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Ketamine vs Etomidate for Tracheal Intubation of Critically Ill Adults

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Abstract

Background: For critically ill adults undergoing tracheal intubation, observational studies suggest that use of etomidate to induce anesthesia may increase the risk of death. Whether using ketamine rather than etomidate decreases the incidence of death is uncertain.

Methods: In a multicenter, randomized trial conducted in 14 emergency departments and intensive care units in the United States, we randomly assigned critically ill adults undergoing tracheal intubation to receive ketamine or etomidate for the induction of anesthesia. The primary outcome was in-hospital death by 28 days. The secondary outcome was cardiovascular collapse during intubation, defined as systolic blood pressure < 65 mm Hg, receipt of new or increased vasopressors, or cardiac arrest.

Results: Among the 2,365 patients in the trial, in-hospital death by 28 days occurred in 330 of 1,173 patients (28.1%) in the ketamine group and 345 of 1,186 patients (29.1%) in the etomidate group (absolute risk difference adjusted for trial site, −0.8 percentage points; 95% confidence interval, −4.5 to 2.9; P=0.65). Cardiovascular collapse during intubation occurred in 260 patients (22.1%) in the ketamine group and 202 patients (17.0%) in the etomidate group (absolute risk difference, 5.1 percentage points; 95% confidence interval, 1.9 to 8.3). Prespecified safety outcomes were similar between groups.

Conclusions: Among critically ill adults undergoing tracheal intubation, use of ketamine to induce anesthesia did not decrease the incidence of in-hospital death by 28 days compared with

use of etomidate. (Funded by the Patient-Centered Outcomes Research Institute and others; RSI ClinicalTrials.gov number, NCT05277896)

INTRODUCTION

More than 13 million critically ill adults undergo emergency tracheal intubation each year worldwide,[1,2] approximately 30% of whom die before hospital discharge.[3,4] Nearly all patients undergoing tracheal intubation in an emergency department (ED) or intensive care unit (ICU) receive a medication to induce anesthesia for the procedure.[3,4] Whether the choice of induction medication for critically ill adults affects the risk of death or other outcomes is uncertain.

Etomidate is the medication most often used to induce anesthesia during emergency tracheal intubation in the United States.[4–10] This imidazole-derived sedative-hypnotic agent, which acts on gamma-aminobutyric acid (GABA) receptors, has been described as an "ideal" induction medication for critically ill adults because of its rapid onset and limited effect on blood pressure and heart rate.[11–13] However, etomidate inhibits 11-β-hydroxylase in the adrenal glands and a single dose decreases cortisol production for up to 72 hours.[14–19] Concern that etomidate-induced corticosteroid insufficiency may cause organ dysfunction and death,[7,17] particularly among patients with sepsis,[20–22] has led regulators to remove etomidate from the market in multiple countries.[23–25]

Ketamine, a dissociative agent that acts on N-methyl-D-aspartate (NMDA) receptors and does not impair cortisol production, is an increasingly used alternative to etomidate for induction of anesthesia in critically ill patients.[7,26,27] Because its administration increases plasma catecholamine concentrations, ketamine has been postulated to maintain hemodynamic stability during intubation better than other induction medications.[24,28,29] However, ketamine is also a negative inotrope and vasodilator,[30–32] and observational studies have reported an association between receipt of ketamine and hypotension,[26,33–35] arrhythmia,[36,37] and cardiac arrest during intubation.[38–40]

Previous small and moderate-sized randomized trials and meta-analyses comparing ketamine and etomidate have reported conflicting results, with some suggesting that the use of ketamine decreases mortality[41–43] and others finding no differences in outcomes.[18,44,45] To determine the effects of using ketamine, as compared with etomidate, for induction of anesthesia during emergency tracheal intubation, we conducted the Randomized trial of Sedative choice for Intubation (RSI). We hypothesized that the use of ketamine would decrease the incidence of death.

METHODS

Trial Design and Oversight

The Pragmatic Critical Care Research Group[4,8,46] conducted this pragmatic, multicenter, unblinded, randomized, parallel-group trial in which the use of ketamine was compared with the use of etomidate for induction of anesthesia during emergency tracheal intubation of critically ill adults. The trial was initiated by the investigators, approved by the

institutional review board at Vanderbilt University Medical Center and the US Food and Drug Administration (IND 141424), and conducted with Exception from Informed Consent Requirements for Emergency Research (EFIC) (details in the Supplementary Appendix).[47] The trial was registered at ClinicalTrials.gov before initiation and was overseen by an independent data and safety monitoring board. The trial protocol and statistical analysis plan were published before the conclusion of enrollment and are available at nejm.org.[48] The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Trial Sites and Patient Population

The trial was conducted at 14 sites (6 emergency departments and 8 intensive care units) in 6 medical centers across the United States. Critically ill adults (age, ≥ 18 years) undergoing tracheal intubation with the use of a medication to induce anesthesia were eligible. Patients were excluded if they were known to be pregnant, were known to be a prisoner, were presenting with a primary diagnosis of trauma, or had an immediate need for tracheal intubation that precluded randomization. Patients were also excluded if the treating clinicians determined that the use of ketamine or etomidate was either necessary or contraindicated. Details of the trial sites and complete lists of inclusion and exclusion criteria are provided in the Supplementary Appendix.

