

PLACE

PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

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di Confindustria

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della Tecnica**

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2022

SCOMPENSO CARDIACO CRONICO: UPDATE 2022

Scompenso cardiaco a funzione cardiaca preservata dal fenotipo alla terapia. L'inizio di una nuova era.

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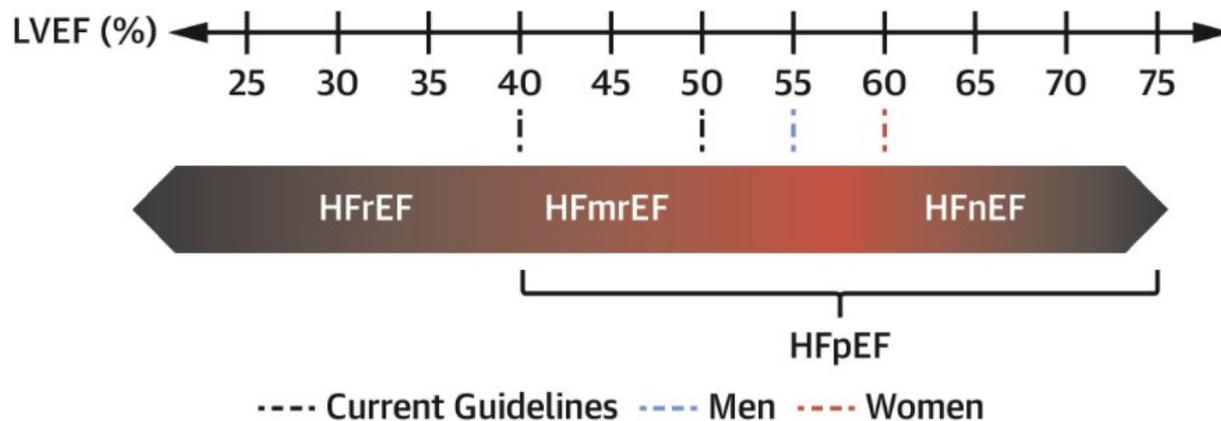
Dipartimento di Medicina e Specialità Mediche

Task Force CardioMetabolica ANMCO





CENTRAL ILLUSTRATION: Proposed Nomenclature in Heart Failure



Lam, C.S.P. et al. J Am Coll Cardiol. 2021;77(25):3217-25.

HF-Recovered if EF on enrollment to Penn HF Study was >50% but prior EF<50%.



A significant portion of HF-Recovered Patients had an abnormal biomarker (NT pro-BNP etc.) profile at baseline including 44% with detectable Troponin I

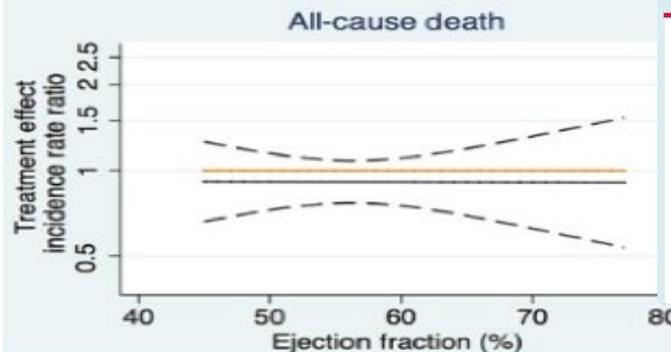
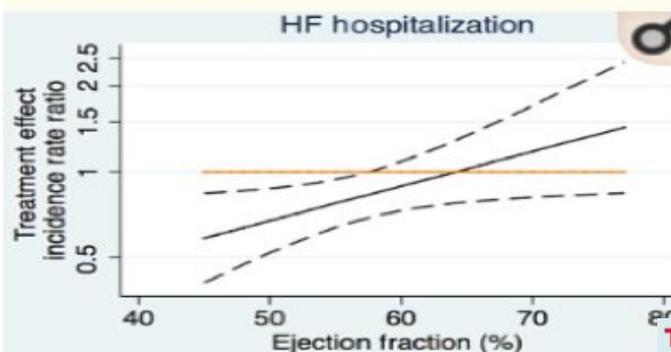
Influence of LVEF on outcomes and efficacy of spironolactone in patients with HFpEF

