A Meta-Analysis of Randomized, Double-Blinded, Placebo-Controlled Clinical Trials

β -Blockers in Heart Failure: Benefits of β -Blockers According to Varying Male Proportions of Study Patients

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ABSTRACT

Background: In patients with heart failure (HF), β -blockers reduce mortality. It's not known whether the beneficial effects of the β -blockers were associated with the differing male proportions of study patients. It also remains to be clarified regarding the true beneficial effects of the 3 β -blockers recommended by the guideline on mortality in the real world.

Hypothesis: The benefits of β -blockers in HF patients were sex-related different.

Methods: Randomized, placebo controlled clinical trials were included if they evaluated the beneficial effects of the three β -blockers on mortality and on hospital admissions on an intention-to-treat basis, and lasted at least 3 months.

Results: Twenty-eighty trials with 14,829 patients were included. The β -blockers significantly reduced all cause mortality by 29.6%, cardiac death by 29.8%, sudden death by 49.4%, respectively. The magnitude of benefits of β -blockers in HF patients was increased with the increased male proportion. A similar magnitude of reduction in all cause mortality was observed among the three β blockers. A trend toward to reduced cardiac death was observed among the three β blockers, but only in bisoprolol was this statistically different (RR, 0.72; 95%CI, [0.59–0.87]). Metoprolol was significantly superior to carvedilol ($P = 0.008$) or bisoprolol ($P = 0.034$) in reduced sudden death.

Conclusions: In patients with HF, the 3 commonly used β -blockers significantly reduced mortality. Greater benefits of β -blockers were observed in the higher male proportion studies. The metoprolol was significantly superior to carvedilol or bisoprolol in reduced sudden death. Additional trials are required to determine whether the benefits of β -blockers will be observed in female HF patients.

Introduction

Compelling evidence now exists that proves adrenergic blockade is at the center of neurohormonal antagonism in heart failure. β -Blocker treatment of heart failure will improve patients' symptoms, left ventricular function, and the rate of hospital admission.^{1,2} The most recently updated ACC/AHA practice guideline published in 2009 recommended that β -blockers should be used in all stable patients with current or prior symptoms of heart failure (HF) and reduced left ventricular ejection fraction (LVEF) unless contraindicated.³ To our knowledge, several high-quality meta-analyses of clinical randomized trials with β -blockers in HF patients were conducted and published from 1998 to 2005.^{4–7} It is legitimate, therefore, to question whether another meta-analysis article is necessary.

The answer seems to be affirmative for the following reasons: 1) The guidelines³ now only recommend the 3 β -blockers carvedilol, metoprolol, and bisoprolol for the treatment of heart failure. In addition to these 3 drugs, the previous meta-analyses or reviews, however, included at least 1 clinical trial with bucindolol,^{4,6} propranolol,⁴ nebivolol,⁷ acebutolol,⁵ or labetalol,⁵ which are now very rarely prescribed for HF patients. Therefore, the results of the previous meta-analyses or reviews including these rarely prescribed β -blockers will not now reflect the true benefits of recommended β -blockers in HF. 2) A statistical method was applied incorrectly in comparing relative risks or odds ratios in subgroup analysis in several meta-analyses.^{4,6,7} 3) Underrepresentation of women in HF clinical trials leads to limited conclusions regarding the beneficial effects of β -blockers on survival and hospitalizations in female HF patients.⁸ Furthermore, those conclusions are from post hoc analyses and are conflicting.^{8–10} Thus, it is not known whether the beneficial effects of β -blockers on all-cause mortality, cardiac

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death, sudden death, and hospital admissions were observed in female HF patients. This meta-analysis was undertaken to address the above-mentioned questions.

Methods

Clinical trials were identified through a computerized bibliographic search of the MEDLINE database and by browsing the bibliography from review articles on heart failure. This search did not reveal any randomized trial that had not been published in either article or abstract form.

Clinical trials were included if they: 1) were randomized and tested any 1 of the following β -adrenergic agents: carvedilol, metoprolol, and bisoprolol; 2) had a placebo-control group; 3) had a parallel design (the first part of crossover studies was included in this study); 4) evaluated mortality on an intention-to-treat basis; and 5) had a minimum therapeutic duration of 3 months. Trials with and without a run-in phase were included.

Sudden death was defined as death occurring within 1 hour without previous worsening of symptoms of heart failure; cardiac death as death occurring as a consequence of progressive deterioration of heart failure, acute pulmonary edema, or cardiogenic shock; and all-cause mortality as any death occurring during the follow-up periods.

