CRITICAL ROUNDS

MICRO LABS LIMITED

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Dear Doctor,

Greetings from Micro Labs limited. We are happy to bring "CRITICAL ROUNDS" containing latest information in the field of Critical care medicine.

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Looking forward to your valuable feedback

Best Regards,
Medical Team, Micro Labs Ltd

CRITICAL ROUNDS

Ceftolozane/tazobactam versus meropenem in patients with ventilated hospital-acquired bacterial pneumonia: subset analysis of the ASPECT-NP randomized, controlled phase 3 trial

Background

Pneumonia, including hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP), is the most common healthcare-acquired infection in the intensive care unit and is associated with high mortality rates of~20–50%. HABP is assessed as bacterial pneumonia that develops in patients who are hospitalized for ≥ 48h, while VABP is defined as bacterial pneumonia developing after ≥ 48h of endotracheal intubation. Patients with HABP who progress to respiratory failure severe enough to require mechanical ventilation (vHABP) represent a more clinically severe subtype of the disease than patients with nonventilated HABP. Randomized controlled trials evaluating antibacterial treatment of HABP/VABP consistently demonstrate higher mortality in participants with vHABP compared with VABP or nonventilated HABP. Clinical research in nosocomial pneumonia has attended focus more on VABP than HABP, with even less focus specifically on the vHABP subgroup. The limited number of obtainable published studies don't report substantial differences between VABP and HABP in terms of underlying microbiology or pathophysiology. Given the especially high mortality associated with vHABP, new treatment options are particularly needed for this nosocomial pneumonia subtype. Ceftolozane/tazobactam is a combination antibacterial agent comprising ceftolozane, an anti-pseudomonal cephalosporin, and tazobactam, a β-lactamase inhibitor active against extended-spectrum β-lactamases (ESBLs). The combination has broad in vitro activity against gram-negative lower tract (LRT) pathogens, including multidrug-resistant P. aeruginosa and ESBL producing Enterobacterales, but lacks activity against strains expressing metallo-β-lactamases (MBLs) and other carbapenemases. Ceftolozane/tazobactam has also demonstrated good intrapulmonary penetration in two clinical trials, including a study conducted exclusively in critically ill, ventilated participants. Ceftolozane/tazobactam was recently approved for the treatment of HABP/VABP in adults employing a regimen of three g (2 g ceftolozane and 1 g tazobactam) every 8 h (q8h), which is double the dose indicated for complicated intrabdominal and complicated urinary tract infections. This approval was supported results from the ASPECT-NP phase 3 trial, which demonstrated ceftolozane/tazobactam to be noninferior to meropenem for treating HABP/VABP in both primary and key secondary endpoints. In participants with vHABP, the higher mortality expected compared with VABP was only seen with meropenem (37% vHABP, 20%

VABP) but not ceftolozane/tazobactam (24% in both vHABP and VABP). To explore the potential survival advantage with ceftolozane/tazobactam in this particular patient population further, we evaluated efficacy and safety outcomes specifically in ASPECT-NP participants with vHABP.

Methods:

ASPECT-NP was a multinational, phase 3, noninferiority trial comparing ceftolozane/tazobactam with meropenem for treating vHABP and VABP.

Primary endpoint: 28-day ACM.

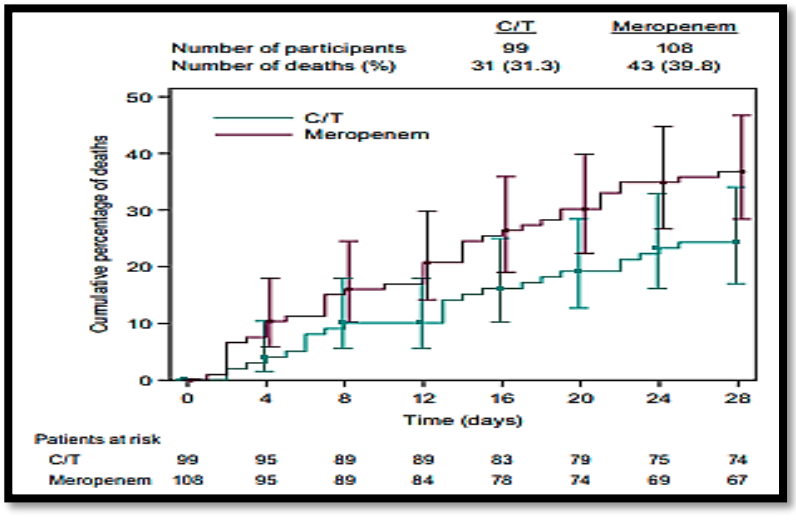
Secondary endpoint: Clinical response at test-of-cure.

