The PREPARE II trial

Embedding a Pragmatic Trial Into Clinical Care During an Emergency Procedure.

Disclosures

Funding:

- None relevant to work discussed today
- Semler: NHLBI K23HL143053
- Russell: NHLBI 1 K08 HL148514

Disclosures or Potential Conflicts of Interest:

- None relevant to work discussed today
- Semler: Consultant to Baxter
- Russell: N/A

Overview

For the Clinician: Does an IV fluid bolus prevent severe hypotension during emergency intubation?

For the Researcher: How to embed an RCT into clinical care during an emergency procedure?

PREPARE II trial

Background

Rationale

Design

Results

Discussion

Background

Emergency Tracheal Intubation

- 2-5 million adults intubated in ED and ICU each year
- 75% of patients are comatose or delirious
- 5% of patients are in cardiac arrest
- Surrogates are frequently unavailable
- Median 5 min from decision-to-intubate to procedure

Choices between available treatments that clinicians must make for every emergency tracheal intubation for which the effect on patient outcomes is unknown

fluid bolus vs none

video vs direct laryngoscopy

hyperangulated vs standard geometry

sedative-first vs NMB-first

NIV vs HFNC vs BMV

Bag-mask ventilation vs none during intubation

neuromuscular blocker vs none

“apneic oxygenation” vs none

etomidate vs ketamine

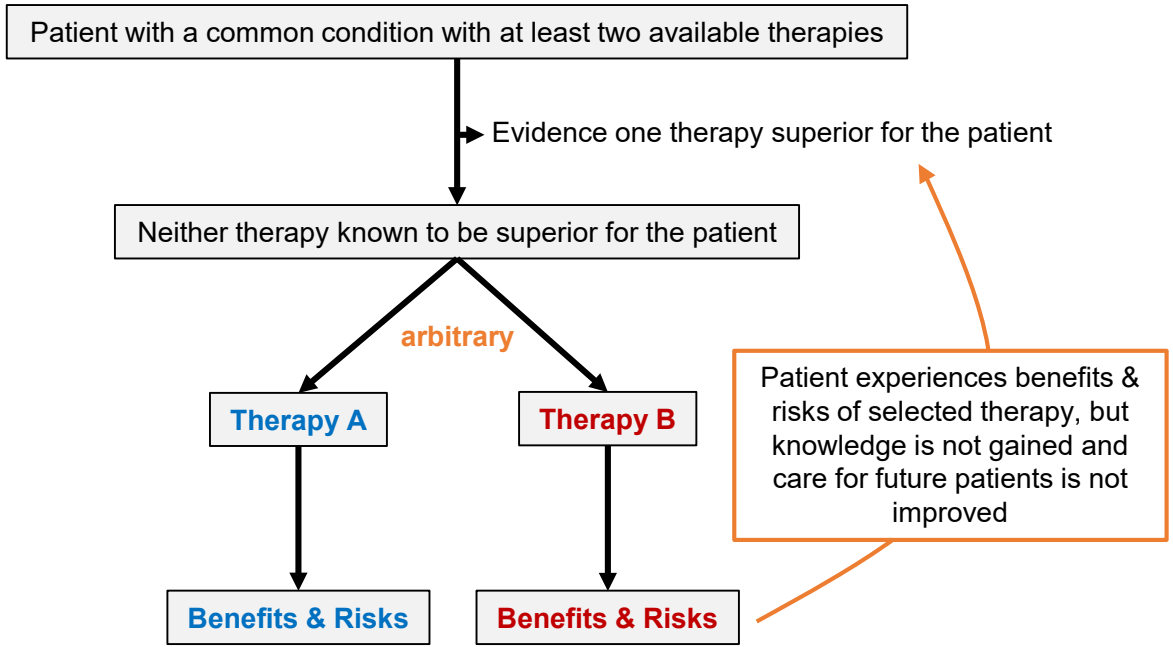
bougie vs stylet

vasopressor vs none

ramped vs sniffing position

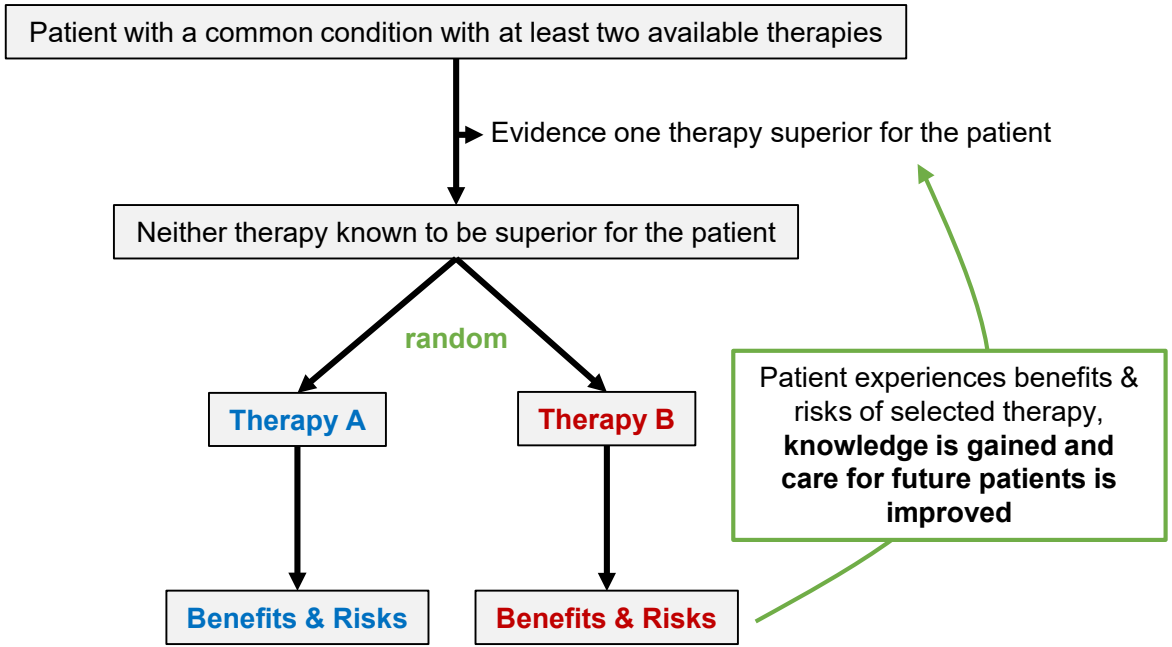
Total number of RCTs of emergency tracheal intubation when we started training: **1**

Arbitrary Variation in Clinical Care



Arbitrary variation (different clinicians choosing different treatments for the same patient) = Clinical Equipoise

