EDITORIAL

Proton-Pump Inhibitor Prophylaxis in the ICU — Benefits Worth the Risks?

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Critical illness can disrupt local and systemic mechanisms that protect against upper gastrointestinal bleeding, a condition that may be associated with increased mortality,[1] particularly among patients receiving extracorporeal life support.[2] On the basis of randomized trials performed over a period of 40 years,[3] most guidelines recommend preventive therapy with either histamine H_2–receptor antagonists or proton-pump inhibitors (PPIs) for patients in the intensive care unit (ICU) who are at risk for the development of stress ulceration and bleeding.

A review of this approach is timely, owing to a number of considerations. First, contemporary observations suggest that stress-ulcer bleeding may be less prevalent than it was in the past, probably as a result of improved care in the ICU. Second, the overall benefit from PPIs may be reduced by adverse events that are associated with the use of these agents, including nosocomial pneumonia, *Clostridium difficile* enteritis, and myocardial ischemia.[1,4] Third, administration of enteral feeding in parallel with bleeding prophylaxis may reduce the risk of gastrointestinal bleeding, possibly obscuring the benefits of PPIs; conversely, the combination may increase the risk of nosocomial pneumonia.[5]

Krag and colleagues address the value of prophylaxis for gastrointestinal bleeding in the ICU in their report, now published in the *Journal*,[6] of a multicenter European trial in which 3298 adult patients were randomly assigned to receive daily, single-bolus, intravenous pantoprazole (40 mg) or placebo during their nonelective ICU stay. The patient population was at high risk for clinically important gastrointestinal bleeding because of a history of liver disease, coagulopathy, shock, treatment with anticoagulant agents, renal replacement therapy, or mechanical ventilation that was expected to last for more than 24 hours.

There was no significant difference between the pantoprazole group and the placebo group in the rate of the primary outcome of death by 90 days after randomization (31.1% and 30.4%, respectively). This finding is similar to the mortality rates found in meta-analyses of similar trials.[7,8] However, the observed mortality rate was higher in the placebo group of the current trial than in the cohorts that were used to calculate the sample size for this trial.[1] It also remains unknown whether there could have been a survival benefit among patients in the ICU who were at especially high risk for death.

Similarly, no difference was found with regard to the secondary, unvalidated composite outcome of clinically important gastrointestinal bleeding, new-onset pneumonia, *C. difficile* infection, or acute myocardial ischemia (21.9% in the pantoprazole group and 22.6% in the placebo group). This composite outcome was designed to capture the net clinical effect of PPI use, but it is difficult to interpret. It encompassed some outcomes that may improve and others that may worsen in association with the intervention. Furthermore, the individual components of the outcome have disparate pathophysiological mechanisms, different expected incidences, and different risks attributable to treatment.[9]

Although the trial was not powered to address each component of the combined secondary outcome, thus limiting conclusions, useful new information can be drawn from the findings.

First, clinically important gastrointestinal bleeding occurred in 2.5% of the patients in the pantoprazole group and in 4.2% of the patients in the placebo group (no P value was reported, since there was no adjustment for multiple comparisons). The magnitude of this possible benefit of pantoprazole is within the range of differences between PPI treatment and placebo for gastrointestinal bleeding prophylaxis that was shown in a recent meta-analysis,[10] although the rate of clinically significant bleeding in the placebo group in this trial was greater than the upper 95% confidence limit of the bleeding rate in a cohort that was analyzed to plan the trial. Moreover, these results highlight the low prevalence of upper gastrointestinal bleeding in modern ICUs. Second, the combined rates of the infectious outcomes of pneumonia and *C. difficile* infection were essentially identical in the two groups (16.8% in the pantoprazole group and 16.9% in the placebo group). These analyses were not stratified according to whether enteral nutrition was administered, which could have modified the outcomes, but the percentages of patients receiving enteral nutrition were balanced between the two groups, with 56 to 85% of the patients receiving it at some point during their ICU stay.

In our view, the take-home message from this trial is that, given the low incidence of clinically important upper gastrointestinal bleeding in the ICU, prophylaxis with a PPI, if initiated, should be reserved for seriously ill patients who are at high risk for this complication. (An important problem, of course, is that the definition of a high risk of bleeding varies between guidelines and needs to be standardized.[3]) Although 90-day mortality was not affected by pantoprazole administration in the current trial, the between-group difference in the rate of important upper gastrointestinal bleeding may still support the recommendation of using a prophylactic PPI, particularly given the absence of a difference in the rate of adverse events between the pantoprazole group and the placebo group. We base this view mainly on the admittedly small (1.7-percentage-point) difference in bleeding rates between the

groups. Additional data are needed to determine the clinical effects of prophylaxis for gastrointestinal bleeding in the ICU, especially in groups of patients who are at very high risk for this complication, and to quantify any protective or harmful effects attributable to the coadministration of enteral nutrition.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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This editorial was published on October 24, 2018, at NEJM.org.

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ORIGINAL ARTICLE

Pantoprazole in Patients at Risk for Gastrointestinal Bleeding in the ICU

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ABSTRACT

BACKGROUND

Prophylaxis for gastrointestinal stress ulceration is frequently given to patients in the intensive care unit (ICU), but its risks and benefits are unclear.

