Published by Elsevier Inc.

ISSN 0735-1097/04/$30.00
doi:10.1016/j.jacc.2003.12.040

Predischarge Initiation of Carvedilol in Patients Hospitalized for Decompensated Heart Failure

Results of the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) Trial

Wendy A. Gattis, PharmD,* Christopher M. O'Connor, MD, FACC,* Dianne S. Gallup, MS,* Vic Hasselblad, PhD,* Mihai Gheorghiade, MD, FACC,† on behalf of the IMPACT-HF Investigators and Coordinators

Durham, North Carolina; and Chicago, Illinois

OBJECTIVES The Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) trial was an investigator-initiated study to evaluate if predischarge carvedilol initiation in stabilized patients hospitalized for heart failure (HF) increased the number of patients treated with beta-blockade at 60 days after randomization without increasing side effects or length of hospital stay.

BACKGROUND Beta-blockers are underused in HF. Predischarge initiation may improve the use of evidence-based beta-blockade.

METHODS The IMPACT-HF was a prospective, randomized open-label trial conducted in 363 patients hospitalized for HF. Patients were randomized to carvedilol initiation pre-hospital discharge or to postdischarge initiation (>2 weeks) of beta-blockade at the physicians' discretion. The primary end point of the study was the number of patients treated with beta-blockade at 60 days after randomization. Secondary end points included the number of patients discontinuing beta-blockade, median dose achieved, and a composite of death, rehospitalization, unscheduled visit for HF, or ≥50% increase in oral diuretic, new oral diuretic, or any intravenous therapy with diuretics, inotropes, or other vasoactive agents.

RESULTS At 60 days 165 patients (91.2%) randomized to predischarge carvedilol initiation were treated with a beta-blocker, compared with 130 patients (73.4%) randomized to initiation postdischarge ($p < 0.0001$). Predischarge initiation was not associated with an increased risk of serious adverse events. The median length of stay was five days in both groups.

CONCLUSIONS Predischarge initiation of carvedilol in stabilized patients hospitalized for HF improved the use of beta-blockade at 60 days without increasing side effects or length of stay. Predischarge initiation may be one approach to improve beta-blocker use in this population. (J Am Coll Cardiol 2004;43:1534–41) © 2004 by the American College of Cardiology Foundation

Data from clinical trials have confirmed the role of specific beta-blockers (carvedilol, metoprolol succinate XL, bisoprolol) in the management of mild, moderate, and severe heart failure (HF) (1–3). The most recent American College of Cardiology/American Heart Association and the Heart Failure Society of America (HFSA) HF guidelines recommend the use of beta-blockade in all patients with chronic HF and reduced systolic function who are without contraindications to beta-blockers (4,5). The HFSA guidelines recommend that, in general, beta-blockers should not be routinely initiated during a hospitalization for worsening HF (5).

Despite the substantial body of evidence demonstrating the lifesaving benefits of beta-blockade as HF treatment, these drugs are underprescribed in the majority of patients (6,7). New strategies are clearly needed to identify effective methods of improving the use of evidence-based therapies because hospitalizations for worsening HF are occurring at an alarming rate, with more than three million patients admitted annually with a primary or secondary HF diagnosis (8). The Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) trial was an investigator-initiated protocol designed to evaluate whether a strategy of carvedilol initiation pre-hospital discharge would be effective at improving the use of beta-blockade at 60 days post-randomization without increasing side effects or length of initial hospital stay in patients hospitalized for HF.

METHODS

The Duke University Cooperative Cardiovascular Studies (DUCCS) investigators conducted the study. The trial operations, site management, data management, and statistical analyses were performed independently of the study sponsor by the Duke Clinical Research Institute (DCRI). The IMPACT-HF study was a prospective, randomized open-label trial of carvedilol initiation predischarge compared with standard practice, which was defined as postdischarge initiation of any beta-blocker no earlier than two weeks after discharge at the physician's discretion. The detailed study design has been published (9). The study

From the *Division of Cardiology, Duke University Medical Center and Duke Clinical Research Institute, Durham, North Carolina; and †Division of Cardiology, Northwestern University/Feinberg School of Medicine, Chicago, Illinois. The IMPACT-HF trial was funded by GlaxoSmithKline, Philadelphia, Pennsylvania.

Manuscript received August 15, 2003; revised manuscript received November 30, 2003, accepted December 2, 2003.

