Adverse Effects of β-Blocker Therapy for Patients With Heart Failure

A Quantitative Overview of Randomized Trials

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Background: β-Blockers substantially improve survival in patients with chronic heart failure (HF) with left ventricular systolic dysfunction, but concerns about cardiovascular adverse effects may deter physicians from prescribing this therapy. We performed an overview of randomized β-blocker trials in patients with HF to quantify the risks of these adverse effects.

Methods: Heart failure trials of β-blockers were identified by electronic searches of the MEDLINE database from 1966 to 2002. The random-effects model was used to combine results from individual trials and calculate estimates of risks associated with therapy.

Results: β-Blocker therapy was associated with significant absolute annual increases in risks of hypotension (11 per 1000; 95% confidence interval [CI], 0-22), dizziness (57 per 1000; 95% CI, 11-104), and bradycardia (38 per 1000; 95% CI, 21-54). There was no significant absolute risk of fatigue associated with therapy (3 per 1000; 95% CI, −2 to 9). β-Blocker therapy was associated with a reduction in all-cause withdrawal of medication (14 per 1000; 95% CI, −2 to 29) as well as significant reductions in all-cause mortality (34 per 1000; 95% CI, 20-49), HF hospitalizations (40 per 1000; 95% CI, 22-58), and worsening HF (52 per 1000; 95% CI, 10-94).

Conclusions: Although β-blocker therapy was associated with hypotension, dizziness, and bradycardia, the absolute increases in risk were small, and overall fewer patients were withdrawn from β-blocker therapy than from placebo. This information should alleviate concerns about prescribing this life-saving therapy to patients with HF.

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ALTHOUGH THE USE OF β-blocker therapy was once thought to be contraindicated in patients with heart failure (HF) with systolic dysfunction, studies have shown that it reduces mortality and hospitalizations in this population.[1-4] Systematic overviews of β-blocker trials in patients with HF have demonstrated reductions in mortality of approximately 30%,[5] and recently published clinical practice guidelines strongly recommend the use of β-blockers.[6,7] The same clinical guidelines, however, highlight common cardiovascular adverse effects associated with β-blocker therapy including HF deterioration, hypotension, dizziness, bradycardia, and fatigue. Concerns about adverse effects may deter clinicians from prescribing this life saving therapy.[8] Although individual HF trials have reported the risks of these adverse effects, no study has combined the available information to obtain the best estimates of these risks during β-blocker therapy.

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The objective of the present study was to quantify the risks of common, potentially serious cardiovascular adverse effects of β-blocker therapy in patients with HF with systolic dysfunction. To address this issue, we performed an overview of the randomized controlled trials of patients with HF comparing β-blockers with placebo. We compared the risk of withdrawal for any reason in patients randomized to β-blocker therapy with that of patients randomized to placebo. In addition, we determined the risks of specific adverse effects including HF deterioration, hypotension, dizziness, bradycardia, and fatigue. This information will allow practitioners and patients to place the risks of β-blocker therapy in proper perspective.

METHODS

SELECTION OF TRIALS

We identified randomized trials of β-blockers in patients with HF with left ventricular systolic dysfunction by electronic searches of the MEDLINE database (1966-2002 through Ovid Medline) using key words "adrenergic beta-antagonists" in combination with "heart failure" and "trial." The search produced 148 English-language articles. We also searched the reference lists of previously published trials and overviews of β-blockers. Inclusion criteria for the overview were as follows: (1) random allocation of study treatments; (2) placebo control; (3) non–crossover design; (4) at least 100 patients enrolled in each treatment group; and (5) a minimum of 6 months of follow-up. The 9 trials[1-4,9-19] that satisfied these criteria and contained information on specified adverse effects were included in the overview.

