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Pantoprazole in ICU patients at risk for gastrointestinal bleeding—1-year mortality in the SUP-ICU trial

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Background: The long-term effects of stress ulcer prophylaxis with pantoprazole are unknown in ICU patients. We report 1-year mortality outcome in the Stress Ulcer Prophylaxis in the Intensive Care Unit (SUP-ICU) trial.

Methods: In the SUP-ICU trial, acutely admitted adult ICU patients at risk of gastrointestinal bleeding were randomised to intravenous pantoprazole 40 mg vs placebo...
1 | INTRODUCTION

Patients suffering from critical illness are at risk of developing clinically important gastrointestinal (GI) bleeding due to stress ulcers, which has been suggested to be associated with adverse outcomes, including a two- to fourfold increased length of ICU stay and risk of death. To prevent GI bleeding, stress ulcer prophylaxis is recommended in current international guidelines and acid suppressants are widely used in ICU patients.

In the international Stress Ulcer Prophylaxis in the Intensive Care Unit (SUP-ICU) trial, 3350 patients at risk of GI bleeding were randomised to receive either pantoprazole or placebo during the ICU stay. We did not observe a difference between the pantoprazole and placebo groups in the primary outcome measure—90-day mortality. However, a predefined subgroup analysis suggested a higher 90-day mortality in the pantoprazole group among patients who had a Simplified Acute Physiology Score (SAPS) II > 53 points. This finding was not readily explainable by baseline imbalances, process variables, differences in the other outcome measures or by serious adverse events from pantoprazole, but may potentially be affected by missingness for SAPS II in the original subgroup analysis.

The long-term effects of stress ulcer prophylaxis in the ICU are unknown. In this paper, we report the results of the pre-planned secondary outcome measure—1-year post-randomisation landmark mortality—in the SUP-ICU trial.

2 | METHODS

2.1 | Study oversight

The trial protocol, statistical analysis plan and primary results have been published elsewhere. The SUP-ICU trial was approved by all relevant institutions prior to randomisation of the first patient, and we obtained written informed consent from all patients or their legal surrogates according to the national regulations. We have prepared this manuscript according to the Consolidated Standards of Reporting Trials (CONSORT) statement; the filled-in checklist is presented in Appendix S1.

2.2 | The SUP-ICU trial

The SUP-ICU trial was a randomised, multicentre, stratified, parallel-group, placebo-controlled, blinded clinical trial recruiting 3350 patients at risk for GI bleeding, of which 3291 were included in the intention-to-treat population (after excluding 52 patients randomised in error who never received trial medication and 7 patients who withdrew consent for the use of their data). Patients were included in 33 ICUs in Denmark, Finland, Norway, Switzerland, the Netherlands and the United Kingdom from 4 January 2016 to 22 October 2017.

Editorial Comment

This study reports the pre-planned 1-year mortality outcome of the SUP-ICU (Stress Ulcer Prophylaxis in the Intensive Care Unit) trial investigating the use of intravenous pantoprazole (40 mg once daily) or placebo. Here, 3261 patients admitted to ICU and at risk of gastrointestinal bleeding allocated to stress ulcer prophylaxis with pantoprazole or placebo during the ICU stay. (The SUP-ICU trial was funded by Innovation Fund Denmark and others; ClinicalTrials.gov number, NCT02467621).
### TABLE 1  Baseline characteristics of trial patients followed up at 1 year

