EVIDENCE-BASED GI
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A PPI a Day Keeps the GI Bleed Away in the ICU

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This summary reviews Cook D, Deane A, Lauzier F et al. Stress ulcer prophylaxis during invasive mechanical ventilation. NEJM 2024; 391(1):9-20 .

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STRUCTURED ABSTRACT

Question: Does 40 mg intravenous pantoprazole daily reduce the risk of clinically important upper gastrointestinal (GI) bleeding in mechanically ventilated patients without increasing all-cause mortality or other adverse events?

Design: Investigator-initiated, randomized, placebo-controlled, multicenter, triple-blinded trial (REVISE trial) conducted between July 2019 to October 2023.

Setting: Sixty-eight hospitals in 8 countries (Australia, Brazil, Canada, England, Kuwait, Pakistan, Saudi Arabia and the United States).

Patients: Adults undergoing invasive mechanical ventilation in the intensive care unit (ICU).

Intervention: Participants received single daily dose of 40 mg pantoprazole IV or an identical placebo until discontinuation of invasive ventilation or 90 day threshold or occurrence of a pre-specified adverse event.

Outcomes: The primary efficacy outcome was clinically important upper GI bleeding defined as overt GI bleeding with evidence of hemodynamic compromise or leading to endoscopic/angiographic/surgical intervention in the ICU, occurring up to 90 days after randomization. The primary safety outcome was all-cause mortality at 90 days. Secondary outcomes included ventilator-associated pneumonia, treatment with renal-replacement therapy, ICU and hospital mortality, patient-important upper GI bleeding (i.e. receipt of at least one blood transfusion, vasopressors, receipt of diagnostic endoscopy, CT angiography, or surgery, outcomes of death, disability, or prolonged hospitalization). Tertiary outcomes included total number of red blood cell transfusions, peak serum creatinine level, duration of mechanical ventilation, hospital and ICU length of stay.

Data Analysis: Cox proportional-hazards analyses were performed for the primary efficacy and safety outcomes after adjusting for receipt of acid suppression before hospitalization. Outcomes were reported as hazard ratios and 95% confidence intervals along with absolute risk differences and Kaplan-Meier curves. Mortality outcomes were adjusted for baseline illness severity using the Acute Physiology and Chronic Health Evaluation (APACHE) II score. For the primary outcomes, subgroup analyses were also performed for: use of acid suppression before hospitalization, diagnosis on ICU admission, SARS-CoV-2 status, and sex.

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Results: During the study period, 4,821 patients were randomized with baseline characteristics similar between both trial arms. Pantoprazole or placebo was administered for a median of 5 days (interquartile range 3-10 days). Clinically important upper GI bleeding occurred significantly less in pantoprazole-treated patients vs placebo-treated patients (**Table 1**): 1% vs 3.5%, respectively; hazard ratio = 0.30, 95% confidence interval [CI], 0.19-0.47, $P<0.001$. Patient-important GI bleeding was also less frequent in pantoprazole-treated patients vs placebo-treated

patients: 1.5% vs 4.2%, respectively; hazard ratio=0.36; 95% CI 0.25-0.53, $P<0.001$.

	Pantoprazole arm	Placebo arm	Hazard Ratio (95% CI)
Clinically important upper GI bleeding	25/2,385 (1.0%)	84/2,377 (3.5%)	0.3 (0.19-0.47)
90-day mortality	696/2,390 (29.1%)	734/2,379 (30.9%)	0.94 (0.85-1.04)
Ventilator-associated pneumonia	556/2,394 (23.2%)	567/2,381 (23.8%)	1.0 (0.89-1.12)
***Clostridioides difficile* infection**	28/2,385 (1.2%)	16/2,377 (0.7%)	1.78 (0.96-3.29)
Patient important upper GI bleeding	36/2,385 (1.5%)	100/2,377 (4.2%)	0.36 (0.25-0.53)
New renal replacement therapy	146/2,385 (6.1%)	142/2,380 (6.0%)	1.04 (0.83-1.31)

Table 1. Efficacy and safety outcomes.

