

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

# Inhaled Sedation in Acute Respiratory Distress Syndrome

## The SESAR Randomized Clinical Trial

Matthieu Jabaudon, MD, PhD; Jean-Pierre Quenot, MD, PhD; Julio Badie, MD; Jules Audard, MD; Samir Jaber, MD, PhD; Benjamin Rieu, MD; Caroline Varillon, MD; Antoine Monsel, MD, PhD; François Thouy, MD; Julien Lorber, MD; Joël Cousson, MD; Stéphanie Bulyez, MD; Jérémy Bourenne, MD; Ghada Sboui, MD; Claire Lhommet, MD; Virginie Lemiale, MD, PhD; Belaïd Bouhemad, MD, PhD; Clément Brault, MD; Sigismond Lasocki, MD, PhD; François Legay, MD; Thomas Lebouvier, MD; Arthur Durand, MD; Julien Pottecher, MD, PhD; Alexandre Conia, MD; Delphine Brégeaud, MD; Lionel Velly, MD, PhD; Arnaud W. Thille, MD, PhD; Fabien Lambiotte, MD; Erwan L'Her, MD, PhD; Mehran Monchi, MD; Antoine Roquilly, MD, PhD; Aziz Berrouba, MD; Franck Verdonk, MD, PhD; Russell Chabanne, MD; Thomas Godet, MD, PhD; Marc Garnier, MD, PhD; Raiko Blondonnet, MD, PhD; Jérémy Vernhes, MD; Vincent Sapin, PharmD, PhD; Lucile Borao, MSc; Emmanuel Futier, MD, PhD; Bruno Pereira, PhD; Jean-Michel Constantin, MD, PhD; for the SESAR Trial Investigators

**IMPORTANCE** Whether the use of inhaled or intravenous sedation affects outcomes differentially in mechanically ventilated adults with acute respiratory distress syndrome (ARDS) is unknown.

**OBJECTIVE** To determine the efficacy and safety of inhaled sevoflurane compared with intravenous propofol for sedation in patients with ARDS.

**DESIGN, SETTING, AND PARTICIPANTS** Phase 3 randomized, open-label, assessor-blinded clinical trial conducted from May 2020 to October 2023 with 90-day follow-up. Adults with early moderate to severe ARDS (defined by a ratio of  $Pao_2$  to the fraction of inspired oxygen of  $<150$  mm Hg with a positive end-expiratory pressure of  $\geq 8$  cm  $H_2O$ ) were enrolled in 37 French intensive care units.

**INTERVENTIONS** Patients were randomized to a strategy of inhaled sedation with sevoflurane (intervention group) or to a strategy of intravenous sedation with propofol (control group) for up to 7 days.

**MAIN OUTCOMES AND MEASURES** The primary end point was the number of ventilator-free days at 28 days; the key secondary end point was 90-day survival.

**RESULTS** Of 687 patients enrolled (mean [SD] age, 65 [12] years; 30% female), 346 were randomized to sevoflurane and 341 to propofol. The median total duration of sedation was 7 days (IQR, 4 to 7) in both groups. The number of ventilator-free days through day 28 was 0.0 days (IQR, 0.0 to 11.9) in the sevoflurane group and 0.0 days (IQR, 0.0 to 18.7) in the propofol group (median difference,  $-2.1$  [95% CI,  $-3.6$  to  $-0.7$ ]; standardized hazard ratio, 0.76 [95% CI, 0.50 to 0.97]). The 90-day survival rates were 47.1% and 55.7% in the sevoflurane and propofol groups, respectively (hazard ratio, 1.31 [95% CI, 1.05 to 1.62]). Among 4 secondary outcomes, sevoflurane was associated with higher 7-day mortality (19.4% vs 13.5%, respectively; relative risk, 1.44 [95% CI, 1.02 to 2.03]) and fewer intensive care unit-free days through day 28 (median, 0.0 [IQR, 0.0 to 6.0] vs 0.0 [IQR, 0.0 to 15.0]; median difference,  $-2.5$  [95% CI,  $-3.7$  to  $-1.4$ ]) compared with propofol.

**CONCLUSIONS AND RELEVANCE** Among patients with moderate to severe ARDS, inhaled sedation with sevoflurane resulted in fewer ventilator-free days at day 28 and lower 90-day survival than sedation with propofol.

**TRIAL REGISTRATION** ClinicalTrials.gov Identifier: [NCT04235608](https://clinicaltrials.gov/ct2/show/study/NCT04235608)

JAMA. doi:[10.1001/jama.2025.3169](https://doi.org/10.1001/jama.2025.3169)  
Published online March 18, 2025.

- [+ Visual Abstract](#)
- [+ Editorial](#)
- [+ Multimedia](#)
- [+ Supplemental content](#)

**Author Affiliations:** Author affiliations are listed at the end of this article.

**Group Information:** The SESAR Trial Investigators appear in Supplement 3.

**Corresponding Author:** Matthieu Jabaudon, MD, PhD, Department of Perioperative Medicine, CHU Clermont-Ferrand and iGReD, CNRS, INSERM, Université Clermont Auvergne, 58 rue Montalembert, 63000 Clermont-Ferrand, France ([mjabaudon@chu-clermontferrand.fr](mailto:mjabaudon@chu-clermontferrand.fr)).

**A**cute respiratory distress syndrome (ARDS) is frequent in patients admitted to an intensive care unit (ICU) and is associated with high hospital mortality rates (35%-46%).<sup>1</sup> Mechanical ventilation remains crucial in managing patients with ARDS,<sup>2</sup> often requiring sedation to improve tolerance and synchrony.<sup>3</sup> However, optimal sedation choice remains unclear.

Guidelines recommend light sedation with nonbenzodiazepine sedatives, such as propofol or dexmedetomidine, in critically ill, ventilated patients (conditional recommendation with a low quality of evidence).<sup>4</sup> However, specific guidance for sedation in patients with ARDS is lacking owing to sparse evidence. Deep sedation and neuromuscular blockade may be required to facilitate lung-protective ventilation during moderate to severe ARDS.<sup>5</sup> Propofol, despite potential adverse effects during high-dose or prolonged use, is often favored for its titratability and organ-independent clearance.<sup>5,6</sup>

Inhaled volatile anesthetics are emerging alternatives, although evidence in patients with ARDS remains scarce. In a pilot trial involving patients with moderate to severe ARDS, inhaled sevoflurane was feasible, improved oxygenation, and decreased markers of inflammation and lung epithelial injury compared with midazolam.<sup>7</sup> A noninferiority trial comparing inhaled isoflurane with propofol in invasively ventilated ICU patients supported the efficacy and safety of inhaled sedation,<sup>8</sup> and a systematic review found that inhaled sedation was associated with faster awakening and extubation than intravenous sedation.<sup>9</sup> However, these findings may not apply to patients with ARDS.

The current study hypothesized that inhaled sedation with sevoflurane could increase the number of days alive and free of mechanical ventilation in patients with ARDS. Thus, the Sevoflurane for Sedation in ARDS (SESAR) trial was conducted to determine the efficacy and safety of early sedation with inhaled sevoflurane compared with propofol in patients with moderate to severe ARDS.

## Methods

### Trial Design and Oversight

We conducted this investigator-initiated, multicenter, open-label, assessor-blinded, randomized trial in 37 ICUs in France. The trial was sponsored by the University Hospital of Clermont-Ferrand (France) and funded by the French Ministry of Health, the European Society of Anesthesiology and Intensive Care, and Sedana Medical.

The trial protocol,<sup>10</sup> which was approved by an ethics committee (Comité de Protection des Personnes Ile-de-France 2) and the French medicines agency (Agence Nationale de Sécurité du Médicament et des Produits de Santé), and initial and modified statistical analysis plans are available in [Supplement 1](#). The trial was registered with ClinicalTrials.gov (NCT04235608) and its report follows the Consolidated Standards of Reporting Trials reporting guidelines and checklist.

Patients or their legally authorized representative provided written informed consent. Additional details on methods are available in the eMethods in [Supplement 2](#).

### Key Points

**Question** Is a strategy of inhaled sedation with sevoflurane safe and associated with improved clinical outcomes in patients with acute respiratory distress syndrome compared with a strategy of intravenous sedation with propofol?

