Milrinone versus Dobutamine in Cardiogenic Shock: A Meta-Analysis

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Introduction: Cardiogenic shock (CS) has remained a common cause of mortality as an end stage manifestation of various cardiac disorders. Despite its prevalence, management still remains challenging. This evidence-based review discusses the differences of milrinone and dobutamine in terms of clinical outcomes so as to better understand and guide therapy for cardiogenic shock.
Objective: To determine the efficacy of milrinone in patients with cardiogenic shock compared to dobutamine by comparing outcomes in terms of mortality, need for mechanical circulatory support devices or heart transplant, length of hospital stay, and readmission rates at one (1) year.
Methods: Randomized controlled trials, observational retrospective and prospective studies which compared clinical outcomes of milrinone and dobutamine.
Results: Milrinone was found to have lower risk for mortality compared to dobutamine (RR 0.75; 95% CI, 0.70-0.80; I^2 42%, p-value <0.00001). In the subgroup analyses for randomized controlled trials, there was a trend favoring milrinone (RR 0.88; 95% CI, 0.62-1.24; I^2 0%, p-value = 0.46) with no significant degree of heterogeneity but the effect did not reach statistical significance. For observational studies, milrinone had decreased risk for mortality (RR 0.75; 95% CI, 0.70-0.80; I^2 49%, p-value <0.00001) with the effect reaching statistical significance however, there was a moderate degree of heterogeneity. In terms of eventual need for mechanical circulatory support or need for cardiac transplantation, there was no significant difference between milrinone and dobutamine (RR 0.88; 95% CI, 0.62-1.24; I^2 0%, p-value = 0.43). Dobutamine was found to have shorter length of hospital stay (RR 1.11; 95% CI, 0.04-2.18; I^2 79%, p-value = 0.04) although milrinone was found to have lower readmission rates at one (1) year (RR 0.79; 95% CI, 0.66-0.94; I^2 0%, p-value = 0.009).
Conclusion: In this meta-analysis, milrinone was shown to have lower risk for mortality and lower rates of readmission. In terms of need for mechanical circulatory support devices or cardiac transplantation, there was no significant difference between milrinone and dobutamine. Dobutamine was associated with shorter length of hospital stay although there was significant heterogeneity between the studies. Larger double-blinded randomized clinical trials can potentially provide more robust evidence regarding choice of inodilator therapy.

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Table 1. Summary of Randomized Controlled Trials on Milrinone vs Dobutamine.				
Trial	**Mortality (No, %)**	**Need for Mechanical Assist Devices or Cardiac Transplantation (No, %)**	**Length of Hospital Stay (Mean, SD)**	**JADAD Score**
Aranda et. al. (2003) Milrinone (n = 19) vs Dobutamine (n = 17)	1 (5) vs 0	16 (84) vs 16 (94)	50 ± 46 vs 63 ± 45	5
	No significant difference in clinical outcomes of mortality and need for mechanical assist devices or cardiac transplantation.			
CAPITAL DOREMI (2021) Milrinone (n = 96) vs Dobutamine (n = 96)	35 (37) vs 41 (43)	11 (12) vs 14 (15)	16 ± 16.4 vs 15 ± 15.6	5
	No significant difference in primary combined outcome of in-hospital death, resuscitated cardiac arrest, receipt of cardiac transplantation or mechanical circulatory support, nonfatal MI, TIA or stroke, and initiation of renal replacement therapy.			

Table 2. Summary of Observational Studies on Milrinone vs Dobutamine				
Study	**Type of Study**	**Mortality (No, %)**	**Length of Hospital Stay (Mean, SD)**	**Readmission Rate (No, %)**
Abraham et. al. (2005) ADHERE Registry Sub-analysis: Milrinone (n = 2021) vs Dobutamine (n = 4226)	Retrospective sub-analysis	248 (12.3) vs 589 (13.9)	10.9 ± 10 vs 10 ± 9	-
	There were similar mortality rates and length of hospital stay with dobutamine and milrinone. Both positive inotropic agents had higher mortality rates than other vasoactive agents (nitroglycerin and nesiritide).			
Arnold et. al. (2005) Milrinone (n = 433) vs Dobutamine (n = 1311) Subgroup	Retrospective cohort	34 (7.9) vs 134 (10.2)	12.2 ± 29.9 vs 10.4 ± 12.9	41 (9.5) vs 65 (5.0) *30 days
	There was lower mortality rate and 30-day readmission rate with milrinone compared to dobutamine. Although dobutamine had a shorter length of hospital stay.			
Gao et. al. (2021) Milrinone (n = 261) vs Dobutamine (n = 558)	Retrospective cohort	74 (28.35) vs 191 (34.23)	17.32 ± 11.91 vs 13.05 ± 10.62	-
	There was increased hospital mortality with inotrope use. Dobutamine was found to have increased hospital mortality while milrinone was found to have decreased risk of hospital mortality.			
Gorodeski et. al. (2009) Milrinone (n = 56) vs Dobutamine (n = 56)	Retrospective analysis	35 (62) vs 47 (84)	-	27 (48) vs 28 (50) *1 year
	There were no differences between dobutamine or milrinone in terms of mortality and readmission rates at 1 year.			
Hauptman et. al.	Retrospective	275 (14.1) vs	-	-

