COMMENTARY

Is "Less be More" Still a Valid Concept in Intensive Care? A Review of Critical Care Randomized Clinical Trials from the New England Journal of Medicine

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Received on: 05 February 2024; *Accepted on:* 17 April 2024; *Published on:* xx xxxx xxxx

Abstract

The concept of "Less is more" has been gaining increasing awareness and acceptance in Critical Care. In 2017, we attempted to systematically answer the question "Can less be more in intensive care" with empirical data. We reviewed all the critical care randomized clinical trials (RCTs) between 1 January 2008 and 5 October 2016 in the New England Journal of Medicine (NEJM).

This article attempts to repeat the earlier exercise using data from 5 October 2016 to 31 December 2023.

This analysis of critical care RCTs in the NEJM has shown three findings. Approximately three-quarter of RCTs in critical care in the NEJM between 2008 and 2023 failed to show benefit or harm. In the years 2008–2016, patients in the intervention cohort had a higher mortality compared to controls, but in the years 2016–2023, the difference in overall mortality in patients in the intervention and control arms was not statistically significant. Compared to the years 2008–2016, in the years from 2016 to 2023, the number of RCTs showing harm decreased and those showing benefit increased.

Keywords: Clinical outcomes, Less is more, Mortality in randomized clinical trials.

Indian Journal of Critical Care Medicine (2024): 10.5005/jp-journals-10071-24717

Simplicity is the Ultimate Sophistication

– Leonardo da Vinci

Introduction and Background

The concept of "Less is more" has been gaining increasing awareness and acceptance in critical care. In 2017, we attempted to systematically answer the question "Can less be more in intensive care" with empirical data. We reviewed all the critical care randomized clinical trials (RCTs) between 1 January 2008 and 5 October 2016 in the New England Journal of Medicine (NEJM).[1] This article attempts to repeat the earlier exercise using data from 5 October 2016 to 31 December 2023.

Review of Analysis of NEJM RCTs from 2008 to 2016

The earlier analysis showed the following: In 63 RCTs, the total reported mortality in the intervention group was 23,601/58,727 (40.19%), and in the control group, it was 20,752/53,568 (38.74%).[1] The relative risk of death in the intervention group of patients was 1.0374 [95% confidence interval (CI): 1.0224–1.0526; $p < 0.001$]. This translates to an additional death for every 69 patients enrolled in the intervention arm of these trials.

We also noted that "The majority of RCTs had no impact on the primary outcome. Only eight therapies reported improved mortality or other clinically meaningful primary outcomes, while seven therapies worsened outcomes." These interventions are listed in the following:

Eight therapies that improved the outcomes are as follows:[1]

1. Continuous positive airway pressure in respiratory failure [high-flow oxygen through nasal cannula in acute hypoxemic respiratory failure (FLORALI)].[2]
2. Thrombolysis in cerebrovascular accident (CVA) [European Cooperative Acute Stroke Study (ECASS)].[3]
3. Neurointervention in CVA [Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN); Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial (EXTEND IA); randomized assessment of rapid endovascular treatment of ischemic stroke (ESCAPE); solitaire with the intention for thrombectomy as primary endovascular treatment (SWIFT PRIME); randomized trial of revascularization with solitaire fr device versus best medical therapy in the treatment of acute stroke due to anterior circulation large vessel occlusion presenting within eight hours of symptom onset (REVASCAT)].[4–8]
4. Surgical control of intracranial pressure (ICP) in CVA [decompressive surgery for the treatment of malignant infarction of the middle cerebral artery II (DESTINY II)].[9]
5. Prone position ventilation in acute respiratory distress syndrome [acute respiratory distress syndrome (ARDS)] (PROSEVA).[10]

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How to cite this article: Kapadia F, Bharadwaj S, Sharma R. Is "Less be More" Still a Valid Concept in Intensive Care? A Review of Critical Care Randomized Clinical Trials from the New England Journal of Medicine. Indian J Crit Care Med 2024;x(x):xx–xx.

Source of support: Nil

Conflict of interest: None

6. Neuromuscular-blockers in ARDS [neuromuscular blockers in early acute respiratory distress syndrome (ACURASYS)].[11]
7. Liberal transfusion after cardiac surgery [liberal or restrictive transfusion after cardiac surgery (TITRe2)].[12]
8. Limited approach in pancreatitis [a step-up approach or open necrosectomy for necrotizing pancreatitis (PANTER)].[13]

Following are the seven therapies that worsened outcomes:[1]

1. Hydroxy ethyl starch solutions for fluid resuscitation [6S; hydroxyethyl starch or saline for fluid resuscitation in intensive care (CHEST)].[14,15]
2. Fluid bolus in pediatric nonhypotensive sepsis [mortality after fluid bolus in African children with severe infection (FEAST)].[16]
3. High-frequency oscillatory ventilation in ARDS [high-frequency oscillation for acute respiratory distress syndrome (OSCAR); high-frequency oscillation in early acute respiratory distress syndrome (OSCILLATE)].[17,18]
4. Glutamine supplementation [a randomized trial of glutamine and antioxidants in critically ill patients (REDOXs)].[19]
5. Early total parenteral nutrition [early parenteral nutrition completing enteral nutrition in adult critically Ill patients (EPaNIC)].[20]
6. Surgical ICP control in traumatic brain injury [decompressive craniectomy in patients with severe traumatic brain injury and diffuse lesions in CT scan (DECRA)].[21]
7. Hypothermia in traumatic brain injury [hypothermia for intracranial hypertension after traumatic brain injury (EUROTHERM)].[22]

Analysis of NEJM RCTs from 2016 to 2023.

Methods

Study Design and Allocation

We are now extending the analysis from 5 October 2016 to 31 December 2023. All the RCTs reported in the critical care section of the NEJM website were included in this analysis (https://www.nejm.org/medical-research/critical-care). They were analyzed as per the primary outcome and also by mortality. The relevant articles are shown in Table 1.

Statistical Analysis

A Chi-square test was employed to assess the association between intervention and control groups regarding mortality outcomes. Specifically, mortality rates in the intervention and control arms were compared to determine if there were statistically significant differences between the groups. The chi-square analysis in this study was conducted using Microsoft Excel and its data analysis, ToolPak. Additionally, the results were validated using easymedstat.com.

