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A Protocol and Statistical Analysis Plan

for a Secondary Analysis of the REVISE (Re-Evaluating the Inhibition of Stress Erosions) Trial

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Abstract
Background: While studies have reported risk factors for clinically-important upper gastrointestinal bleeding among critically ill patients, the risk factors for patient-important upper gastrointestinal bleeding, as defined by ICU survivors and family members, are unknown. Further, although trials show that stress ulcer prophylaxis with pantoprazole decreases the risk of upper gastrointestinal bleeding, some research suggests that mortality may be increased among patients with high illness severity who are exposed to pantoprazole. The risk of death during critical illness is greater than the risk of upper gastrointestinal bleeding.
Objective: To identify risk factors for patient-important upper gastrointestinal bleeding among invasively ventilated critically ill adults, taking into account illness severity and the competing risk of death.
Materials and Methods: This pre-planned secondary analysis of the REVISE trial database will be guided by this protocol. We will use Cox proportional hazards regression analysis to assess the effect of candidate risk factors on the hazard rate of the primary outcome of time to patient-important upper gastrointestinal bleeding, considering the competing risk of death. We propose 2 sensitivity analyses. Secondary analyses will evaluate risk factors for clinically-important upper gastrointestinal bleeding, and another model will evaluate whether enteral nutrition attenuates the effect of pantoprazole on bleeding prevention compared to placebo by including an interaction term between pantoprazole vs. placebo and amount of enteral nutrition received.
Results: This study will identify conditions of critical illness which confer an increased risk of patient-important upper gastrointestinal bleeding in critically ill patients, and factors that decrease the risk.
Conclusions: The findings may inform bedside care, practice guidelines, and the design of future studies.

Introduction

Patients and other members of the public infrequently have input into research priorities, protocol design and study conduct [1]. It has been suggested that patient input is inadequate for outcome selection in many trials conducted in general [2,3] and critical care medicine [4]. Historically, large multicenter trials evaluating upper gastrointestinal bleeding as a complication of critical illness have been focused on the outcome of clinically-important upper gastrointestinal bleeding - an endpoint defined by clinician-researchers [5-9]. In collaboration with survivors of critical illness and family members of patients who were admitted to an intensive care unit (ICU), an outcome of patient-important upper gastrointestinal bleeding was recently developed [10].

This outcome of patient-important bleeding was a secondary endpoint for a recent stress ulcer prophylaxis trial [11]. REVISE (Re-Evaluating the Inhibition of Stress Erosions) was an international, parallel group randomized clinical trial that included 4,821 patients to test the effect of pantoprazole versus placebo on the primary efficacy outcome of clinically-important upper GI bleeding and the primary safety outcome of 90-day mortality [12,13]. Pantoprazole reduced both patient-important and clinically-important upper gastrointestinal bleeding (hazard ratio [HR] 0.36; 95% CI 0.25 to 0.53; p<0.001, and HR 0.30; 95% CI 0.19 to 0.47; p<0.001, respectively), without affecting other endpoints [11].

In REVISE, patient-important upper gastrointestinal bleeding occurred more frequently than clinically-important upper gastrointestinal bleeding. While studies have reported risk factors for clinically-important upper gastrointestinal bleeding [14], the risk factors for patient-important upper gastrointestinal bleeding, as defined by ICU survivors and family members, remain unknown. While some bleeding events confer an increased risk of death [15], most bleeding ICU patients do not die with or from gastrointestinal bleeding [11]. Dying is nonetheless a competing risk for bleeding, and dying is more common than bleeding. Thus, the primary objective of the current study is to identify risk factors for patient-important upper gastrointestinal bleeding among invasively ventilated critically ill adults, taking into account illness severity and the competing risk of death.

Materials and Methods

Risk Factor Analysis

This pre-planned secondary analysis of the REVISE trial data will be guided by this protocol. The inception cohort will comprise the 4,821 participants in the REVISE trial. These were critically ill patients who were receiving invasive mechanical ventilation patients in the ICU, who were expected to remain ventilated beyond the calendar day after randomization, and were without a clear indication or contraindication to pantoprazole [12,13].

We will use Cox proportional hazards regression analysis to assess the effect of candidate risk factors on the hazard rate of the primary outcome of time to patient-important upper gastrointestinal bleeding, considering the competing risk of death [16,17]. In REVISE, approximately 10 times as many patients died at 90-days than experienced upper gastrointestinal bleeding. The main analysis will then be a competing risk analysis for the competing risk of death [18]. The proportional hazards assumption (which states that the effects of the time-dependent variables remain stable over time) will be assessed and handled appropriately using time-varying effects [19]; alternative methods will be used if this is not satisfactory [20]. We will also assess collinearity of the independent variables (e.g., therapeutic anticoagulation and coagulopathy).