Randomization

Patients were randomly assigned in a 1:1 ratio to receive either ketamine or etomidate for induction of anesthesia during tracheal intubation. Randomization was performed with the use of permuted blocks of variable size and was stratified according to trial site. Trial-group assignments were placed in sequentially numbered, opaque envelopes and remained concealed until after enrollment. Clinicians and research personnel were aware of trial-group assignments after randomization.

Trial Interventions

For patients assigned to the ketamine group, clinicians were instructed to administer ketamine intravenously to induce anesthesia for tracheal intubation. A nomogram on the trial group assignment sheet provided doses of ketamine (in milligrams) for a range of patient weights that corresponded to a full dose (2.0 mg/kg), an intermediate dose (1.5 mg/kg), or a reduced dose (1.0 mg/kg) (Supplementary Appendix).[49] Clinicians selected the dose of ketamine to administer.

For patients assigned to the etomidate group, clinicians were instructed to administer etomidate intravenously to induce anesthesia for tracheal intubation. A nomogram on the trial group assignment sheet provided doses of etomidate (in milligrams) for a range of patient weights that corresponded to a full dose (0.3 mg/kg), an intermediate dose (0.25 mg/kg), or a reduced dose (0.2 mg/kg) (Supplementary Appendix). Clinicians selected the dose of etomidate to administer.

All other aspects of the patient's medical care were at the discretion of the treating clinicians, including the administration of vasopressors prior to induction, the choice of

neuromuscular blocking agent for intubation, the approach to sedation and analgesia during mechanical ventilation, and the administration of intravenous fluids, vasopressors, and systemic corticosteroids.

Data Collection

A trained observer who was not involved in the performance of the intubation collected data on the duration of intubation, the systolic blood pressure, and the administration of vasopressors during the interval between induction of anesthesia and 2 minutes after intubation. Immediately after intubation, clinicians recorded whether the patient experienced arrhythmia or cardiac arrest between induction of anesthesia and 2 minutes after intubation. Trial personnel reviewed the medical record to collect data on patients' baseline characteristics, periprocedural care, and clinical outcomes. Trial personnel collected information on death from the medical record, public vital statistics records, and phone calls to patients or family members at 3 and 12 months (details in Supplemental Methods).

Trial Outcomes

The primary outcome was in-hospital death by 28 days, defined as death from any cause occurring between enrollment and 28 days after enrollment with outcome ascertainment ending at hospital discharge. The single prespecified secondary outcome was cardiovascular collapse during intubation, defined as the occurrence of any of the following in the interval between the induction of anesthesia and 2 minutes after tracheal intubation: systolic blood pressure < 65 mm Hg; receipt of new or increased vasopressors; or cardiac arrest. Additional details regarding the trial outcomes are provided in the Supplementary Appendix.

Statistical Analysis

Details regarding the determination of the sample size have been reported previously[48] and are included in the Supplementary Appendix. Assuming an incidence of in-hospital death by 28 days of 30.0% in the etomidate group,[4,8] 80% statistical power, and a two-sided alpha level of 0.05, we calculated that a sample of 2,308 patients would be needed to detect an absolute difference of 5.2 percentage points between the groups in the incidence of in-hospital death by 28 days. To ensure adequate power if data were missing in up to 3% of the patients, we planned to enroll a total of 2,364 patients (1,182 per group). A single interim analysis after 1,182 patients were enrolled used a P value threshold of ≤ 0.001 for the difference between the groups in the primary outcome that would justify stopping the trial.

The primary analysis was an intention-to-treat comparison of the primary outcome between the trial groups that was performed with the use of a generalized linear mixed-effects model with a random effect for trial site and a fixed effect for group assignment (ketamine group vs etomidate group) without adjustment for covariates. The primary analysis included all patients who underwent randomization, except for those who withdrew from follow-up prior to ascertainment of the primary outcome. Sensitivity analyses of the primary outcome included: an unadjusted analysis using a Chi-square test; an analysis adjusting for prespecified baseline covariates; analyses in which patients who withdrew prior to outcome ascertainment were treated as all having experienced the primary outcome or all having not

experienced the primary outcome; an analysis of death in any location by 28 days (including deaths that occurred after hospital discharge); and an analysis of survival to 28 days in any location using the Kaplan-Meier method (details in the Supplemental Appendix).

In accordance with published guidelines,[50,51] we examined whether prespecified baseline variables modified the effect of trial-group assignment on the primary outcome using three approaches: (i) subgroup analyses using a generalized linear mixed-effects model with a random effect for trial site and fixed effects for trial group, the proposed effect modifier, and the interaction between the effect modifier and trial group, without adjustment for covariates; (ii) a risk-modeling approach using previously validated models for patients' baseline risk of the primary outcome;[52] and (iii) an effect-modeling approach using a machine learning model to predict the effect of ketamine versus etomidate on the primary outcome for each patient based on his or her individual characteristics (individualized treatment effect).[53,54] Details of these analyses are provided in the Supplementary Appendix.

