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Meta-analysis: β-Blocker Dose, Heart Rate Reduction, and Death in Patients With Heart Failure

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Background: Guidelines recommend that patients with heart failure receive β-blockers in doses used in the trials that have proven their efficacy. Although the adverse effects of β-blockade are dose-related, it is unclear whether the benefits are.

Purpose: To determine whether the survival benefits of β-blockade in heart failure are associated with the magnitude of heart rate reduction or the β-blocker dose.

Data Sources: MEDLINE, EMBASE, CINAHL, SIGLE, Web of Science, and the Cochrane Central Register of Controlled Trials, supplemented by hand-searches of bibliographies.

Study Selection: Randomized, placebo-controlled heart failure trials that reported all-cause mortality.

Data Extraction: Two reviewers independently extracted data on study characteristics, β-blocker dosing and heart rate reduction, and death.

Data Synthesis: The mean left ventricular ejection fraction in the 23 β-blocker trials ranged from 0.17 to 0.36, and more than 95% of the 19 209 patients had systolic dysfunction. The overall risk ratio for death was 0.76 (95% CI, 0.68 to 0.84); however, heterogeneity testing revealed moderate heterogeneity among trials (I^2 = 30%), which was associated with the magnitude of heart rate reduction achieved within each trial (*P* for meta-regression = 0.006). For every heart rate reduction of 5 beats/min with β-blocker treatment, a commensurate 18% reduction (CI, 6% to 29%) in the risk for death occurred. No significant relationship between all-cause mortality and β-blocker dosing was observed (risk ratio for death, 0.74 [CI, 0.64 to 0.86]) in high-dose β-blocker trials vs. 0.78 [CI, 0.63 to 0.96] in low-dose β-blocker trials; *P* for meta-regression = 0.69).

Limitations: The analysis is based on aggregate data and resting heart rates. Few patients in these trials had bradycardia or diastolic dysfunction at baseline.

Conclusion: The magnitude of heart rate reduction is statistically significantly associated with the survival benefit of β-blockers in heart failure, whereas the dose of β-blocker is not.

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Over the past decade, several randomized clinical trials have established that β-blockers are beneficial in patients with heart failure (1, 2). Although resting heart rate is known to be a prognostic factor in patients with heart failure (3, 4), it remains unclear whether the benefits of β-blockade in patients with heart failure are related to the degree of reduction in heart rate or the dosage of β-blocker administered. This question is important because the adverse effects of β-blockers are dose-related (5). Although heart failure guidelines recommend up-titration of β-blockers to the target doses used in β-blocker trials, outcome studies reveal that only some patients achieve these doses outside of specialized heart failure clinics (6–8).

Secondary analyses of the CIBIS (Cardiac Insufficiency Bisoprolol Study) (9), COMET (Carvedilol Or Metoprolol European Trial) (10), and CIBIS II (11) data suggested that the magnitude of heart rate reduction with β-blockers was an important mediator of β-blocker effect. In addition, a small clinical trial of 49 pacemaker-dependent patients with left ventricular systolic dysfunction demonstrated that patients who were paced at a lower rate (60 beats/min) had improvements in left ventricular function and left ventricular dimensions compared with those paced at a higher rate (80 beats/min) (12). However, other studies have not confirmed a relationship between the magnitude of heart rate reduction and the efficacy of β-blockers (13–15).

We designed this meta-analysis to investigate the between-study heterogeneity in heart failure β-blocker trials. Specifically, we examined whether β-blocker dose or magnitude of heart rate reduction could account for the differences in treatment effects among heart failure β-blocker trials.

See also:

Web-Only
Appendix Table
Conversion of graphics into slides

Methods

Identifying Relevant Studies

We searched for randomized trials in MEDLINE (1966 to 2008), EMBASE (1980 to 2008), CINAHL (1982 to 2008), SIGLE (1980 to 2008), Web of Science, and the Cochrane Central Register of Controlled Trials. We did not apply language restrictions, but we restricted our searches to human studies and clinical trial or randomized, controlled trial publications. We used the keywords and Medical Subject Headings *adrenergic β-antagonists*, *heart failure*, and *congestive (exp)*. We also hand-searched bibliographies of identified studies, recent meta-analyses of β-blockers in heart failure (1, 2), and heart failure guidelines.

Study Selection and Data Abstraction

Two authors independently reviewed the results of the search strategy and selected all studies that reported the effect of β-blockers on all-cause mortality in patients with heart failure. The authors excluded studies if they were published in abstract form only, did not report death, used β-blockers for 1 month or less, or enrolled fewer than 50 patients. Two authors extracted all outcome data independently, with subsequent discussion of any discrepancies. Outcomes from each study were extracted in intention-to-treat categories rather than per-protocol categories (that is, all outcomes were analyzed by randomization group to avoid bias from excluding patients who dropped out, were withdrawn, or did not adhere to treatment).

We calculated the magnitude of heart rate reduction in each trial by comparing the heart rate at the end of the dose titration phase of each trial with the baseline values and subtracted the change in the placebo group from the change in the β-blocker group.

Statistical Analysis

Because of the expected differences in patient samples and length of follow-up in these studies, we did our primary analyses by using the DerSimonian–Laird random-effects model. We did analyses by using Review Manager, version 4.2 (The Cochrane Collaboration, Copenhagen, Denmark), and Stata SE, version 10 (StataCorp, College Station, Texas). Because the outcome of interest was relatively common, we calculated risk ratios (RRs) and 95% CIs. We assessed and quantified statistical heterogeneity for each outcome of interest by using the Cochran Q test and the I^2 statistic, respectively (16). The I^2 statistic quantifies the percentage of statistical heterogeneity due to between-study variability. By convention, values less than 25%, 25% to 50%, and greater than 50% are considered low, moderate, and high amounts of heterogeneity, respectively (17). To explore potential explanations for the between-trial heterogeneity, we did meta-regression analyses by using the weighted least-squares method (16). The logarithm of relative risk for death, weighted by the inverse variance of each study, was regressed against the following variables 1 at a time: sex, age, ischemic cause, left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) class, atrial fibrillation, use of digoxin, heart rate at baseline, magnitude of heart rate reduction achieved with treatment, dose of β-blocker reached, systolic blood pressure (SBP) at baseline, magnitude of treatment-related SBP reduction, and specific β-blocking agent. We explored continuous variables in these meta-regressions both linearly and categorically by using tertiles. We reported the P values from Wald tests. In a sensitivity analysis, we investigated the stability of our meta-regression result by using a Monte Carlo simulation to explore the effect of sampling variability around the point estimates of heart rate reduction in each trial (18). We sampled 5000 data sets, and the mean heart rate reduction was varied along a normal distribution (by using the mean and SE reported by each trial); trial selection remained fixed in each Monte Carlo iteration. In addition, we ran meta-regressions incorporating various combinations of 2 or 3 of these variables to investigate the robustness of our findings (the number of trials was insufficient to run meta-regressions with more than 3 variables).

Role of the Funding Source

There was no specific funding for this project.

Results

Study Selection and Evaluation

Of the 548 citations that we identified in our search, 108 were potentially eligible for inclusion, but we excluded 85 after detailed review (**Figure 1**). Of note, the 34 trials that we excluded because they did not report death but instead evaluated levels of biomarkers or neurohormonal measurements, hemodynamic changes, or echocardiographic measurements, were generally small (mean sample size, 43 patients). The 12 trials that reported death, but were excluded because they included fewer than 50 patients (mean sample size, 28 patients), had a total of only 15 deaths (compared with 2720 deaths in the 23 randomized trials included in our meta-analysis). Disagreement between 2 reviewers about eligibility of the studies occurred on 3 occasions, for a κ value of 0.92. All disagreements were resolved by consensus.

