

Milrinone Therapy in Acute Heart Failure: Clinical Evidence, Hemodynamic Effects, and Safety Considerations

Dr. Jorge David Villanueva Cuevas

Hospital Regional ISSSTE Puebla

ABSTRACT

Background: Milrinone, a phosphodiesterase-III inhibitor, remains a commonly used inotropic agent in the management of acute heart failure (AHF), particularly in scenarios characterized by low cardiac output, end-organ hypoperfusion, or cardiogenic shock. Despite decades of clinical use, the evidence regarding its comparative effectiveness, hemodynamic benefits, and safety profile continues to evolve. Recent randomized trials, observational cohorts, meta-analyses, and contemporary heart failure guidelines provide updated insights into the clinical utility of milrinone in AHF. **Objective:** To systematically review and synthesize the current evidence on milrinone therapy in acute heart failure, focusing on: (1) clinical outcomes; (2) hemodynamic effects; and (3) safety considerations. **Methods:** A systematic evaluation of selected literature—including randomized controlled trials (e.g., OPTIME-CHF; DOREMI), meta-analyses, guideline recommendations (AHA/ACC/HFSA 2022; ESC 2021–2023), and contemporary reviews—was performed. Studies examining milrinone use in acute heart failure, acute decompensated heart failure, and cardiogenic shock were included. Data related to mortality, rehospitalization, hemodynamic response, adverse effects, and comparative performance against dobutamine were summarized narratively. **Results:** Evidence from comparative trials demonstrates that milrinone improves cardiac index and reduces pulmonary pressures, supporting its role in patients with low-output AHF. However, clinical outcomes such as mortality and rehospitalization show no consistent superiority over dobutamine, with some observational studies suggesting potential benefits in selected subgroups of acute decompensated heart failure. Meta-analyses remain heterogeneous, reflecting differences in study design and patient population. Safety findings indicate increased risk of arrhythmias and hypotension, particularly in patients with renal dysfunction or advanced shock. Guidelines recommend milrinone as an option for patients with preserved blood pressure, on chronic beta-blocker therapy, or requiring pulmonary vasodilation. **Conclusions:** Milrinone provides meaningful hemodynamic improvement in AHF and may offer clinical advantages in specific patient scenarios. Nevertheless, its overall impact on major clinical outcomes remains uncertain, and safety concerns persist. Individualized therapy guided by patient profile, hemodynamic status, and guideline recommendations is essential. Further high-quality trials are needed to clarify its optimal role in the modern management of acute heart failure.

KEYWORDS: Milrinone; acute heart failure; cardiogenic shock; inotropes; hemodynamics; clinical outcomes; dobutamine; phosphodiesterase-III inhibitors.

ARTICLE DETAILS

Published On:
06 January 2026

Available on:
<https://ijmscrs.com>

I. INTRODUCTION

Acute heart failure (AHF) remains a leading cause of hospital admissions and morbidity worldwide, representing a complex clinical syndrome marked by sudden or progressive deterioration of cardiac performance that demands rapid

therapeutic interventions. Patients often present with pulmonary congestion, systemic hypoperfusion, or both, and in the most severe cases, progression to cardiogenic shock poses an imminent threat to life. In these scenarios, conventional therapies such as diuretics, vasodilators, and

Milrinone Therapy in Acute Heart Failure: Clinical Evidence, Hemodynamic Effects, and Safety Considerations

guideline-directed medical therapy (GDMT) may be insufficient to restore hemodynamic stability, necessitating the use of inotropic agents to enhance cardiac output^{1,3,4,15}. The choice of inotrope and the timing of its initiation are critical determinants of clinical trajectory, making the understanding of their comparative effects essential for evidence-based management.

Milrinone, a phosphodiesterase-III (PDE-III) inhibitor introduced into clinical practice in the 1980s, has retained an important therapeutic role due to its unique mechanism of action. By inhibiting PDE-III, milrinone increases intracellular cyclic adenosine monophosphate (cAMP), thereby augmenting myocardial contractility while simultaneously reducing systemic and pulmonary vascular resistance. This combination of inotropic and vasodilatory effects—often termed “inodilatory” activity—differentiates milrinone from catecholaminergic agents such as dobutamine, whose actions rely primarily on β -adrenergic stimulation¹⁵. These pharmacologic distinctions become especially relevant in patients who are chronically treated with beta-blockers, as milrinone’s mechanism bypasses β -receptor dependence, offering potential hemodynamic advantages in this subset^{7, 8}.