Secondary and exploratory outcomes were compared between trial groups with the use of the chi-square test for categorical variables and the Wilcoxon rank-sum test for continuous or ordinal variables; between-group differences are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals were not adjusted for multiplicity and should not be used to infer definitive differences in treatment effects between the two groups. All the analyses were performed with the use of R software, version 4.4.2 (R Foundation for Statistical Computing).

RESULTS

Patients

Between April 6, 2022, and August 10, 2025, a total of 3,439 patients were assessed for eligibility, of whom 2,367 (68.8%) were enrolled. The reasons for exclusion are listed in Figure S1. Two patients who were identified after enrollment as being prisoners were excluded from all analyses. The remaining 2,365 patients were included in the trial population. The median age was 60 years, 46.7% of the patients had sepsis or septic shock, and 22.0% of the patients were receiving vasopressors (Table 1). Tracheal intubation was performed in an emergency department for 55.7% of the patients and in an intensive care unit for 44.3% of the patients (Table S1). A total of 1,176 patients (49.7%) were assigned to the ketamine group, and 1,189 patients (50.3%) were assigned to the etomidate group (Tables S2 through S6). The representativeness of the patients is described in the Supplementary Appendix.

Medications for Tracheal Intubation

Of the 1,176 patients in the ketamine group, 1,167 (99.2%) received ketamine, and 1,184 of the 1,189 patients (99.6%) in the etomidate group received etomidate (Table 2 and Tables S7 and S8). The median dose of ketamine was 140 mg (interquartile range [IQR], 100 to 150), equivalent to 1.6 mg/kg (IQR, 1.4 to 2.0) of actual body weight (Figure S2). The median dose of etomidate was 20 mg (interquartile range [IQR], 20 to 25), equivalent to 0.28 mg/kg

(IQR, 0.24 to 0.31) of actual body weight. Approximately 2% of patients in each group received propofol, benzodiazepines, or opiates during the induction of anesthesia. A total of 1,171 patients (99.7%) in the ketamine group and 1,184 patients (99.7%) in the etomidate group received a neuromuscular blocking agent (Table S9). Additional characteristics of the tracheal intubation procedure are shown in Table 2 and Tables S10 and S11.

Primary Outcome

In-hospital death by 28 days occurred in 330 of 1,173 patients (28.1%) in the ketamine group and 345 of 1,186 patients (29.1%) in the etomidate group (absolute risk difference adjusted for trial site, −0.8 percentage points; 95% confidence interval [CI], −4.5 to 2.9; P=0.65) (Figure 1 and Table 3). Death in any location by 28 days occurred in 378 patients (32.2%) in the ketamine group and 384 patients (32.4%) in the etomidate group (absolute risk difference adjusted for trial site, 0.0 percentage points; 95% CI, −3.9 to 3.9). Results were similar in all sensitivity analyses (Figure S3 and Tables S12 and 13) and subgroup analyses (Figure 2 and Figure S4), including among the 1,101 patients with sepsis (38.8% vs 38.2%; absolute risk difference adjusted for trial site, 1.0 percentage points; 95% CI, −4.8 to 6.7). Risk-modeling analyses and effect-modeling analyses did not demonstrate heterogeneity of treatment effect (Figures S5 through S7 and Tables S14 and S15).

Secondary Outcome

Cardiovascular collapse during intubation occurred in 260 patients (22.1%) in the ketamine group and 202 patients (17.0%) in the etomidate group (absolute risk difference, 5.1 percentage points; 95% CI, 1.9% to 8.3%) (Figure S8 and Table S16). Among patients with sepsis, cardiovascular collapse occurred in 30.6% of patients in the ketamine group and 20.9% in the etomidate group (absolute risk difference, 9.7 percentage points; 95% CI, 4.6 to 14.9). Among patients with a high severity of illness (defined as an Acute Physiology and Chronic Health Evaluation II score ≥20), cardiovascular collapse occurred in 31.4% of patients in the ketamine group and 20.7% in the etomidate group (absolute risk difference, 10.7 percentage points; 95% CI, 5.5 to 16.0) (Figure S9).

Exploratory Outcomes

The lowest systolic blood pressure between induction of anesthesia and 2 minutes after tracheal intubation was a median of 112 (IQR, 92 to 138) in the ketamine group and 118 (IQR, 98 to 141) in the etomidate group (median difference, −6; 95% CI, −9 to −1) (Figure S10). A total of 164 patients (14.4%) in the ketamine group and 123 patients (10.6%) patients in the etomidate group experienced a systolic blood pressure < 80 mm Hg (absolute risk difference, 3.8 percentage points; 95% CI, 1.1 to 6.5). A decrease in systolic blood pressure of more than 30 mm Hg occurred in 265 patients (23.9%) in the ketamine group and 165 patients (14.7%) in the etomidate group (absolute risk difference, 9.2 percentage points; 95% CI, 6.0 to 12.5). The median time from induction of anesthesia to successful intubation was 112 seconds (IQR, 86 seconds to 155 seconds) in the ketamine group, compared to 103 seconds (IQR, 80 seconds to 134 seconds) in the etomidate group (median difference, 9 seconds; 95% CI, 5 to 14). The remaining exploratory outcomes, including ventilator-free days, vasopressor-free days, and ICU-free days appeared to be similar between groups (Tables S17 through S19; Figure S11).

