

Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction:

An individual patient-level analysis of double-blind randomized trials

The Beta-blockers in Heart Failure Collaborative Group



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Supplementary Table S1: Baseline characteristics for patients in atrial fibrillation

Characteristic	Left ventricular ejection fraction at baseline					
	<20% N = 494	20-25% N = 868	26-34% N = 1101	35-39% N = 368	40-49% N = 146	≥50% N = 73
LVEF, median (IQR)	0.16 (0.14 - 0.18)	0.23 (0.21 - 0.24)	0.30 (0.28 - 0.32)	0.35 (0.35 - 0.37)	0.41 (0.40 - 0.45)	0.56 (0.52 - 0.64)
Age, median years (IQR)	66 (59 - 73)	67 (59 - 73)	69 (61 - 75)	70 (61 - 74)	75 (71 - 79)	76 (74 - 79)
Women, n (%)	63 (12.8%)	128 (14.7%)	204 (18.5%)	86 (23.4%)	72 (49.3%)	39 (53.4%)
Years with HF diagnosis, median (IQR)	5 (2 - 8)	4 (2 - 8)	3 (1 - 6)	3 (1 - 6)	3 (1 - 5)	1 (0 - 4)
Ischaemic HF aetiology, n (%)	267 (54.0%)	443 (51.0%)	581 (52.8%)	233 (63.3%)	104 (71.2%)	52 (71.2%)
Prior myocardial infarction, n (%)	218 (44.3%)	331 (38.1%)	417 (38.2%)	168 (46.0%)	43 (29.5%)	21 (28.8%)
Diabetes Mellitus, n (%)	108 (24.2%)	200 (23.9%)	243 (22.8%)	72 (20.7%)	32 (22.7%)	19 (26.0%)
NYHA class III/IV, n (%)	434 (88.0%)	765 (88.2%)	819 (74.7%)	209 (57.3%)	56 (38.6%)	31 (42.5%)
Heart rate, median bpm (IQR)	84 (73 - 95)	81 (72 - 92)	80 (72 - 91)	80 (72 - 89)	82 (73 - 92)	84 (78 - 96)
Systolic BP, median mmHg (IQR)	120 (107 - 130)	122 (110 - 138)	130 (118 - 143)	130 (120 - 145)	142 (128 - 155)	140 (130 - 153)
Diastolic BP, median mmHg (IQR)	73 (65 - 80)	78 (70 - 82)	80 (70 - 87)	80 (72 - 87)	80 (75 - 90)	80 (79 - 89)
Body mass index, median kg/m ² (IQR)	27 (24 - 32)	27 (24 - 31)	28 (25 - 31)	28 (25 - 31)	26 (24 - 29)	28 (26 - 31)
Estimated GFR, median mL/min (IQR)	57 (45 - 69)	57 (46 - 70)	64 (52 - 77)	63 (50 - 75)	62 (49 - 76)	60 (49 - 78)
Any diuretic therapy, n (%)	480 (97.2%)	833 (96.0%)	1028 (93.4%)	312 (84.8%)	131 (89.7%)	68 (93.2%)
ACEi or ARB, n (%)	464 (93.9%)	833 (96.0%)	1036 (94.1%)	352 (95.7%)	133 (91.1%)	64 (87.7%)
Aldosterone antagonists, n (%)	78 (16.7%)	176 (20.7%)	136 (12.6%)	62 (17.6%)	27 (18.8%)	16 (21.9%)
Digoxin, n (%)	435 (88.1%)	749 (86.3%)	920 (83.6%)	272 (73.9%)	117 (80.1%)	52 (71.2%)

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; bpm, beats/minute; GFR, glomerular filtration rate; HF, heart failure; IQR, interquartile range; LVEF, left-ventricular ejection fraction; NYHA, New York Heart Association.

