

# $\beta$ -Blockers in Congestive Heart Failure

## A Bayesian Meta-Analysis

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**Purpose:** Congestive heart failure is an important cause of patient morbidity and mortality. Although several randomized clinical trials have compared  $\beta$ -blockers with placebo for treatment of congestive heart failure, a meta-analysis quantifying the effect on mortality and morbidity has not been performed recently.

**Data Sources:** The MEDLINE, Cochrane, and Web of Science electronic databases were searched from 1966 to July 2000. References were also identified from bibliographies of pertinent articles.

**Study Selection:** All randomized clinical trials of  $\beta$ -blockers versus placebo in chronic stable congestive heart failure were included.

**Data Extraction:** A specified protocol was followed to extract data on patient characteristics,  $\beta$ -blocker used, overall mortality, hospitalizations for congestive heart failure, and study quality.

**Data Synthesis:** A hierarchical random-effects model was used to synthesize the results. A total of 22 trials involving 10 135 patients were identified. There were 624 deaths among 4862

patients randomly assigned to placebo and 444 deaths among 5273 patients assigned to  $\beta$ -blocker therapy. In these groups, 754 and 540 patients, respectively, required hospitalization for congestive heart failure. The probability that  $\beta$ -blocker therapy reduced total mortality and hospitalizations for congestive heart failure was almost 100%. The best estimates of these advantages are 3.8 lives saved and 4 fewer hospitalizations per 100 patients treated in the first year after therapy. The probability that these benefits are clinically significant (>2 lives saved or >2 fewer hospitalizations per 100 patients treated) is 99%. Both selective and non-selective agents produced these salutary effects. The results are robust to any reasonable publication bias.

**Conclusions:**  $\beta$ -Blocker therapy is associated with clinically meaningful reductions in mortality and morbidity in patients with stable congestive heart failure and should be routinely offered to all patients similar to those included in trials.

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Congestive heart failure has reached pan-epidemic proportions in industrialized countries and is responsible for vast patient morbidity and mortality (1–4). Mortality associated with moderate to severe congestive heart failure may exceed that associated with many neoplasms, and the 1-year survival rate is as dismal as 50% (5). Quality of life is also adversely affected, and congestive heart failure is the most common cause of hospital admission in elderly persons in North America (6). Clearly, additional therapies are urgently needed.

Randomized clinical trials are the gold standard for comparative research and have been used to investigate both new and old therapies for congestive heart failure. For example, trials have clearly demonstrated the beneficial effect of angiotensin-converting enzyme inhibitors on patient mortality (7), the neutral effect of digitalis (8), and the deleterious effects of other inotropic agents in congestive heart failure (9–11).

Although conventional medical education previously viewed congestive heart failure as a contraindication for the use of  $\beta$ -blockers because of their potential short-term negative inotropic effects, benefits of  $\beta$ -blocker treatment in this condition have been sporadically reported since 1975 (12). Initially, these studies had only modest

samples, thereby limiting definite conclusions. Subsequently, at least four meta-analyses of the cumulative experience of randomized trials with  $\beta$ -blockers in heart failure were published (13–16). It is legitimate, therefore, to question whether another summary article is necessary.

The answer appears to be affirmative for two reasons. First, results of the largest published trials of  $\beta$ -blockers in congestive heart failure (17, 18) have not been included in previously published meta-analyses. With the new larger studies, we can provide a narrower confidence interval, so that clinical benefit is better estimated. Second, unlike previous meta-analyses, we used a Bayesian hierarchical random-effects model. Such a model has several advantages, including the ability to account for possible between-study variation, which may be an important consideration in a meta-analysis of trials covering 15 years and using a variety of  $\beta$ -blockers.

## METHODS

Randomized trials of  $\beta$ -blockers in congestive heart failure were identified by performing a systematic electronic review of the literature. The MEDLINE database

was searched from 1966 to July 2000 by using the key words *adrenergic beta-antagonists*, *congestive heart failure*, and *trial*. This search produced 105 articles, which were hand searched for original randomized clinical trials that compared  $\beta$ -blockers with placebo and had mortality as an outcome. Trials were excluded if they involved crossover designs,  $\beta$ -blockers with intrinsic sympathomimetic activity, follow-up of less than 3 months, or patients admitted for acute myocardial infarction. This procedure identified 17 trials (17–34). The four meta-analyses (13–16) published in 1997 and 1998 were examined and yielded another 5 eligible trials (35–39). Finally, the Cochrane and the Web of Science databases were searched; no further trials were discovered.

