Post-hoc analyses of bleedings, transfusions and coagulation in the 6S-cohort - statistical analysis plan

Descriptive study of presence of bleeding and localisation

3 columns: Full cohort, HES-group, RA-group

8 rows: Intracranial, upper gastric, lower gastric, urine, tracheal, wounds, surgery, total

Numbers are given as n (%).

Statistics:

Primary analysis: Chi2-test of difference between groups in total number of bleedings.

Secondary analyses: Chi2-test of difference in the localisation of bleeding between the groups. Fisher's exact test if numbers are small.

Sensitivity analysis: The severity of the bleedings are assessed by varying the definition of bleeding as follows: Any bleeding, bleeding & 1 unit of RBC, bleeding & 2 units of RBC and bleeding & 3 units of RBC. Since we consider any intracranial bleeding severe, any intracranial bleeding will be included in the total for all bleeding definitions.

Total bleedings will also be evaluated when excluding bleedings during surgery.

Subgroup analysis: Total number of bleedings for medical vs. surgical patients.

Timing of Bleeding

Outcome: time to first bleeding or death in the ICU

Statistics:

Kaplain Meyer analysis of difference between the intervention groups.

Cox-regression with the following covariates (baseline variables)

- Binary variables:
    - Intervention group
    - hematological malignancy at baseline
    - septic shock at baseline
    - admitted to university hospital
    - surgery before randomisation
    - starch before randomisation
- Ordinal variables:

    - SAPS II
    - SOFA-score at baseline
- Continous variables:
    - platelet count at baseline
    - INR at baseline

Sensitivity analysis: The definition of bleeding will be varied as follows: Any bleeding, bleeding and ≥ 3 units of RBC.

The outcome will be changed to "bleeding" only. Dead patients will then be censored.

Timing of Transfusion

Outcome: time to first transfusion of RBC or death in the ICU.

Statistics:

Kaplain Meyer analysis of difference between the intervention groups.

Cox-regression with the following covariates

- Same covariates as in "timing of bleeding" but also
    - previously admitted for MI or heart failure
    - RBC-transfusion given in the 24 hours before randomisation
    - hemoglobin at baseline

Sensitivity analysis: The outcome will be changed to "transfusion" only.

Risk factors for bleeding

Outcome: Composite endpoint of either bleeding or death

Statistics:

    - Multiple logistic regression with the same covariates as in "timing of bleeding"

Sensitivity analysis:

The definition of bleeding will be varied as follows: Any bleeding, bleeding and ≥ 3 units of RBC.

Time course of coagulation measures

Outcomes: INR (5 days), Hgb (5 days), platelets (5 days)

Statistics:

T-test for a difference between mean AUC for each of the two intervention groups. Wilcoxon rank sum test if data are not normally distributed. AUC for each of the two intervention groups

Mixed models (proc mixed, SAS). Covariates

- Primarily (unadjusted analysis)
    - day
    - intervention group
    - intervention group * day
- Secondarily (adjusted analysis)
    - Adjustment for covariates as in "timing of bleeding"

Level of statistically significance

A p-value < 0.05 will be considered statistically significant. Caution will be taken in the interpretation of p-values due to multiple testing.

Missing data

SAPS-score: Lowest and highest possible SAPS scores are calculated. We then perform two worst-best case analyses: One where the starch group is given the highest possible SAPS-score and the Ringer-group is given the lowest possible SAPS-score. Then vice-versa. If these analyses return divergent results, we will perform multiple imputation analysis.

The same applies for the SOFA-score.

Analysis of time course of a variable:

The patient has died: Hgb and platelets will be set to zero. INR will be set to 8.

The patient is discharged from the ICU: last observation will be carried forward.

First observation is missing: Next observation will be carried backward.

Last observation is missing: Last observation will be carried forward.

An observation in between is missing: Imputation with the mean value of the last and next observation.

Model control

Cox-model: log(-log())-plot and cumulative hazards-curves will be used to check for proportional hazards assumption for each variable.

In the analysis of risk factors for bleeding covariates will only be included in the multivariate model if they seem to be associated with the outcome in a univariate model (p-value <10%). In all other models, all pre-defined covariates will be used.