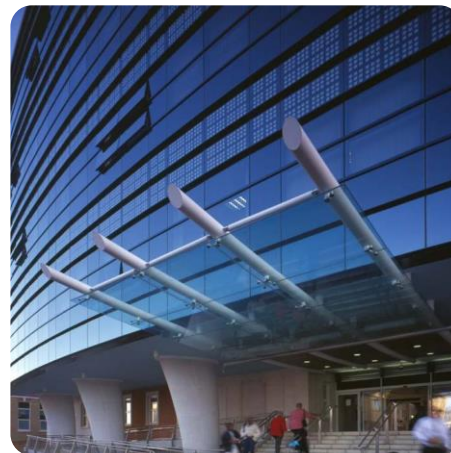


HFmrEF: How should we treat it?

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- What is HFmrEF?
- What is the evidence for disease-modifying therapies?
- Moving towards a treatment algorithm

Chronic Heart Failure Phenotypes

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs ^a	Symptoms ± Signs ^a	Symptoms ± Signs ^a
	2	LVEF ≤40%	LVEF 41–49% ^b	LVEF ≥50%
	3	-	-	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 ^c

The problem with LVEF and treatment

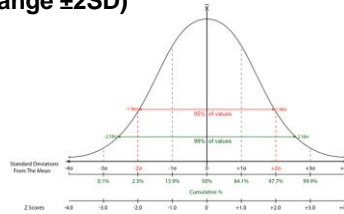
“Normal population”

ASE/EACVI (2015)

Normal EF (normal range $\pm 2SD$)

52-72% men

54-74% women



Problems with LVEF (by echo)

Within patient variability

Measurement-intra and interobserver variability

Method used to measure LVEF

Estimations-“eye-ball”-translating to LVEF

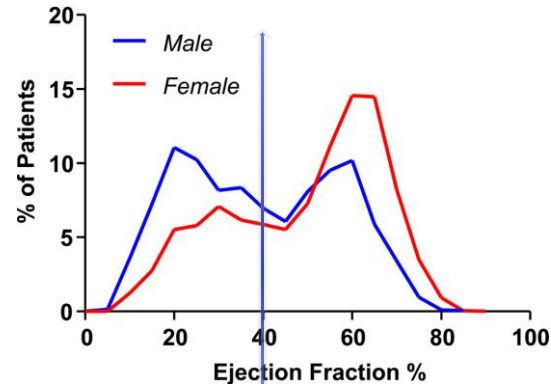
Digit preference etc.

Problematic for a tight window of 41-49%

Could be 30-59%

“Heart Failure” Population

Hospital Based Sample (n = 4910)



HFrEF Trials

LVEF < 40%

Usually $\leq 35\%$

HFpEF

> 40% or 45%

Few > 50%

Mixed bag-mild LVSD, recovered LVSD, low normal, HFpEF

Subgroup Analysis and Meta-Analysis



No specific trials of ACEi in HFmrEF

- **PEP-CHF (Neutral)**

- perindopril in HFpEF
- included patients with LVEF>40%
- did not report outcomes according to LVEF

- **Patients with HFmrEF**

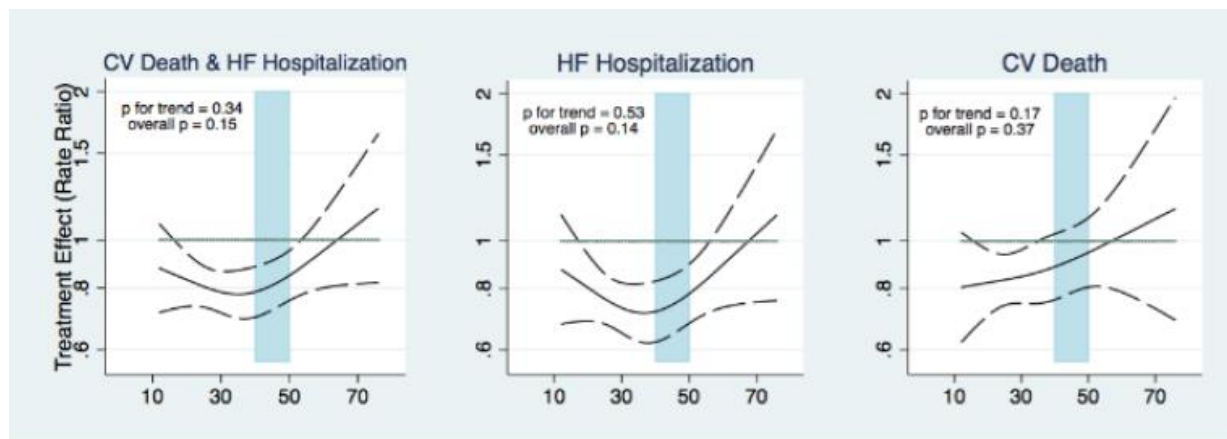
- ACEi for other evidence-based reasons
- CAD, hypertension, or post MI LVSD trials

