What Is Safe Sedation in the ICU?

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For decades, the comfort and safety of patients who are undergoing mechanical ventilation in the intensive care unit (ICU) entailed deep sedation, the nearly ubiquitous administration of opiates, and the liberal use of neuromuscular blockade. Concomitant with rising demands on ICU resources and expenditures, clinical studies started evaluating whether sedation truly mitigated patients' acute discomfort and subsequent unpleasant recall of critical illness or prevented inadvertent extubation or catheter removal.

The development of reliable, psychometrically valid, ICU-based sedation scales[1,2] made it possible to establish that deeper sedation correlates with prolonged mechanical ventilation.[3] A seminal investigation determined that interrupting and lightening pharmacologic sedation reduced the time that patients spent on a ventilator, the frequency of complications, and costs.[3] Cooperative, awake patients could be mobilized within 48 hours after ICU admission, which increased the potential for the outcome that patients value most: returning home to independent living.[4] The risks of early deep sedation were further highlighted in studies in which deep sedation within 48 hours after ICU admission was associated with increased mortality.[5]

The 2018 guidelines of the Society of Critical Care Medicine regarding Pain Agitation/Sedation, Delirium, Immobility, and Sleep Disruption (PADIS) engaged patients who were discharged from the ICU as partners in each guideline section. Their compelling experiences illustrated the adverse effects that sedation can have on patients' communication and comfort and the distress of family members who are unable to connect with loved ones.[6] The PADIS recommendations that were based on these insights included the need for careful, consistent pain assessments, adequate analgesia, and the lightest possible sedation.

In this issue of the *Journal*, Shehabi et al.[7] describe the results of the SPICE (Sedation Practice in Intensive Care Evaluation) III trial, in which the investigators randomly assigned patients in the ICU to receive either early light sedation with dexmedetomidine, an alpha₂ adren-ergic receptor agonist, or usual care with propofol, midazolam, or both.[7] The primary outcome was the rate of death from any cause at 90 days after randomization.

The investigators expected that the pharmacologic properties of dexmedetomidine as a first-line agent would result in lighter sedation than would the usual-care drugs. A pilot study confirmed that enrolling patients and administering early protocol-driven sedation were feasible.[8] As anticipated, 66% of patients in the dexmedetomidine group of the pilot study achieved light sedation within 48 hours, as compared with 38% for standard sedation.

SPICE III was a test of a light sedation strategy in the real world. Among the 4000 trial patients, that reality translated into limited ability to deliver a protocol-defined level of light sedation within 24 hours after study inclusion (Fig. 2A and 2B in the article, available at NEJM.org) or during the first 2 full days after randomization. Clinicians chose deep sedation in more than half the patients. Nearly 75% of the patients in the dexmedetomidine group also received propofol, benzodiazepines, or both, albeit at lower doses than the patients assigned to receive usual care. The duration of sedative administration was similar in the two groups.

The trial's primary outcome of 90-day mortality presupposed that differences in pharmacologic management and adherence to the protocol directives of light sedation in the two groups would result in improved outcomes in the dexmedetomidine group. Unfortunately, the similarity in administered sedatives and the frequent use of deep sedation in the two groups make it challenging to interpret the primary finding that there was no between-group difference in the rate of death at 90 days or in other secondary outcomes.

Nevertheless, the SPICE III trial imparts two important messages. The first cautions researchers about the limitations of pilot studies. Although the pilot study showed timely recruitment and delivery of sedatives in six ICUs in the collaborative culture and common database of the Austra-

lian and New Zealand Intensive Care Society (a process that was duplicated worldwide at SPICE III trial sites), it did not predict clinician behavior in the trial. Pilot studies establish feasibility.[9] Examining the decisions that the physicians made in SPICE III, such as beliefs and behavioral patterns that produced the disruption in prescribed sedation levels and choice of pharmacologic sedative, may help investigators anticipate, and adapt to, such challenges in future trials. Once SPICE III began, opting out of the intended level of light sedation would not have breached the trial protocol because it was acceptable for physicians to choose deep sedation for clinical reasons.

The second caution is that no matter how many well-intentioned guidelines and well-conducted trials indicate the advantages of a change in clinical habits, beliefs drive practice and are slow to change. In this trial, many patients were deeply sedated even in the absence of paralytic agents. Whether this clinical decision was driven by belief or necessity is unclear. Established, well-promulgated guidelines do not change practice. An example of this loss in translation is shown in reports describing the administration of analgesics in the ICU, in which suboptimal pain assessment and insufficient analgesia are observed.[10]

The SPICE III trial should be viewed as a call to study clinical decision making as it pertains to depth of sedation and pharmacologic choices. Understanding these behaviors could enhance trial design and analysis and heighten insight into improving clinical practice. Deep sedation immobilizes patients, limits communication, increases costs and mortality, and reduces the likelihood of meaningful recovery. Understanding the differences in how sedation is administered and what drives these variations is essential in providing improved care. Other areas worthy of investigation include pharmacokinetic and pharmacogenomic guidance — based on age, as noted in SPICE III, but also on sex and other characteristics — on personalizing sedative choices for patients and on assessing the relationship between sedatives and restorative sleep.

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Early Sedation with Dexmedetomidine in Critically Ill Patients

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ABSTRACT

BACKGROUND

Dexmedetomidine produces sedation while maintaining a degree of arousability and may reduce the duration of mechanical ventilation and delirium among patients in the intensive care unit (ICU). The use of dexmedetomidine as the sole or primary sedative agent in patients undergoing mechanical ventilation has not been extensively studied.

METHODS

In an open-label, randomized trial, we enrolled 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 or to receive usual care (propofol, midazolam, or other sedatives). The target range of sedation-scores on the Richmond Agitation and Sedation Scale (which is scored from −5 [unresponsive] to +4 [combative]) was −2 to +1 (lightly sedated to restless). The primary outcome was the rate of death from any cause at 90 days.

