ORIGINAL ARTICLE

Milrinone as Compared with Dobutamine in the Treatment of Cardiogenic Shock

Rebecca Mathew, M.D., Pietro Di Santo, M.D., Richard G. Jung, Ph.D., Jeffrey A. Marbach, M.B., B.S., Jordan Hutson, M.D., Trevor Simard, M.D., F. Daniel Ramirez, M.D., David T. Harnett, M.D., Anas Merdad, M.B., B.S., Aws Almufleh, M.B., B.S., Willy Weng, M.D., Omar Abdel-Razek, M.D., Shannon M. Fernando, M.D., Kwadwo Kyeremanteng, M.D., M.H.A., Jordan Bernick, M.Sc., George A. Wells, Ph.D., Vincent Chan, M.D., Michael Froeschl, M.D., C.M., Marino Labinaz, M.D., Michel R. Le May, M.D., Juan J. Russo, M.D., and Benjamin Hibbert, M.D., Ph.D.

ABSTRACT

BACKGROUND

Cardiogenic shock is associated with substantial morbidity and mortality. Although inotropic support is a mainstay of medical therapy for cardiogenic shock, little evidence exists to guide the selection of inotropic agents in clinical practice.

METHODS

We randomly assigned patients with cardiogenic shock to receive milrinone or dobutamine in a double-blind fashion. The primary outcome was a composite of in-hospital death from any cause, resuscitated cardiac arrest, receipt of a cardiac transplant or mechanical circulatory support, nonfatal myocardial infarction, transient ischemic attack or stroke diagnosed by a neurologist, or initiation of renal replacement therapy. Secondary outcomes included the individual components of the primary composite outcome.

RESULTS

A total of 192 participants (96 in each group) were enrolled. The treatment groups did not differ significantly with respect to the primary outcome; a primary outcome event occurred in 47 participants (49%) in the milrinone group and in 52 participants (54%) in the dobutamine group (relative risk, 0.90; 95% confidence interval [CI], 0.69 to 1.19; P=0.47). There were also no significant differences between the groups with respect to secondary outcomes, including in-hospital death (37% and 43% of the participants, respectively; relative risk, 0.85; 95% CI, 0.60 to 1.21), resuscitated cardiac arrest (7% and 9%; hazard ratio, 0.78; 95% CI, 0.29 to 2.07), receipt of mechanical circulatory support (12% and 15%; hazard ratio, 0.78; 95% CI, 0.36 to 1.71), or initiation of renal replacement therapy (22% and 17%; hazard ratio, 1.39; 95% CI, 0.73 to 2.67).

CONCLUSIONS

In patients with cardiogenic shock, no significant difference between milrinone and dobutamine was found with respect to the primary composite outcome or important secondary outcomes. (Funded by the Innovation Fund of the Alternative Funding Plan for the Academic Health Sciences Centres of Ontario; ClinicalTrials.gov number, NCT03207165.)

From the CAPITAL Research Group, Division of Cardiology (R.M., P.D.S., R.G.J., J.A.M., T.S., F.D.R., D.T.H., O.A.-R., M.F., M.L., M.R.L.M., J.J.R., B.H.), the Cardiovascular Research Methods Centre (J.B., G.A.W.), and the Division of Cardiac Surgery (V.C.), University of Ottawa Heart Institute, and the Faculty of Medicine (R.M., P.D.S., R.G.J., J.H., D.T.H., W.W., O.A.-R., S.M.F., K.K., M.F., M.L., M.R.L.M., J.J.R., B.H.), the Division of Critical Care, Department of Medicine (R.M., J.H., S.M.F., K.K.), the School of Epidemiology and Public Health (P.D.S.), and the Department of Cellular and Molecular Medicine (R.G.J., T.S., B.H.), University of Ottawa, Ottawa, the Division of Cardiology, University of Toronto, Toronto (A.M.), and the Division of Cardiology, University of British Columbia, Vancouver (A.A.) — all in Canada; the Division of Critical Care, Tufts Medical Center, Boston (J.A.M.); the Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN (T.S.); and Hôpital Cardiologique du Haut Lévêque, Centre Hospitalier Universitaire Bordeaux (F.D.R.), and LIRYC (L'Institut de Rythmologie et Modélisation Cardiaque) (F.D.R.) — both in Bordeaux-Pessac, France. Address reprint requests to Dr. Hibbert at the University of Ottawa Heart Institute, 40 Ruskin St., H-4238, Ottawa, ON, Canada K1Y 4W7, or at bhibbert@ottawaheart.ca.

Drs. Mathew and Di Santo contributed equally to this article.

N Engl J Med 2021;385:516-25.
DOI: 10.1056/NEJMoa2026845

Cardiogenic shock is defined as a state of low cardiac output resulting in clinical and biochemical manifestations of end-organ hypoperfusion.[1,2] Although emergency revascularization has been shown to reduce the risk of death in patients with myocardial infarction complicated by cardiogenic shock,[3] there is a paucity of data pertaining to other therapies for cardiogenic shock management. Treatment efforts have focused on improving hemodynamic measures with the use of vasopressor, inotrope, and device-based therapies, with supporting evidence derived predominantly from observational studies.[4]

Although mechanical circulatory support for cardiogenic shock has garnered considerable attention,[5-8] vasopressors and inotropes remain the cornerstone of therapy for most patients with this condition.[9,10] Norepinephrine has emerged as a preferred vasopressor over epinephrine[11,12] and dopamine[13]; however, comparative data on other commonly used and widely available inotropes, such as milrinone and dobutamine, remain scarce.[14] Milrinone is a phosphodiesterase 3 inhibitor that increases cardiac inotropy, lusitropy, and peripheral vasodilatation. In contrast, dobutamine is a synthetic catecholamine that acts as a β_1- and β_2-receptor agonist and improves blood pressure by increasing cardiac output. Both agents are sometimes classified as "inodilators" (inotropes that are also vasodilators).