Abbreviations and Acronyms

ADHERE	= Acute Decompensated Heart Failure National Registry
DCRI	= Duke Clinical Research Institute
DSMB	= Data Safety Monitoring Board
HF	= heart failure
HFSA	= Heart Failure Society of America
IMPACT-HF	= Initiation Management Pre-Discharge: Assessment of Carvedilol Therapy for Heart Failure

enrolled 363 patients from 45 centers across the U.S. Patients could enter the study if they had left ventricular ejection fraction <40% and were hospitalized with a primary diagnosis of HF. Patients were ineligible if they met any of the following criteria: treatment with any beta-blocker within 30 days before randomization; decompensated New York Heart Association functional class IV HF requiring inotropic support at randomization; second- or third-degree atrioventricular block, sick sinus syndrome, or symptomatic bradycardia without a functional pacemaker; bronchial asthma or related bronchospastic conditions; symptomatic hypotension defined by the investigator; cardiogenic shock; expected survival <60 days; hypersensitivity to carvedilol; clinically manifest hepatic impairment; or being pregnant or lactating. The protocol was reviewed and approved by the Data Safety Monitoring Board (DSMB) and the local institutional review board at each institution. All patients provided written informed consent.

Patients were randomized 1:1 using an interactive voice-recognition system to receive either carvedilol initiation predischarge (3.125 mg twice daily) or beta-blocker initiation postdischarge at the physician's discretion. Patients randomized to carvedilol initiation predischarge could receive carvedilol at any point after the principal investigator deemed the patient to be stable from a HF standpoint, but no later than 12 h before discharge. The goal was to administer at least one dose before discharge. The postdischarge initiation arm was based on HFSA HF practice guidelines (5). These guidelines recommended waiting at least two weeks post-hospital discharge before initiating beta-blockade. In this group, physicians could choose whether or not to institute beta-blocker therapy at their discretion provided it was at least two weeks after hospital discharge. Physicians were not required per protocol to see patients in clinic at two weeks post-discharge, nor were they required to initiate beta-blockade at two weeks postdischarge. It was up to the physician's discretion to determine the appropriate time of follow-up for each patient in both groups, and it was the physician's choice to determine when and if to initiate beta-blockade in the postdischarge initiation arm. The protocol did not mandate which beta-blocker should be prescribed in this group; however, the protocol recommended that only those beta-blockers with a Food and Drug Administration-approved indication for HF (carvedilol or metoprolol succinate XL) should be used. The sponsor did not communicate with the investigators to influence the use of beta-blockers in the study groups. All site contact was made by the DCRI. Patients in both groups were contacted by the study coordinator at 30 and 60 days after randomization to determine the patient's current medical regimen. Detailed information on beta-blocker initiation, titration, and discontinuation was collected. The occurrence of clinical events was also documented. The method of contact (i.e., telephone, in-clinic) was determined by each site in the trial. Patients were not required per protocol to be evaluated in clinic at specified time points.

The primary end point of the study was the number of patients treated with any beta-blocker at 60 days after randomization. Several secondary end points were also prespecified, including median beta-blocker dose prescribed; number of patients requiring discontinuation of beta-blockade; median time to discontinuation of beta-blockade; and a composite end point of time to death, recurrent hospitalization, unscheduled visit for HF, ≥50% increase in oral diuretic therapy, addition of new oral diuretic therapy excluding spironolactone, or any intravenous therapy with diuretics, inotropes, inodilators, or other vasoactive agents within 60 days post-randomization.

All nonserious adverse events and serious adverse events were reported to the DCRI Safety Desk. An independent DSMB reviewed all serious adverse events in this study at prespecified time points. At each review point, the DSMB allowed the trial to continue.

The calculated sample size for the study was based on several assumptions. It was estimated that 35% of patients randomized to the physician-discretion postdischarge initiation arm would be treated with beta-blockers at 60 days, and the predischarge initiation of carvedilol would increase the use of beta-blockers at 60 days to 50%. At an alpha level of 0.05, 375 patients would provide 80% power to detect a significant difference in the rate of beta-blocker use between groups.

As the study was nearing completion, the sample size estimates were reevaluated using the pooled blinded rate of beta-blocker use in the study population. This analysis demonstrated the study had adequate power with 360 patients to detect a significant difference as small as 17% between treatment groups. Thus, enrollment was closed after 363 patients had been enrolled.

Statistical methods. Statistical analyses were performed using SAS Version 8.2 on the UNIX system (SAS Institute, Cary, North Carolina). The Pearson chi-square test was used to evaluate the primary end point. Secondary end points represented as continuous variables were analyzed using the Wilcoxon rank-sum test. The secondary end points represented as proportions were analyzed using the Pearson chi-square test. Fisher's exact test was used to test differences in death alone and differences in unscheduled visits for HF alone because the number of these events was small.