Safety Outcomes

Ventricular tachycardia in the interval between induction of anesthesia and 2 minutes after intubation (a *post hoc* outcome added after the enrollment of the first 567 patients) occurred in 9 of 884 patients (1.0%) in the ketamine group and 2 of 905 patients (0.2%) in the etomidate group (absolute risk difference, 0.8 percentage points; 95% CI, 0.1 to 1.5) (Table S20). A total of 420 patients (38.9%) in the ketamine group and 458 patients (42.3%) in the etomidate group were receiving vasopressors at 24 hours after enrollment (absolute risk difference, −3.4 percentage points; 95% CI, −7.5 to 0.7).

DISCUSSION

Among critically ill adults undergoing emergency tracheal intubation in this multicenter, randomized trial, the use of ketamine for induction of anesthesia did not decrease the incidence of death, compared with the use of etomidate. The incidence of cardiovascular complications during intubation appeared to be higher with ketamine than with etomidate. These findings are important because they inform the concern that etomidate-induced corticosteroid insufficiency could affect patients' risk of death, a concern that has led regulators to limit the availability of etomidate and led clinicians to treat patients with less hemodynamically stable induction medications.

Numerous previous studies have demonstrated that the use of etomidate to induce anesthesia impairs cortisol production for up to 72 hours.[14–19] Whether this impairment in cortisol production increases patients' risk of death, however, has been uncertain.[55,56] Large observational studies have reported a lower risk of death in critically ill adults who received ketamine, as compared with etomidate.[7,17] Previous randomized trials have reported inconclusive results. Among 801 patients at a single center in the largest previous trial, the incidence of death by 7 days was 7.8 percentage points (95% CI, 2.4 to 13.0) lower with ketamine compared with etomidate, but the incidence of death by 28 days did not differ significantly between groups.[41] Among 469 patients in the only previous multicenter trial, the incidence of death by 28 days did not differ significantly between groups, but rates of organ dysfunction and death appeared to be lower in the ketamine group than the etomidate group among patients with sepsis.[18] Two recent meta-analyses that included data from all 2,384 patients enrolled in previous randomized trials reached differing conclusions, with one reporting that ketamine likely decreased the risk of death compared to etomidate[43] and one reporting no difference.[44] The concern raised by these prior studies that etomidate might increase patients' risk of death has led to the removal of etomidate from the market in some countries[23–25] and recommendations against its use in some guidelines.[29] Among 2,365 patients in the current trial – approximately as many patients as in all previous trials combined – we observed no difference in the incidence of death between the ketamine and etomidate groups at any timepoint or within any subgroup.

One reason that ketamine has been increasingly used for induction of anesthesia in critically ill adults[7,26,27] is the perception that ketamine maintains hemodynamic stability during intubation better than other induction medications.[24,28,29] Some experts specifically recommend ketamine for intubation of patients with sepsis or shock.[24,29,57,58] Our trial found that hypotension, vasopressor administration, and ventricular tachycardia during

intubation each appeared to be more common with ketamine than with etomidate. These effects appeared to be largest among patients with sepsis and shock. Although discordant with the recommendations in some guidelines,[29] these findings are concordant with the results of two recent observational studies and one previous randomized trial, each of which reported a higher incidence of cardiovascular complications with ketamine, compared with etomidate.[33,34,41]

Our trial has several strengths. The design included randomization to balance baseline characteristics, enrollment of a large sample of patients to provide sufficient statistical power to detect clinically meaningful differences in death between trial groups, and conduct in EDs and ICUs at multiple centers to increase generalizability. The trial population had a sufficiently high severity of illness (nearly 30% of patients died by 28 days) and a sufficiently large number of patients with sepsis (more than 1,100) and shock (more than 500) to credibly evaluate the hypothesized relationship between receipt of etomidate and death. Adherence to the group assignment was excellent, and the percentage of patients with missing data for the primary outcome was low.

Our trial also has limitations. Our trial excluded patients presenting with a primary diagnosis of trauma, and the results may not apply to these patients. Because the trial was not blinded, awareness of group assignment could have influenced the trained observers' assessments of intra-procedural outcomes or clinicians' subsequent treatment decisions. Our findings do not exclude the possibility of small differences in outcomes in favor of either ketamine or etomidate, and for such commonly used medications even small differences in outcomes might be clinically meaningful. Our trial compared ketamine and etomidate, and the results do not inform the effectiveness or safety of other induction medications, such as propofol, benzodiazepines, or barbiturates.