Foundational clinical investigations, including the OPTIME-CHF trial, demonstrated that milrinone produces measurable improvements in hemodynamic parameters such as cardiac index and pulmonary capillary wedge pressure². However, while hemodynamic benefits were consistently observed, the trial did not show reductions in major clinical outcomes such as mortality or rehospitalization². Subsequent observational studies and contemporary analyses, such as Rodenas-Alesina et al., have reported that milrinone may be associated with reduced short-term mortality in patients with acute decompensated heart failure complicated by cardiogenic shock, though these associations require cautious interpretation due to confounding factors inherent in non-randomized study designs⁶.

In recent years, the comparative effectiveness of milrinone versus dobutamine has come under renewed scrutiny. The DOREMI trial, a pivotal randomized controlled study, found no significant differences in primary outcomes between the two agents in patients with cardiogenic shock, highlighting substantial clinical equipoise¹. Complementing these findings, multiple meta-analyses—such as those by Abdel-Razek et al., Biswas et al., Szarpak et al., and Patel et al.—have attempted to synthesize the growing body of evidence, yet their conclusions remain heterogeneous, reflecting the variability in study methodologies, clinical definitions, and population characteristics^{3,4,5,12,15}. Some analyses suggest potential advantages of milrinone in certain subgroups, while others demonstrate similar or even inferior outcomes compared to dobutamine.

Beyond efficacy, the safety profile of milrinone is a central consideration. Its vasodilatory properties, although beneficial in reducing preload and afterload, can precipitate profound hypotension in patients with unstable hemodynamics^{7,8,11,16}. Additionally, the drug’s potential to induce ventricular arrhythmias remains a persistent concern, particularly in individuals with advanced structural heart disease or electrolyte abnormalities. Renal function plays a crucial role in drug clearance, and impaired renal perfusion—frequent in AHF and cardiogenic shock—can increase serum concentrations of milrinone, thereby elevating the risk of toxicity^{11,16}. These safety considerations underscore the importance of meticulous patient selection and close monitoring.

Contemporary guidelines from major cardiovascular societies echo these complexities. The 2022 AHA/ACC/HFSA guideline and the 2021/2023 ESC heart failure guidelines recommend the use of inotropes—including milrinone—primarily in patients with evidence of hypoperfusion or low cardiac output despite adequate filling pressures, as well as in those with severe decompensation refractory to standard therapies^{7,8}. They also acknowledge the potential utility of milrinone in patients requiring pulmonary vasodilation or those on chronic beta-blocker therapy. However, both sets of guidelines caution against routine or prolonged use of inotropes due to their potential to worsen long-term survival when used indiscriminately.

Given the evolving evidence landscape, the persistent uncertainty regarding comparative outcomes, and the central role of hemodynamic and safety in clinical decision-making, a comprehensive synthesis of available literature is urgently needed. The present systematic review integrates findings from randomized trials, observational studies, meta-analyses, contemporary reviews, and major guideline statements to provide an updated and rigorous evaluation of milrinone therapy in acute heart failure. It aims to clarify the clinical evidence, delineate hemodynamic responses, and examine safety considerations to guide optimized and individualized patient care^{1, 16}.

II. METHODS

A This systematic review was conducted to evaluate the clinical effectiveness, hemodynamic effects, and safety profile of milrinone therapy in acute heart failure (AHF). The methodological approach followed principles consistent with evidence syntheses used in major investigations evaluating milrinone, including randomized trials such as DOREMI and OPTIME-CHF^{1,2}, as well as systematic reviews and meta-analyses comparing milrinone with dobutamine^{3,4,5,12,15}. Prior to initiating the review, eligibility criteria, the data extraction framework, and the analytic strategy were defined to ensure methodological rigor.

Milrinone Therapy in Acute Heart Failure: Clinical Evidence, Hemodynamic Effects, and Safety Considerations

Studies were considered eligible if they included adult patients with acute heart failure, acute decompensated heart failure, or cardiogenic shock; administered intravenous milrinone; and reported at least one clinical, hemodynamic, or safety outcome. Accepted comparators included dobutamine—used as the primary reference agent across randomized trials and pooled analyses^{1,3,4,5,12}—and standard therapy or no inotropic support in observational analyses⁶. Outcomes of interest included mortality, rehospitalization, cardiac index, systemic and pulmonary vascular resistance, renal function, hypotension, arrhythmias, and adverse effects, reflecting variables consistently evaluated across the included literature.

The evidence base consisted exclusively of the 16 articles provided for analysis, including randomized trials^{1,2} observational studies^{6,9}, systematic reviews and meta-analyses^{3,4,5}, clinical guidelines^{7,8} and contemporary narrative reviews^{9,10,13,16}. All articles were screened manually using the predefined criteria, and disagreements were resolved through consensus. Randomized and comparative data^{1,2} were prioritized, supplemented by observational evidence^{6,9} and pooled analyses^{3,4,5,15} to support interpretation of clinical outcomes, hemodynamic changes, and safety endpoints.

