CCCTG
Canadian Critical Care Trials Group

ANZICS Clinical Trials Group

McMaster University

The George Institute for Global Health

Re-Evaluating the Inhibition of Stress Erosions: Gastrointestinal Bleeding Prophylaxis In ICU

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clarity
Clinical Advances Through Research and Information Translation

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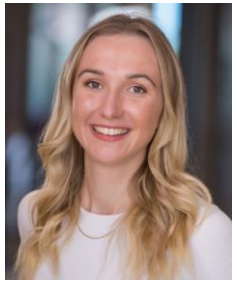

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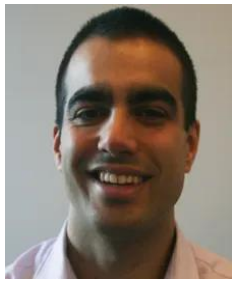

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McMaster University

Research Question

In invasively ventilated critically ill adults, what is the effect of pantoprazole versus placebo on:

- **Clinically important upper GI bleeding** (primary efficacy outcome)
- **90-day mortality** (primary safety outcome)
- VAP, *C difficile* infection, patient-important upper GI bleeding, renal replacement therapy, ICU and hospital mortality (secondary outcomes)
- RBC transfusions, renal function, duration of mechanical ventilation/ICU and hospital stay (tertiary outcomes)

Rationale

- Equipose regarding the **benefit** on clinically- and **patient-important** bleeding with PPI

Krag M et al. *N Engl J Med* 2018;379:2199-208

- Equipose regarding the risk of **death** with PPI
  - Compared to placebo

Krag M et al. *N Engl J Med* 2018;379:2199-208

  - Compared to H2 receptor antagonists

PEPTIC investigators. *JAMA* 2020;323:616-26

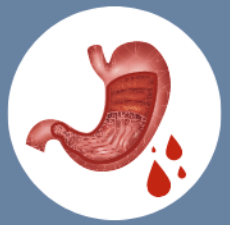
- Equipose regarding the risk of **pneumonia** and ***C difficile*** with PPI

Wang Y et al. *Intensive Care Med* 2020;46:1987-2000

Design

- Investigator-initiated, peer-review funded
- Randomized 1:1, stratified for site *and* prehospital PPI use
- Concealed, double-blind
- 4,821 critically ill patients
- 68 hospitals, 8 countries, 5 continents
- Supported by the CCCTG and ANZICS-CTG

Patient Important Gastrointestinal Bleeding



Objective To elicit views from patients and families regarding features, tests and treatments for gastrointestinal bleeding that are important to them

Study Design

- Sequential mixed-methods
- Qualitative dominant
- Instrument-building aim

Participants

- Adults admitted to the ICU ≥72 hours
- Family members of adult patients in ICU ≥ 72 hours

Recruited From

- Hospitals in Alberta, Ontario and New Brunswick
- Research-affiliated patient or family partners

Sampling Strategies

- Criterion sampling
- Convenience sampling
- Snowball sampling

Sample Size

40-50 participants

Data Collection

- Participants receive an educational presentation on tests and treatments for gastrointestinal bleeding
- Semi-structured interviews or focus groups via videoconferencing

Data Analysis

- Qualitative descriptive analysis of participant views
- Quantitative summary of participant characteristics
- Tool to measure upper gastrointestinal bleeding

