

Appendix D: Clinical Trials for Aims 2 and 3

Appendix D Table 2. Clinical Trial Databases used for External Validation of HF CPMs.

Trial	Sample Size, Enrollment Years	Location	Population	Baseline Characteristics	Baseline Medications	Intervention	Outcome	Effect size	Follow up Duration	Outcome events (rate no/100 person years)
TOPCAT ⁷	N=3445, 2006-2012	233 sites in 6 countries	Chronic HFpEF (LVEF ≥ 45%)	69 (IQR 61-76) yrs 52% female LVEF 56% (IQR 51-61%) 67% NYHA I/II	BB: 78% ACEi/ARB: 84% MRA: 50% Diuretics: 82%	Spirinolactone (15 mg or 45 mg) vs placebo	Composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of HF	Spirinolactone vs placebo: HR 0.89 (95% CI.77-1.04)	Mean 3.3 yrs	Mortality: 15% (4.4) CV Death: 10% (3.0) HF hospitalization: 13% (4.2)
HEAAL ⁸	N=3846, 2001-2005	255 sites in 30 countries	Chronic HFrEF (LVEF≤40%)	66 (IQR 56-73) yrs 30% female LVEF 33% (IQR 28-37%) 70% NYHA Class II (NYHA I excluded)	BB: 72% ACEi/ARB: 100% MRA: 38% Diuretics: 77%	Losartan 150 mg vs Losartan 50 mg	Death or admission for HF	Losartan 150 mg vs Losartan 50 mg: HR 0.90 (95% CI 0.82–0.99)	Median 4.7 yrs	Mortality: 34% (7.9) HF hospitalization: 25% (6.5)
HF-ACTION ⁹	N=2331, 2003-2007	82 sites in US, Canada, and France	Chronic HFrEF (LVEF≤35%)	59 (IQR 51-68) yrs 18% female LVEF 25% (IQR 20-30%) 63% NYHA II (NYHA I excluded)	BB: 95% ACEi/ARB: 94% MRA: 45% Diuretic: 45%	Usual care and aerobic exercise training program vs usual care	All-cause mortality or hospitalization	Usual care and aerobic training vs usual care: HR 0.93 (95% CI 0.84-1.02)	Median 2.5 yrs	Mortality: 17% HF hospitalization: 20%
EVEREST ¹⁰	N=4133, 2003-2006	359 sites in North America, South America, and Europe	Acute HFrEF (LVEF≤40%), enrolled within 48 hrs of admission	65±12 yrs 26% female LVEF 28% ±8% 60% NYHA III (all III/IV)	BB: 70% ACEi/ARB: 84% MRA: 54% Diuretic: 97%	Tolvaptan 30 mg vs placebo	All-cause mortality and cardiovascular death or hospitalization for HF	Tolvaptan vs placebo for all-cause mortality: HR 0.98 (95% CI 0.87-1.11) Cardiovascular death or hospitalization for HF: HR 1.04 (95% CI 0.95-1.14)	Median 0.8 yrs	Mortality: 26% CV Death: 20% HF hospitalization (readmission): 21%
SCD-HeFT ¹¹	N=2521, 1997-2001	NR	Chronic HFrEF (LVEF≤35%), NYHA II-III	60 (IQR 52-68) yrs 24% female LVEF 25% (IQR 20-30%) 70% NYHA Class II (NYHA I excluded)	BB: 69% ACEi/ARB: 100% MRA: 20% Diuretic: 82%	Conventional therapy plus Amiodarone, conservatively programmed, shock only,	All-cause mortality	Amiodarone vs placebo: HR 1.06 (97.5% CI 0.86-1.30) Single-lead ICD vs placebo: HR	Median 3.8 yrs	Mortality: 28%

Trial	Sample Size, Enrollment Years	Location	Population	Baseline Characteristics	Baseline Medications	Intervention	Outcome	Effect size	Follow up Duration	Outcome events (rate no/100 person years)
						single-lead ICD, or placebo		0.77 (97.5% CI 0.62-0.96)		
BEST ¹²	N=2708, 1995-1998	90 sites in US and Canada	Chronic HF _r EF (LVEF≤35%), NYHA III-IV	60±12 yrs 22% female LVEF 23 ±7% 92% NYHA Class III (all III/IV)	BB: 50% ACEi/ARB: 97% MRA: 4% Diuretic: 94%	Bucindolol vs placebo	All-cause mortality	Bucindolol vs placebo: HR 0.90 (95% 0.78-1.02)	Mean 2.0 yrs	Mortality: 31% CV Death: 27% HF hospitalization: 38%
DIG ¹³	N=6800, 1991-1993	302 sites in US and Canada	Chronic HF _r EF (LVEF≤45%), NYHA I-IV	63±11 yrs 22% female LVEF 28 ±9% 67% NYHA Class I/II	BB: 0% ACEi: 95% Diuretics: 81%	Diuretics and ACE inhibitors plus either Digoxin vs placebo	All-cause mortality	Digoxin vs placebo: RR 0.99 (95% CI 0.91-1.07)	Mean 3.1 yrs	Mortality: 35% CV Death: 30% HF hospitalization: 30%
SOLVD ¹⁴	N=2569, 1986-1989	83 sites in US, Canada, and Belgium	Chronic HF _r EF (LVEF≤35%), NYHA I-IV	61 ±10 yrs 20% female LVEF 25 ±7% 68% NYHA Class I/II	BB: 8% ACEi: 50% Diuretics: 86%	Enalapril (2.5 to 20 mg) vs placebo	All-cause mortality	Enalapril vs placebo: HR 0.92 (95% CI 0.92-1.21)	Mean 3.5 yrs	Mortality: 38% CV Death: 32%

HFpEF, heart failure with preserved ejection fraction; HF_rEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; BB, beta-blockers; ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; MRA, mineralocorticoid receptor antagonists; ICD, implantable cardioverter defibrillator; CV, cardiovascular; HF, heart failure; yrs, years, hrs, hours; NR, not reported.