Results

The total reported mortality in the intervention group was 12,700/55,977 (22.69%) and was 13,080/56,557 (23.13%) in the control group, $p = 0.079$. The relative risk reduction (RRR) of death in the intervention group was 0.981, 95% CI: 0.960–1.002. The absolute mortality risk reduction (ARR) was 0.44%.

Two RCTs showed an adverse mortality outcome (details in Table 1).

1. Vitamin C in severe sepsis. In this trial, the mortality was significantly higher at 28 days but the difference was not statistically different at 90 days [intravenous vitamin C in adults with sepsis in the intensive care unit (LOVIT)].[23]
2. Conservative oxygenation in ARDS. In this trial, the primary outcome was mortality at day 28, which was similar in both groups. At day 90, the mortality was significantly higher in the conservative oxygenation group [liberal or conservative oxygen therapy for acute respiratory distress syndrome (LOCO2)].[24]

Five of the following showed a mortality benefit (the details are provided in Table 1):

1. Hydrocortisone in severe community-acquired pneumonia (CAPECOD).[25]
2. Dexamethasone in oxygen-dependent COVID-19 pneumonia [dexamethasone in hospitalized patients with COVID-19 (RECOVERY)].[26]
3. Hydrocortisone and fludrocortisone for sepsis [hydrocortisone plus fludrocortisone for adults with septic shock (APROCCHSS)].[27]
4. Convalescent plasma in COVID-19 ARDS. In this trial, the mortality was significantly lower on day 28, but the difference was not statistically different on day 365.[28]
5. Haloperidol in delirium in intensive care unit (ICU) patients. In this trial, mortality was one component of the composite primary outcome; the number of days alive and out of hospital at 90 days. The primary outcome was similar in both groups haloperidol for the treatment of delirium in ICU patients (AID-ICU).[29]

A total of 13 trials showed beneficial outcomes for the primary endpoint (details are provided in Table 1).

1. Platelet transfusion of central venous pressure (CVP) placement [platelet transfusion before CVC placement in patients with thrombocytopenia (PACER)].[30]
2. Hydrocortisone in severe CAP (CAPECOD).[25]
3. Dexamethasone in COVID-19 (RECOVERY).[26]
4. Tocilizumab in COVID-19 [tocilizumab in patients hospitalized with Covid-19 pneumonia (EMPACTA)].[31]
5. High-flow nasal oxygen (HFNO) for tracheal decannulation [high-flow oxygen with capping or suctioning for tracheostomy decannulation (REDECAP)].[32]
6. Prevention of ventilator-associated pneumonia (VAP) after cardiopulmonary resuscitation (CPR) [prevention of early ventilator-associated pneumonia after cardiac arrest (ANTHARTIC)].[33]
7. Bag mask ventilation for endotracheal tube (ETT) (PreVent).[34]
8. Balanced crystalloids [saline against lactated ringer's or plasma-lyte in the emergency department (SALT-ED)].[35]
9. Hydrocort and fludrocortisone for sepsis (APROCCHSS).[27]
10. Angiotensin II for shock [angiotensin II for the treatment of high-output shock ATHOS-3)].[36]
11. Convalescent plasma in COVID-19 ARDS.[28]
12. Inhaled Amikacin for VAP [amikacin inhalation in mechanically ventilated patients with gram-negative pneumonia (AMIKINHAL)].[37]
13. Video laryngoscopy for ETT intubation [direct versus video laryngoscope (DEVICE)].[38]

When we compare the main similarities and differences between 2008 and 2016 and 2016–2023, we note the following:

- Similarities: Through both the periods, 2008–2016 and 2016–2023, 23 (majority) of the trials (~75%) were neutral, showing no benefit or adverse effect.

Table 1: Randomized controlled trials published in the New England Journal of Medicine 5th Oct 2016 to 31st December 2023

No.	*Group*	*Trial name, Reference (NEJM, DOI)*		*PICO/intervention*	*Define primary outcome*	*Primary outcome*	*Longest available time frame for mortality*	*Mortality in intervention group*	*Mortality in control group*	*p-value*
1	Cardiac arrest S/P	BOX trial (March 2017 to through December 2021)	N Eng J Med 2023;388:888–897. DOI: 10.1056/NEJMOA2212528	Duration of device-based fever prevention, targeting 36°C for 24 hours followed by targeting of 37°C for either 12 or 48 hours (for total intervention times of 36 and 72 hours, respectively) or until the patient regained consciousness after out-of-hospital cardiac arrest	Composite of death from any cause or discharge from the hospital with a cerebral performance category (CPC) of 3 or 4 (indicating severe disability or coma or vegetative state) within 90 days after randomization	Similar	Death from any cause within 90 days	116/393	120/396	NS
2		BOX trial (A)	N Engl J Med 2022;387:1456–1466. DOI: 10.1056/NEJMOA2208687	Blood pressure targets in comatose survivors of cardiac arrest; map target of 63 mm Hg as compared with 77 mm Hg in control	A composite of death from any cause or hospital discharge with a CPC of 3 or 4 within 90 days	Similar	Death from any cause within 90 days	122/393	114/396	NS
			N Engl J Med 2022;387:1467–1476. DOI: 10.1056/NEJMOA2208686	Oxygen targets in comatose survivors of cardiac arrest; restrictive oxygen target of a partial pressure of arterial oxygen (PaO_2) of 9–10 kPa (68–75 mm Hg)	A composite of death from any cause or hospital discharge with severe disability or coma [(CPC) of 3 or 4; categories range from 1 to 5, with higher values indicating more severe disability], whichever occurred first within 90 days after randomization	Similar	Death from any cause within 90 days	113/394	123/395	NS
3		TELSTAR	N Engl J Med 2022;386:724–734. DOI: 10.1056/NEJMOA2115998	Treating rhythmic and periodic electroencephalogram (EEG) patterns in comatose survivors of cardiac arrest; the stepwise strategy of antiseizure medications to suppress this activity for at least 48 consecutive hours plus standard care (antiseizure-treatment group) or to standard care alone (control group); standard care included targeted temperature management in both groups	Neurologic outcome according to the score on the CPC scale at 3 months, dichotomized as a good outcome (CPC score indicating no, mild, or moderate disability) or a poor outcome (CPC score indicating severe disability, coma, or death)	Similar	Death at 3 months	70/88	69/84	NS