Missing data report: n=319 for years with HF diagnosis; n=13 for prior myocardial infarction; n=135 for diabetes mellitus; n=431 for NYHA class; n= 2 for diastolic BP; n=8 heart rate; n= 22 for body mass index; n=101 for GFR; n=85 for any diuretic therapy; n=85 for aldosterone antagonists.

Supplementary Table S2: Baseline characteristics according to randomised treatment allocation in sinus rhythm

Characteristic	LVEF <40%		LVEF 40-49%		LVEF ≥50%	
	PLACEBO N=6582	BETA-BLOCKER N=6861	PLACEBO N=283	BETA-BLOCKER N=292	PLACEBO N=121	BETA-BLOCKER N=123
LVEF, median (IQR)	0.26 (0.20-0.32)	0.26 (0.20-0.32)	0.40 (0.40-0.44)	0.40 (0.40-0.43)	0.58 (0.52-0.65)	0.58 (0.54-0.65)
Age, median years (IQR)	63 (54-71)	63 (54-71)	72 (61-75)	70 (60-74)	75 (72-78)	75 (71-78)
Women, %	23.6%	24.0%	33.6%	35.3%	47.9%	57.7%
Years with HF diagnosis, median (IQR)	3 (1-6)	3 (1-6)	2 (1-5)	2 (1-5)	2 (1-5)	2 (0-6)
Ischaemic HF aetiology, %	67.7%	67.5%	92.6%	89.0%	86.8%	84.6%
Prior myocardial infarction, %	58.0%	58.2%	72.3%	71.2%	39.7%	32.5%
Diabetes Mellitus, %	24.3%	24.6%	23.0%	25.1%	30.6%	27.6%
NYHA class III/IV, %	68.1%	67.7%	21.6%	26.5%	24.0%	29.3%
Heart rate, median bpm (IQR)	80 (72-88)	80 (72-88)	75 (68-82)	76 (70-82)	75 (68-84)	74 (68-80)
Systolic BP, median mmHg (IQR)	122 (110-138)	122 (110-138)	132 (120-148)	130 (120-145)	146 (132-161)	147 (132-160)
Diastolic BP, median mmHg (IQR)	77 (70-82)	77 (70-82)	80 (70-85)	80 (70-84)	80 (79-90)	82 (77-90)
Body mass index, median kg/m ² (IQR)	27 (24-31)	27 (24-31)	27 (25-30)	27 (25-30)	26 (24-31)	27 (25-30)
Estimated GFR, median mL/min (IQR)	64 (52-78)	64 (51-77)	67 (53-78)	66 (53-78)	67 (54-81)	72 (56-85)
Any diuretic therapy, %	85.9%	86.1%	67.1%	63.7%	81.0%	82.1%
ACEi or ARB, %	95.2%	94.4%	90.1%	91.1%	87.6%	87.0%
Aldosterone antagonists, %	8.1%	8.3%	6.4%	5.3%	9.9%	13.9%
Digoxin, %	53.6%	55.5%	26.4%	24.7%	17.1%	25.2%

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; bpm, beats/minute; GFR, glomerular filtration rate; HF, heart failure; IQR, interquartile range; LVEF, left-ventricular ejection fraction; NYHA, New York Heart Association.

Supplementary Table S3: Baseline LVEF and hazard for all-cause and cardiovascular mortality

	All-cause mortality		Cardiovascular death	
	N (events / patients)	HR, 95% CI; p-value	N (events / patients)	HR, 95% CI; p-value
Sinus rhythm; per 5% lower LVEF at baseline	2,160 / 14,261	1.24, 1.21-1.28; p<0.0001	1,768 / 14,260	1.20, 1.22-1.30; p<0.0001
Atrial fibrillation; per 5% lower LVEF at baseline	609 / 3,034	1.09, 1.03-1.15; p=0.002	498 / 3,034	1.10, 1.05-1.18; p<0.0001

Adjusted hazard ratio (HR) analysed using a one-stage Cox regression model, with studies as strata. See also Supplementary Figure B.