Among critically ill adults undergoing tracheal intubation, use of ketamine to induce anesthesia did not decrease the incidence of in-hospital death by 28 days compared with use of etomidate.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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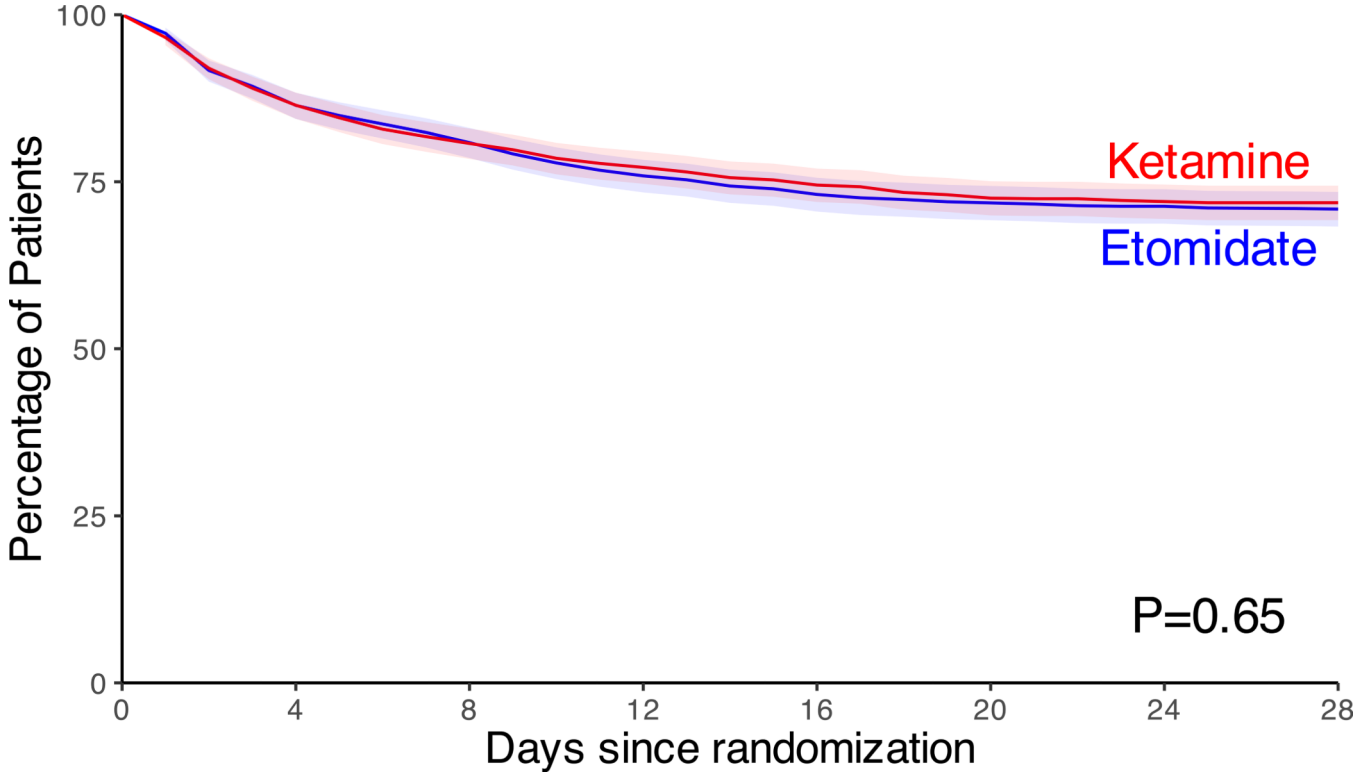

Figure 1. In-Hospital Death by Trial Group.

The percentage of patients without in-hospital death (primary outcome) is displayed for the ketamine group (red) and the etomidate group (blue) from randomization until 28 days after randomization. The incidence of in-hospital death by 28 days did not differ significantly between the ketamine group (28.1%) and the etomidate group (29.1%) (absolute risk difference adjusted for trial site, −0.8 percentage points; 95% CI, − 4.5 to 2.9; P=0.65 using a generalized linear mixed-effects model with a random effect for trial site).