Participants with vHABP were a prospectively defined subgroup, but subgroup analyses were not powered for noninferiority testing.

Results:

Overall, 99 participants in the ceftolozane/tazobactam and 108 in the meropenem arm had vHABP. 28-day ACM was 24.2% and 37.0%, respectively, in the intention-to-treat population and 18.2% and 36.6%, respectively, in the microbiologic intention-to-treat population. Clinical cure rates in the intention-to-treat population were 50.5% and 44.4%, respectively.

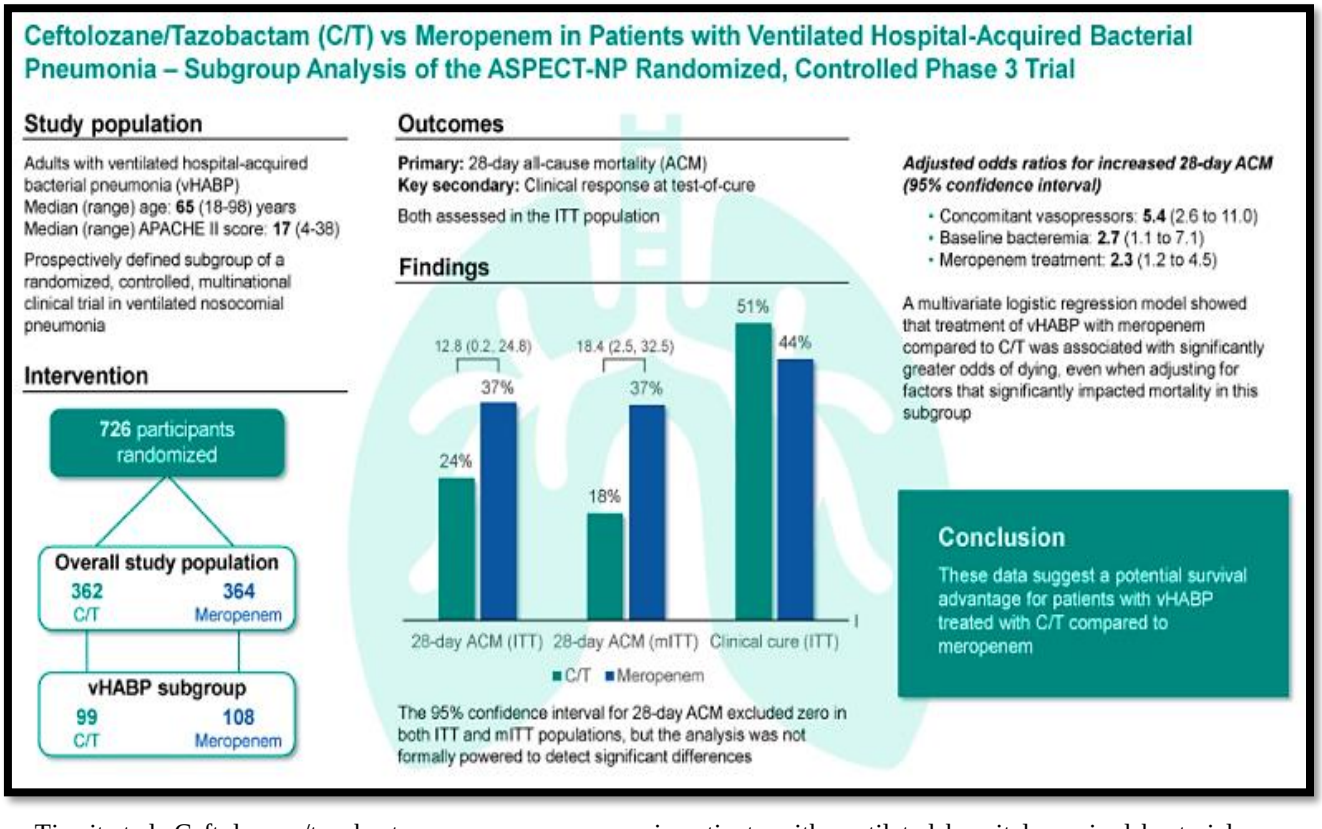
Time to death in participants with vHABP (ITT population). C/T, ceftolozane/tazobactam



