Beta-Blockers in Heart Failure Collaborative Group

Data supplement

Effect of age and sex on efficacy and tolerability of β blockers in patients with heart failure with reduced ejection fraction: individual patient data meta-analysis

Supplementary Table A: Baseline characteristics by sex

Characteristic	Women n=3,283	Men n=10,550
Age, median years (IQR)	66 (58-73)	63 (55-71)
Ischaemic heart failure aetiology, n (%)	1,994 (61%)	7,682 (73%)
Prior myocardial infarction, n (%)	1,639 (50%)	6,644 63%
Prior coronary revascularization, n (%)	425 (14%)	2,474 (25%)
Diabetes Mellitus, n (%)	912 (29%)	2,391 (24%)
Years with heart failure diagnosis, median (IQR)	3 (1-6)	3 (1-6)
LVEF, median % (IQR)	0.28 (0.21-0.34)	0.26 (0.20-0.32)
NYHA class III/IV, n (%)	2,226 (68%)	6,939 (66%)
Systolic blood pressure, median mmHg (IQR)	128 (112-140)	121 (110-137)
Diastolic blood pressure, median mmHg (IQR)	78 (70-83)	77 (70-82)
Heart rate, median bpm (IQR)	80 (73-88)	79 (72-88)
Body mass index, median kg/m2 (IQR)	27 (24-31)	27 (24-31)
Estimated GFR, median mL/min (IQR)	58 (45-70)	65 (53-78)
Any diuretic therapy, n (%)	2, 863 (87%)	8,947 (85%)
ACEi or ARB, n (%)	3,089 (94%)	10,014 (95%)
Aldosterone antagonists, n (%)	286 (9%)	782 (8%)
Digoxin, n (%)	1,746 (54%)	5,456 (53%)

ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; GFR = glomerular filtration rate; IQR = interquartile range; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

Supplementary Table B: Cause of death by age quartile

Cause of death	Quartile 1 (youngest)	Quartile 2	Quartile 3	Quartile 4 (oldest)	All ages
Acute myocardial infarction	5%	5%	6%	6%	6%
Sudden death	50%	45%	40%	34%	41%
Heart failure	16%	25%	27%	31%	26%
Other cardiac	3%	4%	2%	2%	3%
Stroke	1%	2%	1%	3%	2%
Other vascular/thrombo-embolic	5%	5%	5%	4%	5%
Non-cardiovascular	5%	4%	10%	11%	8%
Unknown	13%	11%	10%	10%	11%
Total deaths	**412/3,458 (12%)**	**510/3,590 (14%)**	**581/3,327 (17%)**	**687/3,458 (20%)**	**2190/13,833 (16%)**

Supplementary Table C: Cause of death by sex

Cause of death	Women	Men
Acute myocardial infarction	6%	5%
Sudden death	41%	41%
Heart failure	25%	26%
Other cardiac	3%	2%
Stroke	3%	2%
Other vascular/thrombo-embolic	4%	5%
Non-cardiovascular	7%	8%
Unknown	11%	10%
Total deaths	**462/3,283 (14%)**	**1,728/10,550 (16%)**

Supplementary Table D: All-cause mortality and hospital admission for heart failure according to treatment allocation and age

Age quartile	*All-cause mortality* during median follow-up period of 1.3 years (IQR 0.8-1.9)			*Heart failure hospital admission* during median follow-up period of 1.3 years (IQR 0.8-1.9)		
	Placebo	**Beta-blocker**	**Absolute risk reduction / Number needed to treat (NNT)**	**Placebo**	**Beta-blocker**	**Absolute risk reduction / Number needed to treat (NNT)**
Quartile 1 (youngest)	235/1,682 (14.0%)	177/1,776 (10.0%)	4.0% (NNT=25)	277/1,628 (17.0%)	186/1,720 (10.8%)	6.2% (NNT=16)
Quartile 2	278/1,744 (15.9%)	232/1,846 (12.6%)	3.4% (NNT=29)	330/1,715 (19.2%)	256/1,814 (14.1%)	5.1% (NNT=20)
Quartile 3	333/1,645 (20.2%)	248/1,682 (14.7%)	5.5% (NNT=18)	337/1,631 (20.7%)	231/1,670 (13.8%)	6.8% (NNT=15)
Quartile 4 (oldest)	376/1,702 (22.1%)	311/1,756 (17.7%)	4.4% (NNT=23)	328/1,702 (19.3%)	287/1,756 (16.3%)	2.9% (NNT=34)
All ages	**1,222/6,773 (18.0%)**	**968/7,060 (13.7%)**	**4.3% (NNT=23)**	**1,272/6,676 (19.1%)**	**960/6,960 (13.8%)**	**5.3% (NNT=19)**

