Editorial
Therapeutic strategies for patients hospitalized with worsening heart failure

Liviu Klein, Mihai Gheorghiade*

*Department of Medicine, Advocate Illinois Masonic Medical Center, *Division of Cardiology, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA*

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Address:

Mihai Gheorghiade, MD

Division of Cardiology
Northwestern University
Feinberg School
of Medicine
Galter 10-240
201 E. Huron Street
Chicago, IL 60611
USA
E-mail: m-gheorghiade@
northwestern.edu

Chronic heart failure (HF) affects nearly 5 million individuals in the United States alone and over half a million cases are diagnosed yearly[1]. Despite advances in treatment, the mortality remains very high with nearly 300 000 patients dying of HF as the primary or contributory cause each year[1]. The total number of admissions approaches 1 million yearly, with HF becoming the number one volume diagnosis in the Medicare health system[2]. Patients who have been admitted to a hospital for the treatment of HF have readmission rates as high as 30 to 60% within 3 to 6 months after the initial discharge[3]. The Survival and Ventricular Enlargement (SAVE) trial demonstrated that once patients with HF were hospitalized for an exacerbation, their mortality rate after 4 years increased from 25% to nearly 60%, despite optimal medical management[4].

The presentations of HF that require hospitalization can be classified into three categories: 1) new-onset HF secondary to a precipitating factor, such as a large anterior wall myocardial infarction; 2) end-stage or refractory HF that responds poorly to medical therapy; and 3) worsening of chronic HF (more than 90% of the patients admitted for HF).

The baseline clinical characteristics of patients hospitalized with worsening HF can be described by using data from recent large clinical trials enrolling more than 10 000 patients (ACTIV, ADHERE, IMPACT-HF, OPTIME-CHF, RITZ-4, VMAC) (Table I)[5-12]. These patients are older; many are women and have a preserved ejection fraction. They tend to have less coronary artery disease, more hypertension, atrial fibrillation, diabetes, and renal insufficiency than those enrolled in chronic HF trials (Table II). The mean systolic blood pressure is 110-130 mmHg and the resting heart rate is 80-90 b/min. At the time of hospital admission, around 70% of the patients have jugular venous distension, 70-75% have pulmonary rales and around 50% have an apical systolic ejection murmur. The majority of patients (67%) have elevated left ventricular filling pressures (described as "wet") and adequate systemic perfusion (described as "warm")[13].

While these patients have a low in-hospital mortality (< 4%), their readmission rates within 60 days of discharge range from 20 to 30% and the mortality within 60 days of discharge is 5-10%[5-7,9,12]. In the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) independent baseline predictors of clinical outcome included higher level of blood urea nitrogen, lower systolic blood pressure, male gender, previous hospitalizations, a worse New York Heart Association classification, and the presence of hyponatremia[5]. In addition, changes in levels of brain-type natriuretic peptide following treatment may predict early readmission rates and mortality rates in patients hospitalized with HF[14].

In patients hospitalized with worsening HF, the immediate treatment goals are to alleviate the symptoms of congestion and edema, improve the hemodynamic profile, and preserve renal function without causing myocardial injury (acute therapies should not result in long-term deleterious effects). After the patients are stabilized,

Table I. Recent clinical trials in patients admitted with worsening heart failure.

Trial	
Established therapies	
OPTIME-CHF[5]	Milrinone vs placebo
New therapies	
ACTIV[6]	Tolvaptan (oral vasopressin$_2$ receptor antagonist) vs placebo
RITZ-4[7]	Tezosentan (endothelin-1$_{A/B}$ receptor antagonist) vs placebo
RUSSLAN[8]	Levosimendan vs placebo
VMAC[9]	Nesiritide vs nitroglycerin vs placebo
Established vs new therapies	
LIDO[10]	Levosimendan vs dobutamine
PRECEDENT[11]	Nesiritide vs dobutamine
VMAC[9]	Nesiritide vs nitroglycerin vs placebo
Implementation trials	
IMPACT-HF[12]	Carvedilol initiation predischarge vs beta-blockers usual care postdischarge
OPTIMIZE-HF*	Registry

* to be initiated.

Table II. Characteristics of the majority of patients admitted with worsening heart failure.