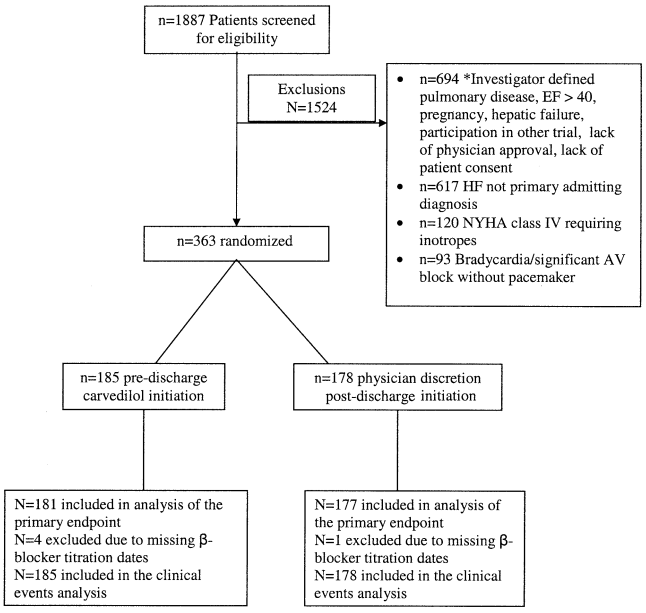

Figure 1. Study outline. Patients with reactive airway disease were excluded per protocol, but patients with chronic obstructive pulmonary disease were allowed. The investigator made the determination of pulmonary disease too severe for the patient to be enrolled. AV = atrioventricular; EF = ejection fraction; HF = heart failure; NYHA = New York Heart Association.

Kaplan-Meier survival curves were produced for the primary composite as well as 60-day death + rehospitalization.

For a difference in proportions between the randomized groups for beta-blocker use at 60 days and clinical events at 60 days, 95% confidence intervals were calculated. The variance was calculated for each proportion to obtain the standard error of the difference. This standard error was then used to calculate 95% asymptotic confidence limits of the difference using the normal approximation to the binomial.

RESULTS

A total of 363 patients were enrolled into the IMPACT-HF trial (Fig. 1). The first patient was enrolled in May 2001. The last patient follow-up was October 2002. The majority of patients were cared for by community-based cardiologists, with a smaller percentage of patients cared for by internal or family medicine. There was no difference in the distribution of physician type between groups. The median age was 67 years, 47% were women, and 35% were of minority ethnic origin. The baseline demographics of the population were similar between groups (Table 1). The baseline clinical characteristics (Table 2) reflect a population of patients with evidence of worsening HF and congestion on admission. The median time from admission to randomization was 60.9 h. The use of standard HF medication was similar between the predischarge initiation and postdischarge physician-discretion groups, respectively: angiotensin-converting enzyme inhibitors (74.6% vs. 74.2%), angiotensin receptor blockers (8.6% vs. 6.2%), digoxin (50.8% vs. 42.1%), diuretic (80% vs. 82.6%), spironolactone (27% vs. 28.1%). On average, symptoms of worsening HF and volume overload improved during the period from admission to randomization; however, patients still had some evidence of congestion at the time of randomization, as reflected by one-third of the population with rales. By the time of discharge, patients' symptoms of HF had improved but had not completely resolved (Table 2).

Table 1. Baseline Characteristics

	Predischarge Carvedilol Initiation (n = 185)	Physician-Discretion Postdischarge Initiation (n = 178)
Median age (25th, 75th)	68 (55, 77)	66 (52, 76)
Male (%)	97 (52.4)	96 (53.9)
Caucasian (%)	118 (63.8)	116 (65.2)
Ischemic etiology (%)	71 (43.6)	78 (48.1)
Median LVEF (25th, 75th)	25 (20, 30)	25 (20, 30)
Hypertension (%)	113 (61.1)	118 (66.3)
Atrial arrhythmia (%)	37 (20)	42 (23.6)
Ventricular arrhythmia (%)	15 (8.1)	18 (10.1)
Hyperlipidemia (%)	54 (29.2)	53 (29.8)
Diabetes (%)	68 (36.8)	73 (41)
Chronic renal insufficiency	20 (10.8)	20 (11.2)
Pulmonary disease (%)	28 (15.1)	21 (11.8)
Median hours from admission to randomization (25th, 75th)	61.9 (30.9, 95.6)	60.0 (34.4, 108.8)

LVEF = left ventricular ejection fraction.

The primary analysis of the trial showed that patients randomized to carvedilol initiation predischarge were more likely to be treated with any beta-blocker at 60 days as compared to patients randomized to the physician-discretion postdischarge beta-blocker initiation arm (91.2% vs. 73.4%, $p < 0.0001$) (Table 3). Patients were also more likely to reach a higher percentage of the target beta-blocker dose if they were randomized to predischarge initiation as compared with those who were not (Table 4). The mean percentage of target dose achieved for the carvedilol initiation group was 36.3% compared with 28.6% for the patients in the postdischarge initiation arm. There was a difference in the distribution of percentage of target beta-blocker dosage between the two treatment groups. A shift towards larger percentages was seen in the predischarge carvedilol initiation arm when compared with the postdischarge initiation arm ($p = 0.02$). The median time to initiation of a beta-blocker after randomization was 0 days for the carvedilol predischarge initiation group versus 17 days in the postdischarge beta-blocker initiation group. There appeared to be no difference in the need for permanent beta-blocker discontinuation between the two groups, with 10.5% of carvedilol predischarge initiation patients having their beta-blocker permanently discontinued during the 60 days of follow-up as compared with 10.6% of the postdischarge beta-blocker initiation group. Of those patients who had their initial beta-blocker discontinued, patients in the arm initiated on a beta-blocker ≥2 weeks postdischarge discontinued beta-blocker therapy sooner (8 days) as compared