Preference is often given to using milrinone in patients with severe pulmonary hypertension because of a purported mechanism of reducing pulmonary-artery pressures and improving right ventricular function.[15,16] Concerns regarding the effects of dobutamine on heart rate and myocardial oxygen consumption have tempered its use in patients who are at risk for tachyarrhythmias or myocardial ischemia. However, in the absence of robust comparative data,[14] the use of each agent is largely based on clinician preference and theoretical benefits related to their mechanisms of action. We therefore sought to compare the efficacy and safety of milrinone and dobutamine in patients with cardiogenic shock in a pragmatic randomized clinical trial.

METHODS

TRIAL OVERSIGHT

We conducted the Dobutamine Compared with Milrinone (DOREMI) trial, a randomized, double-blind clinical trial of milrinone as compared with dobutamine in patients with cardiogenic shock. The protocol is available with the full text of this article at NEJM.org. Ethics approval was obtained from the Ottawa Health Science Network Research Ethics Board, and the trial was conducted in accordance with the principles of the Declaration of Helsinki. An independent data and safety monitoring board regularly monitored enrollment and safety data. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol and statistical analysis plan (available with the protocol).

PATIENT POPULATION

Patients were recruited from a single quaternary care cardiac institute between September 1, 2017, and May 17, 2020. Eligible patients were 18 years of age or older, were admitted to the cardiac intensive care unit (ICU), and had cardiogenic shock meeting the Society for Cardiovascular Angiography and Interventions (SCAI) definition of cardiogenic shock stage B, C, D, or E.[17] Written informed consent was obtained from each participant or their substitute decision maker. A complete list of inclusion and exclusion criteria, the SCAI classification of cardiogenic shock, and details regarding informed consent are provided in the Supplementary Appendix, available at NEJM.org.

TRIAL PROCEDURES

Randomization was performed with the use of a computer-generated random sequence and was stratified according to affected ventricle (left ventricle or both ventricles vs. right ventricle). Participants were assigned in a 1:1 ratio to receive either milrinone or dobutamine. Assignments were given in sealed envelopes, which were opened by the registered nurse who was responsible for preparing the inotrope infusion. Medication bags and intravenous pump screens were concealed. The treating physicians, participants, local investigators, and all research personnel were unaware of the treatment assignments.

After randomization, participants began to receive either milrinone or dobutamine at a dose determined with a standardized dosing scale that ranged from stage 1 to stage 5, which corresponded to 2.5, 5.0, 7.5, 10.0, and greater than 10.0 μg per kilogram of body weight per minute for dobutamine and 0.125, 0.250, 0.375, 0.500,

and greater than 0.500 μg per kilogram per minute for milrinone. Adjustment of the doses according to stage was performed in a blinded fashion by the treating team on the basis of clinical judgment. Pulmonary-artery catheters were not used routinely but were permitted at the discretion of the treating physicians. If at any time the randomly assigned therapy was considered to be unsafe to continue, the treating physician could be made aware of the treatment assignment, reveal the assignment to the participant, and treat the participant with an open-label inotrope.

TRIAL OUTCOMES

All outcomes were limited to the index hospitalization and were adjudicated by members of an outcome adjudication committee who were unaware of the treatment assignments. The primary outcome was the composite of in-hospital death from any cause, resuscitated cardiac arrest, receipt of a cardiac transplant or mechanical circulatory support, nonfatal myocardial infarction, transient ischemic attack or stroke diagnosed by a neurologist, or initiation of renal replacement therapy. A length of stay in the cardiac ICU of 7 days or longer was initially included in the primary composite outcome at the start of the trial; however, it was removed by the trial steering committee in October 2018, given the high incidence of prolonged ICU stays and a reevaluation of its clinical significance relative to the other variables in the composite outcome. Length of stay in the cardiac ICU was therefore converted to a secondary outcome. A complete list of the efficacy and safety outcomes and definitions is provided in Table S1 in the Supplementary Appendix.

STATISTICAL ANALYSIS

On the basis of a previous meta-analysis, the pooled incidence of the composite primary outcome was estimated to be 55% in the dobutamine group.[14] We hypothesized that the percentage of participants with a primary outcome event would be 20 percentage points lower in the milrinone group than in the dobutamine group. This hypothesis was based on the reported reduced incidences of death and arrhythmia with milrinone in observational studies involving patients with acute decompensated heart failure.[14] We calculated that a total of 192 patients would be needed for the trial to have 80% power to detect this difference with the use of a two-sided alpha level of 0.05.

Complete details regarding the statistical analysis are provided in the Supplementary Appendix. In brief, data were analyzed according to the intention-to-treat principle. The statistical analysis plan was reviewed by the trial investigators and finalized before unblinding. An unadjusted chi-square analysis was conducted to compare the treatment groups with respect to the primary composite outcome, and corresponding relative risks and 95% confidence intervals were calculated. Proportional hazards analysis with log-rank testing was also performed for the primary composite outcome and all the individual components of the outcome, with the use of the Fine–Gray method to account for the competing risk of death for the components of the primary outcome, where applicable. For variables measured more than once throughout the trial, a mixed model for repeated measures (for continuous variables) or a cumulative logistic-regression model (for ordinal variables) was used to test the significance of the association between inotrope and outcome.