Baseline clinical, baseline microbiologic, and treatment factors were comparable between treatment arms. Multivariable regression identified concomitant vasopressor use and baseline bacteremia as significantly impacting ACM in ASPECT-NP; adjusting for these two factors, the odds of dying by day 28 were 2.3-fold greater when participants received meropenem instead of ceftolozane/tazobactam.

Conclusions:

There were no underlying differences between treatment arms expected to have biased the observed survival advantage with ceftolozane/tazobactam in the vHABP subgroup. After adjusting for clinically relevant factors found to impact ACM significantly in this trial, the mortality risk in participants with vHABP was over twice as high when treated with meropenem compared with ceftolozane/tazobactam.



Source: Timsit et al. Ceftolozane/tazobactam versus meropenem in patients with ventilated hospital-acquired bacterial pneumonia: subset analysis of the ASPECT-NP randomized, controlled phase 3 trial. Crit Care. 2021;25:290.

CRITICAL ROUNDS

Effect of Intravenous Fluid Treatment With a Balanced Solution vs 0.9% Saline Solution on Mortality in Critically Ill Patients. The BaSICS Randomized Clinical Trial

Introduction:

Intravenous fluids are routinely utilized in critically ill patients to sustain or replenish intravascular volume and to deliver drug infusions. Although saline (0.9% sodium chloride) has remained the first fluid over time, recent evidence from observational studies and a couple of large unblinded cluster-randomized, single-center trials within the US demonstrated that administration of balanced crystalloids (ie, crystalloids whose sodium and chloride concentrations are almost like plasma) resulted in better outcomes. Furthermore, this effect could also be mediated by smaller changes in serum chloride levels. However, these results aren't uniform across clinical trials, and insufficient evidence is out there from large individual randomized multicenter studies.
The Balanced Solutions in medical care Study (BaSICS), a double-blind, factorial, randomized clinical test was conducted to assess whether administration of a balanced solution (Plasma-Lyte 148) during medical care unit (ICU) stay, compared with saline , would end in improved 90-day survival in critically ill patients.**Objective**: To determine the effect of a balanced solution vs saline solution (0.9% sodium chloride) on 90-day survival in critically ill patients.

