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Heart Failure Etiology and Response to Milrinone in Decompensated Heart Failure

Results From the OPTIME-CHF Study

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OBJECTIVES The goal of this study was to assess the interaction between heart failure (HF) etiology and response to milrinone in decompensated HF.

BACKGROUND Etiology has prognostic and therapeutic implications in HF, but its relationship to response to inotropic therapy is unknown.

METHODS The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study randomized 949 patients with systolic dysfunction and decompensated HF to receive 48 to 72 h of intravenous milrinone or placebo. The primary end point was days hospitalized from cardiovascular causes within 60 days. In a post-hoc analysis, we evaluated the interaction between response to milrinone and etiology of HF.

RESULTS The primary end point was 13.0 days for ischemic patients and 11.7 days for nonischemic patients ($p = 0.2$). Sixty-day mortality was 11.6% for the ischemic group and 7.5% for the nonischemic group ($p = 0.03$). After adjustment for baseline differences, there was a significant interaction between etiology and the effect of milrinone. Milrinone-treated patients with ischemic etiology tended to have worse outcomes than those treated with placebo in terms of the primary end point (13.6 days for milrinone vs. 12.4 days for placebo, $p = 0.055$ for interaction) and the composite of death or rehospitalization (42% vs. 36% for placebo, $p = 0.01$ for interaction). In contrast, outcomes in nonischemic patients treated with milrinone tended to be improved in terms of the primary end point (10.9 vs. 12.6 days placebo) and the composite of death or rehospitalization (28% vs. 35% placebo).

CONCLUSIONS Milrinone may have a bidirectional effect based on etiology in decompensated HF. Milrinone may be deleterious in ischemic HF, but neutral to beneficial in nonischemic cardiomyopathy. (J Am Coll Cardiol 2003;41:997–1003) © 2003 by the American College of Cardiology Foundation

Despite their similar presentations, ischemic and nonischemic heart failure (HF) represent distinct diseases with different pathophysiology, response to therapy, and prognosis. It is well-established that patients with ischemic HF have worse long-term outcomes than patients with nonischemic cardiomyopathy (1–4). Substantial heterogeneity in outcomes also exists among patients with nonischemic HF, with some etiologies having significantly better prognosis than others (4).

The response to some chronic medical therapies may differ between patients with ischemic and nonischemic etiology of cardiomyopathy (5). The association between etiology, outcomes, and response to acute therapies in the setting of decompensated HF is unknown. Many potential differences exist in the pathophysiology of HF exacerbations between patients with ischemic and nonischemic etiology, most notably the presence or absence of ischemia as a trigger for decompensation. Positive inotropic agents, especially adrenergic agonists such as dobutamine, may be associated with increasing myocardial oxygen demand and the potential to induce myocardial ischemia or malignant arrhythmias (6). Milrinone, a selective phosphodiesterase III inhibitor, has little effect on myocardial oxygen demand and, therefore, may be better tolerated by patients with ischemic cardiomyopathy (7). Additionally, inotropic stimulation may accelerate HF progression in patients with ischemic heart disease and chronically hibernating myocardium (8–10). Patients with nonischemic HF, on the other hand, may have better tolerance for the potential adverse effects of inotropic therapy and, thus, a more favorable risk/benefit ratio of this therapy. Whether these hypothetical considerations impact the association between the efficacy of short-term inotropic therapy and etiology during HF exacerbations is unknown. In a post-hoc analysis, we sought to evaluate the hypothesis that HF etiology would impact the response to intravenous milrinone in patients enrolled in the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study, a double-blind, randomized,

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Abbreviations and Acronyms

ACE	= angiotensin-converting enzyme
CABG	= coronary artery bypass grafting
HF	= heart failure
MI	= myocardial infarction
OPTIME-CHF	= Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure study
PCI	= percutaneous coronary intervention
QOL	= quality of life

placebo-controlled trial of milrinone during hospitalizations for exacerbations of chronic HF.

