Anaesthesiological Routine Care for Thrombectomy In Cerebral Ischaemia (ARCTIC-I): An International Prospective Observational Study

Statistical Analysis Plan

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Abbreviations

ET	Endovascular Thrombectomy
mRS	modified Rankin Scale

1 Study Overview

For a detailed description of ARCTIC-I, please refer to the study protocol.

1.1 Background and Rationale

Endovascular thrombectomy (ET) is the standard of care for selected patients with acute ischaemic stroke due to large-vessel occlusion.[1,2]

During ET, some patients imperatively require general anaesthesia with intubation and controlled ventilation because of severe agitation, reduced consciousness, loss of airway protective reflexes, or impaired respiratory function. On the other hand, symptoms might be so slight that patients manage to cooperate and lie still. In between, there are patients with preserved airway protective reflexes and stable respiration who need sedation to establish adequate conditions for the intervention.[3] In these cases, ET can be done under sedation with preserved spontaneous ventilation as well as under general anaesthesia with endotracheal intubation and controlled mechanical ventilation.[4] There are still open questions concerning anaesthesiological management of the patient during the intervention.[5] Although current guidelines give gross recommendations,[6] detailed information, like on choice of technique or drugs, are missing.[7]

The present study is intended to describe the variation of routine clinical practice for anaesthesiological care during ET. In the collected data characterising the patients' pre-stroke state of health, the vascular accident itself, the course and success of ET, periprocedural management and physiology, we will look for the factors of anaesthetic management that are independently correlated with a good or bad outcome.

1.2 Objectives

ARCTIC-I aims to describe international differences in anaesthesia care for ET. Based on these data, we will investigate how individual aspects of anaesthesiological support during ET (i.e. anaesthetic technique, substances used, management of haemodynamics, oxygenation and ventilation) influence the functional outcome of patients three months after stroke.

The secondary objectives are to find factors that predict failing sedation with need of conversion to general anaesthesia and controlled mechanical ventilation. Moreover, we will try to define which patients can successfully be extubated at the end of the procedure.

1.3 Patient Population

Any patient undergoing endovascular thrombectomy for out-of-hospital stroke with anaesthesiological support (using either standby, sedation or general anaesthesia) is a candidate for enrolment in ARCTIC-I. Eligibility criteria are as follows.

- Inclusion criterion: ET for acute ischaemic stroke involving anaesthesia care
- Exclusion criteria:
    - In-hospital onset of stroke
    - Inclusion in another study
    - Age under 18 years

Patients who wish to withdraw from the study may do so at any point. Withdrawal will be presented as an absolute frequency.

1.4 Study Design

ARCTIC-I is a prospective, international, observational, multicentre cohort and nested case-control study.

1.5 Endpoints

1.5.1 Primary Endpoint

The proportion of patients able to live independently 3 months after their stroke is the primary endpoint. This corresponds to a modified Rankin scale (mRS) ≤ 2 (see table below).[8] At follow-up on day 90 (range, 80–105 days after ET), the mRS is assessed in a validated structured telephone interview with the patient (or relative), alternatively on the occasion of a clinical follow-up visit.

TABLE: MODIFIED RANKIN SCALE (adapted from Kasner[8]).

mRS	Description	Explanation
0	No symptoms	-
1	No significant disability	Able to carry out all usual activities, despite some symptoms
2	Slight disability	Able to look after own affairs without assistance, but unable to carry out all previous activities
3	Moderate disability	Requires some help, but able to walk unassisted
4	Moderately severe disability	Unable to attend to own bodily needs without assistance, and unable to walk unassisted
5	Severe disability	Requires constant nursing care and attention, bedridden, incontinent
6	Dead	-

1.5.2 Secondary Endpoints

The following secondary endpoints will be used (cf. data collection form, Appendix 9B).