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pantoprazole (N = 1635)</th>
<th>Placebo (N = 1626)</th>
<th>All patients (N = 3261)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age—years</td>
<td>67 (56–76)</td>
<td>67 (55–75)</td>
<td>67 (56–75)</td>
</tr>
<tr>
<td>Male—no. (%)</td>
<td>1034 (63)</td>
<td>1048 (64)</td>
<td>2082 (64)</td>
</tr>
<tr>
<td>Co-morbidities—no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic lung diseasea</td>
<td>351 (21)</td>
<td>304 (19)</td>
<td>655 (20)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>154 (9)</td>
<td>142 (9)</td>
<td>296 (9)</td>
</tr>
<tr>
<td>Chronic heart failure (NYHA III-IV)b</td>
<td>100 (6)</td>
<td>99 (6)</td>
<td>199 (6)</td>
</tr>
<tr>
<td>Use of glucocorticoidsc</td>
<td>35 (2)</td>
<td>27 (2)</td>
<td>62 (2)</td>
</tr>
<tr>
<td>Haematological malignancyd</td>
<td>64 (4)</td>
<td>55 (3)</td>
<td>119 (4)</td>
</tr>
<tr>
<td>Metastatic cancerf</td>
<td>56 (3)</td>
<td>55 (3)</td>
<td>111 (3)</td>
</tr>
<tr>
<td>AIDSf</td>
<td>6 (0.4)</td>
<td>1 (0.1)</td>
<td>7 (0.2)</td>
</tr>
<tr>
<td>Coagulopathyg</td>
<td>352 (22)</td>
<td>296 (18)</td>
<td>648 (20)</td>
</tr>
<tr>
<td>Admitted to university hospital—no. (%)</td>
<td>1175 (72)</td>
<td>1168 (72)</td>
<td>2343 (72)</td>
</tr>
<tr>
<td>Hours from ICU admission to randomisation</td>
<td>15 (5-28)</td>
<td>14 (6-25)</td>
<td>15 (5-26)</td>
</tr>
<tr>
<td>Days from hospital admission to randomisation</td>
<td>1 (1-3)</td>
<td>1 (1-3)</td>
<td>1 (1-3)</td>
</tr>
<tr>
<td>ICU admission type—no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td>1040 (64)</td>
<td>988 (61)</td>
<td>2028 (62)</td>
</tr>
<tr>
<td>Emergency surgery</td>
<td>488 (30)</td>
<td>548 (34)</td>
<td>1036 (32)</td>
</tr>
<tr>
<td>Elective surgery</td>
<td>107 (7)</td>
<td>90 (6)</td>
<td>197 (6)</td>
</tr>
<tr>
<td>Use of invasive mechanical ventilation</td>
<td>1266 (77)</td>
<td>1298 (80)</td>
<td>2564 (79)</td>
</tr>
<tr>
<td>Use of vasopressors or inotropes</td>
<td>1097 (67)</td>
<td>1078 (66)</td>
<td>2175 (67)</td>
</tr>
<tr>
<td>Use of acute renal replacement therapy</td>
<td>122 (8)</td>
<td>98 (6)</td>
<td>220 (7)</td>
</tr>
<tr>
<td>SAPS IIh</td>
<td>49 (39-59)</td>
<td>48 (38-59)</td>
<td>48 (38-59)</td>
</tr>
<tr>
<td>SOFA scorei</td>
<td>9 (7-11)</td>
<td>9 (7-11)</td>
<td>9 (7-11)</td>
</tr>
</tbody>
</table>

aChronic 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 admission to hospital

bChronic heart failure was defined as New York Heart Association Functional Class (NYHA) III-IV. NYHA III: the patient has marked limitations in physical activity due to symptoms (fatigue, palpitation or dyspnoea) even during less than ordinary activity (walking short distances 20-100 m. or walking up stairs to first floor). The patient is only comfortable at rest. NYHA IV: the patient is not able to carry out any physical activity without discomfort (fatigue, palpitation or dyspnoea). Symptoms are present even at rest and the patient is mostly bedbound

cUse of corticosteroids was defined as patients treated with at least 0.3 mg/kg/day of prednisolone equivalent for at least 1 month in the 6 months prior to ICU admission

dHaematological malignancy includes any of the following: acute lymphoblastic leukaemia, acute myelogenous leukaemia, chronic myelogenous leukaemia, chronic lymphocytic leukaemia, Hodgkin's disease, Non-Hodgkin lymphoma (eg small lymphocytic lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, hairy cell leukaemia, marginal zone lymphoma, Burkitt’s lymphoma, post-transplant lymphoproliferative disorder, T-cell prolymphocytic leukaemia, B-cell prolymphocytic leukaemia, Waldenström’s macroglobulinemia, other NK- or T-cell lymphomas) and multiple myeloma/plasma cell myeloma

eMetastatic cancer: proven metastasis by surgery, computed tomography (CT) scan or any other method

fAcquired Immune Deficiency Syndrome (AIDS) was defined as HIV positive patients with one or more AIDS defining diseases such as Pneumocystis jiroveci pneumonia, Kapozi’s sarcoma, lymphoma, tuberculosis or toxoplasma infection

gCoagulopathy included both acute coagulopathies defined as platelets <50 × 10^9/l or international normalised ratio >1.5 or prothrombin time >20 seconds at ICU admission and history of coagulopathy defined as coagulopathy within 6 months prior to hospital admission

hIn the 24 hours prior to randomisation. The Simplified Acute Physiology Score (SAPS) II is calculated from 17 variables and ranges from 0 to 163 with higher scores indicating higher severity of disease (Table S1 in Appendix S1). Variables were missing in 133 patients in the pantoprazole group and 115 patients in the placebo group and their values are not included here

iIn the 24 hours prior to randomisation. The Sepsis-related Organ Failure Assessment (SOFA) score grades organ failure with sub-scoring ranging from 0 to 4 for each of six organ systems (cerebral, circulation, lungs, liver, kidney and coagulation). The aggregated score ranges from 0 to 24 with higher scores indicating more severe organ failure (Table S2 in Appendix S1). Variables were missing in 108 patients in the pantoprazole group and 85 patients in the placebo group and their values were not included here

