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Effects of beta-blocker therapy on mortality in patients with heart failure

A systematic overview of randomized controlled trials

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Aims Several randomized trials have reported that beta-blocker therapy improves left ventricular function and reduces the rate of hospitalization in patients with congestive heart failure. However, most trials were individually too small to assess reliably the effects of treatment on mortality. In these circumstances a systematic overview of all trials of beta-blocker therapy in patients with congestive heart failure may provide the most reliable guide to treatment effects.

Methods and results Details were sought from all completed randomized trials of oral beta-blocker therapy in patients with heart failure of any aetiology. In particular, data on mortality were sought from all randomized patients for the scheduled treatment period. The typical effect of treatment on mortality was estimated from an overview in which the results of all individual trials were combined using standard statistical methods. Twenty-four randomized trials, involving 3141 patients with stable congestive heart failure were identified. Complete data on mortality were obtained from all studies, and a total of 297 deaths were documented during an average of 13 months of follow-up. Overall, there was a 31% reduction in the odds of death among patients assigned a beta-blocker (95% confidence interval 11 to 46%, $2P=0{\cdot}0035$), representing an absolute reduction in mean annual mortality from 9·7% to 7·5%. The effects on mortality of vasodilating beta-blockers (47% reduction SD 15), principally carvedilol, were non-significantly greater ($2P=0{\cdot}09$) than those of standard agents (18% reduction SD 15), principally metoprolol.

Conclusions Beta-blocker therapy is likely to reduce mortality in patients with heart failure. However, large-scale, long-term randomized trials are still required to confirm and quantify more precisely the benefit suggested by this overview.
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Key Words: Meta-analysis, beta-adrenergic antagonists, survival.

Introduction

Randomized trials have clearly demonstrated that beta-adrenergic blockade improves left ventricular function[1]. In the study conducted by the Australia–New Zealand Heart Failure Research Collaborative Group, this effect was observed to persist for at least a year after starting carvedilol therapy[2]. The same trials have not produced consistent evidence of a beneficial effect of beta-blocker therapy on the symptoms of heart failure or on exercise tolerance[1,2]. However, most of the larger trials have reported reductions in the rate of hospital admission among patients assigned treatment with a beta-blocker[2–5].

The effects of beta-blockade on mortality in patients with heart failure remain less certain. In trials of beta-blockers following myocardial infarction, mortality appears to have been reduced in a small subgroup of patients with a history of acute or chronic heart failure[6,7], although in most of these studies, patients with current symptoms or signs of heart failure were excluded. More recently, the combined results of four U.S. trials of carvedilol have suggested improved survival in a heterogeneous group of patients with chronic heart failure[5], but most other randomized trials of beta-blockers in patients with heart failure have not reported reductions in mortality[1].

Since the majority of trials of beta-blockers in patients with heart failure were designed to investigate the effects of treatment on left ventricular function, exercise tolerance or symptoms of heart failure, the size and duration of the individual studies were typically inadequate for the reliable assessment of plausible effects

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of treatment on mortality. In these circumstances, a systematic overview of all randomized trials of beta-blocker therapy in patients with heart failure is likely to provide the most reliable guide to the true effects of treatment on survival. We report here the results of such an overview.

Methods

Criteria for inclusion of trials

All randomized trials of oral beta-blocker therapy in patients with heart failure of any aetiology were sought. Specifically, only studies in which heart failure was a criterion for patient enrolment were included, since it was not possible to obtain complete data on the small subgroups of patients with heart failure who participated in trials of beta-blocker therapy in patients with a primary diagnosis of coronary heart disease or hypertension. Additionally, only trials in which patients were randomized to beta-blocker therapy or no beta-blocker therapy were included; trials in which patients were randomized to beta-blocker therapy or an alternate therapy were not included.

Identification of trials

Published studies were identified by a formal computer-aided literature search (Medline), extensive searches of the references from original trial reports and review articles and screening of abstracts of the major cardiology meetings. Information was also sought from colleagues, investigators and pharmaceutical companies about completed but unpublished studies and this search did not reveal any randomized trial that had not been published in either manuscript or abstract form.

