

Supplementary Table 1: Selected age- and HF-related characteristics in clinical trials on HFrEF patients

Treatment group drug	Trial name	Age inclusion criteria	Age, years (SD or range) in investigated drug group	HF clinical setting/ HF related Inclusion criteria	LVEF % (SD or IQR) in investigated drug group	Mortality subgroup analysis by age
BETA BLOCKERS						
Bisoprolol	CIBIS II ¹	18-80	61 (22-80)	LVEF ≤35%	27.6 (5.5)	No
Carvedilol	US Carvedilol Heart Failure Study ²	Not specified	57.9 (±12.2)	LVEF ≤35%	23 (±7)	All-cause mortality HR <59 y versus ≥59 y 0.30 (0.11–0.80) versus 0.38 (0.19–0.77)
Carvedilol	Carvedilol Prospective Randomized Cumulative Survival Study Group ³	Not specified	63.2 (±11.4)	LVEF <25	19.9 (±4)	All-cause mortality HR higher in ≥59 y versus <59 y
Carvedilol	CAPRICOR N ⁴	≥18	63 (29-88)	LVEF ≤40%, after AMI	32.9 (±6.4)	No
Metoprolol succinate	MERIT HF ⁵	40-80	63.9 (±9.6) age ≥70 (32%)	LVEF ≤40%	28 (±7)	Mortality HR higher in upper versus middle and lower age tertile)
Nebivolol	SENIORS ⁶	≥70	76.1 (±4.8)	Hospital admission due to HF or LVEF ≤35%	36 (±13)	All-cause mortality or cardiovascular hospital admissions<75.2y versus ≥75.2y 16.6 versus 24.6 events per 100 patient-years)
Carvedilol or Metoprolol tartarate	COMET ⁷	Not specified	61.1 (±11.3)	LVEF ≤35% or EDD 60 mm or FS <20%	26 (±7)	All-cause mortality <65 y versus ≥65 y 0.84 (0.70–1.01) versus 0·84 (0.72–0.9))
ANGIOTENSIN CONVERTING ENZYME INHIBITORS						
Enalapril	CONSENS US ⁸	Not specified	71 (N/A)	NYHA IV, cardiomegaly on Chest X-Ray	N/A	No
Enalapril	SOLVD ⁹	18-80	60.7 (N/A)	≤35%	24.8 (N/A)	No
Enalapril	SOLVD prevention ¹⁰	18-80	59.1 (N/A)	≤35%	28 (N/A)	No
Ramipril	AIRE ¹¹	>18	64.9 (±10.8)	HF Signs/symptoms after AMI	N/A	All-cause mortality larger benefit in ≥65 y versus <65 y
Zofenopril	SMILE ¹²	18-80	63.9 (N/A), 29% >70 years	No HF/Post AMI patients	N/A	Mortality RR <65 y versus ≥65 y 0.68 (0.35–1.34) versus 0.68 (0.35–1.34)

Ivabradine	SHIFT ²⁴	≥18	60.7 (±11.2)	Symptomatic HF, LVEF ≤35%	29 (±5.1)	Primary end point CV death and WHF hospitalization; HR reduction larger in <65 y versus ≥65 y (0.76 (0.67–0.87) versus 0.89 (0.77–1.02), p for interaction 0.099)
ANGIOTENSIN RECEPTOR-NEPRILYSIN INHIBITORS						
Sacubitril/valsartan	PARADI GM-HF ²⁵	≥18	63.8 (±11.5)	NYHA II-IV, LVEF ≤40%	29.6 (±6.1)	CV mortality RR reduction larger in <75 y versus ≥75 y (p for interaction 0.62)
Sacubitril/valsartan	PIONEER -HF ²⁶	≥18	61 (N/A), IQR 51–71	LVEF ≤40%, NT-proBNP ≥1600 pg/ml or BNP 400≥ pg/ml	24 (IQR 18–30)	No
SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS						
Dapagliflozin	DAPA-HF ²⁷	≥18	66.2 (±11.0)	NYHA II-IV, LVEF ≤40%	31.2 (±6.7)	Primary outcome (CV death and worsening HF) RR reduction larger in >65 y versus ≤65 y (0.72 (0.60–0.85) versus 0.72 (0.60–0.85))
Empagliflozin	EMPEROR-R-Reduced ²⁸	≥18	67.2 (±10.8)	NYHA II-IV, LVEF ≤40%	27.7 (±6)	Primary outcome (CV death and HF hospitalization) RR reduction larger in <65y versus ≥65 y (0.71 (0.57–0.89) versus 0.78 (0.66–0.93))
Sotagliflozin	SOLOIST -WHF ²⁹	18-85	69 (63-76)	presence of signs and symptoms of HF and received treatment with intravenous diuretic therapy	35 (28-47)	Primary end point: deaths from CV causes and hospitalizations and urgent visits for HF HR <65 y 0.79 (0.51–1.23) versus 0.62 (0.47–0.82) in ≥65 y
OTHER DRUGS						
Digitalis	DIG ³⁰	Not specified	63.4 (±11.2), 26.7% >70 y	LVEF <45%	28.6 (±8.9)	No
Vericiguat	VICTORIA ³¹	≥18	67.5 (±12.2)	NYHA II-IV, LVEF <45%, elevated NPs	29 (±8.3)	Primary outcome (CV death and HF hospitalization) RR <75 y 0.84 (0.75–0.94) versus 1.04 (0.88–1.27) in ≥75 y
Omecamtiv mecarbil	GALACTIC-HF ³²	18-85	64.5 (±11.3)	NYHA II-IV, LVEF ≤35%, elevated NPs, current or recent HF hospitalization (within 1 year)	26.6 (±6.3)	Primary outcome (HF event and CV death) RR reduction larger in <65 y versus ≥65 y; 0.91 (0.82–1.02) versus 0.94 (0.86–1.03)

