APNC
Statistics in Life Science

Statistical Analysis Plan

Outcomes of mechanical thrombectomy with the FlowTriever device in acute pulmonary embolism, results of a national retrospective analysis

FINAL 1.0

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Abbreviations

AUC-ROC	Area under the receiver operating characteristic curve
CT	Computed tomography
ECMO	Extracorporeal membrane oxygenation
ECPR	Extracorporeal cardiopulmonary resuscitation
FAS	Full analysis set
GDPR	General data protection regulation
HR	Hazard ratio
ICU	Intensive care unit
IMU	Intermediate care unit
OR	Odds ratio
PE	Pulmonary embolism
PS	Propensity score
RR	Risk ratio
RV/LV	Right ventricular/left ventricular

1 Background

Current international guidelines recommend intravenous thrombolysis for pulmonary embolism with circulatory shock (high-risk PE). Thrombolysis is a highly effective dissolvent of thromboembolic clots followed by fast improvement in the pulmonary obstruction. The treatment has been shown to decrease the combined outcome of mortality and recurrent PE, but also carries a risk of major bleeding of approximately 10%, including 2% rate of intracranial hemorrhage. Additionally, many PE patients have contraindications to thrombolysis. In high-risk PE where IVT is contraindicated or has failed, surgical embolectomy or catheter-directed interventions (CDI) is recommended. The FlowTriever® retrieval/aspiration system is the first mechanical thrombectomy device to receive PE as an indication from the United States Food and Drug administration agency. It combines large-bore aspiration with expanding mesh disks designed to trap and subsequently retract the blood clots from the pulmonary arteries. The FlowTriever® device is gaining widespread use, but non-industry sponsored studies are small with few high-risk patients.

2 Study Objective and Hypothesis

The objective of this study is to evaluate catheter-directed intervention with the FlowTriever® device by comparison to contemporary systemic thrombolysis in patients with acute PE.

The hypothesis is that patients treated with the FlowTriever® device will have lower incidence of the primary outcome variable, the composite endpoint death at 30 days and/or severe bleeding (according to GUSTO bleeding criteria) within 7 days after treatment, than patients treated with contemporary thrombolysis.

3 Study Design

This is a national multicenter retrospective observational study including patients with acute PE treated between 2021 and 2023 with FlowTriever® in Sweden, to evaluate safety and effects of treatment with the FlowTriever® device. Treated patients will be compared to patients treated with thrombolysis, in the respective hospital during the time period when FlowTriever® has been in use.

Eligible patients will be identified through screening of the relevant clinics/databases at each participating center for:

- Treatment code(s) for thrombolysis and/or pulmonary thrombectomy
- Diagnosis code(s) for pulmonary embolism and/or pulmonary angiography

Data from patients who have been treated for suspected, but not verified, PE may be collected for descriptive purposes but excluded from comparative analyses.

Data will be collected through review of patient records, and subsequently anonymized, organized and analyzed. Collection, handling, and storage of data will be done in accordance with the General Data Protection Regulation (GDPR).

3.1 Inclusion/Exclusion Criteria

Eligible patients are all adult patients (≥18 years) who have been treated with FlowTriever® or thrombolysis for acute PE verified by computed tomography pulmonary angiography (CTPA)or angiography, during the time period from January 1st of the year when FlowTriever® was introduced at each respective participating center, to the end of 2023.

3.2 Study Groups

- Intervention group: Patients treated with FlowTriever®
- Comparison group: Patients treated with thrombolysis
- Intervention group with prior thrombolysis: a subgroup of the intervention group including patients that have received thrombolysis before FlowTriever®. They will be separately described and exploratively analyzed as an own intervention group within the study. No formal statistical comparisons will be made for this group.

4 Study Populations

4.1 Full Analysis Set

The full analysis set (FAS) will include all patients treated with FlowTriever® and thrombolysis at the included centers during the years 2021, 2022 and 2023.

5 Study Variables

5.1 Baseline Characteristics Variables

Following baseline characteristics will be collected and described:

- Age
- Sex (male, female)
- Mechanical ventilation (yes, no)
- Maximum heart rate (0-24 hours before intervention)
- Minimum systolic blood pressure (0-24 hours before intervention)
- Maximum respiratory frequency (0-24 hours before intervention)
- Maximum lactate levels (0-24 hours before intervention)
- Maximum cardiac troponin levels (0-24 hours before intervention)
- Maximum NT-proBNP levels (0-24 hours before intervention)

5.2 Medical History Variables

Following medical history variables will be collected and described:

- Hypertension (yes, no)
- Ischemic heart disease (yes, no)
- Heart failure (yes, no)
- Diabetes (yes, no)

- Chronic obstructive lung disease (yes, no)
- Asthma (yes, no)
- Other lung disease (yes, no)
- Previous stroke (yes, no)
- Liver disease (yes, no)
- Renal disease (yes, no)
- Active cancer (yes, no)
- Previous venous thromboembolism (yes, no)
- Symptomatic COVID-19 infection in the three months prior to intervention (yes, no)
- Other (coded by ICD-10 codes if relevant)