Supplementary Table S4: Mode of death by baseline LVEF category in sinus rhythm

Baseline LVEF	<20%		20-25%		26-34%		35-39%		40-49%		≥50%	
Randomised allocation	PLC	BB	PLC	BB	PLC	BB	PLC	BB	PLC	BB	PLC	BB
Ischaemic cardiomyopathy												
All-cause mortality*	229 / 727 (31.5%)	180 / 756 (23.8%)	254 / 1258 (20.2%)	208 / 1314 (15.8%)	248 / 1697 (14.6%)	214 / 1778 (12.0%)	97 / 776 (12.5%)	62 / 786 (7.9%)	29 / 262 (11.1%)	19 / 260 (7.3%)	9 / 105 (8.6%)	13 / 104 (12.5%)
CV death	201 / 727 (27.6%)	156 / 756 (20.6%)	220 / 1258 (17.5%)	181 / 1314 (13.8%)	207 / 1697 (12.2%)	172 / 1778 (9.7%)	78 / 776 (10.1%)	53 / 786 (6.7%)	22 / 262 (8.4%)	12 / 260 (4.6%)	6 / 105 (5.7%)	9 / 104 (8.7%)
Sudden death	103 / 727 (14.2%)	83 / 756 (11.0%)	117 / 1258 (9.3%)	86 / 1314 (6.5%)	121 / 1697 (7.1%)	88 / 1778 (4.9%)	36 / 776 (4.6%)	29 / 786 (3.7%)	10 / 262 (3.8%)	4 / 260 (1.5%)	2 / 105 (1.9%)	3 / 104 (2.9%)
HF-related death	73 / 727 (10.0%)	45 / 756 (6.0%)	66 / 1258 (5.2%)	63 / 1314 (4.8%)	52 / 1697 (3.1%)	48 / 1778 (2.7%)	20 / 776 (2.6%)	9 / 786 (1.1%)	6 / 262 (2.3%)	3 / 260 (1.2%)	1 / 105 (1.0%)	1 / 104 (1.0%)
Non-CV death	10 / 727 (1.4%)	18 / 756 (2.4%)	16 / 1258 (1.3%)	14 / 1314 (1.1%)	21 / 1697 (1.2%)	19 / 1778 (1.1%)	9 / 776 (1.2%)	4 / 786 (0.5%)	4 / 262 (1.5%)	3 / 260 (1.2%)	1 / 105 (1.0%)	1 / 104 (1.0%)
Non-ischaemic cardiomyopathy												
All-cause mortality*	136 / 508 (26.8%)	118 / 561 (21.0%)	99 / 644 (15.4%)	82 / 669 (12.3%)	113 / 782 (14.5%)	81 / 819 (9.9%)	16 / 189 (8.5%)	18 / 178 (10.1%)	6 / 21 (28.6%)	2 / 32 (6.3%)	2 / 16 (12.5%)	1 / 19 (5.3%)
CV death	99 / 508 (19.5%)	80 / 561 (14.3%)	72 / 644 (11.2%)	61 / 669 (9.1%)	83 / 782 (10.6%)	54 / 819 (6.6%)	11 / 189 (5.8%)	15 / 178 (8.4%)	4 / 21 (19.0%)	1 / 32 (3.1%)	1 / 16 (6.3%)	0 / 19 (0.0%)
Sudden death	48 / 508 (9.4%)	39 / 561 (7.0%)	38 / 644 (5.9%)	27 / 669 (4.0%)	48 / 782 (6.1%)	27 / 819 (3.3%)	9 / 189 (4.8%)	5 / 178 (2.8%)	2 / 21 (9.5%)	1 / 32 (3.1%)	1 / 16 (6.3%)	0 / 19 (0.0%)
HF-related death	38 / 508 (7.5%)	28 / 561 (5.0%)	26 / 644 (4.0%)	17 / 669 (2.5%)	22 / 782 (2.8%)	15 / 819 (1.8%)	2 / 189 (1.1%)	6 / 178 (3.4%)	1 / 21 (4.8%)	0 / 32 (0.0%)	0 / 16 (0.0%)	0 / 19 (0.0%)
Non-CV death	8 / 508 (1.6%)	9 / 561 (1.6%)	8 / 644 (1.2%)	7 / 669 (1.0%)	11 / 782 (1.4%)	13 / 819 (1.6%)	3 / 189 (1.6%)	1 / 178 (0.6%)	0 / 21 (0.0%)	0 / 32 (0.0%)	0 / 16 (0.0%)	1 / 19 (5.3%)