DATA COLLECTION

Information on adverse effects was abstracted from published reports of the trials. In addition, we checked the US Food and Drug Administration Web site (www.fda.gov) and the *Physicians' Desk Reference* for reports of adverse effects in trials of β-blockers. Information on the frequency of adverse effects and associated withdrawals from therapy during the randomized phase of the trials was abstracted, as were the rates of withdrawal owing to adverse effects during the run-in period. None of the trials described the methods used to assess hypotension, dizziness, and fatigue. We abstracted the data when trials used the terms "hypotension," "dizziness," and "fatigue" to report these adverse effects. The definition of bradycardia varied among the trials: 1 trial used "heart rate less than 40 beats per minute,"[10] 1 trial used "bradycardia causing hospital admission,"[3] and 1 trial used "symptomatic bradycardia,"[17] while the rest of the trials did not report their method of assessment.[1,2,4,16,18] Although the assessment of adverse effects among the trials was not standardized, within each trial the same criteria were applied equally to the treatment groups. All the information was abstracted by 1 author and verified by 2 other investigators.

STATISTICAL ANALYSIS

We combined information from the trials using the general variance-based method[20] that incorporates a fixed-effects model and assumes that all the variability is due to random error. The assumption of homogeneity was rejected in some instances when tested using the χ^2 statistic, which implies the presence of significant variation between the studies. To estimate and control for heterogeneity among the trials, we applied a random-effects model to estimate the variance component associated with between-study variation.[21] Hence, the variance for each study in the overview is represented by the sum of the fixed and random study components of variance. Since results from fixed and random-effects models will essentially be equal when there is no heterogeneity, we report results only from the random-effects model throughout this article.

The combined relative risk (RR) estimate was obtained by computing a weighted average of the individual log RR estimates. The weights correspond to the inverse of the total variance (within plus between) for each study. Approximate 95% confidence intervals (CIs) were based on the asymptotic normality of the combined estimates.[22] Confidence intervals for the RRs were obtained by calculating the exponential of the upper and lower confidence limits for the log RRs.

We also examined the absolute increases in risks of adverse effects associated with β-blocker therapy. To account for the variability in follow-up duration (6-24 months), we calculated pooled incidence risk differences as well as numbers needed to treat per year to estimate the absolute risks.[23,24]

Finally, we examined the adverse event rates during the run-in periods. However, since the run-in periods were neither randomized nor controlled, we were able to calculate only the rates of overall withdrawal and withdrawal due to specific adverse effects.

RESULTS

SUMMARY OF TRIALS

Nine trials involving 14 594 patients with follow-up periods ranging from 6 to 24 months were included in the overview (**Table 1**). Carvedilol[1,4,16] and metoprolol[2,9,17] were each tested in 3 trials, bisoprolol[3,10] in 2 trials, and bucindolol[18] in 1 trial. Most trials included relatively few patients with advanced HF, although 1 study included primarily patients with severe HF.[4]

The overall all-cause withdrawal rate was 16.0% in the β-blocker group and 18.0% in the placebo group (Table 1). β-Blocker therapy was associated with a significant 11% relative reduction in all-cause withdrawal of study medication (RR, 0.89; 95% CI, 0.81-0.98), and the associated annual absolute risk reduction for withdrawal was 14 per 1000 patients (95% CI, –2 to 29). Similarly, β-blocker therapy was associated with a significant 27% relative reduction in all-cause mortality (RR, 0.73; 95% CI, 0.62-0.85) and an absolute risk reduction of 34 deaths per 1000 patients per year (95% CI, 20-49), equivalent to 29 patients treated with β-blockers for 1 year to prevent 1 death. Furthermore, the reductions in all-cause withdrawal ($P=.74$) and mortality ($P=.44$) occurred regardless of whether the trials included a run-in period.

β-BLOCKERS AND HF DETERIORATION

Heart failure deterioration was assessed as HF hospitalizations in 8 trials[2-4,9,10,16-18] and worsening HF in 4 trials.[1,4,10,16] As summarized in **Table 2**, for HF hospitalizations, β-blocker therapy was associated with a significant 26% RR reduction (RR, 0.74; 95% CI, 0.66-0.83). The absolute annual reduction in risk was 40 per 1000 patients (95% CI, 22-58), equal to 25 patients treated with β-blockers for 1 year to avoid 1 hospitalization for HF. For worsening HF, β-blocker therapy was also associated with a significant 17% RR reduction (RR, 0.83; 95% CI, 0.71-0.98) and an absolute risk reduction of 52 per 1000 patients per year (95% CI, 10-94), equivalent to 19 patients treated for 1 year to avoid 1 additional case of worsening HF.

