JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Stress Ulcer Prophylaxis With Proton Pump Inhibitors vs Histamine-2 Receptor Blockers on In-Hospital Mortality Among ICU Patients Receiving Invasive Mechanical Ventilation

The PEPTIC Randomized Clinical Trial

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Background

Proton pump inhibitors (PPIs) or histamine-2 receptor blockers (H2RBs) are often prescribed for patients as stress ulcer prophylaxis drugs in the intensive care unit (ICU).

The comparative effect of these drugs on mortality is unknown.

Objective

To compare in-hospital mortality rates using PPIs vs H2RBs for stress ulcer prophylaxis.

- DESIGN, SETTING, AND PARTICIPANTS Cluster crossover randomized clinical trial conducted at 50 ICUs in 5 countries between August 2016 and January 2019.
- Patients requiring invasive mechanical ventilation within 24 hours of ICU admission were followed up for 90 days at the hospital.

- INTERVENTIONS Two stress ulcer prophylaxis strategies were compared (preferential use with PPIs vs preferential use with H2RBs). Each ICU used each strategy sequentially for 6 months in random order; 25 ICUs were randomized to the sequence with use of PPIs and then use of H2RBs and 25 ICUs were randomized to the sequence with use of H2RBs and then use of PPIs (13 436 patients randomized by site to PPIs and 13 392 randomized by site to H2RBs).

- MAIN OUTCOMES AND MEASURES The primary outcomewas all-cause mortality within 90 days during index hospitalization.
- Secondary outcomes were clinically important upper gastrointestinal bleeding, *Clostridioides difficile* infection, and ICU and hospital lengths of stay.

Figure 1. Screening, Randomization, and Follow-up of Participants in the PEPTIC Randomized Trial

