Web Table 7.1 Major clinical trials of therapeutic interventions in patients with heart failure with reduced ejection fraction

Trial	Drug	Major inclusion criteria	Mean follow-up	Impact of treatment on primary endpoint	Other results
ACEIs					
CONSENSUS [2]	Enalapril (*n* = 127) vs placebo (*n* = 126).	Congested HF, NYHA IV, cardiomegaly on chest X-ray.	0.5 y	All-cause mortality reduced by 40% at 6 months (26% vs 44%, *P* =0.002) and by 31% at 12 months (52% vs 36%, *P* =0.001).	-
SOLVD-TREATMENT [168]	Enalapril (*n* = 1285) vs placebo (*n* = 1284).	LVEF ≤35%; NYHA I–IV (90% NYHA II–III).	3.5 y	All-cause mortality reduced by 16% (35% vs 40%) (*P* =0.004).	Reduction in combined all-cause mortality and HF hospitalization rate by 26% (*P* < 0.0001).
ATLAS [169]	High (*n* = 1568) vs low (*n* = 1596) dose of lisinopril.	LVEF ≤30%; NYHA II–IV.	3.8 y	All-cause mortality was non-signficantly reduced by 8% (43% vs 45%, *P* =0.13).	Trend towards a reduction in cardiovascular mortality by 10% (*P* =0.07) Reduction in combined all-cause mortality or HF hospitalization rate by 15% (*P* < 0.001).
Beta-blocker					
COPERNICUS [170]	Carvedilol (*n* = 1156) vs placebo (*n* = 1133).	LVEF <25%, NYHA IV.	0.9 y	All-cause mortality reduced by 35% (11% vs 17%) (*P* < 0.001).	Reduction in combined all-cause mortality and any hospitalization rate by 24% (*P* < 0.001).
CIBIS-II [171]	Bisoprolol (*n* = 1327) vs placebo (*n* = 1320).	LVEF ≤35%, NYHA III–IV.	1.3 y	All-cause mortality reduced by 34% (12% vs 17%) (*P* < 0.001)	Reduction in combined cardiovascular mortality or cardiovascular hospitalization rate by 21% (*P* < 0.001).
MERIT-HF [172]	Metoprolol CR/XL (*n* = 1991) vs placebo (*n* = 2001).	LVEF ≤40%, NYHA II–IV.	1.0 y	All-cause mortality reduced by 34% (7% vs 11%) (*P* < 0.001).	Reduction in the risk of cardiovascular death by 38% (*P* < 0.001), sudden death by 41% (*P* < 0.001) and death from aggravated HF by 49% (*P* =0.002).
SENIORS [173]	Nebivolol (*n* = 1067) vs placebo (*n* = 1061).	Age ≥70 y, HF confirmed as HF hospitalization in recent 12 months and/or LVEF ≤35% in recent 6 months.	1.8 y	Combined all-cause mortality and cardiovascular hospitalization rate reduced by 14% (31% vs 35%, *P* =0.04).	-
MRAs					
RALES [174]	Spironolactone (*n* = 822) vs placebo (*n* = 841).	LVEF≤35%, NYHA III–IV at enrolment and NYHA IV in 6 recent months.	2.0 y	All-cause mortality reduced by 30 (35% vs 46%) (*P* < 0.001).	Reduction in a cardiac hospitalization rate by 35% (*P* < 0.001).
EMPHASIS-HF [175]	Eplerenone (*n* = 1364) vs placebo (*n* = 1373).	NYHA II, LVEF ≤30% or LVEF 30–35% with QRS >130 ms, cardiovascular hospitalization in recent 6 months or BNP ≥250 pg/mL or NT-proBNP ≥500 pg/mL in men and ≥750 pg/mL in women.	1.8 y	Combined cardiovascular mortality or HF hospitalization rate reduced by 37% (18% vs 26%, *P* < 0.001).	Reduction in all-cause mortality by 24% (*P* =0.008) and cardiovascular mortality by 24% (*P* =0.01) Reduction in HF hospitalization rate by 42% (*P* < 0.001).
ARNI					
PARADIGM-HF[167]	Sacubitril/valsartan (*n* = 4187) vs enalapril (*n* = 4212).	NYHA II–IV, LVEF ≤40% (amended to LVEF ≤35%), BNP ≥150 pg/mL or NT-proBNP ≥600 pg/mL, or if HF hospitalization within recent 12 months BNP ≥100 pg/mL or NT-proBNP ≥400 pg/mL.	2.3 y	Composite of death from cardiovascular causes or a first HF hospitalization reduced by 20% (22% vs 27%, *P* < 0.001).	Reduction in all-cause mortality by 16% (*P* < 0.001) and cardiovascular mortality by 20% (*P* < 0.001). Reduction in HF hospitalization rate by 21% (*P* < 0.001).
If-channel blocker					
SHIFT [176]	Ivabradine (*n* = 3268) vs placebo (*n* = 3290).	LVEF ≤35%, NYHA II–IV, HF hospitalization in recent 12 months, sinus rhythm, heart rate ≥70 bpm.	1.9 y	Combined cardiovascular mortality or HF hospitalization rate reduced by 18% (24% vs 29%, *P* < 0.001).	Reduction in HF hospitalization rate by 26% (*P* < 0.001). Reduction in HF-related mortality by 26% (*P* =0.01).
ARB					
CHARM-Added[177]	Candesartan (*n* = 1276) vs placebo (*n* = 1272).	LVEF ≤40%, NYHA II–IV, treatment with ACE-I.	3.4 y	Combined cardiovascular mortality or HF hospitalization rate reduced by 15% (38% vs 42%, *P* =0.01).	-

