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Influence of Beta-Blocker Continuation or Withdrawal on Outcomes in Patients Hospitalized With Heart Failure

Findings From the OPTIMIZE-HF Program

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Objectives This study ascertains the relationship between continuation or withdrawal of beta-blocker therapy and clinical outcomes in patients hospitalized with systolic heart failure (HF).

Background Whether beta-blocker therapy should be continued or withdrawn during hospitalization for decompensated HF has not been well studied in a broad cohort of patients.

Methods The OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) program enrolled 5,791 patients admitted with HF in a registry with pre-specified 60- to 90-day follow-up at 91 academic and community hospitals throughout the U.S. Outcomes data were prospectively collected and analyzed according to whether beta-blocker therapy was continued, withdrawn, or not started.

Results Among 2,373 patients eligible for beta-blockers at discharge, there were 1,350 (56.9%) who were receiving beta-blockers before admission and continued on therapy, 632 (26.6%) newly started, 79 (3.3%) in which therapy was withdrawn, and 303 (12.8%) eligible but not treated. Continuation of beta-blockers was associated with a significantly lower risk and propensity adjusted post-discharge death (hazard ratio [HR]: 0.60; 95% confidence interval [CI]: 0.37 to 0.99, $p = 0.044$) and death/rehospitalization (odds ratio: 0.69; 95% CI: 0.52 to 0.92, $p = 0.012$) compared with no beta-blocker. In contrast, withdrawal of beta-blocker was associated with a substantially higher adjusted risk for mortality compared with those continued on beta-blockers (HR: 2.3; 95% CI: 1.2 to 4.6, $p = 0.013$), but with similar risk as HF patients eligible but not treated with beta-blockers.

Conclusions The continuation of beta-blocker therapy in patients hospitalized with decompensated HF is associated with lower post-discharge mortality risk and improved treatment rates. In contrast, withdrawal of beta-blocker therapy is associated with worse risk and propensity-adjusted mortality. (Organized Program To Initiate Lifesaving Treatment In Hospitalized Patients With Heart Failure [OPTIMIZE-HF]; NCT00344513) (J Am Coll Cardiol 2008; 52:190–9) © 2008 by the American College of Cardiology Foundation

Heart failure (HF) requiring hospitalization is highly lethal, with mortality rates of approximately 25% to 45% within the first year (1,2). Each year in the U.S. there are more than 1.1 million hospitalizations with HF as the primary cause and an additional 2.4 to 3.6 million hospitalizations where HF is a contributing factor (2). Multiple large, placebo-

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controlled, randomized clinical trials (3,4) have demonstrated that certain beta-blockers (carvedilol, metoprolol succinate, and bisoprolol) reduce total mortality by approximately 35% in patients with symptomatic chronic HF and left ventricular systolic dysfunction (LVSD). National guidelines (5,6) recommend the use of one of these specific evidence-based beta-blockers in all patients with current or prior symptoms of HF and reduced left ventricular ejection fraction (LVEF), in the absence of contraindications or intolerance.

Despite the efficacy of HF medical therapy, patients may still decompensate and require hospitalization for HF. An increasing proportion of patients presenting to the hospital with HF (more than two-thirds in recent studies) have been receiving beta-blocker therapy as part of their outpatient medical regimen (7). Unfortunately, whether beta-blocker therapy should be continued or withdrawn during HF hospitalization in such patients has not been well studied. There have been no clinical trials that have randomized HF patients treated with beta-blockers before hospital admission to continuation or withdrawal of beta-blocker therapy. Nor have there been any trials that have assessed initiation of beta-blocker therapy in the first 48 h of hospitalization for HF. A few recent retrospective analyses (8–11) have compared continuation versus withdrawal of beta-blocker therapy among hospitalized HF patients enrolled in randomized clinical trials that were testing other HF treatments or monitoring strategies. However, as randomized clinical trials enroll only select HF patients and generally provide much closer monitoring and follow-up compared with the usual care setting, the generalizability of the findings from these studies may be limited. Furthermore, these studies were not able to document new contraindications or intolerance of beta-blocker therapy during the period of follow-up or able to compare outcomes to HF patients who were otherwise eligible but not treated with beta-blockers.

The OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) is a large, national hospital-based registry and process-of-care improvement initiative for patients hospitalized with HF (12). The present study examines data from OPTIMIZE-HF to explore the relationship of continuation or withdrawal of beta-blocker therapy to post-discharge clinical outcomes in a general population of patients hospitalized with systolic HF.