We will include both baseline variables and time-dependent variables, described further below. All time-dependent risk factors will be defined as existing any time in the preceding 3 days, but not including the day of bleed. For bleeds that occur on day 1 of the study, we will use day 1 data to define the time-dependent covariates. We will consider ICU discharge and consent withdrawal as censoring events.

Dependent Variables:

Primary Outcome

The primary dependent variable will be patient-important upper gastrointestinal bleeding. This was defined in a mixed-methods study of ICU survivors and families [21], with gastrointestinal bleeding judged as important if bleeding resulted in a blood transfusion, vasopressor treatment, diagnostic endoscopy, CT-angiography, surgery, or if it resulted in death, disability, or prolonged hospitalization [10]. These criteria were applied to the REVISE database up to 90 days after randomization [11]. Our main analysis will include all patient-important upper gastrointestinal bleeds that occurred in the ICU.

Among 4,821 patients, 136 (2.8%) had patient-important upper gastrointestinal bleeding, 5 of whom bled on the ward prompting ICU readmission. These 5 patients will be censored at ICU discharge, as daily data for the time-dependent risk factors were not collected beyond the index ICU admission.

Secondary Outcome

A secondary analysis will be to determine risk factors for the secondary outcome of clinically-important upper gastrointestinal bleeding. We defined clinically-important upper gastrointestinal bleeding as the presence of overt bleeding (hematemesis, overt nasogastric bleeding, melena, or hematochezia) and at least one of the following within 24 hours in the absence of another cause: spontaneous decrease in invasively monitored mean arterial pressure or non-invasive systolic or diastolic blood pressure of 20 mmHg or more or an orthostatic increase in pulse rate of 20 beats/minute and a decrease in systolic blood pressure of 10 mmHg, with or without vasopressor initiation or increase; vasopressor initiation; a decrease in hemoglobin of ≥ 20 g/L in a 24-hour period or less; transfusion of ≥2 units of packed red blood cells within 24 hours of bleeding, or therapeutic intervention (e.g., angio-embolization, surgery or endoscopic treatment of bleeding) [12]. Each bleed was reviewed in duplicate by an adjudication committee, blinded to study drug, to determine whether the clinically-important upper gastrointestinal bleeding criteria were fulfilled [22].

Among 4,821 patients, 109 (2.2%) had an event which were adjudicated as clinically-important upper gastrointestinal bleeding, 5 of whom bled on the ward prompting ICU readmission. These 5 patients will be censored at ICU discharge, as daily data for the time-dependent risk factors were not collected beyond the index ICU admission.

Independent Variables:

Bleeding risk factors will include both baseline and time-dependent variables. Factors will draw on pathophysiologic rationale and prior literature. Given the number of patient-important upper gastrointestinal bleeds, we have taken into account the suitable number of independent variables to avoid an over-fitted model [23]. The same risk factors will be analyzed for the secondary outcome of clinically-important upper gastrointestinal bleeding as for the primary outcome of patient-important upper gastrointestinal bleeding.

Baseline Variables

1) APACHE II score (considered as a continuous variable)
2) Medical vs. surgical/trauma (considered as 2 categories)
3) Pantoprazole versus placebo as randomized (considered as 2 categories)

Time-dependent Variables

1) Respiratory failure, defined as receiving invasive mechanical ventilation (considered as 2 categories)
2) Circulatory failure, defined as receiving inotropes or vasopressors (any dose of any of norepinephrine, epinephrine, phenylephrine, vasopressin, dopamine, dobutamine or milrinone) (considered as 2 categories)
3) Renal failure including acute kidney injury or end-stage renal disease, defined as receiving renal replacement therapy (any of intermittent hemodialysis [IHD], continuous renal replacement therapy [CRRT], sustained low efficiency dialysis [SLED] or peritoneal dialysis) (considered as 2 categories)
4) Enteral nutrition in mL/day (considered as a continuous variable)

5) Therapeutic anticoagulation, defined as therapeutic unfractionated heparin or low molecular weight heparin, fondaparinux, warfarin, non-vitamin K antagonist oral anticoagulants including anti-Xa inhibitors and direct thrombin inhibitors, and thrombolytic therapy (considered as 2 categories)
6) Coagulopathy, defined as international normalized ratio (INR) > 3.0 or prothrombin time (PTT) >70 seconds (considered as 2 categories)
7) Severe thrombocytopenia, defined as platelet count <50 × 10^9/L (considered as 2 categories)
8) Platelet aggregation inhibitors, defined as receipt of any of acetyl salicylic acid, clopidogrel, dipyridamole, ticlopidine, tirofiban, P2Y12 inhibitors, or non-steroidal anti-inflammatory drugs (considered as 2 categories)
9) Corticosteroids, defined as any corticosteroid drug or dose, either enteral or intravenous administration (considered as 2 categories)

Sensitivity Analyses

1) To evaluate the effect of the competing risk of death, we will conduct an analysis that does not consider the competing risk of death.
2) To evaluate the influence of risk factors more proximate to the bleed, we will evaluate all time-dependent risk factors defined as any time in the preceding 2 days, instead of the preceding 3 days.