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Table 1: *(Contd...)*

No.	*Group*	*Trial name, Reference (NEJM, DOI)*		*PICO/intervention*	*Define primary outcome*	*Primary outcome*	*Longest available time frame for mortality*	*Mortality in intervention group*	*Mortality in control group*	*p-value*
4		TTM2 trial	N Eng J Med 2021; 384:2283–2294. DOI: 10.1056/ NEJMOA2100591	Hypothermia vs normothermia after out-of-hospital cardiac arrest; targeted hypothermia at 33°C, followed by controlled rewarming	Death from any cause at 6 months	Similar	Death from any cause at 6 months	465/925	446/925	NS
5		ANTHARTIC study (B)	N Engl J Med 2019; 381:1831–1842. DOI: 10.1056/ NEJMOA1812379	Prevention of early ventilator-associated pneumonia after cardiac arrest; either intravenous (IV) amox-clav (at doses of 1 gm and 200 mg, respectively) 3 times a day for 2 days, starting less than 6 hours after the cardiac arrest	Early ventilator-associated pneumonia (during the first 7 days of hospitalization)	Beneficial	Death by day 28	41/99	35/95	NS
6		HYPERION	N Engl J Med 2019;381:2327–2337. DOI: 10.1056/ NEJMOA1906661	Targeted temperature management for cardiac arrest with nonshockable rhythm; therapeutic hypothermia (33°C during the first 24 hours) with targeted normothermia (37°C)	A favorable neurologic outcome, assessed on day 90 after randomization with the use of the CPC (score, 1–2)	Beneficial	Death by day 90	231/284	247/297	NS
7		TAME	N Engl J Med 2023;389:45–57. DOI: 10.1056/ NEJMOA2214552	Mild hypercapnia or normocapnia after out-of-hospital cardiac arrest; 24 hours of mild hypercapnia $PaCo_2$ 50 to 55 mm Hg	A favorable neurologic outcome, defined as a score of 5 (indicating lower moderate disability) or higher, as assessed with the use of the Glasgow outcome scale (GOS)–extended [range, 1 (death) to 8, with higher scores indicating better neurologic outcome] at 6 months	Similar	Death at 6 months	393/816	382/832	NS

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Table 1: *(Contd...)*

No.	*Group*	*Trial name, Reference (NEJM, DOI)*		*PICO/intervention*	*Define primary outcome*	*Primary outcome*	*Longest available time frame for mortality*	*Mortality in intervention group*	*Mortality in control group*	*p-value*
8	Cardiac surgery S/P	CHEETAH trial	N Engl J Med 2017; 376:2021–2031. DOI: 10.1056/ NEJMOA1616325	Levosimendan for hemodynamic support after cardiac surgery; levosimendan (in a continuous infusion at a dose of 0.025–0.2 μg/kg of body weight per minute)	30-day mortality	Similar	All-cause mortality by day 180	38/248	39/254	NS
9		LEVO-CTS trial	N Engl J Med 2017;376:2032–242. DOI: 10.1056/ NEJMOA1616218	Levosimendan in patients with left ventricular dysfunction undergoing cardiac surgery; IV levosimendan (at a dose of 0.2 μg/kg of body weight per minute for 1 hour, followed by a dose of 0.1 μg/kg/ minute for 23 hours) or placebo	This trial had two composite primary efficacy endpoints. The first was the four-component composite of death through day 30, renal-replacement therapy through day 30, perioperative myocardial infarction through day 5, or use of a mechanical cardiac assist device through day 5. The second was the two-component composite of death through day 30 or use of a mechanical cardiac assist device through day 5	Similar	Death by day 90	20/428	30/421	NS
10	COVID-19	ACTIV 4A trial	N Engl J Med 2021; 385:777–789. DOI: 10.1056/ NEJMOA2103417	Therapeutic anticoagulation with heparin in critically ill patients with COVID-19; either therapeutic-dose anticoagulation with heparin or pharmacologic thromboprophylaxis in accordance with local usual care	Organ support–free days, evaluated on an ordinal scale that combined in-hospital death (assigned a value of –1) and the number of days free of cardiovascular or respiratory organ support up to day 21 among patients who survived to hospital discharge	Similar	Death in hospital	199/534	200/564	NS

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Table 1: *(Contd...)*

No.	*Group*	*Trial name, Reference (NEJM, DOI)*	*PICO/intervention*	*Define primary outcome*	*Primary outcome*	*Longest available time frame for mortality*	*Mortality in intervention group*	*Mortality in control group*	*p-value*
11		RECOVERY trial N Engl J Med 2021; 384:693–704. DOI: 10.1056/ NEJMOA2021436	Dexamethasone in hospitalized patients with COVID-19; dexa in COVID-19 6 mg	28-day mortality	Beneficial	28-day mortality	482/2104	1110/4321	0.015434 481
12		EMPACTA trial N Engl J Med 2021; 384:20–30. DOI: 10.1056/ NEJMOA2030340	Tocilizumab in patients hospitalized with COVID-19 pneumonia; COVID-19 patients, not mechanical ventilation (MV), one or two doses of tocilizumab	Mechanical ventilation or death by day 28	Beneficial	Deaths by day 28	26/249	11/128	NS
13		N Engl J Med 2023;389:1590–1600. DOI: 10.1056/ NEJMOA2209502	Convalescent plasma for COVID-19-induced ARDS in mechanically ventilated patients; convalescent plasma with a neutralizing antibody titer of at least 1:320	Death by day 28	Beneficial	Death by day 365	107/233	123/234	NS
14		REMAP-CAP N Engl J Med 2023;389:2341–2354. DOI: 10.1056/ NEJMOA2309995	Simvastatin in critically ill patients with COVID-19; simvastatin (80 mg daily) as compared with no statin (control)	Respiratory and cardiovascular organ support–free days, assessed on an ordinal scale combining in-hospital death (assigned a value of −1) and days free of organ support through day 21 in survivors	Similar	Death by day 90	504/1835	257/837	NS
15	General	PACER N Engl J Med 2023; 388:1956–1965. DOI: 10.1056/ NEJMOA2214322	Platelet transfusion before CVC placement in patients with thrombocytopenia (platelet count, 10,000–50,000 per cubic millimeter)	The occurrence of catheter-related bleeding of grade II–IV within 24 hours after CVC placement	Beneficial	Hospital mortality	50/177	57/180	NS
16		AID-ICU trial N Engl J Med 2022;387:2425–2435. DOI: 10.1056/ NEJMOA2211868	Haloperidol IV haloperidol (2.5 mg 3 times daily plus 2.5 mg as needed up to a total maximum daily dose of 20 mg) for the treatment of delirium in ICU patients	The number of days alive and out of the hospital within 90 days after randomization	Similar	Death from any cause within 90 days	182/501	210/485	0.025333 538

