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Beta-Blocker Use and Outcomes Among Hospitalized Heart Failure Patients

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OBJECTIVES The purpose of this study was to determine the effect of beta-blocker therapy on outcomes of hospitalized heart failure (HF) patients enrolled in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization (ESCAPE).

BACKGROUND The effect of beta-blocker therapy on outcomes among hospitalized HF patients is not well documented.

METHODS We studied the association between beta-blocker therapy and outcomes among 432 hospitalized HF patients in the ESCAPE trial.

RESULTS A total of 268 patients (62%) were on beta-blockers before admission. These patients had a shorter length of stay (7.9 ± 6.3 days vs. 9.4 ± 6.7 days; $p < 0.01$) and a lower six-month mortality rate (16% vs. 24%; $p = 0.03$) compared with those who were not on beta-blockers. Of the patients who were on admission beta-blockers and were discharged alive ($n = 263$), beta-blockers were discontinued in 54 and significantly modified (>50% dose reduction or changed to alternative beta-blocker) in 28 patients during hospitalization. Factors associated with discontinuation of beta-blockers during hospitalization included respiratory rate >24 breaths/min (30.8% vs. 16.9%; $p = 0.03$), heart rate >100 beats/min (19.2% vs. 7.3%; $p = 0.01$), lower ejection fraction (17.9 ± 5.4% vs. 20.2 ± 7.1%; $p = 0.04$), diabetes (21.2% vs. 37.1%; $p = 0.03$), and systolic blood pressure <100 mm Hg during hospitalization (70.3% vs. 54.1%; $p = 0.03$). After adjusting for factors associated with beta-blocker use and those with outcomes, consistent beta-blocker use during hospitalization was associated with a significant reduction in the rate of rehospitalization or death within six months after discharge (odds ratio 0.27, 95% confidence interval 0.10 to 0.71; $p < 0.01$).

CONCLUSIONS Beta-blocker therapy before and during hospitalization for HF is associated with improved outcomes. (J Am Coll Cardiol 2006;47:2462–9) © 2006 by the American College of Cardiology Foundation

Multiple clinical trials have demonstrated that beta-blocker therapy improves morbidity and mortality among patients with heart failure (HF) and reduced ejection fraction (EF) (1–5). However, these studies were done on optimally diuresed patients mostly in the outpatient setting. How best to manage beta-blocker therapy among hospitalized patients with decompensated HF is not well known. Studies addressing beta-blocker use among hospitalized HF patients prospectively have primarily studied the safety of beta-blocker initiation before discharge in patients who were already adequately treated and were ready to be discharged (6,7). Although most experts would agree not to initiate beta-blocker therapy in patients with decompensated HF, there is no consensus on what to do with beta-blockers for patients already on chronic therapy who present with fluid overload. Continuing these drugs may worsen congestion owing to their negative inotropic properties; however, discontinuing beta-blocker therapy may lead to a higher risk of arrhythmia and complications. More importantly, reinitiation and up-titration of therapy is likely to be difficult and may be an impediment in long-term therapy with recommended doses. The impact of beta-blocker therapy on outcomes among hospitalized patients with decompensated HF is an important and unanswered question. Using data from patients enrolled in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization (ESCAPE) (8), we investigated the differences in clinical characteristics and outcomes of patients admitted to the hospital with decompensated HF in whom beta-blocker therapy was continued compared with those in whom it was not.

METHODS

Patient population. Patients enrolled in the ESCAPE trial were studied to assess the impact of beta-blocker

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Abbreviations and Acronyms

BUN = blood urea nitrogen
CI = confidence interval
EF = ejection fraction
ESCAPE = Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization
HF = heart failure
HR = hazard ratio
OR = odds ratio
PAC = pulmonary artery catheter
PCWP = pulmonary capillary wedge pressure

therapy among hospitalized HF patients. The study design and results of the ESCAPE trial have been published (8). The ESCAPE trial assessed pulmonary artery catheter (PAC) use among patients admitted with decompensated HF. Patients were randomly assigned to receive care with PAC placement and hemodynamic guidance or clinical management without hemodynamic monitoring. Data collected included admission signs and symptoms, physical examination findings, laboratory values, hemodynamics (in the PAC arm), medication use (before admission, during hospitalization, and at discharge), complications, length of stay, and outcomes up to 180 days after discharge.