We used unadjusted chi-square testing to conduct an a priori sensitivity analysis that included the primary composite outcome plus a length of stay in the cardiac ICU of 7 days or longer (i.e., the original primary outcome). A post hoc sensitivity analysis of the primary outcome was performed with adjustment for baseline invasive mechanical ventilation, previous myocardial infarction, previous percutaneous coronary intervention, and vasopressor use before randomization, since these baseline characteristics were potentially clinically important and unbalanced between the groups. We assessed the consistency of the treatment effect in prespecified subgroups based on age, sex, affected ventricle, cause of ventricular dysfunction, severity of left ventricular dysfunction, severity of baseline renal dysfunction, and concomitant vasopressor use at the time of randomization (see the Supplementary Appendix).

All reported P values are two-sided, and a P value of less than 0.05 was considered to indicate statistical significance. Analyses were performed with the use of SAS software, version 9.4 (SAS Institute). The widths of the confidence intervals have not been adjusted for multiple

comparisons, and therefore the intervals should not be used to infer definitive treatment effects for secondary outcomes.

RESULTS

TRIAL POPULATION

A total of 319 patients were screened for eligibility, 192 of whom were enrolled (96 in each treatment group) (Fig. S1 in the Supplementary Appendix). Reasons for exclusion included transfer to the ICU after milrinone or dobutamine had already been initiated (47 patients), a decision by the treating physician that the patient was not eligible for the trial (40), an inability to obtain consent (23), presentation with an out-of-hospital cardiac arrest (13), and enrollment in another interventional trial (4).

Baseline characteristics were similar in the milrinone group and the dobutamine group (Tables 1 and S2). The mean (±SD) age of patients was 68.9±13.8 years in the milrinone group and 72.0±11.3 years in the dobutamine group; 38% and 35% of the participants, respectively, were women, and 69% and 65%, respectively, had ischemic cardiomyopathy. The presence of coexisting conditions, including hypertension, diabetes mellitus, and atrial fibrillation, was similar in the two groups. Medical therapy in the 24 hours before randomization was also similar, including the use of beta-blockers in 51% of the participants in the milrinone group and 46% of those in the dobutamine group. At randomization, 10 participants had an intraaortic balloon pump in place and 23 had a pulmonary-artery catheter. The median serum lactate level was elevated to 2.9 mmol per liter (interquartile range, 2.1 to 4.5) (26.1 mg per deciliter [interquartile range, 18.9 to 40.5]) in the milrinone group and to 2.9 mmol per liter (interquartile range, 1.7 to 4.2) (26.1 mg per deciliter [interquartile range, 15.3 to 37.8]) in the dobutamine group. The mean time from admission to the ICU to randomization was 23.4±92.6 hours in the milrinone group and 17.9±50.6 hours in the dobutamine group.

PRIMARY OUTCOME

A primary outcome event occurred in 47 participants (49%) in the milrinone group and in 52 participants (54%) in the dobutamine group (relative risk, 0.90; 95% confidence interval [CI], 0.69 to 1.19; P=0.47) (Table 2). There was no evidence of heterogeneity of the treatment effect across the prespecified subgroups, including those defined according to sex, age, affected ventricle, cause or severity of left ventricular dysfunction, severity of baseline renal dysfunction, or concomitant use of vasopressors at time of inotrope initiation (Fig. 1). A time-to-event analysis also did not show a significant difference between the milrinone group and the dobutamine group with respect to the primary composite outcome (hazard ratio, 0.91; 95% CI, 0.61 to 1.34) (Fig. 2A). There were no significant differences between the groups in the sensitivity analysis that included all components of the primary composite outcome plus a length of stay in the cardiac ICU of 7 days or longer (relative risk, 0.86; 95% CI, 0.72 to 1.04) or in the additional sensitivity analysis with adjustment for unbalanced baseline characteristics (relative risk, 1.00; 95% CI, 0.78 to 1.28).

SECONDARY OUTCOMES

The individual components of the primary outcome are summarized in Table 2. In-hospital death from any cause occurred in 35 participants (37%) in the milrinone group and in 41 participants (43%) in the dobutamine group (relative risk, 0.85; 95% CI, 0.60 to 1.21). Causes of death are shown in Table S3. Time-to-event analyses likewise did not show any significant differences between the two groups in individual components of the primary outcome, including in-hospital death (Fig. 2B). There were no significant differences between the groups with respect to the occurrence of resuscitated cardiac arrest (in 7% of the participants in the milrinone group and 9% of those in the dobutamine group; hazard ratio, 0.78; 95% CI, 0.29 to 2.07) (Fig. S2A), receipt of mechanical circulatory support (in 12% and 15%, respectively; hazard ratio, 0.78; 95% CI, 0.36 to 1.71), occurrence of transient ischemic attack or stroke diagnosed by a neurologist (in 1% and 2%, respectively; hazard ratio, 0.50; 95% CI, 0.05 to 5.50), or the initiation of renal replacement therapy (in 22% and 17%, respectively; hazard ratio, 1.39; 95% CI, 0.73 to 2.67) (Fig. S2B). No participant underwent cardiac transplantation, and only one nonfatal myocardial infarction occurred (in the milrinone group). Given the infrequent use of pulmonary-artery catheters, we did not perform