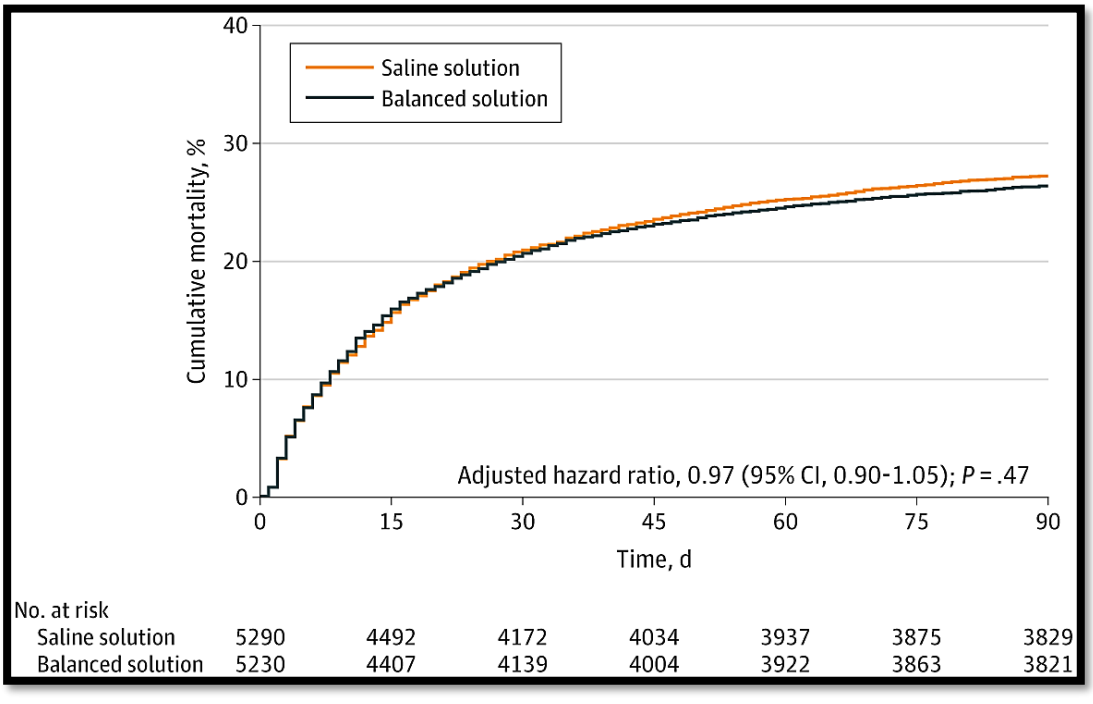
Design, Setting, and Participants: Double-blind, factorial, randomized clinical trial conducted at 75 ICUs. Patients admitted to the ICU with at least 1 risk factor for worse outcomes, who required at least 1 fluid expansion, and who were expected to remain in the ICU for more than 24 hours were randomized to 2 different fluid types (a balanced solution vs saline solution reported in this article) and 2 different infusion rates (reported separately).

Interventions: Patients were randomly assigned 1:1 to receive either a balanced solution (n = 5522) or 0.9% saline solution (n = 5530) for all intravenous fluids.

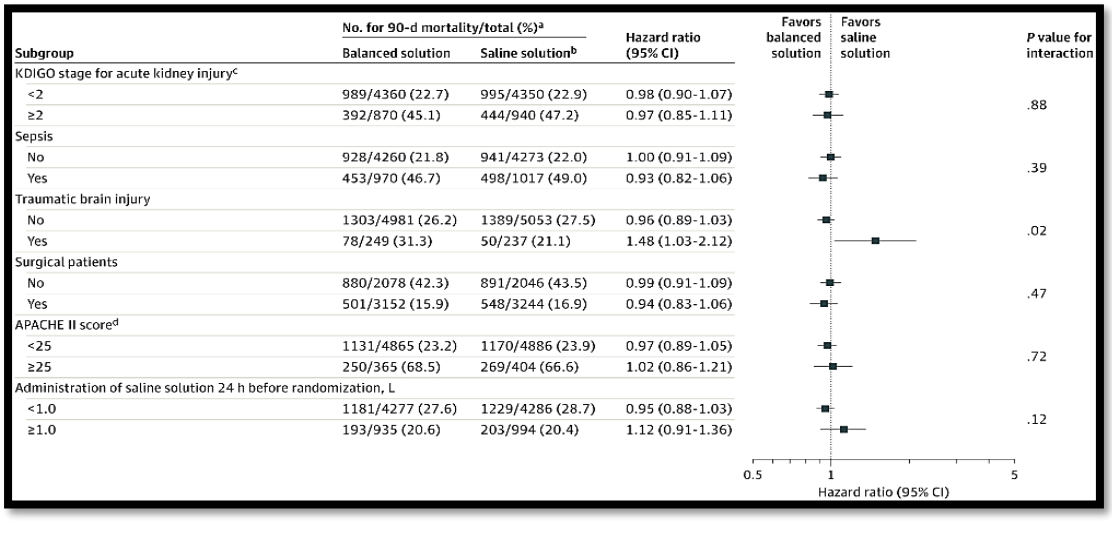
Main Outcomes and Measures: Primary outcome was 90-day survival.