Acquisition of data

Details of the design and results of each study were abstracted from the published reports. The primary endpoint for which data were sought from all randomized patients in all trials was total mortality during the scheduled treatment period. Data were recorded on standard sheets that were sent to all investigators for confirmation. When design details were missing from the published reports or when data on outcome for all randomized patients were not given, the investigators were asked to supply further information. For cross-over trials, only data from the first period comparing active and control treatments were used.

Statistical methods

The statistical methods used to perform this overview have been described in detail elsewhere[8]. The fundamental principle followed was that patients allocated to active treatment in one trial were compared directly only with those allocated to control treatment in the same trial, and not with patients in any other trial. For each trial, the number of deaths observed in the treatment group (O) was contrasted with the number of deaths that would have been expected, if the treatment had no effect (E), on the basis of the overall experience in the treatment and control groups combined. Thus, if the treatment was of no benefit, the observed minus the expected (O − E) number of deaths in the treatment group would only differ randomly from zero [with variance (V) given by the standard formula for 2×2 tables[9]]. The 95% confidence interval of the odds ratio was estimated from the grand total of O − E and its variance using the following formula $e^{[(O-E)/V \pm 1.96/\sqrt{V}]}$[10]. Stratified analyses were performed separately for three subsets of trials: trials using the beta-blocker carvedilol, trials of all vasodilating beta-blockers (including carvedilol) and trials using non-vasodilating beta-blockers. Tests for heterogeneity of treatment effects were performed using a χ^2 test.

Results

This overview included 24 randomized trials[2–5,11–27] involving a total of 3141 patients with clinical congestive heart failure, 1775 of whom were assigned to treatment with the study beta-blocker. These trials provided mortality data from a total of 3312 patients years of follow-up. The design features of the trials included in this overview are summarized in Table 1.

Trial patients

Ten trials included only patients with idiopathic dilated cardiomyopathy (607 patients)[3,11,13–16,18,20,24], two trials included only patients with heart failure due to ischaemic heart disease[2,22] (465 patients) and the remaining 12 trials[4,5,12,17,19,21,23,26,27] included patients with heart failure of various aetiologies including ischaemic heart disease, idiopathic dilated cardiomyopathy, hypertensive heart disease and other causes of heart failure (2069 patients). In general, patients were not eligible for inclusion in any of these trials if they had any of the following: unstable heart failure, unstable angina or myocardial infarction in the preceding month, systolic blood pressure <90 mmHg, heart rate <50 beats . min^{-1}, advanced atrioventricular block (in the absence of a permanent pacemaker), asthma or any non-cardiac life-threatening disease. Hence, typically the patients included in these trials had stable congestive heart failure at entry; the mean NYHA functional class at baseline was 2·5 and the mean left ventricular ejection fraction was 24%. The average age of patients was 58 years and 78% were male.

Table 1 Characteristics of randomized trials of beta-blocker therapy in patients with congestive heart failure

Trial	n	% IHD	Beta-blocker	FU	Primary study end points
Ikram*[11]	17	0	Acebutolol	1	LV function, exercise
Currie*[12]	10	40	Metoprolol	1	LV function, symptoms, exercise
Anderson[13]	50	0	Metoprolol	19	Mortality
Engelmeier*[14]	25	0	Metoprolol	12	LV function, exercise
Sano[15]	22	0	Metoprolol	12	LV function
Leung*[16]	12	0	Labetalol	2	LV function, symptoms, exercise
Pollock[17]	20	37	Bucindolol	3	Exercise, symptoms
Gilbert†[18]	23	0	Bucindolol	3	LV function, symptoms, exercise
Woodley†[19]	50	54	Bucindolol	3	LV function, symptoms, exercise
Paolisso*[20]	10	0	Metoprolol	3	Metabolic and LV function, symptoms
MDC[3]	383	0	Metoprolol	18	Need for transplantation/mortality
Wisenbaugh[21]	29	8	Nebivolol	3	LV function
Fisher[22]	50	100	Metoprolol	6	WHF, LV function, symptoms, exercise
Bristow[23]	139	29	Bucindolol	3	Dose titration study
Eichhorn[24]	25	0	Metoprolol	3	LV function
Metra[25]	40	0	Carvedilol	6	LV function, symptoms, exercise
CIBIS[4]	641	55	Bisoprolol	23	Mortality
Olsen[26]	60	28	Carvedilol	4	LV function, symptoms, exercise
Krum[27]	49	27	Carvedilol	3·5	LV function, symptoms, exercise
ANZ[2]	415	100	Carvedilol	20	LV function, symptoms, exercise
U.S. 'dose ranging'[5]	345	48	Carvedilol	6·5	LV function, exercise QOL
U.S. 'moderate'[5]	278		Carvedilol	6	LV function, symptoms, exercise
U.S. 'severe'[5]	105		Carvedilol	3·5	LV function, QOL
U.S. 'mild'[5]	366		Carvedilol	6	Disease progression
Total	3141	46		12·9	