European Heart Journal Advance Access published May 20, 2016



European Heart Journal
doi:10.1093/eurheartj/ehw128

ESC GUIDELINES



2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

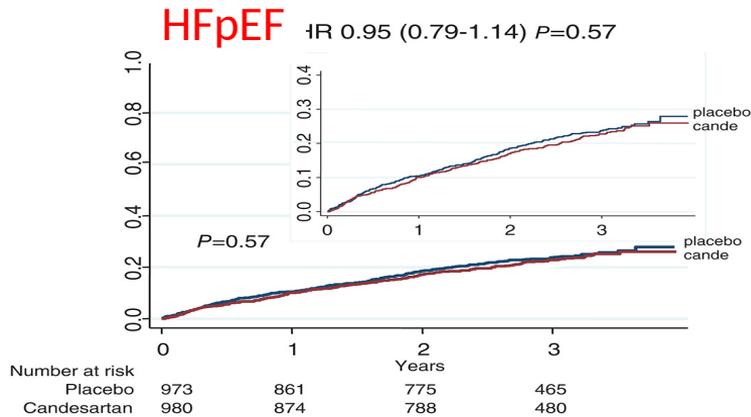
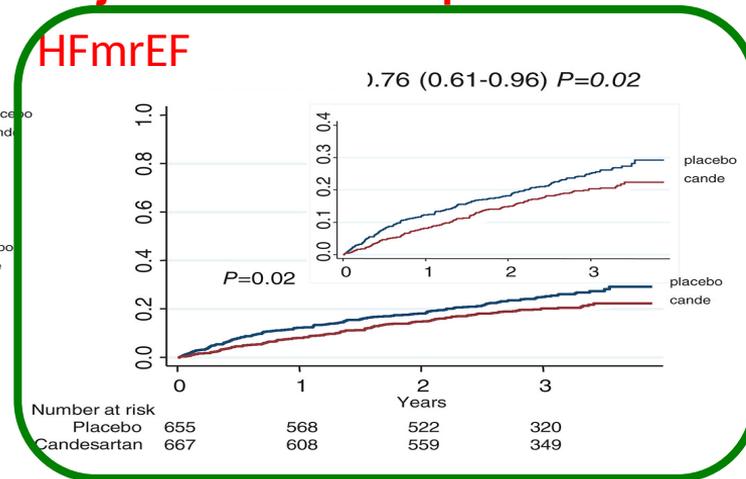
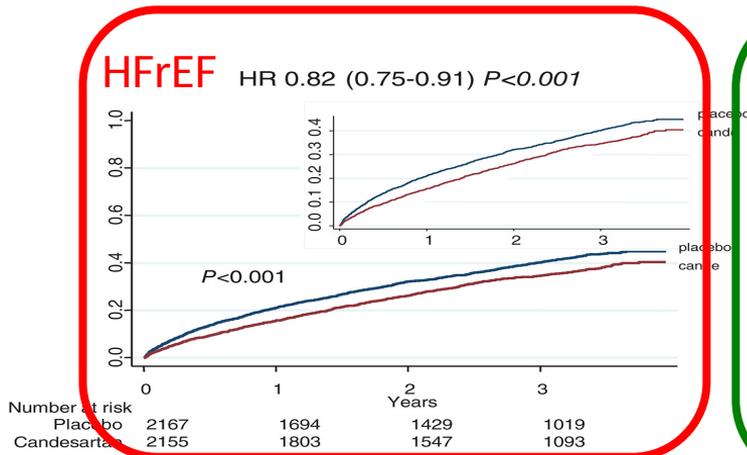
The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Table 3.1 Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

Type of HF	HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs ^a	Symptoms ± Signs ^a
	2	LVEF <40%	LVEF 40–49%
	3	–	1. Elevated levels of natriuretic peptides ^b ; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).
			1. Elevated levels of natriuretic peptides ^b ; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).

