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Dexmedetomidine- or Clonidine-Based Sedation Compared With Propofol in Critically Ill Patients

The A2B Randomized Clinical Trial

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IMPORTANCE Whether α_2-adrenergic receptor agonist–based sedation, compared with propofol-based sedation, reduces time to extubation in patients receiving mechanical ventilation in the intensive care unit (ICU) is uncertain.

OBJECTIVE To evaluate whether dexmedetomidine- or clonidine-based sedation reduces duration of mechanical ventilation compared with propofol-based sedation (usual care).

DESIGN, SETTING, AND PARTICIPANTS Pragmatic, open-label randomized clinical trial conducted at 41 ICUs in the UK including adults who were within 48 hours of starting mechanical ventilation, were receiving propofol plus an opioid for sedation and analgesia, and were expected to require mechanical ventilation for 48 hours or longer. The median time from intubation to randomization was 21.0 (IQR, 13.2-31.3) hours. Recruitment occurred from December 2018 to October 2023; the last follow-up occurred on December 10, 2023.

INTERVENTIONS The bedside algorithms used targeted a Richmond Agitation-Sedation Scale score of −2 to 1 (unless clinicians requested deeper sedation). The algorithms supported uptitration in the dexmedetomidine- and clonidine-based sedation intervention groups and supported downtitration for propofol-based sedation followed by sedation primarily with the allocated sedation (dexmedetomidine or clonidine). If required, supplemental use of propofol was permitted.

MAIN OUTCOMES AND MEASURES The primary outcome was time from randomization to successful extubation. The secondary outcomes included mortality, sedation quality, rates of delirium, and cardiovascular adverse events.

RESULTS Among the 1404 patients in the analysis population (mean age, 59.2 [SD, 14.9] years; 901 [64%] were male; and the mean APACHE II score was 20.3 [SD, 8.2]), the subdistribution hazard ratio (HR) for time to successful extubation was 1.09 (95% CI, 0.96-1.25; P = .20) for dexmedetomidine (n = 457) vs propofol (n = 471) and was 1.05 (95% CI, 0.95-1.17; P = .34) for clonidine (n = 476) vs propofol (n = 471). The median time from randomization to successful extubation was 136 (95% CI, 117-150) hours for dexmedetomidine, 146 (95% CI, 124-168) hours for clonidine, and 162 (95% CI, 136-170) hours for propofol. In the predefined subgroup analyses, there were no interactions with age, sepsis status, median Sequential Organ Failure Assessment score, or median delirium risk score. Among the secondary outcomes, agitation occurred at a higher rate with dexmedetomidine vs propofol (risk ratio [RR], 1.54 [95% CI, 1.21-1.97]) and with clonidine vs propofol (RR, 1.55 [95% CI, 1.22-1.97]). Compared with propofol, the rates of severe bradycardia (heart rate <50/min) were higher with dexmedetomidine (RR, 1.62 [95% CI, 1.36-1.93]) and clonidine (RR, 1.58 [95% CI, 1.33-1.88]). Compared with propofol, mortality was similar over 180 days for dexmedetomidine (HR, 0.98 [95% CI, 0.77-1.24]) and clonidine (HR, 1.04 [95% CI, 0.82-1.31]).

CONCLUSIONS AND RELEVANCE In critically ill patients, neither dexmedetomidine nor clonidine was superior to propofol in reducing time to successful extubation.

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Most critically ill patients receiving mechanical ventilation require sedation. Propofol is the most widely used sedative medication,[1] but some trials suggest the α_2-adrenergic receptor agonist dexmedetomidine may reduce delirium and duration of mechanical ventilation.[2-6] However, evidence is inconclusive and a post hoc analysis of the Sedation Practice in Intensive Care Evaluation (SPICE) III trial[7-9] found heterogeneity in the effects on survival based on patient age, raising concerns about safety for some patients.

Clonidine is an inexpensive α_2-adrenergic receptor agonist with lower α_2-receptor specificity and is widely used as an adjunct sedative in some countries.[10] To our knowledge, no high-quality research has been performed simultaneously evaluating clonidine or dexmedetomidine compared with propofol.[11]

We conducted a pragmatic, multicenter, open-label, randomized clinical trial comparing the effectiveness and safety of dexmedetomidine- and clonidine-based sedation vs propofol-based sedation as the primary sedation in critically ill patients receiving mechanical ventilation. Our primary hypothesis was that α_2-adrenergic receptor agonist–based sedation reduces time to successful extubation.

Key Points

Question Does primary sedation with dexmedetomidine or clonidine (α_2-adrenergic receptor agonists), compared with propofol-based sedation (usual care), decrease the time to successful extubation in critically ill patients receiving mechanical ventilation?

Findings In this pragmatic, multicentered, randomized clinical trial including patients expected to require at least 48 hours of mechanical ventilation, neither dexmedetomidine- nor clonidine-based sedation decreased the time to successful extubation compared with propofol-based sedation.

Meaning Among critically ill patients expected to require at least 48 hours of mechanical ventilation, neither dexmedetomidine- nor clonidine-based sedation was superior to propofol-based sedation.

Methods

The trial protocol was published[12] and appears in Supplement 1. Survivors of intensive care unit (ICU) stays were involved in the choice of the primary outcome and assisted with the conduct of the trial (eAppendix 1 in Supplement 2). The Scotland A Research Ethics Committee (18/SS/0085) provided ethical approval. This trial followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline. Enrollment was paused from March to August 2020 due to the COVID-19 pandemic (during the UK lockdown).

Patient Selection, Consent, and Randomization

Eligible patients were receiving mechanical ventilation in the ICU, were aged 18 years or older, were sedated with propofol (with or without an opioid) after intubation, were within 48 hours of starting mechanical ventilation, and were expected (at randomization) to require a further 24 hours of mechanical ventilation for a total of 48 hours or longer. The exclusion criteria included acute brain injury, neuromuscular paralysis, bradycardia (heart rate <50 beats/min for ≥60 minutes), and an expected survival no longer than 24 hours (eAppendix 2 in Supplement 2).

Signed informed consent was obtained after consultation with surrogate decision-makers; deferred consent was allowed if the decision-makers were unavailable within 2 hours of confirming patient eligibility (eAppendix 3 in Supplement 2).

A remote web-based system was used for randomization, allocating patients in a 1:1:1 ratio to the 3 sedation groups using permuted blocks (randomly arranged block sizes of 3, 6, 9, and 12) stratified by center (**Figure 1**). The allocation sequence was computer-generated by an independent programmer and concealed and stored on a remote server. Randomization was done by local researchers.