Withdrawal of therapy owing to HF deterioration was assessed in 5 trials[1,2,9,16,17] including 6309 patients. In those trials, 3.3% in the β-blocker group and 4.9% in the placebo group were withdrawn from therapy due to HF deterioration. β-Blocker therapy was associated with a significant RR reduction (RR, 0.72; 95% CI, 0.54-0.96) and a nonsignificant absolute annual risk reduction (8/1000; 95% CI, –9 to 25) of withdrawal owing to HF deterioration (**Table 3**).

Table 1. Features of β-Blocker Trials Included in the Overview

Trials	No. of Patients Randomized	Mean Follow-up, mo	β-Blocker	Mean Age, y	Women, %	Withdrawal of Therapy (No. of Patients Withdrawn/No. of Patients Randomized)		Mortality (No. of Deaths/No. of Patients Randomized)	
						β-Blocker	Placebo	β-Blocker	Placebo
MDC,[9] 1993	383	12	Metoprolol	49	28	23/194	31/189	23/194	19/189
CIBIS,[10] 1994	641	23	Bisoprolol	60	17	75/320	82/321	53/320	67/321
US Carvedilol HF Group,[1] 1996	1094	7	Carvedilol	58	23	77/696	68/398	22/696	31/398
Australian–New Zealand Group,[16] 1997	415	19	Carvedilol	67	20	41/207	30/208	20/207	26/208
CIBIS II,[3] 1999	2647	16	Bisoprolol	61	20	194/1327	192/1320	156/1327	228/1320
MERIT-HF,[2] 1999	3991	12	Metoprolol CR/XL	64	23	279/1990	310/2001	145/1990	217/2001
RESOLVD,[17] 2000	426	6	Metoprolol CR	62	18	24/214	25/212	8/214	17/212
BEST,[18] 2001	2708	24	Bucindolol	60	22	311/1354	339/1354	411/1354	449/1354
COPERNICUS,[4] 2001	2289	10	Carvedilol	63	20	171/1156	210/1133	130/1156	190/1133
Total (%)						1195/7458 (16.0)	1287/7136 (18.0)	968/7458 (13.0)	1244/7136 (17.4)
Relative risk (95% CI)						0.89 (0.81 to 0.98)		0.73 (0.62 to 0.85)	
Annual risk reduction per 1000 patients per year (95% CI)						14 (–2 to 29)		34 (20 to 49)	

Abbreviations: BEST, Beta-Blocker Evaluation of Survival Trial; CIBIS, Cardiac Insufficiency Bisoprolol Study; CI, confidence interval; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival Study; CR, controlled release; MDC, Metoprolol in Dilated Cardiomyopathy; MERIT-HF, Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; NZ, New Zealand; RESOLVD, Randomized Evaluation of Strategies for Left Ventricular Dysfunction Pilot Study; XL, extended release.

Table 2. Adverse Events in the β-Blocker and Placebo Groups

Adverse Event	No. of Trials	No. of Events/ No. of Randomized Patients (%)		RR (95% CI)	Annual Absolute Risk Increase*/ 1000 Patients (95% CI)	NNT/y
		β-Blockers	Placebo			
HF hospitalization	8	1169/6752 (17.3)	1541/6726 (22.9)	0.74 (0.66 to 0.83)	–40 (–58 to –22)	25
Worsening HF	4	625/2379 (26.3)	691/2060 (33.5)	0.83 (0.71 to 0.98)	–52 (–94 to –10)	19
Hypotension	7	535/7057 (7.6)	409/6739 (6.1)	1.41 (0.96 to 2.06)	11 (0 to 22)	91
Dizziness	4	1117/5196 (21.5)	810/4886 (16.6)	1.37 (1.09 to 1.71)	57 (11 to 104)	17
Bradycardia	7	400/7057 (5.7)	118/6739 (1.8)	3.62 (2.48 to 5.28)	38 (21 to 54)	26
Fatigue	3	953/4040 (23.6)	840/3753 (22.4)	1.04 (0.97 to 1.11)	3 (–2 to 9)	297

Abbreviations: CI, confidence interval; HF, heart failure; NNT, number needed to treat; RR, relative risk.
*Adverse events with negative annual absolute risk increase represent number to treat to prevent 1 adverse event.