Structured Variation in a Clinical Trial

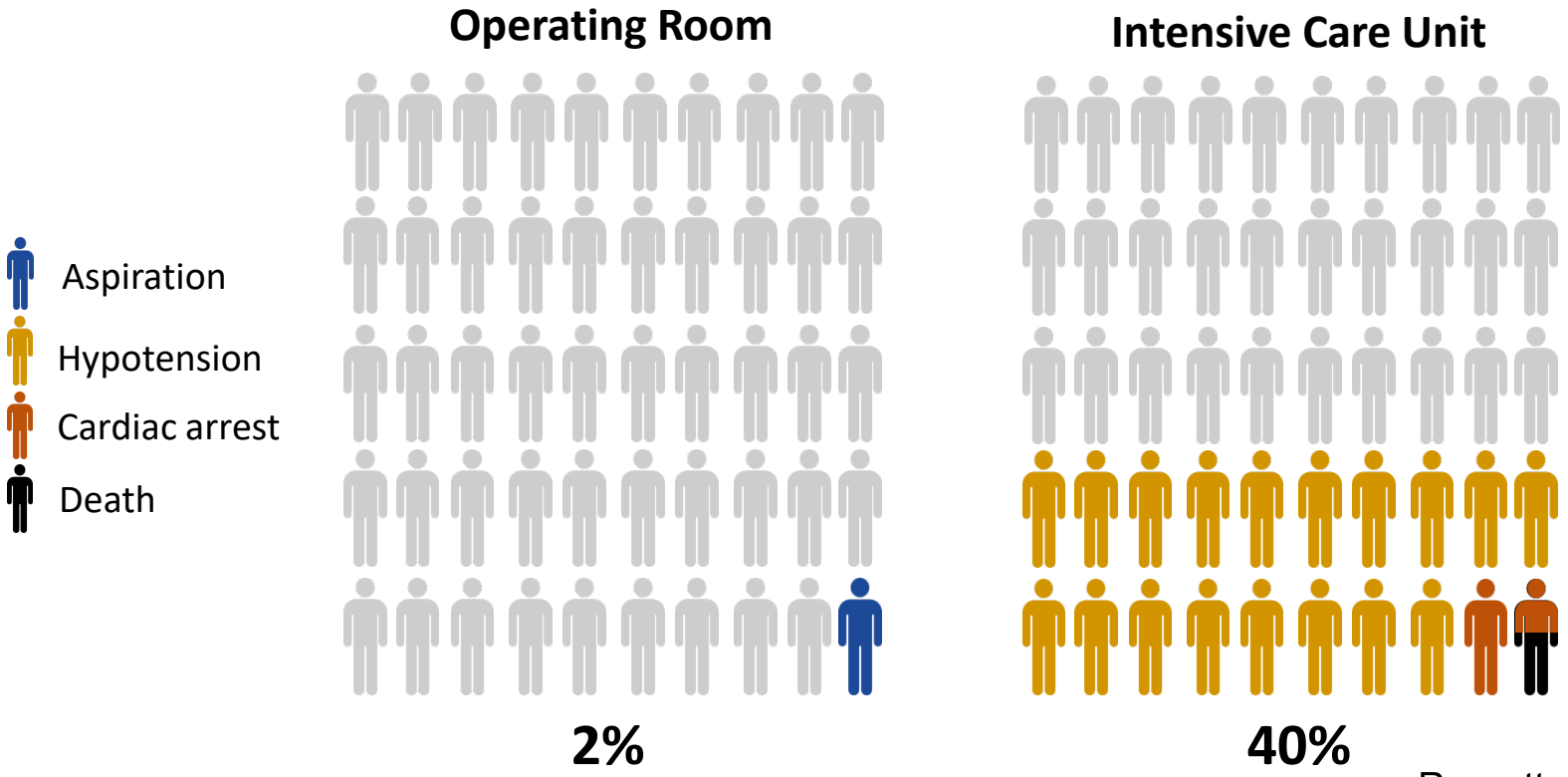


Rationale

Emergency Tracheal Intubation

2 minutes of very high risk for critically ill patients

Complications during tracheal intubation



Russotto et al. JAMA, 2021

Cardiovascular collapse

- Composite of cardiovascular events during tracheal intubation
  - Systolic blood pressure < 65 mmHg
  - New or increased vasopressors

  } between induction & 2 minutes after intubation

  - Cardiac arrest
  - Death

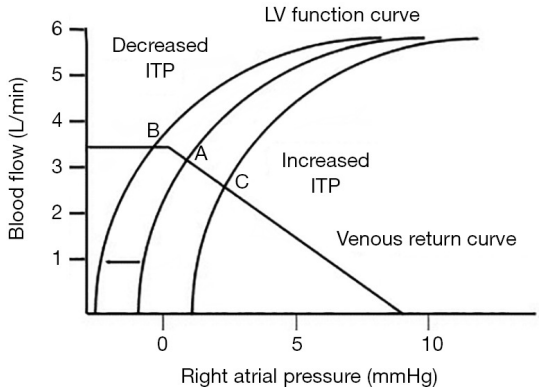
  } between induction & 1 hour after intubation

- **Independently associated with in-hospital mortality**

Russotto et al. AJRCCM, 2022

Physiology of cardiovascular collapse during intubation

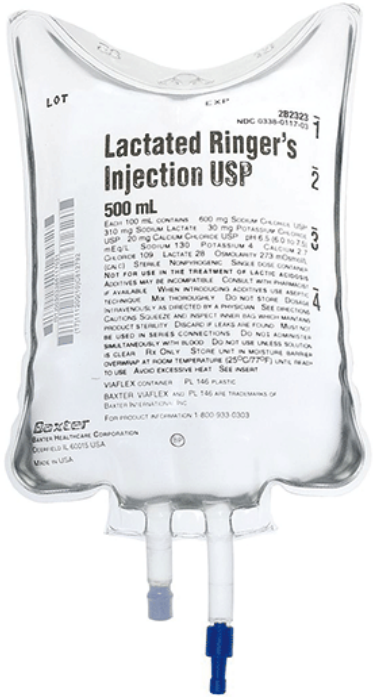
1) Decreased venous return due to increased intrathoracic pressure
2) Sedative-induced venodilation and arterial vasodilation
3) Decreased endogenous catecholamines



All potentially mitigated by a pre-intubation fluid bolus

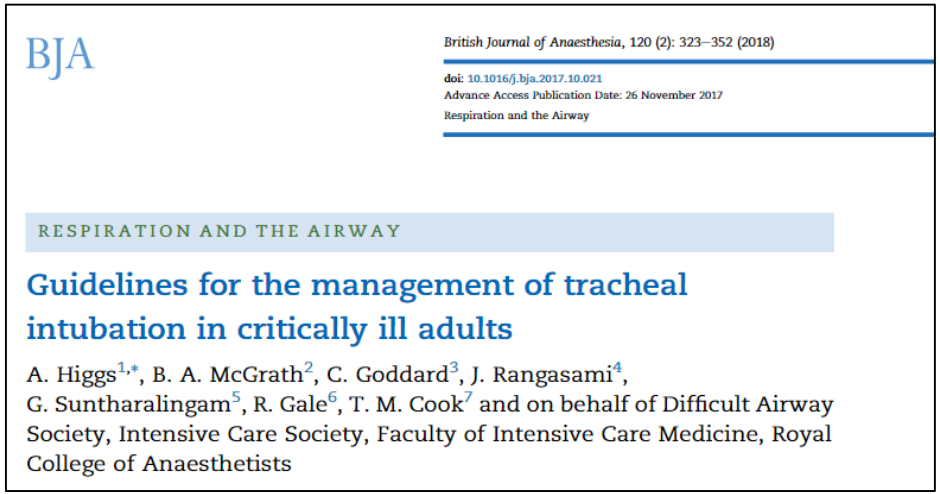
Pre-intubation fluid bolus

- Intravenous infusion of 500 mL of crystalloid solution beginning prior to induction
- Observational studies: ~1/2 of patients receive a pre-intubation fluid bolus



Jaber et al. Intensive Care Med, 2010
Russotto et al. JAMA, 2021

International guidelines recommend a 500 mL fluid bolus before induction



BJA

British Journal of Anaesthesia, 120 (2): 323–352 (2018)

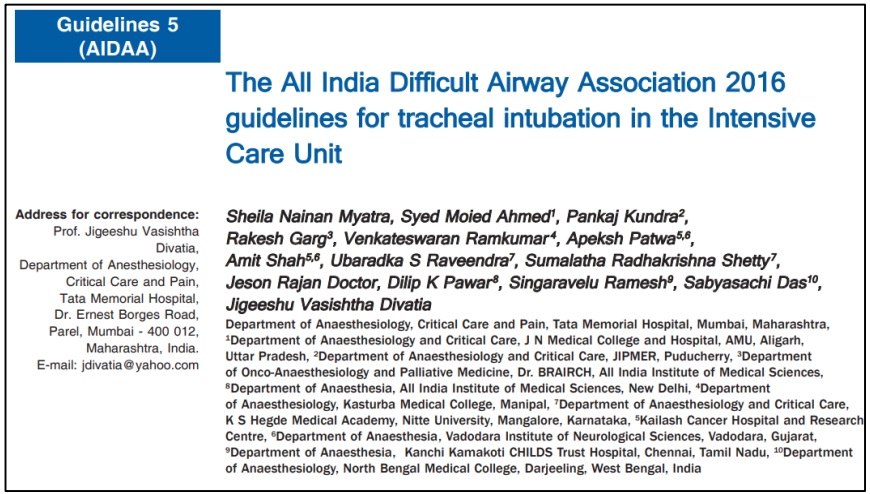
doi: 10.1016/j.bja.2017.10.021
Advance Access Publication Date: 26 November 2017
Respiration and the Airway