Table 1. Baseline Characteristics of the Participants.*

Characteristic	Milrinone (N=96)	Dobutamine (N=96)
Age — yr	68.9±13.8	72.0±11.3
Female sex — no. (%)	36 (38)	34 (35)
Median body-mass index (IQR)†	26.4 (23.7–31.0)	26.0 (22.5–30.5)
Race — no. (%)‡		
White	86 (90)	79 (82)
Non-White	10 (10)	17 (18)
Left ventricular function		
Median left ventricular ejection fraction (IQR) — %	25 (20–40)	25 (20–40)
Cause of ventricular dysfunction — no. (%)		
Ischemic	66 (69)	62 (65)
Nonischemic	30 (31)	33 (34)
Coexisting conditions — no. (%)		
Previous myocardial infarction	39 (41)	29 (30)
Previous percutaneous coronary intervention	30 (31)	19 (20)
Previous coronary-artery bypass grafting	20 (21)	19 (20)
Previous stroke or transient ischemic attack	13 (14)	15 (16)
Atrial fibrillation	49 (51)	46 (48)
Chronic kidney disease§	38 (40)	40 (42)
Chronic liver disease	6 (6)	7 (7)
Chronic obstructive pulmonary disease	11 (11)	14 (15)
SCAI cardiogenic shock class — no. (%)¶		
A	0	0
B	6 (6)	5 (5)
C	77 (80)	78 (81)
D	10 (10)	12 (12)
E	3 (3)	1 (1)
Time from admission to the cardiac ICU to randomization — hr	23.4±92.6	17.9±50.6

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. ICU denotes intensive care unit, and IQR interquartile range.
† Body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Race was reported by the participants.
§ Chronic kidney disease was defined as an estimated glomerular filtration of less than 60 ml per minute per 1.73 m^2 of body-surface area, in accordance with the Chronic Kidney Disease Epidemiology Collaboration creatinine equation.
¶ Society for Cardiovascular Angiography and Interventions (SCAI) class A indicates a risk of the development of cardiogenic shock in the absence of signs or symptoms; class B, compensated shock with relative hypotension; class C, hypoperfusion that requires an initial set of interventions to restore perfusion; class D, deteriorating shock after interventions have failed to stabilize the patient's condition; and class E, cardiovascular collapse with ongoing cardiopulmonary resuscitation.

analyses of changes in cardiac index, pulmonary capillary wedge pressure, or systemic vascular resistance.

Additional secondary outcomes are shown in Table 2. There were no significant differences between the groups with respect to the total duration of inotropic treatment, total hospital length of stay, or ICU length of stay. The number of participants with an ICU stay of 7 days or longer was also similar in the two groups. There were no significant differences in the number of participants who received noninvasive or inva-

Table 2. Primary and Secondary Outcomes.*

Outcome	Milrinone (N=96)	Dobutamine (N=96)	Relative Risk or Hazard Ratio (95% CI)†	P Value‡
Primary outcome: composite of in-hospital death from any cause, resuscitated cardiac arrest, receipt of cardiac transplant or mechanical circulatory support, nonfatal myocardial infarction, transient ischemic attack or stroke diagnosed by a neurologist, or initiation of renal replacement therapy — no. (%)	47 (49)	52 (54)	0.90 (0.69–1.19)	0.47
Secondary outcomes				
In-hospital death from any cause — no. (%)	35 (37)	41 (43)	0.85 (0.60–1.21)	
Resuscitated cardiac arrest — no. (%)	7 (7)	9 (9)	0.78 (0.29–2.07)§	
Receipt of cardiac transplant or mechanical circulatory support — no. (%)	11 (12)	14 (15)	0.78 (0.36–1.71)§	
Nonfatal myocardial infarction — no. (%)	1 (1)	0	—	
Transient ischemic attack or stroke — no. (%)	1 (1)	2 (2)	0.50 (0.05–5.50)§	
Initiation of renal replacement therapy — no. (%)¶	21 (22)	16 (17)	1.39 (0.73–2.67)§	
Median cardiac ICU length of stay (IQR) — days‖	4.5 (2.0–7.0)	5.5 (3.0–10.0)	—	
Cardiac ICU length of stay ≥7 days — no. (%)‖	31 (32)	42 (44)	0.74 (0.51–1.07)	
Median hospital length of stay (IQR) — days‖	16 (6–28)	15 (6–27)	—	
Median total time receiving inotropes (IQR) — hr‖	36 (18–79)	39 (19–64)	—	
Receipt of noninvasive or invasive mechanical ventilation after randomization — no. (%)	6 (6)	7 (7)	0.86 (0.30–2.46)	
Median total time receiving noninvasive or invasive mechanical ventilation (IQR) — hr‖	48 (6–120)	48 (12–120)	—	
Acute kidney injury — no. (%)¶	86 (92)	85 (90)	1.02 (0.94–1.12)	
Normalization of lactate level — no. (%)**	33 (46)	36 (56)	0.80 (0.56–1.15)	
Arrhythmia leading to medical team intervention — no. (%)††	48 (50)	44 (46)	1.19 (0.85–1.57)	

* All analyses were performed in accordance with the intention-to-treat principle.
† Relative risk is shown unless otherwise indicated. The widths of the confidence intervals have not been adjusted for multiple comparisons, and therefore the intervals should not be used to infer definitive treatment effects for secondary outcomes.
‡ The P value for the primary outcome was from an unadjusted chi-square analysis.
§ The point estimate represents a hazard ratio, since analyses taking into consideration the competing risk of death using Fine–Gray model were performed.
¶ Patients with a history of renal replacement therapy before randomization were excluded from the analysis.
‖ Time was measured from the time of randomization.
** Patients with a normal lactate level at the time of randomization were excluded from the analysis, and the analysis was limited to 120 hours from randomization.
†† Medical team intervention was defined as electrical or chemical cardioversion or any intravenous administration of antiarrhythmic medication.

sive mechanical ventilation after inotrope initiation, in the total duration of ventilation, or in the number of participants with arrhythmia leading to intervention by a medical team. The incidence of acute kidney injury was similarly high in both groups.

