Which Multicenter Randomized Controlled Trials in Critical Care Medicine Have Shown Reduced Mortality? A Systematic Review

Carlos A. Santacruz, MD[1]; Adriano J. Pereira, MD, PhD[2]; Edgar Celis, MD[1]; Jean-Louis Vincent, MD, PhD, FCCM[3]

Objectives: To determine which multicenter randomized controlled trials in critically ill patients have shown that the study intervention was associated with a statistically significant reduction in mortality. Our analysis provides an update to a report published 10 years ago.

Data Sources: MEDLINE database and PubMed interface from inception until April 30, 2019.

Study Selection: as a primary or secondary outcome were included.

Data Extraction: Numbers of centers and patients, type of intervention, reported mortality outcome, and rate and level of significance were extracted into predefined tables. Included randomized controlled trials were classified as reporting reduced, increased, or no effect of the intervention on mortality. Methodologic quality of trials was evaluated using the updated Consolidated Standards of Reporting Trials statement.

Data Synthesis: A total of met the inclusion criteria: 27 ( ) reported a significant in , 16 ( ) an and 170 (in (one study was reported in 2 groups). Of the , had assessed interventions likely to , including e, position, and , demonstrating the strategies or improved process of care rather than positive effects of new therapies. trials reported effects of . Results from some positive randomized controlled trials, for example, studies of r , , -1 receptor in sepsis, and in severe acute respiratory distress syndrome were in subsequent randomized controlled trials. Other interventions, for example, , have been .

Conclusions: A systematic literature search provided that has consistently in critically ill patients. Strategies associated with or were associated with . (*Crit Care Med* 2019; 47:00–00)

Key Words: critically ill; heterogeneity; iatrogenicity; outcomes; process of care

Randomized controlled trials (RCTs) are considered the best evidence to guide clinical practice because the randomization process can control for unmeasurable factors that may influence the response to a therapeutic intervention (1). In critical care medicine, mortality is often chosen as the main outcome measure for clinical trials because it is dichotomous, clinically relevant, and relatively high in critically ill patients. However, many factors, in addition to a patient's current disease process, can influence survival, including availability and choice of therapy and personal preferences about end-of-life decisions (2). Biological heterogeneity, including variation in age, sex, genetics/genomics, physiologic response, immunophenotype, and comorbidities, among many others, will also influence the effect of any intervention on mortality (3). Hence, many large RCTs in critically ill patients targeting mortality as an outcome endpoint

[1]Department of Critical and Intensive Care Medicine, Academic Hospital Fundación Santa Fe de Bogotá, Bogotá, Colombia.

[2]Department of Intensive Care, Hospital Israelita Albert Einstein, Sao Paolo, Brazil.

[3]Department of Intensive Care, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium.

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have reported no overall effect of the intervention, that is, have been reported as "negative."

, we performed a systematic review of the literature to determine which RCTs evaluating interventions in critically ill patients had reported statistically significantly reduced mortality rates in the intervention arm (4). The results showed that) included in the review had shown a impact of the intervention on of critically ill patients. Given the large number of RCTs that have been published in the intervening period and increased recognition of the problems with conducting RCTs in ICU patients (5), we decided to update this analysis.

MATERIALS AND METHODS

We conducted a systematic search of the literature from inception up to April 30, 2019, using the MEDLINE database and the PubMed interface, to identify multicenter RCTs that had evaluated any pharmacologic or mechanical intervention or monitoring system in adult critically ill ICU patients and had reported mortality as a predefined primary or secondary outcome.

We used the mesh terms: ((((((((("critical care"[MeSH Terms] OR "critical care"[Text Word]) OR "intensive care"[Text Word]) OR ("critical illness"[MeSH Terms] OR "critical illness"[Text Word])) OR "critically ill"[Text Word]) OR ("sepsis"[MeSH Terms] OR "sepsis"[Text Word])) OR ("respiration, artificial"[MeSH Terms] OR "artificial respiration"[Text Word])) OR "mechanical ventilation"[Text Word]) OR ("respiratory distress syndrome, adult"[MeSH Terms] OR "adult respiratory distress syndrome"[Text Word])) OR ("cardiopulmonary resuscitation"[MeSH Terms] OR "cardiopulmonary resuscitation"[Text Word])) OR ("heart arrest"[MeSH Terms] OR "cardiac arrest"[Text Word])) OR "ards"[Text Word] AND ((Randomized Controlled Trial[ptyp] OR Multicenter Study[ptyp]) AND "Mortality"[Mesh]. Limits: Humans, Clinical trials, Adults +19. We excluded trials that were not multicenter and not randomized, trials involving only pediatric or non-ICU populations or in which the intervention was conducted prior to ICU admission and those in which mortality was not mentioned as an outcome. No date limit or minimum number of patients was applied. Only English-language articles were included. We also searched the references of included articles and related review articles for studies that had been missed in the initial search.