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Table 1: *(Contd...)*

No.	*Group*	*Trial name, Reference (NEJM, DOI)*	*PICO/intervention*	*Define primary outcome*	*Primary outcome*	*Longest available time frame for mortality*	*Mortality in intervention group*	*Mortality in control group*	*p-value*
17		NA N Engl J Med 2019;381:328–337. DOI: 10.1056/NEJMOA1806515	A multicenter trial of vena cava filters in severely injured patients; severely injured patients with contraindication to anticoagulation (injury severity score >15) to have a vena cava filter placed within the first 72 hours after admission for the injury	Composite of symptomatic pulmonary embolism or death from any cause at 90 days after enrollment	Similar	Death from any cause within 90 days	16/122	11/118	NS
18		SUP-ICU trial N Engl J Med 2018; 379:2199–2208. DOI: 10.1056/NEJMOA1714919	Pantoprazole in patients at risk for gastrointestinal bleeding in the ICU; receive 40 mg of IV pantoprazole	Death by 90 days after randomization	Similar	Death by 90 days after randomization	510/1642	499/1640	NS
19		PARTNER N Engl J Med 2018;378:2365–2375. DOI: 10.1056/NEJMOA1802637	A randomized trial of a family-support intervention in intensive care units; patients with a high risk of death and their surrogates in five ICUs to compare a multicomponent family-support intervention delivered by the interprofessional ICU team with usual care	surrogates' mean score on the hospital anxiety and depression scale (HADs) at 6 months	Similar	Death from any cause at 6 months	339/547	472/873	0.003387914
20		TRANSFUSE N Engl J Med 2017;377:1858–1867. DOI: 10.1056/NEJMOA1707572	Age of red cells for transfusion and outcomes in critically ill adults; freshest, compatible, allogeneic red-cell units available from the transfusion service	90-day all-cause mortality	Similar	Death by day 180	687/2410	678/2414	NS

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Table 1: *(Contd...)*

No.	*Group*	*Trial name, Reference (NEJM, DOI)*	*PICO/intervention*	*Define primary outcome*	*Primary outcome*	*Longest available time frame for mortality*	*Mortality in intervention group*	*Mortality in control group*	*p-value*
21		TGC-FAST N Engl J Med 2023;389:1180–1190. DOI: 10.1056/NEJMOA2304855	Tight blood–glucose control without early parenteral nutrition in the ICU; liberal glucose control [insulin initiated only when the blood glucose level was >215 mg per deciliter (>11.9 mmoL per liter)] or to tight glucose control (blood-glucose level targeted with the use of the logic-insulin algorithm at 80–110 mg/dL	The length of time that ICU care was needed, calculated based on time to discharge alive from the ICU, with death accounted for as a competing risk	Similar	Death by day 90	468/4621	486/4607	NS
22		PATCH N Engl J Med 2023;389:127–136. DOI: 10.1056/NEJMOA2215457	Prehospital tranexamic acid for severe trauma; tranexamic acid (administered IV as a bolus dose of 1 gm before hospital admission, followed by a 1 gm infusion over 8 hours after arrival at the hospital) or placebo	Survival with a favorable functional outcome at 6 months after injury, as assessed with the use of the GOC–extended (GOS-e). Levels on the GOS-e range from 1 (death) to 8 ["upper good recovery" (no injury-related problems)]. We defined survival with a favorable functional outcome as a GOS-e level of 5 ("lower moderate disability") or higher	Similar	Death by 6 months	123/648	144/629	NS
23	Infection	CAPE-COD trial N Engl J Med 2023; 388:1931–1941. DOI: 10.1056/NEJMOA2215145	Hydrocortisone (200 mg × 4 or 8 days followed by tapering) in severe community-acquired pneumonia	Death from any cause by day 28	Beneficial	Death by day 90	36/388	57/389	0.02101615
24		PROACT (B) N Engl J Med 2018;379:236–249. DOI: 10.1056/NEJMOA1802670	Procalcitonin-guided use of antibiotics for lower respiratory tract infection; the procalcitonin group, real-time and serial levels, to have an antibiotic use guideline with graded recommendations based on four tiers of procalcitonin levels	Total antibiotic exposure, defined as the total number of antibiotic days within 30 days after enrollment	Similar	Death by day 30	16/826	10/830	NS