Methods

Study design. The OPTIMIZE-HF program is a hospital-based registry and process-of-case improvement program designed to evaluate and enhance the quality of care for patients hospitalized with HF. The OPTIMIZE-HF program has been described in detail elsewhere (12–15) and will be briefly summarized. From March 1, 2003, to December 31, 2004, eligible adult patients hospitalized with HF at participating hospitals were enrolled. All regions of the U.S. were represented, and all types of institutions, from community hospitals to large tertiary medical centers, were included. A list of participating hospitals has been published (14). Hospital teams used HF case-ascertainment methods similar to those of the Joint Commission (16). Patients qualified for enrollment if they were hospitalized for episodes of new or worsening HF as the primary cause of admission or if significant HF symptoms developed during hospitalization for another primary diagnosis, with HF being the primary discharge diagnosis (12–15). Consecutive patients were enrolled irrespective of their ventricular function, including systolic dysfunction documented by a left ventricular ejection fraction (LVEF) <40%, HF symptoms in the setting of preserved left ventricular systolic function (diastolic dysfunction HF), or HF without left ventricular function measurement (12–15).

Abbreviations and Acronyms

CI = confidence interval
HF = heart failure
HR = hazard ratio
LVEF = left ventricular ejection fraction
LVSD = left ventricular systolic dysfunction
OR = odds ratio

Using a web-based information system, data were captured regarding various patient characteristics at admission and discharge, including laboratories, procedures, LVEF, drug contraindications or intolerance, and prescribed medications (12). Automated electronic data checks were used to prevent out-of-range entry or duplicate patients. A database audit was performed, based on predetermined criteria, of a random sample of 5% of the first 10,000 patients verified against source documents (13). A prespecified subgroup (10%) from 91 participating hospitals had 60- to 90-day follow-up data collected. The protocol was approved by each participating center's institutional review board or through the use of a central institutional review board. Written informed consent was obtained before enrollment from patients who participated in the follow-up data collection. The registry coordinating center was Outcome Sciences, Inc. (Cambridge, Massachusetts).

The present study was pre-specified in the study protocol and aimed to compare outcomes in the first 60 to 90 days after HF hospital discharge among patients eligible for beta-blocker therapy who were receiving beta-blockers before hospitalization and continued on therapy through discharge, patients who were eligible for beta-blocker therapy for whom beta-blocker therapy was withdrawn during hospitalization, and patients eligible for beta-blocker therapy who were not treated with beta-blocker therapy before hospitalization or at the time of hospital discharge. The current analysis was confined to those patients who had documented LVEF <40% or moderate-to-severe systolic dysfunction by qualitative assessment. We excluded patients with documented contraindications or intolerance to beta-blockers at the time of hospital discharge. Contraindications included allergy, second- or third-degree heart block without a pacemaker, symptomatic bradycardia, symptomatic

hypotension, cardiogenic shock, or reactive airway disease (14,15). The study also assessed whether continuation of beta-blocker therapy was well tolerated, as gauged by persistence of treatment during 60- to 90-day follow-up.

Statistical analysis. All statistical analyses were performed by Duke Clinical Research Institute (Durham, North Carolina). Eligibility for beta-blocker therapy used specifications similar to the Joint Commission and excluded patients with documented contraindications, intolerance, or other physician documentation. Patient characteristics and evidence-based treatments at hospital discharge were compared using the Pearson chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. The relationship between beta-blocker therapy group and outcomes was evaluated with propensity score and multivariable adjustment. Models of mortality from hospital discharge to 90 days and the combination of post-discharge mortality or rehospitalization have been developed to determine significant factors to use when applying adjusted models, as previously described (13–15). Baseline demographic, clinical, and treatment factors as well as hospital course factors were applied to logistic regression and Cox proportional hazards models using both stepwise and backward variable selection techniques. The assumption of proportional hazards was checked in Cox models for key variables (17). The assumption of linearity was checked in each model for the continuous variables by using restricted cubic splines. When the relationship was found to be nonlinear, appropriate transformations were applied. Propensity score analysis was used to account for potential medication selection bias. The set of all possible covariates that were related to selection was applied to a logistic regression model, with the probability of receiving the medication generated as the score. Each model included 2 treatment indicators plus the propensity score and covariate adjustment. Generalized estimating equations were also performed to account for the correlation of the data within the same hospital in the adjusted models. A previously derived and validated OPTIMIZE-HF post-discharge mortality risk prediction tool was used to estimate mortality based on admission characteristics for the beta-blocker treatment patient groups (18). SAS version 8.2 (SAS Institute Inc., Cary, North Carolina) was used for all statistical analyses.

Results

The OPTIMIZE-HF program enrolled a total of 48,612 patients hospitalized for HF at 259 U.S. hospitals. This analysis was confined to those patients from 91 hospitals participating in the hospital registry and pre-specified 60- to 90-day post-discharge follow-up. Of the 5,791 patients in the pre-specified cohort with 60- to 90-day follow-up data collection, left ventricular function was assessed in 5,117 patients, and 2,720 patients had documented LVSD. Patient demographics for the hospital and follow-up cohort with LVSD are shown in Table 1. The mean patient age in the follow-up group was 69.5 ± 14.5 years; 63% of the patients were men, and 75% were Caucasian. The HF etiology was ischemic in 52% of the patients; the mean LVEF was 24.3 ± 7.8%, and 89.3% of patients had known HF before admission. At hospital admission, pulmonary rales were present in 62% of patients, an S_3 gallop was present in 18%, and lower extremity edema was found in 63%. Medications on admission included a beta-blocker in 57% of patients, an angiotensin-converting enzyme inhibitor in 47%, an angiotensin receptor blocker in 12%, an aldosterone antagonist in 10%, and digoxin in 30%.

