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ORIGINAL RESEARCH

CRITICAL CARE CARDIOLOGY

Milrinone vs Dobutamine for the Management of Cardiogenic Shock

Implications of Renal Function and Injury

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ABSTRACT

BACKGROUND Cardiogenic shock is associated with poor clinical outcomes. There is a paucity of prospective data examining the efficacy and safety of inotropic therapy in patients with cardiogenic shock and renal dysfunction.

OBJECTIVES This study sought to examine the treatment effect of milrinone compared to dobutamine in relation to renal function.

METHODS In this post hoc analysis of the DOREMI (Milrinone as Compared with Dobutamine in the Treatment of Cardiogenic Shock) trial, we examined clinical outcomes with milrinone compared to dobutamine after stratification based on baseline estimated glomerular filtration rate (eGFR) 60 ml/min/1.73 m^2 and acute kidney injury (AKI). 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, or initiation of renal replacement therapy.

RESULTS Baseline eGFR <60 ml/min/1.73 m^2 and AKI were observed in 78 (45%) and 124 (65%) of patients, respectively. The primary outcome and death from any cause occurred in 99 (52%) and 76 (40%) patients, respectively. eGFR <60 ml/min/1.73 m^2 did not appear to modulate the treatment effect of milrinone compared to dobutamine. In contrast, there was a significant interaction between the treatment effect of milrinone compared to dobutamine and AKI with respect to the primary outcome (P interaction = 0.02) and death (P interaction = 0.04). The interaction was characterized by lower risk of primary outcome and death with milrinone compared to dobutamine in patients without, but not with, AKI.

CONCLUSIONS In patients requiring inotropic support for cardiogenic shock, baseline renal dysfunction and AKI are common. A modulating effect of AKI on the relative efficacy of milrinone compared to dobutamine was observed, characterized by attenuation of a potential clinical benefit with milrinone compared to dobutamine in patients who develop AKI. (JACC Adv 2023;2:100393) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

AKI = acute kidney injury

eGFR = estimated glomerular filtration rate

LVEF = left ventricular ejection fraction

RR = relative risk

SCAI = Society for Cardiovascular Angiography and Interventions

Renal dysfunction remains a common clinical challenge in the management of patients with cardiogenic shock.[1] Chronic kidney disease is highly prevalent in patients with cardiovascular disease.[2-4] In addition, acute kidney injury (AKI) is a frequent early sequelae of end-organ hypoperfusion characterizing the cardiogenic shock state.[1] Significant renal dysfunction is both an indicator and a mediator of a worse prognosis in patients with cardiogenic shock, and an important clinical consideration when choosing pharmacotherapies and timing interventions requiring iodinated-contrast agents.[2-5]

In the DOREMI (Milrinone as Compared with Dobutamine in the Treatment of Cardiogenic Shock) trial, clinical outcomes were similar in patients treated with milrinone compared to dobutamine.[6] However, in contrast to dobutamine, elimination of milrinone is highly dependent on renal excretion.[7,8] As a result, milrinone is used with caution in patients with significant renal dysfunction due to the theoretical risks of increased arrhythmias and/or hypotension resulting from decreased clearance of the drug.[8,9] At present, there is a paucity of prospective data examining the efficacy and safety of milrinone in patients with cardiogenic shock with renal dysfunction. We hypothesized that renal dysfunction would modulate the treatment effect of milrinone compared to dobutamine, such that the relative efficacy of milrinone would be lower in patients with vs without renal dysfunction.

Accordingly, in this post hoc analysis of the DOREMI trial, we examined clinical outcomes in patients treated with milrinone compared to dobutamine in relation to baseline renal dysfunction and incident AKI.

