Rehospitalization of Patients with Advanced Heart Failure Receiving Continuous, Palliative Dobutamine or Milrinone

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This study aims to determine the incidence of all-cause hospitalization in patients with advanced heart failure (AHF) receiving ambulatory continuous, intravenous dobutamine versus milrinone for palliative intent. Despite medical optimization, patients with AHF develop refractory symptoms, resulting in frequent hospitalizations. Previous trials precede modern care standards. Data regarding inotrope choice in palliation are limited. This retrospective analysis included 222 patients with AHF and reduced left ventricular ejection fraction discharged on palliative dobutamine (n = 135) or milrinone (n = 87). The primary outcome was incidence of all-cause rehospitalization compared by treatment type. Demographics between groups were similar. In the milrinone arm, more patients were discharged on β blockers (62% vs 22%; p <0.001); fewer patients were discharged to hospice (6% vs 30%). More patients in the milrinone arm than in the dobutamine arm were rehospitalized within 180 days (80% vs 59%; p = 0.002); when patients discharged to hospice were excluded, this difference was no longer significant (83% vs 74%; p = 0.14). Overall mortality was lower in the milrinone arm (63% vs 80%; p = 0.006); survival was longer (median: 228 vs 52 days; p <0.001). Patients receiving milrinone spent more days alive and out of the hospital at 90 days after discharge (70 vs 37 days; p <0.001). In conclusion, in patients with AHF receiving palliative inotropes, there was no difference in rehospitalization when excluding patients discharged to hospice. Milrinone use was associated with decreased mortality and longer survival. Agent selection must closely align with the patient's disease trajectory. **(Am J Cardiol 2022;00:1−10)**

Introduction

Heart failure (HF) affects more than 6.5 million individuals in the United States alone, with particularly high morbidity and mortality in those with advanced disease.[1−4] Despite optimization of guideline-directed medical therapy, patients with advanced HF (AHF) develop refractory symptoms, resulting in frequent hospitalizations and functional limitations.[5,6] For patients who are ineligible or decline advanced therapies, the focus shifts to palliation.[3,6] Previous trials of continuous intravenous inotropes demonstrated beneficial improvement in hemodynamic profile and functional class, albeit with a potential concern for increased mortality and ventricular arrhythmias.[7−12] These studies preceded modern standards of care, such as routine β-blocker use, cardiac resynchronization therapy and implantable cardioverter defibrillators (ICD). Furthermore, these trials used higher doses of inotropes and did not focus exclusively on palliative use. Contrary to these findings, a recent meta-analysis of continuous inotropic therapy use in AHF showed no change in survival; the improvements in functional class were consistent.[13] Incidence of all-cause hospitalization was 22/100 patient-months.[13] Even with continuous inotropes and contemporary treatment modalities, survival remains suboptimal.[13−15] Current guidelines recommend that continuous intravenous inotropes may be considered as palliation for select patients with Stage D HF.[3] Dobutamine and milrinone are the most widely used agents. Data regarding choice of inotrope are limited, with unclear rehospitalization and mortality differences between agents in the palliative population.[14,16−19] There remains a paucity of data for this intervention as advanced palliative therapy.[3] Therefore, we aimed to determine the incidence of all-cause rehospitalization in patients with AHF receiving ambulatory continuous, intravenous dobutamine versus milrinone as palliative therapy.

Methods

This single-center, retrospective cohort study received proper ethical oversight and approval by The Ohio State University Wexner Medical Center Institutional Review

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Board (#2020H0451). The Ohio State University Wexner Medical Center Ross Heart Hospital is a 172-bed, tertiary care center that offers on-site cardiac transplantation and durable mechanical circulatory support to qualifying patients.

Study participants were retrospectively identified through outpatient prescription records upon hospital discharge. Adults (18 to 89 years of age) with Stage D, New York Heart Association Functional Class IV AHF, reduced left ventricular ejection fraction (LVEF <40%) and discharged between January 1, 2015 and April 23, 2020 on continuous, intravenous dobutamine or milrinone for palliation were assessed for inclusion. Patients who were pregnant, incarcerated, receiving inotrope therapy for a nonpalliative indication, receiving more than 1 inotrope during the study period, who had preexisting mechanical circulatory support present at the index admission were excluded from analysis. Patients were not included if they were being considered to receive cardiac transplantation or durable left ventricular assist device, or were listed for cardiac transplantation at the index discharge event. Patients received concurrent guideline-directed medical therapy and cardiac devices as clinically indicated.

The primary outcome was incidence of all-cause rehospitalization within 180 days of the index discharge date, compared by treatment type. For patients with multiple hospitalizations after therapy initiation, the first rehospitalization was assessed. Regarding the primary outcome, patients were followed until 180 days, death, last point of medical contact, until they were no longer receiving inotrope therapy, or until the end of the study period (October 20, 2020); patients were censored for death or loss to follow-up within 180 days. Secondary outcomes include discharge disposition, survival, time to either rehospitalization or death, days alive and out of the hospital, and cause of rehospitalization. Cause of rehospitalization was attributed to worsening HF, arrhythmias, catheter thrombosis, central line infection, or "other." Worsening HF was defined as an increase in necessary diuretic dose relative to home therapy, worsening renal function, elevated B-type natriuretic peptide (BNP), or presenting signs and symptoms of edema leading to weight gain. In regard to secondary outcomes, patients were followed until death, last point of medical contact, or the end of the study period.