**Findings** In this randomized clinical trial that included 687 intensive care unit patients with moderate to severe acute respiratory distress syndrome, inhaled sedation with sevoflurane resulted in fewer ventilator-free days at 28 days and lower survival at 90 days than intravenous sedation with propofol.

**Meaning** These findings do not support a strategy of inhaled sedation with sevoflurane in critically ill patients with moderate to severe acute respiratory distress syndrome.

### Patient Selection and Randomization

We enrolled adult patients ( $\geq 18$  years of age) who were undergoing invasive mechanical ventilation and met the Berlin definition criteria for less than 24 hours,<sup>11</sup> with a ratio of  $P_{aO_2}$  to the fraction of inspired oxygen ( $F_{iO_2}$ ) of less than 150 mm Hg and a positive end-expiratory pressure (PEEP) of 8 cm  $H_2O$  or more. Patients were excluded if they were pregnant; had suspected or proven intracranial hypertension; had long QT syndrome; had history of (or predisposition for) malignant hyperthermia or liver disease from volatile anesthetics; had hypersensitivity to sevoflurane, propofol, or cisatracurium; had persistent bronchopleural fistula; or had received mechanical ventilation for more than 120 hours before enrollment. Further details are provided in the eMethods in [Supplement 2](#).

Patients were randomly assigned by local investigators using a web-based system in a 1:1 ratio to receive sevoflurane or propofol. Randomization was stratified by site, ARDS severity ( $P_{aO_2}:F_{iO_2} < 100$  mm Hg or  $\geq 100$  mm Hg), suspected or proven COVID-19, and shock (defined as the intravenous infusion of vasoactive drugs).

### Trial Interventions and Measurements

All patients initially received deep sedation, targeting a score on the Richmond Agitation-Sedation Scale (RASS) of  $-5$  to  $-4$  (range:  $-5$  [unresponsive] to  $4$  [combative]), with  $0$  meaning alert and calm),<sup>12</sup> with subsequent neuromuscular blockade using continuous cisatracurium infusion for up to 48 hours, or until  $P_{aO_2}:F_{iO_2}$  of at least 150 mm Hg for 4 hours or more with an  $F_{iO_2}$  of  $0.6$  or lower. Then, the use of light sedation (RASS score,  $-1$  to  $0$ ) was recommended with daily awakening and spontaneous-breathing trials. Initial deep sedation with cisatracurium was believed to be a common and clinically relevant approach to patients with severe hypoxemia, as per available guidelines when designing the trial.<sup>13</sup> In both groups, patients received the allocated intervention until the trial drug was permanently discontinued or until the 7-day intervention period, whichever came first. Patients resumed the trial drug if sedation was indicated within the 7-day intervention period. We treated pain on an analgesia-first approach to sedation, with opioid use as necessary.<sup>5</sup> After day 7, clinicians decided on sedation and other interventions. Patients received low-tidal-volume ventilation and a high PEEP strategy.<sup>14</sup>

The protocol involved waiting 12 hours after ARDS onset before prone positioning.<sup>14,15</sup>

In the intervention group, sevoflurane was administered via a miniaturized anesthetic conserving device (Sedaconda ACD-S, Sedana Medical) placed between the endotracheal tube and ventilator circuit, with expired gas scavenged per manufacturer instructions. The control group received intravenous propofol.

### Trial End Points

The primary end point was the number of days alive and off invasive mechanical ventilation (ventilator-free days) from randomization through day 28, as it accounts for both death and the time to extubation. If a patient died prior to day 28, the number of ventilator-free days was zero. The key secondary efficacy end point was 90-day survival. Other secondary efficacy end points were mortality at 7, 14, and 28 days and hospital mortality at 28 days after randomization. Safety end points included changes in hemodynamic measures and in the Kidney Disease: Improving Global Outcomes<sup>16</sup> criteria for acute kidney injury through day 7<sup>17</sup>; new-onset supraventricular tachycardia or atrial fibrillation; severe hypercapnic acidosis with arterial pH less than 7.15; and development of malignant hyperthermia, propofol-related infusion syndrome, pneumothorax, or bronchopleural fistula persistent despite drainage through day 7. Additional details regarding exploratory end points, along with a list of additional end points not reported here, are provided in the eMethods in [Supplement 2](#).

### Statistical Analysis

Under the hypothesis of a 28-day mortality rate of 30% to 35%<sup>18,19</sup> and the assumption that the variability of the number of ventilator-free days at 28 days would follow the properties of the Reevaluation of Systemic Early Neuromuscular Blockade (ROSE) trial,<sup>18</sup> we calculated that enrolling 680 patients would provide the trial with more than 80% power to detect a mean difference of 2 ventilator-free days at 28 days with a standard deviation of 8. We therefore included 350 in each group. After the blinded interim analysis of 350 patients, the independent data and safety monitoring committee recommended continuing the trial.

The primary analysis was an unadjusted, modified intention-to-treat comparison of the primary end point in the 2 groups, with the use of a mixture of generalized gamma distributions with death as the competing event.<sup>20</sup> Results are presented as median differences and standardized hazard ratios with 95% confidence intervals (CIs). The event of interest was successful weaning from invasive mechanical ventilation and the competing event was death. If  $\pi$  is the proportion of the total population of patients who achieve successful weaning from invasive mechanical ventilation and  $(1 - \pi)$  is the complementary proportion of patients who die within 28 days, a mixture according to  $\pi$  and  $(1 - \pi)$  of 2 generalized gamma distributions were used to model times to successful weaning from invasive mechanical ventilation and times to death, considering maximum likelihood for parameter estimation and the likelihood ratio tests to compare nested models.

We also analyzed 2 per-protocol populations and performed 2 adjusted analyses. Day-90 survival was evaluated

using the Kaplan-Meier approach and compared using the log-rank test and marginal Cox proportional hazard regression. Adjusted analyses were conducted, and results were expressed as hazard ratios with 95% CIs. Categorical variables were analyzed using the  $\chi^2$  or Fisher exact test. Continuous parameters were compared using a *t* test or Mann-Whitney *U* test. Longitudinal data were analyzed with a random-effects model. Subgroup analyses were performed to assess the consistency of the treatment effect across prespecified subgroups, including interaction terms. The widths of CIs were not adjusted for multiplicity and should be interpreted as exploratory. A 2-sided *P* value of less than .05 was considered to indicate statistical significance. All analyses were performed using Stata version 15.0 (StataCorp).

## Results

### Patients

From May 2020 through October 2023, we screened 2016 patients, of whom 1316 (65%) met at least 1 exclusion criterion or were not included for other reasons (**Figure 1**). Of the 700 patients who were enrolled and randomized, 13 were excluded (4 in the sevoflurane group and 9 in the propofol group) and 687 patients were included in the primary analysis (346 in the sevoflurane group and 341 in the propofol group). The trial groups had similar characteristics before randomization (**Table 1**; eTable 1 in [Supplement 2](#)). Patients were enrolled a median of 1 day (IQR, 0-3) after ICU admission; 54.9% had a diagnosis of COVID-19 pneumonia, with a median  $\text{PaO}_2\text{:Fio}_2$  at enrollment of 111 mm Hg (IQR, 86-137) and 107 mm Hg (IQR, 80-133) in the sevoflurane and propofol groups, respectively. Additional details are available in the eResults in [Supplement 2](#).