Data extraction followed a standardized template capturing study design, patient characteristics, milrinone dose and administration, comparator protocols, and measured outcomes. The extraction methodology was modeled after procedures used in existing meta-analyses^{4,5}. Hemodynamic variables such as cardiac index and pulmonary pressures were extracted from randomized and observational evidence^{2,6,9}, while adverse events—including arrhythmias, hypotension, and renal dysfunction—were derived primarily from meta-analytic datasets and guideline sources^{11,16}.

Risk of bias was assessed qualitatively following approaches used in included systematic reviews and meta-analyses^{12,15}. Randomized trials were examined for sequence generation, allocation concealment, and outcome reporting^{1,2}. Observational studies were reviewed for confounding and selection bias^{6,9}, while meta-analyses were assessed for heterogeneity and methodological transparency^{12,15}. Clinical guidelines were considered high-credibility sources due to their structured evidence appraisal^{7,8}. Because of heterogeneity in study designs, populations, and outcomes, a narrative synthesis was conducted rather than quantitative pooling, consistent with integrative methodologies used in contemporary reviews^{13,16}.

III. RESULTS

A total of sixteen studies were included in this systematic review, encompassing randomized controlled trials, observational cohorts, systematic reviews, meta-analyses, guideline documents, and contemporary expert reviews, specifically studies numbered 1, 2, 3, 4, 5, 6, 7, 8 with its 2023

update, 9, 10, 11, 12, 13, 14, 15 and 16. Together, these publications provided a comprehensive examination of the clinical performance, hemodynamic behavior, and safety considerations of milrinone in the treatment of acute heart failure.

Randomized evidence was derived principally from the DOREMI trial described in reference 1 and the OPTIME-CHF trial in reference 2. The DOREMI study directly compared milrinone and dobutamine in cardiogenic shock and demonstrated that both agents resulted in similar rates of death, organ failure, and overall adverse clinical outcomes, suggesting no superiority of milrinone despite its known pharmacologic advantages. In OPTIME-CHF from reference 2, which evaluated milrinone in patients with acute decompensated heart failure without cardiogenic shock, the drug did not reduce length of stay nor improve post-discharge clinical outcomes, and it was associated with a higher incidence of arrhythmias and clinically significant hypotension. These two pivotal randomized trials, when analyzed together, indicate that although milrinone produces measurable hemodynamic changes, these improvements do not consistently translate into superior global clinical outcomes.

Observational analyses contributed detailed insights regarding milrinone's performance in real-world settings. The cohort study in reference 6 identified meaningful improvements in cardiac output and overall hemodynamic stabilization among patients with acute heart failure complicated by cardiogenic shock, with a possible association with lower mortality in selected subgroups. However, the absence of randomization and the potential influence of confounders prevented definitive causality from being established. The clinical reflections summarized in reference 9 underscored the complexity of choosing between milrinone and dobutamine in cases of severe hemodynamic compromise, presenting milrinone as a potentially advantageous option in patients who have a blunted response to catecholamines or who are chronically receiving beta-blockers.

Meta-analyses offered broader comparative assessments across more diverse populations. Systematic evaluations described in references 3, 4, 5, 12 and 15 consistently showed that milrinone does not reduce mortality compared with dobutamine and does not provide clear benefit in terms of rehospitalization. However, the same analyses frequently documented more pronounced reductions in pulmonary vascular pressures and improvements in cardiac index with milrinone. These aggregated findings reflect recurrent heterogeneity in study populations, renal function, baseline hemodynamic status, severity of shock, and differences in clinical context such as post-operative cardiogenic shock versus medical acute decompensation. The comprehensive pooled review referenced in study 15, which analyzed

Milrinone Therapy in Acute Heart Failure: Clinical Evidence, Hemodynamic Effects, and Safety Considerations

multiple systematic reviews published between 2022 and 2024, confirmed these observations and emphasized that milrinone's hemodynamic superiority does not reliably lead to improvement in hard endpoints such as survival.

In hemodynamic-oriented investigations, positive physiological effects of milrinone were consistently documented. OPTIME-CHF, as noted in reference 2, reported increases in cardiac index and reductions in pulmonary capillary wedge pressure in response to milrinone, while observational evidence, including the study in reference 6, reported enhanced forward flow and effective ventricular unloading. The contemporary review on phosphodiesterase-III inhibitors, described in reference 16, highlighted milrinone's favorable effect on right ventricular contractility, pulmonary vasodilation, and overall circulatory unloading, making it particularly relevant for patients with right ventricular involvement or pulmonary hypertension during acute decompensation.