RESULTS

We enrolled 4000 patients at a median interval of 4.6 hours between eligibility and randomization. In a modified intention-to-treat analysis involving 3904 patients, the primary outcome event occurred in 566 of 1948 (29.1%) in the dexmedetomidine group and in 569 of 1956 (29.1%) in the usual-care group (adjusted risk difference, 0.0 percentage points; 95% confidence interval, −2.9 to 2.8). An ancillary finding was that to achieve the prescribed level of sedation, patients in the dexmedetomidine group received supplemental propofol (64% of patients), midazolam (3%), or both (7%) during the first 2 days after randomization; in the usual-care group, these drugs were administered as primary sedatives in 60%, 12%, and 20% of the patients, respectively. Bradycardia and hypotension were more common in the dexmedetomidine group.

CONCLUSIONS

Among patients undergoing mechanical ventilation in the ICU, those who received early dexmedetomidine for sedation had a rate of death at 90 days similar to that in the usual-care group and required supplemental sedatives to achieve the prescribed level of sedation. More adverse events were reported in the dexmedetomidine group than in the usual-care group. (Funded by the National Health and Medical Research Council of Australia and others; SPICE III ClinicalTrials.gov number, NCT01728558.)

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SEDATION IS A COMPONENT OF THE CARE of critically ill patients who are undergoing mechanical ventilation,[1,2] but the appropriate choice of a primary sedative agent remains uncertain. Propofol and midazolam, which act mainly through pathways mediated by γ-aminobutyric acid, are widely used for this purpose.[3-7] Dexmedetomidine, a high-affinity adrenergic agonist of the alpha$_2$ receptor, is a potential alternative sedative.[8,9]

Dexmedetomidine induces sedation while preserving a degree of arousability among patients in the intensive care unit (ICU), and its use has resulted in a shorter time to extubation,[10] an increased number of days free from coma or delirium,[11-14] a reduced incidence of agitated delirium,[15] prevention of delirium,[16] and lower mortality than other agents administered in certain populations.[17,18] Hypotension and bradycardia are common side effects.[5,6]

We conducted a multinational, open-label, randomized, controlled trial (Sedation Practice in Intensive Care Evaluation [SPICE] III) to investigate the effect of using dexmedetomidine as the primary and, if possible, sole agent for early sedation among patients receiving ventilatory support. Our hypothesis was that the use of dexmedetomidine would result in a lower rate of death from any cause at 90 days than usual-care sedation.

METHODS

TRIAL DESIGN AND OVERSIGHT

The trial was conducted in 74 ICUs in eight countries (Australia, Ireland, Italy, Malaysia, New Zealand, Saudi Arabia, Switzerland, and the United Kingdom). A complete list of trial sites is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

The protocol and statistical analysis plan, also available at NEJM.org, have been published previously.[19] The trial was designed by the authors, who wrote the manuscript and attest to the accuracy and completeness of the data, the statistical analyses, adherence to the protocol, and complete reporting of adverse events. Approval was obtained from the institutional review board at each participating institution. Prior informed consent or consent to continue to participate in the trial was obtained from all patients or their proxies, according to local regula-

tory requirements. An independent data and safety monitoring committee provided oversight of the trial. A single interim analysis was planned and performed after 2000 patients had been evaluated for the primary outcome, as described in the Supplementary Appendix.

The National Health and Medical Research Council of Australia, the Health Research Council of New Zealand, and the Institut Jantung Negara Foundation of Malaysia funded the trial. Pfizer and Orion Pharma supplied dexmedetomidine but had no role in the design or conduct of the trial, analysis of the data, or writing or review of the manuscript.

PATIENT SELECTION AND RANDOMIZATION

Patients were eligible for inclusion if they were receiving mechanical ventilation through an endotracheal tube, were expected to continue to receive ventilatory support beyond the next full calendar day, and were receiving sedatives for safety and comfort. Key exclusion criteria were an age under 18 years, invasive ventilation in the ICU for longer than 12 hours before enrollment, and suspected or proven acute primary brain injury (Table S1 in the Supplementary Appendix). The patients were randomly assigned in a 1:1 ratio to receive dexmedetomidine or usual care, as described below. Block randomization with a variable block size was implemented by means of a password-protected website. Randomization was stratified according to trial site and the presence or absence of suspected or proven sepsis,[20] as determined by the treating clinician.

TRIAL INTERVENTIONS AND MEASUREMENTS
Sedation Goals

Patients received adequate analgesia as determined by the treating clinician according to the results of pain assessments performed at least every 4 hours with the use of validated scales.[21] The sedation target was light sedation, unless it was deemed to be unsafe or contraindicated by the treating clinician, as defined by the Richmond Agitation and Sedation Scale (RASS), which ranges from –5 (unresponsive) to +4 (combative). The sedation goal was a RASS score of –2 (lightly sedated) to +1 (restless), as assessed at least every 4 hours.[22]

The presence or absence of delirium was assessed daily with the use of the Confusion As-

sessment Method for the Intensive Care Unit (positive or negative)[23] when the RASS score was –2 or higher. Weaning of sedation and ventilation was conducted according to local clinical practices.

Dexmedetomidine

In the dexmedetomidine group, the goal was to administer dexmedetomidine as the primary sedating agent or, once the sedation target was achieved, the sole sedating agent. Intravenous dexmedetomidine was started at a dose of 1 μg per kilogram of body weight per hour without a loading dose and adjusted (maximum dose, 1.5 μg per kilogram per hour) to achieve a RASS score in the target range. Previous data had suggested that dexmedetomidine as the sole agent might not achieve the target sedation in all patients or in all clinical situations, particularly when deep sedation (RASS score of –3 or less) was indicated.[9,12] Thus, the use of propofol at the lowest possible dose was allowed when the maximum dose of dexmedetomidine was insufficient and during the initial adjustment of the dexmedetomidine dose. The use of benzodiazepines was discouraged, although administration was permitted for specific indications of uncontrolled agitation or delirium, seizures, palliative comfort, and procedural sedation or if concomitant neuromuscular blockade was used. The administration of dexmedetomidine was continued as clinically required for up to 28 days after randomization (Fig. S1 in the Supplementary Appendix). All sedatives were administered in an open-label manner.

