

# Short-term Intravenous Milrinone for Acute Exacerbation of Chronic Heart Failure

## A Randomized Controlled Trial

Michael S. Cuffe, MD

Robert M. Califf, MD

Kirkwood F. Adams, Jr, MD

Raymond Benza, MD

Robert Bourge, MD

Wilson S. Colucci, MD

Barry M. Massie, MD

Christopher M. O'Connor, MD

Ileana Pina, MD

Rebecca Quigg, MD

Marc A. Silver, MD

Mihai Gheorghiane, MD

for the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) Investigators

**C**HRONIC HEART FAILURE IS ONE of the most common and life-threatening cardiovascular conditions, affecting nearly 5 million people in the United States.<sup>1</sup> It causes more than 200 000 deaths each year<sup>2-4</sup> and is the leading discharge diagnosis among the Medicare population.<sup>5,6</sup> Treatment costs for chronic heart failure, most of which are incurred by inpatients, are more than \$30 billion yearly.<sup>7</sup> Almost half of the patients with advanced disease will die within 1 year.<sup>8</sup> Hospitalization is common in these patients and is associated with a poor prognosis.<sup>9</sup> From 3 to 6 months

See also pp 1531 and 1578.

**Context** Little randomized evidence is available to guide the in-hospital management of patients with an acute exacerbation of chronic heart failure. Although intravenous inotropic therapy usually produces beneficial hemodynamic effects and is labeled for use in the care of such patients, the effect of such therapy on intermediate-term clinical outcomes is uncertain.

**Objective** To prospectively test whether a strategy that includes short-term use of milrinone in addition to standard therapy can improve clinical outcomes of patients hospitalized with an exacerbation of chronic heart failure.

**Design** Prospective, randomized, double-blind, placebo-controlled trial conducted from July 1997 through November 1999.

**Setting** Seventy-eight community and tertiary care hospitals in the United States.

**Participants** A total of 951 patients admitted with an exacerbation of systolic heart failure not requiring intravenous inotropic support (mean age, 65 years; 92% with baseline New York Heart Association class III or IV; mean left ventricular ejection fraction, 23%).

**Intervention** Patients were randomly assigned to receive a 48-hour infusion of either milrinone, 0.5 µg/kg per minute initially (n=477), or saline placebo (n=472).

**Main Outcome Measure** Cumulative days of hospitalization for cardiovascular cause within 60 days following randomization.

**Results** The median number of days hospitalized for cardiovascular causes within 60 days after randomization did not differ significantly between patients given milrinone (6 days) compared with placebo (7 days;  $P=.71$ ). Sustained hypotension requiring intervention (10.7% vs 3.2%;  $P<.001$ ) and new atrial arrhythmias (4.6% vs 1.5%;  $P=.004$ ) occurred more frequently in patients who received milrinone. The milrinone and placebo groups did not differ significantly in in-hospital mortality (3.8% vs 2.3%;  $P=.19$ ), 60-day mortality (10.3% vs 8.9%;  $P=.41$ ), or the composite incidence of death or readmission (35.0% vs 35.3%;  $P=.92$ ).

**Conclusion** These results do not support the routine use of intravenous milrinone as an adjunct to standard therapy in the treatment of patients hospitalized for an exacerbation of chronic heart failure.

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after discharge, readmission rates for chronic heart failure range from 30% to 50%.<sup>10-12</sup>

Hospitalization for chronic heart failure is often associated with worsening hemodynamic function,<sup>13</sup> which may be

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**Corresponding Author and Reprints:** Mihai Gheorghiane, MD, Northwestern University Medical School, Division of Cardiology, 201 E Huron St, Galter 10-240, Chicago, IL 60611 (e-mail: m-gheorghiane@northwestern.edu).

partly responsible for the volume retention that is usually the precipitating factor. Inotropic agents produce beneficial hemodynamic effects in heart failure patients and may facilitate earlier achievement of hemodynamic improvement and titration of standard oral therapy, particularly when used with hemodynamic monitoring by right-sided heart catheterization.<sup>14,15</sup>

Milrinone, a commonly used inotropic agent that is labeled for use in the short-term intravenous treatment of acute exacerbation of chronic heart failure, has several characteristics that make it physiologically attractive. It has both inotropic and vasodilator properties, which increase cardiac output and reduce systemic vascular resistance and pulmonary capillary wedge pressures.<sup>16</sup> The drug exerts its hemodynamic effects without excessive changes in heart rate or increases in myocardial oxygen consumption,<sup>16</sup> important because coronary artery disease and chronic heart failure often coexist.<sup>17</sup> Although intravenous agents (eg, milrinone and dobutamine) are often used as adjuncts to standard therapy and, with or without hemodynamic guidance, represent a rational approach to treatment of patients with an acute exacerbation of chronic heart failure, no placebo-controlled clinical trials have evaluated their proper role.