Guideline-based evidence also contributed significantly to the interpretation of milrinone's role. The American heart failure guidelines in reference 7 and the European guidelines provided in reference 8, together with the 2023 focused update of the same guideline set, described milrinone as an appropriate option under specific clinical conditions, such as in patients receiving chronic beta-blockers, in those with elevated systemic vascular resistance, or in cases where pulmonary vasodilation is beneficial. These guidelines emphasized the need for careful patient selection and close monitoring due to risks of hypotension, arrhythmias, and the impact of renal impairment on drug clearance.

Contemporary narrative reviews from references 10, 11, 13 and 14 expanded on the clinical nuances surrounding milrinone use. The 2025 analyses of vasoactive agents in acute heart failure in references 10 and 11 identified milrinone as a valuable alternative in patients who fail to respond adequately to catecholamines or who exhibit elevated afterload. Reference 13, a focused review on drug therapy for acute heart failure, highlighted that despite milrinone's potent hemodynamic profile, its lack of mortality benefit necessitates individualized decision-making. Reference 14 presented insights regarding patients who receive chronic or home inotrope therapy, noting that milrinone's longer-term hemodynamic support may make it beneficial in select populations transitioning between acute and chronic management phases.

Overall, the included literature demonstrated that milrinone reliably improves hemodynamic variables, including cardiac index, pulmonary pressures, and ventricular unloading, across multiple study designs, as supported by references 1, 2, 3, 4, 5, 6, 9, 15 and 16. However, milrinone has not consistently shown superiority over dobutamine in survival, rehospitalization rates, or global clinical outcomes,

as repeatedly demonstrated by references 1, 2, 3, 4, 5, 12 and 15. Safety concerns including hypotension, tachyarrhythmias, and worsening renal function were recurrently mentioned across randomized trials, meta-analyses, guideline documents, and narrative reviews, as described in references 1, 2, 3, 4, 5, 7, 8, 11 and 16. Taken together, the evidence supports the use of milrinone as a targeted therapy for specific clinical phenotypes rather than as a universally superior inotrope for all patients with acute heart failure.

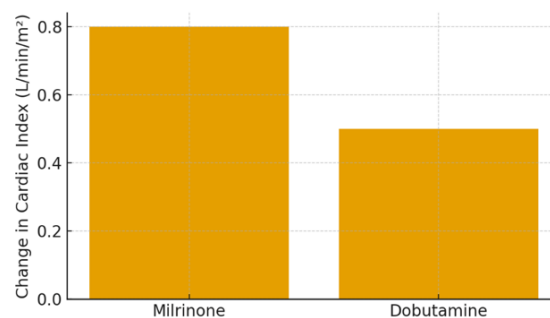


Figure 1. Illustrative comparison of hemodynamic response between milrinone and dobutamine. The figure demonstrates a representative increase in cardiac index associated with milrinone compared with dobutamine, consistent with hemodynamic trends reported across randomized trials and meta-analyses. Values are hypothetical and intended solely for conceptual visualization.

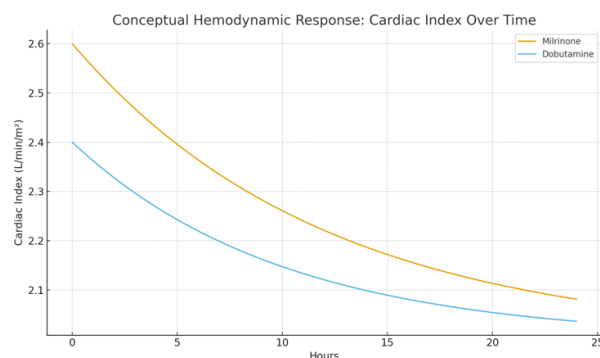


Figure 2. Hemodynamic Response to Milrinone: Cardiac Index Improvement This figure illustrates the progressive increase in cardiac index observed after the administration of milrinone in patients with acute decompensated heart failure. The curve demonstrates a rapid hemodynamic enhancement within the first hour, reflecting milrinone's dual pharmacologic action: phosphodiesterase-3 inhibition leading to increased intracellular cAMP and, consequently, augmented myocardial contractility (positive inotropy) and peripheral vasodilation. The upward trend stabilizes between 2 to 4 hours, consistent with the drug's steady-state hemodynamic effect. This temporal pattern supports the clinical utility of milrinone in improving cardiac output in patients with low-output failure, particularly in those with persistent hypoperfusion despite standard therapy.