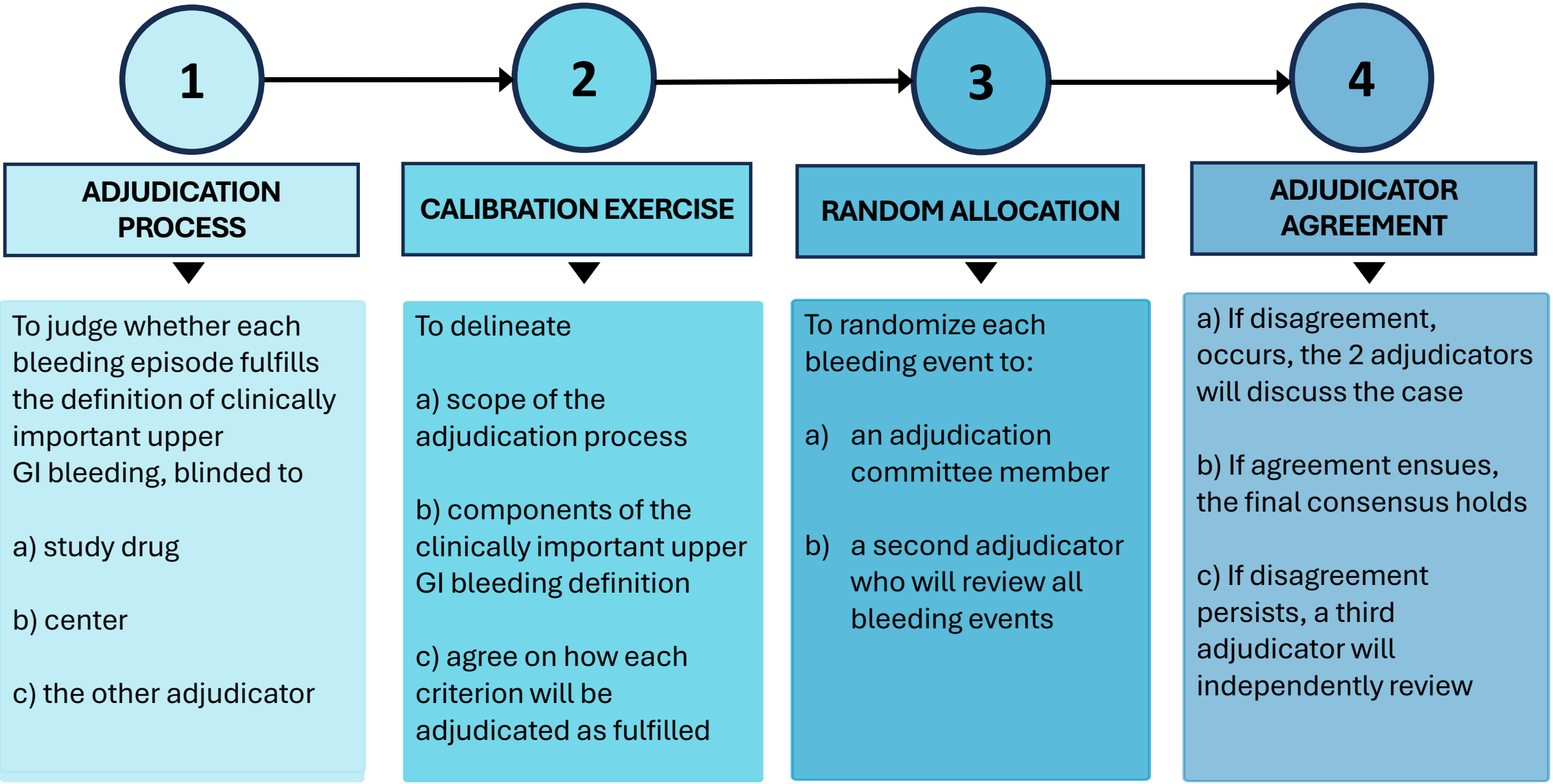
Outcome

Definition of patient important upper gastrointestinal bleeding for a stress ulcer prophylaxis trial

Vanstone MG et al. *J Crit Care 2024*;81:154761

Clinically Important GI Bleeding	Patient Important GI Bleeding
⇩SBP or ⇩DBP or ⇩MAP≥ 20mm/Hg (With/without vasopressor initiation or ⇧)	---
Orthostatic⇩SBP ≥ 10mm/Hg +⇧HR ≥ 20/min (With/without vasopressor initiation or ⇧)	---
Vasopressor initiation	Vasopressor initiation
⇩ Hemoglobin ≥ 2g/dl	---
Transfusion ≥ 2 U RBCs	Transfusion ≥ 1 U RBC
Therapeutic endoscopy	**Diagnostic** or Therapeutic Endoscopy
Angio-embolization	**CT-angio** (with/without embolization)
Surgery	**Surgery**
---	Resulting in **death**
---	Resulting in **disability**
Readmission to ICU for GI bleed	Resulting in prolonged **hospitalization**