Data were collected through retrospective chart review of the electronic medical record and were managed using REDCap (Research Electronic Data Capture) electronic data capture tools. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources.[20,21] Data collection points included baseline demographics, co-morbidities, concurrent medications at initial discharge event, laboratory and vital samples (serum creatinine, systolic blood pressure, mean arterial pressure, BNP), echocardiogram information (LVEF, mean pulmonary artery pressure, right ventricular systolic pressure), etiology of left ventricular dysfunction, inotrope selection and dose at initial discharge event, catheter type, ICD data, time to rehospitalization if event occurred, rehospitalization cause, time to death if event occurred, days alive and out of the hospital, and last point of medical contact.

Patient characteristics and outcomes were reported as count (percentage) or median [first to third quartile] as appropriate, with univariate comparisons between treatments assessed using chi-square tests or Wilcoxon rank-sum tests, respectively. Kaplan-Meier methods were used to compare outcomes of time to rehospitalization and overall survival by treatment. Owing to the high incidence of death within 180 days in the cohort, multiple methods were used to account for death when modeling the rehospitalization outcome. Multivariable Cox proportional hazard models were used to assess outcomes in 2 ways. One model treated death as a censoring event and rehospitalization as the lone event of interest. The second model treated the event of interest as death or rehospitalization during the 180-day follow-up period. Finally, a multivariable Fine-Gray model was used to compare time to rehospitalization between treatments while accounting for death as a competing event. Multivariable Cox proportional hazards regression was also used to compare overall survival by treatment. The effect of treatment type was found to vary over time, so interaction terms between treatment and log (time) were included. Other prespecified confounder variables included inotrope selection, pulmonary hypertension (pHTN), ventricular arrhythmias, β-blocker use, ICD status, systolic blood pressure, and serum creatinine. Systolic blood pressure (mm Hg), mean arterial pressure (mm Hg), and serum creatinine were collected within 24 hours of inotrope initiation for this analysis. pHTN was defined as a mean pulmonary artery pressure>25 on right heart catheterization. Statistical significance was defined as $p<0.05$. All analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, North Carolina).

Results

Figure 1 depicts the patient population selection process that occurred from January 2015 to April 2020. Baseline demographics, co-morbidities, and concurrent discharge medications between the 2 trial groups were similar (Table 1). Patients were predominantly male, with a mean age of 61 years; 53% had HF with reduced EF secondary to nonischemic cardiomyopathy; 92% of patients had concurrent pHTN, and 31% had a history of ventricular arrhythmia. Mean LVEF for both groups was 18%. The mean discharge dose of dobutamine was 3 mcg/kg/minute, and milrinone was 0.3 mcg/kg/minute. Regarding discharge disposition, 41 patients (30%) in the dobutamine group and 5 patients (6%) in the milrinone group were discharged to inpatient or home hospice. The milrinone arm displayed lower baseline age (median: 59 vs 63 years; $p = 0.01$) and BNP (median: 1,207 vs 1,589 pg/mL; $p = 0.03$) than did the dobutamine arm; more patients receiving milrinone were discharged on β blockers (62% vs 22%; $p <0.001$) and aldosterone antagonists (47% vs 30%; $p = 0.01$). No patients in this analysis received concurrent angiotensin receptor-neprilysin inhibitors.

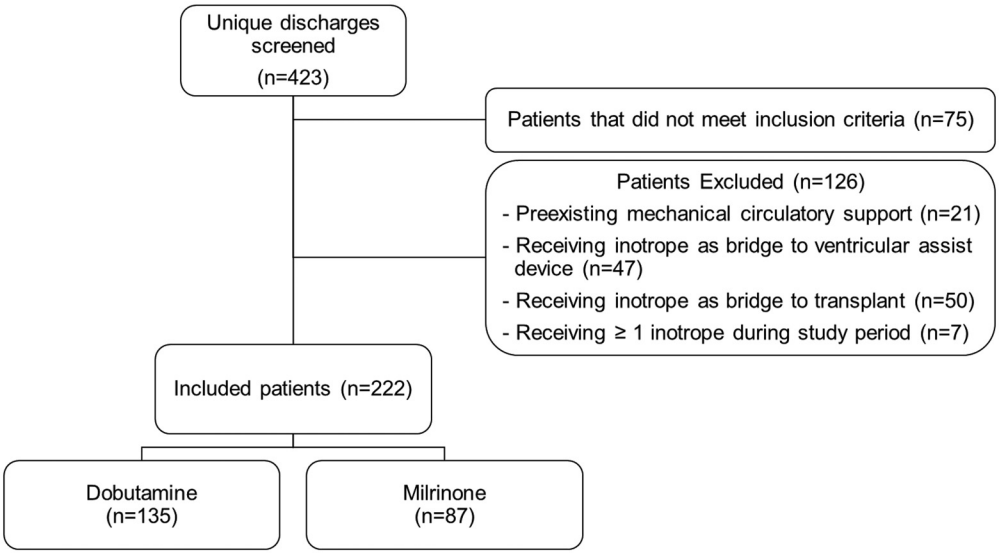

Figure 1. Patient population selection process (Eaton RE, et al).