Two reviewers abstracted data from each study independently. These data included age, gender, mean ejection fraction, ischemic or nonischemic etiology of heart failure, concomitant use of drugs, mean follow-up time, hospital admissions, total mortality, cardiac mortality, and sudden death mortality. Total mortality was the major end point of interest. We programmed a spreadsheet to combine all outcomes. Heterogeneity of treatment effects between studies was tested by using $\alpha\chi^2$ test for heterogeneity. Relative risks (RR) and their 95% confidence intervals (CIs) were calculated using the DerSimonian and Laird random-effects methods with the STATA 11.0 program (StataCorp, College Station, TX). The random-effects model was chosen because, in absence of heterogeneity, the results are the same as those obtained with the fixed-effects model, and they can be more confidently generalized because they are also more conservative. Comparisons between RR estimates were performed using the method described by Altman.¹¹

Results

The data of the first period of 3 crossover design studies were also abstracted.^{12–14} Thus, a total of 28 studies^{12–39} met the pre-established criteria and were included in this meta-analysis. A total of 14 829 patients were studied, 7594 randomized to β -blockers and 7235 to the placebo control. The median duration of treatment was 6 months. In 11 trials, the drug under study was metoprolol; in 15 trials, carvedilol; in 2 trials, bisoprolol (Table 1). Fifteen trials tested a β -blocker with vasodilating properties (6452 patients in trials with carvedilol) and 13 trials without (8377 patients in trials with metoprolol or bisoprolol).

Heart failure due to ischemic heart disease resulted in 3 trials,^{13,22,29} to idiopathic in 7 trials,^{12,14–18,32} and to mixed in 16 trials. The cause was not available in 2 trials.^{25,37} Male proportion <70% was found in 7 trials; 70% to 80%, in 10 trials; and >80%, in 11 trials.

Publication Bias

To evaluate the impact of potential publication bias, the Begg's funnel plot was constructed. As demonstrated in Figure 1, the funnel plot was largely symmetric with no evidence of publication bias. The Egger's test revealed no publication bias ($t = 1.05$, $P = 0.307$).

All-Cause Mortality, Cardiac Death, and Sudden Death

A total of 1677 patients died, 702 (9.24%) of 7594 treated with β -blockers, and 974 (13.46%) of 7235 in the placebo group (RR: 0.71, 95% CI: 0.64–0.77). Thus, 1 death can be prevented by treating 24 patients for a median of 6 months. In 14 trials, a trend toward reduced mortality was seen, but only in 5 trials was this statistically significant.

Information on cardiac death was obtained from 18 studies. There were 464 (7.60%) of 6106 cardiac deaths among patients treated with β -blockers, compared with 647 (11.14%) of 5808 in the control group (RR: 0.71, 95% CI: 0.61–0.82). This corresponds to 1 cardiac death prevented for every 29 patients treated for a median of 6 months.

Information on sudden cardiac death was obtained from 21 studies. There were 232 (3.65%) of 6364 sudden death among patients treated with β -blockers, compared with 448 (7.44%) of 6019 in the control group (RR: 0.51, 95% CI: 0.43–0.59). Thus, 1 sudden death can be prevented for every 26 patients treated for a median of 6 months.

All-Cause Mortality, Cardiac Death, Sudden Death, and Differing Male Proportions

The clinical trials included were assigned to 3 groups based on the differing male proportions in individual clinical trial: male <70%; male 70% to 80%; and male >80%. Then, all-cause mortality, cardiac death, and sudden death were further analyzed. Interestingly, the beneficial effect of β -blockers in chronic HF seems to be related to the gender proportion. The magnitude and significance of the treatment effect on all-cause mortality, cardiac death, and sudden death were increased with the increased male proportion in study patients. In the male >80% group and the male 70% to 80% group, the magnitude of the benefits of β -blockers in terms of all-cause mortality, cardiac death, and sudden death was of the same order with statistical differences. In the male <70% group, however, a nonsignificant trend toward reducing all-cause mortality, cardiac death, and sudden death was seen. In the male <70% group, the point estimate of the reduction of sudden death was particularly low (RR: 0.28, 95% CI: 0.05–1.55), but the CI was wide and the difference was not statistically significant ($P = 0.143$) (Table 2 and Figure 2).