ARBs Effects of Candesartan in CHARM

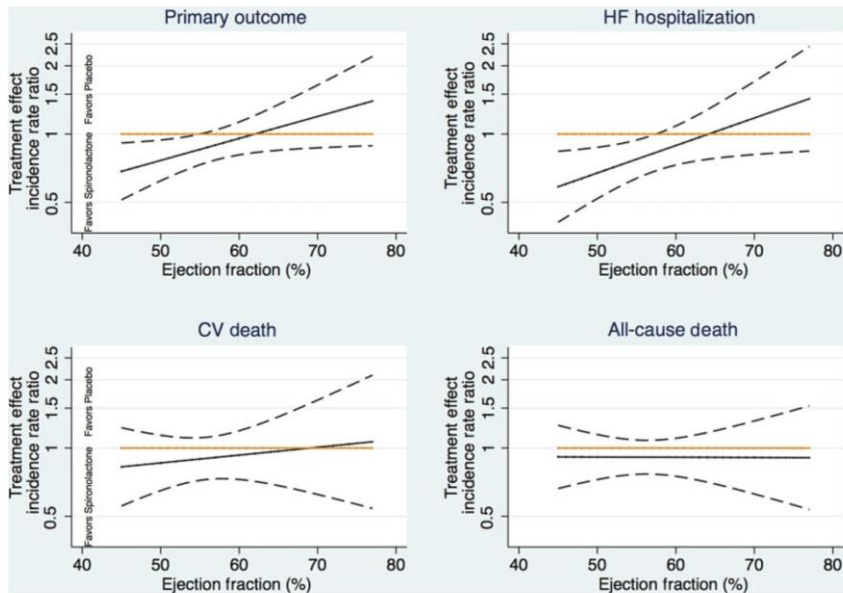
CHARM-Preserved -No significant reduction in CV death or HF hospitalization (HR 0.89, $p=0.118$ unadjusted, HR=0.86, $p=0.051$ adjusted)

CHARM-Programme-the entire spectrum of EF, Candesartan was effective in HFrEF
No heterogeneity with respect to LVEF ($p=0.33$)

HFmrEF subgroup analysis-17%, $n=1322$, CV death or HFH- HR 0.76, (0.6-0.96) $p=0.02$

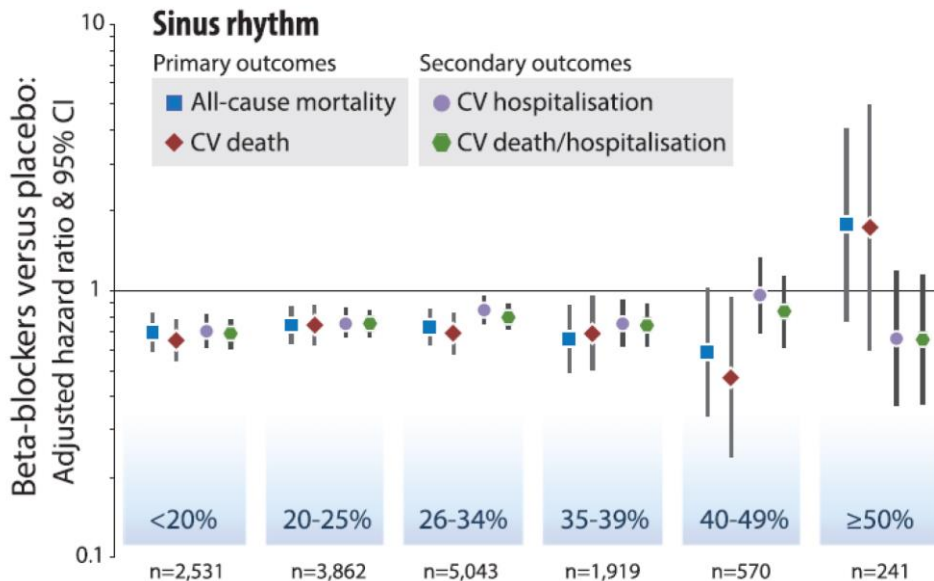


MRA TOPCAT



Spironolactone reduced HF hospitalizations for those with a LVEF < 55%, similar trend for CV death but not all-cause death