Results: Among 11 052 patients who were randomized, 10 520 (95.2%) were available for the analysis (mean age, 61.1 [SD, 17] years; 44.2% were women). There was no significant interaction between the 2 interventions (fluid type and infusion speed; $P = .98$).

Cumulative Incidence of the Primary Outcome of 90-Day Survival for a Balanced Solution vs Saline Solution (0.9% Sodium Chloride)The median follow-up was 90 days (interquartile range, 59.2-90.0 days) for the balanced solution group and 90 days (interquartile range, 54-90 days) for the saline solution group.



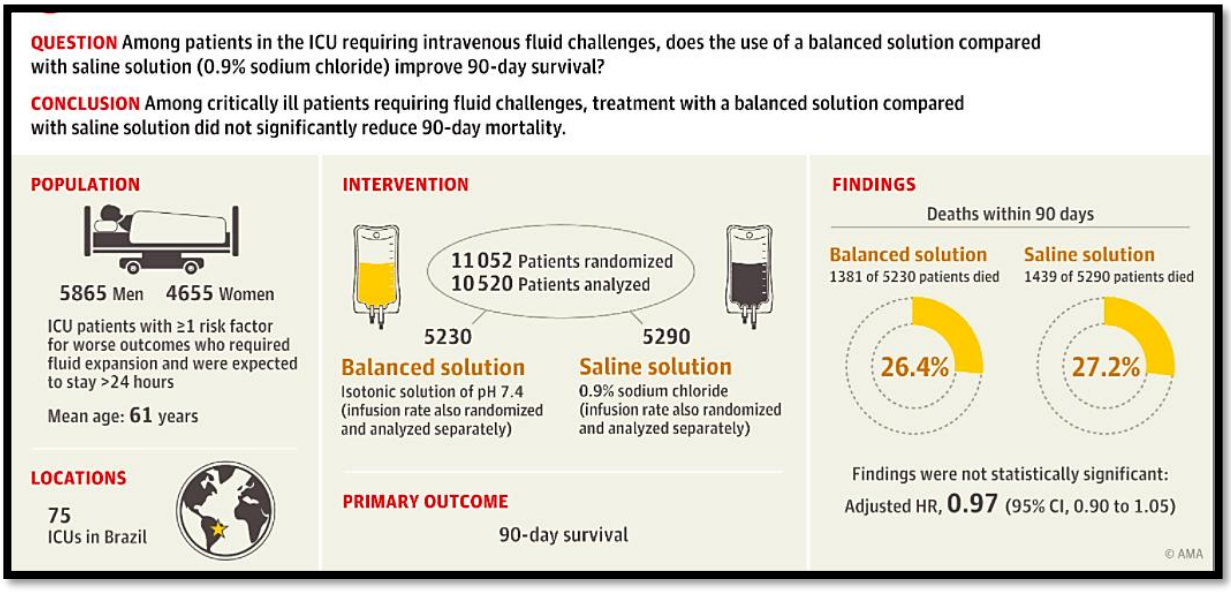
Forest Plot for the Primary Outcome of 90-Day