5.3 Diagnostic, Pre-, Peri- and Post-Intervention Variables

Following diagnostic variables will be collected and described:

- Time between diagnostic radiology and treatment (hours)
- Type of radiology (CT, angiography)
- Clinical presentation of PE (e.g. hypotension, syncope, cardiac arrest) (yes, no)
- Distribution of PE (unilateral, bilateral, saddle)
- Cardiac arrest before treatment (yes, no)
- ROSC before treatment (yes, no)
- Cardiac arrest during treatment (yes, no)
- Cardiac arrest after treatment (yes, no)
- ECMO initiated before treatment (yes, no)
- ECMO initiated during treatment (yes, no)
- ECMO initiated after treatment (yes, no)
- Extracorporeal cardiopulmonary resuscitation (ECPR) (yes, no)

5.4 Intervention

Following variables related to the intervention of FlowTriever® will be summarized:

- Indication for intervention (e.g. contraindication to thrombolysis, unsuccessful thrombolysis, other indication)
- Contraindication to thrombolysis (none, trauma, surgery, ischemic stroke, hemorrhagic stroke, active bleeding, risk for bleeding, ongoing anticoagulation, other indication)
- Use of Cellsaver/*FlowSaver*™ or equivalent
- Rescue treatment after intervention (thrombolysis, surgical embolectomy, ECMO)
- ECMO during intervention (yes, no)
- Technical success (yes, no), defined as achieval of desirable catheter positioning, as assessed by the interventionist
- Procedural success (yes, no), defined as technical success with successful extraction of thrombus material in the absence of major complications, as assessed by the interventionist

- Clinical success (yes, no), defined as hemodynamic or respiratory improvement following intervention, including but not limited to: increase in SaO2, reduced FiO2, regress of hypotension/tachychardia/tachypnoea, reduced need for circulatory support.
- Complications during intervention (bleeding, perforation, other complication)
- Other complications (coded by ICD-10 if relevant)

Following variables related to the treatment with thrombolysis will be summarized:

- Dose of thrombolysis
- Duration of infusion of thrombolysis
- Reason for premature discontinuation of thrombolysis (when relevant)
- Contraindication for thrombolysis (if relevant)
- Rescue treatment after thrombolysis (surgical embolectomy, ECMO)

5.5 Outcome Variables

5.5.1 Primary Outcome Variable

The primary variable in this study is the composite endpoint death at 30 days and/or severe bleeding (according to GUSTO bleeding criteria) within 7 days after treatment with the FlowTriever® device or contemporary thrombolysis.

5.5.2 Secondary Outcome Variables

The secondary variables in this study are:

- Difference in RV/LV-ratio as compared (up to 48h) before, and (up to 48h) after, treatment. RV/LV-ratio before treatment will be assessed on CT, and after treatment on echocardiography.
- Difference in pulmonary artery pressure (systolic, diastolic and mean) as compared (up to 48h) before and (up to 48h) after treatment.
- Incidence of severe bleeding (according to GUSTO bleeding criteria) within 7 days after treatment
- Type of bleeding (severe, moderate, mild GUSTO)
- Intracranial bleeding (yes, no)
- Incidence of all-cause death at 30 days after treatment
- Time to all-cause death within 30 days after treatment
- Causes of death in patients treated with FlowTriever® vs thrombolysis
- Occurrence of cardiac arrest before (within 24 hours), during, or after (within 24
- hours) treatment
- Occurrence of rescue treatment with thrombolysis, ECMO, or surgical thrombectomy
- Length of stay in ICU or IMU (hours)
- Length of hospital admission (days)

5.6 Confounders and Predictors

The confounders and predictors for the outcomes will be used in propensity scores and adjustments. All variables listed below will be included when building propensity scores. For the adjusted analyses, only the

strongest confounders and predictors will be part of the analyses. The number of confounders/predictors in the adjusted analyses will be based on the number of events available in the studied cohort. The general recommendation is to not have more than 1 variable/10 events in a statistical model. We will calculate the maximum number of variables in our study as N events/10.

The following variables will be investigated whether they are statistically defined confounders, i.e. related to both the intervention and the outcome:

- Contraindication for thrombolysis (8 categories)
- Insufficient previous effect of thrombolysis
- Cardiac arrest before treatment

The following variables will be investigated for their relation to the study outcomes:

- Age
- Sex
- Active cancer
- Invasive ventilation before treatment
- Circulatory instability
- Chronic heart failure
- Chronic pulmonary disease (COPD, asthma, other)
- Respiratory rate >30 beats/min
- Center

6 Statistical Methods

6.1 Sample Size

The few non-industry sponsored studies have been performed on a limited number of patients. Furthermore, there is an insufficiency of data concerning the outcomes in this particularly severe group of patients, making it challenging to make informed assumptions for a sample size calculation.

During the planned inclusion period, we anticipate enrolling 60 patients who will undergo the FlowTriever® procedure and 200 patients who will receive thrombolysis intervention. Assuming these group sizes and a 40% incidence rate of the composite outcome in the thrombolysis group, with a two-sided Fisher's exact test and an alpha level of 0.05, the FlowTriever® group would need to demonstrate a 50% reduction, equivalent to a 20% incidence of the composite outcome, to achieve a minimum of 80% statistical power. Our evaluation indicates that achieving such an outcome is feasible within the scope of this study, making it a viable candidate for a positive outcome.