In this cohort, 142 patients were rehospitalized within 180 days of the index discharge event; 54 had the competing event of death within 180 days without previous rehospitalization, and 26 were censored with neither rehospitalization nor death during the follow-up period. Ten patients were alive and not hospitalized but had fewer than 180 days of follow-up and were excluded from the primary end point only; these patients were included in all secondary outcomes, including survival analysis. The primary outcome of rehospitalization within 180 days of the index discharge event occurred in 76 patients in the dobutamine group (59%) and 66 patients in the milrinone group (80%) (p = 0.002) (Figure 2, Table 2). When sensitivity analysis was performed to exclude patients discharged to inpatient or home hospice, there was no longer a difference in the incidence of rehospitalization between dobutamine and milrinone arms (74% vs 83%; p=0.14) (Figure 2, Table 3). When deaths were treated as censored events, the median time to rehospitalization compared by inotrope type was no different between groups (35 [13 to 119] vs 34 [16 to 89] days; p = 0.97) (Table 2). Of all rehospitalized patients, 90% were readmitted by Day 90 after index discharge.

In the milrinone arm, overall mortality was lower (63% vs 80% p = 0.006) and survival was longer (median: 228 vs 52 days; p<0.001) than in the dobutamine group (Figure 3, Table 2). When patients discharged to hospice were excluded, mortality remained significantly lower (61% vs 77%; p = 0.03) and median overall survival (238 vs 85 days; p = 0.03) remained longer in the milrinone group (Table 3). At Day 365, 11% of patients receiving dobutamine and 10% receiving milrinone were known to be alive.

Time to either rehospitalization or death was longer in the milrinone group (median: 29 vs 16 days; p = 0.048); these patients spent more days alive and out of the hospital both 30 days (28 vs 22 days; p = 0.004) and 90 days after discharge (70 vs 37 days; p <0.001) (Figure 4, Table 2). This finding remained consistent when excluding patients discharged to hospice (74 vs 54 d; p = 0.03) (Table 3).

Worsening HF was the leading cause of rehospitalization in this cohort, with 61% of events attributed to increased diuretic doses relative to home therapy, worsening renal function, elevated BNP, or presenting signs and symptoms of edema leading to weight gain (Table 2). All patients readmitted for worsening HF required escalation of intravenous diuretics and showed symptoms of volume overload. The average readmission BNP was 1,792 pg/mL.

Overall, 55% of the cohort had any atrial arrhythmia at baseline, and 31% had history of ventricular arrhythmia (Table 1). Of all patients, 69% of patients were discharged with an activated ICD; 34% had cardiac resynchronization therapy. Of patients who were rehospitalized, 5 patients (7%) in the dobutamine group (n = 3 for atrial; n = 2 for ventricular) and 9 patients (14%) in the milrinone group (n = 5 for atrial; n = 4 for ventricular) were readmitted secondary to arrhythmia (Table 2). All patients admitted with ventricular arrhythmias had activated ICDs, and all underwent device interrogation. Three events required an ICD shock (2 of which were ventricular fibrillation). Two nonsustained ventricular tachycardia events without ICD shock were recorded; 1 interrogation showed no events. Two patients receiving milrinone were inappropriately shocked: 1 for a ventricular tachycardia that was interpreted as atrial fibrillation on interrogation and the other for atrioventricular nodal reentry tachycardia. There was 1 incidence of catheter-related thrombosis leading to rehospitalization (Table 2); this occurred in a patient receiving dobutamine secondary to nonischemic cardiomyopathy who had a tunneled central venous catheter placed.

Of all rehospitalized patients, 11 infections were attributed to central line placement (8%); this was more common in the milrinone group (9 events; 14%) than in the dobutamine group (2 events; 3%). In 73% of infections, patients were bacteremic or fungemic; patients grew predominantly gram-positive organisms.

The “other” designation for rehospitalization included bleeding complications (n = 4), complications secondary to overdiuresis and electrolyte abnormalities (n = 8), and line