The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study sought to further evaluate a strategy that includes the short-term use of milrinone in addition to standard therapy. Although use of milrinone is indicated for and often used in treatment of patients with heart failure, the study population of OPTIME-CHF was not in such a severe state (eg, manifesting cardiogenic shock with end-organ or tissue hypoperfusion) that, in the opinion of the treating physician, inotropic or vasopressor agents were absolutely required. The primary hypothesis of this study was that in this population, short-term treatment with milrinone compared with placebo would result in fewer days of hospitalization for

cardiovascular events within the 60 days following randomization by either reducing the initial length of stay or preventing readmission.

## METHODS

### Study Overview

The design of the study has been described.<sup>18</sup> The OPTIME-CHF was a multicenter, randomized, double-blind, placebo-controlled trial. Patients who had known systolic chronic heart failure and had been hospitalized for exacerbation of chronic heart failure no more than 48 hours earlier were eligible. After approval of each site's institutional review board and written informed consent was obtained, patients were randomly assigned to receive an intravenous infusion of either milrinone or saline placebo. To avoid hypotension, the study drug was administered without a loading dose at an initial infusion of 0.5 µg/kg per minute, and investigators were encouraged to continue this rate for 48 hours. The rate could be adjusted downward to 0.375 µg/kg per minute if hypotension or significant improvement occurred and upward to 0.75 µg/kg per minute if neither occurred. Treatment was to continue for at least 48 hours and could be continued for up to 72 hours at the discretion of investigators.

Patients were otherwise treated at the discretion of their physicians, although recommended guidelines were provided. Guidelines represented steering-committee consensus of the best conventional therapy during hospitalization for exacerbation of chronic heart failure, according to the limited published evidence and outpatient-treatment guidelines.<sup>18</sup> These guidelines were not a formal part of the protocol but rather recommendations to be followed with study drug infusion. Critical components of these guidelines included the initiation and upward titration of angiotensin-converting enzyme (ACE) inhibitors, adequate diuresis, expeditious conversion to oral therapy, and comprehensive discharge planning. The target dose of ACE inhibitor was defined as that shown in randomized trials to reduce mortality, or dose-equivalent for ACE inhibi-

tors for which mortality data were unavailable. Follow-up occurred at 30 and 60 days after randomization, in person or by telephone.

### Patients

Eligible patients were at least 18 years of age and had demonstrated left ventricular ejection fraction below 40% within the past year. Patients were ineligible if the treating physician judged that intravenous inotropic therapy was essential (eg, for shock, metabolic acidosis, or severe hypotension). Patients also were excluded if they had active myocardial ischemia within the past 3 months, atrial fibrillation with poor ventricular rate control (>110/min), or sustained ventricular tachycardia or ventricular fibrillation. Because milrinone is a vasodilator and excreted renally,<sup>16</sup> patients with a baseline systolic blood pressure of less than 80 mm Hg or serum creatinine level higher than 3.0 mg/dL (265 µmol/L) were excluded.

### Study Organization

Patients were recruited at 78 US centers from July 1997 through November 1999. Institutional review boards at the hospitals approved the protocol and consent documents. Data management procedures included source data verification of 20% of all case-report forms, biannual site-monitoring visits, and standard double data entry. The primary end point of cardiovascular hospitalization was monitored against source documents for all patients. A steering committee provided oversight for the scientific conduct of the study. An independent safety committee reviewed the safety data after 250, 500, and 750 patients had completed the in-hospital phase of the protocol to ensure the safety of the active drug and placebo infusion.

### Outcomes

The primary efficacy end point was the total number of days hospitalized for cardiovascular causes (or days deceased) within the 60 days after randomization, a period that represents the highest risk for heart failure rehospitalization.<sup>19</sup> This composite end point reflects the need to

define therapies that safely decrease the length of index heart failure hospitalization and reduce rehospitalization, which is common. Acute intravenous hemodynamic therapy was not expected to affect outcome beyond 60 days. Multi-system disease and social-support problems frequently coexist with heart failure, and the primary efficacy of this investigational hemodynamic strategy was evaluated on cardiovascular hospitalization. Hospital days were defined as inpatient days and emergency department visit days. Days lost to follow-up and days deceased were prospectively included in the primary end point to avoid bias toward a therapy with increased mortality. Site investigators determined whether individual hospital days were related to cardiovascular causes.