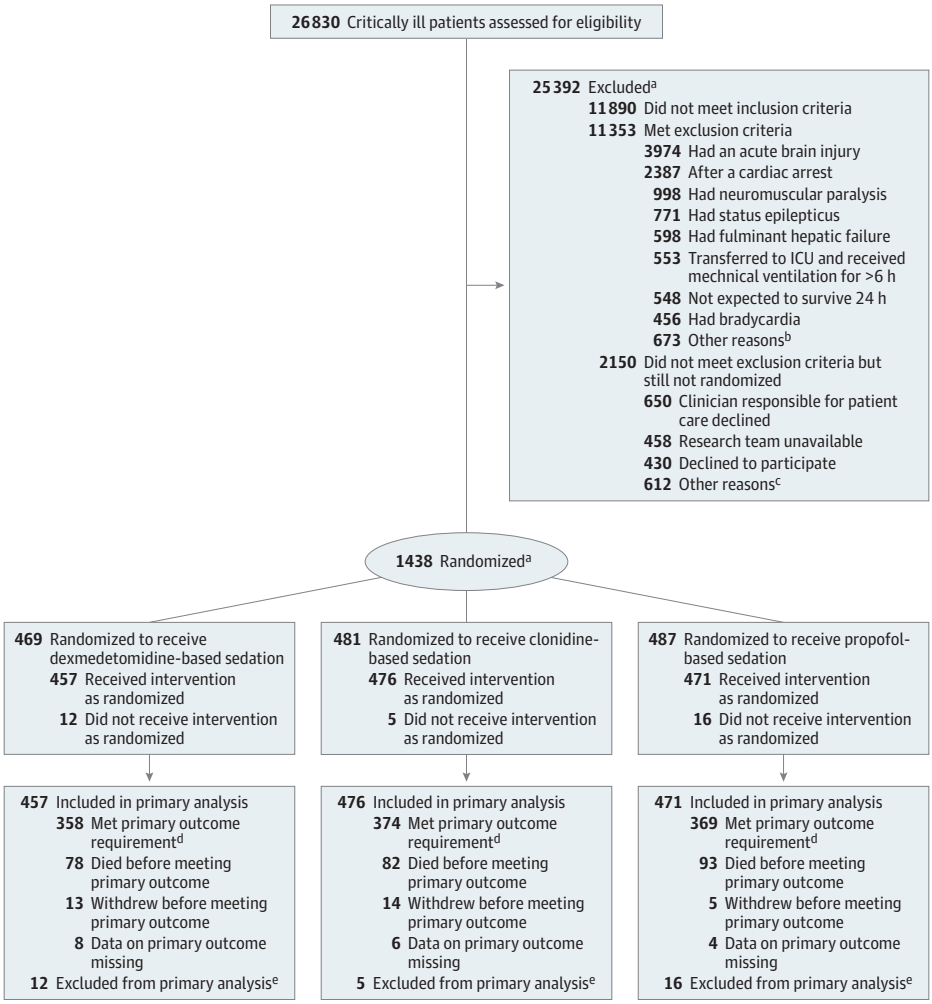
Trial Interventions, Sedation Targets, and Weaning

An intravenous infusion of open-label study drug for patients in the intervention groups (dexmedetomidine or clonidine) was administered using a weight-based dose regimen within 2 hours after randomization (eAppendix 4 in Supplement 2). The medical staff determined whether deep sedation (Richmond Agitation-Sedation Scale [RASS] score of −4 or −5) was clinically indicated and continued to make assessments on a daily basis. Clinical staff used group-specific algorithms to uptitrate dexmedetomidine or clonidine and downtitrate propofol to transition patients to the allocated α_2-adrenergic receptor agonist (dexmedetomidine or clonidine; eAppendix 5 in Supplement 2).

The aim of the study was assessment of α_2-adrenergic receptor agonist–based sedation (dexmedetomidine or clonidine), but propofol was permitted if the maximum α_2-adrenergic receptor agonist dose was reached or because of clinician concerns or dose-limiting adverse effects. For dexmedetomidine, the starting dose was 0.7 µg/kg/h and the maximum dose was 1.4 µg/kg/h; for clonidine, the starting dose was 1.0 µg/kg/h and the maximum dose was 2.0 µg/kg/h. Lower starting doses were recommended for patients with cardiovascular instability. No specific dose guidance was given for propofol-based sedation (usual care).

If deep sedation was not requested by medical staff, bedside algorithms indicated a sedation target based on a RASS score of −2 to 1 (range, −5 [unresponsive] to 4 [combative]), with continuous titration to achieve clinical target sedation status.[13] The choice and dosing of an opioid for analgesia was determined by the clinical team according to usual care and clinical judgment. Other sedatives (especially benzodiazepines) were discouraged and recorded daily as rescue medications, which is consistent with international guidelines.[14] Guidance was provided to medical staff for mechanical ventilation weaning, sedation discontinuation, and assessment of readiness for extubation, which represented best practice (eAppendix 6 in Supplement 2). However, this was not tightly protocolized. Guidance for managing cardiovascular instability and other scenarios also was provided, including pausing

Figure 1. Flow Diagram for Screening, Randomization, and Follow-Up in the Study



ICU indicates intensive care unit.

[a]One patient in the clonidine-based sedation group was randomized twice in error.

[b]There were 307 patients with an unknown reason, 81 were incarcerated individuals, 66 had an untreated heart block, 57 had Guillain-Barre syndrome, 49 were previously enrolled in the trial, 41 had myasthenia gravis, 36 were pregnant, 32 were receiving ventilation assistance at home, and 4 had an allergy to an interventional medicinal product.

[c]There were 574 patients with an unspecified reason, 27 needed an interpreter, 7 died prior to randomization, and 4 were not able to be randomized because the randomization system was unavailable.

[d]The primary outcome was time from randomization to successful extubation (defined as extubation followed by 48 hours of spontaneous breathing without mechanical ventilation).

[e]Data were omitted for 14 patients due to a serious breach at single study site, 7 did not have valid consent recorded, 7 withdrew consent for use of their data, 4 were randomized in error, and 1 was withdrawn by their next of kin.

or decreasing the α_2-adrenergic receptor agonist dose (eAppendices 5-6 in Supplement 2). The interventions continued until the patient (1) was successfully extubated, (2) died, (3) was transferred (before extubation to a nonparticipating ICU), or (4) reached 28 days of receiving mechanical ventilation.

Assessments were made to extrapolate sedation level and agitation (RASS score every 4 hours), delirium status (Confusion Assessment Method for the ICU every 12 hours[15]), and pain behavior (Sedation Quality Assessment Tool every 12 hours[16]); the data were recorded by clinical staff within a 12-hour nursing day (includes separate day and night shifts).

Trial Outcomes

The primary outcome was time from randomization to successful extubation (defined as extubation followed by 48 hours of spontaneous breathing without mechanical ventilation). For patients receiving noninvasive ventilation, a 48-hour period of receiving no more than 5 cm H_2O of continuous positive airway pressure was required to achieve the primary outcome (eAppendix 7 in Supplement 2). The primary outcome was ascertained by unblinded local research teams.

The secondary outcomes included all-cause mortality at 180 days; ICU length of stay; time to first RASS score of −2 or greater; time to first day without agitation, unnecessary deep sedation, or a pain behavior (lack of all 3 was considered overall optimum sedation); and the rates of delirium or coma and delirium when accessible without coma. The key safety outcomes (recorded daily) were rates of severe bradycardia (heart rate <50 beats/min), cardiac arrhythmia, and cardiac arrest. Other predefined daily sedation-related adverse events were also collected along with any other reported adverse events and serious adverse events (eAppendix 8 in Supplement 2).

The longer-term patient-centered outcomes (collected by blinded research staff) were health-related quality of life at 90 and 180 days (assessed using 5-level EuroQol-5 Dimension [EQ-5D-5L] visual analog scale and index scores),[17] anxiety and depression at 180 days (assessed using the Hospital Anxiety and Depression Scale),[18] posttraumatic stress at 180 days (assessed using the Revised Impact of Events Scale),[19] and cognitive function at 180 days (assessed using the Telephone Montreal Cognitive Assessment).[20] Each patient's experience with ICU care was measured descriptively for 4 domains

at 90 days (assessed using the Intensive Care Experience Questionnaire)[21] (eAppendix 9 in Supplement 2). Detailed descriptions of the secondary outcomes appear in eAppendix 7 in Supplement 2.

In addition, we recorded the daily dosages for the intravenous sedative and opioid medications and the rescue medications used for agitation or delirium. This report includes clinical effectiveness outcomes. A subsequent report will detail the health economics, process evaluation, and additional patient-centered outcomes.