Bleeding Adjudication



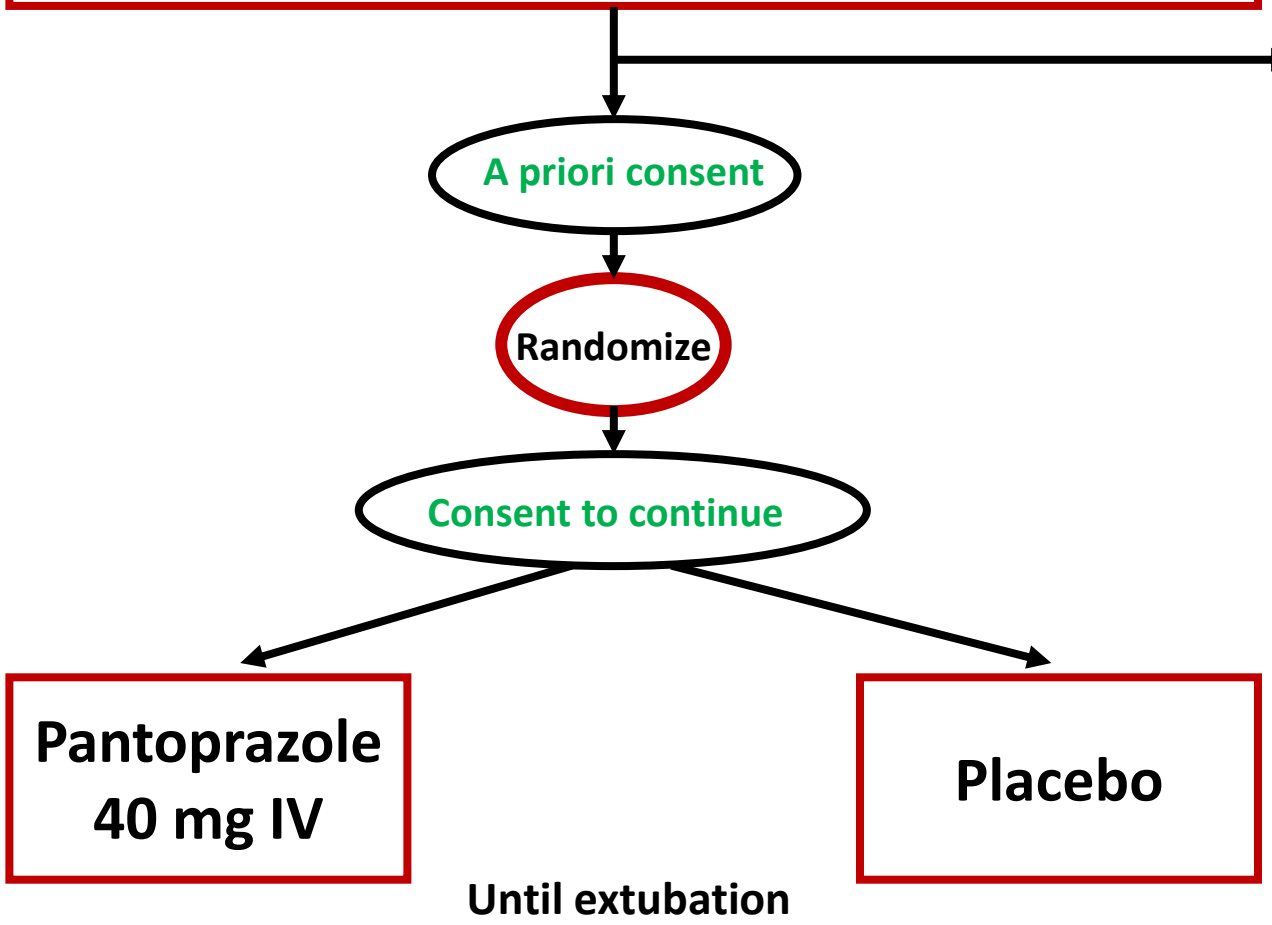
Cook D et al. *Contemp Clin Trials Commun* 2024;39:101284

INCLUSION

- ≥ 18 years old in any ICU
- Expected need of invasive mechanical ventilation ≥48 hours

EXCLUSION

- PPI indicated (DAPT, previous GI bleeding)
- PPI contraindicated
- Mechanical ventilation ≥ 72 hours
- Received ≥ 24 h PPI or H2RA in ICU
- Limitation of life support/palliative care
- Pregnancy
- Patient, proxy, physician decline



Sample size and statistics

- 4800 patients (85% power, absolute risk reduction 1.5%, type 1 error 5%)
- Sequential Holm-Šidak approach to adjust for multiple significance testing (secondary & tertiary outcomes, subgroups)
- No imputation (< 2% with missing data)
- Subgroup analyses (APACHE II, prehospital PPI, age, sex, COVID, type of admission)
- Sensitivity analyses (adjusted for site, unadjusted for prehospital PPI, per protocol, competing risk of death)

Data monitoring Committee

- **Members**
  - Danny McAuley (Belfast, Northern Ireland)
  - Ian Roberts (London, England)
  - George Tomlinson (Toronto, Canada)
- **Mortality review**
  - At 25% sample size (1200 patients)
- **Interim analysis**
  - At 25% sample size (2400 patients)
  - Haybittle-Peto, $p < 0.001$