6.2 General Methodology

Descriptive statistics will be used for group characteristics and outcomes. Mean, standard deviation, median, and range will be described for the continuous variables and frequency and percentage for categorical variables. Intergroup comparisons considering baseline characteristics will be done using Fisher's exact test for

dichotomous variables, Chi-square test for non-ordered categorical variables, and the Mann-Whitney U-test for continuous variables.

The comparative analyses between the groups considering the dichotomous study outcomes will be performed using logistic regression adjusted for known and statistically identified confounders (variables that are related both to the study group and the outcome). Odds-ratios (OR) with associated 95% CI, p-values and area under the receiver operating characteristic curve (AUC-ROC) will be presented. Hosmer-Lemeshow test will be performed as a goodness-of-fit test.

The comparative analyses between the groups considering the continuous study outcomes will be performed using linear regression adjusted for known and statistically identified confounders. Model assumptions will be checked by reviewing diagnostic plots, and if needed transformation (e.g. log) of the outcome variable will be performed. Least square means with associated 95% CI, p-values and R^2 will be presented.

Outcome variables length of stay in ICU (hours) and length of hospital admission (days) will be handled as continuous variables in the case of no censored patients. In case of censored patients in the database, time to discharge will be studied using Cox proportional hazard model, resulting in hazard ratios (HR) with 95% CI and p-value. Proportional hazards assumptions will be checked graphically. Otherwise, the variables will be studied as continuous variables using either linear regression assuming normal distribution if applicable or Poisson or negative binomial regression depending on the distribution of the variables. Results from the Poisson and negative binomial regression result in risk ratio (RR) with 95% CI and p-value.

Time to all-cause mortality will be investigated by using Cox proportional hazard model, describing HR with 95% CI and associated p-value following adjustment. Event rates, the number of events divided by total number of follow-up time will be described, together with the 95% CI obtained using exact 95% Poisson confidence limits. Graphically, this variable will be described applying Kaplan-Meier technique.

The confirmatory analyses will be performed for the following outcome variables, applying Bonferroni-Holm adjustment to minimize the Type I error:

- The primary composite outcome variable, death at 30 days and/or severe bleeding (according to GUSTO bleeding criteria) within 7 days after treatment
- The secondary outcome variable all-cause death at 30 days post-intervention
- The secondary outcome variable severe bleeding (according to GUSTO bleeding criteria) within 7 days after intervention
- The secondary outcome variable difference in RV/LV-ratio as compared before and after treatment

Additionally, the sensitivity analyses will be conducted applying adjustment for propensity score (PS) and PS 1:1 matching for the confirmatory analyses listed above, using the patients' background data to estimate the PS, performed by using logistic regression. Matching will be made applying nearest neighbour matching with the optimal caliper width of 0.2 of the standard deviation of the logit of the PS, as recommended. The performance will be validated by comparing the patient characteristics between the matched groups, that are expected not to differ, and described by standardized mean difference. The potential selection bias in the PS 1:1 matching will be examined in a drop-out analysis comparing included vs excluded FlowTriever® cases.

All non-confirmatory analyses will be evaluated in an exploratory manner at significance level of 0.05. All analyses will be performed using SAS software version 9.4 or later (SAS Institute Inc., Cary, NC, USA).

6.3 Adjustment for Type I Error

As per above in the General Methodology Bonferroni-Holm adjustment will be used for the confirmatory analyses. All other tests will be exploratory.

6.4 Handling of Missing Data

Missing data for the main study outcomes is not expected. Hence no imputation of missing data is pre-planned.

6.5 Primary Analyses

The primary analysis will be performed using logistic regression adjusted for known and statistically identified confounders. OR with associated 95% CI, p-values and AUC-ROC will be presented. Hosmer-Lemeshow test will be performed as a goodness-of-fit test.

The sensitivity analysis of the primary variable will be performed by using:

1) Adjustment for PS
2) PS 1:1 matching – in case match to at least 70% of FT patients is found

6.6 Secondary Analyses

The secondary analyses will be performed applying the general methodology presented above.

6.7 Subgroup Analyses

The investigation of interaction with the intervention group will be performed on following subgroup variables:

- ECMO treatment before, during and after the intervention (yes vs no)
- Cardiac arrest before and during intervention (yes vs no)

These analyses will only be performed if the number of events is at least 10 in each cell.

7 Planned Tables and Figures

Table Number	Table Title
Table 1.1	Patient characteristics by intervention group overall and for propensity score 1:1 matched groups (FAS population and PS 1:1 matched groups).
Table 1.2	Drop-out analysis of included and excluded FlowTriever treated patients in the propensity score matching.
Table 2	Exposure and compliance by intervention group overall and for propensity score 1:1 matched groups (FAS population and PS 1:1 matched groups).
Table 3	Investigational analysis of confounders and predictors (FAS population)