We used hierarchical testing to control for type I error overall, while allowing sequential testing of several hypotheses. Stage 1 testing explored the superiority of clonidine vs propofol (hypothesis 1) and the superiority of dexmedetomidine vs propofol (hypothesis 2); both at the 2.5% level. If hypothesis 1 or 2 was significant (or if both hypotheses were significant), stage 2 testing would be used to test clonidine vs dexmedetomidine for noninferiority (hypothesis 3) and dexmedetomidine vs clonidine for superiority (hypothesis 4). If hypothesis 3 was significant, stage 3 testing would be used to explore the superiority of clonidine vs dexmedetomidine (hypothesis 5). Detailed descriptions of the testing strategies appear in eAppendix 10 in Supplement 2.

Based on published data,[22] we estimated that 53% of patients receiving usual care (propofol-based sedation) would be extubated at 7 days and 14% would die prior to extubation. We expected a heavily skewed median duration of mechanical ventilation of around 7 days in the usual care group and chose an overall mean difference of 2 days for superiority testing. This was consistent with the effects observed in a systematic review,[4] and corresponded to an assumed extubation rate of 63% at 7 days in the dexmedetomidine group or in the clonidine group and a hazard ratio (HR) of 1.37. A detailed description of the sample size modeling appears in eAppendix 10 in Supplement 2.

The sample size was originally 1737 but was decreased to 1437 (479 patients per group) because of the COVID-19 pandemic. The reduced sample size maintained 99% power for the superiority of clonidine vs propofol (hypothesis 1) and the superiority of dexmedetomidine vs propofol (hypothesis 2). The original power was only affected in the noninferiority comparison of clonidine vs dexmedetomidine (hypothesis 3). If required, this had 80% power to conclude noninferiority using a 1-sided significance level of 4% (increased from 2.5% in the original sample size calculation) and a noninferiority margin of 1 day. Based on published data, we estimated that this equates to a survival probability of 63% in the dexmedetomidine group at 7 days and 57% in the clonidine group. The increased significance level of 4% for the noninferiority comparison meant that the upper limit on the family-wise type I error rate increased from 5% to 6.5%. A detailed description of the sample size remodeling because of the COVID-19 pandemic appears in eAppendix 10 in Supplement 2.

Statistical Analysis

All analyses were conducted in accordance with the prespecified statistical analysis plan (Supplement 1). For the primary outcome, the median estimates and 95% CIs of time from randomization until successful extubation were computed within each treatment group using the simple Kaplan-Meier estimator with deaths treated as censored. A Fine and Gray proportional subdistribution hazards regression model was then fitted to the primary outcome and the allocated treatment was included as a fixed effect, adjusting for site and censoring withdrawals at the time of withdrawal.[23] Site was accounted for in the analysis by implementing the marginal model approach to the Fine and Gray method for clustered data.[23] This approach also addressed the potential competing risk of death. The results are reported as the subdistribution HR for each comparison and illustrated using cumulative incidence functions (eAppendix 11 in Supplement 2).

Several sensitivity analyses were undertaken to assess the robustness of the primary analysis (eAppendices 12-13 in Supplement 2). As a post hoc analysis and based on the fitted Fine and Gray primary analysis model, the absolute differences were calculated (difference in percentage of patients successfully extubated within 7 days). The 95% CIs were computed using a nonparametric bootstrap method based on 1000 resamples.

Prespecified subgroup analyses were performed and delineated by age (<64 vs ≥64 years), baseline delirium risk score (above or below the median),[24] baseline Sequential Organ Failure Assessment (SOFA) score (above or below the median),[25] and sepsis status (yes or no) at enrollment. We calculated subdistribution HRs for the dexmedetomidine group vs propofol and the clonidine group vs propofol and *P* values for interaction. We also fitted age as a continuous value in the interaction analyses.

For mortality, Kaplan-Meier survival curves and a mixed-effects proportional hazards regression analysis were used to analyze time to all-cause mortality. The post hoc unadjusted risk differences were also calculated with 95% CIs and computed[26] using the "epiR" package[27] and checked using the "propCI" package.[28]

For ICU length of stay after randomization, the same approach as for the primary outcome was used. For the sedation outcomes, time from randomization to the first 12-hour care period with a RASS score of −2 or greater and the time to the first day achieving overall optimum sedation (no agitation, unnecessary deep sedation, or a pain behavior) were compared using the same method as for the primary outcome. Rates of agitation (defined as a RASS score of 3 or 4), pain (presence of either of the 2 pain behaviors [limb movement or interaction with the ventilator]), unnecessary deep sedation (defined as a RASS score of −4 or −5 without indication for deep sedation), and overall optimum sedation were also compared during the 7 days after randomization using Poisson regression to calculate the rate ratio (RR). A similar approach was used to compare the rates of delirium or coma and delirium when accessible without coma during the 10 days after randomization. Sedation practice in the 3 groups (daily use of sedative and opioid medications and the use of rescue medications) were reported descriptively.

The proportions of patients in each group experiencing an episode of severe bradycardia, cardiac arrhythmia, and cardiac arrest during the intervention were reported. The rates of

these events were compared among the groups using Poisson regression and RRs were calculated. All predefined sedation-related adverse events, other reported adverse events, and serious adverse events were reported descriptively. Subgroup analyses for the mortality and cardiovascular safety outcomes were undertaken by age group (≥64 vs <64 years) and also with age as a continuous variable.

Detailed descriptions of the analytic methods for all the analyses (including the longer-term outcomes) appear in eAppendix 12 in Supplement 2. All analyses (except where indicated above) were undertaken using SAS version 9.4 (SAS Institute Inc). The graphical plots were generated using R software version 4.4.1 (R Foundation for Statistical Computing). Except where specified above, $P < .05$ was considered significant.

Results

Patient Characteristics

From December 2018 to October 2023, 1438 patients were randomized at 41 ICUs in the UK. Of the 1438 patients randomized, the reasons for excluding 34 patients from the primary outcome analysis population (defined in the statistical analysis plan in Supplement 1) were because there was a serious breach at single study site and data were omitted (n = 14), no valid consent was recorded (n = 7), patient withdrew data (n = 7), patients were randomized in error (n = 4), duplicate randomization (n = 1), and next of kin withdrew patient (n = 1). Further details appear in eAppendix 14 in Supplement 2.

The primary outcome analysis population comprised 1404 patients (mean age, 59.2 [SD, 14.9] years; 901 [64%] were male; and the mean APACHE [Acute Physiology and Chronic Health Evaluation] II score was 20.3 [SD, 8.2]). There were 457 patients allocated to receive dexmedetomidine-based sedation, 476 patients allocated to receive clonidine-based sedation, and 471 patients allocated to receive propofol-based sedation (usual care) (Figure 1). The last date of follow-up was December 10, 2023. In the ICU, the median time from mechanical ventilation to randomization was 21.0 hours (IQR, 13.2-31.3 hours).

The baseline characteristics of the patients were well-balanced (**Table 1**). At randomization, prior to commencing group-specific algorithms, 62% of patients had a RASS score of −4 or −5. For the subgroup analyses, 59% of patients were aged 64 years or younger; the median delirium (prediction of delirium in ICU patients [PRE-DELIRIC]) score was 73%; 66% of patients had sepsis; and the median SOFA score was 8 (>75% of patients had severe cardiovascular dysfunction, which was indicated by a SOFA score of 3 or 4).

Primary Outcome

For time to successful extubation, the subdistribution HR was 1.09 (95% CI, 0.96-1.25; $P = .20$) for dexmedetomidine vs propofol and the subdistribution HR was 1.05 (95% CI, 0.95-1.17; $P = .34$) for clonidine vs propofol; an HR greater than 1 favored use of dexmedetomidine or clonidine. The median times to extubation appear in **Table 2** and are illustrated in **Figure 2** (further information appears in eAppendix 11 and eAppendix 15 in Supplement 2). There was no significant difference in the proportion of patients receiving mechanical ventilation 7 days after randomization (Table 2). The findings were supported by the predefined sensitivity analyses (eAppendix 13 in Supplement 2). Because neither test for hypothesis 1 or 2 was significant the hypothesis testing was not undertaken for hypotheses 3 to 5 as per the predefined statistical analysis plan (Supplement 1).