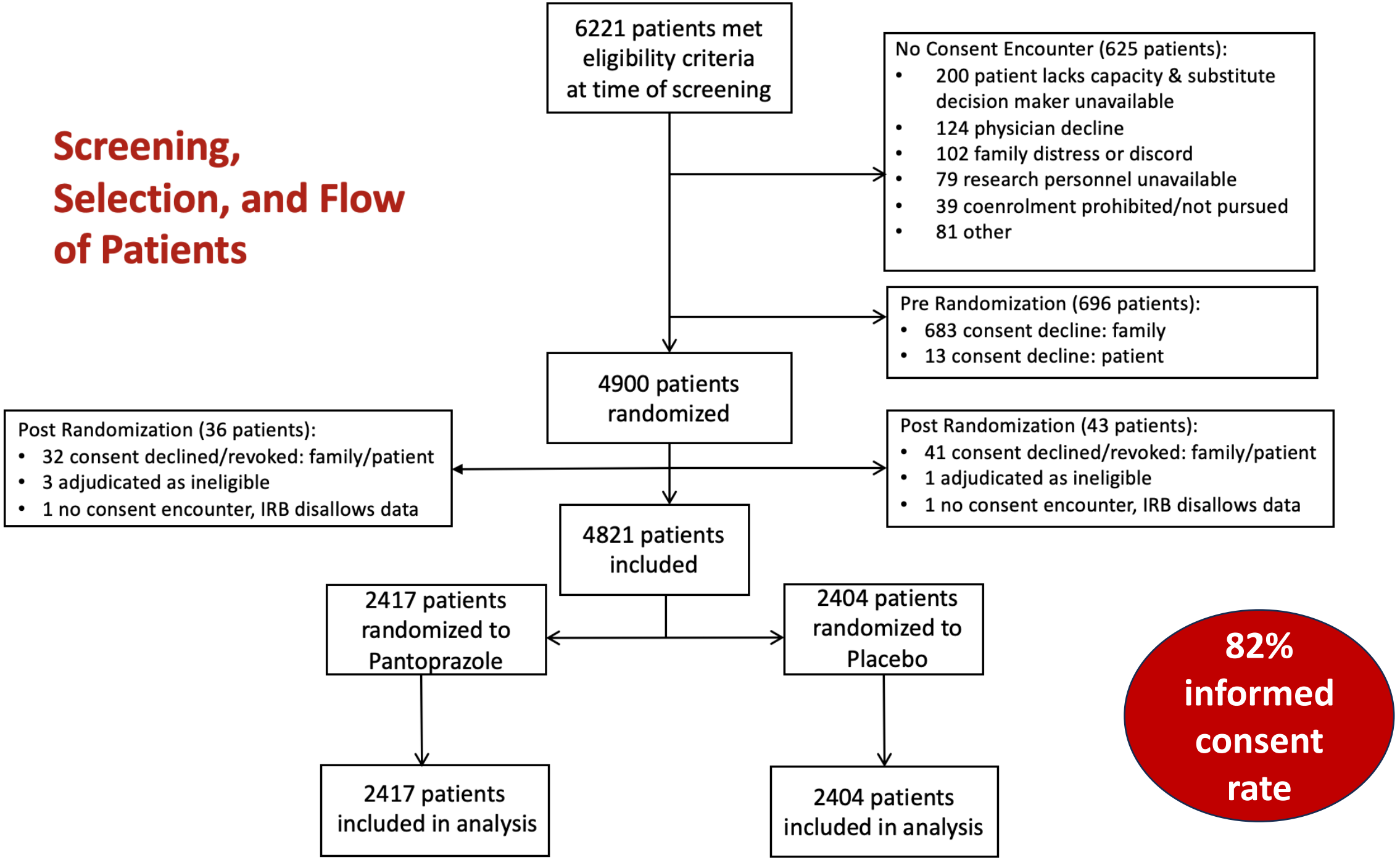
Results

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Stress Ulcer Prophylaxis during Invasive Mechanical Ventilation

Screening, Selection, and Flow of Patients



82% informed consent rate

Baseline characteristics

Characteristic	Pantoprazole (N = 2417)	Placebo (N = 2404)
Age — yr	58.2±16.4	58.3±16.4
APACHE II score†	21.8±8.4	21.7±8.2
Sex — no. (%)		
Female	883 (36.5)	870 (36.2)
Male	1534 (63.5)	1534 (63.8)
Patient status — no. (%)		
Medical	1753 (72.5)	1767 (73.5)
Surgical	295 (12.2)	325 (13.5)
Trauma	369 (15.3)	312 (13.0)
No acid suppression before hospitalization	1847 (76.4)	1854 (77.1)
Glucocorticoid ≥1 wk before randomization — no. (%)‡	856 (35.4)	838 (34.9)
Type of life support — no. (%)		
Invasive mechanical ventilation	2417 (100)	2404 (100)
Inotrope or vasopressor infusion	1680 (69.5)	1709 (71.1)
Renal-replacement therapy	153 (6.3)	155 (6.4)

Intervention	N (%)
At least **one dose**	4650 (96.5%)
≥80% of days on mechanical ventilation	4699 (97.5%)
≥90% of days on mechanical ventilation	4537 (94.1%)
Median 5 days (3 to 10) on the intervention	

Cointerventions	N (%)
Invasive mechanical ventilation	4821 (100%)
Inotropes/vasopressors	3791 (78.6%)
Renal replacement therapy	620 (12.9%)
Corticosteroids	2396 (49.7%)
Prophylactic unfractionated heparin	1313 (12.1%)
Prophylactic low-molecular weight heparin	2973 (61.7%)
Any therapeutic heparin	850 (17.6%)
ASA	896 (18.6%)