Patients were hospitalized for a mean of 6.4 days (median 5.0 days). Of the 2,720 patients with LVSD, 2,373 (87.2%) were eligible for beta-blocker therapy at the time of hospital discharge, with no documented contraindications or intolerance. There were 347 patients (12.8%) ineligible because of contraindications or intolerance to beta-blocker therapy at hospital discharge (n = 299) or discharge to skilled nursing care facility, transfer, or hospice (n = 48). Of the 2,373 patients eligible for beta-blocker therapy at hospital discharge, 1,350 patients (56.9%) were continued on beta-blocker therapy, 79 (3.3%) were withdrawn from beta-blocker therapy, and 303 (12.8%) were not treated. There were 632 patients (26.6%) newly started on beta-blocker therapy and 9 patients with missing treatment data (0.4%). Among the 1,537 patients receiving beta-blocker therapy before hospital presentation, 1,350 (87.8%) were continued on beta-blocker therapy and 187 (12.2%) were withdrawn (108 with documented contraindications or intolerance and 79 without). Patient characteristics for the 4 treatment groups included in this study (continued, newly started, withdrawn, eligible but not treated) are shown in Table 2. Patients in the group continued on beta-blockers were of similar age to those withdrawn but younger than those not treated. Vital signs and lab values were similar in those continued and withdrawn from beta-blocker therapy. The LVEF was lower in patients withdrawn from beta-blockers.

Beta-blocker use and clinical outcomes. UNADJUSTED ANALYSES. In the overall cohort of beta-blocker–eligible patients with HF and LVSD, mortality at 60 to 90 days after hospital discharge was 8.7% (Table 3). Readmission within the 60- to 90-day follow-up period was 30.2%, and death/rehospitalization occurred in 34.8%. Patients continued on beta-blocker therapy from the time of admission had shorter hospital length of stay compared with eligible patients who were not treated with beta-blockers (Table 3). Continued patients were found to have significantly lower post-discharge mortality rates during follow-up compared with those eligible but not treated with beta-blockers (8.7% vs. 13.8%, p = 0.046) (Table 3). The Kaplan-Meier actuarial mortality curves for eligible patients continued, newly started, withdrawn, and not treated with beta-blocker therapy are shown in Figure 1. The unadjusted hazard ratios (HRs) for post-discharge mortality with beta-blocker continuation compared to nonuse among eligible patients was 0.60 (95% confidence interval [CI]: 0.38 to 0.94, p =

Table 1 Patient Demographics at Hospital Admission and Follow-Up Cohort With LVSD

Characteristic	Overall Registry With LVSD (n = 20,118)	Follow-Up Cohort With LVSD (n = 2,720)
Mean age, yrs (SD)	70.3 (14.5)	69.5 (14.5)
Female gender, n (%)	7,797 (39)	1,006 (37)
Race, n (%)		
Caucasian	14,266 (71)	2,037 (75)
African American	4,212 (21)	560 (21)
Native American	73 (<1)	11 (<1)
Unknown	541 (3)	27 (<1)
Other	764 (4)	66 (2)
Hispanic ethnicity, n (%)	789 (4)	80 (3)
HF etiology, n (%)		
Ischemic	10,933 (54)	1,401 (52)
Nonischemic	9,185 (46)	1,319 (48)
Medical history, n (%)		
Hypertension	13,274 (66)	1,832 (67)
CAD	10,869 (54)	1,460 (54)
Hyperlipidemia	6,913 (34)	1,121 (41)
Atrial arrhythmia	5,742 (29)	852 (31)
Pulmonary/COPD	5,057 (25)	740 (27)
Non–insulin-treated diabetes	4,912 (24)	678 (25)
Insulin-treated diabetes	3,110 (15)	447 (16)
Cigarette smoker	3,997 (20)	582 (21)
Renal insufficiency (SCr >2.0)	3,798 (19)	518 (19)
Anemia	2,811 (14)	510 (19)
Peripheral vascular disease	2,754 (14)	401 (15)
Thyroid abnormality	2,621 (13)	400 (15)
CVA/TIA (prior)	2,847 (14)	387 (14)
LVEF (%), mean (SD)	24.3 (7.7)	24.3 (7.8)
Weight admission (kg), mean (SD)	82.0 (24.4)	83.2 (24.2)
Heart rate admission (beats/min), mean (SD)	89.1 (21.7)	88.0 (21.4)
SBP admission (mm Hg), mean (SD)	135.2 (30.9)	133.2 (30.1)
DBP admission (mm Hg), mean (SD)	77.4 (20.0)	75.6 (19.5)
Rales, n (%)	12,502 (63)	1,661 (62)
Lower extremity edema, n (%)	12,132 (62)	1,680 (63)
JVD, n (%)	6,598 (33)	847 (31)
Serum creatinine admission (mg/dl), mean (SD)	1.7 (1.6)	1.6 (1.1)
Serum Na admission (mEq/l), mean (SD)	136.5 (11.4)	136.9 (8.7)
Hemoglobin admission (g/dl), mean (SD)	12.6 (3.2)	12.5 (2.4)
BNP admission (pg/ml), median (25th, 75th)	1,160 (597, 2,270)	1,130 (573, 2,360)
Troponin I admission (ng/ml), median (25th, 75th)	0.13 (0.06, 0.30)	0.19 (0.07, 0.40)