METHODS

Study design. The study design and primary results of OPTIME-CHF have been published elsewhere (11,12). Briefly, the OPTIME-CHF study randomized 949 patients with systolic dysfunction and exacerbations of HF to receive 48 to 72 h of intravenous milrinone therapy (0.5 μg/kg/min without a loading dose) or placebo in a double-blinded fashion. Patients felt to require inotropic therapy and those with evidence of active ischemia within the prior three months, severe renal impairment (serum creatinine >3.0 mg/dl), severe hypotension (systolic blood pressure <80 mm Hg), or unstable arrhythmias were excluded. Background therapy was left to the discretion of the treating physician, but specific recommendations for optimal pharmacotherapy based on current guidelines were included with the study protocol. The primary study end point was days hospitalized from cardiovascular causes within 60 days of study drug infusion. For the purpose of the primary end point, patients who died or were lost to follow-up were considered as hospitalized for the remainder of the time up to 60 days. Secondary end points were 60-day mortality, the composite of death and rehospitalization, the ability to reach target dosing of angiotensin-converting enzyme (ACE) inhibitors, and quality of life (QOL); QOL was assessed using a visual analog scale from 0 (worst) to 100 (best) and a subjective health status questionnaire assessing activity limitations, symptoms, and/or emotions as better, worse, or the same. The present analysis of the OPTIME-CHF data was designed to evaluate the hypothesis that the response to milrinone would differ between patients with ischemic or nonischemic etiology of HF.

Classification of HF etiology. An underlying etiology of HF (ischemic vs. nonischemic) was recorded at the time of randomization based on clinical judgment of the treating physician. In order to evaluate the robustness of our findings in light of potential variability in the criteria used to classify etiology, we also assessed two alternative definitions of ischemic etiology. First, patients were included in the ischemic group if they were classified as ischemic by the enrolling investigator or if they had any history of coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), or myocardial infarction (MI) (broad definition). This reclassification resulted in 101 patients being moved from the nonischemic group to the ischemic group. Alternatively, patients were classified as ischemic only if they had a history of CABG, PCI, or MI, regardless of the enrolling investigator's classification (narrow definition). This reclassification resulted in 41 patients being reclassified into the nonischemic group.

Statistical analysis. Continuous variables are provided as means ± SD, and categorical variables are shown as percentages. Comparisons between groups for continuous variables were performed using Student *t* test or Wilcoxon rank-sum test, as appropriate. Comparisons for categorical variables were performed using the chi-squared test. A multivariable Cox proportional hazards model was used to adjust for differences between groups for both the primary end point and 60-day mortality. Multivariable logistic regression was used for the composite end point of death or rehospitalization. To assess the possibility of a differential effect of milrinone based on HF etiology, the etiology-treatment interaction term was included in the final model for each end point. This process was repeated for each of the two alternative definitions of ischemic etiology.

RESULTS

Baseline characteristics. Four hundred eighty-five patients (51%) had ischemic HF, and 464 (49%) had nonischemic HF, based on the assessment of the enrolling physician. Within the category of nonischemic HF, the most common specific etiologies were idiopathic (38%) and hypertensive (21%). There were multiple baseline differences between the ischemic and nonischemic groups, with ischemic patients more likely to be older, white, male, and diabetic than were nonischemic patients. Complete baseline characteristics are shown in Table 1.

Outcomes by etiology. Study outcomes tended to be worse in the ischemic group than in the nonischemic group (Table 2). The primary end point of days hospitalized for cardiovascular causes or death within 60 days after randomization was 13.0 ± 14.2 days for those with ischemic HF and 11.7 ± 13.9 days for those with nonischemic HF ($p = 0.2$). Overall mortality tended to be greater in the ischemic group than the nonischemic patients. Sixty-day mortality was significantly greater for ischemic patients (11.6%) than for nonischemic patients (7.5%, $p = 0.03$). The combined end point of death or rehospitalization at 60 days was 38.7% in the ischemic patients and 31.5% in the nonischemic patients ($p = 0.02$).