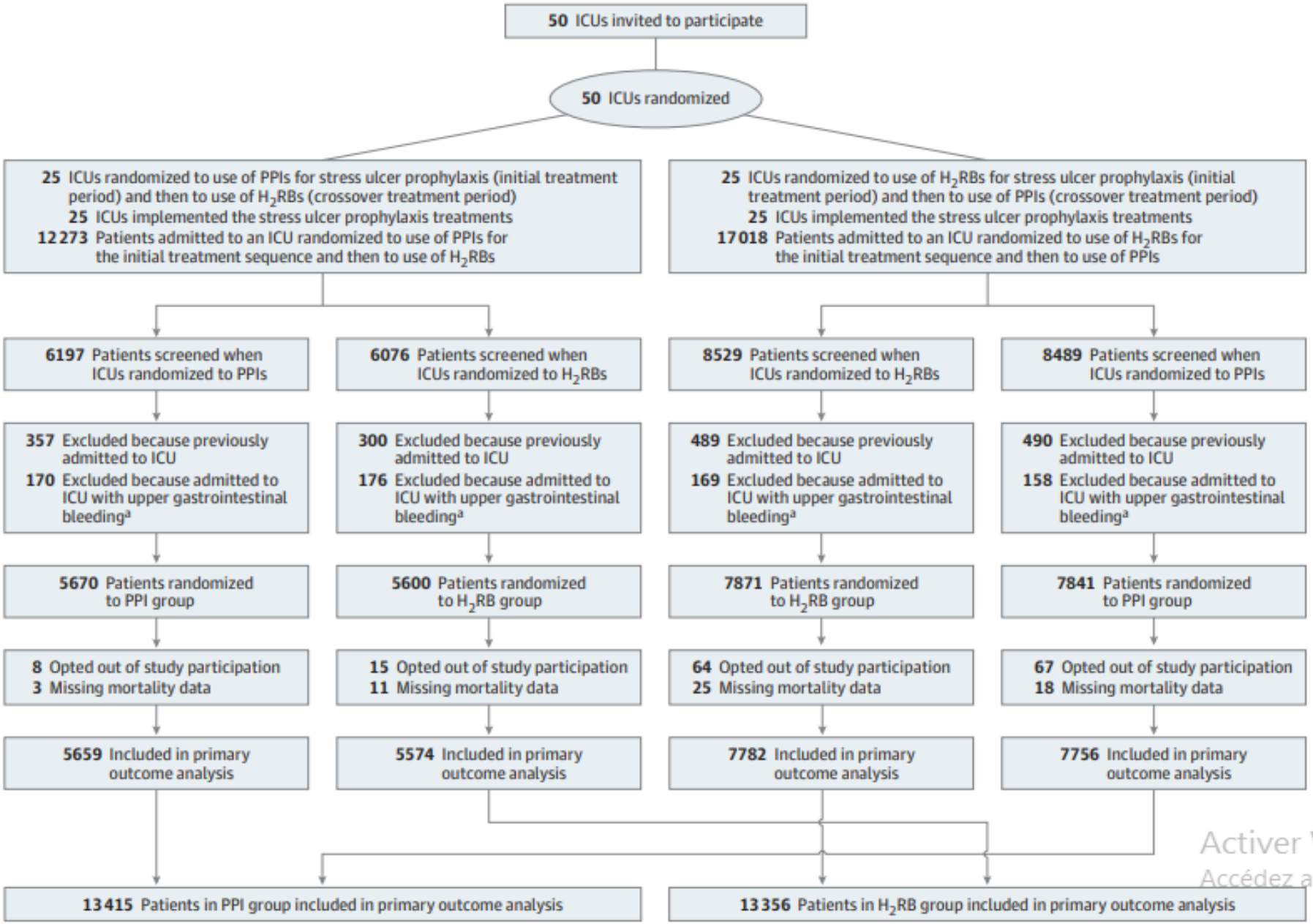

Table 1. Baseline Characteristics

	Proton Pump Inhibitors (n = 13 436)	Histamine-2 Receptor Blockers (n = 13 392)
Age, mean (SD), y	58.6 (17.0)	58.2 (17.1)
Sex, No. (%)		
Male	8577 (63.8)	8560 (63.9)
Female	4859 (36.2)	4832 (36.1)
APACHE II chronic comorbidities, No./total No. (%)		
Respiratory	821/13 425 (6.1)	798/13 375 (6.0)
Cardiovascular	872/13 425 (6.5)	804/13 375 (6.0)
Hepatic	182/13 425 (1.4)	191/13 371 (1.4)
Kidney	252/13 425 (1.9)	277/13 375 (2.1)
Immunosuppression	783/13 425 (5.8)	872/13 375 (6.5)
Metastatic cancer	367/13 425 (2.7)	340/13 371 (2.5)
Source of admission to ICU, No. (%)		
Emergency department	4026 (30.0)	4026 (30.1)
Hospital ward	1479 (11.0)	1406 (10.5)
Transfer from another ICU	322 (2.4)	342 (2.6)
Transfer from another hospital (except from another ICU)	1012 (7.5)	993 (7.4)
After elective surgery	4356 (32.4)	4459 (33.3)
After emergency surgery	2490 (18.5)	2456 (18.3)
Unknown	14 (0.1)	22 (0.2)
Admitted to ICU with lower gastrointestinal bleeding, No. (%)	8 (0.06)	6 (0.04)
APACHE II score		
No. of patients	13 374	13 339
Mean (SD)[a]	18.7 (8.3)	18.7 (8.4)
APACHE III score		
No. of patients	11 214	11 382
Mean (SD)[b]	65.2 (29.9)	65.5 (29.5)
Risk of death for participants living in Australia and New Zealand only[c]		
No. of patients	8818	9078
Mean (SD), %[d]	14.1 (22.4)	13.9 (22.0)
Median (interquartile range), %[d]	3.2 (0.7-16.1)	3.1 (0.8-16.0)
ICNARC risk of death for participants living in Ireland and England only[c]		
No. of patients	2212	1993
Mean (SD), %[d]	31.6 (31.4)	31.5 (31.1)
Median (interquartile range), %[d]	19.8 (4.3-55.7)	19.7 (4.5-54.7)
Patients per site, median (interquartile range)[e]	193 (130-393)	175 (109-416)
By region, No. (%)		
Australia and New Zealand	8826 (65.7)	9088 (67.9)
Canada	2217 (16.5)	2148 (16.0)
Ireland and England	2393 (17.8)	2156 (16.1)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ICNARC, Intensive Care National Audit and Research Centre; ICU, intensive care unit.

[a] Scores range from 0 to 71; higher scores indicate more severe disease and a higher risk of death.

[c] Combines physiology, age, diagnosis, and comorbidities collected during the first 24 hours in the ICU to create predicted risk of death at the hospital.

[d] Scores range from 0% to 99.9%.