Primary outcomes

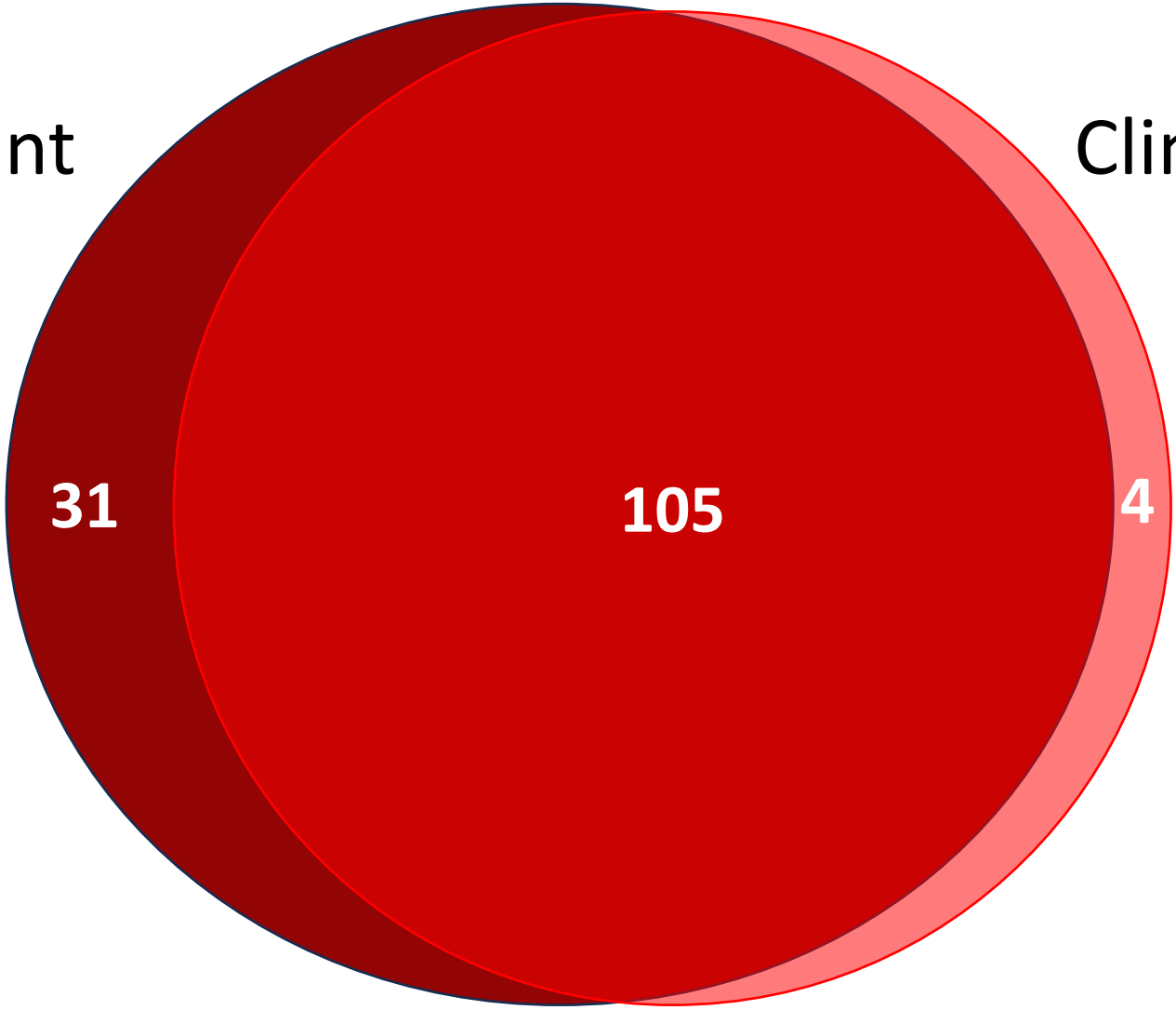
Outcome	Pantoprazole (N = 2417)	Placebo (N = 2404)	Absolute Difference (95% CI)	Hazard Ratio (95% CI)*	P Value
	no./total no. (%)		*percentage points*		
Primary efficacy outcome: clinically important upper gastrointestinal bleeding	25/2385 (1.0)	84/2377 (3.5)	2.5 (1.6 to 3.3)	0.30 (0.19 to 0.47)	<0.001
Primary safety outcome: 90-day mortality	696/2390 (29.1)	734/2379 (30.9)	1.7 (–0.9 to 4.3)	0.94 (0.85 to 1.04)	0.25