METHODS

In this European, multicenter, parallel-group, blinded trial, we randomly assigned adults who had been admitted to the ICU for an acute condition (i.e., an unplanned admission) and who were at risk for gastrointestinal bleeding to receive 40 mg of intravenous pantoprazole (a proton-pump inhibitor) or placebo daily during the ICU stay. The primary outcome was death by 90 days after randomization.

RESULTS

A total of 3298 patients were enrolled; 1645 were randomly assigned to the pantoprazole group and 1653 to the placebo group. Data on the primary outcome were available for 3282 patients (99.5%). At 90 days, 510 patients (31.1%) in the pantoprazole group and 499 (30.4%) in the placebo group had died (relative risk, 1.02; 95% confidence interval [CI], 0.91 to 1.13; P=0.76). During the ICU stay, at least one clinically important event (a composite of clinically important gastrointestinal bleeding, pneumonia, *Clostridium difficile* infection, or myocardial ischemia) had occurred in 21.9% of patients assigned to pantoprazole and 22.6% of those assigned to placebo (relative risk, 0.96; 95% CI, 0.83 to 1.11). In the pantoprazole group, 2.5% of patients had clinically important gastrointestinal bleeding, as compared with 4.2% in the placebo group. The number of patients with infections or serious adverse reactions and the percentage of days alive without life support within 90 days were similar in the two groups.

CONCLUSIONS

Among adult patients in the ICU who were at risk for gastrointestinal bleeding, mortality at 90 days and the number of clinically important events were similar in those assigned to pantoprazole and those assigned to placebo. (Funded by Innovation Fund Denmark and others; SUP-ICU ClinicalTrials.gov number, NCT02467621.)

CRITICALLY ILL PATIENTS IN THE INTENsive care unit (ICU) are at risk for stressrelated gastrointestinal bleeding, which is associated with adverse outcomes.[1] To prevent gastrointestinal bleeding in these patients, prophylaxis for stress ulcers is used and is included in guidelines for patients who are at risk for gastrointestinal bleeding.[2] Risk factors for the development of gastrointestinal bleeding in the ICU include mechanical ventilation, coagulopathy, and hepatic or kidney failure.[3-5] Proton-pump inhibitors are the most commonly used prophylactic acid suppressant in these circumstances,[6] and they are among the most frequently used offlabel medications in ICUs (they have not been approved by the Food and Drug Administration as prophylaxis for stress ulcers).[7] However, the quality of evidence supporting the prophylactic use of proton-pump inhibitors in the ICU is limited.[8,9] Concerns have been raised about adverse effects associated with this class of drugs, including the risk of *Clostridium difficile* infection, pneumonia, and myocardial ischemia, which may counterbalance their potential benefits.[10-12]

We conducted the Stress Ulcer Prophylaxis in the Intensive Care Unit (SUP-ICU) trial to evaluate the effects of and adverse events associated with the prophylactic use of the proton-pump inhibitor pantoprazole in adult patients in the ICU who were at risk for gastrointestinal bleeding. We hypothesized that pantoprazole would be associated with a lower rate of gastrointestinal bleeding but with higher rates of nosocomial infections and myocardial ischemia than placebo among these patients.

METHODS

TRIAL DESIGN AND OVERSIGHT

We performed screening and randomization between January 4, 2016, and October 22, 2017, in 33 ICUs in Denmark, Finland, the Netherlands, Norway, Switzerland, and the United Kingdom after obtaining institutional approval at each site. We obtained written informed consent from the patients or their legal surrogates in accordance with national regulations. In most institutions, if the patient or legal guardian was unable to give consent initially, enrollment of patients was allowed on an emergency basis (e.g., with con-

sent from a doctor who was independent of the trial), followed by consent from relatives and the patient to continue participation. If consent was withdrawn or not granted, we asked the patient or surrogate for permission to continue registration of trial data and for permission to include these data in our analyses. The trial protocol and the statistical analysis plan have been published elsewhere and are available with the full text of this article at NEJM.org.[13,14] All the authors vouch for the adherence of the trial to the protocol, the accuracy and completeness of the data and analyses, and the reporting of adverse events. The members of the steering committee wrote the draft of the manuscript and made the final decision to submit it for publication. The trial was funded by Innovation Fund Denmark, which had no role in the design of the protocol, the trial conduct, or the analyses or reporting of the data. There was no commercial support for the trial.

This trial was a multicenter, stratified, parallelgroup, placebo-controlled, blinded clinical trial. Randomization was performed with a centralized, computer-generated allocation sequence stratified according to trial site and the presence or absence of active hematologic cancer. Patients who were admitted to participating ICUs were screened and, if eligible, were randomly assigned in a 1:1 ratio, with the use of permuted blocks of varying sizes, to receive pantoprazole or placebo. The trial-group assignments were concealed from the patients, clinicians, investigators, trial statisticians, and members of the data and safety monitoring committee. The data and safety monitoring committee oversaw the conduct of the trial and the safety of the participants. Interim analyses were planned to be conducted when 1675 and 2500 patients had been followed for 90 days. The latter interim analysis was not performed, because the target number of patients enrolled was completed before the 90-day follow-up of 2500 patients. The trial data were monitored at the sites by external monitors in accordance with the Good Clinical Practice directive of the European Union and centrally by staff from the coordinating center.