Secondary Analyses

1) To evaluate risk factors for clinically-important upper gastrointestinal bleeding, we will repeat the same analysis [11].
2) To evaluate whether enteral nutrition attenuates the effect of pantoprazole on bleeding prevention compared to placebo, we will include an interaction term between pantoprazole vs. placebo and amount of enteral nutrition received [24,25].
3) To evaluate whether certain baseline conditions are associated with patient-important upper gastrointestinal bleeding, we will include these variables in the main model one at a time: acute hepatic failure [26], traumatic brain injury [27] and female sex [28].

Missing Data

We anticipate little missing data except for 2 risk factors in patients with length of ICU stay greater than 2 weeks. Platelet aggregation inhibitors and corticosteroids were not collected from day 15 onwards 14 on the abbreviated trial case report form. For the primary analysis, if there are any patients remaining in the ICU after 2 weeks who received a platelet aggregation inhibitor on day 14, we will impute that it was continued until ICU discharge, except in the event of bleeding, assuming that the indication persisted over time (e.g., coronary artery disease). For the primary analysis, we will impute that if there are any patients receiving corticosteroid treatment on day 14, it was continued only to day 21, assuming the indication resolved (e.g., septic shock).

Results

We will report independent variables and other characteristics of participants with and without patient-important upper gastrointestinal bleeding using descriptive statistics, including means and standard deviations (or medians with interquartile ranges, if appropriate) for continuous data, and numbers with percentages for categorical data.

Figures we will present include the day of each bleed in the ICU, the concordance between patient-important gastrointestinal bleeding and clinically-important upper gastrointestinal bleeding, and the daily use of invasive ventilation and any enteral nutrition.

Regression results will be presented as adjusted hazard ratios with 95% confidence intervals and corresponding two-tailed p-values for the associations of each independent variable with the primary and secondary outcomes. The criterion for statistical significance will be set at alpha = 0.05. No corrections for multiple testing will be performed because of the exploratory nature of the analyses, but findings will be interpreted in light of confidence intervals and cautiously interpreted.

Discussion

In this study, we will examine baseline and time-dependent risk factors for patient-important upper gastrointestinal bleeding, including the effect of pantoprazole versus placebo. Use of the REVISE trial database will build on risk factor analyses of clinically-important upper gastrointestinal bleeding from prior large trials [25,29].

Strengths of this study include the focus on an outcome developed by ICU survivors and relatives of ICU survivors or decedents. We will minimize the risk of over-fitted regression models caused by evaluation of many admitting diagnoses. Beyond assessing baseline characteristics, we will use Cox models to assess interventions and key laboratory values reflecting events and exposures over the ICU stay. Although proton-pump inhibitors for bleeding prophylaxis do not affect 90-day mortality overall as shown in a recent meta-analysis (RR 0.99 [95% CI, 0.93 to 1.05]) [30], within-trial subgroup analysis suggests a possible heterogeneity of treatment effect based on disease severity. Accordingly, the main analysis will address the competing risk of death and a sensitivity analysis will evaluate whether this impacts the results. In this contemporary database, half of the patients were randomized to no stress ulcer prophylaxis, enabling the evaluation of risk factors with and without stress ulcer prophylaxis. This study will address some issues proposed for future research on this topic [31], including evaluating the volume of enteral nutrition (e.g., trophic versus full feeding) and special populations (e.g., acute hepatic failure). Heterogeneous patients from 68 international centers will increase the generalizability of the results.

Limitations of this study include no information on some uncommon exposures in the REVISE trial (e.g., non-invasive ventilation) and on some rare conditions (e.g., admitting diagnosis of organ transplantation). To focus on events that consume healthcare resources, we will not address overt bleeding, which often resolves; if it evolves into patient-important or clinically-important upper gastrointestinal bleeding, these events will be included in this analysis. This study is not designed to construct or both construct and validate a prediction model, which requires a different design. All analyses such as these are subject to confounding, yielding information on association rather than causation, needing cautious interpretation.

Conclusions

This study will identify conditions of critical illness which confer an increased risk of patient-important upper gastrointestinal bleeding. The findings may inform bedside care, practice guidelines, and the design of future studies.

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