SOLOMON SD et al EHJ 2016;37:455–462

Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum

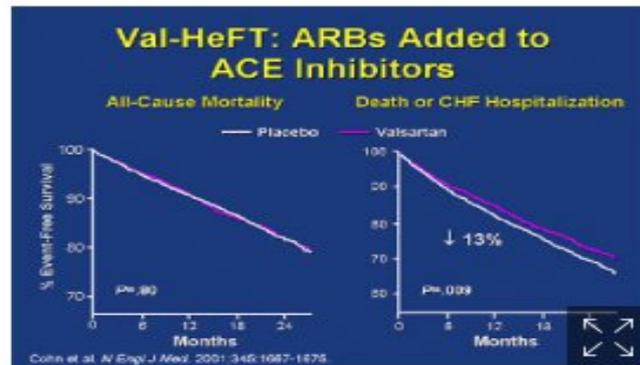
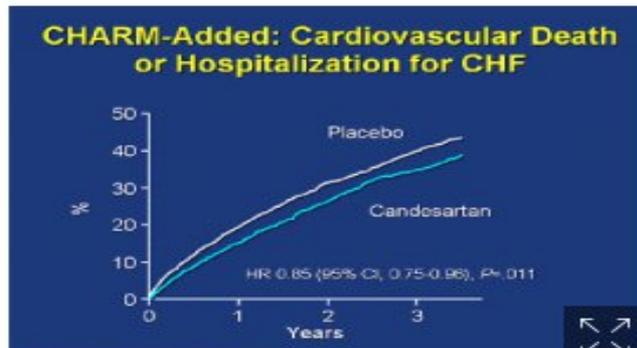


<http://dx.doi.org/10.1714/3285.32584>

Comparing the Results

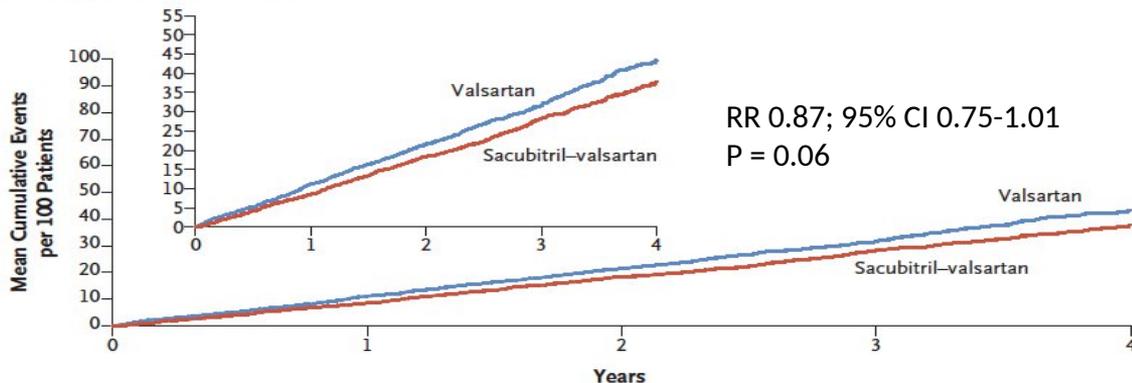
In the CHARM Trial, there was no significant reduction in the risk of cardiovascular death; it was about 10% to 11%. There was a 15% lower risk of the combined end point -- a relatively modest effect and not a mortality effect. The effect was primarily on hospitalizations for heart failure.

In every single trial in which an ARB has been added to an ACE inhibitor and a beta-blocker, we have not seen an incremental effect on mortality.