Usual Care

Patients who were assigned to receive usual care were given propofol, midazolam, or other sedatives, as directed by the treating physician, and with the intention of excluding dexmedetomidine. Rescue dexmedetomidine was permitted for uncontrolled agitation after failure of initial conventional therapies. Intravenous clonidine and remifentanil were prohibited in both groups.

Antipsychotic drugs, including haloperidol and quetiapine, were allowed for the treatment of agitated delirium if the currently administered sedative agents were not sufficient to achieve the target levels of sedation in either group. Other aspects of care, including mobilization and nonpharmacologic interventions to promote comfort, reduce anxiety, and facilitate sleep, were prescribed by the treating clinician in both groups.

TRIAL OUTCOMES

The primary outcome was the rate of death from any cause at 90 days after randomization. Secondary outcomes included 180-day mortality; transfer to a full-time nursing home or rehabilitation center; cognitive function, as evaluated at 180 days by the short form of the Informant Questionnaire on Cognitive Decline in the Elderly (Short IQCODE),[24] with scores ranging from 1 to 5, with higher values indicating worse cognitive function; and the patient-reported health-related quality of life, as assessed by the European Quality of Life 5-Dimensions 3-Level questionnaire (EQ-5D-3L), with scores ranging from 0 to 100, with higher scores indicating a better quality of life, at 180 days.[25] Additional secondary outcomes were the number of days free from coma or delirium and the number of ventilator-free days at day 28 after randomization.

We measured tertiary and process-related outcomes, including daily categories of RASS scores (deeply sedated [–5 to –3], lightly sedated [–2 to +1], and agitated [more than +1]); sedative, analgesic, and adjunct medications; and the patient's indication for deep sedation. Adverse events and serious adverse events were reported by site investigators and were not collected systematically or adjudicated independently.

STATISTICAL ANALYSIS

We conducted all analyses in accordance with the published statistical analysis plan[19] on the basis of a modified intention-to-treat principle, after the exclusion of patients who had withdrawn consent and those with an unknown primary outcome. We assumed a mortality rate of 26%[26] and estimated that the enrollment of 4000 patients would provide the trial with a power of 90% to detect an absolute between-group difference of 4.5 percentage points in the primary outcome at a two-sided significance level of 0.05 and allowing for a 5% loss to follow-up or revocation of consent. The stopping rules for an interim analysis are provided in the Supplementary Appendix.

We determined the effect of trial group on the primary and binomial secondary outcomes using logistic regression to derive odds ratios and binomial regression with an identity-link

function to derive risk differences, with both calculations including 95% confidence intervals. The two models included adjustment for binary stratification according to the presence or absence of sepsis and used an error estimation to account for within-center clustering. Sensitivity analysis of the primary outcome was performed with the use of covariate-adjusted logistic regression that accounted for baseline variables with an imbalance between the two groups with a P value of less than 0.05, with results reported as baseline adjusted odds ratios. Post hoc sensitivity analysis for missing data was performed with the use of multiple imputations (10 replications) and fully conditional specification logistic regression performed on prognostic baseline and post-baseline variables under the assumption that missing data for the primary outcome were conditional on observed covariates and were assumed to be missing at random.

We used median regression after adjustment for the presence or absence of sepsis to analyze the number of ventilator-free days and days free from coma or delirium, with the results presented as medians and differences of medians, both with 95% confidence intervals. We analyzed cognitive function and health-related quality of life in survivors using linear regression after adjustment for sepsis, with the results presented as means and difference of means. Details regarding the post hoc sensitivity analysis with respect to missing data and truncation due to death are provided in the Supplementary Appendix.

We conducted prespecified subgroup analyses of the primary outcome for six baseline variables: clinically suspected or proven sepsis, geographic region, surgical versus medical admission, an age that was older or younger than the median, a score on the APACHE (Acute Physiology and Chronic Health Evaluation) II that was higher or lower than the median,[27] and the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen. Risk differences for subgroups were determined with the use of binomial identity regression, and potential heterogeneity was determined with the use of logistic regression, with the fitting of main effects for sepsis, trial group, subgroup, and an interaction between trial group and subgroup.

The day of randomization was the remainder of the 24-hour ICU chart day. All subsequent days, except for the day of ICU discharge, were 24-hour chart days. On each day, the RASS score was determined in one of three categories: −3 to −5, target sedation (−2 to +1), or more than +1. Comparisons were performed with the use of multinomial logistic regression with robust sandwich errors clustered at an individual patient level. Process-related outcomes and adverse events were compared at a per-patient level with the use of chi-square tests for equal proportion, Student's t-tests for normally distributed data, or Wilcoxon rank-sum tests with results presented as frequency (with percentage), means (with standard deviation), or medians (with interquartile range), respectively. We used repeat-measures logistic and linear modeling with standard errors clustered at an individual patient level to compare daily use and dose of sedatives. All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

CHARACTERISTICS OF THE PATIENTS

From November 2013 through February 2018, we screened 29,502 patients who were being treated in the ICU and randomly assigned 4000 patients to receive either dexmedetomidine (2001 patients) or usual care (1999 patients) (Table S2 in the Supplementary Appendix). Among the patients with baseline data who did not withdraw consent in the two groups (1954 in the dexmedetomidine group and 1964 in the usual-care group), the clinical characteristics were similar (Table 1, and Table S3 in the Supplementary Appendix). Overall, 96 patients (2.4%) either withdrew consent or were lost to follow-up, leaving 1948 patients in the dexmedetomidine group and 1956 in the usual-care group with primary outcome data (Fig. S2 in the Supplementary Appendix). The median time from eligibility to randomization was 4.6 hours (interquartile range, 1.8 to 8.7).