COMMENTARY

Why Is This Important?

Recent randomized trials investigating the benefits of proton pump inhibitor (PPI) prophylaxis among patients on mechanical ventilation in the ICU have shown different results with regards to outcomes of mortality and GI bleeding [1]. The PEPTIC trial (Proton Pump Inhibitors vs Histamine-2 Receptor Blockers for Ulcer Prophylaxis Treatment in the Intensive Care Unit) trial did not show any difference in in-hospital mortality among ICU patients receiving either PPI or H2RB [2]. Another multicenter trial (SUP-ICU) comparing pantoprazole prophylaxis to placebo showed that there was no difference in mortality at 90 days, and no difference in the number of clinically

important events, including GI bleeding, between both groups [3]. However, some of these studies reported composite outcomes. Importantly, these landmark trials suggested that stress ulcer prophylaxis with PPIs may increase mortality among severely ill patients requiring mechanical ventilation and could not exclude an increased risk of ventilator-associated pneumonia and *C. difficile* infection [2]. This potential gap in knowledge led current guidelines to offer only conditional or weak recommendations to use stress ulcer prophylaxis with PPIs in mechanically-ventilated patients.

Cook *et al* definitively address these issues in their large, multicenter, REVISE trial by conducting a rigorously designed RCT with an adequate sample size to overcome the limitations of the prior trials. [4] They are to be congratulated for this huge effort, which clearly demonstrate the benefits of PPI prophylaxis while also demonstrating their safety in this setting, even among patients with higher baseline severity of illness.

Key Study Findings

Stress ulcer prophylaxis 40 mg Pantoprazole IV daily was superior to placebo for lowering rates of clinically important upper GI bleeding (1% vs 3.5%, 95% CI 1.6 to 3.3%) in mechanically ventilated patients without any difference in 90-day mortality (29.1% vs 30.9%, HR = 0.94; 95% CI 0.85-1.04).

Importantly, subgroup analysis did not show an increased risk of death in the most severely ill patients receiving pantoprazole and in the subgroup of patients receiving PPI prior to hospitalization. Also, no difference was observed in infection-related adverse events, including ventilator associated pneumonia and *C. difficile* infection.

Caution

Overall, the REVISE trial is a large, adequately powered trial that addresses limitations from earlier trials which have led to varying results. The authors allude to the lack of patient-reported disability outcomes and the absence of data on microbiome modification in the setting of PPI prophylaxis. While their findings indicate that PPI use does not reduce risk of death in the subgroup of patients who are severely ill, it does underscores the impact of other patient factors such as previous health status on mortality outcomes in this group of patients.

My Practice

In my hospital, the decision to initiate stress ulcer prophylaxis is usually made by the intensive care team. Based on the available research, stress ulcer prophylaxis is appropriate in mechanically-ventilated patients with lower severity of illness (i.e., APACHE II score < 25) [5]. The decision to initiate prophylaxis in patients with higher illness severity (i.e., APACHE II score ≥ 25) may be individualized. Patients with higher illness severity with concurrent dual

antiplatelet therapy or combination anticoagulation are at higher risk of clinically important bleeding and most likely should get prophylaxis, although this group of patients were excluded from the REVISE study.

For Future Research

The REVISE trial was adequately powered to compare the major outcomes of efficacy and safety separately, not as composite outcomes and the conclusion that stress ulcer prophylaxis reduces the risk of upper GI bleeding in patients undergoing mechanical ventilation is based on robust data. The safety results with regards to all-cause mortality and infection-related complications are also reassuring.

Practically, it is common for ICU patients to be on twice a day PPI dosing and the REVISE trial data cannot be extrapolated to those patients, particularly among the subgroup of severely ill patients (APACHE II score ≥ 25) on mechanical ventilation. Also, patients on dual antiplatelet and combination antiplatelet and anticoagulation therapy are a unique group that was excluded from these landmark trials because of their high-risk for clinically important bleeding.

Conflict of Interest

Dr. Okafor reports no conflicts of interest.

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