Supplemental Online Content

Russell DW, Casey JD, Gibbs KW, et al; PREPARE II Investigators and the Pragmatic Critical Care Research Group. Effect of fluid bolus administration on cardiovascular collapse among critically ill patients undergoing tracheal intubation: a randomized clinical trial. *JAMA*. Published online June 16, 2022. doi:10.1001/jama.2022.9792

This supplemental material has been provided by the authors to give readers additional information about their work.

eLists. Manuscript authors; PREPARE II Investigators; Pragmatic Critical Care Research Group Members

Manuscript authors

Wake Forest School of Medicine: *Department of Medicine, Section of Pulmonary, Critical Care, Allergy and Immunologic Disease* — Kevin W. Gibbs, MD; Simanta Dutta, MD
Vanderbilt University Medical Center: *Department of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine*—Jonathan D. Casey, MD, MSc; Janna S. Landsperger, MSN; Todd W. Rice, MD, MSc; Matthew W. Semler, MD, MSc; *Department of Biostatistics* —Li Wang, MS; Christopher J. Lindsell PhD; *Department of Emergency Medicine* —Wesley H. Self, MD, MPH
Baylor Scott & White Medical Center: *Department of Medicine, Division of Pulmonary Disease and Critical Care Medicine* — Shekhar Ghamande, MD; Heath D. White, DO, MS; Alejandro C. Arroliga, MD, MS; Tasnim Lat, DO
Lahey Hospital and Medical Center: *Department of Medicine, Division of Pulmonary and Critical Care Medicine* — James Dargin, MD; Joanne Wozniak, PA-C; Susan Stempek, PA-C
University of Alabama at Birmingham Medical Center: *Department of Medicine, Division of Pulmonary, Allergy and Critical Care Medicine; Pulmonary Section, Birmingham Veteran's Affairs Medical Center* — Derek W. Russell, MD; *Department of Medicine, Division of Pulmonary, Allergy and Critical Care Medicine* — Sarah Robison, MD; Sheetal Gandotra, MD; Swati Gulati, MBBS, MS
Ochsner Health System New Orleans: *Department of Pulmonary and Critical Care Medicine* — Derek J. Vonderhaar, MD; Kevin M. Dischert, MD
University of Washington Harborview Medical Center: *Department of Anesthesiology and Pain Medicine* — Aaron M. Joffe, DO; Christopher Barnes; Itay Bentov, MD, PhD; Andrew M. Walters, MD
Oregon Health and Science University School of Medicine: *Department of Medicine, Division of Pulmonary and Critical Care Medicine* — Akram Khan, MD; Olivia F. Krol, BS; Stephanie Nonas, MD
Hennepin County Medical Center: *Department of Emergency Medicine; Department of Medicine, Division of Pulmonary/Critical Care Medicine* — Matthew E. Prekker, MD, MPH; *Department of Medicine, Division of Pulmonary/Critical Care Medicine* — Brian E. Driver, MD
University of Mississippi Medical Center: *Department of Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine* — Joseph M. Brewer, DO
Louisiana State University School of Medicine, *Department of Medicine, Section of Pulmonary/Critical Care Medicine and Allergy/Immunology;* University Medical Center New Orleans: David R. Janz, MD, MSc

PREPARE II Investigators

Wake Forest School of Medicine—Stephen P. Peters MD, PhD; Muhammad Ali, MBBS; Rita N. Bakhru, MD, MS; Scott Bauer, ANP-BC; Christina R. Bellinger, MD; Amanda M. Brown, PA-C; Blair Brown, MD; Jerri Brown, ADN, RN; Caitlin Bumgarner, ACGNP; Wendy Butcher, RN, BSN; Megan Caudle, ACGNP; Arjun B. Chatterjee, MD; David J. Chodos, MD; Gerardo Corcino, RN, BSN; Nathan S. Cutler, MD; Travis L. Dotson, MD; Daniel C. Files, MD; Jonathan L Forbes, DO; John P. Gaillard, MD; Katherine A. Gershner, DO; Shannon Ginty, PA-C; Kiadrick R. Hood, RN, MSN, CMSRN; April Hazelwood, ADN, RN; Katherine Hendricks, FNP; Kelly Jacobus, PA-C; Jonathan T. Jaffe, MD; Stacy Kay, ACGNP; Chad A. Kloefkorn, MD; Jennifer Krall, MD; Margo T. Lannan, MD; Cornelia Lane, ACGNP; Cynthia Lanning, BSN, RN; Jessica Lyons, PA-C; William I. Mariencheck Jr., MD; Chad R. Marion, DO, PhD; Matthew A. Maslonka, MD; Sara McClintock, ACGNP; Nathaniel M. Meier, MD; Matthew C. Miles, MD, MEd; Peter J. Miller, MD; Sophia Mitchell, PA-C; Wendy C. Moore, MD; Katherine Moss, PA-C; Andrew M. Namen, MD; Dustin L. Norton, MD; Stella B. Ogake, MD; Jill A. Ohar, MD; Victor E. Ortega, MD, PhD; Jessica A. Palakshappa, MD, MS; Rodolfo M. Pascual, MD; Sandi Pascual, ANP-BC; Aaron Pickens, MD; Himanshu Rawal, MBBS; Adam R Schertz, MD; Matt Strong, ADN, RN; Alexander O. Sy, MD; Braghadheeswar Thyagarajan MD; Amy Townsend, ACGNP ; Russell Worthen, FNP-BC; Michael Wlodarski, PA-C ; Charles Yarbrough, ADN, RN; Caroline York, PA-C

Vanderbilt University Medical Center—Bradley Lloyd, RRT-ACCS

Lahey Hospital and Medical Center— Christopher Adler, PA-C; Ahmed Agameya, MD; Michael Colancecco, DO; Daniel Fitelson, MD; Joshua Giaccotto, MD; Gena Han, DO; Louise Kane, MD; Ezra Miller, MD; Timothy Noland, PA-C; Jaqueline Price, PA-C; Joseph Plourde, PA-C; Emily Adams, PA-C; Fraser Mackay, MD; Laura Mahoney, PA-C; Avignat Patel, MD; Michael Plourde, PA-C; Zena Saadeh, PA-C; Sara Shadchehr, DO; Sandeep Somalaraju, MD; Eleanor Summerhill, MD; Ryan Webster, MD; Jordan Winnicki, PA-C; Ekaterina Yavarovich, DO

University of Alabama at Birmingham Medical Center—Anna Altz-Stamm RN, BSN, CCRN; Cristina Bardita, MD, PhD ; Mary Clay Boone RN, BSN; Joe W. Chiles III, MD; Kristina Collins RN, BSN; Abby Drescher RN, BSN; Kevin G. Dsouza, MD; Janna Dunn, RN, AND; Stacy Ejem, MD; Josh Gautney, MD; Nicole Harris, RN, ADN; Savannah Herder, RN, BSN; Tamer Hudali, MD, MPH; R. Chad Wade, MD; Rutwij Joshi, MBBS; Daniel Kelmenson, MD; Anne Merrill Mason RN, BSN; Scott R. Merriman, MD; Takudzwa Mkorombindo, MD; Megan Moore, RN, MSN; Jada Nowak, RN, BSN; Kate O'Connor, DO; David B. Page, MD; Sheylan D. Patel, MD; G. Bruno Pereira, MD, PhD; Lisa Sarratt RN, BSN; Tabitha Stewart RN, BSN; William S. Stigler, MD; Kadambari Vijaykumar, MBBS; Gina White RN, BSN; Micah R. Whitson, MD

University of Washington Harborview Medical Center— Katherine O. Heller, MD

Oregon Health and Science University School of Medicine— C. Cole Malibiran, BS; Milad K. Jouzestani; Chandani Anandkat Zachary Zouyed, BS; Matthew G. Drake, MD; Makrina N. Kamel, BS

Pragmatic Critical Care Research Group Members

Executive Committee: Matthew W. Semler, MD, MSc (Chair); Denver Health Medical Center — Stacy A Trent, MD, MPH; Hennepin County Medical Center — Brian E. Driver, MD; Matthew E. Prekker, MD, MPH; Louisiana State University School of Medicine — David R. Janz, MD, MSc; University of Alabama at Birmingham Medical Center — Sheetal Gandotra, MD; Derek W. Russell, MD; University of Colorado School of Medicine — Adit A. Ginde, MD, MPH; Vanderbilt University Medical Center — Jonathan D. Casey, MD, MSc; Todd W. Rice, MD, MSc; Wesley H. Self, MD, MPH; Matthew W. Semler, MD, MSc; Wake Forest School of Medicine — Kevin W. Gibbs, MD.

Coordinating Center: Jonathan D. Casey, MD, MSc (Director); Christopher J. Lindsell PhD; Todd W. Rice, MD, MSc; Wesley H. Self, MD, MPH; Matthew W. Semler, MD, MSc; Li Wang, MS – all at Vanderbilt University Medical Center.

Steering Committee: Baylor Scott & White Medical Center — Shekhar Ghamande, MD; Denver Health Medical Center — Stacy A. Trent, MD, MPH; Hennepin County Medical Center — Brian E. Driver, MD; Matthew E. Prekker, MD MPH; Lahey Hospital and Medical Center — James M. Dargin, MD; Susan Stempek, PA-C; Lincoln Medical Center — Jason R. West, MD; Louisiana State University School of Medicine — David R. Janz, MD, MSc; Ochsner Health System New Orleans — Derek J. Vonderhaar, MD; Oregon Health and Science University School of Medicine — Akram Khan, MD; University of Alabama at Birmingham Medical Center — Sheetal Gandotra, MD; David B. Page, MD; Micah R. Whitson, MD; Derek W. Russell, MD; University of Colorado School of Medicine — Adit A. Ginde, MD, MPH; University of Iowa Hospitals and Clinics — Kevin Doerschug, MD; Vikas Koppurapu, MD; University of Mississippi Medical Center — Joseph M. Brewer, DO, MS; University of Washington Harborview Medical Center — Steven H. Mitchell, MD; Andrew J. Latimer, MD; Christopher Barnes; Itay Bentov, MD, PhD; Vanderbilt University Medical Center — Matthew W. Semler, MD, MSc; Wesley H. Self, MD, MPH; Todd W. Rice, MD, MSc; Jonathan D. Casey, MD, MSc; Aaron J. Lacy, MD; Wake Forest School of Medicine — Lane M. Smith, MD, PhD; John P. Gaillard, MD; Kevin W. Gibbs, MD.

eMethods. IRB approval and waiver of consent; characteristics of the study intensive care units; inclusion and exclusion criteria; measurement of blood pressure; exploratory outcomes; sample size calculation and re-estimation; modeling of the primary outcome; effect modification (subgroup analyses); sensitivity analyses of the primary outcome; handling of missing data

IRB approval and waiver of consent

Critically ill adults undergoing tracheal intubation in the intensive care unit (ICU) are at significant risk for morbidity and mortality from their critical illness. Patients undergoing emergency tracheal intubation in routine clinical care either receive a fluid bolus or do not receive a fluid bolus during tracheal intubation, experiencing any benefits or risks of these two approaches as a part of clinical care, outside the context of research.