Patient variability and differences in trial design, inclusion and exclusion criteria, and target populations make it unrealistic to assume that the effects of  $\beta$ -blockers estimated from each of these trials will be identical, as implied by a fixed-effects meta-analysis model. We therefore used a Bayesian hierarchical (random-effects) meta-analytic model (40) to analyze these 22 studies. Bayesian analysis produces direct probability statements calculated from the areas under probability distribution function curves, providing clear clinical interpretations of the accumulated data.

In our Bayesian hierarchical model, we assume first that each arm of each study independently estimates the probability  $p_{ij}$  of an event (death or hospitalization), where  $i$  indexes each study (so that  $i$  ranges from 1 to 22) and  $j$  indexes the study group ( $j = 0$  for the placebo control group and 1 for the  $\beta$ -blocker group). Since the follow-up period varied greatly among trials, we initially used the odds ratio as a measure of the effect size. The odds ratio for trial  $i$  is defined as  $or_{(i)} = p_{(i1)}/(1 - p_{(i1)})/p_{(i0)}/(1 - p_{(i0)})$ . The collection of the logarithms of the odds ratios across the different trials is assumed to follow a normal distribution with mean  $\mu$  and variance  $\sigma^2$ . Hence,  $\mu$  represents the overall mean effect (odds ratios in probabilities) across studies, and  $\sigma^2$  represents study-to-study variation. If  $\sigma^2 = 0$ , the model reduces to a fixed-effects model, whereas larger values of  $\sigma^2$  represent increasing evidence of heterogeneity between the studies. We used diffuse prior distributions for  $\mu$  and  $\sigma^2$ , so that all parameter estimates are almost entirely determined by the observed data. Histograms of  $\log(or_{(i)})$  estimates across studies for both death and hospitaliza-

tion outcomes showed that our normality assumptions were reasonable.

Reporting results about  $\mu$  allows us to estimate an overall average effect from all studies combined. Study-to-study variation can be considered by predicting what the odds ratio  $or_{(i)}$  might be for the “next study” by selecting a rate from the normal distribution with mean  $\mu$  and variance  $\sigma^2$ . In a random-effects model, we assume that the effect of the treatment varies from setting to setting. Clinicians must therefore understand that the mean effect does not necessarily apply to their individual practices, because their setting may not be like the “average setting.” By including both the between-study variability and the usual random variability, the clinician can interpret posterior densities and credible intervals (the Bayesian analogue to confidence intervals) as these findings apply to their clinics.

Odds ratios are an attractive means of combining studies that have differing follow-up times; however, as a relative measure, odds ratios do not take into account absolute differences and may thereby obscure the clinical importance of an intervention. We therefore converted our results into probability distributions of the differences in survival at 1 year between patients receiving  $\beta$ -blockers and placebo. To reliably estimate the contemporary annual baseline mortality rate among placebo recipients, we performed a hierarchical meta-analysis of the baseline rates in the three most recent and largest trials (17, 18, 28). Similar results were obtained by using the placebo arms from all trials published from 1993 onward (data not shown).

In creating posterior distributions, we focused on the distribution of the next predicted study. The standard deviation of this distribution is larger than that of the posterior distribution of the mean difference between using  $\beta$ -blockers or placebo because it includes between-study variation. The means of both distributions are, however, equal. Parameters from our models were estimated by using FAST\*PRO software, version 1.0 (41, 42).

Probability density distributions, although unfamiliar to most clinicians, are “clinically friendly” and supply simple, direct probability estimates to pertinent questions by measuring the area under the curve. This approach permits probability calculations not only relating to any interval null or alternative hypotheses but also to any range of clinically meaningful differences.

**Table 1. Randomized, Controlled Clinical Trials Comparing  $\beta$ -Blockers with Placebo in Stable Patients with Congestive Heart Failure\***