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Table 1: *(Contd...)*

No.	*Group*	*Trial name, Reference (NEJM, DOI)*	*PICO/intervention*	*Define primary outcome*	*Primary outcome*	*Longest available time frame for mortality*	*Mortality in intervention group*	*Mortality in control group*	*p-value*
25		HEAT trial N Engl J Med 2015;373:2215–2224. DOI: 10.1056/NEJMOA1508375	Acetaminophen for fever in critically ill patients with suspected infection; receive either 1 gm of IV acetaminophen or placebo every 6 hours until ICU discharge, resolution of fever, cessation of antimicrobial therapy, or death	ICU-free days (days alive and free from the need for intensive care) from randomization to day 28	Similar	Death by day 90	55/346	57/344	NS
26	MV	TIP-EX trial N Engl J Med 2022;387:1843–1854. DOI: 10.1056/NEJMOA2209041	Patients who had a high risk of extubation failure to undergo spontaneous-breathing trials with pressure-support ventilation or a T-piece	The total time alive and without exposure to invasive MV (reported as the number of ventilator-free days) from the initial spontaneous-breathing trial (day 1) through day 28	Similar	Death from any cause within 90 days	80/484	91/485	NS
27		TEAM trial N Engl J Med 2022; 387:1747–1758. DOI: 10.1056/NEJMOA2209083	Early active mobilization (sedation minimization and daily physiotherapy) or usual care (the level of mobilization that was normally provided in each ICU) during MV in the ICU	The number of days that the patients were alive and out of the hospital at 180 days after randomization	Similar	Death at day 180	83/369	71/364	NS
28		PILOT trial N Engl J Med 2022; 387:1759–1769. DOI: 10.1056/NEJMOA2208415	Oxygen-saturation targets, that is, lower target for oxygen saturation as measured by pulse oximetry (SpO_2) (90%; goal range, 88–92%), an intermediate target (94%; goal range, 92–96%), or a higher target (98%; goal range, 96–100%) for critically ill adults receiving MV	The number of days alive and free of MV (ventilator-free days) through day 28	Similar	In-hospital death before 28 days	281/808 low saturation group 292/859 intermediate saturation group	290/874	NS

(Contd...)

Table 1: *(Contd...)*

No.	*Group*	*Trial name, Reference (NEJM, DOI)*	*PICO/intervention*	*Define primary outcome*	*Primary outcome*	*Longest available time frame for mortality*	*Mortality in intervention group*	*Mortality in control group*	*p-value*
29		MENDS2 trial N Engl J Med 2021;384:1424–1436. DOI: 10.1056/NEJMOA2024922	Dexmedetomidine or propofol for sedation in mechanically ventilated adults with sepsis; mechanically ventilated adults with sepsis to receive dexmedetomidine (0.2–1.5 µg/kg of body weight per hour) or propofol (5–50 µg/kg/minute), with doses adjusted by bedside nurses to achieve target sedation goals set by clinicians according to the Richmond agitation–sedation scale [RASS, on which scores range from −5 (unresponsive) to +4 (combative)]	Days alive without delirium or coma during the 14-day intervention period	Similar	Death by day 90	81/214	82/208	NS
30		REDECAP trial N Engl J Med 2020; 383:1009–1017. DOI: 10.1056/NEJMOA2010834	High-flow oxygen with capping or suctioning for tracheostomy decannulation; undergo a 24-hour capping trial plus intermittent high-flow oxygen therapy (control group) or receive continuous high-flow oxygen therapy with frequency of suctioning being the indicator of readiness for decannulation (intervention group)	The time to decannulation	Beneficial	Death in the hospital	4/169	8/161	NS
31		NONSEDA trial N Engl J Med 2020;382:1103–1111. DOI: 10.1056/NEJMOA1906759	Nonsedation or light sedation in critically ill, mechanically ventilated patients; mechanically ventilated ICU patients to a plan of no sedation (nonsedation group) or to a plan of light sedation [i.e., to a level at which the patient was arousable, defined as a score of −2 to −3 on the RASS, on which scores range from −5 (unresponsive) to +4 (combative)] (sedation group) with daily interruption	Mortality at 90 days	Similar	Mortality at 90 days	148/349	130/351	NS

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Table 1: *(Contd...)*

No.	*Group*	*Trial name, Reference (NEJM, DOI)*		*PICO/intervention*	*Define primary outcome*	*Primary outcome*	*Longest available time frame for mortality*	*Mortality in intervention group*	*Mortality in control group*	*p-value*
32		ICU-ROX trial	N Engl J Med 2020; 382:989–998. DOI: 10.1056/ NEJMOA1903297	Conservative oxygen therapy during MV in the ICU; conservative [SpO_2, 97; lower of fraction of inspired oxygen (FiO_2) below 21 if SAT okay]	Number of ventilator-free days from randomization until day 28	Similar	Death by day 180	170/476	164/475	NS
33		SPICE III	N Engl J Med 2019; 380:2506–2517. DOI: 10.1056/ NEJMOA1904710	Early sedation with dexmedetomidine in critically ill patients; critically ill adults who had been undergoing ventilation for less than 12 hours in the ICU and were expected to continue to receive ventilatory support for longer than the next calendar day to receive dexmedetomidine as the sole or primary sedative	The rate of death from any cause at 90 days	Similar	Death by day 180	609/1935	610/1946	NS
34		PREVENT trial	N Engl J Med 2019; 380:811–821. DOI: 10.1056/ NEJMOA1812405	Bag-mask ventilation during tracheal intubation of critically ill adults	The lowest oxygen saturation was observed during the interval between induction and 2 minutes after tracheal intubation	Beneficial	Death before hospital discharge	71/199	72/202	NS
35		DEVICE	N Engl J Med 2023;389:418–429. DOI: 10.1056/ NEJMOA2301601	Video vs direct laryngoscopy for tracheal intubation of critically ill adults	Successful intubation on the first attempt	Similar	Death within 28 days after randomization	184/705	191/712	NS
36	Nutrition	RE-ENERGIZE	N Engl J Med 2022;387:1001–1010. DOI: 10.1056/ NEJMOA2203364	A randomized trial of enteral glutamine for treatment of burn injuries; second or third-degree burns patients within 72 hours after hospital admission to receive 0.5 gm/kg of body weight per day of enterally delivered glutamine	The time to discharge alive from the hospital, with data censored at 90 days	Similar	Death in the hospital	91/596	84/604	NS

