Short-term Intravenous Milrinone for Acute Exacerbation of Chronic Heart Failure
A Randomized Controlled Trial

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Chronic heart failure is one of the most common and life-threatening cardiovascular conditions, affecting nearly 5 million people in the United States. It causes more than 200,000 deaths each year and is the leading discharge diagnosis among the Medicare population. Treatment costs for chronic heart failure, most of which are incurred by inpatients, are more than $30 billion yearly. Almost half of the patients with advanced disease will die within 1 year. Hospitalization is common in these patients and is associated with a poor prognosis. From 3 to 6 months after discharge, readmission rates for chronic heart failure range from 30% to 50%.

Hospitalization for chronic heart failure is often associated with worsening hemodynamic function, which may be caused by systemic congestion and reduced cardiac output.

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partly responsible for the volume reten-
tion that is usually the precipitating fac-
tor. Inotropic agents produce beneficial
hemodynamic effects in heart failure pa-
tients and may facilitate earlier achieve-
ment of hemodynamic improvement and
titration of standard oral therapy, par-
ticularly when used with hemody-
namic monitoring by right-sided heart
catheterization.14,15

Milrinone, a commonly used inotro-
pic agent that is labeled for use in the
short-term intravenous treatment of
acute exacerbation of chronic heart fail-
ure, has several characteristics that
make it physiologically attractive. It has
both inotropic and vasodilator proper-
ties, which increase cardiac output and
reduce systemic vascular resistance and
pulmonary capillary wedge pres-
ures.16 The drug exerts its hemody-
namic effects without excessive changes
in heart rate or increases in myocar-
dial oxygen consumption,16 impor-
tant because coronary artery disease and
chronic heart failure often coexist.17 Al-
though intravenous agents (eg, milri-
none and dobutamine) are often used
as adjuncts to standard therapy and,
with or without hemodynamic guid-
ance, represent a rational approach to
treatment of patients with an acute ex-
acerbation of chronic heart failure, no
placebo-controlled clinical trials have
evaluated their proper role.

The Outcomes of a Prospective Trial
of Intravenous Milrinone for Exacer-
bations of Chronic Heart Failure
(OPTIME-CHF) study sought to fur-
ter evaluate a strategy that includes the
short-term use of milrinone in addition
to standard therapy. Although use of mil-
rinone 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, mani-
festing cardiogenic shock with end-
organ or tissue hypoperfusion) that in
the opinion of the treating physician, ino-
tropic or vasopressor agents were abso-
lutely required. The primary hypoth-
thesis 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 reduc-
ing the initial length of stay or prevent-
ing readmission.

METHODS

Study Overview
The design of the study has been de-
scribed.18 The OPTIME-CHF was a mul-
ticenter, randomized, double-blind, pla-
cebo-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 ap-
proval of each site’s institutional review
board and written informed consent was
obtained, patients were randomly as-
signed to receive an intravenous infu-
sion of either milrinone or saline pla-
cebo. 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 en-
couraged to continue this rate for 48
hours. The rate could be adjusted down-
ward to 0.375 µg/kg per minute if hy-
potension or significant improvement oc-
curred 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 pro-
vided. Guidelines represented steering-
committee consensus of the best con-
ventional therapy during hospitalization
for exacerbation of chronic heart fail-
ure, according to the limited published
evidence and outpatient-treatment guide-
lines.18 These guidelines were not a for-
mal part of the protocol but rather rec-
ommendations to be followed with study
drug infusion. Critical components of
these guidelines included the initiation
and upward titration of angiotensin-
converting enzyme (ACE) inhibitors, ad-
equate diuresis, expeditious conver-
sion to oral therapy, and comprehensive
discharge planning. The target dose of
ACE inhibitor was defined as that shown
in randomized trials to reduce mortal-
ity, or dose-equivalent for ACE inhibi-
tors for which mortality data were un-
available. Follow-up data were collected
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 ven-
tricular ejection fraction below 40%
within the past year. Patients were in-
eligible if the treating physician judged
that intravenous inotropic therapy was
essential (eg, for shock, metabolic aci-
dosis, or severe hypotension). Patients
also were excluded if they had active
myocardial ischemia within the past 3
months, atrial fibrillation with poor ven-
tricular rate control (>110/min), or sus-
tained ventricular tachycardia or ven-
tricular fibrillation. Because milrinone
is a vasodilator and excreted renally,16
patients with a baseline systolic blood
pressure of less than 80 mm Hg or se-
rum 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 hos-
itals approved the protocol and con-
sent documents. Data management pro-
cedures included source data verification
of 20% of all case-report forms, biannu-
al site-monitoring visits, and standard
double data entry. The primary end
point of cardiovascular hospitalization
was monitored against source docu-
ments for all patients. A steering com-
mittee provided oversight for the
scientific conduct of the study. An inde-
pendent 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 car-
diovascular causes (or days deceased)
within the 60 days after randomization,
a period that represents the highest risk
for heart failure rehospitalization.19 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. Multisystem 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), 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 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 α = .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 χ² 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 meaningful difference of 1 hospital day by using a 2-sided test with α = .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. 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,
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.