METHODS

The design and results of the DOREMI trial have been previously published.[6] In brief, the DOREMI trial randomized 192 patients with cardiogenic shock to receive milrinone or dobutamine. Patients ≥18 years of age requiring admission to the cardiac intensive care unit for cardiogenic shock meeting the Society for Cardiovascular Angiography and Interventions (SCAI) definition of cardiogenic shock stage B, C, D, or E were included. Upon randomization, participants were treated with either milrinone or dobutamine at a dose determined with a standardized dosing scale that ranged from stage 1 to stage 5 corresponding to 2.5, 5.0, 7.5, 10.0, and >10.0 μg/kg of body weight per minute for dobutamine and 0.125, 0.250, 0.375, 0.500, and >0.500 μg/kg/min for milrinone. Participants receiving milrinone did not receive a loading dose. Adjustments of the doses according to the stage were made at the discretion of the treating physician. Physicians, patients, local investigators, and research personnel were blinded to treatment allocation. The primary outcome was the composite of in-hospital death from any cause, resuscitated cardiac arrest, receipt of a cardiac transplant or a mechanical circulatory support device, nonfatal myocardial infarction, transient ischemic attack or stroke, or initiation of renal replacement therapy. Study endpoints were limited to the index hospitalization. Written informed consent was obtained from all participants or from their substitute decision-maker. Ethics approval was obtained from the Ottawa Health Science Network Research Ethics Board (20160975-01H) and the study was conducted in accordance with the Declaration of Helsinki.

In this post hoc analysis of DOREMI, we examined the treatment effect of milrinone compared to dobutamine on the primary and secondary outcomes in relation to baseline renal function and AKI during the study period. Renal function definitions for the primary analysis of the study were established a priori based results of observational studies.[4,10,11] Baseline renal function was examined as a categorical variable using an estimated glomerular filtration rate (eGFR) cutoff of 60 ml/min/1.73 m^2 of body-surface area using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation.[12] A cutoff eGFR of 60 ml/min/1.73 m^2 was chosen a priori based on observational studies suggesting worse clinical outcomes in patients with cardiogenic shock and/or acute coronary syndromes with renal function below this threshold.[10,11] Creatinine, urine output, and hemodynamic variables for all patients were collected prospectively at the

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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following time points: 0, 4, 8, 12, 18, 24, 36, 48, 60, 72, and 96 hours from initiation of inotropic therapy. Acute renal dysfunction in the primary analysis was based on the presence of AKI stage ≥2 using definitions put forth in the Kidney Disease Improving Global Outcomes Clinical Practice Guideline for Acute Kidney Injury.[13].

We conducted multivariable analyses to determine whether eGFR <60 ml/min/1.73 m^2 CIs or AKI modified the treatment effect of milrinone compared to dobutamine. Due to a small number of missing eGFR values (n = 19), we used multiple imputation (5 imputations) to address missing values in models containing eGFR. The explanatory variables in our main regression models consisted of: 1) the inotrope used (treatment assignment), eGFR <60 ml/min/1.73 m^2, and the interaction term of inotrope used by eGFR <60 ml/min/1.73 m^2; and 2) the inotrope used (treatment assignment), AKI, and the interaction term of inotrope used by AKI. We conducted separate models with the primary outcome and death as the dependent variables. The *P* value for the interaction term of inotrope used by renal function parameter was used to test the hypothesis of a modulating effect of renal function on the treatment effect of milrinone compared to dobutamine. All models were conducted before and after adjustment for age, sex, left ventricular ejection fraction (LVEF), and SCAI cardiogenic shock stage D or E. These variables were chosen a priori by investigators based on clinical relevance. Lastly, we examined the effect of the specific inotrope used, eGFR <60 ml/min/1.73 m^2, and AKI on cardiac hemodynamics. Given repeated measurements of vasoactive inotrope score, mean arterial pressure, systolic blood pressure, diastolic blood pressure, and heart rate over 96 hours, we performed repeated measures analyses using mixed models with random intercepts and an unstructured variance-covariance matrix. Time was included in the model as a categorical variable.

We present continuous variables using median (IQR), and categorical variables using percentages or frequencies. We compared continuous variables using the Mann-Whitney *U* test and categorical variables using the chi-squared test (or Fisher exact test when appropriate). We provide relative risks (RRs) and 95% CIs for endpoints analyzed. Poisson regression models with robust error variance were used to calculate the RR estimates and their corresponding 95% CI.

Statistical analyses were conducted using SAS (version 9.4, SAS Institute). Two-sided *P* values <0.05 were considered statistically significant.

RESULTS

BASELINE RENAL FUNCTION AND AKI IN PATIENTS WITH CARDIOGENIC SHOCK. Baseline eGFR was available in 173 of 192 (90%) patients enrolled in DOREMI. Of these 173 patients, 78 (45%) had eGFR <60 ml/min/1.73 m^2. Of the 192 patients enrolled in DOREMI, 124 (65%) developed AKI. Baseline patient characteristics in relation to eGFR <60 ml/min/1.73 m^2 and AKI are summarized in **Table 1**. Compared to patients with eGFR ≥60 ml/min/1.73 m^2, patients with eGFR <60 ml/min/1.73 m^2 were older, had a lower body mass index, a higher baseline LVEF, and were more likely to have atrial fibrillation and be nonsmokers. Baseline characteristics, including eGFR, were similar in patients with vs without AKI.