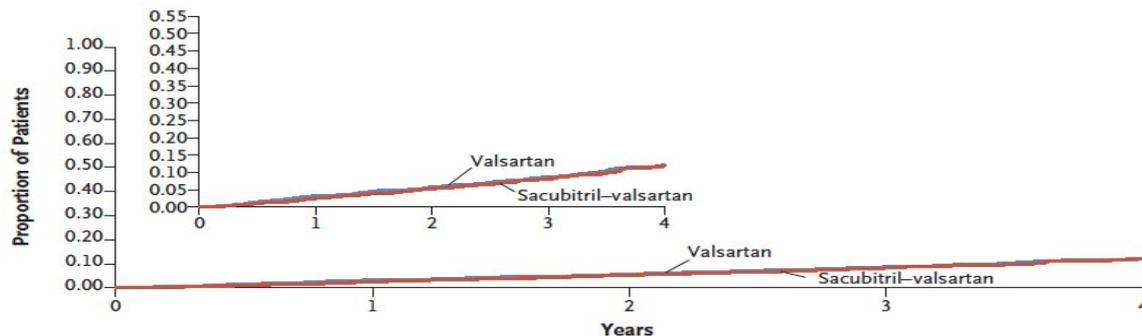


PARAGON HF

B Total Hospitalizations for Heart Failure

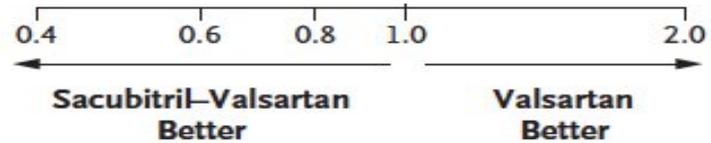


C Death from Cardiovascular Causes



PARAGON-HF

Subgroup	No. of Events/No. of Patients	Rate Ratio (95% CI)
Left ventricular ejection fraction		
≤Median (57%)	1048/2495	0.78 (0.64–0.95)
>Median (57%)	855/2301	1.00 (0.81–1.23)
Sex		
Male	980/2317	1.03 (0.85–1.25)
Female	923/2479	0.73 (0.59–0.90)



Solomon SD et al NEJM DOI: 10.1056/NEJMoa1908655

First HFH 537/658 p <0.001

0.79 (0.71–0.89)

PARADIGM-HF

McMurray JJV NEJM DOI: 10.1056/NEJMoa1409077

Toward Extension to Patients With HF Middle Range Ejection Fraction

TABLE 1 Comparison of PARAGON-HF, CHARM-P, TOPCAT Trials on LVEF Threshold Values and HF Hospital Stay Outcomes

	CHARM-P (n=3,023)	TOPCAT (n=3,445)	PARAGON-HF (n=4,800)
Treatment Arms	Candesartan vs. placebo	Spironolactone vs. Placebo	Sacubitril-Valsartan vs. Valsartan
Key inclusion criteria	LVEF >40% NYHA functional class II-IV, prior CVH	LVEF ≥45% >1 HF symptom, >1 HF sign, elevated NP, or HFH	LVEF >45% NYHA functional class II-IV, Elevated NT-proBNP. Mildly elevated NT-proBNP if prior HFH, structural heart disease (LAE/LVH)
Endpoint	First of either CVD or HFH	First of either CVD, HFH, or RSD	CVD and total HFH (first and recurrent)
Heart failure hospital stays in HFpEF trials based on LVEF	LVEF ≥50% HR: 0.78, 95% CI: 0.59-1.03 LVEF 40%-49% HR: 0.48, 95% CI: 0.33-0.70	LVEF ≥60%: HR: 0.98, 95% CI: 0.74- 1.30 LVEF <50%: HR: 0.76, 95% CI: 0.46-1.27	LVEF 57.6 ± 7.8% HR: 0.85; 95% CI: 0.72-1.00 LVEF <57%: HR: 0.78; 95% CI 0.64-0.95

“Thus, angiotensin aldosterone and peptidases inhibition should be tested in the unexplored HFmrEF currently lacking valid treatment.”

Grona E, Iacoviello M, Napoli C. JACC Heart Fail 10.1016/j.jchf.2020.06.005

“We appreciate the letter from Dr. Grona and colleagues.... The consistency of these observations suggests that....”

Cunningham JW, Vaduganathan M, Claggett BL, McMurray JJV, Solomon SD JACC Heart Fail 10.1016/j.jchf.2020.06.005