Studies Included in the Systematic Review

Table 1 shows the baseline data from 23 randomized trials (19–42). Three trials [23, 28, 38] reported

Figure 1. **Study flow diagram.**

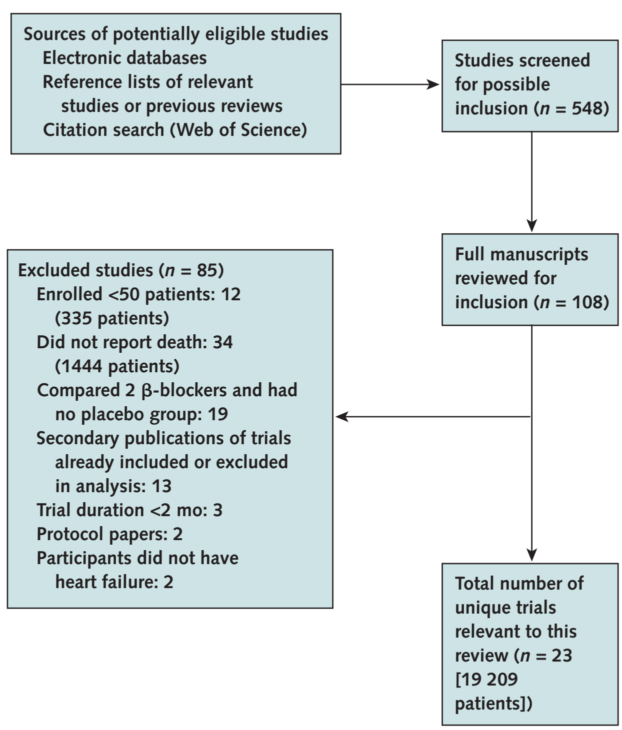


Table 1. **Baseline Data for Included Trials**

Study, Year (Reference)	Sample Size, *n*	Mean Age, *y*	Men, %	Inclusion Criteria
Metoprolol				
Anderson et al, 1985 (19)	50	51	66	LVEF <0.40, idiopathic dilated cardiomyopathy, no coronary disease
MDC, 1993 (20)*	383	49	72	Age 16–75 y, LVEF <0.40, idiopathic dilated cardiomyopathy, no coronary disease, HR >45 beats/min, SBP >90 mm Hg
Fisher et al, 1994 (21)	50	63	96	NYHA class II–IV, LVEF ≤0.40 with coronary disease, stable for 1 mo, HR >60 beats/min
MERIT-HF, 2000 (22) and 2002 (23) (high dose)	3047	63	77	Age 40–80 y, NYHA class II–IV, LVEF ≤0.40, HR >68 beats/min, SBP >100 mm Hg
MERIT-HF, 2000 (22) and 2002 (23) (low dose)	2449	64	78	Age 40–80 y, NYHA class II–IV, LVEF ≤0.40, HR >68 beats/min, SBP >100 mm Hg
RESOLVD, 2000 (24)	426	62	82	NYHA class II–IV, LVEF <0.40, 6-min walk test <500 m
Carvedilol				
Olsen et al, 1995 (25)	60	52	93	Age 18–80 y, NYHA class II–III, LVEF ≤0.35
Colucci et al, 1996 (26)	366	54	85	Age 18–85 y, NYHA class II–IV, LVEF ≤0.35, stable for 1 mo, SBP >85 mm Hg, 6-min walk test 425–550 m
Packer et al, 1996 (27)	278	60	73	NYHA class II–IV, LVEF ≤0.35, stable for 1 mo, HR >68 beats/min, SBP >85 mm Hg, 6-min walk test 150–450 m
MOCHA, 1996 (28) (low dose)	167	59	75	Age 18–85 y, NYHA class II–III, LVEF ≤0.35, stable for 1 mo, HR >68 beats/min, SBP >85 mm Hg, 6-min walk test 150–425 m
MOCHA, 1996 (28) (medium dose)	173	60	76	Age 18–85 y, NYHA class II–III, LVEF ≤0.35, stable for 1 mo, HR >68 beats/min, SBP >85 mm Hg, 6-min walk test 150–425 m
MOCHA, 1996 (28) (high dose)	173	60	77	Age 18–85 y, NYHA class II–III, LVEF ≤0.35, stable for 1 mo, HR >68 beats/min, SBP >85 mm Hg, 6-min walk test 150–425 m
Cohn et al, 1997 (29)	105	61	58	NYHA class III–IV, LVEF ≤0.35, SBP >85 mm Hg, 6-min walk test <450 m
ANZ, 1997 (30)	415	67	80	NYHA class II–IV, LVEF <0.45, ischemic heart disease, HR >50 beats/min, SBP >90 mm Hg
COPERNICUS, 2001 (31)	2289	63	80	NYHA class III–IV, LVEF <0.25, HR >68 beats/min, SBP >85 mm Hg
CHRISTMAS, 2003 (32)	387	63	90	NYHA class I–III, ischemic etiology, stable ≥2 wk, HR >60 beats/min, SBP >85 mm Hg, no specific LVEF criteria beyond "systolic dysfunction"
CARMEN, 2004 (33)	381	62	81	NYHA class I–III, LVEF <0.40, stable for 2 wk, if "no contraindications to β-blocker"
Bisoprolol				
CIBIS, 1994 (34)	641	60	83	NYHA class III–IV, LVEF <0.40, stable for 6 wk, HR >65 beats/min, SBP <160 mm Hg
CIBIS II, 1999 (35) and 2001 (11)	2647	61	80	NYHA class III–IV, LVEF ≤0.35, stable for 6 wk, HR >60 beats/min, SBP >100 mm Hg
CIBIS III, 2005 (36)†	1010	72	68	NYHA class II–III, age >65 y, LVEF ≤0.35, stable for 1 wk, HR >60 beats/min, SBP >100 mm Hg
Bucindolol				
Woodley et al, 1991 (37)	50	52	72	NYHA class II–III, LVEF ≤0.40, stable for 3 wk, HR >50 beats/min, SBP >80 mm Hg, without symptomatic AV block
Bristow et al, 1994 (38) (low dose)	72	53	64	NYHA class I–IV, LVEF
Bristow et al, 1994 (38) (moderate dose)	66	54	58	NYHA class I–IV, LVEF
Bristow et al, 1994 (38) (high dose)	69	54	59	NYHA class I–IV, LVEF
BEST, 2001 (39)	2708	60	78	NYHA class III–IV, LVEF ≤0.35, stable for 4 wk, HR >50 beats/min, SBP >80 mm Hg
Atenolol				
Sturm et al, 2000 (40)	100	52	88	NYHA class II–III, LVEF
Nebivolol				
SENIORS, 2005 (41)	2128	76	63	Age ≥70 y, NYHA class I–IV, hospitalization or LVEF ≤0.35, stable for 6 wk, HR >60 beats/min, SBP >90 mm Hg
ENECA, 2005 (42)	260	72	73	Age ≥65 y, NYHA class II–IV, LVEF ≤0.35, stable for 2 wk, HR >50 beats/min

ACE = angiotensin-converting enzyme; ANZ = Australia/New Zealand heart failure study; AV = atrioventricular; BEST = Beta-blocker Evaluation of Survival Trial; CARMEN = Carvedilol Ace-inhibitor Remodelling Mild chf EvaluatioN; CHRISTMAS = Carvedilol Hibernating Reversible Ischaemia Trial: Marker of Success; CIBIS = Cardiac Insufficiency Bisoprolol Study; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival Study; ENECA = Efficacy of Nebivolol in the treatment of Elderly patients with Chronic heart failure as Add-on therapy; HR = heart rate; LVEF = left ventricular ejection fraction; MDC = Metoprolol in Dilated Cardiomyopathy; MERIT-HF = MEtoprolol CR/XL Randomized Intervention Trial in congestive Heart Failure; MOCHA = Multicenter Oral Carvedilol Heart failure Assessment; NR = not reported; NYHA = New York Heart Association; RESOLVD = Randomized Evaluation of Strategies fOr Left Ventricular Dysfunction study; SBP = systolic blood pressure; SENIORS = Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with heart failure.
* Heart rate data at follow-up were only available for 147 patients (baseline data reported for entire trial; follow-up for only those patients in whom heart rate was measured).
† Monotherapy phase, before the crossover. SDs are listed if they were reported in trial publications.