RESPIRATION AND THE AIRWAY

Guidelines for the management of tracheal intubation in critically ill adults

A. Higgs[1,*], B. A. McGrath[2], C. Goddard[3], J. Rangasami[4], G. Suntharalingam[5], R. Gale[6], T. M. Cook[7] and on behalf of Difficult Airway Society, Intensive Care Society, Faculty of Intensive Care Medicine, Royal College of Anaesthetists

Difficult Airway Society & Royal College of Anaesthetists



Guidelines 5 (AIDAA)

The All India Difficult Airway Association 2016 guidelines for tracheal intubation in the Intensive Care Unit

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The All India Difficult Airway Association

Higgs et al. Br J Anaest, 2018
Myatra et al. Indian J Aneasth, 2016

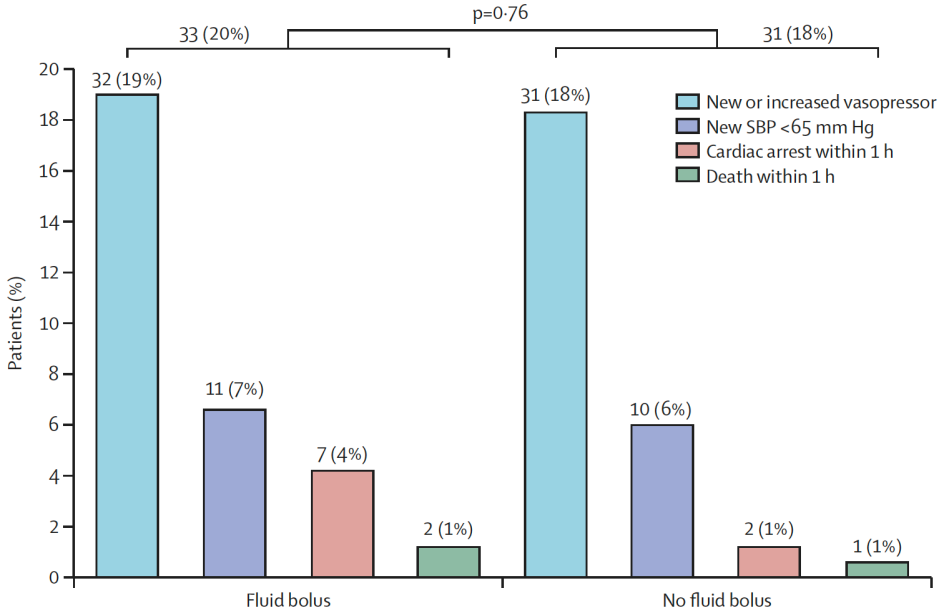
Prior data on a pre-intubation fluid bolus

Effect of a fluid bolus on cardiovascular collapse among critically ill adults undergoing tracheal intubation (PrePARE): a randomised controlled trial

David R Janz, Jonathan D Casey, Matthew W Semler, Derek W Russell, James Dargin, Derek J Vonderhaar, Kevin M Dischert, Jason R West, Susan Stempek, Joanne Wozniak, Nicholas Caputo, Brent E Heideman, Aline N Zouk, Swati Gulati, William S Stigler, Itay Bentov, Aaron M Joffe, Todd W Rice, for the PrePARE Investigators and the Pragmatic Critical Care Research Group*

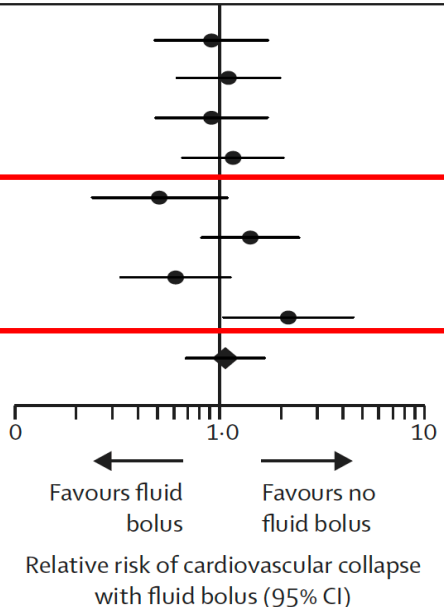
The PrePARE Trial

- **Design:** RCT in 9 U.S. ICUs
- **Population:** ICU patients undergoing intubation
- **Intervention:** Initiation of a 500 mL crystalloid fluid bolus before induction
- **Outcome:** Cardiovascular collapse
- **Result:** Stopped for futility at interim after enrolling 337 patients



Rationale for PREPARE II

	Number of individuals		Number of events		Relative risk (95% CI)	p value for interaction
	Fluid bolus	No fluid bolus	Fluid bolus	No fluid bolus		
Septic shock	39	33	13 (33%)	12 (36%)	0·91 (0·48–1·72)	0·67
No septic shock	129	136	20 (16%)	19 (14%)	1·10 (0·62–1·98)	
On vasopressors	28	28	11 (39%)	12 (43%)	0·91 (0·48–1·71)	0·60
Not on vasopressors	140	141	22 (16%)	19 (14%)	1·16 (0·66–2·05)	
NIV preox	39	30	8 (21%)	12 (40%)	0·51 (0·24–1·09)	0·032
No NIV preox	129	139	25 (19%)	19 (14%)	1·41 (0·82–2·44)	
BMV	81	84	13 (16%)	22 (26%)	0·61 (0·33–1·13)	0·0080
No BMV	87	85	20 (23%)	9 (11%)	2·17 (1·04–4·49)	
Overall	**168**	**169**	**33 (20%)**	**31 (18%)**	**1·07 (0·68–1·66)**	

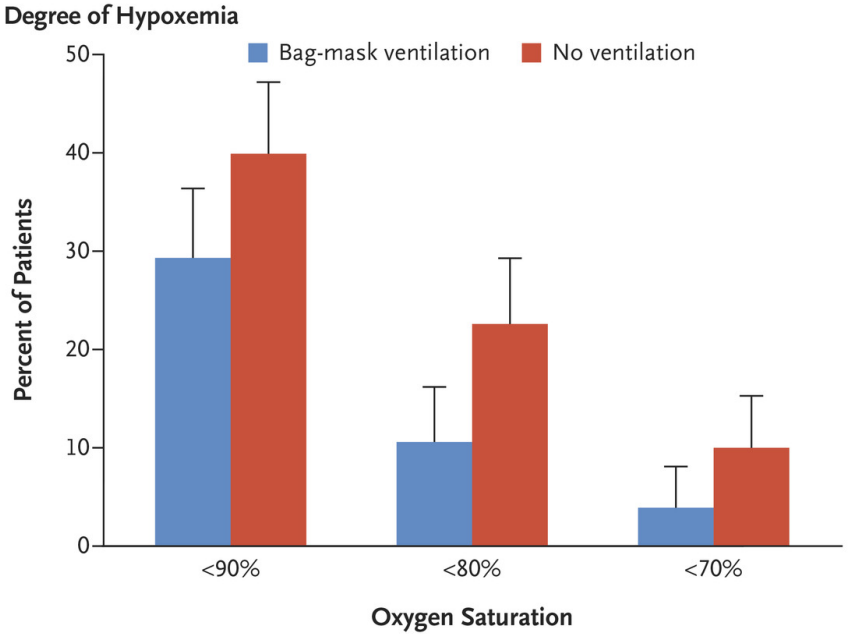


Rationale for PREPARE II

ORIGINAL ARTICLE

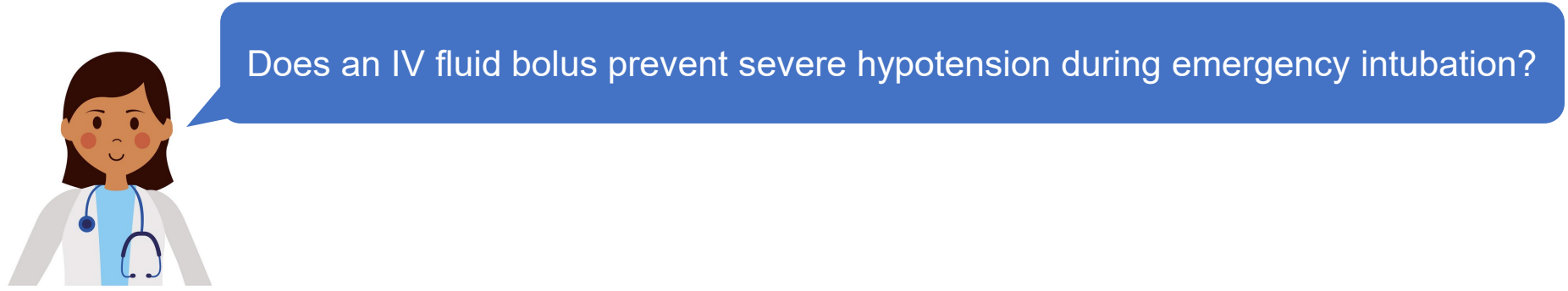
Bag-Mask Ventilation during Tracheal Intubation of Critically Ill Adults