*Cross-over trial; †23 patients appear in both totals from these two trial reports (but are included only once in the column total); n=number of patients; IHD=ischaemic heart disease; FU=follow-up (months); MDC=Metoprolol in Dilated Cardiomyopathy; CIBIS=Cardiac Insufficiency Bisoprolol Study; ANZ=Australia–New Zealand Heart Failure Research Collaborative Group; LV=left ventricular; WHF=worsening heart failure; QOL=quality of life.

Trial treatments

In all trials, the randomized study treatment was provided in addition to whatever was deemed to be standard treatment for heart failure — most frequently this included treatment with one or more of the following: a diuretic, an angiotensin converting enzyme (ACE) inhibitor or digoxin. Overall, 83% of the patients in these trials were receiving ACE inhibitors. The study treatments involved several different beta-blockers and a variety of dosages. Carvedilol was the most frequently used agent, given to 53% of all patients assigned beta-blocker therapy. Overall, beta-blockers with vasodilator properties (carvedilol, bucindolol, nebivolol and labetalol) were given to 61% of all patients assigned beta-blocker therapy in these trials. In general, the study treatment was commenced at a low dose followed by titration up to a target dose (or the maximum tolerated dose) over several weeks. In most trials, patients were randomized to study treatment or control in approximately equal numbers; but in seven trials there was unequal randomization of patients to treatment or control, with larger numbers assigned to beta-blocker therapy[5,17,23,24,27]. The average duration of treatment and follow-up in these trials was approximately 13 months, although 11 of the 24 trials involved less than 6 months of follow- up.

Mortality results

Mortality data by randomized treatment was obtained from all 24 trials for all 3141 randomized patients. During the scheduled treatment period of these trials, there was a total of 135 deaths among the 1775 patients allocated to treatment with a beta-blocker compared with 162 deaths among the 1366 patients allocated to control (Table 2). This represented a 31% (SD 11) reduction in the odds of death in patients assigned beta-blocker therapy (odds ratio 0·69, 95% confidence interval 0·54 to 0·89, $2P=0·0035$), and a reduction in mean annual mortality from 9·7% to 7·5% (Fig. 1). No statistically significant heterogeneity was observed between the results of the individual trials ($\chi^2=16·05$, 15 df, $2P=0·38$).

Mortality by type of beta-blocker

The numbers of deaths observed in subgroups of trials defined by the type of the beta-blocker used were individually small. As a consequence, there is limited statistical power for indirect comparisons between subgroups to detect reliably any true differences between treatments in their effects on mortality. In the trials in which the study treatment was carvedilol, a total of 105