Table 3. Therapy Withdrawal Owing to Adverse Events in the β-Blocker and Placebo Groups

Adverse Event	No. of Trials	No. of Patients Withdrawn From Therapy/ No. of Patients Randomized (%)		RR (95% CI)	Annual Absolute Risk Increase*/ 1000 Patients (95% CI)	NNT per Year
		β-Blockers	Placebo			
HF	5	108/3301 (3.3)	146/3008 (4.9)	0.72 (0.54 to 0.96)	–8 (–25 to 9)	124
Hypotension	5	29/4263 (0.68)	13/3952 (0.33)	1.95 (1.01 to 3.77)	4 (0 to 7)	286
Dizziness	4	33/4049 (0.82)	11/3740 (0.29)	2.57 (1.32 to 5.01)	5 (1 to 8)	213
Bradycardia	5	32/4263 (0.75)	5/3952 (0.13)	3.87 (1.67 to 8.97)	7 (3 to 10)	153
Fatigue	3	20/2893 (0.69)	12/2607 (0.46)	1.40 (0.69 to 2.83)	2 (–2 to 6)	473

Abbreviations: CI, confidence interval; HF, heart failure; NNT, number needed to treat; RR, relative risk.
*Adverse events with negative annual absolute risk increase represent number to treat to prevent 1 adverse event.

β-BLOCKERS AND HYPOTENSION

Hypotension was assessed in 7 trials[1-4,10,17,18] that included 13 796 patients. β-Blockers were associated with a 41% relative increase in risk of hypotension (RR, 1.41; 95% CI, 0.96-2.06) (Table 2). The absolute annual increase in risk was 11 per 1000 patients (95% CI, 0-22), equal to 91 patients treated for 1 year to cause 1 additional report.

In 5 trials[1,2,4,16,17] including 8215 patients that assessed withdrawal of treatment owing to hypotension, 0.68% of patients were withdrawn from β-blocker treatment and 0.33% from placebo. β-Blockers were associ-

zated with a significant 2-fold RR increase (RR, 1.95; 95% CI, 1.01-3.77) and an absolute annual increase of 4 per 1000 patients (95% CI, 0-7) in risk of withdrawal owing to hypotension, equivalent to 286 patients treated for 1 year to cause 1 additional withdrawal (Table 3).

β-BLOCKERS AND DIZZINESS

Dizziness was reported in 4 trials[1,2,4,18] including 10 082 patients. β-Blockers were associated with a significant relative increase in reported dizziness (RR, 1.37; 95% CI, 1.09-1.71) and an absolute annual increase in risk of 57 per 1000 (95% CI, 11-104), equivalent to 17 patients treated for 1 year to cause 1 additional report (Table 2).

There were 4 trials[1,2,4,16] including 7789 patients that assessed withdrawal of therapy owing to dizziness. In those trials, 0.82% in the β-blocker group and 0.29% in the placebo group were withdrawn from therapy. β-Blocker therapy was associated with significant relative increase in risk (RR, 2.57; 95% CI, 1.32-5.01) and an annual absolute increase in risk of 5 per 1000 patients (95% CI, 1-8), equal to 1 additional withdrawal owing to dizziness for every 213 patients treated for 1 year (Table 3).

β-BLOCKERS AND BRADYCARDIA

Bradycardia was assessed in 7 trials[1-4,10,17,18] that included 13 796 patients. β-Blockers were associated with a significant relative increase in risk (RR, 3.62; 95% CI, 2.48-5.28) (Table 2). The annual absolute increase in risk of bradycardia was 38 per 1000 patients (95% CI, 21-54), equal to 1 additional case for every 26 patients treated with β-blockers for 1 year.

Among 5 trials[1,2,4,16,17] including 8215 patients that reported withdrawal of therapy owing to bradycardia, 0.75% of patients were withdrawn from β-blocker treatment and 0.13% from placebo. β-Blockers were associated with a significantly increased risk of withdrawal due to bradycardia (RR, 3.87; 95% CI, 1.67-8.97). There were 7 additional withdrawals per 1000 patients (95% CI, 3-10), equivalent to 1 additional withdrawal owing to bradycardia for every 153 patients treated for 1 year (Table 3).