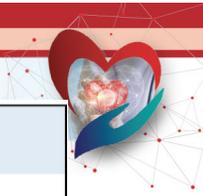
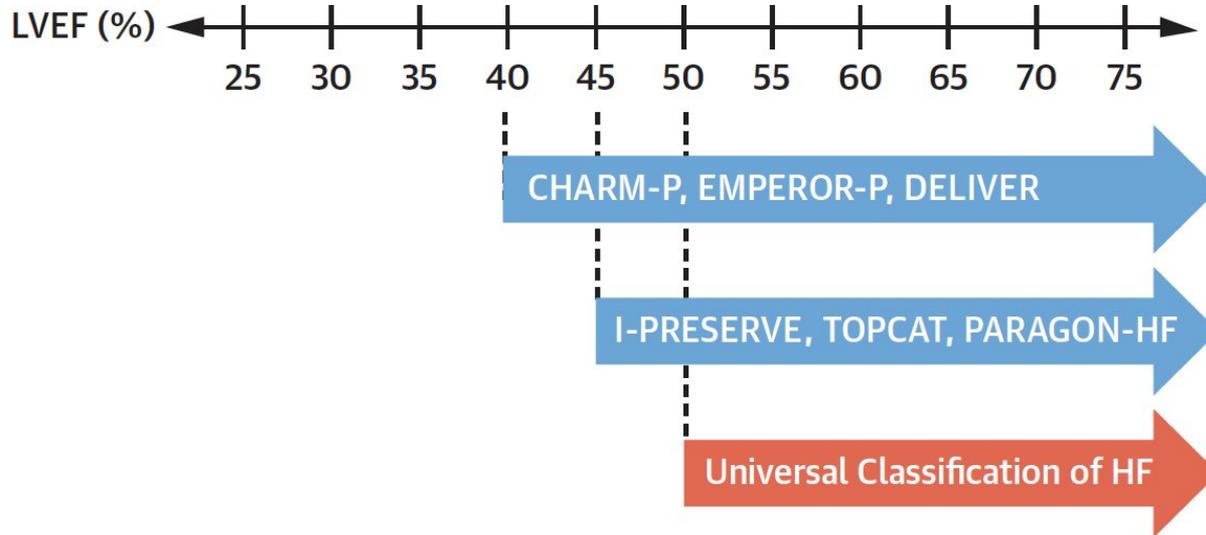
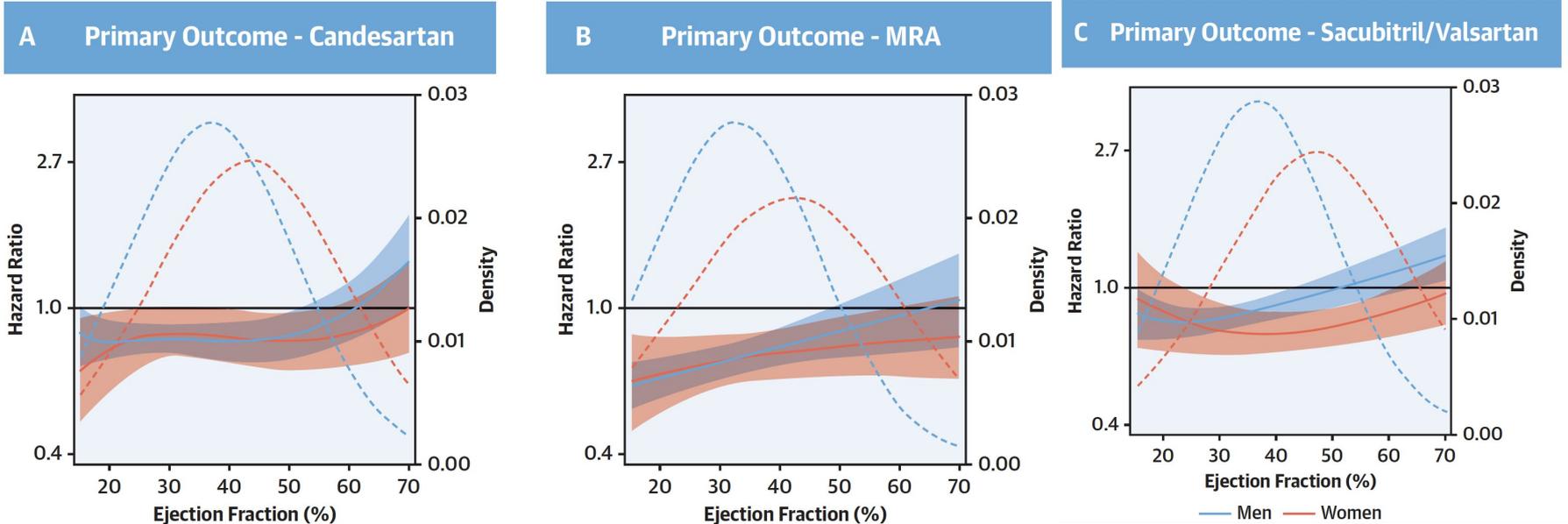


FIGURE 2 LVEF Cutoffs Used as Inclusion Criteria in Clinical Trials and in the Universal Definition of HF