The only patients eligible for the trial were patients for whom their treating clinician considered both initiation of fluid bolus and intubation without a fluid bolus to be safe and reasonable approaches to tracheal intubation of the patient (otherwise the patient was excluded). Thus, for patients who were undergoing tracheal intubation with either a fluid bolus or no fluid bolus as a part of clinical care, and whose treating clinician felt that either approach was a safe and reasonable approach for their care, making the decision between the two approaches using randomization (by trial group assignment) was felt to pose no more than minimal additional risk, compared to the risks the patient would experience in clinical care without participation in the research.

Additionally, obtaining informed consent for participation in the study would be impracticable. In addition to the time-sensitive nature of tracheal intubation in the ED or ICU, critically ill patients requiring intubation are frequently unconscious or delirious due to their critical illness. Further, legally authorized representatives are commonly unavailable during the brief period between the decision to intubate and the completion of the procedure, and the need for emergency tracheal intubation and distress of the patient or LAR from the patient's critical illness precludes a meaningful informed consent process even when an LAR is present. Delaying emergency tracheal intubation for a critically ill adults to attempt a meaningful informed consent process would be unsafe, impracticable, and unethical.

Because the PREPAREII trial was considered to pose minimal incremental risk and obtaining informed consent was considered to be impracticable, the trial was conducted under a waiver of informed consent. This approach is consistent with previous randomized trials comparing the effectiveness of alternative approaches to tracheal intubation commonly used in current clinical care.[1-9] The trial was approved by the central Institutional Review Board (cIRB) at Vanderbilt University Medical Center (reference number 181690) and local institutional review boards at Texas A&M/Baylor Scott and White Medical Center (reference number 019-182) and Lahey Hospital & Medical Center (reference number 20190324), with the remainder of sites ceding review to the cIRB.

Characteristics of the study intensive care units

Characteristic	Vanderbilt MICU	WFU MICU	UAB MICU	Ochsner MICU	UMCNO MICU
Annual admissions	2940	3200	2000	3500	2600
Number of beds	35	45	24	33	24
Annual number of tracheal intubations	200	350	200	400	300
Personnel present at intubation[a]					
Critical Care Attending	Always	Almost Always	Almost Always	Always	Almost Always
Critical Care Fellow	Always	Always	Almost Always	Almost Always	Sometimes
Internal Medicine Resident	Rarely	Rarely	Sometimes	Rarely	Rarely
Emergency Medicine Attending	Never	Never	Never	Never	Never
Emergency Medicine Fellow	Never	Never	Never	Never	Never
Emergency Medicine Resident	Never	Sometimes	Never	Never	Never
Anesthesiology Attending	Never	Sometimes	Never	Sometimes	Never
Anesthesiology Fellow	Never	Never	Never	Never	Never
Anesthesiology Resident	Never	Sometimes	Never	Sometimes	Sometimes
Certified Nurse Anesthetist	Never	Never	Never	Never	Sometimes
Advanced Practice Provider	Sometimes	Sometimes	Rarely	Rarely	Rarely
Laryngoscopes available					
Macintosh Video Laryngoscope	Yes	Yes	Yes	Yes	Yes
Hyperangulated Video Laryngoscope	Yes	Yes	Yes	Yes	Yes
Direct Laryngoscope	Yes	Yes	Yes	Yes	Yes
Pre-medication					
Lidocaine	Never	Never	Never	Never	Never
Atropine	Never	Never	Never	Never	Never
Midazolam	Never	Rarely	Sometimes	Sometimes	Never
Fentanyl	Rarely	Rarely	Rarely	Sometimes	Never
Pre-intubation fluid responsiveness test	Never	Never	Rarely	Never	Never

Characteristic	Vanderbilt MICU	WFU MICU	UAB MICU	Ochsner MICU	UMCNO MICU
Patient Notification Strategy	Information Sheet	Information Sheet	Notification Sheet	Information Sheet	Notification Sheet
IRB Process[b]	Central	Central	Central	Central	Central

Characteristic	UW ICU[c]	UMMC MICU	HCMC MICU	BSW MICU	Lahey MICU	OHSU MICU
Annual admissions	6900	2500	900	2200	1500	1000
Number of beds	89	20	28	70	20	16
Annual number of intubations	1000	300	160	200	200	150
Personnel present at intubation						
Critical Care Attending	Sometimes	Always	Sometimes	Sometimes	Always	Always
Critical Care Fellow	Sometimes	Always	Sometimes	Always	Sometimes	Always
Internal Medicine Resident	Never	Almost Always	Never	Sometimes	Rarely	Sometimes
Emergency Medicine Attending	Sometimes	Never	Sometimes	Never	Never	Never
Emergency Medicine Fellow	Sometimes	Never	Rarely	Never	Never	Never
Emergency Medicine Resident	Sometimes	Sometimes	Sometimes	Sometimes	Never	Sometimes
Anesthesiology Attending	Almost Always	Never	Never	Sometimes	Never	Sometimes
Anesthesiology Fellow	Sometimes	Never	Never	Never	Never	Rarely
Anesthesiology Resident	Almost Always	Never	Never	Rarely	Rarely	Rarely
Certified Nurse Anesthetist	Almost Always	Never	Never	Never	Rarely	Never
Advanced Practice Provider	Never	Almost Always	Never	Sometimes	Sometimes	Never
Laryngoscopes available						
Macintosh Video Laryng.	Yes	No	Yes	Yes	No	Yes
Hyperangulated Video Laryng.	Yes	Yes	Yes	Yes	Yes	Yes
Direct Laryngoscope	Yes	Yes	Yes	Yes	Yes	Yes
Pre-medication						
Lidocaine	Rarely	Never	Never	Never	Never	Sometimes
Atropine	Never	Never	Never	Never	Never	Never

Characteristic	UW ICU[c]	UMMC MICU	HCMC MICU	BSW MICU	Lahey MICU	OHSU MICU
Midazolam	Sometimes	Never	Never	Sometimes	Rarely	Often
Fentanyl	Sometimes	Rarely	Rarely	Sometimes	Rarely	Often
Pre-intubation fluid responsiveness test[d]	Never	Never	Never	Never	Never	Never
Patient Notification Strategy	Information Sheet	Notification Sheet	Notification & Information Sheets	Information Sheet	Admission Information Sheet	Notification Sheets
IRB Process	Central	Central	Central	Local	Local	Central

VUMC is Vanderbilt University Medical Center in Nashville, TN; MICU is medical intensive care unit. UMCNO is Medical Center New Orleans, in New Orleans, LA; Ochsner is Ochsner Medical Center, in New Orleans, LA; UAB is University of Alabama at Birmingham in Birmingham, AL; UW ICU is University of Washington Harborview Medical Center in Seattle, WA; Lahey is Lahey Hospital and Medical Center in Burlington, MA; WFU is Wake Forest University Medical Center in Winston-Salem, NC; BSW is Baylor, Scott & White Medical Center in Temple, TX; OHSU is Oregon Health Sciences University Medical Center in Portland, OR; Hennepin is Hennepin County Medical Center in Minneapolis, MN; UMMC is University of Mississippi Medical Center, in Jackson, MS; IRB is institutional review board. “Notification sheet” is a patient and family notification packet provided to each patient and family following enrollment informing the patient of his or her enrollment and describing the study. “Information Sheet” is a patient and family information sheet containing general information about the study and contact information for the research team displayed in at least three publicly-visible locations within the study unit.

[a.] The PREPARE II trial screened for eligibility 24 hours a day during the enrolling period except at sites for which airways performed at night were performed by a separate group of clinicians not trained in the trial protocol.

[b.] The Vanderbilt IRB served as central IRB for sites utilizing a central IRB process.

[c.] UW ICU includes a neurological ICU, medical ICU, and trauma ICU. Because all intubations are performed by the same group of operators, these three ICUs are treated as one site with regard to study procedures (stratification by site) and analysis.

[d.] In each of the trial ICUs, general fluid management for critically ill adults includes serial multifactorial assessments of intravascular volume status or fluid responsiveness, administration of intravenous crystalloid solutions as the first-line fluid for sepsis, and avoidance of semisynthetic colloid solutions. In none of the trial ICUs does institutional protocol standardize assessment of intravascular volume status or fluid responsiveness in the peri-intubation period.

Inclusion and exclusion criteria

Inclusion Criteria:

1. Patient is undergoing endotracheal intubation in a participating unit
2. Planned operator is a provider expected to routinely perform endotracheal intubation in the participating unit
3. Patient is at least 18 years of age
4. Administration of sedation is planned (with or without neuromuscular blockade)
5. Positive pressure ventilation between induction and laryngoscopy is planned (e.g., non-invasive ventilation or bag-mask ventilation)

Exclusion Criteria:

1. Prisoners
2. Pregnant patients
3. Urgency of intubation precludes safe performance of study procedures
4. Operator feels administration of a fluid bolus is indicated or contraindicated for the safe performance of the procedure

Measurement of blood pressure

Values for systolic blood pressure at induction and between induction and 2 minutes after intubation were measured using either continuous measurement of arterial blood pressure for patients with an indwelling arterial catheter as part of clinical care or intermittent non-invasive measurement via automated sphygmomanometry for patients without an indwelling arterial catheter. When non-invasive blood pressure monitoring was used, observers and operators were advised by trial training materials to set automated sphygmomanometers to cycle every 1-2 minutes after enrollment, including from induction until 2 minutes after tracheal intubation. Observers were trained to monitor the patient's systolic blood pressure throughout the data collection period. The most recent systolic blood pressure reading available at the time of induction (i.e., the moment that an intravenous push of the first intubation anesthetic agent was initiated), as well as the lowest systolic blood pressure reading that occurred after the time of induction but before 2 minutes after placement of an endotracheal tube in the trachea were both recorded on the data collection sheet. If no blood pressure measurement was available for a given timepoint (e.g., as a patient experienced cardiac arrest without a measurable systolic blood pressure), the relevant field was left blank.