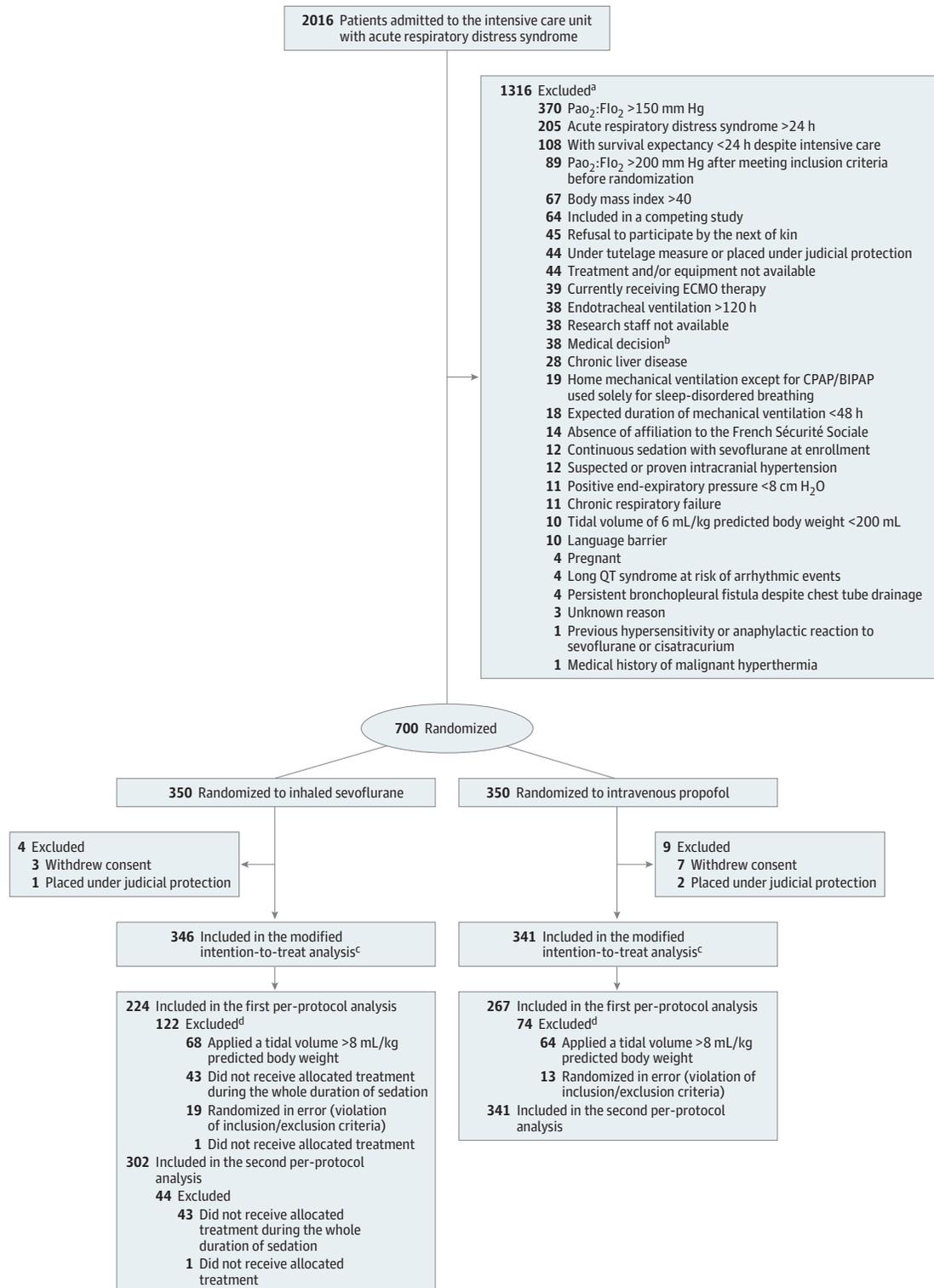
### Trial Interventions and Other Care Processes

The percentage of patients receiving sedation before randomization was similar in the 2 groups (Table 1). Details on trial drugs and sedation regimens are shown in eTable 2 in [Supplement 2](#).

Of the 687 patients who underwent randomization, 1 patient allocated to the sevoflurane group and 1 patient allocated to the propofol group did not receive the assigned trial drug. During the 7-day intervention period, median durations of trial drug administration were 5 days (IQR, 2-7) in the sevoflurane group and 6 days (IQR, 3-7) in the propofol group. The total median sedation duration was 7 days (IQR, 4-7) in both groups.

During the first 48 hours after randomization, deep sedation (RASS score of -5 to -4) was achieved in 93.9% of patients in the sevoflurane group and 89.2% of patients in the propofol group (eFigure 1 and eTable 2 in [Supplement 2](#)). During the 7-day intervention period, additional sedation was used in 148 patients in the sevoflurane group and in 64 patients in the propofol group (eFigure 2 and eTable 2 in [Supplement 2](#)). During the first 48 hours, 72.1% of patients in the sevoflurane group and 70.0% of patients in the propofol group received neuromuscular blockade infusion, with a total median neuromuscular blockade duration of 5 days (IQR, 2-9) in both groups (eTable 2 in [Supplement 2](#)).

Figure 1. Patient Screening, Enrollment, and Follow-Up in the Sevoflurane for Sedation in ARDS (SESAR) Trial



CPAP/BIPAP indicates continuous positive airway pressure/bilevel positive airway pressure; ECMO, extracorporeal membrane oxygenation; and Fio<sub>2</sub>, fraction of inspired oxygen.

<sup>a</sup>Each patient could have more than 1 reason for exclusion.

<sup>b</sup>Reasons included unknown reason (n = 22), clinical deterioration (n = 8),

ventilation or sedation deemed difficult (n = 3), pneumothorax (n = 2), low fraction of inspired oxygen (n = 2), and lung ventilation (n = 1).

<sup>c</sup>Included all patients who underwent randomization except those who withdrew consent or were under judicial protection.

<sup>d</sup>Each patient could have more than 1 protocol violation.

Table 1. Characteristics of the Patients Before Randomization<sup>a</sup>

Characteristic	No. (%)	
	Inhaled sevoflurane (n = 346)	Intravenous propofol (n = 341)
Age, mean (SD), y	64.9 (12.6)	64.4 (12.3)
Sex		
Female	111 (32.1)	92 (27.0)
Male	235 (67.9)	249 (73.0)
BMI, mean (SD)	28.9 (5.4)	28.6 (5.4)
No.	345	337
Time from ICU admission to randomization, median (IQR), d	1 (0-3)	1 (0-3)
Randomization on the same day as ICU admission	108 (31.2)	16 (34.0)
Time from intubation to randomization, median (IQR), d	0 (0-1)	0 (0-1)
Randomization on the same day as intubation	209 (60.4)	221 (64.8)
Primary cause of lung injury		
Pneumonia	288 (83.2)	289 (84.8)
Suspected or confirmed COVID-19 pneumonia	189 (54.6)	188 (55.1)
Aspiration	32 (9.3)	30 (8.8)
Extrapulmonary sepsis	30 (8.7)	25 (7.3)
Other cause <sup>b</sup>	19 (5.5)	26 (7.6)
Pancreatitis	10 (2.9)	9 (2.6)
Drug intoxication	7 (2.0)	2 (0.6)
Severe trauma	4 (1.2)	4 (1.2)
Need for vasopressor or inotropic support before randomization	254 (73.4)	256 (75.1)
Norepinephrine, No./total (%)	253/254 (99.6)	251/256 (98.0)
Dobutamine, No./total (%)	5/254 (2.0)	11/256 (4.3)
Serum lactate, median (IQR), mmol/L <sup>c</sup>	1.6 (1.2-2.3)	1.6 (1.2-2.2)
No.	318	313
KDIGO criteria for acute kidney injury before randomization <sup>d</sup>		
No acute kidney injury	219 (63.3)	224 (65.7)
Stage 1	37 (10.7)	41 (12.0)
Stage 2	47 (13.6)	38 (11.1)
Stage 3	43 (12.4)	38 (11.1)
Need for kidney replacement therapy	10 (2.9)	9 (2.6)
Antibiotic therapy	274 (79.2)	275 (80.7)
Corticosteroid therapy	233 (67.3)	223 (65.4)
Sedation received before randomization, No./total (%)	336/346 (97.1)	332/341 (97.4)
Propofol	289/336 (86.0)	301/332 (90.7)
Dexmedetomidine	5/336 (1.5)	2/332 (0.6)
Benzodiazepine	69/336 (20.5)	51/332 (15.4)
Other (clonidine, ketamine, or levomepromazine)	4/336 (1.2)	2/332 (0.6)
Respiratory support before intubation		
High-flow oxygen therapy	222 (64.2)	230 (67.4)
Noninvasive ventilation	161 (46.5)	161 (47.2)

(continued)

Table 1. Characteristics of the Patients Before Randomization<sup>a</sup> (continued)