Eligibility assessment and data abstraction, including numbers of centers and patients, type of intervention, type of mortality outcome and rate as well as the level of significance was performed by two reviewers (C.A.S., A.J.P.) who completed predefined tables independently in a blinded manner. RCTs were classified as reporting statistically significantly reduced, increased, or no effect of the intervention on mortality. All results were included regardless of the test used to evaluate statistical significance. Discrepancies in the final classification of the RCTs were resolved by consensus among all authors.

Median (interquartile range [IQR] 25–75%) mortality, number of participating centers, and total number of included subjects are reported for each category. Trials were subgrouped according to most frequent populations into "sepsis" (including vasodilatory and distributive shock), "acute respiratory distress syndrome [ARDS]/acute lung injury," "acute respiratory failure" (hypercapnic and hypoxemic respiratory failure), and "general ICU." Trials that reported survival rates were excluded from the overall mortality analysis. The Wilcoxon signed rank test was used to compare the median (IQR) of predicted and observed mortality for the control groups of all RCTs in the three categories. Statistical analyses were performed using the latest version of R program (6).

Trial methodologic quality was assessed by evaluating reports of blinding, use of intention-to-treat analysis, and allocation generation and concealment, according to the directions of the updated Consolidated Standards of Reporting Trials statement (7). Concealment was considered adequate if the author reported a mechanism used to implement the random allocation sequence, describing any steps taken to conceal the sequence until interventions were assigned. We classified the type of analysis (intention to treat or per protocol) as adequate if all randomized patients were included in the analysis in the original group to which they had been allocated. Sample size calculation was not reported in trials where mortality was not the primary outcome.

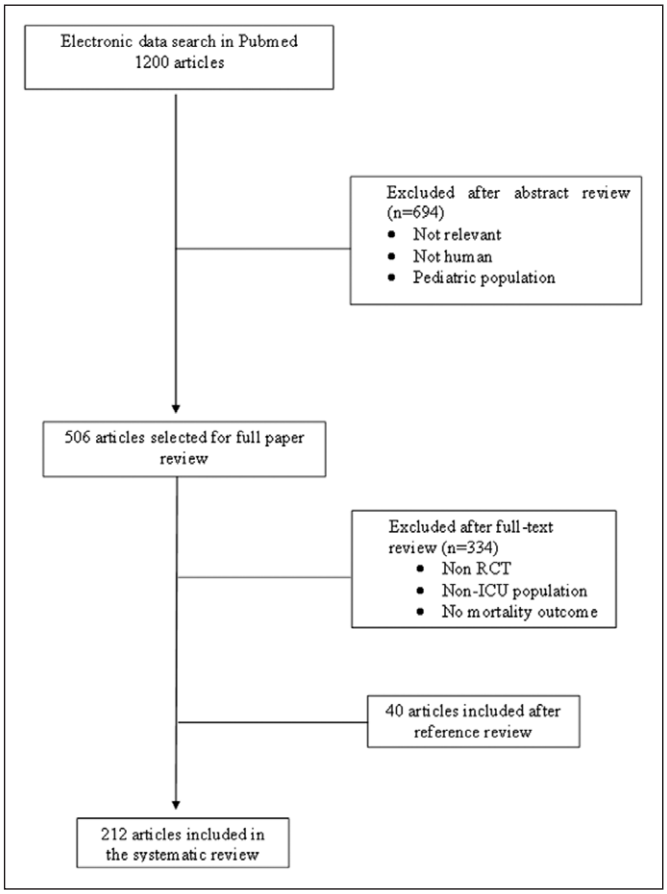

Figure 1. Flow chart of included trials. RCT = randomized controlled trial.