Table 2. Primary, Secondary, and Tertiary Outcomes

	Proton Pump Inhibitors	Histamine-2 Receptor Blockers
Primary Outcome		
Died at the hospital by 90 d, No./total No. (%)	2459/13 415 (18.3)	2333/13 356 (17.5)
Secondary Outcomes		
Types of complications, No./total No. (%)		
Clinically important upper gastrointestinal bleeding[a]	172/13 436 (1.3)	239/13 392 (1.8)
Clostridioides difficile infection[b]	40/13 436 (0.30)	57/13 392 (0.43)
Length of stay variables and duration of ventilation		
Days until discharged alive from the ICU		
No. of patients	13 425	13 384
Median (interquartile range)[c]	3.6 (1.6 to 10.4)	3.3 (1.5 to 10.0)
Days until discharged alive from the hospital		
No. of patients	13 418	13 370
Median (interquartile range)[c]	12.2 (6.0 to 40.0)	12.0 (6.0 to 39.3)
Tertiary Outcomes		
Hours until removed alive from mechanical ventilation		
No. of patients	6047	5438
Median (interquartile range)	48.0 (12.1 to 271)	48.0 (14.3 to 265)
Ventilator-associated conditions, No./total No. (%)[e]	143/2217 (6.5)	124/2148 (5.8)

Abbreviations: ICU, intensive care unit; ROM, ratio of median time to discharge (or extubation); RR, risk ratio.

[a] Defined as overt upper gastrointestinal bleeding (eg, hematemesis, melaena, or frank blood in the nasogastric tube or upper gastrointestinal endoscopy) developing as a complication in the ICU and accompanied by 1 or more of the following features within 24 hours: (1) a spontaneous decline in systolic, diastolic, or mean arterial pressure of 20 mm Hg or greater; (2) initiation of a vasopressor or a 20% increase in dose of ongoing vasopressor; (3) a decrease in hemoglobin level of 20 g/L or greater; or (4) a transfusion of at least 2 U of packed red blood cells.

[b] Defined as a new toxin or culture-positive stool sample collected during an ICU admission (excluding any patients who had positive test results from specimens collected prior to ICU admission).

[c] Calculated from cumulative incidence functions with mortality regarded as a competing risk. A total of 15.1% of patients who received proton pump inhibitors and 13.9% of patients who received histamine-2 receptor blockers died during their index ICU admission; a total of 18.5% and 17.6%, respectively, died during their index hospital admission. Among patients with duration of ventilation data present, a total of 18.5% of patients who received proton pump inhibitors and 17.8% of patients who received histamine-2 receptor blockers died prior to extubation or were determined to have been extubated with palliative intent.

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	Proton Pump Inhibitors	Histamine-2 Receptor Blockers	Estimate (95% CI)
	2459/13 415 (18.3)	2333/13 356 (17.5)	RR, 1.05 (1.00 to 1.10)
	172/13 436 (1.3)	239/13 392 (1.8)	RR, 0.73 (0.57 to 0.92)
	40/13 436 (0.30)	57/13 392 (0.43)	RR, 0.74 (0.51 to 1.09)
	13 425	13 384	
	3.6 (1.6 to 10.4)	3.3 (1.5 to 10.0)	ROM, 1.00 (0.97 to 1.03)[d]
	13 418	13 370	
	12.2 (6.0 to 40.0)	12.0 (6.0 to 39.3)	ROM, 1.01 (0.98 to 1.03)[d]
	6047	5438	
	48.0 (12.1 to 271)	48.0 (14.3 to 265)	ROM, 0.98 (0.92 to 1.04)[d]
	143/2217 (6.5)	124/2148 (5.8)	RR, 1.18 (0.87 to 1.59)

an time to discharge (or extubation); RR, risk ratio.

emesis, melaena, or frank blood in the nasogastric tube lication in the ICU and accompanied by 1 or more of the e in systolic, diastolic, or mean arterial pressure of % increase in dose of ongoing vasopressor; (3) a decrease of at least 2 U of packed red blood cells.