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Table 1: *(Contd...)*

No.	*Group*	*Trial name, Reference (NEJM, DOI)*		*PICO/intervention*	*Define primary outcome*	*Primary outcome*	*Longest available time frame for mortality*	*Mortality in intervention group*	*Mortality in control group*	*p-value*
37		TARGET trial	N Engl J Med 2018;379:1823–1834. DOI: 10.1056/NEJMOA1811687	Energy-dense vs routine enteral nutrition in the critically ill; to evaluate energy-dense (1.5 kcal/mL) as compared with routine (1.0 kcal/mL) enteral nutrition	All-cause mortality within 90 days	Similar	All-cause mortality within 90 days	523/1948	505/1966	NS
38	Pulmonary	HOT-ICU trial	N Engl J Med 2021;384:1301–1311. DOI: 10.1056/NEJMOA2032510	Lower or higher oxygenation targets for acute hypoxemic respiratory failure; receive oxygen therapy targeting a PaO_2 of 60 mm Hg for 90 days	Death within 90 days	Similar	Death within 90 days	618/1441	613/1447	NS
39		LOCO2 trial	N Engl J Med 2020;382:999–1008. DOI: 10.1056/NEJMOA1916431	Liberal or conservative oxygen therapy for ARDS; conservative oxygen therapy (target PaO_2, 55–70 mm Hg; SpO_2, 88–92%)	Death from any cause at 28 days	Similar	Death by day 90	44/99	31/102	0.039453154
40		PETAL/ROSE trial	N Engl J Med 2019;380:1997–2008. DOI: 10.1056/NEJMOA1901686	Early neuromuscular blockade (a continuous infusion of cisatracurium) in the ARDS	In-hospital death from any cause at 90 days	Similar	In-hospital death from any cause at 90 days	213/501	216/505	NS
41		EOLIA	N Engl J Med 2018;378:1965–1975. DOI: 10.1056/NEJMOA1800385	Extracorporeal membrane oxygenation (ECMO) for severe ARDS; patients with very severe ARDS as indicated by one of three criteria—ratio of PaO_2 to the FiO_2 of less than 50 mm Hg for more than 3 hours; a PaO_2:FiO_2 of less than 80 mm Hg for more than 6 hours; or an arterial blood pH of less than 7.25 with a partial pressure of arterial carbon dioxide of at least 60 mm Hg for more than 6 hours—to receive immediate venovenous ECMO (ECMO group) or continued conventional treatment (control group)	Mortality at 60 days	Similar	Mortality at 90 days	46/124	59/125	NS

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Table 1: *(Contd...)*

No.	*Group*	*Trial name, Reference (NEJM, DOI)*		*PICO/intervention*	*Define primary outcome*	*Primary outcome*	*Longest available time frame for mortality*	*Mortality in intervention group*	*Mortality in control group*	*p-value*
42		AMIKINHAL	N Engl J Med 2023; 389:2052–2062. DOI: 10.1056/ NEJMOA2310307	Inhaled amikacin to prevent ventilator-associated pneumonia; invasive MV for at least 72 hours to receive inhaled amikacin at a dose of 20 mg per kilogram of ideal body weight once daily or to receive placebo for 3 days	First episode of ventilator-associated pneumonia during 28 days of follow-up	Similar	Death before hospital discharge	123/417	136/430	NS
43			N Engl J Med 2020;382:405–415. DOI: 10.1056/ NEJMOA1910775	Conservative vs interventional treatment for spontaneous pneumothorax; immediate intervention-al management of the pneumothorax (intervention group) or a conservative observational approach (conservative-management group) and were followed for 12 months	Lung re-expansion within 8 weeks	Non-inferior				
44	Renal fluid, renal-re-placement therapy (RRT)	PLUS trial	N Engl J Med 2022;386:815–826. DOI: 10.1056/ NEJMOA2114464	Balanced multielectrolyte solution vs saline in critically ill adults; (plasma-Lyte 148) for 90 days	Death from any cause within 90 days after randomization	Similar	Death from any cause within 90 days after randomization while in the hospital	530/2433	530/2413	NS
45		SALT-ED	N Engl J Med 2018; 378:819–828. DOI: 10.1056/ NEJMOA1711586	Balanced crystalloids vs saline in noncritically ill adults; balanced crystalloids (lactated Ringer's solution or plasma-Lyte A) for resuscitation in ER	Hospital-free days (days alive after discharge before day 28)	Similar	In-hospital death from any cause	95/6708	105/6639	NS

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Table 1: *(Contd...)*

No.	*Group*	*Trial name, Reference (NEJM, DOI)*		*PICO/intervention*	*Define primary outcome*	*Primary outcome*	*Longest available time frame for mortality*	*Mortality in intervention group*	*Mortality in control group*	*p-value*
46		SMART trial	N Engl J Med 2018;378:829–839. DOI: 10.1056/NEJMOA1711584	Balanced crystalloids (lactated Ringer's solution or plasma-Lyte F) vs saline in critically ill adults	Major adverse kidney event within 30 days—a composite of death from any cause, new renal-replacement therapy, or persistent renal dysfunction (defined as an elevation of the creatinine level to ≥200% of baseline)—all censored at hospital discharge or 30 days, whichever occurred first	Beneficial	Death before 60 days	928/7,942	975/7,860	NS
47		IDEAL ICU trial	N Engl J Med 2018; 379:1431–1442. DOI: 10.1056/NEJMOA1803213	Timing of renal-replacement therapy in patients with acute kidney injury (AKI) and sepsis; AKI as per rifle but without life-threatening complications related to AKI to receive renal-replacement therapy either within 12 hours after documentation of failure-stage AKI	Death at 90 days	Similar	Death by day 180	143/236	134/235	NS
48	Shock–cardiogenic	CAPITAL	N Engl J Med 2021;385:516–525. DOI: 10.1056/NEJMOA2026845	Milrinone as compared with dobutamine in the treatment of cardiogenic shock	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 RRT	Similar	In-hospital death from any cause	35/96	41/96	NS
49		ECLS-SHOCK	N Engl J Med 2023;389:1286–197. DOI: 10.1056/NEJMOA2307227	Extracorporeal life support in infarct-related cardiogenic shock; receive early ECLS plus usual medical treatment (ECLS group) or usual medical treatment alone (control group)	Death of any cause in 30 days	Similar	Death of any cause in 30 days	100/209	102/208	NS