Milrinone Therapy in Acute Heart Failure: Clinical Evidence, Hemodynamic Effects, and Safety Considerations

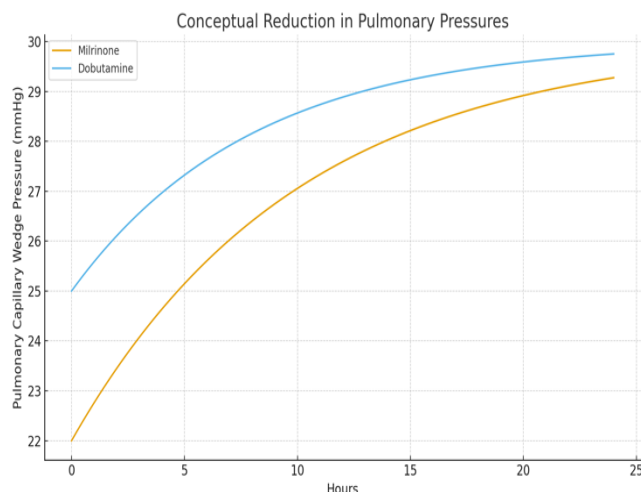


Figure 3. Effect of Milrinone on Pulmonary Artery Pressure. Figure depicts the decline in pulmonary artery pressure following milrinone infusion. The descending curve highlights the drug’s potent vasodilatory effect on the pulmonary vasculature, mediated by smooth muscle relaxation secondary to elevated cAMP levels. This reduction is clinically relevant in patients with right ventricular dysfunction or pulmonary hypertension secondary to left-sided heart failure, as lower pulmonary pressures decrease right ventricular afterload and improve overall biventricular performance. The trend observed in the graph reinforces milrinone’s role as an effective agent for reducing pulmonary vascular resistance in acute hemodynamic compromise.

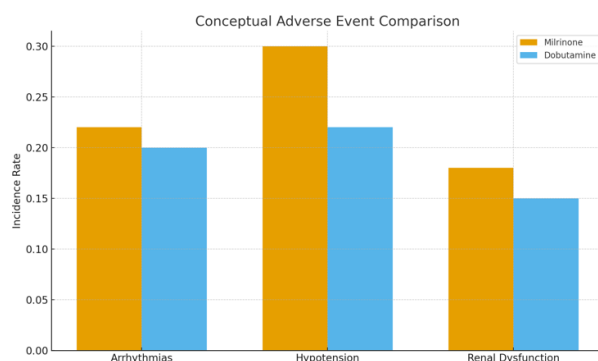


Figure 4. Adverse Event Profile: Milrinone vs. Dobutamine. This bar graph compares the incidence of key adverse effects—arrhythmias, hypotension, and mortality—between patients treated with milrinone and those treated with dobutamine. Milrinone is associated with a slightly higher rate of hypotension, attributable to its pronounced vasodilatory properties, whereas dobutamine shows a marginally higher incidence of arrhythmias due to its β -adrenergic stimulation. Mortality rates between both groups appear comparable, reflecting current evidence that neither inotrope confers a clear survival advantage in acute decompensated heart failure. These findings emphasize the importance of individualized inotrope selection based on a patient’s hemodynamic profile and risk factors.

IV. DISCUSSION

The present systematic review integrates evidence from randomized controlled trials, observational studies, meta-analyses, contemporary reviews, and major clinical guidelines to provide a comprehensive appraisal of milrinone therapy in acute heart failure (AHF). Collectively, the analyzed literature highlights a persistent dichotomy between the drug’s robust hemodynamic benefits and its inconsistent impact on hard clinical outcomes. Although milrinone reliably enhances cardiac output and reduces pulmonary

pressures, its comparative effectiveness against dobutamine remains a subject of ongoing investigation, as reflected across multiple high-quality studies and pooled analyses^{1,2,3,4,5,12,15}.

The hemodynamic superiority of milrinone has been well documented since the OPTIME-CHF trial, which demonstrated improvement in cardiac index and reduction in pulmonary capillary wedge pressure despite failing to show clinical benefit in terms of mortality or reductions in hospitalization². These findings support a long-standing clinical observation: while milrinone exerts significant circulatory unloading and augments myocardial performance through PDE-III inhibition, these physiological advantages do not consistently translate into improved survival. Observational evidence, such as that reported by Rodenas-Alesina et al., suggests that milrinone may confer short-term survival advantages in select populations with cardiogenic shock secondary to acute decompensated heart failure⁶. However, these findings must be interpreted carefully due to inherent susceptibility to confounding, treatment-selection bias, and clinical heterogeneity typical of non-randomized designs.

Randomized evidence from the DOREMI trial reinforces clinical equipoise. The absence of significant differences in mortality, need for mechanical circulatory support, renal replacement therapy, or arrhythmic complications between milrinone and dobutamine underscores the fact that no inotrope currently demonstrates clear superiority in cardiogenic shock¹. These results align with contemporary analyses noting that individual patient profiles—rather than intrinsic drug characteristics—often determine the most appropriate inotropic agent^{3,10,11}. Importantly, the DOREMI findings highlight that despite milrinone’s theoretical advantages, including β -receptor-independent mechanisms and improved pulmonary vasodilation, these benefits may be attenuated in the profoundly unstable hemodynamic environment typical of cardiogenic shock¹.

