The Initiation Management Predischarge Process for Assessment of Carvedilol Therapy for Heart Failure (IMPACT-HF) Study: Design and Implications

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The utilization of β-blockers for the treatment of heart failure in the United States is inadequate despite the available data and the current guidelines that support their use. The ongoing Initiation Management Predischarge Process for Assessment of Carvedilol Therapy for Heart Failure (IMPACT-HF) study was designed to determine if initiation of ß-blockade prior to hospital discharge is safe and effective in improving the 60-day use of ß-blockers in patients with heart failure. IMPACT-HF is a community-based, multicenter, open-label trial of 375 heart failure patients randomized to carvedilol initiated before their hospital discharge or to usual care (Heart Failure Society of America guidelines that recommend waiting 2–4 weeks after hospitalization for heart failure before initiating ß-blocker therapy). The entry criteria are nonrestrictive to ensure inclusion of patients reflective of the general heart failure population. The primary endpoint of the study is the number of patients treated with any ß-blocker at 60 days. A concurrently ongoing pilot registry will enroll 550 patients, admitted with exacerbated heart failure, in three phases to collect demographic, clinical, treatment patterns, and outcome data. The trial will test the tolerability of ß-blocker initiation in the hospital setting, develop strategies to improve the use of evidence-based medicine in clinical practice, and explore the patient's course from hospital admission through discharge and up to 60 days. The trial data will determine if in-hospital initiation of ß-blocker therapy is effective at improving the long-term use of pharmacologic agents proven to reduce morbidity and mortality.
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Consistent evidence from multiple, large, prospective, randomized, controlled clinical trials has confirmed the role of β-blockers as an important therapy for the treatment of heart failure.[1-3] These data have resulted in changes to the American College of Cardiology and the American Heart

Association (ACC/AHA) guidelines for the management of heart failure.[4] Based on the available data and the current guidelines, β-blockers are now recommended as standard treatment for patients with chronic heart failure from systolic dysfunction.

The overall utilization of β-blockers for the treatment of heart failure across the country is inadequate despite the available data and the current guidelines supporting their use. Best estimates suggest that β-blockers are prescribed in only 20%–40% of eligible patients with heart failure; thus, more than one half of heart failure patients are not prescribed a therapy that could reduce mortality and morbidity by 35%.[1-3]

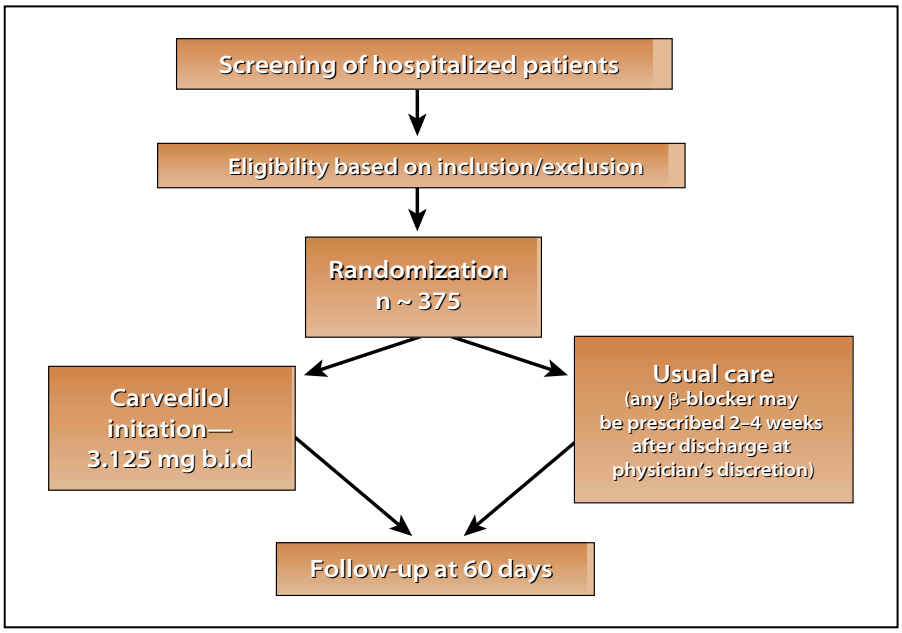

Figure 1. *Design of the Initiation Management Predischarge Process for Assessment of Carvedilol Therapy for Heart Failure (IMPACT-HF) study. Data from Gheorghiade M, Gattis WA, Lukas MA, O'Connor CM. Rationale and design of the initiation management predischarge: process for assessment of carvedilol therapy for heart failure (IMPACT-HF) study.* Am Heart J. *2002; In Press.*