Study design. The impact of beta-blocker therapy on outcomes among patients taking or not taking beta-blockers before admission and among those who were or were not prescribed beta-blockers at discharge was studied. The goal of this post-hoc analysis of the ESCAPE trial, however, was to study the impact of beta-blocker therapy during hospitalization. To identify the patients in whom beta-blocker therapy was continued or discontinued during hospital stay, we identified 268 of the 432 patients in the ESCAPE trial on preadmission beta-blocker therapy. Of these, four patients died during the initial hospitalization, and there was no information on discharge beta-blocker status for one patient. These five patients were excluded from this analysis. Of the remaining 263 patients on preadmission beta-blocker therapy, 209 patients (79%) were discharged on beta-blockers. These patients were compared with the 54 patients in whom beta-blocker therapy was not prescribed at discharge and was discontinued during hospitalization.

Outcomes. Outcomes studied among these patients included need for ventilator or intra-aortic balloon pump support, need for cardiopulmonary resuscitation, length of stay, mortality rate during the index hospitalization, 180-day mortality, rehospitalization, and death or rehospitalization rates.

Statistical analysis. Three separate sets of analyses were performed: 1) among patients on (n = 268) and not on (n = 164) beta-blockers at the time of admission; 2) among patients on beta-blockers at admission and those in whom beta-blockers were continued (n = 209) and discontinued (n = 54) during hospitalization; and 3) among those who were (n = 241) and were not prescribed (n = 182) beta-blockers at discharge.

For the analysis on the group of patients on beta-blockers at admission and whether therapy was continued or discontinued during hospitalization, two separate sets of analyses were performed. It is possible that preadmission beta-blocker therapy may have been discontinued during hospitalization and then re-initiated at discharge. Therefore the presence of beta-blockers on admission and discharge does not guarantee continuous use. In order to take this into account, we identified 28 patients who were either on <50% of the dose of the same beta-blocker at discharge compared with preadmission dose (assuming that beta-blockers were discontinued initially and re-initiated at lower doses) or on different beta-blockers at admission and discharge. Two sets of analyses were performed, either including these patients in the beta-blocker therapy arm (assuming continued therapy) or including them in a broader category of patients in whom beta-blocker therapy was disrupted (modified or discontinued). These 28 patients did not affect the overall result with respect to end points, and only data from the former analysis are shown.

Patient characteristics and outcomes were compared using chi-square tests for categoric and *t* tests for continuous variables. When the assumption of normality for the *t* test was violated, the Wilcoxon rank-sum test was used instead. When expected cell frequencies were too low for the chi-square test, the Fisher exact test was used instead. Continuous variables are presented as mean ± standard deviation. Categoric data are presented as frequencies and percentages. Hemodynamic data were available on only 215 patients, because half of the patients were randomly assigned to receive medical therapy without PAC. Hemodynamic data were studied descriptively but not in the adjusted analyses.

Unadjusted risks for adverse outcomes were assessed and adjusted using multivariable logistic regression analysis for a composite propensity score for beta-blocker use and for a propensity score as well as individual variables that were predictive of various outcomes. Variables associated with the use of beta-blockers were identified based on: 1) clinical considerations; 2) an apparent relation with beta-blocker use; and 3) a reasonable number of non-missing values. The resulting subset included the following variables: age, atrial fibrillation, supine heart rate, ejection fraction (EF), creatinine, blood urea nitrogen (BUN), hematocrit, and in-hospital hypotension (systolic blood pressure <100 mm Hg). A logistic model was then fit to describe the effect of these confounding influences on beta-blocker use, and the propensity score was defined as the quintile of risk (predicted value) associated with a given configuration of these potential confounders in that model. Each end point was first analyzed with an "unadjusted" logistic model (with discharge beta-blocker use as the only predictor). Subsequently, propensity score was added in an "adjusted model." Finally, after examining the previous model for interaction between beta-blocker use and propensity score, other known covariates of the end point were added to a final model.

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Along with propensity score-adjusted analysis, to account for the fact the sicker patients may have preferentially had beta-blockers discontinued and that these patients had mostly adverse outcomes we did a separate analysis after excluding the top 10% of patients with respect to heart rate and respiratory rate (as surrogate measures of severity of disease). The results overall did not change (data not shown). In fact, removing the patients who discontinued beta-blockers and were above the 90th percentile for either heart rate or respiratory rate did not only fail to reverse the trend toward improved outcomes among patients discharged on beta-blockers, it trended toward enhancing it.