Table 1
Baseline demographics

Variable	Dobutamine (n=135)	Milrinone (n=87)	p value
Men	98 (73%)	60 (69%)	0.56
Age (years)	63 [53-72]	59 [49-66]	0.01*
Body mass index (kg/m^2)	28 [25-34]	29 [24-35]	0.28
Mean left ventricular ejection fraction (%)	18 [18-23%]	18 [18-23%]	0.99
Etiology of heart failure			0.30
Ischemic cardiomyopathy	67 (50%)	37 (42%)	
Non-ischemic cardiomyopathy	68 (50%)	50 (58%)	
Systolic blood pressure (mmHg)	103 [95-113]	103 [97-115]	0.30
Mean arterial pressure (mmHg)	78 [71-85]	78 [71-87]	0.58
B-type natriuretic peptide (pg/mL)	1589 [843-2935]	1207 [699-2124]	0.03*
Serum creatinine (mg/dL)	1.7 [1.2-2.6]	1.6 [1.2-2.1]	0.10
Renal replacement therapy	8 (6%)	3 (4%)	0.53
Right ventricular systolic pressure (mmHg)	(n=130); 45 [37-53]	(n=83); 47 [40-59]	0.19
Pulmonary arterial systolic pressure (mmHg)	(n=123); 50 [43-57]	(n=82); 52 [44-65]	0.06
Presence of pulmonary hypertension†	110/123 (89%)	78/82 (95%)	0.15
Hypertension	92 (68%)	59 (68%)	0.96
Hyperlipidemia	84 (62%)	52 (60%)	0.71
Coronary artery disease	86 (64%)	46 (53%)	0.11
Type 2 diabetes mellitus	69 (51%)	36 (41%)	0.16
Atrial fibrillation	62 (46%)	42 (48%)	0.73
Other atrial arrhythmia	14 (10%)	5 (6%)	1.0
Ventricular arrhythmia	43 (32%)	25 (29%)	0.62
Cardiac arrest	9 (7%)	6 (7%)	0.95
Catheter type			0.24
Peripherally inserted central catheter	108 (80%)	75 (86%)	
Tunneled central venous catheter	27 (20%)	21 (14%)	
Implantable cardioverter-defibrillator at discharge			0.04*
On	86 (64%)	67 (77%)	
Off or no implantable cardioverter-defibrillator present	49 (36%)	20 (23%)	
Concurrent Discharge Medications			
Aspirin	90 (67%)	66 (76%)	0.14
Amiodarone	41 (30%)	30 (35%)	0.52
Hydralazine	55 (41%)	40 (46%)	0.44
Nitrate	47 (35%)	40 (46%)	0.10
Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers	27 (20%)	15 (17%)	0.61
Angiotensin receptor-neprilysin inhibitors	0 (0%)	0 (0%)	–
β-blocker	30 (22%)	54 (62%)	<0.001*
Mexiletine	7 (5%)	3 (4%)	0.74
Aldosterone antagonist	41 (30%)	41 (47%)	0.01*
Oral diuretic	117 (87%)	77 (89%)	0.69
Intravenous diuretic	4 (3%)	5 (6%)	0.32
Discharge inotrope dose (mcg/kg/min)	3.0 [2.5-5.0]	0.30 [0.25-0.38]	n/a

Data are presented as count (column %) or median [first to third quartile].
* Denotes statistical significance.
† Denominators shown due to patients with missing data.

malfunctions (n = 8) (Table 2). Three patients were admitted for inotrope wean (2 of whom receiving milrinone) and censored at last day of inotrope therapy. One patient receiving dobutamine was admitted owing to insurance lapse.

Multivariable hazard models were used to account for confounders considering the retrospective nature of this analysis (Tables 4 and 5). With death as a competing event, multivariable hazard models for rehospitalization were tested; the effect of treatment type was found to vary with time (p = 0.02), with an increasing hazard associated with milrinone over time (Table 4). Controlling for their underlying treatment, patients on β blockers had a longer time to rehospitalization (hazard ratio [HR] 0.57 [0.39 to 0.84]; p = 0.004). Table 4 includes hazard models for rehospitalization or death as a composite outcome, and with death treated as a censored event.

Multivariable hazard models for overall survival were also performed (Table 5); treatment type was again found to vary over time for the outcome of overall survival (p = 0.01). In times closer to the initial discharge, the hazard of death was significantly lower in patients receiving milrinone (at Day 30: HR 0.52 [0.34 to 0.80]; p = 0.003). Over time, the differences in survival by treatment became insignificant (at 180 days: HR 0.85 [0.56 to 1.29]; p = 0.45). Higher baseline serum creatinine values (HR 1.16 [1.02 to 1.33]; p = 0.03) and baseline pHTN (HR 2.08 [1.14 to 3.81]; p = 0.02) correlated with higher risk of mortality.