Exploratory outcomes

All outcomes were pre-specified at the time of trial registration and defined as part of the previously published statistical analysis plan.[10]

Pre-specified exploratory outcomes included

- Initiation of an intravenous fluid bolus between induction and 2 minutes after intubation. This outcome was defined as the new administration of an intravenous crystalloid or colloid solution between the first administration of an induction medication and two minutes after the final placement of an endotracheal tube in the tracheal.
- Time from induction to successful intubation. This outcome was defined as the time (in seconds) from the initial administration of an induction medication (start time) until the final placement of an endotracheal tube in the trachea (end time).
- Incidence of successful intubation on the first laryngoscopy attempt. This outcome was defined as placement of an endotracheal tube in the trachea during a single insertion of a laryngoscope blade into the mouth.
- Number of laryngoscopy attempts. This outcome was defined as the number of time a laryngoscope blade was inserted into the mouth between administration of the induction medication and final placement of an endotracheal tube in the trachea.
- Cormack-Lehane grade of glottic view on first attempt. Cormack-Lehane grade of glottic view ranges from grade 1 (best) to grade 4 (worst). Each grade is defined as follows: grade 1 - all or most of the glottic opening seen; grade 2 - only the posterior portion of the glottis or only arytenoid cartilages are visible; grade 3 - only the epiglottis but no portion of the glottis is visible; grade 4 - neither the glottis nor the epiglottis can be seen.
- Operator-assessed difficulty of intubation. This outcome was defined qualitatively by the operator on the basis of the subjective degree of difficulty of the tracheal intubation procedure on a scale of easy (best value), moderate, or difficulty (worst value).
- Need for a second operator. This outcome was considered to have occurred if an individual other than the operator who performed the initial laryngoscopy performed laryngoscopy or intubation of the trachea at any point from initial induction until final placement of an endotracheal tube in the trachea.
- Each individual component of the composite primary endpoint:
    - SBP (systolic blood pressure) < 65 mmHg between induction and 2 minutes after intubation
    - new or increased vasopressor administration between induction and 2 minutes after intubation
    - cardiac arrest between induction and 1 hour after intubation
    - death between induction and 1 hour after intubation.
- Lowest SBP between induction and 2 minutes after intubation. This outcome was defined as the lowest SBP that was measured between initiation of induction medication and 2 minutes after the final placement of an endotracheal tube in the trachea.

- Change in SBP from induction to lowest SBP between induction and 2 minutes after intubation. This outcome was defined as the difference between the lowest SBP between induction and 2 minutes after intubation and the SBP at the time of initiation of induction.
- Lowest arterial oxygen saturation between induction and 2 minutes after intubation. This outcome was defined as the lowest arterial oxygen saturation, as measured by continuous pulse oximetry, between initiation of induction and 2 minutes after the final placement of an endotracheal tube in the trachea.
- Incidence of hypoxemia (oxygen saturation < 90%) between induction and 2 minutes after intubation. This outcome was defined as the occurrence of an oxygen saturation value, as measured by continuous pulse oximetry, of less than 90% between initiation of induction and 2 minutes after the final placement of an endotracheal tube in the trachea.
- Incidence of severe hypoxemia (oxygen saturation < 80%) between induction and 2 minutes after intubation. This outcome was defined as the occurrence of an oxygen saturation value, as measured by continuous pulse oximetry, of less than 80% between initiation of induction and 2 minutes after the final placement of an endotracheal tube in the trachea.
- Oxygen saturation at 24 hours after intubation. This outcome was defined as the arterial oxygen saturation, as measured by continuous pulse oximetry, closest in time to 24 hours after the time of tracheal intubation. This outcome was available only for patients who remained hospitalized at the time of assessment.
- Fraction of inspired oxygen at 24 hours after intubation. This outcome was defined as the fraction of inspired oxygen being administered at the time closest to 24 hours after the time of tracheal intubation. This outcome was available only for patients who remained hospitalized at the time of assessment.
- Positive end expiratory pressure at 24 hours after intubation. This outcome was defined as the positive end-expiratory pressure being administered at the time closest to 24 hours after the time of tracheal intubation. This outcome was available only for patients who remained hospitalized and receiving mechanical ventilation.
- SBP at 24 hours after intubation. This outcome was defined as the SBP, as measured by intermittent non-invasive blood pressure monitoring or continuous invasive blood pressure monitoring, at the time closest to 24 hours after the time of tracheal intubation. This outcome was available only for patients who remained hospitalized at the time of assessment.
- Ventilator-free days to 28 days. This outcome was defined as the number of days alive and free of invasive mechanical ventilation, from the patient's final extubation to 28 days after enrollment. If a patient returned to invasive mechanical ventilation and was subsequently liberated from invasive mechanical ventilation prior to day 28, the number of VFDs were counted from the date of the final liberation from invasive mechanical ventilation before day 28. If the patient is receiving invasive mechanical ventilation at day 28 or dies prior to day 28, the number of VFDs will be counted as 0. If a patient was discharged while receiving assisted ventilation, the number of VFDs will be counted as 0. VFDs were counted as 0 in any patients who died before day 28. All data were censored at hospital

discharge or 28 days, whichever occurred first (i.e., any liberation from invasive mechanical ventilation after day 28 or after a hospital discharge does not affect VFDs).

- ICU-free days to 28 days. This outcome was defined as the number of days alive and not admitted to an intensive care unit service, from the patient's final discharge from the intensive care unit to 28 days after enrollment. If a patient was not discharged from the intensive care unit service by day 28, the number of ICU-FDs were counted as 0. If a patient was discharged but later admitted again to an intensive care unit service but then was subsequently discharged prior to day 28, ICU-FDs were counted as the number of days from the date of the final intensive care unit discharge to day 28. ICU-FDs were counted as 0 in any patients who die before day 28. All data were censored at hospital discharge or 28 days, whichever came first (i.e., any readmission to an intensive care unit service after day 28 or after a hospital discharge does not affect ICU-FDs).

Sample size calculation and re-estimation

Initial Sample Size Estimation

In a prior randomized trial comparing fluid bolus administration beginning prior to induction versus no fluid bolus administration in the same setting as the current trial, the incidence of cardiovascular collapse was 19.6% in the fluid bolus group and 18.3% in the no fluid bolus group overall. However, among the subgroup of patients assigned to receive positive pressure ventilation with a bag-mask device between induction and laryngoscopy, the incidence of cardiovascular collapse was 16.0% in the fluid bolus group and 26.2% in the no fluid bolus group (10% absolute risk difference and 40% relative risk difference). Assuming more conservative rates of cardiovascular collapse of 16.25% in the fluid bolus group and 25.0% in the no fluid bolus group (8.75% absolute risk difference and 35% relative risk difference), we calculated that enrolling 714 patients would provide 80 percent statistical power at a two-sided alpha level of 0.05. Anticipating less than 5% missing data for the primary outcome, the initial planned enrollment for the trial was 750 patients. The study protocol included a pre-specified conditional sample size re-estimation following the single interim analysis.

Sample Size Re-Estimation

The study protocol specified that, assuming the DSMB recommended continuation of the trial following the interim analysis, "*the DSMB will evaluate the rate of the primary outcome in the no fluid bolus group. If the incidence of the primary outcome in the no fluid bolus group differs from the original estimate of 25.0%, the DSMB may ask that the investigators perform a sample size re-estimation to maintain adequate statistical power to detect the planned relative risk difference in the primary outcome between groups*." After completion of the interim analysis and the recommendation to continue enrollment, the DSMB examined the number of patients that would need to be enrolled in order to maintain 80% statistical power to detect the planned relative risk reduction of 35% in the primary outcome. Based on this information, the DSMB recommended increasing the total sample size from 750 to 1,065 patients. The investigators accepted the DSMB's recommendation, revising the planned sample size for the final trial to 1,065 patients. During the sample size re-estimation, both the study investigators and the DSMB remained blind to all outcomes by study group.

Why the observed event rate for cardiovascular collapse in the trial (approximately 20%) was lower than the initially planned event rate (approximately 25%) is uncertain. The planned event rate of 25% was based on the event rate in a prior trial in similar settings, among the subgroup of patients receiving positive pressure ventilation. However, in the overall population of patients from the prior trial, the event rate was 20%. Thus, it is less likely that the difference in event rate observed in the PREPARE II trial represents changes in care over time and more likely that the higher event rate in the subgroup of the prior trial was a chance finding and the observation of a lower rate in the current trial represents regression to the mean. The pre-specified sample size re-estimation and increase in sample size allowed the trial to maintain the planned statistical power despite the lower-than-planned event rate in the no fluid bolus group.

Modeling of the primary outcome

In order to understand the effect of a fluid bolus vs no fluid bolus on the primary outcome of cardiovascular collapse during tracheal intubation, accounting for (1) pre-specified baseline covariates, and (2) correlation of patients within each study site, we fit two regression models.

We fit a logistic regression model with cardiovascular collapse (primary outcome) as the dependent variable and independent variables including study group (fluid bolus group vs no fluid bolus group) and the following pre-specified baseline covariates: age, APACHE II score at enrollment, presence of sepsis or septic shock, vasopressor receipt in the hour prior to enrollment, and receipt of intravenous fluid infusion initiated prior to enrollment. Age and APACHE II score at enrollment were modeled with a nonlinear relationship to the outcome using restricted cubic splines with 3 knots. Location of knots were 10th, 50th, and 90th quantiles. Effect estimates for continuous variables were made by comparing the 75th percentile to the 25th percentile.

Because patients within a specific ICU may be more similar to other patients within the same ICU than to patients in other ICUs, we also fit a generalized linear mixed-effects model with the outcome of cardiovascular collapse, including group assignment as a fixed effect and study unit (stratification variable) as a random effect.

Effect modification (subgroup analyses)

We examined whether pre-specified baseline variables modify the effect of treatment group on the primary outcome using formal tests of statistical interaction in a logistic regression model. Independent variables included study group assignment, the potential effect modifier of interest, and the interaction between the two (e.g., study group * presence of sepsis or septic shock). Significance was determined by the P value for the interaction term, with values less than 0.10 considered a priori to suggest of a potential interaction and values less than 0.05 considered to confirm an interaction. Continuous variables were analyzed using restricted cubic splines and preferentially displayed as continuous variables with 3 knots using a locally weighted regression or partial effects plots. Location of knots were 10th, 50th, and 90th quantiles. A forest plot was used to display the effect of binary covariates. If required for data presentation, continuous variables were dichotomized for inclusion in a forest plot. We examined whether the following baseline variables modified the effect of study group on the primary outcome:

- Risk of death as measured by dichotomized APACHE II score at enrollment
- Presence of sepsis or septic shock at time of enrollment
- Receipt of vasopressors in the 1 hour prior to enrollment
- Predicted probability of cardiovascular collapse as calculated by a pre-specified multivariable model[11]

In addition to the above variables which can be assessed prior to study enrollment, we performed exploratory analyses examining additional potential effect modifiers that are intended to represent patient physiology at baseline, but which are collected between enrollment and induction and therefore have the theoretical potential to be affected by study group assignment. These included:

- Receipt of positive pressure ventilation for pre-oxygenation (via either non-invasive mechanical ventilation or bag-mask ventilation) (yes/no);
- Choice of sedative medication (etomidate, ketamine, propofol, other);
- New or increased vasopressor administration prior to or with induction (yes/no);
- SBP at induction (continuous variable in mm Hg)
- Oxygen saturation at induction (continuous variable in %)

At six of the sites participating in the PREPARE II trial, patients could be co-enrolled in both the PREPARE II trial and the BOugie or Stylet In Patients UnderGoing Intubation Emergently (BOUGIE) trial (NCT03928925). The BOUGIE trial compared the effect of use of bougie tracheal introducer ("bougie") vs. use of endotracheal tube with stylet on the incidence of successful intubation on the first attempt, defined as a single insertion of a laryngoscope blade into the mouth and either a single insertion of a bougie into the mouth followed by a single insertion of an endotracheal tube into the mouth or a single insertion of an endotracheal tube with stylet into the mouth.

