Supplemental Table 1: Diabetes Status Treatment Effect in the Landmark Trials of Guideline-directed Medical Therapy for Heart Failure with Reduced Ejection Fraction

Trial (Year)	Medication	N	% patients with DM	Landmark Trial Result	DM Status Treatment Effect
Beta blockers					
CIBIS-II (1999)	Bisoprolol	2647	12%	All-cause mortality: 12% versus 17% (HR 0.66; 95% CI 0.51-0.81; P<0.0001)[77]	RR of mortality: 0.66 (CI 95% 0.54–0.81) in non-DM versus 0.81 (CI 95% 0.52–1.27) in DM[78] *Meta-analysis pooled estimate of BB trials with significant reduction in mortality: 0.65 (0.57–0.74) in non-DM versus 0.77 (0.61–0.96) in DM
COPERNICUS (2002)	Carvedilol	2287	26%	Annual mortality: 12.8% versus 19.7% (RR 0.65; 95% CI 0.52-0.81; P=0.00013)[79]	RR of mortality: 0.67 (95% CI 0.52-0.85) in non-DM versus 0.68 (95% CI 0.47–1.00) in DM[78] *Pooled estimate per above
MERIT-HF (1999)	Metoprolol Succinate	3991	25%	All-cause mortality: 0.072 versus 0.11 per patient-year (RR 0.34; 95% CI 0.19-0.47; P=0.00009)[80]	RR of mortality: 0.62 (95% CI 0.48–0.79) in non-DM versus 0.81 (95% CI 0.57–1.15) in DM[78] *Pooled estimate per above
Renin-angiotensin system inhibitors					

CONSENSUS (1987)	Enalapril	253	22%	6-month mortality: 26% versus 44% (RR 0.60; P=0.002)[81]	RR of mortality: 0.64 (CI 95% 0.46–0.88) in non-DM versus 1.06 (CI 95% 0.65–1.74) in DM[78] *Meta-analysis pooled estimate of ACEi trials with significant reduction in mortality: 0.85 (0.78–0.92) in non-DM versus 0.84 (0.70–1.00) in DM[78]
SAVE (1992)	Captopril	2,231	22%	All-cause mortality: 20% versus 25% (RR 0.81; 95% CI 0.68-0.97; P=0.019)[82]	RR of mortality: 0.82 (CI 95% 0.68–0.99) in non-DM versus 0.89 (CI 95% 0.68–1.16) in DM[78] *Pooled estimate per above
SOLVD-Treatment (1991)	Enalapril	4,228	15%	All-cause mortality: 35% versus 40% (RR 0.84; 95% CI 0.74-0.95; P=0.0036)[83]	RR of mortality: 0.97 (CI 95% 0.83–1.15) in non-DM versus 0.75 (CI 95% 0.55–1.02) in DM[78] *Pooled estimate per above
SOLVD-Prevention (1992)	Enalapril	2,569	26%	All-cause mortality: 14.8% vs 15.8% (RRR 8%; 95% CI -8%-20%; p=0.3)[84]	RR of mortality: 0.84 (CI 95% 0.74–0.95) in non-DM versus 1.01 (CI 95% 0.85–1.21) in DM[78] *Pooled estimate per above
TRACE (1995)	Trandolapril	1,749	14%	All-cause mortality: 34.7% versus 42.3% (RR 0.78; 95% CI 0.67-0.91; p=0.001)[85]	RR of mortality: 0.85 (CI 95% 0.74–0.97) in non-DM versus 0.73 (CI 95% 0.57–0.94) in DM[78] *Pooled estimate per above

CHARM (2003)	Candesartan	2028	27%	CV death or HF hospitalisation: 33% versus 40% (HR 0.70; 95% CI 0.60-0.81; p<0.0001)[86]	No difference in CV mortality and morbidity outcomes based on DM status(p=0.09)[87]
PARADIGM-HF (2014)	Sacubitril/ Valsartan	8442	35%	CV death or HF hospitalisation: 21.8% versus 26.5% (HR 0.80; 95% CI 0.73-0.87; p<0.001) CV mortality: 13.3% versus 16.5% (HR 0.80; 95% CI 0.71-0.89; P<0.001) HF hospitalisation: 12.8% versus 15.6% (HR 0.79; 95% CI 0.71-0.89 P<0.001) All-cause mortality: 17.0% versus 19.8% (HR 0.84; 95% CI 0.76-0.93; P<0.001)[88]	Similar reductions in CV death or HF hospitalisation, CV death, HF hospitalisation, and all-cause mortality across 3 predefined glycaemic categories[89]
Mineralocorticoid receptor antagonists					
EMPHASIS-HF (2011)	Eplerenone	2737	32%	CV death or HF hospitalisation: 18.3% versus 25.9% (HR 0.63; 95% CI 0.54-0.74; P<0.001)[90]	CV death or HF hospitalisation in patients with DM: 21.7% versus 35.2% (p<0.0001)[91]
EPHESUS (2003)	Eplerenone	6642	32%	CV death or CV hospitalisation: 26.7% versus 30.0% (RR 0.87; 95% CI 0.79-0.85; P=0.002)[92]	CV death or CV hospitalisation in patients with DM: RRR 17% (p=0.031)[93]