PARTICIPANTS

We screened patients 18 years of age or older who were admitted to the ICU for an acute condi-

tion (i.e., excluding elective admissions) and had at least one risk factor for clinically important gastrointestinal bleeding, including shock, use of anticoagulant agents, renal-replacement therapy, mechanical ventilation (expected to last >24 hours), any history of liver disease, or any history of or ongoing coagulopathy (the full definitions of the criteria are provided in the Supplementary Appendix, available at NEJM.org[4,13]). We encouraged the investigators at all the trial sites to systematically complete the screening procedure for all patients who fulfilled the inclusion criteria. Patients were excluded for the reasons shown in Figure 1 and in the Supplementary Appendix.

INTERVENTIONS

Enrolled patients received an intravenous injection of pantoprazole (40 mg suspended in 10 ml of 0.9% sodium chloride) or matching placebo (suspended in 10 ml of 0.9% sodium chloride) (Fig. S1 in the Supplementary Appendix) as a single bolus once daily from randomization until ICU discharge or death, for a maximum of 90 days. If a patient was readmitted to a trial ICU within 90 days, the originally assigned trial regimen was resumed. All other interventions were chosen at the discretion of the clinicians.

OUTCOMES

The primary outcome was death by 90 days after randomization. The secondary outcomes were clinically important events in the ICU (defined as clinically important gastrointestinal bleeding,[4] new-onset pneumonia,[15] *C. difficile* infection, or acute myocardial ischemia; see the Supplementary Appendix); clinically important gastrointestinal bleeding in the ICU (defined as overt gastrointestinal bleeding and at least one of the following four features within 24 hours of gastrointestinal bleeding, in the absence of other causes, in the ICU: a spontaneous decrease in systolic blood pressure, mean arterial pressure, or diastolic blood pressure of 20 mm Hg or more; initiation of treatment with a vasopressor or a 20% increase in vasopressor dose; a decrease in hemoglobin of at least 2 g per deciliter [1.24 mmol per liter]; or transfusion of two or more units of packed red cells); infectious adverse events in the ICU (new-onset pneumonia or *C. difficile* infection); serious adverse reactions in the ICU (see

the Supplementary Appendix); and the percentage of days alive without the use of life support (mechanical ventilation, circulatory support, or renal-replacement therapy; see the Supplementary Appendix) within the 90-day period. Data for outcome measures were obtained from the patients' files by the trial investigators or their delegates. For 90-day mortality, regional and national registries or direct contact with participants or surrogates were used if available.

STATISTICAL ANALYSIS

We estimated that 3350 patients would be required for the trial to have 90% power to detect a between-group difference of 5 percentage points in 90-day mortality, corresponding to a 20% difference in relative risk at a two-sided alpha level of 5%, under the assumption of a baseline 90-day mortality of 25%.[4,13,14] The statistical analysis was performed in accordance with the International Conference on Harmonisation tripartite guideline (Guideline for Good Clinical Practice[16]) and the statistical analysis plan, by an independent statistician who was unaware of the trial-group assignments.[14] We conducted the primary analysis in the intention-to-treat population, defined as all patients who underwent randomization except for the 59 patients who were excluded after randomization; 7 patients did not consent to the use of their data, and 52 patients were excluded immediately after randomization before the first dose of trial medication because they did not meet the inclusion criteria or fulfilled one or more exclusion criteria.[17] In the per-protocol population, we excluded patients with one or more major protocol violations (Table S2 in the Supplementary Appendix).[16]