OUTCOMES

In the modified intention-to-treat analysis, the primary outcome event of death from any cause at 90 days occurred in 566 of 1948 patients (29.1%) in the dexmedetomidine group and in 569 of 1956 (29.1%) in the usual-care group (adjusted risk difference, 0.0 percentage points; 95% confidence interval [CI], −2.9 to 2.8; P=0.98) (Table 2). This result did not change after adjustment for baseline covariates or in a sensitivity

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Dexmedetomidine (N=1954)	Usual Care (N=1964)
Age — yr	61.2±15.5	61.4±15.3
Male sex — no. %	1184 (60.6)	1231 (62.7)
Weight — kg	81.8±23.2	83.5±24.9
Score on APACHE II†	22.1±7.7	21.9±7.7
Suspected or proven sepsis — no. (%)	1248 (63.9)	1256 (64.0)
Median time from eligibility to randomization (IQR) — hr‡	4.7 (1.9 to 8.7)	4.4 (1.7 to 8.6)
Diabetes mellitus treated with insulin — no. (%)	185 (9.5)	205 (10.4)
Type of ICU admission — no. (%)		
Operative	536 (27.4)	550 (28.0)
Nonoperative	1417 (72.6)	1414 (72.0)
Admission diagnosis — no. (%)§		
Respiratory disorder	780 (39.9)	796 (40.5)
Sepsis¶	312 (16.0)	325 (16.5)
Gastrointestinal disorder	315 (16.1)	324 (16.5)
Cardiovascular disorder	300 (15.4)	279 (14.2)
Trauma	83 (4.2)	84 (4.3)
Neurologic disorder	26 (1.3)	24 (1.2)
Metabolic or endocrine disorder	26 (1.3)	21 (1.1)
Renal disorder	19 (1.0)	22 (1.1)
Hematologic disorder	12 (0.6)	9 (0.5)
Musculoskeletal or skin disorder	63 (3.2)	63 (3.2)
Other diagnosis	17 (0.9)	17 (0.9)
Median ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (IQR)‖	197 (136 to 293)	200 (133 to 284)
Median RASS score (IQR)**	−4 (−5 to −2)	−4 (−5 to −2)

* Plus-minus values are ±SD. Listed are available baseline data for patients in the two groups who did not withdraw consent. There were no significant differences in baseline characteristics between the trial groups except for weight (P=0.03). Additional baseline characteristics are listed in Table S2 in the Supplementary Appendix. Data regarding operative status and diagnostic criteria were missing for 1 patient in the dexmedetomidine group, and source data could not be verified. Percentages may not total 100 because of rounding. ICU denotes intensive care unit, and IQR interquartile range.

† The Acute Physiology and Chronic Health Evaluation (APACHE) II score is a prediction tool for death and measures severity of disease in the ICU; scores range from 0 to 71, with higher scores indicating a greater severity of illness.

‡ This interval was calculated from the time of ICU admission to randomization in patients who were intubated outside the ICU or the time from intubation to randomization in patients who were intubated in the ICU. The timing was evaluated in 1940 patients in the dexmedetomidine group and in 1949 in the usual-care group.

§ Conditions are listed according to the major disease categories in the APACHE III diagnostic codes.

¶ Patients with suspected or proven sepsis at randomization may have been assigned to other APACHE III diagnostic categories, such as pneumonia and respiratory disorder.

‖ This ratio was evaluated in 1734 patients in the dexmedetomidine group and in 1760 in the usual-care group.

** The Richmond Agitation and Sedation Scale (RASS) is a tool to assess depth of sedation on a scale of −5 to +4, with negative values denoting increased sedation and positive values denoting increased agitation. This score was evaluated in 1855 patients in the dexmedetomidine group and in 1857 in the usual-care group.

analysis that accounted for missing data (see the Supplementary Appendix). There was no significant difference in the primary outcome between the subgroup of patients with suspected or proven sepsis at randomization and those without sepsis (risk difference favoring the dexmedetomidine group, 1.1 percentage points; 95% CI, −2.6 to 4.8). There also was no significant between-

Table 2. Clinical Outcomes.*

Outcome	Dexmedetomidine (N = 1948)	Usual Care (N = 1956)	Odds Ratio (95% CI)	Adjusted Risk Difference (95% CI)†
Death from any cause at 90 days: primary outcome — no. (%)	566 (29.1)	569 (29.1)	1.00 (0.87 to 1.15)	0.0 (−2.9 to 2.8)
Secondary outcomes				
Death at 180 days — no./total no. (%)	609/1935 (31.5)	610/1946 (31.3)	1.01 (0.88 to 1.16)	0.1 (−2.8 to 3.1)
Institutional dependency at 180 days — no./total no. (%)	89/1323 (6.7)	94/1337 (7.0)	0.96 (0.73 to 1.27)	−0.3 (−2.1 to 1.5)
Mean score on Short IQCODE at 180 days (95% CI)‡	3.14 (3.11 to 3.17)	3.08 (3.05 to 3.11)		0.06 (0.02 to 0.11)
Mean score on the EQ-5D-3L questionnaire (95% CI)§	69.8 (68.5 to 71.1)	70.2 (69.0 to 71.5)		−0.4 (−2.2 to 1.3)
Median no. of days free from coma or delirium (IQR)¶	24.0 (11.0 to 26.0)	23.0 (10.0 to 26.0)		1.0 (0.5 to 1.5)
Median no. of ventilator-free days (IQR)¶	23.0 (0.0 to 26.0)	22.0 (0.0 to 25.0)		1.0 (0.4 to 1.6)