Table 1—**Continued**

Mean LVEF (SD)	Ischemic Etiology, %	Atrial Fibrillation, %	NYHA Class III or IV, %	Digoxin, %	ACE Inhibitor, %
0.28 (0.11)	0	NR	66	NR	NR
0.22 (0.09)	0	NR	52	79	80
0.23 (0.09)	100	20	60	96	94
0.28 (NR)	63	NR	56	64	90
0.28 (NR)	67	NR	60	64	89
0.29 (0.11)	69	NR	24	67	100
0.20 (0.01)	28	NR	50	83	93
0.23 (0.07)	41	NR	14	91	95
0.22 (0.07)	52	NR	60	90	97
0.23 (0.07)	51	NR	55	96	94
0.23 (0.07)	54	NR	59	91	97
0.23 (0.07)	55	NR	53	91	91
0.22 (0.07)	45	NR	99	90	93
0.29 (0.08)	90	NR	73	38	85
0.20 (0.04)	67	NR	100	66	97
0.30 (0.11)	100	NR	29	NR	87
NR	70	17	31	44	0 in β-blocker group
0.25 (0.01)	55	13	100	57	90
0.28 (0.06)	50	20	100	52	96
0.29 (0.05)	62	NR	51	32	0 in β-blocker group
0.22 (0.02)	54	NR	64	71	88
0.25 (0.01)	29	NR	53	71	88
0.25 (0.01)	29	NR	56	79	83
0.24 (0.01)	29	NR	54	84	93
0.23 (0.07)	59	12	100	93	91
0.17 (0.05)	28	16	22	100	100
0.36 (0.13)	68	35	41	39	82
0.26 (0.06)	58	26	51	57	91

outcome data in β-blocker dosage subgroups (each of these subgroups is reported as a separate row in **Table 1**) (19–42). The **Appendix Table** (available at www.annals.org) outlines β-blocker titration schedules, dosing, duration, and effect on SBP and heart rate. Four trials (21, 24, 26, 40) could not be included in the analyses comparing death with physiologic variables because they did not report heart rate data for trial participants.

Qualitative Synthesis

All but 2 (32, 41) trials were restricted to patients with systolic dysfunction, and only 4% of trial participants had preserved systolic function. Two trials enrolled only patients with nonischemic heart failure; 2 trials were restricted to patients with ischemic cardiomyopathy; and in the other trials, the frequency of ischemic heart disease ranged from 27% to 90%, with a median of 59% (**Table 1**).

In addition to standard anti–heart failure therapy except β-blockers, the control groups received placebo in all but 2 trials (in which the control group received an angiotensin-converting enzyme inhibitor but no β-blocker) (33, 36). Use of angiotensin-converting enzyme inhibitors (median, 93% [interquartile range {IQR}, 87% to 96%]) and digoxin (median, 75% [IQR, 57% to 91%]) was high in these trials (**Table 1**). Mean LVEF in these trials ranged from 0.17 to 0.36 (median, 0.24), with all but 1 trial reporting mean LVEF less than 0.30 (**Table 1**). Few trials reported comorbid conditions, but in those that did, 12% to 35% of participants had atrial fibrillation (**Table 1**) and 12% to 36% had diabetes mellitus. Most patients in these trials had NYHA class III or IV symptoms at baseline (median, 54% [IQR, 50% to 66%]). Most of these trials were of relatively short duration—only 6 trials (19, 33–35, 39, 40) followed patients longer than 12 months (**Appendix Table**, available at www.annals.org).

Fifteen trials did not report subgroup analyses, whereas 8 trials did: patients with ischemic versus nonischemic heart failure (22, 31, 34, 35, 39, 41, 43); results by NYHA class (22, 34–36, 39), age (22, 31, 36, 41, 43), sex (22, 31, 39, 41, 43), or race (39); and results for patients with comorbid conditions, such as diabetes (22, 36, 41), hypertension (22, 36), smoking (22), or chronic kidney disease (36). Although 6 trials reported that β-blocker efficacy did not statistically differ between any of the subgroups examined, most of these subgroup analyses were presented as forest plots or Kaplan–Meier curves with no explicit reporting of raw numbers, such that we could not pool subgroup data to examine the consistency across trials with formal interaction tests. One trial (BEST [Beta-Blocker Evaluation of Survival Trial]) reported that β-blockers demonstrated a survival benefit in nonblack patients but not in black patients (*P* for interaction = 0.02) (39). Because no other trials reported outcomes separately for black and nonblack patients, we could not evaluate the consistency of this subgroup finding across trials. The BEST trial enrolled the highest proportion of black patients (23%)—the remaining trials that reported race enrolled fewer than 8% nonwhite patients. One trial (34) reported that β-blockers were beneficial in patients with nonischemic heart failure but not in patients with ischemic heart failure (*P* for interaction = 0.03); however, pooling data across trials that provided outcome data by cause (34, 35, 41, 43) revealed that this subgroup effect was not consistent and that β-blockers exerted similar mortality rate reductions in patients with ischemia (RR, 0.77 [95% CI, 0.55 to 1.07]) and those without ischemia (RR, 0.67 [CI, 0.48 to 0.94]; *P* for comparison = 0.24).

Although SENIORS (Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with heart failure) (41), the U.S. Carvedilol Heart Failure Study Group (43), and MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure) (22) reported nonsignificant trends toward greater survival benefits from β-blockers in patients with lower LVEF (<0.35, <0.23, and <0.25, respectively), this finding was not consistent across trials. No convincing evidence suggested differences in β-blocker efficacy by LVEF; however, these trials enrolled patients within a narrow range of LVEFs (**Table 1**).