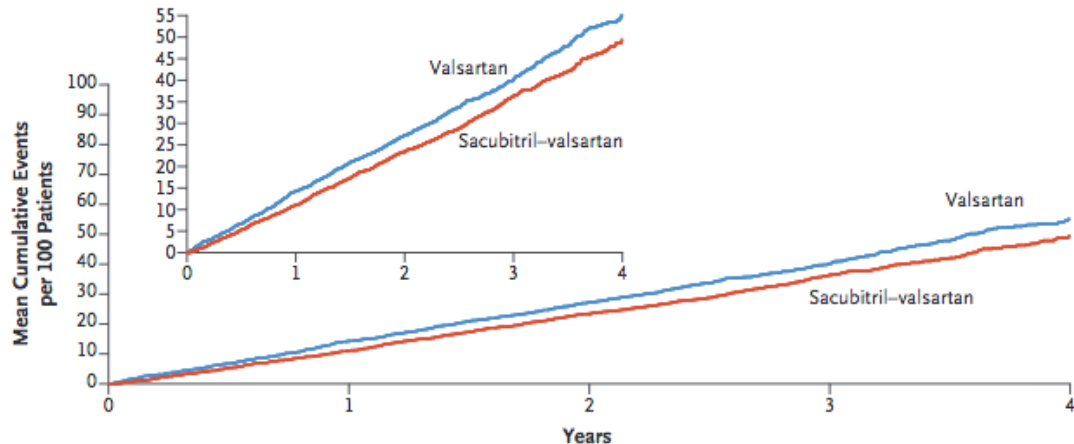
BB: IPD Meta-analysis of landmark trials



***SENIORS** trial- nebivolol significantly ↓ ACM or CV hospital admissions, 35% -LVEF 35-50% . (no significant influence of LVEF on the effect of nebivolol on primary outcome)

ARNI: PARAGON-HF (LVEF \geq 45%)

A Total Hospitalizations for Heart Failure and Death from Cardiovascular Causes



Left ventricular ejection fraction

≤Median (57%)

1048/2495

—■—

0.78 (0.64–0.95)

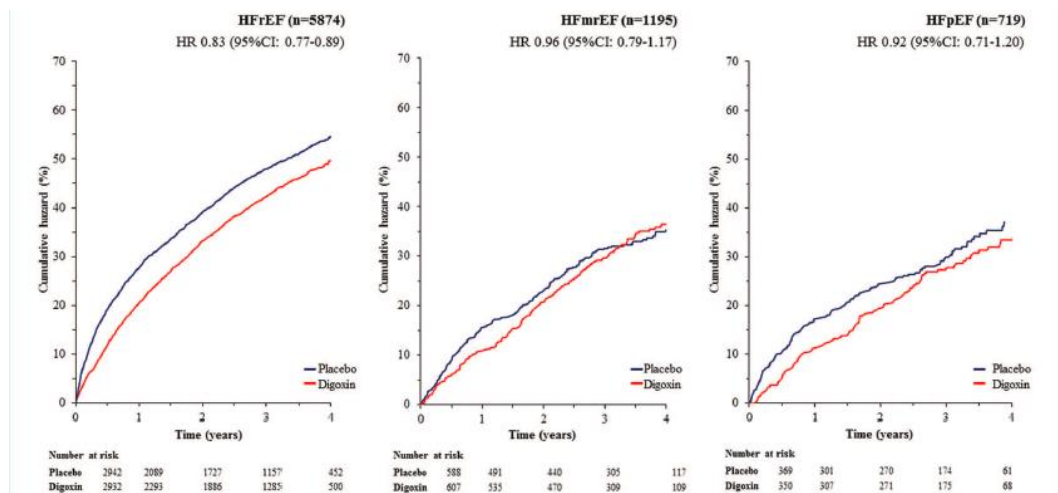
>Median (57%)

855/2301

—■—

1.00 (0.81–1.23)

**DIG trial subgroup analysis, HFmrEF in SR,
Trend to fewer hospitalisations for HF with digoxin, no decrease in mortality**