Table 2. Heart Failure Signs and Symptoms

	Predischarge Carvedilol Initiation n = 185			Physician-Discretion Postdischarge Initiation n = 178		
	Admission	Randomization	Discharge	Admission	Randomization	Discharge
Weight (kg)	80 (64, 95)	79 (65, 95)	79 (63, 92)	82 (70, 99)	81 (68, 99)	80 (66, 97)
Systolic blood pressure (mm Hg)	135 (118, 150)	123 (107, 138)	119 (107, 134)	136 (120, 159)	125 (110, 139)	121 (108, 135)
Diastolic blood pressure (mm Hg)	79 (70, 89)	69 (60, 80)	69 (60, 76)	80 (70, 95)	70 (60, 82)	70 (61, 78)
Heart rate (beats/min)	91 (78, 104)	84 (73, 94)	78 (70, 86)	90 (81, 106)	83 (74, 94)	81 (72, 89)
Serum sodium (mmol/l)	139 (136, 141)	138 (136, 140)	ND	138 (135, 141)	138 (135, 140)	ND
Serum creatinine (μmol/l)	97.20 (79.6, 132.6)	97.2 (79.6, 132.6)	ND	106.1 (79.6, 132.6)	106.1 (79.6, 132.6)	ND
NYHA functional class						
I	8 (5)	13 (7.3)	21 (12.4)	14 (8.6)	15 (8.6)	28 (16.7)
II	47 (29.6)	59 (33.1)	79 (46.7)	46 (28.2)	61 (35.1)	92 (54.8)
III	70 (44)	86 (48.3)	61 (36.1)	77 (47.2)	86 (49.4)	47 (28)
IV	34 (21.4)	20 (11.2)	8 (4.7)	26 (16)	12 (6.9)	1 (0.6)
JVD (%)	57 (35.2)	29 (17.2)	12 (7.7)	46 (28.6)	21 (13)	6 (4.1)
S3 (%)	44 (24.4)	42 (22.7)	22 (12.6)	30 (17)	23 (13.2)	13 (7.6)
Rales (%)	106 (57.9)	60 (32.8)	28 (15.8)	97 (54.5)	55 (31.1)	16 (9.2)
Edema (%)						
1+	50 (49.5)	47 (66.2)	43 (86)	45 (47.9)	40 (52.6)	38 (76)
2+	30 (29.7)	15 (21.1)	5 (10)	27 (28.7)	25 (32.9)	10 (20)
3+	14 (13.9)	8 (11.3)	1 (2)	17 (18.1)	10 (13.2)	1 (2)
4+	7 (6.9)	1 (1.4)	1 (2)	5 (5.3)	1 (1.3)	1 (2)
Fatigue (%)*	95 (51.9)	111 (60)	105 (56.8)	97 (54.5)	120 (67.4)	102 (57.3)
Orthopnea (%)*	90 (49.2)	50 (27)	19 (10.3)	90 (50.6)	63 (35.4)	24 (13.5)
Paroxysmal nocturnal dyspnea (%)*	68 (37.2)	35 (18.9)	7 (3.8)	51 (28.7)	34 (19.1)	6 (3.4)
Dyspnea on exertion (%)*	145 (79.2)	146 (78.9)	110 (59.5)	141 (79.2)	130 (73)	102 (57.3)
Dyspnea at rest (%)*	75 (41)	47 (25.4)	13 (7)	77 (43.3)	36 (20.2)	9 (5.1)

Values are given as median (25th, 75th) percentiles or number (%). *Patients can be double counted.
JVD = jugular venous distention; NYHA = New York Heart Association.

with those patients randomized to carvedilol predischarge initiation (14 days), suggesting that predischarge initiation was not associated with an early withdrawal rate due to intolerance or adverse effects. The rates of worsening HF, hypotension, and bradycardia requiring drug discontinuation were low and did not appear to be different between groups (Table 5). Importantly, the length of hospital stay was not increased in the predischarge initiation arm; the median (25th, 75th percentile) length of stay was five days (3,8) for both groups.

The study was not powered to detect significant differences in clinical outcomes; however, we evaluated a composite clinical secondary end point as described in the methods section to assess whether predischarge initiation might have any early adverse effect. In the predischarge carvedilol initiation arm, 45.4% of patients experienced the composite end point, as compared with 46.1% of patients randomized to the postdischarge beta-blocker initiation arm ($p = 0.9$). Each component of the composite was also evaluated separately, and there was no difference between

Table 3. Beta-Blocker Use at 60 Days Postdischarge

	Carvedilol Initiation Predischarge n = 185	Physician-Discretion Postdischarge Initiation n = 178	95% CI for Difference in Proportions†
Patients treated with any beta-blocker at 60 days (%)	*165 (91.2)	130 (73.4)	−0.2542, −0.1
Carvedilol	159	113	
Metoprolol succinate XL	2	8	
Metoprolol tartrate IR	4	5	
Atenolol	0	4	
Any beta-blocker initiated (%)	185 (100)	142 (79.8)	−0.2613, −0.1432
‡Discontinued and restarted at least once (%)	12 (6.6)	8 (5.7)	−0.0622, 0.0431
Discontinued and never restarted (%)	19 (10.5)	15 (10.6)	−0.663, 0.0691

*$p < 0.0001$; †difference = physician discretion-carvedilol initiation; ‡denominator for predischarge initiation = 181; denominator for postdischarge initiation = 141.
CI = confidence interval.