References

1. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;353:9-13.
2. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N Engl J Med* 1996;334:1349-55.
3. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;344:1651-8.
4. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet* 2001;357:1385-90.
5. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;353:2001-7.
6. Flather MD, Shibata MC, Coats AJ, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J* 2005;26:215-25.
7. Poole-Wilson PA, Swedberg K, Cleland JG, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet* 2003;362:7-13.
8. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. *N Engl J Med* 1987;316:1429-35.
9. SOLVD Investigators; Salim Yusuf, Bertram Pitt, Clarence E Davis, William B Hood, Jay N Cohn. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;325:293-302.
10. SOLVD Investigators; S Yusuf, B Pitt, C E Davis, W B Hood Jr, J N Cohn. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions (SOLVD prevention). *N Engl J Med* 1992;327:685-91.
11. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993; 342:821-8.
12. Ambrosioni E, Borghi C, Magnani B. The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. The Survival of Myocardial Infarction Long-Term Evaluation (SMILE) Study Investigators. *N Engl J Med* 1995;332:80-5.
13. Køber L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. *N Engl J Med* 1995;333:1670-6.
14. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med* 1992;327:669-77.
15. McMurray J JV, Ostergren J, Swedberg K, et al. CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003;362:767-71.
16. Granger CB, McMurray J JV, Yusuf S, et al. CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003;362:772-6.

17. Cohn JN, Tognoni G; Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;345:1667-75.
18. Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan in Acute Myocardial Infarction Trial Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003;349:1893-906.
19. Pitt B, Poole-Wilson PA, Segal R, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomized trial—the Losartan Heart Failure Survival Study ELITE II. *Lancet* 2000;355:1582-7.
20. Møller JE, Dahlström U, Gøtzsche O, et al. OPTIMAAL Study Group. Effects of losartan and captopril on left ventricular systolic and diastolic function after acute myocardial infarction: results of the Optimal Trial in Myocardial Infarction with Angiotensin II AntagonistLosartan (OPTIMAAL) echocardiographic substudy. *Am Heart J* 2004;147:494-501.
21. Pitt B, Zannad F, Remme WJ, et al. Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999;341:709-17.
22. Zannad F, McMurray JJV, van Veldhuisen DJ, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;364:11-21.
23. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;348:1309-21.
24. Swedberg K, Komajda M, Böhm M, et al. SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010;376:875-85.
25. McMurray JJ, Packer M, Desai AS, et al. PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;371:993-1004.
26. Velazquez EJ, Morrow DA, DeVore AD, et al. PIONEER-HF Investigators. Angiotensin- neprilysin Inhibition in Acute Decompensated Heart Failure. *N Engl J Med* 2019;380:539-48.
27. McMurray J JV, Solomon SD, Inzucchi SE, et al. DAPA-HF Trial Committees and Investigators. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med* 2019;381:1995-2008.
28. Packer M, Anker SD, Butler J, et al. EMPEROR-Reduced Trial Investigators. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med* 2020;383:1413-24.
29. Bhatt DL, Szarek M, Steg PG, et al. SOLOIST-WHF Trial Investigators. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. *N Engl J Med* 2021;384:117-28.
30. Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med*. 1997 Feb 20;336(8):525-33.
31. Armstrong PW, Pieske B, Anstrom KJ, et al. VICTORIA Study Group. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med* 2020;382:1883-93.
32. Teerlink JR, Diaz R, Felker GM, et al. GALACTIC-HF Investigators. Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure. *N Engl J Med* 2021;384:105-16.