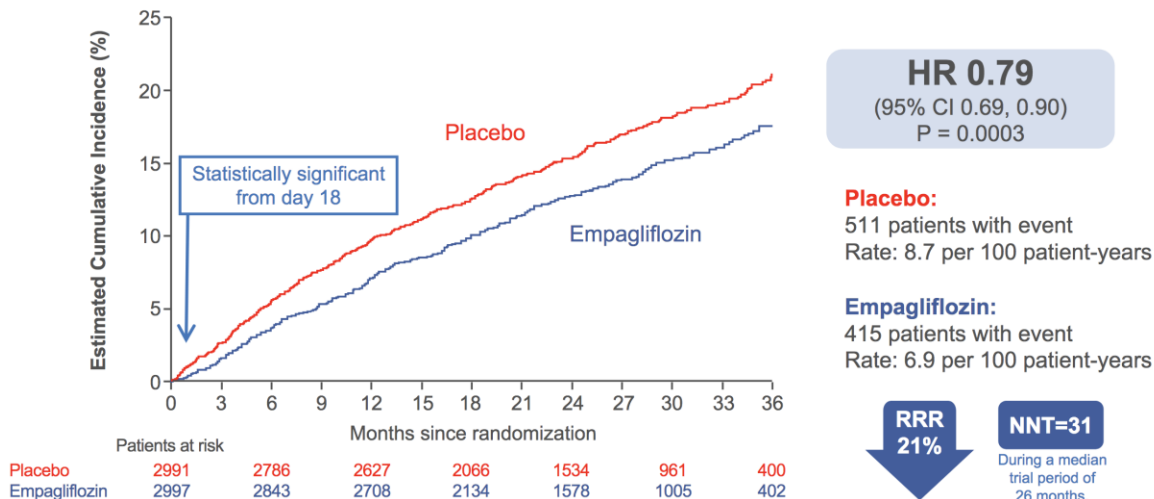
Drug Treatment of HFmrEF

Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs. ¹³⁷	I	C
An ACE-I may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. ¹¹	IIb	C
An ARB may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. ²⁴⁵	IIb	C
A beta-blocker may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. ^{12,119}	IIb	C
An MRA may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. ²⁴⁶	IIb	C
Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. ^{13,247}	IIb	C

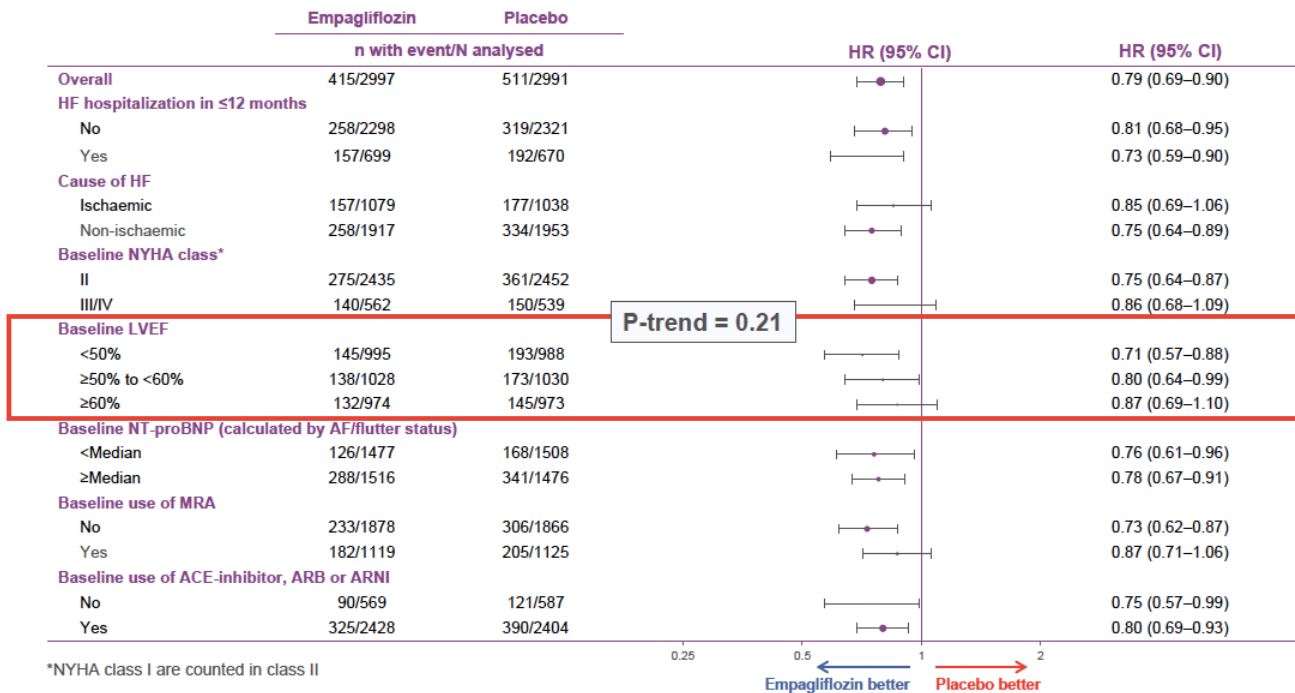
SGLT2i Empagliflozin in HFmrEF and HFpEF