Table 4. Percent of Target Dose Achieved for Carvedilol, Bisoprolol, Metoprolol Tartrate IR or Metoprolol Succinate XL at Day 60

% of Beta-Blocker Target Dosage	Carvedilol Initiation Predischarge n = 165	Physician-Discretion Postdischarge Initiation n = 126
6.25%	3 (1.8)	4 (3.2)
12.5%	35 (21.2)	41 (32.5)
18.75%	8 (4.8)	2 (1.6)
25%	60 (36.4)	45 (35.7)
37.5%	2 (1.2)	0 (0)
50%	38 (23)	30 (23.8)
100%	19 (11.5)	4 (3.2)

Data are presented as n (%). Wilcoxon rank-sum produced a p value of 0.02. Target dose for carvedilol 50 mg/day. Target dose for metoprolol tartrate IR or metoprolol succinate XL 200 mg/day. 6.25% of target = 3.125 mg/day carvedilol; 12.5 mg/day metoprolol tartrate IR or metoprolol succinate XL. 12.5% of target = 6.25 mg/day carvedilol; 25 mg/day metoprolol tartrate IR or metoprolol succinate XL. 18.75% of target = 9.375 mg/day carvedilol; 37.5 mg/day metoprolol tartrate IR or metoprolol succinate XL. 25% of target = 12.5 mg/day carvedilol; 50 mg/day metoprolol tartrate IR or metoprolol succinate XL. 37.5% of target = 18.75 mg/day carvedilol; 75 mg/day metoprolol tartrate IR or metoprolol succinate XL. 50% of target = 25 mg/day carvedilol; 100 mg/day metoprolol tartrate IR or metoprolol succinate XL. 100% of target = 50 mg/day carvedilol; 200 mg/day metoprolol tartrate IR or metoprolol succinate XL.

the groups for any of the individual components (Table 6). A nonsignificant trend towards a lower rate of the composite of death or rehospitalization was observed for the predischarge carvedilol initiation group as compared with patients randomized to the postdischarge physician-discretion arm (Fig. 2). The time to first event in the main composite was longer, but not significantly, for patients randomized to the predischarge carvedilol initiation group (22 days vs. 15.5 days, $p = 0.21$). Thus, there was no evidence of early worsening with predischarge carvedilol initiation based on the individual components or on the composite end point.

DISCUSSION

Several databases have demonstrated the underuse of beta-blockers among HF patients. The recent IMPROVEMENT HF program was conducted in 15 Western European countries among 1,363 primary care physicians and enrolled 11,062 patients. In this population, only 34% were receiving a beta-blocker and only 20% were receiving both an angiotensin-converting enzyme inhibitor and a beta-blocker (6). The Acute Decompensated Heart Failure National Registry (ADHERE) is a prospective observational registry among 250 centers that will enroll more than 100,000 patients hospitalized with a principal diagnosis of HF. Preliminary data from this registry suggest that beta-blockers are prescribed in only 47% of eligible patients at admission. The percentage of patients treated increased to 58% at discharge, an increase of only 11% (7,10).

Table 5. Withdrawal Due to Serious Adverse Events

	Carvedilol Initiation Predischarge n = 185	Physician-Discretion Postdischarge Initiation n = 178
Hypotension (%)	*3 (1.6)	1 (0.6)
Bradycardia (%)	†3 (1.6)	0
Worsening heart failure (%)	1 (0.5)	3 (1.7)

*One patient with a serious adverse event attributed to hypotension also had new-onset atrial flutter with rapid ventricular response and one patient with a serious adverse event attributed to hypotension was receiving milrinone. †One patient who experienced a serious adverse event attributed to bradycardia also had digoxin toxicity.

There are several reasons for the underuse of beta-blockade. First, standard practice guidelines have recommended that beta-blocker initiation should be avoided in patients with a recent decompensation or hospitalization for HF because of a concern that beta-blockers may worsen HF symptoms (5). Second, physicians may be reluctant to initiate beta-blockade in outpatients who appear to be stable because of inexperience with the therapy, reluctance to contribute to polypharmacy, or lack of awareness about the importance of beta-blockade. Moreover, if the beta-blocker was not started before hospital discharge, the primary care physician may believe that the patient was a poor candidate for the drug and forgo initiating this lifesaving therapy during outpatient follow-up. Third, a lag time exists between the availability of clinical data and incorporation of the data into clinical practice among practicing physicians (11,12). Regardless of the cause, the end result is that as many as 60% of HF patients who are candidates for beta-blockers are not receiving this lifesaving evidence-based therapy.