Secondary and tertiary outcomes

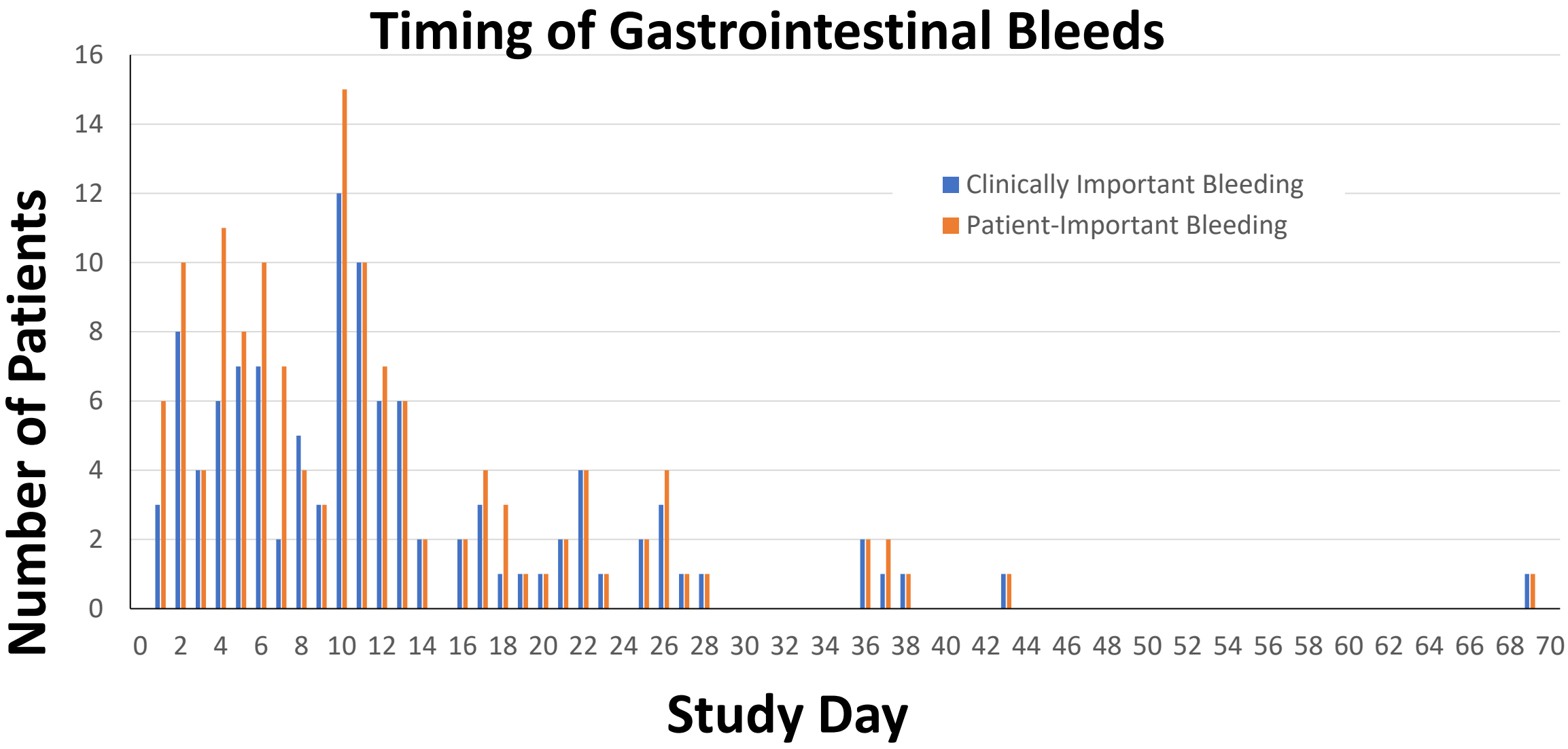
Outcome	Pantoprazole (N = 2417)	Placebo (N = 2404)	Treatment Effect (95% CI)†	P Value‡
Secondary outcome				
Ventilator-associated pneumonia in ICU — no./total no. (%)§	556/2394 (23.2)	567/2381 (23.8)	1.00 (0.89–1.12)	0.93
Clostridioides difficile infection in hospital — no./total no. (%)	28/2385 (1.2)	16/2377 (0.7)	1.78 (0.96–3.29)	0.50
New renal-replacement therapy in ICU — no./total no. (%)	146/2385 (6.1)	142/2380 (6.0)	1.04 (0.83–1.31)	0.98
Death — no./total no. (%)				
In ICU	488/2402 (20.3)	515/2392 (21.5)	0.98 (0.87–1.11)	0.94
In hospital	630/2399 (26.3)	677/2381 (28.4)	0.96 (0.86–1.07)	0.91
Patient-important upper gastrointestinal bleeding in ICU — no./total no. (%)	36/2385 (1.5)	100/2377 (4.2)	0.36 (0.25–0.53)	<0.001
Tertiary outcome				
Median no. of red-cell units transfused in first 14 days in ICU (IQR)	0 (0–1)	0 (0–1)	0.87 (0.74–1.02)	0.51
Median peak serum creatinine level in ICU (IQR) — μmol/liter	99 (70–190)	99 (69–184)	NA	0.91
Median no. of days of mechanical ventilation (IQR)	6 (3–11)	6 (3–11)	NA	0.73
Median no. of days in ICU (IQR)	10 (6–16)	10 (6–16)	NA	0.48
Median no. of days in hospital (IQR)	20 (11–35)	21 (11–38)	NA	0.47

Patient vs clinically important bleeding

Patient Important Bleeding



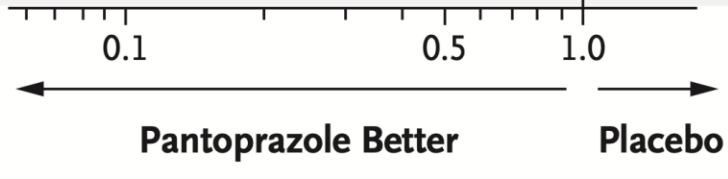
Clinically Important Bleeding


Timing of Gastrointestinal Bleeds
Number of Patients
Study Day
Clinically Important Bleeding
Patient-Important Bleeding
0
2
4
6
8
10
12
14
16
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52 54 56 58 60 62 64 66 68 70