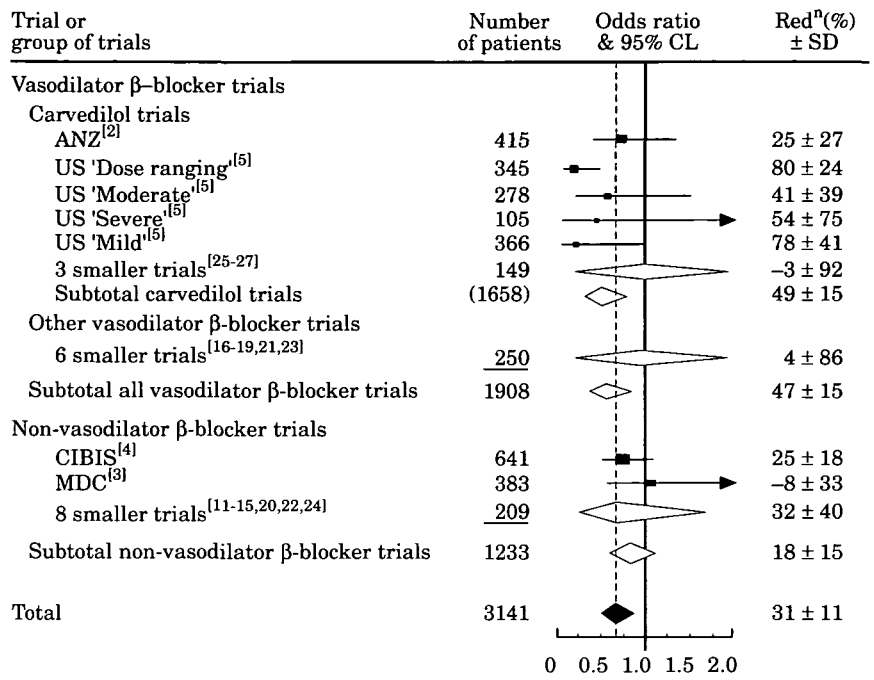

Figure 1 **Total mortality for all trials of beta-blocker therapy in patients with heart failure. CL=confidence limits; SD=standard deviation; Red^{n}=reduction; ◇ represents the odds ratio and 95% confidence interval. Other abbreviations as in Table 1.**

deaths were observed, and among those assigned active treatment, the odds of death were reduced by approximately half (odds ratio 0·51, 95% confidence interval 0·33 to 0·77, $2P=0·0014$). The result for all trials of vasodilator beta-blockers was very similar (odds ratio 0·53, 95% confidence interval 0·35 to 0·79, $2P=0·0018$), since 94% of the 112 deaths observed in these trials occurred in studies of carvedilol. In the trials of other beta-blockers, a total of 185 deaths were observed, and the observed effect of these agents on the odds of death (odds ratio 0·82, 95% confidence interval 0·59 to 1·13, $2P=0·21$) appeared to be about half that observed in the trials of vasodilator beta-blockers. However, there was no clearly significant heterogeneity between the results of these two subgroups of trials ($\chi^2=2·82$, 1 df, $2P=0·09$).

Discussion

This systematic overview included data on mortality from all 24 completed randomized trials of beta-blocker therapy in patients with congestive heart failure. Among the 3141 participants in these trials, a total of 297 deaths were observed during scheduled follow-up, and among those patients randomized to treatment with a beta-blocker, mortality appeared to be reduced by almost a third. The confidence limits for this estimate of treatment effect ranged from a reduction of one tenth to a reduction of one half. This range of possible effects is quantitatively consistent with the one-quarter reduction in mortality observed in trials of beta-blockers after myocardial infarction[8]. Moreover, it is consistent with the approximately one-quarter reduction in hospitalization rates observed in the larger trials of beta-blockers in patients with heart failure[2–5]. The apparent benefit of beta-blocker therapy for survival was achieved against a background of standard care that involved treatment with an ACE inhibitor for most patients. Hence the reduction in mortality conferred by beta-blocker therapy was largely additional to the one-quarter reduction in mortality produced by treatment with an ACE inhibitor[28]. This is consistent with the observed benefits of beta-blocker therapy for left ventricular function, which also appears to be additional to those conferred by ACE inhibition[8].