BNP = B-type natriuretic peptide; BP = blood pressure; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CVA/TIA = cerebral vascular accident/transient ischemic attack; DBP = diastolic blood pressure; HF = heart failure; JVD = jugular venous distention; LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic dysfunction; SBP = systolic blood pressure; SCr = serum creatinine.

0.027). Furthermore, there was no evidence that continuation of beta-blocker therapy was associated with increased risk of early rehospitalization (32.2% vs. 35.6%; HR: 0.86; 95% CI: 0.66 to 1.12, p = 0.25). Continuation of beta-blocker therapy was associated with a significantly lower risk of the combined mortality and/or rehospitalization end point (36.1% vs. 43.2%; odds ratio [OR]: 0.70; 95% CI: 0.54 to 0.91, p = 0.007). In unadjusted analyses, withdrawal of beta-blocker therapy was associated with substantially increased risk of post-discharge death compared with continuation of beta-blocker therapy (24.4% vs. 8.7%, HR: 2.82; 95% CI: 1.46 to 5.48, p = 0.002), but the death/rehospitalization rates were similar (Fig. 1, Table 3). When patients withdrawn from beta-blocker therapy were compared with patients eligible but not treated, mortality risk tended to be higher (HR: 1.69; 95% CI: 0.81 to 3.52, p = 0.16) (Table 3). Patients ineligible for beta-blocker therapy owing to contraindications or intolerance were also at high risk for adverse outcomes, with post-discharge mortality 13.1%, rehospitalization 30.8%, and death/rehospitalization 43.4%.

ADJUSTED ANALYSES. The influence of beta-blocker treatment on follow-up outcomes was tested in risk- and propensity-adjusted models. After adjustment for multiple

Table 2 Patient Characteristics of Follow-Up Cohort With LVSD by Beta-Blocker Treatment Group