5988 patients with HF and LVEF>40% ± T2DM at baseline

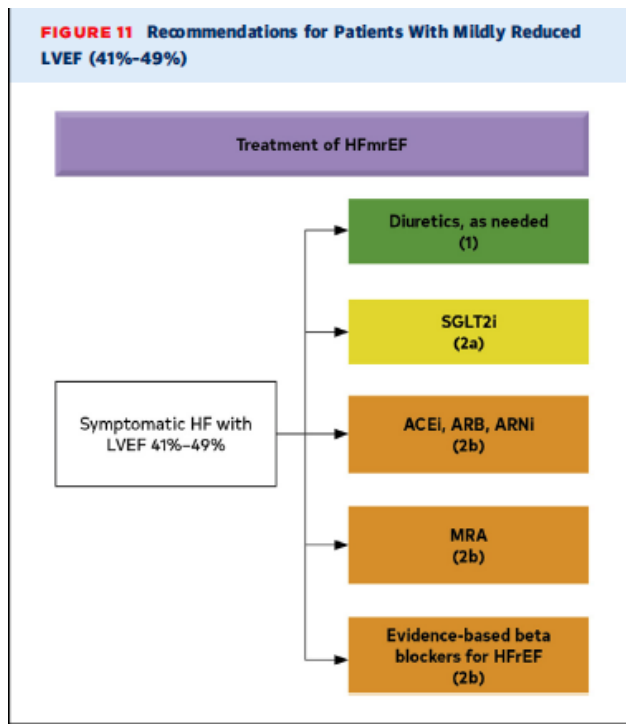
Primary Endpoint – Composite of Cardiovascular Death or Heart Failure Hospitalization



Emperor-Preserved and LVEF



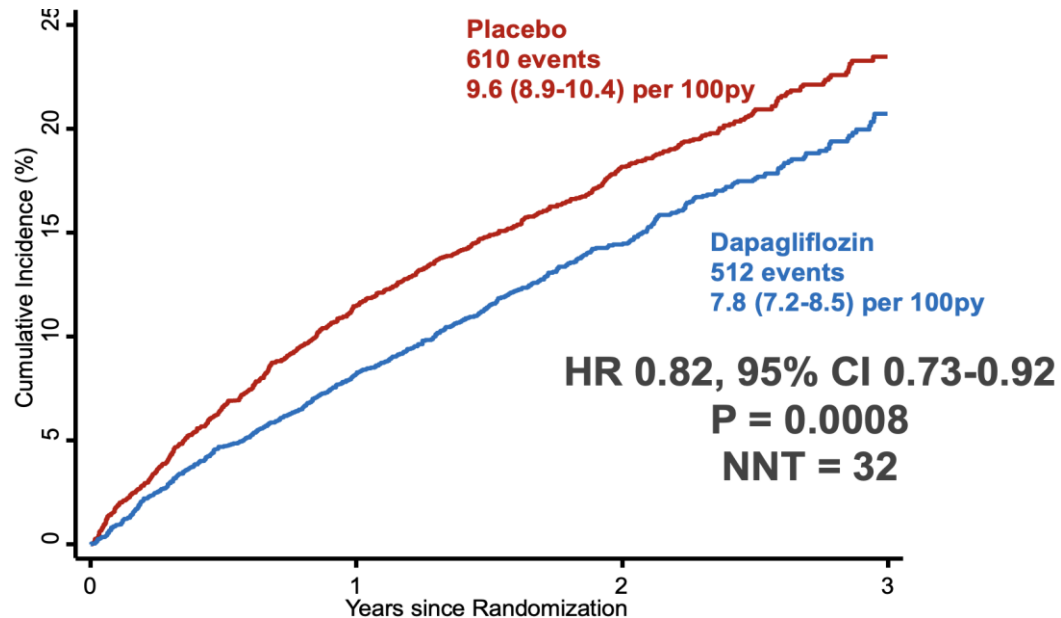
Treatment of HFmrEF-ACC/AHA/HFSA Guideline 2022