Quantitative Data Synthesis

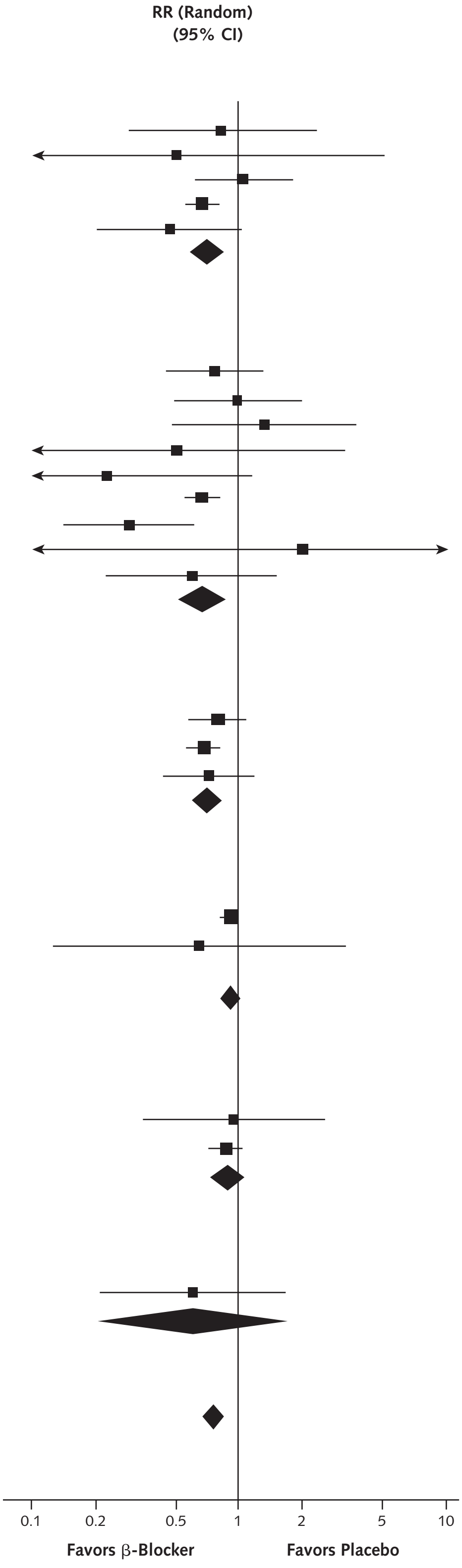
Four of 23 trials reported a significant difference in mortality rates between patients who received β-blocker and those who received placebo (**Figure 2**). For all 23 trials (19 209 patients), the summary RR was 0.76 (CI, 0.68 to 0.84); however, heterogeneity testing revealed moderate heterogeneity (I^2 = 30%; *P* = 0.09) (17).

Examining the results for each β-blocker separately revealed that the choice of β-blocker was associated with the magnitude of the survival benefit (**Table 2**). Patients who received bucindolol exhibited 36% less survival benefit (CI, 9% to 69%; *P* = 0.009) than patients who received carvedilol (pooled RR for the comparisons against placebo, 0.91 [CI, 0.82 to 1.02] vs. 0.66 [CI, 0.51 to 0.87], respectively). Other agents led to survival benefits that did not statistically significantly differ from those of carvedilol (*P* = 0.85 [vs. metoprolol], *P* = 0.68 [vs. bisoprolol], *P* = 0.83 [vs. atenolol, based on very small numbers], and *P* = 0.056 [vs. nebivolol]). However, although metoprolol, carvedilol, and bisoprolol all exhibited statistically significant mortality rate reductions compared with placebo, the data were inconclusive for nebivolol or atenolol (**Figure 2**).

Analyzing these trials by magnitude of heart rate reduction (**Figure 3**) demonstrated minimal heterogeneity within each tertile. Trials in the tertile with greatest heart rate reductions (median, 15 beats/min) reported greater survival benefits with β-blockade (RR, 0.64 [CI, 0.48 to 0.86]) than trials in the tertile with the least heart rate reductions (median, 8 beats/min; RR, 0.91 [CI, 0.83 to 0.99]). Meta-regression confirmed that treatment-related heart rate reduction was statistically significantly associated with the magnitude of the β-blocker survival benefit (*P* for Wald test = 0.01) (**Table 2** and **Figure 4**). In fact, inclusion of heart rate reduction reduced the I^2 value to 0% in this meta-analysis (meaning the between-trial variance was reduced to less than its expected value). The association between heart rate reduction and the benefits of β-blockade were also confirmed by using heart rate reduction as a linear variable in meta-regression (*P* = 0.006). Meta-regression revealed that for every 5 beats/min reduction in heart rate with β-blocker treatment, the relative risk for death decreased by 18% (CI, 6% to 29%).

Figure 2. **All-cause mortality in trials of 50 or more patients, by agent.**

Study, Year (Reference)	β-Blocker, *n/n*	Placebo, *n/n*	RR (Random) (95% CI)
Metoprolol			
Anderson et al, 1985 (19)	5/25	6/25	0.83 (0.29–2.38)
Fisher et al, 1994 (21)	1/25	2/25	0.50 (0.05–5.17)
MDC, 1993 (20)	23/194	21/189	1.07 (0.61–1.86)
MERIT-HF, 2000 and 2002 (22, 23)	145/1990	217/2001	0.67 (0.55–0.82)
RESOLVD, 2000 (24)	8/214	17/212	0.47 (0.21–1.06)
Subtotal	2448	2452	0.70 (0.58–0.83)
Total events: 182 (β-blocker); 263 (placebo)			
Test for heterogeneity: chi-square = 3.50; $P = 0.48$; $I^2 = 0\%$			
Test for overall effect: $z = 3.93$ ($P < 0.001$)			
Carvedilol			
ANZ, 1997 (30)	20/207	26/208	0.77 (0.45–1.34)
CARMEN, 2004 (33)	14/191	14/190	0.99 (0.49–2.03)
CHRISTMAS, 2003 (32)	8/193	6/194	1.34 (0.47–3.79)
Cohn et al, 1997 (29)	2/70	2/35	0.50 (0.07–3.40)
Colucci et al, 1996 (26)	2/232	5/134	0.23 (0.05–1.17)
COPERNICUS, 2001 (31)	130/1156	190/1133	0.67 (0.54–0.83)
MOCHA, 1996 (28)	12/261	13/84	0.30 (0.14–0.63)
Olsen et al, 1995 (25)	1/36	0/24	2.03 (0.09–47.78)
Packer et al, 1996 (27)	6/133	11/145	0.59 (0.23–1.56)
Subtotal	2479	2147	0.66 (0.51–0.87)
Total events: 195 (β-blocker); 267 (placebo)			
Test for heterogeneity: chi-square = 10.00; $P = 0.27$; $I^2 = 20.0\%$			
Test for overall effect: $z = 2.99$ ($P = 0.003$)			
Bisoprolol			
CIBIS, 1994 (34)	53/320	67/321	0.79 (0.57–1.10)
CIBIS II, 2001 and 1999 (11, 35)	156/1327	228/1320	0.68 (0.56–0.82)
CIBIS III, 2005 (36)	23/505	32/505	0.72 (0.43–1.21)
Subtotal (95% CI)	2152	2146	0.71 (0.61–0.83)
Total events: 232 (β-blocker); 327 (placebo)			
Test for heterogeneity: chi-square = 0.64; $P = 0.72$; $I^2 = 0\%$			
Test for overall effect: $z = 4.33$ ($P < 0.001$)			
Bucindolol			
BEST, 2001 (39)	411/1354	449/1354	0.92 (0.82–1.02)
Bristow et al, 1994 (38)	4/105	2/34	0.65 (0.12–3.38)
Woodley et al, 1991 (37)	0/30	0/20	Not estimable
Subtotal	1489	1408	0.91 (0.82–1.02)
Total events: 415 (β-blocker); 451 (placebo)			
Test for heterogeneity: chi-square = 0.17; $P = 0.68$; $I^2 = 0\%$			
Test for overall effect: $z = 1.60$ ($P = 0.11$)			
Nebivolol			
ENECA, 2005 (42)	7/134	7/126	0.94 (0.34–2.61)
SENIORS, 2005 (41)	169/1067	192/1061	0.88 (0.72–1.06)
Subtotal	1201	1187	0.88 (0.73–1.06)
Total events: 176 (β-blocker); 199 (placebo)			
Test for heterogeneity: chi-square = 0.02; $P = 0.89$; $I^2 = 0\%$			
Test for overall effect: $z = 1.38$ ($P = 0.17$)			
Atenolol			
Sturm et al, 2000 (40)	5/51	8/49	0.60 (0.21–1.71)
Subtotal	51	49	0.60 (0.21–1.71)
Total events: 5 (β-blocker); 8 (placebo)			
Test for heterogeneity: NA			
Test for overall effect: $z = 0.96$ ($P = 0.34$)			
Total	9820	9389	0.76 (0.68–0.84)
Total events: 1205 (β-blocker); 1515 (placebo)			
Test for heterogeneity: chi-square = 29.96; $P = 0.09$; $I^2 = 29.9\%$			
Test for overall effect: $z = 5.04$ ($P < 0.001$)			



Trial acronyms are defined in **Table 1.** NA = not applicable; RR = risk ratio.