Reasons for the Underuse of Beta-Blockers in the Treatment of Heart Failure

Although guidelines may be helpful in terms of improving the uptake of evidence-based medicine, additional efforts need to be employed. Several factors are likely to be responsible for the underuse of β-blockers in the heart failure population. First, β-blockers have been traditionally contraindicated in treating heart failure. Educational initiatives are required to re-educate physicians on the benefits of β-blockade. This barrier is especially challenging because it requires physicians to abandon a well-established teaching and to accept a novel concept in heart failure management. Superficially, it is counterintuitive to use β-blockers to treat heart failure, and it is only by recognizing the pathophysiologic processes contributing to the progression of heart failure that the use of β-blockers to care for this condition appears rational. Both education and experience with using β-blockers to treat heart failure are necessary to help physicians make this transition.

Based on the available data and the current guidelines, ß-blockers are now recommended as standard treatment for patients with chronic heart failure from systolic dysfunction.

Second, as the concept for using β-blockers in heart failure emerged, the β-blockers were associated with a negative stigma suggesting that the therapy was extremely time-intensive, difficult to manage, and associated with significant risk to the patient. Although such caution may have been warranted at the time, data from the trials of β-blockers in mild to moderate heart failure showed no evidence of increased risk for worsening heart failure. Importantly, the Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS) demonstrated that even patients with severe heart failure who were without overt evidence of volume overload could be safely initiated, titrated, and maintained on β-blocker therapy without excess risk. In fact, these drugs resulted in significant and meaningful improvements in survival.[1-3]

Best estimates suggest that ß-blockers are prescribed in only 20%–40% of eligible patients with heart failure; thus, at least one half of heart failure patients are not prescribed a therapy that could reduce mortality and morbidity by 35%.

Another potential reason for the

underuse of β-blockers in the heart failure population relates to the timing for the initiation of therapy. Initially, physicians were educated to use β-blockers in patients optimized on angiotensin-converting enzyme (ACE) inhibitors, diuretics, and possibly digoxin, who were without evidence of heart failure symptoms. These parameters describe a patient who is seemingly stable and "doing well." Clinicians are often reluctant to initiate new therapies in stable patients, and in general, they are more likely to prescribe new medications when a patient presents with new or worsening symptoms. Clinicians were also educated to avoid β-blockers in the patient with significant heart failure symptoms. Thus, if physicians are reluctant to start a new therapy when a patient is stable, and they are reluctant to start β-blockers if a patient has heart failure symptoms, then the likelihood that treatment will ever be started is fairly low. Attention must also be paid to educating physicians not only about the benefits of β-blockade, but also about the high risk of sudden cardiac death, even in patients with asymptomatic or minimally symptomatic heart failure, emphasizing the important role of β-blockers in preventing sudden death.

Recognizing the potential reasons why β-blockers are under-prescribed may help identify strategies to improve the overall use of β-blockers in the heart failure population. An early initiation strategy may prove to be the best approach at optimizing β-blocker use among these patients. One time point to consider for initiating β-blockers is during a hospital admission for worsening heart failure after the patient has been stabilized. Hospitalizations among heart failure patients are frequent, and 30% of these patients are readmitted within 3 months after discharge. Implementing β-blocker therapy at this point may contribute to reducing the readmission rates for these patients. Additionally, the in-hospital setting provides an opportunity for closely monitoring the patient if there is concern about worsening heart failure symptoms or side effects such as hypotension or

Table 1
Endpoints of the Initiation Management Predischarge Process for Assessment of Carvedilol Therapy for Heart Failure (IMPACT-HF) Study

