TTM SUB-STUDY PROPOSAL

TRANSITIONS BETWEEN CIRCULATORY STATES IN POST-CARDIAC ARREST SYNDROME

MAIN HYPOTHESES TESTED

Research question 1: What is the development of transitions between different clinical circulatory states during PCAS?

Research question 2: What are the risk factors for the transitions (improvement vs. deterioration) in circulatory status during PCAS?

SINGLE CENTER [ ] , MULTICENTER [X]

Trondheim University Hospital

All TTM-2 sites (information from the eCRF)

PICO

Patients: Patients with sustained ROSC after OHCA, admitted to the intensive care unit or coronary care unit for further treatment.

Intervention/Exposure/Prognostic factor: RCT with two groups, where one group receives therapeutic hypothermia and the other group avoids fever.

Comparison: Categorization based on routine hemodynamic variables (mean arterial pressure, heart rate, serum lactate concentration, central venous oxygen saturation, amount of fluids, dosage of norepinephrine and dobutamine, use of vasopressin, epinephrine, levosimendan or artic balloon pump).

Outcome: Circulatory stability, assessed by circulatory categories.

DATA NEEDED FOR THE ANALYSIS (SPECIFY VARIABLES AND MOTIVATE ANY PROPOSED ADDITIONS TO THE ECRF)

This study is a sub-study of the TTM-II trial and inclusion data are obtained as a part of the TTM-II trial. Information related to medical history and the cardiac arrest is as described in the TTM-II protocol.

Circulatory data registered daily and used in this work are highest pulse rate, lowest mean arterial blood pressure, highest serum lactate concentrations, daily fluid balance, the highest dose of vasoactive medications and use of mechanic circulatory support.

LOGISTICS – HOW WILL ADDITIONAL DATA BE GATHERED?

The required data is obtainable in the proposed eCRF

BRIEF STATISTICAL ANALYSIS PLAN AND SAMPLE SIZE ESTIMATE

The circulatory state after CA will be categorized as undisturbed, disturbed or severely disturbed circulation based on routine hemodynamic variables (**table 1**). This categorization is adapted from an on-going study in Trondheim in order to comply with its use in a large multi-center study. A patient is classified according to the least favorable measurement (e.g. isolated mean arterial pressure (MAP) of 40 mmHg is sufficient to classify a patient as severely disturbed circulation).

	Circulation		
Variables	**Undisturbed**	**Disturbed**	**Severely Disturbed**
MAP, mmHg	≥ 65	45 - 64	< 45
HR, b.p.m.	51 – 100	< 50, 101 – 130	≤ 40, > 130
Lactate, mmol/l	< 2	2 – 4	> 4
$ScvO_2$, %	≥ 65	50 – 64	< 50
Fluid resuscitation, l/hours	< 0.5	0.5 – 1.9	≥ 2
Norepinephrine, $\mu g \cdot kg^{-1} \cdot min^{-1}$	< 0.1	0.1 – 0.29	≥ 0.3
Dobutamine, $\mu g \cdot kg^{-1} \cdot min^{-1}$	No	< 10	≥ 10
Vasopressin	No	No	Yes
Epinephrine	No	No	Yes
Levosimedan	No	No	Yes
Aorta balloon pump	No	No	Yes

Table 1: Circulatory states, without obvious painful stimuli. MAP = mean arterial pressure; HR = heart rate; b.p.m. = beats per minute. Please note that the categories may change after validation in an ongoing study.

Patients may go back and forth between the circulatory states defined above corresponding to the severity and clinical trajectory of PCAS. The transitions can be described as illustrated in **figure 1**.

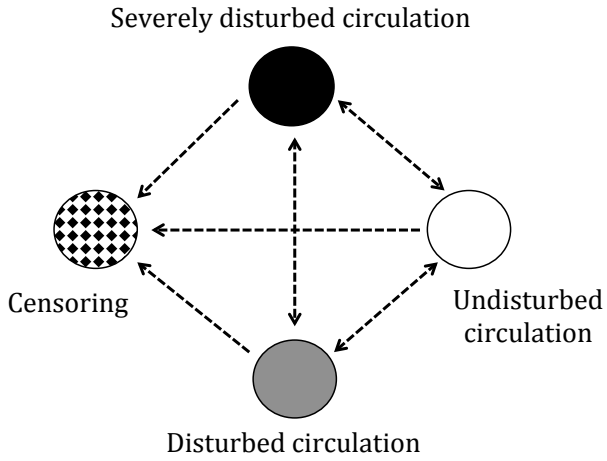

Figure 1: Transitions between circulatory states.

For transitions statistical methods from survival analysis can be applied. Survival analysis allow for right censoring, meaning that information from patients with a limited follow-up time can also be included in the analyses. A patient who is in a certain clinical state at a certain time-point (t) might remain in the same state or move to one of three others at time t+1. In such multi-endpoint settings, the clinical states "compete" with each other, and the transitions over time are studied with methods developed for competing risk analyses. The Kaplan-Meier estimator accurately estimates a transition from one state to another, assuming that these two states describe all possible states. To be useful in a competing risk framework, the Kaplan-Meier estimator is generalized into a matrix version, the Aalen-Johansen estimator. The Nelson-Aalen estimator is a non-parametric estimator of the “cumulative hazard” of a given event, and can be applied in a multi-state model.

We anticipate that not all patients will follow the same circulatory trajectory; some will deteriorate and some will improve their circulatory status, and many will have several state transitions. We will analyze events prior to changes to identify patterns of factors predictive of circulatory deteriorations.

To explore the predictive value of observations to foresee a clinical deterioration we will use two approaches. First, the outcome variable will be dichotomized as deterioration versus no deterioration (unchanged or improvement). For these analyses we will use univariable analyses to identify factors to be included in multivariable logistic

regression. Second, we will use methods from survival analysis to assess continuous alterations in covariates on the outcome. For this analysis, we will use Aalen's linear model, which is an intensity regression model.

FUNDING (IF APPLICBABLE)

Ph.D. student Halvor Langeland, who has a Ph.D. scholarship from the Health Region of Mid-Norway, will perform the analyses.

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Halvor Langeland (Ph.D. student Trondheim), Knut Bjørnstad (cardiologist Trondheim), Magnus Løberg (statistician). Other co-authors in Trondheim to be decided based upon contribution to the TTM-2 study. Co-authors from other TTM-2 sites to be decided by the TTM-2 organization