CLINICAL OUTCOMES IN RELATION TO BASELINE RENAL FUNCTION AND AKI DURING ADMISSION. The primary outcome occurred in 99 patients (52%) enrolled in the DOREMI trial. The rates of primary and secondary outcomes in relation to baseline eGFR and AKI are outlined in **Table 2**. Compared to patients with an eGFR ≥60 ml/min/1.73 m^2, patients with an eGFR <60 ml/min/1.73 m^2 had higher rates of death (RR: 1.70; 95% CI: 1.16-2.49; $P < 0.01$) and a trend toward higher rates of the primary outcome (RR: 1.34; 95% CI: 0.99-1.80; $P = 0.06$). The analysis was repeated adjusting for differences in age, sex, baseline LVEF, and SCAI D or E cardiogenic shock with and without multiple imputation to address missing eGFR values (n = 19). In the adjusted analyses, there was no association between eGFR and death or the primary outcome before ($P = 0.23$ and $P = 0.50$, respectively) or after multiple imputations ($P = 0.42$ and $P = 0.80$, respectively).

Compared to patients without AKI, patients with AKI had comparable rates of death (RR: 1.16; 95% CI: 0.92-1.45; $P = 0.23$) but a trend toward higher rates of the primary outcome (RR: 1.32; 95% CI: 0.99-1.75; $P = 0.07$). The observations were similar for both the primary outcome (RR: 1.34; 95% CI: 0.98-1.84; $P = 0.06$) and death (RR: 1.28; 95% CI: 0.88-1.86; $P = 0.20$) after adjusting for differences in baseline characteristics.

TREATMENT EFFECT OF MILRINONE COMPARED TO DOBUTAMINE IN RELATION TO BASELINE RENAL FUNCTION AND AKI DURING ADMISSION. **Figures 1 and 2** outline the treatment effect of milrinone vs dobutamine on the primary outcome and death, respectively, after stratification by baseline eGFR and AKI. With respect to the primary outcome, there was an interaction (*P* interaction = 0.04) in the efficacy of milrinone compared to dobutamine in relation to AKI.

TABLE 1 Baseline Patient Characteristics in Relation to Baseline Renal Function and Incident AKI

	eGFR <60 ml/min/1.73 m² (n = 78)	eGFR ≥60 ml/min/1.73 m² (n = 95)	*P* Value	No AKI (n = 68)	AKI (n = 124)	*P* Value
Age (y)	78 (71, 84)	64 (57, 73)	<0.001	71 (62, 80)	72 (63, 81)	0.61
Female	33 (42.3)	31 (32.6)	0.19	22 (32.4)	48 (38.7)	0.38
Body mass index (kg/m²)	25 (22, 29)	28 (24, 32)	0.01	26 (22, 30)	26 (24, 31)	0.07
Hypertension	51 (65.4)	62 (65.3)	0.99	41 (60.3)	85 (68.5)	0.25
Diabetes mellitus	45 (57.7)	48 (50.5)	0.35	31 (45.6)	71 (57.3)	0.12
Hyperlipidemia	51 (65.4)	44 (46.3)	0.12	35 (51.5)	67 (54.0)	0.73
Current smoker	6 (7.7)	19 (20.0)	0.02	14 (20.6)	14 (11.3)	0.08
Previous stroke or transient ischemia attack	15 (19.2)	11 (11.6)	0.16	10 (14.7)	18 (14.5)	0.97
Previous myocardial infarction	28 (35.9)	34 (35.8)	0.99	22 (32.4)	46 (37.1)	0.51
Previous percutaneous coronary intervention	19 (24.4)	27 (28.4)	0.55	18 (26.5)	31 (25.0)	0.82
Prior CABG	19 (24.4)	18 (18.9)	0.39	11 (16.2)	28 (22.6)	0.29
Atrial fibrillation	49 (62.8)	42 (44.2)	0.02	31 (45.6)	64 (51.6)	0.43
Chronic liver disease	5 (6.4)	7 (7.4)	0.81	5 (7.4)	8 (6.5)	0.77
Chronic obstructive pulmonary disease	12 (15.4)	12 (12.6)	0.60	7 (10.3)	18 (14.5)	0.41
Etiology of heart failure			0.55			0.19
Ischemic	54 (69.2)	61 (64.9)		49 (73.1)	79 (63.7)	
Nonischemic	24 (30.8)	33 (35.1)		18 (26.9)	45 (36.3)	
Baseline LVEF (%)	28 (20, 40)	23 (18, 40)	0.047	25 (20, 35)	25 (20, 40)	0.51
SCAI D or E shock	10 (12.8)	12 (12.6)	0.97	11 (16.2)	15 (12.1)	0.43
Baseline eGFR (ml/min/1.73 m²)	-	-		63 (43, 101)	65 (42, 86)	0.57