Overall, no significant differences were found in heart rate, mean arterial pressure, vasoactive–inotropic score, serum lactate level, serum creatinine level, or hourly urine output between the treatment groups (Figs. 3 and S3 and Table S4). There was no treatment effect with respect to inotrope dose stage (Fig. S4). Finally, there were no significant differences with respect to secondary safety outcomes, including atrial or ventricular arrhythmias, sustained hypotension, or an increase in dose or the addition of new vasopressor therapy (Table S5).

DISCUSSION

We sought to compare the efficacy and safety of milrinone and dobutamine in patients with cardiogenic shock. In contrast to our hypothesis,

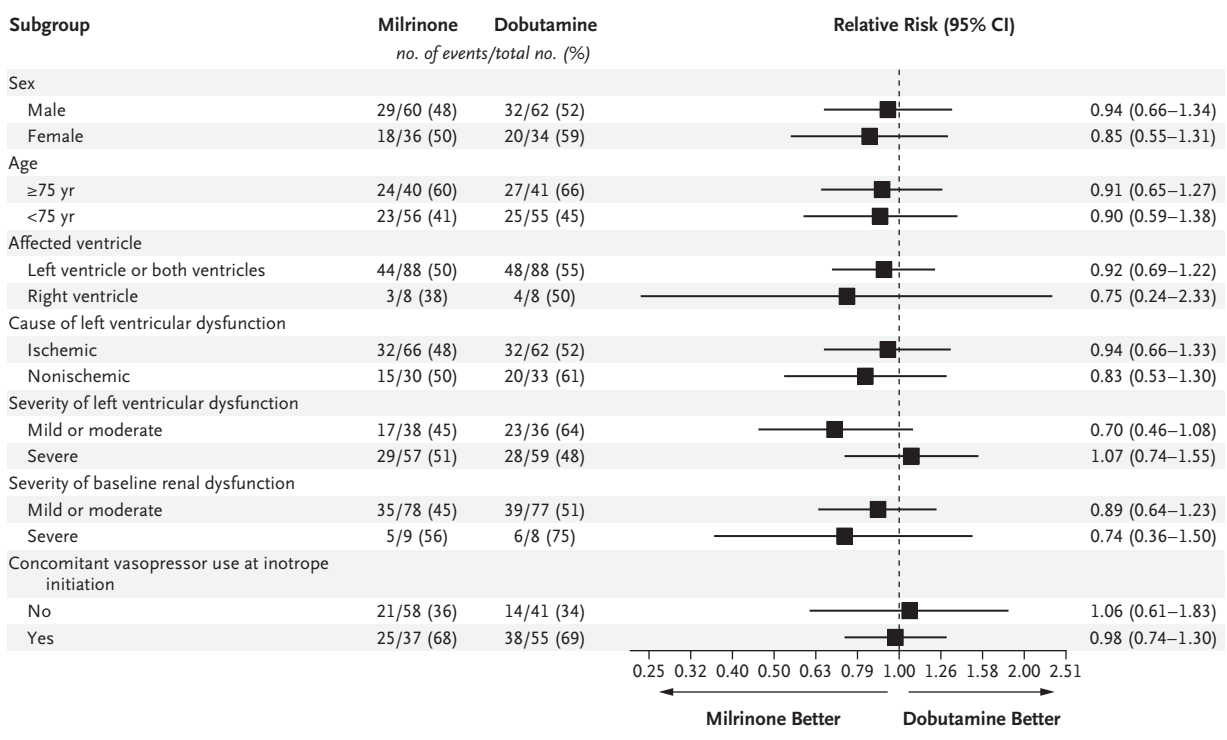

Figure 1. Subgroup Analyses of the Primary Composite Outcome.

Shown are relative risks of the primary composite outcome (in-hospital death from any cause, resuscitated cardiac arrest, receipt of a cardiac transplant or mechanical circulatory support, nonfatal myocardial infarction, transient ischemic attack or stroke diagnosed by a neurologist, or initiation of renal replacement therapy) with 95% confidence intervals from unadjusted chi-square analyses for prespecified subgroups. An ejection fraction of 35% was used as the cutoff value for the definition of subgroups based on the severity of left ventricular dysfunction, and an estimated glomerular filtration rate of 30 ml per minute per 1.73 m^2 of body-surface area was used as the cutoff value for the definition of subgroups based on the severity of baseline renal dysfunction. The widths of the confidence intervals have not been adjusted for multiple comparisons, and therefore the intervals should not be used to infer definitive treatment effects for secondary outcomes.

we did not find a significant advantage of milrinone over dobutamine with respect to the composite primary outcome or secondary outcomes. Moreover, we did not identify any significant between-group differences in safety outcomes or in surrogate markers of resuscitation, including heart rate, blood pressure, and serum lactate level. The incidence of adverse clinical outcomes, including in-hospital death, was high in both groups.