Jonathan D. Casey, M.D., David R. Janz, M.D., Derek W. Russell, M.D., Derek J. Vonderhaar, M.D., Aaron M. Joffe, D.O., Kevin M. Dischert, M.D., Ryan M. Brown, M.D., Aline N. Zouk, M.D., Swati Gulati, M.B., B.S., Brent E. Heideman, M.D., Michael G. Lester, M.D., Alexandra H. Toporek, M.D., et al., for the PreVent Investigators and the Pragmatic Critical Care Research Group*



PREPARE II Research Question

Does the intravenous infusion of a 500 mL crystalloid fluid bolus beginning prior to induction of anesthesia decrease the incidence of cardiovascular collapse for critically ill adults undergoing tracheal intubation with positive pressure ventilation?



PREPARE II Research Methods Question

- Time-to-intervention < 5 minutes
- No research personnel generally present

How to design and conduct an RCT of fluid bolus during emergency intubation?

Design

PREPAREII Trial Design

- **Design:** Multicenter, parallel-group, randomized trial comparing fluid bolus vs none among critically ill adults receiving positive pressure ventilation during intubation
- **Sites:** 11 academic ICU sites across the United States
- **Inclusion Criteria:**
  - Adult undergoing tracheal intubation with sedation
  - Positive pressure ventilation between induction and laryngoscopy is planned
- **Exclusion Criteria:**
  - Pregnant or prisoner
  - Intubation too emergent to perform study procedures
  - Clinicians determined that fluid bolus is either required or contraindicated

Simple eligibility criteria: can be judged by clinicians even during an emergency.

Waiver of Informed Consent

Minimal risk

- Both treatments (fluid bolus and none) are commonly given to patients in clinical care
- Both are interventions to which the patient would likely be exposed even if not participating in a study
- No definitive prior data suggested clinical outcomes were better with one approach relative to another
- Both treatments are consistent with optimal care for that individual patient from the perspective of the treating clinician (otherwise patient is excluded)

Impracticability of obtaining informed consent prior to emergency intervention

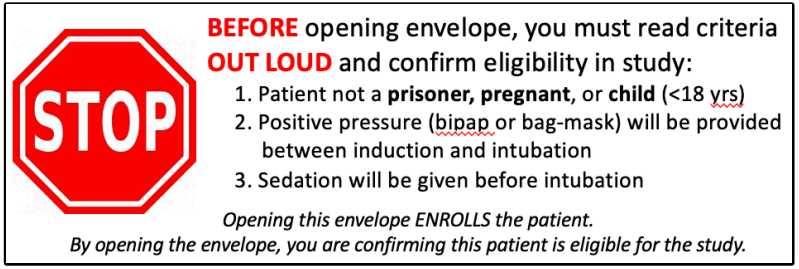
- 75% of patients in coma or delirious; surrogates frequent absent
- 5 minutes from clinical decision to intubate until start of procedure; no study personnel present

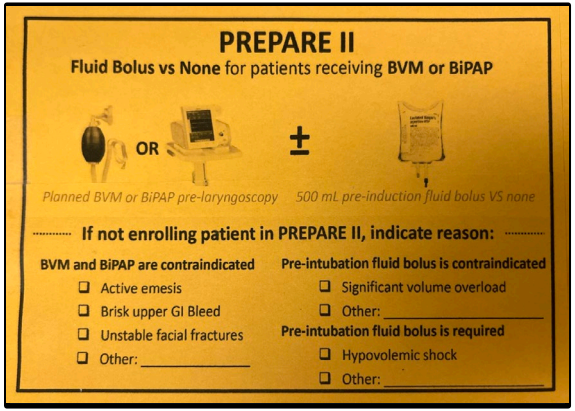
Information for patients and families

- Participants were provided an IRB-approved informational document describing the research and their participation, and providing contact information for investigators for future questions or concerns

Randomization and Blinding

- Allocation concealed until randomization
- 1:1 randomization in blocks of 2, 4, & 6, stratified by site
- Not blinded after randomization



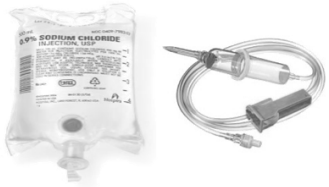


Envelopes with randomized group assignment kept with intubation equipment

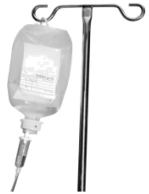
Interventions

Fluid Bolus

1 Obtain 500 ml of crystalloid & gravity IV tubing



2 Hang fluid from top of IV pole, don't use IV pump



3 Start infusion to gravity ASAP
Any IV or IO + squeeze fluid bag

4 Begin procedure whenever ready (don't need to wait for fluid to finish)

Complete 500 mL infusion

NO Fluid Bolus

Do NOT start a new fluid bolus PRIOR to induction (pushing meds)

OK to continue any IV fluids already running or ordered

OK to give IV fluids for treatment of cardiovascular collapse (SBP < 65, new pressor requirement, or cardiac arrest)

Group assignment sheet with succinct instructions to be implemented by clinical personnel

Data Collection

- 1-page data collection sheet
- Site-specific observers
- Rapid feedback from research team on data quality

Box 1: Data to be entered by OBSERVER

1. BEFORE MEDS PUSHED …

NEW fluid bolus started prior to meds pushed: **Yes / No**

Vasopressor bolus or dose increase prior to meds pushed: **Yes / No**

2. AS INTUBATION MEDS PUSHED….

Time first med pushed: _____:_____:_____**(hr/min/sec)**

O2 Sat as meds pushed: _____**%**

SBP as meds pushed: _____ **mmHg**

2. TIME laryngoscope blade first entered mouth: _____:_____:_____**(hr/min/sec)**

3. TIME ET tube successfully placed in airway: _____:_____:_____**(hr/min/sec)**

4. AFTER MEDS PUSHED until 2 MIN AFTER TUBE PLACED IN AIRWAY

Lowest O2 Sat**:** _____**%**

Lowest SBP**:** _____ **mmHg**

NEW Fluid bolus started after meds pushed: **Yes / No**

New or increased vasopressor: **None / Neostick / Levophed / Epi / Other**

OBSERVER Name: _____ OBSERVER Signature _____ Date _____

Box 2: Data to be entered by Intubator **Patient MRN:** _____

1. Estimated # of times you've intubated previously: _____
2. Bag-valve-mask ventilation (bag squeezed) starting at induction: **Yes / No**
3. Bag-valve-mask ventilation (bag squeezed) at any point between induction and intubation: **Yes* / No**
   *If yes, why?: **Study assignment / O_2 sat < 90% / after failed attempt / Other:** _____
4. Airway patency maneuvers (circle all): **oral airway / nasal airway / jaw thrust / head-tilt-chin-lift**
5. Continuous cricoid pressure: **Yes / No**
6. O_2 between induction & laryngoscopy: **none / nasal cannula / HFNC / NRB / BiPAP / Other:** _____
7. Laryngoscope used on first attempt: **DL / McGrath / C-MAC / GlideScope / Other**
8. Best glottic view obtained on the first attempt:

9. Number of laryngoscopy attempts for successful intubation: _____
10. Additional items used (circle all): **Bougie / VL / DL / LMA / Bronch / 2nd proceduralist**
11. Do you think the patient experienced **aspiration** between induction and intubation? **Yes / No**
12. Complications (circle all):
    cardiac arrest / HR<40 / esophageal intubation / airway trauma / Other: _____