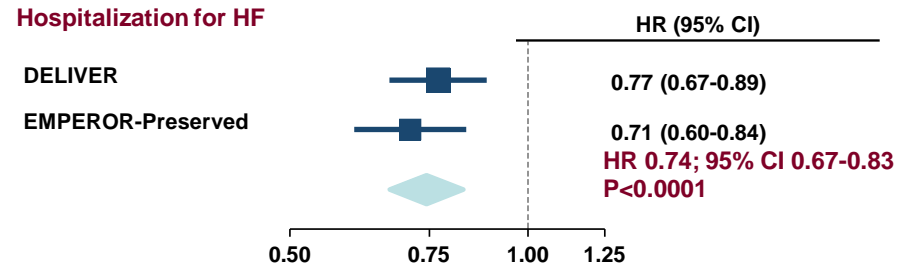
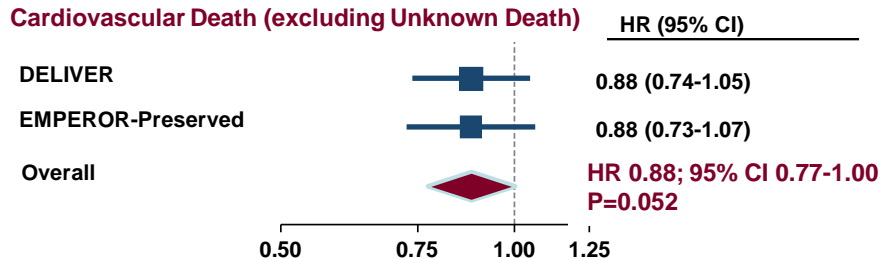
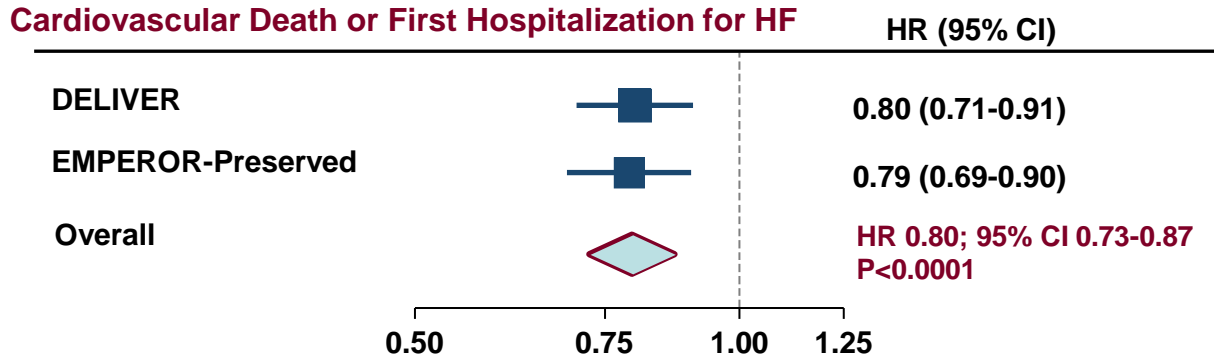
DELIVER-HFpEF and HFmrEF

- Age \geq 40 years
- NYHA class II-IV
- LVEF $>$ 40% (including prior LVEF \leq 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

Primary composite endpoint of CV death or worsening HF



DELIVER and EMPEROR-Preserved Meta-Analysis



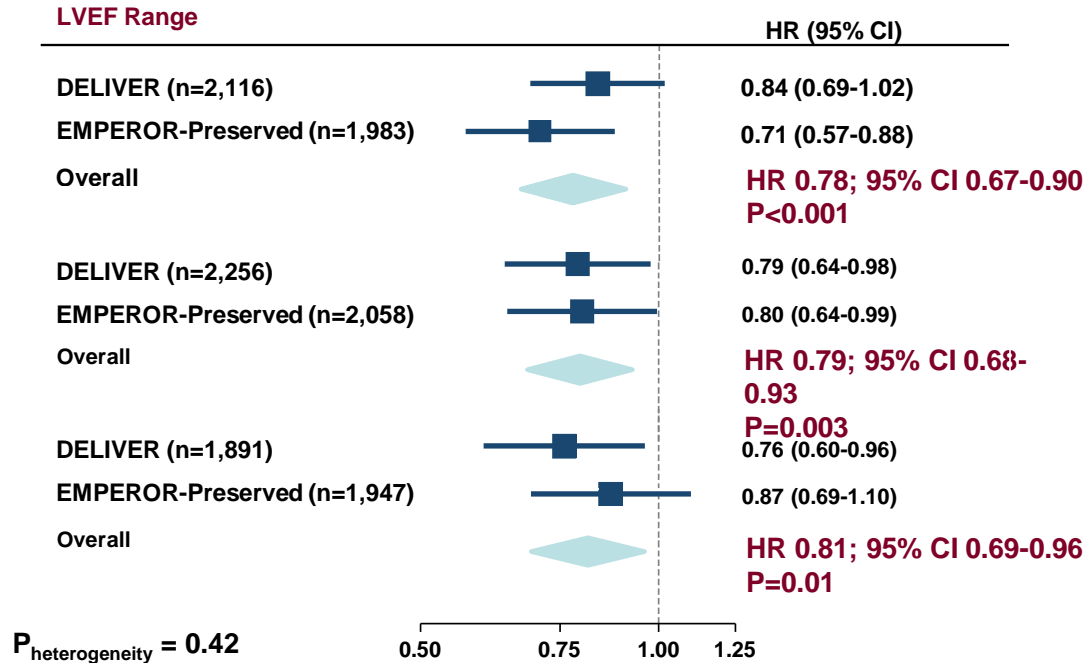
$P_{\text{heterogeneity}} > 0.40$ for all endpoints