Beta-blocker use was significantly increased at one year in patients randomized to a structured outpatient nurse-facilitated program as compared with patients followed by physicians who only received education or notification of their patients' eligibility for beta-blockade (67% vs. 27% vs. 16%, $p < 0.001$) (13). The rate of beta-blocker use among patients randomized to predischarge beta-blocker initiation in the IMPACT-HF trial was higher at 60 days (91%) than the reported rates of beta-blocker use in the study by Ansari et al. (13) at 1 year and in other trials testing outpatient approaches to initiation. This observation suggests that the most effective strategy to improve beta-blocker use may be a combined intervention that initiates therapy before hospital discharge and continues with aggressive follow-up and dose titration in the outpatient setting.

The results of the IMPACT-HF trial have several important implications. The population was older, composed of more women and patients of minority ethnic origin than in previous randomized controlled trials, suggesting that a representative population was enrolled. In addition, the overall 60-day rate of death or rehospitalization was striking (25%) despite the use of background angiotensin-converting enzyme inhibitors, diuretics, and digoxin in the majority of patients. This finding may in part be due to the fact that many patients were discharged with symptoms of congestion. Although the objective of most HF hospitalizations is to relieve congestion, the weight loss in this study was relatively small. The protocol did not mandate how physicians should treat volume overload. Thus, the methods

Table 6. Clinical Events at 60 Days

	Carvedilol Initiation Predischarge n = 185	Physician-Discretion Postdischarge Initiation n = 178	95% CI for Difference in Proportions*
Composite end point (%)	84 (45.4)	82 (46.1)	−0.0959, 0.1091
Death (%)	6 (3.2)	8 (4.5)	−0.0272, 0.0522
Rehospitalization (%)	40 (21.7)	45 (25.3)	−0.0519, 0.1228
Unscheduled visit for heart failure (%)	6 (3.2)	7 (3.9)	−0.0314, 0.0452
Change in heart failure therapy (%)	57 (30.8)	56 (31.5)	−0.0888, 0.1018
Death + rehospitalization (%)	44 (23.8)	48 (27)	−0.0577, 0.1213

None of the differences were statistically different between groups. *Difference = Physician discretion-carvedilol initiation. CI = confidence interval.

used and extent to which patients were decongested in this study may reflect how patients are routinely treated outside of a clinical trial setting. It may also reflect the fact that HF-associated morbidity and mortality are excessively high despite current treatments. Advancements in the medical management of HF are still needed to reduce the burdensome rate of hospitalizations and other morbid events in this patient population.

The IMPACT-HF data show that initiation of carvedilol before hospital discharge in appropriate patients is effective at improving the use of beta-blockade at 60 days. The rate of beta-blocker use in the predischarge initiation arm was extremely high, with 91% of patients receiving beta-blockade at 60 days. The exclusion criteria for IMPACT-HF were minimal and excluded only those patients who would have had a contraindication to carvedilol according to the Food and Drug Administration-approved product labeling. The implication of this finding is that the vast majority of HF patients are candidates for and can tolerate carvedilol therapy. The rate of beta-blocker use in the postdischarge initiation arm was also high; however, this usage rate is likely due in part to the open-label design of the IMPACT-HF trial. One would not expect to see this high rate of beta-blocker use outside of a clinical trial testing this approach. Most recently, the ADHERE registry reported that only 47% of patients admitted to the hospital for worsening HF were treated with a beta-blocker chronically before admission (7). These data are a more realistic indicator of the actual use of beta-blockade because the ADHERE registry is not subject to the open-label limitations that were unavoidably present in the design of the IMPACT-HF trial.

Another important finding of the IMPACT-HF trial is that carvedilol could be initiated before discharge in patients hospitalized for worsening HF without increasing the risk of side effects and without increasing the length of initial hospital stay. Although some data suggest that HF patients already on a beta-blocker may safely be continued on their preexisting therapy during a hospitalization for worsening symptoms, no studies have been conducted to evaluate the safety of initiation of beta-blockade in the hospitalized HF patient (14). Standard guidelines recommended avoiding beta-blocker initiation in patients with a recent episode of decompensated HF. This recommendation was based on a concern that early negative hemodynamic effects of beta-blockers may worsen short-term patient outcomes. Based on the IMPACT-HF data, as well as recently published subgroup analyses from COPERNICUS, there is no evidence that carvedilol initiation predischarge is associated with worsening HF symptoms or other adverse outcomes (15).