* Data regarding the listed primary and secondary outcomes were censored at 28 days after randomization unless otherwise stated. All tertiary outcomes are described in the Supplementary Appendix.
† Confidence intervals were adjusted for sepsis status but were not adjusted for multiple comparisons.
‡ The Short IQCODE (Informant Questionnaire on Cognitive Decline in the Elderly) is a measure of cognitive function as reported by a close friend or relative. The average score on 16 questions is calculated on a scale of 1 to 5, with a score of 3.01 to 3.50 indicating a slight decline and a higher score indicating a worse outcome. This score was evaluated in 1054 patients in the dexmedetomidine group and in 1082 in the usual-care group.
§ Scores on the European Quality of Life 5-Dimensions 3-Level (EQ-5D-3L) questionnaire range from 0 to 100, with higher scores indicating a better quality of life. This score was evaluated in 1144 patients in the dexmedetomidine group and in 1177 in the usual-care group.
¶ The number of days was calculated from the time of randomization to day 28 and was compared by means of quantile regression after adjustment for the sepsis stratum. All the deaths that occurred before day 28 were scored as 0 for ventilator-free days but were scored for the number of days free from coma or delirium on the basis of the 17,282 assessments made with the Confusion Assessment Method for the Intensive Care Unit.
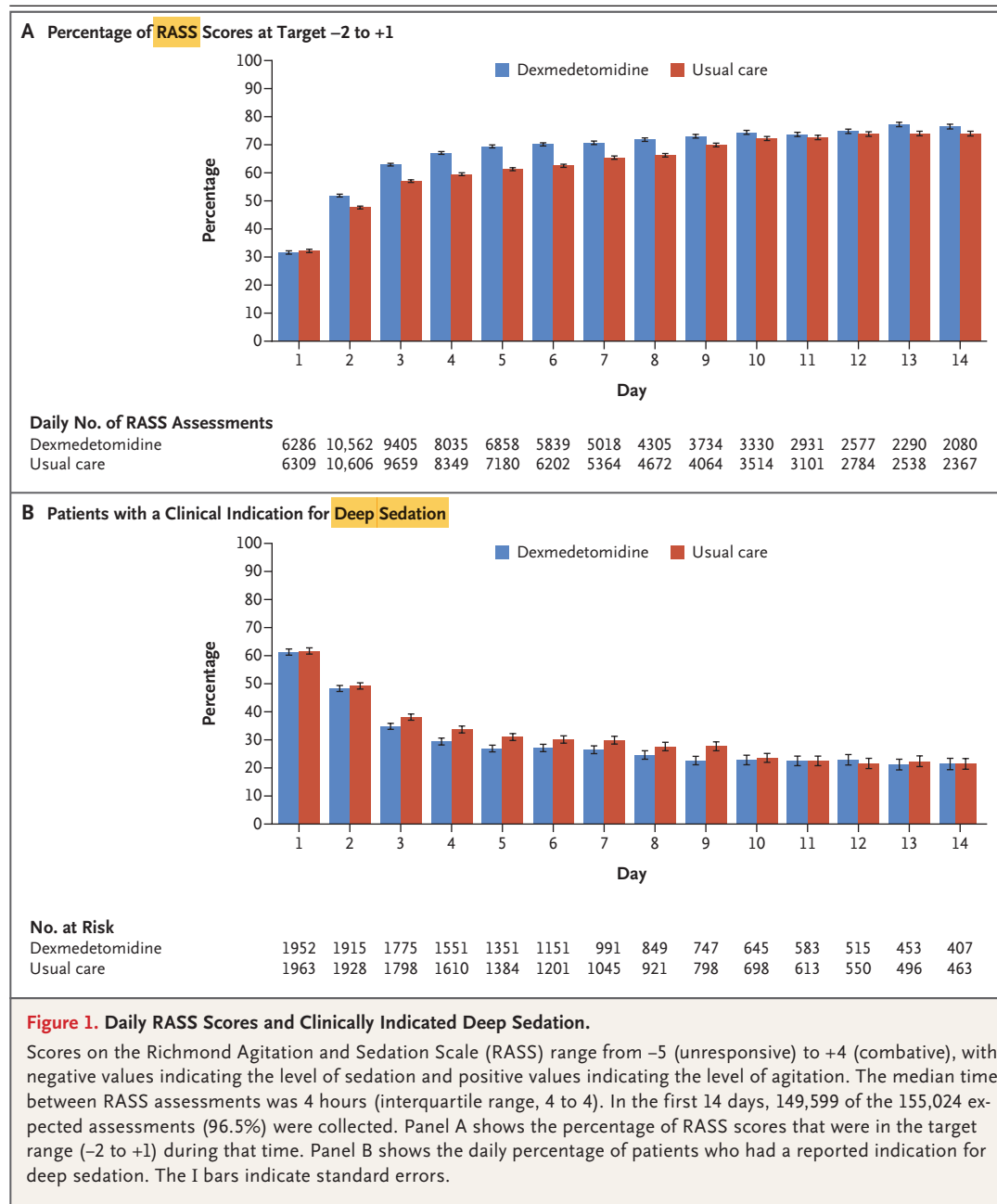
group difference in the primary outcome according to country, overall cause of death, or discharge destination (Tables S4, S5, and S6, respectively, in the Supplementary Appendix).

The between-group differences for secondary outcomes, including 180-day mortality and the percentage of institutionally dependent patients at 180 days, were not significant. Among the patients who were evaluated at 180 days, the score on the Short IQCODE questionnaire was available for 79.5% of the patients in the dexmedetomidine group and 81.0% of those in the usual-care group. There was no significant difference in the mean unadjusted IQCODE score of 3.14 in the dexmedetomidine group and 3.08 in the usual-care group in a sensitivity analysis that accounted for missing data, nor in the score on the EQ-5D-3L questionnaire (Table 2; and Figs. S5 and S6, respectively, in the Supplementary Appendix). As compared with usual care at day 28, the median number of days that patients

were free from coma or delirium and the median number of ventilator-free days were both 1 day higher in the dexmedetomidine group (Table 2). Tertiary outcomes including tracheostomy, re-intubation, use of restraints, unplanned extubation, and lengths of stay in both the ICU and hospital are shown in Table S7 in the Supplementary Appendix.