(2008) Milrinone (n =1949) vs Dobutamine (n = 8762) Subgroup		1735 (19.8)		
	Use of inotropes was associated with higher mortality rates with similar mortality rates between dobutamine and milrinone.			
King et. al. (2015) Milrinone (n = 194) vs Dobutamine (n = 306)	Retrospective cohort	23 (12) vs 55 (18)	-	-
	There was higher risk of death from heart failure with dobutamine compared to milrinone.			
Lewis et. al. (2018) Milrinone (n = 50) vs Dobutamine (n = 50)	Retrospective review	1 (2) vs 5 (10)	11 $\pm$ 5.4 vs 12 $\pm$ 5.9	-
	There was no significant difference in terms of in-hospital mortality and length of hospital stay between milrinone and dobutamine.			
Mazurek et. al. (2010) Milrinone (n = 1012) vs Dobutamine (n = 1141)	Retrospective analysis	245 (24.3) vs 408 (35.8)	-	691 (68.3) vs 843 (73.9) *1 year
	There was higher mortality and readmission rates with dobutamine compared to milrinone.			
Nandkeolyar (2021) Milrinone (n = 70) vs Dobutamine (n = 256)	Retrospective	2 (3) vs 38 (15)	10.6 $\pm$ 9.8 vs 8.8 $\pm$ 7.6	
	Dobutamine was independently associated with in-hospital mortality among SCAI B and C cardiogenic shock.			
Rabinovitz et. al. (2010) Milrinone (n = 65) vs Dobutamine (n = 46)	Retrospective cohort	24 (37) vs 29 (63)	-	32 (49) vs 39 (84) *1 year
	There was increased all-cause mortality and higher 1 year readmission rate in the dobutamine group compared to the milrinone group.			
Scroggins et. al. (2005) Milrinone (n = 27) vs Dobutamine (n = 40) subgroup	Retrospective analysis	5 (18) vs 2 (5)	-	-
	There were similar mortality rates with dobutamine and milrinone.			
Yamani et. al. (2001) Milrinone (n = 60) vs Dobutamine (n = 269)	Retrospective analysis	6 (10) vs 21 (7.8)	3.2 $\pm$ 1.5 vs 3.3 $\pm$ 1.5	
	There was no significant difference in the in-hospital mortality rate and length of hospital stay with milrinone compared to dobutamine.			

RESULTS

Table 3. Baseline Characteristics of Subjects of Randomized Controlled Trials				
Characteristics	**Aranda (2003)**		**DOREMI (2021)**	
	Milrinone	Dobutamine	Milrinone	Dobutamine
Age (years)	61 ± 8	54 ± 9	68.9 ± 13.8	72 ± 11.3
Females (%)	7 (41)	2 (11)	36 (38)	34 (35)
Race (No, %)				
White	16 (94)	18 (95)	86 (90)	79 (82)
Non-white	1 (6)	1 (5)	10 (10)	17 (18)
Left ventricular function				
LV EF (Median, IQR)	-	-	25 (20-40)	25 (20-40)
Cause of LV dysfunction				
Ischemic	11 (65)	9 (47)	66 (69)	62 (65)
Non-ischemic	6 (35)	10 (53)	30 (31)	33 (34)
SCAI cardiogenic shock class (No. %)				
A	-	-	0	0
B	-	-	6 (6)	5(3)
C	19	17	77 (80)	78 (81)
D			10 (10)	12 (12)
E	-	-	3 (3)	3 (3)
Abbreviation: LVEF – left ventricular ejection fraction, SCAI – Society for Cardiovascular Angiography and Interventions				