TABLE 1. Randomized Controlled Trials in Which Decreased Mortality Was Reported (Full Study Details in Table S1, Supplemental Digital Content 1, http://links.lww.com/CCM/E922)

		Intervention	
References	Study Population	Study Group	Control Group
Amendola et al (8)	Acute kidney injury	Goal-directed therapy	Standard practice
Annane et al (9)	Sepsis	Hydrocortisone + udrocortisone	Placebo
de Jong et al (10)	ICU	Procalcitonin-guided therapy	Standard practice
Guérin et al (11)	ARDS	Prone position	Supine position
Guntupalli et al (12)	Sepsis	Talactoferrin	Placebo
Nava et al (13)	AHRF	NIV	Standard practice
Papazian et al (14)	ARDS	Cisatracurium besylate	Placebo
Ferrer et al (15)	AHRF	NIV	Conventional oxygen
de Smet et al (16)	ICU	Selective digestive decontamination/ selective oral decontamination	Standard practice
Ferrer et al (17)	ICU	NIV	Conventional oxygen
Villar et al (18)	ARDS	P ex/low V_T	Standard practice
Panacek et al (19)	Sepsis	Afelimomab	Placebo
Ferrer et al (20)	ICU	NIV during weaning	Conventional weaning
Ferrer et al (21)	Acute hypoxemic respiratory failure	NIV	High-concentration oxygen
Annane et al (22)	Sepsis	Hydrocortisone + udrocorti-sone	Placebo
Bernard et al (23)	Sepsis	Recombinant human activated protein C	Placebo
Brower et al (24)	ARDS	V_T 6 mL/kg PBW	V_T 12 mL/kg PBW
Esteban et al (25)	ARDS	Pressure-controlled ventilation	Volume-controlled ventilation
Fagon et al (26)	Pneumonia	Invasive management in ventilator-associated pneumonia	Clinical management
Nava et al (27)	AHRF	Noninvasive pressure support ventilation	Invasive pressure support ven-tilation
Amato et al (28)	ARDS	Protective ventilation	Conventional ventilation
Baudo et al (29)	Sepsis	Antithrombin III	Placebo
Brochard et al (30)	AHRF	NIV	Standard practice
Fisher et al (31)	Sepsis	Interleukin-1 receptor antagonist	Placebo
Gutierrez et al (32)	ICU	Gastric intramucosal pH	Standard practice
Dominioni et al (33)	Sepsis	High dose immunoglobulin G	Placebo
Ziegler et al (34)	Sepsis and gram-negative bacteremia	Human monoclonal immunoglobulin M antibody	Placebo

AHRF = acute hypercapnic respiratory failure, ARDS = acute respiratory distress syndrome, NIV = noninvasive ventilation, PBW = predicted body weight, V_T = tidal volume.

RESULTS

A total of 1,200 articles were identi ed in the initial search, and 40 after reference review; 212 RCTs met the inclusion criteria (Fig. 1). Of the 212 RCTs, 27 reported reduced mortality (8–34) (Table 1; and Table S1, Supplemental Digital Content 1, http://links.lww.com/CCM/E922), 16 increased mortality (25, 35–49) (Table 2; and Table S2, Supplemental Digital Content 1, http://links.lww.com/CCM/E922), and 170 no effect on mortality (50–219) (Table S3, Supplemental Digital Content 1, http://links.lww.com/CCM/E922). One study (25) that showed

TABLE 2. Randomized Controlled Trials in Which Increased Mortality Was Reported (Full Study Details in Table S2, Supplemental Digital Content 1, http://links.lww.com/CCM/E922)

