Neurological recovery and health related quality of life after cardiac arrest and targeted temperature management – additional exploratory outcomes from the Target Temperature Management (TTM) trial

Background A large clinical trial compared the effect of targeted temperature management at 33°C or 36°C and found no significant differences in mortality or the composite outcome of mortality and a poor neurological outcome defined as modified Rankin Scale 4 and 5 or Cerebral Performance Category 3 and 4. The neurological outcome scales CPC and mRS used in the trial, are well established and the CPC scale is recommended by international guidelines. Nevertheless they are crude and do not exclude more subtle differences in neurological outcome.

Purpose of study To compare the neurological status at 6 months follow up between the two intervention groups in the modified intention-to-treat population. For those outcomes which includes death as a component of the measuring scale the comparison will include the whole modified intention-to-treat population and for those outcomes where this is not the case the comparison will be confined to those patients from the population who were alive at the time of follow-up. In a sensitivity approach the outcomes not including death will also be compared giving the dead patients the worst possible score to compensate for survival bias.

Outcome measures (1 and 2 reported in the main publication)

(1) mRS=modified Rankin Scale: 0-6, 0-3 good neurol outcome, 4-6 poor (6 death)

(2) CPC=Cerebral Performance Category: 1-5, 1, 2 good neurol outcome, 3-5 poor (5 death)

(3) MMSE=mini mental state exam: 0-30 (0 – 22 if interview was performed using a telephone (MMSE_ALFI)). Higher is better. The score was a) analysed as a continuous quantity, b) transformed into a binary quantity using a cut off value of larger than 26 for least or no neurological impairment (or larger than 18 if the interview was by telephone) and c) scores not obtained by telephone were transformed into an ordinal quantity using the following categories: normal (scores 27 to 30), mild cognitive impairment (21 to 26), moderate cognitive impairment (11 to 20) and severe cognitive impairment (0 to 10).

(4) IQCODE= informant questionnaire for the elderly: 26 questions forming a score ranging from 26 to 130. Lower is better. A score of 78 indicates that the patient has not declined or improved after the cardiac arrest. The score was analysed as a continuous quantity, as a binary quantity (cut off value larger than 78) and an ordinal quantity using the following categories: no change or better (26 to 78), minor change (79 to 83), moderate change (84 to 86) and major change (larger than 86)

(5) TSQ-combined (see below for definition) based on the answers of TSQ 1 and TSQ 1.1: 1. In the last two weeks did you require help from another person for your everyday activities?
1.1 If yes, is this a new situation following your heart arrest?
TSQ-combined coded as: 1: yes to both questions, 0: otherwise.

(6) TSQ 2. Do you feel that you have made a complete recovery after your heart arrest 1:yes/0:no?

(7 and 8) SF-36v2: Health related quality of life questionnaire. 36 questions forming 8 health domains all contributing to two main summary scores (Mental Component Summary and Physical Component Summary). The QualityMetrics Inc scoring software 4.0 will be used used. The composite scores of mental health (MCS) (7) and physical health (PCS) (8) will be compared between the intervention group, but all domains will be shown in a descriptive figure.

(9) thegroup of patients with "No detectable deficits" defined as (MMSE scores > 26 (or >17 if MMSE-ALFI = 1)) AND IQCODE lower than 79 AND TSQ-combined=0 AND TSQ2=1

(10) A similar binary division as in (9), using a modified cut-off of IQCODE including patients with minor change defined as (MMSE scores > 26 (or >17 if MMSE-ALFI = 1)) AND IQCODE lower than 84 AND TSQ-combined=0 AND TSQ2=1, to be used as a sensitivity analysis.

Statistical analysis

The analysis is exploratory. To contrast the difference between the intervention groups with the within groups variability statistical tests as explained in the following will be done, and the corresponding P values used as a screening device to identify hypothesis generating differences using a threshold value of $P < 0.05$.

Continuous quantities and binary quantities will be compared between the groups using the general univariate linear model and logistic regression respectively. Ordinal quantities will be compared using the proportional odds model for cumulative probabilities of the type $P(Y \leq j) = P_0 + P_1 .. + P_j$ where the categories of the response variables are indexed by integers and j can attain values between 0 and k-1, where k is the number of possible categories. If the assumption of the model is not fulfilled ($P < 0.05$) the Cochrane-Armitage test for trend will be used. Each regression analysis will be done (a) without adjustment, (b) with adjustment by the protocol specified stratification quantity site and (c) with adjustment by the design variables. If the quantity site proves to include too many parameters to allow convergence or generates unrealistically high parameter estimates and standard errors the site category (one group comprising the two sites with the largest number of patients and another comprising the rest of the sites) will be used instead. However, this does not imply that the intention of an adjustment by the protocol specified stratification variable will be fulfilled, but site category carries some prognostic information which will be combined with that of the design variables.

For patients alive at follow up, missing values will be imputed using multiple imputations (MI) if the percent of patients with missing values (missing outcome value and or missing adjusting covariate values) exceeds 5% for one or more outcomes or P of Little's test < 0.05. Candidate variables for imputation will be age, gender, time to ROSC, initial rhythm shockable or not, circulatory shock on admission present or not, randomisation code, CPC at hospital discharge, CPC score at follow up (fup-CPC), mRS score at follow up (fup-mRS), IQCODE, MMSE, MMSE_ALFI (1 if interview is by phone and 0 otherwise),TSQ-combined, TSQ2, SF-36 summary scores (MCS and PCS) and if possible for technical reasons, site.

Binary MMSE will first be calculated using the information on MMSE and MMSE-ALFI. If MMSE-ALFI = 1 then MMSE will be set equal to missing. Then binary IQCODE, ordinal-MMSE and ordinal-IQCODE will be calculated. In the subsequent MI only MMSE and IQCODE will be included (as continuous quantities) but not binary MMSE or binary IQCODE or ordinal MMSE or ordinal IQCODE. In the files containing imputed values missing binary-MMSE, missing binary-IQCODE, missing ordinal-MMSE and missing ordinal-IQCODE will be calculated. For binary MMSE the cut off value of MMSE > 26 will be used. To assess the span of potential bias caused by values missing not at random missing values among patients with no detectable deficits will be imputed by the worst possible value in one group and the best possible value in the other group and vice versa.

The analyses will be performed both unadjusted and adjusted for site and design variables of the TTM-trial (if technically possible). If this is not technically possible adjustment will be made by design variables and the site category. Because of the exploratory nature of the analysis and the groups not fully balanced by the initial randomization the adjusted analyses will be presented in the manuscript and the unadjusted in the supplementary appendix.