Table 2. **Results of 13 Univariable Meta-regressions Evaluating the Effect of Individual Covariates on Death Benefits of β-Blockers in Heart Failure**

Potential Modifier	Trials, *n*	Patients, *n*	Ratio of Relative Risks (95% CI)	*P* Value
Percentage of men	21	18 773	0.93 (0.79–1.10) per 10% increment	0.38
Mean age	21	18 773	1.04 (0.86–1.24) per decade	0.69
Percentage with an ischemic cause	21	18 773	0.99 (0.86–1.14) per 20% increment	0.88
Mean baseline LVEF	20	18 392	1.04 (0.92–1.18) per 5% increment	0.54
Percentage with NYHA class III or IV symptoms	21	18 773	1.00 (0.96–1.05) per 10% increment	0.84
Percentage with atrial fibrillation	8	8915	1.00 (0.91–1.09) per 5% increment	0.95
Percentage of digoxin use	19	18 336	1.01 (0.96–1.06) per 10% increment	0.64
Baseline heart rate	19	17 981	1.07 (0.88–1.32) per 5 beats/min	0.47
Heart rate reduction*	17	17 831	0.82 (0.71–0.94) per 5 beats/min	0.006
β-Blocker dose	17	17 660	1.02 (0.93–1.10) per increment	0.69
Mean baseline SBP	17	17 516	1.00 (0.73–1.35) per 20 mm Hg	0.99
Mean SBP reduction	10	5462	1.02 (0.87–1.20) per 2 mm Hg	0.78
Agent	21	18 773	–	–
Carvedilol	–	–	Reference	–
Bisoprolol	–	–	1.05 (0.82–1.35)	0.68
Metoprolol	–	–	1.03 (0.77–1.38)	0.85
Atenolol	–	–	0.89 (0.29–2.76)	0.83
Bucindolol	–	–	1.36 (1.09–1.69)	0.009
Nebivolol	–	–	1.30 (0.99–1.71)	0.056

LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SBP = systolic blood pressure.
* For every 5-beat/min reduction in mean heart rate, the risk ratio for death decreases by 18% (relative risk ratio, 0.82 [95% CI, 0.71 to 0.94]). Therefore, starting with our pooled risk ratio of 0.76 for death and our median heart rate reduction of 12 beats/min, it would be reasonable to expect that a mean heart rate reduction of 17 beats/min would confer a relative risk for death of approximately 0.62.

When we tested the robustness of this association in our Monte Carlo sensitivity analysis (allowing heart rate reduction to vary along its observed normal distribution within each trial), we found that the estimated SE (and thus the CI) increased and the estimated effect also increased. For every reduction in heart rate of 5 beats/min, the relative risk for death decreased by 45% (CI, 6% to 63%). The relationship between heart rate reduction and the relative risk for death was also similar, even if heart rate reduction was defined by a relative decrease from baseline value rather than absolute change (RR for death decreased by 15% [CI, 5% to 25%] for every 5% reduction in heart rate; $P = 0.007$). The lack of an inflection point in the meta-regression graph (**Figure 4**) and the narrow range of heart rate reduction values in the included trials limit our ability to speculate about the "optimal" magnitude of heart rate reduction to aim for with β-blocker therapy.

Inclusion of sex, age, ischemic cause, baseline LVEF, use of digoxin, atrial fibrillation, and β-blocker dose in bivariable and trivariable meta-regressions demonstrated that the association between the degree of heart rate reduction and the magnitude of β-blocker benefit was not confounded; the association remained significant ($P \leq 0.025$).

Univariable meta-regressions did not reveal any statistically significant influence of sex ($P = 0.38$), age ($P = 0.69$), ischemic cause ($P = 0.88$), baseline LVEF ($P = 0.54$), NYHA class ($P = 0.84$), atrial fibrillation ($P = 0.95$), use of digoxin ($P = 0.64$), heart rate at baseline ($P = 0.47$), SBP at baseline ($P = 0.99$), or change in SBP ($P = 0.78$) on the size of the death benefit with β-blockers. These findings confirmed our qualitative syntheses of the subgroup results from each trial. Heart rate with β-blockade was not statistically significantly associated with the size of the death benefit in the β-blocker trials (*P* for meta-regression = 0.25), and inclusion of heart rate while receiving treatment in the β-blocker groups did not explain all of the between-trial heterogeneity (residual $I^2 = 14\%$); thus, magnitude of heart rate reduction was a better explanatory variable for the between-trial heterogeneity in survival benefits than heart rate achieved during follow-up.

We observed no statistically significant relationship between β-blocker dosing achieved and the magnitude of all-cause mortality reductions ($P = 0.69$). The RR for death was 0.74 (CI, 0.64 to 0.86) in the 15 trials in which patients were receiving high doses of β-blocker (that is, ≥50% of the target β-blocker dose recommended in guidelines) (44), whereas the RR was 0.78 (CI, 0.63 to 0.96) in the 7 trials in which patients were receiving low doses of β-blocker. β-Blocker dosing was not reported in the remaining trial.

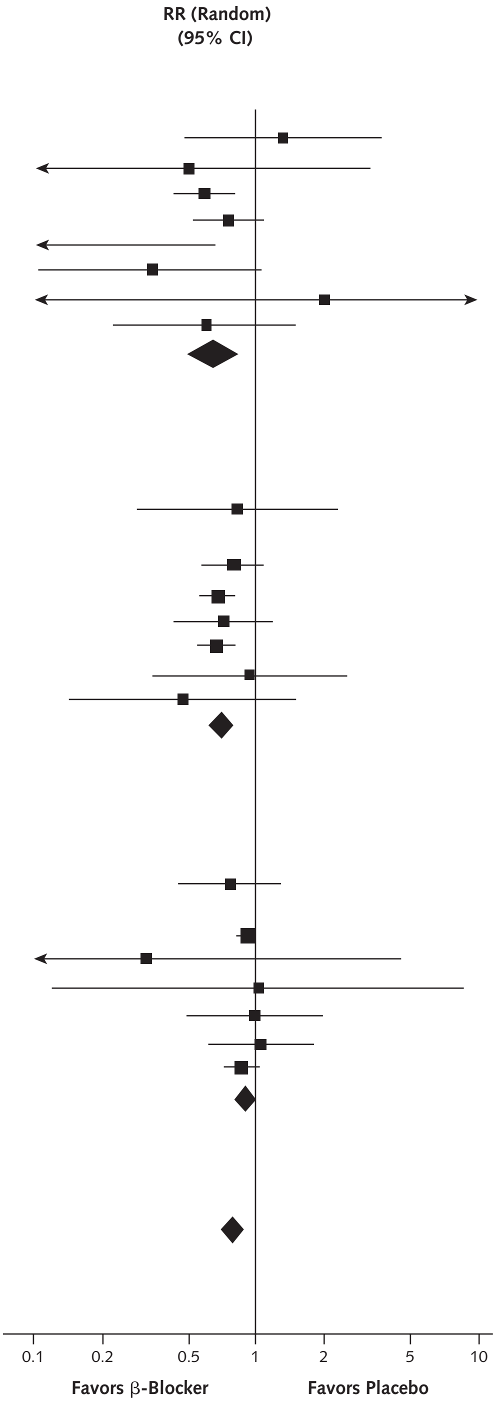
DISCUSSION

β-Blockers reduce the risk for death by approximately 25% in patients with heart failure, and the evidence base is reasonably strong that the benefits of carvedilol, bisoprolol, and metoprolol are similar. Data for death remain inconclusive for atenolol, bucindolol, or nebivolol at this time. Our analyses demonstrate that the benefits of β-blockers are similar regardless of sex, age, cause, use of digoxin, and LVEF (within the restricted range of LVEFs included in these trials). Data are insufficient to make firm conclusions about racial differences in β-blocker efficacy.