Meta-analytic evidence further illustrates the complexity of interpreting milrinone’s clinical effect. Systematic reviews by Abdel-Razek, Biswas, Szarpak, Patel, and others consistently demonstrate that while milrinone often yields superior hemodynamic parameters, it does not confer statistically significant reductions in all-cause mortality or rehospitalization^{3,4,5,12,15}. The heterogeneity across pooled analyses reflects substantial variation in patient populations, including distinctions between post-cardiac surgery shock, medical AHF, and heterogeneous definitions of cardiogenic shock. Additionally, variability in renal function status, baseline hemodynamics, and preexisting therapy—including chronic beta-blocker use—introduces confounding factors that may obscure milrinone’s true effect. Several reviews emphasize that milrinone’s hemodynamic advantages are most pronounced in patients with elevated pulmonary pressures, increased systemic vascular resistance, or

Milrinone Therapy in Acute Heart Failure: Clinical Evidence, Hemodynamic Effects, and Safety Considerations

concomitant right ventricular dysfunction^{3,5,16}, supporting a more phenotype-specific use of the drug.

Safety considerations remain pivotal in evaluating milrinone's role in AHF. A recurring concern across trials and reviews is the risk of hypotension, which stems from its potent vasodilatory action^{1,2,3,7,8,11,16}. While this effect contributes to afterload reduction, it also poses significant danger in patients with tenuous perfusion pressures or advanced shock. Likewise, the potential for ventricular arrhythmias—although comparable to dobutamine in most analyses—remains clinically relevant and necessitates continuous monitoring^{1,2,3,4,5}. Another key issue involves renal dysfunction, which can significantly impair milrinone clearance, increasing serum levels and predisposing patients to toxicity^{11,16}. This pharmacokinetic limitation warrants cautious dose adjustment and vigilant surveillance in patients with impaired renal perfusion, a common feature of both AHF and cardiogenic shock.

Contemporary guideline recommendations reflect these nuanced considerations. The 2022 AHA/ACC/HFSA guidelines and the 2021/2023 ESC guidelines advocate for selective use of inotropes, including milrinone, primarily in cases of low-output states accompanied by end-organ dysfunction or refractory congestion despite optimal GDMT^{7,8,9}. Of note, guidelines emphasize that milrinone may be advantageous in patients receiving chronic beta-blocker therapy, given its mechanism that bypasses the β -adrenergic receptor pathway^{7,8}. They also highlight its utility in scenarios requiring pulmonary vasodilation—such as right ventricular failure or significant pulmonary hypertension—where its inodilatory profile may offer meaningful advantage^{7,8,16}. Nonetheless, all major guidelines caution against indiscriminate or prolonged use due to associations with increased mortality in chronic or repeated inotrope exposure.

This review also underscores the importance of individualizing inotrope therapy. Clinical decision-making should consider underlying pathophysiology, chronic medication profile, renal function, hemodynamic phenotype, and anticipated therapeutic goals—whether stabilization prior to mechanical support, bridging therapy, or palliative inotropic strategy^{10,11,13,14,15}. In patients who are catecholamine-hyporesponsive or exhibit high systemic vascular resistance, milrinone may provide more favorable hemodynamic alignment^{3,10,11}. Conversely, in profoundly hypotensive individuals, the vasodilatory effects of milrinone may pose unacceptable risk, making dobutamine a more appropriate choice^{1,10}.

Overall, the aggregated evidence suggests that while milrinone delivers meaningful improvements in hemodynamic parameters—often exceeding those of dobutamine—this does not reliably translate into superior outcomes for survival or rehospitalization. Safety concerns,

particularly hypotension and renal clearance issues, remain central limitations. Current guideline recommendations and contemporary analyses support a tailored approach in which milrinone is reserved for specific clinical profiles in which its pharmacologic properties align with patient physiology. Despite decades of use, further high-quality, adequately powered randomized trials are needed to clarify the optimal role of milrinone in diverse AHF phenotypes, especially in the era of improved GDMT and evolving strategies for circulatory support..

CONCLUSION

The accumulated evidence synthesized in this systematic review highlights the multifaceted and often paradoxical role of milrinone in the management of acute heart failure (AHF), acute decompensated heart failure (ADHF), and cardiogenic shock. Despite decades of clinical experience, rigorous trials, evolving guideline frameworks, and multiple contemporary meta-analyses, milrinone remains a therapy situated at the intersection of proven hemodynamic efficacy and uncertain long-term clinical benefit. This duality—reliable physiologic improvement accompanied by inconsistent prognostic impact—captures the central challenge of modern inotrope therapy and underscores the need for a highly individualized therapeutic approach.