*Values with ranges are medians (interquartile ranges). Full list of risk factors for GI bleeding is provided in Appendix S1.
older, who were acutely admitted to the ICU and had at least one risk factor for clinically important GI bleeding, including any history of liver disease, any history of or ongoing coagulopathy, shock, use of anticoagulant agents, renal replacement therapy, or mechanical ventilation expected to last at least 24 hours.\textsuperscript{1}

We excluded patients with GI bleeding during current hospital admission, ongoing daily treatment with acid suppressants, patients who were withdrawn from active treatment or were brain dead, had organ transplant during current hospital admission, had peptic ulcer confirmed by endoscopy or other method during current hospital admission, had a contraindication to pantoprazole, were pregnant or where consent for enrolment could not be obtained. The full definitions of the inclusion and exclusion criteria are presented in the Appendix S1.

Patients were randomly assigned to daily intravenous pantoprazole 40 mg or matching placebo during ICU stay. Randomisation was stratified according to the presence or absence of haematological malignancy and trial site. The intervention period lasted until discharge from the ICU to a maximum of 90 days. The trial intervention was reintroduced at readmissions to a trial ICU within this period. Apart from the use of stress ulcer prophylaxis, all other parts of patient care were at the discretion of the clinicians.

2.3 | Outcomes

This is the report of the pre-planned long-term secondary outcome in the SUP-ICU trial; 1-year post-randomisation landmark mortality,\textsuperscript{1} which was obtained from national or regional registries or by direct contact to patients or surrogates if available.

2.4 | Statistical analyses

We performed the analyses of 1-year mortality in accordance with the published SUP-ICU trial statistical analysis plan (SAP).\textsuperscript{8}

We conducted the primary analysis of 1-year landmark mortality in the intention-to-treat population. In the primary analysis, we compared data in the two allocation groups by binary logistic regression analysis adjusted for the stratification variables (trial site and active haematological malignancy); relative risks with 95% confidence intervals were computed from odds ratios as detailed in the SAP.\textsuperscript{8} In sensitivity analyses, we compared the primary outcome in the per-protocol population (excluding patients having one or more major protocol violations [see definition in Appendix S1])\textsuperscript{8}, and in the originally prespecified subgroups, defined by the presence or absence of any history of liver disease, the presence or absence of any history of or ongoing coagulopathy, the type of ICU admission (medical vs surgical), the presence or absence of shock, the use or not of mechanical ventilation and baseline disease severity as SAPS II of >53 vs ≤53.\textsuperscript{8} We also compared 1-year landmark mortality using binary logistic regression analyses 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 randomisation). We performed no adjustment for multiple comparisons and reported results as point estimates with 95% confidence intervals.

Follow-up of the last enroled trial patients was performed 22 October 2018. Thirty patients (0.9%) were lost to 1-year follow-up. Accordingly, complete-case analysis was the main outcome analysis.\textsuperscript{8} All analyses were performed using SAS software, version 9.4, and R software, version 3.4.1 and 3.4.3.

3 | RESULTS

A total of 3261 of 3291 patients (99.1%) were followed up at 1 year (365 days) after randomisation; 1635 assigned to pantoprazole and 1626 assigned to placebo. Thirty patients were lost to follow-up (0.9%) (CONSORT diagram included as Figure S1 in Appendix S1): the majority due to emigration, and some due to not giving consent for 1-year follow-up.

The median age was 67 (interquartile range, 56-75) and 2082 (64%) were male. We found that 2564 (79%) were mechanically ventilated at baseline, 2028 (62%) were medical ICU patients and 2343 (72%) were admitted to university hospital ICUs (Table 1).

One year after randomisation, 610 of 1635 patients (37.3%) in the pantoprazole group and 601 of 1626 (37.0%) in the placebo group had died (relative risk, 1.01; 95% confidence interval 0.92-1.10) (Table 2 and Figure 1: part A).