A total of 294 patients were co-enrolled in the BOUGIE and PREPARE II trials. Although no interaction between these interventions was suspected based on underlying physiological mechanism, the statistical analysis plan for the PREPARE II trial pre-specified an analysis evaluating for potential interactions between the trial interventions.

Among those randomized to the bougie group, 17 of 77 patients (22.1%) experienced cardiovascular collapse in the fluid bolus group compared to 11 of 68 patients (16.2%) in the no fluid bolus group (OR, 1.47; 95% CI, 0.63-3.40); among those randomized to the stylet group, 17 of 75 patients (22.7%) experienced cardiovascular collapse in the fluid bolus group compared to 22 of 74 patients (29.7%) in the no fluid bolus group (OR, 0.69; 95% CI, 0.33-1.45). Formal statistical testing using an interaction term suggested that group assignment in bougie (bougie or stylet) did not significantly modify the relationship between group assignment in PREPARE II (fluid bolus or no fluid bolus) and the outcome of cardiovascular collapse (p-value for interaction = 0.19).

Among those randomized to fluid bolus, 55 of 77 patients (71.4%) experienced first pass success in the bougie group compared to 59 of 75 patients (78.7%) in the stylet group (OR, 1.48; 95% CI, 0.70-3.10); among those randomized to no fluid bolus, 55 of 68 patients (80.9%) experienced first pass success in the fluid bolus group compared to 60 of 74 patients (81.1%) in the no fluid bolus group (OR, 1.01; 95% CI, 0.44-2.34). Formal statistical testing using an interaction term suggested that group assignment in PREPARE II (fluid bolus or no fluid bolus) did not significantly modify the relationship between group assignment in BOUGIE (bougie or stylet) and the outcome of first pass success (p-value for interaction = 0.51).

Sensitivity analyses of the primary outcome

To test the robustness of the primary outcome, we pre-specified a plan to repeat the main analysis using the following alternative definitions of the primary outcome or alternative populations:

- Modifying the threshold for hypotension within cardiovascular collapse from a systolic blood pressure <65mmHg to a systolic blood pressure <90mmHg
- Modifying the death component of cardiovascular collapse from death within 1 hour to death within 28 days of enrollment (28-day in-hospital mortality).
- Repeating the primary analysis using ordinal regression with the components of the primary outcome ranked (from most to least severe) as: (1) death; (2) cardiac arrest; (3) SBP < 65 mmHg; and (4) new or increased vasopressor administration.
- Excluding patients who did not receive positive pressure during intubation.
- Excluding patients who were already receiving intravenous fluid at the time of enrollment.

Handling of missing data

No patient was missing data for the primary or secondary outcome. When data were missing for the exploratory outcomes, we performed complete-case analysis, excluding cases where the data for the analyzed outcome were missing. In the adjusted analysis of the primary outcome, missing data for baseline covariates was imputed using multiple imputations.

Multiple imputations used the R function “aregImpute” in Hmisc package. Variables used in the imputation model include: age, sex, height, weight, BMI, race/ethnicity, indication for intubation, obesity, primary diagnosis of trauma, presence or absence of either sepsis or septic shock at time of enrollment, presence or absence of COVID-19 at time of enrollment, APACHE II score at enrollment, receipt of vasopressors in the hour prior to intubation, and receipt of an intravenous fluid infusion initiated prior to enrollment.

eTable 1. Chronic comorbidities

Comorbidity	Fluid Bolus (N= 538)	No Fluid Bolus (N= 527)
Respiratory conditions – no. (%)		
Chronic obstructive pulmonary disease	101 (18.8)	90 (17.1)
Obstructive sleep apnea	46 (8.6)	43 (8.2)
Asthma	24 (4.5)	14 (2.7)
Pulmonary or pleural malignancy	23 (4.3)	19 (3.6)
Interstitial lung disease	13 (2.4)	17 (3.2)
Pulmonary hypertension	10 (1.9)	7 (1.3)
Neuromuscular weakness	9 (1.7)	14 (2.7)
Recurrent aspiration	6 (1.1)	5 (0.9)
Cystic fibrosis	1 (0.2)	1 (0.2)
Other respiratory condition	17 (3.2)	19 (3.6)
Non-respiratory conditions – no. (%)		
Hypertension	181 (33.6)	180 (34.2)
Diabetes mellitus	141 (26.2)	151 (28.7)
Hepatic cirrhosis	92 (17.1)	81 (15.4)
Atrial fibrillation	60 (11.2)	83 (15.7)
Congestive heart failure	83 (15.4)	73 (13.9)
Coronary artery disease	70 (13.0)	80 (15.2)
Cerebrovascular accident	38 (7.1)	39 (7.4)
Chronic kidney disease	66 (12.3)	50 (9.5)
Solid malignancy, non-pulmonary	51 (9.5)	49 (9.3)
End stage renal disease	22 (4.1)	32 (6.1)
Solid organ transplant	29 (5.4)	23 (4.4)
Hematologic malignancy	39 (7.2)	45 (8.5)
Traumatic brain injury	2 (0.4)	3 (0.6)
Spinal cord injury	6 (1.1)	5 (0.9)

Comorbidity	Fluid Bolus (N= 538)	No Fluid Bolus (N= 527)
Stem cell or bone marrow transplant	6 (1.1)	6 (1.1)
Other non-respiratory condition	66 (12.3)	66 (12.5)

eTable 2. Active medical conditions at the time of intubation

Condition	Fluid Bolus (N= 538)	No Fluid Bolus (N= 527)
Glasgow coma score, median (IQR)[a]	13 (9-15) [N=534]	13 (9-15) [N=526]
Neurologic – no. (%)		
Altered mental status	295 (54.8%)	283 (53.7%)
Seizure	18 (3.3%)	21 (4.0%)
Intracranial hemorrhage	13 (2.4%)	13 (2.5%)
Stroke	14 (2.6%)	15 (2.8%)
Traumatic brain injury	2 (0.4%)	3 (0.6%)
Meningitis or encephalitis	13 (2.4%)	5 (0.9%)
Spinal cord compression	2 (0.4%)	5 (0.9%)
Myasthenic crisis	5 (0.9%)	2 (0.4%)
Cardiac – no. (%)		
Decompensated heart failure	27 (5.0%)	18 (3.4%)
Cardiogenic shock	13 (2.4%)	5 (0.9%)
Acute coronary syndrome	14 (2.6%)	16 (3.0%)
Hypertensive urgency or emergency	8 (1.5%)	7 (1.3%)
Cardiac arrest at time of induction	3 (0.6%)	0 (0.0%)
Pulmonary – no. (%)		
Hypoxemic respiratory failure	290 (53.9%)	289 (54.8%)
Hypercapnic respiratory failure	93 (17.3%)	95 (18.0%)
Pneumonia	133 (24.7%)	123 (23.3%)
Acute respiratory distress syndrome	58 (10.8%)	71 (13.5%)
Acute exacerbation of chronic obstructive pulmonary disease	14 (2.6%)	16 (3.0%)
Aspiration	20 (3.7%)	17 (3.2%)

Condition	Fluid Bolus (N= 538)	No Fluid Bolus (N= 527)
Upper airway obstruction	4 (0.7%)	7 (1.3%)
Asthma exacerbation	1 (0.2%)	1 (0.2%)
Gastrointestinal – no. (%)		
Gastrointestinal bleeding	59 (11.0%)	50 (9.5%)
Acute liver failure	27 (5.0%)	25 (4.7%)
Pancreatitis	14 (2.6%)	12 (2.3%)
Hepatorenal syndrome	9 (1.7%)	8 (1.5%)
Bowel obstruction	6 (1.1%)	2 (0.4%)
Bowel perforation	0 (0.0%)	4 (0.8%)
Trauma as presenting diagnosis – no. (%)	4 (2.6)	5 (3.5)

[a] Most recent Glasgow Coma Score recorded in electronic health record prior to tracheal intubation.

eTable 3. Primary indication for tracheal intubation

Indication – no. (%)	Fluid Bolus (N= 538)	No Fluid Bolus (N= 527)
Hypoxic respiratory failure	222 (41.3)	226 (42.9)
Hypercarbic and hypoxic respiratory failure	61 (11.3)	56 (10.6)
Hypercarbic respiratory failure	37 (6.9)	42 (8.0)
Altered mental status	110 (20.4)	106 (20.1)
Emergency procedure	43 (8.0)	37 (7.0)
Metabolic acidosis	16 (3.0)	14 (2.7)
Upper airway obstruction	9 (1.7)	14 (2.7)
Seizure	8 (1.5)	8 (1.5)
Hemodynamic instability	8 (1.5)	6 (1.1)
Agitation	2 (0.4)	2 (0.4)
Cardiac arrest	3 (0.6)	0 (0.0)
Respiratory arrest	2 (0.4)	3 (0.6)
Hemoptysis	4 (0.7)	2 (0.4)
Other	13 (2.4)	11 (2.1)

eTable 4. Operator characteristics

Characteristic	Fluid Bolus N=538	No Fluid Bolus N=527
No. of unique operators	230	237
Enrollments per operator		
Median (IQR)	2 (1, 4)	1 (1, 2.5)
Range	1 to 13	1 to 15
Operator specialty[a] – no. (%)		
Critical Care	478 (88.8)	464 (88.0)
Anesthesia	29 (5.4)	34 (6.5)
Emergency Medicine	22 (4.1)	25 (4.7)
Other or unknown	14 (2.6)	7 (1.3)
Operator training level – no. (%)		
Resident	50 (9.3)	48 (9.1)
Fellow	406 (75.5)	395 (75.0)
Attending physician	39 (7.2)	36 (6.8)
Nurse anesthetist	11 (2.0)	11 (2.1)
Physician assistant	27 (5.0)	26 (4.9)
Nurse practitioner	9 (1.7)	11 (2.1)
Prior intubation experience[b]		
No. of previous intubations, median (IQR)	50 (30-85)	50 (27-85)

a. Operators could report more than one
b. Prior intubation experience refers to the total number of tracheal intubations the operator has performed previously, as reported by the operator at the time of the enrollment.

eTable 5. Description of patients who did not receive assigned intervention

	Group Assignment	Intervention Received	Reported Reason for Crossover	New or Increased Vasopressors	Lowest SBP (mmHg)	Cardiac Arrest	Death
Patient 1[a]	Fluid Bolus	No Fluid Bolus	Hypertension	Yes	76	No	No
Patient 2	Fluid Bolus	No Fluid Bolus	Operator Error	No	106	No	No
Patient 3	Fluid Bolus	No Fluid Bolus	Pulmonary edema	No	129	No	No
Patient 4	No Fluid Bolus	Fluid Bolus	Hypotension beginning after enrollment	No	81	No	No
Patient 5	No Fluid Bolus	Fluid Bolus	Hypotension beginning after enrollment	No	185	No	No
Patient 6	No Fluid Bolus	Fluid Bolus	Hypotension beginning after enrollment	Yes	77	No	No
Patient 7	No Fluid Bolus	Fluid Bolus	Hypotension beginning after enrollment	No	106	No	No
Patient 8	No Fluid Bolus	Fluid Bolus	Hypotension beginning after enrollment	Yes	72	No	No
Patient 9	No Fluid Bolus	Fluid Bolus	Hypotension beginning after enrollment	Yes	65	No	No

SBP is systolic blood pressure. The time interval for new or increased vasopressors and lowest SBP was defined as between induction and 2 minutes after intubation. The time interval for cardiac arrest and death was defined as between induction and 1 hour after intubation.