**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 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 (\(P=0.04\)), and milrinone-treated patients were more likely to have been treated with a calcium channel blocker (15.9% [milrinone] vs 11.2% [placebo]; \(P=0.03\)). Similarly, apart from the use of intravenous diuretics at 48 hours (76.9% [milrinone] vs 82.2% [placebo]; \(P=0.02\)), 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-treated patients were more likely to have been treated with a calcium channel blocker (15.9% [milrinone] vs 11.2% [placebo]; \(P=0.03\)). Similarly, apart from the use of intravenous diuretics at 48 hours (76.9% [milrinone] vs 82.2% [placebo]; \(P=0.02\)), 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).

**Clinical status was measured by a composite heart failure score, a subjective questionnaire on health status (not previously validated), and a visual analog scale.** 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

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**Table 2. Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 472)</th>
<th>Milrinone (n = 477)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>66 (14)</td>
<td>65 (15)</td>
</tr>
<tr>
<td>Male sex, No. (%)</td>
<td>371 (68.0)</td>
<td>306 (64.2)</td>
</tr>
<tr>
<td>Race, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>314 (66.5)</td>
<td>299 (62.7)</td>
</tr>
<tr>
<td>Black</td>
<td>151 (32.0)</td>
<td>159 (33.3)</td>
</tr>
<tr>
<td><strong>Hours from admission to randomization, mean (SD)</strong></td>
<td>15.0 (14) [n = 471]</td>
<td>15.6 (14) [n = 476]</td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline New York Heart Association classification, No. (%)</td>
<td>33/469 (7.0)</td>
<td>31/474 (6.5)</td>
</tr>
<tr>
<td>II</td>
<td>212/469 (45.2)</td>
<td>219/474 (46.2)</td>
</tr>
<tr>
<td>III</td>
<td>223/469 (47.5)</td>
<td>224/474 (47.3)</td>
</tr>
<tr>
<td>Ischemic etiology of heart failure, No. (%)</td>
<td>243 (51.5)</td>
<td>242 (50.7)</td>
</tr>
<tr>
<td>Qualifying ejection fraction, mean (SD), %</td>
<td>24 (9)</td>
<td>23 (8)</td>
</tr>
<tr>
<td>Hospitalizations in previous year, mean (SD), No.</td>
<td>1.9 (2.0) [n = 465]</td>
<td>2.1 (2.2) [n = 468]</td>
</tr>
<tr>
<td><strong>Medical history, No. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>316/471 (67.1)</td>
<td>325 (68.1)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>227 (48.1)</td>
<td>230 (48.2)</td>
</tr>
<tr>
<td>Myocardial revascularization</td>
<td>198/471 (42.0)</td>
<td>186 (39.0)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>161 (34.1)</td>
<td>141 (29.6)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>104 (22.0)</td>
<td>115 (24.1)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>204 (43.2)</td>
<td>214 (44.9)</td>
</tr>
<tr>
<td>Tobacco use (ever)</td>
<td>312/471 (66.3)</td>
<td>304/476 (63.9)</td>
</tr>
<tr>
<td><strong>Hypercholesterolemia</strong></td>
<td>159/369 (43.1)</td>
<td>164/377 (43.5)</td>
</tr>
<tr>
<td><strong>Physical findings at randomization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure, mean (SD), mm Hg</td>
<td>120 (19)/71 (12)</td>
<td>120 (19)/71 (13)</td>
</tr>
<tr>
<td>Heart rate/min, mean (SD)</td>
<td>85 (15)</td>
<td>84 (16)</td>
</tr>
<tr>
<td>JUGULAR VENOUS PRESSURE &gt;6 cm, No. (%)</td>
<td>322/433 (74.4)</td>
<td>314/441 (71.2)</td>
</tr>
<tr>
<td>Rales, No. (%)</td>
<td>384 (81.4)</td>
<td>387 (81.1)</td>
</tr>
<tr>
<td>S3 gallop, No. (%)</td>
<td>273/465 (58.7)</td>
<td>275/470 (58.5)</td>
</tr>
<tr>
<td><strong>Laboratory findings at randomization, mean (SD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum sodium, mEq/L</td>
<td>138 (4) [n = 470]</td>
<td>138 (4) [n = 473]</td>
</tr>
<tr>
<td>Serum potassium, mEq/L</td>
<td>4.2 (0.6) [n = 470]</td>
<td>4.2 (1.6) [n = 474]</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.5 (0.5) [n = 467]</td>
<td>1.4 (0.5) [n = 471]</td>
</tr>
<tr>
<td>Blood urea nitrogen, mg/dL</td>
<td>11.5 (7.5) [n = 468]</td>
<td>11.3 (7.0) [n = 468]</td>
</tr>
<tr>
<td><strong>Medication use, No. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor</td>
<td>325 (68.9)</td>
<td>340 (71.3)</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>55 (11.7)</td>
<td>64 (13.4)</td>
</tr>
<tr>
<td>ß-Blocker</td>
<td>105 (22.2)</td>
<td>107 (22.4)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>427 (90.5)</td>
<td>429 (89.9)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>333 (70.6)</td>
<td>359 (75.3)</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>53 (11.2)</td>
<td>76 (15.9)†</td>
</tr>
<tr>
<td>Aspirin</td>
<td>220 (47.4)</td>
<td>220 (45.7)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>70 (14.8)</td>
<td>77 (16.1)</td>
</tr>
</tbody>
</table>

*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 µmol/L, multiply by 88.4; to convert urea nitrogen to mmol/L, multiply by 0.357.
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 morbidities, and showed clinical findings of volume overload. Nearly all had New York Heart Association class III or IV symptoms at baseline, had been hospitalized 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 Milrinone for chronic heart failure.