All-Cause Mortality, Cardiac Death, Sudden Death, and β -Blockers With Different Properties

The 3 β -blockers of carvedilol, metoprolol, and bisoprolol reduced all-cause mortality similarly with statistical significances (RR: 0.70, 95% CI: 0.60–0.83; RR: 0.70, 95% CI: 0.60–0.84; and RR: 0.71, 95% CI: 0.60–0.83, respectively). A trend toward reduced cardiac death was observed in the 3 β -blockers, but only in bisoprolol was this statistically significant (RR: 0.72, 95% CI: 0.59–0.87). The CIs were wide in carvedilol and metoprolol and the differences were not

Table 1. Baseline Characteristics of Placebo-Controlled Clinical Trials of β -Blockers in Heart Failure

Source	Year	Official Acronym	β -Blockers	Duration, mo	Male, %	IHD, %	Mean Age, y	Primary End Point
Engelmeier RS ¹²	1985		Metoprolol	12	64%	0%	50	Exercise tolerance
Anderson JL ¹⁵	1985		Metoprolol	19	66%	0%	51	Mortality
Paolisso G ¹⁴	1992		Metoprolol	3	60%	0%	56	NYHA classifications
Waagstein F ¹⁶	1993	MDC	Metoprolol	12	72%	0%	49	All cause mortality
Metra M ¹⁸	1994		Carvedilol	4	90%	0%	51	Exercise tolerance
Fisher ML ¹³	1994		Metoprolol	6	96%	100%	63	Exercise capacity
CIBIS Investigators ³⁹	1994	CIBIS	Bisoprolol	22.8	83%	55%	60	All-cause mortality
Eichhorn EJ ¹⁷	1994		Metoprolol	6	100%	0%	48	EF improvement
Krum H ²⁰	1995		Carvedilol	3.5	78%	27%	55	EF improvement
Olsen SL ²¹	1995		Carvedilol	3	93%	28%	52	EF improvement
ANZ-HeFT Collaborative Group ¹⁹	1995	ANZ-HeFT	Carvedilol	19	80%	100%	67	Deaths and admissions
Krum H ²²	1996		Carvedilol	3.5	80%	33%	57	Endothelin-1 level
Packer M ²³	1996		Carvedilol	6	76%	48%	58	All-cause mortality
CIBIS-II Investigators ²⁴	1999	CIBIS II	Bisoprolol	15.6	81%	50%	60	All cause mortality
Guazzi M ²⁵	1999		Carvedilol	6	77%	na	50	EF improvement
Hjalmarson AS ²⁸	2000	MERIT-HF	Metoprolol	12	77%	66%	64	All-cause mortality
Genth-Zotz S ²⁷	2000		Metoprolol	6	71%	50%	54	6-minute walk test
RESOLVD Investigators ²⁶	2000	RESOLVD	Metoprolol	6	82%	69%	62	All cause mortality
Dargie HJ ²⁹	2001	CAPRICORN	Carvedilol	15.6	74%	100%	63	All cause mortality
Packer M ³¹	2002	COPERNICUS	Carvedilol	10.4	79%	67%	63	All-cause mortality
Palazzuoli A ³²	2002		Carvedilol	12	62%	0%	71	Echocardiographic evaluation
de Milliano PA ³⁰	2002		Metoprolol	6	67%	56%	65	6-minute walk test
Cleland JG ³³	2003	CHRISTMAS	Carvedilol	6	90%	90%	63	EF improvement
Cohen Solal A ³⁵	2004		Carvedilol	6	84%	40%	60	EF improvement
Bergstrom A ³⁴	2004	SWEDIC	Carvedilol	6	57%	11%	67	Regression of diastolic LV dysfunction
Hori M ³⁷	2004	MUCHA	Carvedilol	12	77%	26%	61	Improvement of global assessment
De Matos LD ³⁶	2004		Carvedilol	6	47%	na	49	Exercise tolerance
GrunerSveallv B ³⁸	2007		Metoprolol	12	71%	25%	57	EF improvement

Abbreviations: ANZ-HeFT, Australia-New Zealand Heart Failure Trial; CAPRICORN, Carvedilol Post-Infarct Survival Control in LV Dysfunction; CIBIS, Cardiac Insufficiency Bisoprolol Study; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival; CHRISTMAS, Carvedilol Hibernation Reversible Ischaemia Trial, Marker of Success; EF, ejection fraction; IHD, ischemic heart disease; LV, left ventricular; MDC, Metoprolol in Dilated Cardiomyopathy; MERIT-HF, Metoprolol CR/XI Randomized Intervention Trial in Congestive Heart Failure; MUCHA, Multicenter Carvedilol Heart Failure Dose Assessment; NYHA, New York Heart Association; RESOLVD, Randomized Evaluation of Strategies for Left Ventricular Dysfunction; SWEDIC, Swedish Doppler-Echocardiographic.

statistically significant. The 3 β -blockers reduced sudden death significantly (RR: 0.66, 95% CI: 0.49-0.89; RR: 0.40, 95% CI: 0.32-0.50; and RR: 0.64, 95% CI: 0.44-0.93, respectively). The better beneficial effect on reduced sudden death was observed in metoprolol than in either carvedilol (RR: 0.63, 95% CI: 0.40-0.97) or bisoprolol (RR: 0.61, 95% CI: 0.42-0.88) (Table 3).