[a.] Patient was assigned to the fluid bolus group. They did not receive a fluid bolus before induction due to operator concerns regarding hypertension. A fluid bolus was administered after induction (“rescue” fluid bolus) as treatment of hypotension that developed following induction.

eTable 6. Medications administered for the intubation procedure

Characteristic	Fluid Bolus (N= 538)	No Fluid Bolus (N= 527)	Absolute difference or median difference (95% CI)
Induction medication[a]	536 (99.6)	526 (99.8)	-0.2 (-1.0 to 0.6)
Etomidate	413 (76.8)	416 (78.9)	-2.2 (-7.3 to 3.0)
Dose, median (IQR) – mg	20 (20, 20)	20 (20, 20)	0.0 (0.0 to 0.0)
Dose per weight, median (IQR) – mg/kg	0.26 (0.20, 0.32)	0.26 (0.20, 0.31)	0.00 (0.01 to 0.01)
Ketamine	66 (12.3)	55 (10.4)	1.8 (-2.2 to 5.8)
Dose, median (IQR) – mg	110 (100, 150)	105 (100, 150)	5.0 (-20.0 to 50.0)
Dose per weight, median (IQR) – mg/kg	1.37 (1.11, 1.75)	1.30 (0.97, 1.76)	0.06 (-0.22 to 0.44)
Propofol	53 (9.9)	57 (10.8)	-1.0 (-4.8 to 2.9)
Dose, median (IQR) – mg	80 (50, 100)	70 (50, 100)	10.0 (-5.0 to 40.0)
Dose per weight, median (IQR) – mg/kg	1.03 (0.61, 1.24)	0.91 (0.58, 1.12)	0.12 (-0.01 to 0.28)
Fentanyl	70 (13.0)	63 (12.0)	1.1 (-3.1 to 5.2)
Dose, median (IQR) – mcg	100 (50, 100)	100 (50, 100)	0.0 (-50.0 to 50.0)
Dose per weight, median (IQR) – mcg/kg	0.90 (0.62, 1.27)	0.94 (0.63, 1.26)	-0.04 (-0.21 to 0.20)
Midazolam	48 (8.9)	42 (8.0)	1.0 (-2.6 to 4.5)
Dose, median (IQR) – mg	2 (2, 2)	2 (2, 2)	0.0 (0.0 to 0.0)
Dose per weight, median (IQR) – mg/kg	0.03 (0.02, 0.04)	0.03 (0.02, 0.03)	0.00 (0.00, 0.01)
Morphine	2 (0.4)	0 (0.0)	0.4 (-0.3 to 1.1)
Dose, median (IQR) – mg	--	--	--
Dose per weight, median (IQR) – mg/kg	--	--	--
Lorazepam	2 (0.4)	1 (0.2)	0.2 (-0.6 to 1.0)
Dose, median (IQR) – mg	--	--	--
Dose per weight, median (IQR) – mg/kg	--	--	--
Neuromuscular blocking medication[a,b]	509 (94.6)	492 (93.5)	1.3 (-1.8 to 4.3)
Rocuronium – no. (%)	402 (74.7)	378 (71.7)	3.0 (-2.5 to 8.5)
Dose, median (IQR) – mg	100 (53, 100)	100 (60, 100)	0 (-20.0 to 20.0)

Characteristic	Fluid Bolus (N= 538)	No Fluid Bolus (N= 527)	Absolute difference or median difference (95% CI)
Succinylcholine – no. (%)	105 (19.5)	109 (20.7)	-1.2 (-6.2 to 3.8)
Dose, median (IQR) – mg	100 (75, 100)	100 (90, 100)	0.0 (-0.0 to 0.0)
Cisatracurium – no. (%)	1 (0.2)	1 (0.2)	0.0 (-0.5 to 0.5)
Dose, median (IQR) – mg	--	--	--
Other – no. (%)	3 (0.6)	5 (0.9)	-0.4 (-1.6 to 0.8)
Dose, median (IQR) – mg	--	--	--
Unknown/Not reported	1 (0.2)	4 (0.8)	-0.6 (-1.6 to 0.4)

a. Patients could receive more than one.
b. Data on which neuromuscular blocker was used was missing for 5 patients (0.5%); 1 in the fluid bolus group and 4 in the no fluid bolus group.

eTable 7. Additional characteristics of the intubation procedure

Characteristic	Fluid Bolus (N= 538)	No Fluid Bolus (N= 527)	Absolute difference or median difference (95% CI)
Before induction[a]			
Bilevel positive pressure or high flow nasal cannula use in the hour before intubation, not including preoxygenation – no. (%)	275 (51.1)	265 (50.3)	0.8 (-5.4 to 7.0)
Bilevel positive pressure	171 (31.8)	147 (27.9)	3.9 (-1.8 to 9.6)
High flow nasal cannula	109 (20.3)	125 (23.7)	-3.5 (-8.6 to 1.7)
Preoxygenation device[b] – no. (%)			
Bilevel positive pressure	161 (29.9)	148 (28.1)	1.8 (-3.8 to 7.5)
Bag mask (with ventilation)	80 (14.9)	112 (21.3)	-6.4 (-11.2 to -1.6)
Bag mask (no ventilation)	72 (13.4)	66 (12.5)	0.9 (-3.4 to 5.1)
High flow nasal cannula	102 (19.0)	95 (18.0)	0.9 (-3.9 to 5.8)
Non-rebreather mask	133 (24.7)	129 (24.5)	0.2 (-5.1 to 5.6)
Nasal Cannula	55 (10.2)	43 (8.2)	2.1 (-1.6 to 5.7)
Other	1 (0.2)	3 (0.6)	-0.4 (-1.3 to 0.5)
None	4 (0.7)	2 (0.4)	0.4 (-0.7 to 1.4)
Between induction and laryngoscopy – no. (%)			
Received positive pressure ventilation between induction and laryngoscopy	526 (97.8)	513 (97.3)	0.4 (-1.6 to 2.5)
Reason for not receiving positive pressure – no. (%)			
Emesis occurred after enrollment	0 (0.0)	2 (0.4)	-0.4 (-1.1 to 0.3)
Operator error	8 (1.5)	6 (1.1)	0.3 (-1.2 to 1.9)
Other	4 (0.7)	7 (1.3)	-0.6 (-2.0 to 0.8)
Laryngoscopy			
Initial laryngoscope used – no. (%)			

Characteristic	Fluid Bolus (N= 538)	No Fluid Bolus (N= 527)	Absolute difference or median difference (95% CI)
Direct laryngoscope	162 (30.1)	150 (28.5)	1.6 (-4.0 to 7.3)
C-MAC Macintosh blade	167 (31.0)	171 (32.4)	-1.4 (-7.2 to 4.4)
C-MAC with hyperangulated (“D”) blade	36 (6.7)	36 (6.8)	-0.1 (-3.3 to 3.0)
McGrath MAC Macintosh Blade	83 (15.4)	81 (15.4)	0.1 (-4.3 to 4.5)
GlideScope Titanium MAC blade	18 (3.3)	14 (2.7)	0.7 (-1.5 to 2.9)
Glidescope AVL (hyperangulated)	68 (12.6)	72 (13.7)	-1.0 (-5.3 to 3.2)
Fiberoptic scope	2 (0.4)	2 (0.4)	-0.0 (-0.8 to 0.7)
Unknown/not reported	2 (0.4)	1 (0.2)	0.2 (-0.6 to 1.0)

All values are no. (%) unless otherwise specified
[a.] Patients could receive both bilevel positive pressure and high flow nasal cannula in the hour prior to intubation
[b.] Patients could receive more than one preoxygenation device

eTable 8. Sensitivity analyses

Analysis	Sample Size	Fluid Bolus	No Fluid Bolus	Absolute Difference or Median Difference (95% CI)	P value
		No. with success/total no. in analysis (%)			
The primary analysis	1065	113/538 (21.0%)	96/527 (18.2%)	2.8 (-2.2 to 7.7)	0.25
Repeating the primary analysis while modifying the threshold for hypotension component of cardiovascular collapse from a systolic blood pressure <65mmHg to a systolic blood pressure <90mmHg	1065	142/538 (26.4)	130/527 (24.7)	1.7 (-3.7 to 7.2)	0.52
Repeating the primary analysis while modifying the death component of cardiovascular collapse from death within 1 hour of intubation to 28-day in-hospital mortality	1065	269/538 (50.0)	261/527 (49.5)	0.5 (-5.7 to 6.7)	0.88
Repeating the primary analysis using ordinal regression with the components of the primary outcome ranked (from least to most severe) as: (1) new or increased vasopressor administration; (2) SBP < 65 mmHg; (3) cardiac arrest; and (4) death. Ranks reported as median (IQR) with groups compared using the Wilcoxon rank sum test.	1065	0 (0 to 0)	0 (0 to 0)	0.0 (0.0 to 0.0)	0.28
Repeating the primary analysis while limiting the population to those who received positive pressure ventilation between induction and laryngoscopy	1039	111/526 (21.1)	92/513 (17.9)	3.2 (-1.8 to 8.2)	0.20
Repeating the primary analysis while limiting the population to those not receiving intravenous fluids at enrollment	958	98/483 (20.3)	80/475 (16.8)	3.4 (-1.7 to 8.6)	0.17

eTable 9. Adjusted analyses of the primary outcome

Logistic regression model adjusting for baseline covariates		
Variable	**Odds Ratio**	**95% Confidence Interval**
Age	0.98	0.77-1.24
APACHE II score	1.72	1.28-2.30
Sepsis or septic shock: Neither	1.75	1.19-2.57
Vasopressors or inotropes in the hour before enrollment	3.22	2.23-4.65
Receiving fluids at time of enrollment	1.37	0.84-2.26
Fluid bolus: No fluid bolus	1.24	0.89-1.71
Generalized linear mixed-effects model adjusting for study unit as a random effect		
Variable	**Odds Ratio**	**95% Confidence Interval**
Fluid bolus: No fluid bolus	1.19	0.88-1.61