SEDATION LEVELS

In the first 2 full days after randomization, the percentage of RASS scores in the target range of light sedation (−2 to +1) was 56.6% in the dexmedetomidine group and 51.8% in the usual-care group. (The daily percentage of RASS scores in the target range is provided in Fig. 1A.) The percentage of RASS scores in the deep-sedation range (−5 to −3) was 40.0% in the dexmedetomidine group and 45.6% in the usual-care group (data not shown). The percentage of patients who had an indication for deep sedation as de-

A Percentage of RASS Scores at Target −2 to +1

Daily No. of RASS Assessments														
Dexmedetomidine	6286	10,562	9405	8035	6858	5839	5018	4305	3734	3330	2931	2577	2290	2080
Usual care	6309	10,606	9659	8349	7180	6202	5364	4672	4064	3514	3101	2784	2538	2367

B Patients with a Clinical Indication for Deep Sedation

No. at Risk														
Dexmedetomidine	1952	1915	1775	1551	1351	1151	991	849	747	645	583	515	453	407
Usual care	1963	1928	1798	1610	1384	1201	1045	921	798	698	613	550	496	463

Figure 1. Daily RASS Scores and Clinically Indicated Deep Sedation.

Scores on the Richmond Agitation and Sedation Scale (RASS) range from −5 (unresponsive) to +4 (combative), with negative values indicating the level of sedation and positive values indicating the level of agitation. The median time between RASS assessments was 4 hours (interquartile range, 4 to 4). In the first 14 days, 149,599 of the 155,024 expected assessments (96.5%) were collected. Panel A shows the percentage of RASS scores that were in the target range (−2 to +1) during that time. Panel B shows the daily percentage of patients who had a reported indication for deep sedation. The I bars indicate standard errors.

termined by the treating clinician is shown in Figure 1B.

USE OF ADDITIONAL SEDATIVES

Overall, 1910 of 1954 patients (97.7%) in the dexmedetomidine group received the trial agent for a median duration of 2.56 days (interquartile range, 1.10 to 5.23). In the usual-care group, 1931 of 1964 patients (98.3%) received propofol or midazolam for a median duration of 2.67 days

(interquartile range, 1.36 to 5.70) and 1.51 days (interquartile range, 0.67 to 3.17), respectively.

To achieve clinician-directed or target sedation levels in the 1910 patients who received dexmedetomidine during the first two full days after randomization, supplemental sedation was administered in the form of propofol in 1235 (64.7%), midazolam in 55 (2.9%), or both agents in 132 (6.9%). Among the 1931 patients who received usual care, 1161 (60.1%) received propo-

fol, 230 (11.9%) received midazolam, and 386 (20.0%) received both as primary sedatives.

During the trial, among the patients in the dexmedetomidine group who received supplemental propofol or midazolam, the median daily dose was 9.51 mg per kilogram (interquartile range, 4.20 to 18.70) and 0.11 mg per kilogram (interquartile range, 0.04 to 0.43), respectively; in the usual-care group, the median daily dose was 17.9 mg per kilogram (interquartile range, 8.90 to 30.50) of propofol and 0.31 mg per kilogram (interquartile range, 0.10 to 0.70) of midazolam (Fig. 2, and Table S8 in the Supplementary Appendix).

Fentanyl was the most common opioid used and was administered to 78.5% of the patients in the dexmedetomidine group and 80.7% of those in the usual-care group (Fig. 2D). The regimens of treatment with opioids and adjunct medications are provided in Figure S3 and the administration of dexmedetomidine for agitation or delirium in the usual-care group is shown in Figure S4 in the Supplementary Appendix.

SUBGROUP ANALYSES

Analyses were performed in six prespecified subgroups (Fig. 3). Among these analyses, the only significant difference was heterogeneity between treatment groups and an age above or below the median (63.7 years) with respect to 90-day mortality.

ADVERSE EVENTS

More adverse events and serious adverse events were reported in the dexmedetomidine group than in the usual-care group, most commonly bradycardia and hypotension, along with prolonged sinus arrest (asystole) (in 14 of 1954 patients [0.7%] and in 2 of 1964 patients [0.1%], respectively; P=0.003). Episodes of sinus arrest led to the administration of atropine or epinephrine or cardiac massage (in seven events) or resolved spontaneously (Table S9 in the Supplementary Appendix).

DISCUSSION

In this randomized, controlled, open-label trial, the use of dexmedetomidine as the primary or sole sedative in patients undergoing mechanical ventilation in the ICU did not result in lower 90-day mortality than usual care. Early in the course of the critical illness, most patients who were treated with dexmedetomidine received supplemental sedatives. Although the target level of light sedation was observed more frequently in the dexmedetomidine group, deep sedation was frequently reported in the two groups. The number of days that patients were free from coma or delirium and the number of ventilator-free days were 1 day more in the dexmedetomidine group than in the usual-care group for each of the comparisons; the confidence intervals for the between-group differences did not include zero but were unadjusted for multiple comparisons. Adverse and serious adverse events, mainly bradycardia and hypotension, some of which led to cardiac massage, were reported more frequently during dexmedetomidine sedation than during usual care.

In previous randomized trials comparing dexmedetomidine with several conventionally used sedatives, dexmedetomidine was associated with a shorter time to extubation, a higher number of days free from coma or delirium, and a shorter duration of unresponsive sedation.[11-14] These trials, however, had several limitations, including delayed intervention (up to 96 hours),[12] an unspecified target sedation level,[11] targeting deeper levels of sedation (RASS score of −3 to 0) than currently recommended,[13] a relatively short duration of treatment, and lack of daily data on sedation levels.[11,13] These trials were not powered to evaluate mortality or other patient-centered outcomes.