Our analysis demonstrates a relationship between the magnitude of heart rate reduction and the magnitude of the survival benefit in these trials, which seems to be a more important predictor of outcomes than the dosage of β-blocker. Our findings extend those from a recent meta-analysis of 26 β-blocker trials (including many of those we excluded because they did not report deaths) that reported a strong correlation between magnitude of heart rate reduction and improvements in LVEF ($R^2 = 0.53$; $P < 0.005$) (45). Although the correlation between heart rate reduction and all-cause mortality was nonsignificant in that earlier meta-analysis of 9 trials ($P = 0.06$), our meta-analysis includes 14 additional trials. Our findings also echo those from a recently published meta-regression of

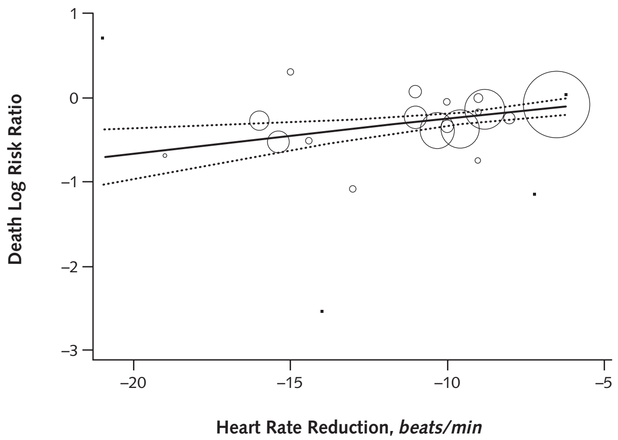
Figure 3. **All-cause mortality, by treatment-related HR reduction tertile.**

Study, Year (Reference)	β-Blocker, *n/n*	Placebo, *n/n*	RR (Random) (95% CI)
Tertile 1 (largest HR reduction)			
CHRISTMAS, 2003 (32)	8/193	6/194	1.34 (0.47–3.79)
Cohn et al, 1997 (29)	2/70	2/35	0.50 (0.07–3.40)
MERIT-HF, 2000 and 2002 (22, 23) (high dose)	59/1202	77/922	0.59 (0.42–0.82)
MERIT-HF, 2000 and 2002 (22, 23) (low dose)	38/604	77/923	0.75 (0.52–1.10)
MOCHA, 1996 (28) (high dose)	1/89	4/28	0.08 (0.01–0.68)
MOCHA, 1996 (28) (low dose)	5/83	5/28	0.34 (0.11–1.08)
Olsen et al, 1995 (25)	1/36	0/24	2.03 (0.09–47.78)
Packer et al, 1996 (27)	6/133	11/145	0.59 (0.23–1.56)
Subtotal	2410	2299	0.64 (0.48–0.86)
Total events: 120 (β-blocker); 182 (placebo)			
Test for heterogeneity: chi-square = 8.35; *P* = 0.30; I^2 = 16.2%			
Test for overall effect: *z* = 3.01 (*P* = 0.003)			
Tertile 2			
Anderson et al, 1985 (19)	5/25	6/25	0.83 (0.29–2.38)
Bristow et al, 1994 (38) (high dose)	0/35	0/11	Not estimable
CIBIS, 1994 (34)	53/320	67/321	0.79 (0.57–1.10)
CIBIS II, 2001 and 1999 (11, 35)	156/1327	228/1320	0.68 (0.56–0.82)
CIBIS III, 2005 (36)	23/505	32/505	0.72 (0.43–1.21)
COPERNICUS, 2001 (31)	130/1156	190/1133	0.67 (0.54–0.83)
ENECA, 2005 (42)	7/134	7/126	0.94 (0.34–2.61)
MOCHA, 1996 (28) (medium dose)	6/89	4/28	0.47 (0.14–1.55)
Subtotal	3591	3469	0.70 (0.62–0.79)
Total events: 380 (β-blocker); 534 (placebo)			
Test for heterogeneity: chi-square = 1.67; *P* = 0.95; I^2 = 0%			
Test for overall effect: *z* = 5.80 (*P* < 0.001)			
Tertile 3			
ANZ, 1997 (30)	20/207	26/208	0.77 (0.45–1.34)
BEST, 2001 (39)	411/1354	449/1354	0.92 (0.82–1.02)
Bristow et al, 1994 (38) (low dose)	1/38	1/12	0.32 (0.02–4.67)
Bristow et al, 1994 (38) (medium dose)	3/32	1/11	1.03 (0.12–8.92)
CARMEN, 2004 (33)	14/191	14/190	0.99 (0.49–2.03)
MDC, 1993 (20)	23/194	21/189	1.07 (0.61–1.86)
SENIORS, 2005 (41)	169/1067	192/1061	0.88 (0.72–1.06)
Woodley et al, 1991 (37)	0/30	0/20	Not estimable
Subtotal	3113	3045	0.91 (0.83–0.99)
Total events: 641 (β-blocker); 704 (placebo)			
Test for heterogeneity: chi-square = 1.48; *P* = 0.96; I^2 = 0%			
Test for overall effect: *z* = 2.12 (*P* = 0.003)			
Total	9114	8813	0.77 (0.70–0.85)
Total events: 1141 (β-blocker); 1420 (placebo)			
Test for heterogeneity: chi-square = 27.20; *P* = 0.16; I^2 = 22.8%			
Test for overall effect: *z* = 4.96 (*P* < 0.001)			



Trial acronyms are defined in **Table 1.** HR = heart rate; RR = risk ratio.

Figure 4. **Meta-regression line for magnitude of heart rate reduction and risk ratio of all-cause mortality.**



The mortality logarithm of relative risk is plotted against the reduction in heart rate. Circles are the observed estimates; size is based on the inverse of the SE of each trial. The 3 lines are the fitted and the upper and lower bounds of the 95% CIs.

the post–myocardial infarction β-blocker trials, which demonstrated that heart rate reduction was the major determinant of the clinical benefit of β-blockers after myocardial infarction (46). Furthermore, our finding that the relative risk for death decreased by 18% (CI, 6% to 29%) for every reduction in heart rate of 5 beats/min with β-blocker treatment is consistent with the recently published BEAUTIFUL (Morbidity-Mortality Evaluation of the I_f Inhibitor Ivabradine in Patients With Coronary Artery Disease and Left Ventricular Dysfunction) Trial (which reported an 8% increase in cardiovascular deaths and a 16% increase in heart failure hospitalizations for every 5-beat/min increase in heart rate in patients with ischemic left ventricular systolic dysfunction) (47). To that end, it is worth noting that the baseline heart rates in the trials we meta-analyzed were substantially higher than those of the participants in the BEAUTIFUL Trial. The only subgroup in the BEAUTIFUL Trial to demonstrate benefits from ivabradine was patients with baseline heart rates greater than 70 beats/min (48).

The benefits of β-blockers in heart failure accrue through several pathophysiologic mechanisms, all of which are potentially responsive in a dose-dependent fashion. In addition to reductions in myocardial ischemia, arrhythmias, and left ventricular wall stress, β-blockers block the sympathetic nervous system, thereby potentially reducing catecholamine-induced myocyte apoptosis. However, calls to simply prescribe β-blockers in trial doses ignore interindividual variations in pharmacodynamics. Previous investigators have demonstrated that patients with heart failure with higher baseline heart rates exhibit the greatest improvements in LVEF with β-blocker therapy (49–51). Moreover, greater reductions in heart rate are associated with greater improvements in LVEF (27, 51). Whether heart rate reduction may serve as a useful surrogate marker for magnitude of LVEF improvement is a hypothesis that requires testing.