Study (Reference)	Year of Publication	Drug Studied	Mean Duration of Follow-up	Cause of Disease	NYHA Class	Entry Criterion for Ejection Fraction (Average Value)
			mo	%		
Anderson et al. (19)	1985	Metoprolol	19	NICM: 100	II–IV	<0.40 (0.28)
Engelmeier et al. (20)	1985	Metoprolol	12	NICM: 100	II–IV	<0.49 (0.17)
Pollock et al. (35)	1990	Bucindolol	3	NICM: 63 ICM: 27	II–IV	<0.40 (0.21)
Woodley et al. (36)	1991	Bucindolol	3	NICM: 45 ICM: 55	II–III	<0.40 (0.22)
Paolisso et al. (37)	1992	Metoprolol	3	NICM: 100	II–III	NA
Waagstein et al. (21)	1993	Metoprolol	18	NICM: 100	I–IV	<0.40 (0.22)
Wisnibaugh et al. (22)	1993	Nebivolol	3	NICM: 92 ICM: 8	II–III	<0.40 (0.24)
Fisher et al. (23)	1994	Metoprolol	6	ICM: 100	II–IV	<0.40 (0.23)
Bristow et al. (24)	1994	Bucindolol	3	NICM: 71	I–IV	<0.40 (0.24)
CIBIS-I (25)	1994	Bisoprolol	23	NICM: 45 ICM: 55	III–IV	<0.40 (0.25)
Eichhorn et al. (26)	1994	Metoprolol	3	NICM: 100	II–III	<0.45 (0.18)
Metra et al. (27)	1994	Carvedilol	4	NICM: 100	II–III	<0.35 (0.20)
Olsen et al. (38)	1995	Carvedilol	4	NICM: 72 ICM: 28	II–IV	<0.35 (0.20)
Krum et al. (39)	1995	Carvedilol	4	NICM: 73 ICM: 27	II–IV	<0.35 (0.16)
Bristow et al. (29)	1996	Carvedilol	6	NICM: 47 ICM: 53	II–IV	<0.35 (0.23)
Packer et al. (30)	1996	Carvedilol	6	NICM: 48 ICM: 52	II–IV	<0.35 (0.23)
Colucci et al. (31)	1996	Carvedilol	15	NICM: 58 ICM: 42	II–III	<0.35 (0.23)
Cohn et al. (32)	1997	Carvedilol	8	NICM: 59 ICM: 41	II–IV	<0.35 (0.23)
Aust/NZ (28)	1997	Carvedilol	19	NICM: 12 ICM: 88	II–III	<0.45 (0.29)
CIBIS-II (17)	1999	Bisoprolol	15	NICM: 35 ICM: 65	III–IV	<0.35 (NA)
MERIT-HF (18)	1999	Metoprolol	12	NICM: 35 ICM: 65	II–IV	<0.40 (0.28)
RESOLVD (34)	2000	Metoprolol	6	NICM: 31 ICM: 69	II–IV	<0.40 (0.28)

\* ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; Aust/NZ = Australia/New Zealand Heart Failure Research Collaborative Group; CIBIS = Cardiac Insufficiency Bisoprolol Study; ICM = ischemic cardiomyopathy; MERIT-HF = Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; NA = not available; NICM = nonischemic cardiomyopathy; NYHA = New York Heart Association; RESOLVD = Randomized Evaluation of Strategies for Left Ventricular Dysfunction Pilot Study.

Table 1—Continued

Men/Women	Mean Age	Additional Therapy	Use of a Run-in Phase; Adverse Events during Run-In Phase
%/%	y		%
66/34	50	NA	No
64/36	50	NA	No
79/21	54	NA	Yes; 5
72/28	52	Digitalis: 73 Diuretics: 84 ACEI: 76	Yes; 0
60/40	55	NA	Yes; 0
72/28	49	Digitalis: 75 Diuretics: 74 ACEI: 80	No
50/50	50	Digitalis: NA Diuretics: NA ACEI: 0	Yes; 0
96/4	63	Digitalis: 96 Diuretics: 100 ACEI: 94	Yes; 0
61/39	55	Digitalis: 76 Diuretics: 94 ACEI: 88	No
83/17	60	Digitalis: 56 Diuretics: 100 ACEI: 90	No
100/0	48	Digitalis: NA Diuretics: NA ACEI: 100	No
90/10	51	Digitalis: 84 Diuretics: 84 ACEI: 94	Yes; 0
94/6	52	Digitalis: 100 Diuretics: 100 ACEI: 98	Yes; 12
78/22	55	Digitalis: NA Diuretics: NA ACEI: 92	Yes; 8
76/24	63	Digitalis: 94 Diuretics: 99 ACEI: 94	Yes; 5
73/27	60	Digitalis: 89 Diuretics: 99 ACEI: 97	Yes; 5
85/15	54	Digitalis: 89 Diuretics: 92 ACEI: 98	Yes; 5
60/40	58	Digitalis: 90 Diuretics: 95 ACEI: 95	Yes; 5
80/20	67	Digitalis: 38 Diuretics: 76 ACEI/ARB: 86	Yes; 6
80/20	61	Digitalis: 52 Diuretics: 99 ACEI/ARB: 96	No
77/23	64	Digitalis: 64 Diuretics: 98 ACEI/ARB: 96	Yes; NA
82/18	62	Digitalis: 67 Diuretics: 83 ACEI/ARB: 100	Yes; 5