References	Study Population	Intervention	
		Study Group	Control Group
Guidet et al (35)	ICU	Systematic ICU admission	Standard practice
Cavalcanti et al (36)	ARDS	Recruitment maneuver and PEEP titration	Low PEEP
Ferguson et al (37)	ARDS	High-frequency oscillatory ventilation	Pressure-controlled ventilation
Heyland et al (38)	ICU	Glutamine, antioxidants, or both	Placebo
Mourvillier et al (39)	Sepsis	Hypothermia	Standard practice
Perner et al (40)	Sepsis	6% hydroxyethyl starch 130/0.42	Ringer´s acetate
Gao Smith et al (41)	ARDS	IV salbutamol	Placebo
Elseviers et al (42)	Acute kidney injury	Renal replacement therapy	Conservative management
López et al (43)	Sepsis	Nitric oxide synthase inhibitor 546C88	Placebo
Esteban et al (44)	Acute respiratory failure	Noninvasive positive pressure ventilation	Standard practice
Mehta et al (45)	ICU	Continuous renal replacement therapy	Intermittent hemodialysis
Esteban et al (25)	ARDS	Volume-controlled ventilation	Pressure-controlled ventilation
Sloan et al (46)	Hemorrhagic shock	Diaspirin cross-linked hemoglobin	Placebo
Takala et al (47)	ICU	Growth hormone	Placebo
Fisher et al (48)	Sepsis	Tumor necrosis factor receptor and Fc portion of immunoglobulin G1	Placebo
Hayes et al (49)	ICU	High Do_2 and Vo_2	Normal Do_2 and Vo_2

ARDS = acute respiratory distress syndrome, Do_2 = oxygen delivery, PEEP = positive end-expiratory pressure, Vo_2 = oxygen consumption.

a difference in mortality was included in both the increased and decreased mortality groups because the interventions were at equipoise so neither could be considered as a standard control or placebo. Hence the results showed an increase or decrease in mortality depending on which group was taken as comparator.

RCTs Reporting Reduced Mortality

Twenty-seven RCTs in a total of 15,612 patients from a median of 10 (3–22) centers reported reduced mortality (or increased survival) with the intervention under study. Four studies in this category reported survival rates (20, 22, 27, 29) and were not included in the mortality analyses. The median (IQR) mortality in the remaining 23 studies was 25.7% (16.7–31.8%) in the intervention group versus 41.9% (30.9–49.9%) in the control group (n = 23 studies). Seven studies were conducted in patients with sepsis (n = 4,480, median mortality 30.0% [24.5–40.5%] intervention vs 47.6% [39.8–49.1%] control) (9, 12, 19, 23, 31, 33, 34). Other frequently studied populations included patients with ARDS (six studies, n = 1,894, mortality 31.5% [30.9–36.5%] vs 49.0% [41.0–66.6%]) (11, 14, 18, 24, 25, 28) and patients with acute hypercapnic or hypoxemic respiratory failure (four studies, n = 377, mortality 10.9% [9.8–13.3%] vs 35.0% [30.5–41.8%]) (13, 15, 21, 30).

The six studies in patients with ARDS evaluated strategies that would reduce ventilator-induced lung injury, assessing a low tidal volume ventilation strategy associated with a high positive end-expiratory pressure (18, 24, 28), pressure versus volume cycle controlled mechanical ventilation (25), prone positioning (11), and IV administration of cisatracurium besylate (14). Seven studies had evaluated use of noninvasive ventilation (NIV) in patients with acute hypercapnic respiratory failure (AHRF) or when weaning from mechanical ventilation in general ICU patients (13, 15, 17, 20, 21, 27, 30). The other 14 trials had evaluated anti-inflammatory or immunomodulatory therapies in patients with sepsis or bacteremia (9, 12, 19, 22, 23, 29, 31, 33, 34), procalcitonin-guided antibiotic therapy (10), digestive decontamination (16), diagnostic strategies for ventilator-associated pneumonia (26), goal-directed therapy in patients with acute kidney injury (8), and hemodynamic optimization monitoring using gastric tonometry (32) (Table 1; and Table S1, Supplemental Digital Content 1, http://links.lww.com/CCM/E922).

RCTs Reporting Increased Mortality

Sixteen RCTs in a total of 10,462 patients from a median of 25 (14–42) centers reported increased mortality with the intervention under study (25, 35–49). One study in this category (43)

reported survival rates and was not included in the mortality analyses. The median mortality in the remaining 15 studies was 50.3% (43.3–53.5%) for the intervention group versus 34.0% (24.1–42.3%) in the control group. Five studies were conducted in general ICU populations (n = 5,043, mortality 45.0% [41.5–54.0%] vs 34.0% [27.2–39.0%]) (35, 38, 45, 47, 49). Other groups frequently studied included patients with ARDS (four studies,n = 1,963, mortality 51.2% [43.8–61.0%] vs 42.2% [32.0–49.7%]) (25, 36, 37, 41) and patients with sepsis (three studies,n = 1,037, mortality 51.0% [51.0–52.0%] vs 34.0% [32.0–38.5%]) (39, 40, 48) (Table 2; and Table S2, Supplemental Digital Content 1, http://links.lww.com/CCM/E922).