The main secondary outcome included the proportion of cases failing therapy because of adverse events or worsening heart failure 48 hours after initiation of therapy. Adverse events included sustained hypotension, defined as a systolic blood pressure below 80 mm Hg for more than 30 minutes, requiring intervention; development of myocardial ischemia; significant atrial arrhythmias; and sustained ventricular arrhythmias (>30 seconds). Investigators determined worsening heart failure or inadequate improvement on the basis of persistent pulmonary congestion, inadequate diuresis, or hypotension with organ hypoperfusion. Other secondary outcomes included the proportion of patients achieving target doses of ACE-inhibitor therapy and time to achieve target dose, symptoms, improvement in heart failure score (TABLE 1),<sup>20</sup> length of initial hospitalization, days of hospitalization for cardiovascular events from initial hospital discharge to 60 days, days of hospitalization for cardiovascular events within 30 days after randomization, all-cause hospitalization, and mortality.

### Statistical Analyses

Analyses were performed with SAS version 6.12 (SAS Institute Inc, Cary, NC) and S-Plus version 3.4 (Insightful Corp, Seattle, Wash). They included all data

**Table 1.** Heart Failure Score\*

Point Value	Criteria			
	Dyspnea	Heart Rate/min	Rales	Right-Sided Heart Failure
1	Exertional	91-110	At bases only	JVP >6 cm H <sub>2</sub> O
2	Nocturnal	>110	More than at bases	JVP >6 cm H <sub>2</sub> O with edema or hepatomegaly
3	Orthopnea	...	...	...
4	Rest	...	...	...
Maximum points per category	4	2	2	2

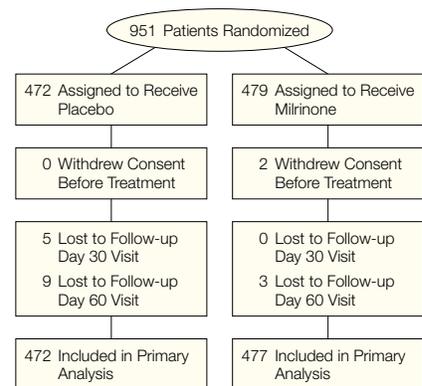
\*The score is calculated as the sum of the number of points for each of the 4 criteria. The maximum possible score, corresponding to the most severe symptomatic state of heart failure, is 10. JVP indicates jugular venous pressure. Derived from data reported by Lee et al.<sup>20</sup>

from all but 2 patients randomized (both had withdrawn consent and had been randomized to the milrinone treatment group) and were performed on an intent-to-treat basis including all other patients as randomized. Analyses were conducted at  $\alpha = .05$  unless otherwise indicated. For the primary analysis, days with uncertain status because of lack of follow-up were prospectively and conservatively included as hospitalized in the primary end point; this principle did not change the outcome results.

Categorical variables were compared between the treatment groups with the likelihood ratio  $\chi^2$  statistic, unless event rates warranted use of the Fisher exact test. The log-rank test was used to compare survival to 60 days between the treatment groups. Continuous variables were compared with the Wilcoxon rank sum test. Treatment groups were compared with a Cox proportional hazards model for the primary outcome. For patients whose clinical course was not followed to 60 days, the number of days hospitalized for cardiovascular causes was augmented by the number of days between the date of death or last contact and day 60. Cox proportional hazards modeling also was used to compare the length of initial hospitalization, the number of days patients were hospitalized for cardiovascular causes between discharge and 60 days, and the number of days patients were hospitalized (all-cause) within 60 days.

The study was designed with an estimated sample size of 500 patients per treatment group, based on an 80% power to observe a clinically meaning-

**Figure.** Study Outline



ful difference of 1 hospital day by using a 2-sided test with  $\alpha = .05$  for comparison. If the primary end point was normally distributed and given an anticipated SD of 5 days, at least 392 patients per group would be required if a 2-sample *t* test was used.

Safety was determined by blinded monitoring of treatment failures and serious adverse events. Because both treatment groups represented accepted care, review of the primary end point occurred only at trial completion. The proportion of patients with treatment failure or at least 1 serious adverse event between treatment groups was compared by using a Bayesian approach assuming a noninformative prior.<sup>21</sup> The safety committee was to recommend early termination of the trial to the steering committee if the Bayesian analyses indicated that  $P > .95$  that the odds ratio of treatment effect for treatment failure or for the rate of serious adverse events differed from 1.0. Similarly,

$P > .90$  that the odds ratio of treatment effect differed from 1.0 for mortality was recommended as a guideline for the safety committee to consider recommending early termination of the trial.

The trial was terminated because of slow enrollment after 951 patients had been randomized, with the steering committee and sponsor's agreement after review of the primary end point in

placebo-treated patients. The variance of the distribution of the primary end point in this group indicated that the study would retain a power of 77% (compared with 79.5% at 1000 patients) if terminated at the 940 patients already enrolled in the trial at the time of calculation.