Among other secondary end points, a significantly greater percentage of patients with nonischemic HF was able to reach target dosing of ACE inhibitors at hospital discharge (49%) when compared with those with ischemic HF (36%, $p = 0.001$). Treatment failure while on the study drug was similar between the two groups (14.2% for ischemic patients

Table 1. Baseline Characteristics by Heart Failure Etiology

	Ischemic (n = 485)	Nonischemic (n = 464)	p Value
Randomized to milrinone	242 (50%)	235 (51%)	
Age	70 ± 11	61 ± 16	0.0001
Gender			
Male	341 (70%)	286 (62%)	0.005
Female	144 (30%)	178 (38%)	
Race			
White	391 (81%)	222 (48%)	0.001
Black	80 (17%)	230 (49%)	
Other	14 (3%)	12 (3%)	
History of arrhythmia	262 (54%)	195 (42%)	0.001
Hospitalizations prior 12 months	2.1 ± 2.1	1.9 ± 2.1	0.06
NYHA functional class			
I	1 (0.2%)	0 (0%)	0.2
II	31 (6%)	33 (7%)	
III	208 (43%)	223 (48%)	
IV	242 (50%)	205 (45%)	
JVP > 6	313 (70%)	323 (76%)	0.05
Rales	405 (84%)	366 (79%)	0.07
S_3	263 (55%)	285 (63%)	0.02
MR murmur	225 (48%)	216 (49%)	0.9
Heart rate	82 ± 15	87 ± 16	0.0001
Systolic blood pressure	120 ± 18	120 ± 18	0.8
Diastolic blood pressure	70 ± 12	73 ± 13	0.0001
Ejection fraction (%)	25 ± 8	22 ± 8	0.0001
Diabetes mellitus	240 (50%)	178 (38%)	0.0001
In-hospital dobutamine treatment	53 (11%)	46 (10%)	0.6
ACE inhibitor on admission	329 (68%)	336 (73%)	0.1
Beta-blocker on admission	120 (25%)	92 (20%)	0.07
Amiodarone on admission	82 (17%)	65 (14%)	0.2
Digoxin on admission	336 (69%)	356 (77%)	0.01
Serum sodium	138 ± 4	138 ± 4	0.1
Serum potassium	4.2 ± 0.6	4.2 ± 1.6	0.5
Serum creatinine	1.5 ± 0.5	1.4 ± 0.5	0.001
Visual analog QOL score (0–100)	42 ± 22	41 ± 22	0.5

ACE = angiotensin-converting enzyme; JVP = jugular venous pressure; MR = mitral regurgitation; NYHA = New York Heart Association; QOL = quality of life; S_3 = third heart sound.

vs. 15.2% for nonischemic patients, p = 0.7). In general, the incidence of in-hospital complications did not differ between the etiologic groups (13.2% for ischemic patients vs. 13.0% for nonischemic patients). Notably, despite the worse overall prognosis in ischemic patients, the incidence of atrial or ventricular arrhythmias did not differ significantly between the groups. The incidence of new atrial fibrillation or flutter during the index hospitalization was 2.7% for the ischemic group and 3.4% for the nonischemic group (p = 0.49). Sustained ventricular tachycardia occurred in 1.6% of ischemic patients and 2.4% of nonischemic patients (p = 0.42), with ventricular fibrillation occurring in 0.6% and 1.7%, respectively (p = 0.11). The most common in-hospital adverse event was sustained hypotension necessitating treatment, which did not differ in incidence between etiologic groups (7.0% for ischemic patients vs. 6.9% for nonischemic patients, p = 0.9).

Baseline QOL data did not differ significantly between the ischemic and nonischemic groups. Visual analog scale rating of QOL was 42 ± 22 for the ischemic group and 41 ± 22 for the nonischemic group (p = 0.5). Both groups had substantial improvement over baseline in visual analog QOL by hospital discharge (mean improvement of 29 for both groups, p = 0.4), which lessened by 60 days follow-up (mean improvement of 23 for ischemic patients vs. 25 for nonischemic patients, p = 0.2). There was a nonsignificant trend towards improved QOL by the subjective health status questionnaire in the nonischemic group compared with the ischemic group (p = 0.053 at 60 days) (Table 2).

Effect of milrinone treatment. To evaluate the hypothesis that the response to milrinone therapy would differ based on HF etiology, etiology-treatment interaction terms were included in the multivariable model for each end point. After multivariable adjustment for baseline differences, there was an interaction identified between treatment assignment (milrinone vs. placebo) and HF etiology (Table 3). This was most pronounced for the composite end point of death or rehospitalization (p = 0.01). Similar trends were identified for other end points but reached nominal statistical significance only for in-hospital mortality (p = 0.04). Kaplan-Meier survival curves by etiology and treatment assignment are shown in Figure 1.