In the primary analyses, we evaluated data in the two groups using a binary logistic regression adjusted for trial site and active hematologic cancer in the intention-to-treat population[18]; relative risks with 95% confidence intervals were computed as described in the statistical analysis plan (see the Supplementary Appendix). We evaluated the primary outcome in the per-protocol population and in prespecified subgroups defined by the presence or absence of any history of liver disease, the presence or absence of any history of coagulopathy or ongoing coagulopathy, the type of ICU admission (medical vs. surgical), the pres-
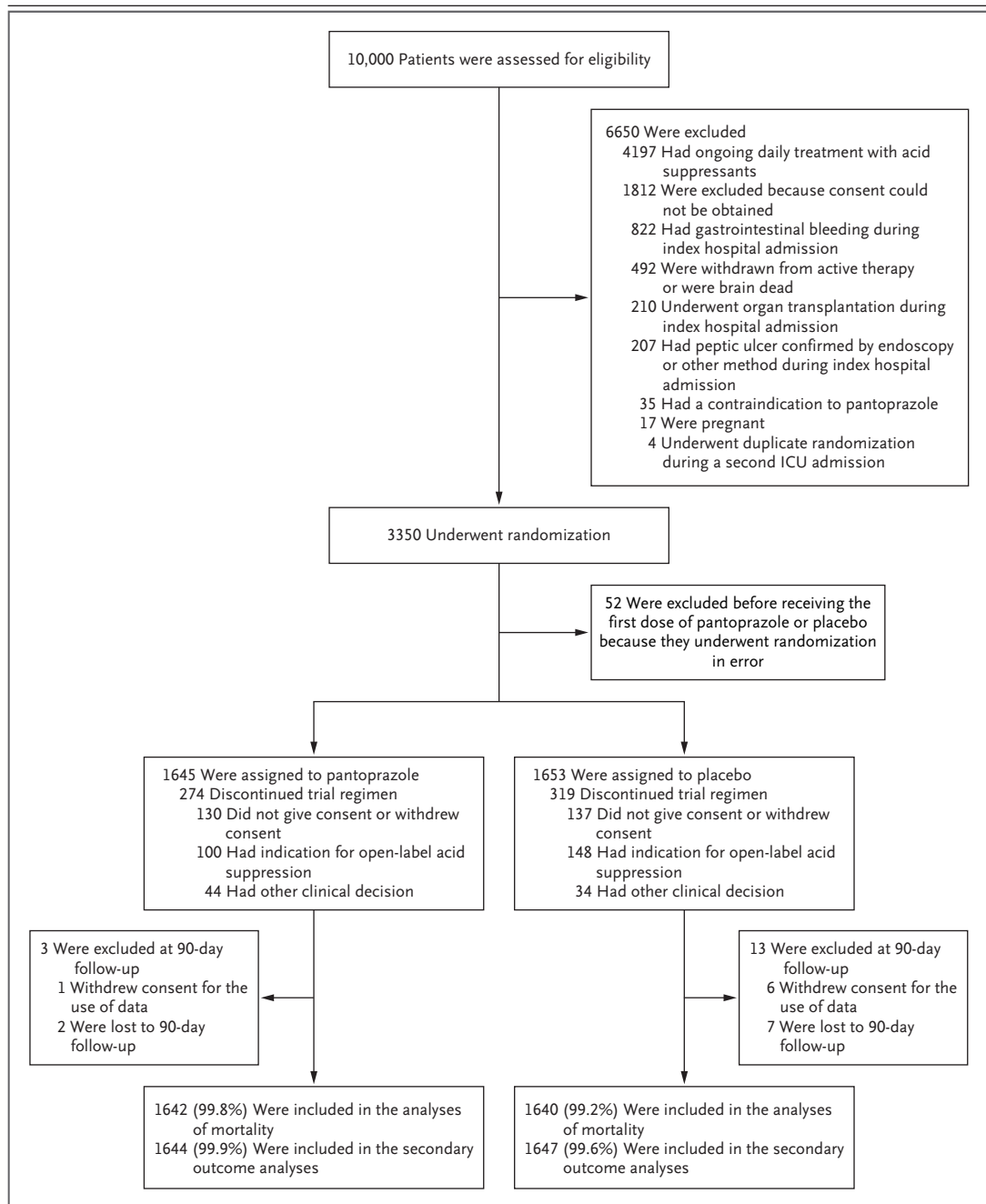
10,000 Patients were assessed for eligibility

6650 Were excluded
   4197 Had ongoing daily treatment with acid
       suppressants
   1812 Were excluded because consent could
       not be obtained
    822 Had gastrointestinal bleeding during
       index hospital admission
    492 Were withdrawn from active therapy
       or were brain dead
    210 Underwent organ transplantation during
       index hospital admission
    207 Had peptic ulcer confirmed by endoscopy
       or other method during index hospital
       admission
     35 Had a contraindication to pantoprazole
     17 Were pregnant
      4 Underwent duplicate randomization
       during a second ICU admission

3350 Underwent randomization

52 Were excluded before receiving the
first dose of pantoprazole or placebo
because they underwent randomization
in error

1645 Were assigned to pantoprazole
  274 Discontinued trial regimen
    130 Did not give consent or withdrew
       consent
    100 Had indication for open-label acid
       suppression
     44 Had other clinical decision

1653 Were assigned to placebo
  319 Discontinued trial regimen
    137 Did not give consent or withdrew
       consent
    148 Had indication for open-label acid
       suppression
     34 Had other clinical decision

3 Were excluded at 90-day
  follow-up
 1 Withdrew consent for the
  use of data
 2 Were lost to 90-day
  follow-up

13 Were excluded at 90-day
   follow-up
  6 Withdrew consent for the
   use of data
  7 Were lost to 90-day
   follow-up

1642 (99.8%) Were included in the analyses
    of mortality
1644 (99.9%) Were included in the secondary
    outcome analyses

1640 (99.2%) Were included in the analyses
    of mortality
1647 (99.6%) Were included in the secondary
    outcome analyses

Figure 1. Screening, Randomization, and Follow-up.

We screened patients who were admitted to the intensive care unit (ICU) for an acute condition (i.e., an unplanned admission), were 18 years of age or older, and had at least one risk factor for gastrointestinal bleeding. Patients were excluded if there were medical reasons, if they were receiving ongoing daily acid-suppressing therapy in the ICU, or if informed consent could not be obtained; 1001 patients met two or more exclusion criteria. A total of 52 patients were excluded immediately after randomization and before the first dose of trial agent because they did not meet the inclusion criteria or fulfilled one or more exclusion criteria; 7 patients were excluded after randomization because the patient or the surrogate did not allow the use of their data. The remaining 267 patients (130 in the pantoprazole group and 137 in the placebo group) who withdrew from the trial at their own or their surrogates' request allowed the use of their data, but 20 patients or surrogates in the pantoprazole group and 20 in the placebo group did not want further data to be registered except for data on mortality, which we obtained from registries. Some of the process variables and some of the secondary outcomes were missing for these 40 patients.

ence or absence of shock, the use or absence of use of mechanical ventilation, and a Simplified Acute Physiology Score (SAPS) II[19] above 53 or 53 or lower at baseline. The SAPS II is calculated from 17 variables and has a total range from 0 to 163, with higher scores indicating greater severity of disease; a score of 53 was chosen as predicting a 50% mortality rate in the original model.