**Table 2.** Baseline Characteristics\*

Characteristic	Placebo (n = 472)	Milrinone (n = 477)
<b>Demographic</b>		
Age, mean (SD), y	66 (14)	65 (15)
Male sex, No. (%)	371 (68.0)	306 (64.2)
Race, No. (%)		
White	314 (66.5)	299 (62.7)
Black	151 (32.0)	159 (33.3)
Hours from admission to randomization, mean (SD)	15.0 (14) [n = 471]	15.6 (14) [n = 476]
<b>Cardiac</b>		
Baseline New York Heart Association classification, No. (%)		
II	33/469 (7.0)	31/474 (6.5)
III	212/469 (45.2)	219/474 (46.2)
IV	223/469 (47.5)	224/474 (47.3)
Ischemic etiology of heart failure, No. (%)	243 (51.5)	242 (50.7)
Qualifying ejection fraction, mean (SD), %	24 (8)	23 (8)
Hospitalizations in previous year, mean (SD), No.	1.9 (2.0) [n = 465]	2.1 (2.2) [n = 468]†
<b>Medical history, No. (%)</b>		
Hypertension	316/471 (67.1)	325 (68.1)
Myocardial infarction	227 (48.1)	230 (48.2)
Myocardial revascularization	198/471 (42.0)	186 (39.0)
Atrial fibrillation	161 (34.1)	141 (29.6)
Chronic obstructive pulmonary disease	104 (22.0)	115 (24.1)
Diabetes mellitus	204 (43.2)	214 (44.9)
Tobacco use (ever)	312/471 (66.3)	304/476 (63.9)
Hypercholesterolemia	159/369 (43.1)	164/377 (43.5)
<b>Physical findings at randomization</b>		
Blood pressure, mean (SD), mm Hg	120 (18)/71 (12)	120 (19)/71 (13)
Heart rate/min, mean (SD)	85 (15)	84 (16)
Jugular venous pressure >6 cm, No. (%)	322/433 (74.4)	314/441 (71.2)
Rales, No. (%)	384 (81.4)	387 (81.1)
S <sub>3</sub> gallop, No. (%)	273/465 (58.7)	275/470 (58.5)
<b>Laboratory findings at randomization, mean (SD)‡</b>		
Serum sodium, mEq/L	138 (4) [n = 470]	138 (4) [n = 473]
Serum potassium, mEq/L	4.2 (0.6) [n = 470]	4.2 (1.6) [n = 474]
Serum creatinine, mg/dL	1.5 (0.5) [n = 467]	1.4 (0.5) [n = 471]
Blood urea nitrogen, mg/dL	11.5 (7.5) [n = 468]	11.3 (7.0) [n = 468]
<b>Medication use, No. (%)</b>		
Angiotensin-converting enzyme inhibitor	325 (68.9)	340 (71.3)
Angiotensin receptor blocker	55 (11.7)	64 (13.4)
β-Blocker	105 (22.2)	107 (22.4)
Diuretic	427 (90.5)	429 (89.9)
Digoxin	333 (70.6)	359 (75.3)
Calcium channel blocker	53 (11.2)	76 (15.9)†
Aspirin	220 (47.4)	220 (45.7)
Amiodarone	70 (14.8)	77 (16.1)

\*Total number of patients listed only when it varies from number randomized as shown.

† $P < .05$ . No other comparisons were significant.

‡To convert creatinine values to  $\mu\text{mol/L}$ , multiply by 88.4; to convert urea nitrogen to  $\text{mmol/L}$ , multiply by 0.357.

## RESULTS

In all, 951 patients were randomized, of whom 2 withdrew consent before treatment, leaving 949 patients available for analysis (FIGURE). The 2 groups were well balanced with respect to all but 2 baseline characteristics (TABLE 2): there were a mean 2.1 hospitalizations in the prior year for patients randomized to milrinone vs 1.9 hospitalizations for patients randomized to placebo ( $P = .04$ ), and milrinone-treated patients were more likely to have been treated with a calcium channel blocker (15.9% [milrinone] vs 11.2% [placebo];  $P = .03$ ). Similarly, apart from the use of intravenous diuretics at 48 hours (76.9% [milrinone] vs 82.2% [placebo];  $P = .02$ ), the care of the 2 treatment groups did not differ significantly at discharge or in regard to the use of medications at 48 hours after randomization or of major procedures, including right-sided heart catheterization (TABLE 3).

Primary efficacy results are shown in TABLE 4. Treatment with milrinone did not reduce the primary end point of days hospitalized for cardiovascular causes within 60 days compared with placebo. The groups did not differ in the length of the initial hospitalization or number of days of readmission. The milrinone and placebo groups did not differ significantly in in-hospital mortality or 60-day mortality. The composite rate of death or readmission within 60 days was similar in the 2 groups (Table 3).