Secondary Outcomes

Mortality and ICU Length of Stay

For mortality during the 180 days after randomization, the HR was 0.98 (95% CI, 0.77-1.24) for dexmedetomidine vs propofol and the HR was 1.04 (95% CI, 0.82-1.31) for clonidine vs propofol (Table 2 and eAppendix 16 in Supplement 2). There was no difference in the time to ICU discharge among the surviving patients (Table 2 and eAppendix 17 in Supplement 2).

Sedation Practice

For all 3 groups, the median number of 12-hour nursing shifts to first achieve a RASS score of −2 or greater was 2 and the median time to the first day without any unnecessary deep sedation, agitation, or pain behaviors was 3 days (Table 2). However, the rates of agitation were higher over the 7 days after randomization with both dexmedetomidine and clonidine compared with propofol (RR, 1.54 [95% CI, 1.21 to 1.97] for dexmedetomidine vs propofol and RR, 1.55 [95% CI, 1.22 to 1.97] for clonidine vs propofol). The rates of pain behaviors, unnecessary deep sedation, and overall optimum sedation were similar during the same period (eAppendix 18 in Supplement 2).

During days 2 to 14 after randomization, the clinician requests for deep sedation of patients ranged from 12% to 26% for dexmedetomidine, from 13% to 28% for clonidine, and from 12% to 29% for propofol. The target RASS score of −2 or greater was achieved in more than 75% of patients on most days in all 3 groups (**Figure 3**). In the propofol group, patients received propofol for a median of 4 days (IQR, 2 to 8 days). During days 2 to 7 after randomization, the median daily dose of propofol ranged from 22 to 26 mg/kg/d.

In the α_2-adrenergic receptor agonist groups (dexmedetomidine and clonidine), uptitration occurred as intended over the 24 hours after randomization. Patients received dexmedetomidine for a median of 4 days (IQR, 2-7 days). During days 2 to 7 after randomization, the median daily dose of dexmedetomidine ranged from 9 to 15 µg/kg/d. Patients in the dexmedetomidine group also received propofol on 77% of the days; the median daily dose of propofol ranged from 4 to 7 mg/kg/d.

Patients received clonidine for a median of 4 days (IQR, 2-7 days). During days 2 to 7 after randomization, the median daily dose ranged from 15 to 22 µg/kg/d. Patients in the clonidine group also received propofol on 76% of the days; the median daily dose of propofol ranged from 8 to 10 mg/kg/d. A further description of the sedation practice appears in eAppendix 19 in Supplement 2.

Alfentanil (54%) and fentanyl (28%) were the most frequently used analgesics at baseline. Subsequent daily doses of analgesics were similar among the groups. The proportion

Table 1. Baseline Characteristics for the Patients Included in the Primary Analysis Population

	Sedation group		
	Dexmedetomidine (n = 457)	Clonidine (n = 476)	Propofol (n = 471)
Age, y	(n =456)	(n = 472)	(n = 475)
Mean (SD)	58.8 (14.8)	59.6 (14.5)	59.2 (15.2)
Group, No. (%)			
18-64	287 (62.9)	272 (57.6)	268 (56.4)
65-84	164 (36.0)	193 (40.9)	203 (42.7)
≥85	5 (1.1)	7 (1.5)	4 (0.8)
Sex, No. (%)	(n =449)	(n = 469)	(n = 469)
Male	292 (65.0)	306 (65.2)	303 (64.6)
Female	157 (35.0)	163 (34.8)	166 (35.4)
Estimated weight, mean (SD), kg	(n =449) 81.7 (21.8)	(n = 469) 83.6 (22.8)	(n = 469) 81.7 (22.0)
Functional Comorbidity Index at admission, No. (%)[a]	(n =449)	(n = 469)	(n = 469)
0	121 (26.9)	115 (24.3)	119 (25.4)
1	123 (27.4)	134 (25.7)	122 (26.0)
2	97 (21.6)	103 (25.3)	120 (25.5)
≥3	108 (24.0)	117 (24.7)	108 (23.0)
APACHE II score, mean (SD)[b]	(n =449) 20.0 (8.0)	(n = 467) 20.3 (8.1)	(n = 467) 20.8 (8.5)
Time from start of mechanical ventilation in ICU to randomization, median (IQR), h	(n =457) 20.7 (12.9-31.4)	(n = 476) 21.0 (13.3-32.1)	(n = 471) 21.0 (13.4-30.5)
SOFA score, median (IQR)[c]	(n =449)	(n = 469)	(n = 469)
Respiratory	3 (2-3)	3 (2-3)	3 (2-3)
Cardiovascular	4 (3-4)	4 (3-4)	4 (3-4)
Coagulation	0 (0-1)	0 (0-1)	0 (0-1)
Kidney	1 (0-3)	1 (0-2)	1 (0-3)
Liver	0 (0-1)	0 (0-1)	0 (0-1)
Total[d]	8 (6-10)	8 (7-10)	8 (7-10)
Lactate level, mean (SD), mmol/L	(n =445) 1.7 (1.4)	(n = 468) 1.7 (1.5)	(n = 468) 1.6 (1.6)
Type of ICU admission	(n =449)	(n = 469)	(n = 469)
Medical			
Planned	10 (2)	6 (1)	9 (2)
Unplanned	271 (60)	275 (59)	286 (61)
Surgical			
Planned	23 (5)	30 (6)	27 (6)
Unplanned	112 (25)	116 (25)	117 (25)
Trauma			
Planned	5 (1)	2 (<1)	2 (<1)
Unplanned	28 (6)	40 (9)	28 (6)
Primary ICU admission diagnosis (by system)			
Cardiovascular	27 (6)	29 (7)	19 (5)
Respiratory	155 (36)	158 (36)	158 (38)
Gastrointestinal	120 (28)	108 (24)	112 (27)
Neurological	15 (4)	13 (3)	16 (4)
Other	110 (26)	133 (30)	111 (27)
Unknown	30 (7)	35 (8)	55 (13)
Sepsis status assessed, No. (%)[e]	(n =449) 297 (66.1)	(n = 469) 303 (64.6)	(n = 469) 308 (65.7)
PRE-DELIRIC (delirium) risk score, median (IQR), %[f]	(n =445) 73 (53-85)	(n = 468) 74 (55-86)	(n = 468) 72 (51-87)

(continued)

Table 1. Baseline Characteristics for the Patients Included in the Primary Analysis Population (continued)

	Sedation group		
	Dexmedetomidine (n = 457)	Clonidine (n = 476)	Propofol (n = 471)
RASS score prior to randomization, No. (%)[g]	(n =449)	(n = 469)	(n = 469)
−5 (Deep sedation)	89 (19.8)	95 (20.3)	90 (19.2)
−4	180 (40.1)	206 (43.9)	195 (41.6)
−3	112 (24.9)	108 (23.0)	119 (25.4)
−2	36 (8.0)	39 (8.3)	44 (9.4)
−1	14 (3.1)	14 (3.0)	11 (2.4)
0	7 (1.6)	4 (1)	4 (0.9)
1	5 (1.1)	0	3 (1)
2 to 4 (Severe agitation)	6 (2)	3 (1)	3 (1)
CAM-ICU status prior to randomization, No. (%)[h]	(n =445)	(n = 468)	(n = 468)
Coma (unable to assess)	339 (76.9)	369 (79.9)	364 (78.7)
Positive for delirium	48 (10.9)	42 (9.1)	39 (8.4)
Negative for delirium	54 (12.2)	51 (11.0)	59 (12.8)
Sedative and opioid use prior to randomization, No. (%)	(n =447)	(n = 467)	(n = 467)
Propofol	447 (100)	464 (99)	466 (>99)
Midazolam	17 (4)	28 (6)	28 (6)
Clonidine	11 (2)	7 (1)	6 (1)
Dexmedetomidine	5 (1)	3 (1)	3 (1)
Fentanyl	116 (26)	144 (31)	132 (28)
Alfentanil	250 (56)	252 (54)	248 (53)
Morphine	23 (5)	22 (5)	25 (5)
Remifentanil	60 (13)	63 (13)	63 (13)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; CAM-ICU, Confusion-Assessment Method for ICU patients; ICU, intensive care unit; PRE-DELIRIC, prediction of delirium in ICU patients; RASS, Richmond Agitation-Sedation Scale; SOFA, Sequential Organ Failure Assessment.