Values are median (25th, 75th percentiles) or n (%).

AKI = acute kidney injury; CABG = coronary artery bypass grafting; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; SCAI = Society for Cardiovascular Angiography and Interventions.

Within the stratum without AKI, the use of milrinone was associated with a lower risk of the primary outcome (RR: 0.48; 95% CI: 0.24-0.97; $P = 0.04$). Within the stratum with AKI, the risk of the primary outcome was comparable between milrinone and dobutamine (RR: 1.06; 95% CI: 0.78-1.46; $P = 0.70$). There was no interaction in the treatment effect of milrinone compared to dobutamine on the primary outcome in relation to baseline eGFR (P interaction = 0.81).

With respect to death from any cause, there was a possible trend towards an interaction (P interaction = 0.06) in the efficacy of milrinone compared to dobutamine in relation to AKI. Within the stratum without AKI, the RR associated with the use of milrinone was of borderline statistical significance (RR: 0.42; 95% CI: 0.18-1.00; $P = 0.05$). Within the stratum with AKI, the risk of death was comparable between milrinone and dobutamine (RR: 1.04; 95% CI: 0.69-1.57; $P = 0.85$). The treatment effect of milrinone compared to dobutamine on additional clinical outcomes after stratification by eGFR and AKI are provided in Supplemental Tables 1 and 2.

In an exploratory analysis, we examined the modulating effect of baseline eGFR and AKI on the treatment effect of milrinone vs dobutamine after: 1)

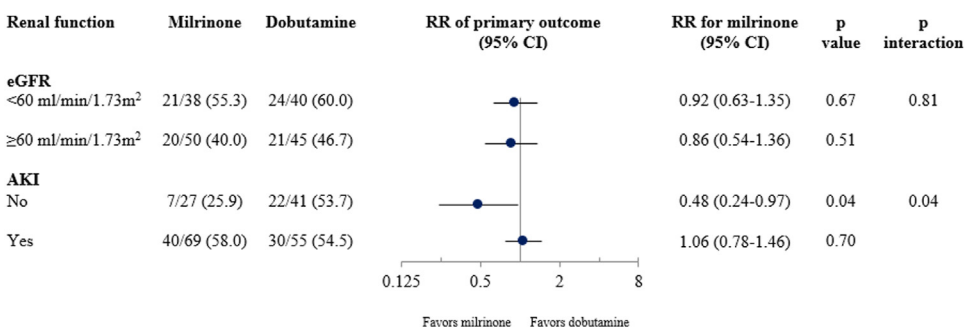
TABLE 2 Clinical Outcomes in Relation to Baseline Renal Function and AKI During Admission

	eGFR ml/min/1.73 m²			AKI		
	<60 (n = 78)	≥60 (n = 95)	*P* Value	No (n = 68)	Yes (n = 124)	*P* Value
Primary outcome	45 (57.7)	41 (43.2)	0.06	29 (42.6)	70 (56.5)	0.07
Death	39 (50.0)	28 (29.5)	<0.01	23 (33.8)	53 (42.7)	0.23
Resuscitated cardiac arrest	7 (9.0)	8 (8.4)	0.90	5 (7.4)	11 (8.9)	0.72
MCS or cardiac transplant	5 (6.4)	17 (17.9)	0.02	8 (11.8)	17 (13.7)	0.70
Myocardial infarction	0 (0)	1 (1.1)	>0.99	0 (0)	1 (0.8)	>0.99
TIA or stroke	1 (1.3)	2 (2.1)	>0.99	0 (0)	3 (2.4)	0.55
Renal replacement therapy	15 (19.2)	15 (15.8)	0.55	8 (11.8)	29 (23.4)	0.06
AKI	48 (61.5)	61 (64.2)	0.72	–	–	–
Vasoactive inotropic score	5.5 (1.9, 10.7)	3.1 (1.5, 7.6)	0.11	2.7 (1.5, 6.3)	5.6 (1.8, 13.6)	0.006

Values are n (%) or median (25th, 75th percentiles).