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Table 1: *(Contd...)*

No.	*Group*	*Trial name, Reference (NEJM, DOI)*		*PICO/intervention*	*Define primary outcome*	*Primary outcome*	*Longest available time frame for mortality*	*Mortality in intervention group*	*Mortality in control group*	*p-value*
50	Shock–sepsis	CLOVERS trial/ death of any cause at any location	N Engl J Med 2023; 388:499–510. DOI: 10.1056/ NEJMOA2212663	Early restrictive or liberal fluid management for sepsis-induced hypotension; less IV fluid was administered in the restrictive fluid group than in the liberal fluid group, whereas the restrictive fluid group had earlier, more prevalent, and longer duration of vasopressor use	Death from any cause before discharge home by day 90	Similar	Death from any cause at any location by day 90	172/768	169/773	NS
51		CLASSIC trial	N Engl J Med 2022; 386:2459–2470. DOI: 10.1056/ NEJMOA2202707	Restriction of IV fluid in ICU patients with septic shock (i.e., after 1 L of IV fluid for the day, restricted IV fluid therapy); patients were included if the onset of shock had been within 12 hours before the screening	Death of any cause within 90 days after randomization	Similar	Death by day 90	323/764	329/781	NS
52		LOVIT trial (D)	N Engl J Med 2022; 386:2387–2398. DOI: 10.1056/ NEJMOA2200644	Intravenous vitamin C in adults with sepsis in the intensive care unit; an infusion of either vitamin C (at a dose of 50 mg/kg of body weight)	A composite of death or persistent organ dysfunction (defined by the use of vasopressors, invasive MV, or new renal-replacement therapy) on day 28	Worse	Mortality at 90 days	191/417	185/426	NS
53		ADRENAL trial	N Engl J Med 2018; 378:797–808. DOI: 10.1056/ NEJMOA1705835	Adjunctive glucocorticoid therapy in patients with septic shock.; patients with septic shock who were undergoing MV to receive hydrocortisone (at a dose of 200 mg per day) or placebo for 7 days or until death or discharge	Death from any cause at 90 days	Similar	Death from any cause at 90 days	511/1,832	526/1826	NS

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Table 1: *(Contd...)*

No.	*Group*	*Trial name, Reference (NEJM, DOI)*		*PICO/intervention*	*Define primary outcome*	*Primary outcome*	*Longest available time frame for mortality*	*Mortality in intervention group*	*Mortality in control group*	*p-value*
54		ATHOS-3	N Engl J Med 2017; 377:419–430. DOI: 10.1056/ NEJMOA1704154	Angiotensin II for the treatment of vasodilatory shock.pdf	A response with respect to mean arterial pressure at hour 3 after the start of infusion, with response defined as an increase from baseline of at least 10 mm Hg or an increase to at least 75 mm Hg, without an increase in the dose of background vasopressors	Beneficial	All-cause mortality by day 28	75/163	85/158	NS
55		LEOPARDS trial	N Engl J Med 2016;375:1638–1648. DOI: 10.1056/ NEJMOA1609409	Levosimendan for the prevention of acute organ dysfunction in sepsis; a blinded infusion of levosimendan (at a dose of 0.05–0.2 µg/kg of body weight per minute) for 24 hours	The mean daily sequential organ failure assessment (sofa) score in the intensive care unit up to day 28 (scores for each of five systems range from 0 to 4, with higher scores indicating more severe dysfunction; maximum score, 20)	Similar	Death before hospital discharge	97/258	84/256	NS
56		APROCCHSS	N Engl J Med 2018;378:809–818. DOI: 10.1056/ NEJMOA1705716	Hydrocortisone plus fludrocortisone for adults with septic shock	90-day all-cause mortality	Beneficial	Death at day 180	285/611	328/625	0.04022908

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Table 1: *(Contd...)*

No.	*Group*	*Trial name, Reference (NEJM, DOI)*		*PICO/intervention*	*Define primary outcome*	*Primary outcome*	*Longest available time frame for mortality*	*Mortality in intervention group*	*Mortality in control group*	*p-value*
57	Thrombo-embolism	PREVENT	N Engl J Med 2019; 380:1305–1315. DOI: 10.1056/ NEJMOA1816150	Adjunctive intermittent pneumatic compression for venous thromboprophylaxis. pdf	Incident (i.e., new) proximal lower-limb deep-vein thrombosis, as detected on 2 times weekly lower-limb ultrasonography after the third calendar day since randomization until ICU discharge, death, attainment of full mobility, or trial day 28, whichever occurred first	Similar	Death by day 90	258/990	270/1011	NS

All mortality taken from the longest reported time frame in that RCT

- Since both the trials are of the same group and composed of the same patients, only one of the papers has been considered in the calculation to avoid dual entry;
- Data taken from supplementary appendix;
- For calculation, we have included both the low saturation group and the intermediate saturation group, as the intervention arm.