Primary Endpoint	• Number of patients treated with any β-blocker at 60 days after randomization
Secondary Endpoints	• Number of patients treated with a specific β-blocker, at 60 days after randomization. β-blockers with data supporting their use in heart failure will be analyzed individually, ie, carvedilol, metoprolol XL, bisoprolol. β-blockers without clinical trial data (all β-blockers other than carvedilol, metoprolol XL, and bisoprolol) will be combined together as one group • Median β-blocker dose prescribed, analyzed as all β-blockers and by specific β-blocker (as in the first bullet), at 60 days after randomization • Median time to β-blocker initiation, analyzed as all β-blockers and by specific β-blocker (as in the first bullet), within 60 days after randomization • Median time to reach the maximum tolerated dose of carvedilol within the range of 6.25 mg–25 mg b.i.d (or 50 mg b.i.d., if >85 kg) within 60 days after randomization • Number of patients requiring discontinuation of β-blocker therapy, analyzed as all β-blockers and by specific β-blocker (as in the first bullet), within 60 days after randomization • Median time to discontinuation of β-blocker therapy, analyzed as all β-blockers and by specific β-blocker (as in the first bullet), within 60 days after randomization (evaluated as all β-blockers and by specific β-blocker) • Time to death, recurrent hospitalization, unscheduled visit for heart failure, or any of the following changes in the patient's medical regimen: ≥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 after randomization • Each component of the composite endpoint in will be also be evaluated individually to evaluate differential effects of treatment

Data from Gheorghiade M, Gattis WA, Lukas MA, O'Connor CM. Rationale and design of the initiation management predischarge: process for assessment of carvedilol therapy for heart failure (IMPACT-HF) study. *Am Heart J.* 2002; In Press.

Table 2
Eligibility Criteria for the Initiation Management Predischarge Process for Assessment of Carvedilol Therapy for Heart Failure (IMPACT-HF) Study

Inclusion Criteria	Exclusion Criteria
• Hospital inpatient with a primary diagnosis of heart failure	• Treatment with any β-blocker within 30 days prior to randomization
• LVEF ≤ 40% by any method within the previous 12 months	• Decompensated New York Heart Association class IV heart failure requiring intravenous inotropic therapy at randomization
• Informed consent	• 2nd or 3rd degree AV block or sick sinus syndrome unless functional pacemaker present
	• Symptomatic bradycardia unless functional pacemaker present
	• Bronchial asthma or related bronchospastic conditions
	• Symptomatic hypotension
	• Cardiogenic shock
	• Expected survival < 60 days
	• Hypersensitivity to carvedilol
	• Clinically manifest hepatic impairment
	• Pregnant or lactating women

Data from Gheorghiade M, Gattis WA, Lukas MA, O'Connor CM. Rationale and design of the initiation management predischarge: process for assessment of carvedilol therapy for heart failure (IMPACT-HF) study. *Am Heart J*. 2002; In Press. LVEF, left ventricular ejection fraction; AV, atrioventricular.

bradycardia. Finally, physicians may be more willing to maintain β-blocker therapy that is initiated in the hospital setting than to initiate the therapy on their own, particularly if their comfort level with using the drug therapy is low.

The Initiation Management Predischarge Process for Assessment of Carvedilol Therapy for Heart Failure (IMPACT-HF) Study

The Initiation Management Predischarge Process for Assessment of Carvedilol Therapy for Heart Failure (IMPACT-HF) study[5] was designed to determine if an early initiation strategy is effective at improving the long-term use of β-blockers in patients with heart failure. A secondary objective was to evaluate the safety of early initiation of β-blockers in hospitalized patients. The rationale for this study was developed from the hypothesis that patients may be more likely to be maintained on therapies that are started during hospitalization, because initiation is not dependent on providers who are less comfortable or less willing to initiate β-blockers. In addition, in-hospital initiation allows closer patient monitoring prior to discharge to observe potential adverse effects that may theoretically occur.

Hospitalizations among heart failure patients are frequent, and 30% of these patients are readmitted within 3 months after discharge. Implementing ß-blocker therapy at this point may contribute to reducing the readmission rates for these patients.