Interaction Between LVEF, Sex, and Neurohormonal Modulators in HF



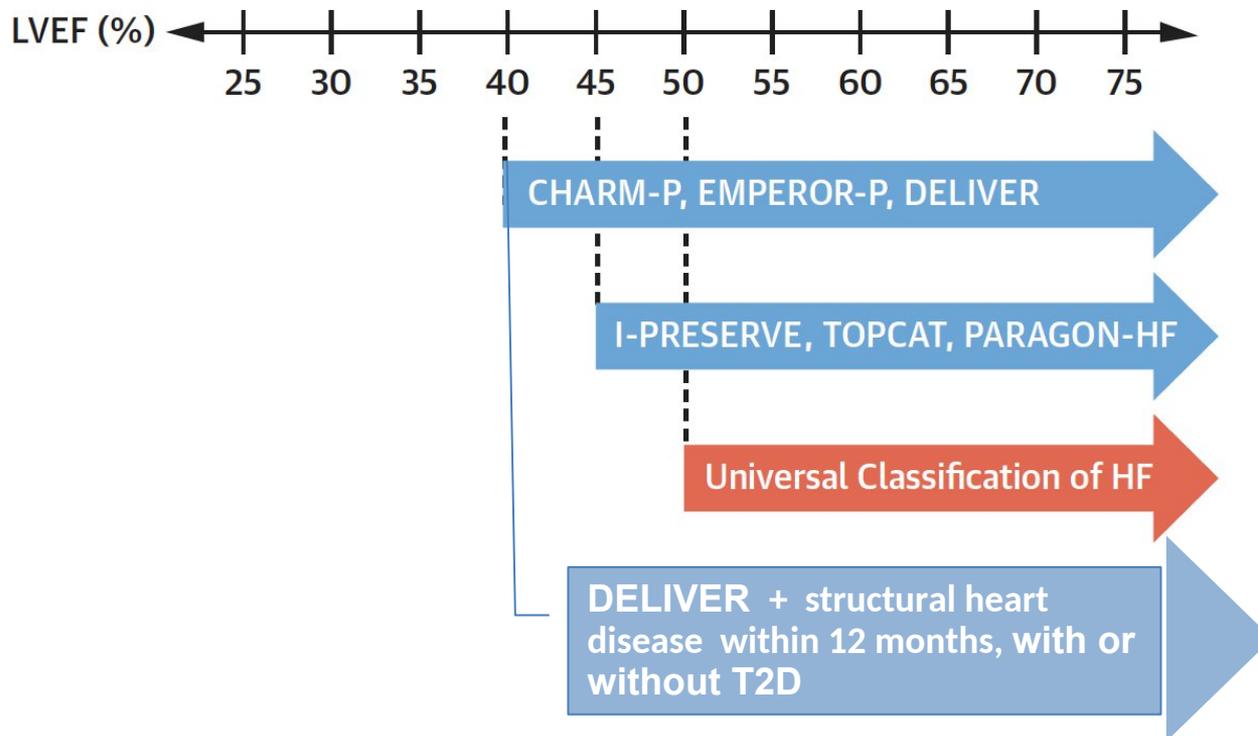
EMPEROR PRESERVED

Subgroup	Empagliflozin <i>no. of patients with events/total no.</i>	Placebo <i>no. of patients with events/total no.</i>	Hazard Ratio (95% CI)
LVEF at baseline			
<50%	145/995	193/988	0.71 (0.57–0.88)
≥50% to <60%	138/1028	173/1030	0.80 (0.64–0.99)
≥60%	132/974	145/973	0.87 (0.69–1.10)

ANKER SD et al. NEJM 2021



FIGURE 2 LVEF Cutoffs Used as Inclusion Criteria in Clinical Trials and in the Universal Definition of HF



Largest and broadest trial to date in patients with heart failure and mildly reduced or preserved ejection fraction¹



6263 Patients²



- Age ≥ 40 with/without T2D
- NYHA class II-IV
- LVEF $>40\%$ ^a with structural heart disease^b
- Ambulatory or hospitalized^c
- Elevated NT-proBNP levels
- eGFR ≥ 25 mL/min/1.73 m²