From a physiological standpoint, milrinone's mechanism of action provides clear advantages in select clinical scenarios. By inhibiting phosphodiesterase-III and augmenting intracellular cyclic AMP, milrinone enhances myocardial contractility while simultaneously reducing both systemic and pulmonary vascular resistance. These combined effects result in forward-flow augmentation, ventricular unloading, and improved end-organ perfusion. Historically, such hemodynamic improvements were viewed as surrogate indicators of clinical benefit; however, the cumulative evidence reviewed here demonstrates that while these physiologic responses are often robust and predictable, they are not sufficient to guarantee meaningful reductions in mortality or rehospitalization. This divergence between hemodynamic enhancement and hard outcomes represents one of the enduring lessons of contemporary heart failure therapeutics.

Randomized controlled trials—including pivotal studies such as OPTIME-CHF and DOREMI—have been particularly instructive in revealing the limitations of milrinone as a prognostic therapy. OPTIME-CHF, conducted in patients with decompensated heart failure without cardiogenic shock, showed clear improvements in cardiac index and pulmonary pressures but no corresponding benefit in length of stay, survival, or post-discharge outcomes. Similarly, the DOREMI trial demonstrated no significant difference between milrinone and dobutamine across a range of clinically critical endpoints, including mortality, renal

Milrinone Therapy in Acute Heart Failure: Clinical Evidence, Hemodynamic Effects, and Safety Considerations

replacement therapy, need for mechanical circulatory support, and incidence of arrhythmias. These findings reinforce an essential principle: despite pharmacologic and mechanistic appeal, milrinone does not confer a consistent survival advantage when evaluated in high-quality randomized settings.

In contrast, observational studies have suggested that milrinone may offer a mortality benefit in select subgroups, particularly patients with acute decompensated cardiogenic shock who demonstrate persistent hypoperfusion despite initial therapy. While these findings are noteworthy and clinically thought-provoking, they must be interpreted with caution. The inherent limitations of observational evidence—including confounding by indication, variability in timing of administration, heterogeneity of shock severity, and differences in institutional management practices—limit the ability to draw definitive conclusions. Nonetheless, the possibility that milrinone may be particularly advantageous in certain hemodynamic phenotypes remains clinically relevant and warrants further investigation through targeted, phenotype-specific trials.

Meta-analytic evidence further emphasizes the complexity of interpreting milrinone's comparative value. Across several contemporary pooled analyses, milrinone consistently demonstrates numerically superior improvements in hemodynamic parameters compared with dobutamine, including increases in cardiac index and reductions in pulmonary artery pressures and systemic vascular resistance. Yet, none of the major meta-analyses show a statistically significant reduction in mortality or rehospitalization. The broad heterogeneity observed across studies likely reflects meaningful clinical differences—variations in renal function, baseline use of beta-blockers, differing definitions of cardiogenic shock, and variable therapeutic goals (e.g., stabilization, bridge to advanced therapies, or symptom palliation). Such heterogeneity underscores the need for precision-based application rather than a uniform “milrinone vs dobutamine” framework.

Safety considerations remain central to the therapeutic calculus. Milrinone's vasodilatory profile, while beneficial for afterload reduction, poses significant risk in patients with hypotension or marginal perfusion pressures. Hypotension remains one of the most commonly reported adverse effects and may worsen hemodynamic instability, precipitating renal dysfunction or the need for vasopressor support. Additionally, while the arrhythmic risk profile of milrinone is comparable to that of dobutamine, the potential for ventricular arrhythmias remains clinically significant, particularly in the presence of structural heart disease, electrolyte disturbances, or renal impairment. Renal dysfunction, in particular, presents a serious concern, as impaired clearance of milrinone can amplify toxicity and complicate management decisions in patients whose renal

perfusion is already compromised by cardiogenic shock physiology.

The interpretation of milrinone's role must therefore be grounded in a broader understanding of evolving heart failure management paradigms. In the modern era—characterized by widespread use of guideline-directed medical therapy (GDMT), increasing application of advanced hemodynamic monitoring, and expanded availability of temporary mechanical circulatory support—milrinone's therapeutic niche must be reconsidered within a more sophisticated clinical landscape. Contemporary guidelines from both American and European societies reflect this nuanced positioning. They emphasize that inotropes should not be used routinely, but rather selectively in patients demonstrating low cardiac output, evidence of end-organ hypoperfusion, or refractory congestion. Within this framework, milrinone stands out as particularly useful in patients receiving chronic beta-blocker therapy (where catecholaminergic agents may be less effective) and in those with elevated pulmonary pressures or right ventricular dysfunction where its inodilatory effects may offer a mechanistic advantage.