	Eligible, Beta-Blocker Therapy Continued (n = 1,350)	Eligible, Beta-Blocker Therapy Newly Started (n = 632)	Eligible, Beta-Blocker Therapy Withdrawn (n = 79)	Eligible, Beta-Blocker Therapy Not Prescribed (n = 303)	p Value*
Mean age, yrs (SD)	69.3 (13.4)	67.0 (15.3)	69.3 (13.1)	72.4 (13.0)	<0.001
Female gender, n (%)	486 (36)	230 (36)	24 (30)	125 (41)	0.224
Race, n (%)					
Caucasian	1,027 (76)	438 (71)	54 (70)	227 (75)	0.025
African American	273 (20)	157 (25)	22 (29)	58 (19)	0.034
Hispanic ethnicity, n (%)	34 (3)	18 (3)	2 (3)	13 (4)	0.416
HF etiology, n (%)					
Ischemic	793 (59)	227 (36)	39 (49)	157 (52)	<0.001
Nonischemic	557 (41)	405 (64)	40 (51)	146 (48)	<0.001
Medical history, n (%)					
Insulin-treated diabetes	265 (20)	75 (12)	20 (25)	35 (12)	<0.001
Non–insulin-treated diabetes	365 (27)	143 (23)	21 (27)	82 (27)	0.197
Hypertension	963 (71)	404 (64)	51 (65)	198 (65)	0.004
CAD	831 (62)	233 (67)	42 (53)	153 (51)	<0.001
Hyperlipidemia	652 (48)	201 (32)	23 (29)	103 (34)	<0.001
Atrial arrhythmia	438 (32)	150 (24)	17 (22)	111 (37)	<0.001
Pulmonary/COPD	354 (26)	144 (23)	16 (20)	86 (28)	0.152
Cigarette smoker	263 (20)	168 (27)	12 (16)	68 (23)	0.003
Renal insufficiency	283 (21)	73 (12)	18 (23)	49 (16)	<0.001
Anemia	265 (20)	100 (16)	8 (10)	54 (18)	0.051
Peripheral vascular disease	226 (17)	64 (10)	12 (15)	42 (14)	0.002
Thyroid abnormality	190 (14)	77 (12)	16 (20)	51 (17)	0.100
CVA/TIA (prior)	204 (15)	58 (9)	12 (15)	52 (17)	0.001
LVEF (%), mean (SD)	24.4 (7.7)	24.1 (7.8)	21.7 (7.9)	25.5 (7.5)	0.001
SBP admission (mm Hg), mean (SD)	132.7 (29.3)	141.5 (30.6)	133.0 (27.4)	132.9 (26.5)	<0.001
DBP admission (mm Hg), mean (SD)	75.0 (18.3)	81.8 (20.1)	75.2 (16.4)	75.4 (16.7)	<0.001
Heart rate admission (beats/min), mean (SD)	84.4 (20.2)	95.9 (22.6)	83.7 (19.7)	90.6 (19.8)	<0.001
Rales admission, n (%)	816 (62)	382 (62)	48 (62)	181 (61)	0.986
Lower extremity edema admission, n (%)	828 (63)	395 (64)	51 (67)	172 (59)	0.464
JVD admission, n (%)	433 (37)	195 (36)	16 (24)	81 (31)	0.097
Serum Na admission (mEq/l), mean (SD)	137.7 (4.5)	138.0 (4.0)	136.4 (4.6)	137.7 (4.6)	0.056
Serum creatinine admission (mg/dl), mean (SD)	1.6 (1.2)	1.4 (1.0)	1.7 (0.9)	1.5 (0.9)	<0.001
Hemoglobin admission (g/dl), mean (SD)	12.6 (2.1)	12.8 (2.1)	12.7 (1.7)	12.5 (2.1)	0.014
BNP admission (pg/ml), median (25th, 75th)	1,120 (577, 2,270)	1,120 (587, 2,140)	1,224 (663, 2,815)	1,150 (668, 2,360)	0.664
Troponin I admission (ng/ml), median (25th, 75th)	0.2 (0.1, 0.4)	0.3 (0.1, 0.5)	0.2 (0.1, 0.3)	0.2 (0.1, 0.4)	0.001
SBP discharge (mm Hg), mean (SD)	118.7 (21.0)	118.8 (20.6)	121.0 (21.3)	119.2 (18.9)	0.519
DBP discharge (mm Hg), mean (SD)	65.7 (12.2)	68.0 (13.4)	68.9 (14.2)	66.4 (11.3)	0.001
Heart rate discharge (beats/min) mean (SD)	74.4 (13.1)	78.3 (14.4)	78.0 (14.6)	79.7 (14.6)	<0.001
Rales discharge, n (%)	169 (14)	59 (10)	5 (7)	37 (14)	0.074
Lower extremity edema discharge, n (%)	300 (26)	120 (22)	21 (31)	69 (27)	0.112
JVD discharge, n (%)	65 (5)	29 (5)	3 (4)	8 (3)	0.403
Post-discharge mortality risk point score (SD)†	42.5 (7.8)	39.4 (8.6)	43.3 (9.0)	42.9 (7.6)	<0.001
Expected post-discharge mortality risk (%), mean (SD)†	5.7 (4.7)	4.6 (4.3)	6.7 (6.9)	5.8 (4.5)	<0.001

*Pearson chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. †OPTIMIZE-HF 60 and 90 days post-discharge mortality risk score and projected mortality based on admission characteristics entered into a previously derived and validated model.

Abbreviations as in Table 1.

variables predictive of post-discharge mortality as well as propensity for beta-blocker use and correlation of data within the same hospital, continuation of beta-blocker therapy, when compared with no beta-blocker use among eligible patients, was still associated with a reduced risk of all-cause mortality in the first 60 to 90 days after hospital discharge (HR: 0.60; 95% CI: 0.37 to 0.99, p = 0.044) (Table 4). Continuation of beta-blocker therapy was also associated with lower post-discharge mortality/rehospitalization. Newly started beta-blocker therapy was also associated with improved outcomes compared to no beta-blocker use among eligible patients (Table 4). In contrast, after risk and propensity adjustment, withdrawal of beta-blocker therapy was associated with a substantially higher risk of death compared with continuation of beta-blocker therapy (HR: 2.34; 95% CI: 1.20 to 4.55, p =

Table 3 Clinical Outcomes of Follow-Up Cohort With LVSD by Beta-Blocker Treatment Group: Unadjusted