Clinical status was measured by a composite heart failure score, a subjective questionnaire on health status (not previously validated), and a visual analog scale.<sup>22</sup> Both groups had a significant and equivalent reduction in heart failure score from baseline at day 3 and even more so at discharge. Milrinone-treated patients reported that they felt

better than placebo-treated patients, as measured by the visual analog scale at one point, 30 days (67 vs 63;  $P = .02$ ); no overall significant differences or trends were identified for other points. There were no differences in procedures between the groups: 5.9% of patients had invasive hemodynamic monitoring by right-sided heart catheterization, 2.5% had mechanical ventilation, and 7.0% had left-sided heart catheterization during the initial hospitalization. There was also no significant difference between the groups' reaching the target dose of ACE inhibitor at 48 hours (40.5% milrinone vs 35.8% placebo;  $P = .14$ ) and at discharge from initial hospitalization (43.8% milrinone vs 40.9% placebo;  $P = .36$ ).

Although there was no significant difference in treatment failures defined by progression of chronic heart failure, treatment failures caused by adverse events by 48 hours were more common in milrinone-treated patients (TABLE 5 and TABLE 6). This treatment failure rate reflects the increased incidence of sustained hypotension and atrial fibrillation in the milrinone-treated patients. During index hospitalization, serious sustained hypotension (systolic blood pressure of  $\leq 80$  mm Hg for at least 30 minutes and requiring intervention) was more common in the milrinone group. Milrinone use was also associated with new atrial arrhythmias during the index hospitalization and trended toward an association with more serious ventricular arrhythmias. Multivariable predictors of any new arrhythmia during the index hospitalization included milrinone use ( $P = .001$ ), lack of previous myocardial infarction ( $P = .04$ ), use of amiodarone ( $P = .02$ ), and systolic blood pressure less than 90 mm Hg ( $P = .047$ ).

In Cox proportional hazards multivariable analysis, independent baseline predictors of increased days hospitalized included higher serum urea nitrogen level ( $P < .001$ ), lower systolic blood pressure ( $P < .001$ ), male sex ( $P = .008$ ), number of previous hospitalizations ( $P = .002$ ), worse New York Heart Association classification ( $P = .008$ ), and hyponatremia ( $P = .03$ ).

## COMMENT

The OPTIME-CHF study is, to our knowledge, the first large, placebo-controlled clinical trial designed to clarify the role of milrinone, a commonly used intravenous inotropic agent approved by the Food and Drug Administration in treatment of patients hospitalized for an exacerbation of chronic heart failure. The underlying rationale for the study was that the known hemodynamic improvements with short-term intravenous milrinone administration would translate into clinical benefit measured by shorter hospitalizations, improved symptoms, or improved dosing of standard therapy. In this study, however, the routine addition of intravenous milrinone, even though labeled for this indication, did not demonstrate any benefit in the duration of hospitalization, dosing of ACE inhibitor, or symptoms. The 48-hour infusion of milrinone was associated with increased early treatment failures, particularly caused by new atrial arrhythmias and significant hypotension. This excess of adverse events did not clearly translate into overall significantly longer hospitalizations, increased readmission, or mortality.

The clinical characteristics of this population were typical of patients with worsening chronic heart failure.<sup>19</sup> They were generally older, had significant comorbidities, and showed clinical findings of volume overload. Nearly all had New York Heart Association class III or IV symptoms at baseline, had been hos-

pitalized the previous year, and were manifesting significant signs of persistent volume overload an average of 15 hours after admission. Such patients with chronic heart failure who required admission would be treated with

**Table 3.** In-Hospital Characteristics and Treatments

Characteristic, No. (%)	Placebo (n = 472)	Milrinone (n = 477)
Dobutamine use	44 (9.3)	55 (11.5)
Cardiac catheterization	29 (7.8)	37 (7.0)
Mechanical ventilation	13 (2.8)	11 (2.3)
Right-sided heart catheter	26 (5.5)	30 (6.3)
Cardioversion/defibrillation	12 (2.5)	11 (2.3)
Medication use at 48 hours		
Oral diuretic	282 (59.7)	292 (61.2)
Intravenous diuretic	388 (82.2)	367 (76.9)*
ACE inhibitor†	347 (73.5)	348 (73.0)
$\beta$ -Blocker	92 (19.5)	97 (20.3)
Calcium channel blocker	48 (10.2)	66 (13.8)
Angiotensin receptor blocker	62 (13.1)	69 (14.5)
Medication use at discharge		
Diuretic	94.1	91.4
ACE inhibitor	74.8	74.2
$\beta$ -Blocker	22.2	24.1
Calcium channel blocker	10.6	14.7
Angiotensin receptor blocker	14.2	13.8
Amiodarone	17.2	19.3
Digoxin	76.7	79.0

\* $P = .02$ . No other comparisons were significant.  
†ACE indicates angiotensin-converting enzyme.