Characteristic	No. (%)	
	Inhaled sevoflurane (n = 346)	Intravenous propofol (n = 341)
Ventilator mode before randomization		
Volume controlled	329 (95.1)	320 (93.8)
Pressure controlled	14 (4.0)	17 (5.0)
Pressure support ventilation	1 (0.3)	3 (0.9)
Airway pressure release ventilation	1 (0.3)	0
Other mode	1 (0.3)	1 (0.3)
Respiratory parameters before randomization		
Pao <sub>2</sub> -Fio <sub>2</sub> , median (IQR), mm Hg	111 (86-137)	107 (80-133)
No.	344	340
Tidal volume, median (IQR), mL/kg of predicted body weight	6.1 (5.7-6.7)	6.0 (5.6-6.6)
No.	339	333
Respiratory rate, median (IQR), breaths/min	26 (22-28)	26 (24-28)
No.	342	334
Positive end-expiratory pressure, median (IQR), cm H <sub>2</sub> O	10 (8-12)	10 (8-13)
No.	343	337
Prone position before randomization, No./total (%)	99/263 (37.6)	97/265 (36.6)
Continuous neuromuscular blockade, No./total (%)	240/264 (90.9)	228/266 (85.7)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); Fio<sub>2</sub>, fraction of inspired oxygen; ICU, intensive care unit; KDIGO, Kidney Disease: Improving Global Outcomes.

SI conversion factors: To convert creatinine to mg/dL, divide by 88.4; and lactate to mg/dL, divide by 0.111.

<sup>a</sup> There were no significant between-group differences before randomization. Percentages may not total 100 because of rounding.

<sup>b</sup> Other causes are reported in eTable 1 in Supplement 2.

<sup>c</sup> Normal serum lactate levels range from 0.5 to 2.0 mmol/L.

<sup>d</sup> Acute kidney injury was defined using the KDIGO criteria for acute kidney injury (increase in serum creatinine level by  $\geq 26.5 \mu\text{mol/L}$  [ $\geq 0.3 \text{ mg/dL}$ ] within 48 hours; or increase in serum creatinine to  $\geq 1.5$  times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume  $<0.5 \text{ mL/kg/h}$  for 6 hours). Higher stages of KDIGO criteria for acute kidney injury reflect higher severity.<sup>16</sup> Stage 1 was defined as an increase in serum creatinine level by  $\geq 26.5 \mu\text{mol/L}$  ( $\geq 0.3 \text{ mg/dL}$ ) or to 1.5 to 1.9 times the baseline value, and/or urine volume  $<0.5 \text{ mL/kg/h}$  for 6 to 12 hours. Stage 2 was defined as an increase in serum creatinine level to 2.0 to 2.9 times the baseline value, and/or urine volume  $<0.5 \text{ mL/kg/h}$  for  $\geq 12$  hours. Stage 3 was defined as an increase in serum creatinine level by  $\geq 353.6 \mu\text{mol/L}$  ( $\geq 4.0 \text{ mg/dL}$ ) or to at least 3.0 times the baseline value or initiation of kidney replacement therapy, and/or urine volume  $<0.3 \text{ mL/kg/h}$  for  $\geq 24$  hours or anuria for  $\geq 12$  hours.

Tidal volumes and PEEP levels during the 7-day intervention period were in accordance with the trial protocol in both groups (Table 2; eTable 3 in Supplement 2). Details regarding respiratory, hemodynamic, kidney, laboratory data, and other treatments received during the 7-day intervention period are provided in eTables 3 through 7 in Supplement 2.

### Primary End Point

At day 28, the median number of ventilator-free days was 0.0 (IQR, 0.0 to 11.9) in the sevoflurane group and 0.0 (IQR,

Table 2. Primary and Secondary End Points<sup>a</sup>

Variable	Inhaled sevoflurane (n = 346)	Intravenous propofol (n = 341)	Between-group difference (95% CI) <sup>b</sup>	Treatment effect (95% CI) <sup>c</sup>
<b>Primary end point</b>				
Ventilator-free days through day 28, median (IQR)	0.0 (0.0 to 11.9)	0.0 (0.0 to 18.7)	-2.1 (-3.6 to -0.7)	0.76 (0.50 to 0.97)
<b>Key secondary end point</b>				
Death at day 90, No./total (%)	183/346 (52.9)	151/341 (44.3)	8.6 (1.2 to 16.1)	1.31 (1.05 to 1.62)
<b>Secondary end points</b>				
Mortality, No./total (%) <sup>d</sup>				
At 28 d	152/345 (44.1)	132/340 (38.8)	5.2 (-2.1 to 12.6)	1.13 (0.95 to 1.36)
At 14 d	104/345 (30.1)	90/340 (26.5)	3.7 (-3.1 to 10.4)	1.14 (0.90 to 1.45)
At 7 d	67/345 (19.4)	46/340 (13.5)	5.9 (0.4 to 11.4)	1.44 (1.02 to 2.03)
ICU-free days through day 28, median (IQR)	0.0 (0.0 to 6.0)	0.0 (0.0 to 15.0)	-2.5 (-3.7 to -1.4)	0.67 (0.52 to 0.86)
No.	345	341		
<b>Safety secondary end points through day 7</b>				
Mean arterial pressure, median (IQR), mm Hg	80 (75 to 86)	81 (76 to 87)	-1.12 (-2.38 to 0.14)	NR
No. of patients/total patient-days <sup>e</sup>	346/2423	346/2501		
Dose of infused norepinephrine, median (IQR), µg/kg/min	0.31 (0.17 to 0.63)	0.23 (0.12 to 0.49)	0.07 (0.03 to 0.10)	NR
No. of patients/total patient-days <sup>e</sup>	330/1480	308/1398		
Dose of infused epinephrine, median (IQR), µg/kg/min	2.2 (2.2 to 2.2)	0.9 (0.1 to 3.0)	Not estimated <sup>f</sup>	NR
No. of patients/total patient-days <sup>e</sup>	1/1	3/4		
Dose of infused dobutamine, median (IQR), µg/kg/min	3.1 (2.5 to 5.0)	4.2 (2.5 to 5.4)	-1.04 (-2.71 to 0.62)	NR
No. of patients/total patient-days <sup>e</sup>	19/56	28/88		
Serum lactate, median (IQR), mmol/L	1.7 (1.4 to 2.2)	1.6 (1.3 to 2.0)	0.12 (0.02 to 0.23)	NR
No. of patients/total patient-days <sup>e</sup>	344/2137	341/2173		
KDIGO criteria for acute kidney injury, No. (%) <sup>g</sup>				
No acute kidney injury	110 (31.8)	146 (42.8)	-0.11 (-0.18 to -0.04)	1 [Reference]
Stage 1	59 (17.1)	41 (12.0)	0.05 (-0.01 to 0.10)	1.91 (1.62 to 2.25)
Stage 2	61 (17.6)	62 (18.2)	-0.01 (-0.06 to 0.05)	1.31 (1.12 to 1.52)
Stage 3	116 (33.5)	92 (27.0)	0.07 (-0.01 to 0.14)	1.67 (1.47 to 1.91)
Predefined adverse events, No. (%)				
Supraventricular tachycardia or atrial fibrillation	27 (7.8)	23 (6.7)	-0.01 (-0.05 to 0.11)	1.16 (0.68 to 1.98)
Severe hypercapnic acidosis with pH <7.15	11 (3.2)	5 (1.5)	1.7 (-0.5 to 4.0)	2.17 (0.76 to 6.18)
Malignant hyperthermia	2 (0.6)	0	0.6 (-0.2 to 1.4)	Not estimated <sup>f</sup>
Propofol-related infusion syndrome	0	3 (0.9)	-0.9 (-1.9 to 0.1)	Not estimated <sup>f</sup>
Pneumothorax or bronchopleural fistula persistent despite drainage	1 (0.3)	0	0.3 (-0.3 to 0.9)	Not estimated <sup>f</sup>

Abbreviations: ICU, intensive care unit; NR, not relevant; KDIGO, Kidney Disease: Improving Global Outcomes.

<sup>a</sup> The primary end point was the number of ventilator-free days as calculated from randomization to day 28. All the patients who had died by day 28 were considered to have had no ventilator-free days. Percentages may not total 100 because of rounding.