Data to guide inotrope selection in patients with cardiogenic shock are limited. The Sepsis Occurrence in Acutely Ill Patients II (SOAP II) trial evaluated dopamine as compared with norepinephrine in the treatment of patients with shock, including a subgroup of 280 patients with cardiogenic shock, and showed no significant difference in mortality between the treatment strategies.[13] Previous comparisons of milrinone and dobutamine include a single randomized trial involving 36 hospitalized patients awaiting cardiac transplantation[19] that was not limited to patients with cardiogenic shock, as well as two observational studies that showed no difference in in-hospital mortality.[20,21] Thus, although inotropes form a foundation of therapy in patients with cardiogenic shock, our trial addresses an important knowledge gap in the management of this condition.

Several studies have suggested that the risk of death is increased with the use of inotropes in patients with chronic heart failure[22,23]; however, this association has not been established in patients with cardiogenic shock. In a propensity-based analysis involving patients with cardiogenic shock, higher 30-day mortality was found

in association with the use of a vasopressor alone (epinephrine, norepinephrine, or dopamine) than with the use of a vasopressor plus an inodilator (dobutamine, levosimendan, or a phosphodiesterase 3 inhibitor).[24] Excessive vasoconstriction, which would increase left ventricular afterload, could in theory be offset with vasodilation by the inodilator. Randomized comparisons between an inotrope and placebo in patients with cardiogenic shock may not be feasible to perform. However, ongoing studies of temporary forms of mechanical circulatory support may offer opportunities to evaluate the need for inotrope therapy in the context of device-based support.

Our trial was intended to be pragmatic and was designed to include a broad range of patients in the phases of shock that are typically treated with inotropes. We set inclusion criteria that were based predominantly on clinical assessment in order to maximize external generalizability. In contrast, the definitions of cardiogenic shock used in previous trials have largely been based on hemodynamic measures, despite the current guidelines advising selective use of a pulmonary-artery catheter[2] and clinical practice reflecting bedside diagnosis. In our trial, relatively few patients underwent hemodynamic assessment with the use of a pulmonary-artery catheter at baseline. Nonetheless, 40% of the patients died while they were hospitalized — a percentage similar to those seen in previous studies in which hemodynamic criteria were used for entry.[3] To reflect the shift to an emphasis on diagnosing cardiogenic shock clinically and to standardize comparisons between trials, the SCAI has recently released a classification system for cardiogenic shock.[17] According to this classification system, most patients in our trial were in class C or D ("classic" or "deteriorating" cardiogenic shock). Future studies focusing on earlier intervention (i.e., with patients in class B or "beginning" cardiogenic shock) may identify therapies capable of altering the natural history of cardiogenic shock — a goal that may be difficult to achieve after hypoperfusion and end-organ dysfunction occurs.

Our trial has important limitations. First, only in-hospital outcomes were evaluated. Although this ensured complete data for analysis, it is possible that differences in outcomes exist beyond the index hospitalization, as was seen in the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial.[3] Second, dose adjustments were based on individual physician assessment rather than guided by a standardized protocol based on biochemical or hemodynamic measures. Although this approach reflects clinical practice, it allowed for potential differences in dose adjustments and resuscitation to arise between the treatment groups. In addition, recruitment for this trial was from a single center, which may limit its external generalizability. Finally, our power cal-

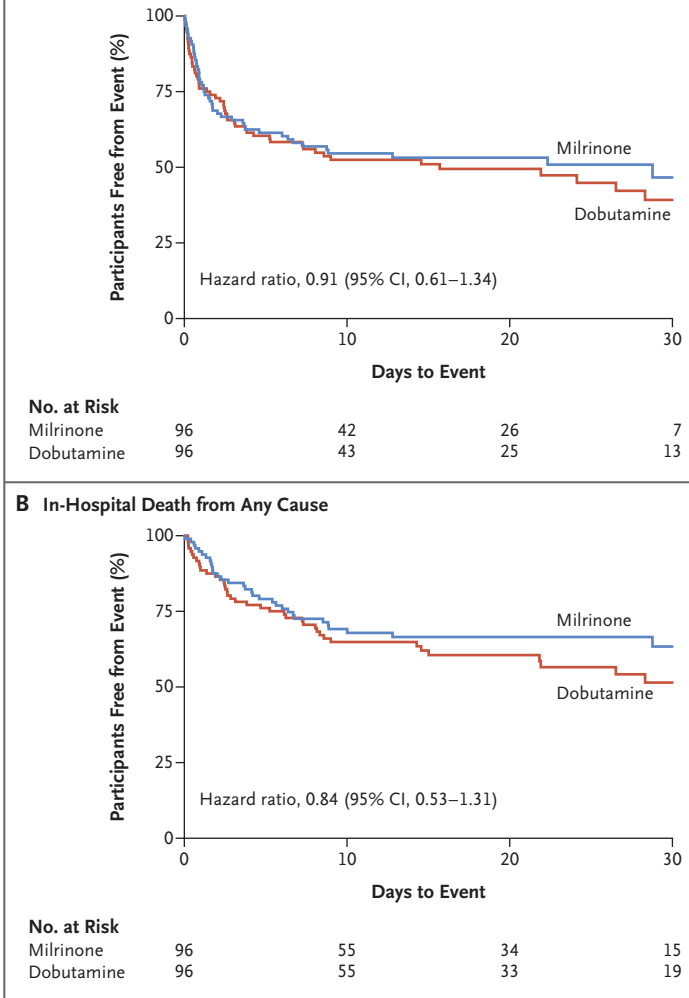

Figure 2. Time-to-Event Analysis of the Primary Composite Outcome and Death.