AKI = acute kidney injury; eGFR = estimated glomerular filtration rate; MCS = mechanical circulatory support; TIA = transient ischemic attack.

FIGURE 1 Treatment Effect of Milrinone Compared to Dobutamine on the Primary Outcome in Relation to Baseline Renal Function and AKI



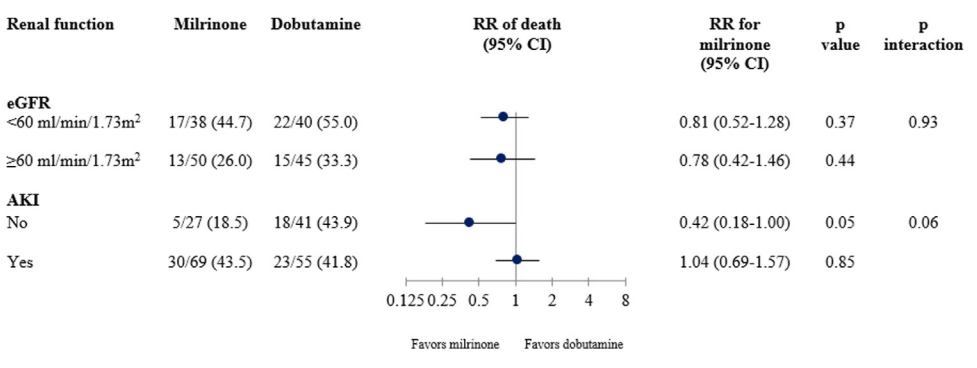
Blue dots and black lines represent relative risks and 95% CIs, respectively. AKI = acute kidney injury; eGFR = estimated glomerular filtration rate; RR = relative risk.

adjusting for baseline differences in age, sex, LVEF, and SCAI D or E cardiogenic shock; and 2) multiple imputation to address missing baseline eGFR values. There was no significant interaction between eGFR and the treatment effect of milrinone vs dobutamine on the primary outcome or death after multiple imputation (P interaction = 0.60 and P interaction = 0.90, respectively) and multiple imputation with adjustment for differences in baseline characteristics (P interaction = 0.78 and P interaction = 0.90, respectively). After adjustment for differences in baseline characteristics, an interaction was observed between AKI and the treatment effect of milrinone compared to dobutamine on both the primary outcome (P interaction = 0.02) and death (P interaction = 0.04). The interaction was characterized by a lower risk of the primary outcome and death with milrinone compared to dobutamine in patients without, but not with, AKI (Figure 3).

CARDIOGENIC SHOCK HEMODYNAMICS IN RELATION TO SPECIFIC INOTROPE USED, BASELINE RENAL FUNCTION, AND AKI. Hemodynamics in patients with cardiogenic shock in relation to specific inotrope used, eGFR, and AKI are provided in Supplemental Table 3 and Supplemental Figures 1A to 1E. Compared to patients treated with dobutamine, patients treated with milrinone had lower vasoactive inotrope scores (estimate −6.08, SE ± 2.07, $P < 0.01$). The mean arterial pressure, systolic blood pressure, diastolic blood pressure, and heart rate were similar in patients treated with milrinone compared to dobutamine.