<sup>b</sup> The between-group difference is reported as the median difference (95% CI) for ventilator-free days, ICU-free days, and continuous variables such as arterial pressure, vasopressor dose, or serum lactate or the absolute difference (95% CI) for categorical variables (such as mortality or stages of acute kidney injury).

<sup>c</sup> The treatment effect is reported as the standardized hazard ratio (95% CI) for ventilator-free days and ICU-free days, the hazard ratio (95% CI) for 90-day survival, or the relative risk (95% CI) for categorical variables (such as mortality or stages of acute kidney injury).

<sup>d</sup> Hospital mortality and all-cause mortality were identical at 28 days as all deaths occurred in the hospital in both groups.

<sup>e</sup> Numbers are reported as the number of patients with the variable available (No.) and the total number of patient-days during which the variable is available from randomization through day 7. Daily values can be found in eTable 20 in Supplement 2.

<sup>f</sup> The between-group difference or relative risk was not estimated due to a limited number of occurrences.

<sup>g</sup> Acute kidney injury was defined using the KDIGO criteria for acute kidney injury. Highest stages of KDIGO criteria for acute kidney injury were recorded through day 7. Higher stages reflect higher severity.<sup>16</sup>

0.0 to 18.7) in the propofol group (median difference,  $-2.1$  [95% CI,  $-3.6$  to  $-0.7$ ]; standardized hazard ratio,  $0.76$  [95% CI,  $0.50$  to  $0.97$ ]) (Table 2; eFigure 3 in Supplement 2). There was no evidence of heterogeneity in predefined subgroups (eTable 8 in Supplement 2). Results were similar in the 2 per-protocol populations, after multivariable adjustments, and in a sensitivity analysis excluding the first 5 patients enrolled at each trial site (eTables 9 through 12 in Supplement 2).

### Secondary End Points

Survival by day 90 (the key secondary end point) was lower in the sevoflurane group (163 survivors/346 patients, 47.1%) than in the propofol group (190 survivors/341 patients, 55.7%) (hazard ratio,  $1.31$  [95% CI,  $1.05$ - $1.62$ ];  $P = .02$  using the log-rank test) (Table 2 and Figure 2). Results were unchanged after adjustment (eTable 13 in Supplement 2). The cumulative number of patients who died, were extubated, or were discharged from the ICU is reported in Figure 3. The main causes of death are reported in eTable 14 in Supplement 2.

Per-protocol analyses showed similar results for all secondary end points. Among all prespecified subgroup analyses, the only significant difference was heterogeneity between treatment groups and suspected or proven COVID-19 before randomization (as defined a priori as a subgroup analysis), with respect to 90-day survival ( $P = .01$  for treatment by subgroup interaction) and 28-day mortality ( $P = .003$  for treatment by subgroup interaction) (eFigures 4 and 5 and eTables 15 through 19 in Supplement 2).

### Safety End Points and Adverse Events

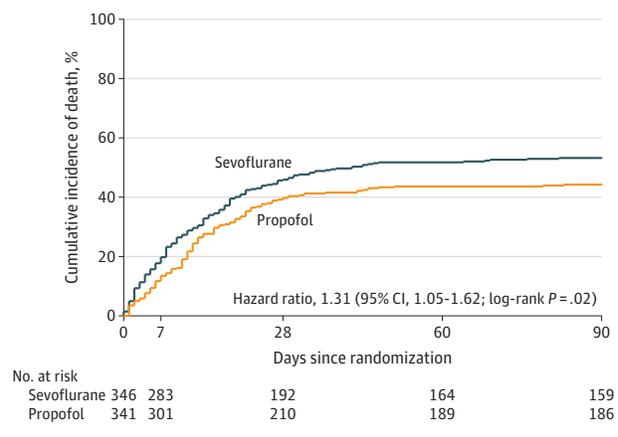
Safety end points are summarized in Table 2 and eTable 20 in Supplement 2. Median norepinephrine doses from randomization to day 3 and changes in median serum lactate levels from randomization to days 1, 2, and 4 were higher in the sevoflurane group than in the propofol group. Similarly, fewer patients in the sevoflurane group than in the propofol group were free from acute kidney injury through day 7 (between-group difference,  $-0.11$  [95% CI,  $-0.18$  to  $-0.04$ ]) (Table 2; eTable 5 and eFigure 6 in Supplement 2). There were no between-group differences in predefined adverse events (Table 2). Nephrogenic diabetes insipidus was reported in 5 patients (1.4%) in the sevoflurane group (median time since randomization, 5.8 days [IQR, 4.3-5.9]) and did not occur in the propofol group (absolute difference,  $1.4$  [95% CI,  $0.2$ - $2.7$ ]). Exploratory end points are reported in eTable 21 in Supplement 2.

## Discussion

Among adults with moderate to severe ARDS enrolled in this multicenter, randomized trial, inhaled sedation with sevoflurane resulted in fewer ventilator-free days at 28 days than intravenous sedation with propofol. Moreover, survival at 90 days was lower among those patients who received inhaled sevoflurane.

The potential benefit of inhaled sedation in ARDS was based on evidence suggesting anti-inflammatory and lung-protective effects of volatile anesthetics.<sup>7,21</sup> Small trials and ob-

Figure 2. Kaplan-Meier Estimates of 90-Day Survival in the Modified Intention-to-Treat Population



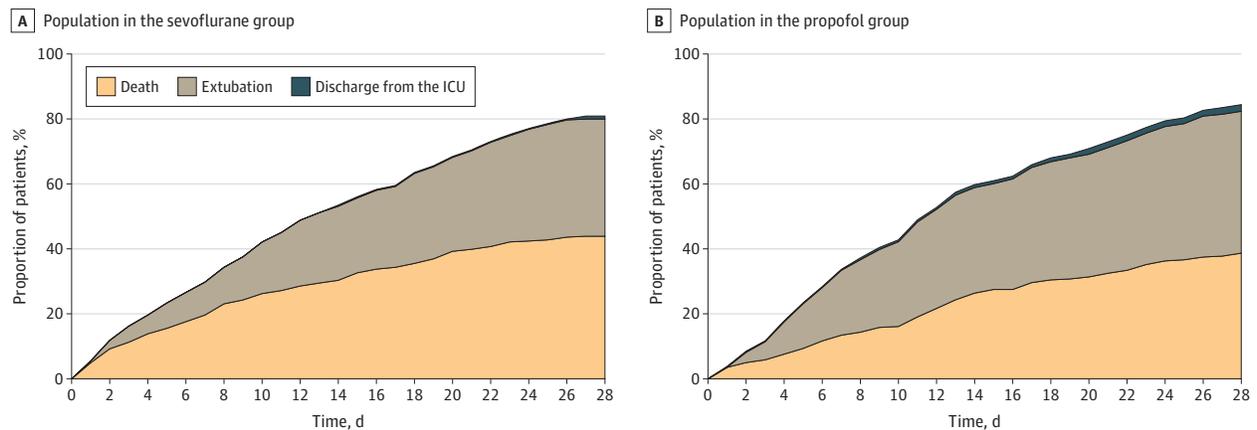
At 90 days, 183 of 346 patients (52.9%) in the sevoflurane group and 151 of 341 patients (44.3%) in the propofol group had died. The median follow-up times were 40.5 days (IQR, 10.0-90.0) in the sevoflurane group and 90.0 days (IQR, 14.0-90.0) in the propofol group.

servational studies in critically ill patients suggested shorter wake-up times and duration on mechanical ventilation with volatile anesthetics compared with intravenous hypnotics.<sup>9</sup> These data supported a potential clinical benefit of sevoflurane in ARDS and the choice of ventilator-free days as the primary end point.