While these results are clearly suggestive of a potentially worthwhile effect of beta-blocker therapy on survival in patients with heart failure, the data available do not provide reliable answers to all the clinically relevant questions. Data on cause-specific mortality were not available from some trials and it was not therefore possible to determine reliably the specific causes of death that were reduced by beta-blocker therapy. Thus, the relative contributions of reductions in death due to worsening heart failure, death due to myocardial infarction and sudden death, all remain unclear. Additionally, data on outcome among the major subgroups of patients with heart failure were also not available from some of the trials. Thus, the specific effects of beta-blockers on survival in patients with idiopathic dilated cardiomyopathy, heart failure due to ischaemic heart disease and hypertensive heart failure,

Table 2 Mortality in the randomized trials of beta-blocker therapy in patients with heart failure

Trial	Basic data (No. dead/No. FU)		Statistical calculations for patients allocated beta-blocker	
	Beta-blocker	Control	Observed–expected deaths (O − E)	Variance of (O − E)
Ikram[11]	0/8	1/9	−0·47	0·2
Currie[12]	0/5	0/5	0	0
Anderson[13]	5/25	6/25	−0·5	2·1
Engelmeier[14]	2/9	2/16	0·56	0·8
Sano[15]	0/8	2/14	−0·73	0·4
Leung[16]	0/6	0/6	0	0
Pollock[17]	0/13	0/7	0	0
Gilbert[18]/Woodley[19]	0/30	0/20	0	0
Paolisso[20]	0/5	0/5	0	0
MDC[3]	23/194	21/189	0·71	9·7
Wisenbaugh[21]	1/15	0/14	0·48	0·2
Fisher[22]	1/25	2/25	−0·5	0·7
Bristow[23]	4/105	2/34	−0·53	1·1
Eichhorn[24]	0/15	0/10	0	0
Metra[25]	0/20	0/20	0	0
CIBIS[4]	53/320	67/321	−6·91	24·4
Olsen[26]	1/36	0/24	0·4	0·2
Krum[27]	3/33	2/16	−0·37	1·0
ANZ[2]	20/207	26/208	−2·94	10·2
U.S. 'dose ranging'[5]	12/261	13/84	−6·91	4·3
U.S. 'moderate'[5]	6/133	11/145	−2·13	4·0
U.S. 'severe'[5]	2/70	2/35	−0·67	0·9
U.S. 'mild'[5]	2/232	5/134	−2·44	1·6
24 Trials	135/1775	162/1366	−22·94	61·9

all remain uncertain. Finally, while the observed effects of vasodilator beta-blockers, principally carvedilol, appeared to be somewhat larger than those of other agents, principally metoprolol, the number of deaths observed in each of these subgroups of trials was too small to exclude the possibility that the difference had occurred by chance alone. Thus, while theoretical advantages of carvedilol and other vasodilator beta-blockers have been proposed[29], it remains uncertain whether these agents confer any real survival advantage over other agents[30].

Patients with heart failure remain at high risk of death despite standard treatment with drugs including ACE inhibitors, and there is therefore much interest in the identification of other agents that might improve prognosis. The principal question raised by the observation of reduced mortality in these trials of beta-blockade is whether or not the evidence is sufficient to warrant the recommendation that this treatment be used widely in patients with heart failure for the prevention of premature death. Following the publication of combined results from four U.S. trials of carvedilol[5], caution has been advised about the strength of the evidence provided by studies in which a total of only 53 deaths were observed, even when the apparent degree of statistical significance was extreme[31]. The present analysis includes more than five times this number of deaths, but its results are still not definitive. By way of comparison, the total number of deaths observed in these 24 trials represents less than one-quarter of the total number of deaths observed in the major randomized controlled trials of ACE inhibitors in patients with heart failure[28]. Moreover, the average follow-up interval was only about 13 months. Recommendations for the life-long treatment of a potentially large proportion of all those with heart failure need to be based on larger and more robust data sets than is provided, even in combination, by these small trials. Large-scale, long-term randomized controlled trials of beta-blockers in patients with heart failure are now required to confirm the benefits suggested by this overview and to determine more reliably the size of effects of treatment on survival. One such study of bucindolol (the Beta-blocker Evaluation Survival Trial[32]) is underway and its results should provide 2–3 times more data than are currently available about the effects of beta-blockers on mortality in heart failure. Other studies are currently being planned. Once completed, these trials should provide separately reliable data on the effects of longer-term beta-blocker therapy on cause-specific mortality in patients with ischaemic or idiopathic heart failure. Any recommendations regarding the routine use of beta-blocker therapy for patients with heart failure should await the results of these trials.

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