- On the day of the intervention (day 0):
  - Duration from patient takeover by the anaesthesia team to arterial puncture (for ET)
  - Duration from arterial puncture to reperfusion (or, in case of futility, last attempt of clot removal)
  - Duration from patient takeover by the anaesthesia team to reperfusion (or last attempt of clot removal)
  - Proportion of technical success as graded by interventionalist (corresponding to an mTICI score[10,11] of 2b or better)
  - Frequency of conversion from sedation to general anaesthesia: proportion of patients primarily treated awake or with sedation that were subsequently intubated
  - Among the intubated patients: ratio of patients breathing spontaneously without endotracheal tube or supraglottic airway device before transfer from the angio suite
- At follow-up (90 days; range, 80–105 days)
  - Proportion of patients able to walk without assistance (i. e., mRS ≤ 3)
  - Mortality at 90 days (equivalent to frequency of mRS 6)
  - Functional outcome using the full ordinal mRS
  - The proportion of patients whose mRS score has not worsened (as compared to their pre-stroke status)

2 Statistical Methods

2.1 Planned Sample Size

A number of 10 observations per parameter of a multivariable model has been recommended for consistent estimation.[12] With a binary outcome this rule refers to the number of observations in the less frequent outcome class. Considering the subgroup of posterior circulation strokes, which represent approximately 20% of cerebral large vessel occlusions,[13] the overall sample size, which is expected to lie within the range of 5,000-10,000 patients for the given recruitment period of 1.5 years, reduces to 1,000-2,000 patients. With a binary outcome representing a rare event, for example occurring in 5% of the patients, there would be 50-100 events observed. This results in 50/10 = 5 to 100/10 = 10 parameters for estimation, which is already a limiting factor against the background of >10 predictor variables and the additional interaction effects that should be simultaneously investigated in a multivariable model. Therefore 5,000 patients overall is a minimum sample size needed for the planned analyses. Sample sizes up to 10,000 patients will be pursued to extend the multiplicity of the model and to thereby increase the information gain.

2.2 Data Sets for Analysis

In the main analyses, all participating patients are evaluated together, taking into account the handling of missing values described below.

2.3 Definitions and Handling of Missing Data

2.3.1 General Time Definitions

Day 0 is defined as the day of groin puncture for ET. All other day definitions are relative to Day 0. All analyses will be performed on day basis unless otherwise specified.

2.3.2 Definition of Days and Time Windows

- Screening: After ET
- Enrolment: Before day 90 (range, day 80–105)
- Data acquisition:
    - Section 1 and 2 of data collection form between enrolment and follow-up
    - Section 3 of data collection form at follow-up around day 90 (range, day 80–105)

2.3.3 Handling of missing values

Missing data might include missing co-variables for the regression models and missing answers upon follow-up. In case of missing values, multiple imputation,[14] conditional imputation by Random Forests[15] or use of nonparametric models[16] that can process missing values will be considered.

2.4 Analysis of endpoints

Exploratory univariable and multivariable regression models will be computed to investigate prognostic and predictive factors associated with treatment for each of the primary and secondary endpoints.[17] Centers will be included as clusters in these analyses, for example by use of robust Huber-White estimators of the covariance matrix or by use of random effects (intercepts) in mixed-effects models. Exploratory hypothesis testing of model coefficients and corresponding linear hypotheses will be performed at two-sided 5% significance levels and will be accompanied by 95% confidence intervals of effect estimates.

Sensitivity analyses will be performed by further parametric and nonparametric models from the field of personalized medicine, e.g. using the ‘Virtual Twins’ method[18] or inverse probability of treatment weighting (IPTW).[19]

A subgroup analysis of patients with occlusions in the anterior and posterior cerebral circulation will be performed by inclusion of interaction effects in the regression models.[20]

The statistical analyses will be performed with R version 4.0.3 or higher (The R Foundation for Statistical Computing, Vienna, Austria).

2.5 Demographics and other Baseline Characteristics

Patient characteristics (such as age, sex, pre-stroke mRS), stroke characteristics (such as symptom severity, location of vessel occlusion, early signs of infarction, latency to reperfusion) and other descriptive variables will be summarized by treatment group.