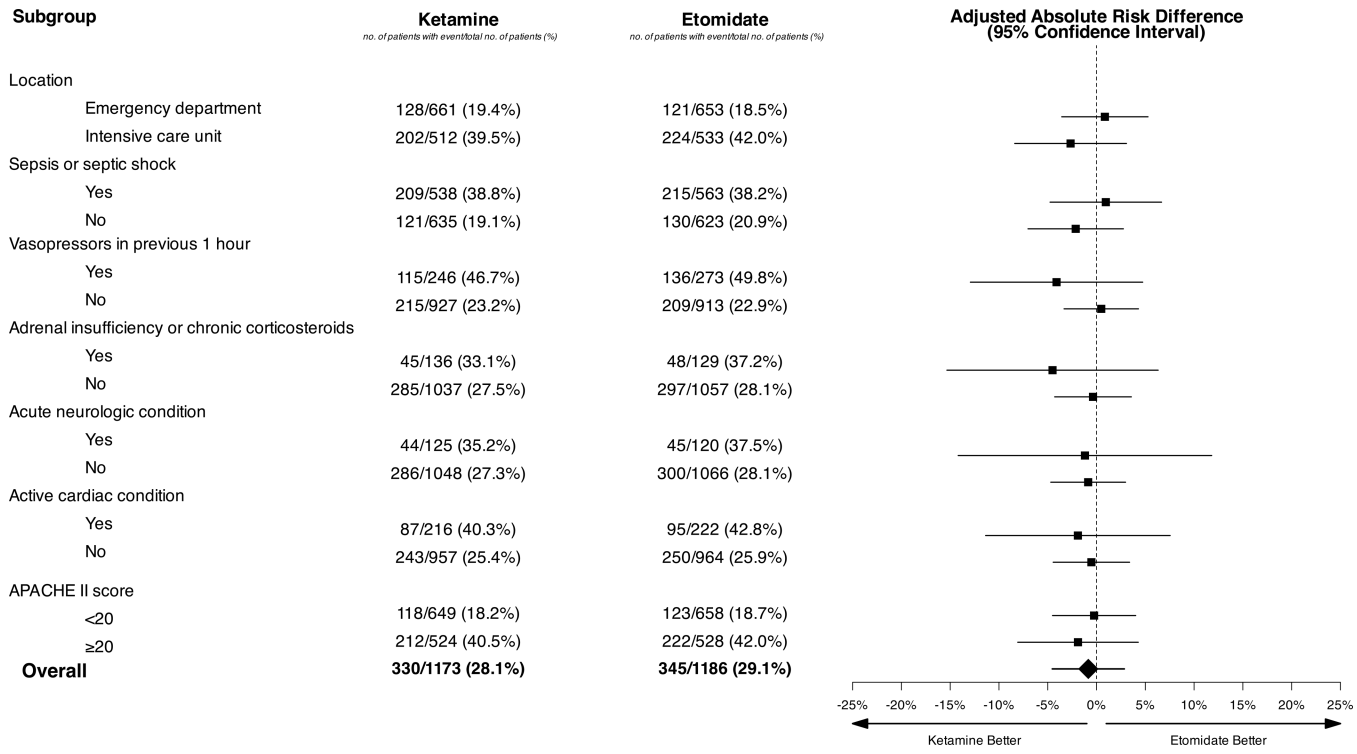

Figure 2. Subgroup Analyses of the Primary Outcome.

Shown are the absolute risk differences and 95% confidence intervals adjusted for trial site for the primary outcome (in-hospital death by 28 days) in the ketamine group as compared with the etomidate group in each prespecified subgroup. Differences between the ketamine group and the etomidate group were calculated with the use of a generalized linear mixed-effects model with a random effect for trial site and fixed effects for trial group, the proposed effect modifier, and the interaction between the trial group and the proposed effect modifier without adjustment for covariates. Differences of less than 0 indicate a lower likelihood of death with the use of ketamine. Sepsis or septic shock at enrollment is defined according to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). Chronic corticosteroid receipt is defined as receiving corticosteroids for at least 3 consecutive weeks prior to enrollment. Acute neurologic condition is defined as intracranial bleeding, meningitis, encephalitis, or stroke. Active cardiac condition is defined as cardiac arrest, cardiogenic shock, congestive heart failure, cardiogenic pulmonary edema, pulmonary hypertension, or myocardial infarction. APACHE II is the Acute Physiology and Chronic Health Evaluation II score, which ranges from 0 to 71, with higher scores indicating a greater severity of illness. The widths of the confidence intervals were not adjusted for multiplicity and should not be used to infer definitive differences in treatment effects between the two groups.

Table 1.

Characteristics of the Patients at Baseline.

Characteristic*	Ketamine (N=1,176)	Etomidate (N=1,189)
Age, years – median (IQR)	60 (45–69)	60 (44–69)
Female sex – no. (%)	498 (42.3)	492 (41.4)
Race or ethnic group – no. (%)†		
Non-Hispanic White	686 (58.3)	706 (59.4)
Non-Hispanic Black	300 (25.5)	287 (24.1)
Hispanic	130 (11.1)	132 (11.1)
Other	60 (5.1)	64 (5.4)
Weight, kg – median (IQR)	78.9 (65.1–95.6)	78.5 (65.3–93.3)
Body mass index – median (IQR)‡	26.9 (23.0–32.4)	26.7 (22.5–32.1)
Location of intubation – no. (%)		
Emergency department	663 (56.4)	655 (55.1)
Intensive care unit	513 (43.6)	534 (44.9)
Chronic conditions – no. (%)		
Adrenal insufficiency or chronic receipt of corticosteroids	136 (11.6)	129 (10.8)
Cirrhosis	165 (14.0)	166 (14.0)
Congestive heart failure	175 (14.9)	158 (13.3)
Coronary artery disease	141 (12.0)	153 (12.9)
Hypertension	536 (45.6)	533 (44.8)
Malignancy	227 (19.3)	215 (18.1)
Acute conditions – no. (%)§		
Acute cardiac condition¶	216 (18.4)	223 (18.8)
Acute respiratory condition‖	678 (57.7)	683 (57.4)
Acute neurologic condition**	125 (10.6)	121 (10.2)
Sepsis or septic shock††	539 (45.8)	565 (47.5)
Glasgow Coma Scale score – median (IQR)‡‡	11 (7–15)	11 (7–15)
APACHE II score – median (IQR)§§	18 (13–24)	18 (13–24)
In the hour before enrollment		
Highest heart rate, beats per minute – median (IQR)	107 (90–125)	108 (92–126)
Lowest systolic blood pressure, mm Hg – median (IQR)¶¶	115 (96–136)	114 (94–135)
Receipt of vasopressors – no. (%)	246 (20.9)	274 (23.0)

*IQR denotes interquartile range. Percentages may not total 100 because of rounding.

