European Journal of Cardio-Thoracic Surgery 2022, 62(2), ezac177
https://doi.org/10.1093/ejcts/ezac177 Advance Access publication 11 March 2022

INVITED COMMENTARY

Cite this article as: Glaser N, Sartipy U. Stress ulcer prophylaxis in the cardiac surgery intensive care unit. Eur J Cardiothorac Surg 2022; doi:10.1093/ejcts/ezac177.

Stress ulcer prophylaxis in the cardiac surgery intensive care unit

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In the current issue of the Journal, van Diepen *et al.* [1] report on the effectiveness and safety of proton pump inhibitors (PPIs) versus histamine-2 receptor blockers (H2RBs) for stress ulcer prophylaxis in the cardiac surgical intensive care unit population. This study question is important because the recent large PEPTIC trial [2] reported a higher risk of mortality in the PPI arm in a pre-specified subgroup analysis of cardiac surgical intensive care unit patients.

Because the current study was a secondary analysis specifically in cardiac surgery patients enrolled in the PEPTIC trial, a short summary of the PEPTIC trial is relevant for understanding, interpretation and assessment of the new findings. The PEPTIC trial was an international open-label, cluster crossover, registry-embedded randomized clinical trial comparing 2 approaches for stress ulcer prophylaxis implemented in the intensive care unit among adults requiring mechanical ventilation [2–4]. The trial compared 2 approaches for stress ulcer prophylaxis; PPI or H2RB by default when stress ulcer prophylaxis was prescribed. Clinicians decided whether individual patients would receive stress ulcer prophylaxis. Each intensive care unit used 1 approach for 6 months and then switched to the alternative approach for the next 6 months. In other words, when clinicians wanted to prescribe stress ulcer prophylaxis, the treatment of either PPI or H2RB was not blinded but determined by randomization status at the respective intensive care unit. The duration of stress ulcer prophylaxis was until discharge from the intensive care unit or the development of an upper gastrointestinal bleeding event, or stopped at the discretion of the treating clinician. The primary outcome was in-hospital all-cause mortality up to 90 days from intensive care unit admission and was obtained from registries. Other outcome measures included upper gastrointestinal bleeding, *Clostridium difficile* infection, and time spent in intensive care or in the hospital. The PEPTIC trial recruited 26 828 adult patients requiring invasive mechanical ventilation within 24 h of intensive care unit admission from 50 centres in Australia, Canada, Ireland, New Zealand and the UK from August 2016 through January 2019. Approximately one-third was admitted to the intensive care unit following elective surgery, and 18% after emergency surgery. The main finding of the PEPTIC trial was that in-hospital mortality was 18.3% vs 17.5% ($P = 0.054$) for patients treated at sites randomized to PPI use versus H2RB use, respectively. The authors therefore concluded that a strategy of PPIs versus H2RBs for stress ulcer prophylaxis among adults requiring mechanical ventilation did not result in a statistically significant difference for in-hospital mortality. Fewer patients in the PPI arm had clinically important upper gastrointestinal bleeding compared to the H2RB arm (1.3% vs 1.8%, $P = 0.009$). However, a pre-specified subgroup analysis in patients who had cardiac surgery showed a higher risk of mortality in the PPI arm versus the H2RB arm (risk ratio 1.27, 95% confidence interval 1.04–1.57).

In the present study [1], the authors report the results of a detailed *post hoc* exploratory analysis using data of the 1628 study participants enrolled at the cardiac surgery intensive care unit at the University of Alberta Hospital in Canada. The original PEPTIC study database was enriched by linking individual-level information from the hospital electronic medical records and 4 other administrative databases. By this procedure, the authors could acquire comprehensive information on demographics, APACHE III and SOFA scores, laboratory measurements, comorbidities and procedures (for the index hospitalization and also up to 5 years prior to surgery) and all prescription medications filled the first month following hospital discharge. As in the original PEPTIC trial, the main outcome measure was in-hospital mortality up to 90 days. A number of secondary outcomes (including upper gastrointestinal bleeding) were also assessed. As in the main PEPTIC trial, cross-over was more frequent in the H2RB arm compared to the PPI arm. The main findings were that no differences in (i) all-cause in-hospital mortality and (ii) upper gastrointestinal bleeding between patients in the PPI or H2RB arms were observed. The incidence of upper gastrointestinal bleeding was higher in the current analysis compared to the original PEPTIC trial. However, as noted by the authors, this may be explained by more chronic kidney disease, aspirin and anticoagulant use. Some caution in interpretation is advised, in particular the results from the subgroup analyses, due to statistical power issues and a limited number of events.

The authors should be commended for performing a rigorous and granular study, initiated by a signal of concern in a subset of patients from a large trial database. It is noteworthy and remarkable that they collected and analysed new information from

several other sources, not available in the original trial. The findings are relevant for clinicians caring for these patients.

Taken together, these results provide some reassurance that stress ulcer prophylaxis using either PPI or H2RB is reasonable in the cardiac surgery intensive care unit. Despite the troubling signal from the main PEPTIC trial of an increased mortality related to PPI use for stress ulcer prophylaxis in the cardiac surgery population, the present study dives deeper into the issue and suggests that both strategies remain sensible options. Going forward, perhaps the best strategy for stress ulcer prophylaxis in the cardiac surgery intensive care unit is to refine our surgical procedures to obviate the need for intensive care altogether.

Funding

Ulrik Sartipy was supported by the Swedish Heart–Lung Foundation (grant number 20190533) and grants provided by Region Stockholm (ALF project) (grant numbers 20180114 and RS2020-0731).

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