The patients studied in the IMPACT-HF trial are representative of the typical patient admitted for worsening HF and can be characterized as "wet" (evidence of congestion) and "warm" (no clinical evidence of a low-output state) (16). On admission, the patients had evidence of volume overload. These symptoms improved but had not completely resolved by the time of randomization. These patients are similar to both the OPTIME-CHF and ADHERE populations (7,17). The IMPACT-HF data do not alter the recommendation that patients not be volume overloaded when initiating beta-blockade, but rather they indicate that the presence of some evidence of volume overload need not preclude initiation at appropriate low doses. Patients presenting with low output states requiring inotropic support at the time of randomization were excluded from the IMPACT-HF trial, and these findings should not be extrapolated to that group. However, this patient type accounts for a small percentage of patients admitted with HF, representing only 1% of the population in ADHERE.

The IMPACT-HF trial was an open-label study, which introduces investigator bias in the results. The design of the study precluded the use of blinding techniques. The bias was bidirectional in both groups. The predischarge carvedilol initiation group may have been adversely biased to have a higher beta-blocker withdrawal rate and fewer titration attempts because the patients had recently experienced HF decompensation. Conversely, this group could have been favorably biased to achieve higher beta-blocker doses because they were initiated on therapy sooner. Similarly, in the postdischarge physician-discretion group one would expect that the bias could have favorably increased the use of beta-blockers because of physician awareness of the study, and it may have favorably biased the tolerability because patients were initiated on beta-blockers a median of 17 days postdischarge when they were

JACC Vol. 43, No. 9, 2004
May 5, 2004:1534–41

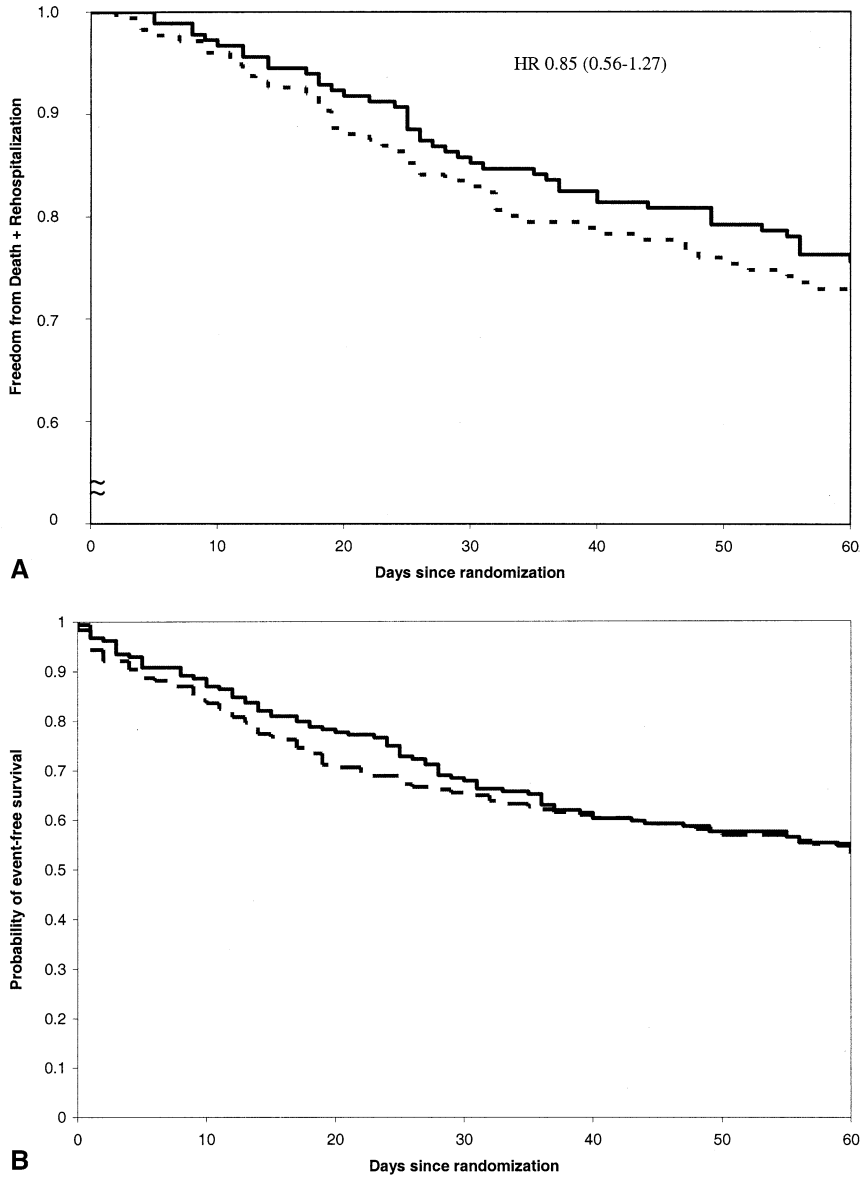

Figure 2. **(A)** Kaplan-Meier curve depicting time to death + rehospitalization. **(B)** Kaplan-Meier curve depicting time to death, recurrent hospitalization, unscheduled visit for heart failure, ≥50% increase in oral diuretic therapy, addition of new oral diuretic therapy excluding spironolactone, or any intravenous therapy with diuretics, inotropes, inodilators, or other vasoactive agents within 60 days post-randomization. **Solid lines** = predischarge carvedilol initiation group; **dashed lines** = physician-discretion postdischarge initiation group. HR = hazard ratio.