Methods

Briefly, the IMPACT-HF trial is a multicenter, open-label trial of heart failure patients randomized to carvedilol initiated before their hospital discharge or to usual care (Figure 1). The definition of usual care is based on the Heart Failure Society of America guidelines that recommend waiting 2–4 weeks after hospitalization for heart failure before initiating β-blocker therapy.[6] The primary endpoint of the study is the number of patients treated with any β-blocker at 60 days. Prespecified secondary analyses include the median β-blocker dose prescribed at 60 days after randomization; the median time to β-blocker initiation; the median time to reach the maximum tolerated β-blocker dose; the number of patients requiring discontinuation of β-blocker therapy within 60 days; the median time to discontinuation of β-blocker therapy within 60 days; and the time to death, recurrent hospitalization, unscheduled visit for heart failure, or any of the following changes in the patient's medical regimen: ≥50% increase in oral diuretic therapy, the addition of new oral diuretic therapy (including spironolactone), or any intravenous therapy with diuretics, inotropes, inodilators,

or other vasoactive agents within 60 days (Table 1).

Approximately 375 patients will be randomized into this study. The study is ongoing at 45 centers across the United States. All patients will be followed for 60 days. Data will be collected on baseline demographics, past medical history, symptoms at admission, symptoms at the time of randomization, medications on admission and throughout 60 days, and specific data on β-blocker initiation, titration, and discontinuation. Patients whose β-blockers were decreased or discontinued will have documented reasons as to why these changes were made, allowing for evaluation of specific issues related to tolerability in this population.

The entry criteria for this study were developed to be nonrestrictive to ensure inclusion of patients reflective of the general heart failure population. Patients must have systolic dysfunction defined as a left ventricular ejection fraction (LVEF) < 40%, they must be inpatients at the time of randomization, and they must have significant symptoms of heart failure during their hospitalization. Patients are excluded if the physician plans to treat the patient with a β-blocker before 2–4 weeks post-discharge, regardless of the randomization arm. In addition, patients requiring inotropic therapy, patients treated with any β-blocker within 30 days prior to randomization, patients with significant heart block, significant bradycardia, bronchospastic pulmonary disease, investigator-defined symptomatic hypotension, cardiogenic shock, clinically manifest hepatic impairment, and pregnant or lactating women are excluded from participation (Table 2).

Pilot Registry

A pilot registry is ongoing concurrently with the main IMPACT-HF trial. A total of 550 patients will be enrolled in the registry in three phases. The purpose of the IMPACT-HF registry is to collect demographic, clinical, treatment patterns, and outcome data on patients admitted with exacerbated heart failure. These data will provide additional insights into the heart failure population that requires admission for worsening heart failure symptoms. All patients admitted with a primary diagnosis of heart failure or with a secondary diagnosis of heart failure when the primary cause was any cardiovascular condition will be eligible for enrollment in the registry. There are no exclusions to participation in the registry. Patients must provide informed consent because follow-up information will be obtained. Baseline data describing clinical history, demographics, medications, presenting symptoms, in-hospital procedures, discharge status, and discharge medications will be captured. Patients will be followed for 60 days, and clinical outcomes, symptoms, and medications will be captured at the 60-day time point. Patients will be enrolled in three phases that will correspond with the first month of enrollment in the main IMPACT trial at each site, within the last month of enrollment in the main IMPACT trial, and within 1 month following the end of

Table 3
Data Variables in the Initiation Management Predischarge Process for Assessment of Carvedilol Therapy for Heart Failure (IMPACT-HF) Study

Time Point	IMPACT-HF Trial	IMPACT-HF Pilot Registry
Admission	Demographics, history, signs/symptoms, NYHA class, medications	Demographics, history, signs/symptoms, NYHA class, medications, labs
Randomization	Signs/symptoms, labs, vital signs, NYHA class, medications	N/A
In-hospital	β-blocker dose, titration, reason for discontinuation or down-titration	Procedures during hospitalization, medications, symptoms, hemodynamics
Discharge	Medications, vital status	Medications, vital status, signs/symptoms, vital signs, NYHA class
30-day and 60-day follow-up	Vital status, clinical events, vital signs, symptoms, NYHA class, β-blocker dose, titration, reason for discontinuation or down-titration, adherence, other medications	Medications, vital status, clinical outcomes

Data from Gheorghiade M, Gattis WA, Lukas MA, O'Connor CM. Rationale and design of the initiation management predischarge: process for assessment of carvedilol therapy for heart failure (IMPACT-HF) study. *Am Heart J.* 2002; In Press. NYHA, New York Heart Association.