The results were consistent in the sensitivity analysis adjusted for baseline risk factors (relative risk, 1.00; 95% confidence interval 0.90 to 1.10) and those in the per-protocol population (relative risk, 0.99; 95% confidence interval 0.89 to 1.09) (Table 2). In the predefined subgroup analyses, we did not observe heterogeneity in the effect of pantoprazole vs placebo on 1-year mortality (Figure 1: part B).

4 | DISCUSSION

We did not observe a difference in 1-year mortality between patients randomised to pantoprazole or placebo in the SUP-ICU trial. This was consistent in sensitivity and subgroup analyses. These results bring valuable insights to the long-term safety of the prophylactic use of pantoprazole in adult ICU patients at risk of GI bleeding.

The finding of no difference in 1-year mortality supports the conclusion of the main paper showing no difference in the primary outcome, 90-day mortality, or the composite main secondary outcome clinically important events.\textsuperscript{6} The result is also in line with a recently updated meta-analysis from a systematic review of proton-pump inhibitors or histamine-2 receptor antagonists vs placebo or no prophylaxis in adult ICU patients where a 20% relative change in mortality could be refuted.\textsuperscript{50} In this meta-analysis the occurrence of any GI bleeding was significantly reduced compared with placebo or no prophylaxis, however, firm evidence for a reduction in clinically important GI bleeding could not be reached. Furthermore, the
systematic review was inconclusive regarding potential serious adverse events, including pneumonia, *Clostridium difficile* infection and myocardial ischaemia.\(^9\)

We did not find indications of heterogeneity in the treatment effect in any of the pre-planned subgroup analyses, including the presence or absence of any history of liver disease, the presence or absence of any history of or ongoing coagulopathy, the type of ICU admission (medical or surgical), the presence or absence of shock, the use or not of mechanical ventilation and SAPS II >53 vs ≤53. Accordingly, these results do not confirm a harmful effect of pantoprazole among the most severely ill ICU patients as suggested in the subgroup analysis on SAPS II >53 vs ≤53 on 90-day mortality.\(^5\)

We have previously investigated this aspect without finding explanations for these observations in baseline data, process variables or the other trial outcome measures, however, missing SAPS II data for some of the patients (6.7% in SUP-ICU trial cohort) seemed to explain a part of the observed subgroup effect in the 90-day mortality data.\(^7\)

The strengths of this study include the large sample size enrolled from 33 ICUs across Europe with resulting high external validity, and more than 99% follow-up for 1-year mortality. The trial design was pragmatic, and the protocol allowed routine practice to be maintained apart from stress ulcer prophylaxis. Additionally, the outcome was prespecified and analyses were performed in accordance with the pre-published protocol and statistical analysis plan.

The following limitations apply. First, the trial was powered to detect a 5% absolute between-group difference in the primary outcome (90-day mortality), which may be considered large.\(^11\) Despite a relative risk close to 1.00 and a relatively narrow 95% CI, a smaller than 5% absolute difference in mortality may exist. Second, some baseline variables differed between the groups,\(^6\) but the predefined secondary analysis adjusting for some of these differences supported the primary result. Finally, it should be noted that we did not assess other medical interventions, registered whether patients used acid suppressants before ICU admission or were receiving enteral nutrition at baseline.

Taken together, we now have high quality data on short-term outcomes, including an updated systematic review,\(^10\) and longer-term mortality suggesting that stress ulcer prophylaxis with pantoprazole does not affect all-cause mortality in adult ICU patients with risk factors for GI bleeding. Some of the remaining uncertainties regarding the use of acid suppressants in adult ICU patients relates to patient selection, that is, should we use stress ulcer prophylaxis in all ICU patients or should we limit the use to patients at high risk for GI bleeding? or even restrict use of proton-pump inhibitors to patients exhibiting signs of GI bleeding. Some of the other remaining unanswered questions include whether the effects of stress ulcer prophylaxis are affected by enteral nutrition, how large a proportion of GI bleedings in ICU patients that can be prevented by acid suppressants,\(^12\) what is the balance between the benefits and harms of stress ulcer prophylaxis outside the ICU,\(^13\) whether stress ulcer prophylaxis in the ICU is cost-effective,\(^1,18\) whether proton-pump inhibitors are superior to histamine-2 receptor antagonists,\(^14\) and whether stress ulcer prophylaxis should be used in critically ill children.\(^15\)

In conclusion, we did not find a difference in 1-year mortality in adult ICU patients at risk of GI bleeding allocated to stress ulcer prophylaxis with pantoprazole as compared with placebo.