Patients who died during the hospitalization were excluded, because they were not classifiable by the study definition, i.e., use of beta-blockers at admission and at discharge. However, this raises the possibility of selection bias, that only the patients destined to do well were included in the study. To address this issue, two sets of additional analyses were performed to assess the impact of in-hospital deaths on outcomes by assuming that: 1) all patients who died during the index hospitalization were continued on beta-blockers; and 2) all these patients were taken off their beta-blockers.

Odd ratios (OR) and 95% confidence intervals (CI) were calculated for discrete end points, and the hazard ratio (HR) was calculated for the continuous end points. Statistical significance was based on an empirical alpha level of 0.05 in all hypothesis tests. All analyses were done using SAS version 8.2 (SAS Institute, Cary, North Carolina).

RESULTS

Patient characteristics. Baseline patient characteristics are described in Table 1. The average age of the study population was 56 ± 14 years with a mean EF of 19.4 ± 6.8%.

Table 1. Baseline Characteristics With Respect to Preadmission Beta-Blocker Therapy

Patient Characteristics	Overall (n = 432)	Beta-Blockers on Admission		p Value
		No (n = 164)	Yes (n = 268)	
Age (mean ± SD), yrs	56.0 ± 14.0	57.0 ± 13.0	55.0 ± 14.0	0.16
Female (%)	25.9	25.6	26.1	0.91
White (%)	59.5	52.4	63.8	0.02
First half of trial (%)	50.0	56.1	46.3	0.05
Systolic blood pressure (mean ± SD), mm Hg	106.0 ± 16.0	106.0 ± 17.0	105.0 ± 16.0	0.59†
Heart rate (mean ± SD), beats/min	82.0 ± 16.0	85.0 ± 14.0	81.0 ± 16.0	0.001†
Pulse rate >100 beats/min (%)	11.5	14.1	9.9	0.18
Ejection fraction (%)	19.4 ± 6.8	18.7 ± 6.1	19.7 ± 6.8	0.15†
Medical history				
Hypertension (%)	47.7	51.6	45.5	0.22
Diabetes (%)	33.3	32.9	33.6	0.89
Atrial fibrillation (%)	30.2	33.9	27.9	0.19
Stroke or transient ischemic attack (%)	12.4	8.1	15.1	0.03
Myocardial infarction (%)	44.2	42.9	44.9	0.69
Signs and symptoms				
Dyspnea at rest or on exertion (%)	98.8	100.0	98.1	0.16*
S3 gallop (%)	65.7	66.5	65.3	0.80
Increased jugular venous pressure (%)	94.4	96.0	93.5	0.54*
Rales (%)	52.3	57.9	48.9	0.07
Respiratory rate ≥24 breaths/min (%)	20.7	22.9	19.4	0.39
Peripheral edema (%)	68.1	73.8	64.5	0.05
Laboratory results				
Sodium (mean ± SD), mmol/l	136.6 ± 4.4	136.4 ± 4.7	136.8 ± 4.2	0.35†
Sodium <135 mmol/l (%)	24.0	29.5	20.7	0.04
Creatinine (mean ± SD), mmol/l	1.5 ± 0.6	1.5 ± 0.6	1.5 ± 0.6	0.83†
Blood urea nitrogen (mean ± SD), mmol/l	34.8 ± 22.6	35.4 ± 23.6	34.5 ± 22.1	0.96†
Hemoglobin (mean ± SD), mg/dl	13.4 ± 14.5	15.4 ± 19.9	12.1 ± 9.6	0.08†
Medications				
ACE inhibitors or ARB (%)	89.3	89.0	89.5	0.86
Calcium channel blockers (%)	4.9	5.5	4.5	0.64
Diuretics (%)	98.4	99.4	97.8	0.26*
Digoxin (%)	73.2	74.7	72.3	0.58
Antiarrhythmic (%)	21.8	27.4	18.4	0.03
Hemodynamic characteristics (PAC arm)	n = 215	n = 75	n = 140	
Right atrial pressure, mm Hg	14 ± 10	14 ± 8	13 ± 11	0.07†
Pulmonary artery systolic pressure, mm Hg	55 ± 14	57 ± 14	54 ± 14	0.15
Pulmonary wedge pressure, mm Hg	25 ± 9	27 ± 9	24 ± 9	0.02†
Cardiac output, l/min	3.9 ± 1.4	3.6 ± 1.1	4.1 ± 1.5	0.04†
Cardiac index, l/min/m^2	2.0 ± 0.6	1.8 ± 0.5	2.1 ± 0.7	0.03†

*Fisher exact test used. †Wilcoxon rank-sum test used.
ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; PAC = pulmonary artery catheter.