For secondary analyses, we evaluated all dichotomous outcomes in binary logistic regression analyses of the intention-to-treat population adjusted for stratification variables and predefined risk factors at baseline (age, type of admission [medical, elective surgery, or emergency surgery], and the Sepsis-related Organ Failure Assessment [SOFA] score assessed in the 24 hours before randomization).[20] The SOFA score is made up of subscores ranging from 0 to 4 for each of six organ systems (cerebral, circulatory, pulmonary, hepatic, renal, and coagulative), resulting in an aggregated score that ranges from 0 to 24, with higher scores indicating more severe organ failure. We also performed unadjusted chi-square testing for the binary outcome measures. We analyzed percentages of days alive without life support in the 90-day period with the van Elteren test (with adjustment for site only), because the assumptions for Poisson or negative binomial distributions were not met.[21] There was no adjustment for multiple comparisons of secondary outcomes, and the results are reported as point estimates with unadjusted 95% confidence intervals. There was no imputation for missing data (details are provided in the Supplementary Appendix). A total of 9 patients were lost to 90-day follow-up. We performed analyses using SAS software, version 9.4 (SAS Institute), and R software, version 3.4.3 (R Foundation), and considered a two-sided P value of less than 0.05 to indicate statistical significance for the primary outcome with 95% confidence intervals.

RESULTS

TRIAL POPULATION

From January 2016 through October 2017, a total of 3298 patients were enrolled in the trial; 1645 were randomly assigned to receive pantoprazole, and 1653 were assigned to receive placebo. We obtained data on 90-day vital status for 3282 patients (99.5%; 1642 in the pantoprazole group and 1640 in the placebo group) (Fig. 1). The characteristics of the patients at baseline were similar in the two groups, with the exception of chronic lung disease, coagulopathy, and emergency surgery (Table 1).

During the 90-day trial period, patients in each group stayed in the ICU for a median of 6 days after randomization (interquartile range, 4 to 11 in each group), and patients in each group received the trial agent for a median of 4 days (interquartile range, 2 to 9 in each group); 274 of 1644 patients (16.7%) in the pantoprazole group and 319 of 1647 (19.4%) in the placebo group discontinued the trial regimen in the ICU for reasons shown in Figure 1. The number of patients with major protocol violations was 46 (2.8%) in the pantoprazole group and 43 (2.6%) in the placebo group (Table S2 in the Supplementary Appendix). On the first trial day, 58.2% of patients in the pantoprazole group and 56.4% in the placebo group received enteral feeding (Table S3 in the Supplementary Appendix); patients in each group received enteral feeding for a median of 4 days (interquartile range, 2 to 10 in each group) in the ICU.

OUTCOMES

At 90 days after randomization, 510 of 1642 patients (31.1%) in the pantoprazole group and 499 of 1640 (30.4%) in the placebo group had died (relative risk, 1.02; 95% confidence interval [CI], 0.91 to 1.13; P=0.76) (Table 2 and Fig. 2). The results were similar in the analysis with adjustment for baseline risk factors and in the per-protocol population (Tables S4, S5, and S6 in the Supplementary Appendix). In predefined subgroup analyses, there was no heterogeneity in the effect of pantoprazole as compared with placebo on mortality at 90 days between patients with and patients without a history of liver disease, a history of or ongoing coagulopathy, shock, or mechanical ventilation, or between patients with different types of ICU admission (Fig. 2). We found heterogeneity in the estimate of the intervention effect among patients with higher as compared with lower baseline severity of disease (defined as a SAPS II of >53 and ≤53, respectively) (Fig. 2).

A total of 360 (21.9%) of 1644 patients in the pantoprazole group and 372 (22.6%) of 1647 in the placebo group had one or more clinically important events in the ICU (relative risk, 0.96; 95% CI, 0.83 to 1.11 [not adjusted for multiple comparisons]) (Table 2). In the pantoprazole group, 41 patients (2.5%) had clinically impor-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Pantoprazole (N = 1644)	Placebo (N = 1647)
Median age (IQR) — yr	67 (56–75)	67 (55–75)
Male sex — no. (%)	1039 (63)	1067 (65)
Coexisting conditions — no. (%)		
Chronic lung disease†	351 (21)	306 (19)
Previous myocardial infarction	156 (9)	142 (9)
Chronic heart failure‡	100 (6)	99 (6)
Use of glucocorticoids§	35 (2)	27 (2)
Hematologic cancer¶	64 (4)	55 (3)
Metastatic cancer ‖	56 (3)	55 (3)
AIDS**	6 (<1)	1 (<1)
Coagulopathy††	352 (21)	299 (18)
Admission to university hospital — no. (%)	1183 (72)	1189 (72)
Median time from ICU admission to randomization (IQR) — hr	15 (5–28)	14 (6–25)
Median time from hospital admission to randomization (IQR) — days	1 (1–3)	1 (1–3)
ICU admission type — no. (%)		
Medical	998 (61)	941 (57)
Emergency surgery	490 (30)	558 (34)
Elective surgery	156 (9)	148 (9)
Use of invasive mechanical ventilation — no. (%)	1273 (77)	1316 (80)
Use of vasopressors or inotropes — no. (%)	1103 (67)	1093 (66)
Use of any renal-replacement therapy — no. (%)	123 (7)	99 (6)
Median SAPS II (IQR)‡‡	49 (39–59)	48 (37–59)
Median SOFA score (IQR)§§	9 (7–11)	9 (7–11)

* There were no significant differences between the groups with regard to any baseline characteristic except chronic lung disease (P=0.05), emergency surgery (P=0.01), and coagulopathy (P=0.02). A full list of risk factors for gastrointestinal bleeding is provided in Table S1 in the Supplementary Appendix.