FELLOW Name: _____ FELLOW Signature _____ Date _____

Clinical data captured into source document in real-time by clinical personnel

Primary Outcome

Cardiovascular collapse

- Systolic blood pressure < 65 mmHg
- New or increased vasopressors

between induction & 2 minutes after intubation

- Cardiac arrest
- Death

between induction & 1 hour after intubation

Sample Size

- Initial Sample Size (**n=750**)
  - Power = 80%
  - Alpha = 0.05
  - Incidence of primary outcome in control group = 25%
  - Absolute difference detectable = 8.75% (35% relative risk difference)
  - Missing data = 5%

- Final Sample Size (**n=1065**)
  - Pre-specified sample size re-estimation by DSMB at interim analysis to maintain 80% power to detect 35% relative risk difference using observed event rate in control group
  - **Increased** sample size by 315 patients (42%)

Statistical Analyses of Primary Outcome

Intention-to-Treat

- Only patients withdrawn from the trial were 2 discovered to be prisoners

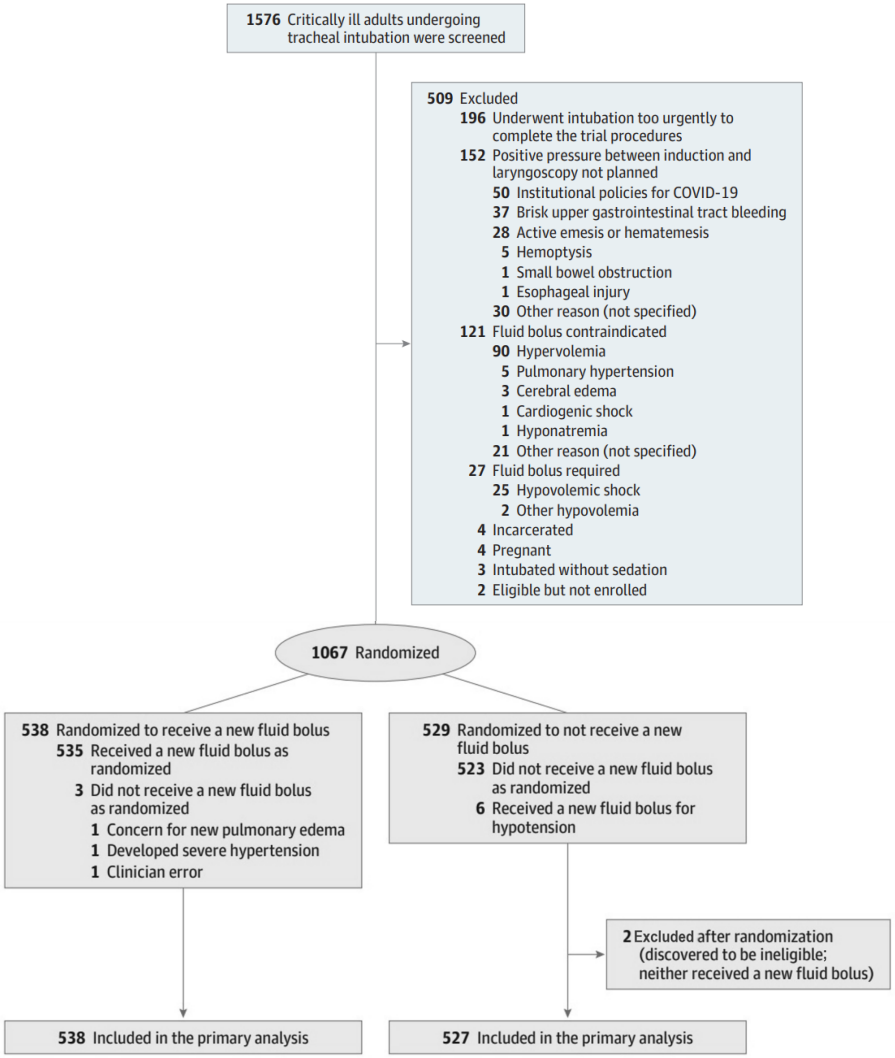
Primary Analysis

- Absolute risk difference between two treatment arms (Chi-square)

Results

Trial Dates

Enrollment start:	1 February 2019
Pause during COVID:	March 2020 to August 2020
Enrollment end:	24 May 2021
Follow up complete:	21 June 2021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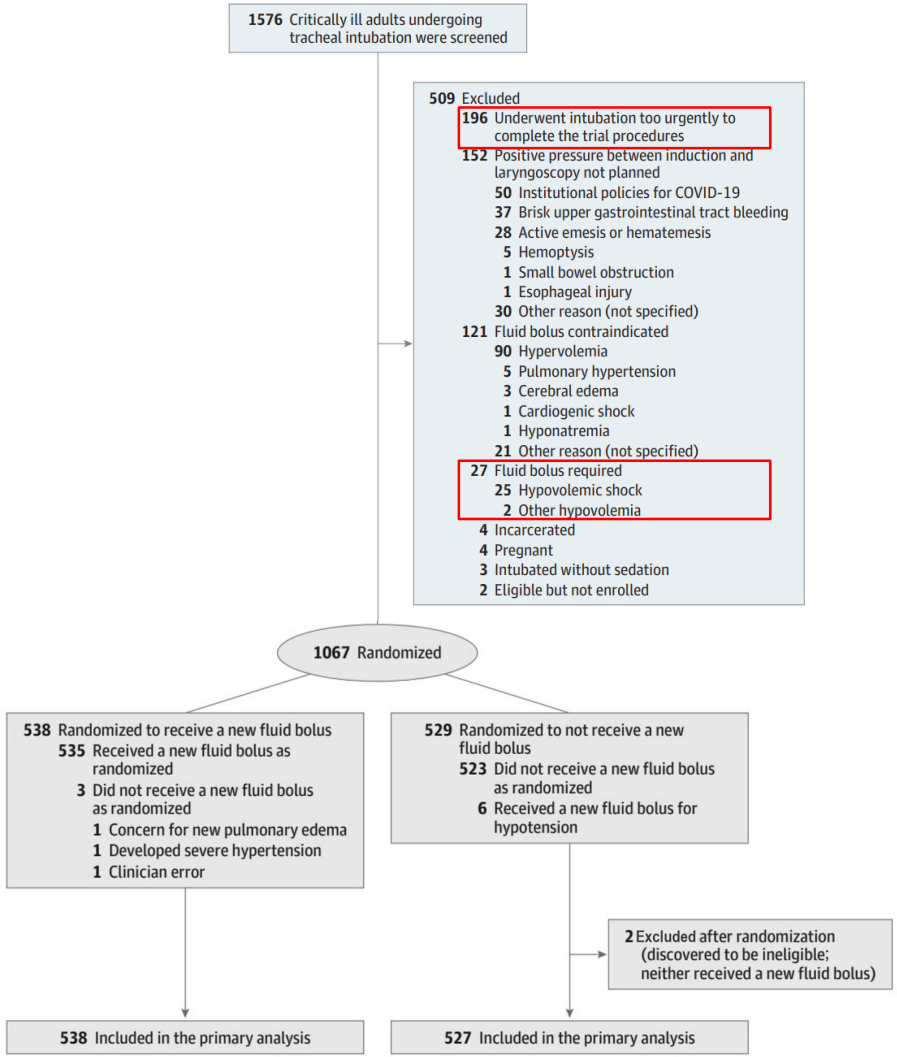
509 Excluded
196 Underwent intubation too urgently to complete the trial procedures
152 Positive pressure between induction and laryngoscopy not planned
50 Institutional policies for COVID-19
37 Brisk upper gastrointestinal tract bleeding
28 Active emesis or hematemesis
5 Hemoptysis
1 Small bowel obstruction
1 Esophageal injury
30 Other reason (not specified)
121 Fluid bolus contraindicated
90 Hypervolemia
5 Pulmonary hypertension
3 Cerebral edema
1 Cardiogenic shock
1 Hyponatremia
21 Other reason (not specified)
27 Fluid bolus required
25 Hypovolemic shock
2 Other hypovolemia
4 Incarcerated
4 Pregnant
3 Intubated without sedation
2 Eligible but not enrolled
1067 Randomized
538 Randomized to receive a new fluid bolus
535 Received a new fluid bolus as randomized
3 Did not receive a new fluid bolus as randomized
1 Concern for new pulmonary edema
1 Developed severe hypertension
1 Clinician error
529 Randomized to not receive a new fluid bolus
523 Did not receive a new fluid bolus as randomized
6 Received a new fluid bolus for hypotension
2 Excluded after randomization (discovered to be ineligible; neither received a new fluid bolus)
538 Included in the primary analysis
527 Included in the primary analysis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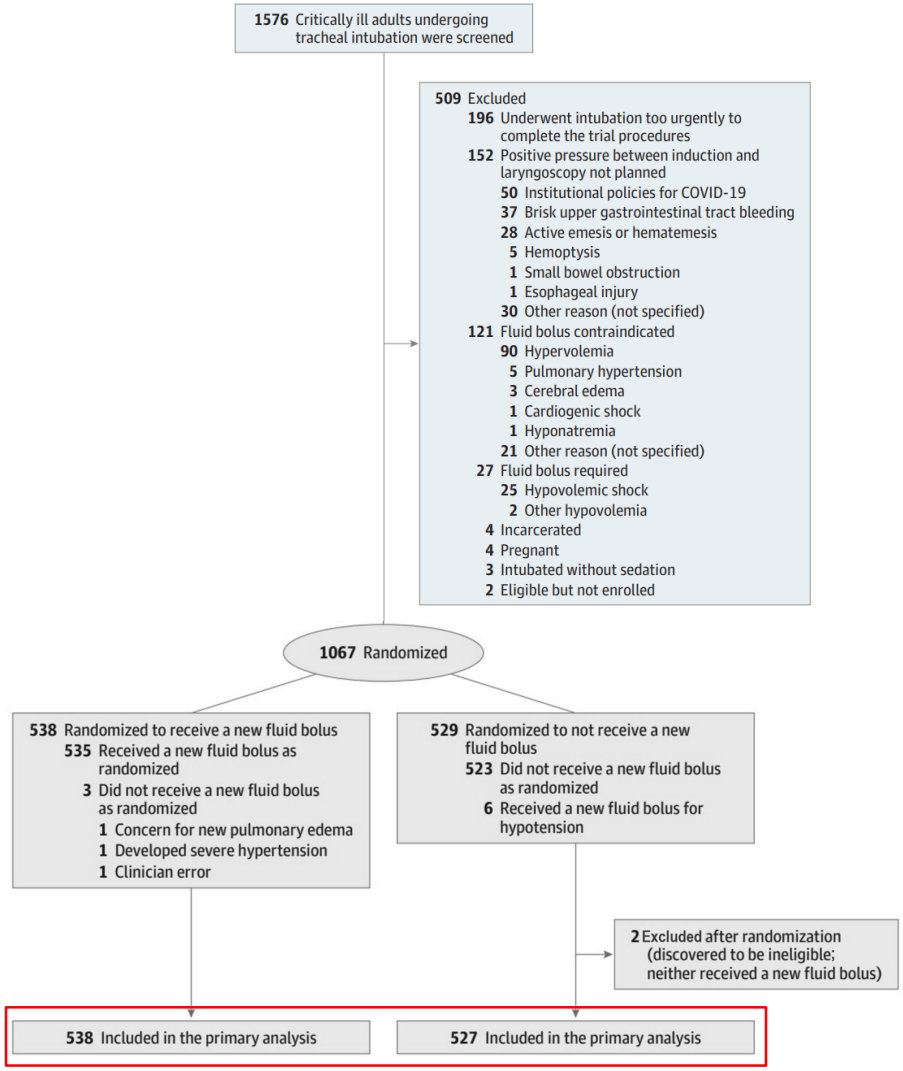
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Patient Characteristics	Fluid Bolus (N= 538)		No Fluid Bolus (N= 527)	
Age (years)	61	(51-70)	62	(51-71)
Female sex	220	(40.9)	228	(43.3)
Body mass index, kg/m^2	28	(24-33)	28	(24-33)
Indication for intubation				
Acute respiratory failure	320	(59.5)	324	(61.5)
Altered mental status	110	(20.4)	106	(20.1)
Other	108	(20.1)	97	(18.4)
APACHE II score	20	(14-25)	18	(14-25)
Vasopressors 1 hour prior	107	(20.0)	102	(19.4)
Sepsis or septic shock	312	(58.0)	318	(60.3)
Etomidate as induction	413	(76.8)	416	(78.9)
Ketamine as induction	66	(12.3)	55	(10.4)