**Table 4.** Primary Outcome and Hospitalization

Outcome	Placebo (n = 472)	Milrinone (n = 477)	P Value
Days of hospitalization for cardiovascular causes within 60 days			
Median (IQR)*	7 (4, 14)	6 (4, 13)	.71
Mean (SD)	12.5 (14.0)	12.3 (14.1)	
Days of hospitalization from infusion to initial discharge			
Median (IQR)	5 (4, 8)	5 (4, 7)	.99
Mean (SD)	7.0 (6.6)	7.0 (6.2)	
Days of hospitalization for cardiovascular causes from discharge to 60 days			
Median (IQR)	0 (0, 5)	0 (0, 5)	.59
Mean (SD)	5.9 (12.5)	5.7 (12.6)	
Days of hospitalization for any cause within 60 days			
Median (IQR)	8 (4, 16)	7 (4, 15)	.83
Mean (SD)	13.5 (14.4)	13.4 (14.7)	
Death or readmission within 60 days, No./Total (%)	164/464 (35.3)	166/474 (35.0)	.92

\*IQR indicates interquartile range.

**Table 5.** Secondary Outcomes\*

Outcome	Baseline		Day 3		Discharge		Day 30		Day 60	
	Placebo	Milrinone	Placebo	Milrinone	Placebo	Milrinone	Placebo	Milrinone	Placebo	Milrinone
Heart failure score†	6 (n = 472)	6 (n = 477)	3 (n = 365)	3 (n = 361)	2 (n = 405)	2 (n = 400)	NA	NA	NA	NA
Visual analog scale‡	42 (n = 469)	42 (n = 466)	NA	NA	70 (n = 397)	72 (n = 398)	63 (n = 384)	67 (n = 373)	67 (n = 369)	68 (n = 363)
Subjective health status§	NA	NA	NA	NA	89 (n = 365)	87 (n = 363)	60 (n = 239)	65 (n = 262)	53 (n = 200)	57 (n = 217)

\*NA denotes not available. Data presented as mean scores and numbers in parentheses are denominators of patients for whom data were available.

†Calculated as the sum of the number of points for each of the 4 criteria. The maximum possible score, corresponding to the most severe symptomatic state of heart failure, is 10.

‡Worst health to best health (scale, 0-100).

§Subjective questionnaire measured as the percentage the patient felt better.

**Table 6.** Adverse Events and Mortality\*

Adverse Event, No. (%)	Placebo (n = 472)	Milrinone (n = 477)	P Value
Treatment failure cause at 48 hours	43/466 (9.2)	97/470 (20.6)	<.001
Progression of heart failure	6.8	7.9	.54
Adverse event	2.1	12.6	<.001
Events during index hospitalization			
Myocardial infarction	2 (0.4)	7 (1.5)	.18
New atrial fibrillation or flutter	7 (1.5)	22 (4.6)	.004
Ventricular tachycardia or fibrillation†	7 (1.5)	16 (3.4)	.06
Sustained hypotension‡	15 (3.2)	51 (10.7)	<.001
Death	11 (2.3)	18 (3.8)	.19
Events within 60 days			
Myocardial infarction	5/448 (1.1)	10/462 (2.2)	.21
New atrial fibrillation or flutter	16/446 (3.6)	26/462 (5.6)	.14
Ventricular tachycardia or fibrillation	20/446 (4.5)	23/461 (5.0)	.72
Death	41/463 (8.9)	49/474 (10.3)	.41

\*Total number of patients listed only when it varies from number randomized as shown.

†Reported by the investigator.

‡Defined as a systolic blood pressure below 80 mm Hg for more than 30 minutes, requiring intervention.

intravenous diuresis and titration of standard oral therapy and, in many cases, with inotropic agents.

Achieving better hemodynamics earlier in hospitalization might allow increases in ACE inhibitor dose to more desirable levels before discharge. Some evidence suggests that the short-term use of milrinone can aid in the upward titration of ACE inhibitors to doses known to improve outcomes.<sup>15,23</sup> If true, long-term benefits could result. In this trial, however, ACE inhibitor dosing was not significantly improved with active milrinone treatment.