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[d] Estimated using censored linear regressio variable. Patients who died were censore as for binary outcomes. Heterogeneity of robust standard errors were used to acco

[e] Only available for participants from the 8 improvement while receiving invasive me of the following indicators of worsening o oxygen of at least 0.20 more than the dail stability that was sustained for at least 2 d pressure of at least 3 cm H_2O more than t period that was sustained for at least 2 da positive end-expiratory pressure during a

	Absolute Risk Difference (95% CI)	*P* Value
	0.93 (−0.01 to 1.88) percentage points	.054
	−0.51 (−0.90 to −0.12) percentage points	.009
	−0.11 (−0.25 to 0.03) percentage points	.13
3)[d]		.85
3)[d]		.66
4)[d]		.43
	1.11 (−0.89 to 3.11) percentage points	.28

egression models with logarithm of time to discharge as the dependent
censored at their time of death. Adjustment was made for the same variables
eneity of variance by treatment group and country was accommodated for and
to account for clustering by ICU.

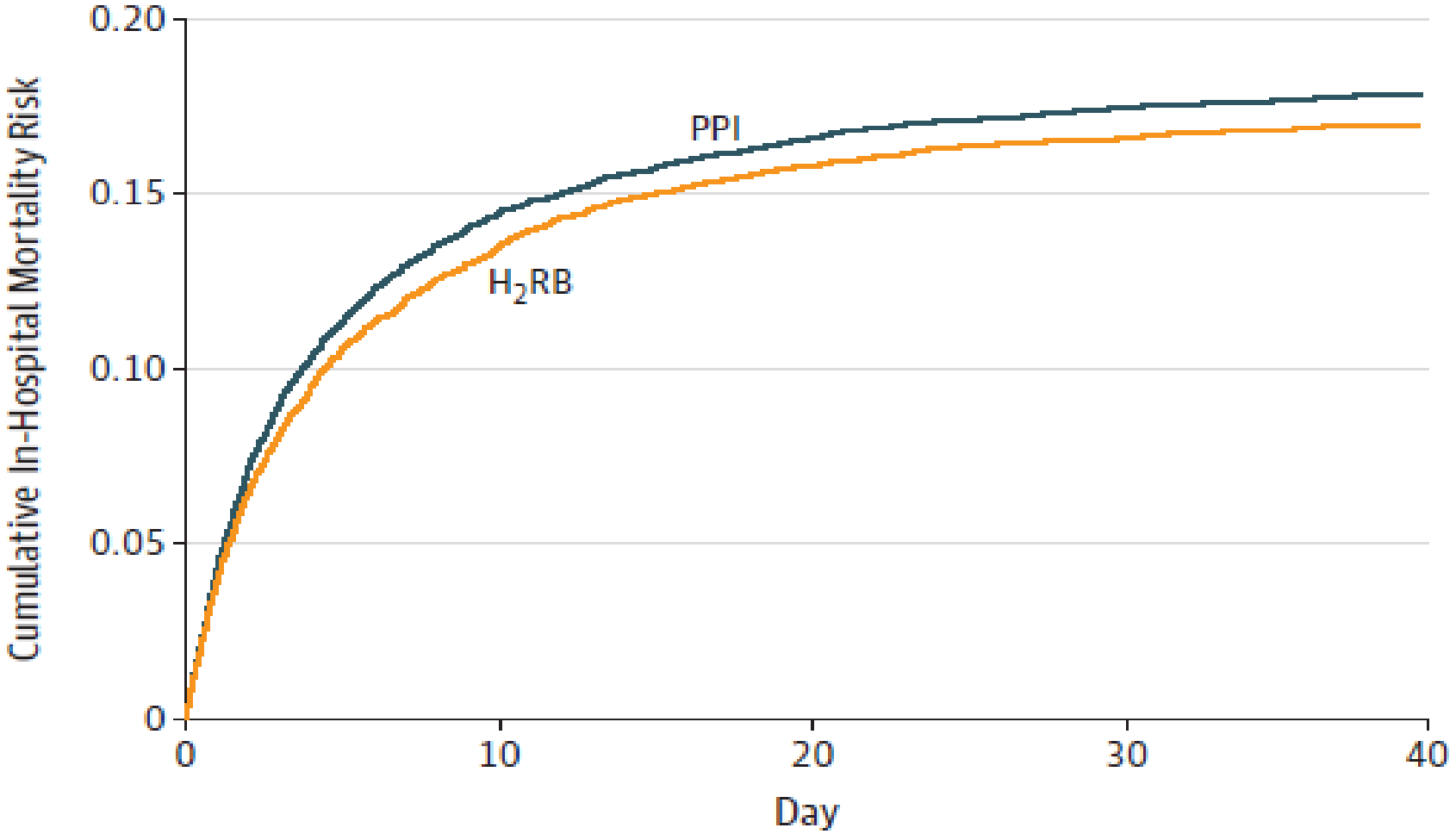
m the 8 Canadian ICUs. Defined as events after a period of stability or
asive mechanical ventilation for at least 2 days in which a patient had at least 1
sening oxygenation: (1) an increase in daily minimum fraction of inspired
n the daily minimum fraction of inspired oxygen during the baseline period of
least 2 days; or (2) an increase in daily minimum positive end expiratory
re than the daily minimum positive end-expiratory pressure during the baseline
east 2 days (daily minimum defined by the lowest fraction of inspired oxygen o
during a calendar day that is maintained for at least 1 hour).