Approximately 60% of the patients were white and 75% were male. Nearly 90% of the patients were on either angiotensin-converting enzyme inhibitors or angiotensin-receptor blocker therapy. Average serum sodium concentration was 137 ± 4 mmol/l, and mean serum creatinine concentration was 1.5 ± 0.6 mmol/dl.

Beta-blocker use. Two hundred sixty-eight patients (62%) were on beta-blockers at admission. The most common beta-blockers were carvedilol (n = 155) and metoprolol (n = 84). Of the 263 patients on preadmission beta-blockers who were discharged alive (and medication information on discharge was complete), 209 were prescribed beta-blockers at discharge; the other 54 were not.

Outcomes. The average length of stay was 8.5 ± 6.4 days. Eight patients (2%) died during the index hospitalization, 21 (4.9%) died during or within 30 days of the index hospitalization, and 83 (19.2%) died within 180 days. A total of 247 patients (57.1%) required rehospitalization within 180 days.

Beta-blocker use and outcomes. PREADMISSION BETA-BLOCKER USE. Table 1 summarizes the characteristics of those patients who were and were not on beta-blocker therapy before admission. Beta-blocker use was significantly higher among whites, patients randomized during the second half of the trial, and those with a history of neurologic events. Patients on beta-blockers were less likely to have edema on exam, to be hyponatremic, or to be on antiarrhythmic therapy. The average heart rate was lower for patients on beta-blocker therapy (80.5 ± 16.3 beats/min vs. 85.1 ± 14.3 beats/min; p = 0.001). For patients in whom hemodynamic data were available (n = 215), patients not on beta-blockers at admission (n = 75) had a higher pulmonary capillary wedge pressure (PCWP) (27 ± 9 mm Hg vs. 24 ± 9 mm Hg; p = 0.02) and lower cardiac index (1.8 ± 0.5 l/min/m^2 vs. 2.1 ± 0.7 l/min/m^2; p = 0.03).

Patients on preadmission beta-blocker therapy had a shorter length of stay (7.9 ± 6.3 days vs. 9.4 ± 6.7 days; p = 0.003), and lower 180-day mortality rate (16.0% vs. 24.4%; p = 0.03). When these outcome analyses were adjusted for differences in patient characteristics associated with baseline beta-blocker use and overall predictors of mortality (detailed data not shown), there was a trend toward lower 180-day mortality with preadmission beta-blocker therapy (OR 0.58, 95% CI 0.32 to 1.06; p = 0.08).

Five of the eight patients who required cardiopulmonary resuscitation, two of the six patients who required intraaortic balloon pump insertion, and five of the eight patients who required mechanical ventilation during the index hospitalization were among those patients who were not on beta-blocker therapy before admission (all p > 0.20).

BETA-BLOCKER USE DURING HOSPITALIZATION. Table 2 shows the differences in characteristics among those patients who were on beta-blocker therapy at both admission and discharge versus those in whom beta-blocker therapy was discontinued before discharge. Patients in whom beta-blocker therapy was discontinued significantly differed from those in whom it was continued in the following characteristics: respiratory rate >24 breaths/min (30.8% vs. 16.9%; p = 0.03), heart rate >100 beats/min (19.2% vs. 7.3%; p < 0.01), lower EF (17.9 ± 5.4% vs. 20.2 ± 7.1%; p = 0.04), diabetes (21.2% vs. 37.1%; p = 0.03), and hypotension (systolic blood pressure <100 mm Hg) during hospitalization (70.3% vs. 54.1%; p = 0.03). Where data were available (n = 134), there were no significant differences in any of the hemodynamic measures among patients in whom beta-blocker therapy was continued (n = 104) and those in whom it was discontinued (n = 30). These included right atrial pressure of 13 ± 7 mm Hg vs. 12 ± 10 mm Hg (p = 0.17), pulmonary wedge pressure of 25 ± 9 mm Hg vs. 23 ± 9 mm Hg (p = 0.14), and a cardiac index of 2.0 ± 0.6 l/min/m^2 vs. 2.1 ± 0.6 l/min/m^2 (p = 0.43) among those who were not versus those who were on continued beta-blocker therapy, respectively.

