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Heterogeneity of treatment effect of stress ulcer prophylaxis in ICU patients: A secondary analysis protocol

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Background: In the Stress Ulcer Prophylaxis in the Intensive Care Unit (SUP-ICU) trial, 3291 adult ICU patients at risk for gastrointestinal (GI) bleeding were randomly allocated to intravenous pantoprazole 40 mg or placebo once daily in the ICU. No difference was observed between the groups in the primary outcome 90-day mortality or the secondary outcomes, except for clinically important gastrointestinal bleeding. However, heterogeneity of treatment effect (HTE) not detected by conventional subgroup analyses could be present.

Methods: This is a protocol and statistical analysis plan for a secondary, *post hoc*, exploratory analysis of the SUP-ICU trial. We will explore HTE in one set of subgroups based on severity of illness (using the Simplified Acute Physiology Score [SAPS] II) and another set of subgroups based on the total number of risk factors for GI bleeding in each patient using Bayesian hierarchical models. We will summarise posterior probability distributions using medians and 95% credible intervals and present probabilities for different levels of benefit and harm of the intervention in each subgroup. Finally, we will assess if the treatment effect interacts with SAPS II and the number of risk factors separately on the continuous scale using marginal effects plots.

Conclusions: The outlined *post hoc* analysis will explore whether HTE was present in the SUP-ICU trial and may help answer some of the remaining questions regarding the balance between benefits and harms of pantoprazole in ICU patients at risk of GI bleeding.

ClinicalTrials.gov registration: NCT02467621.

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1 | INTRODUCTION

Critically ill patients in the intensive care unit (ICU) are at risk of developing stress-related gastrointestinal (GI) ulcers, which may lead to clinically important GI bleeding (CIB) that have been associated with increased risk of death.[1] Despite the low incidence of CIB, the majority of ICU patients receive stress ulcer prophylaxis (SUP) with acid suppressants.[2] The balance between the benefits and harms of SUP has been questioned, and it has been suggested that SUP may increase the risk of infectious complications (including pneumonia and *Clostridium difficile* enteritis) and myocardial ischemia.[3,4]

In the recently published SUP-ICU trial — the largest trial to date comparing SUP (in the form of the proton pump inhibitor pantoprazole) with placebo — there was no difference in the primary outcome of 90-day mortality or the main secondary outcome clinically important events; a lower incidence of CIB was observed in patients allocated to SUP.[5]

Following the SUP-ICU trial, an updated systematic review with meta-analysis and Trial Sequential Analysis[6] reinforced these findings.[7]

While it appears that on average the effect of SUP on mortality was neutral, heterogeneity of treatment effect (HTE) could be present,[8,9] and it is possible that some patients may be more likely to either benefit or be harmed from SUP than others. In the predefined, traditional, one-variable-at-a-time subgroup analyses of the SUP-ICU trial, no heterogeneity between subgroups was found, except when comparing patients with a baseline Simplified Acute Physiology Score (SAPS) II[10] — a severity of illness score and risk prediction model — of ≤53 versus >53.[5] In a detailed secondary exploratory analysis conducted in the subgroup of patients with SAPS II >53, higher 90-day mortality was observed in the group allocated to SUP.[11] However, when accounting for missing data for SAPS II, the 95% confidence intervals included no difference, and it remains uncertain if this represents a chance finding or a true signal.[11]

In the outlined secondary, exploratory, *post hoc* analysis of the SUP-ICU trial, we aim to explore HTE according to severity of illness and the total number of risk factors for CIB. We hypothesise that HTE may be present, and that (a) more severely ill patients may be more likely to be harmed from SUP (increased mortality and infectious adverse events); and (b) patients with more risk factors for CIB may be more likely to benefit from SUP (decreased CIB).

2 | METHODS

2.1 | Study design

This protocol and statistical analysis plan outlines the rationale and methodology for a secondary, exploratory, *post hoc* analysis of the SUP-ICU trial.[5] The protocol has been prepared after the results of the SUP-ICU trial were available, but before any of the analyses described here-in have been conducted. The protocol was prepared according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement[12] (completed checklist included in the Supplement), and concepts specific to the Bayesian analyses adhere to the Reporting Of Bayes Used in clinical STudies (ROBUST) guideline.[13]

2.2 | Patients and the SUP-ICU trial

This study will be conducted using data from all patients included in the intention-to-treat population of the SUP-ICU trial.

The SUP-ICU trial was an international, multicentre, parallel-group, investigator-initiated, blinded clinical trial.[5] Adult patients (≥18 years of age) who were acutely admitted to the ICU with one or more risk factors for GI bleeding were randomised to either SUP (pantoprazole 40 mg) or matching placebo (saline) intravenously once daily while in the ICU for a maximum of 90 days. Exclusion criteria were mainly related to previous GI bleeding during the index hospitalisation, ongoing treatment with acid suppressants or contraindications to pantoprazole. Enrolment took place from 4 January 2016 through 22 October 2017.