	Eligible, Follow-Up Cohort With LVSD (n = 2,373)	Eligible, Beta-Blocker Therapy Continued (n = 1,350)	Eligible, Beta-Blocker Therapy Newly Started (n = 632)	Eligible, Beta-Blocker Therapy Withdrawn (n = 79)	Eligible, Beta-Blocker Therapy Not Prescribed (n = 303)	p Value
Median length of stay, days (IQR)	5.0 (3, 8)	4.0 (3, 7)	5.0 (3, 8)	6.0 (3, 9)	5.0 (3, 8)	<0.001*
Mean length of stay, days (SD)	6.4 (7.0)	6.1 (6.7)	6.7 (6.2)	7.1 (5.4)	7.2 (10.0)	<0.001*
60- to 90-day post-discharge mortality, %	8.7	8.7	4.5	24.4	13.8	<0.001†
60- to 90-day readmission, %	30.2	32.2	24.1	24.1	35.6	<0.001‡
60- to 90-day mortality and/or rehospitalization, %	34.8	36.1	27.5	37.7	43.2	<0.001‡

*Kruskal-Wallis test; †log-rank test; ‡Pearson chi-square test.
IQR = interquartile range; LVSD = left ventricular systolic dysfunction.

0.013). However, these withdrawal patients were at similar post-discharge risk to those eligible but not treated with beta-blockers (Table 4).

TOLERABILITY. During the 60- to 90-day post-discharge follow-up period, continuation of beta-blocker therapy was very well tolerated, as evidenced by 93.6% of patients remaining on beta-blocker therapy after discharge. Newly starting beta-blocker therapy was also well tolerated, with 91.9% of patients remaining on therapy. Of the cohort of eligible patients who were not prescribed beta-blocker therapy either before admission or at time of hospital discharge, only 23.9% were started on beta-blocker therapy after discharge within the 60- to 90-day follow-up period (continued cohort 93.6% vs. not-treated cohort 23.9%, OR: 46.7, 95% CI: 32.1 to 68.0, $p < 0.0001$). Eligible patients in whom beta-blocker therapy was withdrawn during hospitalization were also less likely to be receiving treatment during 60- to 90-day post-discharge follow-up, with only 56.5% restarted on therapy (continued cohort 93.6% vs. withdrawn cohort 56.5%; OR: 11.3, 95% CI: 6.5 to 19.7, $p < 0.0001$). For patients continued on beta-blockers, 88.2% were maintained on at least their admission dose of medication (72.9% same dose and 15.3% increased) during the hospitalization and 11.8% had their dosage reduced. During the first 60 to 90 days of post-discharge follow-up, the discharge dose of beta-blockers was reduced in only 11.7% of patients, maintained in 73.4%, and increased in 15%.

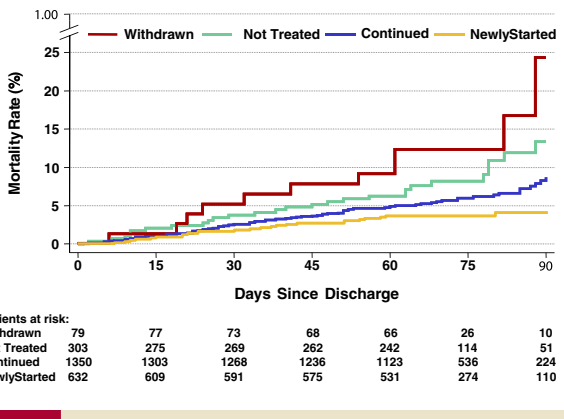

Figure 1 Post-Discharge Survival by Beta-Blocker Treatment Groups

Kaplan-Meier survival curves by beta-blocker treatment groups. Log-rank test: $p < 0.001$.

Subgroups. In the risk- and propensity-adjusted model for mortality and the combined model for mortality and/or rehospitalization, the association of continuation of beta-blocker therapy with improved outcomes was consistent in all clinically relevant subgroups examined, including age, gender, race, diabetes status, chronic obstructive pulmonary disease status, and renal function. The risk-adjusted mortality and mortality/rehospitalization rates were similar for patients in whom the beta-blocker dosage was reduced during hospitalization compared with those in whom beta-blocker dosage was maintained or increased (death/rehospitalization 36.6% vs. 37.2%, OR: 0.91, 95% CI: 0.61 to 1.36, $p = 0.64$).

Discussion

The OPTIMIZE-HF program provides an important opportunity to evaluate the influence of continuation and withdrawal of beta-blocker therapy during hospitalization for HF. This registry contains substantially more detailed information on patient characteristics, presenting symptoms, treatments, and outcomes than has previously been available in administrative datasets or other registries (12). In this detailed analysis, the vast majority of hospitalized HF patients who were treated with beta-blockers before admission were able to be continued on beta-blocker therapy during the hospitalization. Continuation of beta-blocker therapy was associated with substantially lower risk and propensity adjusted post-discharge mortality risk. Withdrawal of beta-blockers was associated with excess adjusted mortality risk. In addition, continuation of beta-blocker therapy was well tolerated after discharge, and substantially more patients were treated as outpatients with this strategy. These findings extend the results of prior observational analyses among select participants in random-

