Pulse Glucocorticoid Therapy in Patients With ST-Segment Elevation Myocardial Infarction

PULSE-MI

NCT05462730

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Statistical Analysis Plan (SAP)

The overall statistical plan was published prior to completion of the trial[1].

Sample Size

The sample size was calculated based on the primary outcome of final infarct size measured by late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) at three months. Based on results of the CMR sub-studies of the DANAMI-3 trial[2,3], the mean final infarct size measured by LGE on CMR is 13% with a standard deviation (SD) of 9% in patients with ST-segment elevation myocardial infarction (STEMI). The trial was powered to demonstrate a reduction in final infarct size of 20% with a two-sided alpha level of 0.05 and a power of 80% requiring 378 patients. A drop-out rate of 30% was expected for the primary outcome but will be adjusted according to the actual drop-out rate. Inclusion of patients will continue until 378 has completed the follow-up CMR.

Statistical Analysis

Due to the inclusion and randomization in the prehospital setting, post-randomization exclusions of patients who do not fulfill criteria is expected. The post-randomization exclusions will include patients who are not eligible or patients with other reasons for ST-segment elevation[1]. A differentiation between a classic type 1 acute myocardial infarction with plaque rupture and thrombosis formation and a type 2 acute myocardial infarction with other reasons for ST-segment elevation (e.g. takotsubo, myocarditis, pericarditis, spontaneous coronary artery dissection, coronary embolism, coronary spasm, anemia, etc.[4]) can only be made after further evaluation including initial coronary angiogram and thus after inclusion. Patients included and subsequently excluded will not be included in the modified intention-to-treat population. The modified intention-to-treat population is prespecified and will not be changed during the trial.

Analyses for the primary and secondary outcomes will be performed in the modified intention-to-treat population[1]. Thus, safety including adverse events and serious adverse events and reactions will be assessed in all randomized patients which will be included in the Supplemental Material. Safety in all randomized patients will be further analyzed by calculating a cumulative incidence curve of all-cause mortality at three months which will be included in the Supplemental Material.

The primary outcome will be tested for normality using Q-Q plot to identify if the observed data is approximate to the expected data[5]. If the primary outcome is normally distributed, mean and standard deviation (SD) will be presented using a Student's t-test to test for differences between treatment groups, whereas median and interquartile range (IQR) and Wilcoxon Rank Sum test will be used if the primary outcome is not normally distributed. Each continuous secondary outcome will be tested for normality and will be presented as either mean and SD or median and IQR. Categorical outcomes will be presented as frequencies and percentages. To assess safety in all randomized patients, the cumulative incidence of adverse events, serious adverse events, and serious adverse reactions will be tested for differences between groups using Chi-Square or Fisher's exact test. Cumulative incidence curve will be calculated for all-cause mortality. Using a Fine and Gray model[6], hospitalization for heart failure will be analyzed with death considered as a competing risk.

Reporting of effect sizes was not prespecified in the protocol. For effect sizes of efficacy outcomes, mean differences with 95% confidence interval (CI) will be calculated if parametric. For non-parametric numeric outcomes, Wilcoxon-Mann-Whitney odds ratio will be calculated including 95% CI (ties are equally split between groups)[7]. To present a change in percent, the effect size for troponin-T and creatine kinase-MB will be calculated using linear regression following log transformation. The effect size of categorial efficacy outcomes will be calculated as relative risk ratios and the 95% CI will be calculated using the Wald method[8]. For all-cause mortality and hospitalization for heart failure, the relative risk will be calculated using Cox proportional hazard analysis and presented as hazard ratios with 95% CI. Hospitalization for heart failure will be calculated with death considered as a competing risk[9].

In the prespecified subgroup analyses of the primary outcome, mean with standard deviation or median and IQR if non-normally distributed will be given for each group. Mean difference or Wilcoxon-Mann-Whitney odds ratio with 95% CI will be used to elucidate the effect size on the primary outcome in each subgroup[7]. A prespecified linear regression analysis of the primary outcome will be evaluated adjusting for the area at risk in the acute cardiac magnetic resonance scan and tested for interaction with the treatment allocation.

Secondary efficacy outcomes in patients assessed for the primary outcome will be presented in a Supplementary Table. To elucidate potential differences between patients who were assessed for the primary and secondary outcomes and patients who were not, baseline tables stratified by competition of acute and follow-up CMR will be included as a sensitivity analysis in the Supplemental Material.

The P-value of the primary outcome will be two-sided and will be considered statistically significant if less than 0.050. All statistical analyses will be performed in R Studio, version 4.3.2 (RStudio Team [2020]. RStudio: Integrated Development for R. RStudio, PBC, Boston, MA; URL: http://www.rstudio.com/) using extension packages *survival* and *effectsize*.

References

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