Supplementary Table E: Sensitivity analyses for all-cause mortality

Analysis	Events/Patients	Beta-blockers versus placebo		Age interaction p-value	Sex interaction p-value
		Hazard ratio, 95% CI	p-value		
Primary adjusted analysis	2,060/13,670	0.70, 0.64 to 0.77	< 0.001	0.10	0.84
Censor at 365 days	1,202/13,670	0.67, 0.59 to 0.75	< 0.001	0.24	0.40
Censor at 770 days	1,844/13,670	0.70, 0.63 to 0.76	< 0.001	0.02	0.87
Exclusion of BEST trial	1,439/11,650	0.64, 0.58 to 0.71	< 0.001	0.02	0.89
Exclusion of CAPRICORN trial	1,881/12,031	0.69, 0.63 to 0.76	< 0.001	0.23	0.96
Per protocol [a]	1,323/11,282	0.67, 0.60 to 0.75	< 0.001	0.22	0.89
LVEF ≤ 0.35	1,882/11,568	0.70, 0.64 to 0.77	< 0.001	0.12	0.65
Additional adjustment for diabetes [b]	1,939/12,964	0.70, 0.64 to 0.77	< 0.001	0.08	0.66
Additional adjustment for digoxin use at baseline [c]	2,058/13,378	0.70, 0.64 to 0.77	< 0.001	0.09	0.86
2 stage [c]; fixed effects	2,058/13,378	0.71, 0.65 to 0.77	< 0.001	-	-
2 stage [c]; random effects [d]	2,058/13,378	0.69, 0.60 to 0.79	< 0.001	-	-
Crude unadjusted analysis	2,119/13,832	0.72, 0.66 to 0.78	< 0.001	0.09	0.81
Including entire age-range available; adjusted	2,164/14,259	0.72, 0.66 to 0.78	< 0.001	0.57	0.76
All patients, regardless of rhythm/LVEF/age [e]	2,984/18,342	0.77, 0.71 to 0.82	<0.001	0.19	0.67

[a] Excludes patients that discontinued study therapy. [b] Excludes the MDC and CIBIS-I trials. [c] Excludes the CHRISTMAS trial. [d] p-value for heterogeneity = 0.04, I^2 = 48%. [e] Post-hoc adjusted analysis of all patients irrespective of baseline heart rhythm, left-ventricular ejection fraction (LVEF) or age. All other sensitivity analyses were pre-defined (for details on study exclusions and analyses, see Design Paper: Kotecha D, Manzano L, Altman DG, et al.; Syst Rev. 2013;2:7).

Supplementary Table F: Beta-blocker discontinuation

Discontinuation of beta-blockers	Quartile 1 (youngest)		Quartile 2		Quartile 3		Quartile 4 (oldest)		All ages	
	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men
- due to any adverse event	47 (14.0%)	167 (11.6%)	51 (12.9%)	183 (12.6%)	59 (14.4%)	186 (14.6%)	86 (15.7%)	233 (19.3%)	243 (14.4%)	769 (14.3%)
- due to hypotension*	2 (0.9%)	8 (0.8%)	4 (1.4%)	14 (1.4%)	5 (1.6%)	12 (1.3%)	3 (0.7%)	13 (1.4%)	14 (1.1%)	47 (1.2%)
- due to bradycardia*	(0.0%)	3 (0.3%)	2 (0.7%)	8 (0.8%)	3 (1.0%)	13 (1.5%)	3 (0.7%)	33 (3.5%)	8 (0.7%)	57 (1.5%)
- due to heart failure exacerbation†	17 (5.4%)	30 (2.2%)	13 (3.5%)	51 (3.7%)	8 (2.0%)	53 (4.4%)	18 (3.3%)	58 (4.9%)	56 (3.5%)	192 (3.7%)
- due to renal impairment*	1 (0.5%)	4 (0.4%)	(0.0%)	2 (0.2%)	(0.0%)	5 (0.6%)	5 (1.2%)	5 (0.5%)	6 (0.5%)	16 (0.4%)
- due to respiratory dysfunction*	1 (0.5%)	6 (0.6%)	3 (1.1%)	8 (0.8%)	3 (1.0%)	10 (1.1%)	2 (0.5%)	11 (1.2%)	9 (0.7%)	35 (0.9%)

* Data not available for MERIT-HF, CIBIS-I and MDC. † Partial data for CIBIS-I and MDC.

Supplementary Table G: Study drug dosage

Sex	Mean beta-blocker dosage as a percentage of maximal dose for that study*				
	Quartile 1 (youngest)	**Quartile 2**	**Quartile 3**	**Quartile 4 (oldest)**	**All ages**
Women	72%	71%	73%	75%	**73%**
Men	76%	74%	71%	70%	**73%**

Data not available for BEST and CHRISTMAS; partial data for other trials (n=1,187 for women and n=3,646 for men randomized to beta-blockers). * Achieved at the interim time point for study in patients receiving therapy (median 172 days [IQR 112-198] from randomization).

Supplementary Figure A: Distribution of patients by age and sex

Frequency histograms for age distribution in men and women (LVEF <0.45 in sinus rhythm; age 40-85).