DELIVER and EMPEROR-Preserved Meta-Analysis

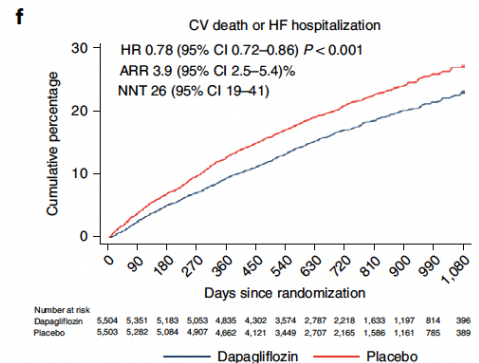
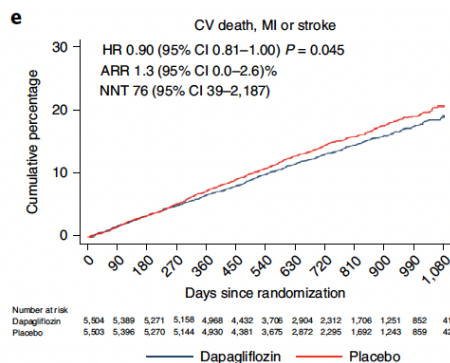
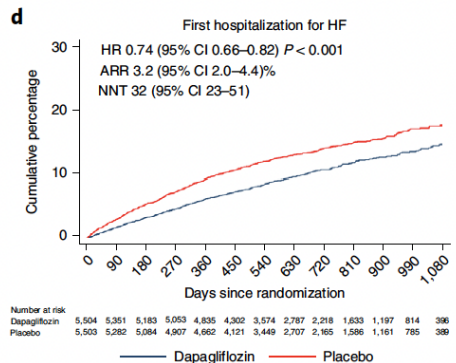
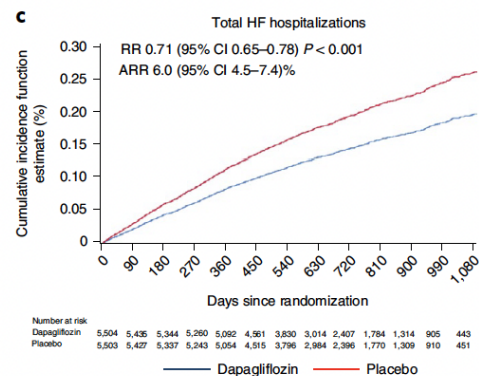
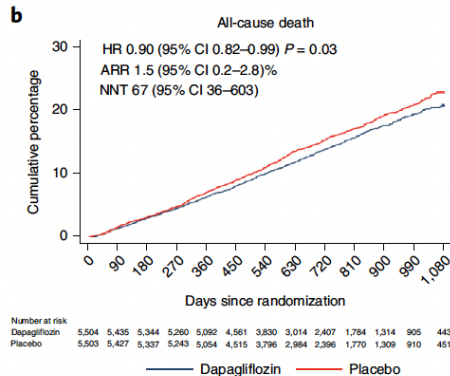
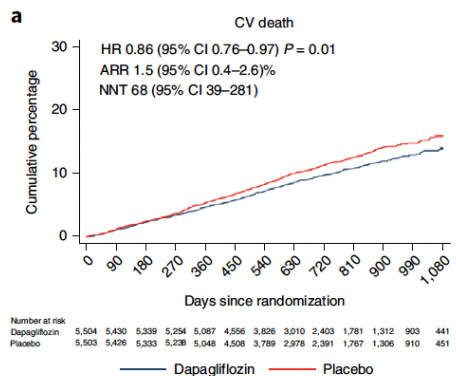
LVEF 41-49%