† Chronic lung disease was defined as any history of chronic obstructive pulmonary disease, asthma, or other chronic lung disease or treatment with any relevant drug indicating this at the time of admission to hospital.

‡ Chronic heart failure was defined as New York Heart Association (NYHA) functional class III or IV. Patients with NYHA class III heart failure have marked limitations in physical activity due to symptoms (fatigue, palpitation, or dyspnea) even during less-than-ordinary activity (e.g., walking short distances of 20 to 100 m or walking up one flight of stairs); patients are comfortable only at rest. Patients with NYHA class IV heart failure are not able to perform any physical activity without discomfort (fatigue, palpitation, or dyspnea); symptoms are present even at rest, and patients are mostly bedbound.

§ Use of glucocorticoids was defined as treatment with at least 0.3 mg per kilogram of body weight per day of prednisolone or equivalent for at least 1 month in the 6 months before ICU admission.

¶ Hematologic cancer included acute lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, Hodgkin's disease, non-Hodgkin's lymphoma (e.g., small lymphocytic lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, mantle-cell lymphoma, hairy-cell leukemia, marginal-zone lymphoma, Burkitt's lymphoma, post-transplantation lymphoproliferative disorder, T-cell prolymphocytic leukemia, B-cell prolymphocytic leukemia, Waldenström's macroglobulinemia, and other natural-killer-cell or T-cell lymphomas), and multiple myeloma or plasma cell myeloma.

‖ Metastatic cancer was defined as metastasis proved by means of surgery, computed tomography, or any other method.

** Acquired immunodeficiency syndrome (AIDS) was defined as one or more AIDS-defining diseases (e.g., *Pneumocystis jiroveci* pneumonia, Kaposi's sarcoma, lymphoma, tuberculosis, and toxoplasma infection) in a patient with human immunodeficiency virus infection.

†† Coagulopathy included both acute coagulopathy (defined as a platelet count of <50×10^9 per liter, an international normalized ratio >1.5, or a prothrombin time of >20 seconds at ICU admission) and a history of coagulopathy (defined as coagulopathy within 6 months before hospital admission).

‡‡ The Simplified Acute Physiology Score (SAPS) II[19] was assessed in the 24 hours before randomization. The score is calculated from 17 variables and ranges from 0 to 163, with higher scores indicating a higher severity of disease (Table S9 in the Supplementary Appendix). Data were missing for 134 patients in the pantoprazole group and 115 patients in the placebo group, and their values are not included here.

§§ The Sepsis-related Organ Failure Assessment (SOFA)[20] score was assessed in the 24 hours before randomization. The score is a measure of organ failure, with subscoring ranging from 0 to 4 for each of six organ systems (cerebral, circulatory, pulmonary, hepatic, renal, and coagulative). The aggregated score ranges from 0 to 24, with higher scores indicating more severe organ failure (Table S10 in the Supplementary Appendix). Data were missing for 108 patients in the pantoprazole group and 85 patients in the placebo group, and their values are not included here. There was no imputation for missing data.

Table 2. Primary and Secondary Outcome Measures.

Outcomes	Pantoprazole	Placebo	Relative Risk (95% CI)*	P Value†
Primary outcome: death by day 90 — no./total no. (%)	510/1642 (31.1)	499/1640 (30.4)	1.02 (0.91–1.13)	0.76
Secondary outcomes				
One or more clinically important events — no./total no. (%)‡	360/1644 (21.9)	372/1647 (22.6)	0.96 (0.83–1.11)	—
One or more episodes of clinically important gastrointestinal bleeding — no./total no. (%)	41/1644 (2.5)	69/1647 (4.2)	0.58 (0.40–0.86)	—
One or more infectious adverse events — no./total no. (%)§	276/1644 (16.8)	279/1647 (16.9)	0.99 (0.84–1.16)	—
Severe adverse reaction — no./total no. (%)¶	0/1644 (0)	0/1647 (0)	—	—
Median percentage of days alive without the use of life support (IQR)‖	92 (60–97)	92 (65–97)	—	—

