HHS Public Access

Author manuscript

JACC Adv. Author manuscript; available in PMC 2024 February 15.

Published in final edited form as:

JACC Adv. 2023 July ; 2(5): . doi:10.1016/j.jacadv.2023.100392.

Trials and Tribulations of Inotrope Choice in Cardiogenic Shock With Renal Dysfunction

Thomas S. Metkus, MD, PHD

Divisions of Cardiology and Cardiac Surgery, Departments of Medicine and Surgery, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.

Keywords

cardiac intensive care unit; cardiogenic; ICU; renal; shock

Patients presenting with cardiogenic shock are among the sickest, most complex, highest risk patients seen in acute cardiac care. Even with contemporary multidisciplinary care innovations, prognosis remains grave—between 1 in 5 to as many as 1 in 2 patients with cardiogenic shock will not survive their hospital stay.[1,2] Patients with cardiogenic shock are more commonly presenting with multisystem organ failure in the contemporary era[3] including renal dysfunction. Once renal dysfunction is established in cardiogenic shock, the prognosis worsens dramatically, even from the high baseline risk.[4,5] Thus, clinicians have impetus to consider the cardiogenic shock patient with renal dysfunction as high clinical risk mandating directed and tailored therapy.

These unique considerations for patients with renal dysfunction in the intensive care unit are shown in the Table 1.[5] Among them is altered drug clearance mandating vigilant pharmacologic management. Inotropes are commonly used in cardiogenic shock, including both dobutamine and milrinone. Dobutamine and milrinone were compared in 192 patients with cardiogenic shock in the pivotal DOREMI (Dobutamine Compared with Milrinone) trial randomized trial.[6] This trial demonstrated no difference between the 2 inotropes with high in-hospital death rate in both groups of approximately 40%. Serum milrinone concentrations have been shown to be higher in patients with lower creatinine clearance, because a majority of milrinone is renally cleared.[7] Higher milrinone concentrations could lead to increased toxicities such as hypotension, tachycardia, and arrhythmias. Thus, Dr Di Santo et al[8] hypothesized that the presence of acute kidney injury (AKI) would be an effect measure modifier[9] of the relationship between milrinone vs dobutamine and outcome in cardiogenic shock.

ADDRESS FOR CORRESPONDENCE: Dr Thomas S. Metkus, Division of Cardiology, Department of Medicine, Johns Hopkins Hospital, Blalock 524, D2, 600 N Wolfe Street, Baltimore, Maryland 21287, USA. tmetkus1@jh.edu.

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

The authors stratified the DOREMI trial population based on both baseline renal dysfunction and the development of AKI.[8] Most patients had AKI—124 of the 192 subjects enrolled. Main clinical findings included the fact that, in the stratum of patients with cardiogenic shock without AKI, milrinone was associated with better outcomes than dobutamine (relative risk: 0.48; 95% CI: 0.24–0.97 for composite primary outcome). Such an effect was not observed in cardiogenic shock patients with AKI, where there was no difference between the strategies (relative risk: 1.06; 95% CI: 0.78–1.46). The authors conclude that a potential clinical benefit of milrinone vs dobutamine in cardiogenic shock could be attenuated by development of AKI.[8]

The author's conclusions have a plausible physiologic mechanism, and they should be congratulated for adding to the evidence base in this understudied area. A second point is that randomized trials are rare in cardiac critical care,[10] and the data from successful randomized trial such as DOREMI should be leveraged to the full extent to increase knowledge and improve care. Limitations of the study include the post hoc nature of the study which was not pre-specified in the DOREMI protocol. As such, the conclusions should be considered hypothesis generating. Subgroup analyses, particularly in small trials such as DOREMI, can be simultaneously underpowered and overpowered leading to risk of false positive and false negative findings.[11] A second consideration is that the exposure of dobutamine vs milrinone was assigned at baseline yet the stratification variable of AKI could occur subsequently at time >0. Thus, interactions between the exposure variable and the stratification variable are possible and could introduce bias.

Despite these limitations, Di Santo et al[8] have provided a study with important implications. The first implication serves as a reminder for scholars to use data from completed randomized trials to generate scientific hypotheses and advance knowledge. Data repositories such as the National Institute of Health Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) exist to facilitate this mission.[12] A second paradigm is reinforced—that to improve cardiogenic shock outcomes, one must consider impact of noncardiac organ failures such as acute renal dysfunction in both prognosis and choice of therapy. Academic networks in acute cardiac care such as the Critical Care Cardiology Trials Network[13] and the Cardiogenic Shock Working Group[14] have recently been developed and these groups and investigators should consider prospective studies of cardiogenic shock therapeutics with particular consideration in those with AKI.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The author has reported that he has no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. Sinha SS, Rosner CM, Tehrani BN, et al. Cardiogenic shock from heart failure versus acute myocardial infarction: clinical characteristics, hospital course, and 1-year outcomes. Circ Heart Fail. 2022;15:e009279. [PubMed: 35510546]
2. Papolos AI, Kenigsberg BB, Berg DD, et al. Management and outcomes of cardiogenic shock in cardiac ICUs with versus without shock teams. J Am Coll Cardiol. 2021;78:1309–1317. [PubMed: 34556316]