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Table 2. Outcomes by Heart Failure Etiology

	Ischemic (n = 485)	Nonischemic (n = 464)	p Value
Primary end point (days)	13.0 ± 14.2	11.7 ± 13.9	0.2
Mortality			
In-hospital	3.3%	2.8%	0.7
60 days	11.6%	7.5%	0.03
Death or rehospitalization at 60 days	38.7%	31.5%	0.02
Treatment failures (during infusion)	14.2%	15.2%	0.7
In-hospital complications (any)	13.2%	13.0%	0.9
Hypotension	7.0%	6.9%	0.9
New atrial fibrillation/flutter	2.7%	3.4%	0.5
Sustained ventricular tachycardia	1.6%	2.4%	0.4
Ventricular fibrillation	0.6%	1.7%	0.1
Reached target ACE dosing	36.0%	49.1%	0.001
Quality of life			
Visual analog scale (0–100)			
Baseline	42 ± 22	41 ± 22	0.5
Δ at hospital D/C	29 ± 24	29 ± 22	0.4
Δ at 30 days	20 ± 28	24 ± 26	0.06
Δ at 60 days	23 ± 29	25 ± 29	0.2
Subjective Health Questionnaire (% better/same or worse)			
Δ at hospital discharge	89/11	92/8	0.2
Δ at 30 days	59/41	66/34	0.1
Δ at 60 days	51/49	59/41	0.053

ACE = angiotensin-converting enzyme; D/C = discharge.

In patients with ischemic HF, milrinone treatment tended to be associated with prolonged hospitalization and higher mortality. Among ischemic patients, the primary end point of days hospitalized or death within 60 days was 13.6 for milrinone versus 12.4 for placebo (p = 0.055 for etiology-treatment interaction). The composite of death or rehospitalization at 60 days was 42% for ischemic patients treated with milrinone and 36% for those treated with placebo (p = 0.01 for etiology-treatment interaction) (Fig. 2). In-hospital mortality for milrinone-treated patients with ischemic HF was 5.0% versus 1.6% for placebo (p = 0.04 for etiology-treatment interaction), and 60-day mortality was 13.3% for milrinone versus 10.0% for placebo (p = 0.21 for etiology-treatment interaction).

In contrast, patients with nonischemic HF demonstrated evidence of benefit with milrinone therapy compared with placebo. The primary end point in the milrinone-treated nonischemic patients was 10.9 days versus 12.6 days for placebo (p = 0.055 for etiology-treatment interaction). The composite of death or rehospitalization at 60 days was 28% for nonischemic patients treated with milrinone versus 35% for those treated with placebo (p = 0.01 for etiology-treatment interaction) (Fig. 2). In-hospital mortality was 2.6% for milrinone versus 3.1% for placebo (p = 0.04 for etiology treatment interaction), with similar results at 60 days (7.3% vs. 7.7%, p = 0.21 for etiology-treatment interaction) (Fig. 2).

Because clinical outcomes after discharge (such as the rate of rehospitalization) were crucial to the end points of interest, we compared discharge medications for each of the treatment-etiology groups (Table 4). Only digoxin was significantly different between groups, with nonischemic patients more likely to receive digoxin at hospital discharge.

Impact of etiology classification. In order to assess the sensitivity of our findings to changes in our assumptions, multivariable analyses were repeated using two alternative definitions of ischemic etiology as previously defined. Reanalysis of the data using the "broad definition" showed small changes in the p values for the milrinone-etiology interaction terms (from 0.055 to 0.12 for the primary end point, from 0.011 to 0.015 for the composite of death or rehospitalization, and from 0.21 to 0.28 for 60-day survival). Alternatively, data were analyzed using the "narrow definition" of ischemic etiology. As in the first alternative analysis,

Table 3. Outcomes by Heart Failure Etiology and Treatment Assignment

	Ischemic		Nonischemic		
	Milrinone	Placebo	Milrinone	Placebo	p Value*
Days hospitalized at 60 days	13.6 ± 15.5	12.4 ± 12.7	10.9 ± 12.4	12.6 ± 15.3	0.055
In-hospital mortality	5.0%	1.6%	2.6%	3.1%	0.04
60-day mortality	13.3%	10.0%	7.3%	7.7%	0.21
Death + rehospitalization	42%	36%	28%	35%	0.02

*p value for the etiology treatment interaction term in the multivariable model.