* Confidence intervals were not adjusted for the comparisons of multiple secondary outcomes.
† Logistic-regression analyses were adjusted for the stratification variables (site and hematologic cancer). The results of the unadjusted outcome analyses and the fully adjusted analyses are presented in Tables S4 and S6 in the Supplementary Appendix. Secondary outcomes are presented without P values because of the lack of adjustment for multiple comparisons.
‡ Clinically important events included clinically important gastrointestinal bleeding, pneumonia, *Clostridium difficile* infection, and myocardial ischemia.
§ Infectious adverse events included pneumonia and *C. difficile* infection.
¶ Severe adverse reactions were defined as anaphylactic reactions, agranulocytosis, pancytopenia, acute hepatic failure, the Stevens–Johnson syndrome, toxic epidermal necrolysis, interstitial nephritis, and angioedema related to the intervention (as judged by the treating clinicians and investigators).[14] Specific events that were adjudicated as not to being related to pantoprazole or placebo, including the reasoning behind each adjudication, are described in Table S11 in the Supplementary Appendix.
‖ The percentage of days alive without the use of life support was calculated as the number of days without the use of invasive or noninvasive mechanical ventilation, infusion of vasopressor or inotropic agents, or any form of renal-replacement therapy, divided by the number of days alive within the 90-day follow-up period.
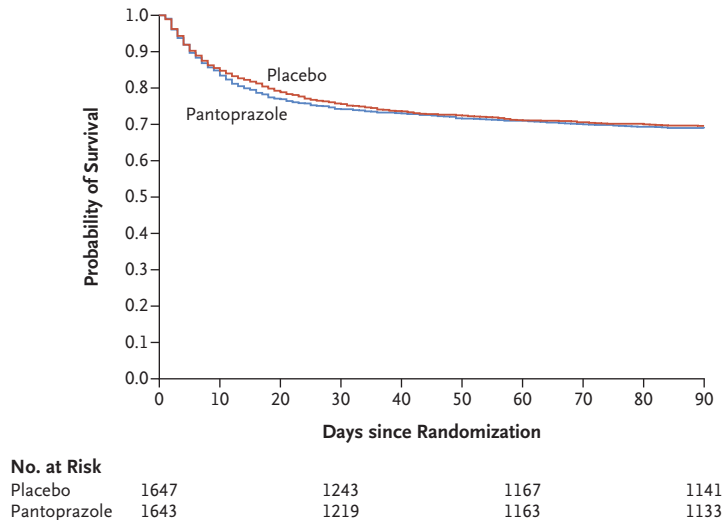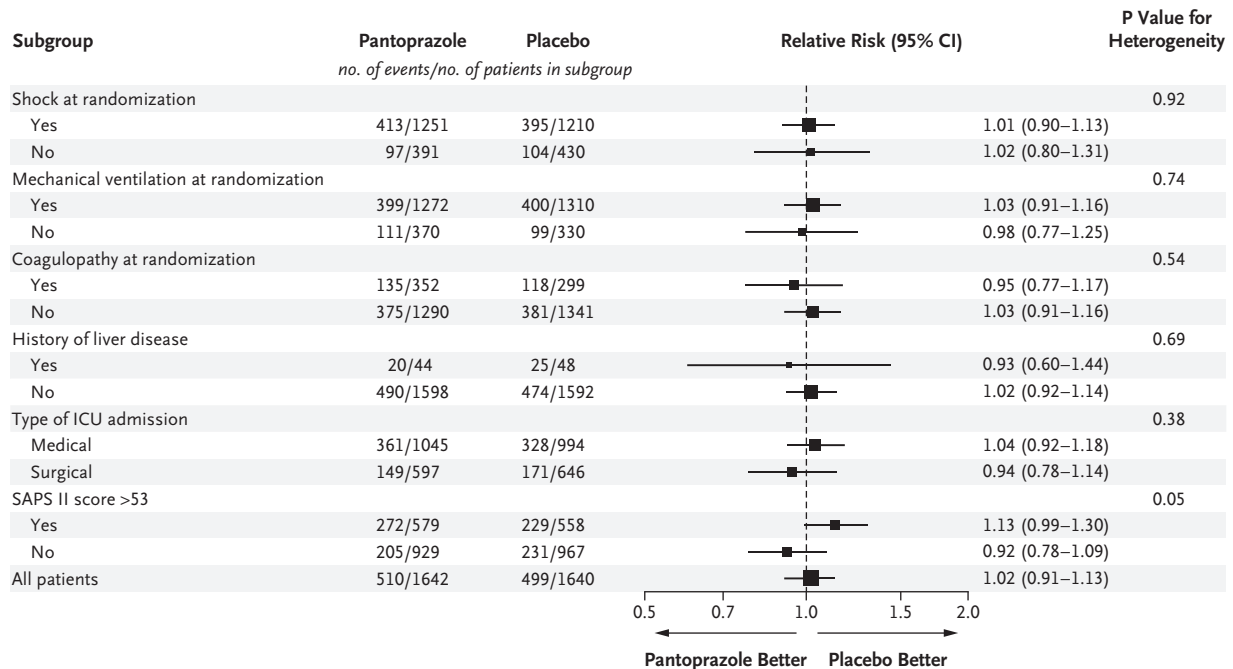
tant gastrointestinal bleeding, as compared with 69 (4.2%) in the placebo group. The proportions of patients in each group with the other secondary outcomes and with single components of the composite outcome were similar in the two groups and are shown in Table 2 without P values because of the lack of adjustment for multiple comparisons (also see Table S7 in the Supplementary Appendix). Details of the episodes of gastrointestinal bleeding are provided in Table S8 in the Supplementary Appendix.

DISCUSSION

In this international, blinded, placebo-controlled, randomized trial involving adult patients in the ICU who were at risk for gastrointestinal bleeding, we found that 90-day mortality, percentages of days alive without the use of life support, and numbers of patients with clinically important events, infectious adverse events, or serious adverse reactions were similar between those treated with pantoprazole and those who received placebo. Fewer patients in the pantoprazole group than in the placebo group had clinically impor-

tant gastrointestinal bleeding in the ICU, and the 95% confidence intervals (which were not adjusted for multiple comparisons) for the relative risk did not cross 1; however, the absence of correction for multiple comparisons of secondary outcomes limits inferences from this observation. The results of this trial apply only to patients who meet the entry criteria used in the trial, including a high risk of gastrointestinal bleeding.