Patients in whom beta-blocker therapy was continued had a lower 180-day rehospitalization and death rate (59.8% vs. 74.1%; p = 0.053). A full logistic propensity model for beta-blocker use in this subset of patients (C-index = 0.069) was based on age, supine heart rate, serum sodium, BUN, hematocrit, and creatinine concentrations, randomization in the first or second half of study, atrial fibrillation, EF, antiarrhythmic use, and in-hospital hypotension (systolic blood pressure <100 mm Hg). As shown in Table 3, when data were adjusted for the resulting propensity score for beta-blocker prescription and for the variables associated with outcomes, continued beta-blocker use was associated with an improved 180-day rehospitalization rate (OR 0.45, 95% CI 0.19 to 1.03; p = 0.048) and 180-day rehospitalization or death rate (OR 0.27, 95% CI 0.10 to 0.71; p < 0.01).

All four patients who required intra-aortic balloon pump insertion were among those in whom beta-blocker therapy was discontinued. One patient requiring mechanical ventilation during hospitalization remained on beta-blocker therapy.

IMPACT OF IN-HOSPITAL DEATHS. There were eight deaths during the index hospitalization. Four of these were in patients who were continued on beta-blocker therapy and four who were not. Therefore, 4 of 268 patients on admission beta-blocker therapy (1.5%) died compared with four of 164 (2.4%) of those not on beta-blocker therapy (p = 0.48). Of the patients who were on beta-blockers on admission, when these four deaths were considered in the group that did not continue beta-blockers, the outcomes were in favor of continued beta-blocker therapy (59.8% vs. 75.9%; p = 0.02; OR 0.22 [95% CI 0.08 to 0.60]; p < 0.01 adjusted). When these deaths were included in the group who were continued on beta-blocker therapy, the overall outcomes still were in favor of beta-blocker therapy (60.6% vs. 74.1; p = 0.06; OR 0.27 [95% CI 0.11 to 0.72]; p < 0.01 adjusted).

BETA-BLOCKER PRESCRIPTION AT DISCHARGE. Among the entire group of patients who were discharged alive (n = 423), 241 (57%) were discharged on beta-blocker therapy. Patient characteristics associated with beta-blocker use at

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Table 2. Baseline Characteristics of Patients on Preadmission Beta-Blockers Stratified by Beta-Blocker Use During Hospitalization