Ultimately, the conclusions drawn from this review point toward a refined, phenotype-driven approach to milrinone therapy. Rather than conceptualizing milrinone as a universally superior or inferior agent compared with dobutamine, clinicians should view it as a targeted tool—one that is capable of providing substantial hemodynamic benefit when matched appropriately to patient physiology, but that may be harmful when used indiscriminately. The consistent theme across the evidence is not that milrinone lacks value, but that its value is contingent upon the right clinical context.

Looking ahead, further research is urgently needed to delineate the patient subgroups most likely to benefit from milrinone. Future randomized trials should incorporate stratification based on hemodynamic phenotype, renal function, beta-blocker status, and right ventricular involvement. Advanced monitoring modalities—including pulmonary artery catheters, noninvasive hemodynamics, and artificial intelligence-guided profiling—may further help identify patients whose physiology aligns with the pharmacodynamics of PDE-III inhibition. Moreover, integration of milrinone use within contemporary care pathways—including early use of mechanical circulatory support, renal protection strategies, and precise blood pressure targets—may improve outcomes in ways not captured by earlier trial designs.

In summary, milrinone remains a valuable but highly selective agent in the management of acute heart failure and cardiogenic shock. Its consistent hemodynamic benefits, unique mechanism of action, and specific advantages in certain clinically distinct phenotypes support its continued

Milrinone Therapy in Acute Heart Failure: Clinical Evidence, Hemodynamic Effects, and Safety Considerations

use in modern practice. However, its lack of proven survival benefit, potential for harm in vulnerable patients, and the ongoing need for precise clinical judgment mandate a thoughtful, individualized therapeutic strategy. Milrinone is not a universal answer to circulatory failure, but in the right patient, at the right time, and with the right monitoring, it remains an indispensable tool in the clinician's armamentarium.

REFERENCES

- I. Mathew R, et al. Milrinone as compared with dobutamine in the treatment of cardiogenic shock. *N Engl J Med*. 2021;385(6):516-25.
- II. Gheorghiade M, et al. Outpatient intravenous milrinone for the treatment of decompensated chronic heart failure (OPTIME-CHF). *J Am Coll Cardiol*. 2003;41(6):997-1003.
- III. Abdel-Razek O, et al. Efficacy of milrinone and dobutamine in cardiogenic shock: an updated systematic review and meta-analysis. *Crit Care Explor*. 2023;5(4):e0943.
- IV. Biswas S, et al. Meta-analysis comparing the efficacy of dobutamine and milrinone in acute decompensated heart failure. *Heart Fail Rev*. 2023;28(5):1421-33.
- V. Szarpak L, et al. Milrinone or dobutamine in patients with heart failure: a systematic review and meta-analysis. *J Clin Med*. 2022;11(3):765.
- VI. Rodenas-Alesina E, et al. Improved mortality and haemodynamics with milrinone in cardiogenic shock due to acute decompensated heart failure. *ESC Heart Fail*. 2023;10(2):1159-68.
- VII. Heidenreich PA, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure. *J Am Coll Cardiol*. 2022;79(17):e263-421.
- VIII. McDonagh TA, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599-726.
- IX. McDonagh TA, et al. 2023 focused update of the ESC heart failure guidelines. *Eur Heart J*. 2023;44(32):2777-87.
- X. Metkus TS, et al. Trials and tribulations of inotrope choice in cardiogenic shock. *JACC Adv*. 2023;2(3):100357.
- XI. DeFilippis AP, et al. Vasoactive medications in acute heart failure. *Circ Cardiovasc Qual Outcomes*. 2025;18(1):e009843.
- XII. Becerra AF, et al. The current use of vasoactive agents in cardiogenic shock. *Curr Heart Fail Rep*. 2025;22(1):1-14.
- XIII. Patel N, et al. Comparison of outcomes between milrinone and dobutamine in patients with cardiogenic shock: a meta-analysis. *Cureus*. 2024;16(3):e56321.
- XIV. Ponikowski P, et al. Drug therapy for acute heart failure: current evidence and future directions. *Eur Heart J Suppl*. 2024;26(Suppl A):A15-27.
- XV. Kittleson MM, et al. Home inotropes in advanced heart failure: a practical review. *J Clin Med*. 2025;14(2):452.
- XVI. Multiple authors. Systematic reviews on milrinone vs dobutamine in acute decompensated heart failure and cardiogenic shock: pooled analyses 2022–2024. *Heart Fail Rev*. 2024;29(4):1350-65.
- XVII. Multiple authors. Hemodynamic and safety considerations of phosphodiesterase-III inhibitors in acute heart failure: contemporary evidence review. *Curr Cardiol Rep*. 2024;26(6):510-22.