

ORIGINAL ARTICLE

Early Sedation with Dexmedetomidine in Critically Ill Patients

Y. Shehabi, B.D. Howe, R. Bellomo, Y.M. Arabi, M. Bailey, F.E. Bass, S. Bin Kadiman, C.J. McArthur, L. Murray, M.C. Reade, I.M. Seppelt, J. Takala, M.P. Wise, and S.A. Webb, for the ANZICS Clinical Trials Group and the SPICE III Investigators*

ABSTRACT

BACKGROUND

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Shehabi at Monash University, School of Clinical Sciences, Level 5, E Block, Monash Medical Centre, Clayton 3168, VIC, Australia, or at yahya.shehabi@monashhealth.org or y.shehabi@unsw.edu.au.

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

*A complete list of the trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

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.

This article was published on May 19, 2019, at NEJM.org.

N Engl J Med 2019;380:2506-17.

DOI: 10.1056/NEJMoa1904710

Copyright © 2019 Massachusetts Medical Society.

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.)

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 α_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-

assessment 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 $1\ \mu\text{g}$ per kilogram of body weight per hour without a loading dose and adjusted (maximum dose, $1.5\ \mu\text{g}$ 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 remifentanyl 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 non-pharmacologic 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 plan¹⁹ 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.

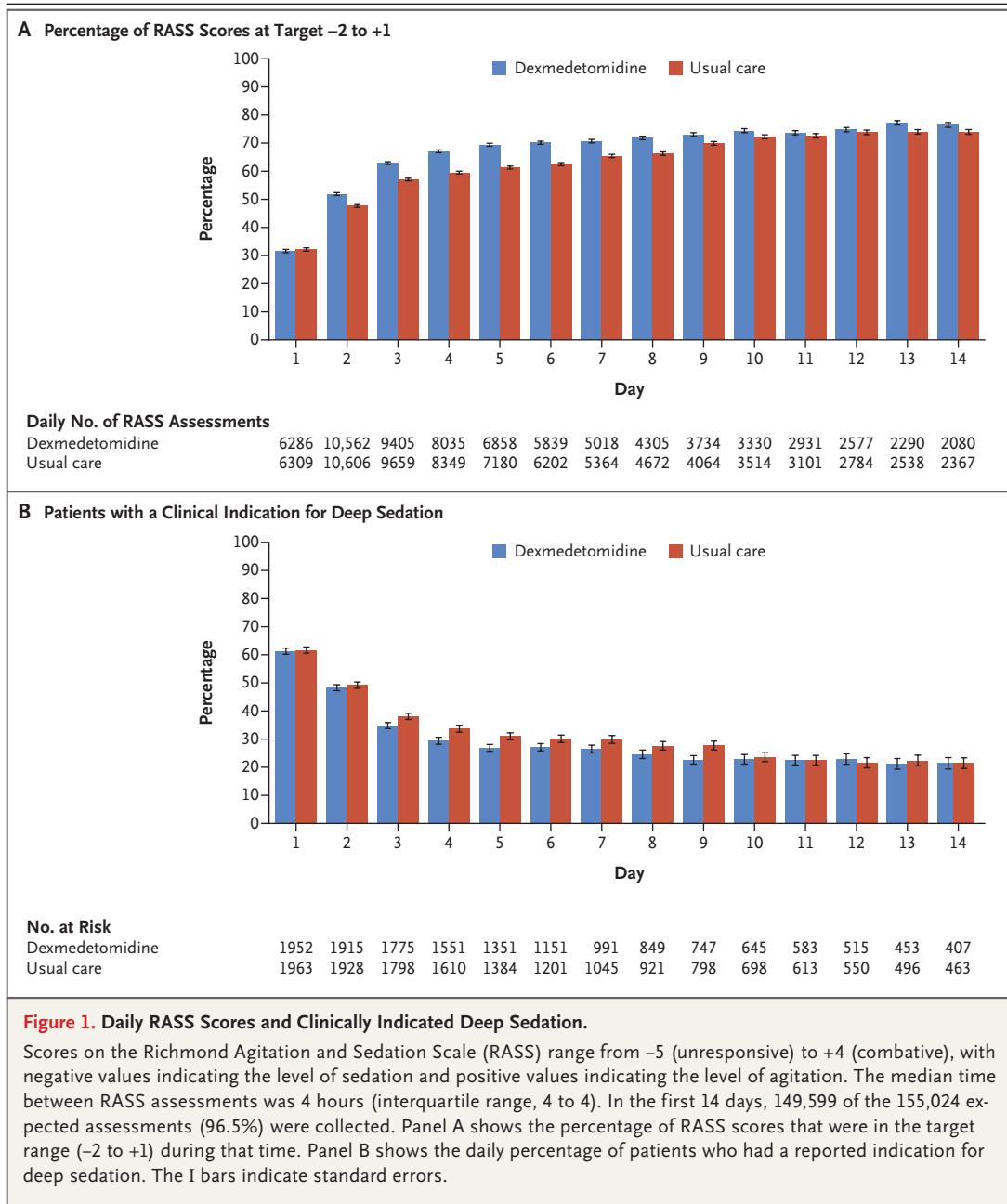
group difference in the primary outcome according to country, overall cause of death, or discharge destination (Tables S4, S5, and S6, respectively, in the Supplementary Appendix).