BB, beta-blockers; CV, cardiovascular; LVEF, left-ventricular ejection fraction; PLC, placebo. * Includes deaths due to an unknown cause. Note that some deaths were ascribed to unknown causes and therefore are attributed neither to cardiovascular or non-cardiovascular deaths.

Supplementary Table S5: Mode of death by baseline LVEF category in atrial fibrillation

Baseline LVEF	<20%		20-25%		26-34%		35-39%		40-49%		≥50%	
Randomised allocation	PLC	BB	PLC	BB	PLC	BB	PLC	BB	PLC	BB	PLC	BB
Ischaemic cardiomyopathy												
All-cause mortality*	47 / 141 (33.3%)	47 / 126 (37.3%)	49 / 224 (21.9%)	44 / 219 (20.1%)	60 / 302 (19.9%)	72 / 279 (25.8%)	29 / 120 (24.2%)	18 / 113 (15.9%)	9 / 50 (18.0%)	14 / 54 (25.9%)	3 / 26 (11.5%)	3 / 26 (11.5%)
CV death	45 / 141 (31.9%)	39 / 126 (31.0%)	41 / 224 (18.3%)	37 / 219 (16.9%)	51 / 302 (16.9%)	60 / 279 (21.5%)	26 / 120 (21.7%)	14 / 113 (12.4%)	7 / 50 (14.0%)	9 / 54 (16.7%)	1 / 26 (3.8%)	2 / 26 (7.7%)
Sudden death	17 / 141 (12.1%)	16 / 126 (12.7%)	22 / 224 (9.8%)	18 / 219 (8.2%)	19 / 302 (6.3%)	28 / 279 (10.0%)	15 / 120 (12.5%)	7 / 113 (6.2%)	1 / 50 (2.0%)	3 / 54 (5.6%)	0 / 26 (0.0%)	0 / 26 (0.0%)
HF-related death	25 / 141 (17.7%)	21 / 126 (16.7%)	13 / 224 (5.8%)	11 / 219 (5.0%)	24 / 302 (7.9%)	18 / 279 (6.5%)	6 / 120 (5.0%)	5 / 113 (4.4%)	2 / 50 (4.0%)	1 / 54 (1.9%)	0 / 26 (0.0%)	0 / 26 (0.0%)
Non-CV death	2 / 141 (1.4%)	5 / 126 (4.0%)	4 / 224 (1.8%)	5 / 219 (2.3%)	4 / 302 (1.3%)	4 / 279 (1.4%)	0 / 120 (0.0%)	2 / 113 (1.8%)	1 / 50 (2.0%)	2 / 54 (3.7%)	1 / 26 (3.8%)	1 / 26 (3.8%)
Non-ischaemic cardiomyopathy												
All-cause mortality*	24 / 106 (22.6%)	31 / 121 (25.6%)	42 / 213 (19.7%)	28 / 211 (13.3%)	50 / 255 (19.6%)	31 / 265 (11.7%)	5 / 70 (7.1%)	8 / 64 (12.5%)	5 / 17 (29.4%)	5 / 25 (20.0%)	1 / 11 (9.1%)	1 / 10 (10.0%)
CV death	18 / 106 (17.0%)	24 / 121 (19.8%)	34 / 213 (16.0%)	25 / 211 (11.8%)	34 / 255 (13.3%)	22 / 265 (8.3%)	4 / 70 (5.7%)	3 / 64 (4.7%)	4 / 17 (23.5%)	2 / 25 (8.0%)	1 / 11 (9.1%)	0 / 10 (0.0%)
Sudden death	11 / 106 (10.4%)	7 / 121 (5.8%)	18 / 213 (8.5%)	16 / 211 (7.6%)	20 / 255 (7.8%)	8 / 265 (3.0%)	2 / 70 (2.9%)	1 / 64 (1.6%)	1 / 17 (5.9%)	0 / 25 (0.0%)	1 / 11 (9.1%)	0 / 10 (0.0%)
HF-related death	6 / 106 (5.7%)	14 / 121 (11.6%)	9 / 213 (4.2%)	6 / 211 (2.8%)	7 / 255 (2.7%)	8 / 265 (3.0%)	2 / 70 (2.9%)	1 / 64 (1.6%)	2 / 17 (11.8%)	2 / 25 (8.0%)	0 / 11 (0.0%)	0 / 10 (0.0%)
Non-CV death	0 / 106 (0.0%)	0 / 121 (0.0%)	2 / 213 (0.9%)	1 / 211 (0.5%)	4 / 255 (1.6%)	3 / 265 (1.1%)	0 / 70 (0.0%)	1 / 64 (1.6%)	0 / 17 (0.0%)	2 / 25 (8.0%)	0 / 11 (0.0%)	1 / 10 (10.0%)