LVEF 50-59%

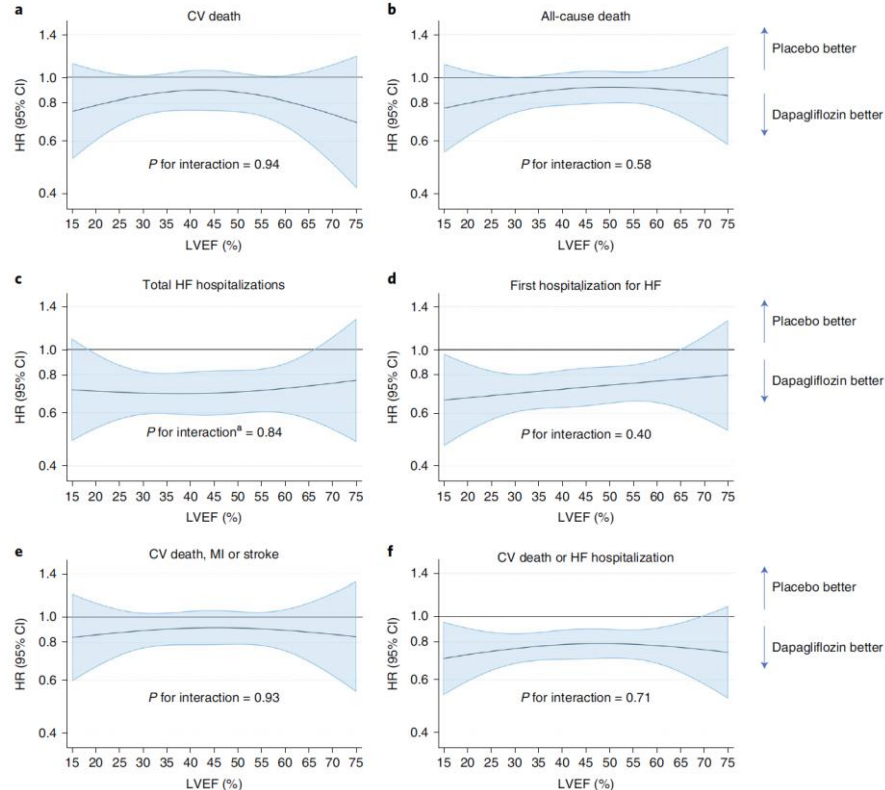
LVEF $\geq 60\%$



DAPA-HF and DELIVER IPD Meta-analysis

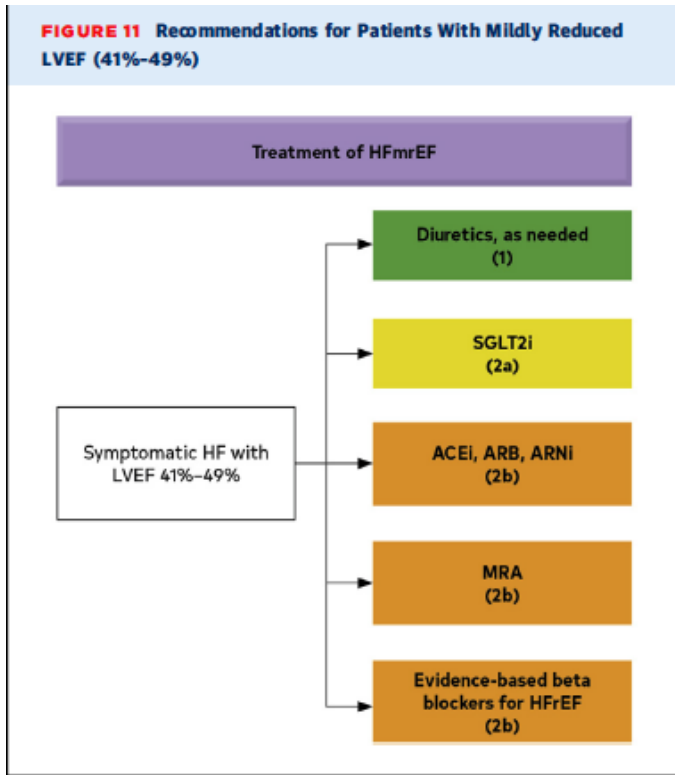


LVEF and Dapagliflozin in DAPA-HF and DELIVER



Treat of HFmrEF-future GLs

FIGURE 11 Recommendations for Patients With Mildly Reduced LVEF (41%-49%)



? SGLT2i | A

Phenotypic approach to the management of HFrmEF?