Table 4. Baseline Characteristics of Observational Studies

	Abraham (2005)		Arnold (2005)		Gao (2021)		Gorodeski (2009)		Hauptman (2008)		King (2015)		Lewis (2018)		Mazurek (2010)		Nandkeolyar (2021)		Rabinovitz (2010)		Scroggins (2005)		Yamani (2001)	
	Mil	**Dob**	**Mil**	**Dob**	**Mil**	**Dob**	**Mil**	**Dob**	**Mil**	**Dob**	**Mil**	**Dob**	**Mil**	**Dob**	**Mil**	**Dob**	**Mil**	**Dob**	**Mil**	**Dob**	**Mil**	**Dob**	**Mil**	**Dob**
N	2021	4226	433	1311	261	558	56	56	1949	8762	194	306	50	50	1012	1141	70	256	65	46	27	40	60	269
Age (years)	67.3 ± 14	70.4 ± 13.5	61 ± 14	63.1 ± 14	64.82 ± 13.18	67.31 ± 14.49	53 ± 12	60 ± 13	≥ 65 (73.2)		62.7		72.5	75	-	-	58 ± 14.2	64 ± 14.7	-	-	-	-	62 ± 12	61 ± 11
Females (No, %)	668 (33)	1559 (37)	122 (28)	486 (37)	98 (37.5)	214 (38.3)	12 (21)	8 (14)	14,7037 (52.9)		173 (34.6)		22 (44)	27 (54)	-	-	30 (43)	80 (31)	-	-	-	-	18 (30)	62 (23)
Race (No, %)																								
White	-	-	296 (68)	696 (53)	201 (77.01)	446 (79.93)	-	-	169,622 (61)		-	-	-	-	-	-	28 (40)	106 (41)	-	-	-	-	-	-
Non-white	-	-	137 (31)	615 (47)	60 (23)	112 (21)	-	-	-	-	-	-	-	-	-	-	42 (60)	150 (59)	-	-	-	-	-	-
Left Ventricular Function																								
LV EF (Median, IQR)	-	-	-	-	-	-	16 ± 8	17 ± 9	-	-	-	-	-	-	-	-	21.9 ± 13.5	21.4 ± 13.5	-	-	-	-	18 ± 5.1	17 ± 4.6
Cause of LV Dysfunction																								
Ischemic	778 (62)	1440 (60)	235 (54)	680 (52)	-	-	23 (41)	23 (41)	-	-	-	-	-	-	-	-	31 (47)	158 (62)	-	-	-	-	34 (57)	140 (52)
Non-ischemic	-	-	-	-	-	-	33 (59)	33 (59)	-	-	-	-	-	-	-	-	37 (54)	96 (38)	-	-	-	-	26 (43)	129 (48)