Patient Characteristics	Overall (n = 263)	Beta-Blockers Continued		p Value
		No (n = 54)	Yes (n = 209)	
Age (mean ± SD), yrs	55.0 ± 14.0	55.0 ± 16.0	55.0 ± 14.0	0.73†
Female (%)	26.2	25.9	26.3	0.95
White (%)	64.3	61.1	65.1	0.59
First half of trial (%)	46.0	57.4	43.1	0.06
Systolic blood pressure (mean ± SD), mm Hg	105.0 ± 16.0	103.0 ± 14.0	106.0 ± 16.0	0.23†
Heart rate (mean ± SD), beats/min	81.0 ± 16.0	83.0 ± 18.0	80.0 ± 16.0	0.22†
Pulse rate >100 beats/min (%)	9.7	19.2	7.3	0.01
Ejection fraction (%)	19.7 ± 6.8	17.9 ± 5.4	20.2 ± 7.1	0.04†
Medical history				
Hypertension (%)	46.4	41.5	47.6	0.43
Diabetes (%)	33.8	21.2	37.1	0.03
Atrial fibrillation (%)	28.5	33.9	27.1	0.32
Stroke or transient ischemic attack (%)	14.6	13.2	14.9	0.75
Myocardial infarction (%)	44.7	40.7	45.7	0.52
Signs and symptoms				
Dyspnea at rest or on exertion (%)	98.1	98.2	98.1	1.00*
S3 gallop (%)	65.0	64.8	65.1	0.97
Increased jugular venous pressure (%)	93.3	93.3	93.3	1.00*
Rales (%)	48.3	55.6	46.4	0.23
Respiratory rate ≥24 breaths/min (%)	19.7	30.8	16.9	0.03
Peripheral edema (%)	63.9	59.3	65.1	0.43
Laboratory results				
Sodium (mean ± SD), mmol/l	137.0 ± 4.0	136.0 ± 4.0	137.0 ± 4.0	0.17†
Sodium <135 mmol/l (%)	20.4	24.5	19.3	0.40
Creatinine (mean ± SD), mmol/l	1.5 ± 0.6	1.5 ± 0.6	1.5 ± 0.6	0.79†
Blood urea nitrogen (mean ± SD), mmol/l	33.7 ± 20.9	34.1 ± 19.6	33.7 ± 21.4	0.52†
Hemoglobin (mean ± SD), mg/dl	12.1 ± 9.7	13.6 ± 19.9	11.7 ± 3.3	0.75†
Medications				
ACE inhibitors or ARB (%)	89.7	90.7	89.5	0.78
Calcium channel blockers (%)	4.2	3.7	4.3	1.00*
Diuretics (%)	97.7	96.2	98.1	0.35*
Digoxin (%)	72.9	68.5	74.0	0.42
Antiarrhythmic (%)	18.4	20.4	17.9	0.67
Hemodynamic characteristics (PAC arm)	n = 124	n = 30	n = 94	
Right atrial pressure, mm Hg	13 ± 9	13 ± 7	12 ± 10	0.17†
Pulmonary artery systolic pressure, mm Hg	54 ± 15	53 ± 12	55 ± 15	0.59
Pulmonary wedge pressure, mm Hg	24 ± 9	25 ± 9	23 ± 9	0.14
Cardiac output, l/min	4.0 ± 1.4	3.8 ± 1.3	4.1 ± 1.4	0.22†
Cardiac index, l/min/m^2	2.1 ± 0.6	2.0 ± 0.6	2.1 ± 0.6	0.43†

*Fisher exact test used. †Wilcoxon rank-sum test used.
Abbreviations as in Table 1.

discharge included randomization in the second half of the trial (57% vs. 41%, p = 0.001), baseline heart rate (81 ± 16 beats/min vs. 84 ± 15 beats/min; p = 0.02), BUN (32 ± 20 vs. 37 ± 23; p = 0.02), hematocrit (37 ± 5% vs. 38 ± 6%; p = 0.05), EF (20 ± 7% vs. 19 ± 6%; p = 0.03), and serum sodium (137 ± 4 mmol/l vs. 136 ± 5 mmol/l; p = 0.03).

Patients discharged on beta-blocker therapy had a significantly lower 180-day death or rehospitalization rate (59% vs. 69%; p = 0.048). This relation remained significant when data were adjusted for propensity to use beta-blocker at discharge and covariates associated with death or rehospitalization (OR 0.51, 95% CI 0.27 to 0.97).

DISCUSSION

There are no clear guidelines on how to manage beta-blocker therapy in patients with decompensated HF. All the major studies that have assessed beta-blocker use among HF patients were conducted among patients either in the outpatient setting or during hospitalization after patients had been adequately diuresed and were deemed ready for discharge (1–7). Although theoretical justifications may be possible for continuation or discontinuation of beta-blocker therapy on admission among hospitalized HF patients, scarce data exist comparing the two approaches. A secondary analysis of the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study by Gattis et al. (9) suggested that beta-blocker discontinuation during hospitalization was associated with a higher mortality rate after discharge within 60 days. Similarly, a retrospective analysis of the Flolan International Randomized Survival Trial (FIRST) database assessed clinical outcomes related to

Table 3. Unadjusted and Adjusted Outcomes Based on Beta-Blocker Use During Hospitalization

	Chi-Square	OR (95% CI)	p Value
Rehospitalization			
Unadjusted	1.2	0.70 (0.38–1.31)	0.27
Adjusted*†	3.6	0.45 (0.19–1.03)	0.048
Rehospitalization or death			
Unadjusted	3.7	0.52 (0.27–1.02)	0.053
Adjusted*‡	7.1	0.27 (0.10–0.71)	<0.01

*Propensity score for beta-blocker use: the full propensity model for beta-blocker use in this subset of patients (C-Index = 0.69) was based on age, heart rate, serum sodium, blood urea nitrogen, hemoglobin, hematocrit, and creatinine levels, randomization in the first or second half of study, atrial fibrillation ejection fraction, antiarrhythmic use, and in-hospital hypotension (systolic blood pressure <100 mm Hg). †Covariates for rehospitalization: pulse pressure, hemoglobin, blood urea nitrogen, sodium, six-minute walk test (Y/N) and distance, supine heart rate, and the propensity score for beta-blocker use. ‡Covariates for death or rehospitalization: same as rehospitalization plus age.