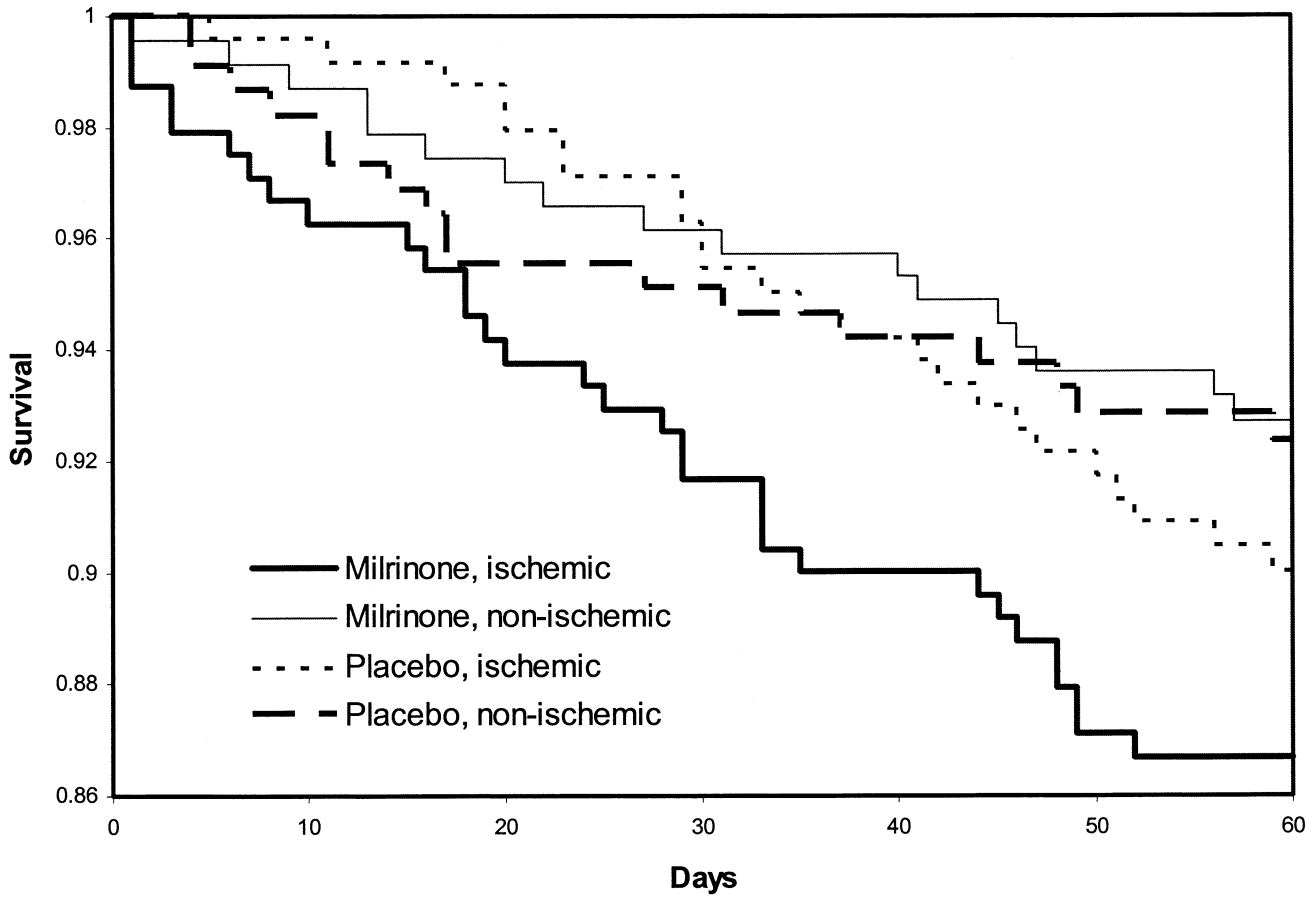

Figure 1. Kaplan-Meier survival curves to 60 days by heart failure etiology and treatment assignment.

this resulted in small changes in the interaction term p values (from 0.055 to 0.22 for the primary end point, from 0.011 to 0.015 for the death + rehospitalization composite, and from 0.21 to 0.12 for 60-day survival). Notably, in all three cases, the p values of the interaction term for the death + rehospitalization end point remained statistically significant.