Regardless of hemodynamic improvement or impact on length of stay, drug efficacy must be balanced with safety. Survival in chronic heart failure relates more closely to severity of left ventricular dysfunction, neurohormonal abnormalities, and the extent and progression of coronary disease than to hemodynamics.<sup>17</sup> Hospitalization more closely relates to worsening of the he-

modynamic profile and volume retention, often the result of a high-sodium diet, hypertension, ischemia, or a combination of these. Particular concern remains over the risks associated with positive inotropic agents: studies with drugs of this and similar classes have shown that short-term improvements in hemodynamics may correlate inversely with mortality.<sup>24</sup> Most agents studied have a common mechanism of action that results in elevated myocardial cyclic adenosine monophosphate through either  $\beta$ -receptor agonism or phosphodiesterase inhibition. Although these agents are hemodynamically effective with short-term use, their long-term use, including use of oral milrinone, particularly in patients with more advanced chronic heart failure, has been strongly associated with increased mortality or morbidity.<sup>25</sup>

The OPTIME-CHF study had several limitations. It did not directly address patients with acutely decompensated

chronic heart failure for whom inotropic therapy was felt to be essential (eg, low cardiac output state with tissue hypoperfusion), although this is an area in which physicians may disagree. For all patients, milrinone was used within its labeled indication. This study was not structured to assess patients for self-limited ventricular tachycardia, a known adverse effect of milrinone. Although the excess adverse events did not result in significantly increased mortality, this study was inadequately powered to evaluate mortality.

## CONCLUSION

The OPTIME-CHF study enrolled a population of patients with severe chronic heart failure and for whom inotropic therapy was indicated but not, in the opinion of the investigators, essential. Literature and practice suggest that the patients enrolled in this study are typical of heart failure patients admitted to US hospitals. No benefit from milrinone treatment was observed in hospital days, other measurements of chronic heart failure improvement, or the ability to institute oral drugs that improve long-term prognosis, although milrinone caused an increase in early adverse events related to hypotension and atrial arrhythmias. Our results do not support the routine use of milrinone in patients hospitalized with an exacerbation of chronic heart failure.

**Author Affiliations:** Duke Clinical Research Institute, Durham, NC (Drs Cuffe, Califf, and O'Connor); Heart Failure Program, University of North Carolina, Chapel Hill (Dr Adams); University of Alabama, Birmingham (Drs Benza and Bourge); Boston University School of Medicine, Boston, Mass (Dr Colucci); Veterans Affairs Medical Center, San Francisco, Calif (Dr Massie); University Hospital of Cleveland, Cleveland, Ohio (Dr Pina); Christ Hospital and Medical Center, Oak Lawn, Ill (Dr Silver); and Northwestern University, Chicago, Ill (Drs Quigg and Gheorghiadu).

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**Drafting of the manuscript:** Cuffe, Califf, O'Connor, Gheorghide.

**Critical revision of the manuscript for important intellectual content:** Cuffe, Califf, Adams, Benza, Bourge, Colucci, Massie, O'Connor, Pina, Quigg, Silver, Gheorghide.

**Statistical expertise:** Cuffe, Califf, Adams, Benza, Bourge, Colucci, Massie, O'Connor, Pina, Quigg, Silver, Gheorghide.

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#### OPTIME-CHF Investigators

**Steering Committee:** M. Gheorghide (chair), R. M. Califf (cochair), K. F. Adams, Jr, W. S. Colucci, C. M. O'Connor, R. Quigg, R. Bourge, B. M. Massie, I. Pina, and M. A. Silver.

**Main Writing Committee:** M. S. Cuffe, R. M. Califf, C. M. O'Connor, and M. Gheorghide.

**Safety Committee:** S. Goldstein (chair), F. E. Harrell, Jr, and L. W. Stevenson.

**Sanofi-Synthelabo Representatives:** A. Akbary and J. Kocsis.

**Statistical Analysis:** J. D. Leimberger.

**Study Coordinators:** K. Lucas and L. Robinson.

**Clinical Sites and Investigators:** University of Alabama, Birmingham; R. Benza; St Thomas Hospital, Nashville, Tenn; D. Pearce; Duke University Medical Center, Durham, NC; C. O'Connor, M. Cuffe; Henry Ford Hospital, Detroit, Mich; S. Borzak; William Beaumont Hospital, Royal Oak, Mich; G. Timmis; Georgia Baptist Medical Center, Atlanta; L. Berger; Baptist Medical Center-Princeton, Birmingham, Ala; M. Wilensky; Osf Saint Francis Medical—Methodist Medical Center, Peoria, Ill; A. Chu; Deborah Heart & Lung Center, Brown Mills, NJ; R. Bender; Sacred Heart Hospital—Baptist Hospital Behavioral Medicine Center, Pensacola, Fla; S. Teague; Northeast Medical Center, Concord, NH; P. Campbell; LSU Medical Center, Shreveport, La; F. Sheridan; Medical University of South Carolina, Charleston; G. Hendrix; Northwestern Memorial Hospital, Chicago, Ill; M. Johnson; Hennepin County Medical Center, Minneapolis, Minn; B. Bart; Saint Luke's Hospital, Kansas City, Mo; D. Bresnahan; University Hospital, Augusta, Ga; B. Chandler; Margaret R. Pardee Memorial Hospital, Hendersonville, NC; P. Goodfield; Rush-Presbyterian-St Luke's Medical Center, Chicago, Ill; W. Kao; James H. Haley Veterans Affairs Hospital, Tampa, Fla; D. Schocken; John L. McClellan Veterans Affairs

