128	119	124	124
	45 to <60	Placebo	78	77	72	74	74
		Empagliflozin	87	86	83	81	81
	<45	Placebo	91	89	82	84	84
		Empagliflozin	82	82	72	75	75

Anker SD et al, Circulation 2021 Oct 12;144(15):1265-1267

Factors associated with bacterial urinary tract infections

	UTI		p
	No (n = 41)	Yes (n = 60)	
	n (%) or median (min-max)	n (%) or median (min-max)	
Sex (female)	23 (56.1)	34 (56.7)	0.558 [c]
Age (year)	57 (45–67)	55.5 (45–67)	0.469 [u]
BMI (kg/m^2)	28 (24–34)	32 (25–41)	**< 0.001** [u]
HbA1c (%)	5.8 (5.6–7.8)	7.7 (5.6–11)	**< 0.001** [u]
FBG (mg/dL)	156 (112–234)	156 (112–234)	0.764 [u]
Glucosuria (present)	11 (26.8)	51 (85.0)	**< 0.001** [c]
SGLT-2i (+)	0 (0.0)	51 (85.0)	**< 0.001** [c]

[u] Mann Whitney U test (Monte Carlo),

[c] Pearson Chi square test (Monte Carlo)

Relative risk of urinary / genital infections in HFpEF with SGLT2-i

Meta-analysis N=12562

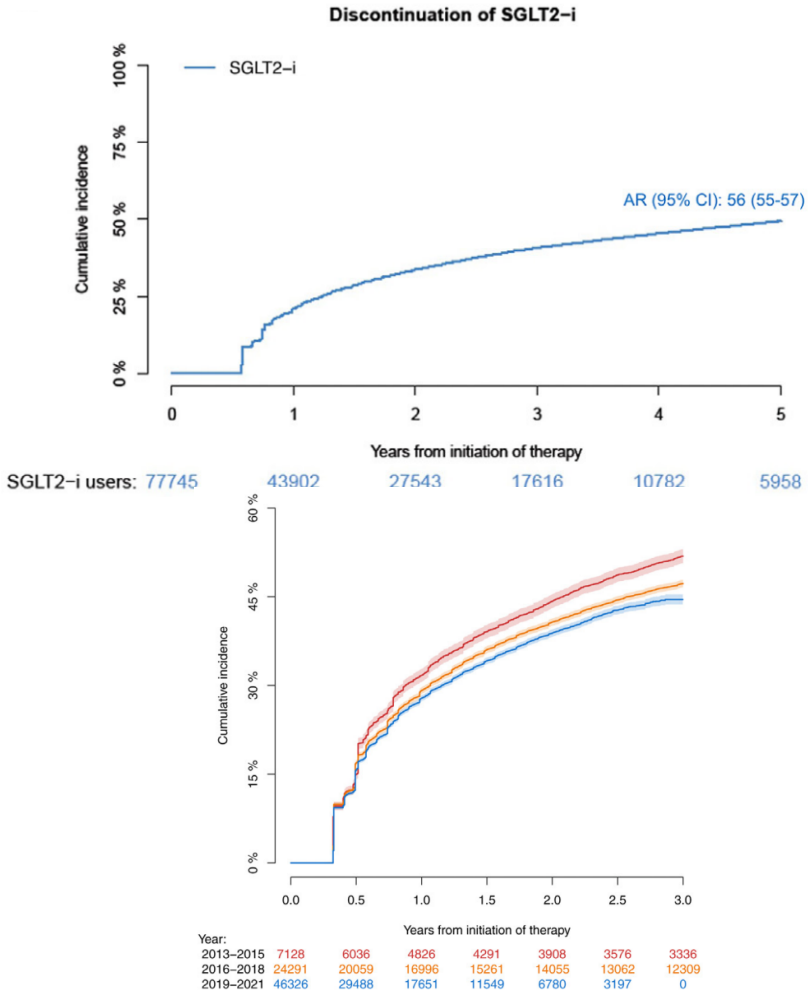
Genital: RR = 3.04 (95% CI 1.88-4.90), p < 0.001

Urinary: RR = 1.19 (95% CI 1.02-1.38), p = 0.029

Pozzi A, et al. Heart Fail Rev. 2024.

BMC endocr disord 2023 Oct 3;23(1):211

Discontinuation of SGLT-2 inhibitors



Covariables	Discontinuation of SGLT2-i	
	HR (95% CI)	P-value
Age		
40–60 years	Reference	
60–70 years	0.97 (0.94–1.00)	0.02*
70–80 years	1.14 (1.11–1.18)	<0.0001***
>80 years	1.39 (1.31–1.47)	<0.0001***
Sex		
Female	Reference	
Male	0.91 (0.89–0.93)	<0.0001***
Year of therapy initiation		
2013–2015	Reference	
2016–2018	0.87 (0.84–0.90)	<0.0001***
2019–2021	0.80 (0.77–0.83)	<0.0001***
Comorbidities		
Acute myocardial infarction	0.93 (0.88–0.98)	<0.01**
Ischemic heart disease	1.07 (1.03–1.11)	<0.0001***
Stroke	0.98 (0.93–1.03)	0.40
Peripheral artery disease	1.05 (0.97–1.14)	0.21
Heart failure	0.88 (0.84–0.93)	<0.0001***
Atrial fibrillation/flutter	0.89 (0.85–0.93)	<0.0001***
Hypertension	0.87 (0.85–0.90)	<0.0001***
Hypercholesterolemia	1.02 (0.99–1.05)	0.25
Chronic kidney disease	1.00 (0.95–1.05)	0.93
Chronic obstructive pulmonary disease	1.10 (1.05–1.16)	<0.0001***
Chronic kidney disease	1.13 (1.06–1.19)	<0.0001***
Malignancy	1.06 (1.02–1.10)	<0.01**

* <0.05; ** <0.01; *** <0.001.

Malik et al. Lancet Reg Health 2023 Mar 17:29:100617

Conclusions

- SGLT2i in HFpEF robustly reduce CV death or hospitalization for HF
- SGLT2i improve symptoms and quality of life rapidly after treatment initiation
- The benefit of SGLT2i is consistent across all subgroups
- The safety profile of SGLTi seems excellent - no significant increase in serious adverse events
- Moderate eGFR decrease at initiation does not need treatment interruption
- Recurrent genital infections are relatively common (elderly / overweight / diabetic)

- **The totality of evidence supports the use of SGLT2 inhibitors in all patients with HFpEF**

Thank you – merci !