DISCUSSION

Exacerbations of HF represent a major component of health care costs, resulting in hospitalizations, emergency department utilization, and unscheduled clinic visits (13). Although 75% of HF costs are related to hospitalizations for decompensated HF (13), the majority of randomized trials in HF have addressed chronic treatment strategies, and relatively little is known about the optimal management of hospitalized patients (14–18). Additionally, although the chronic oral administration of positive inotropic agents has been shown to increase mortality in patients with left ventricular dysfunction (19–22), their efficacy as short-term treatments for HF exacerbations has not been well studied. The OPTIME-CHF study is the first trial to systematically evaluate a strategy of short-term inotrope use during exacerbations of chronic HF , and the current study is the first to evaluate a potential interaction between HF etiology, treatment, and outcomes in such patients.

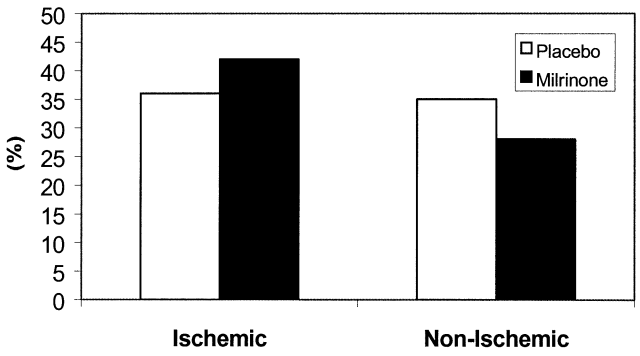

Figure 2. Composite end point of death + rehospitalization by heart failure etiology and treatment assignment. p = 0.01 for etiology-treatment interaction.

Substantial heterogeneity exists among patients with HF in terms of both outcomes and response to specific therapies. The last several decades have seen a shift in the etiologic basis of HF away from hypertension and valvular disease towards ischemic heart disease, which now comprises about 70% of all HF from systolic dysfunction in clinical trials (23). The underlying etiology of HF is among the most important determinants of prognosis in patients with chronic HF, and an ischemic etiology of cardiomyopathy has been shown to be associated with worsened

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Table 4. Discharge Medications by Heart Failure Etiology and Treatment Assignment

	Ischemic		Nonischemic		
	Milrinone	Placebo	Milrinone	Placebo	p Value
Beta-blocker	27%	25%	21%	20%	0.18
ACE inhibitors	74%	74%	75%	76%	0.92
Digoxin	74%	73%	84%	80%	0.02
Amiodarone	20%	18%	19%	16%	0.77
Calcium blocker	14%	10%	16%	11%	0.25

ACE = angiotensin-converting enzyme.

long-term prognosis (3,4). The current study extends this finding to the setting of HF decompensations, demonstrating worsened short- and intermediate-term outcomes in patients with ischemic HF when compared with those with nonischemic cardiomyopathy. Mortality at 60 days was significantly higher in ischemic patients compared with nonischemic, and other measured study outcomes also tended to be worse in the ischemic group.

Milrinone-etiology interaction. This study identified a significant interaction between HF etiology and treatment with milrinone. In patients with ischemic HF, milrinone use was associated with prolonged or recurrent hospitalization and a trend towards increased mortality. Several potential explanations exist for this finding. Patients with ischemic HF may have been more susceptible to malignant arrhythmias than those with nonischemic cardiomyopathy due to greater potential for re-entry around areas of myocardial scar, a risk that could potentially be exacerbated by treatment with milrinone. The current study does not appear to support this explanation, however, as the in-hospital incidence of sustained ventricular tachycardia or ventricular fibrillation was actually greater in the nonischemic patients treated with milrinone (5.9%) than in the ischemic patients treated with milrinone (2.9%).