SI conversion factor: To convert lactate to mg/dL, divide by 0.111.

[a] The score reflects the number of comorbidities (from a list of 18 comorbidities); range, 0 (no comorbidity) to 18 (maximum number).

[b] Illness severity scoring system that predicts hospital mortality based on demographics, number of comorbidities, and acute physiology during first 24 hours in the ICU. Scores range from 0 to 71; a score of 0 to 10 reflects low risk of hospital mortality; 11 to 20, moderate risk; 21 to 30, high risk; and 31 or greater, very high risk.

[c] Assesses organ failure for 6 organs. A score of 0 was given for no organ failure and 4 for severe organ failure. The maximum score was 20; higher scores are associated with greater risk of death in the ICU.

[d] The neurological score was excluded (often omitted in non–neurological populations receiving sedation).

[e] Based on clinical assessment at enrollment and recorded as yes or no.

[f] Comprises 10 risk factors for delirium (available within 24 hours of ICU admission). The score provides an estimated percentage risk (range, 0%-100%); 0% to 20% indicates low risk; 20% to 40%, moderate risk; 40% to 60%, high risk; and greater than 60%, very high risk.

[g] Based on observation, voice, and physical stimulation; score range, −5 (deep sedation) to 4 (severe agitation) using a 10-point scale.

[h] Based on sedation status (RASS score), attention assessment, and disorganized thinking. The score was modified to allow clinicians to judge if they could assess delirium when RASS score was −3.

of patients that received rescue medication for agitation was 31% for dexmedetomidine, 34% for clonidine, and 38% for propofol. Further details of the use of analgesia and rescue medication appear in eAppendices 19 and 20 in Supplement 2.

Delirium or Coma and Delirium When Accessible Without Coma

Compared with the propofol group, there was no difference in the rates of delirium or coma for dexmedetomidine (RR, 0.94 [95% CI, 0.88-1.00]) or clonidine (RR, 0.97 [95% CI, 0.91-1.04]). Compared with the propofol group, there was also no difference in the rates of delirium when accessible without coma for dexmedetomidine (RR, 0.96 [95% CI, 0.84-1.10]) or clonidine (RR, 1.03 [95% CI, 0.91 to 1.18]). Further information appears in eAppendix 18 in Supplement 2.

Safety

The prevalence of severe bradycardia during the intervention was higher in the dexmedetomidine group (33%) and in the clonidine group (33%) than in the propofol group (20%). During the intervention period, the RR for severe bradycardia was 1.62 (95% CI, 1.36-1.93) for dexmedetomidine vs propofol and the RR was 1.58 (95% CI, 1.33-1.88) for clonidine vs propofol. The prevalence and rates of cardiac arrhythmia and cardiac arrest appear in eAppendix 21 in Supplement 2. There was a higher rate of cardiac arrhythmia reported with dexmedetomidine vs propofol (RR, 1.27 [95% CI, 1.15-1.40]). More patients had serious adverse events and adverse events reported in the dexmedetomidine group than in the propofol group or in the clonidine group (Table 2). The rates for the other

Table 2. Primary and Secondary Outcomes

	Sedation group			Absolute difference, % (95% CI)[a]		Relative difference, hazard ratio (95% CI)	
	Dexmedetomidine	Clonidine	Propofol	Dexmedetomidine vs propofol	Clonidine vs propofol	Dexmedetomidine vs propofol	Clonidine vs propofol
No. of patients	457	476	471				
Primary outcome							
Time to successful extubation, median (95% CI), h	136 (117 to 150)	146 (124 to 168)	162 (136 to 170)	3.13 (−2.33 to 8.43)[b]	1.77 (−3.25 to 6.90)[b]	1.09 (0.96 to 1.25)	1.05 (0.95 to 1.17)
P value						.20	.34
Secondary outcomes							
Mortality, No./total (%)							
In ICU	96/454 (21)	103/472 (22)	105/467 (22)	−1.34 (−6.67 to 4.01)	−0.66 (−5.98 to 4.66)	0.95 (0.72 to 1.26)	0.98 (0.74 to 1.28)
At 90 d	122/457 (27)	138/476 (29)	135/471 (29)	−1.97 (−7.71 to 3.80)	0.33 (−5.44 to 6.09)	0.95 (0.74 to 1.21)	1.03 (0.82 to 1.31)
At 180 d	132/457 (29)	145/476 (30)	141/471 (30)	−1.05 (−6.91 to 4.81)	0.53 (−5.32 to 6.37)	0.98 (0.77 to 1.24)	1.04 (0.82 to 1.31)
Time from randomization to ICU discharge, median (95% CI), d	11 (10 to 12)	12 (10 to 13)	12 (11 to 13)			1.05 (0.92 to 1.19)	1.01 (0.91 to 1.12)
Time to optimization of sedation							
No. of 12-h nursing shifts from randomization to first RASS score of ≥−2, median (95% CI)	2 (2 to 2)	2 (2 to 2)	2 (2 to 2)			1.06 (0.96 to 1.17)	1.06 (0.97 to 1.16)
Time from randomization to first day with optimum sedation (no recorded agitation, unnecessary deep sedation, or pain behavior), median (95% CI), d	3 (3 to 4)	3 (3 to 4)	3 (2 to 3)			0.94 (0.83 to 1.07)	0.95 (0.82 to 1.10)
Patients with ≥1 event, No. (%)							
Serious adverse events[c]	20 (4.4)	12 (2.5)	4 (0.8)				
Adverse events[d]	47 (10.3)	26 (5.5)	16 (3.4)				
Long-term patient-centered outcomes at 90 d							
Health-related quality of life (EQ-5D-5L) visual analog scale score, mean (SD)[e,f]	(n = 93) 68 (18)	(n = 105) 60 (21)	(n = 120) 63 (23)	MD, 4.99 (−0.64 to 10.63)	MD, −2.13 (−7.58 to 3.32)		
Health-related quality of life (EQ-5D-5L) index score (excluding deaths), mean (SD)[f,g]	(n = 92) 0.59 (0.29)	(n = 103) 0.57 (0.28)	(n = 118) 0.54 (0.33)	MD, 0.05 (−0.04 to 0.13)	MD, 0.02 (−0.06 to 0.10)		

(continued)

Table 2. Primary and Secondary Outcomes (continued)