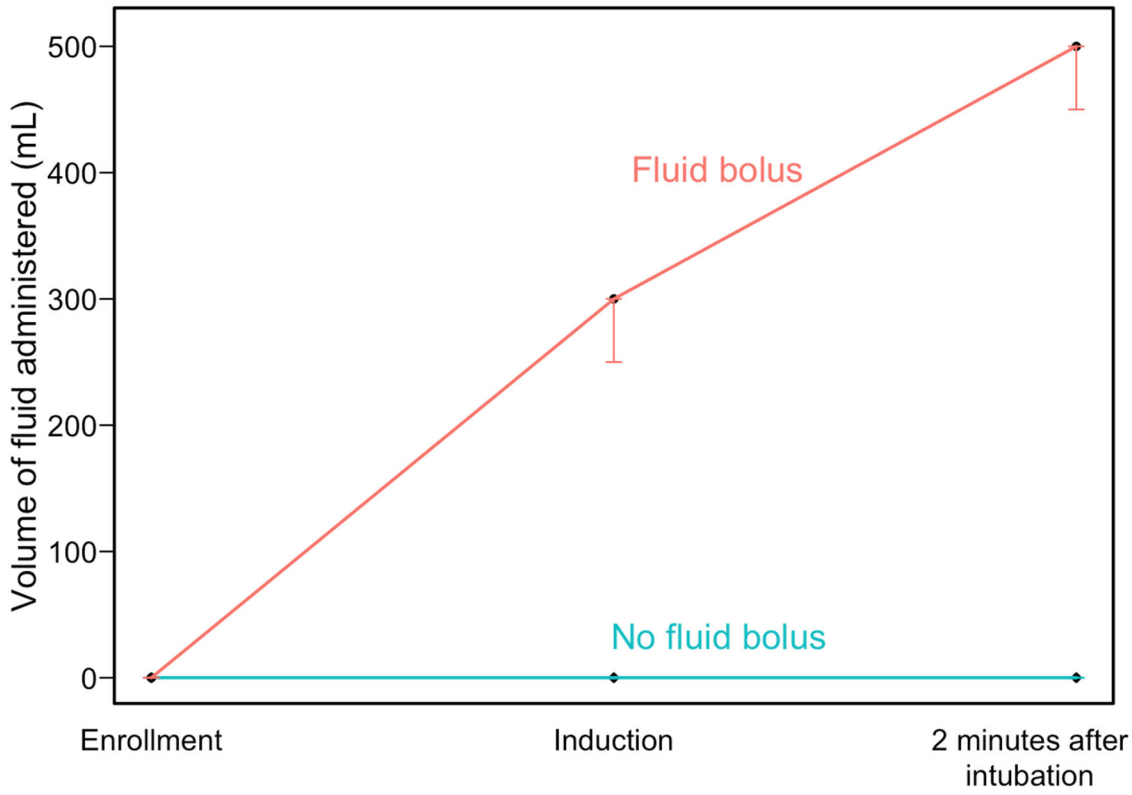
eTable 10. Outcomes of tracheal intubation

	Fluid Bolus (N= 538)	No Fluid Bolus (N= 527)	Absolute difference or median difference (95% CI)
Exploratory procedural outcomes			
Cormack-Lehane grade of glottic view on first attempt – no. (%)[a]			
Grade I (best view)	348 (64.7)	342 (64.9)	-0.2 (-6.1 to 5.7)
Grade II	127 (23.6)	140 (26.6)	-3.0 (-8.4 to 2.4)
Grade III	42 (7.8)	29 (5.5)	2.3 (-0.9 to 5.5)
Grade IV (worst view)	21 (3.9)	16 (3.0)	0.9 (-1.5 to 3.3)
Time from induction to successful intubation, seconds – median (IQR)	149 (108, 217)	142 (103, 209)	7.0 (-4.0 to 17.0)
Incidence of successful intubation on the first laryngoscopy attempt – no. (%)[b]	423 (78.6)	436 (82.7)	-4.1 (-9.0 to 0.8)
Number of laryngoscopy attempts until completed intubation – median (IQR)	1 (1, 1)	1 (1, 1)	0.0 (0.0 to 0.0)
Operator-assessed airway difficulty[c]			
Easy – no. (%)	401 (74.5)	376 (71.3)	3.2 (-2.3 to 8.7)
Moderate – no. (%)	73 (13.6)	88 (16.7)	-3.1 (-7.6 to 1.4)
Difficult – no. (%)	39 (7.2)	27 (5.1)	2.1 (-1.0 to 5.2)
Unknown/Not Reported – no. (%)	25 (4.6)	36 (6.8)	-2.2 (-5.2 to 0.8)
Need for second operator to complete tracheal intubation – no. (%)	24 (4.5%)	16 (3.0)	1.4 (-1.0 to 3.9)
Lowest systolic blood pressure, median (IQR), mm Hg	116 (93, 139) [N=235]	113 (95, 134) [N=235]	3.0 (-3.0 to 7.0)
Change in systolic blood pressure, median (IQR), mm Hg	-7 (-26, 0) [N=235]	-9 (-27, 0) [N=235]	2.0 (-2.0 to 5.0)
Lowest arterial oxygen saturation, median (IQR)	96 (86, 100) [N=531]	96 (88, 100) [N=518]	0.0 (-2.0 to 1.0)
Oxygen saturation < 90%,– no. (%)	178 (33.5) [N=531]	154 (29.7) [N=518]	3.8 (-2.0 to 9.6)

	Fluid Bolus (N= 538)	No Fluid Bolus (N= 527)	Absolute difference or median difference (95% CI)
Oxygen saturation < 80%,– no. (%)	79 (14.9) [N=531]	71 (13.7) [N=518]	1.2 (-3.3 to 5.6)
Exploratory clinical outcomes			
Oxygen saturation at 24 hours, median (IQR)[d]	97 (95, 99) [N=500]	97 (95, 99) [N=486]	0.0 (-0.0 to 0.0)
Fraction of inspired oxygen at 24 hours, median (IQR)[d]	0.4 (0.3, 0.5) [N=499]	0.4 (0.35, 0.5) [N=478]	0.0 (-0.0 to 1.0)
Positive end expiratory pressure at 24 hours after intubation, median (IQR), cm H_2O[d]	5 (5, 8) [N=497]	5 (5,8) [N=483]	0.0 (-0.0 to 1.0)
Systolic blood pressure at 24 hours, median (IQR), mm Hg[d]	115 (101, 129) [N=501]	113 (102, 127) [N=486]	2.0 (-1.5 to 4.0)

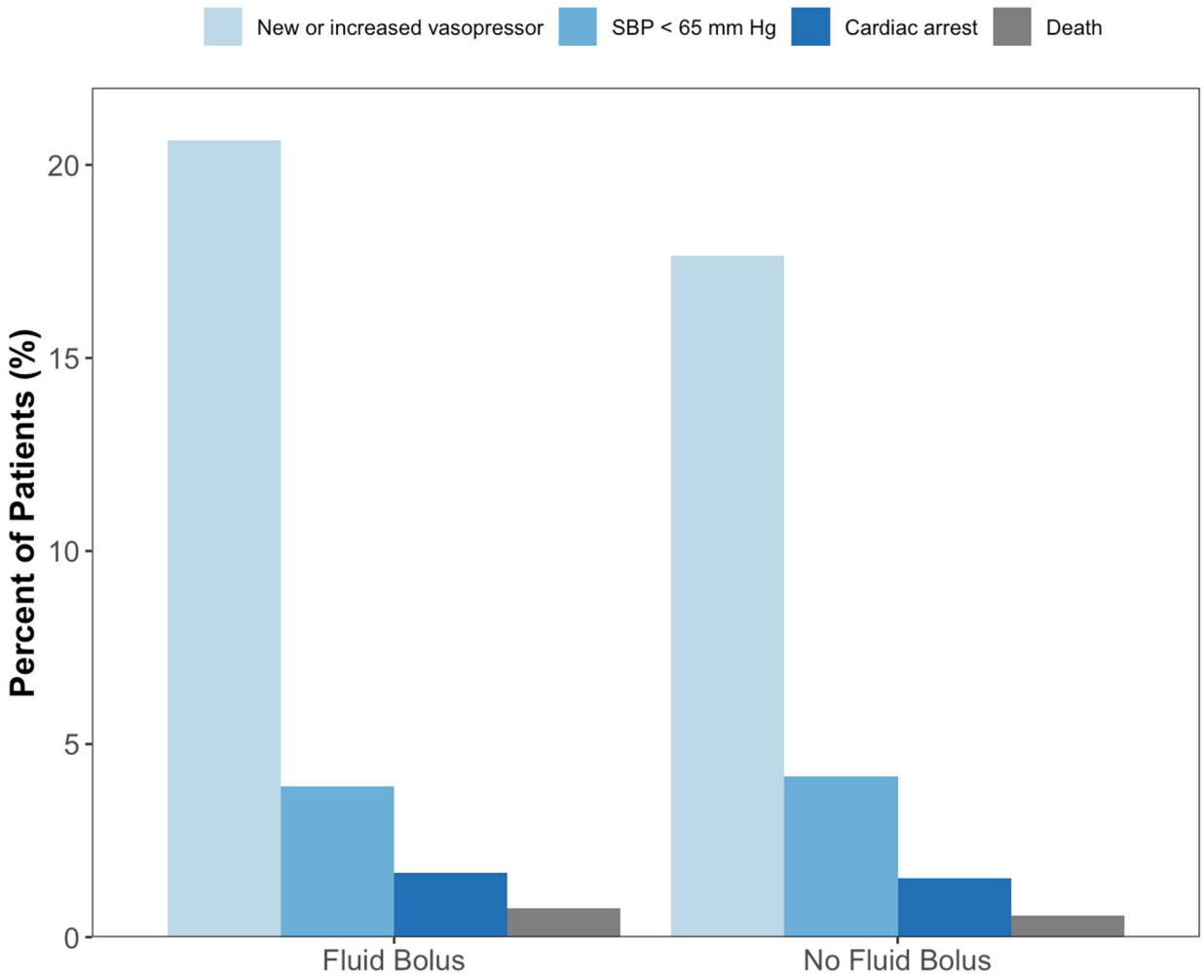
[a.] Cormack-Lehane grade of glottic view, from grade 1 (best) to grade 4 (worst), defined as grade 1: all or most of the glottic opening seen; grade 2: only the posterior portion of the glottis or only arytenoid cartilages are visible; grade 3: only the epiglottis but no portion of the glottis is visible; grade 4: neither the glottis nor the epiglottis can be seen.
[b.] Operator-reported successful tracheal intubation on the first laryngoscopic attempt.
[c.] Operator-assessed difficulty of intubation was defined qualitatively by the operator on the basis of the subjective degree of difficulty of the tracheal intubation procedure.
[d.] Only recorded for patients who were still alive and hospitalized at the 24 hour time point.