Subgroup analyses

Clinically Important Upper Gastrointestinal Bleeding

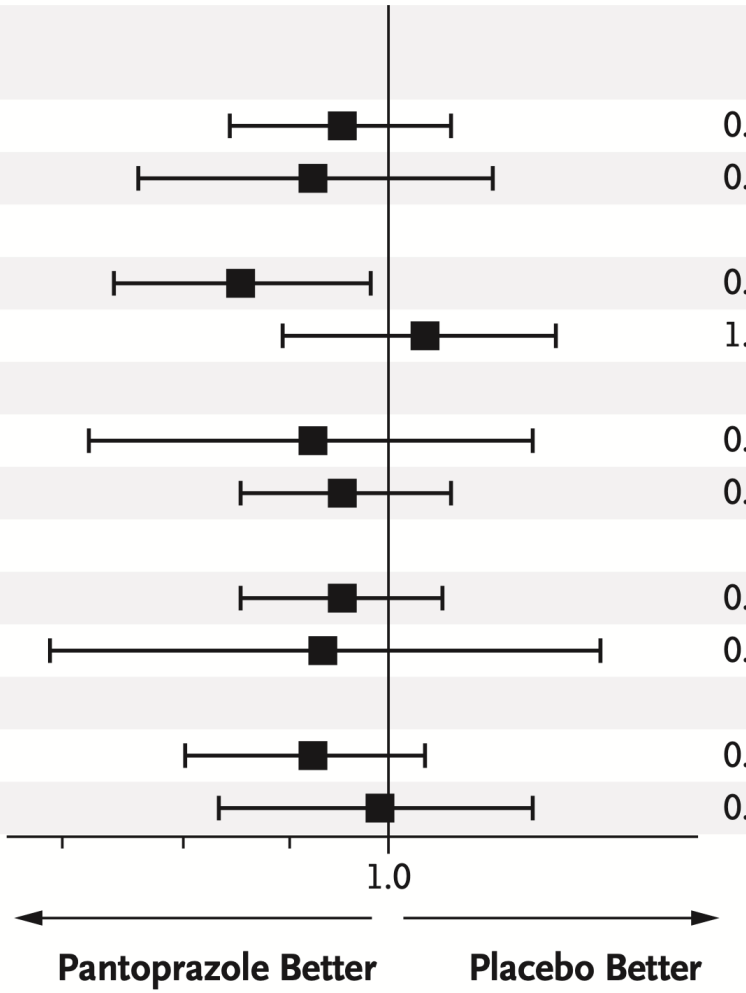
Subgroup	Pantoprazole	Placebo	Hazard Ratio (95% CI)	P Value
	no. of patients with event/total no.			
Use of acid suppression before hospitalization				0.91
No	18/1822	63/1829	0.30 (0.18–0.51)	
Yes	7/563	21/548	0.29 (0.12–0.68)	
APACHE II score				0.12
<25	15/1570	30/1582	0.51 (0.28–0.96)	
≥25	10/815	54/795	0.18 (0.09–0.35)	
Diagnosis on ICU admission				0.75
Surgical or trauma	4/651	20/630	0.20 (0.07–0.57)	
Medical	21/1734	64/1747	0.33 (0.20–0.55)	
SARS-CoV-2 status				0.98
No active infection	21/2145	71/2145	0.30 (0.18–0.48)	
Active infection	4/240	13/232	0.33 (0.11–1.01)	
Sex				0.55
Male	13/1513	56/1519	0.23 (0.13–0.43)	
Female	12/872	28/858	0.43 (0.22–0.85)	



Subgroup analyses

90-Day Mortality

Subgroup	Pantoprazole	Placebo	Hazard Ratio (95% CI)	P Value
	no. of patients with event/total no.			
Use of acid suppression before hospitalization				0.97
No	491/1823	524/1835	0.95 (0.84–1.07)	
Yes	205/567	210/544	0.92 (0.76–1.12)	
APACHE II score				0.27
<25	338/1574	391/1579	0.85 (0.74–0.98)	
≥25	358/816	343/800	1.04 (0.89–1.20)	
Diagnosis on ICU admission				0.99
Surgical or trauma	131/653	139/633	0.92 (0.72–1.17)	
Medical	565/1737	595/1746	0.95 (0.85–1.07)	
SARS-CoV-2 status				0.90
No active infection	613/2150	643/2149	0.95 (0.85–1.06)	
Active infection	83/240	91/230	0.93 (0.69–1.26)	
Sex				0.93
Male	436/1516	469/1522	0.92 (0.80–1.04)	
Female	260/874	265/857	0.99 (0.83–1.17)	



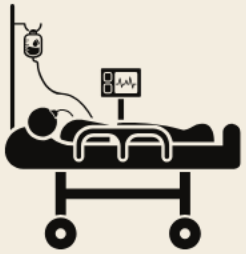
Sensitivity Analyses

	Pantoprazole	Placebo	HR (95% CI)
Adjusted for prehospital PPI			
Clinically important GI bleed	25/2385 (1.0)	84/2377 (3.5)	0.30 (0.19,0.47)
90-Day Mortality	696/2390 (29.1)	734/2379 (30.9)	0.94 (0.85,1.05)
Adjusted for Center			
Clinically important GI bleed	25/2385 (1.0)	84/2377 (3.5)	0.30 (0.19,0.47)
90-Day Mortality	696/2390 (29.1)	734/2379 (30.9)	0.94 (0.85,1.05)
Competing Risk Analysis			
Clinically important GI bleed	25/2385 (1.0)	84/2377 (3.5)	0.30 (0.19,0.47)
≥ 80% intervention exposure			
Clinically important GI bleed	10/1786 (0.6)	21/1671 (1.3)	0.43 (0.20,0.91)
90-Day Mortality	472/1780 (26.5)	472/1669 (28.3)	0.93 (0.82,1.05)