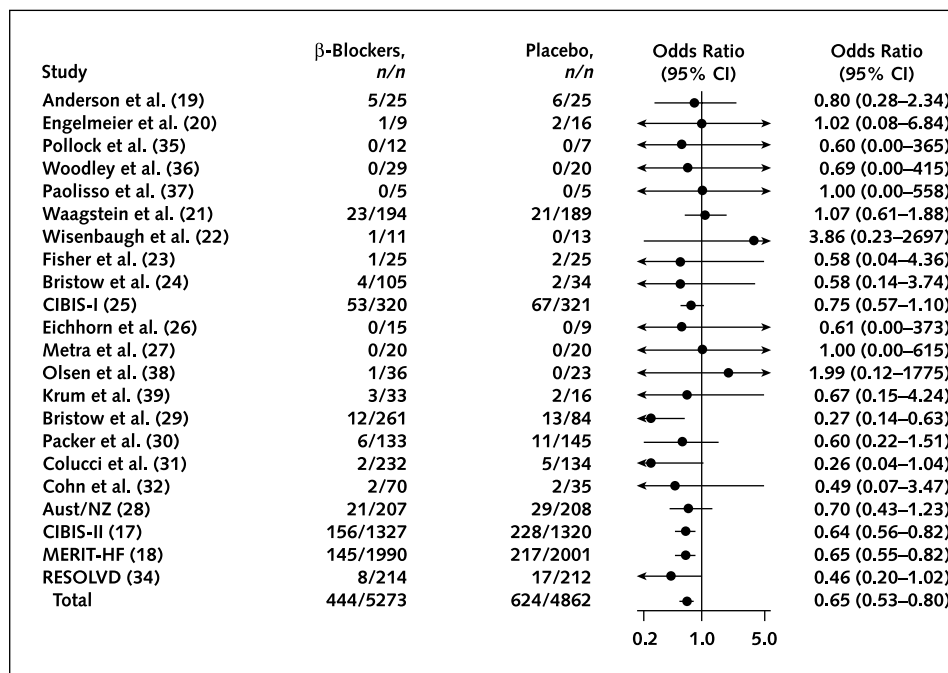
RESULTS

Table 1 shows all of the included trials, along with pertinent patient and study characteristics. Earlier trials focused on patients with idiopathic cardiomyopathy, whereas recent trials have included a preponderance of patients with ischemic cardiomyopathy (Table 1). Overall, the different causes of congestive heart failure have been adequately represented (4127 patients with non-ischemic causes and 6005 patients with ischemic causes). As in most cardiovascular clinical trials, more men (78%) than women were studied, and the average age was younger than is generally seen in routine clinical practice. Although most studies had broad eligibility criteria for functional class, patients with New York Heart Association (NYHA) class IV disease have been under-represented (typically <5% of study samples). Most patients were receiving triple therapy for congestive heart failure; in particular, in recent studies, angiotensin-converting enzymes were used in more than 95% of patients.

Various β-blockers have been studied, but most patients received metoprolol or bisoprolol (up to 200 mg/d); β<sub>1</sub>-selective agents (up to 10 mg/d); or carvedilol, a nonselective agent (up to 25 mg twice daily). Fifteen studies used a run-in period to assess drug tolerability and patient adherence. The overall rate of adverse events in the run-in periods was 5.3%.

The overall quality of the trials was high; each followed a double-blinded protocol, and only one study had possible irregularities in the randomization process (22). Follow-up of randomly assigned patients was almost complete. The only minor methodologic flaw was lack of description of the randomization process in 18 of the 22 trials.

Figures 1 and 2 show the original data on total mortality and need for hospital readmission for congestive heart failure. The obvious difference from earlier meta-analyses is the inclusion of data from the Cardiac Insufficiency Bisoprolol Study II (17) and the Metoprolol CR/XL Randomized Intervention Trial in congestive Heart Failure (18), which tripled the available evidence on which to base our conclusions. Before 1999, 3071 patients had undergone randomization in trials of β-blockers in heart failure, but by July 2000, this number had increased to 10 135. There were 624 deaths among 4862 patients receiving placebo and 444 deaths among 5273 patients receiving β-blocker therapy. Of

Figure 1. Mortality in the placebo and  $\beta$ -blocker groups of 22 studies.

Arrows indicate that the credible interval exceeds the scale; circles indicate point estimates; the bottom circle (in the “Total” row) indicates the overall best estimate of the effect. Aust/NZ = Australia/New Zealand Heart Failure Research Collaborative Group; CIBIS = Cardiac Insufficiency Bisoprolol Study; MERIT-HF = Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; RESOLVD = Randomized Evaluation of Strategies for Left Ventricular Dysfunction Pilot Study.

the 10 135 patients studied, 85% have been enrolled in trials reporting since 1996; most of these trials were ended prematurely on the recommendation of the data and safety boards because large clinical benefits were observed.