β-BLOCKERS AND FATIGUE

Reported fatigue was described in 3 trials[1,2,18] that included 7793 patients. β-Blocker therapy was not associated with a significantly increased RR (RR, 1.04; 95% CI, 0.97-1.11) or absolute risk (3 per 1000 per year; 95% CI, −2 to 9) (Table 2).

In 3 trials[1,2,16] including 5500 patients that assessed withdrawal of therapy owing to fatigue, 0.69% in the β-blocker group and 0.46% in the placebo group were withdrawn from therapy. Similarly, β-blockers were not associated with a significantly increased RR (RR, 1.40; 95% CI, 0.69-2.83) or absolute risk of withdrawal owing to fatigue (2 per 1000 annually; 95% CI, −2 to 6) (Table 3).

RUN-IN PERIODS AND PATIENTS WITH SEVERE HF

Five trials included in the overview had a run-in period: 4 trials used β-blockers,[1,9,16,17] and 1 trial used placebo[2] as test doses. The rates of withdrawal in the run-in periods were 8.6% in β-blocker test doses and 8.5% in placebo test doses. In trials using β-blocker test doses, patients withdrew at rates of 1.5% owing to HF, 1.2% owing to hypotension, 0.7% owing to dizziness, and 0.2% owing to bradycardia. No information was available on withdrawal owing to fatigue.

The risks of adverse effects associated with β-blockers in the randomized phases of the trials did not differ significantly in trials with and without a run-in period (data not shown). Furthermore, the risks of HF deterioration, hypotension, dizziness, and bradycardia in the trial that included primarily patients with severe HF[4] did not differ significantly from the other trials included in the overview.

COMMENT

The principal finding of our quantitative overview is that despite concerns about adverse effects, fewer patients with HF assigned to receive β-blockers were withdrawn from therapy than were those assigned to receive placebo. This difference was primarily owing to a reduction of worsening HF associated with β-blocker therapy. β-Blockers were associated with increased risks of hypotension, dizziness, and bradycardia, although most patients did not experience these adverse effects. Furthermore, the absolute increases in risks were small, and patients were rarely withdrawn from therapy because of these symptoms. Although β-blocker therapy was not associated with a significantly increased risk of fatigue, we cannot exclude the possibility of small absolute increases in risk of fatigue. As previously reported,[1-4] we found that β-blocker therapy is associated with a substantial reduction in mortality.

β-Blockers have negative inotropic effects that could potentially cause decompensation in patients with HF with ventricular dysfunction.[25-27] Until recently, the US Food and Drug Administration approved package inserts and clinical guidelines[28,29] that listed HF as a contraindication for β-blocker therapy. Now that β-blocker therapy has been convincingly shown to reduce mortality in patients with HF, clinicians face the challenge of routinely prescribing a class of medications once thought to be dangerous to most patients with HF. The conventional wisdom that β-blockers are contraindicated because they cause substantial cardiovascular adverse effects in patients with systolic dysfunction may slow the adoption of this practice,[8,25-30] and the opportunity to alter the course of HF may be lost.

Hypotension is of concern in patients with HF because it may impair the perfusion of major organs and has been reported to be associated with poor outcomes.[31] However, the clinical importance of hypotension in patients with HF in the setting of β-blocker therapy is unclear. Dizziness may accompany hypotension and interfere with daily living. Our results indicate that β-blocker therapy was associated with increased risks of reported hypotension and dizziness. This is not surprising because β-blockers lower blood pressure by various mechanisms including reduction of cardiac output and sympathetic output as well as vasodilation in those with

concomitant α-blocking activity.[27] Hypotension and dizziness were commonly reported among patients with HF in the placebo groups in the trials included in the overview, which indicates the difficulty clinicians face in determining the cause of these symptoms. Although the RRs of treatment withdrawal in response to these symptoms were about 2- to 3-fold higher in the β-blocker group, the absolute annual increases in withdrawal were small (4 per 1000 per year for hypotension and 5 per 1000 per year for dizziness) because patients were rarely withdrawn for these symptoms. These results are consistent with clinical experience and indicate that hypotension and dizziness are transient and usually resolve spontaneously or after adjustment of other medications.[6]