Hospitalization

Five trials gave information on all-cause hospitalization. There were 1226 (32.7%) of 3747 hospitalizations treated with β -blockers compared with 1388 (37.2%) of 3731 in the control group. Thus, the β -blockers reduced the rate of hospitalization by 13.8% (RR: 0.86; 95% CI: 0.805-0.918).

Figure 1. The funnel plot for the publication bias test. Abbreviation: s.e., standard error.

Fourteen trials gave information on cardiovascular (CV) hospitalization. The heterogeneity between studies was significant ($\chi^2 = 25.59$, $P = 0.019$, and $I^2 = 49.2\%$). Thus, metaregression was conducted to explore the origin of the heterogeneity with the Knapp-Hartung method using age, male percent, and ischemic heart disease (IHD) percent as covariates, respectively. It was revealed that the male percent was 1 of the origins of the heterogeneity ($t = -2.70$, $P = 0.019$). The male percent was introduced into the regression model, and the I^2 was 22.8%, a reduction by 26.4%. Fourteen trials were then subdivided according to the male proportion into 3 subgroups: male <70%, male 70% to 80%; male >80%, and the meta-analysis of CV hospitalization for these 3 subgroups were conducted, respectively. Only the random-effects model was used for calculating the pooled relative risk of CV hospitalization.

Discussion

Male patients dominated in previous HF clinical trials.^{19,28,31,39} The effects of β -blockers in female HF patients were not fully investigated. The major finding of the present study indicated that the benefits of β -blockers were not found in lower percentages of female HF patients. The benefits of β -blockers were observed in both the male >80% and the male 70% to 80% groups. In the male <70% group, however, the benefits of β -blockers were not revealed. The benefits of β -blockers were observed in both the male >80% and the male 70% to 80% groups. In the male <70% group, the benefits of β -blockers were not revealed. A subgroup analysis in 1 meta study also showed that the benefits of β -blockers were

only observed in the $\geq 75\%$ male group and otherwise in the <75% male group,⁶ which was in accord with our results. A recent small sample study also found that β -blocker therapy may be associated with a higher risk of HF rehospitalization in women compared to men.¹⁰ Patients hospitalized with HF have different clinical characteristics.^{40,41} Women receive comparable quality of care for most, but not all measures; specifically, women were less likely to undergo evaluation of LV function and receive anticoagulation for atrial fibrillation or implantable cardioverter-defibrillator for left ventricular systolic dysfunction (LVSD) with an LVEF <35%.⁴⁰ These may explain the sex-related differences in terms of all-cause mortality, cardiac death, sudden death, and CV hospital admissions treated with these β -blockers in HF patients.

Previously published meta-analyses, which each included from 2986 to 10480 patients, had already suggested a protective effect of β -blockers on all-cause mortality, cardiac death, and sudden death.^{2,4-7} The present study, which encompasses only those clinical trials with the 3 β -blockers of carvedilol, metoprolol, and bisoprolol recommended by the guidelines and includes 14829 patients, confirms previous estimates of the benefit of β -blockers and better reflects the true benefits of β -blockers in terms of all-cause mortality, cardiac death, sudden death, and all-cause hospitalization in the real world. The 3 β -blockers reduced all-cause mortality by 29.6%, cardiac death by 29.8%, sudden death by 49.4%, and all-cause hospitalization by 13.8%, respectively.

Another important finding of the present study indicated that the vasodilating blocking agents were similar to the non-vasodilating ones in terms of reduction of all-cause mortality, cardiac death, and sudden death, which was in sharp contrast to previous meta studies.^{2,4-7} Carvedilol is a vasodilating blocking agent, and metoprolol and bisoprolol are nonvasodilating blocking agents. The vasodilating blocking agents were even not superior to the nonvasodilating blocking agents in terms of reduced sudden death (RR: 0.66, 95% CI: 0.49-0.89 and RR: 0.52, 95% CI: 0.38-0.72, respectively). The subgroup studies in previous meta-analyses revealed that β -blocker agents with a vasodilating property were superior to those without in terms of reduced mortality.^{2,4-7} Unfortunately, the statistical differences were mistakenly reported in 2 meta-analyses,^{4,7} and the remaining meta-analyses did not report the statistical differences.^{2,5,6} Only in the Carvedilol or Metoprolol European Trial trial, were the greater benefits of reduced all-cause mortality, cardiac death, and sudden death observed in carvedilol than in metoprolol.⁴²