	Sedation group			Absolute difference, % (95% CI)[a]		Relative difference, hazard ratio (95% CI)	
	Dexmedetomidine	Clonidine	Propofol	Dexmedetomidine vs propofol	Clonidine vs propofol	Dexmedetomidine vs propofol	Clonidine vs propofol
Long-term patient-centered outcomes at 180 d							
Hospital Anxiety and Depression Scale score, mean (SD)[f,h]	(n = 69) 13.4 (9.9)	(n = 80) 13.6 (9.6)	(n = 85) 14.8 (9.5)	MD, −1.41 (−4.49 to 1.68)	MD, −1.18 (−4.14 to 1.79)		
Revised Impact of Events Scale (posttraumatic stress) score, mean (SD)[f,i]	(n = 62) 24.6 (20.8)	(n = 71) 22.7 (21.7)	(n = 71) 30.6 (24.9)	MD, −6.06 (−13.80 to 1.69)	MD, −7.97 (−15.45 to −0.49)		
Telephone Montreal Cognitive Assessment score, mean (SD)[f,j]	(n = 67) 16.5 (3.5)	(n = 57) 17.0 (3.3)	(n = 63) 16.3 (4.0)	MD, 0.16 (−1.09 to 1.40)	MD, 0.66 (−0.63 to 1.96)		
Health-related quality of life (EQ-5D-5L) visual analog scale score, mean (SD)[e,f]	(n = 71) 68 (23)	(n = 84) 67 (20)	(n = 90) 66 (23)	MD, 0.82 (−6.00 to 7.64)	MD, 0.28 (−6.22 to 6.79)		
Health-related quality of life (EQ-5D-5L) index score, mean (SD)[f,g]	(n = 69) 0.61 (0.35)	(n = 83) 0.61 (0.29)	(n = 88) 0.54 (0.34)	MD, 0.06 (−0.04 to 0.17)	MD, 0.07 (−0.03 to 0.16)		

Abbreviations: EQ-5D-5L, 5-level EuroQol-5 Dimension; ICU, intensive care unit; MD, mean difference; RASS, Richmond Agitation-Sedation Scale.

[a] Unless otherwise indicated. The absolute differences and MDs reflect dexmedetomidine- or clonidine-based sedation minus propofol-based sedation.

[b] Difference in percentage of patients successfully extubated within 7 days.

[c] Defined as an adverse event (defined below in [d]) during ICU stay that was life-threatening, resulted in a prolonged hospitalization, or resulted in significant disability or incapacity. These events were reported at discretion of the local research team. All events were reported to the sponsor within 24 hours, reviewed by the chief investigator, and an agreed upon categorization made: unrelated, possibly related, expected, or unexpected (additional details appear in Supplement 1).

[d] Defined as any untoward medical occurrence not included within the predefined secondary outcome reporting. New or deteriorating organ function, new infections, procedure complications, co-prescribed medication reactions, and additional procedures (eg, surgery) did not require routine reporting. These events were reported at discretion of the local research team during ICU stay only (additional details appear in Supplement 1).

[e] Score range, 0 to 100; 0 indicates the worst possible health state and 100 indicates the best possible health state. The minimum clinically important difference is around 7 points.

[f] Based on data from surviving patients who completed questionnaires.

[g] Score range, −0.59 to 1 (best possible health state). A score of 0 indicates death; negative scores indicate health states worse than death. Only scores for survivors were included.

[h] The combined anxiety and depression subscale scores range from 0 to 42 (0-21 for each subscale); higher scores indicate greater anxiety, depression, or both. Scores from 0 to 14 were considered normal (no anxiety or depression); 15 to 20 (mild anxiety or depression); 21 to 30, moderate; and 31 to 42, severe. The minimum clinically important difference was 2 to 5 points.

[i] Score range, 0 to 88; higher scores indicate greater posttraumatic stress. A score of 33 or greater indicates likely presence of posttraumatic stress disorder. The minimum clinically important difference was around 9 points.

[j] Maximum score of 22; higher scores indicate cognitive impairment. A suggested cutoff of 17 or greater was used to diagnose mild cognitive impairment. The minimum clinically important difference was 1 or 2 points.

predefined sedation-related adverse events collected daily (including severe hypotension) were similar among groups (eAppendix 8 in Supplement 2).

Long-Term Patient-Centered Outcomes

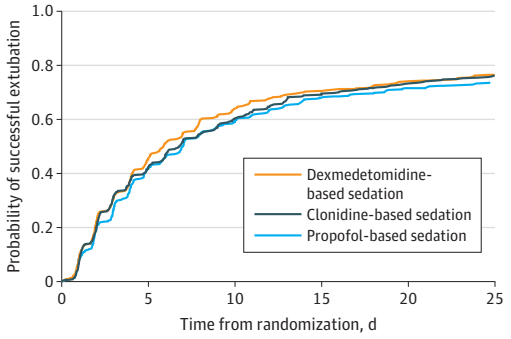
For patients completing long-term follow-up, there were no clinically important differences in the quality of life or psychological outcomes among the groups (Table 2). Responses to the patient experience questionnaire are summarized in eAppendix 9 in Supplement 2.

Subgroup Analyses

For the primary outcome, there was no significant interaction with any of the 4 predefined subgroup analyses (**Figure 4**). A weak interaction with age (when considered as a continuous variable) was observed for dexmedetomidine vs propofol, suggesting reduced benefit on time to extubation with increasing age (HR, 0.90 [95% CI, 0.82-0.99] per 10-year increment of age; eAppendix 13 in Supplement 2). For mortality, no interactions with age were found for either dexmedetomidine or clonidine compared with propofol (eAppendix 16 in Supplement 2).

There were no interactions between age group (<64 years vs ≥64 years) and the rates of severe bradycardia for dexmedetomidine or clonidine, but the association with severe bradycardia for clonidine lessened with increased age per 10-year increment. For dexmedetomidine, the rates of cardiac arrhythmia appeared higher among younger patients. Conversely, the rates of cardiac arrhythmia appeared lower for clonidine among younger patients. Further details appear in eAppendix 21 in Supplement 2.

Figure 2. Cumulative Incidence Plot for Time From Randomization to Successful Extubation



No. at risk

Dexmedetomidine-based sedation	456	325	234	175	129	104
Clonidine-based sedation	476	343	249	195	160	125
Propofol-based sedation	471	357	265	206	158	127

The median duration of follow-up was 4.7 days (IQR, 2.0-9.8 days) for dexmedetomidine; 4.9 days (IQR, 2.0-10.8 days) for clonidine; and 5.0 days (IQR, 2.2-11.2 days) for propofol. There were initially 456 patients at risk in the dexmedetomidine group rather than 457 because information on ultimate extubation status was not available for 1 patient (eAppendix 15 in Supplement 2).