eFigure 1. Fluid volumes given during tracheal intubation



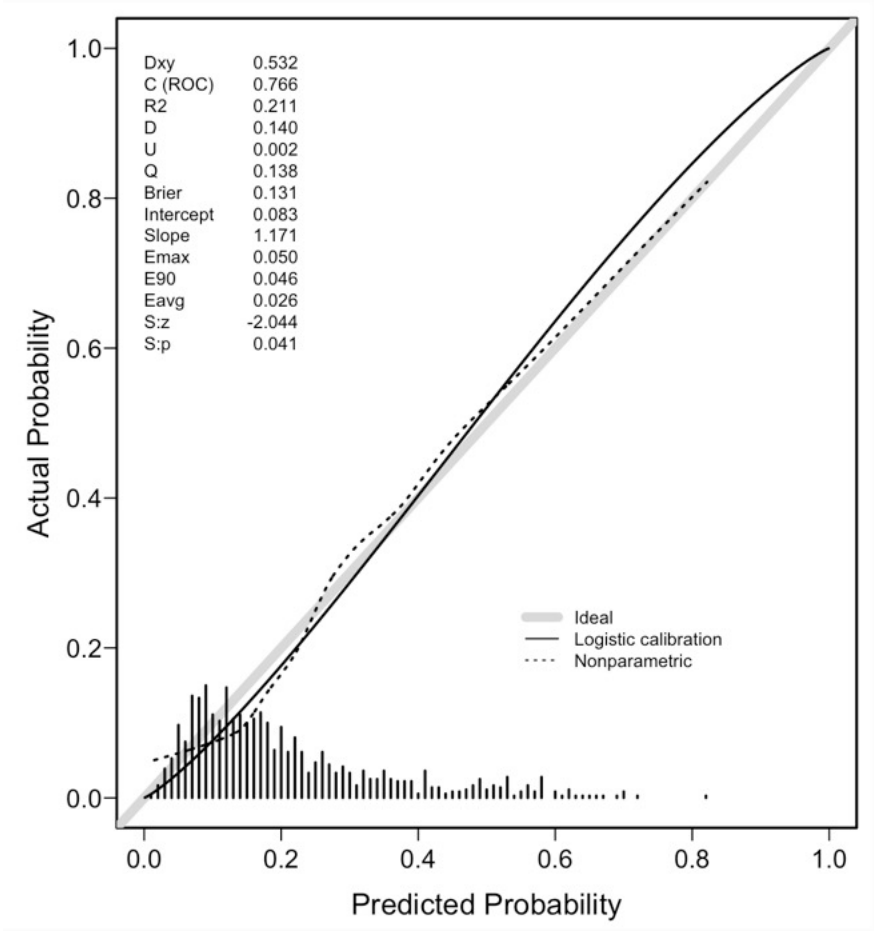
Volume of fluid (mL) received as a new fluid bolus between enrollment and induction of anesthesia and between induction of anesthesia and two minutes after intubation of the trachea. Fluid volume is reported as median and 95% confidence interval around the median at each timepoint.

eFigure 2. Components of the primary outcome by group



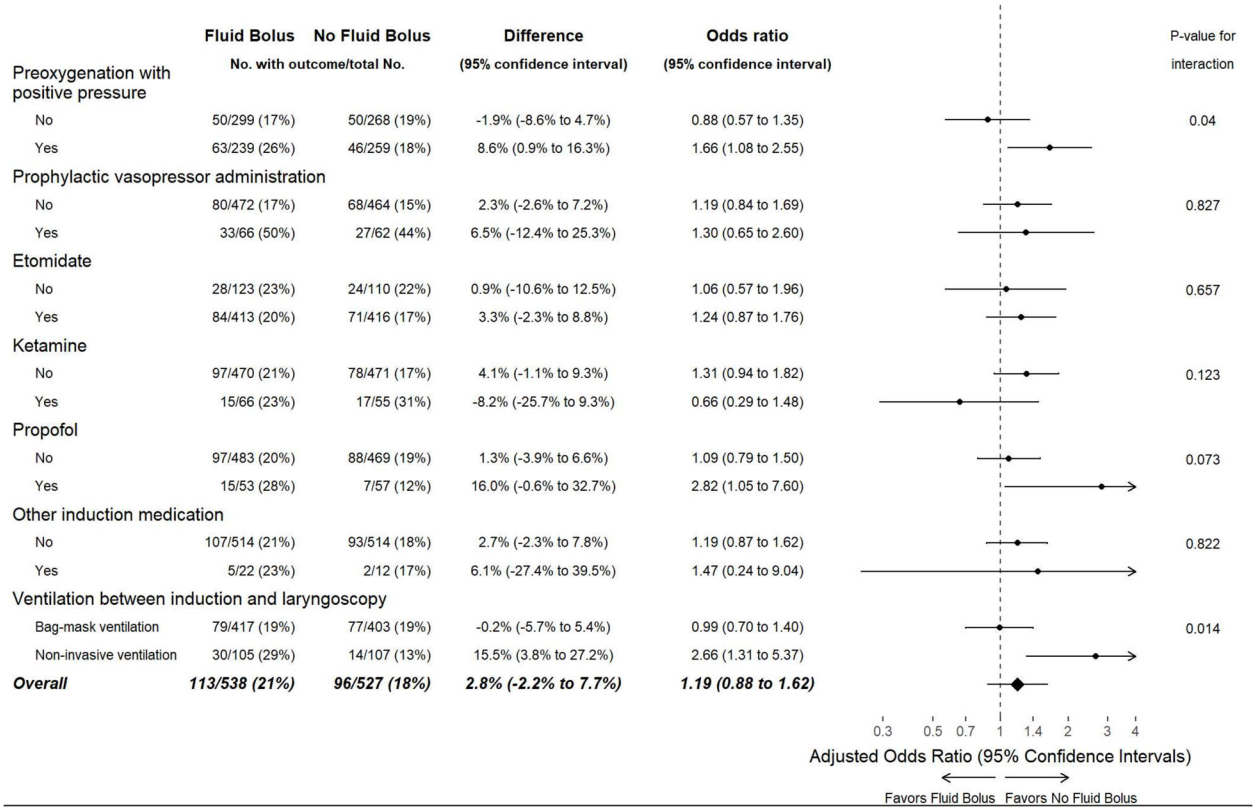
The percent of patients who experienced each component of the primary outcome is shown for the fluid bolus group (left) and no fluid bolus group (right). Patients could experience more than one component of the primary outcome. SBP = systolic blood pressure

eFigure 3. Calibration of prespecified multivariable model



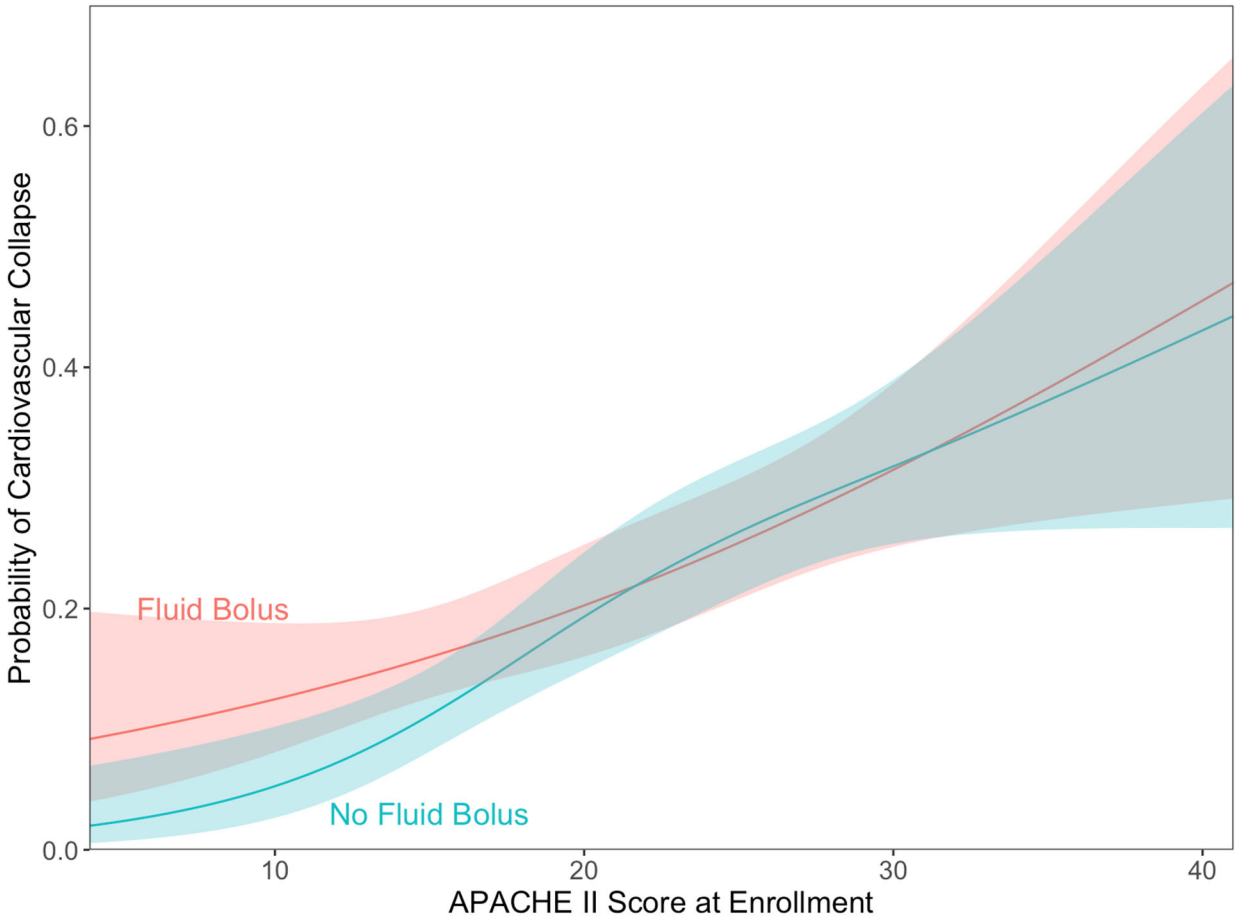
This figure shows the calibration plot for the model fit for the adjusted analysis of the primary outcome (cardiovascular collapse), a logistic regression model with the primary outcome as the dependent variable and independent variables that included group assignment and the following baseline covariates: age, APACHE II score at enrollment, presence of sepsis or septic shock, vasopressor receipt in the hour prior to enrollment, and receipt of intravenous fluid infusion initiated prior to enrollment. Age and APACHE II score at enrollment were modeled with a nonlinear relationship to the outcome using restricted cubic splines with 3 knots. Location of knots were 10th, 50th, and 90th quantiles. Additional details of the model are included in Supplemental Methods section F. Results of the model are shown in eTable 6.