RCTs Showing No Effect on Mortality

In 170 RCTs, in a total of 145,662 patients from a median of 26 (11–55) centers, no statistically significant effect of the intervention under study on mortality was reported (Table S3, Supplemental Digital Content 1, http://links.lww.com/CCM/E922). Nine studies in this category (57, 70, 83, 90, 93, 125, 171, 178, 190) reported survival rates and were not included in the mortality analyses. The median mortality in the remaining 161 studies was 29.0% (21.0–37.0%) for the intervention group versus 30.0% (24.0–38.0%) for the control group. Sixty-five studies were conducted in patients with sepsis (n = 52,005, mortality 30% [26–39%] vs 32% [26–39%]). Other frequently studied groups included general ICU populations (31 studies, n = 58,068, mortality 29.0% [21.0–33.5%] vs 28.0% [22.0–33.0%]) and patients with ARDS (23 studies, n = 9,814, mortality 31.0% [28.5–39.0%] vs 34.0% [28.0–43.5%]). The most recent RCTs to report no effect on mortality were studies assessing the use of lactate levels to guide resuscitation in sepsis (50), probiotics to prevent ventilator-associated pneumonia (51), adjunctive intermittent pneumatic compression to prevent deep-vein thrombosis (52), and levocarnitine in patients with sepsis (53).

Methodologic Quality of Included Trials

Allocation concealment was reported in 25 of the 27 trials (93%) with reduced mortality rates, in 11 of the 16 (69%) with increased mortality and in 148 of 170 neutral trials (87%) (Tables S4–S6, Supplemental Digital Content 1, http://links.lww.com/CCM/E922). Intention to treat or modified intention to treat analyses were reported as having been carried out in 22 of 27 trials (81%) in the reduced mortality group, in 13 of 16 trials (81%) in the increased mortality group, and in 158 of 170 (93%) of the neutral trials group.

There was no statistically significant difference between the control group median assumed and observed mortality rates in the RCTs reporting reduced mortality (45.0% [30.0–50.0%] vs 39.8% [30.2–49.1%]; p = 0.66), increased mortality (35.0% [33.0–34.0%] vs 34.0% [23.0–39.0%]; p > 0.99]), or no effect (40.0% [28.0–48.3%] vs 30.0% [24.0–38.3%]; p = 0.33).

DISCUSSION

This systematic review shows that only 13% of published RCTs demonstrated that the intervention being tested was associated with reduced mortality rates. These observations confirm and extend those of our earlier review 10 years ago (4) in which 14% of the included RCTs had shown a beneficial effect of the intervention on mortality rates. Importantly, it is well known that "negative" trials are less likely to be published than those with significant differences between study arms (220), so the actual percentage of total trials conducted that demonstrate a beneficial effect on survival is likely to be much less than the 13% we identified in published RCTs.

Importantly, many of the RCTs that showed a decrease in mortality studied interventions that reduced iatrogenic conditions, notably in patients with ARDS (11, 14, 18, 24, 25, 28), rather than demonstrating an effect of a new therapy on mortality. The only intervention consistently shown to improve outcomes was use of NIV in patients with AHRF or when weaning from invasive mechanical ventilation (13, 15, 17, 20, 21, 27, 30). For several of the RCTs that reported a decrease in mortality (12, 14, 23), the findings were not replicated in later larger studies (e.g., recombinant activated protein C [121], talactoferrin [97], and neuromuscular blockade in severe ARDS [221]), or, as for gastric tonometry (32), the interventions have been abandoned. In Table 3, we present a simple overview of the current status of the interventions shown by RCT to reduce mortality in ICU patients.

There are multiple reasons why an RCT may not demonstrate a difference between intervention arms apart from the obvious possibility that the intervention is not effective. Notably, lower overall mortality rates in ICU patients in recent years may make it more difficult to detect a mortality difference with any intervention. For example, the control groups of recent studies of early goal-directed therapy in ICU patients had mortality rates of ± 25% (98–100) compared with the initial study by Rivers et al (222) in which mortality was 46% in the control group.