The combined odds ratio for total mortality among all patients in the studies was 0.65 (95% credible interval, 0.53 to 0.80). To fully appreciate the magnitude of benefit associated with  $\beta$ -blocker therapy, it is important to remember the high baseline mortality rate. For example, the hierarchically determined mortality rate among placebo recipients in the three largest and most recent trials (17, 18, 28) was 12% (credible interval, 4% to 26%) in the first year of follow-up. If we assume that mortality rate among placebo recipients is exactly 12%, this implies a best estimate of the absolute mortality reduction of 3.8 lives saved per 100 patients treated (credible interval, 2.1 to 5.3) during the first year of treatment.

An advantage of Bayesian analysis is that the reduction in mortality may be displayed as a probability den-

sity curve, in which the area under the curve between any two points shows the probability that the reduction in mortality is in that interval (Figure 3). From this perspective, the probability that  $\beta$ -blocker therapy saves at least 2 lives per 100 patients is 99%. The probability that 3 or more lives are saved per 100 patients is 85% (Table 2). Although we used the normal distribution to fit these curves, almost identical curves result if a log-normal distribution is fitted.

$\beta$ -Blockers are often categorized according to their adrenergic receptor selectivity. Bisoprolol, metoprolol, and nebivolol are considered to have  $\beta_1$ -selective properties, whereas carvedilol and bucindolol are nonselective agents. All of these agents are lipophilic, although bisoprolol is less so than the others. Other individual characteristics among the  $\beta$ -blockers may be pertinent, but we thought it especially clinically relevant to see whether mortality differed between selective and nonselective agents. Both selective agents, predominately metoprolol and bisoprolol, and nonselective agents, predominately carvedilol, were associated with reduced

mortality (odds ratio, 0.67 [credible interval, 0.57 to 0.79] and 0.52 [credible interval, 0.28 to 0.89], respectively).

β-Blocker therapy in these trials has also been associated with a clear reduction in morbidity; 754 of 4862 placebo recipients required hospitalization for heart failure compared with 540 of 5273 β-blocker recipients (odds ratio, 0.64 [credible interval, 0.53 to 0.79]). Using the trials from 1996 onward, the weighted average number of admissions for congestive heart failure among placebo recipients in the first year of follow-up was 14%. This translates into a best estimate of 4.0 fewer hospitalizations per 100 patients treated (credible interval, 2.4 to 5.6) (Figure 3 and Table 2).

This analysis can easily be repeated as more data become available. For example, it may be updated with the data from the recently reported but as-yet unpublished results of the β-Blockers Evaluation Survival Trial (43). This multicenter, randomized, placebo-controlled trial of bucindolol randomly assigned 2708 patients with a primary end point of all-cause mortality. After 2 years of follow-up, the mortality rate was 33% in the

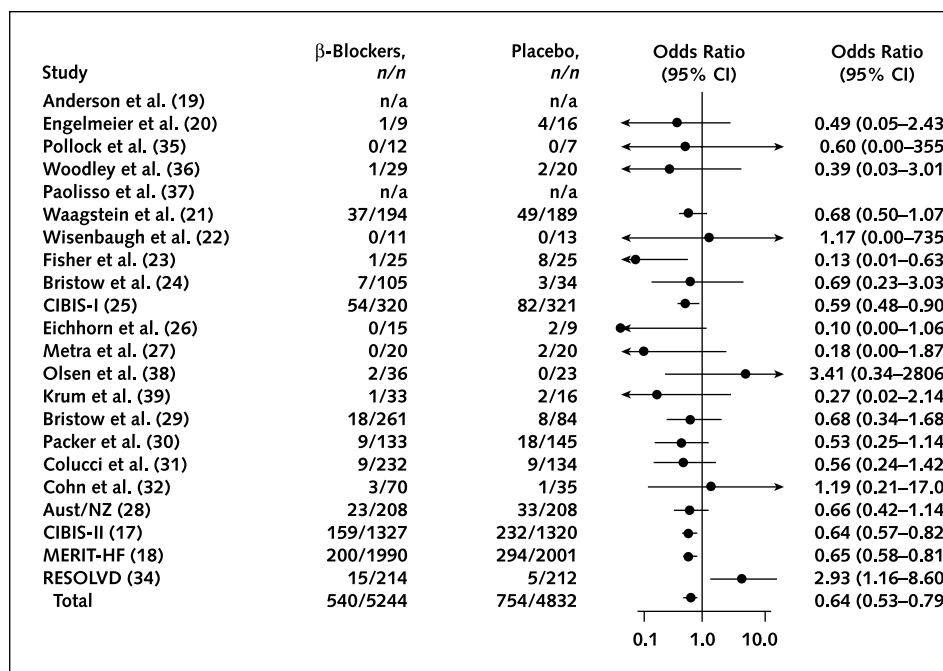
placebo group and 30.2% in the treatment group. The incorporation of these data leads to an accumulative odds ratio of 0.72 (credible interval, 0.61 to 0.84).