CI = confidence interval; OR = odds ratio.

beta-blocker use at randomization and reported no excess risk for patients treated with beta-blockers at the time of hospital presentation (10). In this investigation, we assessed this issue using the ESCAPE trial database and found that continuation of beta-blocker therapy, even after adjusting for potential confounders associated with beta-blocker use or the outcomes studied, was associated with a lower mortality and rehospitalization rate subsequent to discharge.

Beta-blocker therapy before admission and after discharge was also associated with better outcomes, and positive results were seen with continued beta-blocker therapy during hospitalization. Although these data are encouraging, they need to be interpreted with caution. It is possible that discontinuation of beta-blocker therapy in a certain group of hospitalized HF patients may be related to worse HF or other medical reasons, which in turn may be responsible for poor outcomes among these patients rather than lack of beta-blocker use. Patients in whom beta-blockers were discontinued were more tachycardic and tachypneic on admission, had lower EF, and were more likely to develop hypotension during hospitalization. Among patients in whom PAC data were available, PCWP was higher (27 ± 9 mm Hg vs. 24 ± 9 mm Hg; p = 0.02) and cardiac index was lower (1.8 ± 0.5 l/min/m^2 vs. 2.1 ± 0.7 l/min/m^2; p = 0.03) among those who were not on beta-blocker therapy at admission, although no statistically significant hemodynamic differences were noted based on whether or not beta-blockers were continued during hospitalization. Except for extreme hemodynamic alterations such as cardiogenic shock, the decision to discontinue beta-blocker therapy among these patients was based primarily on clinical judgment likely influenced by the provider's experience and bias. Many patients with similar hemodynamics are routinely placed on beta-blocker therapy, especially those awaiting transplantation. In our study, improved outcomes with continued beta-blocker therapy persisted after controlling for factors associated with the decision to discontinue beta-blocker therapy or those associated with the various outcomes assessed that were captured in the data collection. However, with a post-hoc analysis, it is possible that all factors that may have influenced the decision to discontinue beta-blocker therapy may not have been captured in this study and that these factors may influence our results. The fact that some of the outcomes may or may not have improved with beta-blocker therapy (Table 4) could have been related to the number of events and the power to detect differences, but there was no evidence of worsening outcomes with continued beta-blocker use.

Another concern with beta-blocker therapy in patients with decompensated HF is the potential for worsening hemodynamics and respiratory compromise. Although the number of patients needing intra-aortic balloon pump or ventilator support were too few to do adjusted analysis, in univariate analysis there was no suggestion of increased risk during the index hospitalization for either of these two complications with beta-blocker therapy. We can therefore cautiously conclude that continued beta-blocker therapy among these patients was not associated with worsening outcomes and may actually improve them.

Medication prescription at the time of discharge has been shown to be the strongest predictor of long-term adherence to drug therapy (11,12). Discontinuation of medications that may not be absolutely necessary during hospital admission can have potentially inadvertent deleterious effects in the long run, and the full benefit of therapy may not be clinically realized. To improve therapy for cardiovascular medications at discharge, several national initiatives are being conducted by regulatory agencies and professional societies (13–16). In our study, beta-blocker therapy was significantly modified between admission and discharge (discontinued, changed to different beta-blocker, or >50% dose reduction) among 82 patients; 54 of whom (66%) were

Table 4. Outcomes of Patients With Respect to Beta-Blocker Therapy

Outcomes	Beta-Blocker Therapy		p Value
	No	Yes	
Preadmission			
Length of stay (days of initial hospitalization)	9.4 ± 6.7	7.9 ± 6.3	<0.01†
Death, initial hospitalization (%)	2.4	1.5	0.48*
Death, 180 days (%)	24.4	16.0	0.03
Rehospitalization (%)	56.7	57.5	0.88
Death or rehospitalization, 180 days (%)	65.2	63.4	0.70
During hospitalization			
Death, 180 days (%)	16.7	14.4	0.67
Rehospitalization (%)	64.8	56.5	0.27
Death or rehospitalization, 180 days (%)	74.1	59.8	0.053
At discharge			
Death, 180 days (%)	23.1	13.7	0.01
Rehospitalization (%)	60.4	56.4	0.41
Death or rehospitalization, 180 days (%)	68.7	59.3	0.048