RESULTS

Among 26 982 patients who were randomized, 154 opted out, and 26 828 were analyzed (mean [SD] age, 58 [17.0] years; 9691 [36.1%] were women). There were 26 771 patients (99.2%) included in the mortality analysis; 2459 of 13 415 patients (18.3%) in the PPI group died at the hospital by day 90 and 2333 of 13 356 patients (17.5%) in the H2RB group died at the hospital by day 90 (risk ratio, 1.05 [95%CI, 1.00 to 1.10]; absolute risk difference, 0.93 percentage points [95%CI, −0.01 to 1.88] percentage points; $P = .054$). An estimated 4.1% of patients randomized by ICU site to PPIs actually received H2RBs and an estimated 20.1%of patients randomized by ICU site to H2RBs actually received PPIs.

Clinically important upper gastrointestinal bleeding occurred in 1.3%of the PPI group and 1.8%of the H2RB group (risk ratio, 0.73 [95%CI, 0.57 to 0.92]; absolute risk difference, −0.51 percentage points [95%CI, −0.90 to −0.12 percentage points]; $P = .009$). Rates of *Clostridioides difficile* infection and ICU and hospital lengths of stay were not significantly different by treatment group. One adverse event (an allergic reaction) was reported in 1 patient in the PPI group.

Figure 2. Cumulative Incidence of In-Hospital Mortality



No. at risk

PPI	13415	5581	2763	1520	965
H_2RB	13356	5647	2753	1601	1044

- A total of 2459 of 13 415 patients (18.3%) in the proton pump inhibitor (PPI) group and 2333 of 13 356 patients (17.5%) in the histamine-2 receptor blocker (H2RB) group died at the hospital by day 90 (risk ratio, 1.05 [95% CI, 1.00 to 1.10]; absolute risk difference, 0.93 [95% CI, −0.01 to 1.88] percentage points; P = .054).
- The median observation time was 7.99 days (interquartile range, 4.79 to 17.0 days) in the PPI group vs 8.03 days (interquartile range, 4.82 to 17.0 days) in the H2RB group. Curve truncated at 40 days beyond which less than 10% of the study population remained at risk.

LIMITATIONS

This study has several limitations. First, some patients who were excluded from the trial because of an ICU admission diagnosis of upper gastrointestinal bleeding may have actually had lower gastrointestinal bleeding and some patients who were diagnosed as having upper gastrointestinal bleeding in the ICU may have already been bleeding at the time of ICU admission. Second, only data from the index hospitalization were included. Third, because mortality data were obtained from registries, these data may contain random errors. Fourth, clinicians and research staff were aware of treatment assignments. Although mortality rates are unlikely to be subject to bias as a result of this knowledge, such biasmay have affected ascertainment of secondary outcomes including upper gastrointestinal bleeding. Fifth, clinicians were allowed to use any proton pump inhibitor or histamine-2 receptor blocker and to choose the route of administration.

- A range of different drugs were used, increasing the generalizability of the findings. However, it is possible that a trial using different combinations of drugs or different routes of administration would have yielded different findings.

CONCLUSIONS AND RELEVANCE

- Among ICU patients requiring mechanical ventilation, a strategy of stress ulcer prophylaxis with use of proton pump inhibitors vs histamine-2 receptor blockers resulted in hospital mortality rates of 18.3%vs 17.5%, respectively, a difference that did not reach the significance threshold.
- However, study interpretation may be limited by crossover in the use of the assigned medication.