more likely to be stable and tolerate therapy. The rate of hospitalization was higher in the post-discharge initiation group, and it is possible that rehospitalization influenced the lower rate of beta-blocker use in this group. However, in the same way that rehospitalization might cause fewer patients to be initiated in the post-discharge group, rehospitalization might also cause more patients in the pre-discharge group to be discontinued, an action that was not observed. Finally, the IMPACT-HF trial had a follow-up period of 60 days, and initiation or continuation beyond this time point was not assessed.

The IMPACT-HF trial provides the first data demonstrating that a strategy of predischarge beta-blocker initiation effectively improves the use of beta-blockers at 60 days without increasing the risk of side effects or length of initial hospital stay in the population studied. This finding is of significant clinical importance because it allows patients to be initiated on lifesaving therapies earlier. This exposes them to the protective benefits of therapy sooner, and it increases the overall likelihood that they will be treated with the lifesaving therapy of beta-blockade. Both of these factors have important implications for the long-term care of the HF patient. These data also reveal the persistently high short-term event rate among HF patients and underscore the urgent need to identify new treatment strategies for this population.

Reprint requests and correspondence: Dr. Mihai Gheorghiade, Professor of Medicine, Northwestern University, Feinberg School of Medicine, Galter 10-240, 201 East Huron Street, Chicago, Illinois 60611-2908. E-mail: m-gheorghiade@northwestern.edu.

REFERENCES

1. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353:2001–7.
2. CIBIS-II Investigators and Committee. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999;353: 9–13.
3. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344:1651–8.
4. Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). 2001. Available at: http://www.acc.org/clinical/guidelines/failure/hf.htm. Accessed March 1, 2001.
5. Heart Failure Society of America Guideline Committee. HFSA guidelines for the management of patients with heart failure caused by left ventricular systolic dysfunction: pharmacologic approaches. J Card Fail 1999;5:357–82.
6. Cleland JGF, Cohen-Solal A, Aguilar JC, et al. Management of heart failure in primary care (the IMPROVEMENT of Heart Failure Programme): an international survey. Lancet 2002;360:1631–9.
7. Fonarow GC, Adams KF, Strausser BP. ADHERE (Acute Decompensated Heart Failure National Registry): rationale, design, and subject population. J Card Fail 2002;8:S49.
8. Haldeman GA, Croft JB, Giles WH, et al. Hospitalizations of patients with heart failure: National Hospital Discharge Survey, 1985–1995. Am Heart J 1999;137:352–60.
9. Gheorghiade M, Gattis WA, Lukas MA, O'Connor CM. Initiation management predischarge: process for assessment of carvedilol therapy for heart failure investigators. Rationale and design of the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy for Heart Failure (IMPACT-HF) study. Am Heart J 2003;145(2 Suppl):S60–1.
10. Fonarow GC, Yancy CW, Chang SF. Variation in heart failure quality of care indicators among US hospitals: analysis of 230 hospitals in the ADHERE registry. J Card Fail 2003;9:S82.
11. Bart BA, Gattis WA, Diem SJ, et al. Reasons for underuse of angiotensin-converting enzyme inhibitors in patients with heart failure and left ventricular dysfunction. Am J Cardiol 1997;79:1118–20.
12. Fonarow GC, Gawlinski A, Moughrabi S, et al. Improved treatment of coronary heart disease by implementation of a cardiac hospitalization atherosclerosis management program (CHAMP). Am J Cardiol 2001;87:819–22.
13. Ansari M, Ghlipak GM, Heidenreich PA, et al. Improving guideline adherence: a randomized trial evaluating strategies to increase beta-blocker use in heart failure. Circulation 2003;107:2799–804.
14. Gattis WA, O'Connor CM, Leimberger JD, et al. Clinical outcomes in patients on beta-blocker therapy admitted with worsening chronic heart failure. Am J Cardiol 2003;91:169–74.
15. Krum H, Roecker EB, Mohacsi P, et al. Effects of initiating carvedilol in patients with severe chronic heart failure: results from the COPERNICUS study. JAMA 2003;289:712–8.
16. Stevenson LW, Massie BM, Francis GS. Optimizing therapy for complex or refractory heart failure: a management algorithm. Am Heart J 1998;135 Suppl:S293–309.
17. Cuffe MS, Califf RM, Adams KF Jr, et al. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. JAMA 2002;287:1541–7.

APPENDIX

For a list of the Steering Committee, Data and Safety Monitoring Board, Investigators, and Duke Clinical Research Institute Coordinating Center, please see the May 5, 2004, issue of *JACC* at www.cardiosource.com/jacc.html.