*Fisher exact test used. †Wilcoxon rank-sum test used.

not prescribed these drugs at discharge. If beta-blocker therapy is disrupted during hospitalization, it is possible that it may not be initiated later. Another major problem in discontinuing or altering beta-blocker therapy is that their up-titration in HF patients is a difficult and slow process. If beta-blocker therapy is altered, even if beta-blockers are continued, the patients may remain on suboptimal doses, whereas higher doses of beta-blockers have been associated with incremental improvements in outcomes (1). Whether or not beta-blocker therapy is continued during hospitalization among HF patients is an important consideration for which little data exist. The present study suggests that routinely discontinuing beta-blocker therapy among hospitalized HF patients may not be necessary.

We excluded four patients who were on beta-blockers on admission who died during the index hospitalization. These patients were excluded because they cannot be classified in the study definition, i.e., use of beta-blockers at admission and at discharge. However, this does raise an important question regarding selection bias, that only the patients destined to do well were included in the study. However, this was not the case. There were eight deaths overall during the index hospitalization in the ESCAPE trial. Four of these were in patients who were continued on beta-blocker therapy and four who were not. Proportionally speaking, only 4 of 268 patients on admission beta-blocker therapy (1.5%) died compared with 4 of 164 (2.4%) among those not on beta-blocker therapy. Studying the patients who were on beta-blockers on admission specifically, if we exclude these four patients from the analysis, we see an outcome difference (death or rehospitalization rate at 6 months) in favor of beta-blocker use (59.8% vs. 74.1%; $p = 0.053$ unadjusted; OR 0.27 [95% CI 0.10 to 0.71]; $p < 0.01$ adjusted). To further study the impact of these four deaths, we did two sets of additional analyses: 1) counting these four patients who died as those who continued on beta-blocker therapy; and 2) counting these four as patients who did not continue beta-blockers during hospitalization. If we consider them in the group not continued on beta-blockers, the outcomes are in favor of those who continued beta-blockers (59.8% vs. 75.9%; $p = 0.02$; OR 0.22 [95% CI 0.08 to 0.60]; $p < 0.01$ adjusted). However, if we assume that all four deaths occurred in the group who were continued on beta-blocker therapy, the overall outcomes still trend in favor of beta-blocker therapy (60.6% vs. 74.1%; $p = 0.06$; OR 0.27 [95% CI 0.11 to 0.72]; $p < 0.01$ adjusted). The overall results with respect to at least no worsening outcomes and possible beneficial outcomes with beta-blocker therapy did not change based on the four hospital deaths.

Study limitations. We do recommend being cautious with beta-blockers in patients with decompensated HF. This investigation, though provocative and suggestive of improved outcomes with beta-blocker therapy in this group of patients, is not definitive, because it was a retrospective analysis. Several important data are missing, the most important of which is why beta-blocker therapy was discontinued. Intolerance, symptomatic hypotension, bradycardia, and heart block are all recognized reasons for altering beta-blocker therapy. The appropriateness of discontinuing beta-blocker therapy cannot be commented on in this study. Although these data are adjusted for baseline differences between the two groups, they are retrospective in nature and one cannot be completely certain that some measured and unmeasured differences between the two groups may not have influenced the outcomes. Other limitations include the fact that these patients were treated in a clinical trial that focused on centers with considerable experience in managing patients with advanced HF. Whether similar results can be expected in the general group of patients is not known. Similarly, beta-blockers were discontinued on admission in a minority of patients, which may not be the case in general practice outside of clinical trials. Either prospective randomized studies or carefully designed registries are needed to answer these questions more accurately.

Conclusions. We found no worsening, but instead better, HF outcomes with continuation of beta-blocker therapy among hospitalized patients with decompensated HF. These results persisted even after controlling for differences between the two groups, suggesting that routine discontinuation of beta-blocker therapy on admission may not be necessary. However, the appropriateness of discontinuing beta-blocker therapy in certain settings needs to be assessed prospectively.

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