Medical Center and University Hospital of Arkansas for Medical Sciences, Little Rock; E. Smith; North Shore University Hospital, Manhasset, NY; D. Grossman; Michigan Heart and Vascular Institute, Ypsilanti; M. Leonen; Saint Vincent Hospital and Health Care Center, Indianapolis, Ind; E. Fry; Washington University-Barnes Jewish Hospital, St Louis, Mo; J. Rogers; Jefferson Hospital, Pittsburgh, Pa; S. Tauber; Lawrence Memorial Hospital, Lawrence, Kan; K. M. Zabel; Williamsport Hospital & Medical Center-Susquehanna Heart Center, Williamsport, Pa; J. Burks; Robert Wood Johnson University Hospital, New Brunswick, NJ; R. Hilkert; Cedars-Sinai Medical Center, Los Angeles, Calif; R. Davidson; Medical College of Virginia, Richmond; M. Hess; Baptist Memorial Hospital, Memphis, Tenn; F. McGrew; Loyola University Medical Center, Maywood, Ill; J. Mendez; Abbott Northwestern Hospital, Minneapolis, Minn; M. Pritzker; Good Samaritan Regional Medical Center, Phoenix, Ariz; E. Selsky; Wuesthoff Hospital, Rockledge, Fla; K. Sheikh; Evanston Hospital, Evanston, Ill; R. Williams; South Jersey Hospital System, Elmer, NJ; J. Kramer; Oakwood Hospital and Medical Center, Dearborn, Mich; A. Riba; Chesapeake General Hospital, Chesapeake, Va; C. Ashby; Westchester County Medical Center, Valhalla, NY; R. Belkin; Sarasota Memorial Hospital, Sarasota, Fla; M. Frey; Harper Hospital, Detroit, Mich; P. Gordon; Virginia Beach General Hospital, Virginia Beach, Va; S. Jones; University of Minnesota, Minneapolis; L. Miller; Columbia University Hospital, Tamarac, Fla; R. Schneider, L. Simkins; Mercy Hospital of Pittsburgh, Pa; P. Bannon; Providence Hospital, Mobile, Ala; C. Brown; North Ridge Medical Center, Ft Lauderdale, Fla; L. Cioci; Medical Center of Delaware, Newark; E. Marshall; Roper Hospital, Charleston, SC; B. Reeves; Lutheran General Hospital, Park Ridge, Ill; L. Brookfield; University of Pennsylvania Medical Center, Braddock; S. Tauber; Jewish Hospital, Louisville, Ky; J. Adams; Columbia-Blake Hospital, Bradenton, Fla; S. Mehanny; Riverside Methodist Hospital, Columbus, Ohio; R. Frazier; University of Utah Health Science Center, Salt Lake City; D. Renlund; Illinois Masonic Medical Center, Chicago; C. Chiu; Mary Washington Hospital, Fredericksburg, Va; T. Martyak; Tulane University School of Medicine, New Orleans, La; H. Ventura; Memorial Hospital, Chattanooga, Tenn; K. Wright; University of North Carolina, Chapel Hill; K. Adams; University of Illinois Medical Center, Chicago; S. Dunlap; Lakeview Regional Medical Center, Covington, La; M. Gomez; Mount Sinai Medical Center, New York, NY; M. Kukin; Louis A. Weiss Memorial Hospital, Chicago, Ill; A. Sheikh; Glenbrook Hospital, Glenview, Ill; R. Williams; Allegheny University Hospital-Graduate, Philadelphia, Pa; B. Berger; Middletown Regional Hospital, Middletown, Ohio; G. Brown; Morton Plant Hospital, Clearwater, Fla; M. Hepp; Christ Hospital, Cincinnati, Ohio; D. Kereiakes; Bayfront Medical Center, St Petersburg, Fla; M. McIvor; Erlanger Medical Center, Chattanooga, Tenn; M. Mutter; Sentara Hampton General Hospital, Hampton, Va; K. Newby; Latter-Day Saints Hospital, Salt Lake City, Utah; D. Renlund; and Madigan Army Medical Center, Tacoma, Wash; M. Yandel.

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