Table 4 Effect of Beta-Blocker Treatment Group on All-Cause Mortality and Death/Rehospitalization at 60 to 90 Days After Discharge: Risk- and Propensity-Adjusted Analyses

	n	Hazard Ratio	95% Confidence Interval	p Value
Mortality				
Continued on beta-blocker therapy versus eligible but not treated	1,350 vs. 303	0.60	0.37–0.99	0.044
Newly started on beta-blocker therapy versus eligible but not treated	632 vs. 303	0.41	0.22–0.78	0.006
Withdrawn from beta-blocker therapy versus eligible but not treated	79 vs. 303	1.41	0.76–2.61	0.277
Withdrawn from beta-blocker therapy versus continued on beta-blocker therapy	79 vs. 1,350	2.34	1.20–4.55	0.013
Mortality/rehospitalization				
Continued on beta-blocker therapy versus eligible but not treated	1,350 vs. 303	0.69	0.52–0.92	0.012
Newly started on beta-blocker therapy versus eligible but not treated	632 vs. 303	0.61	0.44–0.83	0.002
Withdrawn from beta-blocker therapy versus eligible but not treated	79 vs. 303	0.77	0.44–1.35	0.360
Withdrawn from beta-blocker therapy versus continued on beta-blocker therapy	79 vs. 1,350	1.11	0.67–1.85	0.689

ized clinical trials to a diverse cohort of patients hospitalized with HF in the usual care setting from all regions of the country and have significant clinical implications.

Neurohormonal inhibition is the foundation of modern systolic HF management. A meta-analysis of 22 placebo-controlled randomized beta-blocker trials involving 10,132 chronic systolic HF patients demonstrated an OR for total mortality of 0.65 (95% CI: 0.53 to 0.80) in favor of beta-blocker use (19). Accordingly, national practice guidelines (5,6) recommend use of beta-blockers in all stable outpatients with systolic HF in the absence of contraindications on the basis of their proven ability to significantly reduce mortality in these patients. In contrast to the compelling evidence for beta-blocker use in the chronic stable setting, whether beta-blocker therapy should be continued during hospitalization among decompensated HF patients is a commonly encountered and important clinical issue for which little data exist.

There have been no randomized clinical trials and relatively little observational data on the impact of continuing or withdrawing beta-blocker therapy after hospitalization for worsening HF. A retrospective analysis of patients enrolled in the OPTIME-CHF (Outcomes of the Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure) study (8) reported worse outcomes for the 47 patients in whom beta-blocker were withdrawn of the 212 patients treated with beta-blockers at the time of the admission for acute decompensated HF. A retrospective analysis of patients enrolled in FIRST (Flolan International Randomized Survival Trial) (9) reported no excess risk for patients treated with beta-blockers at the time of hospital presentation for HF. A study of patients receiving beta-blockers at the time of HF hospitalization in the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization) trial showed that 268 of 432 patients who remained on beta-blocker therapy had a shorter length of stay and lower 6-month mortality rate (11). Continuation versus withdrawal of beta-blocker therapy remained independently associated with lower mortality in a multivariable analysis (11). In an analysis of COMET (Carvedilol or Metoprolol European Trial), 752 of 3,029 patients had a nonfatal HF hospitalization while receiving study beta-blocker treatment (10). Of these, 529 (70%) of patients were continued on beta-blocker therapy at the same dose, 162 (22%) had a dose reduction, and 61 patients (8%) had beta-blocker treatment withdrawn. The risk of death was higher in patients in whom beta-blocker therapy was discontinued or for whom the dose was reduced compared with those patients who were continued on beta-blocker therapy (10).

Each of these prior analyses included select patients enrolled and followed in randomized clinical trials. The mean age of the patients was approximately 64 years, 75% were men, and comorbidities were relatively infrequent (8–11). As these patients were treated in clinical trials with investigators and coordinators with considerable experience in managing patients with HF, these studies cannot provide information as to whether similar results can be expected in the general group of patients hospitalized with HF. Our results in real-world patients in the usual care setting

involving clinicians and hospitals from all regions of the country show that discontinuation of beta-blocker therapy during a HF hospitalization is associated with substantially worse risk-adjusted outcomes compared to continuation. These findings were derived from a broad cohort with a high proportion of older HF patients with multiple comorbidities who are more representative of those seen in general practice (12,13).