The findings of the current study contrast with evidence suggesting benefits of volatile anesthetics, such as sevoflurane or isoflurane, in patients without ARDS.<sup>9</sup> They also challenge proposed oxygenation benefits in ARDS, suggested by smaller and preclinical studies.<sup>7,22-24</sup> This lack of effect was confirmed in subsequent clinical studies in patients with hypoxemic acute respiratory failure.<sup>25,26</sup> While a single-center trial showed improved oxygenation with sevoflurane vs midazolam in moderate to severe ARDS (but no mortality difference),<sup>7</sup> inhaled anesthetic use, popularized during COVID-19 sedative shortages<sup>27</sup> and associated with reduced sedative and analgesic needs,<sup>28</sup> yielded mixed results regarding oxygenation and mortality in patients with COVID-19.<sup>29-31</sup> Although between-group differences in 90-day survival and 28-day mortality were greater in patients without COVID-19, possibly reflecting worse prognosis in controls with COVID-19, no significant treatment-by-subgroup interactions were found for the primary and other secondary end points, suggesting relevance of current findings regardless of ARDS etiology.

A particular feature of the SESAR trial was the use of early deep sedation with neuromuscular blockade, before transitioning to lighter sedation as oxygenation improved.<sup>32</sup> A stabilization period before prone positioning of at least 12 hours after the onset of ARDS was recommended, as suggested by current evidence.<sup>18,32</sup> Despite standardized training, variability in expertise with inhaled sedation could have influenced results. The enrolled population is unlikely to explain the findings, as both groups had similar ARDS severity and vasopressor needs, with control group mortality aligning with the ROSE

**Figure 3. Cumulative Numbers of Patients Dead, Extubated (Alive), and Discharged (Alive) From the Intensive Care Unit From Randomization Through Day 28 in the Modified Intention-to-Treat Population**



Extubation (alive) was counted as the end of the last period of assisted breathing to day 28. ICU indicates intensive care unit.

trial.<sup>18</sup> The prolonged sedation and cisatracurium use in SESAR may raise concerns about generalizability, but the alignment of clinical outcomes in the control group with those in recent trials<sup>18,19</sup> suggests the current findings remain applicable to contemporary ARDS management, despite variations in sedation practices.

Several hypotheses may explain the worse clinical outcomes in the sevoflurane group. Sevoflurane was associated with modest yet significant increases in serum lactate and norepinephrine dose within the first week after randomization. Whether this reflects more severe shock or vasoplegia due to sevoflurane or could account for the clinical outcomes observed with sevoflurane remains unclear. Prolonged sevoflurane use was associated with increased acute kidney injury, contrasting with the results from a systematic review<sup>33</sup> but aligning with those from a recent COVID-19 trial in which 39% of patients developed acute kidney injury.<sup>25</sup> Differences in prerandomization characteristics are unlikely to explain such differences. Consistent with previous studies after prolonged sevoflurane use,<sup>21</sup> the current study observed an increased incidence of nephrogenic diabetes insipidus, the precise mechanisms of which remain unknown.<sup>34</sup> Although their association with nephrotoxicity remains discussed,<sup>21</sup> high fluoride levels may have developed under sevoflurane, which was not verified in this study. This study's findings also differ from those of a recent systematic review of inhaled sedation in ICU patients, which included 9 smaller trials evaluating the same vaporizer device as in this trial.<sup>9</sup> Elevated arterial carbon dioxide and lower pH suggest issues with dead space (50 mL according to the manufacturer) or carbon dioxide retention from the device, potentially leading to the observed increases in ventilatory ratio, a predictor of ARDS mortality.<sup>35</sup> While the device used in the trial has low dead space and carbon dioxide retention risk,<sup>21,36</sup> it may have contributed to these issues. Although dead space volumes of heat and moisture exchangers or use of active humidifiers in the propofol group were not collected, whether the intervention increased mechanical

power due to higher respiratory rates and influenced the risk of ventilator-induced lung injury deserves further investigation (eTables 3 and 21 in Supplement 2).<sup>37</sup> The Sedating With Volatile Anesthetics Critically Ill COVID-19 Patients in ICU (SAVE-ICU) trial (NCT04415060) will provide more safety data.

Our findings may have important clinical implications because inhaled sedation has garnered growing attention in ICU patients with ARDS or those at risk for the syndrome.<sup>29</sup> However, this trial does not inform whether outcomes would have differed with shorter durations of sevoflurane or with the use of other volatile anesthetics such as isoflurane. Such knowledge gaps may be addressed by ongoing trials of inhaled isoflurane sedation for mechanically ventilated ICU patients (NCT05312385 and NCT05327296).

### Limitations

The trial has limitations. First, double-blinding was impossible due to the intervention's nature, though similar sedation scores in both groups suggest minimal performance bias. Second, data on volumes of fluid administered, sevoflurane's expired fractions, corticosteroid dosing, or concomitant opioid analgesia were not collected. Third, adherence with the ABCDEF (awakening and breathing coordination, delirium monitoring/management, and early exercise/mobility) bundle was not assessed,<sup>4</sup> anticipating consistent care between groups. Fourth, COVID-19 pneumonia was the predominant ARDS cause; generalizability across ARDS causes or subphenotypes remains unknown. Fifth, the trial was unable to assess sevoflurane's impact on delirium,<sup>38</sup> and long-term and biological outcomes will be explored in future analyses.

### Conclusions

In this trial involving patients with moderate to severe ARDS, inhaled sedation with sevoflurane resulted in fewer ventilator-free days and lower 90-day survival than did intravenous propofol.

## ARTICLE INFORMATION

**Accepted for Publication:** February 27, 2025.

**Published Online:** March 18, 2025.  
doi:10.1001/jama.2025.3169

**Author Affiliations:** Department of Perioperative Medicine, CHU Clermont-Ferrand, Clermont-Ferrand, France (Jabaudon, Audard, Rieu, Chabanne, Godet, Garnier, Blondonnet, Vernhes, Borao, Futier); iGREd, CNRS, INSERM, Université Clermont Auvergne, Clermont-Ferrand, France (Jabaudon, Garnier, Blondonnet, Sapin, Futier); The Lipness Team, INSERM Lipids, Nutrition, Cancer-Unité Mixte de Recherche I231 and LabEx LipSTIC, INSERM Centre d'Investigation Clinique 1432, Clinical Epidemiology, Université de Bourgogne, and Médecine Intensive Réanimation, CHU Dijon, Dijon, France (Quenot); Réanimation Polyvalente, Hôpital Nord Franche-Comté, Trévenans, France (Badie); Centre Hospitalier Universitaire (CHU) Montpellier, Département Anesthésie Réanimation B, Hôpital Saint Eloi and PhyMedExp, INSERM U1046, Université de Montpellier, Montpellier, France (Jaber); Department of Medical Intensive Care, Dunkerque Hospital, 59240 Dunkerque, France (Varillon); Multidisciplinary Intensive Care Unit, Department of Anesthesiology and Critical Care, La Pitié-Salpêtrière Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), and INSERM UMRS 959, Immunology-Immunopathology-Immunotherapy (I3), Biotherapy (CIC-BTI), Sorbonne University, Paris, France (Monsel); Réanimation Médicale Polyvalente, CHU Gabriel Montpied, Clermont-Ferrand, France (Thouy); Department of Intensive Care Medicine, Hospital of Saint-Nazaire, Saint-Nazaire, France (Lorber); Department of Critical Care Medicine, University Hospital (CHU) of Reims, Reims, France (Cousson); Department of Anesthesiology, Pain, and Critical Care Medicine, Carêmeau Hospital, University Hospital (CHU) of Nîmes, Nîmes, France (Bulyez); Department of Intensive Care Medicine, Timone Hospital, Assistance Publique-Hôpitaux de Marseille (AP-HM), Marseille, France (Bourenne); Department of Intensive Care Medicine, Hospital of Béthune, Béthune, France (Sboui); Department of Anesthesiology and Critical Care Medicine, Diaconesses-La Croix Simon Hospital, Paris, France (Lhommet); Department of Intensive Care Medicine, Saint-Louis University Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France (Lemiale); Department of Anesthesiology and Critical Care Medicine, University Hospital (CHU) of Dijon and the Lipness Team, INSERM UMR1231, Dijon, France (Bouhemad); Department of Intensive Care Medicine, University Hospital (CHU) of Amiens, Amiens, France (Brault); Department of Anesthesiology and Critical Care Medicine, University Hospital (CHU) of Angers, Angers, France (Lasocki); Department of Intensive Care Medicine, Hospital of Saint-Brieuc, Saint-Brieuc, France (Legay); Department of Anesthesiology and Critical Care Medicine, University Hospital (CHU) of Rennes, Rennes, France (Lebouvier); Department of Critical Care Medicine, Salengro Hospital, University Hospital (CHU) of Lille, Lille, France (Durand); Department of Anesthesiology and Critical Care Medicine, Hautepierre Hospital, University Hospital (CHU) and UR3072, FHU Omicare, FHU Data-Surge, FMTS, Strasbourg