The biologic rationale for a potential benefit of dexmedetomidine is based on experimental evidence of protective effects against neuronal, myocardial, and renal injury,[28,29] along with a reduction in inflammatory mediators after cardiopulmonary bypass[30] and reduced mortality in animal models.[31] Several studies and trials have shown lower mortality associated with dexmedetomidine than with other agents in patients with sepsis[17,18] along with lower rates and shorter durations of coma and delirium,[12,16,17] both of which are associated with increased mortality.[32,33] Taken together, these findings have provided a rationale for a possible mortality benefit of the drug.[26,34-36] However, in our trial, we found no difference in overall mortality with the use of dexmedetomidine as compared with usual care. There was heterogeneity with respect to the treatment effect on mortality for an age above or
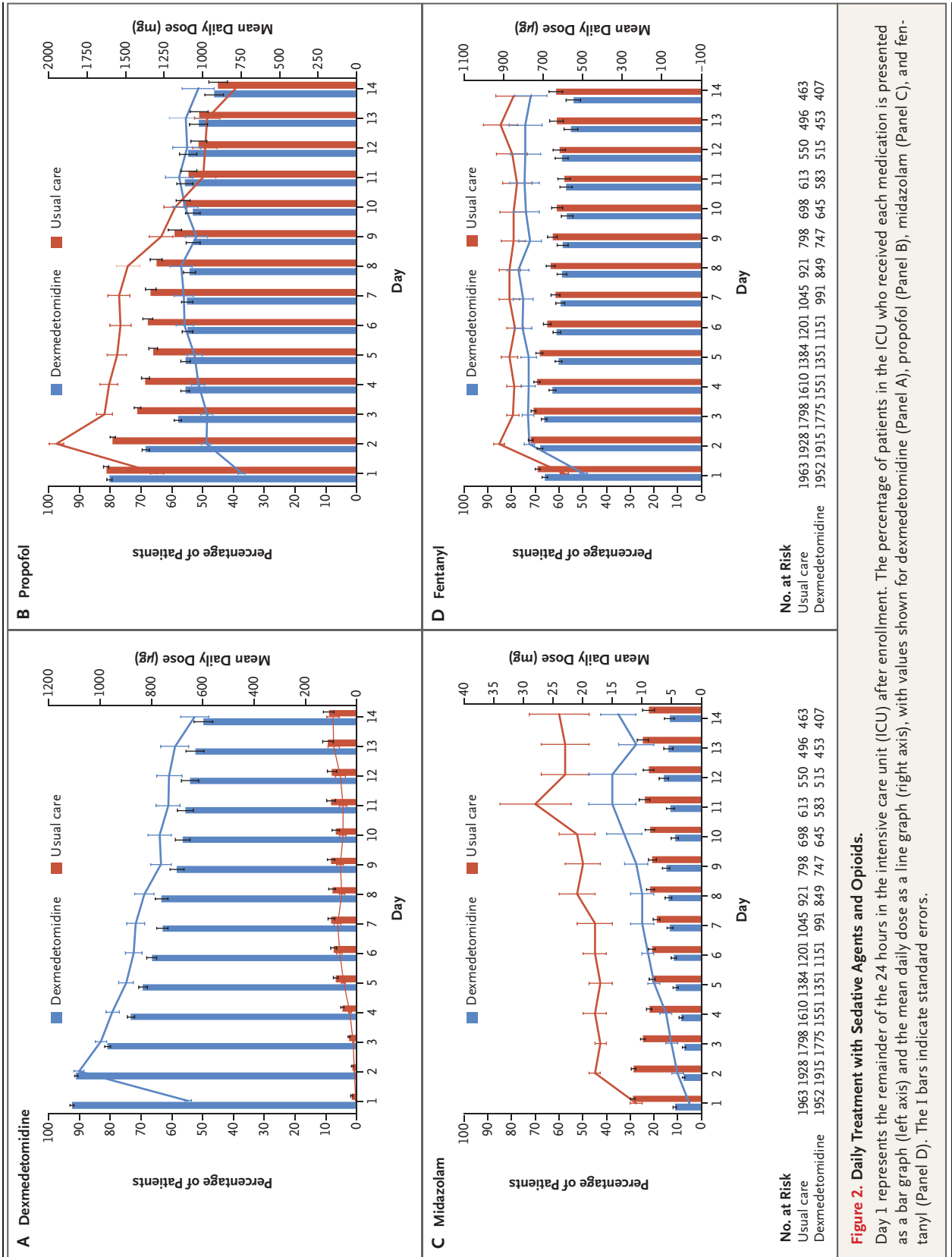
Figure 2. Daily Treatment with Sedative Agents and Opioids.

Day 1 represents the remainder of the 24 hours in the intensive care unit (ICU) after enrollment. The percentage of patients in the ICU who received each medication is presented as a bar graph (left axis) and the mean daily dose as a line graph (right axis), with values shown for dexmedetomidine (Panel A), propofol (Panel B), midazolam (Panel C), and fentanyl (Panel D). The I bars indicate standard errors.

No. at Risk

Usual care	1963	1928	1798	1610	1384	1201	1045	921	798	698	613	550	496	463
Dexmedetomidine	1952	1915	1775	1551	1351	1151	991	849	747	645	583	515	453	407

Subgroup	Dexmedetomidine	Usual Care	Risk Difference (95% CI)	
	no. of patients/total no. (%)		percentage points	
Age				
≤Median	219/976 (22.4)	176/975 (18.1)		4.4 (0.8 to 7.9)
>Median	347/972 (35.7)	393/981 (40.1)		−4.4 (−8.7 to −0.1)
APACHE II score				
≤Median	177/977 (18.1)	204/1018 (20.0)		−1.9 (−5.4 to 1.5)
>Median	389/971 (40.1)	365/938 (38.9)		1.1 (−3.2 to 5.5)
Geographic region				
Australia and New Zealand	330/1250 (26.4)	319/1246 (25.6)		0.8 (−2.6 to 4.2)
United Kingdom and Europe	148/428 (34.6)	155/430 (36.0)		−1.5 (−7.9 to 4.9)
Malaysia	50/171 (29.2)	57/176 (32.4)		−3.1 (−12.9 to 6.6)
Saudi Arabia	38/99 (38.4)	38/104 (36.5)		1.8 (−11.5 to 15.2)
Pao₂:Fio₂ ratio				
≤Median	303/881 (34.4)	290/862 (33.6)		0.8 (−3.7 to 5.2)
>Median	205/848 (24.2)	230/892 (25.8)		−1.6 (−5.7 to 2.5)
Sepsis suspected or proved				
No	157/703 (22.3)	172/706 (24.4)		−2.0 (−6.4 to 2.4)
Yes	409/1245 (32.9)	397/1250 (31.8)		1.1 (−2.6 to 4.8)
Admission type				
Nonoperative	442/1390 (31.8)	430/1389 (31.0)		0.8 (−2.6 to 4.3)
Operative	124/556 (22.3)	139/566 (24.6)		−2.3 (−7.2 to 2.7)
Overall				−0.2 (−1.4 to 1.1)