The SUP-ICU trial was approved by the Danish Health and Medicine Agency (2015030166), the Committee on Health Research Ethics in the Capital Region of Denmark (H-16036586; with additional local/national ethics approvals as required),[14] by the Danish Data Protection Agency (RH-2015-3203695) and registered at ClinicalTrials.gov (NCT02467621).

2.3 | Definitions

- 90-day mortality: vital status 90 days after randomisation
- Clinically important GI bleeding (CIB): overt GI bleeding (haematemesis, coffee ground emesis, melaena, haematochezia or bloody nasogastric aspirate) and at least one of the following four features within 24 hours of GI bleeding in the absence of other causes: spontaneous decrease in systolic/diastolic/mean arterial blood pressure of ≥20 mmHg; vasopressor treatment or increase in vasopressor dose of ≥ 20%; decrease in haemoglobin of ≥2 g/dL [1.24 mmol/L]; or transfusion of ≥ 2 units of packed red blood cells
- Infectious adverse events: new-onset pneumonia or *Clostridium difficile* infection
- Clinically important events: composite outcome consisting of one or more of the following: CIB, infectious adverse events or acute myocardial ischemia

Additional details and definitions are available in the supplement and elsewhere.[5,14,15]

2.4 | Outcomes

We will assess the following outcomes of the SUP-ICU trial in this study:

Primary outcome:
- 90-day mortality

Secondary outcomes:

1. Clinically important events
2. Clinically important GI bleeding (CIB)
3. Infectious adverse events

Ninety-day mortality data were obtained by local trial investigators (including use of national and regional registries where possible) and all secondary outcomes were followed-up in-ICU only (including transfers to other participating ICUs and re-admissions) for a maximum of 90 days.

2.5 | Statistical analyses

All statistical analyses will be conducted using R (R Core Team, R Foundation for Statistical Computing) and Stan[16] primarily through the *brms*[17] R package. This statistical analysis plan has been prepared according to recent recommendations[8,9] and informed by a recent HTE analysis of the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial[18] by Zampieri and colleagues.[19]

2.5.1 | Subgrouping

We will assess the presence of HTE in the SUP-ICU trial based on two subgrouping schemes.

First, we will subgroup patients in fifths based on SAPS II quintiles. Second, we will subgroup patients based on their total number of risk factors (trial inclusion criteria) for CIB:

- shock
- renal replacement therapy (RRT; acute or chronic intermittent or continuous RRT)
- invasive mechanical ventilation
- coagulopathy (acute *or* within 6 months prior to hospitalization)
- ongoing treatment with anticoagulant drugs (prophylactic doses excluded)
- history of chronic liver disease

Accordingly, 6 mutually exclusive subgroups will be created based on the total number of risk factors in each patient (from 1 to 6). If any subgroup contains few (<300) patients, we will pool adjacent subgroups.

2.5.2 | Baseline data

We will present baseline data including the risk factors mentioned above, age, sex, SAPS II, Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score,[20] presence or absence of haematological malignancy and admission type (medical, elective surgical or emergency surgical) in all patients and in each subgroup as medians with interquartile ranges (IQRs) for numeric variables and numbers with percentages for categorical variables.

We will graphically present the distribution of SAPS II according to the number of risk factors. We expect these variables to be linearly correlated and have not planned analyses incorporating both subgrouping schemes.

2.5.3 | HTE in subgroups

We will present the percentages of patients with each outcome according to treatment allocation in each subgroup.

We will assess the presence of HTE separately in each of the two sets of subgroups using Bayesian hierarchical logistic regression models via the *brms* R package.[17,21] Hierarchical models partially pool data and shrink effect estimates in each subgroup towards the overall estimate, with more shrinkage for more extreme and less certain estimates (eg, for smaller subgroups or subgroups with fewer events). Compared to a fully stratified analysis, this may produce more reliable subgroups effects due to partial pooling of information from the full sample.

We will specify the model (using *brms* syntax) as:

$$outcome \sim 1 + treatment + (1 + treatment \mid\mid subgroup)$$

where *outcome* specifies the outcome assessed, *1 + treatment* means that an *intercept* (denoted *1* and corresponding to the baseline risk in the control group) and the treatment effect (allocation to PPI) will be assessed. Both the overall (population-level, "fixed") effect and the separate subgroup ("random") effects will be estimated for both the intercept and the treatment effect.

The outlined model is similar to the *simple shrinkage* models for HTE analysis described elsewhere.[22-24] In addition to the hierarchical model, a similar model including only the overall effects and using the same priors will be used for comparison with the subgroup findings.

