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EDITORIAL

Could stress ulcer prophylaxis increase mortality in high-acuity patients?

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Clinically important upper gastrointestinal (GI) bleeding occurs in 1.6–3.6% of critically ill adults [1]. This complication is associated with prolonged intensive care unit (ICU) and hospital lengths of stay, and high mortality [1]. To reduce the risk of upper GI bleeding, nearly 75% of critically ill patients are given stress ulcer prophylaxis [1]. However, because clinically important upper GI bleeding is very uncommon in some patient groups, there remains uncertainty about the ubiquity of benefit from prophylaxis. Moreover, although the risks of nosocomial pneumonia [2–4] and *Clostridioides difficile* infection [2] associated with exposure to proton pump inhibitors (PPIs) in observational studies have not been confirmed in RCTs [5], the potential for harm in some patient groups still exists. Overall, it remains highly plausible that the balance of risks and benefits for stress ulcer prophylaxis differs depending on the patient's circumstances.

This background information highlights the importance of considering not only average treatment effects, but also whether there is heterogeneity of treatment effect (HTE), when evaluating data on the safety and efficacy of stress ulcer prophylaxis. The average treatment effect of an intervention is the difference in outcomes between the intervention and comparator groups when comparing all patients. HTE is when the treatment effect varies by one or more baseline characteristics in what appears to be a non-random fashion [6]. In the Stress Ulcer Prophylaxis in the Intensive Care Unit (SUP-ICU) trial [7], the largest placebo-controlled randomized clinical trial of stress ulcer prophylaxis in critically ill patients, there was no statistically significant mortality difference between the PPI and placebo groups, but patients randomized to receive PPIs had less clinically important upper GI bleeding. While these data suggest that PPIs are effective at preventing clinically important upper GI bleeding, how clinicians should act on them is complicated when one considers the possibility of HTE.

In relation to 90-day mortality, which was the primary outcome in the SUP-ICU trial [7], there was evidence of HTE in a pre-planned analysis evaluating the impact of baseline illness severity on the mortality treatment effect. Illness severity was determined using the Simplified Acute Physiology Score II (SAPS-II), which is a multivariable mortality risk score. The primary study findings raised concerns about the use of PPI prophylaxis for the sickest critically ill patients because such patients appeared to have a possible increase in mortality when randomized to receive PPIs (relative risk and 95% confidence interval (CI) for PPI vs. placebo, 1.13 (0.99–1.30) in those with a SAPS-II > 53 points vs. 0.92 (0.78–1.09) in those with a SAPS-II ≤ 53 points; $P = 0.05$ for interaction). Unfortunately, while HTE is intuitive clinically, it is notoriously difficult to identify empirically. A central problem is that trials are almost universally designed with sample sizes that are only sufficient to assess differences in average treatment effects. Thus, analyses among subgroups, even pre-planned ones, can lead to false-negative findings from inadequate power and false-positives from multiple testing [8–11]. Small sample sizes in subgroups also introduce imprecision in treatment effect estimates. In addition, subgroup analyses typically focus on a single characteristic that is similar within strata, when many other characteristics vary and may influence the observed HTE.

Because of these concerns, the signal towards harm in patients with high illness severity as measured by SAPS-II has motivated additional analyses. The SUP-ICU

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investigators have previously demonstrated that the observed HTE did not appear to be due to chance baseline imbalances between groups in high-acuity patients [12]. In this issue of *Intensive Care Medicine* [13], Granholm and colleagues provide a major methodological extension to their prior analysis [12] by incorporating Bayesian priors into the HTE analyses using Bayesian hierarchical logistic regression models [13]. The current approach [13] offers two substantial strengths. First, compared to the previous analysis [12], it further reduces the risk of type 1 errors. Second, it permits the concurrent assessment of the existence of HTE using several "prior" distributions. These prior distributions provide an empirical approach of impacting the effect estimate by formally weighting the analysis with assumptions regarding potential effect distributions [14]. The authors included a weakly informative prior centered on effect sizes informed by previous RCTs, but wide enough to encompass all plausible effect sizes, as well as a pessimistic prior favoring the placebo arm. By evaluating all these prior distributions, the authors were able to examine the robustness of the empirical result suggesting higher mortality among sicker patients (i.e., HTE). All of the analyses conducted suggested a small, but harmful impact of PPIs in patients with high illness acuity [13]. This included effects not just on 90-day mortality, but also on infectious adverse events. Importantly, HTE was observed both among patients with high illness severity (as measured by SAPS-II) and also in those with more risk factors for clinically important upper GI bleeding [13].

The results of the analysis by Granholm and colleagues [13] are particularly compelling when viewed together with the recently published Proton Pump Inhibitors versus Histamine-2 Receptor Blockers for Ulcer Prophylaxis Therapy in the Intensive Care Unit (PEPTIC) study [15]. The PEPTIC trial was a randomized, open-label, cluster-crossover trial that compared PPIs and histamine 2 receptor blockers (H_2RBs) for stress ulcer prophylaxis in 26,982 mechanically ventilated adults. In the PEPTIC trial [15], similar to the SUP-ICU trial [7], patients with high illness severity who were assigned to PPIs had higher mortality than comparator patients.

Based on the available evidence, we surmise that, although considerable uncertainty remains, the inferences from SUP-ICU and PEPTIC are consistent with the hypothesis that PPIs increase the risk of death in patients with higher illness severity. While, the overall evidence that PPIs reduce upper GI bleeding in the critically ill is unequivocal [5, 15], it appears that most upper GI bleeds are not fatal, and the attributable mortality from such bleeds appears to be low [16]. Therefore, we suspect that most patients would exchange the small increased risk of upper GI bleeding to avoid a therapy that might increase their risk of death, despite the uncertainty. These data are not definitive and further research is warranted, but for now, they are likely to be sufficient to prompt a shift by many clinicians away from the routine use of PPIs for stress ulcer prophylaxis in patients with high illness severity.

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Compliances with ethical standards

Conflicts of interest
MS-H is on the Editorial Board for ICM and declares no other competing interests. PY is the Chief Investigator for the PEPTIC trial and declares this as an academic conflict of interest.

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