The decision to discontinue beta-blocker therapy in certain patients hospitalized with HF may be related to a greater state of patient decompensation, which may account for poor outcomes among these patients rather than the withdrawal of beta-blocker therapy per se (10). Though withdrawal of beta-blockers was associated with a few indicators of more severe HF, it remained significantly and independently associated with increased mortality after adjustment for multiple covariates and propensity score. In the absence of symptomatic bradycardia, symptomatic hypotension, or cardiogenic shock, the decision to discontinue beta-blocker therapy among these patients is based primarily on clinical judgment, likely influenced by individual clinician experience (11). Patients who were continued on beta-blocker therapy had similar admission vital signs, physical exam findings, and laboratories to those in whom beta-blocker therapy was discontinued. In this study, improved outcomes with continued beta-blocker therapy persisted after controlling for factors associated with the decision to discontinue beta-blocker therapy and those associated with post-discharge outcomes. However, with an observational analysis, it is possible that not all factors that may have influenced the decision to continue, withdraw, or not initiate beta-blocker therapy have been fully captured, and these unmeasured factors may influence the findings.

Abrupt cessation of beta-blockers has been reported to be associated with ischemia, hypertension, ventricular arrhythmias, and, in some cases, myocardial infarction (20,21). Withdrawal of beta-blocker therapy in patients hospitalized with HF thus could be associated with outcomes worse than having never been treated in the first place. In this study, HF patients in whom beta-blocker therapy was withdrawn were at higher risk for mortality and death/rehospitalization in the first 60 to 90 days compared with those continued, but this risk was not significantly different from those eligible but not treated. However, as there was a trend for worse outcomes, further study will be necessary to determine whether withdrawal of beta-blockers is associated with increased risk beyond that of not deriving the benefits on ongoing beta-blocker treatment in this patient population.

Several recent studies (22–24) have reported that many HF patients who are candidates for beta-blockers do not receive them. In addition, the rate of beta-blocker prescriptions at hospital discharge is lowest for patients at the greatest risk of death, who in fact derive the most benefit from their use (24). In an analysis of 103 acute-care hospitals in Ontario, Canada, comprising 1,418 patients with LVEF ≤40%, beta-blockers were prescribed to 40% of the lowest-risk patients but to only 23% with the highest risk of death on the basis of a previously derived and validated 1-year mortality risk prediction model (24). Medication prescription at the time of discharge has been shown to be the strongest predictor of long-term adherence to drug therapy (25,26). Discontinuation of evidence-based HF medications during hospital admission, when not absolutely necessary, thus can have deleterious effects on treatment rates and long-term clinical outcomes. As shown in this study, when beta-blocker therapy was disrupted during hospitalization, a substantial proportion of patients did not have this therapy re-initiated after discharge. In a prospective longitudinal follow-up study in a cohort of consecutive patients with chronic HF seen at a specialized HF outpatient clinic (23), the most common reason for systolic HF patients not to be treated with beta-blocker therapy was discontinuation during hospitalization and failure to restart treatment despite the absence of contraindications. Continuation of beta-blocker therapy during HF hospitalization, whenever possible, represents an important strategy to improve overall treatment rates with this guideline-recommended therapy.

Study limitations. The reason(s) for beta-blocker continuation and withdrawal during hospitalization were not collected; therefore, we cannot determine the specific rationale for these treatment decisions. Contraindications and intolerance were as documented in the medical record. A proportion of patients reported to be eligible for beta-blocker therapy but not treated may have had contraindications or intolerance (before hospitalization or in-hospital) that were present but not documented. Medication use in this study was as reported by patients and as documented in the medical record; actual adherence rates may have been lower. Follow-up data were limited to the first 60 to 90 days after discharge, and only a subset of hospitals and patients participated in the collection of follow-up data. OPTIMIZE-HF was not a randomized clinical trial, and, therefore, interpretation of results is subject to limitations. Despite covariate adjustment and propensity matching, other measured and unmeasured factors may have influenced improvements in clinical outcomes associated with continuation of beta-blocker therapy. These findings may not apply to hospitals that differ in patient characteristics or care patterns from OPTIMIZE-HF hospitals, although a recent study (27) suggests that patients enrolled in OPTIMIZE-HF have similar demographics to those hospitalized nationally.

Conclusions

Data from this study of a large, representative cohort of HF patients indicate that continuation of beta-blocker therapy among patients hospitalized with HF is associated with better outcomes than those in whom beta-blocker therapy is withdrawn or never initiated. These results persisted even after controlling for differences between the patient groups. In addition, continuation of beta-blocker therapy was very well tolerated, with 93.6% of those continued and dis-

charged on beta-blocker therapy remaining on treatment during follow-up. The HF patients withdrawn from beta-blockers during hospitalization were substantially less likely to be treated with beta-blockers after discharge, which likely contributed to these patients' poor outcomes. These findings suggest that routine discontinuation of beta-blocker therapy on hospital admission is neither necessary nor advisable, and the majority of patients hospitalized for HF are eligible for beta-blocker therapy to be continued. The present study provides real-world support of recent guideline recommendations that, whenever possible, beta-blocker therapy should be continued in patients hospitalized with HF.

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Key Words: heart failure ■ beta-blockers ■ mortality ■ registry.

APPENDIX

For a list of variables included in multivariable analysis, please see the online version of this article.