Our results are similar to those obtained in a recent network meta-analysis, in which no significant differences were found in the rates of death or infectious complications between patients receiving placebo or no prophylaxis and those receiving proton-pump inhibitors; the latter group, however, did have lower rates of clinically important gastrointestinal bleeding.[22] The results of the current trial did not reproduce those of observational studies, which have suggested an increased risk of infectious complications and myocardial ischemia in association with the use of proton-pump inhibitors.[10-12] We found no significant differences between the pantoprazole group and the placebo group in the rates of these events in the full trial population, but we

A Time to Death

B Relative Risk of the Primary Outcome

Subgroup	Pantoprazole	Placebo	Relative Risk (95% CI)	Relative Risk (95% CI)	P Value for Heterogeneity
	no. of events/no. of patients in subgroup				
Shock at randomization					0.92
Yes	413/1251	395/1210		1.01 (0.90–1.13)	
No	97/391	104/430		1.02 (0.80–1.31)	
Mechanical ventilation at randomization					0.74
Yes	399/1272	400/1310		1.03 (0.91–1.16)	
No	111/370	99/330		0.98 (0.77–1.25)	
Coagulopathy at randomization					0.54
Yes	135/352	118/299		0.95 (0.77–1.17)	
No	375/1290	381/1341		1.03 (0.91–1.16)	
History of liver disease					0.69
Yes	20/44	25/48		0.93 (0.60–1.44)	
No	490/1598	474/1592		1.02 (0.92–1.14)	
Type of ICU admission					0.38
Medical	361/1045	328/994		1.04 (0.92–1.18)	
Surgical	149/597	171/646		0.94 (0.78–1.14)	
SAPS II score >53					0.05
Yes	272/579	229/558		1.13 (0.99–1.30)	
No	205/929	231/967		0.92 (0.78–1.09)	
All patients	510/1642	499/1640		1.02 (0.91–1.13)	

did find an interaction between the intervention effect and disease severity that suggested higher 90-day mortality among patients who had more severe disease and received pantoprazole. This may be a chance finding, but it warrants further study.

The strengths of our trial include the large sample size and variety of ICUs and countries involved, reflecting different practice patterns. The trial protocol was pragmatic, so that routine practice was maintained except for the prophylactic use of gastric acid suppressors.

Figure 2 (facing page). Time to Death and Relative Risk of Death at Day 90.

Panel A shows the survival curves with data censored at day 90 for the two groups in the intention-to-treat population. The nine patients who were lost to 90-day follow-up — two patients in the pantoprazole group and seven patients in the placebo group — were included in the survival curves until the last day they were known to be alive; at that time point, data from these patients were censored. One patient in the pantoprazole group was known to be dead at day 90, but the date of death was unknown. This patient was excluded from the survival curves. Panel B shows relative risks with 95% confidence intervals for the primary outcome measure of death at day 90 in the pantoprazole group as compared with the placebo group, among all the patients and in the six predefined subgroups, assessed by logistic-regression analysis with adjustment for the stratification variables. Shock was defined as at least one of the following: systolic blood pressure of less than 90 mm Hg, mean arterial pressure of less than 70 mm Hg, use of vasopressors or inotropes (norepinephrine, epinephrine, phenylephrine, vasopressin or dopamine, dobutamine, milrinone, or levosimendan), or a lactate level of more than 4 mmol per liter. Coagulopathy included both acute coagulopathy, defined as a platelet count of less than 50×10^9 per liter, an international normalized ratio of more than 1.5, or a prothrombin time of more than 20 seconds at ICU admission, and a history of coagulopathy, defined as coagulopathy within 6 months before hospital admission. A history of liver disease was defined as portal hypertension; cirrhosis proved by biopsy, computed tomography, or ultrasonography; history of variceal bleeding; or hepatic encephalopathy in the medical history. A medical admission was defined as a hospital admission during which no surgery was performed or an ICU admission in which surgery had been performed more than 1 week before admission. The Simplified Acute Physiology Score (SAPS) II was calculated from 17 baseline variables and ranges from 0 to 163, with higher scores indicating greater severity of disease. One or more variables were missing for 134 patients in the pantoprazole group and 115 patients in the placebo group for the calculation of the SAPS II; these patients were not included in the SAPS II subgroup analysis.

The limitations of the trial include the lack of assessment of other medical interventions and the limited power of the trial to detect differences in some outcome measures and in the subgroup analyses; in addition, the absence of reported serious adverse reactions to pantoprazole suggests underreporting, as may have occurred in another large trial of glucocorticoids in the ICU setting.[23] We did not mandate diagnostic endoscopy to assess the source of bleeding and were therefore unable to differentiate between stress ulcers and other causes of gastrointestinal bleeding. Some baseline variables differed between the groups, but the predefined secondary analysis adjusting for some of these differences supported the primary result. We did not determine whether patients had used acid suppressants before ICU admission or were receiving enteral nutrition at baseline. The composite secondary outcome we used is not one that is normally reported. Finally, the trial was powered for an absolute between-group difference in 90-day mortality of 5 percentage points, a margin that may be considered large.[24]

In conclusion, in this trial involving adult patients who were admitted to the ICU for an acute condition and were at risk for gastrointestinal bleeding, we found no significant differences between pantoprazole and placebo with regard to either 90-day mortality or the number of patients with a composite outcome of four clinically important events.

APPENDIX

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