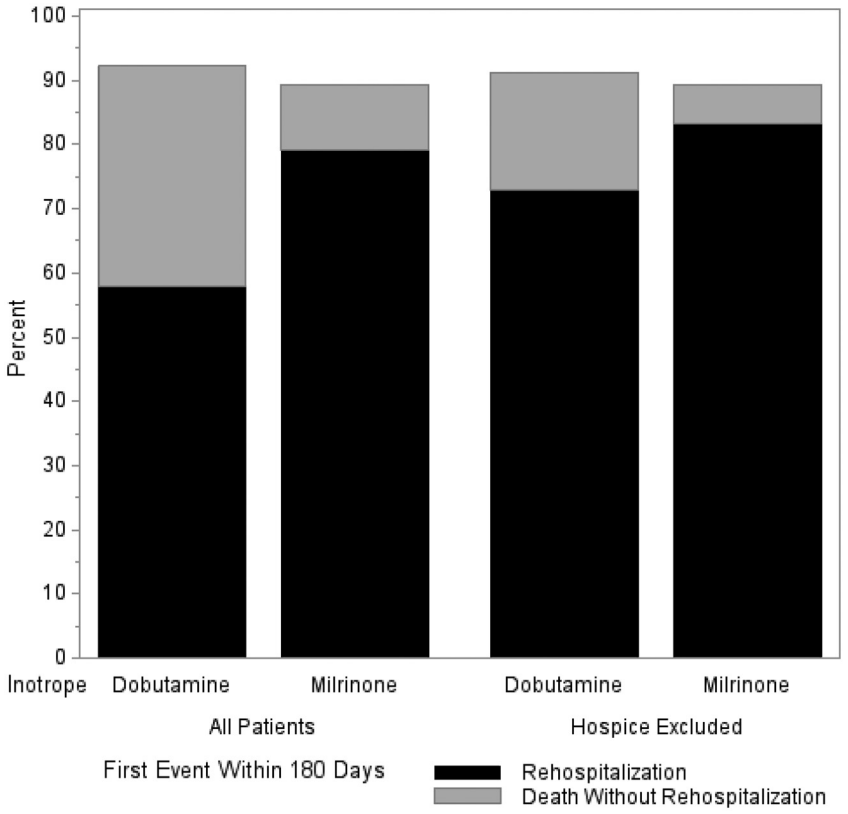

Figure 2. Outcomes in overall cohort compared with overall cohort excluding patients discharged to hospice (Eaton RE, et al).

After exclusion of patients discharged to hospice, treatment differences in these models for rehospitalization with death as a competing event (p = 0.36) and overall survival (p = 0.22) were no longer statistically significant. In regard to rehospitalization, use of β blockers (HR 0.54 [0.36 to 0.81]; p = 0.002) and baseline pHTN (HR 2.65 68 [1.26 to 5.67]; p = 0.01) remained significant.

Discussion

To the authors' knowledge, this is the largest study to date to find no difference in rehospitalization between dobutamine and milrinone in patients with AHF receiving ambulatory continuous intrope therapy solely for palliative intent when patients discharged to hospice were excluded. Both inotrope agents increase cardiac contractility but exhibit differing hemodynamic effects, adverse event profiles, and clinical considerations for use. Limited evidence exists to guide inotrope selection, regardless of indication, and is of high clinical significance.[14,16–19] Although the trial population differed, 1 recent trial found no significant difference in in-hospital death from any cause, stroke, or cardiovascular or renal events between milrinone and dobutamine in patients presenting with cardiogenic shock.[22] Gottlieb et al[23] recommend better evidence and consistent guidelines for outpatient inotrope use regardless of indication. One retrospective, single-center cohort (n = 98 palliative care patients) reported longer median survival with milrinone than with dobutamine; however, 85% of the total cohort received milrinone, and the authors comment on differences in patient selection that limit the ability to conclude independent survival benefit with milrinone.[14,19] Another retrospective study (n = 197) compared dobutamine with milrinone in patients with Stage D HF who were not transplant candidates at enrollment with mortality as a primary outcome; after adjusted analysis, there were no mortality differences between treatment groups.[18] These previous studies used survival as the primary outcome; however, our investigation shifted to focus on rehospitalization. Despite documented preferences for home death, more than 75% of all deaths attributed to HF occur in a medical facility.[6] Prevention of symptom exacerbation leading to rehospitalization is paramount in preserving quality at the end of life, which drove the decision to select this as our primary outcome.

In patients with AHF who were discharged on dobutamine or milrinone for palliation, patients receiving dobutamine were less likely to be rehospitalized within 180 days of the initial discharge event, with no difference in time to rehospitalization between groups. When interpreting this finding in the context of the baseline differences in our study arms, it is pertinent to discuss that 31% of the dobutamine versus only 6% of the milrinone group was discharged to inpatient or home hospice, likely eliminating their likelihood of rehospitalization in the study period. When patients discharged to hospice were excluded, the benefit initially seen in the dobutamine group versus the milrinone group was no longer significant. There was no difference in the incidence of rehospitalization between study groups when those discharged to hospice were

Table 2
Clinical outcomes in overall cohort

	Overall Cohort		
	Dobutamine (n=135)	Milrinone (n=87)	p value
Rehospitalization Outcomes			
Rehospitalization within 180 days (excluding patients alive and not hospitalized with <180 days follow-up)	76/129 (59%)	66/83 (80%)	0.002*
Median days to rehospitalization (deaths treated as censored)†	35 [13-119]	34 [16-89]	0.97
Discharge Disposition			<.001*,‡
Home health care	82 (61%)	72 (83%)	
Hospice (inpatient or home)	41 (30%)	5 (6%)	
Long term care	5 (4%)	6 (7%)	
Rehab	0 (0%)	1 (1%)	
Skilled nursing facility	7 (5%)	3 (4%)	
Survival Outcomes			
Overall mortality	108 (80%)	55 (63%)	0.006*
Median overall survival (days) †	52 [15-279]	228 [62-415]	<0.001*
Either Rehospitalization or Death			
Median time to rehospitalization or death † (days)	16 [6-45]	29 [11-76]	0.048*
Days spent alive and out of hospital at 30 days	22 [10-30]	28 [20-30]	0.004*
Days spent alive and out of hospital at 90 days	37 [11-76]	70 [29-84]	<0.001*
Cause of Rehospitalization			
Arrhythmia	5 (7%)	9 (14%)	
Catheter-related thrombosis	1 (1%)	0 (0%)	
Central line infection	2 (3%)	9 (14%)	
Other	18 (24%)	12 (18%)	
Worsening heart failure	50 (66%)	36 (55%)	