Figure 4 shows the progression of our knowledge of the effect of β-blockers on mortality in congestive heart failure with the publication of large trials since 1999. The accumulation of data leads to improved estimation of the benefits of β-blockers, as demonstrated by narrowing of the probability density curves, and an increased probability that the benefits are clinically meaningful, demonstrated by the shift of the curves to the right.

**DISCUSSION**

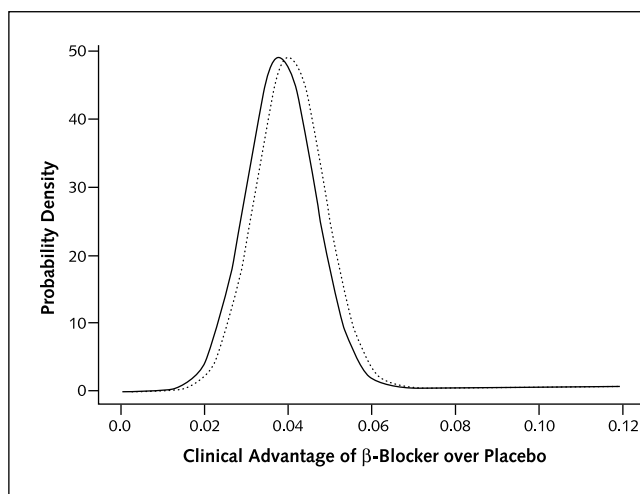
Our meta-analysis demonstrates that β-blockers have a large beneficial effect on mortality (3.8 lives saved per 100 patients treated) and morbidity (4.0 fewer hospitalizations per 100 patients treated) in stable patients with NYHA class II or III congestive heart failure. This benefit is statistically and clinically significant and is obtained with selective and nonselective β-blockers. The

Figure 2. Hospital admission for congestive heart failure in the placebo and β-blocker groups of 22 studies.



Arrows indicate that the credible interval exceeds the scale; circles indicate point estimates; the bottom circle (in the “Total” row) indicates the overall best estimate of the effect. Aust/NZ = Australia/New Zealand Heart Failure Research Collaborative Group; CIBIS = Cardiac Insufficiency Bisoprolol Study; MERIT-HF = Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; n/a = not available; RESOLVD = Randomized Evaluation of Strategies for Left Ventricular Dysfunction Pilot Study.

**Figure 3. Probability density curves for improvement in mortality rate (solid line) and hospital admission (dotted line) due to congestive heart failure among patients taking  $\beta$ -blockers.**



The probability density functions for the number of lives saved and hospitalizations for congestive heart failure were calculated assuming a baseline annual mortality rate of 12% and a hospitalization rate of 14%. The area under the curve and to the right of any specified point on the abscissa is proportional to the probability of that event. For example, the probability of saving at least 2 lives per 100 patients treated is approximately 99% (almost the entire area to the right); the probability of saving 3 or more lives is 85%.

benefits of  $\beta$ -blockers go beyond those provided by angiotensin-converting enzyme inhibitors (since almost all patients were receiving angiotensin-converting enzyme inhibitors at the time of randomization).

Of note, the totality of the evidence for the utility of  $\beta$ -blockers in chronic congestive heart failure (more than 10 000 patients, excluding BEST) now exceeds that for angiotensin-converting enzyme inhibitors (7600 patients) (7). Indeed, the evidence is strong enough that little ethical justification exists for pursuing ongoing trials of  $\beta$ -blockers versus placebo in similar patients with heart failure. This factor may have been partially responsible for the decision to prematurely stop BEST (43).

The role of  $\beta$ -blocker therapy in patients with NYHA class IV disease is uncertain. Evidence is limited for such patients because they account for fewer than 5% of those studied to date. In addition, it is ethically correct to continue comparative randomized trials of different  $\beta$ -blockers. With the amount of evidence already available showing substantial and similar benefits of different classes of  $\beta$ -blockers, it seems unlikely that a

clinically significant difference could be detected without an exceedingly large mega-trial.