Discussion

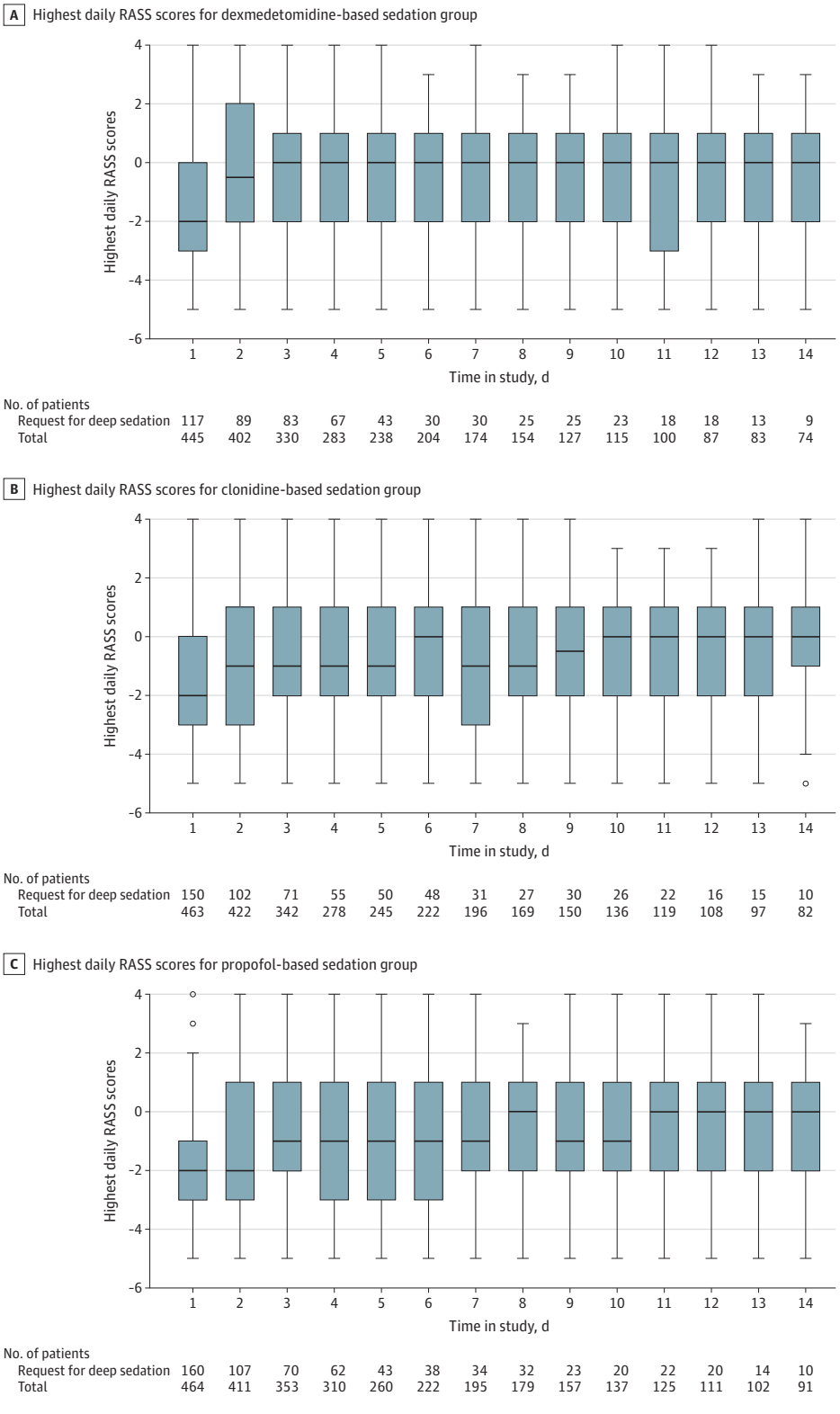
We found that dexmedetomidine and clonidine were not superior to propofol-based sedation for reducing time to successful extubation in critically ill patients when either intervention was introduced within 48 hours of initiating mechanical ventilation. We found no evidence of improved sedation quality or less delirium. The rates of agitation and severe bradycardia were higher in both the dexmedetomidine and clonidine groups.

Our findings were consistent in the sensitivity analyses. No interactions were found in the predefined subgroup analyses of baseline organ failure severity, delirium risk, or the presence of sepsis with either dexmedetomidine or clonidine. Given the SPICE III trial findings,[7] we explored interactions with age for the primary outcome, mortality, and cardiovascular adverse events. Several interactions were found between age and the primary outcome, severe bradycardia, and cardiac arrhythmia, but not mortality. However, these findings should be interpreted with caution because they are secondary analyses.

We observed 60% higher rates of severe bradycardia with both dexmedetomidine and clonidine. Bradycardia occurred in one-third of patients, which is substantially higher than the rates reported in previous trials. A possible explanation is the daily recording of cardiovascular safety events in the current trial, whereas previous trials[7,29] had nonsystematic recording of cardiovascular safety events. The higher rates of cardiac arrhythmia were reported with dexmedetomidine, but not clonidine, and occurred more frequently in younger patients. Whether these cardiovascular adverse effects directly affect clinical outcomes is uncertain and merits further study, but they likely limited dose escalation and might explain the continued use of propofol in many of the patients.

Sedation is a complex intervention involving medications, guidelines, clinician behaviors, and organizational culture.[30,31] In the current pragmatic trial, clinicians implemented group-specific algorithms that were adapted to individual patient needs and dose-limiting effects. Treatment allocation was well maintained, with low rates of crossover to dexmedetomidine or clonidine as rescue medication in the propofol group. The quality of sedation achieved appeared similar with all 3 sedation methods, with the exception of agitation which occurred at a 55% higher rate with both dexmedetomidine and clonidine. Clinician request for deep sedation occurred on 25% to 30% of days in all groups, which is similar to the rates in the SPICE III trial.[7] Clinician request for deep sedation might reflect resistance to lighter sedation in clinical practice, although the median time to achieving the RASS score target of −2 or greater was within 24 hours for all groups, and around 75% of patients achieved this target on most study days. Overall, patients also had high levels of illness severity, which may have influenced the clinicians' choice of deeper sedation for some patients. The higher observed rates of agitation with dexmedetomidine and clonidine was surprising, given rescue medication use was similar. These increased rates of agitation might reflect less clinician experience using dexmedetomidine and clonidine for primary sedation.

Figure 3. Box-and-Whisker Plots Showing the Highest Richmond Agitation-Sedation Scale (RASS) Scores Achieved

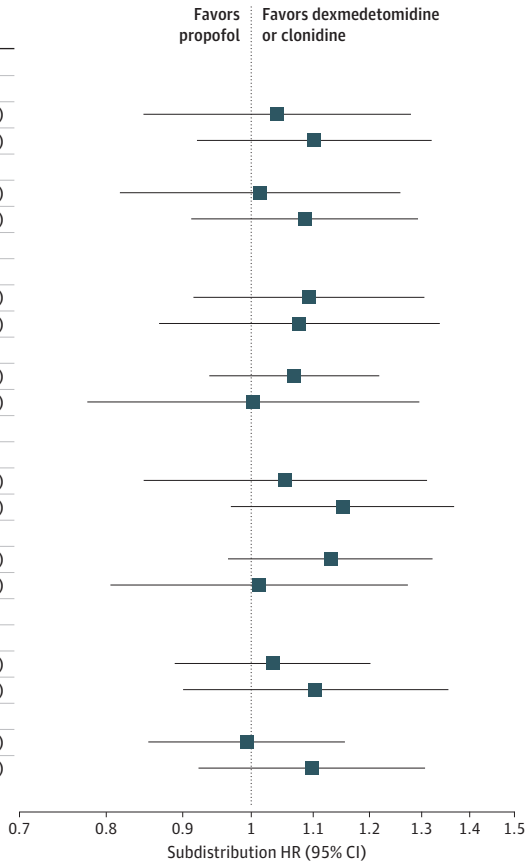


Includes patients who have not yet achieved the primary outcome. Each box represents the IQR; the bottom and top of the boxes are the first and third quartiles, respectively, with the median shown as a horizontal line inside each box. The whiskers extend to the minimum and maximum values within 1.5 times the IQR from the quartiles. Any values outside the whiskers are represented by circles to identify them as potential outliers. Unless deep sedation was requested by medical staff, bedside algorithms indicated a target RASS score of −2 to 1; score range, −5 (unresponsive) to 4 (combative).