RALES (1999)	Spironolactone	1663	22%	All-cause mortality: 35% versus 46% (RR 0.70; 95% CI 0.59-0.82; P<0.001) CV mortality: 27% versus 37% (RR 0.69; 95% CI 0.58-0.82; P<0.001)[94]	No subgroup analysis performed
Ivabradine					
SHIFT (2010)	Ivabradine	6558	30%	CV death or HF hospitalisation: 24% versus 29% (HR 0.82; 95% CI, 0.75-0.90; P<0.0001)[95]	CV death or HF hospitalisation: HR 0.80 (95% CI, 0.68-0.94) in non-DM versus HR 0.84 (95% CI, 0.75-0.95) in DM[96]
Digoxin					
DIG (1997)	Digoxin	6800	28%	HF hospitalisation: 26.8% versus 34.7% (RR 0.72; 95% CI, 0.66-0.79; P<0.001)[97]	HF hospitalisation: HR 0.79 (95% CI, 0.68-0.91) in non-DM versus HR 0.69 (95% CI, 0.62-0.77) in DM[98]

ACEi = angiotensin-converting enzyme inhibitor; BB = beta blocker; CV = cardiovascular; DM = diabetes; HF = heart failure; HR = hazard ratio; RR = relative risk; RRR = relative risk reduction. Landmark trial results presented as medication versus placebo or alternative therapy.

References

77. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;353:9-13.
https://doi.org/10.1016/S0140-6736(98)11181-9
PMID: 10023943

78. Shekelle PG, Rich MW, Morton SC, et al. Efficacy of angiotensin-converting enzyme inhibitors and beta-blockers in the management of left ventricular systolic dysfunction according to race, gender, and diabetic status: a meta-analysis of major clinical trials. *J Am Coll Cardiol* 2003;41:1529-38.
https://doi.org/10.1016/S0735-1097(03)00262-6

79. Packer M, Fowler MB, Roecker EB, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. *Circulation* 2002;106:2194-9.
https://doi.org/10.1161/01.CIR.0000035653.72855.BF
PMid:12390947

80. MERIT-HF Study Group. 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.
https://doi.org/10.1016/S0140-6736(99)04440-2
PMID: 10376614

81. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987;316:1429-35.
https://doi.org/10.1056/NEJM198706043162301
PMid:2883575

82. Pfeffer MA, Braunwald E, Moyé 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.
https://doi.org/10.1056/NEJM199209033271001
PMid:1386652

83. SOLVD Investigators, Yusuf S, Pitt B, et al. 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.
https://doi.org/10.1056/NEJM199108013250501
PMid:2057034

84. SOLVD Investigators, Yusuf S, Pitt B, et al. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992;327:685-91.
https://doi.org/10.1056/NEJM199209033271003
PMid:1463530

85. 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.
https://doi.org/10.1056/NEJM199512213332503
PMid:7477219

86. Granger CB, McMurray JJV, Yusuf S, et al. 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.
https://doi.org/10.1016/S0140-6736(03)14284-5
PMID: 13678870

87. MacDonald MR, Petrie MC, Varyani F, et al. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme. *Eur Heart J* 2008;29:1377-85.
https://doi.org/10.1093/eurheartj/ehn153
PMid:18413309

88. McMurray JJV, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;371:993-1004.
https://doi.org/10.1056/NEJMoa1409077
PMid:25176015

89. Kristensen SL, Preiss D, Jhund PS, et al. Risk Related to Pre-Diabetes Mellitus and Diabetes Mellitus in Heart Failure With Reduced Ejection Fraction: Insights From Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial. *Circ Heart Fail* 2016;9:e002560.

https://doi.org/10.1161/CIRCHEARTFAILURE.115.002560
PMid:26754626

90. Zannad F, McMurray JJV, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;364:11-21.
https://doi.org/10.1056/NEJMoa1009492
PMid:21073363

91. Eschalier R, McMurray JJV, Swedberg K, et al. Safety and efficacy of eplerenone in patients at high risk for hyperkalemia and/or worsening renal function: analyses of the EMPHASIS-HF study subgroups (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure). *J Am Coll Cardiol* 2013;62:1585-93.
https://doi.org/10.1016/j.jacc.2013.04.086
PMid:23810881

92. 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.
https://doi.org/10.1056/NEJMoa030207
PMid:12668699

93. O'Keefe JH, Abuissa H, Pitt B. Eplerenone improves prognosis in postmyocardial infarction diabetic patients with heart failure: results from EPHESUS. *Diabetes Obes Metab* 2008;10:492-7.
https://doi.org/10.1111/j.1463-1326.2007.00730.x
PMid:17490427

94. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;341:709-17.
https://doi.org/10.1056/NEJM199909023411001
PMid:10471456

95. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010;376:875-85.
https://doi.org/10.1016/S0140-6736(10)61198-1
https://doi.org/10.1016/S0140-6736(10)62287-8
PMID: 20801500

96. Komajda M, Tavazzi L, Francq BG, et al. Efficacy and safety of ivabradine in patients with chronic systolic heart failure and diabetes: an analysis from the SHIFT trial. *Eur J Heart Fail* 2015;17:1294-301.
https://doi.org/10.1002/ejhf.347
PMid:26377342

97. Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997;336:525-33.
https://doi.org/10.1056/NEJM199702203360801
PMid:9036306

98. Abdul-Rahim AH, MacIsaac RL, Jhund PS, et al. Efficacy and safety of digoxin in patients with heart failure and reduced ejection fraction according to diabetes status: An analysis of the Digitalis Investigation Group (DIG) trial. *Int J Cardiol* 2016;209:310-6.
https://doi.org/10.1016/j.ijcard.2016.02.074
PMid:26913372