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, reintubation, 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-



terminated 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 bypass³⁰ 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

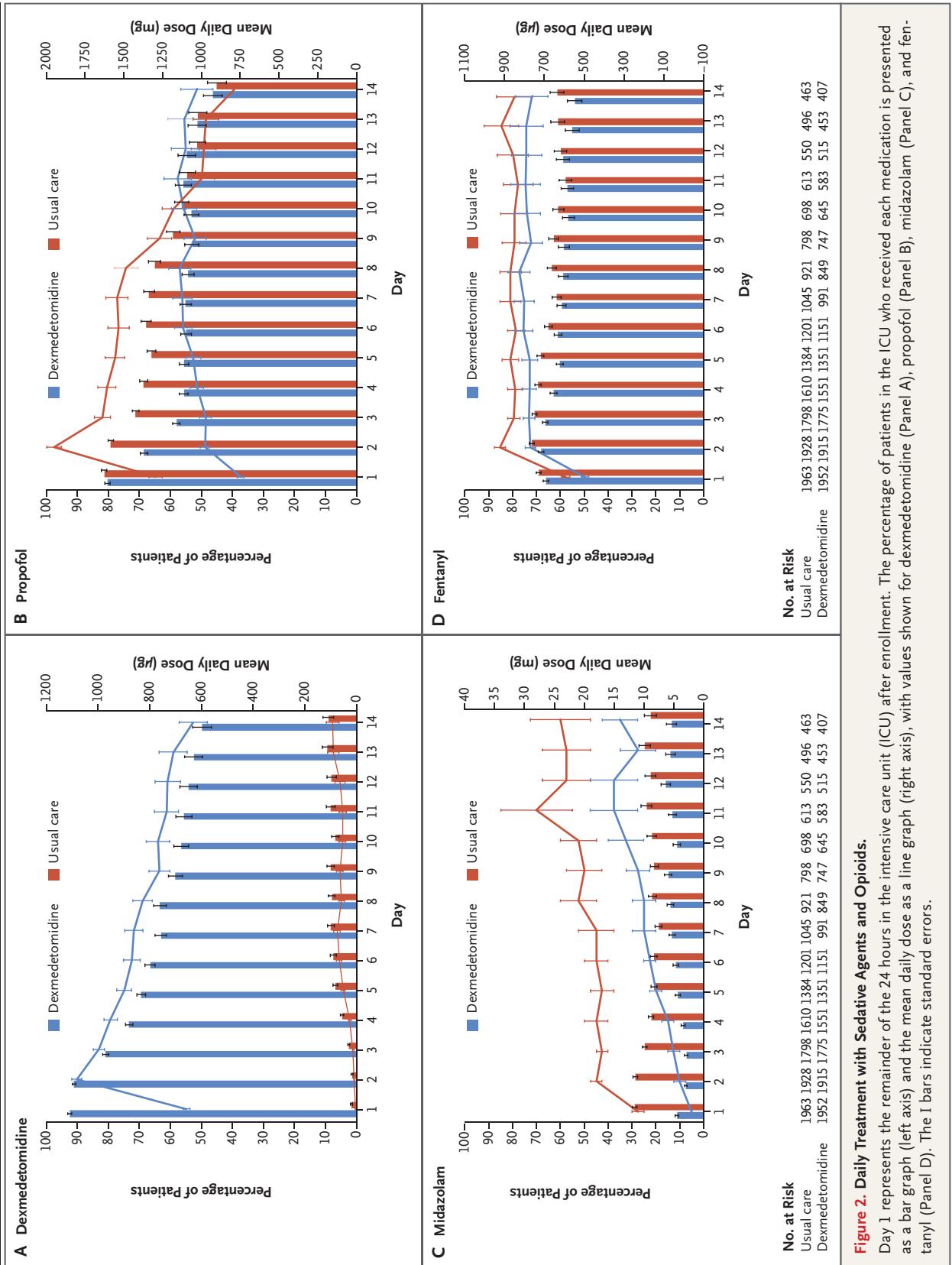


Figure 2. Daily Treatment with Sedative Agents and Opioids.