IMPACT enrollment. Each site will have 2 weeks to enroll consecutive patients. The strategy of phase enrollment will allow changes in practice patterns resulting from the presence of the IMPACT-HF trial to be detected and will enhance the likelihood for enrollment of consecutive patients during each of the specified enrollment windows.

The registry population will represent a larger and more heterogenous group of patients than the group in the main IMPACT-HF trial because of the lack of exclusion criteria for participation. Patients will be allowed in the registry even if they are receiving β-blockers on admission, which is an exclusion in the main IMPACT-HF trial. Differences in characteristics, treatment patterns, and outcomes will be explored between the IMPACT-HF trial and the IMPACT-HF pilot registry (Table 3).

Implications

The IMPACT-HF trial is important for several reasons. First, outside the setting of a rigorous clinical trial, the tolerability of β-blocker initiation in the hospital setting is unknown. Second, strategies to improve the use of evidence-based medicine have not been rigorously tested. Although the need to improve the uptake of evidence-based medicine into clinical practice is widely discussed, it is unknown whether the implementation of pathways, standard orders, intensive discharge planning, education, or protocols to specify initiation of a given drug therapy are effective at improving the use of proven therapies.

Further, the IMPACT-HF trial includes only those patients who have not been treated with a β-blocker prior to enrollment, whereas patients in the registry may or may not be receiving β-blocker therapy. A review of these data and the differences between the populations may provide hypotheses-generating data to support further study.

The IMPACT-HF trial is also important because it will allow the exploration of the patient's course from hospital admission through discharge and up to 60 days. Clinical characteristics, concomitant diseases, symptoms, treatment patterns, medications, and clinical outcome will be evaluated. The data collected will provide a rich database to assess issues related to β-blocker tolerability, patient selection, and dosing strategies used by community practitioners. The IMPACT-HF protocol suggests initiating therapy at a low-dose with titration by doubling the dose at biweekly intervals, but it does not mandate this dosing regimen. Thus, data describing different dosing regimens may be available, and observations will be made regarding the β-blocker prescribing patterns among practicing clinicians in daily practice. The clinical sites for both the IMPACT-HF trial and the pilot registry are community-based practices, allowing important observations to be made within a community setting rather than solely at large academic centers.

Main Points

- The use of β-blockers for the treatment of heart failure across the country is inadequate despite the available data and the current guidelines supporting their employment.
- The Initiation Management Predischarge Process for Assessment of Carvedilol Therapy for Heart Failure (IMPACT-HF) study was designed to determine if treatment with β-blockers during hospitalization would be safe and effective in improving the long-term use of β-blockers in patients with heart failure.
- IMPACT-HF is a community-based, multicenter, open-label trial of approximately 375 heart failure patients randomized to carvedilol initiated before their hospital discharge or to usual care (Heart Failure Society of America guidelines that recommend waiting 2–4 weeks after hospitalization for heart failure before initiating β-blocker therapy). The primary endpoint of the study is the number of patients treated with any β-blocker at 60 days. The entry criteria are nonrestrictive to ensure inclusion of patients reflective of the general heart failure population.
- A concurrently ongoing pilot registry will enroll 550 subjects in three phases to collect demographic, clinical, treatment patterns, and outcome data on patients admitted with exacerbated heart failure.
- The IMPACT-HF trial will test the tolerability of β-blocker initiation in the hospital setting, develop strategies to improve the use of evidence-based medicine in clinical practice, and explore the patient's course from hospital admission through discharge and up to 60 days.
- The trial data will determine if in-hospital initiation of β-blocker therapy is effective at improving the long-term use of pharmacologic agents proven to reduce morbidity and mortality.

The IMPACT-HF trial will provide the foundation for the development of other research strategies targeted at improving the use of evidence-based medicine among various populations. Important data will be gathered from this trial and will determine if in-hospital initiation of β-blocker therapy is effective at improving the long-term use of pharmacologic agents proven to reduce morbidity and mortality. ■

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