The earlier meta-analyses (13–16) had suggested a statistical benefit with  $\beta$ -blockers, but appropriate caution was recommended in the interpretation of these preliminary findings (44). The mathematical justification for this early caution is shown in our analysis, in which the probability of reaching a clinically significant benefit can be assessed (Table 2). Before 1999, the uncertainty that this benefit exceeded a clinically meaningful level, given the theoretical risks associated with this treatment, mandated prudence. Furthermore, discrepancies between meta-analyses and subsequent large randomized, controlled trials have been shown to occur in 35% of cases (45). Finally, many previously published trials used a run-in protocol in which only patients who could tolerate  $\beta$ -blocker therapy eventually underwent randomization. This protocol is not a threat to internal trial validity, but it complicates the generalizability of the results.

As with any meta-analysis, exclusion of pertinent trials, particularly negative trials, because publication bias is a concern. Although we are reasonably confident in our search procedure and although funnel plots did not suggest any publication bias (data not shown), an appropriate safeguard would be to perform a sensitivity analysis. Consider an extreme situation in which further trials involving 2000 patients (equally divided between  $\beta$ -blocker therapy and placebo) were included in our analysis and that mortality in the treatment group was double that in the placebo group (for example, 20% vs. 10%). Inclusion of this information in our meta-analysis

**Table 2. Probability of Improvement in Mortality and Hospitalization with  $\beta$ -Blocker Therapy\***

Difference in Events per 100 Persons Treated	Death		Hospitalization for Congestive Heart Failure	
	From Data before 1999	From All Data	From Data before 1999	From All Data
	←————— % —————→			
>0	99	100	100	100
>1	94	100	99	100
>2	82	99	96	99
>3	61	85	87	90
>4	36	42	69	52
>5	5	8	45	1

\* The data are based on a baseline mortality rate of 12% and a baseline hospitalization rate of 14%.

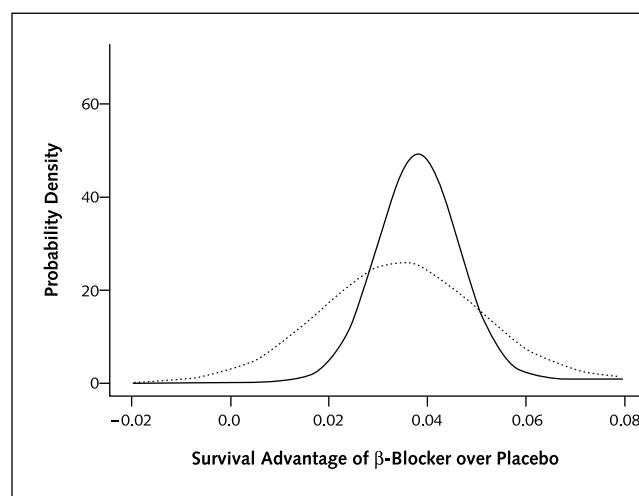
would still suggest that  $\beta$ -blockers reduce the odds ratio for mortality by 16% (odds ratio, 0.84 [credible interval, 0.74 to 0.94]). This demonstrates the robustness of this analysis to unfavorable future or unpublished results.

Before incorporating these results into clinical practice, one must consider the settings in which the data were obtained, as it would be dangerous to extrapolate these results to different clinical situations. Patients were enrolled only if they were clinically stable for at least 2 to 3 weeks. Nevertheless, the degree of systolic dysfunction could be pronounced; in the two largest trials (17, 18), the mean ejection fraction was 0.28. Patients experiencing acute cardiac decompensation or those with congestive heart failure immediately after myocardial infarction were excluded, as were patients with pure diastolic dysfunction. Patients were usually receiving standard triple-drug therapy (diuretics, digitalis, and angiotensin-converting enzyme inhibitors) and started receiving very small doses of  $\beta$ -blockers (for example, metoprolol, 12.5 mg twice daily, or carvedilol, 3.125 mg twice daily) that were titrated slowly (for example, at weekly intervals) under close medical supervision. Physicians must be prepared to manage potential short-term deterioration in clinical status, most commonly dizziness, hypotension, and worsening heart failure. This reality was confirmed by the 5% withdrawal rate in the run-in periods.

Patients with contraindications to  $\beta$ -blocker therapy (atrioventricular block worse than first-degree, significant hypotension, or reversible airways disease) were excluded from the trials. In addition, few data are available on patients with very severe symptoms (NYHA class IV). As in most clinical research, patients with advanced renal or hepatic dysfunction were also excluded. Finally,  $\beta$ -blockers with intrinsic sympathomimetic activity and *d*-sotalol, a  $\beta$ -blocker with predominant class III antiarrhythmic effects, should be avoided because they have been shown to increase mortality (46, 47).