Data are presented as count (column %) or median [first to third quartile].
* Denotes statistical significance.
† Data presented are median [twenty-fifth to seventy-fifth percentiles] of survival from the Kaplan Meier curves.
‡ p value is from a chi-square test with discharge disposition grouped as hospice (home or inpatient) or any other location.

Table 3
Clinical outcomes in overall cohort excluding patients discharged to inpatient or home hospice

	Overall Cohort Excluding Patients Discharged to Hospice		
Variable	Dobutamine (n=94)	Milrinone (n=82)	p value
Rehospitalization Outcomes			
Rehospitalization within 180 days (excluding patients alive and not hospitalized with <180 days follow-up)	68/92 (74%)	65/78 (83%)	0.14
Median days to rehospitalization (deaths treated as censored)†	32 [18-47]	34 [23-56]	0.50
Survival Outcomes			
Overall mortality	72 (77%)	50 (61%)	0.03*
Median overall survival (days) †	85 [54-166]	238 [138-284]	0.03*
Either Rehospitalization or Death			
Median time to rehospitalization or death (days) †	20 [14-32]	32 [21-50]	0.11
Days spent alive and out of hospital at 30 days	26 [15-30]	29 [21-30]	0.09
Days spent alive and out of hospital at 90 days	54 [17-82]	74 [37-85]	0.03*
Cause of Rehospitalization			
Arrhythmia	5 (7%)	9 (14%)	
Catheter-related thrombosis	1 (2%)	0 (0%)	
Central line infection	2 (3%)	8 (12%)	
Other	16 (24%)	12 (19%)	
Worsening heart failure	44 (65%)	36 (55%)	

Data are presented as count (column percentage) or median [first to third quartile].
* Denotes statistical significance.
† Data presented are median [twenty-fifth to seventy-fifth percentiles] of survival from the Kaplan Meier curves.

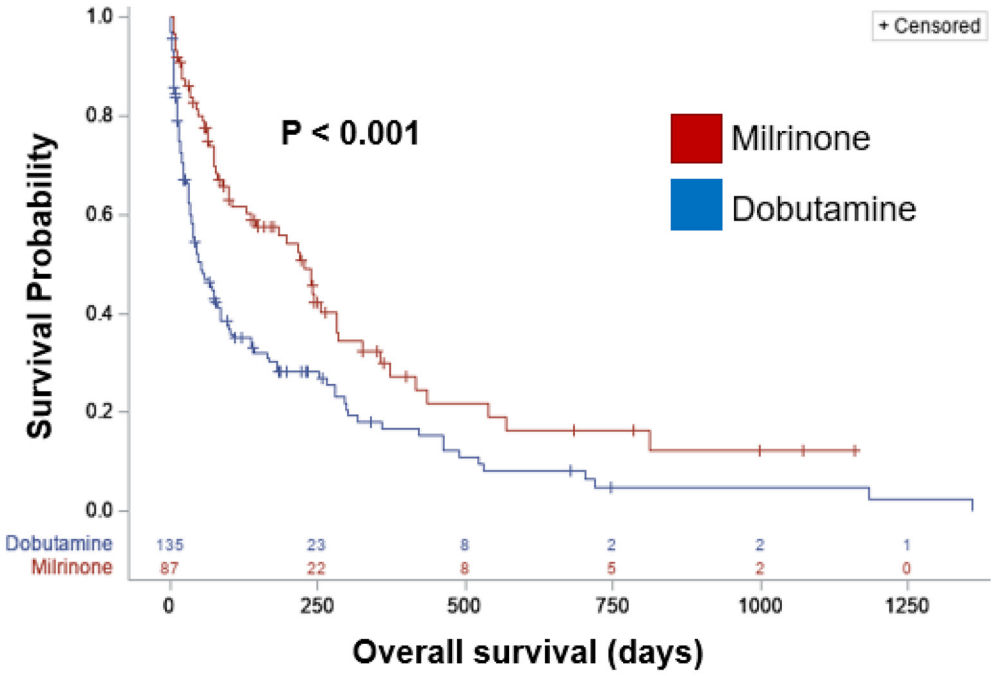

Figure 3. Overall survival compared by inotrope type (Eaton RE, et al).