Marked bradycardia is of concern in patients with HF because of the potential to decrease cardiac output and cause clinical decompensation. It is also not surprising that β-blockers were associated with an increased risk of bradycardia owing to the reduction of sympathetic output. We did not have complete information on the severity or timing of bradycardia, although adverse effects resulting in withdrawal of therapy may be a surrogate for marked bradycardia. In our overview, 0.8% of patients assigned to β-blockers were withdrawn owing to bradycardia compared with 0.1% of patients assigned to placebo. This translates to a small absolute risk of 7 additional withdrawals for bradycardia per 1000 patients treated for 1 year. Experimental studies have suggested that bradycardia is a major mechanism through which β-blockers can restore contractile function,[32] and a reduction in heart rate is a predictor of benefits associated with β-blocker therapy.[33] Therefore, bradycardia without accompanying dizziness, hypotension, or heart block may not be a sufficient reason to withdraw therapy. Placing the risk of bradycardia into perspective, the clinical guidelines[6] recommend consideration of pacemaker implantations in patients who would derive substantial benefits from therapy.

Another major concern about β-blocker therapy is that improvements in survival may be associated with decrements in quality of life due to fatigue. Fatigue is considered a known adverse effect of β-blocker therapy, hypothesized to be related to the reduction in cardiac output and effects on the central nervous system.[27] This association is supported by early randomized trials of hypertension testing β-blockers[34,35] and our recent quantitative overview that included a broader patient population in which we found a 12% relative increase in risk of reported fatigue associated with therapy.[36] Despite this evidence, the association of fatigue with β-blocker therapy has not been convincingly established in patients with HF. Our results do not support a substantial increased risk of fatigue associated with β-blocker therapy in patients with HF. Even at the upper confidence limit, the absolute increase in risk of fatigue associated with β-blockers was small (9 per 1000 per year for reported fatigue, 6 per 1000 per year for withdrawal). Although we did not examine symptoms such as depression and sexual dysfunction, a previous report examining these symptoms found no increased risk of depression and only a small absolute increased risk of sexual dysfunction associated with β-blockers.[36]

Owing to concern that β-blockers might cause substantial adverse events at initiation of therapy, several early clinical trials incorporated run-in periods to address tolerability of therapy initiation. In our overview, test doses of β-blockers were used in 4 trials and of placebo in a single trial. Although no direct comparison was possible, the withdrawal rates in this period were similar between β-blocker and placebo test doses, and the number of patients who required withdrawal of therapy owing to adverse effects was modest. However, these numbers may represent overestimations because they are limited by the lack of blinding and placebo control as well as the likelihood that physicians withdrew patients who were experiencing adverse effects and would be unlikely to maintain participation throughout the trial.

We found that the risks of adverse effects during the randomized phase did not differ significantly in trials with and without run-in periods. Since all the trials included in the overview excluded patients already taking β-blockers, the comparison between trials with and without run-in periods allows an opportunity to examine the potential excess risks at initiation. Furthermore, concerns about selection biases in trials with run-in periods may limit the generalization of the demonstrated mortality benefits. Contrary to this belief, we found no significant differences in the observed reductions in all-cause withdrawal or mortality.

Several issues in this study merit consideration. Compared with a community cohort of patients with HF, randomized HF trials included in our overview enrolled healthier and relatively few female and elderly patients. In addition, trial physicians were experienced in managing patients with HF. As such, our results may not be generalizable to all patients with HF. Finally, we had insufficient data to perform subgroup analyses by the individual preparations or dosages for any of the adverse effects.

In conclusion, β-blocker therapy in patients with HF was well tolerated and associated with fewer overall withdrawals and less HF deterioration than placebo. β-Blocker therapy was associated with small absolute increased risks of hypotension, dizziness, and bradycardia but not of fatigue. Our findings should alleviate concerns of physicians who are reluctant to prescribe β-blockers because of their cardiovascular adverse effects and support the implementation of this lifesaving therapy to appropriate candidates with HF.

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