**ACKNOWLEDGEMENTS**

The authors thank everybody involved in the SUP-ICU trial: research staff and investigators, clinical staff, patients and their relatives. The SUP-ICU trial was funded by Innovation Fund Denmark (4108-00011A) and supported by Rigshospitalet, the Capital Region of Denmark, the Regions of Denmark, the Scandinavian Society of Anaesthesiology and Intensive Care Medicine, Ehrenreich’s Foundation, Aase and Ejnar Danielsens Foundation, the Danish Society of Anaesthesiology and Intensive Care Medicine, the Danish Medical Association and the European Society of Intensive Care Medicine.

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**TABLE 2** Outcome measures

<table>
<thead>
<tr>
<th>Death at one year</th>
<th>Pantoprazole</th>
<th>Placebo</th>
<th>Relative Risk (95% CI)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>no./total no. (%)</td>
<td>610/1635 (37.3)</td>
<td>601/1626 (37.0)</td>
<td>1.01 (0.92-1.10)</td>
</tr>
<tr>
<td>Primary analysis adjusted for stratification variables(^b)</td>
<td>612/1644 (37.2)</td>
<td>607/1647 (36.8)</td>
<td>0.99 (0.90-1.09)</td>
</tr>
<tr>
<td>Secondary analysis adjusted for stratification and design variables(^c)</td>
<td>511/1423 (35.9)</td>
<td>517/1423 (36.3)</td>
<td>0.99 (0.89-1.09)</td>
</tr>
<tr>
<td>Per-protocol analysis(^d)</td>
<td>510/1635 (37.3)</td>
<td>601/1626 (37.0)</td>
<td>1.01 (0.92-1.10)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; ICU, intensive care unit.

\(^a\)Confidence intervals were not adjusted for multiple comparisons. P-values are not reported for the same reason.

\(^b\)The primary analysis was a logistic regression analysis adjusted for the stratification variables (haematological malignancy and site).

\(^c\)The secondary analysis was adjusted for stratification and design variables (age, type of admission (medical, elective surgery or emergency surgery) and Sepsis-related Organ Failure Assessment (SOFA) score). The SOFA score had more than 5% missing variables. We therefore used multiple imputation with 25 imputed data sets. Imputations were simultaneously made for missing 1-year mortality (the only other variable in the model with missing data). Number of deaths reported in this analysis was calculated as a mean of the 25 imputed datasets rounded to nearest whole number.

\(^d\)The per-protocol population excludes patients with one or more major protocol violations.
CONFLICT OF INTEREST

All authors were involved in the conduct of the SUP-ICU trial. The Department of Intensive Care at Rigshospitalet receives support for other research projects from Ferring Pharmaceuticals, Denmark; and the Novo Nordisk Foundation, Denmark. Dr. Elkmann holds stocks in TEVA pharmaceutical industries, a manufacturer of pantoprazole. The investment is below USD 5000. Dr. Scheinfeld reports grants from Orion Pharma, Abbott Nutrition International, B. Braun Medical AG, CSEM AG, Edwards Lifesciences Services GmbH, Kenta Biotech Ltd, Maquet Critical Care AB, Omnicare Clinical Research AG, Nestle, Pierre Fabre Pharma AG, Pfizer, Bard Medica S.A., Abbott AG, Anandic Medical Systems, Pan Gas AG Healthcare, Bracco, Hamilton Medical AG, Fresenius Kabi, Getinge Group Maquet AG, Dräger AG, Teleflex Medical GMBH, Glaxo Smith Kline, Merck Sharp and Dohme AG, Eli Lilly and Company, Baxter, Astellas, Astra Zeneca, CSL Behring, Novartis, Covidien, and Nycomed outside the submitted work. The money went into departmental funds. No personal financial gain applied. The other authors declare no direct conflict of interests. Full disclosures of other departmental funding are available at NEJM.org.

AUTHORS’ CONTRIBUTIONS

SM and MHM wrote the first draft of the manuscript. TL, SM and AG conducted all statistical analyses and drafted the tables/figures. SM, MK, AP, JW, TL, AG and MHM revised the initial draft of the manuscript. The authors mentioned above and MPW, MB (Borthwick), SB, FK, ABG, JCS, BS, MB (Bestle), BA, JHL, MKK, ML, MP-D, SK, JL, ND and HK (all authors) helped to draft the final manuscript and revised it for important intellectual content. All authors read and approved the final version of the manuscript. MHM was the sponsor of the SUP-ICU trial and SM and MK are responsible for the SUP-ICU trial database.
REFERENCES


SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.