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.

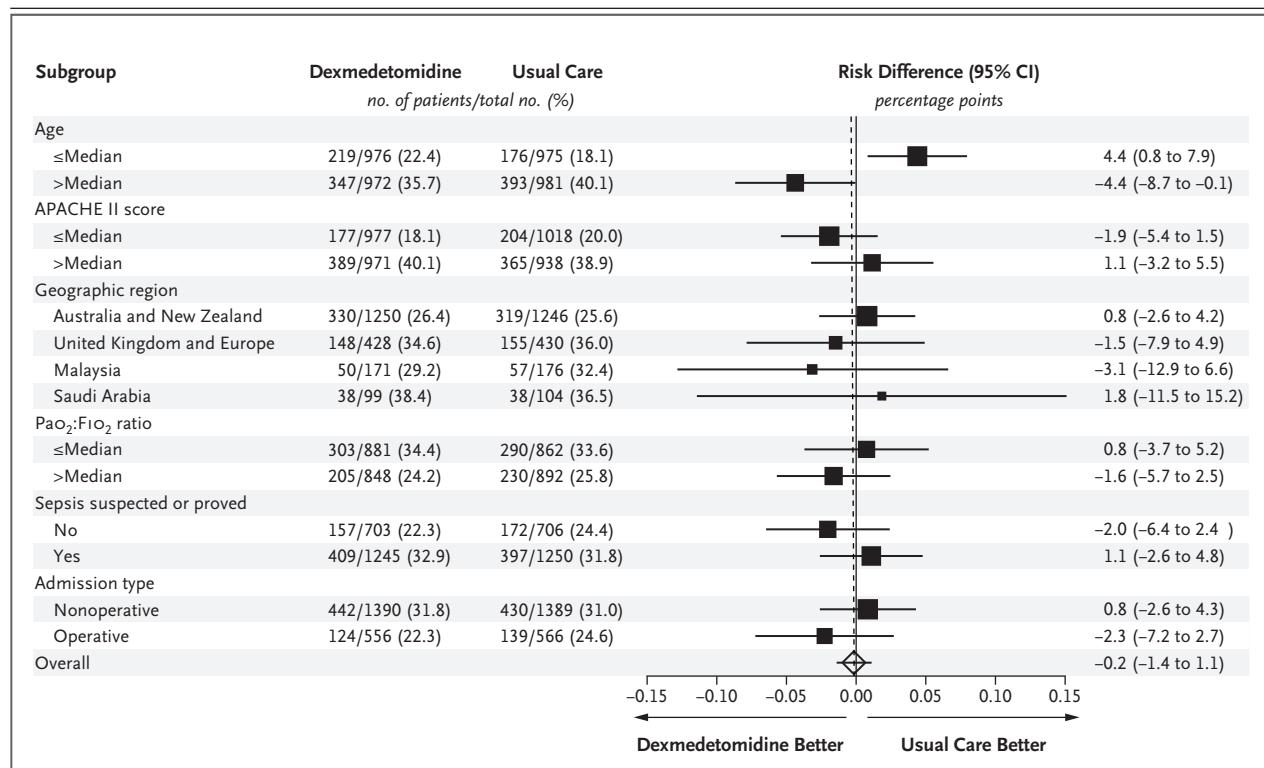


Figure 3. Subgroup Analysis of the Primary Outcome.

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 ran-

domization. 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.

Supported by the National Health and Medical Research Council of Australia, the Health Research Council of New Zealand, and the National Heart Institute Foundation of Malaysia. Pfizer and Orion Pharma provided dexmedetomidine to trial sites.

Dr. Shehabi reports receiving travel support and lecture fees, paid to Monash Health, and lecture fees from Pfizer (Malaysia) and Orion Pharma and fees for expert testimony from Stephens Lawyers and Consultants, Melbourne; Dr. Bellomo, receiving

fees for expert testimony from Pfizer; and Dr. Takala, receiving consulting fees from Nestec. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank all patients and their relatives who participated in the trial and acknowledge the support of the doctors and nurses across all trial sites.