DAPA 10 mg
n=3131

Placebo
n=3132

Median follow-up: 2.3 years

Baseline characteristics^{1,2}



1011 pg/mL

Median NT-proBNP



54%

Average LVEF



55%

Without T2D



50%

With an eGFR
 <60 mL/min/1.73 m²



10%

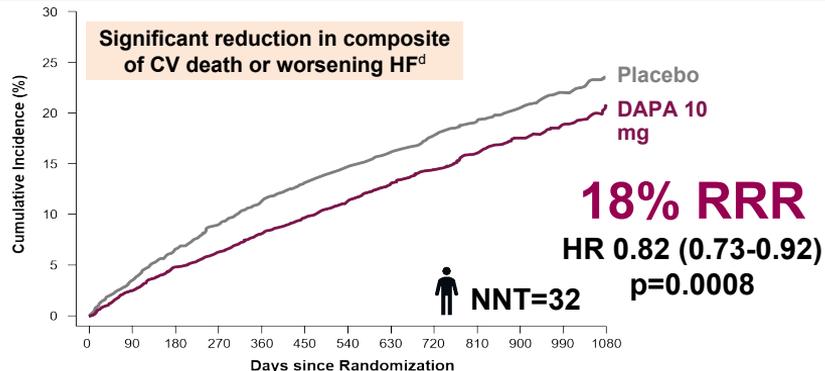
Hospitalized or
recently discharged



~18%

With prior
LVEF $\leq 40\%$

Primary Endpoint^{2,3}



- ❖ All individual components occurred less frequently in the DAPA group
- ❖ Treatment benefit was consistent across all prespecified subgroups

Secondary Endpoints²



Significant reduction in total^e worsening HF events^d and CV deaths



Significant improvement in HF symptoms



Mortality rates numerically lower

Safety



Results **consistent with the well-established safety profile²⁻⁴**



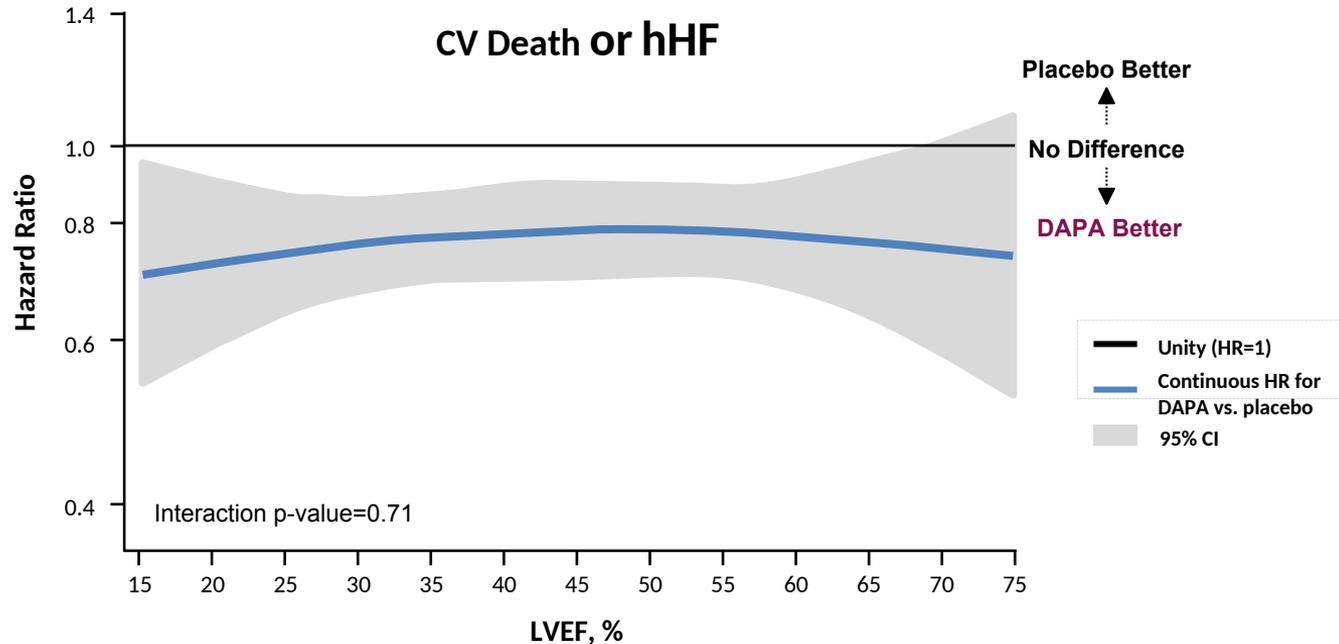
SGLT2 inhibitors, including **dapagliflozin**, are **recommended in patients with HF regardless of LVEF** in Treatment Guidelines⁵

^aPrior LVEF $\leq 40\%$ also included; ^bLV hypertrophy or LA enlargement; ^cOff IV HF therapy (including diuretics) for ≥ 24 hours; ^dhHF or urgent HF visit; ^eFirst and recurrent.