Subgroup	No. for 90-d mortality/total (%)[a] Balanced solution	Saline solution[b]	Hazard ratio (95% CI)	P value for interaction
KDIGO stage for acute kidney injury[c]				
<2	989/4360 (22.7)	995/4350 (22.9)	0.98 (0.90-1.07)	.88
≥2	392/870 (45.1)	444/940 (47.2)	0.97 (0.85-1.11)	
Sepsis				
No	928/4260 (21.8)	941/4273 (22.0)	1.00 (0.91-1.09)	.39
Yes	453/970 (46.7)	498/1017 (49.0)	0.93 (0.82-1.06)	
Traumatic brain injury				
No	1303/4981 (26.2)	1389/5053 (27.5)	0.96 (0.89-1.03)	.02
Yes	78/249 (31.3)	50/237 (21.1)	1.48 (1.03-2.12)	
Surgical patients				
No	880/2078 (42.3)	891/2046 (43.5)	0.99 (0.91-1.09)	.47
Yes	501/3152 (15.9)	548/3244 (16.9)	0.94 (0.83-1.06)	
APACHE II score[d]				
<25	1131/4865 (23.2)	1170/4886 (23.9)	0.97 (0.89-1.05)	.72
≥25	250/365 (68.5)	269/404 (66.6)	1.02 (0.86-1.21)	
Administration of saline solution 24 h before randomization, L				
<1.0	1181/4277 (27.6)	1229/4286 (28.7)	0.95 (0.88-1.03)	.12
≥1.0	193/935 (20.6)	203/994 (20.4)	1.12 (0.91-1.36)	

Planned surgical admissions represented 48.4% of all patients. Of all the patients, 60.6% had hypotension or vasopressor use and 44.3% required mechanical ventilation at enrollment. Patients in both groups received a median of 1.5 L of fluid during the first day after enrollment. By day 90, 1381 of 5230 patients (26.4%) assigned to a balanced solution died vs 1439 of 5290 patients (27.2%) assigned to saline solution (adjusted hazard ratio, 0.97 [95% CI, 0.90-1.05]; *P* = .47). There were no unexpected treatment-related severe adverse events in either group.

Conclusion and Relevance Among critically ill patients requiring fluid challenges, use of a balanced solution compared with 0.9% saline solution did not significantly reduce 90-day mortality. The findings do not support the use of this balanced solution.



Source: Zampieri FG, et al. BaSICS investigators and the BRICNet members. Effect of Intravenous Fluid Treatment With a Balanced Solution vs 0.9% Saline Solution on Mortality in Critically Ill Patients: The BaSICS Randomized Clinical Trial. JAMA. 2021 Aug 10.

CRITICAL ROUNDS

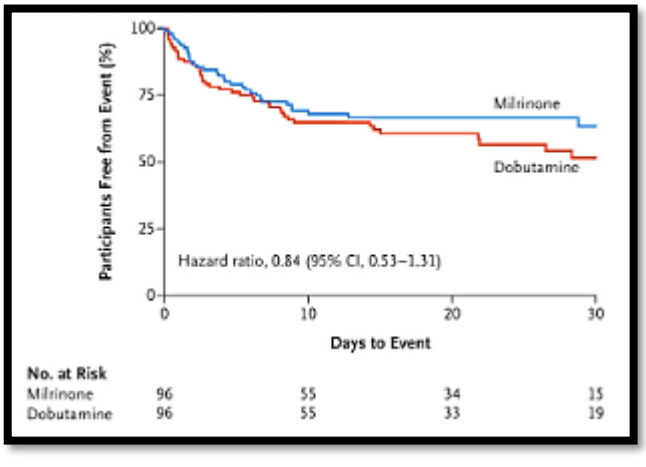
Milrinone as Compared with Dobutamine in the Treatment of Cardiogenic Shock

Background

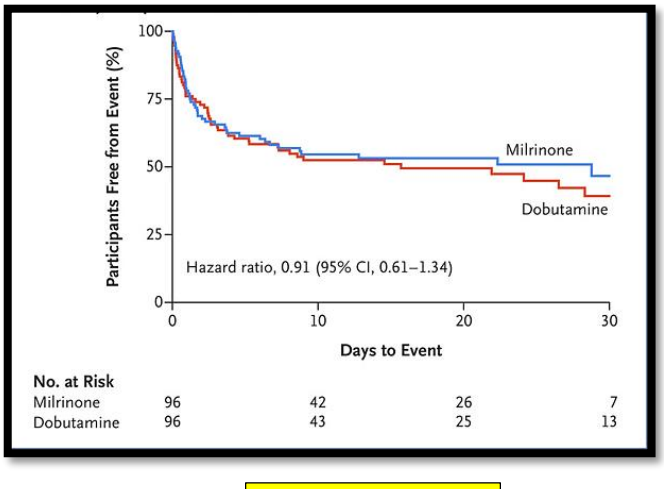
Cardiogenic shock is associated with substantial morbidity and mortality. Although inotropic support is a mainstay of medical therapy for cardiogenic shock, little evidence exists to guide the selection of inotropic agents in clinical practice.