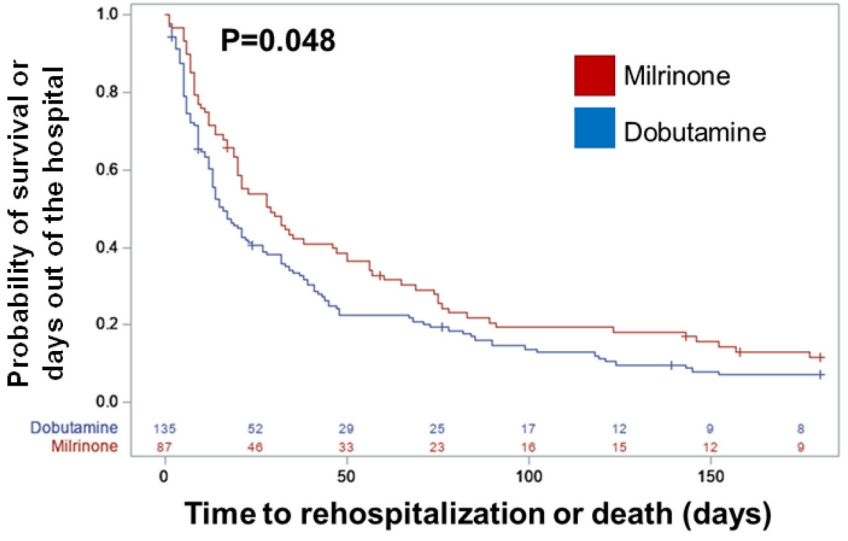

Figure 4. Time to first rehospitalization or death compared by inotrope type (Eaton RE, et al).

excluded from analysis. Among all patients who were rehospitalized, those receiving dobutamine were hospitalized sooner. Patients receiving dobutamine displayed a higher incidence of death and lower overall survival. Patients receiving milrinone, however, spent more days overall alive and out of the hospital, and were more likely to continue on guideline-directed medical therapy. During the study period, being alive longer was predictive of rehospitalization and being on milrinone.

The effect of milrinone versus dobutamine was variable as time progressed from the index discharge event. Patients receiving milrinone had a higher hazard of hospitalization late in the study period but decreased mortality earlier in the study period. These findings have important implications and can be extrapolated to real-world practice in conjunction with the patient's goals of care at advanced stages of disease. Selection of milrinone may be more appropriate for those who do not qualify for advanced therapies but have a longer anticipated trajectory of survival.

One year after the index discharge event, approximately 10% of our trial population was known to be alive. Median overall survival in the dobutamine group was 52 days, and 228 days in the milrinone group. This is consistent with 1 previous trial that reported a median survival time of 9.0

Table 4
Multivariable hazard models for rehospitalization and death within 180 days in the full cohort

	Outcome					
	Rehospitalization or death		Rehospitalization (death treated as censored)		Rehospitalization (death treated as competing event)	
Variable	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Treatment-specific models						
Milrinone (Ref=dobutamine)		0.10		0.72		0.007*
1 day (At risk n=205)	0.47 (0.20−1.08)		0.71 (0.27−1.89)		0.50 (0.18−1.42)	
15 day (At risk n=121)	0.73 (0.54−0.99)		0.99 (0.69−1.41)		1.30 (0.91−1.85)	
30 day (At risk n=85)	0.82 (0.59−1.13)		1.08 (0.75−1.54)		1.65 (1.16−2.33)	
90 day (At risk n=35)	0.98 (0.59−1.62)		1.23 (0.71−2.14)		2.42 (1.39−4.22)	
180 day (At risk n=15)	1.10 (0.57−2.12)		1.34 (0.65−2.78)		3.08 (1.47−6.47)	
Multivariable models						
Milrinone (Ref=dobutamine)		0.44		0.18		0.02*
1 day (At risk n=205)	0.61 (0.26−1.42)		0.82 (0.30−2.21)		0.51 (0.18−1.47)	
15 day (At risk n=121)	0.98 (0.69−1.39)		1.29 (0.86−1.91)		1.30 (0.87−1.94)	
30 day (At risk n=85)	1.10 (0.76−1.60)		1.44 (0.96−2.16)		1.65 (1.11−2.46)	
90 day (At risk n=35)	1.34 (0.77−2.32)		1.73 (0.95−3.17)		2.42 (1.32−4.42)	
180 day (At risk n=15)	1.51 (0.75−3.05)		1.95 (0.90−4.23)		3.07 (1.40−6.75)	
Presence of pulmonary hypertension	2.13 (1.18−3.84)	0.01*	2.61 (1.24−5.48)	0.01*	2.08 (1.08−4.01)	0.03*
Ventricular arrhythmia	1.04 (0.75−1.43)	0.84	1.07 (0.73−1.55)	0.74	1.04 (0.71−1.50)	0.86
Beta blocker utilization	0.51 (0.35−0.74)	<0.001*	0.45 (0.30−0.68)	<0.001*	0.57 (0.39−0.84)	0.004*
Systolic blood pressure†	1.00 (0.99−1.01)	0.58	1.00 (0.99−1.01)	0.94	1.01 (1.00−1.02)	0.20
Serum creatinine†	1.20 (1.03−1.39)	0.02*	1.12 (0.94−1.35)	0.25	0.94 (0.72−1.23)	0.64
Implantable cardioverter-defibrillator turned on	0.97 (0.70−1.36)	0.87	1.53 (1.00−2.36)	0.05*	2.15 (1.38−3.35)	<0.001*

* Denotes statistical significance.
† Hazard ratios correspond to a 1 unit increase in the continuous variable.