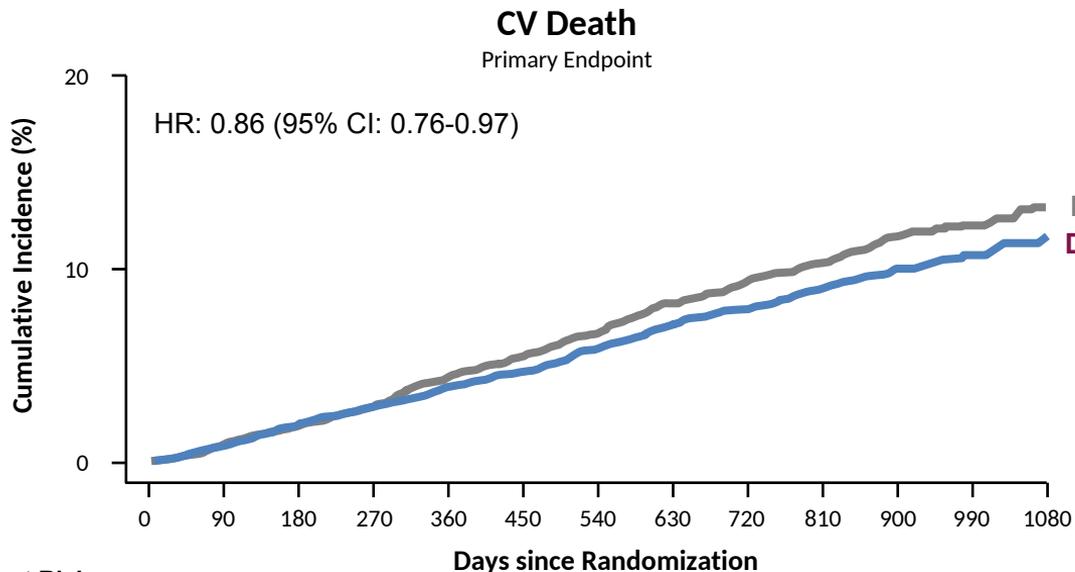
Dapagliflozin Demonstrated Benefit in the Composite of CV Death or hHF Across the Range of LVEF



CV = cardiovascular; DAPA = dapagliflozin; hHF = heart failure hospitalization; HR= hazard ratio; LVEF = left ventricular ejection fraction.

Jhund PS et al. Online ahead of print. *Nat Med.* 2022.

Dapagliflozin Significantly Reduced CV Death Across the Range of LVEF



14% RRR
1.5% ARR
p=0.01

Number at Risk

	0	90	180	270	360	450	540	630	720	810	900	990	1080
DAPA 10 mg	5504	5430	5339	5254	5087	4556	3826	3010	2403	1781	1312	903	441
Placebo	5503	5426	5333	5238	5048	4508	3789	2978	2391	1767	1306	910	451

Results were unchanged when undetermined deaths were excluded from the definition of CV death or if the definition of CV death used in each trial was examined.

ARR = absolute risk reduction; CV = cardiovascular; DAPA = dapagliflozin; HF = heart failure; HR = hazard ratio; RRR = relative risk reduction.

CONCLUSIONI

- I FARMACI INIBITORI DEL RAAS CONSENTONO DI RIDURRE LA PROGRESSIONE DELLO SCOMPENSO CARDIACO, CON INSUFFICIENZA CARDIACA MANIFESTA IN TUTTI I SOGGETTI:
 - DI GENERE FEMMINILE CON FRAZIONE D'EIEZIONE < DEL 60%
 - DI GENERE MASCHILE CON FRAZIONE D'EIEZIONE < DEL 55%
 - I FARMACI SGLT2i EMPAGLIFLOZIN E DAPAGLIFLOZIN (10 MG OID) HANNO DIMOSTRATO DI RIDURRE LA PROGRESSIONE DELLO SCOMPENSO CARDIACO E LA MORTALITA' CARDIOVASCOLARE IN TUTTO LO SPETTRO DEI VALORI DELLA FRAZIONE D'EIEZIONE
- NELL' ANALISI PREDEFINITAPOST HOC, CONDOTTA NEGLI STUDI CON DAPAGLIFLOZIN **NON È STATA RILEVATA ALCUNA MODIFICA DELL'EFFETTO DEL FARMACO** PER LA FE ESAMINATA COME VARIABILE CATEGORICA O CONTINUA (P per INTERAZIONE, RISPETTIVAMENTE 0,63 E 0,94).