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.

Result: 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).



In Hospital Death from Any cause

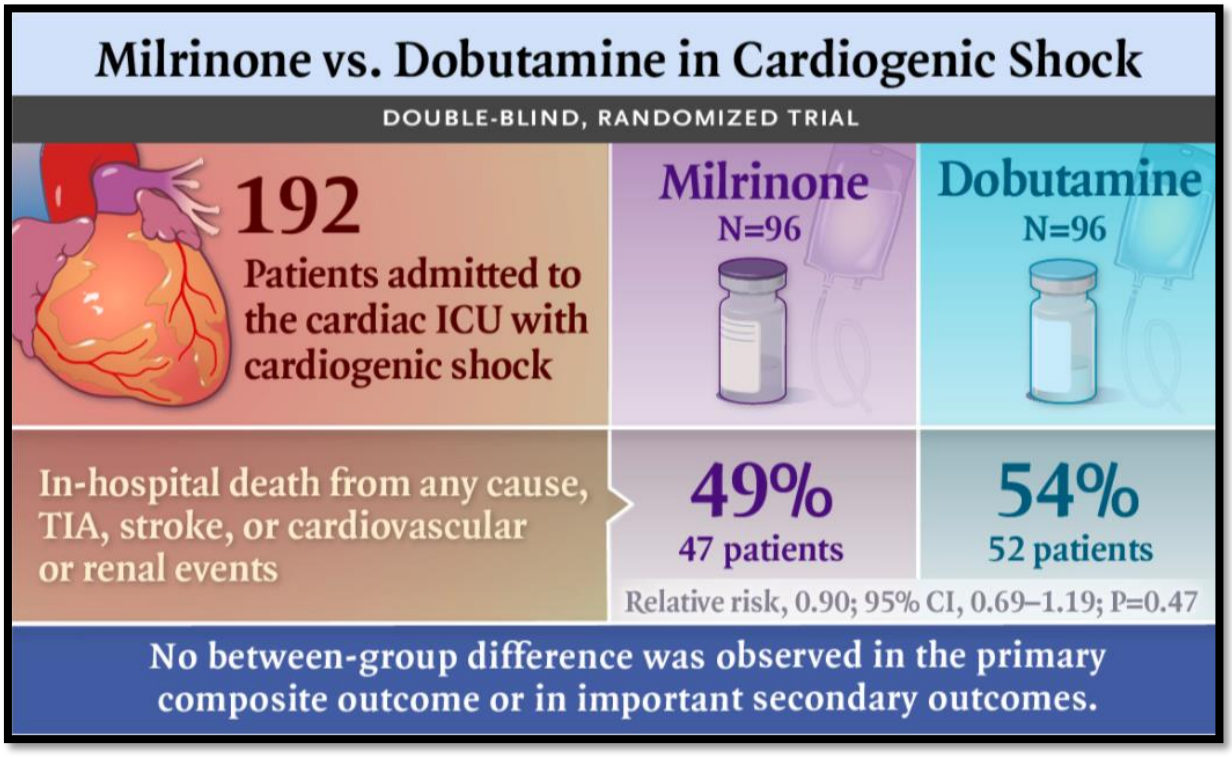


Primary Outcome

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



Source: Mathew R, et al. Milrinone as Compared with Dobutamine in the Treatment of Cardiogenic Shock. N Engl J Med. 2021 Aug 5;385(6):516-525

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