Data given as no. (%) or median [IQR]

Receipt of a Fluid Bolus

	Fluid Bolus (N= 538)	No Fluid Bolus (N= 527)
Fluid bolus	**535 (99.4)**	6 (1.1)
No fluid bolus	3 (0.6)	**521 (98.9)**

Receipt of a Fluid Bolus

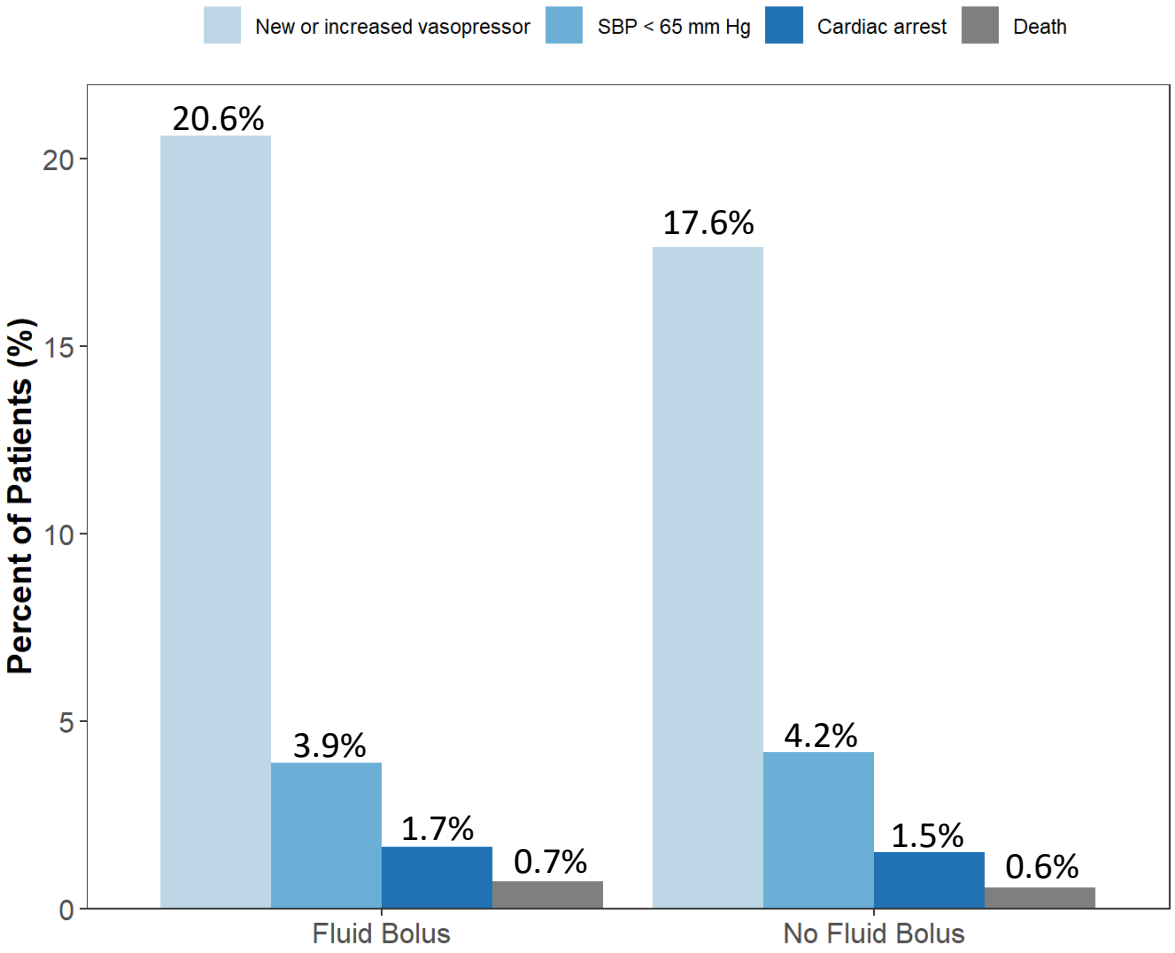
	Fluid Bolus (N= 538)	No Fluid Bolus (N= 527)
Fluid bolus	535 (99.4)	6 (1.1)
No fluid bolus	3 (0.6)	521 (98.9)
Volume of intravenous fluid from enrollment to 2 minutes after intubation, mL	**500 (300-500)**	**0 (0-0)**

