Stress ulcer prophylaxis in the intensive care unit
A multicentre 7-day inception cohort study

Statistical Analysis Plan

CONFIDENTIAL

VERSION #4, DATE 12/03/2014

Study 1. Use of stress ulcer prophylaxis in the intensive care unit. An international unit evaluation

OUTCOME MEASURE

- Use of stress ulcer prophylaxis
    - Proton pump inhibitor (PPI)
    - Histamine-2-receptor antagonist (H2RA)
    - Sucralfate
    - Antacid
    - Prostanoids

VARIABLES

- Country
    - Demark
    - Sweden
    - Norway
    - Iceland
    - Finland
    - Italy
    - The Netherlands
    - United Kingdom
    - New Zealand
    - Australia
    - Canada

- Type of hospital
    - University
    - Teaching
    - District
    - General
    - Specialist

- Type of ICU
    - Surgical
    - Medical
    - Mixed
    - Cardiothoracic
    - Neurosurgical
    - Cardiology
    - Burn

- Size of ICU
    - Small (<10 beds)
    - Medium (10-20 beds)
    - Large (>20 beds)

- Unit guideline/protocol for use of SUP
    - Yes
    - No

- Patient groups receiving SUP

  - A (most frequent)
  - B (second most frequent)
  - C (third most frequent)
  - D (fourth most frequent)
  - E (fifth most frequent)

- Criteria for discontinuing SUP
  - Enteral feeding
  - Suspension of mechanical ventilation
  - Discharge from ICU
  - No discontinuation
  - Other
    - A (most frequent)
    - B (second most frequent)
    - C (third most frequent)
    - D (fourth most frequent)
    - E (fifth most frequent)

- Adverse effects worried about
  - Nosocomial pneumonia
  - Clostridium difficile enteritis
  - C (third most frequent)
  - D (fourth most frequent)
  - E (fifth most frequent)

ANALYSES

Data will be presented as distribution frequencies and per cent.

Tabulation of the outcome measure and 1) country, 2) type of hospital, 3) type of ICU, and 4) size of ICU will be performed. Chi-square-test will be used to assess statistical significant difference between groups (2-tailed $P<.05$ is considered statistically significant).

Study 2. International study of the prevalence and outcome of gastrointestinal bleeding and use of stress ulcer prophylaxis in adult critically ill patients in the intensive care unit

OUTCOME MEASURES

- Primary
  - Clinically significant GI bleeding (overt GI bleeding AND ≥1 of the following features within 24 hours of GI bleeding: 1) spontaneous drop of systolic, mean arterial pressure or diastolic blood pressure of 20 mmHg or more; 2) start of vasopressor or a 20% increase in vasopressor dose; 3) decrease in hemoglobin of at least 2 g/dl (1.24 mmol/L); or 4) transfusion of 2 units of packed red blood cells or more)

- Secondary
  - Overt GI bleeding (hematemesis, coffee ground emesis, melena, hematochezia or bloody nasogastric aspirate)
  - 90-day mortality

VARIABLES

- Age (years)

- Gender

- SOFA score on index day

- Surgery prior to ICU admission
  - Emergency
  - Elective
  - None

- Treatment with ulcer prophylactic drugs prior to hospital admission
  - Yes
  - No

- Treatment with NSAID or acetylsalicylic acid prior to hospital admission
  - Yes
  - No

- Treatment with anticoagulant drugs prior to hospital admission
  - Yes
  - No

- Treatment with NSAID or acetylsalicylic acid initialised during current hospital admission
  - Yes
  - No

- Treatment with anticoagulant drugs initialised during current hospital admission
  - Yes
  - No

- Comorbid conditions
  - COPD

  - Previous myocardial infarction
  - Severe chronic heart failure (NYHA 3-4)
  - Chronic renal failure
  - Liver cirrhosis or structural damage
  - Metastatic cancer
  - Active hematologic cancer
  - AIDS
  - Immunosuppression
  - Coagulopathy (Platelets < 50 and/or INR > 1,5 during current hospital admission)

- Number of comorbid conditions
  - 0
  - 1
  - 2
  - 3
  - > 3

- Mechanical ventilation on ICU admission
  - Yes
  - No

- Renal replacement therapy on ICU admission
  - Yes
  - No

- Shock on ICU admission (vasopressors and/or inotropes)
  - Yes
  - No

- Coagulopathy on ICU admission (Platelets < 50 and/or INR > 1,5 during current hospital admission)
  - Yes
  - No

- Treatment with NSAID or acetylsalicylic acid on ICU admission
  - Yes
  - No

- Treatment with anticoagulant drugs on ICU admission
  - Yes
  - No

- Treatment with thrombolysis on ICU admission
  - Yes
  - No

- Use of stress ulcer prophylaxis on ICU admission
  - Proton pump inhibitor (PPI)
  - Histamine-2-receptor antagonist (H2RA)
  - Sucralfate
  - Antacid
  - Prostanoids

ANALYSES

Data will be presented as mean (95% confidence interval), median (interquartile range [IQR]), or number (%) as appropriate. All statistical tests will be 2-tailed, and $P<.05$ is considered statistically significant.

Primary analysis

Multivariate logistic regression analysis will be used to determine baseline (ICU admission) risk factors for GI bleeding (clinically significant and overt). Data will be presented as crude and adjusted odds ratios (95% confidence intervals). The variables above will be investigated as independent risk factors for GI bleeding. Odds ratios will be adjusted for 1) country, 2) type of hospital, 3) type of ICU, 4) size of ICU, and 5) length of hospital stay prior to index day. Statistically significant independent risk factors will be tabulated with GI bleeding.

Secondary analysis

Multivariate logistic regression analysis will be used to determine the crude and adjusted odds ratio (95% confidence interval) for the association between the primary outcome measure and 90-day mortality. The odds ratio will be adjusted for the following covariates:

Covariates:

- Categorical
    - Comorbidity (one or more)
    - Gender
    - Surgery prior to ICU admission
    - Mechanical ventilation on ICU admission
    - Renal replacement therapy on ICU admission
    - Shock on ICU admission (vasopressors and/or inotropes)
    - Coagulopathy on ICU admission

- Continuous
    - Age on ICU admission
    - SOFA score on ICU admission

MISSING DATA

The frequency and percentage of missing values for each variable will be collected, analysed and reported (missing value analysis). If there are missing values for the variables of interest/outcome, exclusion of observations with missing values for the variables of interest/outcome will be considered. Highly incomplete covariates (>33% of observations missing) will be excluded from analyses. If missing values are Missing Completely At Random (MCAR), exclusion of patients with missing observations will be considered. If missing values are Missing At Random (MAR) or not at random (MNAR), multiple imputation will be performed. Missing values, selection or exclusion of observations and variables and handling of missing values in the statistical analysis will be describes carefully and sensitivity analysis will be provided. (1-4)

References

1. Schafer JL. Multiple imputation: a primer. Stat Methods Med Res. 1999;8(1):3-15.

2. Schafer JL, Graham JW. Missing data: our view of the state of the art. Psychol Methods. 2002;7(2):147-77.

3. Vesin A, Azoulay E, Ruckly S, Vignoud L, Rusinova K, Benoit D, et al. Reporting and handling missing values in clinical studies in intensive care units. Intensive Care Med. 2013;39(8):1396-404.

4. Vickers AJ, Altman DG. Statistics notes: missing outcomes in randomised trials. BMJ. 2013;346:f3438.