Although we included data from all sizeable β-blocker heart failure trials, our study has some limitations. First, our analysis was restricted to resting heart rates measured at baseline and after the drug-titration phase of these trials because this was the variable and the timing most frequently reported in this body of literature. We acknowledge that heart rates at peak exercise or 24-hour averages provide a more accurate assessment of β-blockade (52); however, resting heart rate is easier for the clinician to monitor and follow in the clinic. Second, because most of these trials did not report causes of death, we could not explore the effect of β-blockade on cardiovascular deaths and specifically on the balance between sudden cardiac deaths versus deaths from progressive heart failure. However, more than 90% of all deaths in patients with moderate to advanced heart failure (such as those in this meta-analysis) are from cardiovascular causes, and approximately 50% of these cardiovascular deaths are sudden cardiac deaths (53, 54). Third, because all of these trials excluded patients with bradycardia at baseline and data in patients with atrial fibrillation or diastolic dysfunction are lacking, we cannot draw firm inferences for these important patient subgroups. Moreover, because most of these trials predated the device era in heart failure, the modulating effect of cardiac resynchronization therapy or implantable cardioverter-defibrillators in patients receiving β-blockers is unknown and a topic worthy of future research. Because data on physiologic measurements and death were available for only 17 trials, our results are driven by a relatively small number of trials; however, exclusion of individual trials in 16 cases did not change the statistical significance of the association between heart rate reduction and the survival benefits of β-blockers. Although exclusion of the BEST data did change the *P* value to 0.22, the direction of the association was maintained (risk ratio for death, 0.88 [CI, 0.71 to 1.09] for every 5-beat/min reduction in heart rate), suggesting that this was merely an issue with sample size. Finally, our analyses are based on aggregate data, and therefore our comparisons are ecological (although the use of randomized trial data and a meta-regression based on intratrial comparisons ensures that we have controlled for time period and other potential confounders, such as location and concomitant health care). Some have argued that it is impossible to truly separate the prognostic impact of the indirect effects of an intervention (for example, heart rate reduction in patients exposed to β-blockers) from the direct effects when only the exposure (that is, β-blocker or placebo) is randomized (55). To that end, ongoing studies, such as SHIFT (Effects of Ivabradine on Cardiovascular Events in Patients with Moderate to Severe Chronic Heart Failure and Left Ventricular Systolic Dysfunction Trial), in which heart rate (the intermediate outcome in our analysis) will be modified by using the non–β-blocker compound ivabradine, will provide valuable information to further inform this issue.

In summary, our meta-regression analyses of β-blocker heart failure trials demonstrate that the magnitude of survival benefit seen with β-blockers is statistically significantly associated with the magnitude of heart rate reduction achieved but not the dosage of β-blocker administered. However, because no heart failure trials have randomly assigned participants who receive β-blockers to different target heart rates and we did not find an inflection point in our meta-regression for heart rate reduction, the optimal heart rate (and thus target heart rate reduction) is unknown. Thus, 2 questions remain unanswered: Is there any additional benefit to up-titrating β-blocker dose to trial doses if substantial heart rate reduction has already been achieved with a lower dose? Is there any additional benefit to increasing β-blocker dose above trial doses if heart rate reduction is minimal? We hope that this exploratory analysis will encourage the heart failure β-blocker trial investigators to pool their individual patient data to definitively answer these important questions.

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Appendix Table. **Changes in Clinical Variables During Trials***

Study, Year (Reference)	β-Blocker Titration Schedule	Mean Daily Dose Achieved, *mg*	Treatment Duration, *mo*	Baseline SBP (SD), *mm Hg*
Metoprolol				
Anderson et al, 1985 (19)	12.5 mg up to 50 mg twice daily	61	19	Intervention: 118; control: 118
MDC, 1993 (20)†	10 mg/d up to 150 mg/d (given 2–3 times daily)	108	12	Intervention: 118 (17); control: 118 (18)
Fisher et al, 1994 (21)	6.25 mg up to 50 mg twice daily	87	6	Intervention: 117 (25); control: 117 (19)
MERIT-HF, 2000 (22) and 2002 (23) (high dose)	Initial 12.5 mg/d (for NYHA class III or IV) or 25 mg/d (for NYHA class II) up to 200 mg/d of the controlled-release formulation	192	12	Intervention: 131; control: 130
MERIT-HF, 2000 (22) and 2002 (23) (low dose)	Initial 12.5 mg/d (for NYHA class III or IV) or 25 mg/d (for NYHA class II) up to 200 mg/d of the controlled-release formulation	76	12	Intervention: 127; control: 130
RESOLVD, 2000 (24)	12.5 mg/d up to 200 mg/d of the controlled-release formulation	156	6	NR
Carvedilol				
Olsen et al, 1995 (25)	6.25 mg up to 25 mg twice daily (<75 kg) or 50 mg twice daily (>75 kg)	80	4	Intervention: 84 (2); control: 85 (1)
Colucci et al, 1996 (26)	12.5 mg up to 25 mg twice daily (<85 kg) or 50 mg twice daily (≥85 kg)	NR	12	NR
Packer et al, 1996 (27)	6.25 mg twice daily during open-label phase, then 12.5 mg when randomly assigned up to 25 mg twice daily (≤85 kg) or 50 mg twice daily (>85 kg)	28	6	Intervention: 117 (18); control: 117 (18)
MOCHA, 1996 (28) (low dose)	6.25 mg twice daily	12.5	6	Intervention: 115 (19); control: 114 (17)
MOCHA, 1996 (28) (medium dose)	6.25 mg up to 12.5 mg twice daily	24.6	6	Intervention: 113 (16); control: 114 (17)
MOCHA, 1996 (28) (high dose)	6.25 mg up to 25 mg twice daily	47.4	6	Intervention: 117 (18); control: 114 (17)
Cohn et al, 1997 (29)	6.25 mg up to 25 mg twice daily	46	6	Intervention: 117; control: 115
ANZ, 1997 (30)	3.125 mg up to 25 mg twice daily	41	12	NR
COPERNICUS, 2001 (31)	3.125 mg up to 25 mg twice daily	37	10	Intervention: 123 (19); control: 123 (19)
CHRISTMAS, 2003 (32)	3.125 mg up to 25 mg twice daily (<85 kg) or 50 mg twice daily (>85 kg)	NR	6	Intervention: 127 (18); control: 125 (17)
CARMEN, 2004 (33)	3.125 mg up to 25 mg twice daily (<85 kg) or 50 mg twice daily (>85 kg)	48	22	Intervention: 129 (18) control: 132 (19)
Bisoprolol				
CIBIS, 1994 (34)	1.25 mg/d up to 5 mg/d	3.6	23	Intervention: 128 (2); control: 126 (2)
CIBIS II, 1999 (35) and 2001 (11)	1.25 mg/d up to 10 mg/d	8.6	16	Intervention: 129 (19); control: 130 (20)
CIBIS III, 2005 (36)‡	1.25 mg/d up to 10 mg/d	8.3	6	Intervention: 135 (17); control:134 (17)
Bucindolol				
Woodley et al, 1991 (37)	12.5 mg up to 100 mg twice daily	181	3	NR
Bristow et al, 1994 (38) (low dose)	6.25 mg/d	12.5	3	Intervention: 114 (3); control: 116 (4)
Bristow et al, 1994 (38) (moderate dose)	6.25 mg up to 25 mg twice daily	44	3	Intervention: 122 (4); control: 116 (4)
Bristow et al, 1994 (38) (high dose)	6.25 mg/d up to 100 mg/d	192	3	Intervention: 117 (3); control: 116 (4)
BEST, 2001 (39)	3 mg up to 50 mg twice daily (or 100 mg twice daily if >75 kg)	152	24	Intervention: 117 (18); control: 117 (18)
Atenolol				
Sturm et al, 2000 (40)	12.5 mg up to 50 mg twice daily	NR	12	Intervention: 115 (18); control: 118 (15)
Nebivolol				
SENIORS, 2005 (41)	1.25 mg/d up to 10 mg/d	7.7	21	Intervention: 139 (20); control: 140 (21)
ENECA, 2005 (42)	1.25 mg/d up to 10 mg/d	NR	8	Intervention: 136 (18); control: 135 (17)