Table 2. Effects of β -Blockers on Mortality in Patients With Heart Failure Based on Differing Male Proportions

Subgroup	All-Cause Mortality		Cardiac Death		Sudden Death	
	No. of Trials	RR (95% CI), <i>P</i>	No. of Trials	RR (95% CI), <i>P</i>	No. of Trials	RR (95% CI), <i>P</i>
Male <70%	5	0.73(0.35–1.53), 0.410	2	0.89(0.21–3.71), 0.871	2	0.28(0.05–1.55), 0.143
Male 70%–80%	7	0.72(0.64–0.81), 0.000	5	0.78(0.62–0.99), 0.038	5	0.59(0.38–0.91), 0.016
Male >80%	8	0.67(0.55–0.83), 0.000	4	0.63(0.48–0.82), 0.001	5	0.61(0.46–0.80), 0.000
Overall	20	0.71(0.64–0.77), 0.000	11	0.71(0.61–0.82), 0.000	12	0.51(0.43–0.59), 0.000

Abbreviations: RR, relative risk; CI, confidence interval.

Figure 2. Effects of β -blockers on all-cause mortality based on differing male proportions. Squares indicates point estimates. The diamonds indicate the subtotal or overall best estimates of the effects in the subtotal or the overall rows. Abbreviations: CI, confidence interval; CIBIS, Cardiac Insufficiency Bisoprolol Study; RESOLVD, Randomized Evaluation of Strategies for Left Ventricular Dysfunction; RR, relative risk.

Table 3. Benefits of Different β -Blockers in Terms of Mortality

Groups	Carvedilol RR (95% CI)	Metoprolol RR (95% CI)	P^a	Bisoprolol RR (95% CI)	P^b	Noncarvedilol RR (95% CI)	P^c
All-cause mortality	0.70 (0.60-0.83)	0.70 (0.60-0.84)	1.00	0.71 (0.60-0.83)	0.90	0.71 (0.63-0.80)	0.88
Cardiac death	0.65 (0.42-1.01)	0.78 (0.54-1.13)	0.54	0.72 (0.59-0.87)	0.68	0.71 (0.62-0.81)	0.70
Sudden death	0.66 (0.49-0.89)	0.40 (0.32-0.50)	0.008	0.64 (0.44-0.93)	0.90	0.52 (0.38-0.72)	0.28

P = carvedilol vs bisoprolol. a Indicates comparison of relative risk of effects of carvedilol vs metoprolol on mortality; b Carvedilol vs noncarvedilol; c Carvedilol vs noncarvedilol. Noncarvedilol indicates metoprolol and bisoprolol.

A similar magnitude of reduction in all-cause mortality was observed in carvedilol, metoprolol, and bisoprolol. A trend toward reduced cardiac death was observed in carvedilol, metoprolol, and bisoprolol, but only in bisoprolol was this statistically different (RR:0.72, 95% CI: 0.59-0.87). All of the 3 β -blockers reduced sudden death significantly,

and the metoprolol was prominent in reduced sudden death (RR:0.40, 95% CI: 0.32-0.50). Metoprolol was significantly superior to carvedilol ($z = 2.63$, $P = 0.008$) or bisoprolol ($z = 2.11$, $P = 0.034$) in terms of reduced sudden death.

The results of the present meta-analysis should be interpreted cautiously. The publication bias, which is a

tendency not to submit or publish studies demonstrating nonsignificant differences in therapy, may invalidate our findings. The majority of studies had follow-up durations of ≤ 12 months. The long-term effects of β -blockers on survival are unclear. It is also difficult to distinguishing between sudden death and non-sudden cardiac death, and our findings are therefore limited by the accuracy of each trial's classification.

Conclusion

β -Blockers significantly reduce all-cause mortality, cardiac death, sudden death, and rates of all-cause or CV hospital admissions. The magnitude of benefit from β -blockers in HF patients was increased with the increased male proportion of study subjects. No benefits from β -blockers were observed in the male $<70\%$ group. The 3 β -blockers of carvedilol, metoprolol, and bisoprolol reduced all-cause mortality and sudden death with statistical differences. Of these 3 β -blockers, metoprolol was prominent in reduced sudden death compared with carvedilol or bisoprolol. Benefits of β -blockers in reduced cardiac death were observed, but only in bisoprolol was this significant. No greater benefits were observed in vasodilating β -blocking agents (carvedilol in this study) than in the nonvasodilating blocking agents (metoprolol and bisoprolol). Additional trials are required to determine whether the benefits of β -blockers will be observed in female HF patients.

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