Another potential mechanism of adverse outcomes in ischemic patients treated with milrinone could be the presence of hibernating myocardium. Although the OPTIME-CHF study excluded patients with clinical evidence of ischemia, patients with ischemic HF may have chronically ischemic hibernating myocardium in the absence of overt ischemia (24). Data using positron emission tomography scanning suggest that up to 50% of patients with systolic dysfunction and ischemic heart disease may have demonstrable myocardial hibernation (25). While treatment with inotropic agents may increase contractility and cardiac performance in patients with hibernating myocardium (the mechanism for the utility of dobutamine echocardiography in assessing myocardial viability), this may come at the expense of the acceleration of apoptosis and underlying HF progression (8,10,26). Whether short-term treatment with milrinone (48 to 72 h) may have resulted in acceleration of HF progression in patients with ischemic HF and hibernating myocardium is unknown.

In contrast with patients with ischemic HF, the use of milrinone appeared to have a neutral to beneficial impact on outcomes in patients with nonischemic cardiomyopathy, with less hospitalization and trends towards decreased mortality with milrinone therapy in this subgroup. A similar pattern of drug efficacy (more effective in nonischemic HF) has been suggested for other pharmacologic agents, most notably amiodarone (27,28). These data suggest the hypothesis that milrinone may have a bi-directional effect in decompensated HF based on etiology. This hypothesis would need to be confirmed prospectively before being incorporated into clinical practice.

Classification of etiology. The classification of patients into ischemic or nonischemic categories in the OPTIME-CHF study was done based on the judgment of the enrolling physician rather than on prespecified objective criteria (such as coronary angiography), so some variability in the classification of etiology may have occurred. In reality, the development of left ventricular dysfunction is a complex process in which many potential etiologies may coexist and contribute to the clinical syndrome of HF in a given patient. A binary classification system, while attractive due to its simplicity, is clearly an oversimplification of a complex physiologic process. Additionally, no standardized definition of ischemic etiology of HF exists, although a classification system based on the results of clinical history and angiography has recently been proposed (29). Indeed, the terms "ischemic" and "nonischemic" are imprecise because demonstrable myocardial ischemia (particularly in the subendocardium) may exist in patients with cardiomyopathy and no obstructive coronary disease (30,31). Our alternative analyses suggest that the finding of an interaction between HF etiology and treatment with milrinone is relatively insensitive to the method used for classification of etiology.

Study limitations. This study is limited by its retrospective nature, and, as such, should be considered hypothesis-generating rather than definitive. Data were not collected on the level of care that patients received (i.e., intensive care unit vs. monitored bed), which potentially could have affected the results of our study, particularly with regard to the recognition and treatment of arrhythmias. Because the reasons for rehospitalization are frequently multifactorial in HF patients, we did not attempt to assign a specific reason for rehospitalization (i.e., cardiovascular vs. noncardiovascular) in evaluating study end points. Based on the assessment of the site investigator, 93% of all hospital days during the study period were considered to be due to cardiovascular causes, suggesting that the impact of noncardiovascular hospitalizations was low. Finally, although follow-up was

99% complete for the study, there was an imbalance between etiologic groups (four patients in the ischemic group vs. eight patients in the nonischemic group lost to follow-up), which could potentially have influenced our conclusions regarding differences in outcomes. This analysis is strengthened by the standardized ascertainment of baseline characteristics and outcomes in a large, well-characterized cohort of patients with exacerbations of HF.

Conclusions. In patients hospitalized for decompensated HF in the OPTIME-CHF trial, those with nonischemic HF had a better short- and intermediate-term prognosis than those with ischemic HF. Intravenous milrinone treatment appeared to have a bidirectional effect in acute HF based on etiology, with worsened outcomes in those with ischemic HF and neutral to improved outcomes in those with nonischemic HF. This finding provides support for the importance of carefully defining the etiology of HF, which has important implications not only for prognosis but also for therapy. Although the specific determination of etiology for a given patient with HF may be imprecise, our data suggest that particular caution should be used when contemplating inotropic therapy in patients with ischemic heart disease and HF. The morbidity and mortality seen in the overall OPTIME-CHF study were substantial, with a mortality rate at 60 days of 9.6% and a rate of death or rehospitalization at 60 days of 35.2%. This poor short-term prognosis underscores the need for more research into risk stratification and optimal treatment strategies for this increasingly prevalent clinical problem.

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