continued

Web Table 7.1 Major clinical trials of therapeutic interventions in patients with heart failure with reduced ejection fraction (continued)

Trial	Drug	Major inclusion criteria	Mean follow-up	Impact of treatment on primary endpoint	Other results
ARB (continued)					
CHARM-Alternative[178]	Candesartan (n = 1013) vs placebo (n = 1015).	LVEF ≤40%, NYHA II–IV, intolerant to ACE-I.	2.8 y	Combined cardiovascular mortality or HF hospitalization rate reduced by 23% (33% vs 40%, P < 0.001).	-
Val-HeFT[179]	Valsartan (n = 2511) vs placebo (n = 2499).	LVEF <40%, NYHA II–IV, treatment with ACE-I, LVID >2.9 cm/BSA.	1.9 y	All-cause mortality was similar in both groups (19.7% vs 19.4%, P =0.80) Reduction in a co-primary combined endpoint of all-cause death, cardiac arrest with resuscitation, HF hospitalization, or i.v. administration of inotropic or vasodilator drugs for ≥4 hours without hospitalization by 13% (29% vs 32%, P =0.009).	-

ACE = angiotensin-converting enzyme; ACEI = angiotensin-converting enzyme inhibitor; AMI = acute myocardial infarction; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; ATLAS = Assessment of Treatment with Lisinopril And Survival; BNP = B-type natriuretic peptide; bpm = beats per minute; BSA = body surface area; CHARM-Added = Candesartan Cilexetil in Heart Failure Assessment of Reduction in Mortality and Morbidity; CHARM-Alternative = Candesartan in heart failure assessment of reduction in mortality and morbidity; CIBIS II = Cardiac Insufficiency Bisoprolol Study II; CONSENSUS = Cooperative North Scandinavian Enalapril Survival Study; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival; EMPHASIS-HF = Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; HF = heart failure; i.v. = intravenous; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; LVID = left ventricular internal dimension; MERIT-HF = Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B type natriuretic peptide; NYHA = New York Heart Association; PARADIGM-HF = Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial; QRS = Q, R, and S waves (combination of three of the graphical deflections); RALES = Randomized Aldactone Evaluation Study; SENIORS = Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisations in Seniors with Heart Failure; SHIFT = Systolic Heart failure treatment with the If inhibitor ivabradine Trial; SOLVD = Studies of Left Ventricular Dysfunction; Val-HeFT = Valsartan Heart Failure Trial; y = years.