Table 5
Multivariable Cox proportional hazard model for overall survival

Variable	HR (95% CI)	p Value
Milrinone (Reference=dobutamine)		0.01*
30 days	0.52 (0.34−0.80)	
90 days	0.70 (0.49−1.01)	
180 days	0.85 (0.56−1.29)	
1 year	1.03 (0.61−1.76)	
2 years	1.25 (0.64−2.45)	
Presence of pulmonary hypertension	2.08 (1.14−3.81)	0.02*
Ventricular arrhythmia	1.25 (0.87−1.78)	0.22
Beta blocker utilization	0.75 (0.51−1.11)	0.15
Systolic blood pressure†	1.00 (0.98−1.01)	0.64
Serum creatinine†	1.16 (1.02−1.33)	0.03*
Implantable cardioverter-defibrillator turned on	0.76 (0.51−1.12)	0.17

* Denotes statistical significance.
† Hazard ratios correspond to a 1 unit increase in the continuous variable.

months, with 85% of this trial population receiving milrinone.[19]

Days alive and out of the hospital is an outcome that accounts for multiple events and event severity in a patient-centered approach.[24] For our patient population in particular, it also represents precious time spent potentially at home with loved ones in the last days of life. Determining the length of rehospitalization, in conjunction with the cause, is vital in understanding the impact on quality of life. In our analysis, we analyzed Day 30 and Day 90 after the index discharge event, and determined total number of days spent alive and out of the hospital at both time points. This finding was most pronounced at Day 90, when patients receiving milrinone spent over a month longer alive and out of the hospital relative to those receiving dobutamine. Although the differences are on the scale of days, this time is clinically significant to a patient and their family at the end of life.

Patients may display baseline characteristics that influence treatment selection. Both agents increase heart rate and cardiac output.[2,25] Dobutamine, an alpha1, beta1, and beta2 agonist, increases contractility through beta receptors; however, it also increases myocardial oxygen demand.[25] In practice, it is typically the preferred agent in acute kidney injury; however, it displays a higher risk of ventricular tachyarrhythmias.[2,25] Concurrent β-blocker use with dobutamine is not common. Milrinone, a phosphodiesterase-3 inhibitor, decreases the mean arterial pressure, causing vasodilation.[2,25] Owing to vasodilatory action in the pulmonary arteries, it is preferred in patients with pHTN and displays a lower risk of ventricular tachyarrhythmias.[2,25] Because of its mechanism of action, concurrent β-blocker use can occur, as evidenced in our trial. Previous trials of β blockers alone have shown reduction in all-cause mortality and hospitalization in patients with HF with reduced EF.[3] In our adjusted analysis, independent of treatment type, β-blocker use was associated with decreased risk of hospitalization. Regardless of treatment type at baseline, the presence of pHTN and increased serum creatinine was associated with poorer survival.

Finally, the overall incidence of rehospitalization secondary to arrhythmias was low (10%) and similar between groups; this finding could be due to the relatively low doses of dobutamine (mean discharge dose 3 mcg/kg/min) and milrinone (mean discharge dose 0.3 mcg/kg/min) used in this cohort. Previous studies in similar patient populations used a mean dobutamine dose of at least 4 mcg/kg/min.[18,19] There was a higher incidence of central line infections in the milrinone arm; this finding could be attributed to the longer median therapy duration in this group.

This retrospective analysis from a single, tertiary care center has several limitations. The dobutamine arm likely represents a higher acuity population at baseline, with this group being older, presenting with a significantly higher BNP, and a larger proportion being discharged to hospice. To account for the retrospective nature of this study, multivariable models were performed to account for confounders and baseline differences between groups. The potential benefits seen with milrinone in this population could be attributed to selection bias and differences in patient selection and characteristics. Follow-up was collected through our electronic medical record, representing a potentially limited ability to capture all events and patient information. We could only assess ICD status at point of discharge and could not capture if they were turned off after index discharge event. We collected data from 2015 to 2020; a minimum of 180 days of data were collected for all patients; however, those patients discharged earlier in the period have longer overall duration of follow-up. Because data were collected over 5 years, there is the potential that nonclinical factors influenced therapy selection, such as insurance coverage or discharge site formulary restrictions.

In conclusion, there are limited data available on outcomes associated with continuous, intravenous inotrope therapy as palliation in patients with AHF. In our cohort of patients with AHF receiving palliative inotropes, there was no difference in rehospitalization when patients discharged to hospice were excluded. Although dobutamine showed favor in rehospitalization as the primary end point in the overall population, milrinone was associated with decreased mortality and longer survival, with a higher hazard of hospitalization late in the period but decreased mortality early in the period. Agent selection must closely align with the patient's trajectory of disease. More trial data are needed to validate mortality and quality of life outcomes.

Disclosures

Kevin Kissling is a consultant for Nuwellis Inc. The remaining authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2022.08.019.

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