

Table 1. Completed phase 3-4 randomised clinical trials in patients with HFpEF

Trial	Phase	N	Intervention	Major inclusion criteria	Duration	Primary end-point(s)/outcome
Diuretics						
CHAMPION trial HFpEF substudy: Adamson et al. ¹ , 2014 Abraham et al. ² , 2011 Costanzo et al. ³ , 2016	3	119	Ambulatory PAP-guided HF care vs. standard of care	EF≥40%, NYHA III, recent HF hospitalisation	≥6 months	More changes in diuretics and vasodilator therapies with knowledge of PAP. Reduced HF hospitalisation overall (and in HFpEF substudy). NNT=2 to prevent 1 HFpEF hospitalisation over 18 months.
Angiotensin converting enzyme inhibitors/angiotensin receptor blockers						
CHARM-Preserved Yusuf et al. ⁴ , 2003	3	3023	Candesartan vs placebo	EF≥40%, NYHA II-IV, previous HF hospitalisation [age 67.1±11y, 60% male, 45% prior MI]	36 months (median)	Non-significant reduction in composite endpoint (CV death or HF hospitalisation). No difference in CV mortality but fewer single and multiple HF hospitalisations in the Candesartan group.
I-PRESERVE Massie et al. ⁵ , 2008	3	4128	Irbesartan vs placebo	EF≥45%, age≥60y, NYHA II-IV, sinus rhythm	49 months (mean)	Neutral across all endpoints: composite (all-cause mortality or CV hospitalisation), death, CV hospitalisation. Post hoc analysis of patients with NT-proBNP below the median – showed benefit for the composite outcome and new composite outcome of HF events (death due to worsening HF, SCD; HF hospitalisation) ⁶
PEP-CHF Cleland et al. ⁷ , 2006	3	850	Perindopril vs placebo	EF≥40%, age≥70y, diastolic dysfunction (echo)	2 years (median)	Enrollment and event rates lower than expected. Insufficient power for primary endpoint (all-cause mortality/HF hospitalisation). Substantial crossover between groups. Cross-over to open label ACEI after 1 year (≈26-28%). Trend towards decreased mortality and HF hospitalisation at 1y. No change at 3y. Improved 6MWD and NYHA class.

Mineralocorticoid receptor antagonists						
RAAM-PEF Deswal et al. ⁸ , 2011	4	44	Eplerenone vs placebo	EF≥50%, NYHA II-III, BNP>62pg/mL, on ACEI/ARB for >4 weeks	6 months	No change in 6MWD. Some improvement in diastolic function (echocardiography) and markers of collagen turnover.
TOPCAT Pitt et al. ⁹ , 2014	3	3445	Spirolactone vs placebo	EF≥45%, controlled hypertension, HF hospitalisation <12 months and/or elevated BNP	3.3 years	No reduction in primary endpoint (CV death/HF hospitalisation/ aborted cardiac death). Modest reduction in HF hospitalisation. Increased serum creatinine and rates of hyperkalaemia. Signal of benefit in high-risk populations e.g. raised BNP and lower EF benefited vs EF>55% ¹⁰ , and regional differences in patient characteristics and benefit.
Beta-blockers						
SENIORS Flather et al. ¹¹ , 2005	3	2128	Nebivolol vs placebo	Age ≥70y, HF hospitalisation ≤12 months or EF≤35%, [35% patients had EF>35%]	21 months (mean)	Reduction in primary endpoint (CV death/CV hospitalisation) with nebivolol. No interaction between EF (> or < 35%) and benefits of nebivolol, but underpowered to assess effect in true HFpEF
SWEDIC Bergstrom et al. ¹² , 2004	3	113	Carvedilol vs placebo	EF>45%	6 months	No change in primary endpoint; but trend towards benefit in those with HR>71bpm. Improved mitral E/A, but not other echocardiographic markers.
Yamamoto et al., 2013 ¹³	3	245	Carvedilol vs placebo	Age ≥20y (mean age 72y), EF>40%, clinical heart failure (modified Framingham criteria)	3.2 years (median)	No change in the composite primary endpoint: cardiovascular death and unplanned hospitalization for heart failure. In subgroup analysis, a significant reduction in the primary endpoint was seen in patients treated with carvedilol>7.5mg/day vs placebo (not among patients receiving a standard dose ≤ 7.5mg/day)
Digoxin						
HFpEF substudy of DIG trial Ahmed et al. ¹⁴ , 2006	Post hoc	988	Digoxin vs placebo	EF>45% (median 53%), ambulatory, sinus rhythm	37 months	Trend towards decreased HF hospitalisation negated by increased admissions for unstable angina. No effect on mortality. No effect on all-cause or cause-specific mortality or all-cause or CV hospitalisation

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