Demographics	
Age (years)	65-75
Women (%)	40-50
Medical history	
Coronary artery disease (%)	40-55
Hypertension (%)	65-70
Preserved ejection fraction (%)	30-40
Atrial fibrillation (%)	35-40
Diabetes mellitus (%)	40-45
Chronic renal insufficiency (%)	15-20
Clinical characteristics at the time of admission	
Systolic blood pressure (mmHg)	110-130
Heart rate (b/min)	80-90
Jugular venous distension (%)	70
Apical systolic ejection murmur (%)	50
Pulmonary rales (%)	70-75
Leg edema (%)	70-80
Serum sodium (mEq/l)	137-138
Serum potassium (mEq/l)	4.1-4.2
Serum blood urea nitrogen (mg/dl)	20-25
Serum creatinine (mg/dl)	1.2-1.4

the goals are to implement long-term life-saving therapies that include: a) angiotensin-converting enzyme (ACE)-inhibitors, beta-blockers, and spironolactone; b) implantable cardiac defibrillators and biventricular pacing; c) for patients with coronary artery disease, antiplatelet agents, statins, and revascularization-therapeutic strategy that is presently tested in the National Institute of Health funded Surgical Treatment for Ischemic Heart Failure trial (NIH-STICH).

Hospitalizations for worsening HF present unique opportunities to: a) examine the utility and safety of established therapies (e.g. milrinone), b) examine new therapies aimed at treating these patients (e.g. levosimendan, nesiritide, tolvaptan), and c) compare existing and new therapies (e.g. dobutamine and levosimendan, dobutamine and nesiritide). It is also an opportunity to improve patient care and ultimately the outcomes by implementing life-saving therapies.

The OPTIME-CHF was the first carefully designed randomized placebo-controlled trial to assess the utility and safety of short-term use of intravenous milrinone in patients admitted with worsening HF. The trial randomized 951 patients to a 48-72 hour infusion of intravenous milrinone or placebo in addition to standard therapy that included diuretics, ACE-inhibitors, digoxin and beta-blockers. All patients had an indication for milrinone, but they did not absolutely require inotropic support for low cardiac output. The results showed that the addition of milrinone to standard therapies did not decrease the median number of days hospitalized for cardiovascular causes (the primary endpoint) or the rate of readmission/death at 60 days[5]. The HF score declined to a similar degree in both groups. Milrinone use was associated with increased incidence of treatment failures (mainly due to hypotension) and new atrial fibrillation and with a trend in increase mortality[5]. Based on these findings, the investigators for OPTIME-CHF trial concluded that milrinone should not be routinely used as an adjunct to standard therapy in patients admitted with worsening HF[5].

Recent trials examined the role of new medications in the management of patients hospitalized with worsening HF. The Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) trial compared the effects of intravenous nesiritide to intravenous nitroglycerin and placebo in addition to standard chronic medications (ACE-inhibitors, beta-blockers and digoxin) and standard intravenous treatment (diuretics and, if needed, intravenous dobutamine and dopamine) in patients admitted with worsening HF[9]. Addition of nesiritide, significantly decreased the pulmonary capillary wedge pressure at 24 hours when compared to nitroglycerin or placebo[9]. No statistically significant difference was noted between treatment with nitroglycerin and nesiritide with regard to improvement in dyspnea. However, nesiritide significantly reduced dyspnea when compared with placebo[9].

The Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natrecor Therapy (PRECEDENT) trial found that nesiritide was not proarrhythmic when compared with dobutamine. Specifically, treatment with nesiritide for 24 hours did not aggravate preexisting ventricular tachycardia nor did it increase the frequency of premature ventricular beats when compared with patient measurements taken from a baseline 24-hour Holter tape[11]. Low-dose nesir-

itide treatment was also associated with a lower readmission rate at 3 weeks (8 vs 20%) and 6-month mortality when compared with dobutamine (18 vs 31%)[15].

The Levosimendan Infusion versus Dobutamine trial (LIDO) randomized 203 patients admitted for worsening HF who were judged to have low cardiac output and require inotropic support to a 24-hour infusion of levosimendan (a novel calcium sensitizer) or dobutamine[10]. Although the number of patients who achieved hemodynamic improvement (the primary endpoint) was greater in the levosimendan group compared with dobutamine (28 vs 15%), there was little difference in the improvement in symptoms between the two groups[10]. The hemodynamic effects of levosimendan, unlike those of dobutamine, were not attenuated with the concomitant use of beta-blockers. At 6 months, the mortality rate was also lower in the levosimendan-treated patients when compared with dobutamine (26 vs 38%)[10].

In patients admitted with acute coronary syndromes complicated by HF, a 6-hour low-dose infusion of levosimendan did not result in significantly more episodes of ischemia and/or hypotension than placebo (13.4 vs 10.8%)[8]. The combined risk of death and worsening HF was lower in the levosimendan-treated patients during the first 24 hours after the start of the infusion. Fourteen-day and 6-month mortality rates were also lower in the levosimendan group[8].

The Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist (Tolvaptan) in Congestive Heart Failure (ACTIV in CHF) trial randomized 320 patients admitted for worsening HF to three doses of tolvaptan (a selective vasopressin$_2$ receptor antagonist) or placebo in addition to the best medical therapy. Treatment was initiated within 72 hours of admission and was continued for 60 days. The primary objective was to determine whether therapy with tolvaptan further reduces body weight at 24 hours and the rate of worsening HF (death, readmissions, unscheduled visits for HF) within 60 days following discharge. The results will be available in 2003.

Morbidity and mortality in HF patients remain high, particularly in patients recently hospitalized for HF. Despite overwhelming clinical trial evidence, expert opinion, national guidelines, and a vast array of educational conferences, evidence-based, life-saving therapies continue to be underutilized. In the Acute Decompensated Heart Failure National Registry (ADHERE), only 55% of the eligible HF patients were using an ACE-inhibitor or an angiotensin receptor blocker and only 41% were treated with a beta-blocker[12]. Patients are frequently discharged without these vital medications being initiated and often the community physicians fall short of initiating these therapies. A strategy that targets the in-hospital initiation of these medications is likely to yield better results, because the patients are more likely to view therapy as essential and be more compliant, they are more likely to achieve treatment dosing goals and the long-term therapy is more likely to be continued by community physicians.

Despite the results from four major clinical trials (US Carvedilol, CIBIS II, MERIT-HF and COPERNICUS)[16-19] showing that beta-blockers decrease the mortality and readmission rates in HF patients, this life-saving therapy is used in only 30-40% of the eligible patients. Present American College of Cardiology/ American Heart Association and Heart Failure Society of America guidelines recommend that beta-blockers be started 2 to 4 weeks after discharge[20,21]. However, beta-blockers are often not started as the community physicians might still perceive these medications as deleterious and be reluctant to initiate them or have too little time to spend with the patients and adjust their HF medications.

Initiation Management Predischarge Process for Assessment of Carvedilol Therapy for Heart Failure (IMPACT-HF) trial was conducted to determine if starting carvedilol prior to hospital discharge in patients admitted with a primary diagnosis of HF and ejection fraction ≤ 40% is safe and improves the overall use of beta-blockers at 60 days after randomization as compared with usual care[12]. Three hundred and sixty three patients admitted with worsening HF were randomized to carvedilol started in hospital (3.125 mg bid and adjusted to target dose) or any beta-blocker initiated at physician discretion at least 2 weeks after the patients have been discharged. The results, recently presented at a Satellite Symposium at the 2002 American Heart Association Annual Scientific Session, showed that significantly more patients randomized to carvedilol predischarge were receiving a beta-blocker at 60 days as compared to beta-blocker initiation at physician discretion. In addition, the predischarge initiation of carvedilol was not associated with an increased risk of worsening HF or other serious adverse events[12]. Thus because hospital setting is the ideal opportunity to increase utilization and avoid delay in providing life-saving benefits of beta-blockers, initiation of beta-blocker therapy predischarge should be considered as a recommendation in future guidelines.

A large treatment gap between guidelines and practice exists for HF patients. A strategy that targets the in-hospital initiation of these medications is likely to yield better results and to improve patient care and outcomes. Therefore, hospital-based management programs can significantly increase the utilization of life-saving therapies. The Organized Program To Initiate Life-Saving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) is a hospital-based process of care improvement program and web based registry in HF. For this project, approximately 500 hospitals will work collaboratively to measure and improve the management of care for HF patients. Up to 50 000 patients with HF as primary or secondary diagnosis will be included in this registry. The objectives are to improve medical

care and education of patients hospitalized with HF and to accelerate initiation of the HF evidence-based, guideline-recommended therapies by starting the life-saving therapies before hospital discharge in appropriate patients without contraindications. OPTIMIZE-HF will be the largest HF quality of care improvement project ever undertaken and if successfully implemented, it will improve the standard of care in HF in the hospital and outpatient settings, increase utilization of evidence-based therapies, and save lives.

More randomized clinical trials are needed in patients hospitalized with HF to examine current and new therapies that assess not only acute, but also long-term effects on these patients. Such endeavor should eventually result in publication of treatment guidelines for hospitalized patients with HF. New approaches to improve the use of proven life-saving therapies are needed.

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