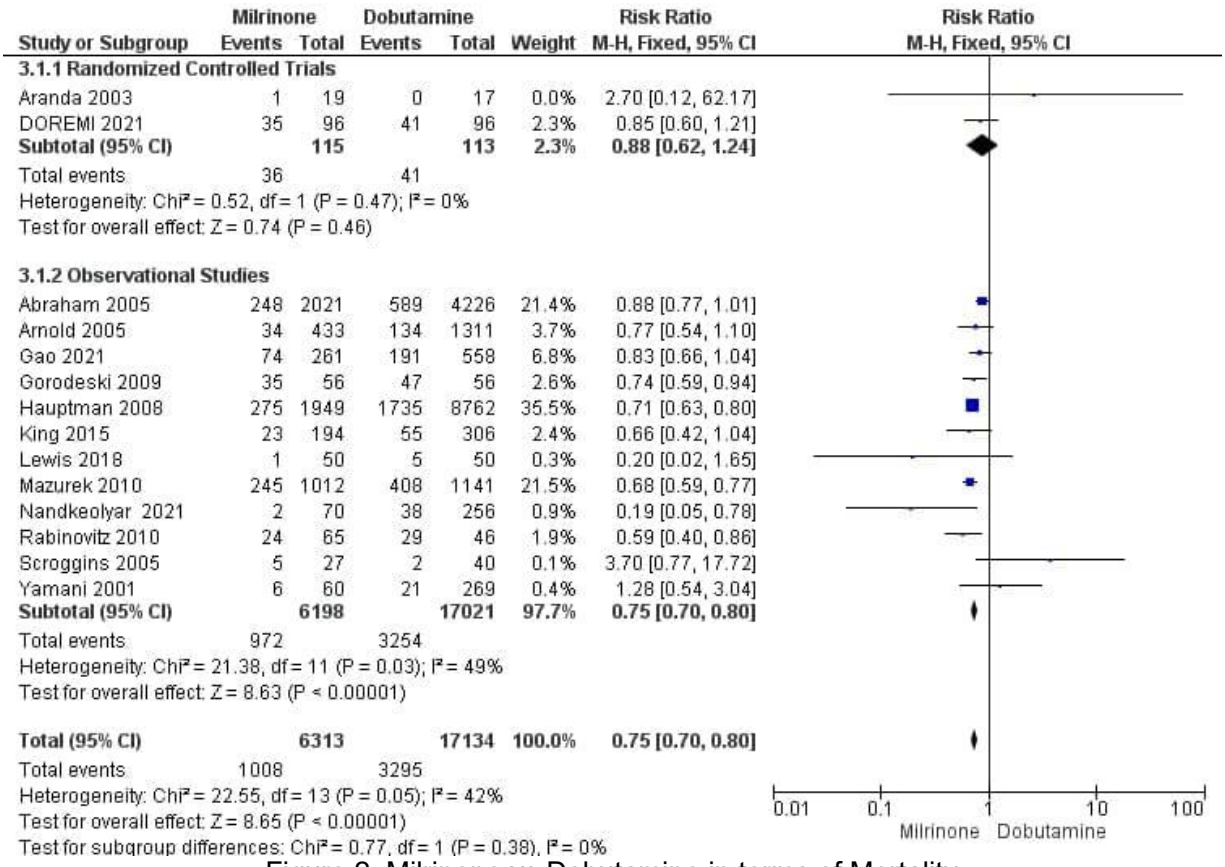

Figure 2. Milrinone vs Dobutamine in terms of Mortality

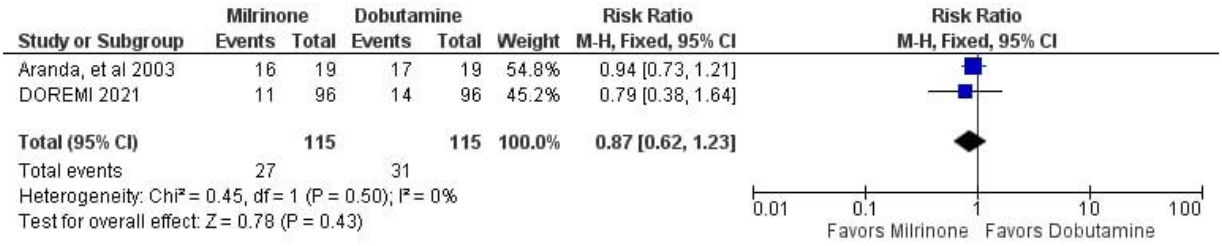

Figure 3. Milrinone vs Dobutamine in terms of Need for Mechanical Circulatory Support or Cardiac Transplantation

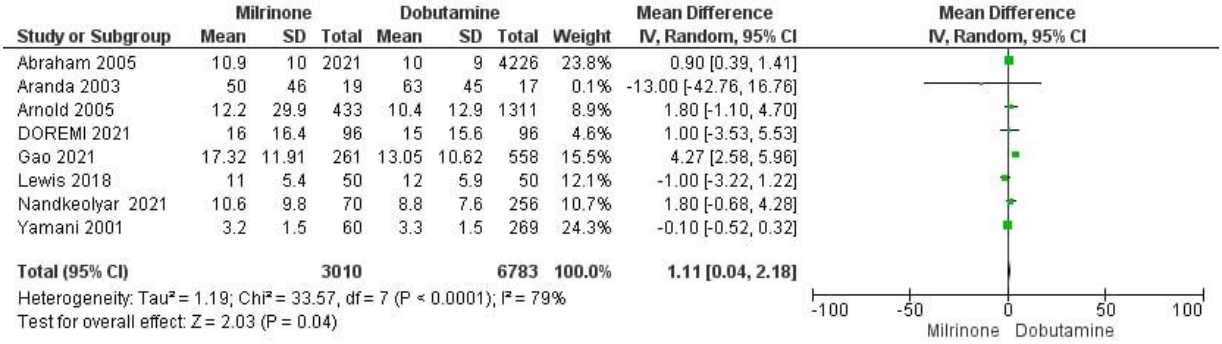

Figure 4. Milrinone versus Dobutamine in terms of Length of Hospital Stay

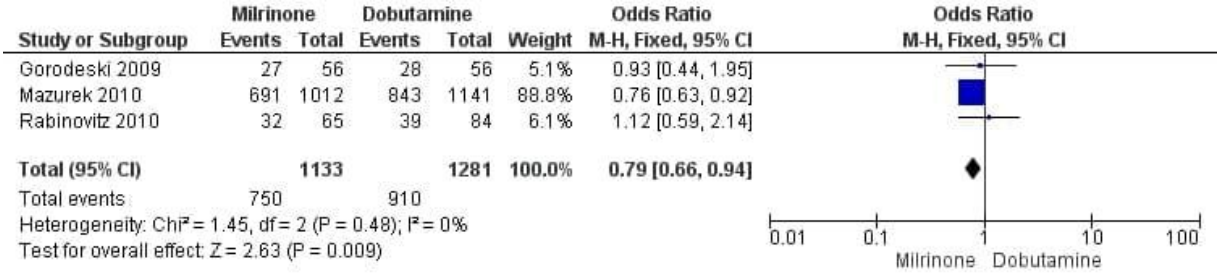

Figure 5. Milrinone versus Dobutamine in terms of Readmission Rates at 1 Year