†Race and ethnic group were reported by the patients or their surrogates as part of clinical care and were obtained from the electronic health record by research personnel using fixed categories.

‡Data on body-mass index (the weight in kilograms divided by the square of the height in meters) were missing for 19 patients (0.8%) – 8 in the ketamine group and 11 in the etomidate group.

[§] Data on acute conditions were abstracted from the electronic health record and grouped into prespecified categories. Patients could have had more than one acute condition.

[¶] Acute cardiac condition is defined as the presence of one or more of the following at the time of enrollment: cardiac arrest; cardiogenic shock; congestive heart failure; cardiogenic pulmonary edema; pulmonary hypertension; or myocardial infarction.

[‖] Acute respiratory condition is defined as the presence of one or more of the following at the time of enrollment: acute respiratory distress syndrome; hypercapnic respiratory failure; hypoxemic respiratory failure; or pneumonia.

[**] Acute neurologic condition is defined as the presence of one or more of the following at the time of enrollment: intracranial bleeding; meningitis; encephalitis; or stroke.

[††] Sepsis or septic shock at enrollment is defined according to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).

[‡‡] Data on Glasgow Coma Scale score were missing for 10 patients (0.4%) – 6 in the ketamine group and 4 in the etomidate group.

[§§] Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II range from 0 to 71, with higher scores indicating a greater severity of illness.

[¶¶] Data on lowest systolic blood pressure in the hour before enrollment were missing for 22 patients (0.9%) – 11 in the ketamine group and 11 in the etomidate group.

Table 2.

Characteristics of the Intubation Procedure.

Characteristic	Ketamine (N=1,176)	Etomidate (N=1,189)	Difference (95% CI)*
Primary induction medication – no. (%)†			
Ketamine	1,167 (99.2)	3 (0.3)	99.0 (98.4 to 99.6)
Etomidate	6 (0.5)	1,184 (99.6)	−99.1 (−99.6 to −98.5)
None	3 (0.3)	2 (0.2)	0.1 (−0.3 to 0.5)
Neuromuscular blocking agent – no. (%)‡			
Rocuronium	810 (69.0)	819 (69.0)	0.0 (−3.7 to 3.7)
Succinylcholine	362 (30.8)	365 (30.7)	0.1 (−3.6 to 3.8)
None	3 (0.3)	3 (0.3)	0.0 (−0.4 to 0.4)
Measurements or treatments at induction of anesthesia			
Oxygen saturation – median (IQR)§	99 (97–100)	99 (97–100)	0 (−1 to 1)
Preoxygenation – no. (%)	1,172 (99.7)	1,186 (99.7)	−0.1 (−0.5 to 0.4)
Systolic blood pressure, mm Hg – median (IQR)¶	127 (110–147)	127 (110–148)	0 (−3 to 3)
Vasopressor bolus or increased infusion rate – no. (%)	207 (17.6)	234 (19.7)	−2.1 (−5.2 to 1.1)
Laryngoscope used on the first attempt – no. (%)			
Video	1,124 (95.6)	1,127 (94.8)	0.8 (−0.9 to 2.5)
Direct	49 (4.2)	60 (5.0)	−0.9 (−2.6 to 0.8)
Other‖	3 (0.3)	2 (0.2)	0.1 (−0.3 to 0.5)
Instrument used on the first attempt — no. (%)**			
Endotracheal tube with stylet	672 (57.3)	689 (58.1)	−0.8 (−4.7 to 3.2)
Bougie	455 (38.8)	446 (37.6)	1.2 (−2.7 to 5.1)
Neither	45 (3.8)	51 (4.3)	−0.5 (−2.1 to 1.1)

*The unadjusted difference is reported in percentage points for categorical variables, and the unadjusted difference in the median value is reported for continuous variables.

†One patient in the ketamine group received ketamine and then also received etomidate as a second induction medication. A total of 35 patients (1.5%) received either propofol or a benzodiazepine in addition to ketamine or etomidate – 18 in the ketamine group and 17 in the etomidate group. A total of 5 patients experienced hemodynamic instability or cardiac arrest before induction and were intubated without an induction medication – 3 in the ketamine group and 2 in the etomidate group.

‡One patient received both rocuronium and succinylcholine. Data on neuromuscular blocking agents were missing in 4 patients (0.2%) – 2 patients in the ketamine group and 2 patients in the etomidate group.

§Data on oxygen saturation at induction were missing in 108 patients (4.6%) – 54 patients in the ketamine group and 54 patients in the etomidate group.

¶Data on systolic blood pressure at induction were missing in 112 patients (4.7%) – 59 patients in the ketamine group and 53 patients in the etomidate group.

‖Three patients in the ketamine group and 2 in the etomidate group were intubated using a bronchoscope or an intubating laryngeal mask airway.

**Among the 2,360 patients intubated with a laryngoscope, data on the instrument used on the first attempt were missing in 2 patients (0.1%) – 1 patient in the ketamine group and 1 patient in the etomidate group.