99% compliance with group assignment during an emergency procedure

Primary Outcome

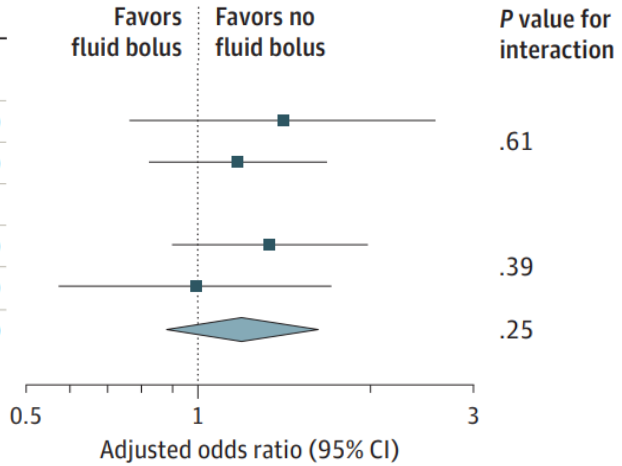
	Fluid Bolus (N= 538)	No Fluid Bolus (N= 527)	Absolute risk difference (95% CI)	P value
Primary outcome: Cardiovascular collapse				

Data given as no. (%) or median [IQR]


New or increased vasopressor
SBP < 65 mm Hg
Cardiac arrest
Death
Percent of Patients (%)
0
5
10
15
20
20.6%
3.9%
1.7%
0.7%
17.6%
4.2%
1.5%
0.6%
Fluid Bolus
No Fluid Bolus

Effect Modification

	No. with outcome/total No. (%)		Difference, % (95% CI)	Adjusted odds ratio (95% CI)
	Fluid bolus	No fluid bolus		
Sepsis				
No	28/226 (12)	19/209 (9)	3.3 (-3.0 to 9.6)	1.41 (0.76 to 2.62)
Yes	85/312 (27)	77/318 (24)	3.0 (-4.1 to 10.2)	1.17 (0.82 to 1.68)
Vasopressors or inotropes[b]				
No	66/429 (15)	51/425 (12)	3.4 (−1.5 to 8.2)	1.33 (0.90 to 1.98)
Yes	47/107 (44)	45/102 (44)	-0.2 (-13.8 to 13.5)	0.99 (0.57 to 1.71)
Overall	113/538 (21)	96/527 (18)	2.8 (-2.2 to 7.7)	1.19 (0.88 to 1.62)



Exploratory Clinical Outcomes	Fluid Bolus (N= 538)	No Fluid Bolus (N= 527)	Absolute difference (95% CI)
Secondary Outcome			
In-hospital mortality	218 (40.5)	223 (42.3)	-1.8% (-7.9% to 4.3%)
Exploratory clinical outcomes			
Ventilator-free days	14 (0-25)	12 (0-2)	2.0 (-10 to 15)
ICU-free days	9 (0-22)	9 (0-22)	-0.5 (-9.0 to 9.5)
Lowest SBP, mmHg	116 (93-139)	113 (95-134)	3 (-3.0 to 7.0)
Change in SBP, mmHg	-7 (-26-0)	-9 (-27-0)	2.0 (-2.0 to 5.0)

Data given as no. (%) or median [IQR]

Discussion

PREPAREII Summary

- 1,065-patient trial with 99% protocol compliance
- Administration of a fluid bolus during emergency tracheal intubation did not prevent cardiovascular collapse (21.0% vs 18.2%)
- No significant difference in in-hospital mortality (40.5% vs. 42.3%)

Strengths

- Conduct at multiple centers
- Severely-ill population (mortality 40%)
- Collection of trial endpoints by an independent observer
- High protocol compliance
- No missing data for primary outcome

Limitations

- Cardiovascular collapse is a surrogate outcome that may not be meaningful to patients
- Does not inform the effectiveness of fluid administration for other indications (“rescue fluids”)

So, why DIDN’T a fluid bolus work?

The right Patient Population?

- ***Did the trial enroll patients likely to benefit from fluid bolus administration?***
  - PREPAREII used predictive enrichment to target patients most likely to benefit
  - No evidence of benefit from fluid bolus overall or in any subgroup

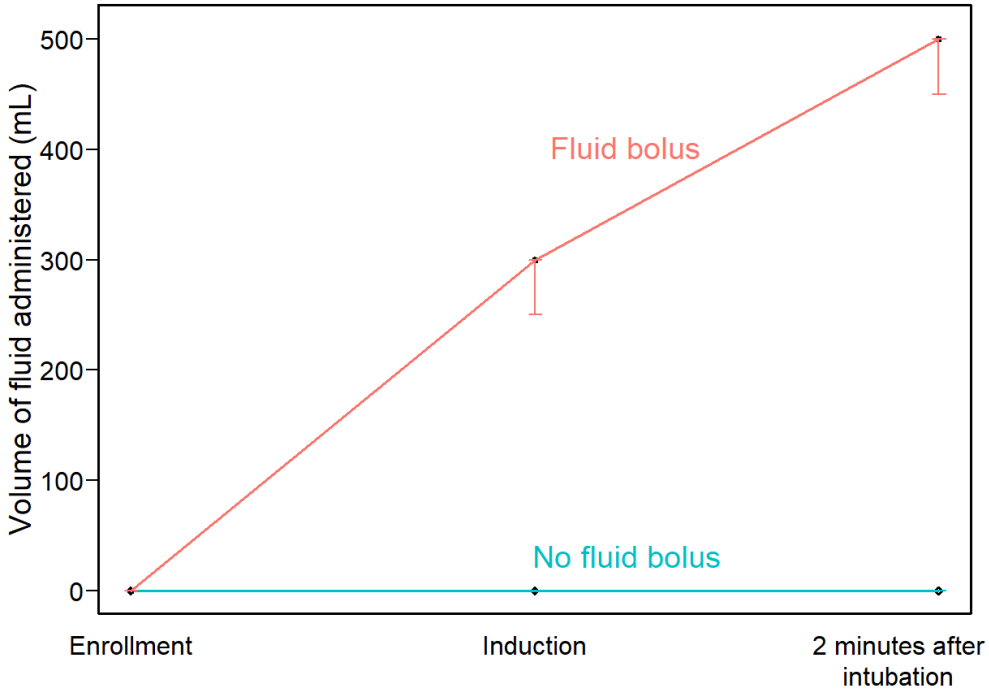
- ***Did the trial exclude patients for whom clinicians felt fluid would be beneficial?***
  - Only 27 patients (1.7% of the screened population) were excluded from PREPAREII because a fluid bolus was felt by clinicians to be requisite

- ***Did the trial enroll patients likely to experience the outcome?***
  - High event rate: cardiovascular collapse in 20% (and 40% mortality)
  - No evidence of benefit from fluid bolus in patients at high or low risk of the outcome

Was the assigned intervention delivered?
(Did adequate separation between groups occur?)

- Intervention (500cc fluid bolus)
  - Same as in prior studies
  - Same as in guidelines

- Median fluid volume given
  - 500 mL in fluid bolus group
  - 0 mL no fluid bolus group



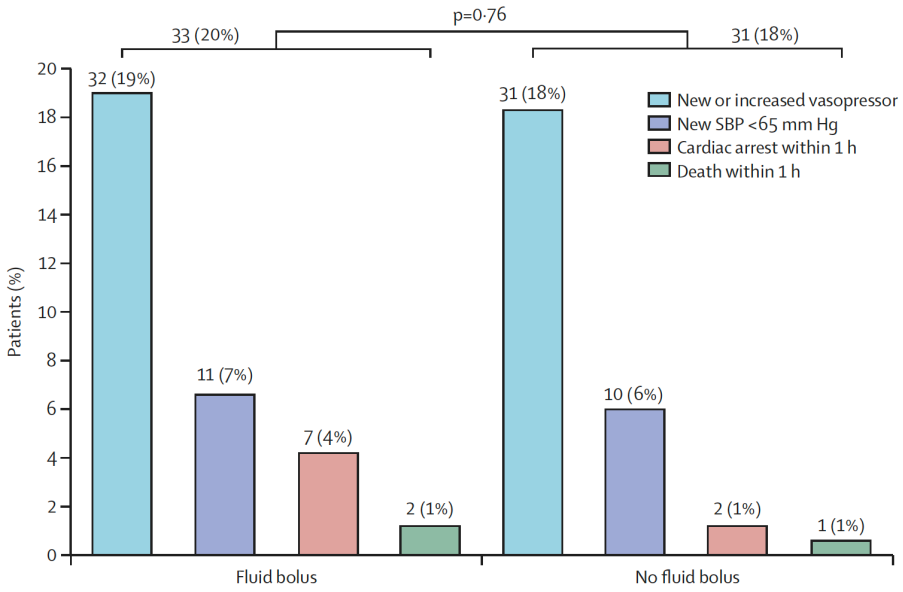
Was the sample size too small?