The following priors will be used:

- For the population-level intercept: a normally distributed prior with mean 0 and standard deviation (SD) 1.5 for all outcomes except CIB. This corresponds to a prior baseline risk that with 95% probability is between 5% and 95%. For CIB, a mean of −4 will be used, corresponding to a prior baseline risk that with 95% probability is between 0.01% and 25.7%.
- For the population-level treatment effect: a normally distributed prior with mean 0 and SD of 0.5 for all outcomes except CIB, corresponding to an odds ratio (OR) that with 95% probability is between 0.38 and 2.66 and with mean probability of 1.00. For CIB, a mean of −0.4 will be used, corresponding to an OR that with 95% probability is between 0.25 and 1.79 with a mean of 0.67.
- For both group-level effects: a normally distributed prior with mean 0 and SD *omega*, with *omega* being the shrinkage factor and having a half-normally distributed prior with SD of 1.

These priors are only weakly informative, are centred on effect sizes informed by previous trials, and are wide enough to encompass all plausible effect sizes. Given the sample size, we expect the likelihoods to dominate the posteriors, with the shrinkage factor limiting exaggerated subgroup effects. Additional justifications are presented in the Supplement.

The posterior distributions of the overall and subgroup treatment effects will be exponentiated to ORs and presented using median values and 95% percentile-based credible intervals. For

the primary analysis, posterior distributions of the effect sizes will also be presented graphically. Additionally, we will present the probabilities of an OR <1.00 or >1.00 (no difference), <0.90 or >1.11 (a 10% relative reduction or the corresponding increase) and <.80 or >1.25 (a 20% relative reduction or the corresponding increase), in order to asses both the presence and magnitude of HTE.

2.5.4 | Effect of severity of illness (SAPS II) and number of risk factors

Finally, we will use Bayesian logistic regression models (through *brms*) to assess the interaction between treatment allocation and (a) SAPS II; and (b) the number of risk factors in turn and on the continuous scale for each outcome. Results will be presented graphically as marginal effects plots for the interaction. Marginal effects express how the probabilities of an outcome changes with changes in a risk factor (when all other variables are kept constant) and are easier to interpret than ORs or beta coefficients for interactions.[25]

The models will be specified as:

$$outcome \sim 1 + treatment + variable + treatment{:}variable$$

With *variable* being either SAPS II or the number of risk factors. Weakly informative priors will be used for these analyses; exact priors are specified in the Supplement.

2.5.5 | Missing data handling

For the outcomes of interest in this study, 9 patients (0.3%) had missing 90-day mortality data; no data were missing for the remaining outcomes.[5] Only patients with available outcome data will be included in these analyses.

While no data for the included risk factors were missing, *missingness* for SAPS II in the SUP-ICU trial was 7.6%.[5] Consequently, we will perform multiple imputations[26,27] for the missing SAPS II values. Multiple imputation with chained equations will be conducted separately in each treatment group using *predictive mean matching* and 25 imputed datasets through the *mice* R package.[28] To use as much of the available data as possible, we will impute missing SAPS II subscores followed by recalculation of the complete scores. We will include all SAPS II subscores, all outcomes and risk factors mentioned above, age, SOFA score, haematological malignancy and admission type in the imputation model.

Missing data for SAPS II are likely not *missing completely at random*, as missing biochemical or physiological variables may be related to severity of illness, with not all variables measured in, eg, less severely ill patients. Using the non-missing SAPS II subscores (all associated with severity of illness) and the variables outlined above in the imputation model justifies an assumption of data being *missing at random* and the use of multiple imputation.[29,30]

The SAPS II quintiles used to subgroup patients will be calculated after pooling all SAPS II values from the 25 imputed datasets. For presenting baseline data and the percentages of patients with each outcome in the subgroups stratified by SAPS II, we will use the mean

number of patients/events across the 25 imputed datasets rounded to the nearest whole number for categorical data and medians and IQRs from the pooled imputed datasets for numerical data.

Where missing data are present, the Bayesian analyses will be conducted separately in each imputed dataset, followed by pooling the posterior distributions before summary results are calculated.

2.5.6 | Model diagnostics

We will assess chain convergence visually with overlain trace and density plots, and numerically with the potential scale reduction factor (Rhat),[31] requiring Rhat to be ≤1.1 for all parameters[32] and no divergent transitions in any of the chains. Where multiply imputed datasets are used, chain convergence will be assessed separately in each imputed dataset.

We will conduct graphical posterior predictive checks to assess if the models adequately fit the original input data,[32] and estimate out-of-sample predictive accuracy using Pareto-smoothed importance sampling leave-one-out cross-validation (PSIS-LOO-CV).[33,34] In case the PSIS-LOO-CV method fails, we will use normal K-fold cross-validation.