−0.15 −0.10 −0.05 0.00 0.05 0.10 0.15
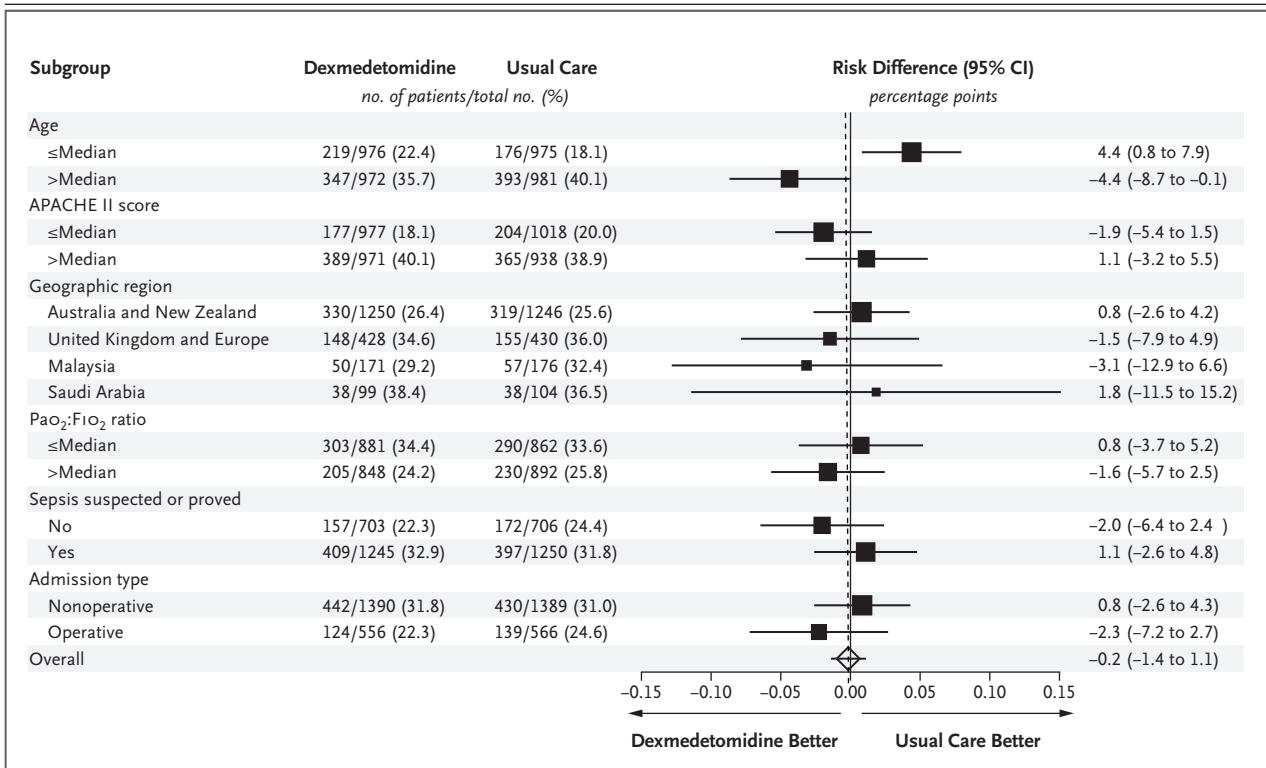
Dexmedetomidine Better | Usual Care Better

Figure 3. Subgroup Analysis of the Primary Outcome.

The forest plot shows the risk difference for the primary outcome (the rate of death from any cause at 90 days) in six prespecified subgroups, as calculated with the use of binomial identity regression. The size of the square representing the risk difference reflects the relative number of patients in each subgroup, and the horizontal bars represent the 95% confidence intervals. The diamond indicates the overall risk difference, as represented by the dashed vertical line, and the solid vertical line indicates no between-group difference. Heterogeneity after adjustment for multiple comparisons was observed only for age, with a divergent effect above and below the median age of the patients (63.7 years). The median score on the APACHE (Acute Physiology and Chronic Health Evaluation) II was 21 on a scale ranging from 0 to 71, with higher scores indicating a greater severity of illness. The median ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO₂:FIO₂) was 198.

below the median of 63.7 years, with lower mortality in older patients and higher mortality in younger patients, but the significance of the difference could not be determined. If this finding is confirmed in future trials, it could be due to age-related changes in the pharmacokinetics of sedatives.[37,38]

Patients who were treated with dexmedetomidine received additional drugs to achieve the target level of sedation. The use of multiple agents, however, was common in both groups. This may reflect sedation requirements during the acute phase of a critical illness.

The administration of medications in our trial was unblinded. We did not exclude patients who required deep sedation, a factor that might have influenced the overall RASS scores and the need for sedative agents administered after randomization. We did not mandate a daily interruption in sedation or adherence to a particular strategy for managing sedation or delirium in the ICU (e.g., the ABCDEF bundle).[39,40] In addition, we did not assess in detail other aspects of ICU care (e.g., vasopressor use, administration of fluids, or renal-replacement therapy).

In conclusion, among critically ill adults undergoing mechanical ventilation in the ICU, the early administration of dexmedetomidine as the sole or primary sedative did not result in lower 90-day mortality than usual care. Dexmedetomidine was insufficient alone or as the primary agent to achieve clinically desired target sedation levels and was associated with more reported adverse events than usual care.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

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