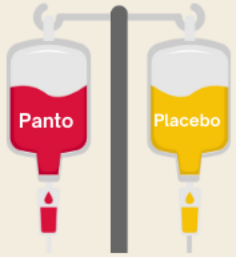
Stress ulcer prophylaxis during invasive ventilation

REVISE
Re-Evaluating the Inhibition of Stress Erosions: Gastrointestinal Bleeding Prophylaxis In ICU

Design



Randomized blinded trial of 4821 critically ill patients in 68 ICUs in 8 countries



Invasively ventilated patients allocated to IV pantoprazole or placebo while ventilated

Results

Patient-important upper GI bleeding occurred in 36 **(1.5%)** of patients receiving pantoprazole and 100 **(4.2%)** patients receiving placebo.

Results

Clinically important bleeding occurred in 25 **(1.0%)** of patients receiving pantoprazole and in 84 **(3.5%)** of patients receiving placebo.

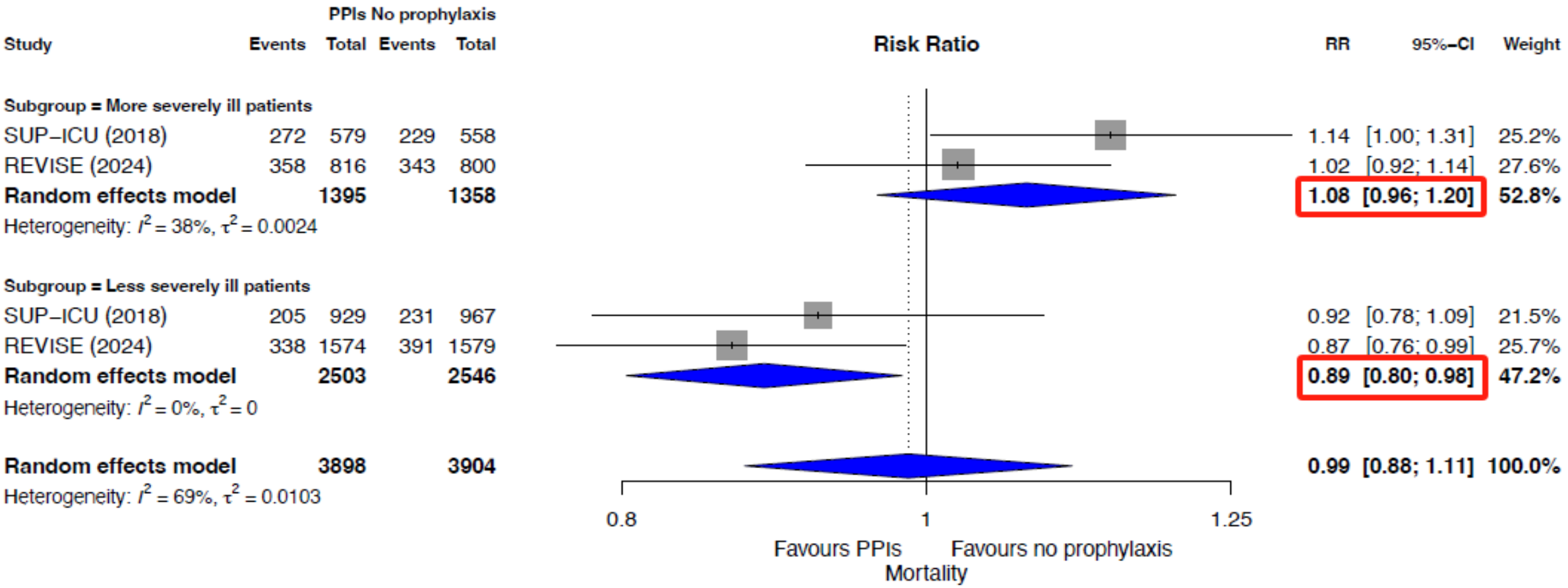
Death at 90 days occurred in 696 **(29.1%)** of patients receiving pantoprazole and 734 **(30.9%)** of patients receiving placebo.

No difference in other outcomes

- Ventilator-associated pneumonia
- *Clostridioides difficile* infection
- ICU & Hospital Length of Stay

Summary: In invasively ventilated critically ill patients, pantoprazole significantly reduced clinically important upper GI bleeding and patient important upper GI bleeding but did not affect mortality or other outcomes.

Updated meta-analysis



PPIs may increase mortality in more severely ill patients and decrease mortality in less severely ill patients (low to moderate credibility)

Wang Y et al. *NEJM Evid* 2024;3:EVIDoa2400134

Next steps

- Risk factors of patient-important bleeding
- Cost-effectiveness analysis
- Pandemic adaptation analysis
- COVID-19 cohort substudy
- And more…