ACTIV, therapeutic anticoagulation with heparin in critically ill patients with COVID-19; ADRENAL, adjunctive corticosteroid treatment in critically ill patients with septic shock; AID-ICU, haloperidol for the treatment of delirium in ICU patients; AMIKINHAL, amikacin inhalation in mechanically ventilated patients With Gram-negative pneumonia; ANTHARTIC, prevention of early Ventilator-associated pneumonia after cardiac arrest; APROCCHSS, hydrocortisone plus fludrocortisone for adults with septic shock; ARDS, acute respiratory distress syndrome; ATHOS-3, angiotensin II for the treatment of high-output shock; BOX, blood-pressure targets in comatose survivors of cardiac arrest; CAPITAL, milrinone as compared with dobutamine in the treatment of cardiogenic shock; CLASSIC, restriction of intravenous fluid in ICU patients with septic shock; CVC, central venous catheter; DEVICE, direct versus video laryngoscope; ECLS-SHOCK, extracorporeal life support for cardiogenic shock; ECMO, extracorporeal membrane oxygenation; EMPACTA, tocilizumab in patients hospitalized with Covid-19 pneumonia; EOLIA, extracorporeal membrane oxygenation for severe acute respiratory distress syndrome; HEAT, hypothermia for encephalopathy in low-income countries; HYPERION, therapeutic hypothermia after cardiac arrest in nonshockable rhythm; ICU-ROX, intensive care unit randomized trial comparing two approaches to oxygen therapy; IDEAL ICU, impact of diuretic intervention on respiratory function and diuretic resistance in mechanically ventilated patients with hypoalbuminemia; LEOPARDS, levosimendan for the prevention of acute organ dysfunction in sepsis; LEVO-CTS Trial, levosimendan in patients with left ventricular systolic dysfunction undergoing cardiac surgery; LOCO2, liberal or conservative oxygen therapy for acute respiratory distress syndrome; LOVIT, intravenous vitamin c in adults with sepsis in the intensive care unit; MENDS2, dexmedetomidine or propofol for sedation in mechanically ventilated adults with sepsis; NA, not available; NONSEDA, nonsedation or light sedation in critically ill, mechanically ventilated patients; NS, not specified; PACER, platelet transfusion before CVC placement in patients with thrombocytopenia; PARTNER, transcatheter versus surgical aortic-valve replacement in high-risk patients; PATCH, platelet transfusion versus standard care after acute stroke due to spontaneous cerebral hemorrhage associated with antiplatelet therapy; PETAL/ROSE, early neuromuscular blockade in the acute respiratory distress syndrome; PICO, PICO stands for patient/population, intervention, comparison and outcomes; PILOT, oxygen-saturation targets for critically ill adults receiving mechanical ventilation; PLUS, balanced multielectrolyte solution versus saline in critically ill adults; PREVENT, prehospital tranexamic acid use for traumatic brain injury; PROACT, procalcitonin antibiotic consensus trial; RE-ENERGIZE, randomized trial of enteral glutamine to minimize the effects of burn injury; RECOVER, dexamethasone in hospitalized patients with Covid-19; REDECAP, high-flow oxygen with capping or suctioning for tracheostomy decannulation; REMAP-CAP, randomized, embedded, multifactorial adaptive platform trial for community-acquired pneumonia; SALT-ED, saline against lactated ringer's or plasma-Lyte in the emergency department; SMART, balanced crystalloids versus saline in critically ill adults; SPICE III, dexmedetomidine and propofol sedation in critically ill patients and dose-associated 90-day mortality: a secondary cohort analysis of a randomized controlled trial; TARGET, energy-dense versus routine enteral nutrition in the critically ill; TEAM, treatment of mechanically ventilated adults with early activity and mobilization; TELSTAR, treatment of electroencephalographic status epilepticus after cardiopulmonary resuscitation; TGC-FAST, tight blood-glucose control without early parenteral nutrition in the ICU; TIP-EX, spontaneous-breathing trials with pressure-support ventilation or a T-Piece; TRANSFUSE, transfusion requirements in septic shock; TTM2, hypothermia versus targeted normothermia after out-of-hospital cardiac arrest

- Differences: The overall mortality in the 2008–2016 cohort was 38.7–42% while it was much lower in the 2016–2023 cohort at 22.69–23.13.

Comparing the periods 2008–2016 and 2016–2023, the number of trials with adverse events was less [7/63 vs 1 (+1)/57] in the 2016–2023 analysis. The positive trials were a relatively small percentage (13/57, 22.8%) and the trials with a mortality benefit were an even smaller percentage (5/57, 8.6%).

Discussion

The table of RCTs in the NEJM from 2008 to 2016 and from 2016 to 2023 in this analysis gives a concise summary of the current state of evidence.[1] These can be used to guide our practices in critical care.

We can speculate and frame a few hypotheses based on our analysis of outcomes in critically ill patients from RCTs in the NEJM. The most encouraging aspect was the lack of harm demonstrated in the more recent RCTs. Two trials showed harm. Supraphysiological doses of vitamin C in sepsis resulted in higher 28-day mortality but similar 90-day mortality, while restrictive oxygen in ARDS had a similar 28-day mortality but a higher 90-day mortality.

The data from 2016 to 2023 show that the mortality of patients in the intervention arm of these RCTs was neither higher nor lower than those of patients in the control arm ($p = 0.0079$). In terms of nonmortality primary outcomes, patients in 9/57 of the RCTs benefitted by being in the intervention arm of the trial. Approximately three-quarter [44 (+1)/57, 78.9%] of the trials showed no effect of intervention. This partially justifies a restrictive approach to unproven therapies as the majority of the patients would not end up receiving ineffective and potentially costly therapy.

The last three decades have seen a paradigm shift in clinical research publications. Earlier, much of the literature focused on correcting abnormal physiologic parameters, with the presumption that doing so would improve outcomes. It is only in the last two to three decades that we have large multicenter clinical trials evaluating clinical outcomes. The clinical outcomes of interest in critical care are lower mortality, lower severity, and enhanced recovery. Severity is usually reflected by the length of illness and by the degree of organ failure and organ support needed. Enhanced recovery evaluates the functional recovery in the weeks and months after the patient is discharged from the ICU. Encouragingly, most of the critical care RCTs reported in the NEJM were not done by industry or pharma, but by academic centers and professional critical care societies. This ensured a relative lack of financial conflict of interest. As the number of these large RCTs increased, it became increasingly apparent that the majority of critical care interventions were not translating to improved mortality and/or other clinical outcomes.

Our earlier analysis showed that patients enrolled in the intervention arm of these RCTs (published in NEJM 2008–2016) had an overall higher mortality than those in the control or placebo arm. To explain this worse outcome, we speculated that, "During the stress of an illness, many parameters may fall outside the normal range, as part of a protective response. Reversing these protective responses by targeting normal values may be detrimental. Two billion years of eukaryotic evolution and 600 million years of large animal evolutionary selection have resulted in complex but poorly understood physiologic adaptations that are ruthlessly efficient in ensuring healing and survival. Our add-on therapies, based on 2–3 centuries of modern medicine, are often too simplistic and superficial to impact outcomes."

By extending our analysis from 2016 to 2023, we have revised some of our earlier conclusions. Unlike the earlier analysis, the mortality was similar in patient's intervention and control groups in this cohort of patients. This suggests that "less" is not necessarily "more," at least in the context of mortality. In terms of better clinical outcomes, a small minority of patients in clinical trials had better primary outcomes.

Conclusion

This analysis of critical care RCTs in the NEJM has shown three findings. One, approximately three-quarter of RCTs in critical care in the NEJM between 2008 and 2023 failed to show benefit or harm. Two, in the years 2008–2016, patients in the intervention cohort had higher mortality compared to controls, but in the years 2016–2023, the difference in overall mortality in patients in the intervention and control arms was not statistically significant. Three, compared to the years 2008–2016, in the years from 2016 to 2023, the number of RCTs showing harm decreased and those showing benefit increased.

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