3. Vallabhajosyula S, Dunlay SM, Prasad A, et al. Acute noncardiac organ failure in acute myocardial infarction with cardiogenic shock. J Am Coll Cardiol. 2019;73:1781–1791. [PubMed: 30975295]
4. van Diepen S, Tymchak W, Bohula EA, et al. Incidence, underlying conditions, and outcomes of patients receiving acute renal replacement therapies in tertiary cardiac intensive care units: an analysis from the Critical Care Cardiology Trials Network Registry. Am Heart J. 2020;222: 8–14. [PubMed: 32006910]
5. Jentzer JC, Bihorac A, Brusca SB, et al. Contemporary management of severe acute kidney injury and refractory cardiorenal syndrome: JACC Council perspectives. J Am Coll Cardiol. 2020;76:1084–1101. [PubMed: 32854844]
6. Mathew R, Di Santo P, Jung RG, et al. Milrinone as compared with dobutamine in the treatment of cardiogenic shock. N Engl J Med. 2021;385:516–525. [PubMed: 34347952]
7. Cox ZL, Calcutt MW, Morrison TB, Akers WS, Davis MB, Lenihan DJ. Elevation of plasma milrinone concentrations in stage D heart failure associated with renal dysfunction. J Cardiovasc Pharmacol Ther. 2013;18:433–438. [PubMed: 23695773]
8. Di Santo P, Dehghan K, Mao B, et al. Milrinone vs dobutamine for the management of cardiogenic shock: implications of renal function and injury. JACC Adv. 2023;2(5): 100393.
9. Knol MJ, VanderWeele TJ. Recommendations for presenting analyses of effect modification and interaction. Int J Epidemiol. 2012;41:514–520. [PubMed: 22253321]
10. van Diepen S, Granger CB, Jacka M, Gilchrist IC, Morrow DA, Katz JN. The unmet need for addressing cardiac issues in intensive care research. Crit Care Med. 2015;43:128–134. [PubMed: 25243816]
11. Burke JF, Sussman JB, Kent DM, Hayward RA. Three simple rules to ensure reasonably credible subgroup analyses. BMJ. 2015;351:h5651. [PubMed: 26537915]
12. Giffen CA, Wagner EL, Adams JT, et al. Providing researchers with online access to NHLBI biospecimen collections: the results of the first six years of the NHLBI BioLINCC program. PLoS One. 2017;12:e0178141. [PubMed: 28614402]
13. Metkus TS, Baird-Zars VM, Alfonso CE, et al. Critical Care Cardiology Trials Network (CCCTN): a cohort profile. Eur Heart J Qual Care Clin Outcomes. 2022;8:703–708. [PubMed: 36029517]
14. Zweck E, Thayer KL, Helgestad OKL, et al. Phenotyping cardiogenic shock. J Am Heart Assoc. 2021;10:e020085. [PubMed: 34227396]

TABLE 1

Clinical Considerations Relevant to Acute Renal Dysfunction in the ICU and Implications for ICU Care Teams[5]

Clinical Manifestation	Implication for ICU Clinicians
Vascular access for renal replacement	• Placement of access at proper anatomic site to facilitate uninterrupted continuous renal replacement • Bleeding avoidance strategies during placement of large bore catheter • Catheter maintenance to avoid infection • Facilitation of early mobility in the ICU while access is in place
Altered pharmacokinetics	• Reduced drug clearance with exaggerated clinical effects • Increased risk of drug-drug interaction • Increased risk of toxicities • Expanded need for critical care pharmacy services for guidance and management
Facilitating renal recovery	• Avoiding nephrotoxins • Hemodynamic optimization • Vigilant attention to fluid balance
Expanded consultative team, including nephrology and other consultants	• Team based, multidisciplinary rounds • Direct and closed loop communication
Electrolyte disturbance, acidosis	• Laboratory monitoring at appropriate frequency • Electrolyte replacement and maintenance via appropriate route
Volume overload	• Early and appropriate diuretic challenge • Provision of renal replacement therapy as needed
Uremia and altered mentation	• Consideration of uremia in the differential diagnosis of altered mental status in the intensive care unit • Correction of uremia to facilitate patient awakening and progression of intensive care unit clinical care
Patient and family centered care	• Inclusion of risk assessment for chronic renal replacement needs as part of goals of care discussions in the ICU • Identification and acknowledgment of renal dysfunction as a syndrome that worsens the prognosis of patients with acute cardiac illness