eFigure 4. Additional analyses of effect modification



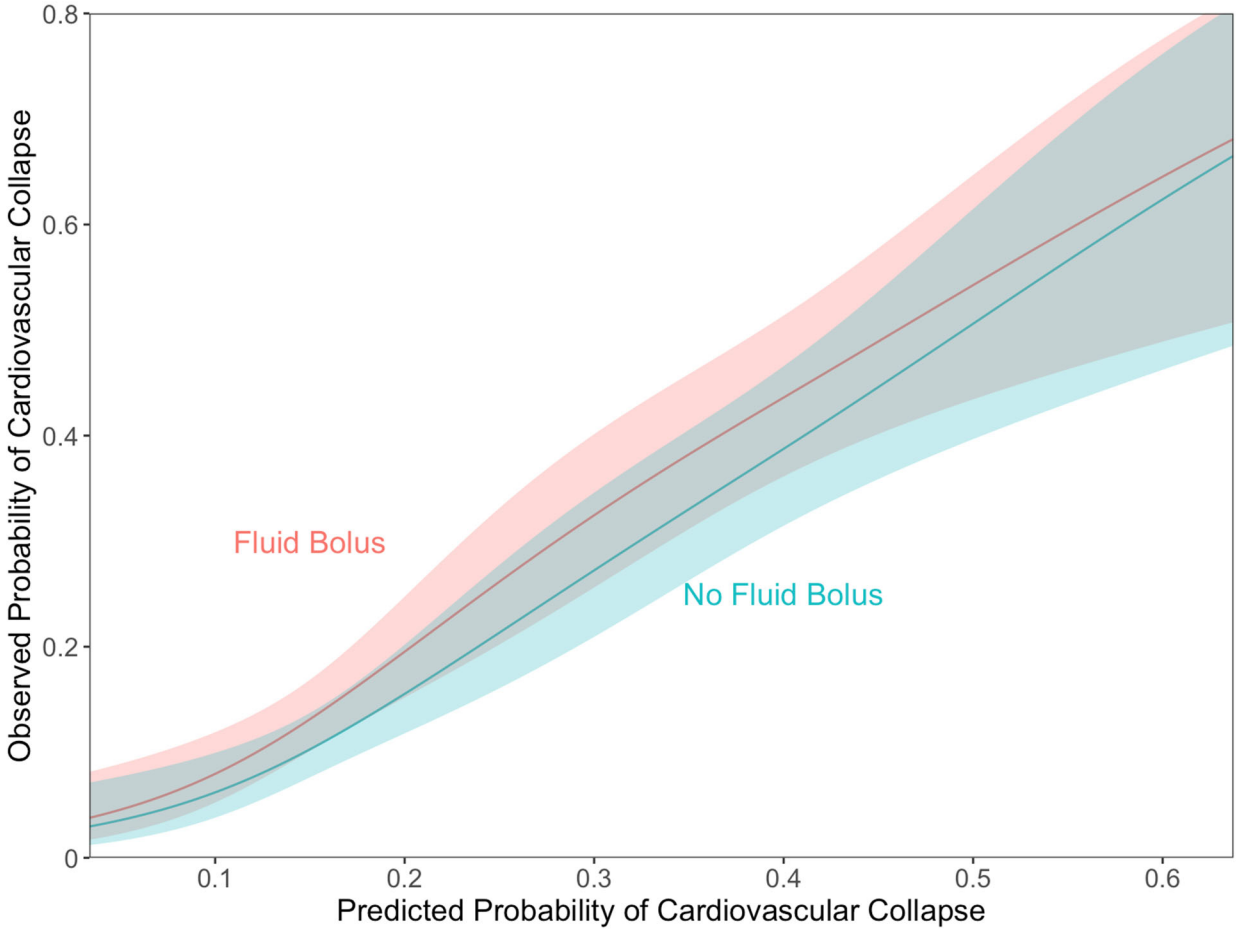
This figure displays the odds ratio and 95% confidence interval for the primary outcome (cardiovascular collapse) for fluid bolus group compared to the no fluid bolus group, overall and for subgroups. The device used to provide positive pressure ventilation (bag-mask ventilation or non-invasive ventilation) was added post-hoc. All other subgroups were pre-specified.

eFigure 5. Effect modification by APACHE II score



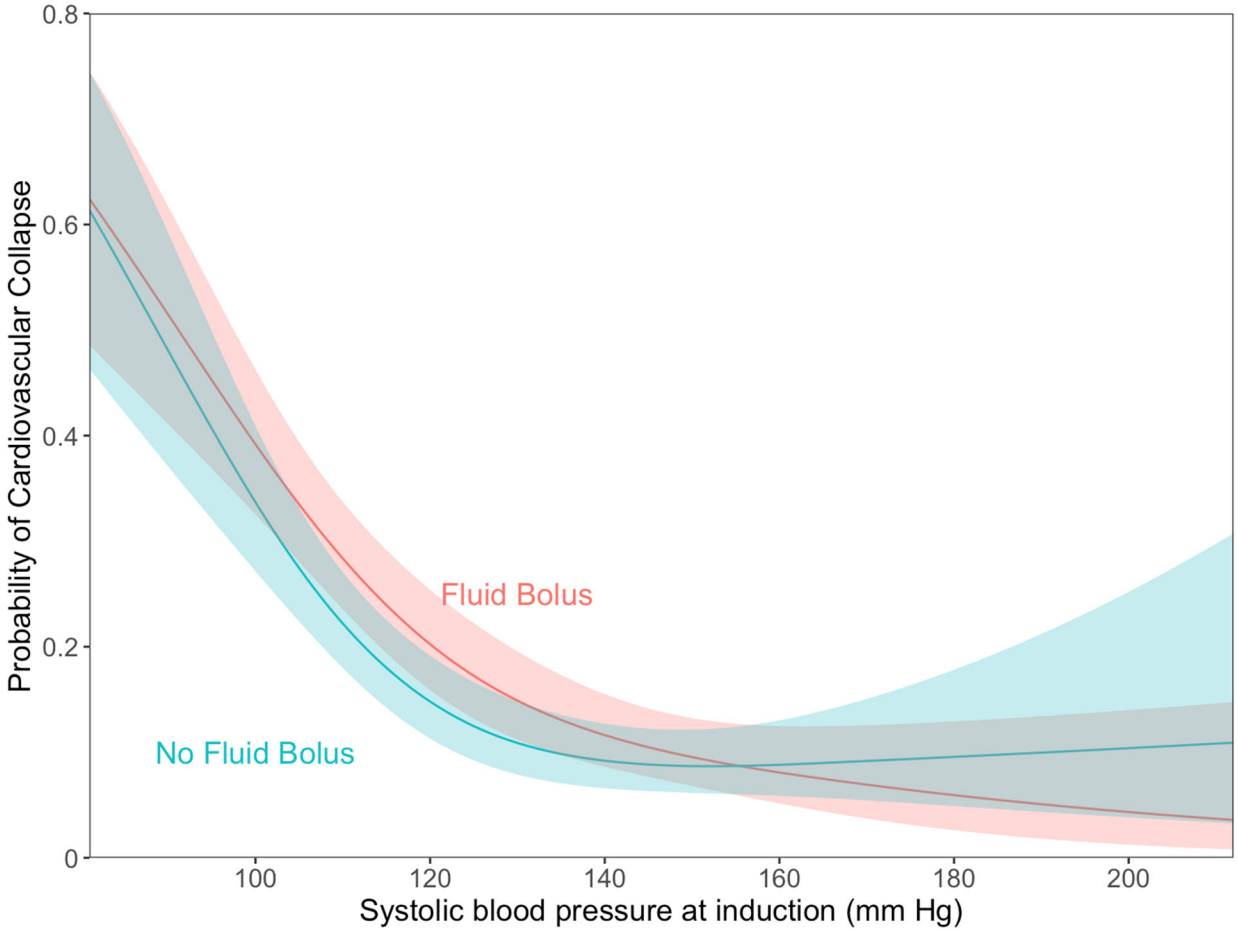
The mean and 95% confidence interval for the predicted probability of the primary outcome (cardiovascular collapse) is displayed for patients randomized to the fluid bolus group (red line) and the no fluid bolus group (blue line) across the spectrum of APACHE II scores at the time of enrollment. Acute Physiology and Chronic Health Evaluation (APACHE) II range from 0 to 71, with higher scores indicating a greater severity of illness.[12] This partial effect plot suggests that among patients with lower severity of illness scores a fluid bolus is associated with a higher probability of cardiovascular collapse while among patient with higher severity of illness scores, a fluid bolus has no effect on the probability of cardiovascular collapse.

eFigure 6. Effect modification by probability of cardiovascular collapse



The mean and 95% confidence interval for the predicted probability of the primary outcome (cardiovascular collapse) is displayed for patients randomized to the fluid bolus group (red line) and the no fluid bolus group (blue line) across the spectrum of predicted probability of cardiovascular collapse, as calculated by a previously published model.[11] This partial effect plot shows that a fluid bolus was not associated with a significant difference in the incidence of cardiovascular collapse among patients at high or low risk of cardiovascular collapse.

eFigure 7. Effect modification by systolic blood pressure at induction



The mean and 95% confidence interval for the predicted probability of the primary outcome (cardiovascular collapse) is displayed for patients randomized to the fluid bolus group (red line) and the no fluid bolus group (blue line) across the spectrum of systolic blood pressures at the time of induction. This partial effect plot shows that a fluid bolus was not associated with a significant difference in the incidence of cardiovascular collapse among patients with low or high systolic blood pressures at induction.

eReferences

1. Driver BE, Prekker ME, Klein LR, et al. Effect of Use of a Bougie vs Endotracheal Tube and Stylet on First-Attempt Intubation Success Among Patients With Difficult Airways Undergoing Emergency Intubation: A Randomized Clinical Trial. *JAMA.* 2018;319(21):2179-2189.
2. Janz DR, Semler MW, Joffe AM, et al. A Multicenter Randomized Trial of a Checklist for Endotracheal Intubation of Critically Ill Adults. *Chest.* 2018;153(4):816-824.
3. Tekwani KL, Watts HF, Sweis RT, Rzechula KH, Kulstad EB. A comparison of the effects of etomidate and midazolam on hospital length of stay in patients with suspected sepsis: a prospective, randomized study. *Ann Emerg Med.* 2010;56(5):481-489.
4. Janz DR, Casey JD, Semler MW, et al. Effect of a fluid bolus on cardiovascular collapse among critically ill adults undergoing tracheal intubation (PrePARE): a randomised controlled trial. *Lancet Respir Med.* 2019;7(12):1039-1047.
5. Jabre P, Combes X, Lapostolle F, et al. Etomidate versus ketamine for rapid sequence intubation in acutely ill patients: a multicentre randomised controlled trial. *Lancet.* 2009;374(9686):293-300.
6. Semler MW, Janz DR, Lentz RJ, et al. Randomized Trial of Apneic Oxygenation during Endotracheal Intubation of the Critically Ill. *Am J Respir Crit Care Med.* 2016;193(3):273-280.
7. Janz DR, Semler MW, Lentz RJ, et al. Randomized Trial of Video Laryngoscopy for Endotracheal Intubation of Critically Ill Adults. *Crit Care Med.* 2016;44(11):1980-1987.
8. Caputo N, Azan B, Domingues R, et al. Emergency Department use of Apneic Oxygenation Versus Usual Care During Rapid Sequence Intubation: A Randomized Controlled Trial (The ENDAO Trial). *Acad Emerg Med.* 2017;24(11):1387-1394.
9. Driver B, Semler MW, Self WH, et al. BOugie or stylet in patients UnderGoing Intubation Emergently (BOUGIE): protocol and statistical analysis plan for a randomised clinical trial. *BMJ Open.* 2021;11(5):e047790.
10. Russell DW, Casey JD, Gibbs KW, et al. Protocol and statistical analysis plan for the PREventing cardiovascular collaPse with Administration of fluid REsuscitation during Induction and Intubation (PREPARE II) randomised clinical trial. *BMJ Open.* 2020;10(9):e036671.
11. Halliday SJ, Casey JD, Rice TW, et al. Risk Factors for Cardiovascular Collapse during Tracheal Intubation of Critically III Adults. *Ann Am Thorac Soc.* 2020;17(8):1021-1024.
12. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med.* 1985;13(10):818-829.