Another key reason for the many studies that report no effect of an intervention is the heterogeneity of the patients included. Despite broad clinical and biological heterogeneity in study groups, particularly in patients with sepsis and ARDS, most studies still report an "average" treatment effect, which assumes that the effect of treatment would have been the same in all patients. The heterogeneity of treatment effect is examined primarily by subgroup analyses, some of which have indeed shown decreased mortality in RCTs in which the overall outcome effect was negative. For example, Ziegler et al (34) reported no overall effect of human monoclonal antibody against endotoxin in patients with presumed Gram-negative sepsis, but reduced mortality in patients with proven Gram-negative bacteremia. And Bone et al (218) reported no overall difference in 14-day mortality in patients with sepsis treated with high dose methylprednisolone, but a significant decrease in mortality in a subgroup of patients with elevated serum creatinine levels. Nevertheless, subgroup analyses have reduced power compared with analyses involving the full study cohort and must be interpreted with some caution.

Several approaches to study design have been suggested to overcome the problem of heterogeneity. Performing larger RCTs may increase the credibility of subgroup analysis, but enrolling more patients prolongs study duration and costs. Alternatively, adaptive design RCTs (223–225) have been proposed to try and improve the likelihood of detecting a difference between study arms. Such studies adapt the study design while the study is in

TABLE 3. A Simple Overview of the Current Status of the Interventions Shown by Randomized Controlled Trial to Reduce Mortality in ICU Patients

Type of Intervention	Well Accepted	Still Debated [a]	Largely Unaccepted/ Disproved
Limiting iatrogenicity/respiratory support			
Limited tidal volume in ARDS	X		
NIV in hypercapnic respiratory failure	X		
NIV following extubation in complex cases	X		
Prone positioning in severe ARDS		X	
Muscle relaxants in severe ARDS			X
Monitoring systems			
Gastric tonometry			X
New therapeutic interventions			
Interleukin-1 receptor antagonist in sepsis			X
Drotrecogin alfa (activated) in sepsis			X
Talactoferrin in sepsis			X
Polymyxin B hemoperfusion in sepsis			X
Other strategies			
Selective digestive decontamination		X	
Corticosteroids in septic shock		X	
Early goal-directed therapy in acute kidney injury		X	

ARDS = acute respiratory distress syndrome, NIV = noninvasive ventilation.
[a]Perhaps applicable in some patients, but not for routine use.

progress, either by halting recruitment to study arms in which no benefit is shown at interim analysis, thus focusing the rest of the study on those arms most likely to demonstrate reduced mortality, or by recalculating sample sizes so that studies showing potential benefit, but which are underpowered can continue and ineffective interventions can be stopped early. However, such trials necessitate more complex statistical techniques (225). Alternatively, more careful patient characterization and selection is needed such that populations are more homogeneous and only patients most likely to respond to the intervention are included. This option will become increasingly possible as 'omics technology develops.

Finally, mortality may not be the best endpoint for RCTs in critically ill patients because it is difficult to influence outcomes partly because mortality rates have decreased over time as mentioned earlier, but also because mortality is a heterogeneous outcome, which can be influenced by many factors beyond the intervention target, including patient end-of-life treatment preferences. Although patient survival is of course important, other patient-centered outcomes, such as improvement in organ function (226) or quality-of-life (227), should also be considered. Indeed, RCTs that report a reduction in mortality but have a high risk of bias may lead to excessive, potentially unnecessary interventions (8). Importantly, although the "at-a-glance" interpretation of so-called negative trials is that the intervention is not effective and should therefore not be used, RCTs with negative results in terms of mortality endpoints may still have important implications for daily ICU practice when other outcomes are considered, and results should still be published.

This review has several limitations. First is the simple classification we used to characterize study results, using a decrease, increase, or no effect on mortality, although there may be some subjectivity in the way in which study results are interpreted, and others may have classified some studies differently. Second, our search strategy was limited to the MEDLINE database, but we also carefully reviewed reference lists of the included articles and of relevant review articles and do not believe that important published RCTs escaped our search. Third, we did not study results of subgroup analyses as we were interested only in global study results. Finally, publication bias was not formally assessed.

CONCLUSIONS

Although 20% of studies have reported a statistically significant difference in survival, the large proportion of neutral trials suggests that careful thought is necessary when designing RCTs in terms of selection of patients and choice of outcomes. RCTs should target other outcomes than just mortality, and other study designs could also be considered.

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