Most patients in the dexmedetomidine group or clonidine group continued to receive some propofol. The median daily doses of propofol in the dexmedetomidine and clonidine groups were generally small (25%-30% of the dose used in the propofol group), indicating propofol was used as an adjunct sedative. Several factors may explain this. First, the high rates of

Figure 4. Predefined Subgroup Analyses

Subgroup analyses	Dexmedetomidine or clonidine		Propofol		Subdistribution HR (95% CI)
	No. of events	No. of patients	No. of events	No. of patients	
Age, y					
Dexmedetomidine vs propofol					
≥64	127	183	153	212	1.04 (0.85-1.28)
<64	231	273	216	259	1.10 (0.92-1.32)
Clonidine vs propofol					
≥64	153	212	153	212	1.01 (0.82-1.26)
<64	221	264	216	259	1.09 (0.91-1.29)
Sepsis					
Dexmedetomidine vs propofol					
Yes	230	296	238	308	1.09 (0.92-1.31)
No	128	152	131	161	1.08 (0.87-1.34)
Clonidine vs propofol					
Yes	238	303	238	308	1.07 (0.94-1.22)
No	136	166	131	161	1.00 (0.78-1.30)
PRE-DELIRIC (delirium) risk score[a]					
Dexmedetomidine vs propofol					
≥Median	160	220	166	227	1.05 (0.85-1.31)
<Median	197	225	197	235	1.15 (0.97-1.37)
Clonidine vs propofol					
≥Median	185	238	166	227	1.13 (0.97-1.32)
<Median	184	224	197	235	1.01 (0.81-1.27)
SOFA score[b]					
Dexmedetomidine vs propofol					
≥Median	181	247	206	278	1.03 (0.89-1.20)
<Median	153	172	145	168	1.10 (0.90-1.35)
Clonidine vs propofol					
≥Median	199	273	206	278	0.99 (0.86-1.15)
<Median	156	175	145	168	1.10 (0.92-1.31)



PRE-DELIRIC indicates prediction of delirium in intensive care unit (ICU) patients; SOFA, Sequential Organ Failure Assessment.

[a]Comprises 10 risk factors for delirium (available within 24 hours of ICU admission). The score provides an estimated percentage of risk (range, 0%-100%); 0% to 20% indicates low risk; 20% to 40%, moderate risk; 40% to 60%, high risk; and greater than 60%, very high risk. The median score was 73%.

[b]Assesses organ failure for 6 organs. A score of 0 was given for no organ failure and 4 for severe organ failure. The maximum score was 20; higher scores are associated with greater risk of death in the ICU. The median score (excluding neurological score) was 8. The neurological score is often omitted in non–neurological populations receiving sedation.

shock in the trial population and the significantly higher observed rates of severe bradycardia with both dexmedetomidine and clonidine likely limited dosing, and propofol was required to achieve sedation targets. Second, the higher rates of observed agitation may have required supplemental propofol, especially given benzodiazepine use was avoided, which is consistent with guidelines.[14] Third, the COVID-19 pandemic had a major effect on staff numbers and experience during the conduct of the trial, and nurses may have lacked confidence when administering dexmedetomidine or clonidine alone.

The use of opioid analgesia, which was based on clinical discretion, was similar among the groups despite the known analgesic properties of dexmedetomidine and clonidine. Pain behaviors were reported on 35% to 45% of days in all groups, with no differences among the groups, indicating the importance of balancing light sedation with adequate analgesia. We found no reduction in delirium despite the high delirium risk and prevalence. This finding is consistent with the lack of significant effects found in other recent trials.[7,29]

The current trial adds to the uncertainty[2,3,6,7,29] about the clinical effectiveness of dexmedetomidine as a primary sedative. Caution exists for use of dexmedetomidine in younger patients because higher mortality was found in the SPICE III trial.[7,32] In the current trial, 59% of patients were aged 64 years or younger. We found no interactions between mortality and age, but these were secondary analyses. If dexmedetomidine causes harm, it could be dose-related and the individual clinical judgment allowed in the current trial might have decreased dose-related toxicity.[9,32,33]

The most recent international practice guideline[34] recommends only using dexmedetomidine "when desirable effects are valued over undesirable effects." The current trial is the first, to our knowledge, of clonidine-based sedation. Our findings do not support the routine early use of either a dexmedetomidine- or a clonidine-based sedation strategy as an alternative to propofol.

The strengths of the current trial include the broad population studied and the use of a pragmatic design, which

increases generalizability. The primary outcome was relevant to clinicians and patients, and we described sedation, delirium, and safety outcomes in detail. Sedation practice was comprehensively described, we systematically recorded important adverse effects, and primary outcome completeness was greater than 95%. We met most expert recommendations recently described for sedation trial design and conduct.[35]

Limitations

Our trial has important limitations. First, the intervention was unblinded and the primary outcome was measured by unblinded researchers, which could have resulted in bias. Second, although clear separation in treatment exposure was achieved, the continued use of low-dose propofol in the dexmedetomidine and clonidine groups may have influenced outcomes. Third, best practice for sedation targets, weaning of mechanical ventilation, and the use of analgesia were encouraged, but could not be tightly controlled. We cannot exclude different effects if these were more tightly protocolized. Fourth, although our trial had high statistical power for the chosen minimum clinically important difference, we cannot exclude smaller effects on the primary outcome with certainty. Fifth, our findings cannot be extrapolated to all critically ill patients (eg, those with less severe illness) or excluded patients (such as those who had cardiac surgery or a brain injury).

Conclusions

In critically ill patients, neither dexmedetomidine nor clonidine was superior to propofol in reducing time to successful extubation.

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Author Contributions: Drs Walsh and Weir had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Walsh, Parker, Aitken, McKenzie, Lone, Kydonaki, Norrie, Creagh-Brown, McAuley, Dark, Wise, Gordon, Perkins, Reade, Blackwood, MacLullich, Glen, Page, Weir.
Acquisition, analysis, or interpretation of data: Walsh, Parker, Aitken, McKenzie, Emerson, Boyd, Macdonald, Beveridge, Giddings, Hope, Irvine, Tuck, Lone, Norrie, Brealey, Antcliffe, Reay, Williams, Bewley, McAuley, Dark, Wise, Perkins, Reade, Blackwood, MacLullich, Page, Weir.
Drafting of the manuscript: Walsh, McKenzie, Irvine, Lone, Bewley, Creagh-Brown, McAuley, Blackwood, MacLullich, Glen, Page, Weir.
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Statistical analysis: Walsh, Parker, Tuck, Lone, Norrie.
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Administrative, technical, or material support: Walsh, Aitken, McKenzie, Boyd, Macdonald, Beveridge, Giddings, Hope, Irvine, Bewley, McAuley, Gordon.
Supervision: Boyd, Beveridge, Giddings, Bewley, McAuley, MacLullich, Glen, Weir.

Conflict of Interest Disclosures: Dr McKenzie reported receiving a senior clinical practitioner research award from the National Institute for Health and Care Research and receiving personal fees from Pharmaceutical Press for serving as editor in chief of *Critical Illness*. Dr Lone reported being the director of research and the intensive care society chair for the Scottish Intensive Care Society Audit Group, Public Health Scotland. Dr Norrie reported receiving grants from the University of Edinburgh and serving as chair of the National Institute for Health and Care Research funding committee. Dr Bewley reported serving as a consultant to Bayer PLC. Dr McAuley reported receiving personal fees for serving as a consultant to Bayer, GlaxoSmithKline, Boehringer Ingelheim, Novartis, Eli Lilly, Vir Biotechnology, Aptarion, Aviceda, and Direct Biologics; receiving grants from Wellcome Trust, Innovate UK, Medical Research Council, and the HSC Public Health Agency; having a patent for an anti-inflammatory treatment that was issued to Queen's University Belfast; and serving as codirector of research for the Intensive Care Society and serving as program director for the National Institute for Health and Care Research/Medical Research Council. Dr Wise reported receiving personal fees from the National Institute for Health and Care Excellence and Diagnostics for the Real World. Dr Gordon reported receiving personal fees from AstraZeneca that were paid to his institution. No other disclosures were reported.

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