The primary composite outcome was in-hospital death from any cause, resuscitated cardiac arrest, receipt of a cardiac transplant or mechanical circulatory support, nonfatal myocardial infarction, transient ischemic attack or stroke diagnosed by a neurologist, or initiation of renal replacement therapy.

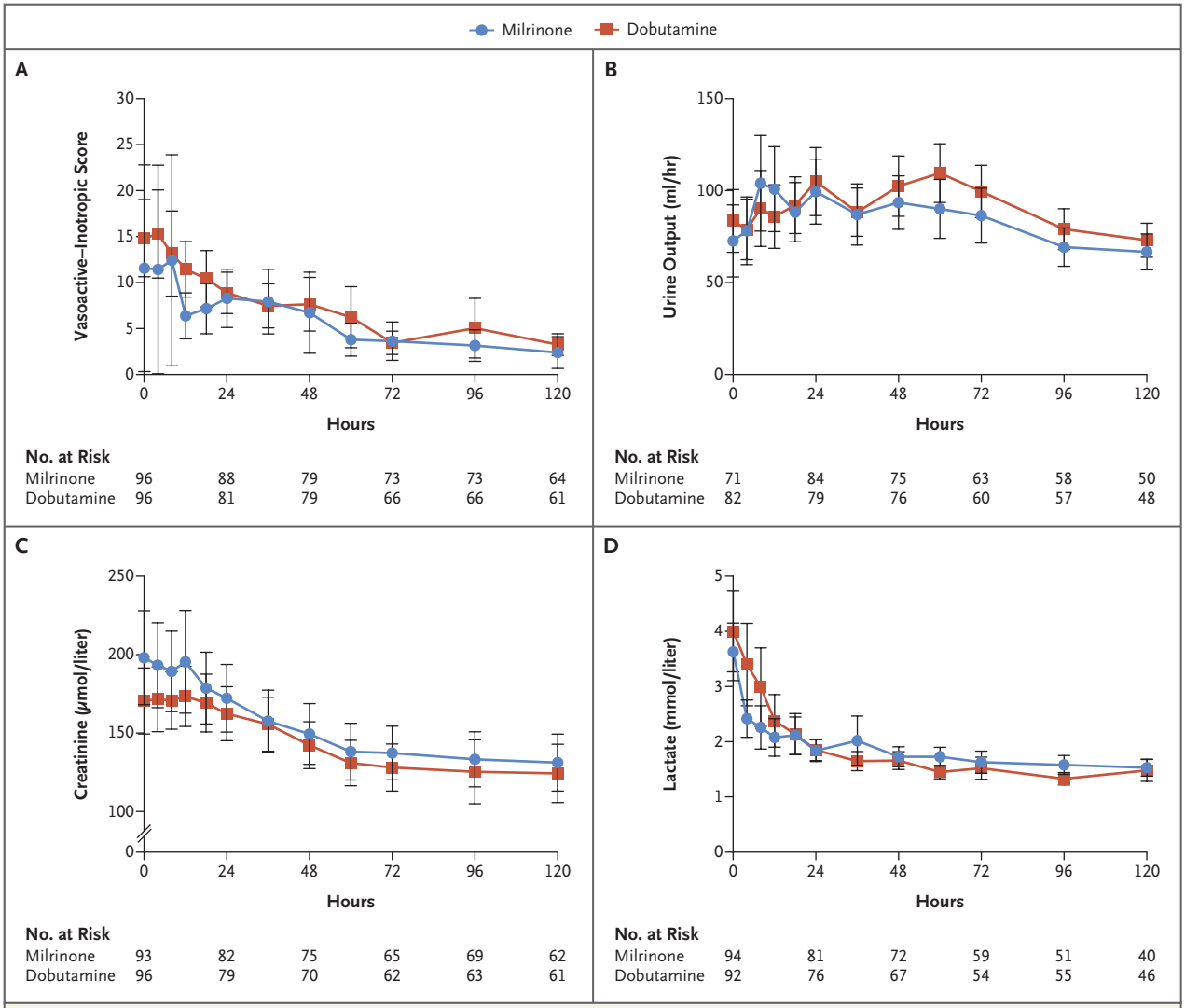

Figure 3. Key Clinical, Biochemical, and Hemodynamic Measures.

A mixed model for repeated measures was used to evaluate differences in continuous variables between the groups. The mean at each interval for the milrinone group and the dobutamine group is shown; I bars indicate 95% confidence intervals. Panel A shows the vasoactive–inotropic score[18] (which reflects the total amount of combined pharmacologic cardiovascular support provided by vasopressor and inotropic agents, as described in the Supplementary Appendix; higher scores indicate larger amounts of support), Panel B the hourly urine output, Panel C the serum creatinine level, and Panel D the serum lactate level. To convert the values for creatinine to milligrams per deciliter, divide by 88.4. To convert the values for lactate to milligrams per deciliter, divide by 0.1110.

culation was based on the expectation of a large treatment effect. As a consequence, the trial was underpowered to detect smaller effects, as reflected in the wide confidence interval for the primary outcome, which is compatible with a 31% lower risk or a 19% higher risk with milrinone than with dobutamine. The trial accordingly had even less power for the comparisons of the components of the primary outcome.