APPENDIX

The authors' full names and academic degrees are as follows: Yahya Shehabi, Ph.D., M.B., B.S., Belinda D. Howe, R.N., M.P.H., Rinaldo Bellomo, M.D., Ph.D., Yaseen M. Arabi, M.D., Michael Bailey, Ph.D., Frances E. Bass, R.N., Suhaini Bin Kadiman, M.D., Colin J. McArthur, M.B., Ch.B., Lynette Murray, B.S., Michael C. Reade, M.B., B.S., M.P.H., D.Phil., Ian M. Seppelt, M.B., B.S., Jukka Takala, M.D., Ph.D., Matt P. Wise, M.D., D.Phil., and Steven A. Webb, M.P.H., Ph.D.

The authors' affiliations are as follows: the School of Clinical Sciences (Y.S.) and the Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine (B.D.H., R.B., M.B., L.M., S.A.W.), Monash University, Monash Health (Y.S.), the Faculty of Medicine, University of Melbourne (R.B., M.B.), Melbourne, VIC, Heidelberg, VIC (R.B.), the Prince of Wales Clinical School of Medicine, University of New South Wales (Y.S.), Royal North Shore Hospital, the George Institute for Global Health (F.E.B.), the Sydney Medical School—Nepean, University of Sydney, and the Department of Clinical Medicine, Macquarie University (I.M.S.), Sydney, the Faculty of Medicine, University of Queensland, Royal Brisbane and Women's Hospital, Brisbane (M.C.R.), the Joint Health Command, Australian Defence Force, Canberra, ACT (M.C.R.), and St. John of God Subiaco Hospital, Subiaco, WA (S.A.W.) — all in Australia; the College of Medicine, King Saud Bin Abdulaziz University for Health Sciences and King Abdullah International Medical Research Center, King Abdulaziz Medical City, Riyadh, Saudi Arabia (Y.M.A.); the Department of Anesthesiology and Intensive Care, IJN-UTM Cardiovascular Engineering Center, National Heart Institute, Kuala Lumpur, Malaysia (S.B.K.); the Department of Critical Care Medicine, Auckland City Hospital, University of Auckland, Auckland, New Zealand (C.J.M.); Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland (J.T.); and Adult Critical Care, University Hospital of Wales, Cardiff, United Kingdom (M.P.W.).

REFERENCES

1. Shehabi Y, Bellomo R, Mehta S, Riker R, Takala J. Intensive care sedation: the past, present and the future. *Crit Care* 2013;17:322.
2. Reade MC, Finfer S. Sedation and delirium in the intensive care unit. *N Engl J Med* 2014;370:444-54.
3. Mehta S, McCullagh I, Burry L. Current sedation practices: lessons learned from international surveys. *Crit Care Clin* 2009;25:471-88.
4. Wunsch H, Kahn JM, Kramer AA, Rubenfeld GD. Use of intravenous infusion sedation among mechanically ventilated patients in the United States. *Crit Care Med* 2009;37:3031-9.
5. Gommers D, Bakker J. Medications for analgesia and sedation in the intensive care unit: an overview. *Crit Care* 2008;12:Suppl 3:S4.
6. Roberts DJ, Haroon B, Hall RI. Sedation for critically ill or injured adults in the intensive care unit: a shifting paradigm. *Drugs* 2012;72:1881-916.
7. Devlin JW, Fraser GL, Ely EW, Kress JP, Skrobik Y, Dasta JF. Pharmacological management of sedation and delirium in mechanically ventilated ICU patients: remaining evidence gaps and controversies. *Semin Respir Crit Care Med* 2013;34:201-15.
8. Carollo DS, Nossaman BD, Ramadhyani U. Dexmedetomidine: a review of clinical applications. *Curr Opin Anaesthesiol* 2008;21:457-61.
9. Keating GM. Dexmedetomidine: a review of its use for sedation in the intensive care setting. *Drugs* 2015;75:1119-30.
10. Constantin J-M, Momon A, Mantz J, et al. Efficacy and safety of sedation with dexmedetomidine in critical care patients: a meta-analysis of randomized controlled trials. *Anaesth Crit Care Pain Med* 2016;35:7-15.
11. Pandharipande PP, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA* 2007;298:2644-53.
12. Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA* 2009;301:489-99.
13. Jakob SM, Ruokonen E, Grounds RM, et al. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. *JAMA* 2012;307:1151-60.
14. Fraser GL, Devlin JW, Worby CP, et al. Benzodiazepine versus nonbenzodiazepine-based sedation for mechanically ventilated, critically ill adults: a systematic review and meta-analysis of randomized trials. *Crit Care Med* 2013;41:Suppl 1:S30-S38.
15. Reade MC, Eastwood GM, Bellomo R, et al. Effect of dexmedetomidine added to standard care on ventilator-free time in patients with agitated delirium: a randomized clinical trial. *JAMA* 2016;315:1460-8.
16. Skrobik Y, Duprey MS, Hill NS, Devlin JW. Low-dose nocturnal dexmedetomidine prevents ICU delirium: a randomized, placebo-controlled trial. *Am J Respir Crit Care Med* 2018;197:1147-56.
17. Pandharipande PP, Sanders RD, Girard TD, et al. Effect of dexmedetomidine versus lorazepam on outcome in patients with sepsis: a priori-designed analysis of the MENDS randomized controlled trial. *Crit Care* 2010;14:R38.
18. Kawazoe Y, Miyamoto K, Morimoto T, et al. Effect of dexmedetomidine on mortality and ventilator-free days in patients requiring mechanical ventilation with sepsis: a randomized clinical trial. *JAMA* 2017;317:1321-8.
19. Shehabi Y, Forbes AB, Arabi Y, et al. The SPICE III study protocol and analysis plan: a randomised trial of early goal-directed sedation compared with standard care in mechanically ventilated patients. *Crit Care Resusc* 2017;19:318-26.
20. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest* 1992;101:1644-55.
21. Gélinas C, Fillion L, Puntillo KA, Viens C, Fortier M. Validation of the Critical-Care Pain Observation tool in adult patients. *Am J Crit Care* 2006;15:420-7.
22. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002;166:1338-44.
23. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *JAMA* 2001;286:2703-10.
24. Jorm A. Short form of the Informant