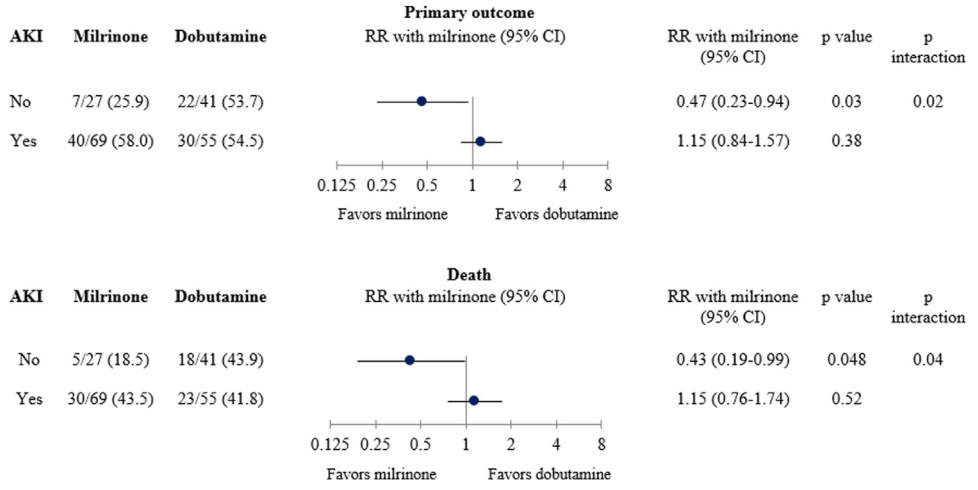
Compared to patients with an eGFR ≥60 ml/min/1.73 m^2, patients with an eGFR <60 ml/min/1.73 m^2 had a lower mean arterial pressure (estimate −2.77,

FIGURE 2 Treatment Effect of Milrinone Compared to Dobutamine on Death in Relation to Baseline Renal Function and AKI



Blue dots and black lines represent relative risks and 95% CIs, respectively. AKI = acute kidney injury; eGFR = estimated glomerular filtration rate; RR = relative risk.

FIGURE 3 Treatment Effect of Milrinone Compared to Dobutamine on Death in Relation to Baseline Renal Function and AKI After Adjustment for Differences in Baseline Characteristics



Blue dots and black lines represent relative risks and 95% CIs, respectively. AKI = acute kidney injury; RR = relative risk.

SE ± 1.26, P = 0.03), diastolic blood pressure (estimate −5.43, SE ± 1.46, P < 0.001), and heart rate (estimate −7.04, SE ± 2.42, P = 0.004). The specific inotrope used did not appear to modulate the association between eGFR <60 and mean arterial pressure (P interaction = 0.36), diastolic blood pressure (P interaction = 0.44), or heart rate (P interaction = 0.95). Systolic blood pressure and vasoactive inotrope scores were similar in patients with eGFR <60 vs ≥60 ml/min/1.73 m^2.