Table 3.

Outcomes.

Outcome	Ketamine (N=1,176)	Etomidate (N=1,189)	Difference (95% CI)*
Primary outcome†			
In-hospital death by 28 days – no. (%)	330 (28.1)	345 (29.1)	−0.8 (−4.5 to 2.9)‡
Secondary outcome			
Cardiovascular collapse between induction and 2 minutes after intubation – no. (%)	260 (22.1)	202 (17.0)	5.1 (1.9 to 8.3)
Systolic blood pressure < 65 mmHg§	73 (6.4)	64 (5.5)	0.9 (−1.0 to 2.8)
New or increased vasopressor receipt	251 (21.3)	189 (15.9)	5.4 (2.3 to 8.6)
Cardiac arrest¶	12 (1.0)	10 (0.8)	0.2 (−0.6 to 1.0)
Additional Procedural outcomes			
Lowest systolic blood pressure, mm Hg – median (IQR) §	112 (92–138)	118 (98–141)	−6 (−9 to −1)
Lowest systolic blood pressure <80 mm Hg – no. (%)§	164 (14.4)	123 (10.6)	3.8 (1.1 to 6.5)
Highest systolic blood pressure, mm Hg – median (IQR) §	140 (115–164)	141 (118–168)	−2 (−7 to 2)
Highest systolic blood pressure > 180 mm Hg – no. (%)§	154 (13.5)	191 (16.5)	−2.9 (−5.9 to −0.0)
Lowest oxygen saturation, % – median (IQR)‖	97 (90–100)	97 (89–100)	0 (0 to 2)
Lowest oxygen saturation <80% – no./total no. (%)‖	125 (11.1)	126 (11.1)	0.0 (−2.6 to 2.6)
Successful intubation on the first attempt – no. (%)**	1,005 (85.7)	1,029 (86.7)	−1.0 (−3.8 to 1.8)
Median time from induction to intubation (IQR) – seconds††	112 (86–155)	103 (80–134)	9 (5 to 14)
Safety outcomes			
Systolic blood pressure at 24 hours, mm Hg – median (IQR) ‡‡	114 (102–130)	114 (103–129)	0 (−2 to 3)
Receipt of vasopressors at 24 hours – no. (%)§§	420 (38.9)	458 (42.3)	−3.4 (−7.5 to 0.7)
Clinical outcomes†,¶¶			
Ventilator-free days – median (IQR)	23 (0–26)	23 (0–26)	0 (−1 to 1)
Vasopressor-free days – median (IQR)	25 (0–28)	25 (0–28)	0 (−1 to 1)
ICU-free days – median – median (IQR)	20 (0–24)	19 (0–24)	1 (−1 to 2)

*For the primary outcome, the absolute risk difference adjusted for trial site is presented, which was generated using a general linear mixed-effects model with a random effect for trial site without adjustment for covariates. For other outcomes, the unadjusted absolute risk difference is reported in percentage points for categorical variables, and the unadjusted difference in the median value is reported for continuous and ordinal variables; the widths of the confidence intervals were not adjusted for multiplicity and should not be used to infer definitive differences in treatment effects between the two groups.

†A total of 6 patients (0.3%) withdrew from follow-up prior to 28 days and were missing data for 28-day outcomes — 3 in the ketamine group and 3 in the etomidate group.

‡P=0.65.

§Data on systolic blood pressure during the interval between induction of anesthesia and 2 minutes after intubation were missing for 68 patients (2.9%) — 38 in the ketamine group and 30 in the etomidate group.

¶Of the 22 patients (0.9%) who experienced cardiac arrest during the interval between induction of anesthesia and 2 minutes after intubation, 5 patients (0.2%) died within one hour of intubation — 3 in the ketamine group and 2 in the etomidate group.

[//] Data on the oxygen saturation during the interval between induction of anesthesia and 2 minutes after intubation were missing for 106 patients (4.5%) — 49 in the ketamine group and 57 in the etomidate group.

[**] Successful intubation on the first attempt is reported among the 2,360 patients intubated with a laryngoscope

[††] Data on the time from induction to intubation were missing for 26 patients (1.1%) — 14 in the ketamine group and 12 in the etomidate group.

[‡‡] Data on systolic blood pressure at 24 hours were unavailable for the 204 patients (8.6%) who died or were discharged prior to 24 hours and were missing for 9 patients (0.4%) – 4 in the ketamine group and 5 in the etomidate group.

[§§] Data on receipt of vasopressors at 24 hours were unavailable for the 204 patients (8.6%) who died or were discharged prior to 24 hours — 97 in the ketamine group and 107 in the etomidate group. Among the 878 patients who were receiving vasopressors at 24 hours, the *post hoc* outcome of median vasopressor dose in norepinephrine equivalents was 0.09 μg/kg/min (IQR, 0.04−0.20) in the ketamine group and 0.12 μg/kg/min (IQR, 0.06−0.27) in the etomidate group (median difference, −0.03; 95% CI, −0.06 to −0.01).

[¶¶] Ventilator-free days, vasopressor-free days, and ICU-free days were assessed at 28 days, with follow-up data censored at the time of hospital discharge.