3 References

1. Goyal M, Menon BK, Zwam WH Van, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet (London, England)*. 2016;387:1723-1731. doi:10.1016/S0140-6736(16)00163-X

2. Wahlgren N, Moreira T, Michel P, et al. Mechanical thrombectomy in acute ischemic stroke: Consensus statement by ESO-Karolinska Stroke Update 2014/2015, supported by ESO, ESMINT, ESNR and EAN. *Int J Stroke*. 2016;11(1):134-147. doi:10.1177/1747493015609778

3. Davis MJ, Menon BK, Baghirzada LB, et al. Anesthetic management and outcome in patients during endovascular therapy for acute stroke. *Anesthesiology*. 2012;116(2):396-405. doi:10.1097/ALN.0b013e318242a5d2

4. Schönenberger S, Hendén PL, Simonsen CZ, et al. Association of General Anesthesia vs Procedural Sedation With Functional Outcome Among Patients With Acute Ischemic Stroke Undergoing Thrombectomy. *JAMA*. 2019;322(13):1283. doi:10.1001/jama.2019.11455

5. Venema AM, Uyttenboogaart M, Absalom AR. Land of confusion: anaesthetic management during thrombectomy for acute ischaemic stroke. *Br J Anaesth*. 2019;122(3):300-304. doi:10.1016/j.bja.2018.12.004

6. Talke PO, Sharma D, Heyer EJ, Bergese SD, Blackham KA, Stevens RD. Society for Neuroscience in Anesthesiology and Critical Care Expert consensus statement: anesthetic management of endovascular treatment for acute ischemic stroke. *J Neurosurg Anesthesiol*. 2014;26(2):95-108. doi:10.1097/ANA.0000000000000042

7. Hindman BJ, Dexter F. Anesthetic Management of Emergency Endovascular Thrombectomy for Acute Ischemic Stroke, Part 2: Integrating and Applying Observational Reports and Randomized Clinical Trials. *Anesth Analg*. 2019;128(4):706-7017. doi:10.1213/ANE.0000000000004045

8. Kasner SE. Clinical interpretation and use of stroke scales. *Lancet Neurol*. 2006;5(7):603-612. doi:10.1016/S1474-4422(06)70495-1

9. Bruno A, Akinwuntan AE, Lin C, et al. Simplified modified Rankin scale questionnaire: reproducibility over the telephone and validation with quality of life. *Stroke*. 2011;42(8):2276-2279. doi:10.1161/STROKEAHA.111.613273

10. Zaidat OO, Yoo AJ, Khatri P, et al. Recommendations on angiographic revascularization grading standards for acute ischemic stroke: A consensus statement. *Stroke*. 2013;44(9):2650-2663. doi:10.1161/STROKEAHA.113.001972

11. Almekhlafi MA, Mishra S, Desai JA, et al. Not all “successful” angiographic reperfusion patients are an equal validation of a modified TICI scoring system. *Interv Neuroradiol*. 2014;20(1):21-27. doi:10.15274/INR-2014-10004

12. Harrell FEJ. *Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis.* Springer International Publiching Switzerland 2015; 2015. doi:10.1007/978-3-319-19425-7_3

13. Nouh A, Remke S, Ruland S. Ischemic posterior circulation stroke: a review of anatomy, clinical presentations, diagnosis, and current management. *Front Neurol*. 2014;5(30). doi:10.3389/fneur.2014.00030

14. van Buuren S. *Flexible Imputation of Missing Data*. Second Edi. Chapman & Hall/CRC

Interdisciplinary Statistics. Boca Raton, FL; 2018.

15. Stekhoven DJ, Buehlmann P. MissForest - nonparametric missing value imputation for mixed-type data. *Bioinformatics*. 2012;28(1):112-118. doi:10.1093/bioinformatics/btr597

16. Hastie T, Tibshirani R, Friedman J. *The Elements of Statistical Learning: Data Mining, Inference, and Prediction*. Second Edi. New York, NY, USA: Springer US; 2009.

17. Steyerberg EW. *Clinical Prediction Models - A Practical Approach to Development, Validation, and Updating*. Springer International Publishing; 2009.

18. Foster JC, Taylor JM, Ruberg SJ. Subgroup identification from randomized clinical trial data. *Stat Med*. 2011;30(24):2867-2880.

19. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med*. 2015;34(28):3661-3679.

20. Zhang Z, Seibold H, Vettore MV, Song WJ, François V. Subgroup identification in clinical trials: an overview of available methods and their implementations with R. *Ann Transl Med*. 2018;6(7). doi:10.21037/atm.2018.03.07

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