NR = not reported; NYHA = New York Heart Association; SBP = systolic blood pressure.
* Trial acronyms are defined in **Table 1.**
† Heart rate data at follow-up were only available for 147 patients (baseline data reported for entire trial; follow-up for only those patients in whom heart rate was measured).
‡ Monotherapy phase, before the crossover.

Appendix—**Continued**

Change in SBP, *mm Hg*	Baseline Heart Rate (SD), *beats/min*	Follow-up Heart Rate (SD), *beats/min*	Change in Heart Rate, *beats/min*
NR	Intervention: 85 (12); control: 85 (11)	Intervention: 75 (12) at 19 mo; control: 84 (21) at 19 mo	Intervention: −10 at 19 mo; control: −1 at 19 mo
Intervention: +7 at 6 mo; control: +2 at 6 mo	Intervention: 90 (17); control: 91 (18)	Intervention: 75 (14) at 6 mo; 77 (15) at 12 mo; control: 84 (17) at 6 mo; 89 (14) at 12 mo	Intervention: −15 at 6 mo; −13 at 12 mo; control: −7 at 6 mo; −2 at 12 mo
NR	Intervention: 82 (12); control: 86 (12)	NR	NR
NR	Intervention: 83; control: 83	Intervention: 68 at 3 mo; control: 83 at 3 mo	Intervention: −15.4 at 3 mo; control: no change at 3 mo
NR	Intervention: 81; control: 83	Intervention: 65 at 3 mo; control: 83 at 3 mo	Intervention: −16.0 at 3 mo; control: no change at 3 mo
NR	NR	NR	NR
Intervention: 0 at 4 mo; control: −1 at 4 mo	Intervention: 87 (17); control: 83 (14)	Intervention: 67 (17) at 4 mo; control: 84 (14) at 4 mo	Intervention: −20 at 4 mo; control: +1 at 4 mo
NR	NR	NR	NR
Intervention: −5.8 at 6 mo; control: −0.7 at 6 mo	Intervention: 85 (12); control: 83 (12)	Intervention: 69 at 6 mo; control: 81 at 6 mo	Intervention: −16.3 at 6 mo; control: −1.9 at 6 mo
Intervention: +1 at 6 mo; control: +3 at 6 mo	Intervention: 86 (15); control: 83 (16)	Intervention: 70 (21) at 6 mo; control: 80 (12) at 6 mo	Intervention: −16 at 6 mo; control: −3 at 6 mo
Intervention: +5 at 6 mo; control: +3 at 6 mo	Intervention: 80 (13); control: 83 (16)	Intervention: 68 (12) at 6 mo; control: 80 (12) at 6 mo	Intervention: −12 at 6 mo; control: −3 at 6 mo
Intervention: +1 at 6 mo; control: +3 at 6 mo	Intervention: 84 (17); control: 83 (16)	Intervention: 67 (13) at 6 mo; control: 80 (12) at 6 mo	Intervention: −17 at 6 mo; control: −3 at 6 mo
Intervention: −4.4 at 6 mo; control: +1.5 at 6 mo	Intervention: 85; control: 79	Intervention: 68 at 6 mo; control: 81 at 6 mo	Intervention: −17 at 6 mo; control: +2 at 6 mo
Intervention: +5.2 at 6 mo; control: +10.8 at 6 mo	Intervention: 76 (13); control: 77 (13)	Intervention: 66 (12) at 6 mo; control: 75.5 (12) at 6 mo	Intervention: −9.5 at 6 mo; control: −1.5 at 6 mo
NR	Intervention: 83 (12); control: 83 (13)	Intervention: 71 at 2 mo; control: 81 at 2 mo	Intervention: −12.5 at 2 mo; control: −2.2 at 2 mo
Intervention: −11 at 6 mo; control: 0 at 6 mo	Intervention: 77 (11); control: 78 (13)	Intervention: 65 (13) at 6 mo; control: 81 (13) at 6 mo	Intervention: −12 at 6 mo; control: +3 at 6 mo
Intervention: −5 at 3 mo; control: −6 at 3 mo	Intervention: 77 (11); control: 78 (11)	Intervention: 68 at 3 mo; control: 78 at 3 mo	Intervention: −9 at 3 mo; control: 0 at 3 mo
NR	Intervention: 83 (14); control: 83 (15)	Intervention: 67 at 1 mo; control: 78 at 1 mo	Intervention: −15.7 at 1 mo; control: −4.1 at 1 mo
NR	Intervention: 80 (15); control: 81 (16)	Intervention: 70 (15) at 2 mo; control: 81 (14) at 2 mo	Intervention: −9.8 at 2 mo; control: −0.2 at 2 mo
Intervention: −6 at 6 mo; control: −5.5 at 6 mo	Intervention: 79 (14); control: 80 (13)	Intervention: 68 (14) at 6 mo; control: 79 (15) at 6 mo	Intervention: −10.9 at 6 mo; control: −0.9 at 6 mo
NR	Intervention: 84.7 (13); control: 84.4 (21)	Intervention: 72 (9) at 3 mo; control: 81 (20) at 3 mo	Intervention: −11.6 at 3 mo; control: −3.2 at 3 mo
Intervention: −3.4 at 1 mo; control: +5.5 at 1 mo	Intervention: 86 (12); control: 87 (12)	Intervention: 80 (7) at 3 mo; control: 88 (16) at 3 mo	Intervention: −6 at 3 mo; control: +1.2 at 3 mo
Intervention: −6 at 1 mo; control: +5.5 at 1 mo	Intervention: 87 (11); control: 87 (12)	Intervention: 82 (8) at 3 mo; control: 88 (15) at 3 mo	Intervention: −5 at 3 mo; control: +1.2 at 3 mo
Intervention: −2.8 at 1 mo; control: +5.5 at 1 mo	Intervention: 88 (12); control: 87 (12)	Intervention: 81 (7) at 3 mo; control: 88 (15) at 3 mo	Intervention: −7.2 at 3 mo; control: +1.2 at 3 mo
NR	Intervention: 81 (13); control: 82 (13)	Intervention: 72 (13) at 3 mo; control: 81 (13) at 3 mo	Intervention: −9 at 3 mo; control: −1 at 3 mo
NR	Intervention: 89 (15); control: 91 (15)	NR	NR
Intervention: −7 at 4 mo; control: −5 at 4 mo	Intervention: 79 (14); control: 79 (14)	Intervention: 69 (13) at 4 mo; control: 77 (14) at 4 mo	Intervention: −10.3 at 4 mo; control: −1.5 at 4 mo
Intervention: −1 at 8 mo; control: 0 at 8 mo	Intervention: 77 (11); control: 75 (10)	Intervention: 67 (9) at 8 mo; control: 75 (10) at 8 mo	Intervention: −10 at 8 mo; control: 0 at 8 mo