**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. 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 hospitalized 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 Milrinone for chronic heart failure.

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

<table>
<thead>
<tr>
<th>Characteristic, No. (%)</th>
<th>Placebo (n = 472)</th>
<th>Milrinone (n = 477)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobutamine use</td>
<td>44 (9.3)</td>
<td>51 (11.5)</td>
</tr>
<tr>
<td>Intravenous diuretic</td>
<td>388 (82.2)</td>
<td>367 (76.9)*</td>
</tr>
<tr>
<td>ACE inhibitor†</td>
<td>347 (73.9)</td>
<td>348 (73.0)</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>92 (19.5)</td>
<td>97 (20.3)</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>48 (10.2)</td>
<td>66 (13.8)</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>62 (13.1)</td>
<td>69 (14.5)</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>14.2</td>
<td>13.8</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>17.2</td>
<td>19.3</td>
</tr>
<tr>
<td>Digoxin</td>
<td>76.7</td>
<td>79.0</td>
</tr>
</tbody>
</table>

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

### Table 4. Primary Outcome and Hospitalization

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

*IQR indicates interquartile range.
intra venous 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. 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. Hospitalization more closely relates to worsening of the hemodynamic 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.24 Most agents studied have a common mechanism of action that results in elevated myocardial cyclic adenosine monophosphate through either β-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.25

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.

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**Table 5. Secondary Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Baseline (n = 472)</th>
<th>Milrinone (n = 477)</th>
<th>Placebo (n = 469)</th>
<th>Milrinone (n = 466)</th>
<th>Placebo (n = 466)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure score†‡§</td>
<td>6 (n = 472)</td>
<td>6 (n = 477)</td>
<td>3 (n = 365)</td>
<td>3 (n = 361)</td>
<td>2 (n = 405)</td>
</tr>
<tr>
<td>Visual analog scale‡‡‡</td>
<td>42 (n = 469)</td>
<td>42 (n = 466)</td>
<td>NA</td>
<td>NA</td>
<td>70 (n = 397)</td>
</tr>
<tr>
<td>Subjective health status NA</td>
<td>NA</td>
<td>NA</td>
<td>70 (n = 397)</td>
<td>72 (n = 398)</td>
<td>63 (n = 384)</td>
</tr>
</tbody>
</table>

**Table 6. Adverse Events and Mortality**

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n = 472)</th>
<th>Milrinone (n = 477)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failure cause at 48 hours</td>
<td>43/466 (9.2)</td>
<td>97/470 (20.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Progression of heart failure</td>
<td>6.8</td>
<td>7.9</td>
<td>.54</td>
</tr>
<tr>
<td>Adverse event</td>
<td>2.1</td>
<td>12.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Events during index hospitalization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2 (0.4)</td>
<td>7 (1.5)</td>
<td>.18</td>
</tr>
<tr>
<td>New atrial fibrillation or flutter</td>
<td>7 (1.5)</td>
<td>22 (4.6)</td>
<td>.004</td>
</tr>
<tr>
<td>Ventricular tachycardia or fibrillation‡</td>
<td>7 (1.5)</td>
<td>16 (3.4)</td>
<td>.06</td>
</tr>
<tr>
<td>Sustained hypotension‡§</td>
<td>15 (3.2)</td>
<td>51 (10.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Death</td>
<td>11 (2.3)</td>
<td>18 (3.8)</td>
<td>.19</td>
</tr>
</tbody>
</table>

**Events within 60 days**

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n = 472)</th>
<th>Milrinone (n = 477)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>5/448 (1.1)</td>
<td>10/462 (2.2)</td>
<td>.21</td>
</tr>
<tr>
<td>New atrial fibrillation or flutter</td>
<td>16/446 (3.6)</td>
<td>26/462 (5.6)</td>
<td>.14</td>
</tr>
<tr>
<td>Ventricular tachycardia or fibrillation</td>
<td>20/446 (4.5)</td>
<td>23/461 (5.0)</td>
<td>.72</td>
</tr>
<tr>
<td>Death</td>
<td>41/463 (8.9)</td>
<td>49/474 (10.3)</td>
<td>.41</td>
</tr>
</tbody>
</table>

**Notes:**

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

1 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.

2 Worst health to best health (scale, 0–100).

3 Subjective questionnaire measured as the percentage the patient felt better.
MILRINONE FOR CHRONIC HEART FAILURE

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