- Sample size increased from 750 to 1,065 to ensure adequate power
- Effect estimate favored the no fluid bolus group
- No suggestion of benefit in any subgroup
- No suggestion of benefit in any secondary analysis

PrePARE

Effect of a fluid bolus on cardiovascular collapse among critically ill adults undergoing tracheal intubation (PrePARE): a randomised controlled trial

David R Janz, Jonathan D Casey, Matthew W Semler, Derek W Russell, James Dargin, Derek J Vonderhaar, Kevin M Dischert, Jason R West, Susan Stempek, Joanne Wozniak, Nicholas Caputo, Brent E Heideman, Aline N Zouk, Swati Gulati, William S Stigler, Itay Bentov, Aaron M Joffe, Todd W Rice, for the PrePARE Investigators and the Pragmatic Critical Care Research Group*

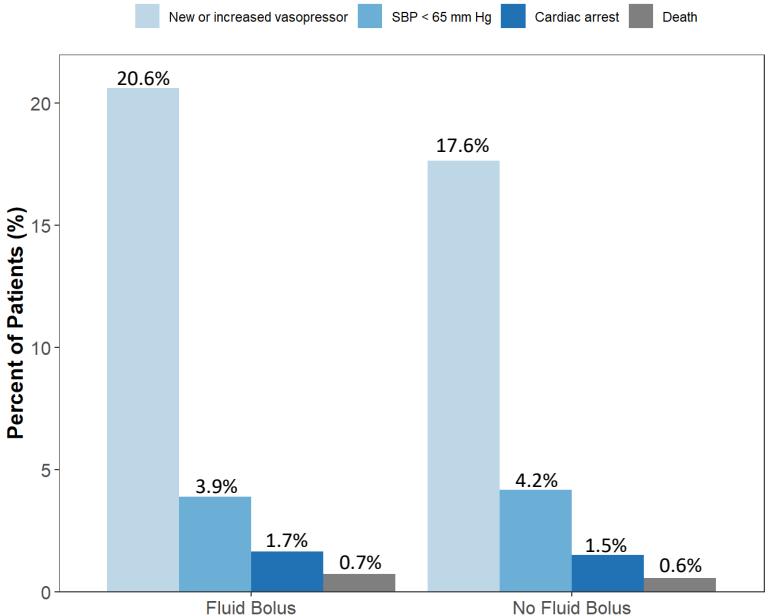


PrePARE II

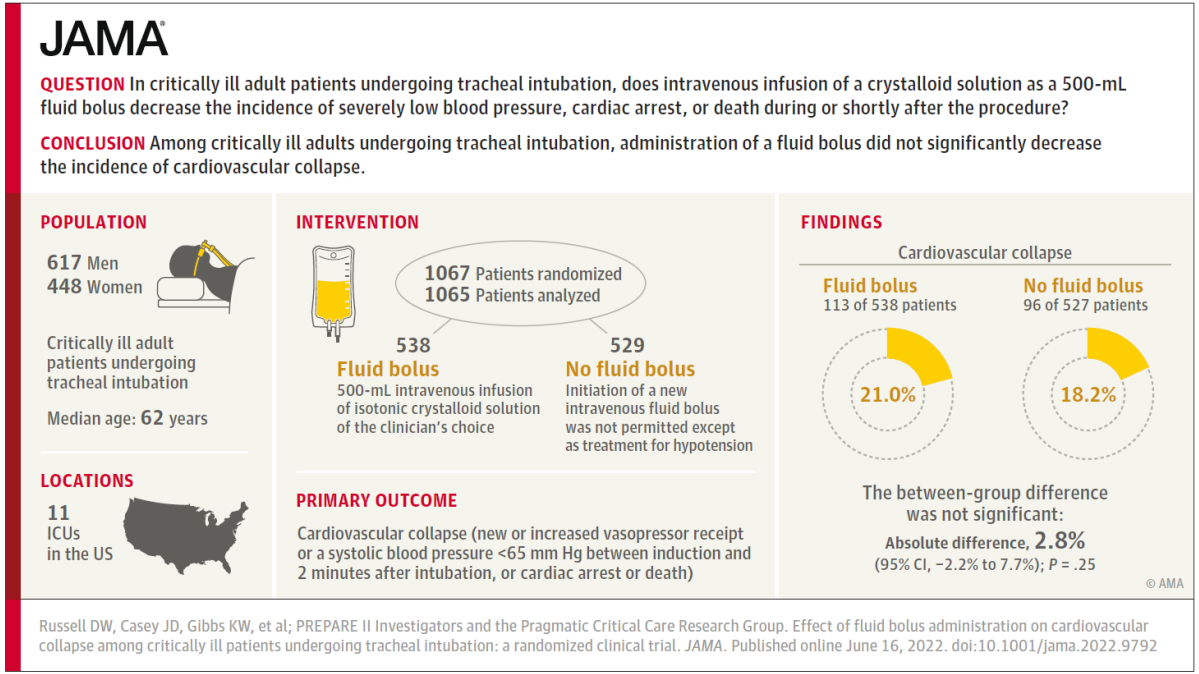
Effect of Fluid Bolus Administration on Cardiovascular Collapse Among Critically Ill Patients Undergoing Tracheal Intubation

A Randomized Clinical Trial

Derek W. Russell, MD; Jonathan D. Casey, MD, MSc; Kevin W. Gibbs, MD; Shekhar Ghamande, MD; James M. Dargin, MD; Derek J. Vonderhaar, MD; Aaron M. Joffe, DO; Akram Khan, MD; Matthew E. Prekker, MD, MPH; Joseph M. Brewer, DO; Simanta Dutta, MD; Janna S. Landsperger, MS, ACNP-BC; Heath D. White, DO, MS; Sarah W. Robison, MD; Joanne M. Wozniak, MS, PA-C; Susan Stempek, MMSc, PA-C; Christopher R. Barnes, MD; Olivia F. Krol, BS; Alejandro C. Arroliga, MD, MS; Tasnim Lat, DO; Sheetal Gandotra, MD; Swati Gulati, MBBS, MS; Itay Bentov, MD, PhD; Andrew M. Walters, MD; Kevin M. Dischert, MD; Stephanie Nonas, MD; Brian E. Driver, MD; Li Wang, MS; Christopher J. Lindsell, PhD; Wesley H. Self, MD, MPH; Todd W. Rice, MD, MSc; David R. Janz, MD, MSc; Matthew W. Semler, MD, MSc; for the PREPARE II Investigators and the Pragmatic Critical Care Research Group



Conclusion



Among critically ill adults undergoing tracheal intubation, administration of a fluid bolus does not prevent cardiovascular collapse.

Takeaways for the Researcher

- The Imperative
  - In clinical care, patients are receiving treatments that are ineffective (or harmful).
  - Without RCTs, we cannot know which treatments are helpful and which are not.
  - Emergency research has largely focused on a small number of conditions (e.g., cardiac arrest, stroke) and neglected many common treatments (e.g., intubation).
  - We must establish the regulatory and logistical methods needed to examine in RCTs the full range of emergency treatments patients are receiving in clinical care.
- Embedding RCT procedures within emergency care can:
  - Deliver treatments in the manner that they are delivered in clinical care.
  - Collect the data on which clinicians and patients base decisions.
  - Enroll diverse and representative trial populations (to understand H.T.E.).

How can we improve acute and emergency care through more broadly embedding RCTs into clinical care?

Thank you!

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