- Questionnaire on Cognitive Decline in the Elderly (Short IQCODE). Canberra, ACT: Australian National University Centre for Mental Health Research, 2004.
25. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20:1727-36.
 26. Shehabi Y, Bellomo R, Reade MC, et al. Early intensive care sedation predicts long-term mortality in ventilated critically ill patients. *Am J Respir Crit Care Med* 2012; 186:724-31.
 27. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;13:818-29.
 28. Ren X, Ma H, Zuo Z. Dexmedetomidine postconditioning reduces brain injury after brain hypoxia-ischemia in neonatal rats. *J Neuroimmune Pharmacol* 2016;11: 238-47.
 29. Si YN, Bao HG, Xu L, et al. Dexmedetomidine protects against ischemia/reperfusion injury in rat kidney. *Eur Rev Med Pharmacol Sci* 2014;18:1843-51.
 30. Ueki M, Kawasaki T, Habe K, Hamada K, Kawasaki C, Sata T. The effects of dexmedetomidine on inflammatory mediators after cardiopulmonary bypass. *Anaesthesia* 2014;69:693-700.
 31. Taniguchi T, Kidani Y, Kanakura H, Takemoto Y, Yamamoto K. Effects of dexmedetomidine on mortality rate and inflammatory responses to endotoxin-induced shock in rats. *Crit Care Med* 2004; 32:1322-6.
 32. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA* 2004;291:1753-62.
 33. Shehabi Y, Riker RR, Bokesch PM, et al. Delirium duration and mortality in lightly sedated, mechanically ventilated intensive care patients. *Crit Care Med* 2010;38:2311-8.
 34. Shehabi Y, Chan L, Kadiman S, et al. Sedation depth and long-term mortality in mechanically ventilated critically ill adults: a prospective longitudinal multicentre cohort study. *Intensive Care Med* 2013;39:910-8.
 35. Shehabi Y, Bellomo R, Kadiman S, et al. Sedation intensity in the first 48 hours of mechanical ventilation and 180-day mortality: a multinational prospective longitudinal cohort study. *Crit Care Med* 2018; 46:850-9.
 36. Stephens RJD, Dettmer MR, Roberts BW, et al. Practice patterns and outcomes associated with early sedation depth in mechanically ventilated patients: a systematic review and meta-analysis. *Crit Care Med* 2018;46:471-9.
 37. Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol* 2004;57: 6-14.
 38. Kim J, Kim WO, Kim H-B, Kil HK. Adequate sedation with single-dose dexmedetomidine in patients undergoing transurethral resection of the prostate with spinal anaesthesia: a dose-response study by age group. *BMC Anesthesiol* 2015;15:17.
 39. Mehta S, Burry L, Cook D, et al. Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial. *JAMA* 2012;308:1985-92.
 40. Pun BT, Balas MC, Barnes-Daly MA, et al. Caring for critically ill patients with the ABCDEF bundle: results of the ICU Liberation Collaborative in over 15,000 adults. *Crit Care Med* 2019;47:3-14.

Copyright © 2019 Massachusetts Medical Society.