In this randomized clinical trial of milrinone as compared with dobutamine in patients with cardiogenic shock, we did not find a significant advantage of milrinone over dobutamine with respect to the primary composite outcome or important secondary outcomes.

Supported by the Innovation Fund of the Alternative Funding Plan for the Academic Health Sciences Centres of Ontario.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

REFERENCES

1. Thiele H, Ohman EM, de Waha-Thiele S, Zeymer U, Desch S. Management of cardiogenic shock complicating myocardial infarction: an update 2019. Eur Heart J 2019;40:2671-83.
2. van Diepen S, Katz JN, Albert NM, et al. Contemporary management of cardiogenic shock: a scientific statement from the American Heart Association. Circulation 2017;136(16):e232-e268.
3. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. N Engl J Med 1999;341:625-34.
4. Vahdatpour C, Collins D, Goldberg S. Cardiogenic shock. J Am Heart Assoc 2019;8(8):e011991.
5. Rihal CS, Naidu SS, Givertz MM, et al. 2015 SCAI/ACC/HFSA/STS clinical expert consensus statement on the use of percutaneous mechanical circulatory support devices in cardiovascular care (endorsed by the American Heart Association, the Cardiological Society of India, and Sociedad Latino Americana de Cardiologia Intervencion; affirmation of value by the Canadian Association of Interventional Cardiology-Association Canadienne de Cardiologie d'intervention). J Card Fail 2015; 21:499-518.
6. Burkhoff D, Cohen H, Brunckhorst C, O'Neill WW. A randomized multicenter clinical study to evaluate the safety and efficacy of the TandemHeart percutaneous ventricular assist device versus conventional therapy with intraaortic balloon pumping for treatment of cardiogenic shock. Am Heart J 2006;152(3):469.e1-469.e8.
7. Ouweneel DM, Eriksen E, Sjauw KD, et al. Percutaneous mechanical circulatory support versus intra-aortic balloon pump in cardiogenic shock after acute myocardial infarction. J Am Coll Cardiol 2017;69: 278-87.
8. Combes A, Price S, Slutsky AS, Brodie D. Temporary circulatory support for cardiogenic shock. Lancet 2020;396:199-212.
9. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129-200.
10. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2013;128:1810-52.
11. Levy B, Perez P, Perny J, Thivilier C, Gerard A. Comparison of norepinephrine-dobutamine to epinephrine for hemodynamics, lactate metabolism, and organ function variables in cardiogenic shock. A prospective, randomized pilot study. Crit Care Med 2011;39:450-5.
12. Levy B, Clere-Jehl R, Legras A, et al. Epinephrine versus norepinephrine for cardiogenic shock after acute myocardial infarction. J Am Coll Cardiol 2018;72:173-82.
13. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med 2010;362:779-89.
14. Mathew R, Visintini SM, Ramirez FD, et al. Efficacy of milrinone and dobutamine in low cardiac output states: systematic review and meta-analysis. Clin Invest Med 2019;42(2):E26-E32.
15. Anderson JL, Baim DS, Fein SA, Goldstein RA, LeJemtel TH, Likoff MJ. Efficacy and safety of sustained (48 hour) intravenous infusions of milrinone in patients with severe congestive heart failure: a multicenter study. J Am Coll Cardiol 1987;9: 711-22.
16. Eichhorn EJ, Konstam MA, Weiland DS, et al. Differential effects of milrinone and dobutamine on right ventricular preload, afterload and systolic performance in congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 1987;60: 1329-33.
17. Baran DA, Grines CL, Bailey S, et al. SCAI clinical expert consensus statement on the classification of cardiogenic shock: this document was endorsed by the American College of Cardiology (ACC), the American Heart Association (AHA), the Society of Critical Care Medicine (SCCM), and the Society of Thoracic Surgeons (STS) in April 2019. Catheter Cardiovasc Interv 2019;94:29-37.
18. Belletti A, Lerose CC, Zangrillo A, Landoni G. Vasoactive-inotropic score: evolution, clinical utility, and pitfalls. J Cardiothorac Vasc Anesth 2020 September 22 (Epub ahead of print).
19. Aranda JM Jr, Schofield RS, Pauly DF, et al. Comparison of dobutamine versus milrinone therapy in hospitalized patients awaiting cardiac transplantation: a prospective, randomized trial. Am Heart J 2003;145:324-9.
20. Yamani MH, Haji SA, Starling RC, et al. Comparison of dobutamine-based and milrinone-based therapy for advanced decompensated congestive heart failure: hemodynamic efficacy, clinical outcome, and economic impact. Am Heart J 2001; 142:998-1002.
21. Lewis TC, Aberle C, Altshuler D, Piper GL, Papadopoulos J. Comparative effectiveness and safety between milrinone or dobutamine as initial inotrope therapy in cardiogenic shock. J Cardiovasc Pharmacol Ther 2019;24:130-8.
22. Felker GM, Benza RL, Chandler AB, et al. Heart failure etiology and response to milrinone in decompensated heart failure: results from the OPTIME-CHF study. J Am Coll Cardiol 2003;41:997-1003.
23. Abraham WT, Adams KF, Fonarow GC, et al. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). J Am Coll Cardiol 2005;46:57-64.
24. Pirracchio R, Parenica J, Resche Rigon M, et al. The effectiveness of inodilators in reducing short term mortality among patient with severe cardiogenic shock: a propensity-based analysis. PLoS One 2013;8(8):e71659.