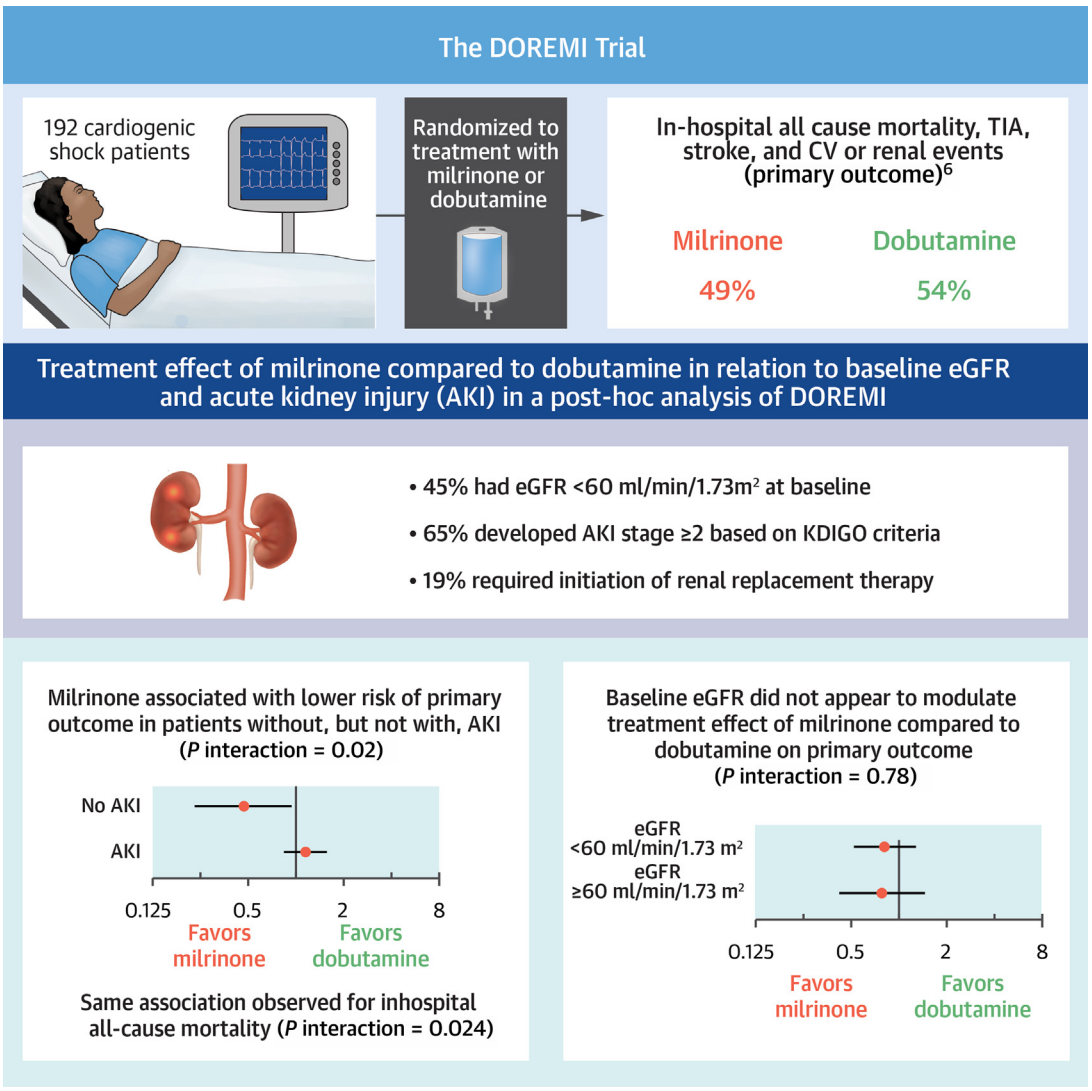
Compared to patients without AKI, patients with AKI had lower diastolic blood pressures (estimate −3.11; SE ± 1.54; P = 0.04) and a trend toward higher vasoactive inotropic scores (estimate +4.12; SE ± 2.19; P = 0.06). The specific inotrope used did not appear to modulate the association between AKI and diastolic blood pressure (P interaction = 0.22) or vasoactive inotropic score (P interaction = 0.41). The mean arterial pressure, systolic blood pressure, and heart rate were similar in patients with vs without AKI.

DISCUSSION

In this post hoc analysis of DOREMI, we sought to examine clinical and treatment implications of baseline renal function and incident AKI in patients with cardiogenic shock. Moderate chronic kidney disease (45% of patients) and Kidney Disease Improving Global Outcomes AKI stage ≥2 (65% of patients) were common in our cohort of patients admitted with cardiogenic shock. Baseline renal function did not appear to modulate the treatment effect of milrinone compared to dobutamine. However, there was an interaction between AKI and the treatment effect of milrinone vs dobutamine on the primary outcome and death. This interaction was characterized by a lower risk of the primary outcome and death with milrinone compared to dobutamine in patients without, but not with, AKI (**Central Illustration**). Lastly, we did not find any substantial evidence of a differential treatment effect of milrinone vs dobutamine on cardiac hemodynamics in relation to baseline renal function or AKI.

Renal dysfunction is a prevalent comorbidity and a common sequelae of end-organ hypoperfusion in patients with cardiogenic shock.[2-4] Renal dysfunction secondary to chronic kidney disease and/or AKI is associated with increased mortality in this patient population. However, it is unclear to what extent renal dysfunction represents a marker as opposed to a mediator of a poor prognosis in cardiogenic shock.[2-5] Patients with cardiogenic shock and renal dysfunction represent a high-risk population due to significant comorbidities and a higher severity of cardiogenic shock on presentation.[3,4] Additionally, renal dysfunction (both chronic and acute) can propagate myocardial dysfunction in patients with cardiogenic shock through several neurohormonal,

CENTRAL ILLUSTRATION **Evaluating Milrinone vs Dobutamine in Patients With Cardiogenic Shock in Relation to Renal Function**



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CV = cardiovascular; eGFR = estimated glomerular filtration rate; KDIGO = Kidney Disease Improving Global Outcomes; TIA = transient ischemic attack.

immunological, and inflammatory pathways.[4,14] At present, there are no proven renal protective therapies to safeguard renal function and improve clinical outcomes in patients with cardiogenic shock.[14]