2.5.7 | Sensitivity to priors

To assess the influence of priors on the analyses, we will re-run the same analyses using optimistic (favouring pantoprazole) and pessimistic priors (favouring placebo) weakly informed by previous trials.[35] Exact priors and additional justifications are presented in the Supplement.

2.6 | Reporting

Results from this study will be submitted to an international peer-reviewed journal regardless of findings and reported according to the STROBE statement.[12]

3 | DISCUSSION

The outlined secondary, *post-hoc* analysis aims to explore whether HTE was present in the SUP-ICU trial. As these analyses were not pre-specified before results of the SUP-ICU trial were known, the results should be considered exploratory and interpreted with caution. Despite this limitation, results from the study will add knowledge and further elaborate on the uncertainty about the benefits and harms of SUP in general and in the most severely ill patients.[5,11]

The conventional and commonly reported one-variable-at-a-time subgroup analyses are imperfect. Due to multiple testing the risk of chance findings is increased (increased risk of type 1 errors). Also, most trials are only adequately powered for the primary analysis, and subgroup analyses may be unable to detect true differences (increased risk of type 2 errors).[8] Furthermore, risk factors are often additive, which may lead to clinical heterogeneity and large variation in risks.

Thus, potentially different balances between benefits and harms of an intervention in different patients may not be detected by traditional, one-variable-at-a-time subgroup analyses of heterogeneity.[9]

With this study, we will explore whether HTE was present in the SUP-ICU trial, which may help inform future studies, clinical decision-making and guidelines on the use of SUP.

3.1 | Strengths and limitations

The planned study will have several strengths. First, strengths of the SUP-ICU trial also apply to this study, including the large sample size, pragmatic design, few protocol violations, low number of missing data and high external validity.[5] Second, we will assess the influence of SAPS II on the effect of SUP with greater detail than done previously,[5,11] using five subgroups and by assessing the interaction of treatment and SAPS II on a continuous scale using marginal effects. Third, we will assess the influence of risk factors for CIB in a cumulative way instead of one-at-a-time, which is expected to lead to estimates in patients with multiple risk factors that better reflect the clinical reality.[8] Fourth, compared to conventional, frequentist subgroup analyses, the Bayesian approach allows us to present results as probabilities, which are intuitively easier to interpret. Furthermore, this approach may be preferable to dichotomizing results as statistically significant or not based on an arbitrary threshold that is difficult to reach in conventional subgroup analyses with less power than full trial population analyses.[8] Fifth, the Bayesian hierarchical model decreases potential exaggerated subgroup findings due to shrinkage, and thus decreases the risk of chance findings in small subgroups with low power.[23]

Our study has limitations. First, some subgroups may contain few events, which may lead to uncertain estimates and wide posterior probability distributions. This limitation is mitigated by shrinkage in the hierarchical models. Second, in the analyses of subgroups stratified by the number of risk factors, all risk factors will be equally weighted. This approach could be refined by using an internal, dedicated risk model[8]; however, this would increase complexity, be more difficult to communicate and the model would only be fitted to predict one of the included outcomes—likely CIB—and risk factors may be differently associated with the other included outcomes. Third, only subgrouping schemes based on two variables will be considered. Assessing different variables or combinations of variables, for example, using clustering methods to create novel subgroups, could further elaborate on the results. However, we believe the outlined approach represents a rational and logical starting point for assessing HTE in the SUP-ICU trial that is in line with recent recommendations.[8,9] Finally, for the subgroup-based analyses, patients will be grouped according to SAPS II quintiles. Categorisation of continuous variables always leads to information loss; however, this approach is also in line with recent recommendations for conducting HTE analyses, [8,9] and has the advantage of being easier to interpret. Further, the interaction between SAPS II on a continuous scale, treatment allocation and outcomes will also be assessed using marginal effects.

In conclusion, this secondary, exploratory, *post hoc* analysis of the SUP-ICU trial will further elaborate on whether HTE was present in the SUP-ICU trial and may help answer some of the remaining questions regarding the balance between benefits and harms of SUP according to disease severity and the number of risk factors for GI bleeding. Additionally, it may help outline a standardised approach for assessing the presence of HTE in ICU trials in general.

AUTHORS' CONTRIBUTIONS

The idea for this project was conceived by AG, FGZ, AP and MHM. AG wrote the first draft for this protocol, which was critically revised by all authors. SM and MK were responsible for the SUP-ICU trial database. AG, SM, MK, ICCH, TL, JW, AP and MHM were all involved in the conduct of the SUP-ICU trial.

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SUPPORTING INFORMATION

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

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