Our study design has several advantages. The interval estimates calculated from our random-effects model are not artificially narrow, as would happen in a simple pooled analysis that did not take into account between-study variation. Whereas conventional meta-analysis provides almost identical results (for example, the odds ratio for death according to the method of Peto is 0.65 [95% confidence interval, 0.50 to 0.85]), a Bayesian approach permits the reporting of direct probability

**Figure 4. Probability density curves for improvement in survival with  $\beta$ -blocker therapy, according to sequential accumulation of data from trials published before 1999 (dotted line) and including those published in 1999 and 2000 (solid line).**



The probability density functions for the number of lives saved on the basis of data available before 1999 (at the time of previous meta-analyses) and by the end of 2000 (after publication of the Cardiac Insufficiency Bisoprolol Study II [17], the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure trial [18], and the Randomized Evaluation of Strategies for Left Ventricular Dysfunction Pilot Study [34]) were calculated assuming a baseline annual mortality rate of 12%. The progressive narrowing of the curves shows the improved precision in estimation of the benefit of  $\beta$ -blocker therapy. This benefit is not only statistically but also clinically significant, as indicated by the virtual lack of an area under the curve to the left of 0.02 (that is, at least 2 lives saved per 100 persons).

statements about any clinically meaningful differences (represented graphically as the percentage of the area under the probability density curve to the right of the selected point), providing clear and up-to-date conclusions that mirror our normal learning and decision-making processes. In contrast, standard statistical analysis frequently concludes with a *P* value, which relates information only about the null hypothesis, is a poor measure for evaluating evidence and making clinical decisions (48, 49), and is often misinterpreted by clinicians (50). Even the more revered standard confidence interval is not without its shortcomings (48, 49). The transparency and flexibility of our analysis avoid these limitations and may facilitate the acceptance and integration of these compelling results into routine clinical practice.

A limitation of our meta-analysis was our inability to obtain the exact patient data from each individual trial, which would have permitted detailed analysis of



treatment effect according to pertinent clinical and demographic subgroups. Such an analysis may be important because patients enrolled in clinical trials may differ meaningfully from those seen in routine clinical practice. This idea is highlighted by the 1-year mortality rates among patients randomly assigned to placebo, which varied from 4% to 28%. Nevertheless, the overall strength of the evidence from our meta-analysis, results of post hoc analysis showing beneficial results of  $\beta$ -blockers in patients with heart failure after myocardial infarction (51), and the theoretical underpinnings of improvement in patient outcomes with deactivation of the neurohormonal response suggest that  $\beta$ -blockers should be offered to most stable patients with mild to moderate congestive heart failure.

In contemporary medical research, it is common practice to evaluate the cost-effectiveness of a new technology. The cost-effectiveness of  $\beta$ -blocker therapy remains to be analyzed formally, but the large treatment benefits and the low cost of this therapy indicate that it will be cost attractive. Of note, a treatment advantage was realized rapidly, with an average follow-up of only 12 months, and independently of the benefits of angiotensin-converting enzyme inhibitors. In contrast, other cardiovascular benefits, such as angiotensin-converting enzyme inhibition in congestive heart failure, often take longer to materialize. The imperative to offer  $\beta$ -blocker therapy to patients would be accentuated if it were shown that benefits are sustained or increased with longer follow-up.

The transition of scientific results from the experimental phase to clinical practice is a complex and poorly understood process. The sound design of randomized clinical trials has been shown to influence practice patterns (52), although penetration of the trial results has sometimes been less than optimal (52, 53), particularly for  $\beta$ -blockers after myocardial infarction (54). In theory, meta-analyses that represent the cumulative experience of randomized trials should be expected to most influence medical decision making and practice patterns. We hope that this meta-analysis will thereby assist in bridging any gap between research and practice in the use of  $\beta$ -blockers for the treatment of all eligible patients with congestive heart failure.

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Three drachmas of dry leaves (of digitalis), picked up at the time of expansion of flowering, boiled in twelve to eight ounces of water. Two spoons of this medicine, delivered each two hours, sooner or later, will produce nausea . . . I think that digitalis, thus provided, constitutes the truest diuretic that I know . . . I use it for ascites, anasarca, and dropsy pectoris . . . The medicine should be administered until it acts on the kidneys, the stomach, the pulse, or the intestines; it must be interrupted when any of these effects appear. . . ."

William Withering

*An Account of the Foxglove and Some of Its Medicinal Uses with Practical Remarks on Dropsy and Other Diseases*

London; 1785

Submitted by:

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