Acute worsening of cardiac function resulting in AKI is commonly categorized as a type 1 cardiorenal syndrome.[14] Although the mechanisms underlying renal injury in patients with cardiogenic shock are complex, and likely vary from patient to patient, hemodynamic-mediated renal injury secondary to inadequate renal perfusion is a common offender and a treatment target in the intensive care unit. Milrinone and dobutamine remain the most widely used pharmacotherapies to augment cardiac output in patients with cardiogenic shock. The selection of these agents remains largely operator and/or center

dependent as there are no prospective trials suggesting the superiority of one agent compared to the other. However, renal dysfunction is a common clinical consideration when selecting vasoactive agents. In contrast to dobutamine, milrinone is primarily excreted in the urine and, as a result, its half-life and pharmacological effects can be prolonged in patients with renal dysfunction.[15] In theory, increased plasma milrinone concentrations in patients with significant renal dysfunction could result in excess rates of arrhythmias and hypotension, although this has not been demonstrated in prospective trials.[8,16]

The present analysis suggests a possible heterogeneity in the treatment effect of milrinone compared to dobutamine on clinical outcomes in relation to AKI. Compared to dobutamine, milrinone was associated with reduced rates of the primary outcome and death in the stratum of patients without AKI. These results should be interpreted with caution given that DOREMI was a negative trial. However, a plausible explanation requiring further investigation is that milrinone, compared to dobutamine, may offer therapeutic benefits which are attenuated in patients who develop AKI. Due to the high rates of AKI observed in DOREMI, this treatment effect would have been diluted in DOREMI resulting in comparable outcomes between treatment arms. Cardiogenic shock is a heterogeneous syndrome with variable etiologies and phenotypes requiring nuanced risk stratification and management.[17,18] Exploring the role of individualized patient care, including patients with renal dysfunction, to improve clinical outcomes in cardiogenic shock remains a research priority.

STUDY LIMITATIONS. Our findings should be considered in the context of several limitations. The DOREMI trial was not designed or adequately powered to examine the modulating effect of renal function on the efficacy and safety of milrinone compared to dobutamine in patients with cardiogenic shock. In addition, it is important to note that DOREMI did not show a difference in the rate of the primary outcome with milrinone compared to dobutamine.[6] Despite the negative trial findings in DOREMI, a subgroup analysis in relation to renal function was deemed to be a research priority by investigators and reviewers due to its clinical relevance. For the baseline renal function analysis, an eGFR prior to the index hospitalization was not available in approximately 10% of patients enrolled in DOREMI. When examining AKI, the first documented serum creatinine was used as a baseline as per the European Renal Best Practice workgroup recommendations.[19] Examining renal function and injury using additional biomarkers not collected in DOREMI, such as Cystatin C and neutrophil gelatinase-associated lipocalin, may have been informative.[20] However, the use of these biomarkers in clinical practice has not been standardized, remains uncommon, and has not been shown to be superior to serum creatinine in predicting clinical outcomes.[21]

To our knowledge, this is the first study examining the impact of renal function on the treatment effect of milrinone compared to dobutamine for the management of cardiogenic shock in a randomized controlled trial setting. The observed treatment effect heterogeneity of milrinone compared to dobutamine in relation to AKI warrants further investigation due to its physiological plausibility and clinical relevance.

CONCLUSIONS

Baseline renal dysfunction and AKI are common in patients with cardiogenic shock treated with inotropes. We observed an interaction between the treatment effect of milrinone compared to dobutamine and AKI in this patient population. The interaction was characterized by lower risk of the primary outcome and death with milrinone compared to dobutamine in patients who did not develop AKI, but not in those who did.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Renal dysfunction is a prevalent comorbidity and a common sequelae of end-organ hypoperfusion in patients with cardiogenic shock. Significant renal dysfunction is both an indicator and a mediator of a worse prognosis in patients with cardiogenic shock and an important clinical consideration when choosing pharmacotherapies and timing interventions requiring iodinated-contrast agents.

At present, there is a paucity of prospective data examining the relative efficacy and safety of milrinone in patients with cardiogenic shock and renal dysfunction.

TRANSLATIONAL OUTLOOK: Future studies should further explore the association between milrinone and outcomes in patients with cardiogenic shock and renal dysfunction.

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KEY WORDS acute kidney injury, cardiogenic shock, inotropes, renal dysfunction

APPENDIX For supplemental tables and figures, please see the online version of this paper.