BB, beta-blockers; CV, cardiovascular; LVEF, left-ventricular ejection fraction; PLC, placebo. * Includes deaths due to an unknown cause. Note that some deaths were ascribed to unknown causes and therefore are attributed neither to cardiovascular or non-cardiovascular deaths.

Supplementary Table S6: Absolute mortality difference and observed change in LVEF according to aetiology in sinus rhythm

Classification	‘Reduced’ LVEF				‘Mid-range’ LVEF	‘Preserved’ LVEF
	<20%	20-25%	26-34%	35-39%	40-49%	≥50%
Sinus rhythm: Ischaemic aetiology						
Change in absolute mortality; beta-blockers vs placebo (95% CI) †	n=1483 -7.7% (-12.2% to -3.1%)	n=2572 -4.4% (-7.3% to -1.4%)	n=3475 -2.6% (-4.8% to -0.3%)	n=1562 -4.6% (-7.6% to -1.6%)	n=522 -3.8% (-8.7% to +1.2%)	n=209 +3.9% (-4.4% to +12.2%)
Change in LVEF from baseline to follow-up; mean difference (SE) beta-blockers vs placebo ‡	n=593 +3.1% (0.6%)	n=667 +3.3% (0.6%)	n=1070 +3.0% (0.5%)	n=277 +4.4% (1.0%)	n=227 +2.5% (1.2%)	n=177 +0.6% (1.3%)
Sinus rhythm: Non-ischaemic aetiology						
Change in absolute mortality; beta-blockers vs placebo (95% CI) †	n=1069 -5.7% (-10.9% to -0.6%)	n=1313 -3.1% (-6.8% to +0.6%)	n=1601 -4.6% (-7.8% to -1.4%)	n=367 +1.6% (-4.3% to +7.6%)	n=53 -22.3% (-43.4% to -1.3%)	n=35 -7.2% (-26.3% to +11.8%)
Change in LVEF from baseline to follow-up; mean difference (SE) beta-blockers vs placebo ‡	n=513 +6.2% (0.9%)	n=401 +5.6% (1.0%)	n=530 +6.2% (0.9%)	n=98 +6.3% (2.0%)	n=24 -4.2% (4.3%)	n=24 -4.4% (4.5%)

† Median follow-up of 1.3 years (IQR 0.8-1.9)

‡ Median 1.0 years after baseline assessment (IQR 0.3-2.0)

CI = confidence interval; LVEF = left ventricular ejection fraction; SE = standard error of the mean difference.