University, Strasbourg, France (Pottecher); Department of Intensive Care Medicine, Hospital of Chartres, Chartres, France (Conia); Department of Intensive Care Medicine, Hospital of Saintes, Saintes, France (Brégeaud); Department of Anesthesiology and Critical Care Medicine, Timone Hospital, Assistance Publique-Hôpitaux de Marseille and Institut des Neurosciences de la Timone, CNRS, Aix Marseille University, Marseille, France (Velly); Department of Intensive Care Medicine, University Hospital of Poitiers, Poitiers, France (Thille); Department of Intensive Care Medicine, Hospital of Valenciennes, Valenciennes, France (Lambiotte); Department of Intensive Care Medicine, Cavale Blanche University Hospital (CHU) and Laboratoire de Traitement de l'Information Médicale, Unité Mixte de Recherche 1101, INSERM, Université de Bretagne Occidentale, Brest, France (L'Her); Department of Intensive Care Medicine, Hospital of Melun-Sénart, Melun, France (Monchi); University of Nantes, CHU Nantes, Department of Anesthesiology and Intensive Care Unit, CIC Immunology and Infection, and INSERM UMR 1064 CR2TI, Nantes, France (Roquilly); Department of Critical Care Medicine, Hospital of Martigues, Martigues, France (Berrouba); Department of Anesthesiology and Intensive Care, Hôpital Saint-Antoine and Hôpital Tenon, GRC 29, DMU DREAM, Assistance Publique-Hôpitaux de Paris (AP-HP) and UMRS 938, Centre de Recherche Saint-Antoine (CRSA), Sorbonne Université, INSERM, Paris, France (Verdonk); Department of Healthcare Simulation and NEURO-DOL, UMR 1107, INSERM, Université Clermont Auvergne, Clermont-Ferrand, France (Godet); Department of Biochemistry and Molecular Genetics, CHU Clermont-Ferrand, Clermont-Ferrand, France (Sapin); Biostatistics and Data Management Unit, Department of Clinical Research and Innovation, CHU Clermont-Ferrand, Clermont-Ferrand, France (Pereira); Sorbonne University, GRC 29, AP-HP, DMU DREAM, Department of Anesthesiology and Critical Care, Pitié-Salpêtrière Hospital, Paris, France (Constantin).

**Author Contributions:** Drs Jabaudon, Pereira, and Constantin 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:** Jabaudon, Audard, Cousson, Berrouba, Blondonnet, Sapin, Borao, Futier, Pereira, Constantin.

**Acquisition, analysis, or interpretation of data:** Jabaudon, Quenot, Badie, Jaber, Rieu, Varillon, Monsel, Thouy, Lorber, Bulyez, Bourenne, Sboui, Lhommet, Lemiale, Bouhemad, Brault, Lasocki, Legay, Lebouvier, Durand, Pottecher, Conia, Brégeaud, Velly, Thille, Lambiotte, L'Her, Monchi, Roquilly, Verdonk, Chabanne, Godet, Garnier, Blondonnet, Vernhes, Sapin, Futier, Pereira, Constantin.

**Drafting of the manuscript:** Jabaudon, Quenot, Monsel, Cousson, Bouhemad, Brégeaud, Futier, Pereira.

**Critical review of the manuscript for important intellectual content:** Jabaudon, Quenot, Badie, Audard, Jaber, Rieu, Varillon, Monsel, Thouy, Lorber, Bulyez, Bourenne, Sboui, Lhommet, Lemiale, Bouhemad, Brault, Lasocki, Legay, Lebouvier, Durand, Pottecher, Conia, Velly, Thille, Lambiotte, L'Her, Monchi, Roquilly, Berrouba, Verdonk, Chabanne, Godet, Garnier,

Blondonnet, Vernhes, Sapin, Borao, Futier, Pereira, Constantin.

**Statistical analysis:** Jabaudon, Vernhes, Pereira.

**Obtained funding:** Jabaudon, Brégeaud.

**Administrative, technical, or material support:** Jabaudon, Badie, Audard, Bouhemad, Lambiotte, L'Her, Godet, Blondonnet, Sapin, Borao, Pereira.

**Supervision:** Jabaudon, Jaber, Roquilly, Futier, Pereira, Constantin.

**Other-participation:** Berrouba.

**Other-patient inclusion:** Brault.

**Other-enrolling and including patients in the trial:** Monsel.

**Conflict of Interest Disclosures:** Dr Jabaudon reported personal fees from AbbVie and Sedana Medical outside the submitted work. Dr Jaber reported personal fees from Fisher & Paykel, Mindray, Dräger, Baxter, and Medtronic outside the submitted work. Dr Pottecher reported personal fees from Takeda, Edwards Lifesciences, Masimo, AOP Orphan, and RDS outside the submitted work. Dr Thille reported personal fees from Fisher & Paykel outside the submitted work. Dr L'Her reported grants from Sedana Medical for conferences and is funded by Sedana Medical for the ongoing Inased trial and receiving personal fees from GE Medical; he is also a cofounder and shareholder of Oxynov Inc and Ivanae Medical. Dr Godet reported personal fees from Fisher & Paykel Healthcare, Edwards Healthcare, Dräger, AOP Health, GE Healthcare, and Aspen Pharma outside the submitted work. Dr Garnier reported personal fees from LFB Biomedicaments and Shionogi outside the submitted work. Dr Futier reported personal fees from Dräger and GE Healthcare outside the submitted work. No other disclosures were reported.

**Funding/Support:** This study was funded by research grants from the French Ministry of Health (Programme Hospitalier de Recherche Clinique National 2018), the European Society of Anaesthesiology and Intensive Care (ESAIC\_GR\_2019\_MJ), and Sedana Medical.

**Role of the Funder/Sponsor:** The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Group Information:** The SESAR Trial Investigators appear in [Supplement 3](#).

**Meeting Presentation:** This study was presented at the International Symposium on Intensive Care and Emergency Medicine; March 18, 2025; Brussels, Belgium.

**Data Sharing Statement:** See [Supplement 4](#).

**Additional Contributions:** We thank the patients and their families, the clinical and research staff at the participating sites, and the staff at the clinical coordinating center. Coinvestigator Christophe Vinsonneau, MD (Department of Intensive Care Medicine, Hospital of Béthune, Béthune, France), died on April 7, 2024.

## REFERENCES

- Bellani G, Laffey JG, Pham T, et al; LUNG SAFE Investigators; ESICM Trials Group. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive

- care units in 50 countries. *JAMA*. 2016;315(8):788-800. doi:10.1001/jama.2016.0291
2. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. *N Engl J Med*. 2013;369(22):2126-2136. doi:10.1056/NEJMra1208707
  3. Northam KA, Phillips KM. Sedation in the ICU. *NEJM Evid*. 2024;3(11):a2300347. doi:10.1056/EVIDra2300347
  4. Devlin JW, Skrobik Y, Gélinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med*. 2018;46(9):e825-e873. doi:10.1097/CCM.0000000000003299
  5. Chanques G, Constantin JM, Devlin JW, et al. Analgesia and sedation in patients with ARDS. *Intensive Care Med*. 2020;46(12):2342-2356. doi:10.1007/s00134-020-06307-9
  6. Shehabi Y, Bellomo R, Kadiman S, et al; Sedation Practice in Intensive Care Evaluation (SPICE) Study Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group. 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(6):850-859. doi:10.1097/CCM.0000000000003071
  7. Jabaudon M, Boucher P, Imhoff E, et al. Sevoflurane for sedation in acute respiratory distress syndrome: a randomized controlled pilot study. *Am J Respir Crit Care Med*. 2017;195(6):792-800. doi:10.1164/rccm.201604-0686OC
  8. Meiser A, Volk T, Wallenborn J, et al; Sedaconda Study Group. Inhaled isoflurane via the anaesthetic conserving device versus propofol for sedation of invasively ventilated patients in intensive care units in Germany and Slovenia: an open-label, phase 3, randomised controlled, non-inferiority trial. *Lancet Respir Med*. 2021;9(11):1231-1240. doi:10.1016/S2213-2600(21)00323-4
  9. Al Aseri Z, Alansari MA, Al-Shami SA, Alaskar B, Aljumaiah D, Elhazmi A. The advantages of inhalational sedation using an anesthetic-conserving device versus intravenous sedatives in an intensive care unit setting: a systematic review. *Ann Thorac Med*. 2023;18(4):182-189. doi:10.4103/atm.atm\_89\_23
  10. Blondonnet R, Simand LA, Vidal P, et al; On Behalf of the Sesar Collaborative Group. Design and rationale of the sevoflurane for sedation in acute respiratory distress syndrome (SESAR) randomized controlled trial. *J Clin Med*. 2022;11(10):2796. doi:10.3390/jcm11102796
  11. Ranieri VM, Rubenfeld GD, Thompson BT, et al; ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin Definition. *JAMA*. 2012;307(23):2526-2533.
  12. 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(10):1338-1344. doi:10.1164/rccm.2107138
  13. Papazian L, Aubron C, Brochard L, et al. Formal guidelines: management of acute respiratory distress syndrome. *Ann Intensive Care*. 2019;9(1):69. doi:10.1186/s13613-019-0540-9
  14. Qadir N, Sahetya S, Munshi L, et al. An update on management of adult patients with acute respiratory distress syndrome: an official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med*. 2024;209(1):24-36. doi:10.1164/rccm.202311-2011ST
  15. Grasselli G, Calfee CS, Camporota L, et al; European Society of Intensive Care Medicine Taskforce on ARDS. ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies. *Intensive Care Med*. 2023;49(7):727-759. doi:10.1007/s00134-023-07050-7
  16. Summary of recommendation statements. *Kidney Int Suppl (2011)*. 2012;2(1):8-12. doi:10.1038/kisup.2012.7
  17. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract*. 2012;120(4):c179-c184. doi:10.1159/000339789
  18. Moss M, Huang DT, Brower RG, et al; National Heart, Lung, and Blood Institute PETAL Clinical Trials Network. Early neuromuscular blockade in the acute respiratory distress syndrome. *N Engl J Med*. 2019;380(21):1997-2008. doi:10.1056/NEJMoa1901686
  19. Beitler JR, Sarge T, Banner-Goodspeed VM, et al; EPVent-2 Study Group. Effect of titrating positive end-expiratory pressure (PEEP) with an esophageal pressure-guided strategy vs an empirical high PEEP-Fio2 strategy on death and days free from mechanical ventilation among patients with acute respiratory distress syndrome: a randomized clinical trial. *JAMA*. 2019;321(9):846-857. doi:10.1001/jama.2019.0555
  20. Checkley W, Brower RG, Muñoz A; NIH Acute Respiratory Distress Syndrome Network Investigators. Inference for mutually exclusive competing events through a mixture of generalized gamma distributions. *Epidemiology*. 2010;21(4):557-565. doi:10.1097/EDE.0b013e3181e090e0
  21. O'Gara B, Bonyck C, Meiser A, et al. Volatile anesthetic sedation for critically ill patients. *Anesthesiology*. 2024;141(1):163-174. doi:10.1097/ALN.0000000000004994
  22. Voigtsberger S, Lachmann RA, Leutert AC, et al. Sevoflurane ameliorates gas exchange and attenuates lung damage in experimental lipopolysaccharide-induced lung injury. *Anesthesiology*. 2009;111(6):1238-1248. doi:10.1097/ALN.0b013e3181bdf857
  23. Schläpfer M, Leutert AC, Voigtsberger S, Lachmann RA, Booy C, Beck-Schimmer B. Sevoflurane reduces severity of acute lung injury possibly by impairing formation of alveolar oedema. *Clin Exp Immunol*. 2012;168(1):125-134. doi:10.1111/j.1365-2249.2012.04562.x
  24. Ferrando C, Aguilar G, Piqueras L, Soro M, Moreno J, Belda FJ. Sevoflurane, but not propofol, reduces the lung inflammatory response and improves oxygenation in an acute respiratory distress syndrome model: a randomised laboratory study. *Eur J Anaesthesiol*. 2013;30(8):455-463. doi:10.1097/EJA.0b013e32835f0aa5
  25. Beck-Schimmer B, Schadde E, Pietsch U, et al. Early sevoflurane sedation in severe COVID-19-related lung injury patients: a pilot randomized controlled trial. *Ann Intensive Care*. 2024;14(1):41. doi:10.1186/s13613-024-01276-4
  26. Becher T, Meiser A, Guenther U, et al. Isoflurane vs propofol for sedation in invasively ventilated patients with acute hypoxemic respiratory failure: an a priori hypothesis substudy of a randomized controlled trial. *Ann Intensive Care*. 2022;12(1):116. doi:10.1186/s13613-022-01090-w
  27. Jerath A, Slessarev M. The impact of the coronavirus pandemic on sedation in critical care: volatile anesthetics in the ICU. *Curr Opin Crit Care*. 2023;29(1):14-18. doi:10.1097/MCC.0000000000001011
  28. Landoni G, Belloni O, Russo G, Bonaccorso A, Carà G, Jabaudon M. Inhaled sedation for invasively ventilated COVID-19 patients: a systematic review. *J Clin Med*. 2022;11(9):2500. doi:10.3390/jcm11092500
  29. Coupet R, Schläpfer M, Neff TA, et al; ISCA Study Group. Inhaled sedation in patients with COVID-19-related acute respiratory distress syndrome: an international retrospective study. *J Clin Med*. 2022;12(1):12. doi:10.3390/jcm12010012
  30. Consales G, Cappellini I, Freschi B, Campiglia L, Parise M, Zamidei L. Sevoflurane sedation in COVID-19 acute respiratory distress syndrome: an observational study with a propensity score matching model. *Front Med (Lausanne)*. 2023;10:1267691. doi:10.3389/fmed.2023.1267691
  31. Martínez-Castro S, Monleón B, Puig J, et al. Sedation with sevoflurane versus propofol in COVID-19 patients with acute respiratory distress syndrome: results from a randomized clinical trial. *J Pers Med*. 2023;13(6):925. doi:10.3390/jpm13060925
  32. Guérin C, Reignier J, Richard JC, et al; PROSEVA Study Group. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med*. 2013;368(23):2159-2168. doi:10.1056/NEJMoa1214103
  33. Taylor B, Scott TE, Shaw J, Chockalingam N. Renal safety of critical care sedation with sevoflurane: a systematic review and meta-analysis. *J Anesth*. 2023;37(5):794-805. doi:10.1007/s00540-023-03227-y
  34. Dupuis C, Robert A, Gerard L, Morelle J, Laterre PF, Hantson P. Nephrogenic diabetes insipidus following an off-label administration of sevoflurane for prolonged sedation in a COVID-19 patient and possible influence on aquaporin-2 renal expression. *Case Rep Anesthesiol*. 2022;2022:3312306. doi:10.1155/2022/3312306
  35. Sinha P, Calfee CS, Beitler JR, et al. Physiologic analysis and clinical performance of the ventilatory ratio in acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2019;199(3):333-341. doi:10.1164/rccm.201804-0692OC
  36. Bomberg H, Meiser F, Daume P, et al. Halving the volume of AnaConDa: evaluation of a new small-volume anesthetic reflector in a test lung model. *Anesth Analg*. 2019;129(2):371-379. doi:10.1213/ANE.0000000000003452
  37. Pellet PL, Stevic N, Degivry F, et al. Effects on mechanical power of different devices used for inhaled sedation in a bench model of protective ventilation in ICU. *Ann Intensive Care*. 2024;14(1):18. doi:10.1186/s13613-024-01245-x
  38. Bailly P, Egreteau PY, Ehrmann S, et al. Inhaled (inhaled sedation in ICU) trial protocol: a multicentre randomised open-label trial. *BMJ Open*. 2021;11(2):e042284. doi:10.1136/bmjopen-2020-042284